**List of supplementary data**

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**Supplementary data 10:** Results of ‘leave-one-out’ sensitivity analyses

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**Supplementary data 12:** Sub-group analyses (limited to outcomes with more than 10 effect sizes)

**Supplementary data 13:** Contour funnel plots and results of Egger’s test (limited to outcomes with more than 10 effect sizes)

**Supplementary data 14:** GRADE assessment of the quality of the body of evidence

**Supplementary data 1:** PRISMA checklist

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| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 - 5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 - 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplementary Data 2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6 - 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6 - 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | 7 - 8 |

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| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 - 8 |
| **RESULTS** | | |  |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Figure 2, Supplementary data 9 - 10 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 2, Supplementary data 3 - 4 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Table 2, Supplementary data 4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 11, Supplementary data 8, 11 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 10, Supplementary data 5 - 7 |
| **DISCUSSION** | | |  |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11 - 15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 14 - 15 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 15 |
| **FUNDING** | | |  |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

**Supplementary data 2:** Example search strategy

Pubmed:

((((((((((((((((((((((((((((((((((((((((((((("Glucose"[Mesh]) OR "Blood Glucose"[Mesh]) OR glucose) OR"plasma glucose") OR "blood glucose") OR "Insulin"[Mesh]) OR insulin\*) OR "Insulin Resistance"[Mesh]) OR insulin resistan\*) OR "Glycated Hemoglobin A"[Mesh]) OR "glycosylated hemoglobin") OR "glycosylated haemoglobin") OR "glycated hemoglobin") OR "glycated haemoglobin") OR HbA1c) OR "Diabetes Mellitus"[Mesh]) OR diabet\*) OR "Glucose Metabolism Disorders"[Mesh]) OR glucose metabolism disorder\*) OR "Glucose Intolerance"[Mesh]) OR glucose intoleran\*) OR "Prediabetic State"[Mesh]) OR prediabet\*) OR impaired glucose toleran\*) OR "Hyperglycemia"[Mesh]) OR glycemi\*) OR glycaemi\*) OR hyperglycemi\*) OR hyperglycaemi\*) OR dysglycemi\*) OR dysglycaemi\*) OR "Hyperinsulinism"[Mesh]) OR hyperinsulin\*) OR dysinsulin\*) OR HOMA) OR "homeostatic model assessment") OR "blood sugar")))))) AND ((((((("Juglans"[Mesh]) OR walnut\*) OR "Nuts"[Mesh]) OR nut) OR nuts)))

**Supplementary data 3:** Reasons for full-text exclusions

|  |  |  |  |
| --- | --- | --- | --- |
| **Author** | **Year** | **Title** | **Reason** |
| L. Wu, K. Piotrowski, T. Rau, E. Waldmann, U. C. Broedl, C. Mantzoros and K. G. Parhofer | 2012 | Walnut-enriched diet reduces fasting non-HDL-cholesterol in healthy Caucasian subjects | Conference abstract (full text included in review) |
| B. M. McArthur, R. D. Mattes and R. V. Considine | 2018 | Mastication of Nuts under Realistic Eating Conditions: implications for Energy Balance | Does not compare walnut intake to control |
| S. Kalgaonkar, R. U. Almario, D. Gurusinghe, E. M. Garamendi, W. Buchan, K. Kim and S. E. Karakas | 2011 | Differential effects of walnuts vs almonds on improving metabolic and endocrine parameters in PCOS | Does not compare walnut intake to control |
| M. V. Selma, A. González-Sarrías, J. Salas-Salvadó, C. Andrés-Lacueva, C. Alasalvar, A. Örem, F. A. Tomás-Barberán and J. C. Espín | 2018 | The gut microbiota metabolism of pomegranate or walnut ellagitannins yields two urolithin-metabotypes that correlate with cardiometabolic risk biomarkers: Comparison between normoweight, overweight-obesity and metabolic syndrome | Does not compare walnut intake to control |
| E. K. Song, Y. Liu, H.S. Kim, H. Park | 2018 | Daily Walnut Consumption Favourably Changed Lipid Profiles among Korean Subjects with Higher Waist Circumference | Does not compare walnut intake to control |
| S. Bo, N. Milanesio, C. Schiavone, P. Villois, M. Durazzo, L. Gentile, M. Cassader and P. Cavallo-Perin | 2011 | Magnesium and trace element intake after a lifestyle intervention | Does not investigate the effect of walnuts |
| A. Kennedy, J. P. Spiers, V. Crowley, E. Williams and F. E. Lithander | 2015 | Postprandial adiponectin and gelatinase response to a high-fat versus an isoenergetic low-fat meal in lean, healthy men | Does not investigate the effect of walnuts |
| L. J. Moran, C. J. Wilson, J. D. Buckley, M. Noakes, P. M. Clifton and G. D. Brinkworth | 2013 | Changes in endothelial function and depression scores are associated following long-term dietary intervention: a secondary analysis | Does not investigate the effect of walnuts |
| S. D. Poppitt, G. F. Keogh, F. E. Lithander, Y. Wang, T. B. Mulvey, Y. K. Chan, B. H. McArdle and G. J. Cooper | 2008 | Postprandial response of adiponectin, interleukin-6, tumor necrosis factor-alpha, and C-reactive protein to a high-fat dietary load | Does not investigate the effect of walnuts |
| S. Rajaie, L. Azadbakht, M. Khazaei, M. Sherbafchi and A. Esmaillzadeh | 2014 | Moderate replacement of carbohydrates by dietary fats affects features of metabolic syndrome: a randomized crossover clinical trial | Does not investigate the effect of walnuts |
| L. C. Tapsell, A. Hokman, A. Sebastiao, S. Denmeade, G. Martin, G. D. Calvert and A. B. Jenkins | 2004 | The impact of usual dietary patterns, selection of significant foods and cuisine choices on changing dietary fat under 'free living' conditions | Does not investigate the effect of walnuts |
| K. N. Aronis, M. T. Vamvini, J. P. Chamberland, L. L. Sweeney, A. M. Brennan, F. Magkos and C. S. Mantzoros | 2012 | Short-term walnut consumption increases circulating total adiponectin and apolipoprotein A concentrations, but does not affect markers of inflammation or vascular injury in obese humans with the metabolic syndrome: data from a double-blinded, randomized, placebo-controlled study | Does not report relevant outcome |
| D. J. Baer, S. K. Gebauer and J. A. Novotny | 2016 | Walnuts Consumed by Healthy Adults Provide Less Available Energy than Predicted by the Atwater Factors | Does not report relevant outcome |
| L. Djousse, B. Lu and J. M. Gaziano | 2016 | Effects of Walnut Consumption on Endothelial Function in People with Type 2 Diabetes: a Randomized Pilot Trial | Does not report relevant outcome |
| O. M. Farr, D. Tuccinardi, J. Upadhyay, S. M. Oussaada and C. S. Mantzoros | 2018 | Walnut consumption increases activation of the insula to highly desirable food cues: a randomized, double-blind, placebo-controlled, cross-over fMRI study | Does not report relevant outcome |
| L. J. Gillen, L. C. Tapsell, C. S. Patch, A. Owen and M. Batterham | 2005 | Structured dietary advice incorporating walnuts achieves optimal fat and energy balance in patients with type 2 diabetes mellitus | Does not report relevant outcome |
| R. Holt, S.J. Yim, G. C. Shearer, R. M. Hackman, D. Djurica, J. W. Newman, A. W. Shindel, C. L. Keen | 2015 | Effects of short-term walnut consumption on human microvascular function and its relationship to plasma epoxide content | Does not report relevant outcome |
| John W. Newmana,g, Alan W. Shindelc, Carl L. Keena | 2012 | Short-term effect of macronutrient composition and glycemic index of a yoghurt breakfast on satiety and mood in healthy young men | Does not report relevant outcome |
| B. Burton-Freeman | 2005 | Sex and cognitive dietary restraint influence cholecystokinin release and satiety in response to preloads varying in fatty acid composition and content | Does not report relevant outcome |
| A. Lozano, P. Perez-Martinez, C. Marin, F. J. Tinahones, J. Delgado-Lista, C. Cruz-Teno, P. Gomez-Luna, F. Rodriguez-Cantalejo, F. Perez-Jimenez and J. Lopez-Miranda | 2013 | An acute intake of a walnut-enriched meal improves postprandial adiponectin response in healthy young adults | Does not report relevant outcome |
| C. L. Rock, S. W. Flatt, H.-S. Barkai, B. Pakiz and D. D. Heath | 2017 | A walnut-containing meal had similar effects on early satiety, CCK, and PYY, but attenuated the postprandial GLP-1 and insulin response compared to a nut-free control meal | Does not report relevant outcome |
| P. A. Megdal, D. Siemsen, D. Sands, E. A. Dratz and G. J. Handelman | 2010 | Facile fingerstick insulin analysis: Application to monitoring postprandial insulin responses to snack foods | Not appropriate study design |
| B. A. Kogan | 2005 | A complementary approach to type 2 diabetes | Not appropriate study design |
| F. Kaseb, M. Rashidi, M. Afkhami-Ardekani and H. Fallahzadeh | 2013 | Effect of olive, almond and walnut oil on cardiovascular risk factors in type 2 diabetic patients | Not appropriate study design |
| M. G. Campos Mondragon, R. M. Oliart Ros, A. Martinez Martinez, G. F. Mendez Machado and J. O. Angulo Guerrero | 2013 | [Metabolic syndrome reversion by polyunsaturated fatty acids ingestion] | Not appropriate study design |
| L. Tene, I. Shelef, D. Schwarzfuchs, Y. Gepner, A. Yaskolka Meir, G. Tsaban, H. Zelicha, A. Bilitzky, O. Komy, N. Cohen and et al. | 2018 | The effect of long-term weight-loss intervention strategies on the dynamics of pancreatic-fat and morphology: an MRI RCT study | Not possible to isolate the effect of walnuts |
| Y. Gepner, I. Shelef, D. Schwarzfuchs, H. Zelicha, L. Tene, A. Y. Meir, G. Tsaban, N. Cohen, N. Bril, M. Rein and et al. | 2018 | Effect of distinct lifestyle interventions on mobilization of fat storage pools CENTRAL magnetic resonance imaging randomized controlled trial | Not possible to isolate the effect of walnuts |
| G. Tsaban, A. Wolak, H. Avni-Hassid, Y. Gepner, I. Shelef, Y. Henkin, D. Schwarzfuchs, N. Cohen, N. Bril, M. Rein, D. Serfaty, S. Kenigsbuch, L. Tene, H. Zelicha, A. Yaskolka-Meir, O. Komy, A. Bilitzky, Y. Chassidim, U. Ceglarek, M. Stumvoll, M. Blüher, J. Thiery, D. Dicker, A. Rudich, M. J. Stampfer and I. Shai | 2017 | Dynamics of intrapericardial and extrapericardial fat tissues during long-term, dietary-induced, moderate weight loss | Not possible to isolate the effect of walnuts |
| A. Camargo, O. A. Rangel-Zúñiga, P. Peña-Orihuela, C. Marín, P. Pérez-Martínez, J. Delgado-Lista, F. M. Gutierrez-Mariscal, M. M. Malagón, H. M. Roche, F. J. Tinahones, F. Perez-Jimenez and J. Lopez-Miranda | 2013 | Postprandial changes in the proteome are modulated by dietary fat in patients with metabolic syndrome | Not possible to isolate the effect of walnuts |
| D. J. A. Jenkins, C. W. C. Kendall, B. Lamarche, M. S. Banach, K. Srichaikul, E. Vidgen, S. Mitchell, T. Parker, S. Nishi, B. Bashyam and et al. | 2018 | Nuts as a replacement for carbohydrates in the diabetic diet: a reanalysis of a randomised controlled trial | Not possible to isolate the effect of walnuts |
| D. J. A. Jenkins, C. W. C. Kendall, B. Lamarche, M. S. Banach, K. Srichaikul, E. Vidgen, S. Mitchell, T. Parker, S. Nishi, B. Bashyam, R. J. de Souza, C. Ireland, S. C. Pichika, J. Beyene, J. L. Sievenpiper and R. G. Josse | 2019 | Correction to: Nuts as a replacement for carbohydrates in the diabetic diet: a reanalysis of a randomised controlled trial | Not possible to isolate the effect of walnuts |
| P. López-Uriarte, R. Nogués, G. Saez, M. Bulló, M. Romeu, L. Masana, C. Tormos, P. Casas-Agustench and J. Salas-Salvadó | 2010 | Effect of nut consumption on oxidative stress and the endothelial function in metabolic syndrome | Not possible to isolate the effect of walnuts |
| C. Agebratt, E. Ström, T. Romu, O. Dahlqvist-Leinhard, M. Borga, P. Leandersson and F. H. Nystrom | 2016 | A Randomized Study of the Effects of Additional Fruit and Nuts Consumption on Hepatic Fat Content, Cardiovascular Risk Factors and Basal Metabolic Rate | Not possible to isolate the effect of walnuts |
| Y. Gepner, I. Shelef, D. Schwarzfuchs, N. Cohen, N. Bril, M. Rein, G. Tsaban, H. Zelicha, A. Yaskolka Meir, L. Tene, B. Sarusy, P. Rosen, J. R. Hoffman, J. R. Stout, J. Thiery, U. Ceglarek, M. Stumvoll, M. Blüher, M. J. Stampfer and I. Shai | 2017 | Intramyocellular triacylglycerol accumulation across weight loss strategies; Sub-study of the CENTRAL trial | Not possible to isolate the effect of walnuts |
| E. Mullner, M. Wallner, H. Brath and K. H. Wagner | 2013 | Dna damage and chromosomal stability in healthy and diabetic individuals and the impact of vegetables and walnut oil | Not possible to isolate the effect of walnuts |
| S. K. Nishi, C. W. C. Kendall, R. P. Bazinet, B. Bashyam, C. A. Ireland, L. S. A. Augustin, S. Blanco Mejia, J. L. Sievenpiper and D. J. A. Jenkins | 2014 | Nut consumption, serum fatty acid profile and estimated coronary heart disease risk in type 2 diabetes | Not possible to isolate the effect of walnuts |
| F. J. Ortega, M. I. Cardona-Alvarado, J. M. Mercader, J. M. Moreno-Navarrete, M. Moreno, M. Sabater, N. Fuentes-Batllevell, E. Ramírez-Chávez, W. Ricart, J. Molina-Torres, E. L. Pérez-Luque and J. M. Fernández-Real | 2015 | Circulating profiling reveals the effect of a polyunsaturated fatty acid-enriched diet on common microRNAs | Not possible to isolate the effect of walnuts |
| S. Rajaram, E. L. Yip, R. Reghunathan, S. Mohan and J. Sabaté | 2017 | Effect of Altering Dietary n-6: n-3 Polyunsaturated Fatty Acid Ratio with Plant and Marine-Based Supplement on Biomarkers of Bone Turnover in Healthy Adults | Not possible to isolate the effect of walnuts |
| J. L. Stevenson, C. M. Paton and J. A. Cooper | 2017 | Hunger and satiety responses to high-fat meals after a high-polyunsaturated fat diet: a randomized trial | Not possible to isolate the effect of walnuts |
| S. Tulipani, M. Urpi-Sarda, R. García-Villalba, M. Rabassa, P. López-Uriarte, M. Bulló, O. Jáuregui, F. Tomás-Barberán, J. Salas-Salvadó, J. C. Espín and et al. | 2012 | Urolithins are the main urinary microbial-derived phenolic metabolites discriminating a moderate consumption of nuts in free-living subjects with diagnosed metabolic syndrome | Not possible to isolate the effect of walnuts |
| N. W. Badri, S. W. Flatt, H. S. Barkai, B. Pakiz, D. D. Heath and C. L. Rock | 2018 | Insulin Resistance Improves More in Women than In Men in Association with a Weight Loss Intervention | Relevant outcomes reported in article already included in review |
| A. Martin, E. P. Neale and L. C. Tapsell | 2019 | The clinical utility of the AUSDRISK tool in assessing change in type 2 diabetes risk in overweight/obese volunteers undertaking a healthy lifestyle intervention | Relevant outcomes reported in article already included in review |
| V. Y. Njike, N. Yarandi, P. Petraro, R. G. Ayettey, J. A. Treu and D. L. Katz | 2016 | Inclusion of walnut in the diets of adults at risk for type 2 diabetes and their dietary pattern changes: a randomized, controlled, cross-over trial | Relevant outcomes reported in article already included in review |
| V. Y. Njike, V. C. Costales, P. Petraro, R. Annam, N. Yarandi and D. L. Katz | 2018 | The Resulting Variation in Nutrient Intake With the Inclusion of Walnuts in the Diets of Adults at Risk for Type 2 Diabetes: A Randomized, Controlled, Crossover Trial | Relevant outcomes reported in article already included in review |
| B. K. Rana, S. W. Flatt, D. D. Health, B. Pakiz, E. L. Quintana, L. Natarajan and C. L. Rock | 2017 | The IL6 Gene Promoter SNP and Plasma IL-6 in Response to Diet Intervention | Relevant outcomes reported in article already included in review |
| M. J. Zibaeenezhad, P. Farhadi, A. Attar, A. Mosleh, F. Amirmoezi and A. Azimi | 2017 | Effects of walnut oil on lipid profiles in hyperlipidemic type 2 diabetic patients: a randomized, double-blind, placebo-controlled trial | Relevant outcomes reported in article already included in review |
| L. Davis, W. Stonehouse, T. Loots du, J. Mukuddem-Petersen, F. H. van der Westhuizen, S. M. Hanekom and J. C. Jerling | 2007 | The effects of high walnut and cashew nut diets on the antioxidant status of subjects with metabolic syndrome | Relevant outcomes reported in article already included in review |
| T. Le, S. W. Flatt, L. Natarajan, B. Pakiz, E. L. Quintana, D. D. Heath, B. K. Rana and C. L. Rock | 2016 | Effects of Diet Composition and Insulin Resistance Status on Plasma Lipid Levels in a Weight Loss Intervention in Women | Relevant outcomes reported in article already included in review |
| M. Pieters, W. Oosthuizen, J. C. Jerling, D. T. Loots, J. Mukuddem-Petersen and S. M. Hanekom | 2005 | Clustering of haemostatic variables and the effect of high cashew and walnut diets on these variables in metabolic syndrome patients | Relevant outcomes reported in article already included in review |
| A. E. Schutte, J. M. Van Rooyen, H. W. Huisman, J. Mukuddem-Petersen, W. Oosthuizen, S. M. Hanekom and J. C. Jerling | 2006 | Modulation of baroreflex sensitivity by walnuts versus cashew nuts in subjects with metabolic syndrome | Relevant outcomes reported in article already included in review |
| H. Moravej, A. Salehi, Z. Razavi, M. R. Moein, H. Etemadfard, F. Karami and F. Ghahremani | 2016 | Chemical Composition and the Effect of Walnut Hydrosol on Glycemic Control of Patients With Type 1 Diabetes | Walnut extract |

**Supplementary data 4:** Risk of bias assessment summary



**Supplementary data 5:** Justification for risk of bias judgements, using the Cochrane Risk of Bias tool 2.0 (Y: Yes, PY: Probably Yes, N: No, PN: Probably No, NI: No information, NA: Not applicable)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Unique ID** | 1 | **Study ID** | Bamberger et al (2017) | **Assessor** | EN/VG |
| **Reference** |  | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Fasting glucose, HbA1c | **Results** | Supplementary table S1 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | PY | "Randomization (blocking of 12; SAS proc factex) and statistical analysis were performed using SAS 9.3 (SAS Institute, Cary, NC, USA)" - text implies computer generated randomisation sequence    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PY | Given the nature of the foods provided, which could not be masked, the study was unblinded - also, given the design was a cross-over study, participants would likely be aware of which group they were in    Given the nature of the foods provided, which could not be masked, the study was unblinded for personnel | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | Y | ITT used - manuscript states: "In addition, we also performed intention to treat analyses (ITT) of all 204 randomized subjects with all of the missing values imputed using single Markov chain Monte Carlo (MCMC) imputation" | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | Y | 95% completion rate | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | NA |  | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA |  | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose samples measured (considered to be appropriate) | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | N | "Data were blinded for laboratory analysis" | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | NA |  | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available (NCT02329067), HOMA listed but not published | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Data reported suggests outcomes reported as planned. HOMA not reported in manuscript, however this is addressed in 5.1 | |
| 5.3 ... multiple analyses of the data? | | NI | Data analysed multiple ways (ITT, PP). Only ITT results reported for glucose and HbA1c, however given this method is likely to be more appropriate, this was not judged as increasing the risk of bias. Change data reported (post data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| **Unique ID** | 2 | **Study ID** | Brennan et al (2010) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Fasting glucose, fasting insulin | **Results** | Table 4 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | PY | "Subjects were randomly assigned by a blinded statistician to either receive walnut-containing diet or placebo diet on the first visit", suggests randomisation sequence    States "randomly assigned by a blinded statistician", however this appears to be referring to random-sequence generation, rather than allocation concealment | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | "In order to allow for blinding of subjects and study staff, 48g of walnuts were incorporated into a liquid meal with similar macronutrient composition" - based on incorporation of walnuts, suggests blinding    "In order to allow for blinding of subjects and study staff, 48g of walnuts were incorporated into a liquid meal with similar macronutrient  composition" - judged to indicate intervention deliverers were blinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PN |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | NA |  | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | N | Per-protocol used | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | PY | 25% drop-out rate in study, suggesting per protocol analysis may have impacted on results | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 75% completion rate | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NI | No information on reasons for missing data or when pts withdrew | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NI | No information on reasons for missing data or when pts withdrew | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose samples measured (considered to be appropriate) | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Stated as "double-blind", however not clear if this refers to personnel or outcome assessors | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available (NCT00525629), glucose and insulin not listed, HOMA listed but not available | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Data reported suggests outcomes reported as planned. HOMA not reported in manuscript, however this is addressed in 5.1 | |
| 5.3 ... multiple analyses of the data? | | PY | ITT analysis also conducted but not reported | |
| **Risk of bias judgement** | | **High** |  | |
| **Overall bias** | **Risk of bias judgement** | | **High** |  | |
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| **Unique ID** | 3 | **Study ID** | Damasceno et al (2011) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Fasting glucose | **Results** | Table 4 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | Y | "Randomization was simple (not stratified) and was based on a random number table prepared  by a biostatistician, resulting in six possible diet sequences" (page 15)  "…resulting in six possible diet sequences,which were coded and introduced into sealed envelopes" - judged to be allocation concealment | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | PY |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | NI | Baseline characteristics given for all participants (cross-over), not possible to identify if differences between those who started on walnuts, or olive oil | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PY | Given the nature of the foods provided, which could not be masked, the study was unblinded - also, given the design was a cross-over study, participants would likely be aware of which group they were in    Given the nature of the foods provided, which could notbe masked, the study was unblinded. | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | N | Analysis appears to be per-protocol | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | PN | 10% drop-out, however as outcome not rare and exclusions not related to prognostic factors (drop-outs were due to study burden) | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 90% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | PN | "After randomization, two participants completed one and two diet sequences, respectively, but left the study because they felt it was too demanding" (page 17) - suggests that withdrawal was not based on outcome's true value | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose samples measured (considered to be appropriate) | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | N | Investigators involved in preparation of databases and laboratory (pg 16) determinations,however, were masked with respect to treatment sequence | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | NA |  | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available (ISRCTN68210440), however glucose not listed | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Text suggests only fasting glucose measured (minimal opportunity for alternate measurement methods) (pg 16). Pg 16 also indicates only baseline and 4 week data collected | |
| 5.3 ... multiple analyses of the data? | | NI | Final data reported (change data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 4 | **Study ID** | Holscher et al (2018) | **Assessor** | EN/VG |
| **Reference** |  | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Fasting glucose | **Results** | table 4 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | Y | "The treatment order was randomized by  dividing participants by sex and by using a random-number generator."    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | NI | Baseline characteristics given for all participants (cross-over), not possible to identify if differences between those who started on walnuts, or control | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PY | Given the nature of the foods provided, which could not be masked, the study was unblinded - also, given the design was a cross-over study, participants would likely be aware of which group they were in    Given the nature of the foods provided, which could notbe masked, the study was unblinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherance to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | PY | Analysis method not reported, appears to be per-protocol, however considered to be appropriate as design was controlled feeding study, with no drop-outs | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | Y | 100% data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | NA |  | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA |  | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose samples measured (considered to be appropriate) | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Not stated | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available, however glucose not listed | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Text suggests only fasting glucose measured (minimal opportunity for alternate measurement methods), also indicates only baseline and 3 week data collected | |
| 5.3 ... multiple analyses of the data? | | NI | Final data reported (change data not reported), with LSM reported, insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 5 | **Study ID** | Katz et al (2012) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol; Personal communication with trialist |
| **Outcome** | Fasting glucose, insulin, HOMA-IR | **Results** | Table 3 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | NI | Stated to be randomised, no details of randomisation method given    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | NI | Baseline characteristics given for all participants (cross-over), not possible to identify if differences between those who started on walnuts, or control | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PY | Given the nature of the foods provided, which could not be masked, the study was unblinded - also, given the design was a cross-over study, participants would likely be aware of which group they were in    Given the nature of the foods provided, which could notbe masked, the study was unblinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | |  |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | PY | "All analyses of endpoints were based  on the intention-to-treat principle." (pg 418 | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 87% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | PY | ITT used (confirmed by authors that all participants included in analysis) - corrects for bias | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA |  | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose and insulin samples measured (considered to be appropriate). "Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) values were generated from FPG and fasting serum insulin levels (HOMA calculator version 2.2.1)" | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | States that measurement of endothelial function conducted by assessor blinded to treatment assignments, but not stated for blood glucose measurements | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available (NCT01413646), however HOMA-IR not listed | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Text suggests only fasting glucose, insulin, HOMA-IR measured (minimal opportunity for alternate measurement methods), also indicates only baseline and 8 week data collected | |
| 5.3 ... multiple analyses of the data? | | NI | Change data reported (post data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 6 | **Study ID** | Ma et al (2010) | **Assessor** | EN/VG |
| **Reference** |  | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol; Personal communication with trialist |
| **Outcome** | Fasting glucose, insulin, A1c, HOMA-IR | **Results** | Table 2 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | NI | Stated to be randomised, no details of randomisation method given    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | NI | Baseline characteristics given for all participants (cross-over), not possible to identify if differences between those who started on walnuts, or control | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PY | Given the nature of the foods provided, which could not be masked, the study was unblinded - also, given the design was a cross-over study, participants would likely be aware of which group they were in    Given the nature of the foods provided, which could notbe masked, the study was unblinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | PY | "All analyses of end points were based on the intention-to-treat principle" (pg 229\_ | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 88% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | PY | ITT used (confirmed by authors that all participants included in analysis) - corrects for bias | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA |  | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose, A1c, and insulin samples measured (considered to be appropriate). "insulin resistance (HOMA-IR) values were calculated (HOMA calculator version 2.2.1) from fasting serum glucose and serum insulin levels to gauge the degree of insulin resistance" | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | States that measurement of endothelial function conducted by assessor blinded to treatment assignments, but not stated for blood glucose measurements | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available ( NCT00901043), however HOMA-IR not listed | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Text suggests only fasting glucose, insulin, HOMA-IR measured (minimal opportunity for alternate measurement methods), also indicates only baseline and 8 week data collected | |
| 5.3 ... multiple analyses of the data? | | NI | Change data reported (post data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 7 | **Study ID** | Mukuddem-Peterson et al (2007) | **Assessor** | EN/VG |
| **Reference** |  | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; “Grey literature” (e.g. unpublished thesis) |
| **Outcome** | Fasting glucose, insulin, HOMA-IR | **Results** | Table 5, pg 67 of Mukuddem-Peterson PhD thesis | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | Y | "participants  were grouped according to gender and age and then into  three groups by randomly drawing numbers from a hat" - judged to be randomised method    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants received foods, and as design was parallel study it is likely participants were not aware of their intervention  Given the nature of the foods provided, which could not be masked, personnel would be aware | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | N | Analysis appears to be per protocol | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | PN | 6% drop-out, however outcome not rare and exclusions not related to prognostic factors (drop-outs were due to study burden) | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | PN | 94% had data available (not clear which group participants dropped out of however, resulting in uncertainty of how this might affect results) | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | PN | Reasons for missing data suggest not related to true value. It should be noted that the study does not state which group participants withdrew from, however based on the reasons for withdrawal given, and the fact that the final numbers are similar across groups, it is assumed that the reasons for missing data are not related to its true value | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose and insulin samples measured (considered to be appropriate). "Insulin resistance was determined by using the HOMA method (24). The use of the current HOMA model performed well in comparison with the hyperglycaemic clamp, the frequently sampled intravenous glucose tolerance test (IVGTT) or the oral glucose tolerance test (OGTT) (25-28). The formula is as follows (24): HOMA = (Insulin (yIU/mi) x glucose (mmo1/1))/22.5." | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Not stated | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | NI | Protocol not available | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Test suggests fasting glucose, insulin and HOMA measured. Insulin and HOMA not reported in manuscript, but reported in thesis accessed for RoB appraisal | |
| 5.3 ... multiple analyses of the data? | | NI | Does not appear to be analysed using multiple methods (data reported for both change and post). Protocol not available therefore analysis intentions not available | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 8 | **Study ID** | Mullner et al (2014) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial |
| **Outcome** | Fasting glucose, HbA1c, insulin, HOMA-IR | **Results** | Table 3 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | NI | Stated to be randomised, method of randomisation not specified    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances in outcomes of interest at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants provided with oil. No detail provided on whether colour/taste was the same, however as parallel design study, implies participants not aware    Study stated to be "double-blind" however not clearly stated who was blinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | NI |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | N | Analysis appears to be per protocol | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | PY | >10% drop-out rate in study, suggesting per protocol analysis may have impacted on results | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | Average 87% had data available, some variation between groups (mean drop-out in intervention group: 11%, mean drop-out in control group: 15.5%), however reasons for drop-outs similar between groups and do not seem to reflect true values | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | PN | Reasons for missing data provided. Participants excluded for non-compliance, however as this was similar across control and intervention, not considered to reflect true outcome | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose and insulin, and HbA1c samples measured (considered to be appropriate). "Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as the product of fasting plasma glucose (mM) and insulin (lU mL 1) concentrations, divided by 22.5" | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Stated as "double-blind", however not clear if this refers to personnel or outcome assessors | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | NI | Protocol not available | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | NI | "Blood samples were taken and  anthropometric measurements were performed before the  intervention, after 4, 10 (end of intervention period) and  18 weeks" - text suggests measures were also taken after 18 weeks. Paper only states that changes were reversed after 18 weeks (data not shown). However, protocol not available, not possible to determine if all reported results correspond to intended outcome measurements | |
| 5.3 ... multiple analyses of the data? | | NI | Final data reported (change data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **High** |  | |
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| **Unique ID** | 9 | **Study ID** | Njike et al (2015) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol; Personal communication with trialist |
| **Outcome** | Fasting glucose, HbA1c | **Results** | Table 2 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | Y | The study participants were randomized using a SAS-generated random table."     Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | NI | Baseline characteristics given for all participants (cross-over), not possible to identify if differences between those who started on walnuts, or control | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PY | Given the nature of the foods provided, which could not be masked, the study was unblinded - also, given the design was a cross-over study, participants would likely be aware of which group they were in    Given the nature of the foods provided, which could not be masked, the study was unblinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | PY | All analyses of end points were based on the  intention-to-treat principle" | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 87% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | PY | ITT used (confirmed by authors that all participants included in analysis) - corrects for bias | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA |  | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose, HbA1c samples measured (considered to be appropriate). | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Not stated | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PY | Protocol available, lists measurements and timepoints as reported in the paper | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Measures taken at baseline, 3mo, and 6 mo, however 6 mo primary outcome (and reported here) | |
| 5.3 ... multiple analyses of the data? | | NI | Change data reported (post data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 10 | **Study ID** | Rock et al (2016) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Fasting glucose, insulin, HOMA-IR | **Results** | Table 3 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | PY | Method of randomisation not stated, however Le et al (2016) refers to stratified randomisation, implying computer generated method used    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants received dietary advice, and as design was parallel study it is likely participants were not aware of their intervention    Given the nature of the foods provided, which could not be masked, personnel would be aware | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | PN | Unclear what method of analysis used. Figure suggests all participants included in the analysis, however Table 3 has lower sample sizes implying analysis was restricted to completers only | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | Y | >20% drop-out rate in study, suggesting per protocol analysis may have impacted on results | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 78% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NI | No information on reasons for missing data (only stated as "lost to follow up") | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NI | 21% missing in intervention group, 24% missing in control group - similar proportion, however without reasons for missing data cannot conclude that missingness in the outcome does not depend on the true value | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose and insulin samples measured (considered to be appropriate). HOMA-IR "calculated from the homeostasis model assessment — insulin resistance (HOMA-IR) index ([fasting glucose, mmol/L] × [insulin, mIU/L]/22.5) with HOMA-IR >3.0 considered indicative of insulin resistance" | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Not stated | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available (NCT01424007), however does not list specific blood measures | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Measures taken at baseline, 6mo, and 12 mo, however 12 mo primary outcome (and reported here) | |
| 5.3 ... multiple analyses of the data? | | NI | Final data reported (change data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **High** |  | |
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| **Unique ID** | 11 | **Study ID** | Tapsell et al (2004) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial |
| **Outcome** | HbA1c | **Results** | Table 1 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | NI | Stated to be randomised, however method of randomisation not stated    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants received dietary advice, and as design was parallel study it is likely participants were not aware of their intervention    Given the nature of the foods provided, which could not be masked, personnel would be aware | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | Y | "Changes in clinical outcomes were analyzed  with an intention-to-treat model" | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | Y | 94 - 95% had data available (1 participant withdrew from each group) | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | NA |  | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA |  | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | PN | "Trained venipuncturists drew blood samples and sent them to a quality assured pathology laboratory (Southern IML Pathology)." - specific detail not given on HbA1c, but based on this information, judgement made that it was appropriate | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | PN | "Two research dietitians undertook all dietary  assessments, all at the University Clinic at 0, 3, and 6 months. Another three experienced  dietitians provided advice only; two were randomly allocated to see subjects on a monthly basis" and "Trained venipuncturists drew blood samples and sent them to a quality assured pathology laboratory (Southern IML Pathology)." - suggests that outcome assessors were different staff to those providing advice | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | NA |  | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | NI | Protocol not available | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | NI | Protocol not available, not possible to determine if all reported results correspond to intended outcome measurements | |
| 5.3 ... multiple analyses of the data? | | NI | Analysis intentions not available | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 12 | **Study ID** | Tapsell et al (2009) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Fasting glucose, HbA1c, fasting insulin | **Results** | Table 4 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | Y | "Randomization was conducted using a computerized random number generator, by a researcher independent of the subject interface (MB)."    Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants received dietary advice, and as design was parallel study it is likely participants were not aware of their intervention    Given the nature of the foods provided, which could not be masked, personnel would be aware | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | N | Completers only analysis appears to be used | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | Y | 30% drop-out rate in study, suggesting per protocol analysis may have impacted on results | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 65% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | PY | Reasons for missing data provided. Although overall amount of missing data similar between groups, reasons for missing data differs between group - in particular participants in the walnut group were excluded for non-compliance, which may indicate that the missing data depends on its true outcome | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | PY | participants in the walnut group were excluded for non-compliance, which may indicate that the missing data depends on its true outcome | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose and insulin samples measured (considered to be appropriate). HOMA "Insulin sensitivity was assessed using the homeostasis model assessment (HOMA) method: glucose (mmol per 100ml) insulin (mU/ml)/22.5 (Matthews et al., 1985)." | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Not stated | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available (ACTRN12607000600448), however HbA1c not listed | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | All time points reported in paper | |
| 5.3 ... multiple analyses of the data? | | NI | Protocol refers to change, however only final data reported. Insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **High** |  | |
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| **Unique ID** | 13 | **Study ID** | Tapsell et al (2017) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Glucose, HbA1c | **Results** | Table 2 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | Y | "Randomisation was conducted after the second screen for eligibility  and performed remotely by an investigator unrelated to the clinic using  a computer generated randomisation sequence (STATA V12, StataCorp  LP, College Station, TX)"     "The randomisation list was provided to the study team who added eligible participants sequentially for each of the effect sizes." - suggests allocation not concealed | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | N |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants received dietary advice, and as design was parallel study it is likely participants were not aware of their intervention    Given the nature of the foods provided, which could not be masked, personnel would be aware | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | Y | "The study was testing an  approach applicable to primary care, so the analysis was  conducted on an intention-to-treat basis rather than on  compliance to treatment" | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | <50% had data available at 12 months | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Sensitivity analyses performed for weight, but not for outcomes of interest (glucose, HbA1c) | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NI | Detailed reasons for missing data not provided, unclear if due to true value | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | Y | Greater proportion of missing data in intervention groups (~40%) compared to walnut group (~50%) | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | "fasting blood glucose and serum HbA1c were assessed through a registered pathology service (Southern IML Pathology) quarterly" - appropriate method used | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | PN | "For each participant, a different APD that was blinded  to study allocation undertook assessments to the one providing  counselling, to reduce the risk of cross-contamination between study  arms." - judged as suggesting blinded | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | NA |  | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PY | Protocol available and protocol paper available. Analysis judged to be conducted according to plan | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | Measures taken at baseline, 3mo, 6 mo, 9 mo, 12 mo, however 12 mo primary outcome (and reported here) | |
| 5.3 ... multiple analyses of the data? | | PN | Data appears to be analysed in accordance with analysis plan in protocol publication | |
| **Risk of bias judgement** | | **Low** |  | |
| **Overall bias** | **Risk of bias judgement** | | **High** |  | |
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| **Unique ID** | 14 | **Study ID** | Wu et al (2010) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Fasting glucose, HbA1c, insulin | **Results** | Table 4 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | PY | Stated to be block randomised. Based on this information assumed to be computer generated.     Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants provided with bread. Manuscript states "It should be noted that the flaxseed and walnut  breads could be differentiated by their appearance and taste; therefore,  the participants were not necessarily unaware of the intervention arms", however as parallel study it was judged to be low risk that participants could be aware    Manuscript states: "However, researchers, dietitians, laboratory technicians, and statisticians were unaware of the group assignment" | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | N |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | NA |  | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | Y | Intention-to-treat analysis used: "The analyses were based on the intention-to-treat principle" | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | Y | Data available for 97.9% of participants | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | NA |  | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA |  | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Methods of measuring outcome judged to be appropriate as use standard measurement methods  "Serum glucose, total cholesterol, HDL cholesterol, LDL cholesterol,  triglycerides, and apolipoprotein (Apo) A-1, B, and E were measured  enzymatically on an automatic analyzer"  "Hemoglobin A1C  (HbA1c) was quantified from resolved erythrocyte with automated  immunoassay (Roche Diagnostics)."  "Serum insulin levels were determined  by a sandwich ELISA (Linco Research)" | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | N | Manuscript states: "However, researchers, dietitians, laboratory technicians, and statisticians  were unaware of the group assignment" | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | NA |  | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PN | Protocol available (NCT00742742), however does not describe flaxseed group (described in separate protocol). While this group was not included in the current analysis, may have affected analysis plan | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | All time points reported in paper | |
| 5.3 ... multiple analyses of the data? | | NI | Change data reported (post data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **Some concerns** |  | |
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| **Unique ID** | 15 | **Study ID** | Wu et al (2014) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial; Trial protocol |
| **Outcome** | Glucose, insulin, HbA1c, HOMA | **Results** | Table 5 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | PY | "Subject randomization  (using a complete block design) and statistical analysis were  performed on SAS 9.2." - implies computer generated sequence      Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PY | Given the nature of the foods provided, which could not be masked, the study was unblinded - also, given the design was a cross-over study, participants would likely be aware of which group they were in    Given the nature of the foods provided, which could not be masked, the study was unblinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | N | Completers only analysis used | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | Y | 38% drop-out rate in study, suggesting per protocol analysis may have impacted on results | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 62% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | PY | Reasons for missing data provided, and unclear whether data missingness related to true value (eg n=5 participants excluded due to protocol violations, n=1 excluded due to persistent hypertension). | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | PY | Reasons for missing data provided, and unclear whether data missingness related to true value (eg n=5 participants excluded due to protocol violations, n=1 excluded due to persistent hypertension). | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose, HbA1c, and insulin samples measured (considered to be appropriate). HOMA "HOMA-IR = glucose (mg/dL) × insulin  (μU/mL)/405." | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Not stated | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | PY | Protocol available (NCT01188902) and all outcomes of interest reported in manuscript | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | PN | All time points reported in paper | |
| 5.3 ... multiple analyses of the data? | | NI | Change data reported (post data not reported), insufficient information in protocol to tell if this was original intention | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **High** |  | |
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|  |  |  |  |  |  |
| **Unique ID** | 16 | **Study ID** | Zibaeenezhad et al (2016) | **Assessor** | EN/VG |
| **Reference** | Individually Randomized, Parallel Group Trials | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | **Source** | Journal article(s) with results of the trial |
| **Outcome** | Glucose, HbA1c | **Results** | Table 2 | **Weight** | 1 |
| **Domain** | **Signalling question** | | **Response** | **Description** | |
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | | PY | Stated to be block randomised. Based on this information assumed to be computer generated.     Allocation concealment not stated | |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | N | No imbalances apparent between groups at baseline | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | | PN | All participants received dietary advice, and as design was parallel study it is likely participants were not aware of their intervention    Given the nature of the trial (oil provided to intervention group but not control), which could not be masked, the study was unblinded | |
| 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | PY |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | PN | Any deviations reported (ie non-adherence to the intervention) would be expected to arise in usual care | |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA |  | |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA |  | |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | N | Completers only analysis used | |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | PY | 10% drop-out, however reasons for drop-out differed between study groups not given | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | N | 90% had data available | |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | N | Analysis methods did not correct for bias, and no sensitivity analyses conducted | |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | PY | Participants excluded for non-compliance (minimal detail provided), therefore missingness could reflect true outcome | |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | | PY | 10% missing data in both groups, however reasons for dropout differed between groups, implying missing data may have been related to true outcome | |
| **Risk of bias judgement** | | **High** |  | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | | N | Fasting glucose and HbA1c measured using standard techniques: "Measurement of fasting blood sugar (FBS) and  hemoglobin A1c (HbA1c) values were done using enzymatic  assay kits (Parsazmoon, Iran)." | |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | | PN | Suggests same method used for all participants | |
| 4.3 Were outcome assessors aware of the intervention received by study participants? | | NI | Not stated | |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | | PN | Objective measurement unlikely to be affected by knowledge | |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA |  | |
| **Risk of bias judgement** | | **Low** |  | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | | NI | Protocol not available | |
| 5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | NI | Protocol not available, not possible to determine if all reported results correspond to intended outcome measurements | |
| 5.3 ... multiple analyses of the data? | | NI | Analysis intentions not available | |
| **Risk of bias judgement** | | **Some concerns** |  | |
| **Overall bias** | **Risk of bias judgement** | | **High** |  | |

**Supplementary data 6:** Summary data for each study

**Table S1**: Summary data, fasting blood glucose (mg/dL)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Post-intervention/ change from baseline | Mean (intervention) | Standard deviation (intervention) | n (intervention) | Mean (control) | Standard deviation (control) | n (control) |
| Bamberger et al (2017) | post | 93.3 | 7.141428 | 204 | 92.2 | 7.141428 | 204 |
| Brennan et al (2010) | change | -0.86 | 6.584072 | 15 | -4.21 | 6.584072 | 15 |
| Damasceno et al (2011) | post | 87.96 | 12.88741 | 18 | 90 | 11.29459 | 18 |
| Holscher et al (2018) | post | 99.5 | 6.788225 | 18 | 99.7 | 6.788225 | 18 |
| Katz et al (2012) | change | -0.2 | 8.8 | 46 | -1.5 | 6.8 | 46 |
| Ma et al (2010) | change | 10 | 20.5 | 24 | 2.9 | 21.5 | 24 |
| Mukuddem-Petersen et al (2005/2007) | change | 3 | 18.60379 | 21 | -8.1 | 31.38252 | 22 |
| Müllner et al (2014) (a) | post | 144.18 | 40.72085 | 18 | 157.68 | 55.73672 | 16 |
| Müllner et al (2014) (b) | post | 138.78 | 30.99535 | 29 | 144.18 | 41.406 | 29 |
| Njike et al (2015) (a) | change | 0.02 | 9.67 | 56 | -1.08 | 7.27 | 56 |
| Njike et al (2015) (b) | change | -1.75 | 7.29 | 56 | -0.33 | 5.42 | 56 |
| Rock et al (2016) | post | 93 | 8.062258 | 65 | 93 | 15.6205 | 61 |
| Tapsell et al (2009) | post | 160.2 | 50.4 | 18 | 136.8 | 37.8 | 17 |
| Tapsell et al (2017) | post | 96 | 9.556142 | 64 | 95.4 | 9.717436 | 37 |
| Wu et al (2010) | change | -7.2 | 18.253 | 94 | -7.92 | 20.58762 | 95 |
| Wu et al (2014) | change | -0.7 | 5.91608 | 35 | 1.3 | 8.282512 | 35 |
| Zibaeenezhad et al (2016) | post | 137.91 | 23.24 | 45 | 153.93 | 42.06 | 45 |

**Table S2**: Summary data, HbA1c (%)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Post-intervention or change from baseline | Mean (intervention) | Standard deviation (intervention) | n (intervention) | Mean (control) | Standard deviation (control) | n (control) |
| Bamberger et al (2017) | post | 5.53 | 0.142829 | 204 | 5.48 | 0.142829 | 204 |
| Ma et al (2010) | change | 0 | 0.3 | 24 | 0 | 0.3 | 24 |
| Müllner et al (2014) (a) | post | 7.54 | 0.914962 | 18 | 7.89 | 1.13538 | 16 |
| Müllner et al (2014) (b) | post | 7.03 | 0.80183 | 29 | 7.03 | 0.867554 | 29 |
| Njike et al (2015) (a) | change | 0.1 | 0.21 | 56 | 0.04 | 0.17 | 56 |
| Njike et al (2015) (b) | change | 0.05 | 0.14 | 56 | 0.06 | 0.14 | 56 |
| Tapsell et al (2004) | post | 6.89 | 0.82 | 16 | 6.97 | 0.95 | 19 |
| Tapsell et al (2009) | post | 7.1 | 1.5 | 18 | 6.7 | 1.5 | 16 |
| Tapsell et al (2017) | post | 5.13333 | 0.37935 | 63 | 5.13333 | 0.385613 | 37 |
| Wu et al (2010) | change | 0.05 | 0.346263 | 94 | 0.06 | 0.795657 | 95 |
| Wu et al (2014) | change | 0.06 | 0.177482 | 35 | -0.02 | 0.236643 | 35 |
| Zibaeenezhad et al (2016) | post | 6.37 | 1.29 | 45 | 6.98 | 1.33 | 45 |

**Table S3**: Summary data, fasting insulin (μIU/mL)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Post-intervention or change from baseline | Mean (intervention) | Standard deviation (intervention) | n (intervention) | Mean (control) | Standard deviation (control) | n (control) |
| Brennan et al (2010) | change | 4.33 | 9.64373 | 15 | 7.62 | 11.3478 | 15 |
| Katz et al (2012) | change | -0.3 | 19.6 | 46 | -1.7 | 6.6 | 46 |
| Ma et al (2010) | change | 3.6 | 10.4 | 24 | -3.4 | 8 | 24 |
| Mukuddem-Petersen et al (2005/2007) | change | 37.3333 | 28.6212 | 21 | 41.5 | 45.1718 | 22 |
| Müllner et al (2014) (a) | post | 8.208 | 9.04908 | 18 | 17.28 | 12.0526 | 16 |
| Müllner et al (2014) (b) | post | 15.264 | 5.33782 | 29 | 17.712 | 13.0417 | 29 |
| Rock et al (2016) | post | 13.8 | 9.67471 | 65 | 13 | 7.81025 | 61 |
| Tapsell et al (2009) | post | 15.9 | 8.5 | 18 | 12.3 | 5.2 | 17 |
| Wu et al (2010) | change | 0.52704 | 3.56868 | 94 | 0.59616 | 9.10152 | 95 |
| Wu et al (2014) | change | 0.48 | 2.66224 | 35 | 1.56 | 3.43133 | 35 |

**Table S4**: Summary data, HOMA-IR

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Post-intervention or change from baseline | Mean (intervention) | Standard deviation (intervention) | n (intervention) | Mean (control) | Standard deviation (control) | n (control) |
| Katz et al (2012) | change | -0.5 | 5.7 | 46 | -0.3 | 1.8 | 46 |
| Ma et al (2010) | change | 0.2 | 0.9 | 24 | -0.2 | 0.7 | 24 |
| Mukuddem-Petersen et al (2007) | change | 8.96667 | 9.71531 | 21 | 7.29667 | 8.72529 | 22 |
| Müllner et al (2014) (a) | post | 4.66 | 3.28783 | 18 | 6.01 | 6.07099 | 16 |
| Müllner et al (2014) (b) | post | 4.84 | 2.41864 | 29 | 5.57 | 5.12646 | 29 |
| Rock et al (2016) | post | 3 | 2.41868 | 65 | 3 | 2.34307 | 61 |
| Wu et al (2014) | change | 0.06 | 0.76909 | 35 | 0.35 | 0.946573 | 35 |

**Supplementary data 7:** Sensitivity analyses using the random-effects model with Hartung-Knapp-Sidik-Jonkman adjustment

|  |  |  |
| --- | --- | --- |
| Outcome | DerSimonian and Laird  (original analysis)  Weighted mean difference (95% CI) | Hartung-Knapp-Sidik-Jonkman Weighted mean difference (95% CI) |
| Fasting blood glucose (mg/dL) | 0.331 (-0.817, 1.479), p=0.572 | 0.331 (-0.946, 1.608), p=0.590 |
| HbA1c (%) | 0.031 (-0.001, 0.063), p=0.057 | 0.031 (-0.005, 0.067), p=0.084 |
| Fasting insulin (μIU/mL) | 0.032 (-1.826, 1.889), p=0.973 | 0.032 (-2.498, 2.562), p=0.978 |
| HOMA-IR | -0.010 (-0.319, 0.298), p=0.947 | -0.010 (-0.374, 0.354), 0.949 |

**Supplementary data 8:** Sensitivity analyses using correlation coefficient of 0.25, 0.5, and 0.75 for cross-over studies

**Table S5:** sensitivity analyses using varying correlation coefficients for cross-over studies, fasting blood glucose (mg/dL)

|  |  |  |
| --- | --- | --- |
| Outcome | Weighted mean difference (95% CI) | Inconsistency (I2) |
| Paired analysis (original analysis) | 0.331 (-0.817, 1.479), p=0.572 | 17.4% |
| Correlation coefficient: 0.25 | 0.330 (-0.808, 1.467), p=0.570 | 28.1% |
| Correlation coefficient: 0.5 | 0.351 (-0.781, 1.484), p=0.543 | 42.4% |
| Correlation coefficient: 0.75 | 0.422 (-0.691, 1.534), p=0.458 | 63% |

**Table S6:** sensitivity analyses using varying correlation coefficients for cross-over studies, HbA1c (%)

|  |  |  |
| --- | --- | --- |
| Outcome | Weighted mean difference (95% CI) | Inconsistency (I2) |
| Paired analysis (original analysis) | 0.031 (-0.001, 0.063), p=0.057 | 16.4% |
| Correlation coefficient: 0.25 | 0.030 (-0.002, 0.063), p=0.070 | 27.1% |
| Correlation coefficient: 0.5 | 0.031 (-0.002, 0.064), p=0.068 | 40.7% |
| Correlation coefficient: 0.75 | 0.031 (-0.001, 0.063), p=0.061 | 61.7% |

**Table S7:** sensitivity analyses using varying correlation coefficients for cross-over studies, fasting insulin (μIU/mL)

|  |  |  |
| --- | --- | --- |
| Outcome | Weighted mean difference (95% CI) | Inconsistency (I2) |
| Paired analysis (original analysis) | 0.032 (-1.826, 1.889), p=0.973 | 53% |
| Correlation coefficient: 0.25 | 0.074 (-1.843, 1.991), p=0.940 | 60.2% |
| Correlation coefficient: 0.5 | 0.135 (-1.857, 2.126), p=0.895 | 68.2% |
| Correlation coefficient: 0.75 | 0.139 (-2.029, 2.307), p=0.900 | 79.5% |

**Table S8:** sensitivity analyses using varying correlation coefficients for cross-over studies, HOMA-IR

|  |  |  |
| --- | --- | --- |
| Outcome | Weighted mean difference (95% CI) | Inconsistency (I2) |
| Paired analysis (original analysis) | -0.010 (-0.319, 0.298), p=0.947 | 6.8% |
| Correlation coefficient: 0.25 | -0.012 (-0.373, 0.349), p=0.947 | 25.8% |
| Correlation coefficient: 0.5 | -0.020 (-0.430, 0.391), p=0.925 | 46.4% |
| Correlation coefficient: 0.75 | -0.032 (-0.494, 0.430), p=0.892 | 69.8% |

**Supplementary data 9:** Sensitivity analyses pooling separate intervention groups within the same study (in the case of studies which included more than one eligible intervention group and corresponding control groups)

|  |  |  |
| --- | --- | --- |
| Outcome | Original analysis – weighted mean difference (95% CI), I2 | Sensitivity analysis pooling separate intervention groups within the same study - weighted mean difference (95% CI), I2 |
| Fasting blood glucose (mg/dL) | 0.331 (-0.817, 1.479), p=0.572, 17.4% | 0.428 (-0.751, 1.608), p=0.476, 18.2% |
| HbA1c (%) | 0.031 (-0.001, 0.063), p=0.057, 16.4% | 0.040 (0.017, 0.063), p=0.001, 1.2% |
| Fasting insulin (μIU/mL) | 0.032 (-1.826, 1.889), p=0.973, 53% | 0.175 (-1.676, 2.027), p=0.853, 54.2% |
| HOMA-IR | -0.010 (-0.319, 0.298), p=0.947, 6.8% | -0.015 (-0.384, 0.353), p=0.936, 22.5% |

**Supplementary data 10:** Results of ‘leave-one-out’ sensitivity analyses



**Figure S1:** Estimates for effect of walnut consumption on fasting blood glucose (mg/dL) if one study was omitted



**Figure S2:** Estimates for effect of walnut consumption on HbA1c (%) if one study was omitted



**Figure S3:** Estimates for effect of walnut consumption on fasting insulin (μIU/mL) if one study was omitted

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**Figure S4:** Estimates for effect of walnut consumption on fasting HOMA-IR if one study was omitted

**Supplementary Data 11:** Sensitivity analyses restricting analyses to studies using whole walnuts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | Number of studies | Number of effect sizes | Weighted mean difference (95% CI) | Inconsistency (I2) |
| Fasting blood glucose (mg/dL) | 13 | 14 | 0.538 (-0.354, 1.431), p=0.237 | 0% |
| HbA1c (%) | 8 | 9 | 0.039 (0.017, 0.061), p=0.000 | 0% |
| Fasting insulin (μIU/mL) | 8 | 8 | 0.678 (-1.062, 2.419), p=0.445 | 44.6% |
| HOMA-IR | 5 | 5 | 0.025 (-0.349, 0.399), p=0.896 | 24.9% |

**Supplementary data 12:** Sub-group analyses

**Table S9:**  Results of sub-group analyses for fasting blood glucose (mg/dL)

|  |  |  |  |
| --- | --- | --- | --- |
| **Sub-group analysis category** | **Sub-group** | **Number of effect sizes** | **Weighted mean difference (95% CI)** |
| Risk of bias | Some concerns | 9 | 0.633 (-0.365, 1.630), p=0.214 |
| High | 8 | -0.382 (-3.429, 2.665), p=0.806 |
| Duration | Less than three months | 10 | 0.842 (-0.254, 1.938), p=0.132 |
| More than three months | 7 | -0.206 (-2.359, 1.947), p=0.851 |
| Health status | Healthy | 3 | 0.177 (-1.714, 2.068), p=0.855 |
| MetS or other chronic disease risk factors | 8 | 0.332 (-1.051, 1.715), p=0.638 |
| T2DM | 5 | -1.754 (-14.887, 11.378), p=0.793 |
| Combination | 1 | 0.600 (-3.310, 4.510), p=0.764 |
| Walnut dose\* | <50g/day | 8 | 0.733 (-0.348, 1.814), p=0.184 |
| >50g/day | 6 | 0.318 (-1.599, 2.235), p=0.745 |
| Total fat percentage | <37% | 5 | 0.342 (-2.104, 2.788), p=0.784 |
| >37% | 7 | 0.906 (-0.517, 2.329), p=0.212 |
| Not reported | 5 | -1.509 (-5.088, 2.070), p=0.409 |

\* limited to studies examining the effect of whole walnuts only

**Table S10:**  Results of sub-group analyses for HbA1c (%)

|  |  |  |  |
| --- | --- | --- | --- |
| **Sub-group analysis category** | **Sub-group** | **Number of effect sizes** | **Weighted mean difference (95% CI)** |
| Risk of bias | Some concerns | 6 | 0.037 (0.014, 0.060), p=0.001 |
| High | 6 | -0.012 (-0.160, 0.137), p=0.879 |
| Duration | Less than three months | 5 | 0.050 (0.024, 0.076), p=0.000 |
| More than three months | 7 | 0.008 (-0.053, 0.068), p=0.799 |
| Health status | Healthy | 2 | 0.052 (0.026, 0.079), p=0.000 |
| MetS or other chronic disease risk factors | 3 | 0.016 (-0.034, 0.065), p=0.537 |
| T2DM | 6 | -0.085 (-0.277, 0.106), p=0.384 |
| Combination | 1 | 0.000 (-0.156, 0.156), p=1.000 |
| Walnut dose\* | <50g/day | 6 | 0.049 (0.023, 0.075), p=0.000 |
| >50g/day | 3 | -0.016 (-0.032, 0.065), p=0.516 |
| Total fat percentage | <37% | 4 | -0.002 (-0.115, 0.111), p=0.970 |
| >37% | 3 | 0.051 (0.025, 0.077), p=0.000 |
| Not reported | 5 | -0.004 (-0.099, 0.092), p=0.941 |

\* limited to studies examining the effect of whole walnuts only

**Table S11:**  Results of sub-group analyses for fasting insulin (μIU/mL)

|  |  |  |  |
| --- | --- | --- | --- |
| **Sub-group analysis category** | **Sub-group** | **Number of effect sizes** | **Weighted mean difference (95% CI)** |
| Risk of bias | Some concerns | 4 | 2.077 (-1.860, 6.014), p=0.301 |
| High | 6 | -0.957 (-3.323, 1.409), p=0.428 |
| Duration | Less than three months | 7 | -0.880 (-4.141, 2.381), p=0.597 |
| More than three months | 3 | 0.594 (-1.010, 2.198), p=0.468 |
| Health status | Healthy | 1 | -1.080 (-2.519, 0.359), p=0.141 |
| MetS or other chronic disease risk factors | 5 | 0.098 (-1.458, 1.655), p=0.902 |
| T2DM | 4 | 0.129 (-6.046, 6.305), p=0.967 |
| Walnut dose\* | <50g/day | 5 | -0.214 (-1.512, 1.084), p=0.747 |
| >50g/day | 3 | 4.098 (-0.534, 8.729), p=0.083 |
| Total fat percentage | <37% | 3 | 0.594 (-1.010, 2.198), p=0.468 |
| >37% | 5 | 0.849 (-2.980, 4.678), p=0.664 |
| Not reported | 2 | -5.248 (-11.662, 1.165), p=0.109 |

\* limited to studies examining the effect of whole walnuts only

**Supplementary data 13:** Contour funnel plots and results of Egger’s test (limited to outcomes with more than 10 effect sizes)

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**Figure S5**: Contour funnel plot of the effect of walnut consumption on fasting blood glucose (mg/dL)

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**Figure S6**: Contour funnel plot of the effect of walnut consumption on HbA1c (%)



**Figure S7**: Contour funnel plot of the effect of walnut consumption on fasting insulin (μIU/mL)

**Table S12:** Results of Egger’s test

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Bias | 95% CI | p-value |
| Fasting blood glucose (mg/dL) | -0.090 | -1.034, 0.854 | 0.842 |
| HbA1c (%) | -0.626 | -1.514, 0.262 | 0.147 |
| Fasting insulin (μIU/mL) | 0.167 | -1.763, 2.097 | 0.847 |

**Supplementary data 14:** GRADE assessment of the quality of the body of evidence

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **walnut** | **control** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Fasting blood glucose** | | | | | | | | | | | | |
| 17 | randomised trials | serious a | not serious b | not serious | not serious c | none | -/826 | -/794 | not estimable |  | ⨁⨁⨁◯ MODERATE | IMPORTANT |
| **Fasting insulin** | | | | | | | | | | | | |
| 10 | randomised trials | serious d | serious e | not serious | not serious f | none | -/365 | -/360 | not estimable |  | ⨁⨁◯◯ LOW | IMPORTANT |
| **HbA1c** | | | | | | | | | | | | |
| 12 | randomised trials | serious g | not serious h | not serious | not serious i | none | -/658 | -/632 | not estimable |  | ⨁⨁⨁◯ MODERATE | IMPORTANT |
| **HOMA-IR** | | | | | | | | | | | | |
| 7 | randomised trials | serious j | not serious k | not serious | not serious l | none | -/238 | -/233 | not estimable |  | ⨁⨁⨁◯ MODERATE | IMPORTANT |

**CI:** Confidence interval

#### Explanations

a. The studies were viewed as being in the category of 'serious limitation'. This category was selected as the risk of bias assessments for each study resulted in both 'some concerns' and 'high risk' (no studies were considered to be 'low risk' of bias (see risk of bias assessment charts). In accordance with the GRADE guidelines, this would be categorised as either 'serious limitations' or 'very serious limitations'. In view of the potential implications of the 'high risk' aspects on the quality of the body of evidence, 'serious limitations' was selected

b. I-squared value of 17.4%, considered to indicate very low heterogeneity

c. Sample size in review exceeds estimated Optimal Information Size of 400 pts. 95% confidence intervals in analysis do not cross appreciable harm/benefit and no effect. As a result, this outcome was not downgraded for imprecision

d. The studies were viewed as being in the category of 'serious limitation'. This category was selected as the risk of bias assessments for each study resulted in both 'some concerns' and 'high risk' (no studies were considered to be 'low risk' of bias (see risk of bias assessment charts). In accordance with the GRADE guidelines, this would be categorised as either 'serious limitations' or 'very serious limitations'. In view of the potential implications of the 'high risk' aspects on the quality of the body of evidence, 'serious limitations' was selected

e. I-squared value of 53%, which is considered to indicate moderate heterogeneity. As the cause of the heterogeneity was not able to be explained, this was judged to reflect serious inconsistency

f. Sample size in review exceeds estimated Optimal Information Size of 400 pts. 95% confidence intervals in analysis do not cross appreciable harm/benefit and no effect. As a result, this outcome was not downgraded for imprecision

g. The studies were viewed as being in the category of 'serious limitation'. This category was selected as the risk of bias assessments for each study resulted in both 'some concerns' and 'high risk' (no studies were considered to be 'low risk' of bias (see risk of bias assessment charts). In accordance with the GRADE guidelines, this would be categorised as either 'serious limitations' or 'very serious limitations'. In view of the potential implications of the 'high risk' aspects on the quality of the body of evidence, 'serious limitations' was selected

h. I-squared value of 16.4%, considered to indicate very low heterogeneity

i. Sample size in review exceeds estimated Optimal Information Size of 400 pts. 95% confidence intervals in analysis do not cross appreciable harm/benefit and no effect. As a result, this outcome was not downgraded for imprecision

j. The studies were viewed as being in the category of 'serious limitation'. This category was selected as the risk of bias assessments for each study resulted in both 'some concerns' and 'high risk' (no studies were considered to be 'low risk' of bias (see risk of bias assessment charts). In accordance with the GRADE guidelines, this would be categorised as either 'serious limitations' or 'very serious limitations'. In view of the potential implications of the 'high risk' aspects on the quality of the body of evidence, 'serious limitations' was selected

k. I-squared value of 6.8%, considered to indicate very low heterogeneity

l. Sample size in review exceeds estimated Optimal Information Size of 400 pts. 95% confidence intervals in analysis do not cross appreciable harm/benefit and no effect. As a result, this outcome was not downgraded for imprecision