

Consumption of nuts and seeds and health outcomes including cardiovascular, diabetes and metabolic disease, cancer, and mortality: an umbrella review

Rajiv Balakrishna¹, Tonje Bjørnerud^{1§}, Mitra Bemanian^{1,2§}, Dagfinn Aune^{3,4,5,6}, Lars T. Fadnes^{1,2*}

Affiliations

¹ Department of Global Public Health and Primary Care, University of Bergen, Norway

² Department of Addiction Medicine, Haukeland University Hospital

³ Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, Paddington, London, W2 1PG, UK

⁴ Department of Nutrition, Oslo New University College, Oslo, Norway

⁵ Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway

⁶ Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

§ Authors contributed equally

* Corresponding author: Lars Fadnes, email: Lars.Fadnes@uib.no, phone +47 55 97 01 73, Address: Post box 7804, 5020 Bergen, Norway.

Funding: The authors were funded by their respective institutions. The study had no additional funding. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interests: All authors have no competing interests.

Abbreviations: AMSTAR-2: A MeaSurement Tool to Assess systematic Reviews (version 2),

g/d: grams per day, I²: Heterogeneity, RR: relative risk, p: probability value.

ORIGINAL UNEDITED MANUSCRIPT

Abstract: Consumption of nuts and seeds is associated with a range of health outcomes. Summarizing the best evidence on essential health outcomes from the consumption of nuts is essential to provide optimal recommendations. Our objective is to comprehensively assess health outcomes associations related to the consumption of nuts and seeds, using a culinary definition including tree nuts and peanuts (registered in PROSPERO: CRD42021258300). Health outcomes of interest include cardiovascular disease, cancer, diabetes, obesity, respiratory disease, mortality, and their biomarker for disease. We present associations for high versus low consumption, per serving, and dose-response relationships. Medline, Embase, Cochrane, and Epistemonikos were searched and screened for systematic reviews and meta-analyses. Evidence was extracted from 89 articles on the consumption of nuts and relevant health outcomes, including 23 articles with meta-analysis on disease and mortality, 66 articles on biomarkers for disease, and 9 articles on allergy/adverse outcomes. Intake of nuts was associated with reduced risk of cardiovascular diseases and related risk factors, with moderate quality of evidence. An intake of 28 grams of nuts per day compared to not eating nuts was associated with a 21% relative risk reduction of cardiovascular disease (including coronary heart disease incidence and mortality, atrial fibrillation, and stroke mortality), 11% risk reduction of cancer deaths, and 22% reduction in all-cause mortality. Nut consumption was also inversely associated with mortality from respiratory diseases, infectious diseases, and diabetes: however, associations between nut consumption and diabetes incidence were mixed. Meta-analyses of trials on biomarkers for disease generally mirrored meta-analyses from observational studies on cardiovascular disease, cancers, and diabetes. Allergy and related adverse reactions to nuts were observed among 1-2% of adult populations, with substantial heterogeneity between studies. Overall, the current

evidence supports dietary recommendations to consume a handful of nuts and seeds per day for people without allergies to these foods.

Key words: nuts; cardiovascular diseases; cancers; diabetes mellitus, type 2

Statement of Significance: This umbrella review provides comprehensive and up-to-date evidence on nut consumption and the risk of cardiovascular disease, cancers, diabetes, and mortality. It also presents per serving and dose-response relationships, and evidence on biomarkers for diseases.

ORIGINAL UNEDITED MANUSCRIPT

Introduction

Nuts and seeds have been part of diets worldwide for millennia (1). Nuts and seeds are highly nutrient-dense dietary components, rich in macronutrients including mono- and polyunsaturated fatty acids, proteins, and fibres (2, 3). They are also rich in vitamins and minerals, and a range of active metabolites such as phenolic acids, phytosterols, carotenoids, and polyphenolic compounds (2, 4-6). Some of the compounds present in nuts, including polyphenols, have been found to have antioxidant, antimicrobial and antiproliferative properties (4, 7, 8). Nuts were utilized in ancient medicinal traditions, an example being Hippocrates' description of almonds as a treatment for colds and coughs (1).

Nuts are botanically categorized as tree nuts and peanuts. Nuts have hard shells covering the seed, and examples of frequently consumed tree nuts include almonds, walnuts, hazelnuts, cashews, Brazil nuts, macadamias, and pistachios. Tree nuts and peanuts have many compositional/nutritional similarities, and even though peanuts are botanically classified as a legume, their culinary use is similar to tree nuts (9). Further, seeds such as sesame and sunflower are related food groups (10). Consumption of nuts and seeds varies between cultural settings, both in preference in nut and seed types and the amount consumed (11, 12), with higher consumption generally reported in Canada, some African countries, parts of Europe, and the Middle East, and lower intakes in South America.

Consumption of nuts and seeds has been inversely associated with the risks of cardiovascular disease, cancers, and respiratory diseases (13-18). Cardiovascular disease, cancer, respiratory diseases, diabetes, and neurodegenerative diseases, are globally among the leading causes of

death and life years lost (19-21), contributing to 32/20%, 16/13%, 11/10%, 3/2%, 5/2% and 2/2% of deaths/life years lost from these outcomes, respectively. On the other hand, nut allergies and related reactions are potential unintended effects (22). Some compounds, such as phytates, might also reduce the bioavailability of some nutrients in the gastrointestinal tract (23). Nuts might also impact the microbiota, but the results are uncertain whether it tends to have more prebiotic properties and stimulate the growth of non-pathogenic gut bacteria or pathogenic bacteria (24, 25). To contribute to optimizing intake levels through diet recommendations, both positive and adverse effects need to be considered. Therefore, summarizing the best evidence on health outcomes from consumption of nuts and seeds is essential. Umbrella reviews have been conducted focusing on cardiovascular and metabolic outcomes (26-28). However, these do not cover all relevant morbidities, and a large proportion of relevant meta-analyses have been published since these. Thus, a comprehensive update could give more precise estimates and balance various health outcomes.

This umbrella review provides a systematic and comprehensive overview of the evidence on the consumption of nuts and seeds and the associations with various diseases, including high versus low consumption, per serving, and dose-response relationships. We have used a culinary definition of nuts, and seeds, thus including both tree nuts, peanuts, and seeds, and presenting data on biomarker for diseases as intermediate causal factors contributing to understanding of evidence.

Methods

To summarize the evidence from meta-analyses and systematic reviews on the consumption of nuts and relevant health outcomes such as cardiovascular disease, cancer, diabetes, obesity, respiratory disease, mortality, and their intermediate factors, we used an umbrella review framework (29, 30). The protocol for the study has been registered in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021258300).

Eligibility criteria

Types of studies: We evaluated meta-analysis and systematic reviews presenting analyses from cohorts and trials on the consumption of nuts and seeds and associations with incidence and mortality of different diseases and intermediary factors related to these diseases. For inclusion and exclusion criteria, see below. Studies with cross-sectional design or only presenting regional estimates not representative of a general population were excluded. No search restrictions were imposed on the publication date or publication status. We excluded papers written in languages other than English, German, French, Norwegian, Danish, or Swedish.

Inclusion criteria:

- Study types: meta-analysis and systematic reviews presenting analyses from longitudinal observation studies (e.g., cohorts, nested case-control), and trials
- Exposure: consumption of nuts and seeds (using a culinary definition)

- Comparators: High versus low consumption, per serving, and dose-response relationship between exposure and outcomes
- Outcome: cardiovascular diseases, cancer, diabetes and metabolic disease, respiratory, infectious, and other diseases, adverse effects including allergies, and mortality, as well as intermediary factors for these diseases.
- Language: English, German, French, Norwegian, Danish, or Swedish
- Publication status: Published articles indexed in Medline, Embase, Cochrane, and Epistemonikos from inception to the 27th of May 2021

Exclusion criteria:

- Non-systematic reviews
- Studies not presenting results for nuts separately but only as part of a combined diet

Types of outcome measures

Outcomes included were the following:

Coronary heart disease, coronary heart disease mortality, cardiovascular disease, cardiovascular disease mortality, cancer mortality, diabetes mellitus, diabetes mortality, obesity or overweight, metabolic syndrome, heart failure, stroke and subtypes including hemorrhagic stroke incidence, ischemic stroke incidence, stroke mortality, infectious disease and related mortality, kidney disease and related mortality, neurodegenerative disease mortality, respiratory

disease mortality, adverse effects including allergies and anaphylactic reactions, and all-cause mortality, Supplementary Table 1. We also assessed biomarkers for disease (intermediate factors), including blood lipids, cholesterol, endothelial function, blood pressure, body composition & weight, hunger and fullness, glucose and insulin, inflammation, and gut microbiota.

Information sources

Overall, in collaboration with an experienced librarian, 1546 records were retrieved in the databases from Medline, Embase, Cochrane, and Epistemonikos (also extracting through CINAHL, PsycINFO, LILACS, DARE, The Campbell Collaboration online library, JBI Database, and EPPI-Centre Evidence Library). The search period was from inception to the 27th of May 2021. After automatic deduplication in EndNote, 1009 records remained (see Figure 1 and details for search in Supplementary text 1). No limits were applied for language or publication date. This systematic review has made efforts to adhere to the PRISMA criteria (31).

Search

The search included the following terms (at least one of 1, 2, and 3):

1. Nut, almond, Brazil nut, cashew nut, hazelnut, pecan, pistachio, walnut, peanut, macadamia, sesame, oilseed, hickory, seeds, pine seed, sunflower seed, chia, poppy seed, hemp seed, quinoa, pumpkin seed, or flaxseed
2. Intake, consumption, eat, or diet
3. systematic review or meta-analysis

For further details on search, see Supplementary text. The references were imported into EndNote X9.

Study selection

The two first authors screened the imported references. The screening was done by reading the title, abstract, and assessing of full-text articles assumed to be relevant. Two authors read all obtainable relevant papers in full text by, and possible differences in assessment were discussed between the authors and resolved by consensus. None of the available meta-analyses reported on total cancer incidence, although some meta-analyses combined different cancer types in an overall analysis (32-35), none of the original studies included in these meta-analyses reported on total cancer incidence, but only on the incidence of specific cancers, and because of this the results for different cancers combined were not considered reliable and were not used in the current analysis. Data values extracted were also double-checked.

Data collection process and data items

Data considered relevant was extracted into a Microsoft Excel table, and information was gathered on the first author, title, primary outcome(s), aims of the studies, conclusion, exposure (types of nuts/seeds), inclusion and exclusion criteria, design, type and number of studies, number of participants, number of cases/outcomes, outcome measures, heterogeneity, findings (high vs. low intake) and findings (dose-response or per serving of 28 g), or findings categorized otherwise, per serving or high/low, Supplementary table 1. We used the data from the source

published last for duplicate data identified. A total of 148 full-text articles were assessed in detail.

Risk of bias in individual studies and across studies

The risk of bias was assessed with the AMSTAR-2 tool (36). The quality of the reviews is categorized into high/moderate/low (e.g., AMSTAR-2: high). A list of details from the assessments is listed in Supplementary table 2.

Analysis

Tables with extracted data from included studies were made. These data were summarized in figures visualizing the associations between nuts and various health outcomes for low versus high comparison, per serving, and dose-response. For per serving, when other units were used than per serving of 20-30 grams per day (g/d), a conversion of the risk ratios (RR) was estimated (for four servings of 28g per week: $RR^{(7/4)}$; for one serving per week: RR^4 ; for servings of 20g/d: RR^1 ; for servings of 12g/d: RR^2). We present forest plots for the most comprehensive meta-analysis for each outcome measure (and similar emphasizing the most recent meta-analyses). The most comprehensive was defined as the relevant meta-analysis including the most relevant studies and having the most participants with the relevant outcomes. The forest plots include information on source/reference, the number of participants and cases, included studies, and heterogeneity. We also present data for nuts and subgroups of nuts and groups of outcomes, including:

1. Cardiovascular disease/coronary heart disease/stroke/heart failure/atrial fibrillation
2. All-cause mortality

3. Diabetes, diabetes mortality, and metabolic syndrome
4. Cancer mortality
5. Other morbidities including infectious disease mortality, kidney disease mortality, neurodegenerative disease mortality, respiratory disease mortality

For dose-response, we present data from meta-analyses with dose-response data, extracted values through the Web Plot Digitizer tool (<https://apps.automeris.io/wpd/>), and present these through supplementary figures. Stata SE 17 was used for data analysis and graphical presentation.

Results

Twenty-three meta-analysis articles provided 190 outcome measures for disease and disease-related mortality (Supplementary table 1 and 3) (13-16, 32-35, 37-52). Most outcome measures were available for all-cause mortality, cancer mortality, and cardiovascular disease, with subcategories including related incidence and mortality, coronary heart disease, and stroke. Sixty-six full-text articles provided data on biomarkers for disease and disease mechanisms (53-118), and most of these were trials.

Cardiovascular disease

Meta-analyses indicate inverse associations between a high compared to low consumption of nuts and cardiovascular diseases, Figure 2, Supplementary figure 1-4 (16, 37-39, 43-45, 48-50, 52). Similar findings are also seen for coronary heart disease and related mortality. For per serving data, a daily intake of 28g nuts is associated with a RR of 0.79 (0.70–0.89, I^2 :60%, AMSTAR-2: high) for overall cardiovascular disease, 0.75 (0.64–0.88, I^2 :74%, AMSTAR-2: high) for coronary heart disease, and 0.78 (0.73–0.83, I^2 :60%, AMSTAR-2: moderate) for

cardiovascular mortality, Figure 3. The associations were generally similar between the intake of tree nuts versus peanuts and cardiovascular outcomes. An inverse association was observed between intake of peanuts and stroke, while this was non-significant for tree nuts. Dose-response associations between nut consumption and risk of cardiovascular diseases and coronary heart diseases suggest optimal intake levels of around 15-20 g/d of nuts and limited benefits in increasing intake beyond one serving of 28 g/d, Figure 4 and Supplementary figure 13-15. There were 376,228 participants and 18,655 cases in the overall cardiovascular disease analyses for all nuts.

Mechanisms related to cardiovascular disease

Meta-analyses investigating nut and seed consumption on biomarkers for disease (intermediary outcomes) related to cardiovascular disease generally reported favorable effects on blood lipid profile (linked with reduced risk of diseases), particularly for total cholesterol, low-density lipoprotein, triglycerides, and apolipoprotein B (56, 59, 62, 69-71, 75, 77, 79, 81, 85, 93, 99-101, 105), Table 1. In contrast, some reported no significant biomarker change (66, 72, 73, 77, 81, 90, 109). Evidence on vascular endothelial function and blood pressure outcomes either indicated favorable (55, 63, 65, 66, 73, 77, 78, 86, 95, 108, 112, 116), or neutral/no significant biomarker change (55, 56, 62, 63, 65, 66, 69, 71-73, 79, 80, 85, 89, 109). However, the duration of many of these trials may have been too short to identify potential effects on changes in blood pressure and hypertension (60, 62, 63, 72, 73, 80, 89). Meta-analyses of observational studies reported an inverse association between consumption of nuts and risk of hypertension (41, 107, 118).

Diabetes, obesity, and metabolic disease

Meta-analyses reported mixed associations between a high compared to low consumption of nuts and diabetes, obesity, and metabolic disease (15, 34, 37, 42, 43, 47, 51), Supplementary figure 9-10. For per serving data, a daily intake of 28g of nuts was associated with a RR of 0.89 (0.71–1.12, I^2 :77%, AMSTAR-2: high) for diabetes mellitus type 2, and 0.61 (0.43–0.87, I^2 :0%, AMSTAR-2: high) for diabetes-related mortality. For obesity there was a non-significant association 0.81 (0.62–1.07, I^2 :74%, AMSTAR-2: moderate), while when assessing obesity/overweight, a significant association 0.89 (0.83–0.94, I^2 :0%, AMSTAR-2: moderate) was observed. There were no significant non-linear dose-response associations between consumption of nuts and diabetes, Supplementary figure 16. There were 27,016 cases in the analysis of nut consumption and type 2 diabetes incidence.

Neither tree nuts nor peanuts separately were significantly associated with diabetes mortality. Most meta-analyses were adjusted for body-mass index, and these results might have been over-adjusted. When not adjusting for body-mass index, an association between diabetes and nut consumption was seen with a RR of 0.80 (0.69–0.94, I^2 :51%, two large cohorts, AMSTAR-2: high) that could indicate that weight reduction might be a potential effect mediator for a potential effect on diabetes incidence (119).

Mechanisms related to diabetes, obesity, and metabolic disease

Trials and cohort studies have shown that diets enriched with nuts do not increase body weight, body mass index, or waist circumference (60, 64, 68, 74, 87, 115, 120-125), with a tendency to a slight reduction in all of these. Overall nuts and seeds showed a favorable trend in improving fasting blood glucose levels, glycemic control, and insulin sensitivity (60, 74, 88, 97, 98, 114, 123) (74, 88, 92, 97, 98, 123). Furthermore, nuts have been found to contribute positively to satiety and reducing hunger (125), which might be one of the reasons studies have not found nuts to be linked with obesity (115, 126).

Cancer

Meta-analyses indicated substantial inverse associations between a high compared to low consumption of nuts and cancer-related mortality (16, 32-35), Supplementary figure 7-8. For per serving data, a daily intake of 28g/d of nuts was associated with a RR of 0.89 (0.83–0.94, I^2 :23%, AMSTAR-2: moderate) for cancer mortality. For meta-analysis on cancer mortality, 1 serving of 28 g/d is associated with the lowest risk of cancer mortality, Figure 4, and Supplementary figure 17. There were 49,161 cancer mortality cases in the overall analysis for all nuts.

There was a tendency towards stronger associations between tree nuts and cancer mortality than for peanuts. There is more uncertainty regarding the association between nut consumption and specific cancers. However, inverse associations were reported between nut consumption and

endometrial, colon, pancreatic, gastric, and lung cancers, with less clear associations for rectal, esophageal, liver, endometrial, prostate, and breast cancer (35, 127, 128).

Mechanisms related to cancer

Trials assessing inflammatory outcomes from nut consumption have generally found a slightly favorable or neutral change in inflammatory markers such as c-reactive proteins, interleukins, tumor necrosis factor alpha (TNF- α), cell adhesion molecules, and antioxidant defense system (58, 67, 84, 95, 102, 103, 113, 129-132). Further, insulin sensitivity, glycemic control, and obesity (covered under the section on diabetes), might also be relevant for cancers.

All-cause mortality and other cause-specific mortality

Meta-analyses have shown substantial inverse associations between nut intake and all-cause mortality, Supplementary figure 5-6 (13, 14, 16, 33, 40, 43, 45, 46). A daily intake of 28g/d nuts was associated with a RR of 0.78 (0.72–0.84, I^2 :66%, AMSTAR-2: high) – with the dose-response curves plateauing from around 20 g/d, Supplementary figure 18. There were 819,448 participants and 85,870 deaths in the mortality analyses. There were no clear differences in mortality outcomes between tree nuts and peanuts.

Relating to other cause-specific mortality, there were also observed inverse associations between nut consumption and mortality from respiratory disease (RR: 0.48; 0.26–0.89, I^2 :61%, AMSTAR-2: high), and infectious disease (RR: 0.25; 0.07–0.87, I^2 :54%, AMSTAR-2: high) (16), Supplementary figure 11-12. A non-significant association was observed for neurodegenerative disease mortality 0.65 (0.40–1.07, p =0.086, I^2 :6%, AMSTAR-2: high). No significant association was seen for kidney-related disease mortality. For these four outcomes, 2551/397/367/2056 deaths were included in each analysis.

Allergy and adverse reactions to nuts and seeds

Nine meta-analyses and systematic review articles provided data on allergies and adverse reactions. Using the gold standard diagnostic methods of peanut allergy, the prevalence ranged between 0 to 2.8%, with heterogeneity between age groups and (9, 133-135), Supplementary table 4. Food challenge tests indicated the following age-specific prevalence of allergies to tree nuts: 0-6 years of 0.03% to 0.2%, 6-18 years of 0.2% to 2.3%, and adults of 0.4% to 1.4% (136). Challenge-proven data is sparse for non-European countries. Anaphylactic reactions were rare, but among these peanut seems to be the leading food allergen (22), and can be life-threatening if not handled promptly and correctly. Among individuals with peanut allergy, 1 to 6 anaphylaxis events are estimated per 2500 patients exposed to low-dose nuts protein (137). Consumption of cashew nuts is also a relatively common cause of anaphylactic reactions, commonly with cross-reactions to pistachio nuts (138). The prevalence of allergy to sesame seeds was estimated as 0.1–0.2% (139).

Discussion

An intake of a serving size of 28 g/d of nuts per day compared to not eating nuts was associated with a 21% relative risk reduction of cardiovascular disease (including coronary heart disease incidence and mortality, atrial fibrillation, and stroke mortality), 11% risk reduction of cancer deaths, and 22% reduction in all-cause mortality. Nut consumption was also associated with a reduced risk of mortality from respiratory diseases, infectious diseases, and diabetes: however, associations between nut consumption and diabetes incidence were mixed. Generally, these associations seem to be relatively similar for different nuts, including different tree nuts and peanuts. Meta-analyses of trials on biomarkers for disease (intermediate factors) generally mirrored meta-analyses from observational studies on cardiovascular disease, cancer mortality, and diabetes. Dose-response relationships suggest optimal intake levels between 15-40 g/d with generally limited benefits in increasing intake beyond 28 g/d.

We observed mixed associations between consumption of nuts and diabetes incidence or diabetes mortality. It is possible that a potential inverse association between consumption of nuts and diabetes incidence may largely be mediated by body weight, and that meta-analyses adjusting for body mass index might have over-adjusted analyses masking associations between consumption of nuts and diabetes incidence (119). This assumption is supported by studies that generally showed weaker associations between nuts and diabetes incidence when adjusting for body mass index (119). Consumption of a handful of nuts per day is unlikely to contribute to overweight and obesity based on the current evidence (126). Around half of the meta-analyses conducted indicate slightly favorable effects of nuts on body weight and fat mass.

Allergies for nuts are reported among around 1-2%, with substantial heterogeneity between populations (134). Allergies to seeds are relatively uncommon (139). Severe allergic reactions, and particularly anaphylactic reactions, can be life-threatening if not handled promptly and correctly (9, 138). However, many reactions are also milder cross-reactions (140). Roasting generally reduces the allergenicity of some nut allergies (e.g., hazelnut and almonds) (140). As avoidance of known allergens is the cornerstone among people with allergies, labelling of food to ensure transparency is essential (22). Legislation for allergen disclosure generally reflects allergens commonly responsible for food anaphylaxis (133). Some nuts, such as Brazil nuts, are more prone to contain potentially harmful fungal toxins when stored after inadequate drying (such as aflatoxin) (23). The presence of potentially harmful fungal toxins such as aflatoxin can generally be limited by regulations in the processing and distribution of nuts reduce this threat (23).

The current evidence strongly supports nut consumption as part of healthy but also sustainable diets, both in terms of greenhouse gas emissions, land and energy use, and potential for acidification and eutrophication (141-146). Furthermore, an increased intake of nuts to at least 20 g/d could have averted 4.4 million deaths in North and South America, Europe, Southeast Asia, and the Western Pacific (16). This is estimated from probable reductions in premature deaths related to cardiovascular disease and cancers and possible reductions in mortality from respiratory disease and diabetes. Some systematic reviews have further suggested that nut consumption is positively associated with cognitive function tests (54, 147), and nuts might have a role both in child development and in slowing some age-related cognitive decline. For children, less evidence is available relating to the effect of nut consumption on disease patterns, but the

studies generally show some similarities in trends to what is presented for adults (148). Intake amounts can be adapted to the age, and the youngest children generally need less energy. Recommending an intake of a handful of nuts per day will to some degree take this into consideration as hand size will also grow relatively parallel with body size.

This study has several strengths and some limitations. This is the most comprehensive umbrella review conducted on nut and seed consumption and its associations with disease and mortality outcomes. For many of the included outcomes, no umbrella reviews are presently available, and for the remainder, many studies have been published after the relevant umbrella reviews. We have included both disease and mortality outcomes, and biomarkers for disease as intermediate outcomes with mechanistic studies to better identify causal effects. We have strived to adhere to the PRISMA criteria (31). Still, some data might have been missed due to inadequate indexing in Medline and Embase, or titles and abstracts not indicating the articles to be relevant. The former is less uncommon for older studies, but these are probably few. Some trials have included nuts as a component of a complex intervention (83, 149). For several of the interventions with several components that can contribute to the outcomes of interest, the duration of these trials may also have been too short of achieving relevant effects on many of these chronic diseases (83, 150). Relating to cancer, one might argue against assessing all cancers combined as cancers are heterogeneous. On the other hand, cancers generally share a range of mechanisms, and assessing all cancers separately increases the risk of random variability errors. In meta-analyses on cancer incidence, there might have been studies including data on assessing cancer-related mortality (mixing different outcomes). Thus, the validity of the cancer incidence is uncertain, and some studies have questioned whether nut intake is associated with cancer incidence (150, 151).

However, it is more agreement on the inverse associations between nut intake and cancer mortality. There are also many studies on diet patterns that include nuts but do not assess the effect of nuts and other food groups individually. Our assessment omitted these as it is difficult to ascribe effects to separate food groups. Finally, inadequately described study methods, such as lacking specification, might have been the cause for the rejection of otherwise relevant studies. Double controlling has contributed to preventing mistakes, and when there is room for different interpretations, these have been discussed among the authors.

Conclusion

Intake of nuts is inversely associated with the risk of cardiovascular diseases. This is mirrored with experimental studies on biomarkers for cardiovascular disease, with the overall quality of evidence considered moderate. Compared to not eating nuts, a handful of nuts per day is associated with a risk reduction of cardiovascular disease and mortality by a fifth, and cancer deaths by a tenth. Nut consumption is also associated with a substantial reduction in mortality risk from respiratory diseases, infectious diseases, and diabetes; however, associations between nut consumption and diabetes incidence are mixed and may be explained by adiposity differences. Meta-analyses of trials on intermediate factors of other chronic diseases also generally mirror meta-analyses from observational studies on cardiovascular, cancer, metabolic, and infectious diseases.

In conclusion, the current evidence supports dietary recommendations to consume a handful of nuts and seeds per day for people without allergies to these foods. Different types of nuts and seeds seem to have broadly similar benefits.

Acknowledgements: We thank the librarian Elisabeth Ebner who assisted us with the search.

Contributors: All authors contributed to conceiving and designing the study, RB, TB, MB led screening and data extractions, LTF led the analysis, supervised the study, and drafted the first manuscript, all authors have read and approved the final manuscript, have had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: The authors were funded by their respective institutions. The study had no additional funding. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: All authors have no competing interests.

Ethical approval: Not required.

Data sharing: Data are available in supplementary data file.

References

1. Casas-Agustench P, Salas-Huetos A, Salas-Salvado J. Mediterranean nuts: origins, ancient medicinal benefits and symbolism. *Public health nutrition* 2011;14(12A):2296-301. doi: 10.1017/S1368980011002540.
2. Bolling BW--C, C. Y.-/-/McKay, D. L.-/-/Blumberg, J. B. Tree nut phytochemicals: composition, antioxidant capacity, bioactivity, impact factors. A systematic review of almonds, Brazils, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. *Nutr Res Rev* 2011;24(2):244-75. doi: 10.1017/s095442241100014x.
3. Ros E, Mataix J. Fatty acid composition of nuts--implications for cardiovascular health. *Br J Nutr* 2006;96 Suppl 2:S29-35. doi: 10.1017/bjn20061861.

4. Ros E, Izquierdo-Pulido M, Sala-Vila A. Beneficial effects of walnut consumption on human health: role of micronutrients. *Curr Opin Clin Nutr Metab Care* 2018;21(6):498-504. doi: 10.1097/MCO.0000000000000508.
5. Terzo S, Baldassano S, Caldara GF, Ferrantelli V, Lo Dico G, Mule F, Amato A. Health benefits of pistachios consumption. *Nat Prod Res* 2019;33(5):715-26. doi: 10.1080/14786419.2017.1408093.
6. Alasalvar C, Salvado JS, Ros E. Bioactives and health benefits of nuts and dried fruits. *Food Chem* 2020;314:126192. doi: 10.1016/j.foodchem.2020.126192.
7. Baptista A--G, R. V.-/-/Bressan, J.-/-/Pelúzio, Mdcg. Antioxidant and Antimicrobial Activities of Crude Extracts and Fractions of Cashew (*Anacardium occidentale* L.), Cajui (*Anacardium microcarpum*), and Pequi (*Caryocar brasiliense* C.): A Systematic Review. *Oxid Med Cell Longev* 2018;2018:3753562. doi: 10.1155/2018/3753562.
8. Kim Y, Keogh JB, Clifton PM. Benefits of Nut Consumption on Insulin Resistance and Cardiovascular Risk Factors: Multiple Potential Mechanisms of Actions. *Nutrients* 2017;9(11). doi: 10.3390/nu9111271.
9. McWilliam V--K, J.-/-/Lodge, C.-/-/Tang, M.-/-/Dharmage, S.-/-/Allen, K. The Prevalence of Tree Nut Allergy: A Systematic Review. *Curr Allergy Asthma Rep* 2015;15(9):54. doi: 10.1007/s11882-015-0555-8.
10. Cardoso CA--O, G. M. M.-/-/Gouveia, L. A. V.-/-/Moreira, A. S. B.-/-/Rosa, G. The effect of dietary intake of sesame (*Sesamum indicum* L.) derivatives related to the lipid profile and blood pressure: A systematic review. *Crit Rev Food Sci Nutr* 2018;58(1):116-25. doi: 10.1080/10408398.2015.1137858.
11. de Souza RJ, Dehghan M, Mente A, Bangdiwala SI, Ahmed SH, Alhabib KF, Altuntas Y, Basiak-Rasała A, Dagenais GR, Diaz R, et al. Association of nut intake with risk factors, cardiovascular disease, and mortality in 16 countries from 5 continents: analysis from the Prospective Urban and Rural Epidemiology (PURE) study. *The American journal of clinical nutrition* 2020;112(1):208-19. doi: 10.1093/ajcn/nqaa108.
12. . Internet: https://www.nutfruit.org/files/tech/1587539172_INC_Statistical_Yearbook_2019-2020.pdf.
13. Chen GC, Zhang R, Martínez-González MA, Zhang ZL, Bonaccio M, van Dam RM, Qin LQ. Nut consumption in relation to all-cause and cause-specific mortality: a meta-analysis 18 prospective studies. *Food & function* 2017;8(11):3893-905. doi: 10.1039/c7fo00915a.
14. Grosso G, Yang J, Marventano S, Micek A, Galvano F, Kales SN. Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. *The American journal of clinical nutrition* 2015;101(4):783-93. doi: 10.3945/ajcn.114.099515.
15. Becerra-Tomás N, Paz-Graniel I, Hernández-Alonso P, Jenkins DJA, Kendall CWC, Sievenpiper JL, Salas-Salvadó J. Nut consumption and type 2 diabetes risk: a systematic review and meta-analysis of observational studies. *The American journal of clinical nutrition* 2021. doi: 10.1093/ajcn/nqaa358.
16. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC medicine* 2016;14(1):207. doi: 10.1186/s12916-016-0730-3.
17. de Souza RGM--S, R. M.-/-/Pimentel, G. D.-/-/Mota, J. F. Nuts and Human Health Outcomes: A Systematic Review. *Nutrients* 2017;9(12). doi: 10.3390/nu9121311.

18. Schwingshackl L, Hoffmann G, Missbach B, Stelmach-Mardas M, Boeing H. An Umbrella Review of Nuts Intake and Risk of Cardiovascular Disease. *Curr Pharm Design* 2017;23(7):1016-27. doi: 10.2174/1381612822666161010121356.
19. Institute for Health Metrics and Evaluation (IHME). University of Washington. Internet: <http://vizhub.healthdata.org/gbd-compare> (accessed 13.08.2020 2020).
20. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018;392(10159):2052-90. doi: 10.1016/S0140-6736(18)31694-5.
21. Collaborators GBDCoD. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392(10159):1736-88. doi: 10.1016/S0140-6736(18)32203-7.
22. Versluis A--K, A. C.-/-/Kruizinga, A. G.-/-/Michelsen, A.-/-/Houben, G. F.-/-/Baumert, J. L.-/-/van Os-Medendorp, H. Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review. *Clin Exp Allergy* 2015;45(2):347-67. doi: 10.1111/cea.12328.
23. Cardoso BR, Duarte GBS, Reis BZ, Cozzolino SMF. Brazil nuts: Nutritional composition, health benefits and safety aspects. *Food Res Int* 2017;100(Pt 2):9-18. doi: 10.1016/j.foodres.2017.08.036.
24. Creedon AC, Hung ES, Berry SE, Whelan K. Nuts and their effect on gut microbiota, gut function and symptoms in adults: A systematic review and meta-analysis of randomised controlled trials. *Nutrients* 2020;12(8):1-21. doi: 10.3390/nu12082347.
25. Fitzgerald E, Lambert K, Stanford J, Neale EP. The effect of nut consumption (tree nuts and peanuts) on the gut microbiota of humans: a systematic review. *The British journal of nutrition* 2020;125(5):1-27. doi: 10.1017/S0007114520002925.
26. Kim Y, Keogh J, Clifton PM. Nuts and Cardio-Metabolic Disease: A Review of Meta-Analyses. *Nutrients* 2018;10(12). doi: 10.3390/nu10121935.
27. Kwok CS, Gulati M, Michos ED, Potts J, Wu P, Watson L, Loke YK, Mallen C, Mamas MA. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *European journal of preventive cardiology* 2019;26(13):2047487319843667. doi: 10.1177/2047487319843667.
28. Schwingshackl L, Hoffmann G, Missbach B, Stelmach-Mardas M, Boeing H. An Umbrella Review of Nuts Intake and Risk of Cardiovascular Disease. *Curr Pharm Des* 2017;23(7):1016-27. doi: 10.2174/1381612822666161010121356.
29. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc* 2015;13(3):132-40. doi: 10.1097/XEB.0000000000000055.
30. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. *Evid Based Ment Health* 2018;21(3):95-100. doi: 10.1136/ebmental-2018-300014.
31. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLOS Medicine* 2009;6(7):e1000100. doi: 10.1371/journal.pmed.1000100.
32. Long J, Ji Z, Yuan P, Long T, Liu K, Li J, Cheng L. Nut Consumption and Risk of Cancer: A Meta-analysis of Prospective Studies. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2020;29(3):565-73. doi: 10.1158/1055-9965.EPI-19-1167.

33. Naghshi S, Sadeghian M, Nasiri M, Mobarak S, Asadi M, Sadeghi O. Association of Total Nut, Tree Nut, Peanut, and Peanut Butter Consumption with Cancer Incidence and Mortality: A Comprehensive Systematic Review and Dose-Response Meta-Analysis of Observational Studies. *Advances in nutrition* (Bethesda, Md) 2020. doi: 10.1093/advances/nmaa152.
34. Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH. Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis. *Nutrition reviews* 2015;73(7):409-25. doi: 10.1093/nutrit/nuv006.
35. Zhang D, Dai C, Zhou L, Li Y, Liu K, Deng YJ, Li N, Zheng Y, Hao Q, Yang S, et al. Meta-analysis of the association between nut consumption and the risks of cancer incidence and cancer-specific mortality. *Aging* 2020;12. doi: 10.18632/aging.103292.
36. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj* 2017;358:j4008. doi: 10.1136/bmj.j4008.
37. Afshin A, Micha R, Khatibzadeh S, Mozaffarian D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *The American journal of clinical nutrition* 2014;100(1):278-88. doi: 10.3945/ajcn.113.076901.
38. Becerra-Tomás N, Paz-Graniel I, C WCK, Kahleova H, Rahelić D, Sievenpiper JL, Salas-Salvadó J. Nut consumption and incidence of cardiovascular diseases and cardiovascular disease mortality: a meta-analysis of prospective cohort studies. *Nutrition reviews* 2019;77(10):691-709. doi: 10.1093/nutrit/nuz042.
39. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, Henauw S, Michels N, Devleeschauwer B, Schlesinger S, et al. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. *Critical reviews in food science and nutrition* 2019;59(7):0. doi: 10.1080/10408398.2017.1392288.
40. van den Brandt PA, Schouten LJ. Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis. *International journal of epidemiology* 2015;44(3):1038-49. doi: 10.1093/ije/dyv039.
41. Guo K, Zhou Z, Jiang Y, Li W, Li Y. Meta-analysis of prospective studies on the effects of nut consumption on hypertension and type 2 diabetes mellitus. *Journal of Diabetes* 2015;7(2):202-12. doi: 10.1111/1753-0407.12173.
42. Li H, Li X, Yuan S, Jin Y, Lu J. Nut consumption and risk of metabolic syndrome and overweight/obesity: a meta-analysis of prospective cohort studies and randomized trials. *Nutrition & metabolism* 2018;15(1):46. doi: 10.1186/s12986-018-0282-y.
43. Luo C, Zhang Y, Ding Y, Shan Z, Chen S, Yu M, Hu FB, Liu L. Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. *The American journal of clinical nutrition* 2014;100(1):256-69. doi: 10.3945/ajcn.113.076109.
44. Ma L, Wang F, Guo W, Yang H, Liu Y, Zhang W. Nut consumption and the risk of coronary artery disease: a dose-response meta-analysis of 13 prospective studies. *Thrombosis research* 2014;134(4):790-4. doi: 10.1016/j.thromres.2014.06.017.
45. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. *The British journal of nutrition* 2016;115(2):1-14. doi: 10.1017/S0007114515004316.
46. Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi AM, Knüppel S, Iqbal K, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *The American journal of clinical nutrition* 2017;105(6):1462-73. doi: 10.3945/ajcn.117.153148.

47. Schwingshackl L, Hoffmann G, Lampousi AM, Knüppel S, Iqbal K, Schwedhelm C, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *European journal of epidemiology* 2017;32(5):1-13. doi: 10.1007/s10654-017-0246-y.
48. Shao C, Tang H, Zhao W, He J. Nut intake and stroke risk: A dose-response meta-analysis of prospective cohort studies. *Scientific reports* 2016;6:30394. doi: 10.1038/srep30394.
49. Shi ZQ, Tang JJ, Wu H, Xie CY, He ZZ. Consumption of nuts and legumes and risk of stroke: A meta-analysis of prospective cohort studies. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2014;24(12):1262-71. doi: 10.1016/j.numecd.2014.06.009.
50. Weng YQ, Yao J, Guo ML, Qin QJ, Li P. Association between nut consumption and coronary heart disease: A meta-analysis. *Coronary Artery Disease* 2016;27(3):227-32. doi: 10.1097/MCA.0000000000000331.
51. Zhang Y, Zhang DZ. Relationship Between Nut Consumption and Metabolic Syndrome: A Meta-Analysis of Observational Studies. *Journal of the American College of Nutrition* 2019;38(6):1-7. doi: 10.1080/07315724.2018.1561341.
52. Zhang Z, Xu G, Wei Y, Zhu W, Liu X. Nut consumption and risk of stroke. *European Journal of Epidemiology* 2015;30(3):189-96. doi: 10.1007/s10654-015-9999-3.
53. Altamimi M, Zidan S, Badrasawi M. Effect of Tree Nuts Consumption on Serum Lipid Profile in Hyperlipidemic Individuals: A Systematic Review. *Nutrition and metabolic insights* 2020;13:1178638820926521. doi: 10.1177/1178638820926521.
54. Arias-Fernández L, López García E, Struijk EA, Rodríguez Artalejo F, Lana Pérez A. [Nut consumption and cognitive function: a systematic review]. *Nutricion hospitalaria* 2019;36(5):1179-88. doi: 10.20960/nh.02566.
55. Asbaghi O, Hadi A, Campbell MS, Venkatakrishnan K, Ghaedi E. Effects of pistachios on anthropometric indices, inflammatory markers, endothelial function, and blood pressure in adults: A systematic review and meta-analysis of randomized controlled trials. *The British journal of nutrition* 2020:1-27. doi: 10.1017/S0007114520004523.
56. Asbaghi O, Moodi V, Hadi A, Eslampour E, Shirinbakhshmasoleh M, Ghaedi E, Miraghajani M. The effect of almond intake on lipid profile: a systematic review and meta-analysis of randomized controlled trials. *Food & function* 2021. doi: 10.1039/d0fo02878a.
57. Askari G, Rouhani MH, Ghaedi E, Ghavami A, Nouri M, Mohammadi H. Effect of *Nigella sativa* (black seed) supplementation on glycemic control: A systematic review and meta-analysis of clinical trials. *Phytother Res* 2019;33(5):1341-52. doi: 10.1002/ptr.6337.
58. Askarpour M, Karimi M, Hadi A, Ghaedi E, Symonds ME, Miraghajani M, Javadian P. Effect of flaxseed supplementation on markers of inflammation and endothelial function: A systematic review and meta-analysis. *Cytokine* 2020;126:154922. doi: 10.1016/j.cyto.2019.154922.
59. Banel DK, Hu FB. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: a meta-analysis and systematic review. *The American journal of clinical nutrition* 2009;90(1):56-63. doi: 10.3945/ajcn.2009.27457.
60. Blanco Mejia S, Kendall CW, Viguiliouk E, Augustin LS, Ha V, Cozma AI, Mirrahimi A, Maroleanu A, Chiavaroli L, Leiter LA, et al. Effect of tree nuts on metabolic syndrome criteria: a systematic review and meta-analysis of randomised controlled trials. *BMJ open* 2014;4(7):e004660. doi: 10.1136/bmjopen-2013-004660.
61. De Lira C, Jimenez-Cruz A, Bacardi-Gascon M. Effectiveness of long-term consumption of nuts, seeds and seeds' oil on glucose and lipid levels in people with type 2 diabetes: Systematic review. *Obesity* 2011;19:S225. doi: <http://dx.doi.org/10.1038/oby.2011.225>.
62. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61

- controlled intervention trials. *The American journal of clinical nutrition* 2015;102(6):1347-56. doi: 10.3945/ajcn.115.110965.
63. Eslampour E, Asbaghi O, Hadi A, Abedi S, Ghaedi E, Ghaedi E, Lazaridi AV, Miraghajani M, Miraghajani M. The effect of almond intake on blood pressure: A systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med* 2020;50:102399. doi: 10.1016/j.ctim.2020.102399.
 64. Flores-Mateo G, Rojas-Rueda D, Basora J, Ros E, Salas-Salvadó J. Nut intake and adiposity: meta-analysis of clinical trials. *The American journal of clinical nutrition* 2013;97(6):1346-55. doi: 10.3945/ajcn.111.031484.
 65. Fogacci F, Cicero AFG, Derosa G, Rizzo M, Veronesi M, Borghi C. Effect of pistachio on brachial artery diameter and flow-mediated dilatation: a systematic review and meta-analysis of randomized, controlled-feeding clinical studies. *Critical reviews in food science and nutrition* 2019;59(2):0. doi: 10.1080/10408398.2017.1368007.
 66. Ghanavati M, Ghanavati M, Rahmani J, Hosseinabadi SM, Clark CCT, Rahimlou M. Pistachios and cardiometabolic risk factors: A systematic review and meta-analysis of randomized controlled clinical trials. *Complement Ther Med* 2020;52:102513. doi: 10.1016/j.ctim.2020.102513.
 67. Gouveia Lde A, Cardoso CA, de Oliveira GM, Rosa G, Moreira AS. Effects of the Intake of Sesame Seeds (*Sesamum indicum* L.) and Derivatives on Oxidative Stress: A Systematic Review. *J Med Food* 2016;19(4):337-45. doi: 10.1089/jmf.2015.0075.
 68. Guarneiri LL, Cooper JA. Intake of Nuts or Nut Products Does Not Lead to Weight Gain, Independent of Dietary Substitution Instructions: A Systematic Review and Meta-Analysis of Randomized Trials. *Advances in nutrition (Bethesda, Md)* 2020. doi: 10.1093/advances/nmaa113.
 69. Guasch-Ferré M, Li J, Hu FB, Salas-Salvadó J, Tobias DK. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: an updated meta-analysis and systematic review of controlled trials. *The American journal of clinical nutrition* 2018;108(1):174-87. doi: 10.1093/ajcn/nqy091.
 70. Hadi A, Askarpour M, Salamat S, Ghaedi E, Symonds ME, Miraghajani M. Effect of Flaxseed Supplementation on Lipid Profile: An Updated Systematic Review and Dose-Response Meta-Analysis of Sixty-Two Randomized Controlled Trials. *Pharmacological research* 2020;152:104622. doi: 10.1016/j.phrs.2019.104622.
 71. Huang Y, Zheng S, Wang T, Yang X, Luo Q, Li H. Effect of oral nut supplementation on endothelium-dependent vasodilation - a meta-analysis. *VASA Zeitschrift fur Gefasskrankheiten* 2018;47(3):1-5. doi: 10.1024/0301-1526/a000693.
 72. Jafari Azad B, Daneshzad E, Azadbakht L. Peanut and cardiovascular disease risk factors: A systematic review and meta-analysis. *Critical reviews in food science and nutrition* 2019;60(7):1-18. doi: 10.1080/10408398.2018.1558395.
 73. Jalali M, Karamizadeh M, Jalali M, Karamizadeh M, Zare M, Akbarzadeh M, Ferns GA, Moosavian SP. The effects of cashew nut intake on lipid profile and blood pressure: A systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med* 2020;50:102387. doi: 10.1016/j.ctim.2020.102387.
 74. Jamshidi S, Moradi Y, Nameni G, Mohsenpour MA, Vafa M. Effects of cashew nut consumption on body composition and glycemic indices: A meta-analysis and systematic review of randomized controlled trials. *Diabetes & metabolic syndrome* 2021;15(2):605-13. doi: 10.1016/j.dsx.2021.02.038.
 75. Karimian J, Abedi S, Shirinbakhshmasoleh M, Moodi F, Moodi V, Ghavami A. The effects of quinoa seed supplementation on cardiovascular risk factors: A systematic review and meta-analysis of controlled clinical trials. *Phytotherapy research : PTR* 2020. doi: 10.1002/ptr.6901.

76. Kendall C, Mejia SB, Viguiliouk E, Augustin L, Ha V, Cozma A, Mirahimi A, Maroleanu A, Chivaroli L, Leiter L, et al. Tree nuts improve criteria of the metabolic syndrome: A systematic review and meta-analysis of randomized controlled dietary trials. *FASEB Journal* 2014.
77. Khalesi S, Irwin C, Schubert M. Flaxseed Consumption May Reduce Blood Pressure: A Systematic Review and Meta-Analysis of Controlled Trials. *The Journal of nutrition* 2015;145(4):758-65. doi: 10.3945/jn.114.205302.
78. Khosravi-Boroujeni H, Nikbakht E, Natanelov E, Khalesi S. Can sesame consumption improve blood pressure? A systematic review and meta-analysis of controlled trials. *Journal of the science of food and agriculture* 2017;97(10):3087-94. doi: 10.1002/jsfa.8361.
79. Lee-Bravatti MA, Wang J, Avendano EE, King L, Johnson EJ, Raman G. Almond Consumption and Risk Factors for Cardiovascular Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Advances in nutrition (Bethesda, Md)* 2019;10(6):1076-88. doi: 10.1093/advances/nmz043.
80. Li J, Jiang B, H OS, Santos D, Singh A, Wang L. Effects of walnut intake on blood pressure: A systematic review and meta-analysis of randomized controlled trials. *Phytotherapy research : PTR* 2020;34(11):2921-31. doi: 10.1002/ptr.6740.
81. Liu K, Hui S, Wang B, Kaliannan K, Guo X, Liang L. Comparative effects of different types of tree nut consumption on blood lipids: a network meta-analysis of clinical trials. *The American journal of clinical nutrition* 2020;111(1):219-27. doi: 10.1093/ajcn/nqz280.
82. Mahboobi S. The Effect of Cashew Nut on Cardiovascular Risk Factors and Blood Pressure: A Systematic Review and Meta-analysis (P06-117-19). *Current developments in nutrition* 2019;3(Suppl 1). doi: 10.1093/cdn/nzz031.P06-117-19.
83. Martin N, Germanò R, Hartley L, Adler AJ, Rees K. Nut consumption for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2015;9(9):CD011583. doi: 10.1002/14651858.CD011583.pub2.
84. Mazidi M, Rezaie P, Ferns GA, Gao HK. Impact of different types of tree nut, peanut, and soy nut consumption on serum C-reactive protein (CRP): A systematic review and meta-analysis of randomized controlled clinical trials. *Medicine* 2016;95(44):e5165. doi: 10.1097/MD.0000000000005165.
85. Mejia SB, Kendall CW, Viguiliouk E, Augustin LS, Ha V, Cozma AI, Mirrahimi A, Chivaroli L, De Souza RJ, Jenkins DJ, et al. Tree nut consumption on metabolic syndrome criteria: A systematic review and meta-analysis of randomized controlled trials. *Canadian Journal of Diabetes* 2015;39:S56.
86. Mohammadi-Sartang M, Bellissimo N, Totosy de Zepetnek JO, Bazyar H, Mahmoodi M, Mazloom Z. Effects of walnuts consumption on vascular endothelial function in humans: A systematic review and meta-analysis of randomized controlled trials. *Clinical nutrition ESPEN* 2018;28:52-8. doi: 10.1016/j.clnesp.2018.07.009.
87. Mohammadi-Sartang M, Mazloom Z, Raeisi-Dehkordi H, Barati-Boldaji R, Bellissimo N, Totosy de Zepetnek JO. The effect of flaxseed supplementation on body weight and body composition: a systematic review and meta-analysis of 45 randomized placebo-controlled trials. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2017;18(9):1096-107. doi: 10.1111/obr.12550.
88. Mohammadi-Sartang M, Sohrabi Z, Barati-Boldaji R, Raeisi-Dehkordi H, Mazloom Z. Flaxseed supplementation on glucose control and insulin sensitivity: a systematic review and meta-analysis of 25 randomized, placebo-controlled trials. *Nutrition reviews* 2018;76(2):125-39. doi: 10.1093/nutrit/nux052.
89. Mohammadifard N, Salehi-Abarghouei A, Salas-Salvadó J, Guasch-Ferré M, Humphries K, Sarrafzadegan N. The effect of tree nut, peanut, and soy nut consumption on blood pressure: a

- systematic review and meta-analysis of randomized controlled clinical trials. *The American journal of clinical nutrition* 2015;101(5):966-82. doi: 10.3945/ajcn.114.091595.
90. Morvaridzadeh M, Sepidarkish M, Farsi F, Akbari A, Mostafai R, Omidi A, Potter E, Heshmati J. Effect of Cashew Nut on Lipid Profile: A Systematic Review and Meta-Analysis. *Complementary medicine research* 2020;1-9. doi: 10.1159/000506348.
 91. Mukuddem-Petersen J, Oosthuizen W, Jerling JC. A systematic review of the effects of nuts on blood lipid profiles in humans. *The Journal of nutrition* 2005;135(9):2082-9. doi: 10.1093/jn/135.9.2082.
 92. Muley A, Fernandez R, Ellwood L, Muley P, Shah M. Effect of tree nuts on glycemic outcomes in adults with type 2 diabetes mellitus: a systematic review. *JBIM Evid Synth* 2020;19(5):966-1002. doi: 10.11124/jbisrir-d-19-00397.
 93. Musa-Veloso K, Paulionis L, Poon T, Lee HY. The effects of almond consumption on fasting blood lipid levels: a systematic review and meta-analysis of randomised controlled trials. *Journal of nutritional science* 2016;5:e34. doi: 10.1017/jns.2016.19.
 94. Neale EP, Guan V, Tapsell LC, Probst YC. Effect of walnut consumption on markers of blood glucose control: a systematic review and meta-analysis. *The British journal of nutrition* 2020;124(7):1-33. doi: 10.1017/S0007114520001415.
 95. Neale EP, Tapsell LC, Guan V, Batterham MJ. The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. *BMJ open* 2017;7(11):e016863. doi: 10.1136/bmjopen-2017-016863.
 96. Neelakantan N, Narayanan M, de Souza RJ, van Dam RM. Effect of fenugreek (*Trigonella foenum-graecum* L.) intake on glycemia: a meta-analysis of clinical trials. *Nutrition journal* 2014;13(1):7. doi: 10.1186/1475-2891-13-7.
 97. Nowrouzi-Sohrabi P, Sisakht M, Hassanipour S, Daryabeygi-Khotbehsara R, Savardashtaki A, Fathalipour M, Fathalipour M. The effectiveness of pistachio on glycemic control and insulin sensitivity in patients with type 2 diabetes, prediabetes and metabolic syndrome: A systematic review and meta-analysis. *Diabetes Metab Syndr Clin Res Rev* 2020;14(5):1589-95. doi: 10.1016/j.dsx.2020.07.052.
 98. Ntzouvani A, Antonopoulou S, Nomikos T. Effects of nut and seed consumption on markers of glucose metabolism in adults with prediabetes: a systematic review of randomised controlled trials. *Br J Nutr* 2019;122(4):361-75. doi: 10.1017/s0007114519001338.
 99. Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids. *The American journal of clinical nutrition* 2009;90(2):288-97. doi: 10.3945/ajcn.2009.27469.
 100. Perna S, Giacosa A, Bonitta G, Bologna C, Isu A, Guido D, Rondanelli M. Effects of Hazelnut Consumption on Blood Lipids and Body Weight: A Systematic Review and Bayesian Meta-Analysis. *Nutrients* 2016;8(12):747-63. doi: 10.3390/nu8120747.
 101. Phung OJ, Makanji SS, White CM, Coleman CI. Almonds have a neutral effect on serum lipid profiles: a meta-analysis of randomized trials. *Journal of the American Dietetic Association* 2009;109(5):865-73. doi: 10.1016/j.jada.2009.02.014.
 102. Rahimlou M, Jahromi NB, Hasanyani N, Ahmadi AR. Effects of Flaxseed Interventions on Circulating Inflammatory Biomarkers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Advances in nutrition (Bethesda, Md)* 2019;10(6):1108-19. doi: 10.1093/advances/nmz048.
 103. Ren GY, Chen CY, Chen GC, Chen WG, Pan A, Pan CW, Zhang YH, Qin LQ, Chen LH. Effect of Flaxseed Intervention on Inflammatory Marker C-Reactive Protein: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients* 2016;8(3):136. doi: 10.3390/nu8030136.

104. Ribeiro PVM, da Silva A, de Almeida AP, Hermsdorff HHM, Alfenas RCG. Effect of chronic consumption of pistachios (*Pistacia vera* L.) on glucose metabolism in pre-diabetics and type 2 diabetics: a systematic review. *Critical reviews in food science and nutrition* 2019;59(7):0. doi: 10.1080/10408398.2017.1392290.
105. Sabaté J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials. *Arch Intern Med* 2010;170(9):821-7. doi: 10.1001/archinternmed.2010.79.
106. Sahebkar A, Katsiki N, Ward N, Reiner Ž. Flaxseed Supplementation Reduces Plasma Lipoprotein(a) Levels: A Meta-Analysis. *Alternative therapies in health and medicine* 2019.
107. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, Andriolo V, Bechthold A, Schlesinger S, Boeing H. Food Groups and Risk of Hypertension: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. *Advances in nutrition (Bethesda, Md)* 2017;8(6):793-803. doi: 10.3945/an.117.017178.
108. Smeets E, Mensink RP, Joris PJ. Effects of tree nut and groundnut consumption compared with those of l-arginine supplementation on fasting and postprandial flow-mediated vasodilation: Meta-analysis of human randomized controlled trials. *Clinical nutrition (Edinburgh, Scotland)* 2020. doi: 10.1016/j.clnu.2020.09.015.
109. Teoh SL, Lai NM, Vanichkulpitak P, Vuksan V, Ho H, Chaiyakunapruk N. Clinical evidence on dietary supplementation with chia seed (*Salvia hispanica* L.): a systematic review and meta-analysis. *Nutrition reviews* 2018;76(4):219-42. doi: 10.1093/nutrit/nux071.
110. Theodore LE, Kellow NJ, McNeil EA, Close EO, Coad EG, Cardoso BR. Nut Consumption for Cognitive Performance: A Systematic Review. *Advances in nutrition (Bethesda, Md)* 2020. doi: 10.1093/advances/nmaa153.
111. Tindall AM, Johnston EA, Kris-Etherton PM, Petersen KS. The effect of nuts on markers of glycemic control: a systematic review and meta-analysis of randomized controlled trials. *The American journal of clinical nutrition* 2019;109(2):297-314. doi: 10.1093/ajcn/nqy236.
112. Ursoniu S, Sahebkar A, Andrica F, Serban C, Banach M, Lipid, Blood Pressure Meta-analysis Collaboration G. Effects of flaxseed supplements on blood pressure: A systematic review and meta-analysis of controlled clinical trial. *Clinical nutrition (Edinburgh, Scotland)* 2016;35(3):615-25. doi: 10.1016/j.clnu.2015.05.012.
113. Ursoniu S, Sahebkar A, Serban MC, Pinzaru I, Dehelean C, Noveanu L, Rysz J, Banach M, Lipid, Blood Pressure Meta-Analysis Collaboration G. A systematic review and meta-analysis of clinical trials investigating the effects of flaxseed supplementation on plasma C-reactive protein concentrations. *Archives of medical science : AMS* 2019;15(1):12-22. doi: 10.5114/aoms.2018.81034.
114. Vigiouliouk E, Kendall CW, Blanco Mejia S, Cozma AI, Ha V, Mirrahimi A, Jayalath VH, Augustin LS, Chiavaroli L, Leiter LA, et al. Effect of tree nuts on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled dietary trials. *PloS one* 2014;9(7):e103376. doi: 10.1371/journal.pone.0103376.
115. Xia K, Yang T, An LY, Lin YY, Qi YX, Chen XZ, Sun DL. The relationship between pistachio (*Pistacia vera* L) intake and adiposity: A systematic review and meta-analysis of randomized controlled trials. *Medicine* 2020;99(34):e21136. doi: 10.1097/MD.00000000000021136.
116. Xiao Y, Huang W, Peng C, Zhang J, Wong C, Kim JH, Yeoh EK, Su X. Effect of nut consumption on vascular endothelial function: A systematic review and meta-analysis of randomized controlled trials. *Clinical nutrition (Edinburgh, Scotland)* 2018;37(3):831-9. doi: 10.1016/j.clnu.2017.04.011.
117. Yang L, Zhu H, Guo Z, Qi S, Fang T, Santos HO, Khani V, Wong CH, Qiu Z. Walnut intake may increase circulating adiponectin and leptin levels but does not improve glycemic biomarkers: A systematic review and meta-analysis of randomized clinical trials. *Complement Ther Med* 2020;52:102505. doi: 10.1016/j.ctim.2020.102505.

118. Zhou D, Yu H, He F, Reilly KH, Zhang J, Li S, Zhang T, Wang B, Ding Y, Xi B. Nut consumption in relation to cardiovascular disease risk and type 2 diabetes: a systematic review and meta-analysis of prospective studies. *The American journal of clinical nutrition* 2014;100(1):270-7. doi: 10.3945/ajcn.113.079152.
119. Luo C--Z, Y.-/-/Ding, Y.-/-/Shan, Z.-/-/Chen, S.-/-/Yu, M.-/-/Hu, F. B.-/-/Liu, L. Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. *Am J Clin Nutr* 2014;100(1):256-69. doi: 10.3945/ajcn.113.076109.
120. Eslami O, Shidfar F, Dehnad A. Inverse association of long-term nut consumption with weight gain and risk of overweight/obesity: a systematic review. *Nutrition research (New York, NY)* 2019;68:1-8. doi: 10.1016/j.nutres.2019.04.001.
121. Eslampour E, Moodi V, Asbaghi O, Ghaedi E, Shirinbakhshmasoleh M, Hadi A, Miraghajani M. The effect of almond intake on anthropometric indices: a systematic review and meta-analysis. *Food & function* 2020;11(9):7340-55. doi: 10.1039/d0fo00470g.
122. Fogelholm M, Anderssen S, Gunnarsdottir I, Lahti-Koski M. Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. *Food & nutrition research* 2012;56:1-45. doi: 10.3402/fnr.v56i0.19103.
123. Hajiahmadi S, Hosseinzadeh E, Hosseinzadeh M, Maryam k, Hosseinzadeh M. Flaxseed and its products improve glycemic control: A systematic review and meta-analysis. *Obes Med* 2021;22. doi: 10.1016/j.obmed.2020.100311.
124. Fang Z, Dang M, Zhang W, Wang Y, Kord-Varkaneh H, Nazary-Vannani A, H OS, Tan SC, C CTC, Zanghelini F, et al. Effects of walnut intake on anthropometric characteristics: A systematic review and dose-response meta-analysis of randomized controlled trials. *Complement Ther Med* 2020;50:102395. doi: 10.1016/j.ctim.2020.102395.
125. Akhlaghi M, Ghobadi S, Zare M, Foshati S. Effect of nuts on energy intake, hunger, and fullness, a systematic review and meta-analysis of randomized clinical trials. *Critical reviews in food science and nutrition* 2020;60(1):1-10. doi: 10.1080/10408398.2018.1514486.
126. Flores-Mateo G--R-R, D.-/-/Basora, J.-/-/Ros, E.-/-/Salas-Salvadó, J. Nut intake and adiposity: meta-analysis of clinical trials. *Am J Clin Nutr* 2013;97(6):1346-55. doi: 10.3945/ajcn.111.031484.
127. Wu L--W, Z.-/-/Zhu, J.-/-/Murad, A. L.-/-/Prokop, L. J.-/-/Murad, M. H. Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis. *Nutr Rev* 2015;73(7):409-25. doi: 10.1093/nutrit/nuv006.
128. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Laure Preterre A, Iqbal K, Bechthold A, De Henauw S, Michels N, Devleeschauwer B, et al. Food groups and risk of colorectal cancer. *Int J Cancer* 2018;142(9):1748-58. doi: 10.1002/ijc.31198.
129. Silveira BKS, da Silva A, Hermsdorff HHM, Bressan J. Effect of chronic consumption of nuts on oxidative stress: a systematic review of clinical trials. *Critical reviews in food science and nutrition* 2020:1-12. doi: 10.1080/10408398.2020.1828262.
130. Mazidi M--R, P.-/-/Ferns, G. A.-/-/Gao, H. K. Impact of different types of tree nut, peanut, and soy nut consumption on serum C-reactive protein (CRP): A systematic review and meta-analysis of randomized controlled clinical trials. *Medicine (Baltimore)* 2016;95(44):e5165. doi: 10.1097/md.00000000000005165.
131. Neale EP--T, L. C.-/-/Guan, V.-/-/Batterham, M. J. The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2017;7(11):e016863. doi: 10.1136/bmjopen-2017-016863.
132. Xiao Y, Xia J, Ke Y, Cheng J, Yuan J, Wu S, Lv Z, Huang S, Kim JH, Wong SY, et al. Effects of nut consumption on selected inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Nutrition* 2018;54:129-43. doi: 10.1016/j.nut.2018.02.017.

133. Conrado AB, Patel N, Turner PJ. Global patterns in anaphylaxis due to specific foods: a systematic review. *J Allergy Clin Immunol* 2021. doi: 10.1016/j.jaci.2021.03.048.
134. Nwaru BI--H, L.-/-Panesar, S. S.-/-Roberts, G.-/-Muraro, A.-/-Sheikh, A. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014;69(8):992-1007. doi: 10.1111/all.12423.
135. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, et al. The prevalence of food allergy: a meta-analysis. *The Journal of allergy and clinical immunology* 2007;120(3):638-46. doi: 10.1016/j.jaci.2007.05.026.
136. Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C, Sodergren E, Dahlstrom J, Lindner T, Sigurdardottir ST, et al. The prevalence of plant food allergies: a systematic review. *The Journal of allergy and clinical immunology* 2008;121(5):1210-8.e4. doi: 10.1016/j.jaci.2008.02.019.
137. Patel N, Adelman DC, Anagnostou K, Baumert JL, Blom WM, Campbell DE, Chinthrajah RS, Mills ENC, Javed B, Purington N, et al. Using data from food challenges to inform management of food-allergic consumers: a systematic review with individual participant data meta-analysis. *The Journal of allergy and clinical immunology* 2021. doi: 10.1016/j.jaci.2021.01.025.
138. van der Valk JP--D, A. E.-/-Gerth van Wijk, R.-/-Wichers, H. J.-/-de Jong, N. W. Systematic review on cashew nut allergy. *Allergy* 2014;69(6):692-8. doi: 10.1111/all.12401.
139. Patel A, Bahna SL. Hypersensitivities to sesame and other common edible seeds. *Allergy* 2016;71(10):1405-13. doi: 10.1111/all.12962.
140. Masthoff LJ--H, R.-/-Verhoeckx, K. C.-/-van Os-Medendorp, H.-/-Michelsen-Huisman, A.-/-Baumert, J. L.-/-Pasmans, S. G.-/-Meijer, Y.-/-Knulst, A. C. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. *Allergy* 2013;68(8):983-93. doi: 10.1111/all.12185.
141. Barre T, Perignon M, Gazan R, Vieux F, Micard V, Amiot MJ, Darmon N. Integrating nutrient bioavailability and co-production links when identifying sustainable diets: How low should we reduce meat consumption? *PLoS one* 2018;13(2):e0191767. doi: 10.1371/journal.pone.0191767.
142. Bertoluci G, Masset G, Gomy C, Mottet J, Darmon N. How to Build a Standardized Country-Specific Environmental Food Database for Nutritional Epidemiology Studies. *PLoS One* 2016;11(4):e0150617. doi: 10.1371/journal.pone.0150617.
143. van Dooren C, Tyszler M, Kramer GFH, Aiking H. Combining Low Price, Low Climate Impact and High Nutritional Value in One Shopping Basket through Diet Optimization by Linear Programming. *Sustainability* 2015;7:12837-55. doi: 10.3390/su70912837.
144. Fischer CG, Garnett T. Plates, pyramids and planets. Developments in national healthy and sustainable dietary guidelines: a state of play assessment. . *FAO: Food and Agriculture Organization of the United Nations & The Food Climate Research Network at The University of Oxford.* , 2016:80.
145. Willett W, Rockstrom J, Loken B, Springmann M, Lang T, Vermeulen S, Garnett T, Tilman D, DeClerck F, Wood A, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet* 2019;393(10170):447-92. doi: 10.1016/S0140-6736(18)31788-4.
146. Vanham D, Mekonnen MM, Hoekstra AY. Treenuts and groundnuts in the EAT-Lancet reference diet: Concerns regarding sustainable water use. *Glob Food Sec* 2020;24:100357. doi: 10.1016/j.gfs.2020.100357.
147. Solfrizzi V--C, C.-/-Lozupone, M.-/-Imbimbo, B. P.-/-Valiani, V.-/-Agosti, P.-/-Schilardi, A.-/-D'Introno, A.-/-La Montagna, M.-/-Calvani, M.-/-Guerra, V.-/-Sardone, R.-/-Abbrescia, D. I.-/-Bellomo, A.-/-Greco, A.-/-Daniele, A.-/-Seripa, D.-/-Logroscino, G.-/-Sabbá, C.-/-Panza, F. Relationships of Dietary Patterns, Foods, and Micro- and Macronutrients with Alzheimer's

- Disease and Late-Life Cognitive Disorders: A Systematic Review. *J Alzheimers Dis* 2017;59(3):815-49. doi: 10.3233/jad-170248.
148. Mead LC-H, A. M.-/-/Carter, S.-/-/Coates, A. M. The Effect of Nut Consumption on Diet Quality, Cardiometabolic and Gastrointestinal Health in Children: A Systematic Review of Randomized Controlled Trials. *Int J Environ Res Public Health* 2021;18(2). doi: 10.3390/ijerph18020454.
149. Abdelhamid AS--M, N.-/-/Bridges, C.-/-/Brainard, J. S.-/-/Wang, X.-/-/Brown, T. J.-/-/Hanson, S.-/-/Jimoh, O. F.-/-/Ajabnoor, S. M.-/-/Deane, K. H.-/-/Song, F.-/-/Hooper, L. Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018;7(7):Cd012345. doi: 10.1002/14651858.CD012345.pub2.
150. Nieuwenhuis L, van den Brandt PA. Nut and Peanut Butter Consumption and the Risk of Total Cancer: A Prospective Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2020;29(10):2100-4. doi: 10.1158/1055-9965.EPI-20-0456.
151. Fang Z, Wu Y, Li Y, Zhang X, Willett WC, Eliassen AH, Rosner B, Song M, Mucci LA, Giovannucci EL. Association of nut consumption with risk of total cancer and 5 specific cancers: evidence from 3 large prospective cohort studies. *The American journal of clinical nutrition* 2021. doi: 10.1093/ajcn/nqab295.

ORIGINAL UNEDITED MANUSCRIPT

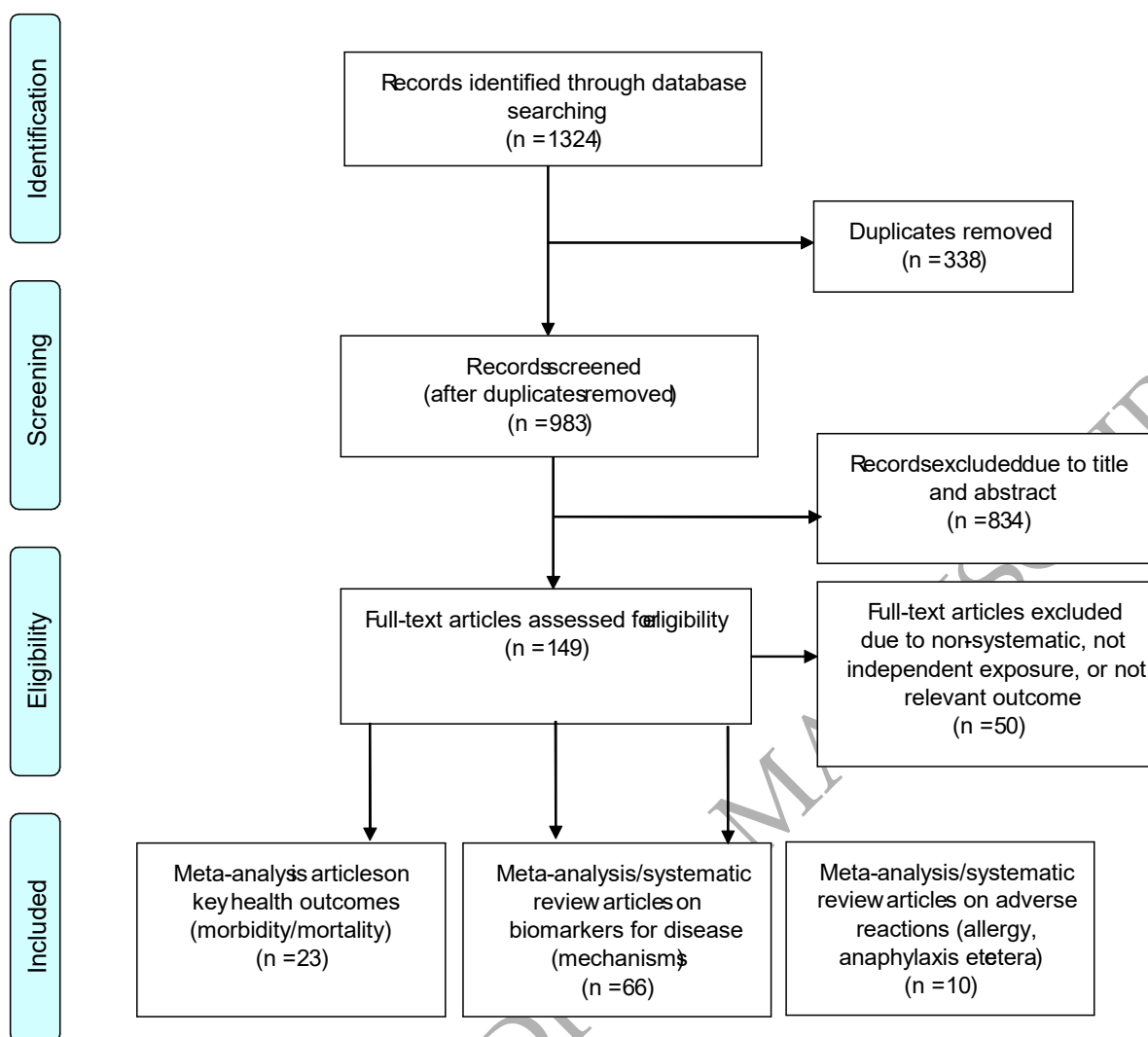


Figure 1: Study selection for the umbrella analysis of health outcomes of nuts and seeds.

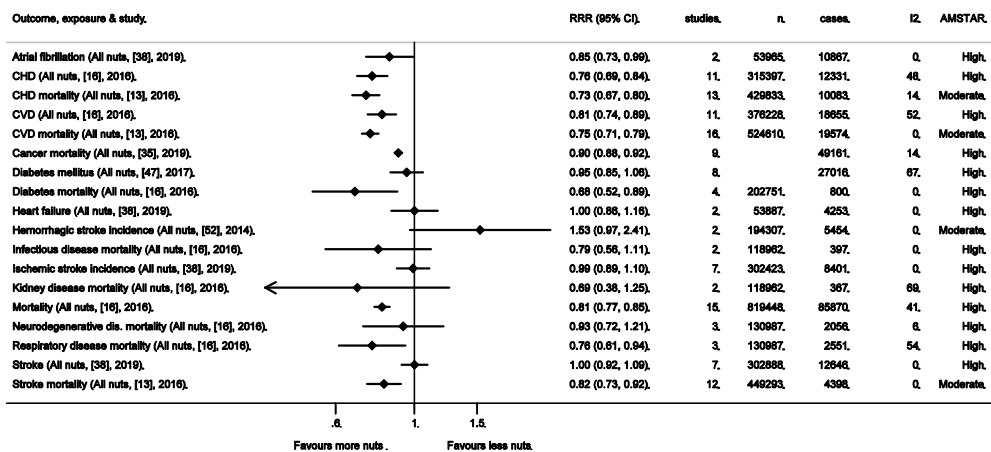


Figure 2: Summary of associations from the most comprehensive meta-analyses between high compared to low consumption of nuts and risk of various morbidities and mortalities. Reference number is listed in brackets and search year is listed within the parentheses.

ORIGINAL UNEDITED MANUSCRIPT

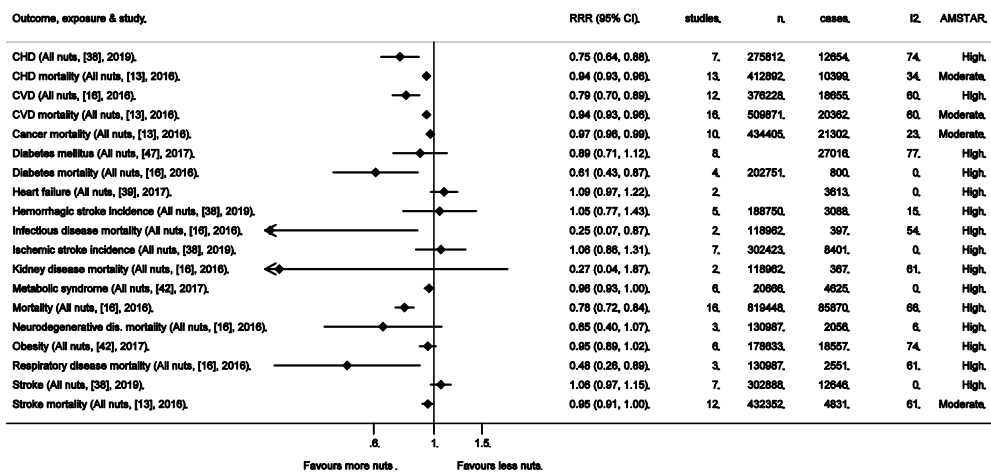


Figure 3: Summary of per serving associations from the most comprehensive meta-analyses between consumption of 28g/d nuts and risk of various morbidities and mortalities. Reference number is listed in brackets and search year is listed within the parentheses.

ORIGINAL UNEDITED MANUSCRIPT

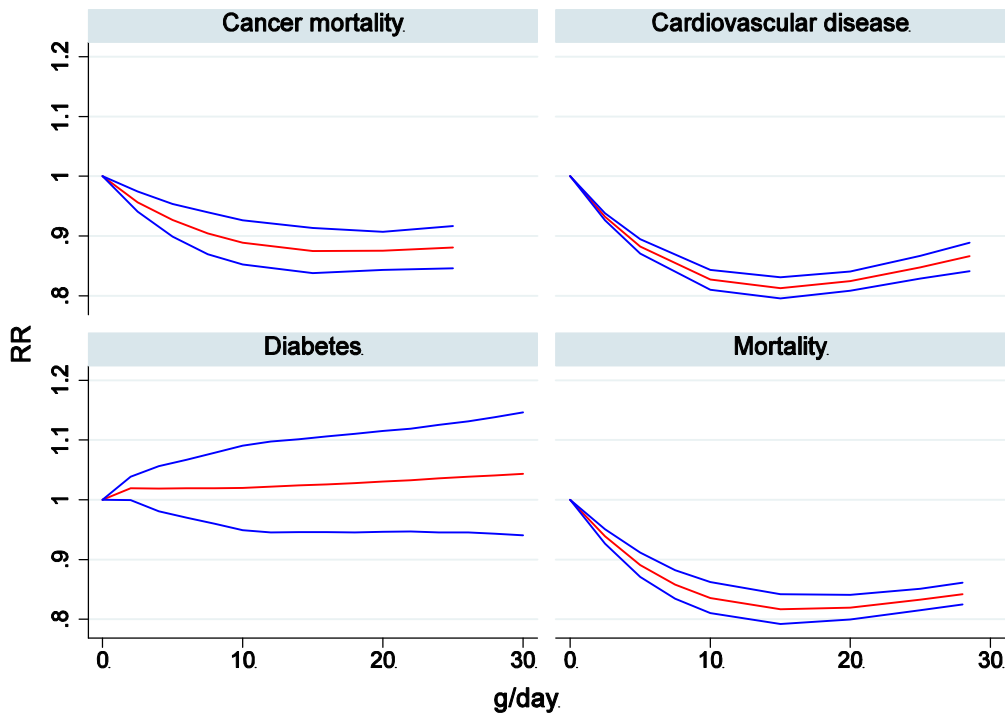


Figure 4: Summary of dose-response associations from the most comprehensive meta-analyses between consumption of nuts and risk of cancer mortality, cardiovascular disease, diabetes, and all-cause mortality.

* The red lines indicate the relative risk associations estimate while the blue lines represent the confidence interval of the relative risks.

Table 1: List of biomarkers for various disease and intermediate mechanisms for various morbidities from systematic reviews and meta-analyses including cardiovascular, diabetes and weight, and other outcomes.

	Favorable ¹	Neutral ¹	Unfavorable ¹
Blood lipids			
High-density lipoprotein	(72)	(59), (85), (62), (69), (70), (71), (73), (77), (81), (90), (93), (99), (100), (101), (105), (66), (75), (109), (56)	(79)
Low-density lipoprotein	(62), (69), (70), (81), (93), (99), (100), (105), (75), (79), (56)	(71), (73), (77), (90), (101), (72), (66), (109)	
Triglycerides	(59), (85), (62), (69), (70), (71), (77), (81), (93), (75), (56)	(59), (73), (81), (90), (99), (100), (101), (105), (72), (66), (79), (109)	
Total cholesterol	(59), (62), (69), (70), (71), (81), (81), (93), (99), (100), (101), (105), (75), (79), (56)	(73), (77), (81), (90), (72), (66), (109)	
Lipoprotein A	(106), (70)		
Apolipoprotein A		(62), (79)	
Apolipoprotein B	(62), (69), (79)		
Endothelial function			
Brachial artery diameter	(65)		
Flow mediated dilatation	(116), (86), (95), (108)	(85), (62), (65), (56)	
Blood pressure			
Systolic blood pressure (trials)	(55), (73), (78), (112), (66), (77)	(63), (69), (71), (80), (89), (72), (79), (109), (62), (85)	
Diastolic blood pressure (trials)	(63), (78), (112), (77)	(85), (62), (69), (71), (73), (80), (89), (55), (72), (79), (109), (66)	
Hypertension (observational)	(107), (41), (118)		
Body composition & weight			
Body composition		(74)	
Body weight	(120), (121), (122), (123), (68, 87), (124)	(125), (124), (68), (115), (64), (74)	
Body mass index (BMI)	(123), (115), (124)	(121), (124), (68), (64), (74)	
Energy intake	(125)		
Fat mass	(68), (121)	(124), (68)	
Overweight/obesity risk	(120), (121)		
Waist circumference	(120), (124)	(60), (121), (68), (115), (64), (74)	

Hunger and fullness			
Fullness		(125)	
Hunger	(125)		
Leptin	(84)		
Glucose & insulin			
Fasting blood glucose	(60), (97), (98), (60), (123), (88)	(74)	
Glycemic control	(88), (114), (123)		
Insulin sensitivity	(98)		
Fasting plasma insulin	(98)	(97)	
Adiponectin		(84), (94)	
HOMA-IR	(123), (88)	(74)	
HbA1C		(97), (98), (88)	
Glycemic indices	(92)	(74), (92)	
Inflammation			
C-reactive protein (CRP)	(58), (102)	(84), (95), (102), (103), (113)	
Tumor necrosis factor alpha (TNF- α)	(58), (102)	(84), (95)	
Interleukin 6 and 10 (IL-6, IL-10)	(58)	(84), (95), (102)	
Vascular, intercellular and endothelial-leukocyte cell adhesion proteins 1 (VCAM-1, ICAM-1, E-selectin)	(58)	(95)	
Antioxidant defense system	(67), (129)		
Gut microbiota			
Fecal microbiota		(24), (25)	
Cognitive function			
Cognitive performance	(54)	(110)	

¹ Studies are categorized based on biomarker change [favorable/ reduced disease risk, neutral (no significant change), or unfavorable/ increased risk], and listed by reference number.