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

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Abstract

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

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic disease increasing in global prevalence. While habitual consumption of walnuts is associated with reduced risk of cardiovascular disease, 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 2nd 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 haemoglobin, 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 18 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% confidence intervals: -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 cardiovascular disease 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.

Keywords: nuts; walnuts; glycaemic control; blood glucose; systematic review; meta-analysis

Introduction

Nutrition plays an increasingly important role in the prevention of chronic diseases including coronary heart disease 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 polyunsaturated fatty acid content [5] which is aligned to cholesterol lowering effects. This, and other components in walnuts and nuts generally contribute to reduced risk of coronary heart disease. For the food category of nuts, habitual consumption has been associated with the reduced risk of coronary heart disease [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 haemoglobin (HbA1c) and fasting glucose levels, with no impact on fasting insulin or homeostasis 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 polyunsaturated fatty acid content, including alpha-linolenic acid, while also delivering dietary fibre and phytochemicals [5,14]. 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 body mass index [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 (PRISMA) statement [19] (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 crossover 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, HOMA-IR); (4) studies where the effect of walnut consumption could be isolated from other food sources or interventions such as physical activity programs. 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 EN. Date restrictions were not applied, and the databases were searched on 2 March 2019. Both MEDLINE and PubMed were searched to ensure recent studies were detected, in line with recommendations by Rosen and 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 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 body mass index, 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 was extracted from each study. Where possible, the mean changes in the relevant biomarker outcomes and the respective standard deviation (or standard error/95% confidence interval) were obtained. When these data were not available, the mean final values and the respective standard deviation (or standard error/95% confidence interval) were retrieved as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [18]. Where median and interquartile range were provided, these were converted to 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 was 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 were considered in the risk of bias assessment (outlined below).

Abstract screening, full text review, and data extraction were conducted independently by two authors (EN and VG), with any disagreements were resolved via consensus. Where consensus could not be reached a third author was consulted (YP).

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. EN and VG 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, USA) 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 effect 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% confidence intervals) 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 10 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 three months versus more than three 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 g per day vs >50 g per day, 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% vs ≥37% per day, 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 10 effect sizes per outcome in total [18], although the number of effect sizes per individual sub-group were not restricted. The relationship between the nut dose (in studies exploring whole nuts only) and the study duration, as continuous characteristics, were 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 68 full-text articles were reviewed for eligibility. A total of 51 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) (Figure 1, Supplementary Data 3). This resulted in a total of 17 articles describing 16 studies included in this review. Through these articles, n=18 effect sizes were available for inclusion in the meta-analysis (Figure 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 range from four days [46], to one year [39,43,44]. Studies were conducted in Germany [45,50], the United States [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 metabolic syndrome or other risk factors for chronic disease [17,38,41-43,46-48], had type 2 diabetes mellitus [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 14 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 grams (1.06 oz) [39-41,44] to 56 grams (1.98 oz) per day [48,49]. In three studies walnuts were consumed to provide a prescribed proportion of dietary energy (ranging from 18 – 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 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 (for

example 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 (for example olive oil [47]).

Risk of bias assessment

The risk of bias assessments are shown in Figure 2 and 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, are shown in Table 2 and Figures 3 - 6. Summary data for each study is available in 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 Figures 3 - 6). Similar results were found when conducting sensitivity analyses using Hartung-Knapp-Sidik Jonkman adjustment[26] (Supplementary Data 7), and when using correlation coefficients of 0.25, 0.5, and 0.75 for cross-over studies (Supplementary Data 8).

Sensitivity analyses demonstrated that pooling separate intervention groups within the same study did not substantially the magnitude of the pooled change effect, nor did removing each individual study, or restricting analysis to studies exploring whole walnuts only (Supplementary Data 9, 10 and 11, respectively). Sub-group analyses and meta-regression were conducted where sample size permitted (fasting blood glucose, HbA1c, fasting insulin). Overall, the sub-group analyses indicated that a similar magnitude of effect was found across the different sub-groups (Supplementary Data 12). Variation in the magnitude of effect was observed for the risk of bias (some concerns versus high) and walnut dose (<50g/day versus ≥

50g/day) 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=0.953, HbA1c: p=0.576; fasting insulin: p=0.711) or study duration, also treated as a continuous variable (fasting blood glucose: p=0.663; HbA1c: p=0.300; fasting insulin: p=0.375).

Small study effects

Contour funnel plots were generated for outcomes with ten or more effect sizes (fasting blood glucose, HbA1c, fasting insulin) (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] (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 to 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 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 cardiovascular disease [6-8,51], and a recent report of reduced risk of cardiovascular disease 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 cardiovascular disease have been described [53], one of which is dietary fat modification which has resultant impacts on blood cholesterol levels, a major risk factor for cardiovascular disease [54]. For walnuts specifically, a previous systematic review found improvements in total and low-density lipoprotein 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 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 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 polyunsaturated fatty 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, magnesium, and potassium [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 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 to previous reviews on this topic [12,13]. There were also potential limitations, such as the small number of studies available for inclusion, limiting the generalizability 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 (for example 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 30g mixed nuts, half of which were walnuts, and this may have influenced results. As outlined previously, none of the included studies were found to be at low risk of bias, which may have resulted in either under or over-estimating 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], and 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 cardiovascular disease 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.

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Conflict of Interest: Elizabeth Neale, Yasmine Probst, and Linda Tapsell have previously received funding or hold current grants from Nuts for Life, the International Nut and Dried Fruit Council, and the California Walnut Commission.

Authorship: EPN, VG, LCT, YCP designed the study, EPN, VG conducted study screening, application of eligibility criteria, and data extraction, EPN conducted statistical analyses, EPN drafted the manuscript, LCT, YCP, VG provided critical review of the manuscript.

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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, (gender)	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 (%)°	FBG (units)	HbA1c (units)	Insulin (units)	HOMA-IR
Bamberger et al. (2017), Germany (43)	204 (M, F)‡	63 (0.54)§	25.4 (0.29)§	Healthy (including overweight)	X	8	W	43g/day	Western diet	Nuts replacing 70g carbohydrate or 30g saturated fat	43 – 46	mg/dL	%	-	-
Brennan et al. (2010), United States (44)	15 (M: 9, F: 6)	58.0 (2.5)§	36.9 (1.7)§	MetS	X	0.6	W	48g/day	Placebo meal containing 2.14% protein, 48.55% fat, and 49.31% carbohydrate	Isocaloric diet, controlled	46.05	mg/dL	-	µIU/mL	-
Damasceno et al. (2011), Spain (45)	18 (M: 9, F: 9)	56 ± 13¶	25.7 ± 2.3¶	HC	X	4	W*	40 - 65g/day §§ (22% energy)	35 – 50g/day virgin olive oil	Mediterranean-style diet (isocaloric)	32	mmol/L •	-	-	-
Holscher et al. (2018), United States (22)	18 (M: 10, F: 8)	53.1 (2.2)§	28.8 (0.9)§	Healthy (including overweight)	X	3	W	42g/day	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	mg/dL	-	-	-
Katz et al. (2012), United States (46)	46 (M: 18, F: 28)	57.4 ± 11.9¶	33.2 ± 4.4¶	Overweight plus risk factors for MetS	X	8	W	56g/day	No nuts	Ad libitum, participants advised to substitute	41.4	mg/dL	-	µIU/mL	HOMA-IR

										walnuts for other foods					
Ma et al. (2010), United States (47)	24 (M: 10, F: 14)	58.1 ± 9.2¶	32.5 ± 5.0¶	T2DM	X	8	W	56g/day	No nuts	Ad libitum, participants advised to substitute walnuts for other foods	45	mg/dL	%	µIU/mL	HOMA-IR
Mukuddem-Peterson (2005), and Mukuddem-Petersen et al. (2007), South Africa (36, 40)	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 (isocaloric)	40.3	mmol/L •	-	µIU/mL	HOMA-IR
Mullner et al. (2014), Austria (30)	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	9g oil/day	Mixed oil (corn, sunflower, linseed oil)	Usual diet	NR	mM•,	%	pM•	HOMA-IR
Njike et al. (2015), United States (17)	112 (M: 31, F: 81)	*Ad libitum:* 56.5 ± 11.7¶ *Energy adjusted:* 53.3 ±	*Ad libitum:* 30.0 ± 4.0 ¶ *Energy adjusted:* 30.2 ± 4.1¶	Overweight, pre-diabetic or MetS	X••	24	W	56g/day	No nuts	1. Ad libitum diet 2. Isocaloric diet (energy adjusted for walnuts)	NR	mg/dL	%	-	-

		11.1¶													
Rock et al. (2016), United States (41)	126 (F)	50 (range: 22 - 72)††	33.5 (range: 27 - 40)††	Overweight and obese	P	52	W	42g/day ¶¶ (18% energy)	Higher fat (35% energy) lower CHO (45% energy) diet, no nuts*	Hypocaloric diet (500 - 1000 kcal/day deficit)	35	mg/dL	-	µIU/mL	HOMA-IR
Tapsell et al. (2004), Australia (38)	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	30g/day	<30% fat, modified fat†	<30% fat, modified fat	~32	-	%	-	-
Tapsell et al. (2009), Australia (37)	35 (M,F) ‡	54 ± 8.7††	I: 33.2 ± 4.4 C: 33.0 ± 4.0	T2DM	P	52	W	30g/day	Low-fat advice (weight maintenance)	Low-fat advice (weight maintenance)	~34	mmol/L •	%	µU/L•	
Tapsell et al. (2017), Australia (42)	101 (M, F) ‡ 100 (M, F) ¶¶	45 (37–51) ‣ **	32 (29–35) ‣ **	Overweight and obese (including T2DM)	P	52	W	30g/day	Interdisciplinary intervention (dietitian, exercise physiologist, psychologist support)†	Individualized dietary advice based on Australian Guide to Healthy Eating	~33	mmol/L •	%	-	-
Wu et al. (2010), China (39)	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*	30g/day	Bread (no walnuts incorporated)	Counselling and written materials based on American Heart Association guidelines	36.5	mmol/L •	%	pmol/L	-
Wu et al. (2014), Germany (48)	35 (M, F)‡	60 (1)§ **	24.9 (0.6)§ **	Healthy (including overweight)	X	8	W	43g/day	No nuts	Western diet with walnuts substituted for saturated fat	39.2	mg/dL	%	µU/mL	HOMA-IR

										(isocaloric)					
Zibaeenezhad et al. (2016), Iran (31)	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	15g/day	No intervention	Dietetic consultation on eating a balanced diet (advised according to weight maintenance requirements)	NR	mg/dL	%	-	-

°In intervention group

‡Gender breakdown for analysed participants not available

§ Mean (standard error)

¶ Mean ± standard deviation

‣Median (interquartile range)

*Study included other intervention group which was not relevant to this review, therefore this group was not included in this analysis

†Treated as comparison group for this analysis

•Unit reported in study, converted to consistent unit for analysis

§§Gram weight for dose sub-analysis based on mid-point of range of doses used

‡‡Body weight (kg) is reported when BMI was not available

††Characteristics reported for participants who met inclusion criteria

••Participants were randomised to one of two parallel groups (ad libitum or calorie adjusted). Within each group participants completed a 'walnut included' and 'walnut excluded' period in a cross-over design

¶¶ HbA1c

**Characteristics reported for randomised participants

Abbreviations: BMI: body mass index; CI: confidence intervals; F: female; HC: hypercholesterolemia; 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

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

Outcome	Number of studies	Number of effect sizes	Number of participants	Weighted mean difference (95% CI)	Inconsistency (I^2)
Fasting blood glucose (mg/dL)	15	17	1620	0.331 (-0.817, 1.479), p=0.572	17.4%
HbA1c (%)	10	12	1290	0.031 (-0.001, 0.063), p=0.057	16.4%
Fasting insulin (µIU/mL)	9	10	725	0.032 (-1.826, 1.889), p=0.973	53%
HOMA-IR	6	7	471	-0.010 (-0.319, 0.298), p=0.947	6.8%

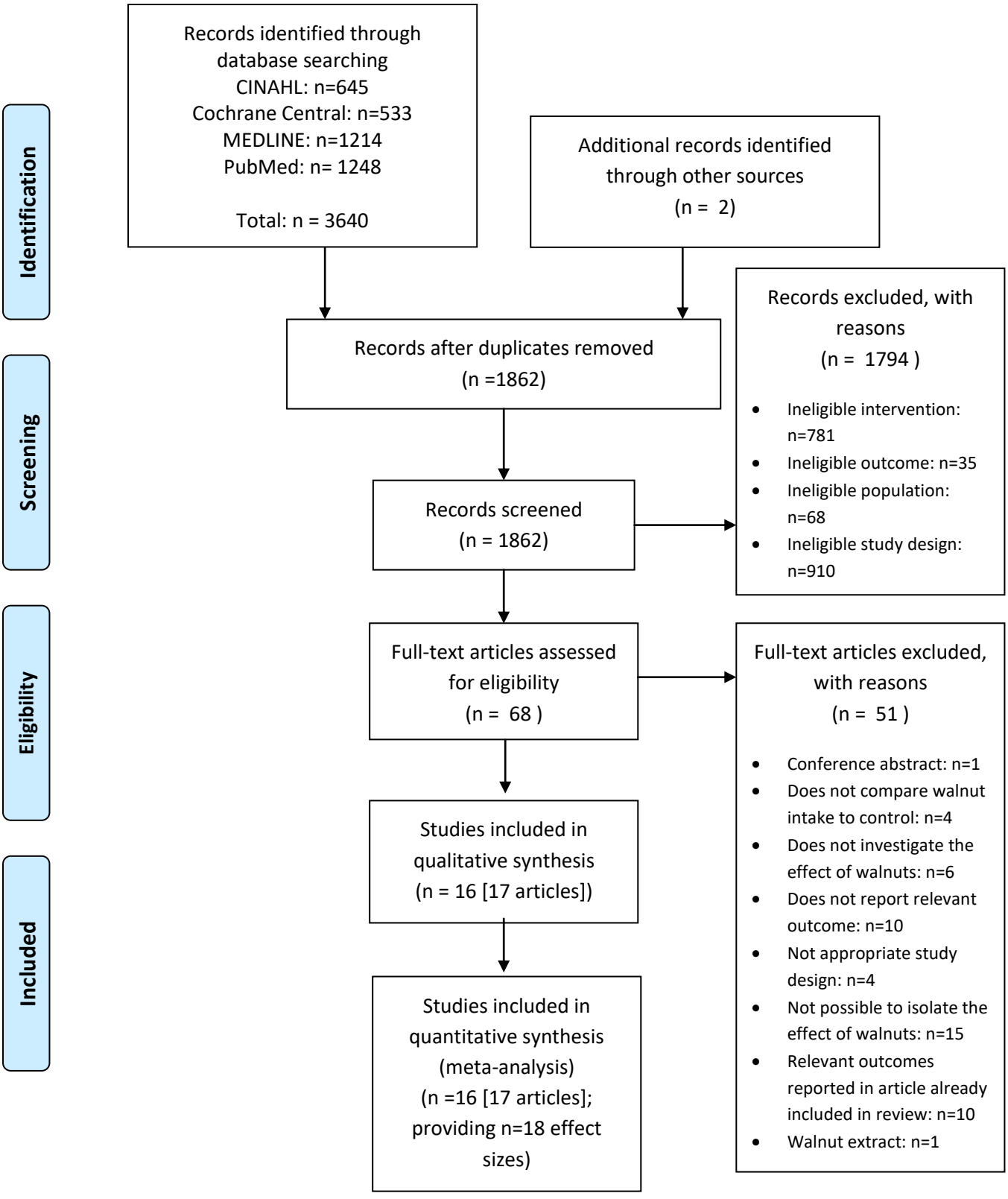

Figure 1: PRISMA flow diagram of study selection

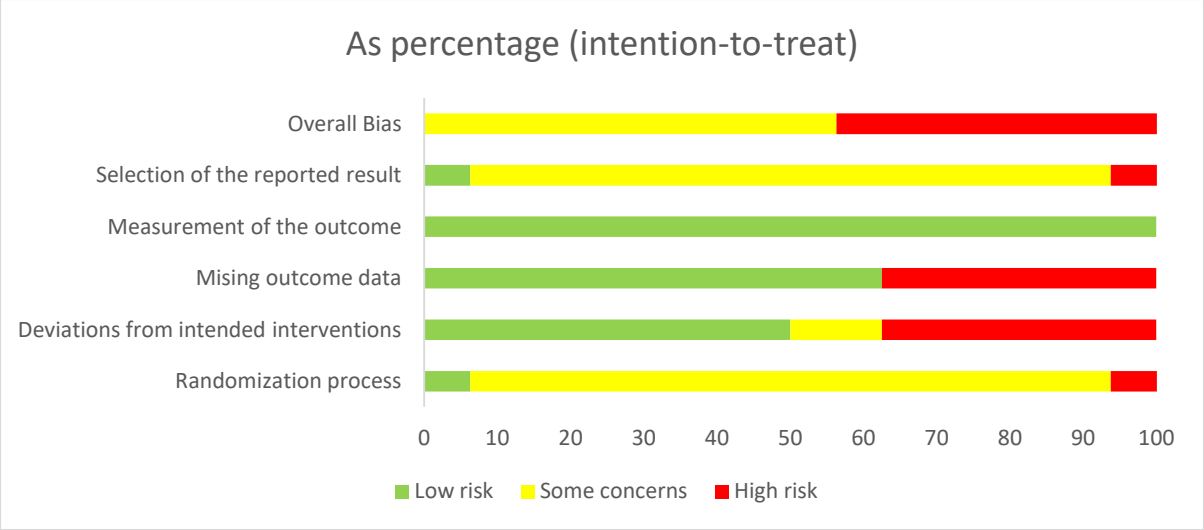

Figure 2: Risk of bias assessment as a proportion of total studies

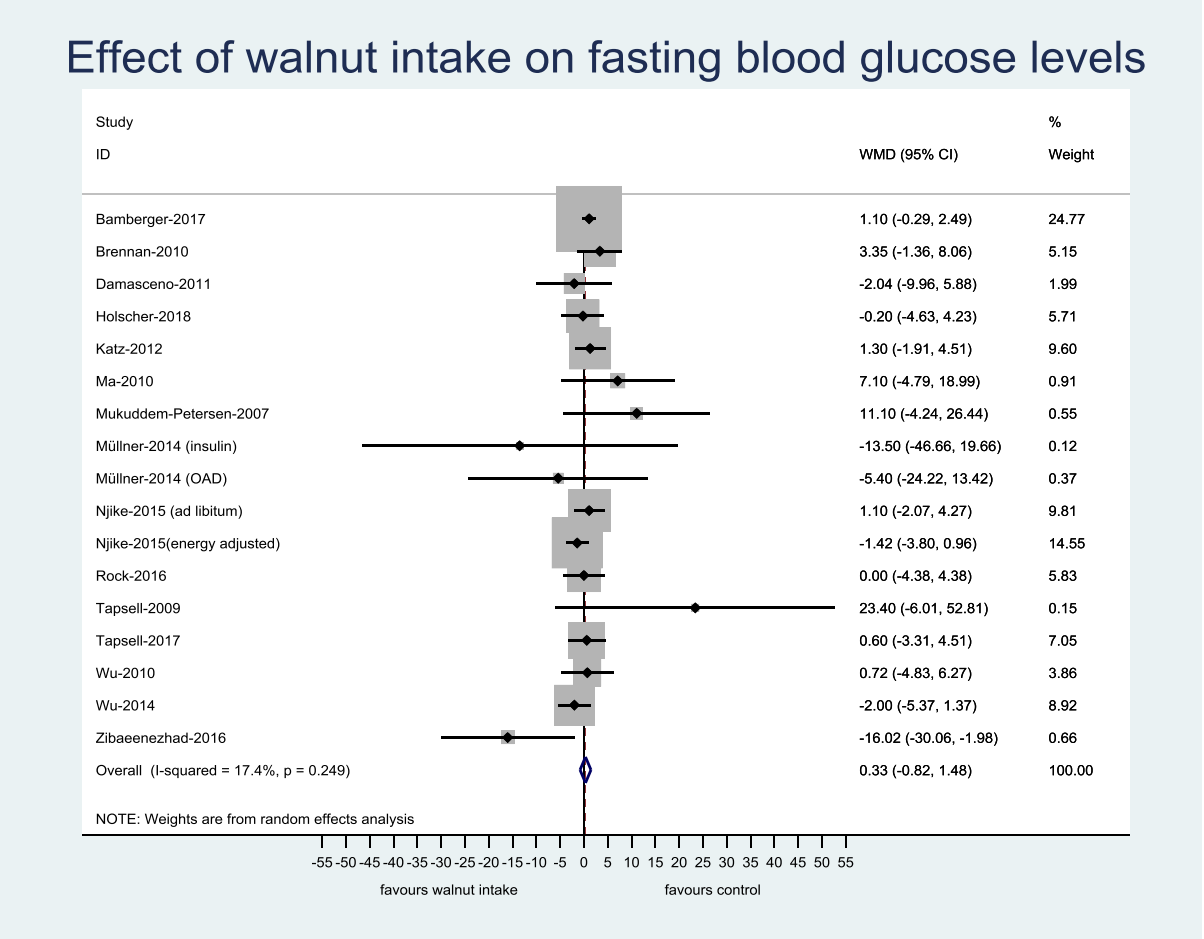

Figure 3: Difference in fasting blood glucose (mg/dL) between walnut consumption and control. Diamond indicates weighted mean difference with 95% confidence intervals

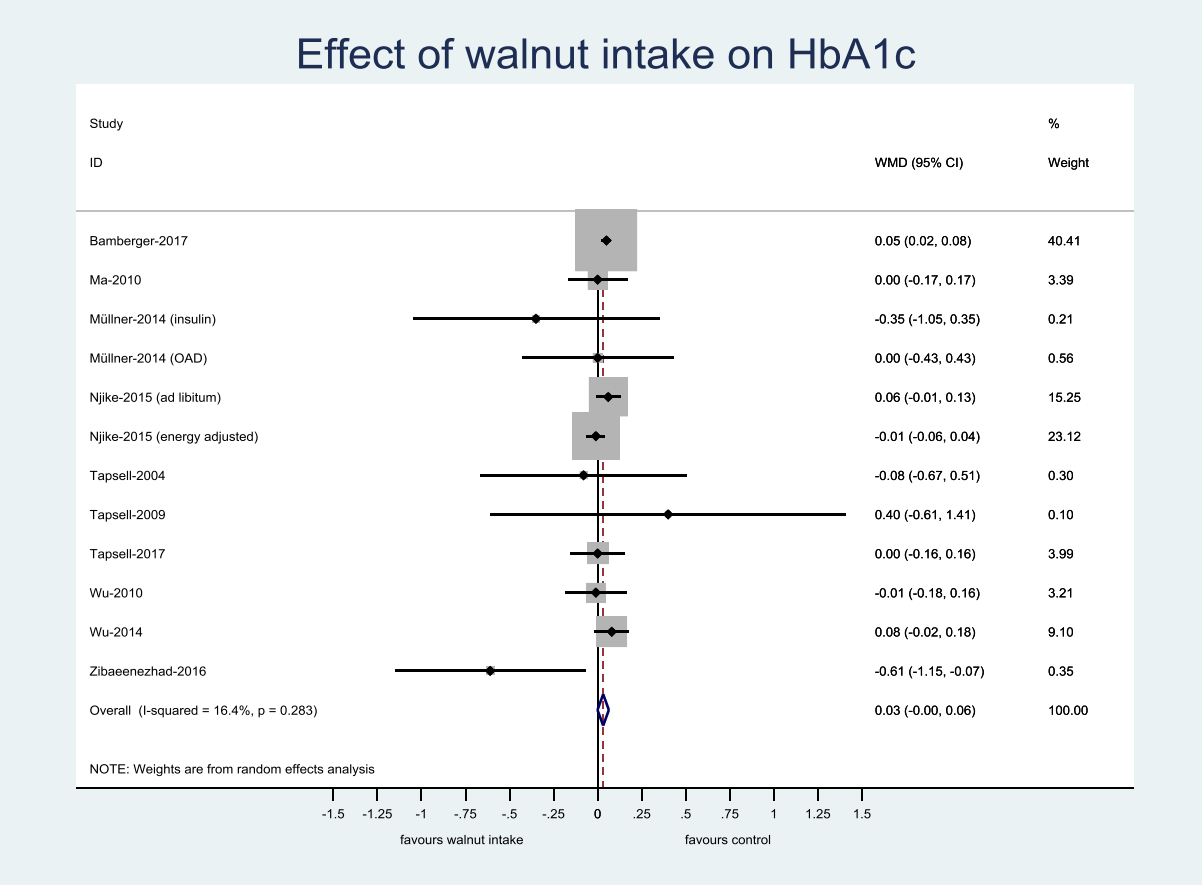

Figure 4: Difference in HbA1c (%) between walnut consumption and control. Diamond indicates weighted mean difference with 95% confidence intervals.

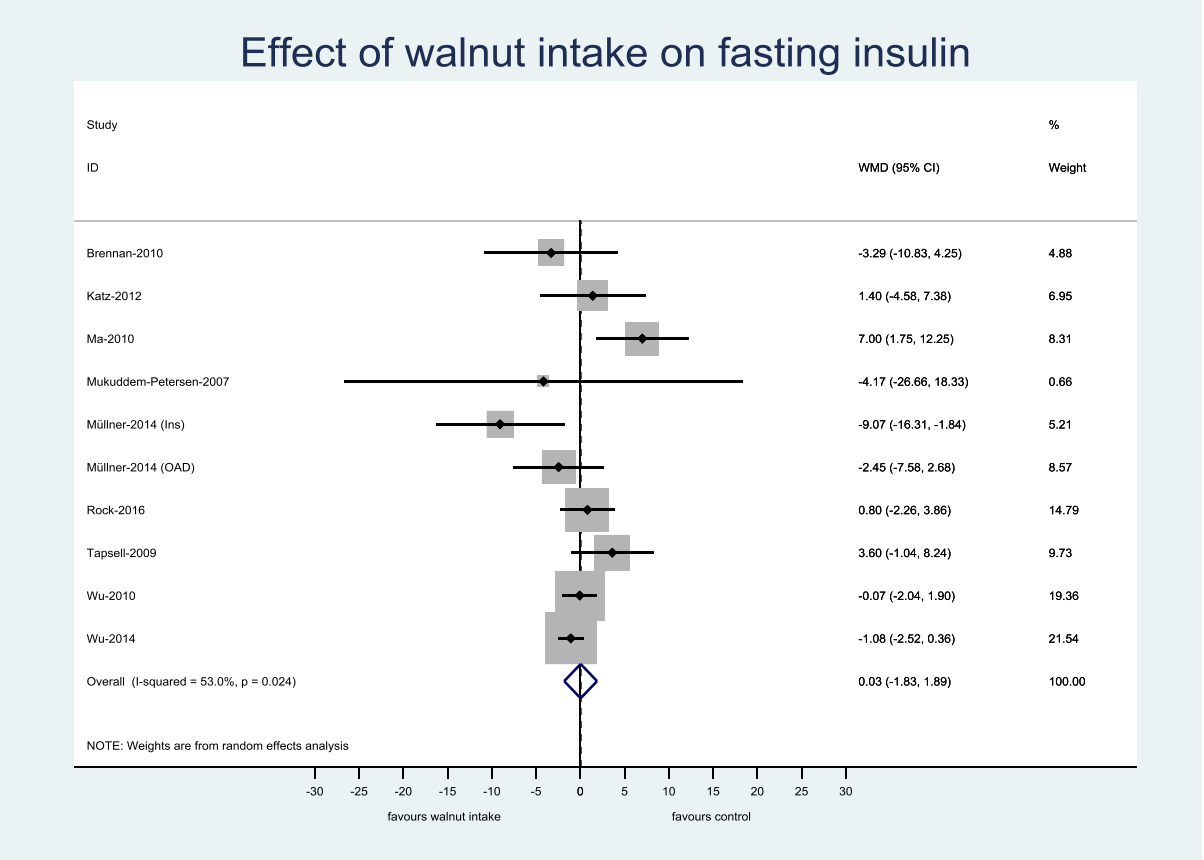

Figure 5: Difference in fasting insulin (μIU/mL) between walnut consumption and control. Diamond indicates weighted mean difference with 95% confidence intervals.

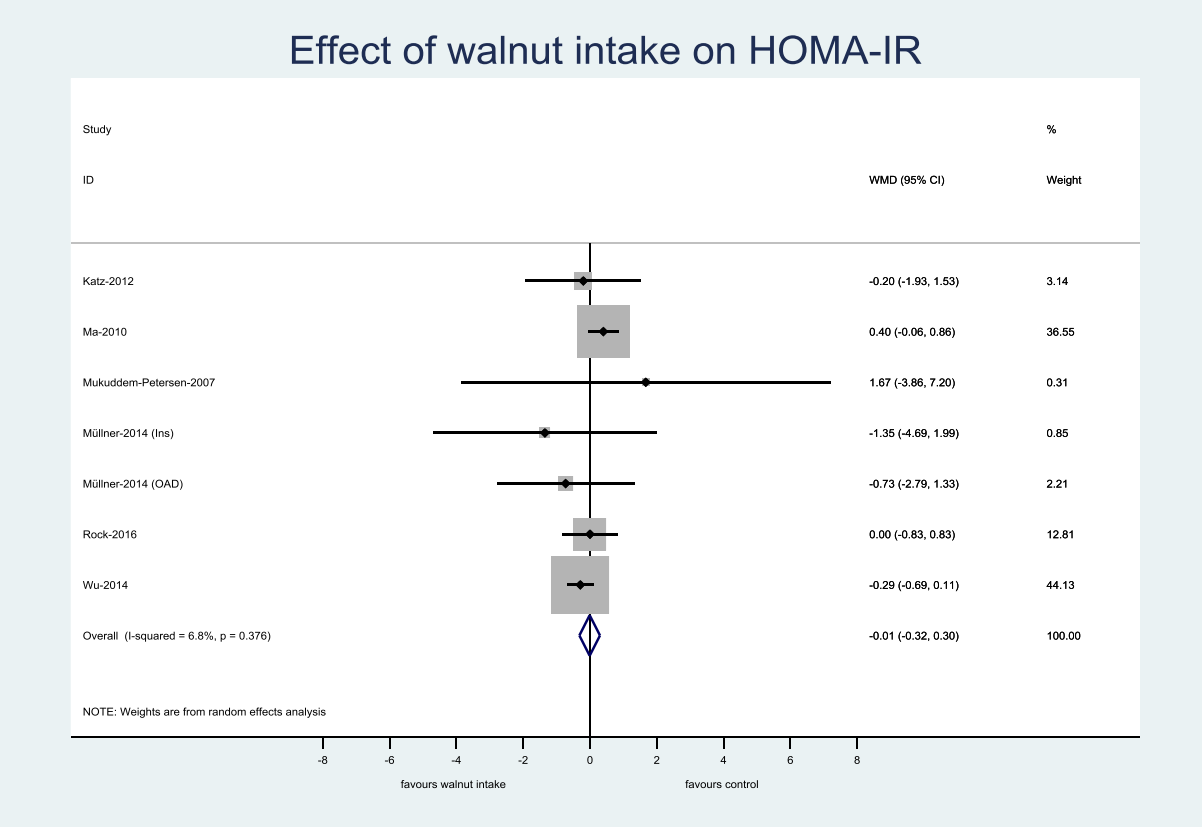

Figure 6: Difference in HOMA-IR between walnut consumption and control. Diamond indicates weighted mean difference with 95% confidence intervals.