British Journal of Nutrition (2020), 124, 641–653
doi:10.1017/S0007114520001415

Effect of walnut consumption on markers of blood glucose control: a systematic review and meta-analysis

Elizabeth P. Neale[1,2]*, Vivienne Guan[1,2], Linda C. Tapsell[1,2] and Yasmine C. Probst[1,2]

[1]*School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, NSW 2522, Australia*
[2]*Illawarra Health and Medical Research Institute, University of Wollongong, NSW 2522, Australia*

(Submitted 23 October 2019 – Final revision received 24 March 2020 – Accepted 5 April 2020 – First published online 21 April 2020)

Abstract

Type 2 diabetes mellitus is a chronic disease increasing in global prevalence. Although habitual consumption of walnuts is associated with reduced risk of CVD, there is inconsistent evidence for the impact of walnut consumption on markers of glycaemic control. This systematic review and meta-analysis aimed to examine the effect of walnut consumption on markers of blood glucose control. A systematic search of Medline, PubMed, CINAHL and Cochrane databases (to 2 March 2019) was conducted. Inclusion criteria were randomised controlled trials conducted with adults which assessed the effect of walnut consumption on fasting blood glucose and insulin, glycated Hb and homeostatic model assessment of insulin resistance. Random effects meta-analyses were conducted to assess the weighted mean differences (WMD) for each outcome. Risk of bias in studies was assessed using the Cochrane Risk of Bias tool 2.0. Sixteen studies providing eighteen effect sizes were included in the review. Consumption of walnuts did not result in significant changes in fasting blood glucose levels (WMD: 0·331 mg/dl; 95 % CI −0·817, 1·479) or other outcome measures. Studies were determined to have either 'some concerns' or be at 'high risk' of bias. There was no evidence of an effect of walnut consumption on markers of blood glucose control. These findings suggest that the known favourable effects of walnut intake on CVD are not mediated via improvements in glycaemic control. Given the high risk of bias observed in the current evidence base, there is a need for further high-quality randomised controlled trials.

Key words: **Nuts: Walnuts: Glycaemic control: Blood glucose: Systematic reviews: Meta-analyses**

Nutrition plays an increasingly important role in the prevention of chronic diseases including CHD and type 2 diabetes mellitus (T2DM)[1,2]. The global prevalence of T2DM is increasing. In 2017, 424·9 million adults globally had diabetes and this is projected to increase to 628·6 million by 2045[3]. Research has demonstrated that lifestyle strategies such as dietary changes are effective for the prevention and management of T2DM[4]. While dietary patterns exert the effect, they are the sum of individual food choices. There is therefore a need to establish the evidence for individual foods which may aid in the prevention of T2DM, as well as improve disease management for persons already diagnosed.

Walnuts are part of the nut category of foods but stand out for their high PUFA content[5] which is aligned to cholesterol lowering effects. This and other components in walnuts and nuts generally contribute to reduced risk of CHD. For the food category of nuts, habitual consumption has been associated with the reduced risk of CHD[6–10], but the evidence base for T2DM is less consistent. Recent systematic reviews of observational and clinical studies have reported conflicting results, with an inverse relationship between nut intake and risk of T2DM found by one review[7], yet no association reported in others[6,8,11]. Inconsistent results have also been reported when the effect of nut consumption on markers of glycaemic control has been investigated. In a systematic review restricted to individuals with T2DM, nut consumption was found to improve glycated Hb (HbA1c) and fasting glucose levels, with no impact on fasting insulin or homeostatic model assessment of insulin resistance (HOMA-IR)[12]. Conversely, favourable effects of nut intake on fasting insulin and HOMA-IR were found in another review, although no effect on HbA1c or fasting glucose was found[13]. To our knowledge, an umbrella review of systematic reviews specifically exploring the effect of nut consumption in T2DM or markers of glycaemic control has not been conducted to clarify these inconsistent results.

Given the variation in composition of different types of nuts, there is value in considering the impact of individual nut categories. As stated earlier, walnuts are distinguishable from other nuts by virtue of a high PUFA content, including α-linolenic acid, while also delivering dietary fibre and phytochemicals[5,14].

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; T2DM, type 2 diabetes mellitus.

* **Corresponding author:** Elizabeth P. Neale, email elizan@uow.edu.au

A past analysis of the Nurses' Health Study found increased consumption of walnuts was associated with reduced incidence of T2DM, although the relationship may be partly mediated by BMI[15]. There may be a number of reasons for this observation. For example, secondary analysis from dietary trials[16,17] demonstrated that provision of walnuts appeared to support changes in overall diet quality. Here, the consumption of walnuts could be implicated in whole-of-diet effects for behavioural as well as biological reasons. With these issues in mind, the aim of this systematic review and meta-analysis was to examine the effect of walnut consumption on markers of blood glucose control (fasting blood glucose, fasting insulin, HbA1c and HOMA-IR) in adults.

Methods

This systematic review was conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[18] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[19] (online Supplementary Data 1). The protocol for the review was prospectively registered with PROSPERO, the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/, CRD42019123636).

Study eligibility

To be eligible for inclusion in this review, studies were required to meet the following inclusion criteria: (1) randomised controlled trial study design (including parallel and cross-over designs, and studies where participants were randomised at either the individual or cluster level); (2) studies conducted with humans aged 18 years or older; (3) studies assessing the effect of consuming walnuts (as a whole or processed nut, or oil form) on biological markers of blood glucose control (fasting blood glucose, HbA1c, fasting insulin and HOMA-IR) and (4) studies where the effect of walnut consumption could be isolated from other food sources or interventions such as physical activity programmes. Eligible studies were not limited to those published in English, or by study duration.

Data sources

A systematic search of the databases MEDLINE (EBSCO), PubMed, Cumulative Index to Nursing and Allied Health Literature (EBSCO) and Cochrane Central Register of Controlled Trials was conducted by E.P.N. Date restrictions were not applied, and the databases were searched on 2 March 2019. Both MEDLINE and PubMed were searched to ensure that recent studies were detected, in line with recommendations by Rosen & Suhami[20]. Where possible Medical Subject Headings in addition to free-text search terms were used in the search[20]. Reference lists of eligible articles and relevant review articles were also reviewed for potential studies. An example of the search strategy is available in online Supplementary Data 2. Articles were initially processed using Endnote X8 (2017, Endnote X8.1 (software)) including removal of duplicates, before being transferred into Microsoft Excel (2016, Microsoft Excel version 16.0 (software)) for screening and full-text review.

Study selection

Articles were screened in duplicate based on the title and abstract. In the case that an abstract was not available or did not provide sufficient information to draw a conclusion regarding eligibility, the full-text articles were retrieved for further review. Following screening, full-text articles were reviewed in duplicate against the eligibility criteria. In the case that multiple articles reported results from a single study, all associated articles were checked to avoid duplication of study populations in the analysis. Where multiple articles reported different information for the outcomes of the same study, all relevant articles were included and linked together, as recommended by the Cochrane Handbook[18]. When multiple articles reported the same outcomes from a single study, the article reporting the longest follow-up period was included in the review.

Data extraction

The following data were extracted from each study: citation, country, study design, sample size, participant age and BMI, participant health status, study duration, walnut form, dose of walnuts, details of control arm, background diet and the percentage dietary fat consumed in the intervention diet. Aggregate outcome data were extracted from each study. Where possible, the mean changes in the relevant biomarker outcomes and the respective standard deviation (or standard error/95 % CI) were obtained. When these data were not available, the mean final values and the respective standard deviation (or standard error/95 % CI) were retrieved as outlined in the Cochrane Handbook for Systematic Reviews of Interventions[18]. Where median and interquartile range were provided, these were converted into mean and standard deviation using the formula developed by Wan *et al.*[21]. As one study[22] provided only pooled standard error for the intervention and the control groups, this pooled standard error was used for both groups. In the case that the published study did not provide adequate information, study authors were contacted for additional details. Where available, data from intention-to-treat analyses were extracted for use in the meta-analysis. Where this was not available, data from per protocol analyses were used and the impact of these approaches on study results was considered in the risk of bias assessment (outlined below).

Abstract screening, full-text review and data extraction were conducted independently by two authors (E. P. N. and V. G.), with any disagreements were resolved via consensus. Where consensus could not be reached, a third author was consulted (Y. C. P.).

Risk of bias assessment

The Cochrane Collaboration Risk of Bias tool 2.0[23] was used to determine the risk of bias in the included studies, with the effect of assignment to the interventions considered. E. P. N. and V. G. independently appraised the risk of bias, and disagreements were resolved by discussion until consensus was reached.

Data synthesis

Stata IC (version 15.1; StataCorp LLC) was used to conduct random effects meta-analyses, using the metan command (using the randomi option for random effects). This command uses the DerSimonian and Laird method with the heterogeneity estimate taken from the inverse variance fixed effects model[24,25]. Sensitivity analyses were also conducted using the random effects model with Hartung–Knapp–Sidik–Jonkman adjustment[26]. Weighted mean differences (with 95 % CI) in change or final mean values for each outcome were calculated. As both parallel and cross-over studies were included in the review, both study designs were initially analysed the same way, using a paired analysis. This approach was used as it is the most conservative method for managing cross-over studies in meta-analysis[18]. In addition, sensitivity analyses were conducted using paired analysis of cross-over studies with correlation coefficients of 0·25, 0·5 and 0·75, in order to determine if this analysis underweighted the cross-over studies, as conducted in our previous review on nuts as a food group[27]. In the case of two studies which included more than one eligible intervention group and corresponding control groups[17,28], study groups were included in meta-analyses as separate effect sizes. Sensitivity analyses were then further conducted to examine the effect of pooling these separate study groups on results. Meta-analyses were conducted using available cases analyses, with attrition addressed as part of the risk of bias assessment (outlined below).

The I^2 test statistic was used to estimate the proportion of total variation attributable to the between-study heterogeneity[29]. In line with the guidance of Higgins *et al.*[29], I^2 values of 25, 50 and 75 % were taken to indicate low, moderate and high heterogeneity. Contour funnel plots were created to determine the presence of small study effects for outcomes with ten or more effect sizes[30]. An Egger's test was then conducted to examine the extent of funnel plot asymmetry[31]. 'Leave-one-out' sensitivity analyses were conducted to explore the effect of removing each individual study from the meta-analyses. In addition, to explore the effects in whole walnuts only, sensitivity analyses were conducted excluding studies using walnut oil[28,32]. Pre-specified sub-group analyses (based on study quality, study duration (less than 3 months *v.* more than 3 months, aligning with the approaches used in previous meta-analyses of nut consumption[12,33]) and health status of participants) were conducted to explore differences in the magnitude of effects between the sub-groups. In addition, *post hoc* sub-group analyses were conducted based on the dose of walnuts consumed (<50 *v.* >50 g/d, based on dose sub-groups used in a previous meta-analysis of nut consumption[33]) and the percentage of total dietary fat provided by the intervention diet (<37 *v.* ≥37 %/d, based on previous research which found beneficial effects of fat substitution at total fat intakes <37 %[34]). Sub-group analyses were conducted where there were at least ten effect sizes per outcome in total[18], although the number of effect sizes per individual sub-group was not restricted. The relationship between the nut dose (in studies exploring whole nuts only) and the study duration, as continuous characteristics, was then explored via random effects meta-regression using the metareg command[35] which uses the Knapp–Hartung variance estimator[36], where sample size permitted, as recommended by the Cochrane Handbook[18].

Quality of the body of evidence

The quality of the body of evidence (also known as certainty) was then determined using GRADE[37] (GRADEpro GDT: GRADEpro Guideline Development Tool (Software). McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from www.gradepro.org)

Results

A total of 3642 records were identified from the systematic search and the review of reference lists and review articles. After the removal of duplicates, 1862 records were screened and sixty-eight full-text articles were reviewed for eligibility. A total of fifty-one articles were excluded after full-text review, with the most common reasons for exclusion being an inability to isolate the effects of walnuts on the outcome of interest (*n* 15), for example, when walnuts were provided as part of a suite of dietary changes, the article did not report relevant outcomes (*n* 10), and relevant study outcomes were reported in another article included in the review (*n* 10) (Fig. 1, online Supplementary Data 3). This resulted in a total of seventeen articles describing sixteen studies included in this review. Through these articles, eighteen effect sizes were available for inclusion in the meta-analysis (Fig. 1).

Study characteristics

Characteristics of included studies are outlined in Table 1. Eight studies[28,32,38–44] had a parallel study design, while seven[22,45–50] had a cross-over study design. In addition, one study[17] included features from both a parallel and cross-over design, where the participants were randomised to a parallel group (either energy adjusted or *ad libitum* diet), and each group was intervened with a walnut-included diet period and a walnut-excluded diet period. The duration of the included studies ranges from 4 d[46] to 1 year[39,43,44]. Studies were conducted in Germany[45,50], the USA[17,22,43,46,48,49], Spain[47], Austria[28], South Africa[38,42], Australia[39,40,44], China[41] and Iran[32]. Studies included participants who were healthy (inclusive of overweight participants)[22,45,50], had the metabolic syndrome or other risk factors for chronic disease[17,38,41–43,46–48], had T2DM[28,32,39,40,49] or included participants with a mixture of these factors[44].

Consumption of walnuts

Walnuts were consumed as whole nuts in fourteen of the included studies[17,22,38–50] and as an oil in two of the studies[28,32]. The dose of whole walnuts consumed by participants ranged from 30 g (1·06 oz)[39–41,44] to 56 g (1·98 oz) per d[48,49]. In three studies, walnuts were consumed to provide a prescribed proportion of dietary energy (ranging from 18 to 22 % of total energy)[38,42,43,47], meaning the dose of walnuts differed between the participants. The energy value of the walnuts was accounted for in thirteen studies[22,38–50], either by modelling the energy of the walnuts into the dietary prescription, or by encouraging the

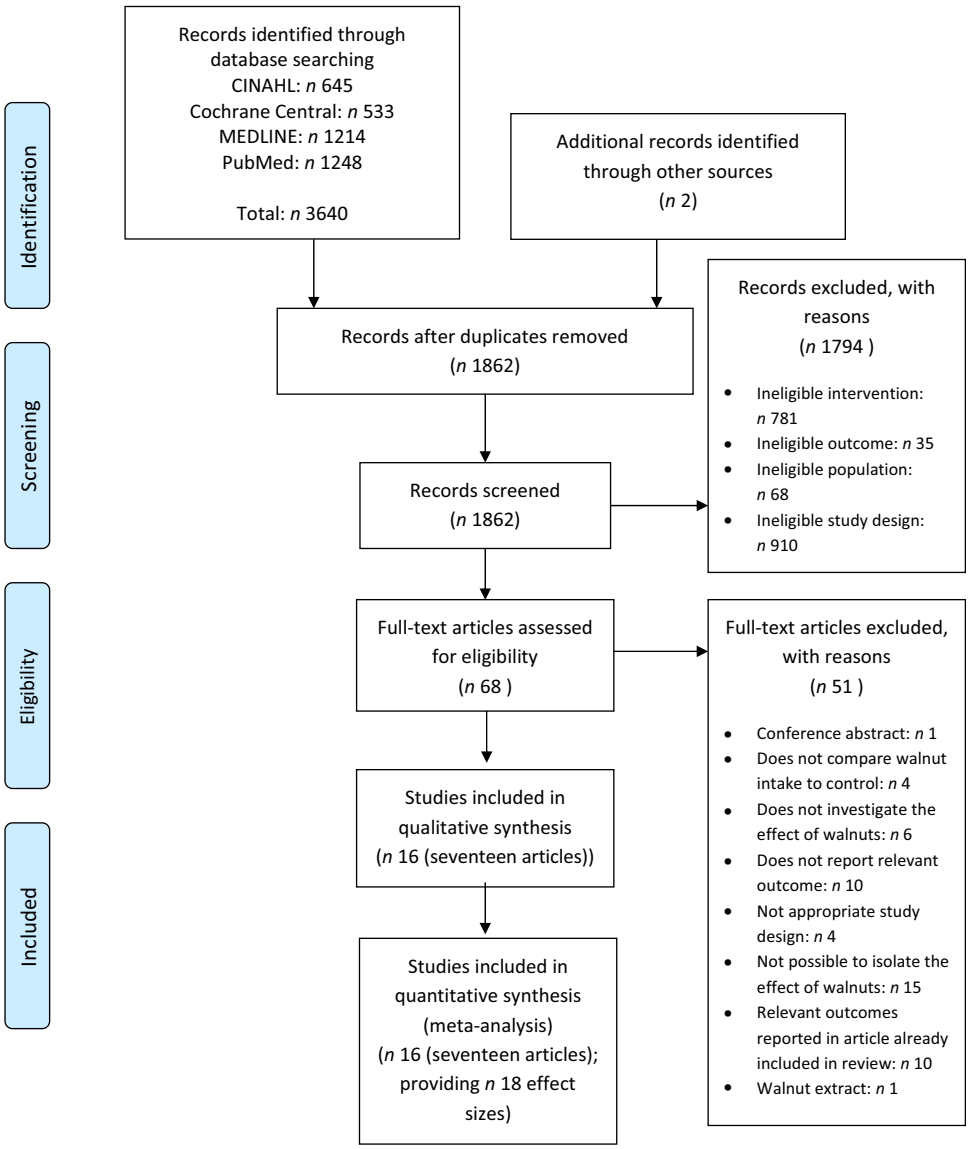

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

participants to substitute walnuts for other food in their diet. One study[17] included two different intervention groups, with one group accounting for the added energy from the walnuts, whereas another group added the walnuts in addition to their regular diet. The background diets used in the studies included dietary advice based on healthy eating guidelines (e.g. the Australian Guide to Healthy Eating), as well as habitual diets (with the addition of walnuts for the intervention groups). Control groups typically followed the same background diet as the intervention group, with the exception of the added walnuts, although some studies included a comparison food in their control group (e.g. olive oil[47]).

Risk of bias assessment

The risk of bias assessments is shown in Fig. 2 and online Supplementary Data 4 and 5. Studies were determined to have either 'some concerns' regarding the risk of bias, or be at 'high risk' of bias, with no studies found to be at 'low risk' of bias.

Effect of nut consumption on study outcomes

The number of effect sizes and studies, as well as the results of each meta-analysis, is shown in Table 2 and Figs. 3–6. Summary data for each study are available in online Supplementary Data 6. Walnut consumption did not result in significant differences in the fasting blood glucose, HbA1c, fasting insulin or HOMA-IR (Table 2 and Figs. 3–6). Similar results were found when conducting sensitivity analyses using Hartung–Knapp–Sidik–Jonkman adjustment[26] (online Supplementary Data 7), and when using correlation coefficients of 0·25, 0·5 and 0·75 for cross-over studies (online Supplementary Data 8).

The results of sensitivity analyses indicated that pooling separate intervention groups within the same study did not

British Journal of Nutrition

Table 1. Characteristics of included randomised controlled trials examining the effect of walnut consumption on blood glucose measures

Citation and country	Sample size for analysis (sex)	Mean age (years)	Mean BMI (kg/m^2)	Population	Design	Study duration (weeks)	Whole walnut or oil	Nut dose	Control group details	Background diet	Dietary fat intake (%)*	Blood glucose measures (units)
Bamberger *et al.*[45], Germany	204 (M, F)†	63 (0·54)‡	25·4 (0·29)‡	Healthy (including overweight)	X	8	W	43 g/d	Western diet	Nuts replacing 70 g carbohydrate or 30 g saturated fat	43–46	FBGL (mg/dl) HbA1c (%)
Brennan *et al.*[46], USA	15 (M: 9, F: 6)	58·0 (2·5)‡	36·9 (1·7)‡	MetS	X	0·6	W	48 g/d	Placebo meal containing 2·14 % protein, 48·55 % fat and 49·31 % carbohydrate	Isoenergetic diet, controlled	46·05	FBGL (mg/dl) Insulin (μIU/ml)
Damasceno *et al.*[47], Spain	18 (M: 9, F: 9)	56 ± 13§	25·7 ± 2·3§	HC	X	4	W‖	40–65 g/d¶ (22 % energy)	35–50 g/d virgin olive oil	Mediterranean-style diet (isoenergetic)	32	FBGL (mmol/l**)
Holscher *et al.*[22], USA	18 (M: 10, F: 8)	53·1 (2·2)‡	28·8 (0·9)‡	Healthy (including overweight)	X	3	W	42 g/d	Base diet (17 % protein, 29 % fat, 54 % CHO) of typical American foods, unsupplemented with walnuts	Base diet (17 % pro, 29 % fat, 54 % CHO) of typical American foods. Energy reduced proportionally to incorporate walnuts	>50	FBGL (mg/dl)
Katz *et al.*[48], USA	46 (M: 18, F: 28)	57·4 ± 11·9§	33·2 ± 4·4§	Overweight plus risk factors for MetS	X	8	W	56 g/d	No nuts	*Ad libitum*, participants advised to substitute walnuts for other foods	41·4	FBGL (mg/dl) Insulin (μIU/ml) HOMA-IR
Ma *et al.*[49], USA	24 (M: 10, F: 14)	58·1 ± 9·2§	32·5 ± 5·0§	T2DM	X	8	W	56 g/d	No nuts	*Ad libitum*, participants advised to substitute walnuts for other foods	45	FBGL (mg/dl) HbA1c (%) Insulin (μIU/ml) HOMA-IR
Mukuddem-Peterson and Mukuddem-Petersen *et al.*[38,42], South Africa	43 (M: 21, F: 22	I: 45 (95 % CI 40·4, 50·2) C: 45 (95 % CI 40·8, 49·3)	I: 36 (95 % CI 33·3, 38·7) C: 35·1 (95 % CI 32·8, 37·4)	MetS	P	8	W‖	20 % energy from walnuts ¶	No nuts	Controlled feeding protocol (isoenergetic)	40·3	FBGL (mmol/l**) Insulin (μIU/ml) HOMA-IR
Mullner *et al.*[28], Austria	92 (*nut oil*: M: 20, F: 27; *mixed oil*: M: 18, F: 27)	*Insulin treated:* I: 63 (95 % CI 58·5, 67·5) C: 66·1 (95 % CI 62·5, 69·7) *OAD treated*: I: 62·3 (95 % CI 59·5, 65·2) C: 60·9 (95 % CI 57·8, 63·9)	*Insulin treated* I: 90·1 (95 % CI 79·4, 100·7) C: 93·7 (95 % CI 84·2, 103·1)†† *OAD treated*: I: 86·3 (95 % CI 79·6, 92·9) C: 87·6 (95 % CI 81·2–93·9) ††	T2DM (treated with OAD or insulin)	P	1	O	9 g oil/d	Mixed oil (maize, sunflower, linseed oil)	Usual diet	NR	FBGL (mM**) HbA1c (%) Insulin (pM**) HOMA-IR
Njike *et al.*[17], USA	112 (M: 31, F: 81)	*Ad libitum:* 56·5 ± 11·7§ *Energy adjusted:* 53·3 ± 11·1§	*Ad libitum:* 30·0 ± 4·0§ *Energy adjusted:* 30·2 ± 4·1§	Overweight, pre-diabetic or MetS	X‡‡	24	W	56 g/d	No nuts	1. *Ad libitum* diet 2. Isoenergetic diet (energy adjusted for walnuts)	NR	FBGL (mg/dl) HbA1c (%)
Rock *et al.*[43], USA	126 (F)	50 (range: 22–72)§§	33·5 (range: 27–40)§§	Overweight and obese	P	52	W	42 g/d‖‖ (18 % energy)	Higher fat (35 % energy) lower CHO (45 % energy) diet, no nuts‖	Hypoenergetic diet (500–1000 kcal/d deficit)	35	FBGL (mg/dl) Insulin (μIU/ml) HOMA-IR
Tapsell *et al.*[40], Australia	35 (M: 21, F: 16)	I: 57·71 ± 8·97§ C: 59·30 ± 7·11§	I: 30·72 ± 3·85§ C: 30·16 ± 4·51§	T2DM	P	26	W	30 g/d	<30 % fat, modified fat¶¶	<30 % fat, modified fat	Approximately 32	HbA1c (%)

Table 1. (*Continued*)

Citation and country	Sample size for analysis (sex)	Mean age (years)	Mean BMI (kg/m^2)	Population	Design	Study duration (weeks)	Whole walnut or oil	Nut dose	Control group details	Background diet	Dietary fat intake (%)*	Blood glucose measures (units)
Tapsell *et al.*[39], Australia	35 (M, F) †	54 ± 8·7§§	I: 33·2 ± 4·4 C: 33·0 ± 4·0	T2DM	P	52	W	30 g/d	Low-fat advice (weight maintenance)	Low-fat advice (weight maintenance)	Approximately 34	FBGL (mmol/l**) HbA1c (%) Insulin (μU/l**)
Tapsell *et al.*[44], Australia	101 (M, F) † 100 (M, F) ‖‖	45 (37–51)*** †††	32 (29–35)*** †††	Overweight and obese (including T2DM)	P	52	W	30 g/d	Interdisciplinary intervention (dietitian, exercise physiologist, psychologist support)¶¶	Individualised dietary advice based on Australian Guide to Healthy Eating	Approximately 33	FBGL (mmol/l**) HbA1c (%)
Wu *et al.*[41], China	189 (M: 105, F: 84)	I: 48·2 ± 8·4§ C: 48·6 ± 8·0§	I: 25·7 ± 2·9§ C: 25·4 ± 2·4§	MetS	P	12	W‖	30 g/d	Bread (no walnuts incorporated)	Counselling and written materials based on American Heart Association guidelines	36·5	FBGL (mmol/l**) HbA1c (%) Insulin (pmol/l)
Wu *et al.*[50], Germany	35 (M, F)†	60 (1)‡ †††	24·9 (0·6)‡ †††	Healthy (including overweight)	X	8	W	43 g/d	No nuts	Western diet with walnuts substituted for saturated fat (isoenergetic)	39·2	FBGL (mg/dl) HbA1c (%) Insulin (μU/ml) HOMA-IR
Zibaeenezhad *et al.*[32], Iran	90 (M: 43, F: 47)	I: 55·5 ± 10·75§ C: 54 ± 11·37§	I: 27·60 ± 2·47§ C: 27·21 ± 2·27§	T2DM	P	12	O	15 g/d	No intervention	Dietetic consultation on eating a balanced diet (advised according to weight maintenance requirements)	NR	FBGL (mg/dl) HbA1c (%)

F, female; FBGL, fasting blood glucose levels; HC, hypercholesterolaemia; HOMA-IR, homeostatic model assessment of insulin resistance; M, male; MetS, metabolic syndrome; O, walnut oil; OAD, oral antidiabetic medication; P, parallel; T2DM, type 2 diabetes mellitus; W, whole walnut; X, cross-over.
* In intervention group.
† Breakdown by sex for analysed participants not available.
‡ Mean (standard error).
§ Mean ± standard deviation.
‖ Study included other intervention group which was not relevant to this review, therefore this group was not included in this analysis.
¶ Gram weight for dose sub-analysis based on mid-point of range of doses used.
** Unit reported in study, converted to consistent unit for analysis.
†† Body weight (kg) is reported when BMI was not available.
‡‡ Participants were randomised to one of two parallel groups (*ad libitum* or energy adjusted). Within each group participants completed a 'walnut included' and 'walnut excluded' period in a cross-over design.
§§ Characteristics reported for participants who met inclusion criteria.
‖‖ HbA1c.
¶¶ Treated as comparison group for this analysis.
*** Median (interquartile range).
††† Characteristics reported for randomised participants.

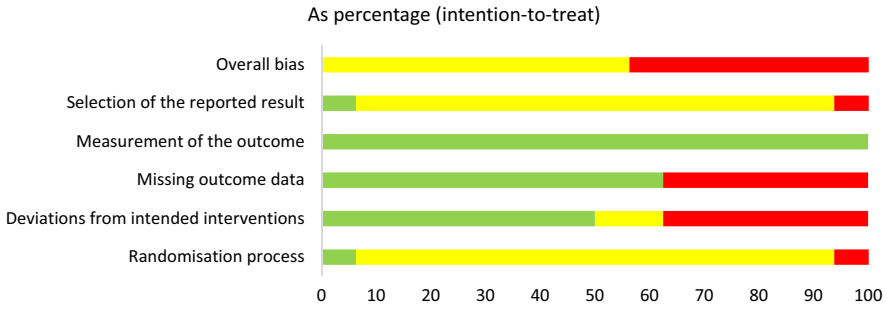

Fig. 2. Risk of bias assessment as a proportion of total studies. ■, Low risk; ■, some concerns; ■, high risk.

Table 2. Changes in outcomes following walnut consumption, compared with control

Outcome	Number of studies	Number of effect sizes	Number of participants	Weighted mean difference	95 % CI	*P*	Inconsistency (I^2) (%)
Fasting blood glucose (mg/dl)	15	17	1620	0·331	–0·817, 1·479	0·572	17·4
HbA1c (%)	10	12	1290	0·031	–0·001, 0·063	0·057	16·4
Fasting insulin (μIU/ml)	9	10	725	0·032	–1·826, 1·889	0·973	53
Homeostatic model assessment of insulin resistance	6	7	471	–0·010	–0·319, 0·298	0·947	6·8

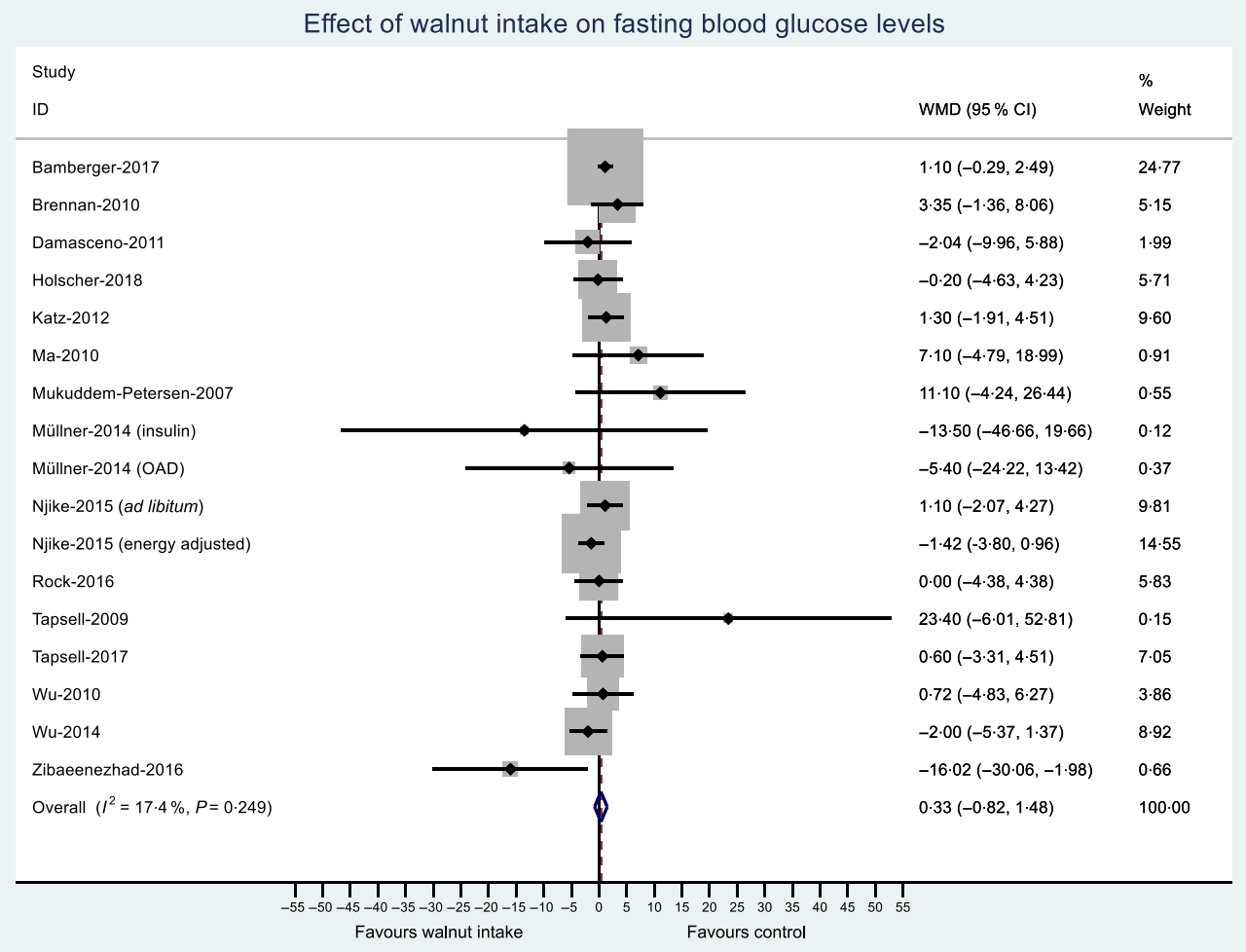

Fig. 3. Difference in fasting blood glucose (mg/dl) between walnut consumption and control. Diamonds indicate weighted mean differences (WMD) with 95 % confidence intervals. Weights are from random effects analysis. OAD, oral antidiabetic medication.

British Journal of Nutrition

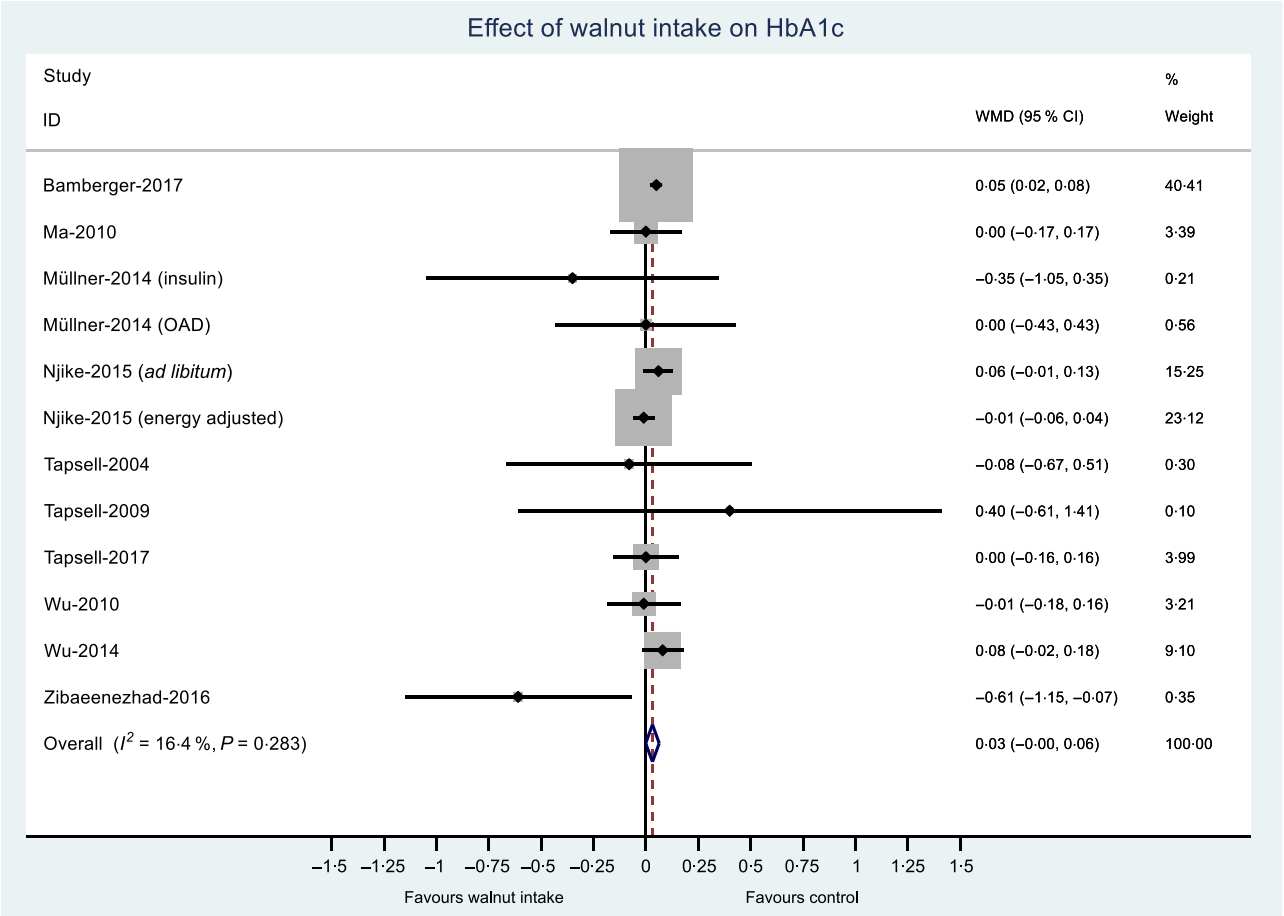

Fig. 4. Difference in HbA1c (%) between walnut consumption and control. Diamonds indicate weighted mean differences (WMD) with 95 % confidence intervals. Weights are from random effects analysis. OAD, oral antidiabetic medication.

substantially the magnitude of the pooled change effect, nor did removing each individual study, or restricting analysis to studies exploring whole walnuts only (online Supplementary Data 9, 10 and 11, respectively). Sub-group analyses and meta-regression were conducted where sample size permitted (fasting blood glucose, HbA1c and fasting insulin). Overall, the sub-group analyses indicated that a similar magnitude of effect was found across the different sub-groups (online Supplementary Data 12). Variation in the magnitude of effect was observed for the risk of bias (some concerns *v.* high) and walnut dose (<50 *v.* ≥50 g/d) for insulin; however, these results should be interpreted with caution due to the small number of studies included in the sub-groups. Similar results were observed for the meta-regression, which found no significant relationship between the outcomes of interest and the walnut dose, treated as a continuous variable (fasting blood glucose: $P = 0{\cdot}953$; HbA1c: $P = 0{\cdot}576$; fasting insulin: $P = 0{\cdot}711$) or study duration, also treated as a continuous variable (fasting blood glucose: $P = 0{\cdot}663$; HbA1c: $P = 0{\cdot}300$; fasting insulin: $P = 0{\cdot}375$).

Small study effects

Contour funnel plots were generated for outcomes with ten or more effect sizes (fasting blood glucose, HbA1c and fasting insulin) (online Supplementary Data 13). Visual inspection of funnel plots and the results of Egger's test did not indicate funnel plot asymmetry.

The quality of the body of evidence

The quality of the body of evidence was determined using GRADE[37] (online Supplementary Data 14). The quality of the body of evidence was 'moderate' for fasting blood glucose, HbA1c and HOMA-IR, after being downgraded due to risk of bias. The quality of the body of evidence for fasting insulin was 'low', as a result of being downgraded for both risk of bias and inconsistency.

Discussion

This systematic review and meta-analysis pooled the evidence base from randomised controlled trials examining the impact of walnut consumption on markers of blood glucose control (fasting glucose, HbA1c, fasting insulin and HOMA-IR). When compared with control groups without walnuts, no evidence of a significant effect of walnut consumption on the markers of blood glucose control was observed. These results did not appear to be affected by sensitivity analyses, suggesting the

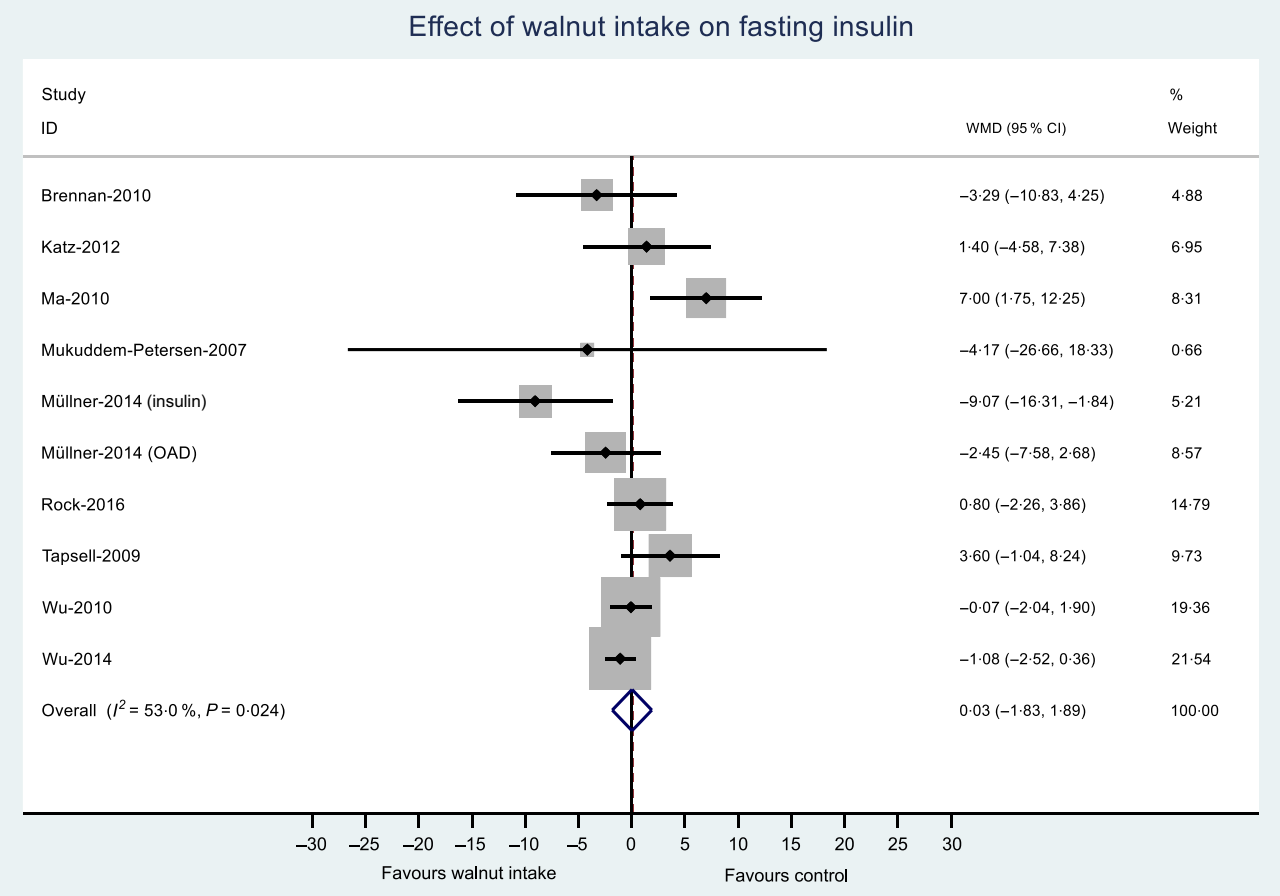

Fig. 5. Difference in fasting insulin (μIU/ml) between walnut consumption and control. Diamonds indicate weighted mean differences (WMD) with 95 % confidence intervals. Weights are from random effects analysis. OAD, oral antidiabetic medication.

findings were robust across different scenarios for study inclusion and analysis[18].

The findings are consistent with research on nuts generally. Although there is a strong body of evidence linking habitual consumption of nuts with reduced risk of CVD[6–8,51], and a recent report of reduced risk of CVD associated with nut intake amongst people with T2DM[10], evidence is less consistent for the effect of nut consumption on incident T2DM and markers of blood glucose control. This may be due to the relative effects of foods and diets on progression to these two disease states, as well as the study designs aimed at exposing any relationships. Foods deliver bioactive compounds which have varying influences on disease mechanisms, and the combination of foods (i.e. diet) determines the set of nutrients which deliver a form of polypharmacy or food synergy[52]. Although plant-based diets are by nature high carbohydrate, nuts are largely comprised of fat and protein. The component effects of nuts on CVD have been described[53], one of which is dietary fat modification which has resultant impacts on blood cholesterol levels, a major risk factor for CVD[54]. For walnuts specifically, a previous systematic review found improvements in total and LDL-cholesterol levels with consumption[55]. A further prospective study has highlighted the specific areas of heart disease in which nut consumption may be having its impact[56]. On the other hand, although fatty acids have been implicated in insulin sensitivity[34], glycaemic control is more immediately influenced by carbohydrate in the diet, so any effect of nuts is likely to be seen as part of a preventive dietary pattern, as outlined below.

Importantly, study designs vary in terms of the extent to which the total dietary pattern is controlled, and this may influence the ability to expose the influence of a particular food on health outcomes[57]. Where observational studies (with greater variation in dietary intake) form the basis of a systematic review, no association between the consumption of nuts and risk of T2DM[6,8] has been found, but when intervention studies are the focus, conflicting results emerge[7,11]. From a methodological perspective, these inconsistencies may reflect differences in the eligibility criteria between reviews, resulting in differences in the number and type of studies included. In view of the above, it is interesting to note that only one systematic review[7] included an analysis from the Prevención con Dieta Mediterránea (PREDIMED) trial[58] (which showed a favourable effect of a Mediterranean diet inclusive of nuts or olive oil on incidence of T2DM[59]). Importantly, the background diets in the PREDIMED study were controlled, and this may have enabled relationships to be better exposed[57]. Nevertheless, conflicting findings are also reported by systematic reviews of trials examining the impact of nut consumption on markers of blood

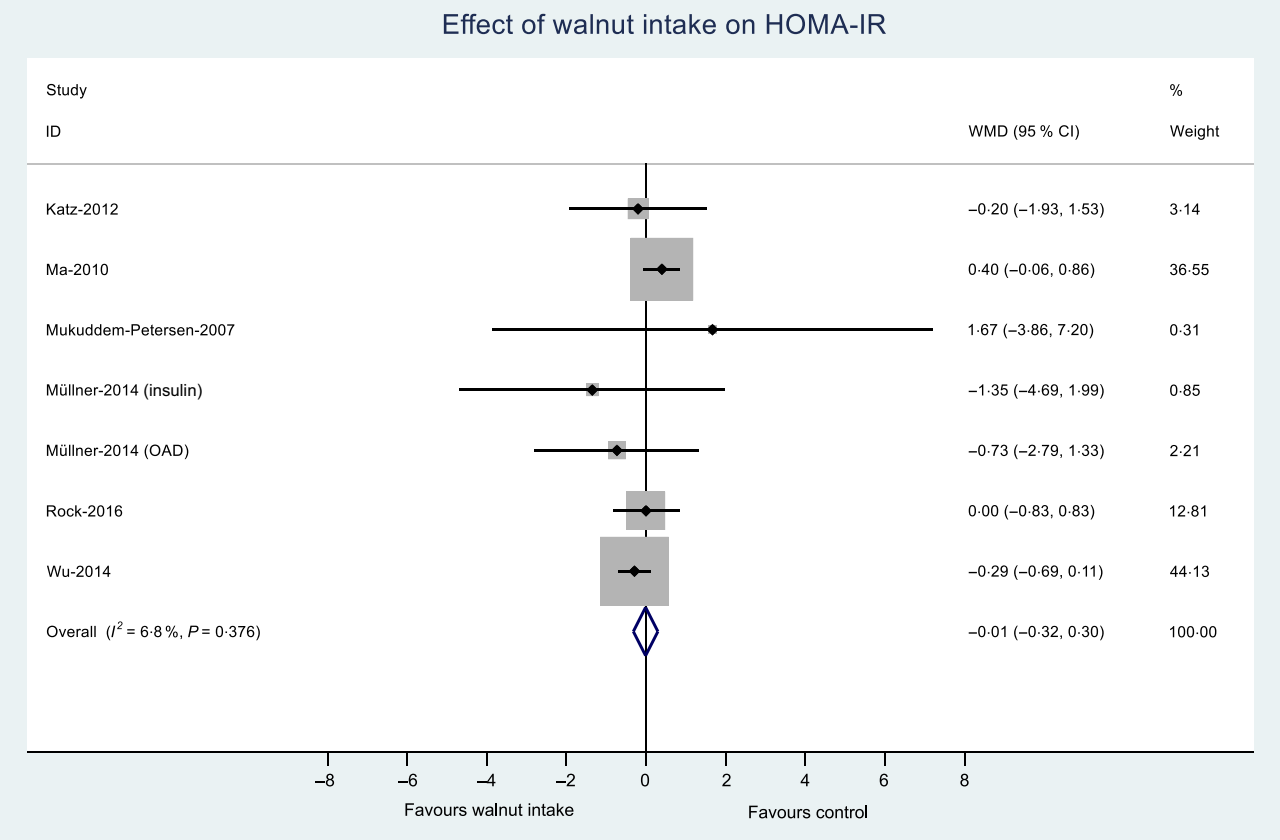

Fig. 6. Difference in homeostatic model assessment of insulin resistance (HOMA-IR) between walnut consumption and control. Diamonds indicate weighted mean differences (WMD) with 95 % confidence intervals. Weights are from random effects analysis. OAD, oral antidiabetic medication.

glucose control, both in individuals with T2DM[12], and the broader adult population[13]. Our findings are consistent with the latter review[13] where it was limited to analyses specifically examining the impact of walnuts. We build on these findings by including the most recent studies, considering the broader at-risk population, addressing all available durations of study[22] and using the most up-to-date risk of bias tool[60].

The relative impact of walnuts within a preventive dietary pattern is another way to consider the food–disease relationship. As walnuts are differentiated from other nuts by their high PUFA acid content, a desirable impact on cholesterol levels in a low-fat diet would be expected. However, like other nuts, they also deliver dietary fibre, phytochemicals and a number of vitamins and minerals including folate, niacin, Mg and K[61]. Consumption of tree nuts including walnuts has been found to be associated with favourable overall nutrient intakes[62,63], and in one study, the provision of walnuts specifically increased the overall quality of the diets chosen by participants[16,17]. Thus, for cuisine reasons, the inclusion of walnuts may help drive better meal and snack choices producing a diet more aligned with preventive health outcomes. This behavioural concept could also be considered in trials of diets related to the prevention of T2DM, where appreciating the significance of single food choices in a total dietary pattern can be overlooked.

From a methodological perspective, the assessment of the risk of bias within individual studies is essential when considering the overall quality of the body of evidence on a topic[64]. We evaluated the risk of bias using the Cochrane Collaboration Risk of Bias tool 2.0, which was updated in July 2019[23]. This updated tool was released to overcome challenges associated with the previous tool[18], including inconsistent use amongst researchers, difficulties in determining risk of bias in some domains and difficulties in assessing overall risk of bias[60]. Applying the 2.0 tool in our review, we found all studies had either 'some concerns' regarding the risk of bias or were at 'high risk' of bias. Potential bias particularly emerged in relation to the randomisation process often due to a lack of information on allocation concealment. It also emerged with the lack of pre-registered protocols detailing sufficient information to determine if the results were selectively reported. The literature confirms a general trend for insufficient reporting of allocation concealment in randomised controlled trials[65] and problems in identifying selective reporting of outcomes due to the lack of pre-registered study protocols[66]. This may reflect the time in which the studies were conducted relative to demands by the scientific literature for these standards, but this resulted in downgrading the quality of the body of evidence (evaluated using GRADE[37]), for all outcomes. These findings suggest a need for more randomised controlled trials with pre-registered study protocols and better reporting of all aspects of study methodology in accordance with current standards.

There were several strengths to this review. It was conducted and reported according to current guidelines[18,19] and included an evaluation of results using a number of sensitivity analyses, and examination of the risk of bias using an updated assessment tool. The review was also not limited by study duration, in comparison with previous reviews on this topic[12,13]. There were also potential limitations, such as the small number of studies available for inclusion, limiting the generalisability of results and interpretations of the results of the sub-group analyses and meta-regression (known to be influenced by the number of available observations[18]). Heterogeneity was also observed in participant characteristics, particularly health status, and in background and control diets. This variation in control diets has been highlighted as a common issue in nutrition meta-analyses, where adding or removing one food from the diet will lead to variation in overall kilojoule, macro- and micronutrient content[67]. Furthermore, in order to ensure the effect of walnut consumption could be isolated, studies which tested walnut consumption in combination with other nuts (e.g. mixed nuts) were not eligible for inclusion. While this allowed for the identification of the effect of walnut consumption, separated from that of other nuts, this approach resulted in the exclusion of several studies such the PREDIMED study[58] which used a dose of 30 g mixed nuts, half of which were walnuts, and this may have influenced results. As outlined previously, none of the included studies was found to be at low risk of bias, which may have resulted in either under- or overestimating the true intervention effects. In addition, limitations associated with meta-analysis methodology should be considered. One such limitation is Simpson's paradox, an ecological effect which can occur in meta-analyses of randomised controlled trials, particularly when there are imbalances in the size of study groups[68]. While this appears unlikely in the present review due to the characteristics of the studies[69], it is possible in some circumstances. Finally, while the present review followed current guidelines for conducting meta-analyses, it should be noted that alternatives to random effects meta-analyses[70–72], funnel plots and Egger's test[73] have been proposed. Further consideration of these advances as a component of research focused on meta-analysis methodologies is recommended.

This systematic review and meta-analysis did not find evidence of an effect of walnut consumption on markers of blood glucose control, namely fasting glucose, HbA1c, fasting insulin and HOMA-IR. These findings suggest that favourable effects of walnut intake on health outcomes such as CVD observed elsewhere may not be mediated via improvements in glucose control. Given the high risk of bias observed in the current evidence base, there is a need for further research on this topic, with a particular emphasis on meeting current standards for registering and reporting on randomised controlled trials to reduce the risk of bias.

Acknowledgements

This study was funded by the California Walnut Commission. The funding body was not involved in the planning, analysis, interpretation or interpretation of results.

E. P. N., V. G., L. C. T. and Y. C. P. designed the study, E. P. N. and V. G. conducted study screening, application of eligibility criteria and data extraction, E. P. N. conducted statistical analyses, E. P. N. drafted the manuscript, L. C. T., Y. C. P. and V. G. provided critical review of the manuscript.

E. P. N., Y. C. P. and L. C. T. have previously received funding or hold current grants from Nuts for Life, the International Nut and Dried Fruit Council, and the California Walnut Commission.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114520001415

References

1. Tapsell L & Probst Y (2008) Nutrition in the prevention of chronic diseases. In *Nutrition and Fitness: Cultural, Genetic and Metabolic Aspects*, vol. 98, pp. 94–105 [A Simopoulos, editor]. Basel, Switzerland: Karger.
2. Tapsell LC, Neale EP & Probst Y (2019) Dietary patterns and cardiovascular disease: insights and challenges for considering food groups and nutrient sources. *Curr Atheroscler Rep* **21**, 9.
3. International Diabetes Federation (2017) *IDF Diabetes Atlas*, 8th ed. Brussels: IDF.
4. Ley SH, Hamdy O, Mohan V, *et al.* (2014) Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet* **383**, 1999–2007.
5. Food Standards Australia New Zealand (2014) *AUSNUT 2011–13 – Australian Food Composition Database*. Canberra: Food Standards Australia New Zealand.
6. Luo C, Zhang Y, Ding Y, *et al.* (2014) Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. *Am J Clin Nutr* **100**, 256–269.
7. Afshin A, Micha R, Khatibzadeh S, *et al.* (2014) Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr* **100**, 278–288.
8. Zhou D, Yu H, He F, *et al.* (2014) Nut consumption in relation to cardiovascular disease risk and type 2 diabetes: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* **100**, 270–277.
9. Guasch-Ferré M, Liu X, Malik VS, *et al.* (2017) Nut consumption and risk of cardiovascular disease. *J Am Coll Cardiol* **70**, 2519–2532.
10. Liu G, Guasch-Ferré M, Hu Y, *et al.* (2019) Nut consumption in relation to cardiovascular disease incidence and mortality among patients with diabetes mellitus. *Circ Res* **124**, 920–929.
11. Wu L, Wang Z, Zhu J, *et al.* (2015) Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis. *Nutr Rev* **73**, 409–425.
12. Viguiliouk E, Kendall CWC, Blanco Mejia S, *et al.* (2014) Effect of tree nuts on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled dietary trials. *PLOS ONE* **9**, e103376–e103376.
13. Tindall AM, Johnston EA, Kris-Etherton PM, *et al.* (2019) The effect of nuts on markers of glycemic control: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* **109**, 297–314.
14. Chen CO & Blumberg JB (2008) Phytochemical composition of nuts. *Asia Pac J Clin Nutr* **17**, 329–332.

15. Pan A, Sun Q, Manson JE, *et al.* (2013) Walnut consumption is associated with lower risk of type 2 diabetes in women. *J Nutr* **143**, 512–518.
16. Neale EP, Tapsell LC, Martin A, *et al.* (2017) Impact of providing walnut samples in a lifestyle intervention for weight loss: a secondary analysis of the HealthTrack trial. *Food Nutr Res* **61**, 1344522.
17. Njike VY, Ayettey R, Petraro P, *et al.* (2015) Walnut ingestion in adults at risk for diabetes: effects on body composition, diet quality, and cardiac risk measures. *BMJ Open Diabetes Res Care* **3**, e000115.
18. Higgins JPT & Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane Collaboration.
19. Moher D, Liberati A, Tetzlaff J, *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* **6**, e1000097.
20. Rosen L & Suhami R (2016) The art and science of study identification: a comparative analysis of two systematic reviews. *BMC Med Res Methodol* **16**, 24.
21. Wan X, Wang W, Liu J, *et al.* (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* **14**, 135.
22. Holscher HD, Guetterman HM, Swanson KS, *et al.* (2018) Walnut consumption alters the gastrointestinal microbiota, microbially derived secondary bile acids, and health markers in healthy adults: a randomized controlled trial. *J Nutr* **148**, 861–867.
23. Sterne JAC SJ, Page MJ, Elbers RG, *et al.* (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* **366**, l4898.
24. Bradburn MJ, Deeks JJ & Altman DG (1999) Metan – an alternative meta-analysis command. *Stata Tech Bull* **8**.
25. Harris RJ, Deeks JJ, Altman DG, *et al.* (2008) Metan: fixed-and random-effects meta-analysis. *Stata J* **8**, 3–28.
26. IntHout J, Ioannidis JPA & Borm GF (2014) The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* **14**, 25.
27. Neale EP, Tapsell LC, Guan V, *et al.* (2017) The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* **7**, e016863.
28. Müllner E, Plasser E, Brath H, *et al.* (2014) Impact of polyunsaturated vegetable oils on adiponectin levels, glycaemia and blood lipids in individuals with type 2 diabetes: a randomised, double-blind intervention study. *J Hum Nutr Diet* **27**, 468–478.
29. Higgins JPT, Thompson SG, Deeks JJ, *et al.* (2003) Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560.
30. Sterne JAC, Sutton AJ, Ioannidis JPA, *et al.* (2011) Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* **343**, d4002.
31. Egger M, Smith GD, Schneider M, *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.
32. Zibaeenezhad M, Aghasadeghi K, Hakimi H, *et al.* (2016) The effect of walnut oil consumption on blood sugar in patients with diabetes mellitus type 2. *Int J Endocrinol Metab* **14**, e34889.
33. Mejia SB, Kendall CW, Viguiliouk E, *et al.* (2014) Effect of tree nuts on metabolic syndrome criteria: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* **4**, e004660.
34. Vessby B, Uusitupa M, Hermansen K, *et al.* (2001) Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU Study. *Diabetologia* **44**, 312–319.
35. Harbord RM & Higgins JP (2008) Meta-regression in Stata. *Stata J* **8**, 493–519.
36. Knapp G & Hartung J (2003) Improved tests for a random effects meta-regression with a single covariate. *Stat Med* **22**, 2693–2710.
37. Guyatt GH, Oxman AD, Vist GE, *et al.* (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–926.
38. Mukuddem-Petersen J, Stonehouse W, Jerling JC, *et al.* (2007) Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: a controlled feeding trial. *Br J Nutr* **97**, 1144–1153.
39. Tapsell LC, Batterham M, Teuss G, *et al.* (2009) Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes. *Eur J Clin Nutr* **63**, 1008.
40. Tapsell LC, Gillen LJ, Patch CS, *et al.* (2004) Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes. *Diabetes Care* **27**, 2777–2783.
41. Wu H, Pan A, Yu Z, *et al.* (2010) Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. *J Nutr* **140**, 1937–1942.
42. Mukuddem-Petersen J (2005) *The Effects of Nuts on Markers of the Metabolic Syndrome*, PhD thesis, North-West University (Potchefstroom Campus).
43. Rock CL, Flatt SW, Pakiz B, *et al.* (2016) Effects of diet composition on weight loss, metabolic factors and biomarkers in a 1-year weight loss intervention in obese women examined by baseline insulin resistance status. *Metabolism* **65**, 1605–1613.
44. Tapsell LC, Lonergan M, Batterham MJ, *et al.* (2017) Effect of interdisciplinary care on weight loss: a randomised controlled trial. *BMJ Open* **7**, e014533.
45. Bamberger C, Rossmeier A, Lechner K, *et al.* (2017) A walnut-enriched diet reduces lipids in healthy Caucasian subjects, independent of recommended macronutrient replacement and time point of consumption: a prospective, randomized, controlled trial. *Nutrients* **9**, 1097.
46. Brennan AM, Sweeney LL, Liu X, *et al.* (2010) Walnut consumption increases satiation but has no effect on insulin resistance or the metabolic profile over a 4-day period. *Obesity* **18**, 1176–1182.
47. Damasceno N, Pérez-Heras A, Serra M, *et al.* (2011) Crossover study of diets enriched with virgin olive oil, walnuts or almonds. Effects on lipids and other cardiovascular risk markers. *Nutr Metab Cardiovasc Dis* **21**, S14–S20.
48. Katz DL, Davidhi A, Ma Y, *et al.* (2012) Effects of walnuts on endothelial function in overweight adults with visceral obesity: a randomized, controlled, crossover trial. *J Am Coll Nutr* **31**, 415–423.
49. Ma Y, Njike VY, Millet J, *et al.* (2010) Effects of walnut consumption on endothelial function in type 2 diabetic subjects: a randomized controlled crossover trial. *Diabetes Care* **33**, 227–232.
50. Wu L, Piotrowski K, Rau T, *et al.* (2014) Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: a randomized controlled cross-over clinical trial. *Metabolism* **63**, 382–391.
51. Aune D, Keum N, Giovannucci E, *et al.* (2016) Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med* **14**, 207.

British Journal of Nutrition

52. Jacobs DR Jr, Gross MD & Tapsell LC (2009) Food synergy: an operational concept for understanding nutrition. *Am J Clin Nutr* **89**, 1543S–1548S.
53. Ros E (2019) Contrasting effects on mortality of monounsaturated fatty acid intake depending on vegetable or animal sources. *Circ Res* **124**, 1154–1156.
54. Sacks FM, Lichtenstein AH, Wu JH, *et al.* (2017) Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation* **136**, e1–e23.
55. Banel DK & Hu FB (2009) Effects of walnut consumption on blood lipids and other cardiovascular risk factors: a meta-analysis and systematic review. *Am J Clin Nutr* **90**, 56–63.
56. Larsson SC, Drca N, Björck M, *et al.* (2018) Nut consumption and incidence of seven cardiovascular diseases. *Heart* **104**, 1615–1620.
57. Tapsell LC (2014) Foods and food components in the Mediterranean diet: supporting overall effects. *BMC Med* **12**, 100.
58. Estruch R, Ros E, Salas-Salvadó J, *et al.* (2018) Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* **378**, e34.
59. Salas-Salvadó J, Bulló M, Babio N, *et al.* (2011) Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* **34**, 14–19.
60. Sterne J, Savović, J & Higgins J (2018) Launching the new Cochrane tool for assessing risk of bias in randomised trials. In *25th Cochrane Colloquium*. Edinburgh.
61. Nuts for Life (2018) Nutrient composition of tree nuts. https://d131k5wuh4trw5.cloudfront.net/uploads/2020/03/NFL606-NFL-Ready-Reckoner-LR.pdf (accessed May 2020).
62. Brown RC, Tey SL, Gray AR, *et al.* (2016) Nut consumption is associated with better nutrient intakes: results from the 2008/09 New Zealand Adult Nutrition Survey. *Br J Nutr* **115**, 105–112.
63. O'Neil CE, Keast DR, Fulgoni VL, *et al.* (2010) Tree nut consumption improves nutrient intake and diet quality in US adults: an analysis of National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Asia Pac J Clin Nutr* **19**, 142.
64. Guyatt GH, Oxman AD, Vist G, *et al.* (2011) GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). *J Clin Epidemiol* **64**, 407–415.
65. Pildal J, Hróbjartsson A, Jørgensen K, *et al.* (2007) Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol* **36**, 847–857.
66. Savović J, Weeks L, Sterne JAC, *et al.* (2014) Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst Rev* **3**, 37.
67. Barnard ND, Willett WC & Ding EL (2017) The misuse of meta-analysis in nutrition research. *JAMA* **318**, 1435–1436.
68. Rücker G & Schumacher M (2008) Simpson's paradox visualized: the example of the Rosiglitazone meta-analysis. *BMC Med Res Methodol* **8**, 34.
69. Altman DG & Deeks JJ (2002) Meta-analysis, Simpson's paradox, and the number needed to treat. *BMC Med Res Methodol* **2**, 3.
70. Doi SA, Barendregt JJ, Khan S, *et al.* (2015) Advances in the meta-analysis of heterogeneous clinical trials II: the quality effects model. *Contemp Clin Trials* **45**, 123–129.
71. Doi SAR, Barendregt JJ, Khan S, *et al.* (2015) Advances in the meta-analysis of heterogeneous clinical trials I: the inverse variance heterogeneity model. *Contemp Clin Trials* **45**, 130–138.
72. Furuya-Kanamori L, Thalib L & Barendregt JJ (2017) Meta-analysis in evidence-based healthcare: a paradigm shift away from random effects is overdue. *Int J Evid Based Healthc* **15**, 152–160.
73. Furuya-Kanamori L, Barendregt JJ & Doi SAR (2018) A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid Based Healthc* **16**, 195–203.

British Journal of Nutrition