RESEARCH
Review

The Effect of Replacing Refined Grains with Whole Grains on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with GRADE Clinical Recommendation

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ABSTRACT

Background Observational data have established a link between the consumption of whole grains and reduced risk of cardiovascular disease (CVD); however, there is a need to review interventional research.

Objective Our aim was to determine whether interventions providing whole grain or whole pseudo-grain for dietary consumption improved CVD-related outcomes compared with refined grain or placebo in adults with or without chronic disease and/or associated risk factors.

Methods A systematic review and meta-analysis of randomized controlled trials that compared whole-grain vs refined-grain or placebo consumption by human adults was conducted. PubMed, CINAHL, Embase, Web of Science, and Cochrane CENTRAL were searched for studies of 12 weeks (or 2 weeks for inflammatory outcomes) duration until 21 February 2020. Data were extracted for 14 types of CVD risk factors (40 outcomes in total). Risk of bias was assessed using the Cochrane Risk-of-Bias tool. Meta-analysis was performed using *Comprehensive Meta-Analysis* software. The Grading of Recommendations Assessment, Development and Evaluation method was used to determine confidence in the pooled effects and to inform a clinical recommendation.

Results Twenty-five randomized controlled trials were included and 22 were meta-analyzed. Interventions ranged from 2 to 16 weeks; most samples were healthy (n = 13 studies) and used mixed whole grains (n = 11 studies). Meta-analysis found that whole-grain oats improved total cholesterol (standardized mean difference [SMD] = −0.54, 95% CI −0.95 to −0.12) and low-density lipoprotein cholesterol (SMD = −0.57, 95% CI −0.84 to −0.31), whole-grain rice improved triglycerides (SMD = 0.22, 95% CI −0.44 to −0.01), and whole grains (all types) improved hemoglobin A1c (SMD = −0.33, 95% CI −0.61 to −0.04) and C-reactive protein (SMD = −0.22, 95% CI −0.44 to −0.00).

Conclusions For adults with or without CVD risk factors, consuming whole grains as opposed to refined grains can improve total cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, and C-reactive protein. There is insufficient evidence to recommend the whole grains as opposed to refined grains for the prevention and treatment of CVD. Further interventional research is needed to better understand the preventive and treatment potential of whole-grain and whole pseudo-grain dietary intake for cardiovascular disease, particularly among those with existing CVD risk factors.

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A RELATIONSHIP BETWEEN WHOLE GRAINS AND overall health has been well established using observational data, with cohort studies linking whole grains to reduced risk of type 2 diabetes mellitus, gastrointestinal cancers, and cardiovascular disease (CVD).[1-3] Whole grains are a category of cereal foods in which the grain is intact or the constituents are present in proportions that represent the intact grain.[4] The most common grains consumed by humans are durum wheat, oats, barley, rice, rye, sorghum, and maize/corn.[5] In addition, pseudo-grains, such as buckwheat, quinoa, and amaranth, are often considered as grains due to their nutritional, culinary,

and flavor profile similarities to true grains.[4] The consumption of whole grains as opposed to refined grains, which contain the endosperm starch primarily, is recommended in dietary guidelines internationally[1,6,7] due to the strong nutritional profile of the bran and germ, which contain protein, dietary fiber, magnesium, potassium, selenium, zinc, iron, iodine, folate, niacin, and vitamin E.[8] Whole grains are also an important source of phytochemicals and antioxidants, such as phenols, flavonoids, zeaxanthin, lutein, and β-cryptoxanthin, and provide additional health benefits, such as reduced risk of CVD, type 2 diabetes, and some cancers, beyond the consumption of essential nutrients.[9]

Cardiovascular disease is an umbrella term for a range of diseases that involve the heart and blood vessels, of which coronary heart disease, also known as ischemic heart disease, is the most common.[10] Four recent systematic reviews and meta-analyses of prospective cohort studies reported that a high intake of whole grains is associated with a 19% to 22% risk reduction in CVD and coronary heart disease incidence[11] and 15% to 32% risk reduction in CVD mortality.[3,11-14] Dose–response relationships were identified at 50 g[14] and 90 g[11,13] for risk reduction in CVD mortality. Conversely, a recent systematic review and meta-analysis of randomized controlled trials (RCTs) by Kelly and colleagues[15] found that there were no RCTs that measured outcomes of cardiovascular events or cardiovascular mortality.

Due to the long-term diet-related etiological development of chronic disease, the incidence and subsequent complications of CVD, such as myocardial infarctions, stroke, and death, are difficult outcomes to measure in dietary intervention studies with short durations. Therefore, dietary intervention studies have measured modifiable CVD risk factors, such as blood pressure, cholesterol, or glucose intolerance. The systematic review of RCTs by Kelly and colleagues[15] found insufficient evidence for an effect of whole grains on CVD risk factors. Although the review by Kelly and colleagues was of high quality, it applied stringent eligibility criteria to the intervention duration ($\geq$12 weeks), which led to only 9 RCTs being included. In addition, the review considered blood pressure and blood lipid outcomes only, and other CVD risk factors, including inflammatory markers, oxidative stress markers, metabolic disease incidence, glycemic and insulin markers, and other markers of hemodynamics, were excluded.

Therefore, in order to guide clinical practice and public health strategies, there is a need to review interventional research more broadly to determine the effect of whole grains vs refined grains on the risk of CVD and CVD-related outcomes in samples both with and without pre-existing chronic disease. Finally, no systematic review to date has examined the effect of whole pseudo-grains on CVD-related outcomes.

RESEARCH QUESTION

In adults with or without chronic disease and/or associated risk factors, do interventions providing whole grain or whole pseudo-grain for dietary consumption improve cardiovascular-related outcomes compared with placebo or refined-grain dietary consumption?

RESEARCH SNAPSHOT

Research Question: In adults with or without chronic disease and/or associated risk factors, do interventions providing whole grain or whole-pseudo-grain for dietary consumption improve cardiovascular disease–related outcomes compared with refined grain or placebo?

Key Findings: This systematic review and meta-analysis found that for adults with or without cardiovascular disease risk factors, consuming whole grain as opposed to refined grain can improve some cardiovascular risk factors, including total and low-density lipoprotein cholesterol, triglycerides, hemoglobin A1c, and C-reactive protein.

MATERIALS AND METHODS

Study Design

A systematic review of randomized or pseudorandomized controlled trials with a meta-analysis was undertaken and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This study was prospectively registered at the International Prospective Register of Systematic Reviews (CRD42019129403).

Whole Grains and Pseudo-Grains

All grains and pseudo-grains were included in this review according to the international definition by the HEALTHGRAIN European Union Consortium.[4] Specifically, these were wheat (including spelt, emmer, einkorn, Khorasan or kamut, durums, and faro), rye, oats, barley, corn/maize, rice, teff, canary seed, Job's tears, fonio, sorghum, millet, and triticale. The included pseudo-grains were amaranth, buckwheat, quinoa, and wild rice. A food product was considered whole grain according to the HEALTHGRAIN European Union Consortium definition as follows: "the intact grain or the dehulled, ground, milled, cracked or flaked grain where the constituents—endosperm, germ and bran—are present in such proportions that represent the typical ratio of those fractions occurring in the whole cereal, and includes wholemeal."[4] For pseudo-grains, the same concept was applied, where a whole pseudo-grain was considered as the intact pseudo-grain or a ground, milled, cracked, or flaked pseudo-grain was present with equal constituents as found in the intact pseudo-grain.[4] Food products, such as bread, wraps, and breakfast cereals were considered a source of whole grain (herein referred to as whole grains or whole pseudo-grains) if they contained >50% whole grain.[4]

Eligibility Criteria

Studies were deemed eligible if they were RCTs, cross-over trials, or pseudorandomized controlled trials. Other study designs, such as reviews, observational cohort studies, or uncontrolled intervention studies, were excluded. Figure 1 outlines other eligibility criteria according to the PICO (participant, intervention, comparator, and outcome) concept. Intervention duration of $\geq$8 weeks was chosen to allow for diet-related changes to impact CVD-related risk factors; however, studies that examine inflammatory and/or oxidative stress markers have study durations ranging from a

	Inclusion criteria	Exclusion criteria
Participants	Humans Healthy adults, adults with CVD[a] risk factors, CVD, metabolic syndrome, or T2DM.[b]	The sample population exclusively includes participants who are pregnant or have any other chronic diseases not directly associated with CVD risk.
Interventions	Whole grain or pseudo-grain met the HEALTHGRAIN[c] EU[d] Consortium definition and food products contained >50% whole grain. The background diet between groups was standardized or controlled. Other intervention factors could be included if they were implemented in both groups, for example, energy restriction, voluntary fortification. Intervention length ≥2 weeks for studies that reported inflammatory or oxidative stress markers as outcomes, or ≥8 weeks for studies that reported all other eligible outcomes.[e]	Does not meet the HEALTHGRAIN EU criteria for whole grain. Does not describe the whole-grain intervention product in sufficient detail as to ascertain whether it meets the HEALTHGRAIN EU criteria. Whole-grain product is fortified with additional nutrients or functional ingredients that are not subject to mandatory fortification. The intervention was implemented by dietary recommendations where the whole-grain product was not provided to participants. The intervention co-administers other non–whole-grain aspects not implemented in the control group, for example, other dietary products or lifestyle modifications.
Comparators and outcomes	Control group receiving refined grain or placebo.	No outcomes of interest are included.

[a]CVD = cardiovascular disease.

[b]T2DM = type 2 diabetes mellitus.

[c]"The intact grain or the dehulled, ground, milled, cracked or flaked grain where the constituents—endosperm, germ and bran—are present in such proportions that represent the typical ratio of those fractions occurring in the whole cereal, and includes wholemeal."[4]

[d]EU = European Union.

[e]For studies with a duration between 2 and 8 weeks that reported inflammatory and oxidative markers as well as other relevant outcomes, only inflammatory and oxidative stress outcomes were retrieved and considered in this review.

Figure 1. Inclusion and exclusion criteria of a systematic review and meta-analysis of randomized controlled trials that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans.

single meal to <1 month. Therefore, for outcomes related to inflammatory and/or oxidative stress markers, intervention duration ≥2 weeks was chosen to be able to review the impact of whole grains on these important CVD risk factors, as this duration should allow for assessment of impact, feasibility, and safety, while capturing a sufficient number of studies. No minimum dosage was considered as part of the eligibility criteria due to the large heterogeneity in whole-grain dosage-reporting methods across the literature.

Study Selection

Five electronic databases were searched from database inception to March 8, 2019: PubMed, CINAHL, Embase, Web of Science, and Cochrane CENTRAL. The search strategy (Figure 2, available at www.jandonline.org) was designed in PubMed and translated for other databases using Polyglot Search Translator.[16] After translation, the final search algorithm for each database was checked and modified to improve sensitivity and specificity by the study authors and a librarian. The search in PubMed was updated and searched to February 21, 2020. Grey literature and trial registries were not included as part of the search strategy. The reference lists of included studies and similar reviews were examined to identify records that the systematic strategy may have missed. Two investigators (S.M., F.F.M.) independently screened studies for eligibility via title and abstract, then full text (S.M., E.D.) using *Covidence* systematic literature review software.[17] Full-text disagreements that could not be resolved by discussion were decided by a third independent investigator (F.F.M.). Although the search strategy and eligibility screening mistakenly included chia seeds, studies including chia seeds were excluded at the full-text stage, as they are not considered pseudo-grains according to the HEALTHGRAIN definition.[4]

Outcomes and Data Extraction

This review considered outcomes of CVD, CVD-related complications, and CVD risk factors, including CVD events and

symptoms, hemodynamic measures, serum plasma lipids, comorbidity incidence, inflammatory markers, oxidative stress markers, body composition, and glycemic and insulin markers. In addition, alkylresorcinol was extracted as a biomarker of whole-grain intake to report intervention fidelity, and adverse events were recorded. Data were extracted from publications into a Microsoft Excel (version 1908) spreadsheet by 1 investigator (S.M. or E.D.) and checked for accuracy thrice by 2 investigators (E.D. or S.M.). Data extracted were study and participant characteristics, baseline, follow-up, change in outcome, and *P* value for between-group comparisons. When the change from baseline to follow-up was not reported, it was calculated by the investigators. The data associated with this review are available at Dryad (https://datadryad.org).[18]

Review of Study Quality and Grading of Recommendations Assessment, Development and Evaluation Assessment

Included studies were critically appraised independently by 2 investigators (S.M. and E.D.) using the Cochrane Risk-of-Bias tool.[19] When an outcome was pooled by meta-analysis, all studies included in the meta-analysis were appraised by the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[20] method using *GRADEpro GDT: GRADEpro Guideline Development Tool*[21] to determine the level of confidence in the body of evidence. The GRADE approach considers the internal validity and external validity of all studies reporting on a particular outcome so as to judge confidence in the estimated effect across the body of research.[21] Publication bias of pooled outcomes was further assessed by funnel plots.

GRADE Clinical Recommendation for Populations

To make the clinical recommendation for populations, the findings of this study were considered in addition to other literature, stakeholder values, issues of equity, access, and feasibility, risk of benefit and harm, and other judgements made by the review investigators using *GRADEpro* software.[21] The GRADE assessment and recommendation were led by 1 investigator (S.M.), discussed and revised by a second investigator (M.B.), and the recommendation was discussed and agreed upon by all authors.

Meta-Analytical Approach

Outcome data for which sufficient information was reported by publications were meta-analyzed by an applied statistician (P.P.) using *Comprehensive Meta-Analysis* software.[22] The data used in the meta-analyses were sample size (post attrition), change in means (ie, change from baseline to follow-up), and standard deviations (SDs) in intervention groups (IGs) and control groups (CGs) that were either reported or imputed. Where SD change was not reported (most cases), it was imputed from the baseline and follow-up SDs assuming a baseline to follow-up correlation of 0.7, which was derived from a rounded average of the few cases where SD change was reported. A priori moderator variables considered in the meta-analyses were type of grain (mixed, oats, rice, and wheat), health status (healthy or at risk of CVD), and study quality (high risk of bias, moderate risk of bias, and low risk of bias). Other types of grains were not included as moderators, as there were insufficient studies testing their efficacy. Dosage of whole grains was not included as a moderator due to large variation in the method of reporting. Values of $P < 0.05$, or equivalently 95% CIs not crossing the null (0.0), were considered to indicate a statistically significant result. The analyses were performed both by study (combining subgroups) and then by subgroup (treating each subgroup as an independent study).

The pooled outcomes were obtained as standardized mean differences (SMDs; mean difference divided by the pooled standard error from the 2 groups) to account for differences in measurement units and measurement techniques, and to improve generalizability of consistent (ie, low heterogeneity) results. SMD effect sizes of <0.4 were considered small, 0.4 to 0.7 moderate, and >0.7 large.[23] Where clinical interpretation of SMD was required, SMD effect sizes were re-expressed into the units by multiplying the SMD by the baseline SD of 1 of the included studies.[24] The study chosen to inform the re-expressed units was based on the highest-quality study that reported variance data, with consideration of sample size. Random-effects models were used for all meta-analyses.

One-study-removed sensitivity analyses were obtained to determine whether removing any individual study or subgroup caused significant change to the results. Analyses were then carried out using grouping by each of the moderator variables. A further sensitivity analysis was performed to determine the effect of the assumption that baseline to follow-up correlation was 0.7. For 2 outcome variables (hemoglobin A1c [HbA1c %] and triglycerides) analyses were repeated using a correlation of 0.9 followed by 0.5.

Bootstrapped meta-analyses were carried out using the metafor[25] and boot[26] packages in *R* software.[27] Nonparametric bootstrapping was carried out using the approach described by Viechtbauer and colleagues,[28] with the outcomes in which the meta-analytical models approached significance but may be subject to bias[29]: HbA1c %, C-reactive protein (CRP)/high-sensitivity CRP, and waist circumference. A variety of CIs, representing different distributional assumptions, were obtained in each case.

RESULTS

Results of the Search Strategy

The search strategy identified 10,623 records from PubMed, CINAHL, Embase, Web of Science, and Cochrane CENTRAL. Among these, 194 full-text studies were reviewed, and 30 publications were included (Figure 3). Of the 30 publications,[30-60] 25 were unique RCTs.[31,33,36-58,60] One RCT had 2 eligible intervention arms,[59,60] leading to a total of 26 included interventions. The main reason for exclusion was "wrong intervention," when the test product did not meet the HEALTHGRAIN European Union Consortium[4] definition for whole grain, and/or the study duration did not meet the eligibility criteria. The other main reason for exclusion was ineligible CG, where many RCTs compared the whole grain of interest against another whole grain (eg, oats vs wheat) or against usual diet.

Study Samples

Of the 25 included RCTs, 13 were conducted in healthy adult populations, and 12 were in adults with CVD risk factors (Table 1). None of the studies exclusively recruited

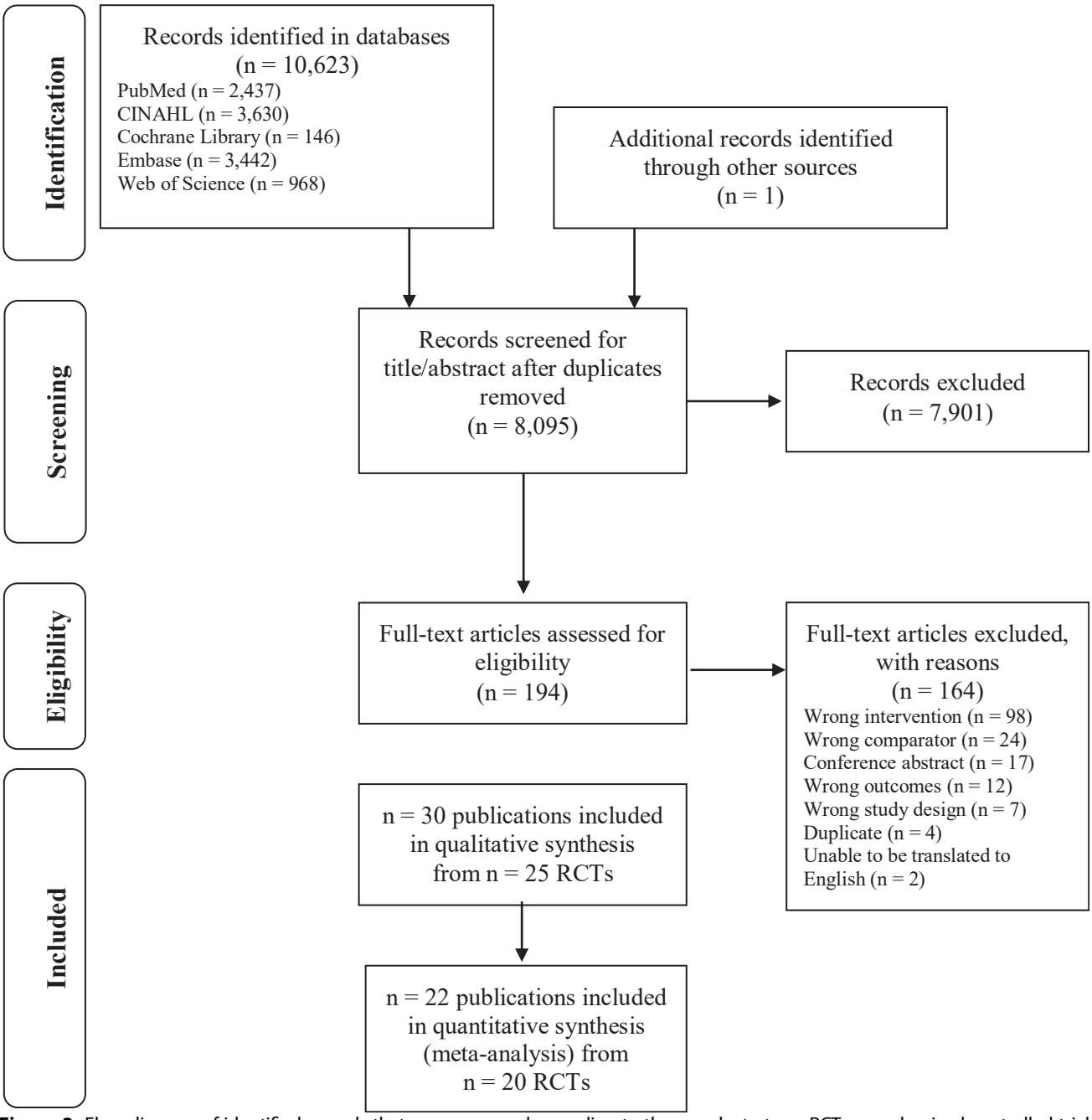

Figure 3. Flow diagram of identified records that were screened according to the search strategy. RCT = randomized controlled trial.

participants with existing CVD. The CVD risk factors across studies were highly diverse and included metabolic syndrome, type 2 diabetes mellitus, hyperlipidemia, hypertension, or a combination of these. The mean age of participants ranged from 27 to 67 years, and most (16 RCTs) reported a majority of females. Across all included RCTs, there were 1,186 intervention participants and 1,109 control participants, with individual study total sample sizes ranging from 12 to 226 (Table 1). Three studies[30-32] appeared to have some of the same participants, as did the 3 studies reported by Kirwan and colleagues[33] and Malin and colleagues,[34,35] but the exact number of duplicate participants is unclear. Attrition ranged from 0% (n = 7 studies) to 30% and was either equal between groups or higher in the CG. RCTs were included from Europe (n = 8), Asia (n = 7), North America (n = 7), the United Kingdom (n = 2), and the Middle East (n = 1); none were from Africa, South America, or Oceania (Table 1).

Study Design and Quality

There were 10 cross-over RCTs and 15 parallel RCTs (Table 1). Twenty-four RCTs had 2 arms (IG: n = 1, CG: n = 1), and 1 RCT had 3 arms (IG: n = 2, CG: n = 1). Three RCTs were double-

Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
Barley								
Pick, 1998,[57] Canada	Open-label, cross-over, 2 arms (1 IG[b], 1 CG[c])	n = 12 (IG: n = 12; CG: n = 12) Attrition: IG: 8%, CG: 8% μ51[d] ± 7 y 0% female CVD[e] risk factors	12 wk Run-in: none Washout: none	Grain: barley Food source: barley bread, buns, muffins, cookies, pasta, cereal Made with waxy hull-less barley Dosage: 83 g/d	Grain: wheat Food source: white bread Dosage: ND[f]	Isocaloric Controlled by cross-over design	NM[g]	Inflammatory markers, glycemic and insulin markers, body composition
Mixed grains								
Ampatzoglou, 2016,[36] United Kingdom	Open-label, cross-over, 2 arms (1 IG, 1 CG).	n = 33 (IG: n = 33; CG: n = 33). Attrition: IG: 0%, CG: 0% μ49 ± 1 y 65% female Healthy	6 wk Run-in: 2 wk Washout: 4 wk	Grain: mixed (59% wheat, 40% oats, 1% corn and rice) Food source: commercially available pasta, rice, snacks, and breakfast cereals Dosage: μ168 g/d (range, 67-335 g/d).	Grain: mixed (not further specified) Food source: commercially available pasta, rice, snacks, and breakfast cereals Dosage: unspecified; consumed RG[h]; mean WG[i] intake was 0.1 g/d	Pre- and probiotics were prohibited Habitual low WG intake Controlled by cross-over design and run-in diet	IG: μ161.1 (176.8) nmol/L, CG: μ38 (29.4) nmol/L, $P < 0.001$	Inflammatory markers
Andersson, 2007,[54] Sweden	Open-label, cross-over, 2 arms (1 IG, 1 CG)	n = 34 (IG: n = 34; CG: n = 34) Attrition: IG: 12%, CG: 12% μ59 ± 5y 73% female CVD risk factors	6 wk Run-in: none Washout: 6-8 wk	Grain: mixed (wheat, rye, oat, rice) Food source: commercially available bread, breakfast cereal, pasta, rice, flour Dosage: μ112 g/d	Grain: Mixed (wheat, rye, corn, rice) Food source: Commercially available bread, breakfast cereal, pasta, rice, flour Dosage: Unspecified; provides 3340 kJ/d	Encouraged to maintain habitual diet; controlled by cross-over design	NM	Inflammatory markers, oxidative stress markers

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
Enright, 2010,[37] United States	Open-label, cross-over, 2 arms (1 IG, 1 CG)	n = 20 (IG: n = 20; CG: n = 20) Attrition: IG: 0%, CG: 0% μ27 ± 4 y 50% female Healthy	2 wk Run-in: none Washout: none	Grain: mixed (wheat, oat, rye) Food source: commercially available: bread, cereals, cookies, crackers, buns, bagels Dosage: males: 8 servings/d, females: 6 servings/d Standard serving: 1 slice of bread, $^1/_2$ cup cereal, others not specified	Grain: mixed (wheat, rice) Food source: commercially available: bread, cereals, cookies, crackers, buns, bagels Wheat and rice, mostly puffed Dosage: males: 8 servings/d, females: 6 servings/d Standard serving: 1 slice of bread, $^1/_2$ cup cereal, others not specified	Usual diet maintained but no counseling provided; controlled by cross-over design	NM	Oxidative stress markers
Giacco, 2013,[31] Finland and Italy	Open-label, parallel, 2 arms (1 IG, 1 CG)	n = 146 (IG: n = 75; CG: n = 71) Attrition: IG: 19%, CG: 13% Age ND 53% female CVD risk factors	12 wk Run-in: 4 wk	Grain: mixed (wheat, barley, oat, rye) Food source: bread, pasta, soup, biscuits, breakfast cereal Bread was sourdough Dosage: μ136 ± 18 g/d	Grain: mixed (wheat, rice, corn) Food source: Commercially available bread, rice, pizza, porridge, breakfast cereal Dosage: 60%-80% of carbohydrate intake; 0 g WG intake	Isocaloric controlled via 4-wk run-in period in which both groups had similar background diets	IG: μ122 (96) nmol/L; CG: μ40 (32) nmol/L; P = 0.0001	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition
Giacco, 2014,[30] Italy	—	n = 61 (IG: n = 30; CG: n = 31)	—	—	—	—	IG: μ140.2 (102.0) nmol/L; CG: μ43.7	Glycemic and insulin markers, blood lipids,

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
		Attrition: IG: 7%, CG: 16% μ57 ± 9 y 57% female CVD risk factors					(38.0) nmol/L; $P = 0.0001$	body composition
Vetrani, 2016,[32] Finland and Italy	—	n = 40 (IG: n = 21; CG: n = 19) Attrition: IG: 0%, CG: 0% μ58 ± 2 y 60% female CVD risk factors	—	—	—	—	ND	Inflammatory markers, glycemic and insulin markers, blood lipids
Harris Jackson, 2014,[39] United States	Open-label, parallel, 2 arms (1 IG, 1 CG)	n = 60 (IG: n = 28; CG: n = 32) Attrition: IG: 11%, CG: 22% μ46 ± 6 y 50% female CVD risk factors	12 wk Run-in: None	Grain: mixed (wheat, rice, oat) Food source: pancakes, bread roll, pasta, cookies; others ND Dosage: μ163-301 g/d	Grain: mixed (wheat, rice, corn) Food source: Pancakes, bread rolls, pasta, cookies; others ND Dosage: ND; 0 g WG	Diets were tailored to individual; hypocaloric	Data presented graphically only; $P < 0.05$ between groups	Inflammatory markers, glycemic and insulin markers, blood lipids, body composition
Kirwan, 2016,[33] United States	Double-blind, cross-over, 2 arms (1 IG, 1CG)	n = 40 (IG: n = 40; CG: n = 40) Attrition: IG: 18%, CG: 18% μ39 ± 7 y 82% female Healthy	8 wk Run-in: none Washout: 10 wk	Grain: mixed (wheat, rice, oat)[j] Food source: Commercially available breakfast cereal, rice Dosage: 50 g/1,000 kJ/d	Grain: mixed (wheat, rice)[j] Food source: commercially available breakfast cereal, rice Dosage: ND; 0 g WG	Isocaloric, individualized, matched macronutrient composition	IG: μ change 85.2 (95% CI 38.2 to 132.2) nM; CG: μ change −36.8 (95% CI −51.1 to −22.5) nM; $P < 0.001$	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, CVD comorbidity incidence, body composition

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
Malin, 2018,[34] United States	—	n = 14 (IG: n = 14; CG: n = 14) Attrition: IG: 0%, CG: 0% μ38 ± 2 y 79% female Healthy	—	—	—	—	—	Glycemic and insulin markers, body composition
Malin, 2019,[35] United States	—	n = 13 (IG: n = 13; CG: n = 13) Attrition: IG: 0%, CG: 0% 78% female Healthy	—	—	—	—	—	Glycemic and insulin markers, body composition
Kondo, 2017,[42] Japan	Open-label, parallel, 2 arms (1 IG, 1 CG)	n = 29 (IG: n = 14; CG: n = 15) Attrition: IG: 0%, CG: 7% μ67 ± 8 y 36% female CVD risk factors	8 wk Run-in: 4-8 wk	Grain: mixed (brown rice, amaranth, barley) Food source: packet of mixed grain to cook as per preference Dosage: staple food for 10/21 meals/wk	Grain: white rice Food source: ND Dosage: Staple food for 10/21 meals/wk	Isocaloric; controlled with run-in period	NM	Inflammatory markers, oxidative stress markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition
Kristensen, 2017,[50] France	Single-blind, parallel, 2 arms (1 IG, 1CG)	n = 178 (IG: n = 89; CG: n = 89) Attrition: IG: 9%, CG: 1% μ36 ± 9 y 100% female Healthy	12 wk Run-in: 8 wk	Grain: mixed (wheat, rice, rye, oat) Food source: commercially available bread, bulgur, couscous, rice, pasta, rusks, crispbread, breakfast	Grain: mixed (wheat, rice, corn) Food source: commercially available bread, couscous, rice, pasta, rusks, breakfast cereal	Hypocaloric, controlled with run-in period, all food provided, dietitian counseling throughout	IG: μ119 (181) nmol/L[k]; CG: μ33 6 (38.9) nmol/L; $P <$ 0.00001.	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
				cereal, cereal bar Dosage: μ124 ± 1.7 g/d	Dosage: ND Mean 0.5 g/d of WG			
Roager, 2019,[44] Denmark	Open-label, cross-over, 2 arms (1 IG, 1 CG)	n = 60 (IG: n = 60; CG: n = 60) Attrition: IG: 17%, CG: 17% μ49 ± 11 y 64% female CVD risk factors	8 wk Run-in: none Washout: 6 wk	Grain: mixed (oat, rye, wheat, bulgur) Food source: breakfast cereal, bread, buns, pasta, crisps Dosage: >122 g/d	Grain: mixed (wheat, rice, oat, rye, spelt, bulgur) Food source: breakfast cereal, bread, buns, pasta, crisps Dosage: >128 g/d	Usual diet maintained Controlled by cross-over design and washout period	NM	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition
Tighe, 2010,[60] United Kingdom	Single-blind, parallel, 3 arms (2 IG, 1CG)	n = 226 (IG: n = 73; IG: n = 77; CG: n = 76) Attrition: IG: 5%, IG: 4%, CG: 17% μ52 ± 1 y 50% female Healthy	12 wk Run-in: 4 wk	IG: 1 Grain: Mixed (wheat, oat) Food source: Bread, cereal, rolled oats Dosage: >60 g/d IG: 1 reported below	Grain: refined wheat Food source: Bread, cereal Dosage: >6 g/d	Dietary advice to maintain regular diet; controlled with run-in period	NM	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics
Tighe, 2013,[59] United Kingdom	—	—	—	—	—	—	—	Blood lipids
Vanegas, 2017,[46] United States	Open-label, parallel, 2 arms (1 IG, 1 CG)	n = 90 (IG: n = 45; CG: n = 45) Attrition: IG: 9%, CG: 11% μ55 ± 1 y 40% female Healthy	6 wk Run-in: 2 wk	Grain: mixed (mostly wheat) Food source: bread Dosage: 16 g/1,000 kcal	Grain: mixed (mostly wheat) Food source: white bread Dosage: 8 g/1,000 kcal	Isocaloric; controlled by run-in phase and then all food provided during intervention phase	IG: μ198.03 (24.27) nmol/L; CG: μ30.60 (3.76) nmol/L; $P <$ 0.0001	Inflammatory markers

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
Oat								
Maki, 2010,[51] United States	Open-label, parallel, 2 arms (1 IG, 1 CG)	n = 204 (IG: n = 101; CG: n = 103) Attrition: IG: 24%, CG: 35% μ49 ± 1 y 79% female Healthy	12 wk Run-in: none	Grain: oat Food source: ready-to-eat commercially available oat cereal (Cheerios) Dosage: 3 cups/d	Grain: mixed (corn, wheat, rice) Food source: ready-to-eat commercially available breakfast cereal, bread, bagel, muffin, chips, crackers, or rice cakes Dosage: ND; kJ consumption of RG matched that provided by the WG	Hypocaloric; diet prescribed but not well described	NM	Inflammatory markers, blood lipids, hemodynamics, body composition
Pins, 2002,[58] United States	Single-blind, parallel, 2 arms (1 IG, 1 CG)	n = 88 (IG: n = 45; CG: n = 43) Attrition: IG: 0%, CG: 0% μ48 y (range, 33-67 y) 49% female CVD risk factors	12 wk Run-in: none	Grain: oat Food source: oatmeal and oat squares Dosage: 137 g/d	Grain: mixed (wheat, corn, barley) Food source: breakfast cereal Dosage: 146 g/d	Isocaloric; poorly described	IG: μ380 (95% CI 255 to 505) nmol/L; CG: μ134 (95% CI 107 to 161) nmol/L; $P <$ 0.0001	Glycemic and insulin markers, blood lipids, hemodynamics, body composition
Rice								
Araki, 2017,[49] Japan	Open-label, parallel, 2 arms (1 IG, 1 CG)	n = 41 (IG: n = 20; CG: n = 21) Attrition: IG: 5%, CG: 14% μ54 ± 7 y 54% female CVD risk factors	12 wk Run-in: none	Grain: brown rice Food source: partially abraded Dosage: μ400 g/d	Grain: white rice Food source: ND Dosage: 400 g/d	Study provided 2 main meals; participants able to eat staple foods for third meal	NA[l]	Glycemic and insulin markers, blood lipids, hemodynamics, body composition

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
Kazemzadeh, 2014,[40] Iran	Open-label, cross-over, 2 arms (1 IG, 1 CG)	n = 38 (IG: n = 38; CG: n = 38) Attrition: IG: 8%, CG: 8% μ33 ± 6 y 100% female Healthy	6 wk Run-in: 2 wk Washout: 2 wk	Grain: brown rice Food source: Iranian rice variety (Tarom) Dosage: 150 g/d	Grain: white rice Food source: Iranian rice variety (Tarom) Dosage: 150 g/d	Hypocaloric prescribed diet; controlled by cross-over design, run-in and washout periods	NA	Inflammatory markers, glycemic and insulin markers
Kim, 2008,[56] South Korea	Open-label, parallel, 2 arms (1 IG, 1 CG)	47 (IG: n = 23; CG: n = 24) Attrition: IG: 13%, CG: 17% 20-35 y 100% female Healthy	6 wk Run-in: none	Grain: brown and black rice Food source: served within a meal substitute Dosage: 3 servings/d; ND further	Grain: white rice Food source: served within a meal substitute Dosage: 3 servings/d; ND further	Hypocaloric diet provided by study	NA	Oxidative stress markers
Nakayama, 2017,[52] Japan	Open-label, cross-over, 2 arms (1 IG, 1 CG)	n = 18 (IG: n = 18; CG: n = 18) Attrition: IG: 11%, CG: 11% μ64 ± 9 y 25% female CVD risk factors	8 wk Run-in: 1 wk Washout: none	Grain: brown rice Food source: glutenous brown rice Dosage: 2 servings/d; serving size ND	Grain: white rice Food source: ND Dosage: 2 servings/d; serving size ND	Usual diet; instructed by nutritionist; controlled by run-in period	NA	Glycemic and insulin markers, blood lipids
Shimabukuro, 2014,[53] Japan	Open-label, cross-over, 2 arms (1 IG, 1 CG)	n = 28 (IG: n = 28; CG: n = 28) Attrition: IG: 4%, CG: 4% μ46 ± 5 y 0% female CVD risk factors	8 wk Run-in: none Washout: none	Grain: brown rice Food source: ND Dosage: consumed daily; ND further	Grain: white rice Food source: ND Dosage: consumed daily; ND further	Unchanged from usual diet Controlled by cross-over design	NA	Inflammatory markers, oxidative stress markers, glycemic and insulin markers, blood lipids, hemodynamics,

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
								body composition
Zhang, 2011,[48] China	Single-blind, parallel, 2 arms (1 IG, 1 CG)	n = 202 (IG: n = 101; CG: n = 101) Attrition: IG: 3%, CG: 6% μ50 ± 7 y 47% female CVD risk factors	16 wk Run-in: none	Grain: brown rice Food source: soaked in water for 1hr before cooking Dosage: 225 g/d	Grain: white rice Food source: ND Dosage: 225 g/d	Isocaloric Usual dietary pattern maintained	NA	Glycemic and insulin markers, blood lipids, hemodynamics, CVD comorbidity incidence, body composition
Wheat								
Giacco, 2010,[38] Italy	Open-label, cross-over, 2 arms (1 IG, 1 CG)	n = 15 (IG: n = 15; CG: n = 15) Attrition: IG: 0%, CG: 0% μ55 ± 8 y 20% female Healthy	3 wk Run-in: 2 wk Washout: none	Grain: WG what Food source: commercially available pasta, bread, rusks, crackers Dosage: ND; included WG at every meal	Grain: Refined wheat Food source: commercially available pasta, bread, rusks, crackers Dosage: not specified; included RG at every meal	Encouraged to maintain isogenic habitual diet; controlled by cross-over design and run-in period	NM	Inflammatory markers, oxidative stress markers
Kikuchi, 2018,[41] Japan	Double blind, parallel, 2 arms (1 IG, 1 CG)	n = 50 (IG: n = 25; CG: n = 25) Attrition: IG: 4%, CG: 0% μ48 ± 2 y 35% female Healthy	12 wk Run-in: none	Grain: WG wheat Food source: bread prepared for the study Dosage: μ100 g/d	Grain: refined wheat Food source: refined bread dyed brown, prepared for the study Dosage: ND; assumed equal intake of bread as IG	Maintained background diet; no counseling provided	NM	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
Kristensen, 2012,[55] Denmark	Open-label, parallel, 2 arms (1 IG, 1 CG)	n = 79 (IG: n = 42; CG: n = 37) Attrition: IG: 10%, CG: 8% μ60 ± 5 y 100% female Healthy	12 wk Run-in: 2 wk	Grain: WG wheat Food source: commercially available pasta, bread, biscuits Dosage: μ105 g/d	Grain: refined wheat Food source: commercially available pasta, bread, biscuits Dosage: grain foods were the same portion sizes as WG	Hypocaloric, controlled with run-in period, all food provided, dietitian counseling throughout	Data presented graphically only; $P < 0.001$ between groups	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition
Schutte, 2018,[45] Netherlands	Double-blind, parallel, 2 arms (1 IG, 1 CG)	n = 50 (IG: n = 25; CG: n = 25) Attrition: IG: 0%, CG: 0% μ61 y (range, 51-69 y) 48% female CVD risk factors	12 wk Run-in: 4 wk	Grain: WG wheat Food source: bread, cereal, buns Dosage: 98 g/d	Grain: refined wheat Food source: white bread, buns, cereal Dosage: 98 g/d	Unchanged from usual diet, asked to maintain not gain or lose weight; controlled with run-in period	IG: μ209.2 (94) nmol/L; CG: μ41.8 (19) nmol/L; $P <$ 0.001	Inflammatory markers, glycemic and insulin markers, blood lipids, body composition
Tighe, 2010,[60] United Kingdom	Single-blind, parallel, 3 arms (2 IG, 1CG)	n = 226 (IG: n = 73; IG: n = 77; CG: n = 76) Attrition: IG: 5%, IG: 4%, CG: 17% μ52 ± 1 y 50% female Healthy	12 wk Run-in: 4 wk	IG: 2 Grain: WG wheat Food source: bread, cereal Dosage: >60 g/d IG: 2 reported above	Grain: Refined wheat Food source: Bread, cereal Dosage: >6 g/d	Dietary advice to maintain regular diet; controlled with run-in period	NM	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics

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Table 1. Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

First author, year, country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresorcinol	Outcomes measured
Tighe, 2013,[59] United Kingdom	—	—	—	—	—	—	—	Blood lipids
Vitaglione, 2015,[47] Italy	Single-blind, parallel, 2 arms (1 IG, 1 CG)	n = 80 (IG: n = 40; CG: n = 40) Attrition: IG: 10%, CG: 20% μ39 ± 2 y 66% female Healthy	8 wk Run-in: none	Grain: WG wheat Food source: biscuits Dosage: 70 g/d	Grain: refined wheat Food source: bread and crackers Dosage: 60 g/d	Isocaloric Diet was tailored for individual Habitual diet largely retained	NM	Inflammatory markers, glycemic and insulin markers, blood lipids, body composition

[a]RCT = randomized controlled trial.
[b]IG = intervention group.
[c]CG = comparator group.
[d]μ = sample mean.
[e]CVD = cardiovascular disease.
[f]ND = not described.
[g]NM = not measured.
[h]RG = refined grain.
[i]WG = whole grain.
[j]Corn was not considered as a grain by the study investigators, and was therefore provided as part of the background diet to both groups.
[k]62% of participants had insufficient alkyresorcinol levels indicating nonadherence.
[l]NA = not applicable.

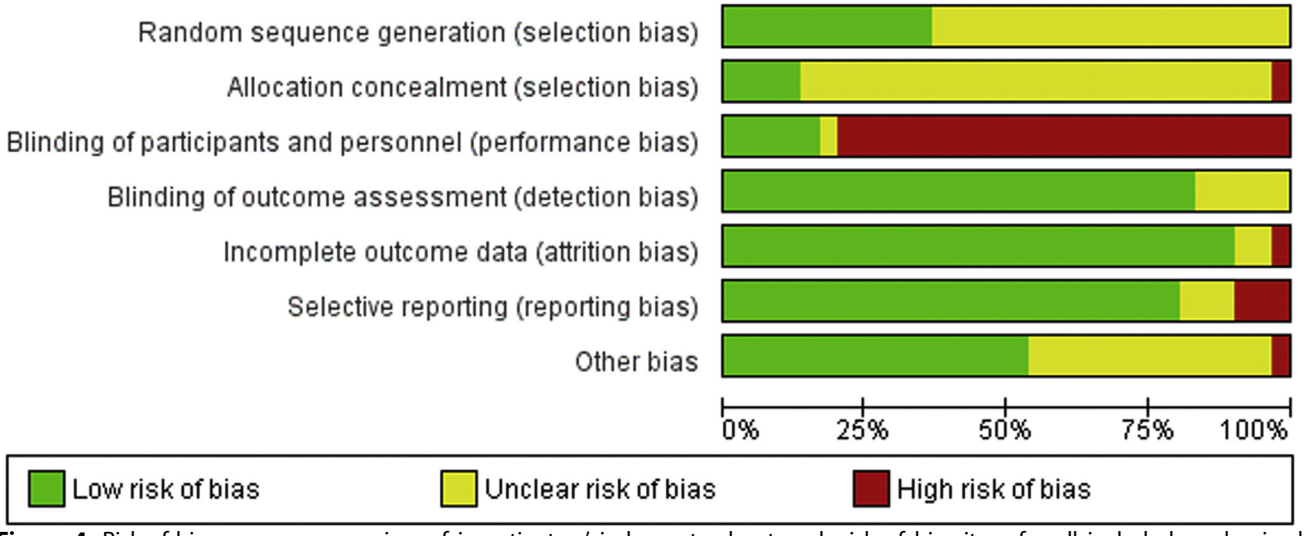

Figure 4. Risk-of-bias summary: a review of investigators' judgments about each risk of bias item for all included randomized controlled trials, as guided by the Cochrane Risk-of-Bias tool,[19] which compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans.

blinded, 5 were single-blinded, and the remaining 17 RCTs were open-label (Table 1).

Of the 25 included studies, 7 had an intervention duration longer than 8 weeks, which reported inflammatory and/or oxidative stress markers that were extracted as outcomes (Table 1). The remaining 18 RCTs ranged in duration from 8 to 16 weeks. To stabilize the diet before intervention, 11 RCTs used a run-in period, which varied from 1 to 8 weeks. The washout period of the 10 cross-over RCTs ranged from 2 to 10 weeks; however, 50% of cross-over studies did not use a washout period (Table 1). Other approaches to control the background diet were usually the recommendation or provision of isocaloric diets; however, 5 studies prescribed hypocaloric diets to all intervention arms. Beyond hypocaloric diets, no other interventions were co-administered to both groups.

Risk of bias across RCTs was generally low for detection bias, attrition bias, and reporting bias (Figure 4; justifications in Table 2 [available at www.jandonline.org). Despite all RCTs being randomized, few reported the randomization method, leading to an unclear risk of bias. Although most RCTs did not blind participants and personnel, it must be recognized this is not usually possible in dietary studies and therefore allocation concealment would not be possible. Therefore, if an RCT had a low risk of bias on all domains except allocation concealment and blinding of participants and personnel, it was considered to have a low risk of bias. If an RCT was rated as having a high risk of bias in any other domain, or had only 1 other domain rated a low risk of bias, then it was considered to have a high risk of bias overall. There were 16 publications evaluated as having low risk of bias,[30-34,38-48] 5 had a high risk of bias,[49-53] and 8 had an unclear risk of bias.[48,54-60] None of the funnel plots for pooled outcomes detected evidence of publication bias.

Whole-Grain Intervention Characteristics

Of the 26 different interventions included, most whole grains were mixed (n = 11 studies); followed by rice (n = 6), wheat (n = 6), oats (n = 2), and barley (n = 1) (Table 1). No pseudo-grain RCTs were identified that met this review's eligibility criteria. The daily dose of whole grains varied widely and was reported heterogeneously. Of those that reported whole-grain dosage in grams per day, it ranged from 60 g to 150 g, except for cooked rice, which ranged from 150 g to 400 g. Where whole grains were not prescribed in a daily dose to all participants, whole grains may have been provided without a specific gram target (eg, use in main meals twice per day) or calculated as a proportion of total daily energy or carbohydrate requirement. No RCTs used placebo as control. Whole grains were compared against their refined counterpart for most RCTs (eg, brown rice vs white/refined rice; mixed whole grain vs mixed refined grains) (Table 1). The exceptions were the studies by Kondo and colleagues,[42] which compared mixed whole grains against refined rice, Maki and colleagues[51] and Pins and colleagues,[58] which compared whole-grain oats against mixed refined grains, and Pick and colleagues,[57] which compared whole-grain barley against refined wheat. Daily doses of refined grains were reported rarely, but among those that did report them, it ranged from 60 g to 150 g, and 15 g to 400 g for cooked rice, which aligns with the range in dose of the whole-grain intervention. Plasma alkylresorcinol was measured by 9 RCTs; all of which reported a significantly higher level in the intervention arms (ranging from 122 to 380 nmol/L) compared with control arms (ranging from 30 to 134 nmol/L), indicating intervention fidelity (Table 1).

The number of RCTs that reported a statistically significant improvement between groups is reported in Table 1. There were 40 outcome variables reported across all included RCTs, which could be grouped into the following outcome

Table 3. Summary of outcomes reported by the 26 included randomized controlled trials[a] that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans

Outcomes category[b]	RCTs[c] reporting outcomes, n	RCTs reporting significant improvements favoring whole grain	RCTs reporting significant improvements favoring refined grain
		n (%)	
Inflammatory markers (n = 10)	21		
CRP[d]		2/5 (40)	0/5 (0)
hsCRP[e]		1/11 (9)	1/11 (9)
IL[f]-β		1/2 (50)	0/2 (0)
IL-6		1/9 (11)	0/9 (0)
TFN[g]-α		1/6 (17)	0/6 (0)
PAI[h]-1		1/5 (20)	0/5 (0)
IL-8		0/2 (0)	0/2 (0)
IL-10		0/2 (0)	0/2 (0)
Adiponectin		0/5 (0)	0/5 (0)
Leptin		0/4 (0)	0/4 (0)
Oxidative stress markers (n = 7)	6		
TBARS[i]		1/2 (50)	0/2 (0)
GSH-Px[j]		1/1 (100)	0/1 (0)
FRAP[k]		0/1 (0)	0/1 (0)
8-iso PGF2a[l]		0/4 (0)	0/4 (0)
ORAC[m]		0/1 (0)	0/1 (0)
SOD[n]		0/1 (0)	0/1 (0)
ADMA[o]		0/1 (0)	0/1 (0)
Glycemic and insulin markers (n = 6)	19		
HOMA-IR[p]		1/12 (8)	0/12 (0
Postprandial plasma insulin		2/5 (40)	0/5 (0)
Fasting plasma glucose		2/14 (14)	0/14 (0)
Postprandial plasma glucose		2/4 (50)	0/4 (0)
Fasting plasma insulin		0/14 (0)	0/14 (0)
HbA1c%		0/9 (0)	0/9 (0)
Blood lipids (n = 5)	18		
Total cholesterol		3/16 (19)	3/16 (19)
LDL[q] cholesterol		4/16 (25)	1/16 (6)
HDL[r] cholesterol		2/17 (12)	1/17 (6)
Triglycerides		2/17 (12)	1/17 (6)
VLDL[s] cholesterol		0/1 (0)	0/1 (0)
Hemodynamics (n = 4)	12		
Pulse pressure[t]		3/3 (100)	3/3 (100)
SBP[u]		3/13 (23)	0/13 (0)
DBP[v]		1/13 (8)	1/13 (8)
Mean arterial pressure		0/1 (0)	0/1 (0)

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Table 3. Summary of outcomes reported by the 26 included randomized controlled trials[a] that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Outcomes category[b]	RCTs[c] reporting outcomes, n	RCTs reporting significant improvements favoring whole grain	RCTs reporting significant improvements favoring refined grain
		←——————*n (%)*——————→	
CVD[w] comorbidity (n = 2)	2		
Prediabetes incidence		1/2 (50)	0/2 (0)
MetS[x] incidence		0/2 (0)	0/2 (0)
Body composition (n = 6)	15		
Total body weight		2/13 (15)	0/13 (0)
Fat mass (kg)		1/3 (0)	0/3 (0)
WC[y]		2/12 (17)	1/12 (8)
BMI[z]		0/9 (0)	0/9 (0)
Fat mass		0/4 (0)	0/4 (0)
FFM[aa] (kg)		0/4 (0)	0/4 (0)

[a]RCTs that measured an outcome but did not compare groups were excluded from Table 3. Data included were from 25 unique RCTs that had 26 intervention arms, but were reported across 30 publications.
[b]Number of different outcomes reported within the outcome category.
[c]RCT = randomized controlled trial.
[d]CRP = C-reactive protein.
[e]hsCRP = high-sensitivity C-reactive protein.
[f]IL = interleukin.
[g]TNF = tumor necrosis factor.
[h]PAI = plasminogen activator inhibitor.
[i]TBARS = thiobarbituric acid reactive substances.
[j]GSH-px = glutathione peroxidase.
[k]FRAP = total antioxidant capacity of plasma.
[l]8-iso PGF2a = 8-iso-prostaglandin F2α.
[m]ORAC= oxygen radical absorbance capacity.
[n]SOD = superoxide dismutase.
[o]ADMA = asymmetric dimethylarginine.
[p]HOMA-IR = Homeostatic Model Assessment of Insulin Resistance.
[q]LDL = low-density lipoprotein.
[r]HDL = high-density lipoprotein.
[s]VLDL = very low-density lipoprotein.
[t]Although there was a significant difference between groups for this outcome it is not clear whether the changes favored intervention or control in any study, as all values were within the normal range (ie, between 40 and 60 mmHg), effect sizes were small, and/or data were only presented graphically.
[u]SBP = systolic blood pressure.
[v]DBP = diastolic blood pressure.
[w]CVD = cardiovascular disease.
[x]MetS = metabolic syndrome.
[y]WC = waist circumference.
[z]BMI = body mass index; calculated as kg/m^2.
[aa]FFM = fat-free mass.

categories: hemodynamics (12 RCTs), body composition (15 RCTs), blood lipids (18 RCTs), glycemic and/or insulin markers (19 RCTs), and inflammatory markers (21 RCTs). Only 6 RCTs reported oxidative stress markers and 2 RCTs reported incidence of CVD comorbidities. No RCTs reported CVD and CVD-related complication outcomes.

Outcomes of Whole Grains Compared to Refined Grains Reported by Included Studies

Of the 40 outcomes measured across all RCTs, 23 (58%) were found to have 1 or more RCTs report a statistically significant improvement in the whole-grain intervention compared to refined-grain comparator. For 6 outcomes (15%), a significant difference between groups was reported to favor whole grain in some studies and refined grain in others; and 1 outcome (fat-free mass) was reported to favor refined grain alone (Table 3). Blood lipids had the largest number of studies that reported beneficial effects of whole grains compared to refined grains (11 RCTs); however, they also had the largest number of RCTs that reported results favoring refined grains (5 RCTs).

Most publications did not report on adverse events. Four studies reported minor gastrointestinal symptoms, with low incidence varying from 2% to 16%, which was comparable between intervention and control arms.[46,51,54,58] There was also 1 case of faintness reported in the IG[38] and 1 case of gastroenteritis in the CG.[51]

Table 4. Pooled effects and confidence in the body of evidence based on 20 randomized controlled trials (reported across 22 publications) that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans

Outcome	No. of intervention groups	No. of participants (IG[a]/CG[b])	SMD[c] (95% CI)	Model	I^2 (%)	*P* value	GRADE[d]
CRP/hsCRP[e]	14	658/644	−0.19 (−0.57 to 0.20)	RE[f]	88.9	0.542	Moderate[g]
IL[h]-6	9	458/432	−0.08 (−0.29 to 0.13)	RE	51.0	0.457	Moderate
Fasting blood glucose	16	742/722	−0.01 (−0.19 to 0.16)	RE	60.4	0.875	Very low
Fasting blood insulin	13	649/626	0.07 (−0.05 to 0.18)	RE	0	0.265	Moderate
HOMA-IR[i]	12	528/500	−0.03 (−0.17 to 0.10)	RE	0	0.603	Moderate
Hemoglobin A1c	10	404/403	−0.24 (−0.53 to 0.06)	RE	75.0	0.122	Moderate[g]
Total cholesterol (Figure 5)	16	791/757	−0.10 (−0.29 to 0.09)	RE	67.3	0.291	Very low[g]
HDL[j] cholesterol	18	775/750	−0.0 (−0.03 to 0.03)	RE	38.7	0. 896	Low[k]
LDL[l] cholesterol (Figure 6)	15	783/751	−0.07 (−0.25 to 0.10)	RE	59.6	0.405	Very low[g]
Triglycerides	16	753/727	−0.06 (−0.21 to 0.10)	RE	49.9	0.477	Very low[g]
SBP[m]	11	482/481	−0.04 (−0.28 to 0.21)	RE	71.3	0.781	Very low
DBP[n]	12	515/514	0.05 (−0.26 to 0.37)	RE	83.1	0.730	Very low
Total body weight[o]	16	602/587	−0.02 (−0.24 to 0.19)	RE	70.8	0.826	Very low
Waist circumference	14	641/625	−0.10 (−0.25 to 0.05)	RE	35.5	0.117	Moderate

[a]IG = intervention group.
[b]CG = control group.
[c]SMD = standardized mean difference.
[d]GRADE = Grading of Recommendations Assessment, Development and Evaluation.
[e]CRP/hsCRP = C-reactive protein/high-sensitivity C-reactive protein.
[f]RE = random effect.
[g]GRADE assessment reflects confidence in the statistically significant subgroup rather than the overall analytical model.
[h]IL = interleukin.
[i]HOMA-IR = Homeostatic Model Assessment of Insulin Resistance.
[j]HDL = high-density lipoprotein.
[k]GRADE assessment reflects confidence in the statistically significant subgroup grain type: mixed, rather than the overall analytical model or the subgroup study quality: unclear.
[l]LDL = low-density lipoprotein.
[m]SBP = systolic blood pressure.
[n]DBP = diastolic blood pressure.
[o]Weight change was meta-analyzed for total body weight change in preference to body mass index (BMI) as fewer studies reported BMI change.

Pooled Effects of Whole Grains Compared to Refined Grains on Cardiovascular Disease Risk Factors

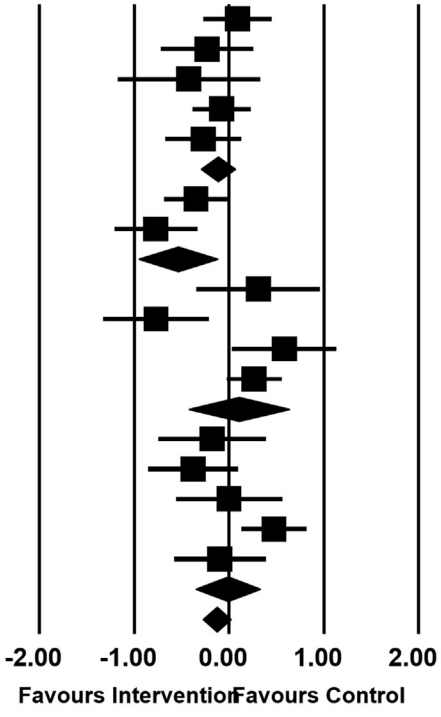
There were 20 RCTs (across 22 publications) included to meta-analyze 14 outcomes (Table 4). Three publications[40,41,53] reported results for the IGs and/or CGs by subgroup (eg, male and female participants separately); leading to 23 IGs included in the models. A further sensitivity analysis was carried out to evaluate the effect of the assumption that baseline to follow-up correlation was 0.7. For the 2 variables HbA1c% and triglycerides, analyses repeated using correlation of first 0.9 and then 0.5 led to no appreciable difference in results.

In initial models, which ranged between 9 and 18 RCTs (or RCT subgroups) per outcome, we were unable to reject the null hypothesis for any pooled effect; sensitivity analysis did not indicate any change. Confidence that the pooled estimated effect reflects the true effect ranged from very low to moderate (Table 4; justifications in Table 5 [available at www.jandonline.org); the most common reason for decreased confidence was due to risk of bias in individual studies, statistical heterogeneity, and some imprecision.

Subgroup analysis by type of grain found that whole-grain oats significantly decreased total cholesterol (SMD = −0.54, 95% CI −0.95 to −0.12, re-expressed as −20.8 mg/dL [−0.54 mmol/L]; $P = 0.011$, n = 232; IG: n = 122, CG: n = 110, $I^2 = 56.9\%$, GRADE level of evidence: Very low; Figure 5) and low-density lipoprotein (LDL) cholesterol (SMD = −0.57, 95% CI −0.84 to −0.31, re-expressed as −16.7 mg/dL [−0.43 mmol/L]; $P < 0.0001$, n = 232 [IG: n = 122, CG: n = 110], $I^2 = 0\%$; GRADE level of evidence: Very low) (Figure 6) compared to refined grains. SDs of baseline total and LDL cholesterol in the intervention group reported by Pins and colleagues[58] were used to re-express SMD to mg/dL for clinical interpretation. Compared to white rice, brown rice decreased triglycerides (SMD = −0.22, 95% CI −0.44 to −0.01, re-expressed as −1.6 mg/dL [−0.02 mmol/L]; $P = 0.040$, n = 338 [IG: n = 171, CG: n = 167], $I^2 = 0\%$, GRADE level of evidence: Very low). The triglyceride SD from the IG in Araki and colleagues[49] was used to re-express SMD to mg/dL.

Subgroup analysis found that mixed whole grains decreased (ie, negative direction) high-density lipoprotein (HDL) cholesterol in comparison to mixed refined grains (SMD = −0.17, 95%

Group by Grain	Study name	Statistics for each study		
		Std diff in means	Standard error	p-Value
mixed	Giacco 2013	0.09	0.18	0.623
mixed	Kirwan 2016	-0.23	0.25	0.349
mixed	Kondo 2017	-0.42	0.38	0.269
mixed	Kristensen 2017	-0.08	0.15	0.621
mixed	Roager 2019	-0.27	0.20	0.177
mixed		-0.11	0.09	0.206
oats	Maki 2010	-0.35	0.17	0.039
oats	Pins 2002	-0.77	0.22	0.000
oats		-0.54	0.21	0.011
rice	Araki 2017	0.31	0.33	0.352
rice	Shimabukuro 2014 per1	-0.77	0.28	0.006
rice	Shimabukuro 2014 per2	0.58	0.28	0.036
rice	Zhang 2011	0.27	0.14	0.067
rice		0.10	0.27	0.700
wheat	Kikuchi 2018	-0.18	0.29	0.530
wheat	Kristensen 2012	-0.38	0.24	0.113
wheat	Schutte 2018	0.00	0.28	1.000
wheat	Tighe 2010	0.47	0.17	0.006
wheat	Vitaglione 2015	-0.09	0.24	0.696
wheat		-0.01	0.17	0.960
Overall		-0.13	0.07	0.072



Total cholesterol

Figure 5. Whole-grain oats compared with refined mixed grains had a significant effect on total cholesterol (standardized mean difference = −0.54, 95% CI −0.95 to −0.12; I^2 = 56.9%, P = 0.011) when pooling results of 2 randomized controlled trials during subgroup analysis by grain type. Std diff = standard difference.

CI −0.33 to −0.01, re-expressed as −2.0 mg/dL [−0.06 mmol/L]; P = 0.037, n = 590 [IG: n = 292, CG: n = 298], I^2 = 0%, GRADE level of evidence: High). However, in moderate-quality studies (ie, unclear risk of bias), whole grains improved HDL cholesterol (SMD = 0.33, 95% CI 0.05 to 0.62, re-expressed as 3 mg/dL [0.08 mmol/L]; P = 0.022, n = 490 [IG: n = 255, CG: n = 235], I^2 = 5.1%, GRADE level of evidence: Low) compared to refined grains. To re-express HDL cholesterol SMDs into a clinically interpretable value, SDs from Giacco and colleagues[30] and Pins and colleagues[58] were used.

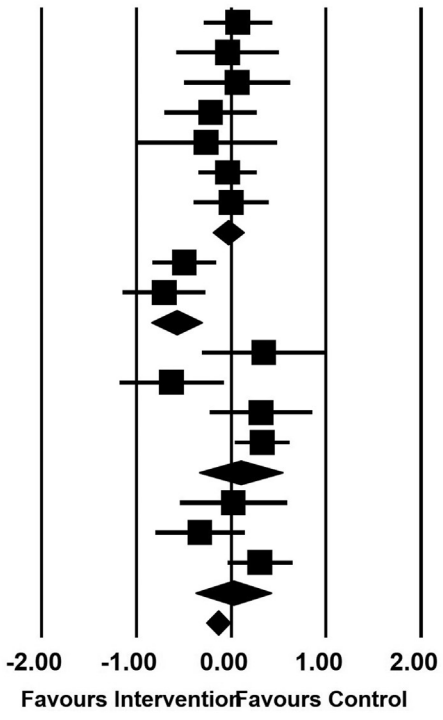
Further subgroup analysis by study quality found that in higher-quality studies (ie, low risk of bias), whole grains improved CRP (SMD = −0.22, 95% CI −0.44 to −0.00, re-expressed as −0.7 mg/L; P = 0.048, n = 671 [IG: n = 311, CG: n = 360], I^2 = 45.7%, GRADE level of evidence: Moderate); and decreased HbA1c (SMD = −0.33, 95% CI −0.61 to 0.04, re-expressed as −0.2%; P = 0.025, n = 194 [IG: n = 97, CG: n = 97], I^2 = 0%, GRADE level of evidence: Moderate). CRP and HbA1c SDs from the IG reported by Kirwan and colleagues[33] were used to re-express the CRP and HbA1c SMD for clinical interpretation. No other subgroup analyses found significant findings; however, study samples that had CVD risk factors approach a significant decrease in triglycerides (SMD = −0.13, 95% CI −0.23 to 0.03; P = 0.065, n = 10 studies).

The nonparametric bootstrapped meta-analyses were HbA1c SMD = −0.27 (95% CI −0.44 to 0.39), for CRP/high-sensitivity CRP SMD = −0.25 (95% CI −0.45 to 0.25), and waist circumference SMD = −0.10 (95% CI −0.21 to 0.08).

DISCUSSION

The benefits of consuming whole grains to human health are well established, due to their nutrient and antioxidant profile and strong association with improved chronic disease outcomes, including reduced type 2 diabetes mellitus and gastrointestinal cancer risk.[1,2,9] Despite the dose−response relationship for decreased risk of CVD-related death reported by meta-analyses of observational data,[11,13] the current review of RCTs found insufficient evidence to conclude that dietary intake of whole grains has a clinically relevant effect on CVD risk factors in comparison to refined grains. Although this review's meta-analytical models found some improvements in triglycerides, HbA1c, and CRP, there was very low to moderate confidence in the body of evidence, and the re-expressed effect sizes have no clinical significance. Whole-grain oats had clinically relevant improvements on LDL and total cholesterol, aligning with other literature,[61] but had very low confidence that this estimated effect represented the true effect.

Group by Grain	Study name	Statistics for each study		
		Std diff in means	Standard error	p-Value
mixed	Giacco 2013	0.07	0.18	0.693
mixed	Giacco 2014	-0.04	0.27	0.886
mixed	Harris Jackson 2014	0.06	0.28	0.819
mixed	Kirwan 2016	-0.22	0.25	0.377
mixed	Kondo 2017	-0.26	0.38	0.488
mixed	Kristensen 2017	-0.04	0.15	0.807
mixed	Roager 2019	0.00	0.20	1.000
mixed		-0.03	0.08	0.709
oats	Maki 2010	-0.50	0.17	0.003
oats	Pins 2002	-0.71	0.22	0.001
oats		-0.57	0.13	0.000
rice	Araki 2017	0.34	0.33	0.300
rice	Shimabukuro 2014 per1	-0.63	0.28	0.025
rice	Shimabukuro 2014 per2	0.32	0.27	0.250
rice	Zhang 2011	0.33	0.14	0.025
rice		0.10	0.22	0.648
wheat	Kikuchi 2018	0.02	0.29	0.938
wheat	Kristensen 2012	-0.33	0.24	0.165
wheat	Tighe 2010	0.30	0.17	0.078
wheat		0.02	0.20	0.906
Overall		-0.14	0.06	0.032



LDL cholesterol

Figure 6. Whole-grain oats compared with mixed refined grains had a significant effect on low-density lipoprotein cholesterol (standardized mean difference = −0.57, 95% CI −0.84 to −0.31; $P < 0.0001$, n = 232 [intervention group: n = 122, control group: n = 110], $I^2 = 0\%$) when pooling results of 2 randomized controlled trials during subgroup analysis by grain type. LDL = low-density lipoprotein; Std diff = standard difference.

Unexpectedly, there was high confidence that mixed whole grains had a small (re-expressed as −2.0 mg/dL) but significant decrease in cardioprotective HDL cholesterol compared to refined grains. HDL cholesterol is predominately regulated through hepatic synthesis and cholesterol ester transfer protein activity, which replaces cholesterol esters in HDL particles with triglycerides. Triglyceride-rich HDL particles are substrates for hepatic lipase, which promotes HDL cholesterol clearance.[62] There was no effect of mixed grains on triglyceride levels, suggesting that an effect on cholesterol ester transfer protein activity does not explain the observed difference in HDL cholesterol. Most mixed-grain studies used wheat, rye, rice, and/or oats, and 2 studies included barley. However, oats, rice, and wheat did not show any independent effects on HDL cholesterol in the meta-analysis and are unlikely to explain this effect. Conversely, the subgroup by study design meta-analysis found that studies with an unclear risk of bias, which represented RCTs using mixed, rice, barley, and wheat test products, significantly increased HDL cholesterol with a similar effect size (3 mg/dL). However, this finding should be rejected as relevant in the light that the positive estimated effect had a low confidence and the studies with low risk of bias found no significant effect. Given the unclear mechanism of action, this finding should be interpreted with caution.

The present findings align with those reported by Kelly and colleagues,[15] who reviewed 9 whole-grain RCTs with durations of ≥12 weeks, in that the included studies have inherent limitations and findings may be subject to change with additional research. This is particularly the case among those with existing CVD, as the study populations in this review were predominantly healthy or had only mild-to-moderate CVD risk factors. Having relatively healthy samples may explain both the finding of no overall pooled effect of whole grains compared to refined grains on CVD risk factors, as well as the finding that some subgroup improvement CVD risk factors were of statistical but not clinical significance. For example, it is unlikely that an improvement in CRP, systolic blood pressure, or HbA1C would occur among those who do not have elevated CRP, systolic blood pressure, or HbA1C at baseline. Similarly, the systematic review and meta-analysis by Hollænder and colleagues,[63] which evaluated the effect of whole grains on blood lipids in healthy populations only, found no significant pooled effects of whole grains, except for the β-glucan–containing subgroups. Although some studies measured adherence to the allocated groups objectively through plasma alkylresorcinol, many RCTs did not measure adherence to the intervention and/or

control and dietary intake could have possibly been too low to detect a significant change in CVD risk factors. Interpretation of findings is substantially limited by the poor reporting of whole-grain daily dose; where doses of both intervention and test products are not able to be determined. Few studies reported whole-grain intake as dose per day as recommended by Ross and colleagues.[64] Other limitations include poorly reported dosage of refined grains, inadequately controlled and/or measured background diet, and the possibility of underpowered models due to the small number of included studies in each model, particularly in subgroups.

Differences between meta-analyses of RCTs and prospective cohort studies on whole grain and CVD must also be acknowledged. Pooled data from prospective cohort studies are derived from participants who have been following a dietary pattern either rich or poor in whole grains for many years, and sometimes decades,[11,13] and the potential for whole grains to have a preventive and/or treatment effect is increased. This contrasts with the identified interventional research, which is limited by study duration ranging between 2 and 16 weeks. Recalling that diet-related etiologies of chronic disease have long latency periods, it is difficult to detect significant effects in a short timeframe. Considering some subgroups found significant improvements in inflammation, glycemia, and blood lipids, it is possible that with an increased intervention duration and investigations targeted at those with elevated risk factors, improvements in CVD incidence and death may be observed. Additional research is required to confirm this hypothesis. The importance of intervention duration is emphasized by the types of outcomes measured in prospective cohort studies, which include CVD-related death and events, including myocardial infarctions and strokes.[11,13] This is in contrast with RCTs that are limited to measuring CVD risk markers, and thus, indirect CVD outcomes.

Despite attempts to control for confounding variables in observational data, the improved CVD outcomes in the meta-analyses of observational data may represent the effects of broader dietary and lifestyle patterns. Participants in cohort studies who reported consuming whole grains as opposed to refined grains may be those who adhere to a healthier lifestyle; and over many years this lifestyle presents multiple confounding factors that are inherently difficult to measure and account for.[65] The finding that some refined-grain arms of RCTs had higher attrition than the whole-grain arms also suggests that low whole-grain consumers in observational studies may not necessarily be high refined-grain consumers. In observational research, it is possible that low whole-grain consumers replace whole grains with discretionary foods rather than refined-grain core foods, thereby creating a greater discrepancy in the diet quality of the 2 groups, leading to a greater observed effect size in high whole-grain consumers. It must be remembered that grains are recommended by dietary guidelines as a core food group; although guidelines recommend they be consumed mostly as whole grains and/or higher-fiber varieties, refined grains are not considered discretionary foods.[1,6,7]

Of clinical significance, the RCTs in this review reported that participants had either equal or lower attrition in the whole-grain group, as well as high compliance to the whole-grain intervention when measured by plasma alkylresorcinol. This suggests that dietary intake of whole grains is a feasible dietary strategy in culturally diverse populations and strengthens the need to test other types of grains that are important to certain cultural groups in RCTs.

GRADE Clinical Recommendation for Populations

A conditional recommendation was made for the intervention: For adults with or without CVD risk factors, the findings of this review conditionally recommend whole grains for improved CVD risk based on very weak to moderate evidence. In line with the GRADE approach, this conditional recommendation is subject to change with new evidence.

This recommendation was based on the balance of beneficial effects, which tended toward the intervention and is strengthened by observational and economic research (Figure 7, available at www.jandonline.org).[11,13,14,66] However, due to inherent limitations and risk of bias found in the interventional research, even when drawing upon other research, a strong recommendation cannot yet be made. There is no uncertainty that prevention of CVD is valued by all stakeholders and is feasible to implement, considering grains are a staple food to many cultures and countries, and dietary guidelines already recommend that grains be consumed as whole grains. Healthy food basket research suggests that whole-grain foods may be unavailable to some small communities and may be associated with a higher cost, which is likely to impact low-income families[71] (Figure 7, available at www.jandonline.org).

Limitations of This Review

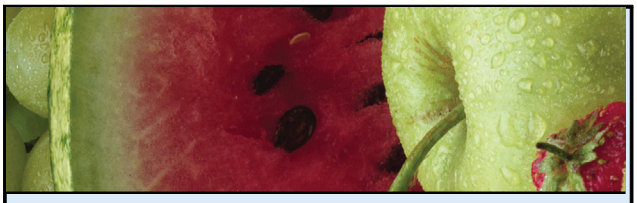
Although eligibility criteria included 40 broad outcomes related to CVD risk, outcomes such as short-chain fatty acids or metabolites of the gut microbiome were beyond the capacity of this review. The review was not able to evaluate the effect of whole grains on CVD outcomes; and it should be highlighted that all outcomes reported are indirect measures of CVD risk only. It was beyond the scope of this review to examine a dose–response relationship through meta-regression. Finally, although funnel plots did not detect publication bias, this may have been due to the small number of included studies in each model.

Implications for Future Research

The effect of whole-grain intake on CVD is of high interest to both the people and to governments, as CVD is the leading cause of noncommunicable disease deaths worldwide.[75] Future RCTs are required that compare whole grain with refined grain for all grain and pseudo-grain varieties, especially rye, maize, teff, amaranth, triticale, or unique varieties of wheat, such as kamut or spelt. Future RCTs need to be well powered and use parallel design to allow for substantially longer intervention durations, such as that used in the PREDIMED (Prevención con Dieta Mediterránea) trial.[76] In addition, whole-grain products should be tested for the potential to improve both CVD risk factors and events in samples with existing CVD at baseline. Studies should control and/or measure background diet and medications carefully so that the effect of the whole grain as opposed to other diet and lifestyle factors can be understood. The dosage of whole-grain intake should be reported in grams per day, as recommended by Ross and colleagues.[64] Finally, CVD-related outcomes should be accompanied by feasibility evaluations to better inform dietary guidelines and public health policy.

CONCLUSIONS

For adults with or without CVD risk factors, consuming whole grain as opposed to refined grain may improve total cholesterol, LDL cholesterol, HbA1c, and CRP. However, there is insufficient interventional evidence to recommend the use of whole grains as opposed to refined grains for the prevention and treatment of CVD. Further interventional research is needed to better understand the preventive and treatment potential of whole-grain and whole pseudo-grain dietary intake for CVD, particularly among those with existing CVD risk factors.



PRACTICE IMPLICATIONS

• What Is the Current Knowledge on the Topic?

Whole grains have a higher nutrient density than refined grains, and observational studies have identified an association between whole-grain intake and improved CVD risk.

• How Does this Research Add to Knowledge on this Topic?

This systematic review of RCTs examines the cause-and-effect relationship between whole-grain intake and CVD risk.

• How Might this Knowledge Impact Current Dietetics Practice?

Choosing whole grains is recommended for populations to improve CVD risk, but evidence is not convincing enough to use whole grains as a CVD treatment approach.

References

1. *Australian Dietary Guidelines*. Canberra: National Health and Medical Research Council, Australian Government; 2013.
2. McRae MP. Health benefits of dietary whole grains: An umbrella review of meta-analyses. *J Chiropr Med*. 2017;16(1):10-18.
3. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: A series of systematic reviews and meta-analyses. *Lancet*. 2019;393(10170):434-445.
4. Van Der Kamp JW, Poutanen K, Seal CJ, Richardson DP. The HEALTHGRAIN definition of "whole grain." *Food Nutr Res*. 2014;58(1):22100.
5. Arterburn D, Flum D, Westbrook E, et al. A population-based, shared decision-making approach to recruit for a randomized trial of bariatric surgery versus lifestyle for type 2 diabetes. *Surg Obes Relat Dis*. 2013;9(6):837-844.
6. 2015 Intergenerational Report. Commonwealth of Australia. Published March 2015. Accessed July 8, 2020, https://treasury.gov.au/sites/default/files/2019-03/2015_IGR.pdf.
7. The Eatwell Guide. Public Health England. Published 2016. Accessed July 8, 2020, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/742750/Eatwell_Guide_booklet_2018v4.pdf.
8. Australian Food Composition Database. Food Standards Australia New Zealand. https://www.foodstandards.gov.au/science/monitoringnutrients/afcd/Pages/default.aspx.
9. Liu RH. Whole grain phytochemicals and health. *J Cereal Sci*. 2007;46(3):207-219.
10. Mendis S, Puska P, Norrving B, eds. *Global Atlas on Cardiovascular Disease Prevention and Control*. Geneva: World Health Organization; 2011.
11. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: Systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016;353:i2716.
12. Zhang B, Zhao Q, Guo W, Bao W, Wang X. Association of whole grain intake with all-cause, cardiovascular, and cancer mortality: A systematic review and dose–response meta-analysis from prospective cohort studies. *Eur J Clin Nutr*. 2018;72(1):57.
13. Wei H, Gao Z, Liang R, Li Z, Hao H, Liu X. Whole-grain consumption and the risk of all-cause, CVD and cancer mortality: A meta-analysis of prospective cohort studies. *Br J Nutr*. 2016;116(3):514-525.
14. Chen GC, Tong X, Xu JY, et al. Whole-grain intake and total, cardiovascular, and cancer mortality: A systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2016;104(1):164-172.
15. Kelly SA, Hartley L, Loveman E, et al. Whole grain cereals for the primary or secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2017;8(8):CD005051.
16. Baretta D, Nardino M, Carvalho IR, et al. Estimates of genetic parameters and genotypic values prediction in maize landrace populations by REML/BLUP procedure. *Genet Mol Res*. 2017;16(2).
17. *Covidence Systematic Review Software* [computer program]. Melbourne, Australia: Veritas Health Innovation. Accessed 2019.
18. Marshall S, Poetocz P, Duve E, et al. Systematic review data of whole grains versus placebo or refined grains on cardiovascular disease risk factors. Dryad. 2000. https://doi.org/10.5061/dryad.n2z34tmth
19. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
20. Handbook for Grading the Quality of Evidence and the Strength of Recommendations Using the GRADE approach. Updated October 2013. Accessed January 15, 2019. http://gdt.guidelinedevelopment.org
21. *GRADEpro GDT: GRADEpro Guideline Development Tool* [computer program]. Hamilton, ON, Canada: McMaster University; 2015.
22. Borenstein M, Hedges VL, Higgins JPT, et al. *Comprehensive Meta-Analysis* [computer program]. Version 2. Englewood, NJ: Biostat; 2006.
23. Study summaries using more than one patient-reported outcome. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. Updated March 2011. Accessed July 8, 2020. www.cochrane-handbook.org
24. Re-expressing SMD using a familiar instrument. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. Updated March 2011. Accessed July 8, 2020. www.cochrane-handbook.org
25. *metafor: A Meta-Analysis Package for R* [computer program]. Version 2.1-0. Vienna, Austria: R Foundation for Statistical Computing; 2019.
26. *Bootstrap Functions* [computer program]. Version 1.3-23. Vienna, Austria: R Foundation for Statistical Computing; 2019.
27. *R: A Language and Environment for Statistical Computing* [computer program]. Version 3.6.1. Vienna, Austria: R Foundation for Statistical Computing; 2019. Accessed July 1, 2020. http://www.R-project.org/
28. Viechtbauer W. Bootstrapping with meta-analytic models. Accessed January 20, 2019, http://www.metafor-project.org/doku.php/tips:bootstrapping_with_ma.
29. Van Den Noortgate W, Onghena P. Parametric and nonparametric bootstrap methods for meta-analysis. *Behav Res Methods*. 2005;37(1):11-22.
30. Giacco R, Costabile G, Della Pepa G, et al. A whole-grain cereal-based diet lowers postprandial plasma insulin and triglyceride levels in individuals with metabolic syndrome. *Nutr Metab Cardiovasc Dis*. 2014;24(8):837-844.
31. Giacco R, Lappi J, Costabile G, et al. Effects of rye and whole wheat versus refined cereal foods on metabolic risk factors: A randomised controlled two-centre intervention study. *Clin Nutr*. 2013;32(6):941-949.
32. Vetrani C, Costabile G, Luongo D, et al. Effects of whole-grain cereal foods on plasma short chain fatty acid concentrations in individuals with the metabolic syndrome. *Nutrition*. 2016;32(2):217-221.
33. Kirwan JP, Malin SK, Scelsi AR, et al. A whole-grain diet reduces cardiovascular risk factors in overweight and obese adults: A randomized controlled trial. *J Nutr*. 2016;146(11):2244-2251.

34. Malin SK, Kullman EL, Scelsi AR, et al. A whole-grain diet reduces peripheral insulin resistance and improves glucose kinetics in obese adults: A randomized-controlled trial. *Metabolism*. 2018;82:111-117.

35. Malin SK, Kullman EL, Scelsi AR, Godin JP, Ross AB, Kirwan JP. A whole-grain diet increases glucose-stimulated insulin secretion independent of gut hormones in adults at risk for type 2 diabetes. *Mol Nutr Food Res*. 2019;63(7):1800967.

36. Ampatzoglou A, Williams C, Atwal K, et al. Effects of increased whole-grain consumption on immune and inflammatory markers in healthy low habitual wholegrain consumers. *Eur J Nutr*. 2016;55(1):183-195.

37. Enright L, Slavin J. No effect of 14 day consumption of whole grain diet compared to refined grain diet on antioxidant measures in healthy, young subjects: A pilot study. *Nutr J*. 2010;9:12.

38. Giacco R, Clemente G, Cipriano D, et al. Effects of the regular consumption of wholemeal wheat foods on cardiovascular risk factors in healthy people. *Nutr Metab Cardiovasc Dis*. 2010;20(3):186-194.

39. Harris Jackson K, West SG, Vanden Heuvel JP, et al. Effects of whole and refined grains in a weight-loss diet on markers of metabolic syndrome in individuals with increased waist circumference: A randomized controlled-feeding trial. *Am J Clin Nutr*. 2014;100(2):577-586.

40. Kazemzadeh M, Safavi SM, Nematollahi S, Nourieh Z. Effect of brown rice consumption on inflammatory marker and cardiovascular risk factors among overweight and obese non-menopausal female adults. *Int J Prev Med*. 2014;5(4):478-488.

41. Kikuchi Y, Nozaki S, Makita M, et al. Effects of whole grain wheat bread on visceral fat obesity in Japanese subjects: A randomized double-blind study. *Plant Foods Hum Nutr*. 2018;73(3):161-165.

42. Kondo K, Morino K, Nishio Y, et al. Fiber-rich diet with brown rice improves endothelial function in type 2 diabetes mellitus: A randomized controlled trial. *PLoS One*. 2017;12(6):16.

43. Nieman DC, Cayea EJ, Austin MD, Henson DA, McAnulty SR, Jin F. Chia seed does not promote weight loss or alter disease risk factors in overweight adults. *Nutr Res*. 2009;29(6):414-418.

44. Roager HM, Vogt JK, Kristensen M, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: A randomised cross-over trial. *Gut*. 2019;68(1):83-93.

45. Schutte S, Esser D, Hoevenaars FPM, et al. A 12-wk whole-grain wheat intervention protects against hepatic fat: The Graandioos study, a randomized trial in overweight subjects. *Am J Clin Nutr*. 2018;108(6):1264-1274.

46. Vanegas SM, Meydani M, Barnett JB, et al. Substituting whole grains for refined grains in a 6-wk randomized trial has a modest effect on gut microbiota and immune and inflammatory markers of healthy adults. *Am J Clin Nutr*. 2017;105(3):635-650.

47. Vitaglione P, Mennella I, Ferracane R, et al. Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: Role of polyphenols bound to cereal dietary fiber. *Am J Clin Nutr*. 2015;101(2):251-261.

48. Zhang G, Pan A, Zong G, et al. Substituting white rice with brown rice for 16 weeks does not substantially affect metabolic risk factors in middle-aged chinese men and women with diabetes or a high risk for diabetes. *J Nutr*. 2011;141(9):1685-1690.

49. Araki R, Ushio R, Fujie K, et al. Effect of partially-abraded brown rice consumption on body weight and the indicators of glucose and lipid metabolism in pre-diabetic adults: A randomized controlled trial. *Clin Nutr*. 2017;19:9-15.

50. Kristensen M, Pelletier X, Ross AB, Thielecke F. A high rate of non-compliance confounds the study of whole grains and weight maintenance in a randomised intervention trial—The case for greater use of dietary biomarkers in nutrition intervention studies. *Nutrients*. 2017;9(1):55.

51. Maki KC, Beiseigel JM, Jonnalagadda SS, et al. Whole-grain ready-to-eat oat cereal, as part of a dietary program for weight loss, reduces low-density lipoprotein cholesterol in adults with overweight and obesity more than a dietary program including low-fiber control foods. *J Acad Nutr Diet*. 2010;110(2):205-214.

52. Nakayama T, Nagai Y, Uehara Y, et al. Eating glutinous brown rice twice a day for 8 weeks improves glycemic control in Japanese patients with diabetes mellitus. *Nutr Diabetes*. 2017;7(5):e273.

53. Shimabukuro M, Higa M, Kinjo R, et al. Effects of the brown rice diet on visceral obesity and endothelial function: The BRAVO study. *Br J Nutr*. 2014;111(2):310-320.

54. Andersson A, Tengblad S, Karlstrom B, et al. Whole-grain foods do not affect insulin sensitivity or markers of lipid peroxidation and inflammation in healthy, moderately overweight subjects. *J Nutr*. 2007;137(6):1401-1407.

55. Kristensen M, Toubro S, Jensen MG, et al. Whole grain compared with refined wheat decreases the percentage of body fat following a 12-week, energy-restricted dietary intervention in postmenopausal women. *J Nutr*. 2012;142(4):710-716.

56. Kim JY, Kim JH, Lee DH, Kim SH, Lee SS. Meal replacement with mixed rice is more effective than white rice in weight control, while improving antioxidant enzyme activity in obese women. *Nutr Res*. 2008;28(2):66-71.

57. Pick ME, Hawrysh ZJ, Gee MI, Toth E. Barley bread products improve glycemic control of type 2 subjects. *Int J Food Sci Nutr*. 1998;49(1):71-78.

58. Pins JJ, Geleva D, Keenan JM, Frazel C, O'Connor PJ, Cherney LM. Do whole-grain oat cereals reduce the need for antihypertensive medications and improve blood pressure control? *J Fam Pract*. 2002;51(4):353-359.

59. Tighe P, Duthie G, Brittenden J, et al. Effects of wheat and oat-based whole grain foods on serum lipoprotein size and distribution in overweight middle aged people: A randomised controlled trial. *PLoS One*. 2013;8(8). 2013;e70436.

60. Tighe P, Duthie G, Vaughan N, et al. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: A randomized controlled trial. *Am J Clin Nutr*. 2010;92(4):733-740.

61. Ho HV, Sievenpiper JL, Zurbau A, et al. The effect of oat β-glucan on LDL-cholesterol, non-HDL-cholesterol and apoB for CVD risk reduction: A systematic review and meta-analysis of randomised-controlled trials. *Br J Nutr*. 2016;116(8):1369-1382.

62. Zhou L, Li C, Gao L, Wang A. High-density lipoprotein synthesis and metabolism. *Mol Med Rep*. 2015;12(3):4015-4021.

63. Hollænder PL, Ross AB, Kristensen M. Whole-grain and blood lipid changes in apparently healthy adults: A systematic review and meta-analysis of randomized controlled studies. *Am J Clin Nutr*. 2015;102(3):556-572.

64. Ross AB, Kristensen M, Seal CJ, Jacques P, McKeown NM. Recommendations for reporting whole-grain intake in observational and intervention studies. *Am J Clin Nutr*. 2015;101(5):903-907.

65. McEvoy CT, Temple N, Woodside JV. Vegetarian diets, low-meat diets and health: A review. *Public Health Nutr*. 2012;15(12):2287-2294.

66. Rahkovsky I, Gregory CA. Food prices and blood cholesterol. *Econ Hum Biol*. 2013;11(1):95-107.

67. World Health Organization. Top 10 causes of death. Published May 24, 2018. Accessed July 9, 2020, https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

68. Ryan M, Farrelly M. Living with an unfixable heart: A qualitative study exploring the experience of living with advanced heart failure. *Eur J Cardiovasc Nurs*. 2009;8(3):223-231.

69. Davidson PM, Daly J, Leung D, et al. Health-seeking beliefs of cardiovascular patients: a qualitative study. *Int J Nurs Stud*. 2011;48(11):1367-1375.

70. Mancino L, Kuchler F, Leibtag E. Getting consumers to eat more whole-grains: The role of policy, information, and food manufacturers. *Food Policy*. 2008;33:489-496.

71. Jetter KM, Cassady DL. The availability and cost of healthier food alternatives. *Am J Prev Med*. 2006;30(1):38-44.

72. Barton P, Andronis L, Briggs A, McPherson K, Capewell S. Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modelling study. Version 2. *BMJ*. 2011;343:d4044.

73. Brunner E, Cohen D, Toon L. Cost effectiveness of cardiovascular disease prevention strategies: a perspective on EU food based dietary guidelines. *Public Health Nutr*. 2001;4(2B):711-715.

74. World Health Organization. Global Health Observatory (GHO) data. NCD mortality and morbidity. https://www.who.int/gho/ncd/mortality_morbidity/en/. Accessed July 9, 2020.

75. World Health Organization. *Global Status Report on Noncommunicable Diseases*. Geneva: World Health Organization; 2014.

76. Martínez-González MÁ, Corella D, Salas-Salvadó J, et al. Cohort profile: Design and methods of the PREDIMED study. *Int J Epidemiol*. 2010;41(2):377-385.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

Grains & Legumes Nutrition Council of Australia provided critical revision and feedback on the proposed review methodology; but had no contribution to the analysis or interpretation of results. All authors declare no existing or potential conflicts of interest.

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AUTHOR CONTRIBUTIONS

F. Fayet-Moore, S. Marshall, and T. Cassettari designed the research; S. Marshall, K. Abbott, and E. Duve conducted the research; S. Marshall and P. Petocz analyzed the data; S. Marshall drafted the manuscript and led the GRADE assessment and clinical guideline; M. Blumfield contributed to the GRADE assessment; T. Cassettari, M. Blumfield, K. Abbott, E. Duve contributed to the GRADE clinical guideline; all authors critically appraised the manuscript. All authors have read and approved the manuscript.

Set	Search terms
	MEDLINE (via PubMed): Searched March 8, 2019 using keywords (title and abstract) and MeSH[a] terms. Result = 2,437 records
#1	(((clinical trial[MeSH Terms]) OR (("clinical trial"[Title/Abstract] OR "controlled trial"[Title/Abstract] OR "equivalence trial"[Title/Abstract] OR intervention[Title/Abstract] OR "cross-over"[Title/Abstract] OR randomized[Title/Abstract] OR randomized[Title/Abstract] OR "control trial"[Title/Abstract] OR placebo[Title/Abstract]))))) AND ((((("edible grain"[Title/Abstract] OR secale[Title/Abstract] OR triticale[Title/Abstract] OR triticum[Title/Abstract] OR avena [Title/Abstract] OR "setaria plant"[Title/Abstract] OR hordeum[Title/Abstract] OR oryza[Title/Abstract] OR "zea mays"[Title/Abstract] OR eragrostis[Title/Abstract] OR teff[Title/Abstract] OR sorghum[Title/Abstract] OR johnsongrass[Title/Abstract] OR "kaffir corn"[Title/Abstract] OR kafir[Title/Abstract] OR sudangrass[Title/Abstract] OR triticale[Title/Abstract] OR triticosecale[Title/Abstract] OR triticum[Title/Abstract] OR Fagopyrum[Title/Abstract] OR buckwheat[Title/Abstract] OR celosia[Title/Abstract] OR durum[Title/Abstract] OR rye[Title/Abstract] OR barley [Title/Abstract] OR maize[Title/Abstract] OR teosinte[Title/Abstract] OR zea[Title/Abstract] OR cereal*[Title/ Abstract] OR grain*[Title/Abstract] OR *grain[Title/Abstract] OR *germ[Title/Abstract] OR *bran[Title/Abstract] OR endosperm[Title/Abstract] OR wholegrain*[Title/Abstract] OR wholemeal[Title/Abstract] OR wheat[Title/Abstract] OR oat[Title/Abstract] OR oats[Title/Abstract] OR millet[Title/Abstract] OR setaria[Title/Abstract] OR panicum[Title/ Abstract] OR rice[Title/Abstract] OR corn[Title/Abstract] OR flour[Title/Abstract] OR semolina[Title/Abstract] OR bulgar[Title/Abstract] OR groats[Title/Abstract] OR bread[Title/Abstract] OR porridge[Title/Abstract] OR cracker [Title/Abstract] OR biscuit[Title/Abstract] OR muesli[Title/Abstract] OR pancake*[Title/Abstract] OR pasta[Title/ Abstract] OR noodle*[Title/Abstract] OR polenta[Title/Abstract] OR muffin*[Title/Abstract] OR roll[Title/Abstract] OR dough[Title/Abstract] OR durum[Title/Abstract] OR spelt[Title/Abstract] OR spelta[Title/Abstract] OR emmer[Title/ Abstract] OR dicoccon[Title/Abstract] OR khorasan[Title/Abstract] OR turanicum[Title/Abstract] OR einkorn[Title/ Abstract] OR monococcum[Title/Abstract] OR "hard red spring"[Title/Abstract] OR "hard red winter"[Title/Abstract] OR "soft red winter"[Title/Abstract] OR "hard white"[Title/Abstract] OR "soft white"[Title/Abstract] OR teff[Title/ Abstract] OR eragrostis[Title/Abstract] OR "Williams lovegrass"[Title/Abstract] OR "annual bunch grass"[Title/ Abstract] OR pumpernickel[Title/Abstract] OR Fagopyrum[Title/Abstract] OR quinoa[Title/Abstract] OR amaranth* [Title/Abstract] OR chia[Title/Abstract] OR chiaseed[Title/Abstract] OR granola[Title/Abstract] OR tortilla*[Title/ Abstract] OR "maya nut"[Title/Abstract] OR *bread[Title/Abstract] OR colosia[Title/Abstract] OR cockscomb[Title/ Abstract] OR "quail grass"[Title/Abstract] OR soko[Title/Abstract] OR "pitseed goosefoot"[Title/Abstract] OR berlandieri[Title/Abstract] OR kaniwa[Title/Abstract] OR "Chenopodium pallidicaule"[Title/Abstract] OR canihua [Title/Abstract] OR qaniwa[Title/Abstract] OR wattleseed[Title/Abstract] OR "acacia seed"[Title/Abstract] OR "wattle seed"[Title/Abstract] OR kamut[Title/Abstract] OR Fagopyrum[Title/Abstract]))) AND (((((((edible grain[MeSH Terms]) OR secale[MeSH Terms]) OR ((((((((((triticale[MeSH Terms]) OR triticum[MeSH Terms]) OR flour[MeSH Terms]) OR bread[MeSH Terms]) OR avena[MeSH Terms]) OR setaria plant[MeSH Terms]) OR hordeum[MeSH Terms]) OR oryza[MeSH Terms]) OR zea mays[MeSH Terms]) OR eragrostis[MeSH Terms])) OR ((((((((((teff[MeSH Terms]) OR sorghum[MeSH Terms]) OR johnsongrass[MeSH Terms]) OR kaffir corn[MeSH Terms]) OR kafir[MeSH Terms]) OR sorghum bicolor[MeSH Terms]) OR sorghum halepense[MeSH Terms]) OR sudangrass[MeSH Terms]) OR triticale[MeSH Terms]) OR triticosecale[MeSH Terms])) OR (((((((triticum x secale[MeSH Terms]) OR Fagopyrum [MeSH Terms]) OR Fagopyrum esculentum[MeSH Terms]) OR Fagopyrum sagittatum[MeSH Terms]) OR Fagopyrum tataricum[MeSH Terms]) OR buckwheat[MeSH Terms]) OR Chenopodium quinoa[MeSH Terms])) OR ((((((((quinoa [MeSH Terms]) OR amaranthus[MeSH Terms]) OR celosia[MeSH Terms]) OR durum wheat[MeSH Terms]) OR triticum aestivum[MeSH Terms]) OR triticum durum[MeSH Terms]) OR triticum spelta[MeSH Terms]) OR triticum turgidum[MeSH Terms])) OR ((((((((((((((((triticum turgidum subsp. Durum[MeSH Terms]) OR triticum vulgare[MeSH Terms]) OR wheat[MeSH Terms]) OR rye[MeSH Terms]) OR secale cereale[MeSH Terms]) OR barley[MeSH Terms]) OR hordeum vulgare[MeSH Terms]) OR oats[MeSH Terms]) OR cultivated oat[MeSH Terms]) OR avena sativa[MeSH Terms]) OR rice[MeSH Terms]) OR oryza sativa[MeSH Terms]) OR corn[MeSH Terms]) OR Indian corn[MeSH Terms]) OR maize[MeSH Terms]) OR teosinte[MeSH Terms]))))

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Figure 2. Search strategy implemented across 5 electronic databases and results of total records retrieved when searching for randomized controlled trials that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans.

Set	Search terms
	CINAHL (via Ebscohost): Searched on March 8, 2019 using keywords (title and abstract) and CINAHL Subject Headings. Result = 3,630 records
#1	(MH "clinical trials+") OR (TI "clinical trial" or "controlled trial" or "equivalence trial" or intervention or "cross-over" or randomized or randomized or "control trial" or placebo) OR (AB "clinical trial" or "controlled trial" or "equivalence trial" or intervention or "cross-over" or randomized or randomized or "control trial" or placebo) AND ((MH "Cereals+") or (MH "barley") or (MH "corn") or (MH "oats") or (MH "rice") or (MH "wheat") or (MH "bread")) OR (TI "edible grain" or secale or triticale or triticum or avena or "setaria plant" or hordeum or oryza or "zea mays" or eragrostis or teff or sorghum or johnsongrass or "kaffir corn" or kafir or sudangrass or triticale or triticosecale or triticum or Fagopyrum or buckwheat or celosia or durum or rye or barley or maize or teosinte or zea or cereal* or grain* or *grain or *germ or *bran or endosperm or wholegrain* or wholemeal or wheat or oat or oats or millet or setaria or panicum or rice or corn or flour or semolina or bulgar or groats or bread or porridge or cracker or biscuit or muesli or pancake* or pasta or noodle* or polenta or muffin* or roll or dough or durum or spelt or spelta or emmer or dicoccon or khorasan or turanicum or einkorn or monococcum or "hard red spring" or "hard red winter" or "soft red winter" or "hard white" or "soft white" or teff or eragrostis or "Williams lovegrass" or "annual bunch grass" or pumpernickel or Fagopyrum or quinoa or amaranth* or chia or chiaseed or granola or tortilla* or "maya nut" or *bread or colosia or cockscomb or "quail grass" or soko or "pitseed goosefoot" or berlandieri or kaniwa or "Chenopodium pallidicaule" or canihua or qaniwa or wattleseed or "acacia seed" or "wattle seed" or kamut or Fagopyrum) OR (AB "edible grain" or secale or triticale or triticum or avena or "setaria plant" or hordeum or oryza or "zea mays" or eragrostis or teff or sorghum or johnsongrass or "kaffir corn" or kafir or sudangrass or triticale or triticosecale or triticum or Fagopyrum or buckwheat or celosia or durum or rye or barley or maize or teosinte or zea or cereal* or grain* or *grain or *germ or *bran or endosperm or wholegrain* or wholemeal or wheat or oat or oats or millet or setaria or panicum or rice or corn or flour or semolina or bulgar or groats or bread or porridge or cracker or biscuit or muesli or pancake* or pasta or noodle* or polenta or muffin* or roll or dough or durum or spelt or spelta or emmer or dicoccon or khorasan or turanicum or einkorn or monococcum or "hard red spring" or "hard red winter" or "soft red winter" or "hard white" or "soft white" or teff or eragrostis or "Williams lovegrass" or "annual bunch grass" or pumpernickel or Fagopyrum or quinoa or amaranth* or chia or chiaseed or granola or tortilla* or "maya nut" or *bread or colosia or cockscomb or "quail grass" or soko or "pitseed goosefoot" or berlandieri or kaniwa or "Chenopodium pallidicaule" or canihua or qaniwa or wattleseed or "acacia seed" or "wattle seed" or kamut or Fagopyrum)
	The Cochrane Library: Searched on March 8, 2019 using keywords and MeSH Headings. Result = 146 "Trials" records
#1	'MeSH descriptor: [Clinical Trials as Topic] explode all trees'
#2	("edible grain" or secale or triticale or triticum or avena or "setaria plant" or hordeum or oryza or "zea mays" or eragrostis or teff or sorghum or johnsongrass or "kaffir corn" or kafir or sudangrass or triticale or triticosecale or triticum or Fagopyrum or buckwheat or celosia or durum or rye or barley or maize or teosinte or zea or cereal* or grain* or *grain or *germ or *bran or endosperm or wholegrain* or wholemeal or wheat or oat or oats or millet or setaria or panicum or rice or corn or flour or semolina or bulgar or groats or bread or porridge or cracker or biscuit or muesli or pancake* or pasta or noodle* or polenta or muffin* or roll or dough or durum or spelt or spelta or emmer or dicoccon or khorasan or turanicum or einkorn or monococcum or "hard red spring" or "hard red winter" or "soft red winter" or "hard white" or "soft white" or teff or eragrostis or "Williams lovegrass" or "annual bunch grass" or pumpernickel or Fagopyrum or quinoa or amaranth* or chia or chiaseed or granola or tortilla* or "maya nut" or *bread or colosia or cockscomb or "quail grass" or soko or "pitseed goosefoot" or berlandieri or kaniwa or "Chenopodium pallidicaule" or canihua or qaniwa or wattleseed or "acacia seed" or "wattle seed" or kamut or Fagopyrum):ti
3	("edible grain" or secale or triticale or triticum or avena or "setaria plant" or hordeum or oryza or "zea mays" or eragrostis or teff or sorghum or johnsongrass or "kaffir corn" or kafir or sudangrass or triticale or triticosecale or

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Figure 2. *(continued)* Search strategy implemented across 5 electronic databases and results of total records retrieved when searching for randomized controlled trials that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans.

Set	Search terms
	triticum or Fagopyrum or buckwheat or celosia or durum or rye or barley or maize or teosinte or zea or cereal* or grain* or *grain or *germ or *bran or endosperm or wholegrain* or wholemeal or wheat or oat or oats or millet or setaria or panicum or rice or corn or flour or semolina or bulgar or groats or bread or porridge or cracker or biscuit or muesli or pancake* or pasta or noodle* or polenta or muffin* or roll or dough or durum or spelt or spelta or emmer or dicoccon or khorasan or turanicum or einkorn or monococcum or "hard red spring" or "hard red winter" or "soft red winter" or "hard white" or "soft white" or teff or eragrostis or "Williams lovegrass" or "annual bunch grass" or pumpernickel or Fagopyrum or quinoa or amaranth* or chia or chiaseed or granola or tortilla* or "maya nut" or *bread or colosia or cockscomb or "quail grass" or soko or "pitseed goosefoot" or berlandieri or kaniwa or "Chenopodium pallidicaule" or canihua or qaniwa or wattleseed or "acacia seed" or "wattle seed" or kamut or Fagopyrum):ab
#4	#2 or #3
#5	#1 and #4
	EMBASE: Searched March 8, 2019 for citations from both Embase and MEDLINE using keywords (abstract and title) and Emtree terms. Result = 3,442 records
#1	[Emtree] 'clinical trial'/exp
#2	[Emtree] 'food grain'/exp OR 'cereal'/exp OR 'barley'/exp OR 'bread'/exp OR 'breakfast cereal'/exp OR 'finger millet'/exp OR 'foxtail millet'/exp OR 'maize'/exp OR 'field corn'/exp OR 'sweet corn'/exp OR 'malt'/exp OR 'millet'/exp OR 'oat'/exp OR 'pearl millet'/exp OR 'rice'/exp OR 'Indian rice'/exp OR 'Japonica rice'/exp OR 'rye'/exp OR 'sorghum'/exp OR 'sudangrass'/exp OR 'wheat'/exp OR 'emmer'/exp OR 'spelt'/exp OR 'spring wheat'/exp OR 'triticale'/exp OR 'Triticum aestivum'/exp OR 'Triticum durum'/exp OR 'Triticum monococcum'/exp OR 'Triticum turgidum'/exp OR 'wheat germ'/exp OR 'winter wheat'/exp OR 'grain flour'/exp OR 'barley flour'/exp OR 'corn flour'/exp OR 'oatmeal'/exp OR 'rice flour'/exp OR 'rye flour'/exp OR 'semolina'/exp OR 'sorghum flour'/exp OR 'wheat flour'/exp OR 'pseudocereal'/exp OR 'buckwheat'/exp OR 'Chenopodium quinoa'/exp OR 'chia'/exp OR 'refined grain'/exp OR 'whole grain'/exp OR 'dough'/exp OR 'bakery product'/exp OR 'biscuit'/exp OR 'cookie'/exp OR 'dough'/exp
#3	"edible grain":ab,ti or secale:ab,ti or triticale:ab,ti or triticum:ab,ti or avena:ab,ti or "setaria plant":ab,ti or hordeum:ab,ti or oryza:ab,ti or "zea mays":ab,ti or eragrostis:ab,ti or teff:ab,ti or sorghum:ab,ti or johnsongrass:ab,ti or "kaffir corn":ab,ti or kafir:ab,ti or sudangrass:ab,ti or triticale:ab,ti or triticosecale:ab,ti or triticum:ab,ti or Fagopyrum:ab,ti or buckwheat:ab,ti or celosia:ab,ti or durum:ab,ti or rye:ab,ti or barley:ab,ti or maize:ab,ti or teosinte:ab,ti or zea:ab,ti or cereal*:ab,ti or grain*:ab,ti or grain:ab,ti or germ:ab,ti or bran:ab,ti or endosperm:ab,ti or wholegrain*:ab,ti or wholemeal:ab,ti or wheat:ab,ti or oat:ab,ti or oats:ab,ti or millet:ab,ti or setaria:ab,ti or panicum:ab,ti or rice:ab,ti or corn:ab,ti or flour:ab,ti or semolina:ab,ti or bulgar:ab,ti or groats:ab,ti or bread:ab,ti or porridge:ab,ti or cracker:ab,ti or biscuit:ab,ti or muesli:ab,ti or pancake*:ab,ti or pasta:ab,ti or noodle*:ab,ti or polenta:ab,ti or muffin*:ab,ti or roll:ab,ti or dough:ab,ti or durum:ab,ti or spelt:ab,ti or spelta:ab,ti or emmer:ab,ti or dicoccon:ab,ti or khorasan:ab,ti or turanicum:ab,ti or einkorn:ab,ti or monococcum:ab,ti or "hard red spring":ab,ti or "hard red winter":ab,ti or "soft red winter":ab,ti or "hard white":ab,ti or "soft white":ab,ti or teff:ab,ti or eragrostis:ab,ti or "Williams lovegrass":ab,ti or "annual bunch grass":ab,ti or pumpernickel:ab,ti or quinoa:ab,ti or amaranth*:ab,ti or chia:ab,ti or granola:ab,ti or tortilla*:ab,ti or "maya nut":ab,ti or bread:ab,ti or colosia:ab,ti or cockscomb:ab,ti or "quail grass":ab,ti or soko:ab,ti or "pitseed goosefoot":ab,ti or berlandieri:ab,ti or kaniwa:ab,ti or "Chenopodium pallidicaule":ab,ti or canihua:ab,ti or qaniwa:ab,ti or wattleseed:ab,ti or "acacia seed":ab,ti or "wattle seed":ab,ti or kamut:ab,ti
#4	#2 or #3
#5	#1 and #4

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Figure 2. *(continued)* Search strategy implemented across 5 electronic databases and results of total records retrieved when searching for randomized controlled trials that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans.

Set	Search terms
#6	#5 and ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim) AND ('clinical article'/de OR 'clinical trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'human'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'normal human'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial'/de OR 'pilot study'/de OR 'randomized controlled trial'/de OR 'single blind procedure'/de) AND ('article'/it OR 'article in press'/it)
	Web of Science: Searched March 8, 2019 for the following keywords in title. Results = 968 records
#1	TITLE: "edible grain" or secale or triticale or triticum or avena or "setaria plant" or hordeum or oryza or "zea mays" or eragrostis or teff or sorghum or johnsongrass or "kaffir corn" or kafir or sudangrass or triticale or triticosecale or triticum or Fagopyrum or buckwheat or celosia or durum or rye or barley or maize or teosinte or zea or cereal* or grain* or *grain or *germ or *bran or endosperm or wholegrain* or wholemeal or wheat or oat or oats or millet or setaria or panicum or rice or corn or flour or semolina or bulgar or groats or bread or porridge or cracker or biscuit or muesli or pancake* or pasta or noodle* or polenta or muffin* or roll or dough or durum or spelt or spelta or emmer or dicoccon or khorasan or turanicum or einkorn or monococcum or "hard red spring" or "hard red winter" or "soft red winter" or "hard white" or "soft white" or teff or eragrostis or "Williams lovegrass" or "annual bunch grass" or pumpernickel or Fagopyrum or quinoa or amaranth* or chia or chiaseed or granola or tortilla* or "maya nut" or *bread or colosia or cockscomb or "quail grass" or soko or "pitseed goosefoot" or berlandieri or kaniwa or "Chenopodium pallidicaule" or canihua or qaniwa or wattleseed or "acacia seed" or "wattle seed" or kamut or Fagopyrum
#2	TITLE: "clinical trial" or "controlled trial" or "equivalence trial" or intervention or "cross-over" or randomized or randomized or "control trial" or placebo
#3	#1 and #2
	Total = 10,623 records

[a]MeSH = Medical Subject Headings.

Figure 2. *(continued)* Search strategy implemented across 5 electronic databases and results of total records retrieved when searching for randomized controlled trials that compared whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans.

Problem

Is the problem a priority?

Judgment	Research evidence and justification
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Ischemic heart disease and stroke, both forms of CVD,[a] are the top 2 causes of morbidity and death worldwide.[67] Qualitative research has shown significant impacts on the lived experience of people with CVD. Important themes include "living in the shadow of fear," "living a restricted life," and "battling the system".[68]

Desirable effects

How substantial are the desirable anticipated effects?

Judgment	Research evidence and justification
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Based on the results of this systematic review: Of the 40 outcomes on which data were reported, 23 were found to have 1 or more RCT[b] report a beneficial effect of the intervention. There were 7 outcomes which reported any beneficial effect for the refined group. Pooled effects found some significant beneficial outcomes when investigating by subgroups (type of grain, study quality) for total cholesterol, LDL[c] cholesterol, triglycerides, CRP,[d] and HbA1c.[e] Although most models were not significant, this shows there is a trend towards desirable effects on cardiovascular risk factors. However, despite statistical significance, effect sizes were small, with most having clinically insignificant effect sizes. When drawing upon other literature, such as the systematic reviews and meta-analyses of observational studies which have reported a dose–response relationship between whole-grain intake and reduced risk of CVD death,[11,13,14] the effects strongly favor the intervention. However, observational research has a lower level of evidence in the evidence hierarchy, as it is accompanied by confounding variables that are not properly or easily accounted for in multivariable models. Therefore, strong conclusions cannot be drawn in favor of the intervention. There was one pooled estimated effect that favored the refined grains, which was a decrease in HDL[f] cholesterol. However, the effect size was clinically insignificant. Other considerations are side effects/adverse events. Four studies reported minor gastrointestinal symptoms (likely related to the intervention), which are of trivial consideration, and occurred in both groups. Other adverse events were unlikely to be related to the intervention.

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgment	Research evidence and justification
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Based on the results of this systematic review: Of the 40 outcomes on which data were reported, 23 were found to have 1 or more RCT report a beneficial effect of the intervention. There were only 7 outcomes that reported any beneficial effect for the refined group. Pooled effects found some significant beneficial outcomes when investigating by subgroups (type of grain, study quality) for total cholesterol, LDL cholesterol, triglycerides, CRP, and HbA1c. Although most models were not significant, this shows there is a trend towards desirable effects on cardiovascular risk factors. However, despite statistical significance, effect sizes were small, with most having clinically insignificant effect sizes. When drawing upon other literature, such as the systematic reviews and meta-analyses of observational studies which have reported a dose-response relationship between whole-grain intake and reduced risk of CVD death,[11,13,14] the effects strongly favor the intervention.

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Figure 7. Recommendations assessment and justification for the use of whole grains to improve cardiovascular disease risk using Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical recommendations for populations software on *GRADEpro*.

However, observational research has a lower level of evidence in the evidence hierarchy, as it is accompanied by confounding variables that are not properly or easily accounted for in multivariable models. Therefore, still prevent strong conclusions being drawn in favor of the intervention.
There was 1 pooled estimated effect that favored the refined grains, which was a decrease in HDL cholesterol. However, the effect size was clinically insignificant.
Other considerations are side effects/adverse events. Four studies reported minor gastrointestinal symptoms (likely related to the intervention), which are of trivial consideration, and occurred in both groups. Other adverse events were unlikely to be related to the intervention.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgment	Research evidence and justification
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The GRADE assessment of confidence in the body of evidence ranged from very low to moderate; looking across all outcomes, this was considered to be a low level of certainty in the evidence overall.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgment	Research evidence and justification
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The outcomes of this review ranged from cardiovascular risk factors through to cardiovascular disease events and death. However, only data were found on cardiovascular risk factors. Although some biomarkers may be highly clinical in nature and not readily interpreted by patients; investigators considered there was no variability or uncertainty in the value of preventing CVD (although the prevention/treatment of risk factors) by any stakeholder group: patients, clinicians, health services, governments, or industry. Qualitative research shows that individuals hold diverse values that must be interpreted through an appropriate cultural lens. Although values are diverse, commonality is the broad value for health and well-being.[69]

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgment	Research evidence and justification
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the	As described above, although beneficial and undesirable effects were reported by individual studies and in pooled estimates, the balance of effects favors the intervention. It should be noted that the effects are of marginal clinical significance, and therefore it is not possible to strongly conclude that the effects favor the intervention. This review has highlighted and discussed in detail the limitations in the existing body of interventional research that may explain such a finding. When interpreted alongside systematic

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Figure 7. *(continued)* Recommendations assessment and justification for the use of whole grains to improve cardiovascular disease risk using Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical recommendations for populations software on *GRADEpro*.

intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	reviews and meta-analyses of observational studies, which have reported a dose—response relationship between whole-grain intake and reduced risk of CVD death,[11,13,14] the effects favor the intervention. However, observational research has a lower level of evidence in the evidence hierarchy, as it is accompanied by confounding variables that are not properly or easily accounted for in multivariable models. Therefore, still prevent strong conclusions being drawn in favor of the intervention.

Resources required

How large are the resource requirements (costs)?

Judgment	Research evidence and justification
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Grains are an affordable staple food, with whole-grain sources available in the majority of countries, to all socioeconomic levels and geographical areas. Many countries and cultures also have locally grown and lesser-known grains and pseudo-grains available for consumption (eg, Khorasan wheat, teff). However, it must be acknowledged in small communities with limited access to the food supply, whole-grain sources may not be a readily available alternative, but should be attainable by alternative methods such as bulk purchasing raw ingredients or products with long shelf-lives (eg, brown rice, wholemeal flour). Availability of whole grains has also increased in recent years due to the impact of dietary guidelines on food policies and competition among food suppliers.[70] No additional resources are required to implement the intervention, as consuming whole grains simply replaces refined grains, and is therefore a negligible intervention for most communities/populations. A judgment of negligible costs and savings was made by the review authors, but it must be acknowledged that this may not be the case for some vulnerable groups.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgment	Research evidence and justification
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Although the recommendation replaces one food (refined grains) with another (whole grains), it is acknowledged that there is some variation in the direct cost to consumers, with variation in the significance of this cost dependent of socioeconomic and geographical circumstances.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgment	Research evidence and justification
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison	Food basket studies have identified that whole-grain products may be more expensive than refined-grain alternatives. Although the cost difference is small to most families in developed countries, there could be a substantial cost to low-income families.[71] Epidemiological research has further linked the varying cost of whole grains to variations in cholesterol levels, identifying that for every dollar of subsidies to whole-grain products, that there is a medical cost savings of $13.20.[66] Population economic modeling using data from the United Kingdom strongly advocates for any intervention that prevents CVD incidence, as even interventions with effect sizes of −1% incidence result in a cost saving of $48m/annum; and that dietary interventions are one of the most

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Figure 7. *(continued)* Recommendations assessment and justification for the use of whole grains to improve cardiovascular disease risk using Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical recommendations for populations software on *GRADEpro*.

○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	cost-effective approaches to achieve a reduction in incidence.[72,73] Despite this, due to this review finding that the evidence from RCTs (based on short intervention durations) show only trivial to small clinical significance, the authors felt that there is insufficient evidence to state that replacing refined grains with whole grains is cost-effective. This may change with further long-term intervention studies that show a greater clinical impact.

Equity

What would be the impact on health equity?

Judgment	Research evidence and justification
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	The effect of the intervention is not dependent on sociocultural or socioeconomic circumstances. Baseline differences in socioeconomic groups would not result in a different effect. Many alternatives for CVD prevention and treatment have a higher cost and have greater barriers, such as medications or frequent health care consultations. Therefore, if effective, the choice of replacing refined grains with whole grains would increase access to CVD prevention strategies for vulnerable groups. The current review drew on literature from across Europe, the United States, and Asia, finding that attrition was either equal between groups or higher in the control group, suggesting that whole grains were equally or better preferred across these diverse cultures. The current reviewers judged was that if effective and recommended to all populations, whole grains are an accessible, feasible, and acceptable intervention to help meet the disproportionate rise in CVD deaths amount low- to middle-income countries.[74]

Acceptability

Is the intervention acceptable to key stakeholders?

Judgment	Research evidence and justification
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Of clinical significance, the RCTs in this review reported that participants had either equal or lower attrition in the whole-grain group, as well as high compliance to the whole-grain intervention when measured by plasma alkylresorcinol. This suggests that dietary intake of whole grains is a feasible dietary strategy in culturally diverse populations and strengthens the need to test other types of grains that are important to certain cultural groups in RCTs.

Feasibility

Is the intervention feasible to implement?

Judgment	Research evidence and justification
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Of clinical significance, the RCTs in this review reported that participants had either equal or lower attrition in the whole-grain group, as well as high compliance to the whole-grain intervention when measured by plasma alkylresorcinol. This suggests that dietary intake of whole grains is a feasible dietary strategy in culturally diverse populations and strengthens the need to test other types of grains that are important to certain cultural groups in RCTs. The strategy of promoting whole grains as opposed to refined grains may require high-level strategic approaches from governments. For example, food subsidies,[66] population policy interventions,[72] and national dietary guidelines promoting whole grains[70] have demonstrated effectiveness and broad impact. From an individual point of view, whole-grain consumption is in line with national dietary guidelines of many countries and is therefore already considered an important part of dietary recommendations made by health professionals and in public health strategies.

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Figure 7. *(continued)* Recommendations assessment and justification for the use of whole grains to improve cardiovascular disease risk using Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical recommendations for populations software on *GRADEpro*.

[a]CVD = cardiovascular disease.
[b]RCT = randomized controlled trial.
[c]LDL = low-density lipoprotein.
[d]CRP = C-reactive protein.
[e]HbA1c = hemoglobin A1c.
[f]HDL = high-density lipoprotein.

Figure 7. *(continued)* Recommendations assessment and justification for the use of whole grains to improve cardiovascular disease risk using Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical recommendations for populations software on *GRADEpro*.

Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ampatzoglou, 2016[36]							
Rating	Low risk of bias	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	"Subjects were randomized based on age, gender and BMI by a research assistant, who was not involved in the analysis, using covariate adaptive randomization software"	No description of allocation concealment	No parties were blinded There were no measures taken to minimize risk of bias in regards to blinding	There is no blinding; however, all measures are objective serum biomarkers	0% attrition for both groups	None detected	None detected
Andersson, 2007[54]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Unclear	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	No parties were blinded There were no measures taken to minimize risk of bias in regards to blinding	There is no blinding; however, all measures are objective serum biomarkers	12% (cross-over design), reason for withdrawal was not related to study	4 participants dropped out; but there are an additional 2 for whom data are not reported with no explanation	None detected
Araki, 2017[49]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Unclear
Evidence	No description of how randomization allocation was generated: "The participants were	No description of how randomization allocation was generated:	No parties were blinded There were no measures taken to minimize risk of bias in	There is no blinding; however, most measures are objective serum biomarkers	Although attrition was higher in IG[b] (14%) compared to CG[c] (5%), attrition was not	Outcomes measured, including blood pressure and BMI were not reported	Analysis of findings found no statistically significant results; however,

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
	allocated to receive either PABR or WR with an allocation table prepared by a data coordinator based on simple randomization method with stratification by sex and low-density lipoprotein cholesterol (LDL-C) levels (>140 mg/dL or not)."	"The participants were allocated to receive either PABR or WR with an allocation table prepared by a data coordinator based on simple randomization method with stratification by sex and low-density lipoprotein cholesterol (LDL-C) levels (>140 mg/dL or not)."	regards to blinding		due to study factors	at follow-up despite being measured Several measures, particularly for the CG, did not report final values but only change values Many of the statistically significant results were presented in figures only with no report of actual data	there is a very high level of sub-analysis using per-protocol analysis (where several participants were excluded due to an error in the study product at the commencement of the study), which suggests analysts were mining for results Background diet was not well controlled beyond basic advice, and was not tested as a confounding variable
Enright, 2010[37]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	No parties were blinded There were no measures	There is no blinding; however, most measures are	No attrition for either group	None detected	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
			taken to minimize risk of bias in regards to blinding	objective serum biomarkers			
Giacco, 2010[38]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	No parties were blinded There were no measures taken to minimize risk of bias in regards to blinding	There is no blinding; however, most measures are objective serum biomarkers	No attrition for either group	None detected	None detected
Giacco, 2013[31]							
Rating	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	"Randomization was carried out with stratification for sex, age, and body mass index (BMI) by means of a computerized random allocation list."	"Allocation was carried out by personnel not involved in the study; investigators and dieticians were aware of the participants' group allocation only after completion of the randomization process"	"Investigators and dieticians were aware of the participants' group allocation"; no description of participant blinding	"Investigators and dieticians were aware of the participants' group allocation" however, the outcome of interest is an objective biomarker	Attrition <20%; lowest in the IG group; none related to study procedures	None detected.	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Giacco, 2014[30]							
Rating	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence	As per Giacco and colleagues, 2013[31]	As per Giacco and colleagues, 2013[31]	As per Giacco and colleagues, 2013[31] Laboratory analyses were performed blind with respect to the assigned treatment	"Investigators and dieticians were aware of the participants' group allocation" however, the outcome of interest is an objective biomarker	Attrition <20%; lowest in the IG group; none related to study procedures	Blood pressure was reported as measured in the methods but no results presented; however, blood pressure results were pooled with the Finland sample and reported in Giacco and colleagues, 2013[31]	This study reports outcomes not of interest to this study using a subgroup of Giacco and colleagues, 2013[31]; however, also repeats other clinical outcomes already reported for the whole cohort. This may lead to results being over-or mis-interpreted.
Vetrani, 2016[32]							
Rating	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence	As per Giacco and colleagues, 2013[31]	As per Giacco and colleagues, 2013[31]	Investigators and dieticians were aware of the participants' group allocation"; no description of participant blinding	"Investigators and dieticians were aware of the participants' group allocation"; however, the outcome of interest is an objective biomarker	No attrition for either group; as only completers were selected for the subanalysis	None detected	This study reports outcomes not of interest to this study using a subgroup of Giacco and colleagues, 2013[31]; however, also repeats other clinical

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
							outcomes already reported for the whole cohort. This may lead to results being over- or mis-interpreted.
Harris Jackson, 2014[39]							
Rating	Low risk of bias	High risk of bias	High risk of bias	Low risk of bias	Unclear	Low risk of bias	Low risk of bias
Evidence	"Eligible individuals (n = 60) were randomly assigned to either the WG or RG diet group for the entire 12 wk by using a computer-generated random-number assignment"	"An unblended study coordinator stratified participants by age, sex, and BMI and conducted all data analyses"	"Participants could not be blinded to their group assignment"	"Outcome assessors (i.e., nurses and technicians) were blinded"	Attrition <20%; lowest in the IG group; 2 participants in IG withdrew for reason related to diet—1 caused minor adverse event, 1 could not comply. There may be some bias in the results, but numbers are very low so unlikely to substantially affect outcomes.	None detected	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kazemzadeh, 2014[40]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	"In the present work participant were not blinded"	No description of blinding the personnel/ researchers; however, the outcome of interest is an objective biomarker	3 (7%) withdrawals occurred during the brown rice due to noncompliance; however, this rate is very low and unlikely to bias the results	None detected	None detected
Kikuchi, 2018[41]							
Rating	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence	No description of randomization technique	No description of allocation concealment	"We added malt extract to refined wheat bread (RW diets) and colored it brown. RW diets and WW diets had almost same appearance. And we decided formulation of tasteful bread (oil-rich and sugar-rich), it was hard to feel difference in taste. As a	"We added malt extract to refined wheat bread (RW diets) and colored it brown. RW diets and WW diets had almost same appearance. And we decided formulation of tasteful bread (oil-rich and sugar-rich), it was hard to feel difference in taste. As a	4% attrition in IG, 0% in CG; very low attrition and none related to study	None detected	Background diet not well controlled; may have introduced bias

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
			result, blindness is properly maintained." and "A randomized double-blind placebo-controlled intervention study was conducted."	result, blindness is properly maintained." and "A randomized double-blind placebo-controlled intervention study was conducted."			
Kim, 2008[56]							
Rating	Unclear	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence	No description of randomization technique	No description of allocation concealment	The test products were contained within a meal replacement, and it should not have been able to detect if they had RG or WG. But there is no description of concealment or blinding, so it is unclear.	Although not blinded, outcomes were objective (serum biomarkers)	Both groups had low attrition (<15%). Some dropped out because of a "dislike" of the diet, but exact numbers for withdrawal related to study procedures is not reported; regardless, it was equal across groups and was a low rate.	None detected	The test products were poorly described and contained within a meal replacement, therefore, not indicative of WG intake or consumed in a way that would be recommended Exact doses were unclear

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kirwan, 2016[33]							
Rating	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	"Blinding and "We conducted a double-blind, randomized, controlled crossover study" and " Blinding was achieved by covering whole-grain foods with sauce and by packaging meals into identical containers so that entrees appeared similar for both diets. Entrees were assembled at the Nestle Product Technology Center in Solon, Ohio."	"We conducted a double-blind, randomized, controlled crossover study" plus use of objective markers	Overall attrition was 18%, reasons stated show that were unrelated to study.	None detected.	None detected.
Malin, 2018[34], 2019[35]							
Rating	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	As per Kirwan and colleagues, 2016[33]	As per Kirwan and colleagues, 2016[33]	As per Kirwan and colleagues, 2016[33]	As per Kirwan and colleagues, 2016[33]	No attrition was reported for this sub-sample of Kirwan and colleagues, 2016[33]	None detected.	None detected.

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kondo, 2017[42]							
Rating	Low risk of bias	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	"We used the minimization method for randomization." Investigators were provided with a random allocation sequence made by a research assistant, who was independent of the investigators, using computer-generated random digits"	No description of allocation concealment	"The study was a randomized, open-labeled, parallel-controlled trial"	Although not blinded, outcomes were objective (serum biomarkers)	Attrition was 7% in the CG, none in the IG. No attrition related to study processes.	No systematic reporting bias was detected although an error was identified with the results of triglycerides	None detected
Kristensen, 2012[55]							
Rating	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	"We used an open-labeled design"	Not blinded, but most outcomes were objective. However, outcomes around anthropometry were subjective and may have been influenced.	Both groups had 1 participant withdraw for reasons related to the test products. Overall attrition was low (<10%) and equal between groups.	None detected	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kristensen, 2017[50]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	"Open-label researcher-blinded parallel design"	"Open-label researcher-blinded parallel design"; many outcomes were objective biomarkers	1 withdrawal related to study; 6 unexplained. ITT[d] analysis used. Low attrition in both groups.	None detected	61% of IG were noncompliant according to plasma alkylresorcinol concentrations; this was found to have a significant effect on the outcome
Maki, 2010[51]							
Rating	Unclear	Unclear	High risk of bias	Unclear	High risk of bias	High risk of bias	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	No attempt at blinding	Not blinded, but most outcomes were objective. However, outcomes around anthropometry were subjective and may have been influenced.	Both groups had >20% attrition with reasons for withdrawal not adequately described to determine if related to the study, but it appears several were related to the study. An ITT was attempted but the ITT results were reported	Only data for statistically significant results were reported. Baseline values for some outcomes were not reported.	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
					inadequately to allow for any true review of the results. Attrition was high in the control group.		
Nakayama, 2017[52]							
Rating	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Evidence	No description of randomization technique	No description of allocation concealment	No attempt at blinding	Not blinded, but most outcomes were objective. However, outcomes around anthropometry were subjective and may have been influenced.	Only 2 participants withdrew, none due to study factors	Data for many outcomes were presented graphically only, and only significant results tended to be reported, but as data is not presented as numerals it is had to detect if this biases the outcome	Background diet not well controlled; may have introduced bias
Pick, 1998[57]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Unclear	Low risk of bias
Evidence	No description of randomization technique	No description of allocation concealment	No attempt at blinding	Not blinded, but most outcomes were objective	0 attrition. One participant was excluded from data analysis.	Data were reported poorly and insufficiently, but no systematic or purposeful bias detected	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Pins, 2002[58]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence	No description of randomization technique	No description of allocation concealment	No attempt at blinding	"Cereals were dispensed in unlabeled bulk containers to facilitate physician blinding"	0 attrition	None detected	Background diet not well controlled; may have introduced bias
Roager, 2019[44]							
Rating	Low risk of bias	Low risk of bias	High risk of bias	Unclear	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	"Using a variable block size, the randomization list was generated by an investigator without contact to the participants, and a dietitian allocated participants to sequence of intervention matching the list of participant identifications with the randomization list."	"Using a variable block size, the randomization list was generated by an investigator without contact to the participants, and a dietitian allocated participants to sequence of intervention matching the list of participant identifications with the randomization list."	"It was not feasible to blind during the intervention, but participants and investigators involved in outcome assessment were blinded until the first examination day and during sample analysis and the initial data analysis."	Not blinded, but most outcomes were objective. However, outcomes around anthropometry were subjective and may have been influenced.	2 withdrawals related to the study product (not clear if IG or CG); but overall attrition was low and compliance with products was good	None detected	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Schutte, 2018[45]							
Rating	Low risk of bias	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence	"Randomization of the participants over the intervention groups was conducted by block randomization with the use of Microsoft Excel by a researcher who was not involved in the study"	No description of allocation concealment	"Both researchers and participants were blinded with regard to the intervention received."	"Both researchers and participants were blinded with regard to the intervention received."	0% attrition. Test products reported as well tolerated.	None detected	Background diet not well controlled; may have introduced bias
Shimabukuro, 2014[53]							
Rating	Low risk of bias	Unclear	High risk of bias	Unclear	Low risk of bias	High risk of bias	Unclear
Evidence	"The participants were randomized by a computer-generated random number table into either the BR group followed by the WR group (BR-WR, n 14) or the WR group followed by the BR group (WR-BR, n 13)."	No description of allocation concealment	No attempt at blinding	Not blinded, but most outcomes were objective. However, outcomes around anthropometry were subjective and may have been influenced.	Only 1 participant withdrew. No description of reason.	There appears to be a purposeful bias towards reporting favorable results; were both IG and CG reported identical follow-up values for BMI, but only the IG was statistically significant; or otherwise the final value for CG was an error. CG	Test products were severely under-described

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
						and IG were not compared, and the cross-over groups were not pooled but reported separately. However, perhaps more likely mis-reporting to favor IG as the waist circumference decreased further in CG than IG, but only the IG was reported as significant.	
Tighe, 2010[60]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence	No description of allocation concealment	No description of allocation concealment	No attempt at blinding. Products were commercially available and familiar.	"16-wk randomized, single-blind, controlled, parallel-designed trial that involved 3 treatment groups (refined, wheat, and oat + wheat diets)"	Largest attrition was from the controlled group. Only 1 participant withdrew due to the study; unclear which group they were in.	None detected	Background diet not well controlled; may have introduced bias
Tighe, 2013[59]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Unclear	Unclear

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Evidence	As per Tighe and colleagues, 2010[60]	As per Tighe and colleagues, 2010[60]	As per Tighe and colleagues, 2010[60]	As per Tighe and colleagues, 2010[60]	As per Tighe and colleagues, 2010[60]	Many outcomes were only compared at baseline and not follow-up including hemodynamics and body composition	As per Tighe and colleagues, 2010[60]
Vanegas, 2017[46]							
Rating	Low risk of bias	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	"Participants were randomly assigned to the WG or RG group with the use of block random assignment with stratification by BMI (20-25, 25-30, and 30-35), age (40-55 and 55-65 y), sex, and race (Caucasian, African American, Asian American, Hispanic, and other). The statistician, who had no contact with participants and had no role in the data collection, assigned	No description of allocation concealment	No attempt at blinding	Not blinded, but most outcomes were objective	Attrition was low (<15%) for both groups, and only one participant in each group withdrew due to reasons related to the study. No bias detected.	None detected	None detected

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
	the random-assignment coding for the WG and RG groups."						
Vitaglione, 2015[47]							
Rating	Low risk of bias	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Evidence	"Once enrolled by the study nutritionist and physician, subjects were randomly assigned by the dietitian to the WG or the control group on the basis of a randomization sequence that was previously generated by the statistician with the use of a computer-generated permuted blocks (n = 5) randomization scheme"	No description of allocation concealment	No attempt at blinding	"In addition, in this study, unblinded participants might have led to possible biases in psychological response and compliance to the dietary interventions, whereas the blinded outcome assessors guaranteed unbiased interaction with participants and data collection"	Attrition was low for both groups and none was related to the study	None detected	None detected
Zhang, 2011[48]							
Rating	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Evidence			No attempt at blinding	"All the researchers not directly in	Attrition was low for both groups	None detected	Background diet not well

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Table 2. Justification for the risk of bias assessment according to the Cochrane Risk-of-Bias tool[19] of randomized controlled trials that compare whole-grain or whole pseudo-grain interventions and placebo or refined-grain controls in humans (*continued*)

Study, first author, year	Random sequence generation (selection bias)[a]	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
	No description of randomization technique	No description of allocation concealment		contact with study participants (dietitians, laboratory technicians, and statisticians) were unaware of group allocations". Unclear if outcome assessors were blinded. Outcomes are objective.	and none was related to the study		controlled; may have introduced bias

[a]BMI = body mass index; BR = brown rice; PABR = partially abraded brown rice; RG = refined grain; RW = refined wheat; WG = whole grain; WR = white rice.
[b]IG = intervention group.
[c]CG = comparator group.
[d]ITT = intention-to-treat.

Table 5. Grading of Recommendations Assessment, Development and Evaluation evidence and summary of findings table: whole grains compared to refined grains for cardiovascular disease risk

Certainty Assessment							No. of Patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole grain	Refined grain	Absolute (95% CI)	Certainty	Importance
CRP/hs-CRP[a]: Study quality (high) subgroup											
8	Randomized trials	Not serious[b]	Serious[cd]	Not serious[e]	Not serious	None	311	360	SMD[f] 0.22 SD[g] lower (0.44 lower to 0)	⊕⊕⊕◯ MODERATE	IMPORTANT
IL-6[h]											
9	Randomized trials	Not serious	Serious[d]	Not serious[e]	Not serious	None	458	432	SMD 0.08 SD lower (0.29 lower to 0.13 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Fasting blood glucose											
16	Randomized trials	Serious[b]	Very serious[i]	Not serious[e]	Not serious	None	742	722	SMD 0.01 SD lower (0.19 lower to 0.16 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting blood insulin											
13	Randomized trials	Serious[b]	Not serious	Not serious[e]	Not serious[j]	None	649	626	SMD 0.07 SD higher (0.05 lower to 0.18 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

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Table 5. Grading of Recommendations Assessment, Development and Evaluation evidence and summary of findings table: whole grains compared to refined grains for cardiovascular disease risk (*continued*)

Certainty Assessment							No. of Patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole grain	Refined grain	Absolute (95% CI)	Certainty	Importance
HOMA-IR[k]											
11	Randomized trials	Serious[b]	Not serious	Not serious[e]	Not serious	None	528	500	SMD 0.03 SD lower (0.17 lower to 0.1 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
HbA1c[l]**: Study quality (high) subgroup**											
3	Randomized trials	Not serious[b]	Not serious[c]	Not serious[e]	Serious[j]	None	97	97	SMD 0.33 SD lower (0.61 lower to 0.04 lower)	⊕⊕⊕○ MODERATE	IMPORTANT
Total cholesterol: Grain type (oats) subgroup											
2	Randomized trials	Serious[b]	Very serious[im]	Not serious[e]	Serious[j]	None	122	110	SMD 0.54 SD lower (0.95 lower to 0.12 lower)	⊕○○○ VERY LOW	IMPORTANT
HDL[n] **cholesterol: Grain type (mixed) subgroup**											

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Table 5. Grading of Recommendations Assessment, Development and Evaluation evidence and summary of findings table: whole grains compared to refined grains for cardiovascular disease risk (*continued*)

Certainty Assessment							No. of Patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole grain	Refined grain	Absolute (95% CI)	Certainty	Importance
7	Randomized trials	Not serious	Not serious[c]	Not serious[e]	Not serious	None	292	298	SMD 0.17 SD lower (0.33 lower to 0.01 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
HDL cholesterol: Study design (moderate) subgroup											
4	Randomized trials	Serious[b]	Not serious[c]	Not serious[e]	Serious[j]	None	255	235	SMD 0.33 SD higher (0.05 higher to 0.62 higher)	⨁⨁◯◯ LOW	IMPORTANT
LDL[o] cholesterol: Grain type (oat) subgroup											
2	Randomized trials	Serious[b]	Serious[cm]	Not serious[e]	Serious[j]	None	122	110	SMD 0.57 SD lower (0.84 lower to 0.31 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Triglycerides: Grain type (rice) subgroup											

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Table 5. Grading of Recommendations Assessment, Development and Evaluation evidence and summary of findings table: whole grains compared to refined grains for cardiovascular disease risk (*continued*)

Certainty Assessment							No. of Patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole grain	Refined grain	Absolute (95% CI)	Certainty	Importance
3	Randomized trials	Very serious[p]	Serious[cm]	Not serious[e]	Not serious	None	171	167	SMD 0.22 SD lower (0.44 lower to 0.01 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Systolic blood pressure											
10	Randomized trials	Serious[b]	Very serious[i]	Not serious[e]	Not serious	None	482	481	SMD 0.04 SD lower (0.28 lower to 0.21 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Diastolic blood pressure											
11	Randomized trials	Serious[b]	Very serious[i]	Not serious[e]	Not serious	None	515	514	SMD 0.05 SD higher (0.26 lower to 0.37 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Total body weight											
15	Randomized trials	Serious[b]	Very serious[i]	Not serious[e]	Not serious	None	602	587	SMD 0.02 SD lower (0.24 lower to 0.19 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

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Table 5. Grading of Recommendations Assessment, Development and Evaluation evidence and summary of findings table: whole grains compared to refined grains for cardiovascular disease risk (*continued*)

Certainty Assessment							No. of Patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Whole grain	Refined grain	Absolute (95% CI)	Certainty	Importance
Waist circumference											
14	Randomized trials	Serious[b]	Not serious	Not serious[e]	Not serious	None	641	625	SMD 0.1 SD lower (0.25 lower to 0.05 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

[a]CRP/hsCRP = C-reactive protein/high-sensitivity CRP.
[b]Some studies had unclear or high risk of bias.
[c]Although the initial model had higher heterogeneity, this was explained by the subgroup analysis upon which this Grading of Recommendations Assessment, Development and Evaluation assessment is being performed.
[d]There was some statistical heterogeneity (I^2 between 30% and 60%).
[e]Although this outcome is a risk factor for CVD, and does not directly represent CVD; all outcomes in this review are CVD risk factors and therefore the decision was made to not downgrade all markers on this basis. This measure was considered to be a direct measure of the risk factor.
[f]SMD = standardized mean difference.
[g]SD = standard deviation.
[h]IL-6 = interleukin 6.
[i]There was high statistical heterogeneity (I^2 between 60% and 100%).
[j]The upper or lower 95% CI crosses an effect size of 0.5 in either direction.
[k]HOMA-IR = Homeostatic Model Assessment of Insulin Resistance.
[l]HbA1C = hemoglobin A1c.
[m]There is a risk of inconsistency due to there being fewer than 400 participants in this subgroup.
[n]HDL = high-density lipoprotein.
[o]LDL = low-density lipoprotein.
[p]All studies have high or unclear risk of bias.