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

Marshall, Skye; Petocz, Peter; Duve, Emily; Abbott, Kylie; Cassettari, Tim; Blumfield, Michelle; Fayet-Moore, Flavia

Published in:
Journal of the Academy of Nutrition and Dietetics

DOI:
10.1016/j.jand.2020.06.021

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

Skye Marshall[1,2], Peter Petocz[3], Emily Duve[4], Kylie Abbott[5,6], Tim Cassettari[7], Michelle Blumfield[8], Flavia Fayet-Moore[9*]

1. BNutrDiet(Hons), PhD, Accredited Practising Dietitian, Scientific and Education Director, Nutrition Research Australia, Sydney, New South Wales, Australia. skye@nraus.com
2. Senior Postdoctoral Research Fellow, Bond University Nutrition and Dietetics Research Group, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia.
3. PhD, Statistician, Nutrition Research Australia, Sydney, New South Wales, Australia. Peter.petocz@mq.edu.au
4. BPESS, MPH, Research Nutritionist, Nutrition Research Australia, Sydney, New South Wales, Australia. emily@nraus.com
5. Nutraceuticals Research Group, School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia. kylie@nraus.com
6. BNutrDiet (Hons), PhD, Research Dietitian, Nutrition Research Australia, Sydney, New South Wales, Australia.
7. BSc(Hons), BAppSc, Project Director, Nutrition Research Australia, Sydney, New South Wales, Australia. tim@nraus.com
8. BNutrDiet(Hons), PhD, Research Dietitian, Nutrition Research Australia, Sydney, New South Wales, Australia. michelle@nraus.com
9. BSc(Hons), MNutrDiet, PhD, Chief Executive Officer, Nutrition Research Australia, Sydney, New South Wales, Australia.

*Corresponding author and reprint contact: Flavia Fayet-Moore, flavia@nraus.com, Level 10, 20 Martin Place Sydney, New South Wales, Australia.

Manuscript words: 5360

Abstract words: 270

Keywords: Systematic review, meta-analysis, cardiovascular disease, whole grains, wholemeal.

Author contributions: FFM, SM, and TC designed the research; SM, KA, and ED conducted the research; SM and PP analysed the data; SM drafted the manuscript and led the GRADE assessment and clinical guideline; MB contributed to the GRADE assessment; TC, MB, KA, ED contributed to the GRADE clinical guideline; all authors critically appraised the manuscript. All authors have read and approved the manuscript.

Declaration of interests: 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.

Acknowledgements: The authors would like to acknowledge Mr David Honeyman, Librarian at Bond University, and Sara Grafenauer and Felicity Curtain from Grains & Legumes Nutrition Council of Australia for their feedback on the draft methods.

David and Sara have given their approval to be acknowledged this manuscript.

Funding statement: This study received funding from Grains & Legumes Nutrition Council of Australia.

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 CVD-related outcomes compared with refined grain or placebo?

Key findings: This systematic review and meta-analysis found that for adults with or without CVD risk factors, consuming whole grain as opposed to refined grain may improve some cardiovascular risk factors, including total and low-density lipoprotein cholesterol, triglycerides, HbA1c, and C-reactive protein.

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: In adults with or without chronic disease and/or associated risk factors, determine if interventions providing whole grain or whole pseudo-grain for dietary consumption improve CVD-related outcomes compared with refined grain or placebo.

Methods: A systematic review and meta-analysis of randomized controlled trials which compared whole grain versus 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. GRADE was used to determine the confidence in the pooled effects and to inform a clinical recommendation.

Results: 25 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 whole grain oats improved total cholesterol (SMD:-0.54[95%CI:-0.95,-0.12]) and LDL-cholesterol (SMD:-0.57[95%CI:-0.84,-0.31]) whole grain rice improved triglycerides (SMD:-0.22[95%CI:-0.44,-0.01]); and whole grains (all types) improved HbA1c (SMD:-0.33[95%CI:-0.61,-0.04]) and CRP (SMD:-0.22[95%CI:--0.44, -0.00]).

Conclusions: For adults with or without CVD risk factors, consuming whole grains as opposed to refined grains may improve total cholesterol, LDL-cholesterol, HbA1c, and CRP. 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.

Introduction

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 II diabetes mellitus (T2DM), gastrointestinal cancers, and cardiovascular disease (CVD) [1-3]. Whole grains are a category of cereal foods in which the grain is intact, or where the constituents are present in proportions which represent the intact grain [4]. The most common grains consumed by humans are durum wheat, oats, barley, rice, rye, sorghum, and maize/corn [5,6]. In addition, pseudo-grains such as buckwheat, quinoa, and amaranth are often considered as grains due to their nutritional, culinary, and flavor profile similarities with true grains [4]. The consumption of whole grains as opposed to refined grains, which contain primarily the endosperm starch, is recommended in dietary guidelines internationally [1,7,8] due to the strong nutritional profile of the bran and germ, which contain protein, dietary fiber, magnesium, potassium, selenium, zinc, iron, iodine, folate, niacin, folate, and vitamin E [9]. Whole grains are also an important source of phytochemicals and antioxidants, such as phenols, flavonoids, zeaxanthin, lutein, and beta-cryptoxanthin, and provide additional health benefits, such as reduced risk of CVD, type II diabetes, and some cancers, beyond the consumption of essential nutrients [10].

Cardiovascular disease is an umbrella term for a range of diseases which involve the heart and blood vessels, of which coronary heart disease (CHD), also known as ischemic heart disease, is the most common [11]. Four recent systematic reviews and meta-analyses of prospective cohort studies reported that a high intake of whole grains is associated with a 19-22% risk reduction in CVD and CHD incidence [12] and 15-32% risk reduction in CVD mortality [3,12-15]. Dose response relationships were identified at 50g [15] and 90g [1214] for risk reduction in CVD-mortality. Conversely, a recent systematic review and meta-analysis of randomized controlled trials (RCTs) by Kelly et al [16] found that there are no randomized

controlled trials (RCTs) which 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 et al [16] found insufficient evidence for an effect of whole grains on CVD risk factors. Although the review by Kelly et al [16] was of high quality, it applied a stringent eligibility criteria on the intervention duration (≥12 weeks) which led to only nine RCTs being included. Additionally, the review only considered blood pressure and blood lipid outcomes, 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 versus 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?

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 PRISMA guidelines. This study was prospectively registered at PROSPERO (CRD42019129403).

Whole grains and pseudo-grains

All grains and pseudo-grains were included in this review according to the international definition by the HEALTHGRAIN EU Consortium [4]. Specifically, these were wheat (including spelt, emmer, einkorn, Khorasan or kamut, durums, 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 EU Consortium definition: *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 referring to whole grains or whole pseudo-grains) if they contained >50% whole grain [4].

Eligibility criteria

Studies were deemed eligible if they were randomized controlled trials, cross-over trials, or pseudorandomized controlled trials. Other study designs such as reviews, observational cohort studies, or uncontrolled intervention studies were excluded. Table 1 outlines other

eligibility criteria according to the Participant, Intervention, Comparator, and Outcome (PICO) concept. An intervention duration of ≥8-weeks was chosen to allow for diet-related changes to impact upon CVD-related risk factors; however, studies which examine inflammatory and/or oxidative stress markers have study durations starting from a ranging from a 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 whilst capturing a sufficient number of studies. No minimum dose was considered as part of the eligibility criteria due to the large heterogeneity in whole grain dose reporting methods across the literature.

Study selection

Five electronic databases were searched from database inception to 8 March 2019: Pubmed, CINAHL, Embase, Web of Science, and Cochrane CENTRAL. The search strategy (Table 2) was designed in Pubmed and translated for other databases using Polyglot [17]. Following 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 21 February 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 which the systematic strategy may have missed. Two investigators ([redacted]) independently screened studies for eligibility via title and abstract, then full text ([redacted]) using Covidence systematic literature review software [Veritas Health Innovation, Melbourne, Australia] [18]. Full-text disagreements which could not be resolved by discussion were decided by a third independent investigator ([redacted]). 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; Excel for Office 365] spreadsheet by one investigator ([redacted]) and checked for accuracy thrice by two investigators ([redacted]). Data extracted were study and participant characteristics, baseline, follow-up, change in outcome, and p-value for between group comparisons. Where the change from baseline to follow-up was not reported it was calculated by the investigators. The data associated with this review have been published in Dryad [dataset] [19].

Review of study quality and GRADE assessment

Included studies were critically appraised using the Cochrane Risk of Bias tool [20] independently by two investigators ([redacted]). When an outcome was pooled by meta-analysis, all studies included in the meta-analysis were appraised by GRADE [21] using GRADEpro Guideline Development Tool [McMaster University, 2015, Evidence Prime, Inc] [22] 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 [22]. Publication bias of pooled outcomes were 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 [22]. The GRADE assessment and recommendation was led by one investigator ([redacted]), discussed and revised by a second investigator ([redacted]); 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 ([redacted]) using Comprehensive Meta-Analysis [23]. The data used in the meta-analyses were sample size (post-attrition), change in means (i.e. change from baseline to follow-up), and standard deviations (SD) in intervention and control groups 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; wheat), health status (healthy; at risk of CVD), and study quality (high risk of bias; moderate risk of bias; 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% confidence intervals (CI) 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 (SMD, the mean difference divided by the pooled standard error from the two groups) to account for differences in measurement units and measurement techniques, and to improve generalizability of consistent (i.e. low heterogeneity) results. SMD effect sizes of <0.4 were considered small, 0.4 – 0.7 moderate, and >0.7 large [24]. Where clinical interpretation of SMD was required, SMD effect sizes were re-expressed into the units by multiplying the SMD by the baseline standard deviation of one of the included studies [25]. The study chosen to inform the re-expressed units was based on the highest quality study which 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 if 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 two outcome variables (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 [26] and boot [27] packages in R [28]. Non-parametric bootstrapping was carried out using the approach described by Viechtbauer et al 2018 [29] with the outcomes in which the meta-analytical models approached significance but may be subject to bias [30]: HbA1c %, CRP/hCRP, and waist circumference. A variety of confidence intervals, representing different distributional assumptions, were obtained in each case.

Results

Results of the search strategy

The search strategy identified 10,706 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 1). Of the 30 publications, 25 were unique RCTs. One RCT had two eligible intervention arms, leading to a total of 26 included interventions. The main reason for exclusion was "wrong intervention", where the test product did not meet the HEALTHGRAIN EU 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 comparator group, where many RCTs compared the whole grain of interest against another whole grain (e.g. oats versus 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 3). None of the studies exclusively recruited participants with existing CVD. The CVD risk factors across studies were highly diverse, and included metabolic syndrome, T2DM, 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 n=1186 intervention participants and n=1109 control participants, with individual study total sample sizes ranging from n=12 to n=226 (Table 3). The three studies Giacco et al 2013, Giacco et al 2014, and Vetrani et al 2016 [31-33] appeared to have some of the same participants, as did three studies reported by Kirwan et al 2016, Malin et al 2019, and Malin et al 2019 [34-36], but the exact number of duplicated participants is unclear. Attrition ranged from 0% (n=7 studies) to 30%; and was either equal between groups or higher in the control group. 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 3).

Study design and quality

There were 10 cross-over RCTs and 15 parallel RCTs (Table 3). Twenty-four RCTs had two-arms (n=1 intervention group, n=1 control group), and one RCT had three-arms (n=2 intervention group, n=1 control group). Three RCTs were double-blinded, five were single-blinded, and the remaining 17 RCTs were open-label (Table 3).

Of the 25 included studies, n=7 had an intervention duration <8-weeks, which reported inflammatory and/or oxidative stress markers that were extracted as outcomes (Table 3). The remaining 18 RCTs ranged in duration from 8- to 16-weeks. To stabilize the diet prior to 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 3). Other approaches to control the background diet were usually the recommendation or provision of isocaloric diets; however, n=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 2; justifications in Table 4). 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 one 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 [31,33,35,37-51] , five had a high risk of bias [52-56], and eight had an unclear risk of bias [57-63]. 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 3). No pseudo-grain RCTs were identified which met this reviews' eligibility criteria. The daily dose of whole grains varied widely and was reported heterogeneously. Of those that reported whole grain dose in grams per day, it ranged from 60g to 150g; except for cooked rice which ranged from 150g to 400g. Where whole grains were not prescribed in a daily dose to all participants, whole grains may have been provided without a specific gram target (e.g. 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 (e.g. brown rice versus white/refined rice; mixed whole grain versus mixed refined grains) (Table 3). The exceptions were Kondo et al [45] which compared mixed whole grains against refined rice, Maki et al [54] and Pins et al [61] which compared whole grain oats against mixed refined grains, and Pick et al [60] which compared whole grain barley against refined wheat. Daily doses of refined grains were rarely reported; but among those that did report them, it ranged from 60g to 150g, and 15g to 400g for cooked rice, which aligns with the range in dose of the whole grain intervention. Plasma alkylresorcinol was measured by nine RCTs; all of which reported a significantly higher level in the intervention arms (ranging from 122 to 380nmol/L) compared to control arms (ranging from 30 to 134nmol/L), indicating intervention fidelity (Table 3).

The number of RCTs which reported a statistically significant improvement between groups is reported in Table 3. There were 40 outcome variables reported across all included RCTs; which could be grouped into the following outcome 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 six RCTs reported oxidative stress markers, and two 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 one or more RCT report a statistically significant improvement in the whole grain intervention compared to refined grain comparator. For six outcomes (15%), a significant difference between groups was reported to favor whole grain in some studies and refined grain in others; and one outcome (fat free mass) was reported to favor refined grain alone (Table 5). 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 2-16% which was comparable between intervention and control arms [49,54,57,61]. There was also one case of faintness reported in the intervention group [41] and one case of gastroenteritis in the control group [54].

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 6). Three publications [42,43,56] reported results for the intervention and/or comparator groups by

subgroup (e.g. males and females separately); leading to 23 intervention groups 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 two 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 9-18 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 6; justifications in Table 7); 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, -0.12] re-expressed as -20.8mg/dL [-0.54mmol/L], p=0.011, n=232 [IG: 122, CG: 110], I^2: 56.9%, GRADE level of evidence: very low; Figure 3) and LDL cholesterol (SMD: -0.57 [95%CI: -0.84, -0.31] re-expressed as -16.7mg/dL [-0.43mmol/L], p<0.0001, n=232 [IG: 122, CG: 110], I^2: 0%; GRADE level of evidence: very low; Figure 4) compared to refined grains. Standard deviations of baseline total and LDL cholesterol in the intervention group reported by Pins et al. [61] was 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, -0.01] re-expressed as -1.6mg/dL [-0.02mmol/L], p=0.040, n=338 [IG: 171, CG: 167], I^2: 0%, GRADE level of evidence: very low). The triglyceride standard deviation from the intervention group in Araki et al [49] was used to re-express SMD to mg/dL.

Subgroup analysis found that mixed whole grains decreased (i.e. negative direction) HDL cholesterol in comparison to mixed refined grains (SMD: -0.17 [95%CI: -0.33, -0.01] re-

expressed as -2.0mg/dL [-0.06 mmol/L], p=0.037, n=590 (IG: 292, CG: 298), I^2: 0%, GRADE level of evidence: high). However, in moderate quality studies (i.e. unclear risk of bias), whole grains improved HDL cholesterol (SMD: 0.33 [95%CI: 0.05, 0.62] re-expressed as 3mg/dL [0.08mmol/L], p=0.022, n=490 (IG: 255, CG: 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, standard deviations from Giacco et al 2013 [32] and Pins et al [61] were used respectively.

Further subgroup analysis by study quality found that in higher quality studies (i.e. low risk of bias), whole grains improved CRP (SMD: -0.22 [95%CI: -0.44, -0.00] re-expressed as -0.7mg/L, p=0.048, n=671 (intervention group (IG): 311, comparator group (CG): 360), I^2: 45.7%, GRADE level of evidence: moderate); and decreased HbA1c (SMD: -0.33 [95%CI: -0.61, -0.04] re-expressed as -0.2%, p=0.025, n=194 (IG: 97, CG: 97), I^2: 0%, GRADE level of evidence: moderate). CRP and HbA1c standard deviation from the intervention group reported Kirwan et al [34] was used to re-express the CRP and HbA1c SMD for clinical interpretation. No other subgroup analyses found significant findings; however, study samples which had CVD risk factors approach a significant decrease in triglycerides (SMD: -0.13 [95%CI: -0.23, 0.03], p=0.065, n=10 studies).

The non-parametric bootstrapped meta-analyses were HbA1c SMD: -0.27 (95%CI: -0.44, 0.39), for CRP/hs-CRP SMD: -0.25 (95%CI: -0.45, 0.25), and waist circumference SMD: -0.10 (95%CI: -0.21, 0.08).

Discussion

The benefits of consuming whole grains to human health is well established, due to their nutrient and antioxidant profile and strong association with improved chronic disease outcomes, including reduced T2DM and gastrointestinal cancer risk [1,2,10]. Despite the dose-

response relationship for decreased risk of CVD-related death reported by meta-analyses of observational data [12,14]; 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 [64], but had very low confidence that this estimated effect represented the true effect.

Unexpectedly, there was high confidence that mixed whole grains had a small (re-expressed as -2.0mg/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 (CETP) activity, which replaces cholesterol esters in HDL particles with triglycerides. Triglyceride-rich HDL particles are substrates for hepatic lipase, which promotes HDL cholesterol clearance [65]. There was no effect of mixed grains on triglyceride levels, suggesting that an effect on CETP activity does not explain the observed difference in HDL-cholesterol. Most mixed grain studies used wheat, rye, rice, and/or oats, while two studies included barley. However, neither oats, rice, nor wheat showed independent effects on HDL-cholesterol in the meta-analysis and are thus 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 (3mg/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.

374 The present findings align with those reported by Kelly et al. [16], who reviewed nine whole
375 grain RCTs with durations ≥12-weeks, in that the included studies have inherent limitations,
376 and findings may be subject to change with additional research. This is particularly the case
377 among those with existing CVD, as the study populations in this review were predominantly
378 healthy or had only mild-to-moderate CVD risk factors. Having relatively healthy samples
379 may explain both the finding of no overall pooled effect of whole grains compared to refined
380 grains on CVD risk factors, as well as the finding that some subgroup improvement CVD risk
381 factors were of statistical but not clinical significance. For example, it is unlikely that an
382 improvement in CRP, SBP, or HbA1C would occur among those who do not have elevated
383 CRP, SBP, or HbA1C at baseline. Similarly, the systematic review and meta-analysis by
384 Hollander et al [66], which evaluated the effect of whole grains on blood lipids in healthy
385 populations only, found no significant pooled effects of whole grains, except for the beta-
386 glucan containing subgroups. Although some studies measured adherence to the allocated
387 groups objectively through plasma alkylresorcinol, many RCTs did not measure adherence to
388 the intervention and/or control and dietary intake could have possibly been too low to detect a
389 significant change in CVD risk factors. Interpretation of findings is substantially limited by
390 the poor reporting of whole grain daily dose; where dosages of both intervention and test
391 products is not able to be determined. Few studies reported whole grain intake as dose per
392 day as recommended by Ross et al. [67] Other limitations include poorly reported dosage of
393 refined grains, inadequately controlled and/or measured background diet, and the possibility
394 of underpowered models due to the small number of included studies in each model,
395 particularly in subgroups.
396 Differences between meta-analyses of RCTs and prospective cohort studies on whole grain
397 and CVD must also be acknowledged. Pooled data from prospective cohort studies is derived
398 from participants who have been following a dietary pattern either rich or poor in whole

399 grains for many years, and sometimes decades [12,14]; and the potential for whole grains to have
400 a preventive and/or treatment effect is increased. This contrasts with the identified
401 interventional research, which is limited by study duration ranging between 2- to 16-weeks.
402 Recalling that diet-related etiologies of chronic disease have long latency periods; it is
403 difficult to detect significant effects in a short timeframe. Considering some subgroups found
404 significant improvements in inflammation, glycemia, and blood lipids, it is possible that with
405 an increased intervention duration and investigations targeted at those with elevated risk
406 factors, improvements in CVD incidence and death may be observed. Additional research is
407 required to confirm this hypothesis. The importance of intervention duration is emphasized
408 by the types of outcomes measured in prospective cohort studies, which include CVD-related
409 death and events, including myocardial infarctions and strokes [12,14]. This is in contrast with
410 RCTs which are limited to measuring CVD risk markers, and thus, indirect CVD outcomes.
411 Despite attempts to control for confounding variables in observational data, the improved
412 CVD outcomes in the meta-analyses of observational data may represent the effects of
413 broader dietary and lifestyle patterns. Participants in cohort studies who reported consuming
414 whole grains as opposed to refined grains may be those who adhere to a healthier lifestyle;
415 and over many years this lifestyle presents multiple confounding factors which are inherently
416 difficult to measure and account for [68]. The finding that some refined grain arms of RCTs had
417 higher attrition than the whole grain arms also suggests that low whole grain consumers in
418 observational studies may not necessarily be high refined grain consumers. In observational
419 research, it is possible that low whole grain consumers replace whole grains with
420 discretionary foods rather than refined grain core foods, thereby creating a greater
421 discrepancy in the diet quality of the two groups, leading to a greater observed effect size in
422 high whole grain consumers. It must be remembered that grains are recommended by dietary
423 guidelines as a core food group; although guidelines recommend they should be consumed

mostly as whole grains and/or higher fiber varieties, refined grains are not considered discretionary foods [1,7,8].

Of clinical significance, the RCTs in this review reported that participants either had equal or lower attrition in the whole grain group, as well as a 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 towards the intervention and is strengthened by observational and economic research (Table 8) [12,14,15,69]. 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 cardiovascular disease is valued by all stakeholders and is feasible to implement considering grains being a staple food to many cultures and countries, and dietary guidelines already recommending that grains should be consumed as a whole grain. 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 upon low income families [70] (Table 8).

Limitations of this review

Whilst 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

449 review. The review was not able to evaluate the effect of whole grains on CVD outcome; and
450 it should be highlighted that all outcomes reported are indirect measures of CVD risk only. It
451 was beyond the scope of this review to examine a dose-response relationship through meta-
452 regression. Finally, although funnel plots did not detect publication bias, this may have been
453 due to the small number of included studies in each model.

454 Implications for future research

455 The effect of whole grain intake on CVD is of high interest to both the individual and to
456 governments, as CVD is the leading cause of noncommunicable disease deaths worldwide [71].
457 Future RCTs are required which compare whole grain versus refined grain for all grain and
458 pseudo grain varieties, especially rye, maize, teff, amaranth, triticale, or unique varieties of
459 wheat such as kamut or spelt. Future RCTs need to be well-powered and use parallel design
460 so as to allow for substantially longer intervention durations; such as that used in
461 PREDIMED [72]. Additionally, whole grain products should be tested for the potential to
462 improve both CVD risk factors and events in samples with existing CVD at baseline. Studies
463 should control and/or measure background diet and medications carefully, so the effect of the
464 whole grain as opposed to other diet and lifestyle factors can be understood. The dosage of
465 whole grain intake should be reported in grams per day as recommended by Ross et al. [67]
466 Finally, CVD related outcomes should be accompanied by feasibility evaluations to better
467 inform dietary guidelines and public health policy.

Conclusion

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 cardiovascular disease, particularly among those with existing CVD risk factors.

Figure Legends

Figure 2: Risk of bias summary: a review of investigators' judgements about each risk of bias item for all included randomized controlled trials, as guided by the Cochrane risk of bias tool [20]which compared whole grain or whole pseudo-grain interventions and placebo or refined grain controls in humans.

Figure 3: Whole grain oats compared with refined mixed grains had a significant effect on total cholesterol (SMD: -0.54 [95%CI: -0.95, -0.12], I^2: 56.9%, p=0.011) when pooling results of two randomized controlled trials during subgroup analysis by grain type.

Figure 4: Whole grain oats compared with mixed refined grains had a significant effect on LDL cholesterol (SMD: -0.57 [95%CI: -0.84, -0.31], p<0.0001, n=232 [IG: 122, CG: 110], I^2: 0%) when pooling results of two randomized controlled trials during subgroup analysis by grain type.

References

1. *Australian Dietary Guidelines.* Canberra: NHMRC, 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. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/571/CN-01015571/frame.html. Accessed Nov-Dec.
6. Arterburn D, Flum DR, Westbrook EO, 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.
7. 2015 Intergenerational Report. In. treasury.gov.au: Commonwealth of Australia; 2015.
8. Choices N. The Eatwell Guide. In:2016.
9. Australian Food Composition Database. In: Zealand FSAN, ed. foodstandards.gov.au: Food Standards Australia New Zealand; 2019.
10. Liu RH. Whole grain phytochemicals and health. *J Cereal Sci.* 2007;46(3):207-219.
11. Global atlas on cardiovascular disease prevention and control In: Organisation WH, ed. https://www.who.int: World Health Organisation; 2011.
12. 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.
13. 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.
14. 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.
15. 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.
16. Kelly SA, Hartley L, Loveman E, et al. Whole grain cereals for the primary or secondary prevention of cardiovascular disease. *Cochrane Database Sys Rev.* 2017(8).
17. 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).

18. *Covidence systematic review software* [computer program]. Melbourne, Australia: Veritas Health Innovation.
19. Marshall S, Poetocz P, Duve E, et al. Systematic review data of whole grains versus placebo on cardiovascular disease risk factors, Dryad [dataset]. https://doi.org/10.5061/dryad.n2z34tmth2020
20. 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.
21. *Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013.* http://gdt.guidelinedevelopment.org2013.
22. *GRADEpro GDT: GRADEpro Guideline Development Tool [Software]* [computer program]. McMaster University; 2015.
23. Borenstein M, Hedges VL, Higgins JPT, et al. *Comprehensive Meta-Analysis; version 2* [computer program], Englewood, New Jersey: Biostat; 2006.
24. Higgins, Julian, Green. 17.8.2 Study summaries using more than one patient-reported outcome. In: *Cochrane handbook for systematic reviews of interventions;* 2011.
25. Higgins, Julian, Green. 12.6.4 Re-expresing SMD using a familiar instrument. In: *Cochrane handbook for systematic reviews of interventions.*2011.
26. *metafor: A Meta-Analysis Package for R, Version 2.1-0* [computer program]. 2019.
27. *Bootstrap Functions, Version 1.3-23* [computer program]. 2019.
28. *R: A language and environment for statistical computing; version 3.6. 1* [computer program]. Vienna: R Foundation for Statistical Computing; 2019. Retrieved from: http://www.R-project.org/.
29. Viechtbauer W. Bootstrapping with Meta-Analytic Models. 2018. Accessed 01.20.2019.
30. Van Den Noortgate W, Onghena P. Parametric and nonparametric bootstrap methods for meta-analysis. *Behav Res Methods.* 2005;37(1):11-22.
31. 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.
32. 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.
33. 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. *Nutr.* 2016;32(2):217-221.
34. 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.
35. 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.
36. 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.

37. Ampatzoglou A, Williams C, Atwal K, et al. Effects of increased wholegrain consumption on immune and inflammatory markers in healthy low habitual wholegrain consumers. *Eur J Nutr.* 2016;55(1):183-195.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. 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.
47. 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.
48. 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.
49. 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.
50. 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.

51. 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.
52. 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.
53. 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.
54. 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.
55. 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.
56. Shimabukuro M, Higa M, Kinjo R, et al. Effects of the brown rice diet on visceral obesity and endothelial function: The BRAVO study. *Brit J Nutr.* 2014;111(2):310-320.
57. 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.
58. 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.
59. 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.
60. 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.
61. 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.
62. 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):e70436.
63. 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.
64. 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. *Brit J Nutr.* 2016;116(8):1369-1382.
65. Zhou L, Li C, Gao L, Wang A. High-density lipoprotein synthesis and metabolism. *Mol Med Rep.* 2015;12(3):4015-4021.
66. 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.

67. 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.
68. McEvoy CT, Temple N, Woodside JV. Vegetarian diets, low-meat diets and health: a review. *Public Health Nutr.* 2012;15(12):2287-2294.
69. Rahkovsky I, Gregory CA. Food prices and blood cholesterol. *Econ Hum Biol.* 2013;11(1):95-107.
70. Jetter KM, Cassady DL. The availability and cost of healthier food alternatives. *Am J Prev Med.* 2006;30(1):38-44.
71. Global status report on noncommunicable diseases. In. who.int: WHO; 2014.
72. 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.

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 cardiovascular disease risk.

How does this research add to knowledge on this topic? This systematic review of randomised controlled trials examines the cause-and-effect relationship between whole grain intake and cardiovascular disease risk.

How might this knowledge impact current dietetics practice? Choosing whole grains is recommended for populations to improve cardiovascular disease risk but evidence is not convincing enough to use whole grains as a cardiovascular disease treatment approach.

Online Supplementary Material 1

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

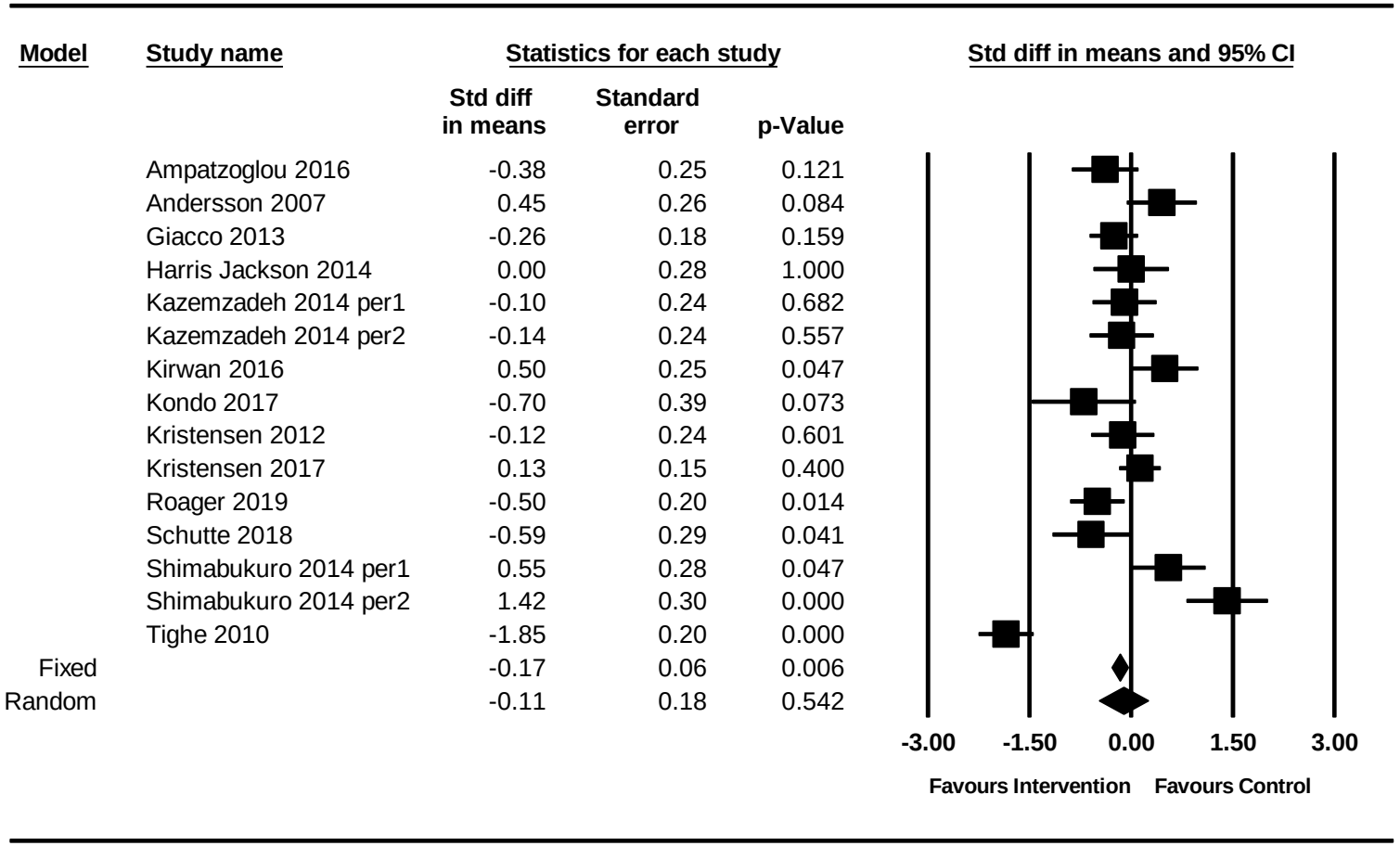
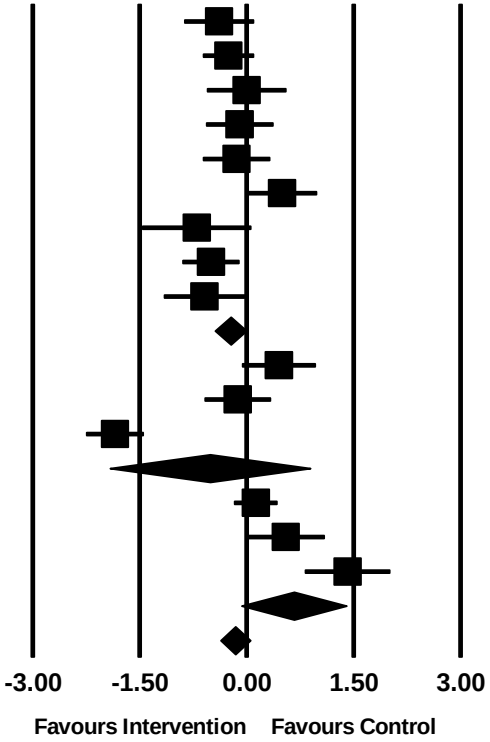


Figure S1: Whole grains compared with refined grains has no significant effect on CRP/hs-CRP (SMD: -0.11 [95%CI: -0.47, 0.25], I^2: 88.9%, p=0.542).

Online Supplementary Material 1

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

Group by Quality	Study name	Std diff in means	Standard error	p-Value
A	Ampatzoglou 2016	-0.38	0.25	0.121
A	Giacco 2013	-0.26	0.18	0.159
A	Harris Jackson 2014	0.00	0.28	1.000
A	Kazemzadeh 2014 per1	-0.10	0.24	0.682
A	Kazemzadeh 2014 per2	-0.14	0.24	0.557
A	Kirwan 2016	0.50	0.25	0.047
A	Kondo 2017	-0.70	0.39	0.073
A	Roager 2019	-0.50	0.20	0.014
A	Schutte 2018	-0.59	0.29	0.041
A		-0.22	0.11	0.048
B	Andersson 2007	0.45	0.26	0.084
B	Kristensen 2012	-0.12	0.24	0.601
B	Tighe 2010	-1.85	0.20	0.000
B		-0.51	0.72	0.475
C	Kristensen 2017	0.13	0.15	0.400
C	Shimabukuro 2014 per1	0.55	0.28	0.047
C	Shimabukuro 2014 per2	1.42	0.30	0.000
C		0.67	0.38	0.076
Overall		-0.16	0.11	0.140

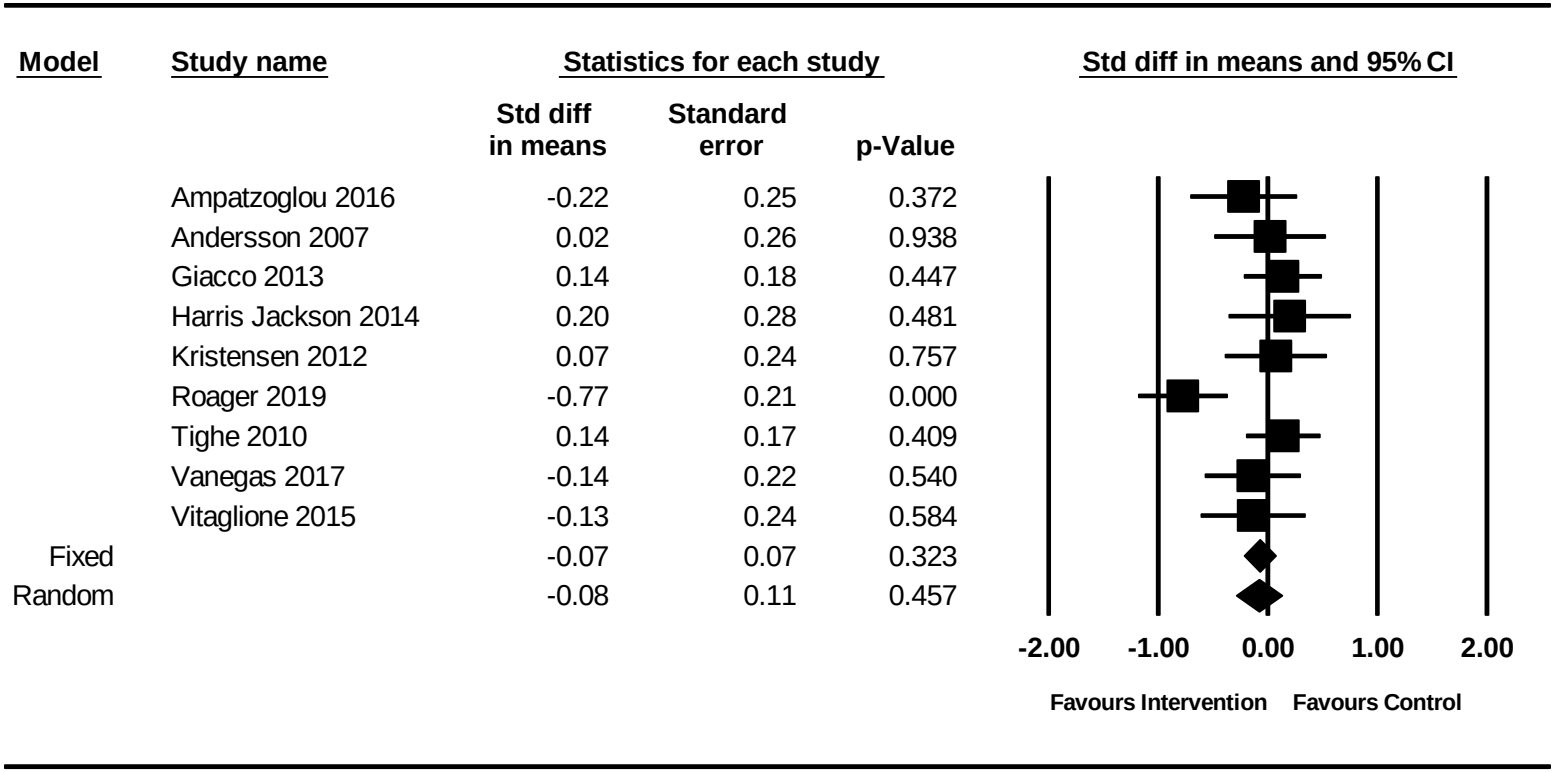


CRP and hsCRP

Online Supplementary Material 1

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

Figure S2: Whole grains compared with refined grains has a significant effect on CRP/hs-CRP (SMD: -0.22 [95%CI: -0.44, -0.00, p=0.048, I^2: 45.7%) for the high quality study subgroup only (A, high quality; B, unclear quality; C, low quality).



IL-6

Figure S3: Whole grains compared with refined grains has no significant effect on IL-6 (SMD: -0.08 [95%CI: -0.29, 0.13], I^2: 51.0%, p=0.450).

Online Supplementary Material 1

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

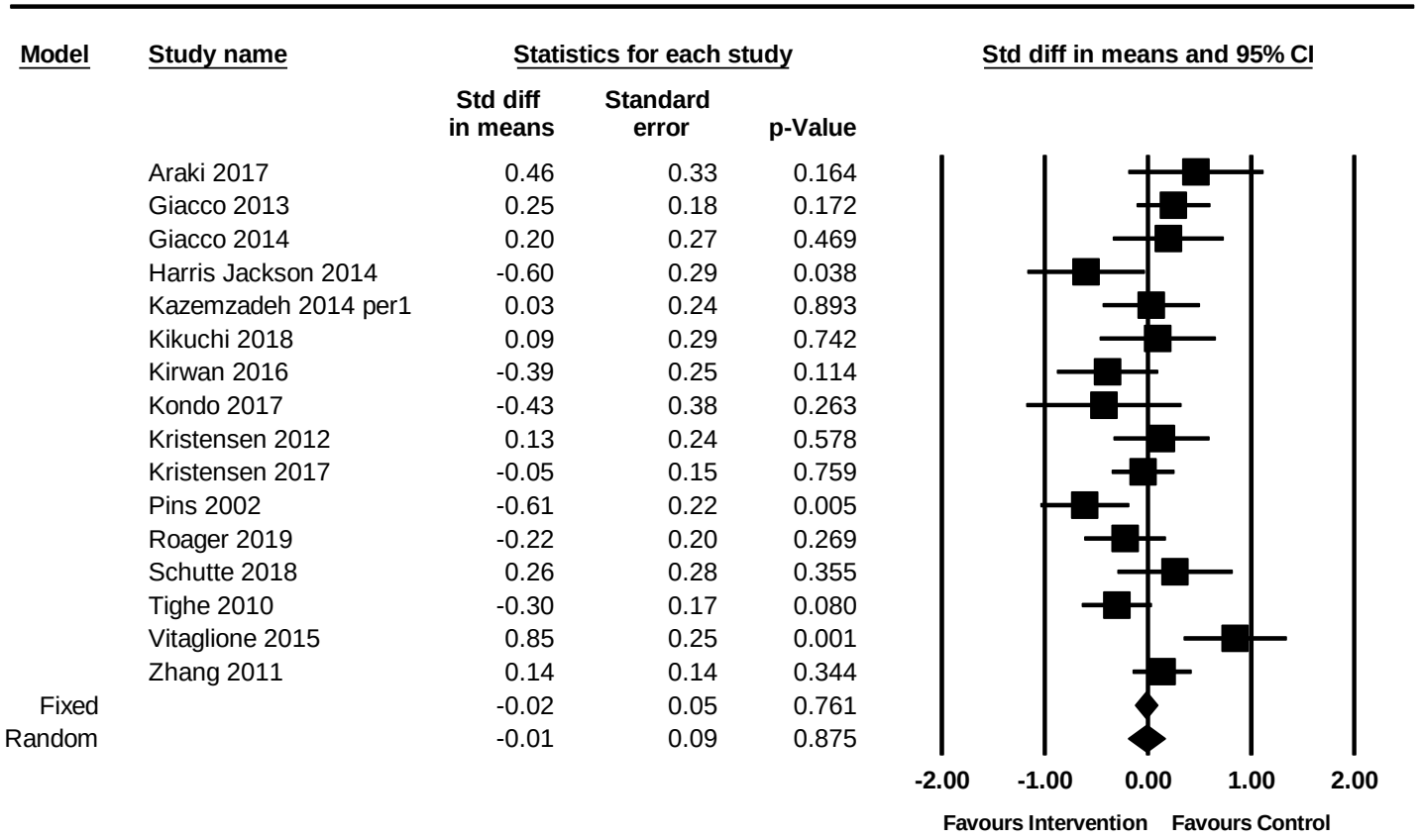


Figure S4: Whole grains compared with refined grains has no significant effect on fasting plasma glucose (SMD: -0.01 [95%CI: -0.19, 0.16], I^2: 60.4%, p=0.875).

Online Supplementary Material 1

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

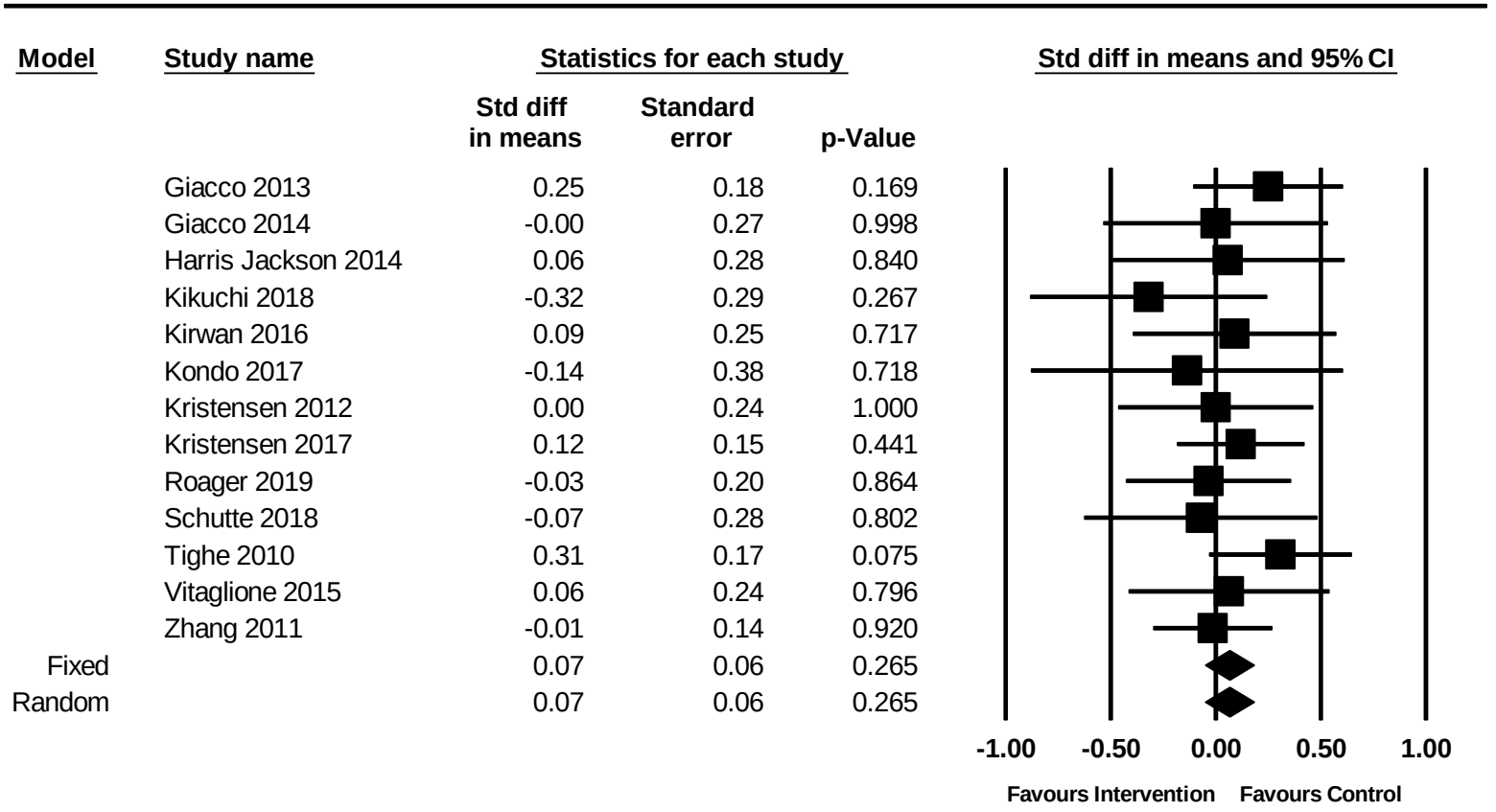


Figure S5: Whole grains compared with refined grains has no significant effect on fasting plasma insulin (SMD: 0.07 [95%CI: -0.05, 0.18], I^2: 0%, p=0.265).

Online Supplementary Material 1

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

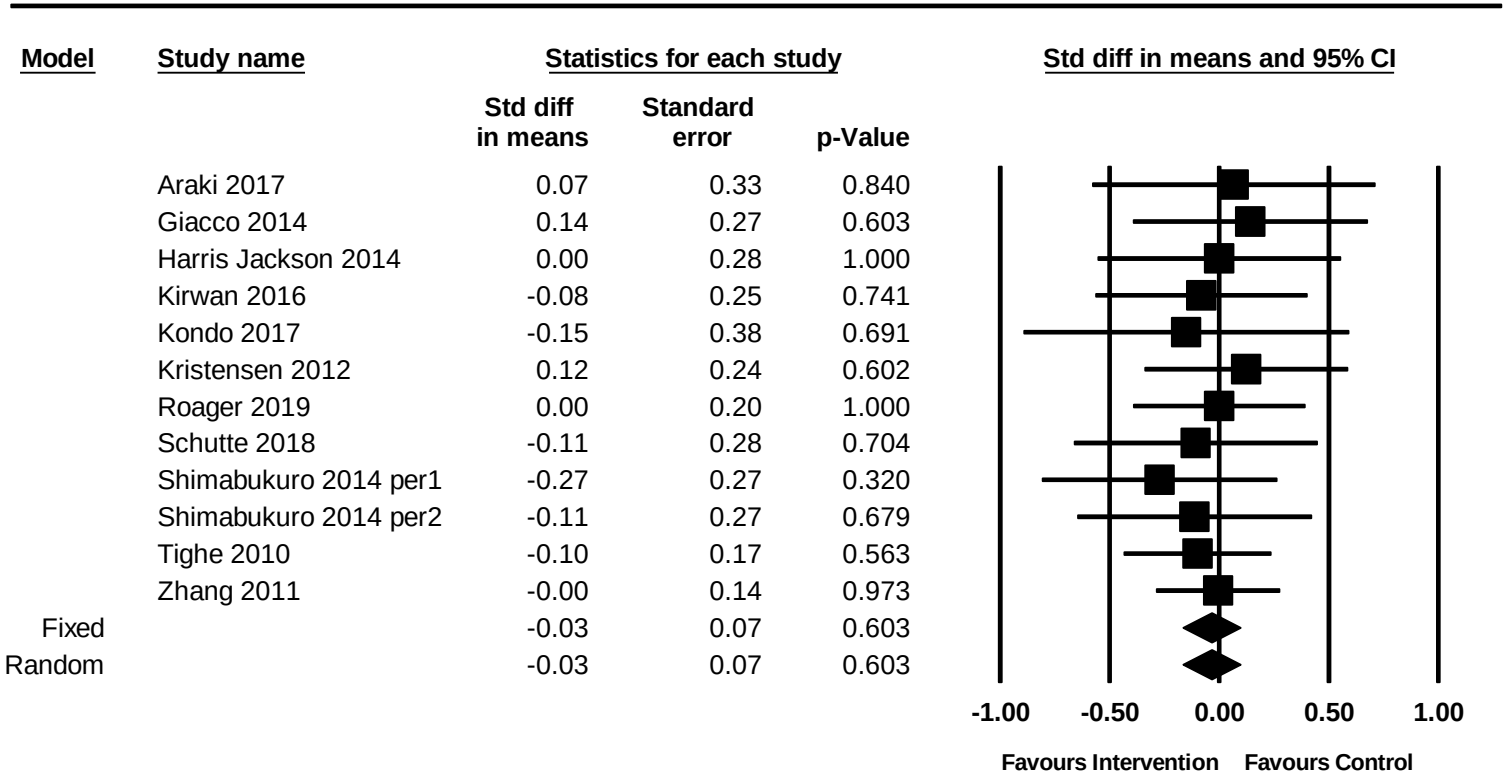


Figure S6: Whole grains compared with refined grains has no significant effect on HOMA-IR (SMD: -0.03 [95%CI: -0.17, 0.10], I^2: 0%, p=0.603).

Online Supplementary Material 1

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

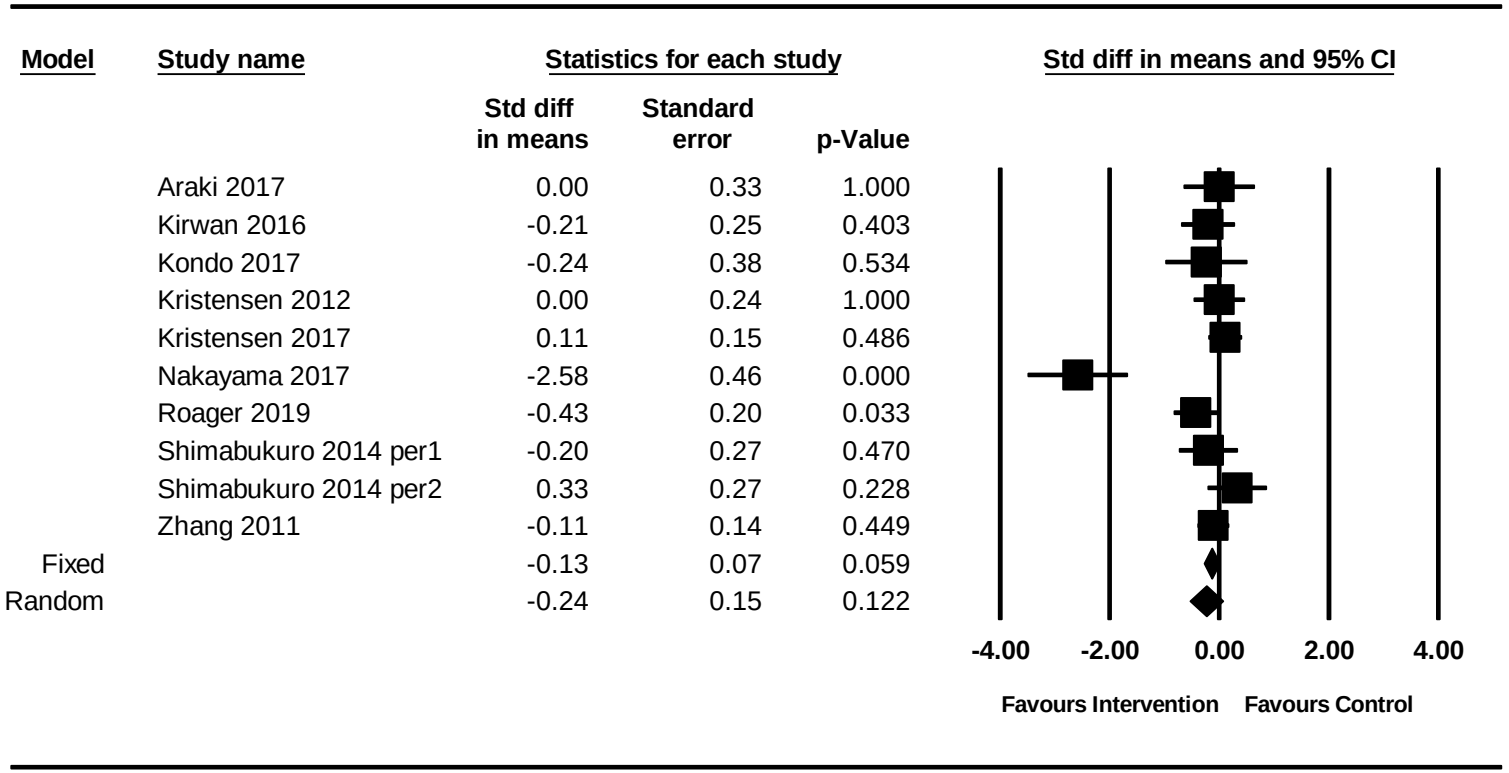


Figure S7: Whole grains compared with refined grains has no significant effect on HbA1c (SMD: -0.24 [95%CI: -0.53, 0.06] %, I^2: 75.0%, p=0.122).

Online Supplementary Material 1

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

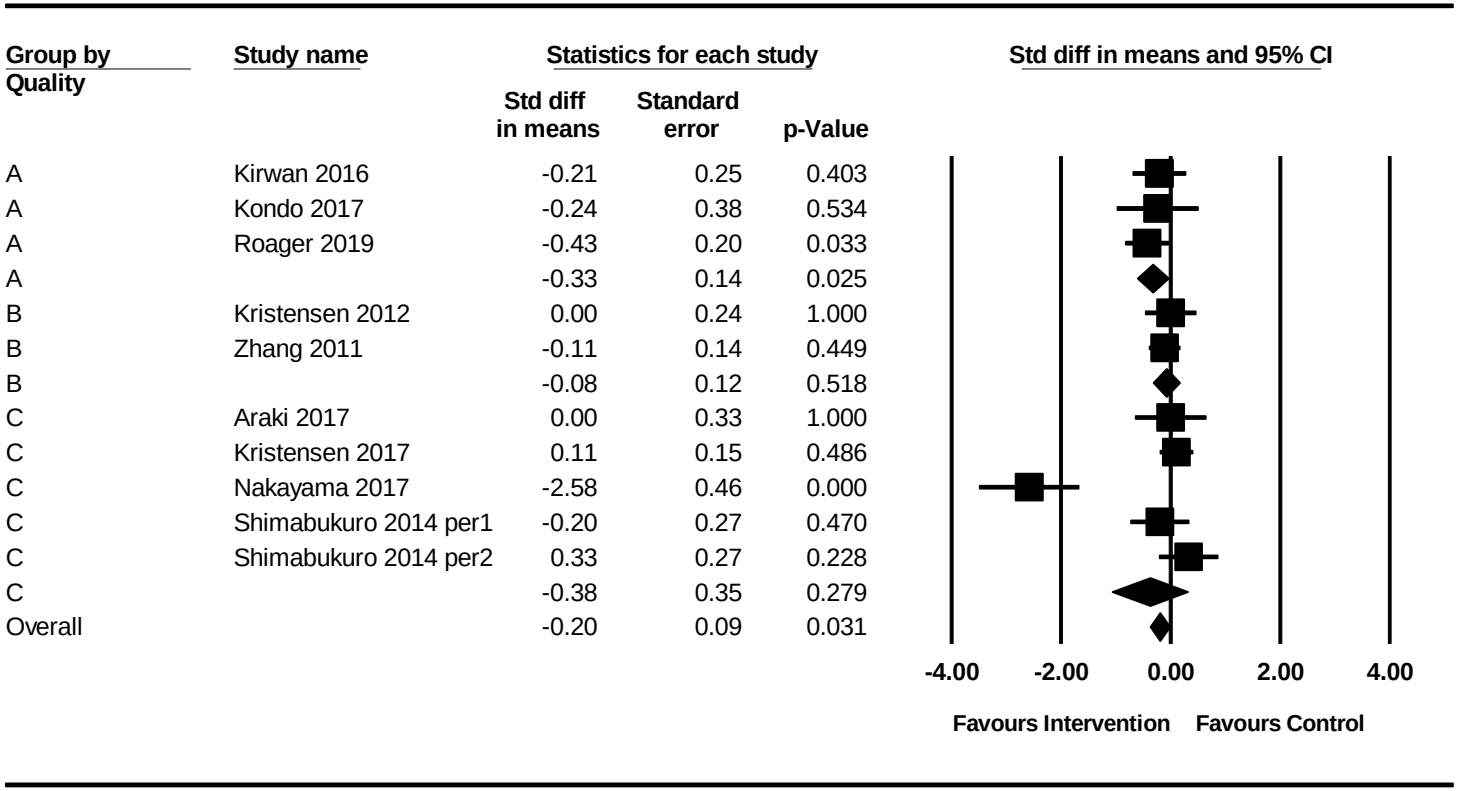


Figure S8: Whole grains compared with refined grains has a significant effect on HbA1c (SMD: -0.33 [95%CI: -0.61, -0.04] %, I^2: 0%, p=0.025) for the high quality study subgroup only (A, high quality; B, unclear quality; C, low quality).

Online Supplementary Material 1

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

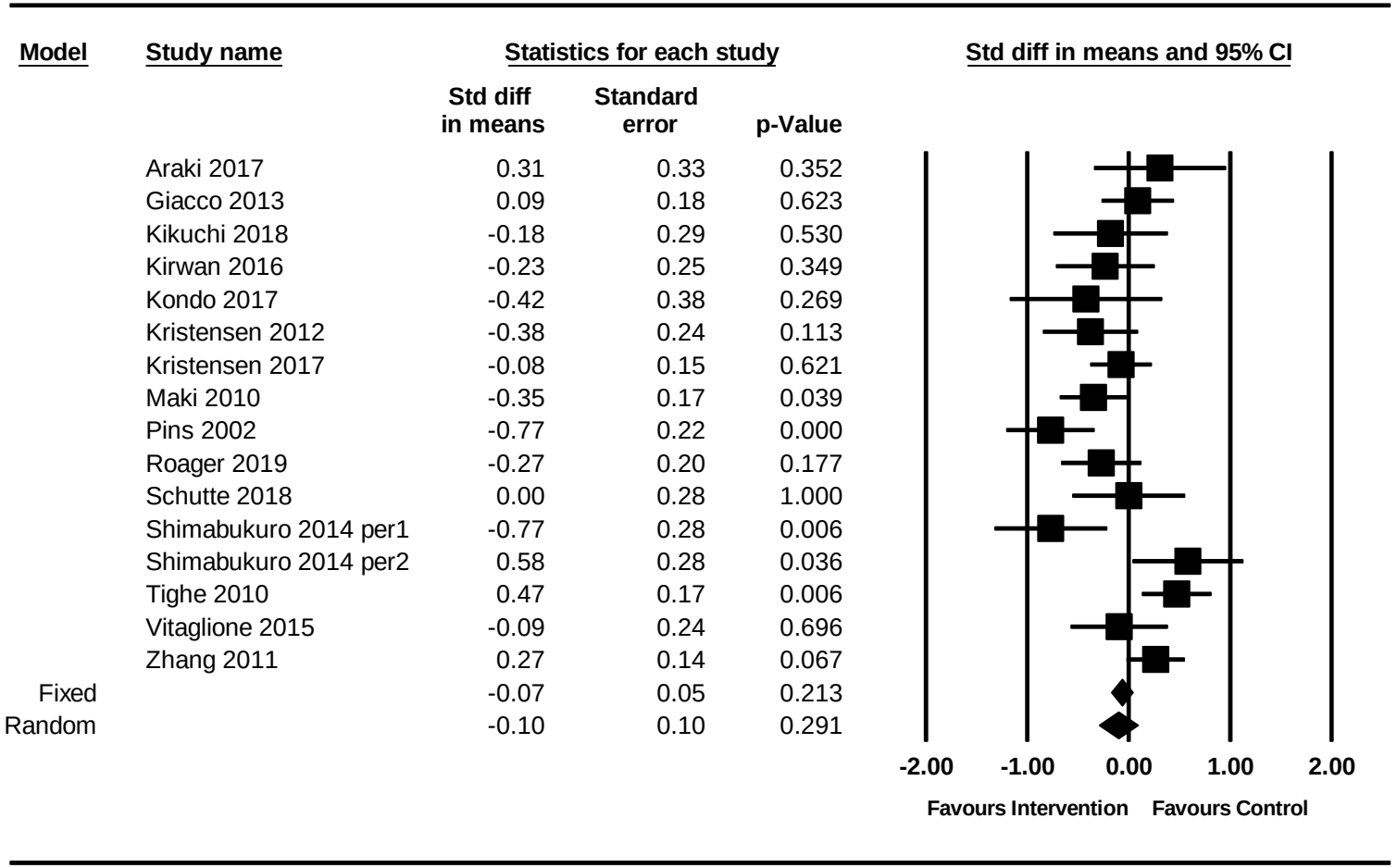


Figure S9: Whole grains compared with refined grains has no significant effect on total cholesterol (SMD: -0.10 [95%CI: -0.29, 0.09] mmol/L, I^2: 67.3%, p=0.291).

Online Supplementary Material 1

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

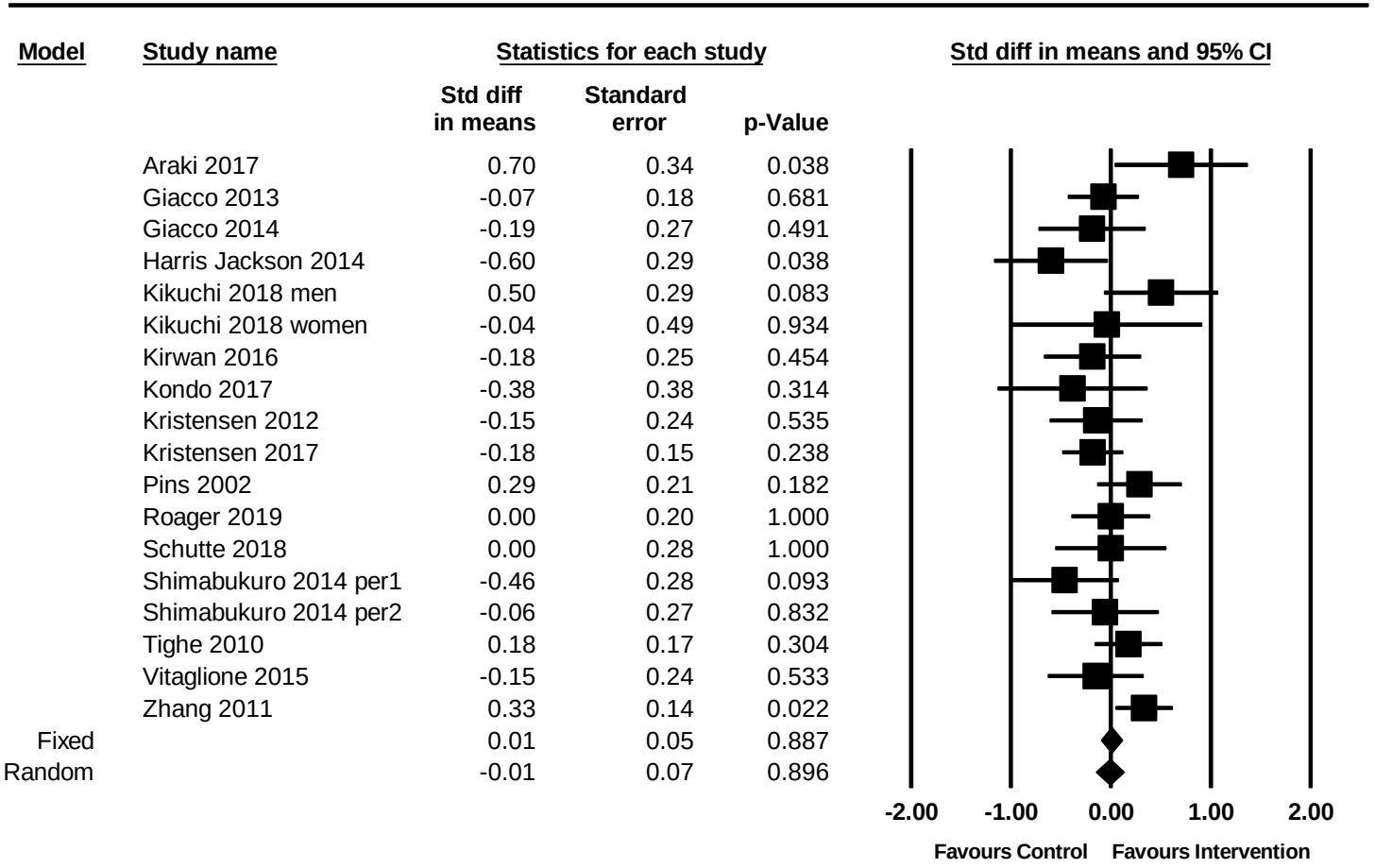


Figure S10: Whole grains compared with refined grains has no significant effect on HDL-cholesterol (SMD: -0.01 [95%CI: -0.15, 0.13], I^2: 38.7%, p=0.896).

Online Supplementary Material 1

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

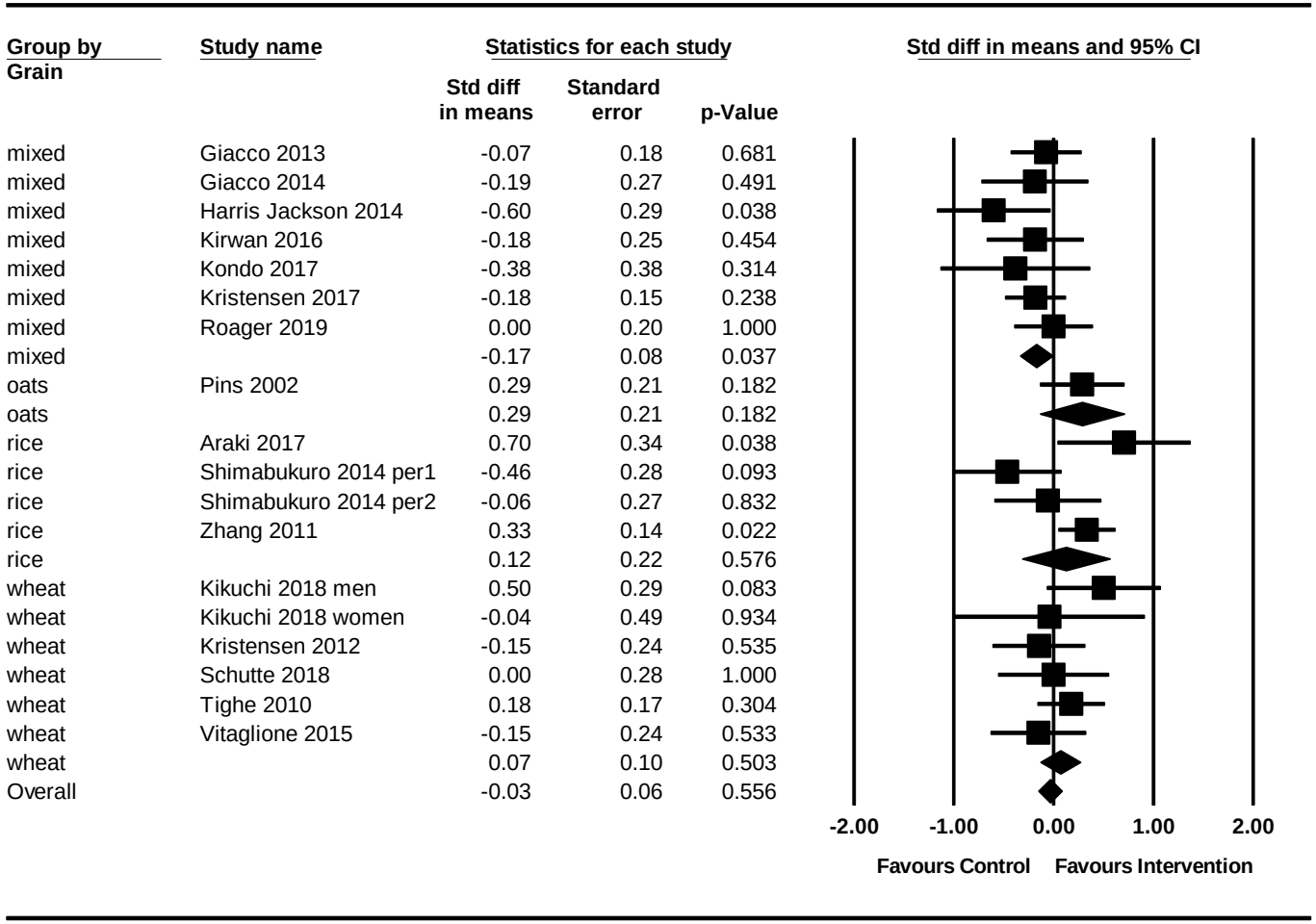
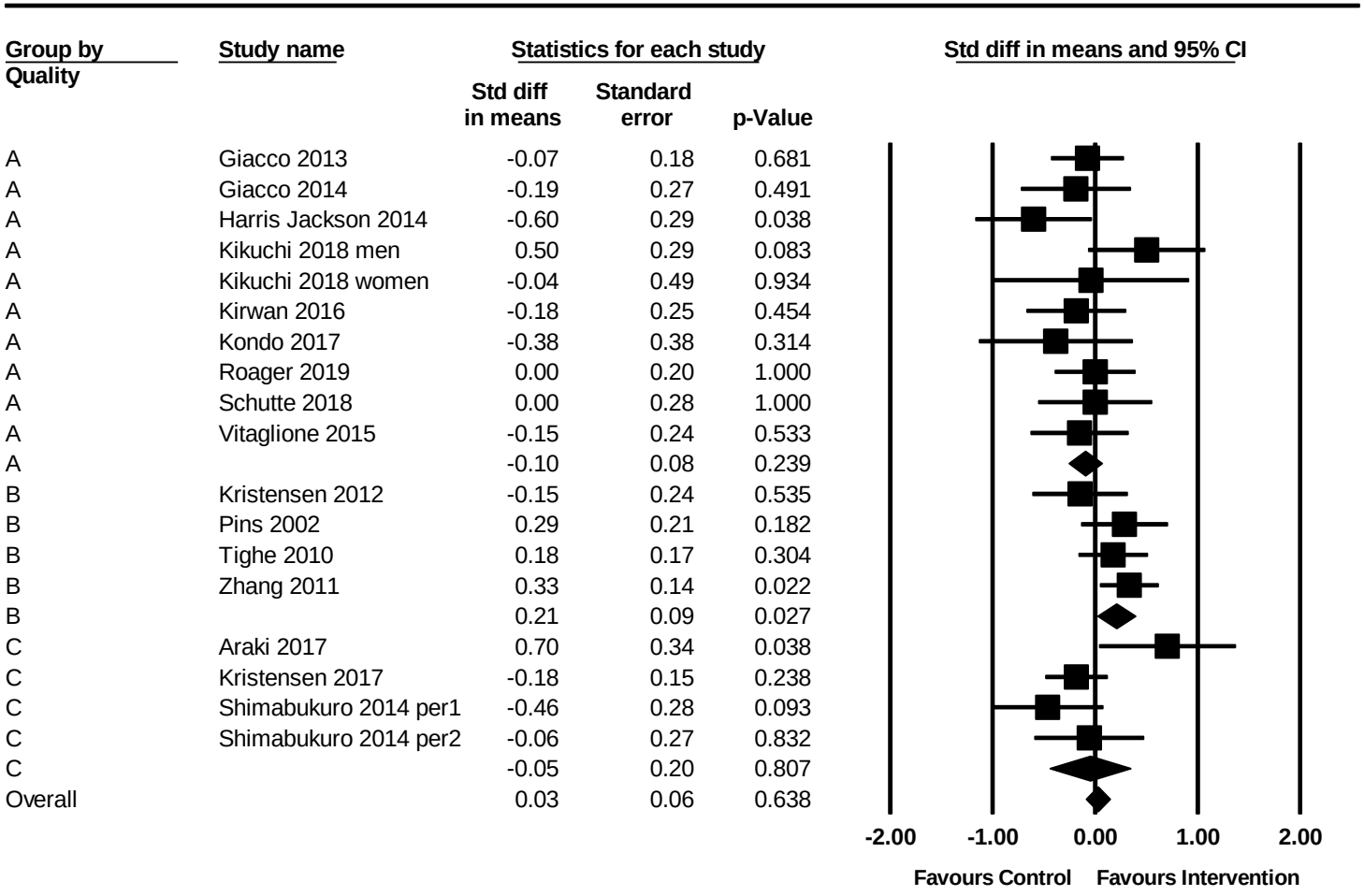


Figure S11: Mixed whole grains compared with refined grains has decreases HDL cholesterol (SMD: -0.17 [95%CI: -0.33, -0.01], I^2: 0%, p=0.037) for the high quality study subgroup only (A, high quality; B, unclear quality; C, low quality).

Online Supplementary Material 1

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

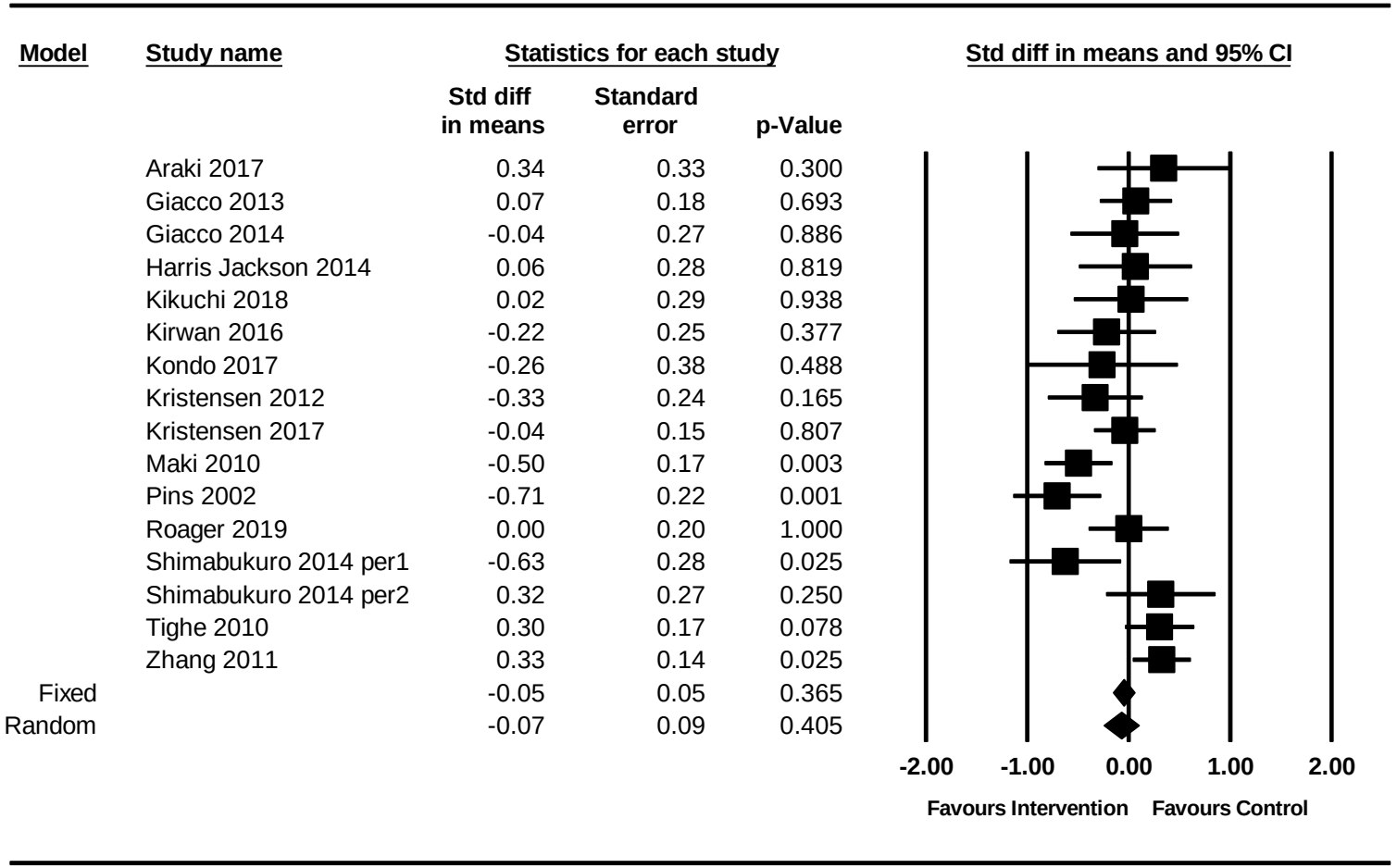


Group by Quality	Study name	Std diff in means	Standard error	p-Value
A	Giacco 2013	-0.07	0.18	0.681
A	Giacco 2014	-0.19	0.27	0.491
A	Harris Jackson 2014	-0.60	0.29	0.038
A	Kikuchi 2018 men	0.50	0.29	0.083
A	Kikuchi 2018 women	-0.04	0.49	0.934
A	Kirwan 2016	-0.18	0.25	0.454
A	Kondo 2017	-0.38	0.38	0.314
A	Roager 2019	0.00	0.20	1.000
A	Schutte 2018	0.00	0.28	1.000
A	Vitaglione 2015	-0.15	0.24	0.533
A		-0.10	0.08	0.239
B	Kristensen 2012	-0.15	0.24	0.535
B	Pins 2002	0.29	0.21	0.182
B	Tighe 2010	0.18	0.17	0.304
B	Zhang 2011	0.33	0.14	0.022
B		0.21	0.09	0.027
C	Araki 2017	0.70	0.34	0.038
C	Kristensen 2017	-0.18	0.15	0.238
C	Shimabukuro 2014 per1	-0.46	0.28	0.093
C	Shimabukuro 2014 per2	-0.06	0.27	0.832
C		-0.05	0.20	0.807
Overall		0.03	0.06	0.638

HDL cholesterol

Figure S12: Whole grains compared with refined grains increases HDL cholesterol (SMD: 0.21 [95%CI: 0.02, 0.39], I^2: 5.1%, p=0.027) for the

unclear quality study subgroup only (A, high quality; B, unclear quality; C, low quality).

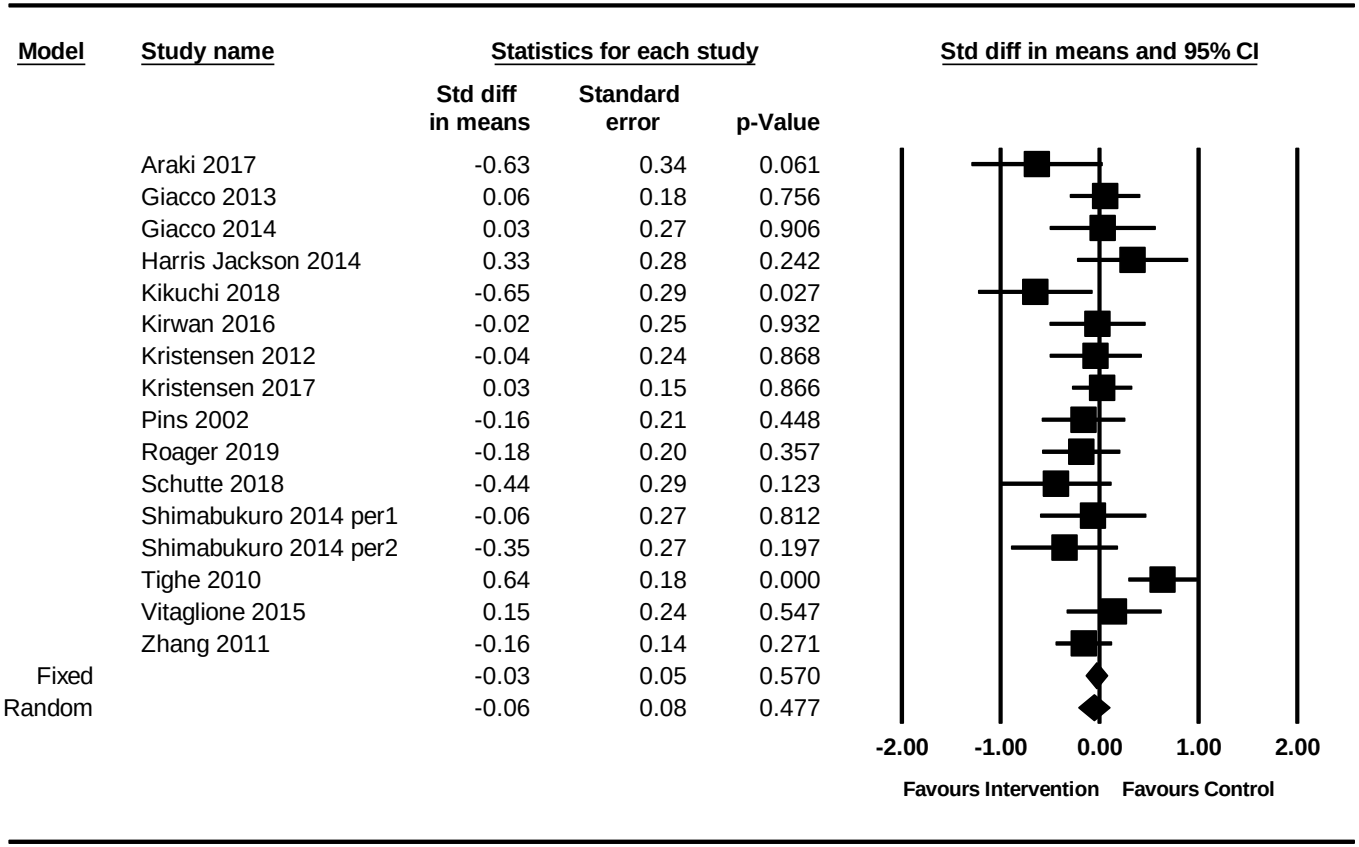


LDL cholesterol

Online Supplementary Material 1

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

Figure S13: Whole grains compared with refined grains has no significant effect on LDL cholesterol (SMD: -0.07 [95%CI: -0.25, 0.10], I^2: 59.6%, p=0.405).

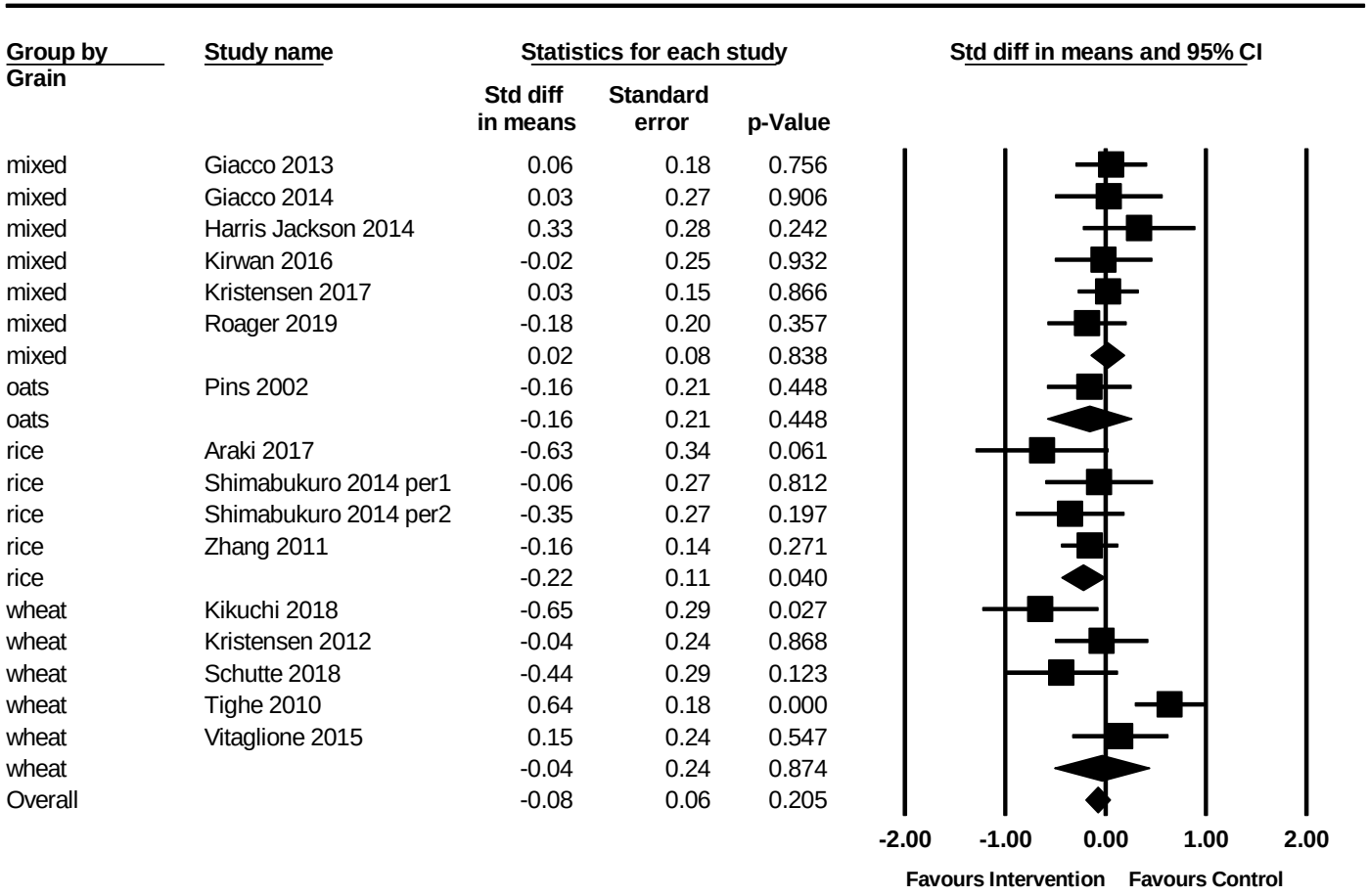


Triglycerides

Figure S14: Whole grains compared with refined grains has no significant effect on triglycerides (SMD: -0.06 [95%CI: -0.21, 0.10], I^2: 49.9%, p=0.477).

Online Supplementary Material 1

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



Triglycerides

Figure S15: Whole grain rice compared with refined rice decreased triglycerides (SMD: -0.22 [95%CI: -0.44, -0.01], I^2: 0%, p=0.040).

Online Supplementary Material 1

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

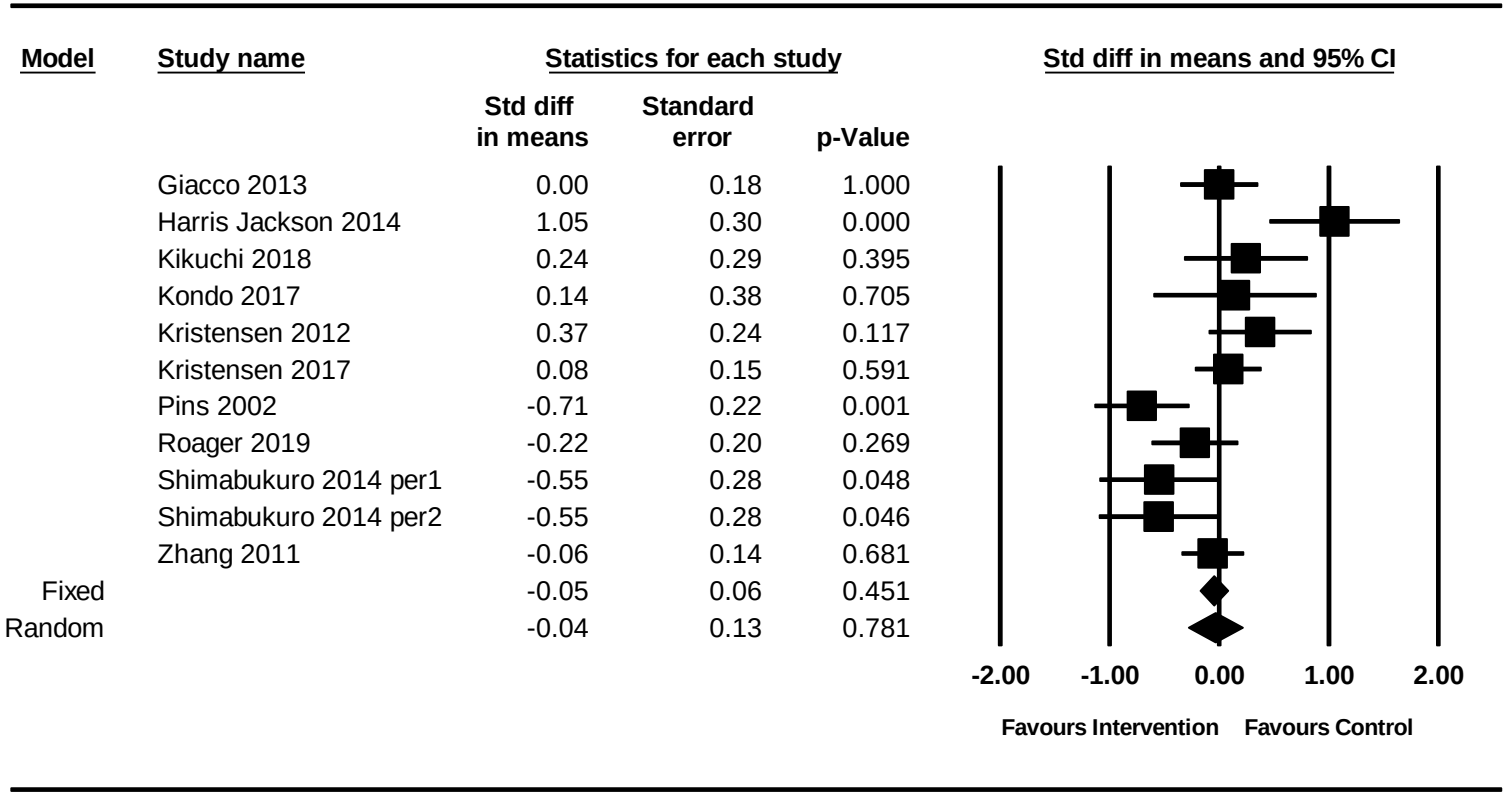


Figure S16: Whole grains compared with refined grains has no significant effect on systolic blood pressure (SMD: -0.04 (95%CI: -0.28, 0.21], I^2: 71.3%, p=0.781).

Online Supplementary Material 1

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

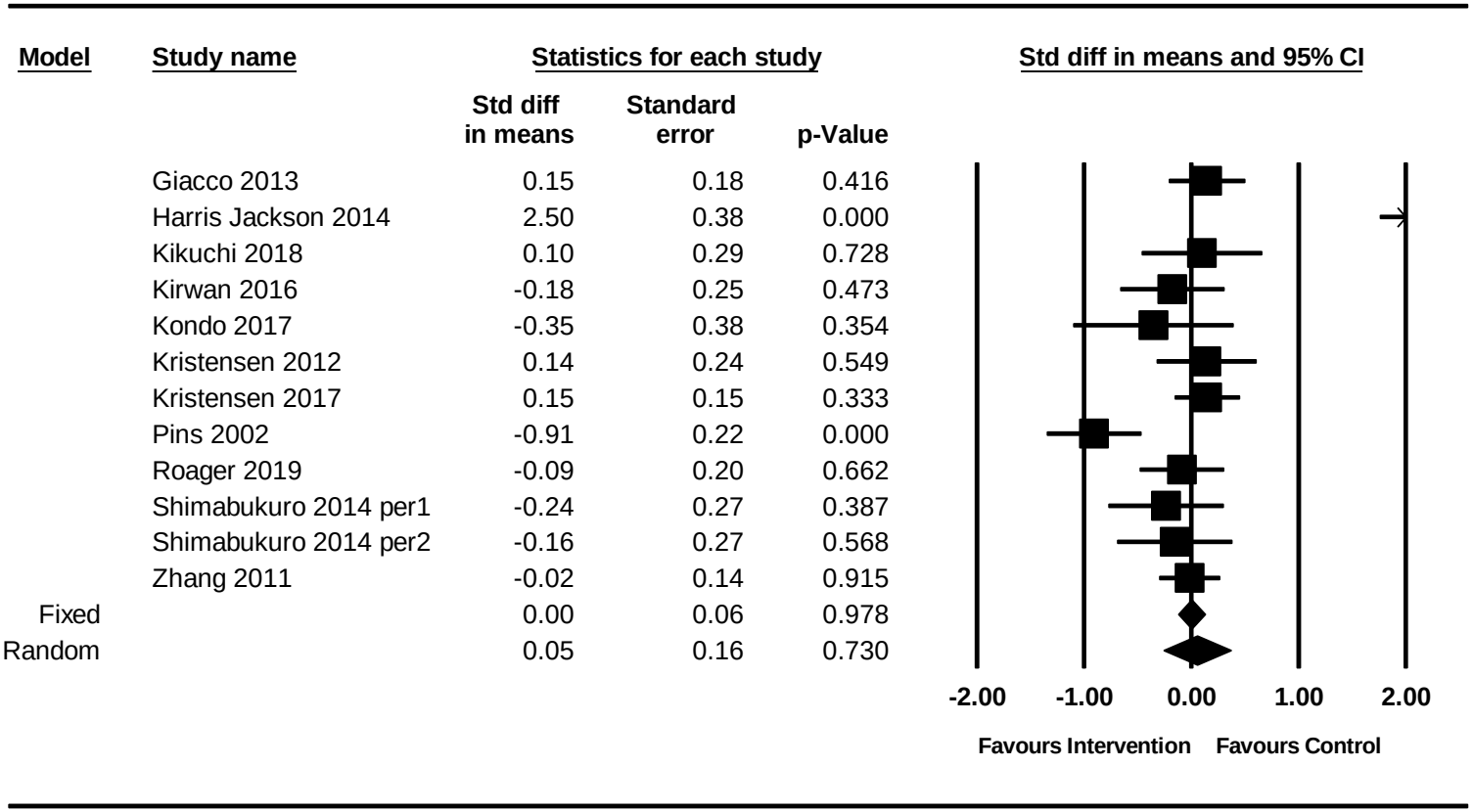


Figure S17: Whole grains compared with refined grains has no significant effect on diastolic blood pressure (SMD: 0.05 [95%CI: -0.26, 0.37], I^2: 83.1%, p=0.730).

Online Supplementary Material 1

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

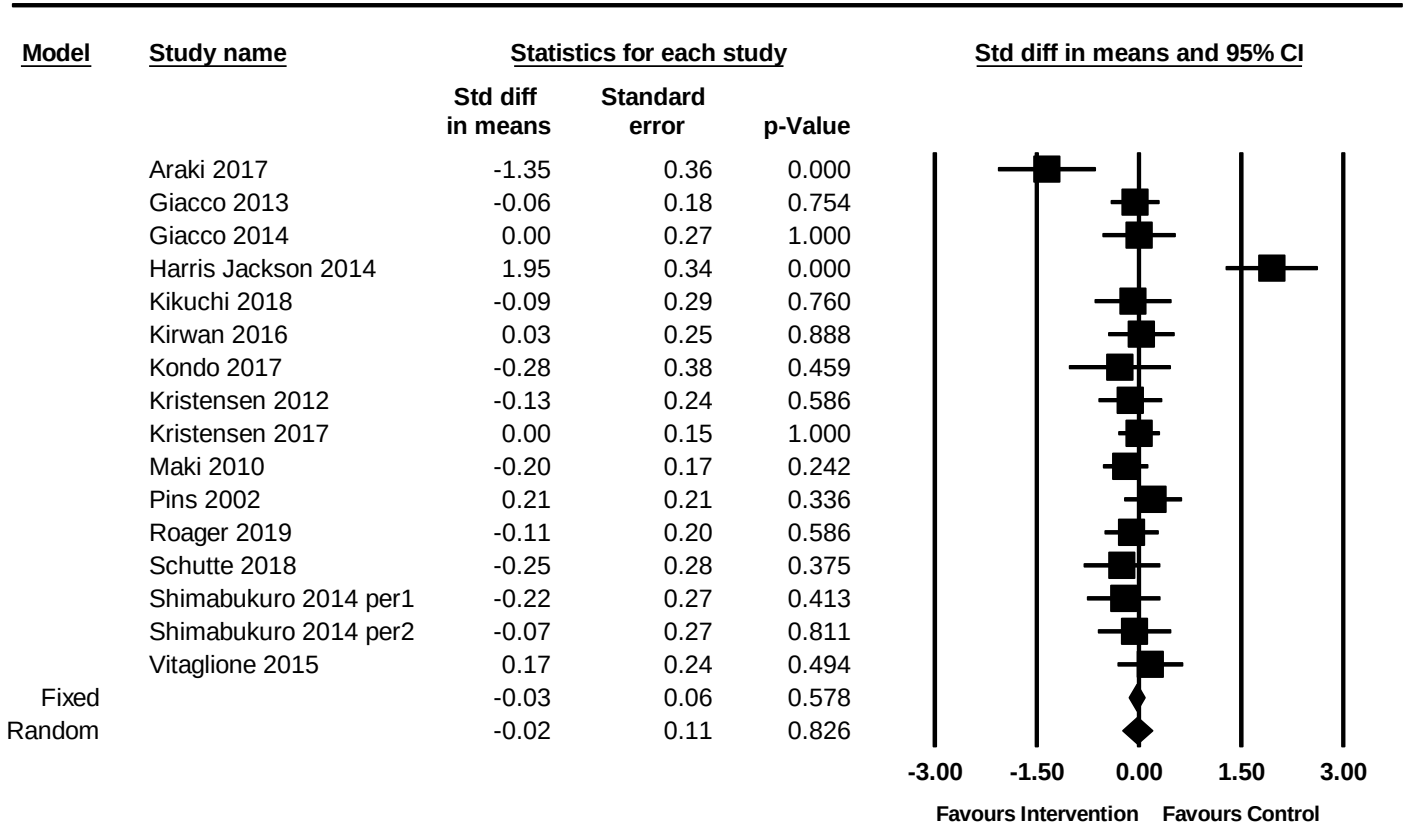


Figure S18: Whole grains compared with refined grains has no significant effect on total body weight (SMD: -0.02 [95%CI: -0.24, 0.19], I^2: 70.8%, p=0.826).

Online Supplementary Material 1

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

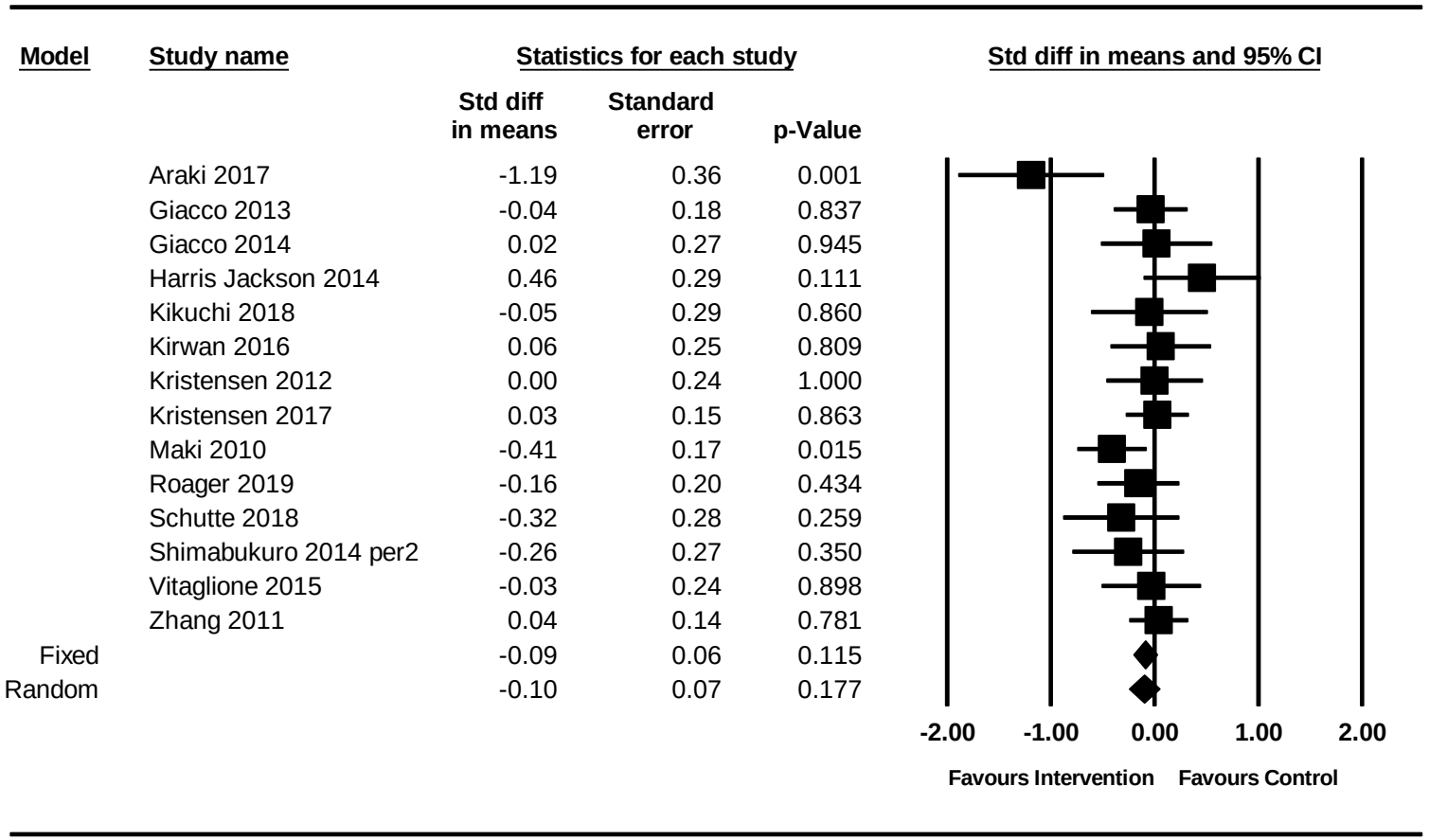


Figure S19: Whole grains compared with refined grains had a significant effect on waist circumference (SMD: -0.09 [95%CI: -0.25, 0.05], I^2: 35.5%, p=0.117).

Online Supplementary Material 1
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

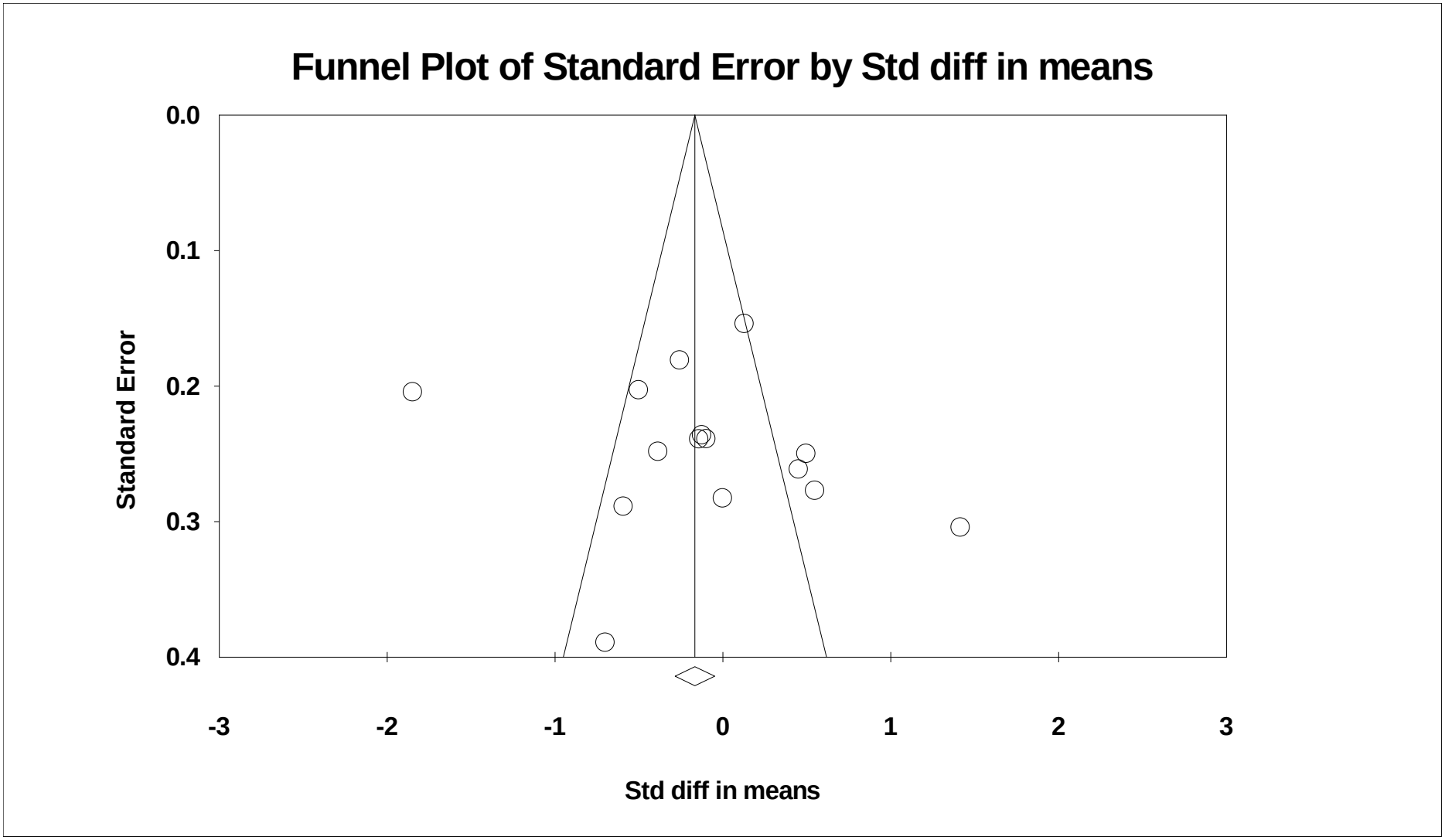


Figure S20: Funnel plot assessing publication bias of studies pooled to determine the effect of whole grains compared to refined grains on CRP/hs-CRP.

Online Supplementary Material 1
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

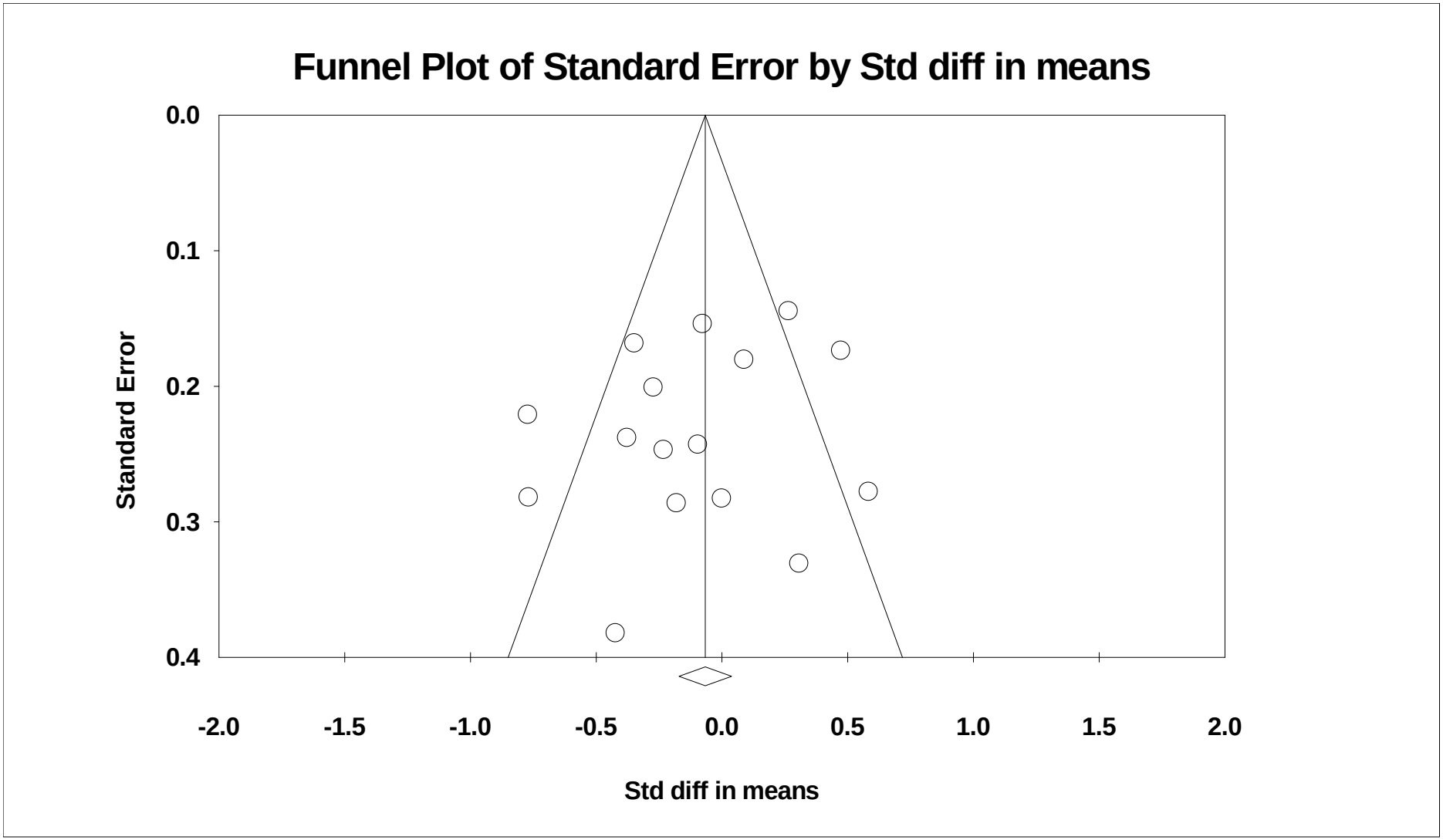


Figure S21: Funnel plot assessing publication bias of studies pooled to determine the effect of whole grains compared to refined grains on total cholesterol.

Online Supplementary Material 1
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

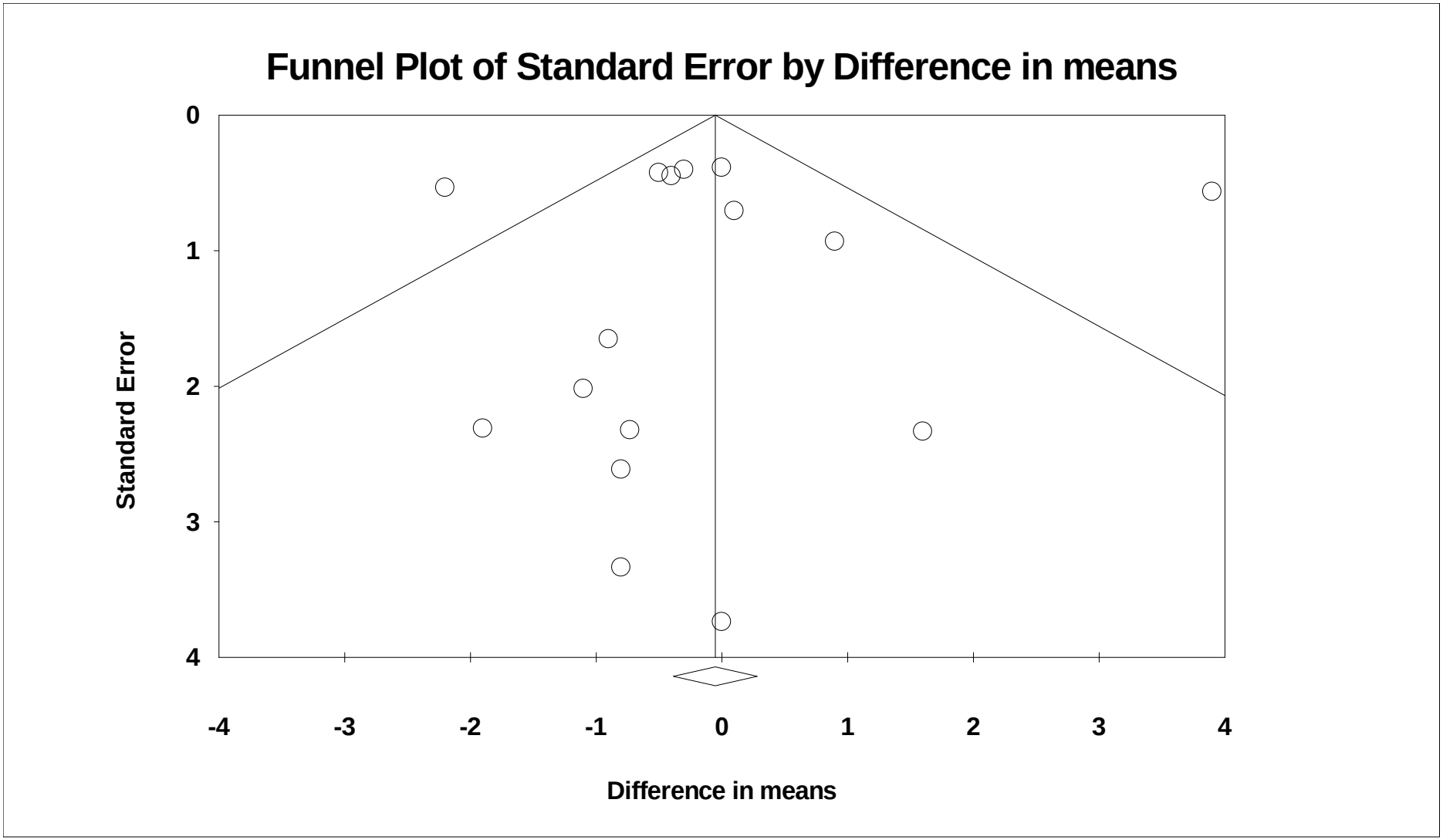


Figure S22: Funnel plot assessing publication bias of studies pooled to determine the effect of whole grains compared to refined grains on total body weight change.

Online Supplementary Material 1
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

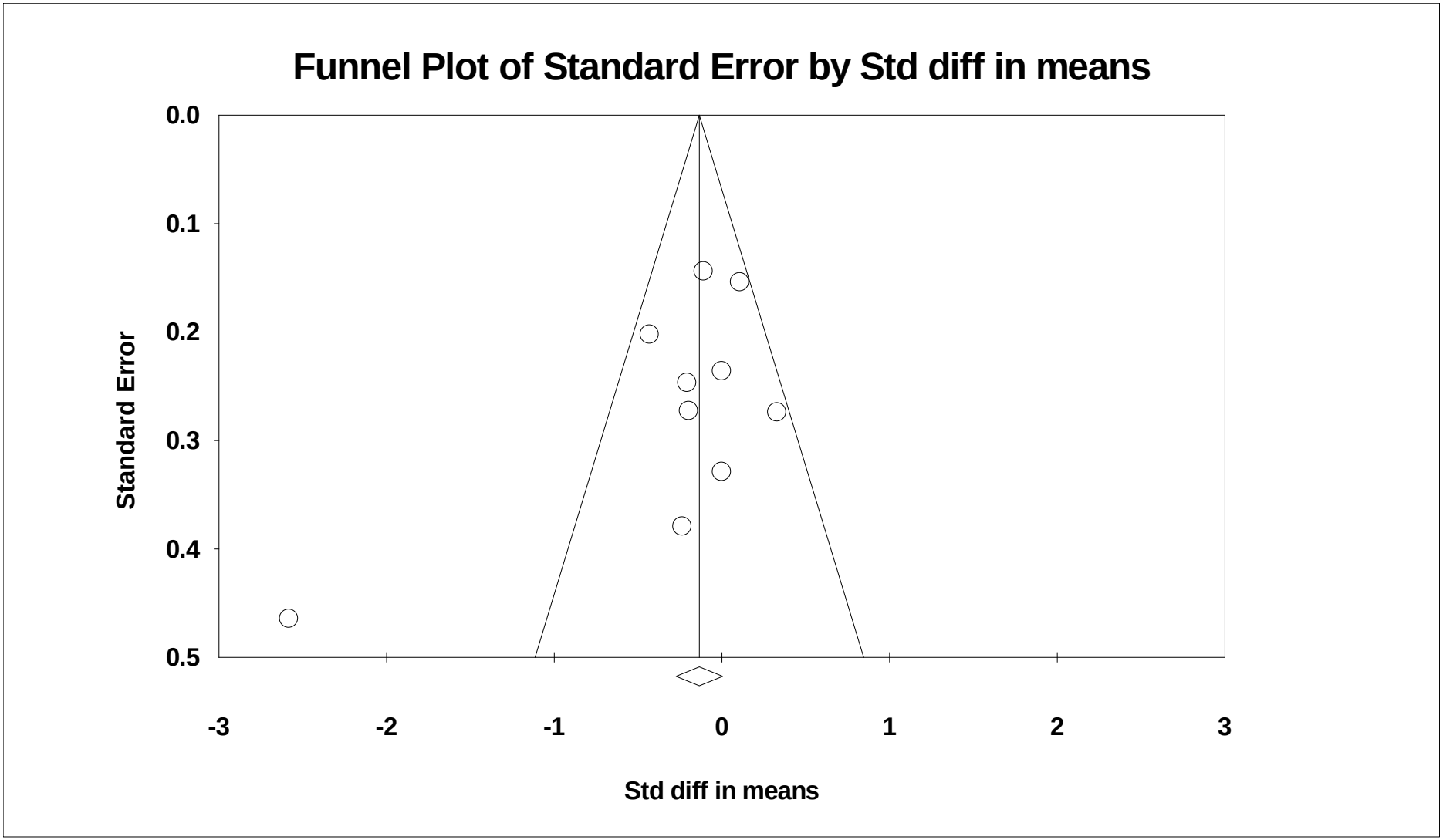


Figure S22: Funnel plot assessing publication bias of studies pooled to determine the effect of whole grains compared to refined grains on HbA1c%.

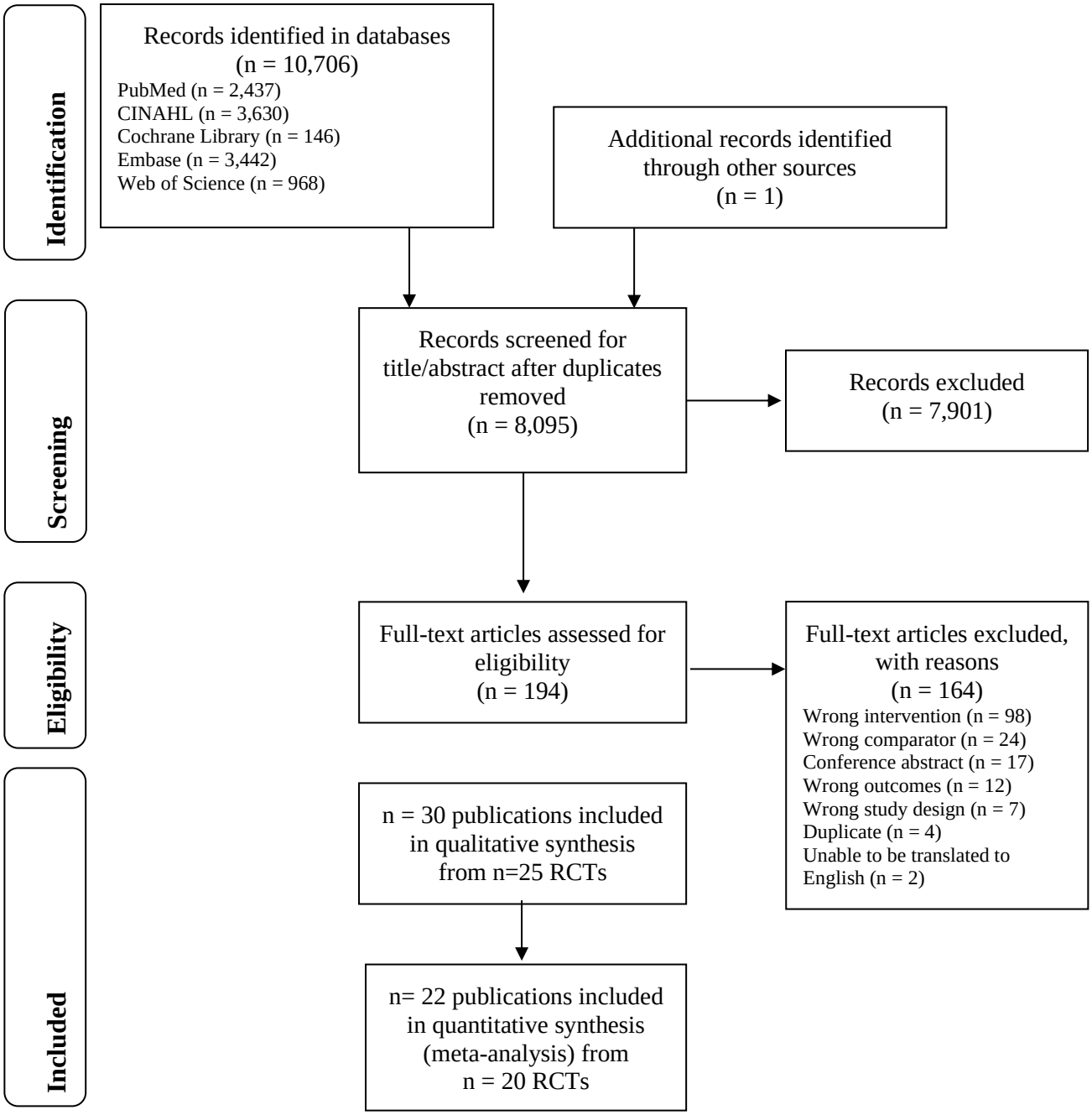
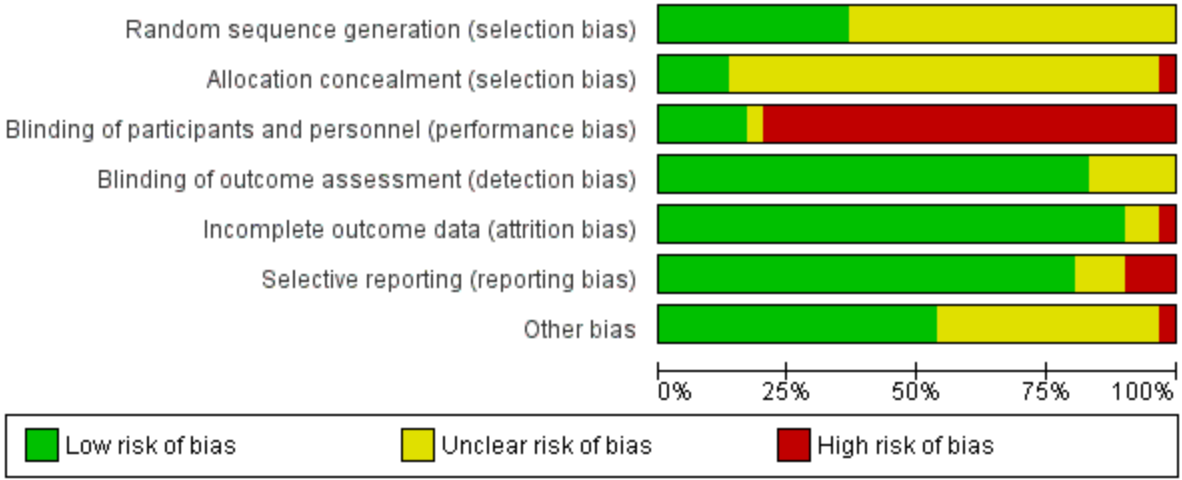
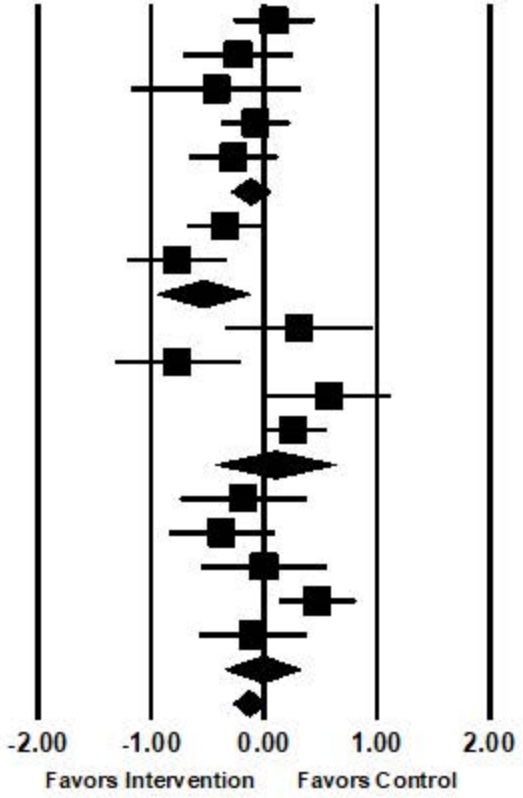


Figure 1: Flow diagram of identified records which were screened according to the search strategy.

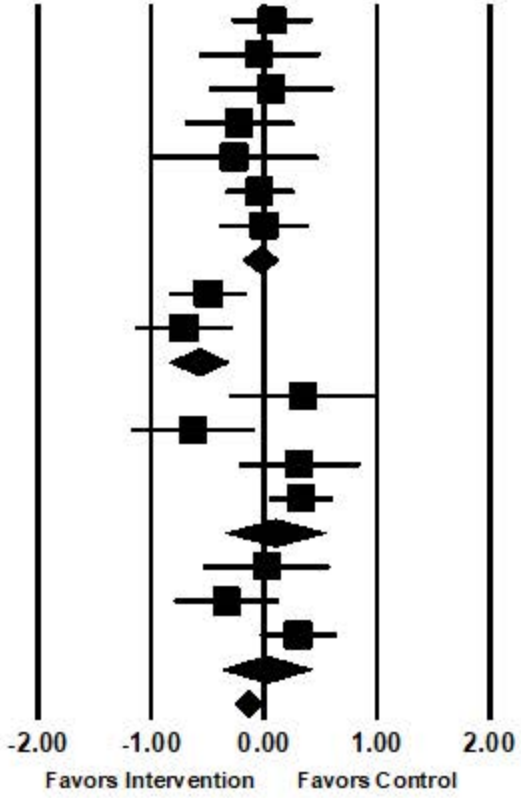

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Group by Grain	Study name	Statistics for each study			Std diff in means and 95% CI
		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

Group by Grain	Study name	Statistics for each study			Std diff in means and 95% CI
		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

Table 1: Inclusion and exclusion criteria of a systematic review and meta-analysis of randomized controlled trials which compare whole grain or whole pseudo-grain interventions and placebo or refined grain controls in humans.

	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 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 e.g. energy-restriction, voluntary fortification. ・Intervention length ≥2 weeks for studies which reported inflammatory or oxidative stress markers as outcomes; or ≥8 weeks for studies which reported all other eligible outcomes[b].	・Does not meet the HEALTHGRAIN EU criteria for whole grain. ・Does not describe the whole grain intervention product in sufficient detail as to ascertain if it meets the HEALTHGRAIN EU criteria. ・Whole grain product is fortified with additional nutrients or functional ingredients which 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 e.g. 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 II diabetes mellitusc
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]

For studies with a duration between two and eight weeks which reported inflammatory and oxidative markers as well as other relevant outcomes, only inflammatory and oxidative stress outcomes were retrieved and considered in this review.

Table 2: Search strategy implemented across five electronic databases and results of total records retrieved when searching for randomized controlled trials which compare whole grain or whole pseudo-grain interventions and placebo or refined grain controls in humans.

Set	Search Terms
MEDLINE (via PubMed) - searched 8 March 2019 using keywords (title and abstract) and MeSH 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

Set	Search Terms
	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]))) ***CINAHL (via Ebscohost) was searched on 8 March 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 was searched on 8 March 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

Set	Search Terms
	"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 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 was searched 8 March 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

Set	Search Terms
	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 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 was searched 8 March 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***

Table 3: Sample and study design characteristics of the 25 included randomized controlled trials (reported across 30 publications) which compare whole grain or whole pseudo-grain interventions and placebo or refined grain controls in humans.

Author & Country	RCT[a] Design	Sample	Duration	Intervention	Comparator	Background diet	Plasma alkyresor-cinol	Outcomes measured
Barley								
Pick et al 1998 [60]. Canada.	Open label, cross-over, 2-arms (1 IG[b], 1 CG[c]).	N=12 (IG=12; CG=12). Attrition: IG 8%, CG 8%. µ51 ± 7y[d]; 0% F[e]. CVD[f] risk factors.	12wks[g]. **Run-in**: none. **Washout**: none.	**Grain**: Barley. **Food source**: Barley bread, buns, muffins, cookies, pasta, cereal. Made with waxy hull less barley. **Dose**: 83g[h]/d[i].	**Grain**: Wheat. **Food source**: white bread. **Dose**: ND[j].	Isocaloric. Controlled by cross-over design.	NM[k]	Inflammatory markers, glycemic and insulin markers, body composition.
Mixed grains								
Ampatzoglou et al 2016 [37]. UK[l].	Open label, cross-over, 2-arms (1 IG, 1 CG).	N=33 (IG=33; CG=33). Attrition: IG 0%, CG 0%. µ49 ±1 y; 65% F. Healthy.	6wks. **Run-in**: 2wks. **Washout**: 4wks.	**Grain**: Mixed (59% wheat, 40% oats, 1% corn and rice). **Food source**: Commercially available pasta, rice, snacks, and breakfast cereals. **Dose**: µ168g/d (range 67-335g/d).	**Grain**: Mixed (not further specified). **Food source**: Commercially available pasta, rice, snacks, and breakfast cereals. **Dose**: Unspecified; consumed RG[m]; mean WG[n] intake was 0.1g/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 et al 2007 [57]. Sweden.	Open label, cross-over, 2-arms (1 IG, 1 CG).	N=34 (IG=34; CG=34). Attrition: IG 12%, CG 12%. µ59 ± 5y, 73% F. CVD risk factors.	6wks. **Run-in**: None. **Washout**: 6-8wks.	**Grain**: Mixed (wheat, rye, oat, rice). **Food source**: Commercially available bread, breakfast cereal, pasta, rice, flour. **Dose**: µ112g/d.	**Grain**: Mixed (wheat, rye, corn, rice). **Food source**: Commercially available bread, breakfast cereal, pasta, rice, flour. **Dose**: Unspecified; provides 3340kJ/d.	Encouraged to maintain habitual diet; controlled by cross-over design.	NM.	Inflammatory markers, oxidative stress markers.

Enright et al 2010 [38]. USA[o].	Open label, cross-over, 2-arms (1 IG, 1 CG).	N=20 (IG=20; CG=20). Attrition: IG 0%, CG 0%. µ27 ± 4y. 50% F. Healthy.	2wks. **Run-in:** none **Washout**: none.	**Grain**: Mixed (wheat, oat, rye) **Food source**: Commercially available: bread, cereals, cookies, crackers, buns, bagels. **Dose**: M: 8 servings/d, F:6 servings/d. Standard serving: 1 slice of bread, 1/2C[q] cereal, others not specified.	**Grain**: Mixed (wheat, rice) **Food source**: Commercially available: bread, cereals, cookies, crackers, buns, bagels. Wheat and rice mostly puffed. **Dose**: M[p]: 8 servings/d, F:6 servings/d. Standard serving: 1 slice of bread, 1/2C cereal, others not specified.	Usual diet maintained but no counselling provided; controlled by cross-over design.	NM.	Oxidative stress markers.
Giacco et al 2013 [40]. Finland and Italy.	Open label, parallel, 2-arms (1 IG, 1 CG).	N=146 (IG=75; CG=71). Attrition: IG 19%, CG 13%. Age ND. 53% F. CVD risk factors	12wks. **Run-in**: 4wks.	**Grain**: Mixed (wheat, barley, oat, rye). **Food source**: Bread, pasta, soup, biscuits, breakfast cereal. Bread was sourdough. **Dose**: µ136 ±18g/d.	**Grain**: Mixed (wheat, rice, corn). **Food source**: Commercially available bread, rice, pizza, porridge, breakfast cereal. **Dose**: 60-80% of carbohydrate intake; 0g WG intake.	Isocaloric. Controlled via 4-week 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 et al 2014 [31]. Italy.		N=61 (IG=30; CG=31). Attrition: IG 7%, CG 16%. µ57 ± 9y. 57% F. CVD risk factors.					IG µ140.2 (102.0) nmol/L; CG µ43.7 (38.0) nmol/L; p=0.0001.	Glycemic and insulin markers, blood lipids, body composition.
Vetrani et al 2016 [33]. Finland and Italy.		N=40 (IG=21; CG=19). Attrition: IG 0%, CG 0%. µ58 ± 2y. 60% F. CVD risk factors.					ND.	Inflammatory markers, glycemic and insulin markers, blood lipids.
Harris Jackson et al 2014 [41]. USA.	Open label, parallel, 2-	N=60 (IG=28; CG=32). Attrition: IG 11%, CG 22%. µ46 ±	12wks. **Run-in**: None.	**Grain**: Mixed (wheat, rice, oat). **Food source**: Pancakes, bread roll,	**Grain**: Mixed (wheat, rice, corn). **Food source**: Pancakes, bread rolls,	Diets were tailored to individual; hypocaloric.	data presented graphically only;	Inflammatory markers, glycemic and insulin markers, blood

	arms (1 IG, 1 CG).	6y. 50% F. CVD risk factors.		pasta, cookies; others ND. **Dose**: µ163-301g/d.	pasta, cookies; others ND. **Dose**: ND; 0g WG.		p<0.05 between groups.	lipids, body composition.
Kirwan et al 2016 [44]. USA.	Double blind, cross-over, 2-arms (1 IG, 1CG)	N=40 (IG=40; CG=40). Attrition: IG 18%, CG 18%. µ39 ± 7y. 82% F. Healthy.	8wks. **Run-in**: none. **Washout**: 10wks.	**Grain**: Mixed (wheat, rice, oat)[r]. **Food source**: Commercially available breakfast cereal, rice. **Dose**: 50g/1000kJ/d.	**Grain**: Mixed (wheat, rice)[r]. **Food source**: Commercially available breakfast cereal, rice. **Dose**: ND; 0g WG.	Isocaloric, individualized, matched macronutrient composition.	IG µ change 85.2 (95%CI: 38.2, 132.2) nM; CG µ change -36.8 (95%CI: -51.1, -22.5) nM; p<0.001.	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, CVD comorbidity incidence, body composition
Malin et al 2019 [37]. USA.		N=14 (IG=14; CG=14). Attrition: IG 0%, CG 0%. µ38 ± 2y. 79% F. Healthy.						glycemic and insulin markers, body composition.
Malin et al 2019 [35]. USA		N13 (IG=13; CG=13). Attrition: IG 0%, CG 0%. 78%F. Healthy.						glycemic and insulin markers, body composition.
Kondo et al 2017 [45]. Japan.	Open label, parallel, 2-arms (1 IG, 1 CG).	N=29 (IG=14; CG=15). Attrition: IG 0%, CG 7%. µ67 ± 8y. 36% F. CVD risk factors.	8wks. Run-in: 4-8wks.	**Grain**: Mixed (brown rice, amaranth, barley). **Food source**: Packet of mixed grain to cook as per preference. **Dose**: Staple food for 10/21 meals/wk.	**Grain**: White rice. **Food source**: ND. **Dose**: 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 et al 2017 [53]. France.	Single blind, parallel, 2-arms (1 IG, 1CG).	N=178 (IG=89; CG=89). Attrition: IG 9%, CG 1%. µ36 ± 9y. 100% F. Healthy.	12wks, **Run-in:** 8wks	**Grain**: Mixed (wheat, rice, rye, oat). **Food source**: Commercially available bread, bulgur, couscous, rice, pasta, rusks, crispbread, breakfast cereal, cereal bar.	**Grain**: Mixed (wheat, rice, corn). **Food source**: Commercially available bread, couscous, rice, pasta, rusks, breakfast cereal. **Dose**: ND, Mean 0.5g/d of WG.	Hypocaloric, controlled with run-in period, all food provided, dietitian counselling throughout.	IG µ119 (181) nmol/L[s]; CG µ33.6 (38.9) nmol/L; p<0.00001.	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition.

				Dose: µ124 ±1.7g/d.				
Roager et al 2019 [47]. Denmark.	Open label, cross-over, 2-arms (1 IG, 1 CG).	N=60 (IG=60; CG=60). Attrition: IG 17%, CG 17%. µ49 ± 11y. 64% F. CVD risk factors.	8wks Run-in: none Washout: 6wks	**Grain**: Mixed (oat, rye, wheat, bulgur) **Food source**: Breakfast cereal, bread, buns, pasta, crisps **Dose**: >122g/d.	**Grain**: Mixed (wheat, rice, oat, rye, spelt, bulgur) **Food source**: Breakfast cereal, bread, buns, pasta, crisps **Dose**: >128g/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 et al 2010 [63]. UK.	Single-blind, parallel, 3-arms (2 IG, 1CG).	N=226 (IG=73; IG=77; CG=76). Attrition: IG 5%, IG 4%, CG 17%. µ52 ± 1y. 50% F. Healthy.	12wks. **Run-in**: 4wks.	IG 1. **Grain**: Mixed (wheat, oat) **Food source**: Bread, cereal, rolled oats. **Dose**: >60g/d IG 1 reported below.	**Grain**: Refined wheat. **Food source**: Bread, cereal. **Dose**: >6g/d.	Dietary advice to maintain regular diet; controlled with run-in period.	NM.	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics.
Tighe et al 2013 [62]. UK.								Blood lipids.
Vanegas et al 2017 [49]. USA.	Open label, parallel, 2-arms (1 IG, 1 CG).	N=90 (IG=45; CG=45). Attrition: IG 9%, CG 11%. µ55 ± 1y. 40% F. Healthy.	6wks **Run-in**: 2wks	**Grain**: Mixed (mostly wheat). **Food source**: Bread. **Dose**: 16g/1000kcal.	**Grain**: Mixed (mostly wheat). **Food source**: White bread. **Dose**: 8g/1000kcal.	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.
Oat								
Maki et al 2010 [54]. USA.	Open label, parallel, 2-arms (1 IG, 1 CG).	N=204 (IG=101; CG=103). Attrition: IG 24%, CG 35%. µ49 ± 1y. 79% F. Healthy.	12wks **Run-in**: none.	**Grain**: Oat. **Food source**: Ready-to-eat commercially available oat cereal (Cheerios). **Dose**: 3C/d.	**Grain**: Mixed (corn, wheat, rice). **Food source**: Ready-to-eat commercially available breakfast cereal, bread, bagel, muffin, chips, crackers, or rice cakes. **Dose**: ND; kJ consumption of RG	Hypocaloric; diet prescribed but not well described.	NM.	Inflammatory markers, blood lipids, hemodynamics, body composition.

					matched that provided by the WG.			
Pins et al 2002 [61]. USA.	Single blind, parallel, 2-arms (1 IG, 1 CG).	N=88 (IG=45; CG=43). Attrition: IG 0%, CG 0%. µ48y (range: 33-67y). 49% F. CVD risk factors.	12wks. **Run-in**: none	**Grain**: Oat. **Food source**: oatmeal and oat squares. **Dose**: 137g/d.	**Grain**: Mixed (wheat, corn, barley). **Food source**: Breakfast cereal. **Dose**: 146g/d.	Isocaloric; poorly described.	IG µ380 (95%CI 255, 505) nmol/L; CG µ134 (95%CI: 107, 161) nmol/L; p<0.0001.	Glycemic and insulin markers, blood lipids, hemodynamics, body composition.
Rice								
Araki et al 2017 [52]. Japan.	Open label, parallel, 2-arms (1 IG, 1 CG)	N=41 (IG=20; CG=21). Attrition: IG: 5%, CG 14%. µ54 ± 7y. 54% F. CVD risk factors.	12wks. **Run-in**: none.	**Grain**: Brown rice. **Food source**: partially abraded. **Dose**: µ400g/d.	**Grain**: White rice. **Food source**: ND. **Dose**: 400g/d.	Study provided 2 main meals; participants able to eat staple foods for 3rd meal.	N/A[t].	Glycemic and insulin markers, blood lipids, hemodynamics, body composition.
Kazemzadeh et al 2014 [42]. Iran.	Open label, cross-over, 2-arms (1 IG, 1 CG)	N=38 (IG=38; CG=38). Attrition: IG 8%, CG 8%. µ33 ± 6y. 100% F. Healthy.	6wks. **Run-in**: 2wks. **Washout**: 2wks.	**Grain**: Brown rice **Food source**: Iranian rice variety (Tarom) **Dose**: 150g/d.	**Grain**: White rice **Food sour**ce: Iranian rice variety (Tarom) **Dose**: 150g/d	Hypocaloric prescribed diet; controlled by cross-over design, run-in and washout periods.	N/A.	Inflammatory markers, glycemic and insulin markers.
Kim et al 2008 [59]. South Korea.	Open label, parallel, 2-arms (1 IG, 1 CG).	47 (IG=23; CG=24) Attrition: IG 13%, CG 17%. 20-35y. 100% F. Healthy.	6wks. **Run-in**: none.	**Grain**: Brown and black rice. **Food source**: served within a meal substitute. **Dose**: 3 servings/d; ND further.	**Grain**: White rice. **Food source**: served within a meal substitute. **Dose**: 3 servings/d; ND further.	Hypocaloric diet provided by study.	N/A.	Oxidative stress markers.
Nakayama et al 2017 [55]. Japan.	Open label, cross-over, 2-arms (1 IG, 1 CG).	N=18 (IG=18; CG=18). Attrition: IG 11%, CG 11%. µ64 ± 9y. 25% F. CVD risk factors.	8wks. **Run-in**: 1wk. **Washout**: none.	**Grain**: Brown rice. **Food source**: Glutenous brown rice. **Dose**: 2 servings/d; serving size ND.	**Grain**: White rice. **Food source**: ND. **Dose**: 2 servings/d; serving size ND.	Usual diet; instructed by nutritionist; controlled by run-in period.	N/A.	Glycemic and insulin markers, blood lipids.

Shimabukuro et al 2014 [56]. Japan.	Open label, cross-over, 2-arms (1 IG, 1 CG).	N=28 (IG=28; CG=28). Attrition: IG 4%, CG 4%. µ46 ± 5y. 0% F. CVD risk factors.	8wks. **Run-in**: none. **Washout**: none.	**Grain**: Brown rice. **Food source**: ND. **Dose**: consumed daily; ND further.	**Grain**: white rice. **Food source**: ND. **Dose**: consumed daily; ND further.	Unchanged from usual diet. Controlled by cross-over design.	N/A.	Inflammatory markers, oxidative stress markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition.
Zhang et al 2011 [13]. China.	Single blind, parallel, 2-arms (1 IG, 1 CG).	N=202 (IG=101; CG=101). Attrition: IG 3%, CG 6%. µ50 ± 7y. 47% F. CVD risk factors.	16wks. **Run-in**: none.	**Grain**: Brown rice **Food source**: soaked in water for 1hr before cooking. **Dose**: 225g/d.	**Grain**: White rice **Food source**: ND **Dose**: 225g/d	Isocaloric. Usual dietary pattern maintained.	N/A.	Glycemic and insulin markers, blood lipids, hemodynamics, CVD comorbidity incidence, body composition.
Wheat								
Giacco et al 2010 [39]. Italy.	Open label, cross-over, 2-arms (1 IG, 1 CG).	N=15 (IG=15; CG=15). Attrition: IG: 0%, CG 0%. µ55 ± 8y. 20% F. Healthy.	3wks. **Run-in**: 2wks **Washout**: none.	**Grain**: WG Wheat. **Food source**: Commercially available pasta, bread, rusks, crackers. **Dose**: ND; included WG at every meal.	**Grain**: Refined wheat. **Food source**: Commercially available pasta, bread, rusks, crackers. **Dose**: 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 et al 2018 [43]. Japan.	Double blind, parallel, 2-arms (1 IG, 1 CG).	N=50 (IG=25; CG=25). Attrition: IG 4%, CG 0%. µ48 ± 2y. 35% F. Healthy.	12wks. **Run-in**: none.	**Grain**: WG wheat. **Food source**: Bread prepared for the study. **Dose**: µg/day (range -g/d).	**Grain**: Refined wheat. **Food source**: Refined bread dyed brown, prepared for the study. **Dose**: ND; assumed equal intake of bread as IG.	Maintained background diet; no counselling provided.	NM.	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition.
Kristensen et al 2012 [58]. Denmark.	Open label, parallel, 2-arms (1 IG, 1 CG).	N=79 (IG=42; CG=37). Attrition: IG 10%, CG 8%. µ60 ± 5y. 100% F. Healthy.	12wks **Run-in**: 2wks.	**Grain**: WG wheat. **Food source**: Commercially available pasta, bread, biscuits. **Dose**: µ105g/d.	**Grain**: Refined wheat. **Food source**: Commercially available pasta, bread, biscuits.	Hypocaloric, controlled with run-in period, all food provided, dietitian counselling throughout.	Data presented graphically only; $p<0.001$ between groups.	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics, body composition

					Dose: Grain foods were the same portion sizes as WG.			
Schutte et al 2018 [48]. Netherlands.	Double blind, parallel, 2-arms (1 IG, 1 CG).	N=50 (IG=25; CG=25). Attrition: IG 0%, CG 0%. µ61y (range: 51-69y). 48% F. CVD risk factors.	12wks. **Run-in**: 4wks.	**Grain**: WG wheat **Food source**: Bread, cereal, buns **Dose**: 98g/d.	**Grain**: Refined wheat **Food source**: White bread, buns, cereal **Dose**: 98g/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 et al 2010 [60]. UK.	Single-blind, parallel, 3-arms (2 IG, 1CG).	N=226 (IG=73; IG=77; CG=76). Attrition: IG 5%, IG 4%, CG 17%. µ52 ± 1y. 50% F. Healthy.	12wks. **Run-in**: 4wks.	IG 2. **Grain**: WG wheat **Food source**: Bread, cereal **Dose**: >60g/d IG 2 reported above	**Grain**: Refined wheat. **Food source**: Bread, cereal. **Dose**: >6g/d.	Dietary advice to maintain regular diet; controlled with run-in period	NM.	Inflammatory markers, glycemic and insulin markers, blood lipids, hemodynamics
Tighe et al 2013 [62]. UK.								Blood lipids.
Vitaglione et al 2015 [50]. Italy.	Single-blind, parallel, 2-arms (1 IG, 1CG).	N=80 (IG=40; CG=40). Attrition: IG 10%, CG 20%. µ39 ± 2y. 66% F. Healthy.	8wks. **Run-in:** none.	**Grain**: WG wheat. **Food source**: biscuits. **Dose**: 70g/d.	**Grain**: Refined wheat. **Food source**: Bread and crackers. **Dose**: 60g/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. y, year.
e. F, females
f. CVD, cardiovascular disease
g. wks, weeks
h. g, grams
i. d, day
j. ND, not described
k. NM, not measured
l. UK, United Kingdom
m. RG, refined grain

n. WG, whole grain
o. USA, United States of America
p. M, males
q. C, cup
r. Corn was not considered as a grain by the study investigators, and was therefore provided as part of the background diet to both groups.
s. 62% of participants had insufficient alkyresorcinol levels indicating non-adherence.
t. N/A, not applicable

;;;;;;;;;;;;;;;

Table 4: Justification for the risk of bias assessment according to the Cochrane Risk of Bias tool [20] of randomized controlled trials which compare whole grain or whole pseudo-grain interventions and placebo or refined grain controls in humans.

	Study	Random sequence generation (selection bias)	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
Rating	Ampatzoglou 2016 [37]	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.
Rating	Andersson 2007 [57]	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 is not reported with no explanation	None detected.

	Study	Random sequence generation (selection bias)	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
Rating	Araki 2017 [52]	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 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)."	No description of how randomization allocation was generated: "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)."	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.	Although attrition was higher in IG (14%) compared to CG (5%), attrition was not due to study factors.	Outcomes measured, including blood pressure and BMI were not reported 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.	Analysis of findings found no statistically significant results; however, 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 advise, and was not tested as a confounding variable.
Rating	Enright 2010 [38]	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	No attrition for either group.	None detected.	None detected.

	Study	Random sequence generation (selection bias)	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
					objective serum biomarkers.			
Rating	Giacco 2010 [39]	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.
Rating	Giacco 2013 [40]	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.
Rating	Giacco 2014 [31]	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 2013	As per Giacco 2013	As per Giacco 2013. Laboratory analyses were performed blind in respect to the assigned treatment.	"investigators and dieticians were aware of the participants' group allocation" ; however, the outcome of interest is an	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	This study reports outcomes not of interest to this study using a subgroup of Giacco 2013; however, also repeats other clinical outcomes

	Study	Random sequence generation (selection bias)	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
					objective biomarker		sample and reported in Giacco 2013	already reported for the whole cohort. This may lead to results being over- or mis-interpreted.
Rating	Vetrani 2016 [33]	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 2013	As per Giacco 2013	"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 sub analysis	None detected.	This study reports outcomes not of interest to this study using a subgroup of Giacco 2013; however, also repeats other clinical outcomes already reported for the whole cohort. This may lead to results being over- or mis-interpreted.
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

	Study	Random sequence generation (selection bias)	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	Harris Jackson 2014 [41]	"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 unblinded 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.
Rating	Kazemzadeh 2014 [42]	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 non-compliance; however, this rate is very low and unlikely to bias the results.	None detected.	None detected.
Rating		Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear

	Study	Random sequence generation (selection bias)	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	Kikuchi 2018 [43]	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 result, blindness is properly maintained." and "A randomized double-blind placebo-controlled intervention study was conducted"	"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 result, blindness is properly maintained." and "A randomized double-blind placebo-controlled intervention study was conducted"	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.
Rating		Unclear	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Unclear

	Study	Random sequence generation (selection bias)	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	Kim 2008 [59]	No description of randomization technique	No description of allocation concealment	The test products were contained within a meal replacement, and it shouldn't 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
Rating	Kirwan 2016 [44]	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.
Rating		Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

	Study	Random sequence generation (selection bias)	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	Malin 2019 [35, 36]	As per Kirwan 2016	As per Kirwan 2016	As per Kirwan 2016	As per Kirwan 2016	No attrition was reported for this sub-sample of Kirwan 2016	None detected.	None detected.
Rating	Kondo 2017 [45]	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.
Rating	Kristensen 2012 [58]	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 n=1 participant withdraw for reasons related to the test products. Overall attrition was low (<10%) and equal between groups.	None detected.	None detected.
Rating		Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias

	Study	Random sequence generation (selection bias)	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	Kristensen 2017 [53]	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 analysis used. Low attrition in both groups.	None detected.	61% of IG were non-compliant according to plasma alkylresorcinol concentrations; this was found to have a significant effect on the outcome.
Rating	Maki 2010 [54]	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 inadequately to allow for any true review of the results. Attrition was high in the control group.	Only data for statistically significant results were reported. Baseline values for some outcomes were not reported.	None detected.
Rating		Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear

	Study	Random sequence generation (selection bias)	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	Nakayama 2017 [55]	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.
Rating	Pick 1998 [60]	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 was reported poorly and insufficiently, but no systematic or purposeful bias detected.	None detected.
Rating	Pins 2002 [61]	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.
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

	Study	Random sequence generation (selection bias)	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	Roager 2019 [47]	"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.
Rating	Schutte 2018 [48]	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.

	Study	Random sequence generation (selection bias)	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
Rating	Shimabukuro 2014 [56]	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 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.	Test products were severely under-described.
Rating		Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear

	Study	Random sequence generation (selection bias)	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	Tighe 2010 [63]	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.
Rating	Tighe 2013 [62]	Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Unclear	Unclear
Evidence		As per Tighe 2010	As per Tighe 2010	As per Tighe 2010	As per Tighe 2010	As per Tighe 2010	Many outcomes were only compared at baseline and not follow-up including hemodynamics and body composition.	As per Tighe 2010
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

	Study	Random sequence generation (selection bias)	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	Vanegas 2017 [49]	"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 the random-assignment coding for the WG and RG groups."	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.
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

	Study	Random sequence generation (selection bias)	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	Vitaglione 2015 [50]	"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.
Rating		Unclear	Unclear	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear

	Study	Random sequence generation (selection bias)	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	Zhang 2011 [13]	No description of randomization technique	No description of allocation concealment	No attempt at blinding	"all the researchers not directly in contact with study participants (dietitians, laboratory technicians, and statisticians) were unaware of group allocations". Unclear if outcome assessors were blinded. Outcomes are objective.	Attrition was low for both groups and none was related to the study.	None detected.	Background diet not well controlled; may have introduced bias.

Table 5: Summary of outcomes reported by the 26 included randomized controlled trials[a] which compare whole grain or whole pseudo-grain interventions and placebo or refined grain controls in humans.

Outcome category (n)[b]	**RCTs**[c] **reporting outcomes**	**RCTs reporting significant improvements favoring whole grain**	**RCTs reporting significant improvements favoring refined grain**
Inflammatory markers (10)	n=21	CRP[d] n=2/5 (40%) hsCRP[e] n=1/11 (9%) IL[f]-β n=1/2 (50%) IL-6 n=1/9 (11%) TFN[g]-α n=1/6 (17%) PAI[h]-1 n=1/5 (20%) IL-8 n=0/2 (0%) IL-10 n=0/2 (0%) Adiponectin n=0/5 (0%) Leptin n=0/4 (0%)	CRP n=0/5 (0%) hsCRP n=1/11 (9%) IL-β n=0/2 (0%) IL-6 n=0/9 (0%) TFN-α n=0/6 (0%) PAI-1 n=0/5 (0%) IL-8 n=0/2 (0%) IL-10 n=0/2 (0%) Adiponectin n=0/5 (0%) Leptin n=0/4 (0%)
Oxidative stress markers (7)	n=6	TBARS[i] n=1/2 (50%) GSH-Px[j] n=1/1 (100%) FRAP[k] n=0/1 (0%) 8-iso PGF2a[l] n=0/4 (0%) ORAC[m] n=0/1 (0%) SOD[n] n=0/1 (0%) ADMA[o] n=0/1 (0%)	TBARS n=0/2 (0%) GSH-Px n=0/1 (0%) FRAP n=0/1 (0%) 8-iso PGF2a n=0/4 (0%) ORAC n=0/1 (0%) SOD n=0/1 (0%) ADMA n=0/1 (0%)
Glycemic and insulin markers (5)	n=19	HOMA-IR n=1/12 (8%) Postprandial plasma insulin n=2/5 (40%) Fasting plasma glucose n=2/14 (14%) Postprandial plasma glucose n=2/4 (50%) Fasting plasma insulin n=0/14 (0%) HbA1c% n=0/9 (0%)	HOMA-IR n=0/12 (0%) Postprandial plasma insulin n=0/5 (0%) Fasting plasma glucose n=0/14 (0%) Postprandial plasma glucose n=0/4 (0%) Fasting plasma insulin n=0/14 (0%) HbA1c% n=0/9 (0%)
Blood lipids (5)	n=18	Total cholesterol n=3/16 (19%) LDL[p] cholesterol n=4/16 (25%) HDL[q] cholesterol n=2/17 (12%) Triglycerides n=2/17 (12%) VLDL[r] cholesterol n=0/1 (0%)	Total cholesterol n=3/16 (19%) LDL cholesterol n=1/16 (6%) HDL cholesterol n=1/17 (6%) Triglycerides n=1/17 (6%) VLDL cholesterol n=0/1 (0%)
Hemodynamics (4)	n=12	Pulse pressure[s] n=3/3 (100%) SBP[t] n=3/13 (23%) DBP[u] n=1/13 (8%) Mean arterial pressure n=0/1 (0%)	Pulse pressure[c] n=3/3 (100%) SBP n=0/13 (0%) DBP n=1/13 (8%) Mean arterial pressure n=0/1 (0%)
CVD[v] comorbidity (2)	n=2	Prediabetes incidence n=1/2 (50%) MetS[w] incidence n=0/2 (0%)	Prediabetes incidence n=0/2 (0%) MetS incidence n=0/2 (0%)
Body composition (7)	n=15	Total body weight n=2/13 (15%) Fat mass (kg)n=1/3 (0%) WC[x] n=2/12 (17%) BMI[y] n=0/9 (0%) Fat mass (%) n=0/4 (0%) FFM[z] (kg[aa]) n=0/4 (0%)	Total body weight n=0/13 (0%) Fat mass (kg)n=0/3 (0%) WC n=1/12 (8%) BMI n=0/9 (0%) Fat mass (%) n=0/4 (0%) FFM (kg) n=0/4 (0%)

a. RCTs which measured an outcome but did not compare groups were excluded from Table 3. Data included were from 25 unique RCTs which had 26 intervention arms, but were reported across 30 publications.
b. Number of different outcomes reported within the outcome category
c. Randomized controlled trial
d. C-reactive protein
e. high-sensitivity C-reactive protein
f. Interleukin
g, Tumor necrosis factor

h. Plasminogen activator inhibitor
i. Thiobarbituric acid reactive substances
j. Glutathione peroxidase
k. Total antioxidant capacity of plasma
l. 8-iso-prostaglandin F2 alpha
m. Oxygen radical absorbance capacity
n. Superoxide dismutase
o. Asymmetric dimethylarginine
p. Low-density lipoprotein
q. High-density lipoprotein
r. Very low-density lipoprotein
s. 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 (i.e. between 40 and 60mmHg), effect sizes were small, and/or data was only presented graphically.
t. Systolic blood pressure
u. Diastolic blood pressure
v. Cardiovascular disease
w. Metabolic syndrome
x. Waist circumference
y. Body mass index
z. Fat free mass
aa. Kilogram

Table 6: Pooled effects and confidence in the body of evidence based on 20 randomized controlled trials (reported across n=22 publications) which compare whole grain or whole pseudo-grain interventions and placebo or refined grain controls in humans.

Outcome	Number of intervention groups	Number of participants (IG[a]/CG[b])	SMD[c] (95%CI[d])	Model	I^2 (%)	p-value	GRADE
CRP[e]/hsCRP	14	658/644	-0.19 (-0.57, 0.20)	RE[f]	88.9	0.542	Moderate[h]
IL[g]-6	9	458/432	-0.08 (-0.29, 0.13)	RE	51.0	0.457	Moderate
Fasting blood glucose	16	742/722	-0.01 (-0.19, 0.16)	RE	60.4	0.875	Very low
Fasting blood insulin	13	649/626	0.07 (-0.05, 0.18)	RE	0	0.265	Moderate
HOMA-IR	12	528/500	-0.03 (-0.17, 0.10)	RE	0	0.603	Moderate
HbA1c	10	404/403	-0.24 (-0.53, 0.06)	RE	75.0	0.122	Moderate [h]
Total cholesterol (Figure 3)	16	791/757	-0.10 (-0.29, 0.09)	RE	67.3	0.291	Very low [h]
HDL[i] cholesterol	18	775/750	-0.0 (-0.03, 0.03)	RE	38.7	0. 896	Low[j]
LDL[k] cholesterol (Figure 4)	15	783/751	-0.07 (-0.25, 0.10)	RE	59.6	0.405	Very low [h]
Triglycerides	16	753/727	-0.06 (-0.21, 0.10)	RE	49.9	0.477	Very low [h]
SBP[l]	11	482/481	-0.04 (-0.28, 0.21)	RE	71.3	0.781	Very low
DBP[m]	12	515/514	0.05 (-0.26, 0.37)	RE	83.1	0.730	Very low
Total body weight[n]	16	602/587	-0.02 (-0.24, 0.19)	RE	70.8	0.826	Very low
Waist circumference	14	641/625	-0.10 (-0.25, 0.05)	RE	35.5	0.117	Moderate

a. IG, intervention group
b. CG, control group
c. SMD, standardized mean difference
d. CI, confidence intervals
e. CRP, C-reactive protein;
f. RE, random effects
g. IL, interleukin
h. GRADE assessment reflects confidence in the statistically significant subgroup rather than the overall analytical model.
i. HDL, high density lipoprotein
j. GRADE assessment reflects confidence in the statistically significant subgroup grain type: mixed, rather than the overall analytical model or the subgroup study quality: unclear
k. LDL, low density lipoprotein
l. SBP, systolic blood pressure
m. DBP, diastolic blood pressure
n. Weight change was meta-analyzed for total body weight change in preference to BMI as fewer studies reported BMI change.

Table 7: GRADE evidence and summary of findings table: whole grains compared to refined grains for cardiovascular disease risk.

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Whole grain**	**Refined grain**	**Absolute (95% CI[a])**		
CRP[b]/hs-CRP - Study quality (high) subgroup											
8	randomized trials	not serious [c]	serious [d,e]	not serious [f]	not serious	none	311	360	SMD[g] **0.22 SD[h] lower** (0.44 lower to 0)	⊕⊕⊕◯ MODERATE	IMPORTANT
IL-6											
9	randomized trials	not serious	serious [e]	not serious [f]	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 [c]	very serious [i]	not serious [f]	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 [c]	not serious	not serious [f]	not serious [j]	none	649	626	SMD **0.07 SD higher** (0.05 lower to 0.18 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
HOMA-IR											
11	randomized trials	serious [c]	not serious	not serious [f]	not serious	none	528	500	SMD **0.03 SD lower** (0.17 lower to 0.1 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
HbA1c - Study quality (high) subgroup											

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Whole grain**	**Refined grain**	**Absolute (95% CI[a])**		
3	randomized trials	not serious [c]	not serious [d]	not serious [f]	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 [c]	very serious [i,k]	not serious [f]	serious [j]	none	122	110	SMD **0.54 SD lower** (0.95 lower to 0.12 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
HDL cholesterol - Grain type (mixed) subgroup											
7	randomized trials	not serious	not serious [d]	not serious [f]	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 [c]	not serious [d]	not serious [f]	serious [j]	none	255	235	SMD **0.33 SD higher** (0.05 higher to 0.62 higher)	⨁⨁◯◯ LOW	IMPORTANT
LDL cholesterol - Grain type (oat) subgroup											
2	randomized trials	serious [c]	serious [d, k]	not serious [f]	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											

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Whole grain**	**Refined grain**	**Absolute (95% CI[a])**		
3	randomized trials	very serious [l]	serious [d, k]	not serious [f]	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 [c]	very serious [i]	not serious [f]	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 [c]	very serious [i]	not serious [f]	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 [c]	very serious [i]	not serious [f]	not serious	none	602	587	SMD **0.02 SD lower** (0.24 lower to 0.19 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Waist circumference											
14	randomized trials	serious [c]	not serious	not serious [f]	not serious	none	641	625	SMD **0.1 SD lower** (0.25 lower to 0.05 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

a. CRP, c-reactive protein.
b. CI, confidence intervals

c. Some studies had unclear or high risk of bias
d. Although the initial model had higher heterogeneity, this was explained by the subgroup analysis upon which this GRADE assessment is being performed.
e. There was some statistical heterogeneity (I2 between 30 and 60%)
f. 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.
g. SMD, standardized mean difference
h. SD, standard deviation
i. There was high statistical heterogeneity (I2 between 60 and 100%)
j. The upper or lower 95%CI crosses an effect size of 0.5 in either direction
k. There is a risk of inconsistency due to there being fewer than 400 participants in this subgroup
l. All studies have high or unclear risk of bias

Table 8: Recommendations assessment and justification for the use of whole grains to improve cardiovascular disease risk using GRADE clinical recommendations for populations software on GRADEpro

Problem Is the problem a priority?	
JUDGEMENT	**RESEARCH EVIDENCE & JUSTIFICATION**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Ischemic heart disease and stroke, both forms of CVD[a], are the top two causes of morbidity and death worldwide (WHO, Top 10 Causes of death, https://www.who.int/). 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" (Ryan and Farrelly, Euro J Cardiovas Nurs, 2009, 8:223-231).
Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE & 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 one 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. 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 (Aune et al, BMJ, 2016, 353; Wei et al, Br J Nutr, 2016, 116; Chen et al, Am J Clin Nutr, 2016, 3), 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 which 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 which favored the refined grains, which was a decrease in HDL[e] 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?

JUDGEMENT	RESEARCH EVIDENCE & 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 one or more RCT report a beneficial effect of the intervention. There were only 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 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 (Aune et al, BMJ, 2016, 353; Wei et al, Br J Nutr, 2016, 116; Chen et al, Am J Clin Nutr, 2016, 3), 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 which are not properly or easily accounted for in multivariable models. Therefore, still prevent strong conclusions being drawn in favor of the intervention. There was one pooled estimated effect which 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?

JUDGEMENT	RESEARCH EVIDENCE & 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?	
JUDGEMENT	**RESEARCH EVIDENCE & JUSTIFICATION E**
○ 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 cardiovascular disease (though 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 which must be interpreted through an appropriate cultural lens. Although values are diverse, commonality is the broad value for health and well-being (Davidson, Int J Nurs Stud, 2011, 11:1367-1375).
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	**RESEARCH EVIDENCE & JUSTIFICATION**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	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 which may explain such a finding. When interpreted alongside 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 (Aune et al, BMJ, 2016, 353; Wei et al, Br J Nutr, 2016, 116; Chen et al, Am J Clin Nutr, 2016, 3), 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 which 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)?	
JUDGEMENT	**RESEARCH EVIDENCE & 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 (e.g. 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 (e.g. 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 (Mancino et al, Food Policy, 2008, 33). 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 judgement 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)?	
JUDGEMENT	**RESEARCH EVIDENCE & JUSTIFICATION**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Whilst 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?

JUDGEMENT	RESEARCH EVIDENCE & JUSTIFICATION
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	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 (Jetter and Cassady, Am J Prevent Med, 2006, 30). 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 $13.2 (Rahkovsky and Gregory, Econ Hum Biol, 2013, 11). Population economic modelling using data from the UK[f] strongly advocates for any intervention which 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 cost-effective approaches to achieve a reduction in incidence (Barton et al, BMJ, 2011, 343 and Brunner et al, Public Health Nutr, 2001). 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 which show a greater clinical impact.

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE & 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 results 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 USA[g], 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 (WHO, NCD mortality and morbidity, who.int).

Acceptability Is the intervention acceptable to key stakeholders?	
JUDGEMENT	**RESEARCH EVIDENCE & JUSTIFICATION**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Of clinical significance, the RCTs in this review reported that participants either had equal or lower attrition in the whole grain group, as well as a 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?	
JUDGEMENT	**RESEARCH EVIDENCE & JUSTIFICATION**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Of clinical significance, the RCTs in this review reported that participants either had equal or lower attrition in the whole grain group, as well as a 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 (Rahkovsky and Gregory, Econ Hum Biol, 2013, 11), population policy interventions (Barton et al, BMJ, 2011, 343), and national dietary guidelines promoting whole grains (Mancino et al, Food Policy, 2008, 33) 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.

a. CVD, cardiovascular disease
b. RCT, randomized controlled trial
c. LOL, low density lipoprotein
d. CRP, c-reactive protein
e. HDL, high density lipoprotein
f. UK, United Kingdom
g. United States of America