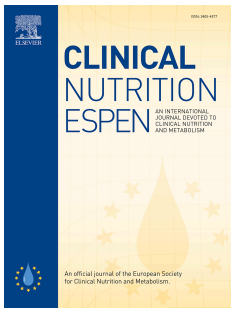
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Title	The separate effects of whole oats and isolated beta-glucan on lipid profile: a systematic review and meta-analysis of randomized controlled trials
Authors	de Morais Junior, Alcides C.;Schincaglia, Raquel M.;Viana, Ricardo B.;Armet, Anissa M.;Prado, Carla M.;Walter, Jens;Mota, João F.
Publication date	2022-12-19
Original Citation	de Morais Junior, A. C., Schincaglia, R. M., Viana, R. B., Armet, A. M., Prado, C. M., Walter, J., Mota, J. F. (2022) 'The separate effects of whole oats and isolated beta-glucan on lipid profile: a systematic review and meta-analysis of randomized controlled trials', Clinical Nutrition ESPEN, 53, pp. 224-237. https://doi.org/10.1016/j.clnesp.2022.12.019
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1016/j.clnesp.2022.12.019
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The separate effects of whole oats and isolated beta-glucan on lipid profile: a systematic review and meta-analysis of randomized controlled trials

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PII: S2405-4577(22)01429-2

DOI: https://doi.org/10.1016/j.clnesp.2022.12.019

Reference: CLNESP 1589

To appear in: *Clinical Nutrition ESPEN*

Received Date: 12 December 2022

Accepted Date: 15 December 2022

Please cite this article as: de Morais Junior AC, Schincaglia RM, Viana RB, Armet AM, Prado CM, Walter J, Mota JF, The separate effects of whole oats and isolated beta-glucan on lipid profile: a systematic review and meta-analysis of randomized controlled trials, *Clinical Nutrition ESPEN*, https://doi.org/10.1016/j.clnesp.2022.12.019.

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The separate effects of whole oats and isolated beta-glucan on lipid profile: a systematic review and meta-analysis of randomized controlled trials

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Running title: Oat or isolated β-glucan on lipid profile

Abbreviations list:

TC, total cholesterol;

LDL, low density lipoprotein;

HDL, high density lipoprotein;

TG, triglycerides;

SMD, standardized mean difference;

CI, confidence interval;

PRISMA, preferred reporting items for systematic review and meta-analysis protocols;

PROSPERO, international prospective register of systematic reviews;

MESH, medical subject heading;

RCT, randomized clinical trial;

BMI, body mass index;

RoB2, cochrane risk-of-bias tool 2;

SD, standard deviation;

Registration: This review was registered at PROSPERO under the identification number CRD42021249983.

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Abstract

Background & Aims: It is well known that dietary fiber positively impacts the microbiome and health as a whole. However, the health effects of β-glucan, a dietary fiber extracted from oats, have been questioned when administered alone or incorporated into other foods. The purpose of this systematic review and meta-analysis was to evaluate the impact of oats or β-glucan supplements on the lipid profile. **Methods:** Randomized controlled trials with parallel-arm or crossover blinded interventions at least two weeks in duration, for hyperlipidemic or non-hyperlipidemic men and women ≥ 18 years of age were selected. Only single (participants blinded) or double-blinded studies that compared oat or isolated β-glucan with a placebo/control group were considered for this review. The databases EMBASE, PubMed, Web of science and CINHAL were searched, from the earliest indexed year available online to the end of January 2022. Random-effects models were used to combine the estimated effects extracted from individual studies, and data were summarized as standardized mean difference (SMD) and 95% confidence interval (95%CI). **Results:** A total of 811 articles were screened for eligibility, and relevant data were extracted from 28 studies, totaling 1494 subjects. Oat interventions TC (-0.61, 95%CI: -0.84;-0.39, $p<0.00001$, and -0.70, 95%CI: -1.07;-0.34, $p=0.0002$, respectively) and LDL (-0.51, 95%CI: -0.71;-0.31, $p<0.00001$, and -0.38, 95%CI: -0.60;-0.15, $p=0.001$, respectively). Moreover, isolated β-glucan interventions from parallel-arm studies decreased TC (-0.73, 95%CI: -1.01;-0.45, $p<0.00001$), LDL (-0.58, 95%CI: -0.85;-0.32, $p<0.0001$) and triglycerides (-0.30, 95%CI: -0.49;-0.12, $p=0.001$). HDL was not altered by either oat or isolated β-glucan ($p>0.05$). **Conclusion:** Overall, this review showed that both oat and isolated β-glucan interventions improved lipid profiles. Furthermore, the ingestion of oats or isolated β-glucan supplements are effective tools to combat dyslipidemia and should be considered in cardiovascular disease prevention.

Keywords: *Avena sativa*; oats; beta-glucan; dietary fiber; blood cholesterol; meta-analysis

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Introduction

Nutraceuticals have been used as lipid-lowering agents and have safely and successfully improved plasma lipid levels [1]. Among the nutraceuticals applied for improvement of the lipid profile is found dietary fiber, particularly a type of fiber called β-glucan. The term dietary fiber is believed to have been coined by Hipsley in 1953 [2] and it is usually related to the non-digestible carbohydrates found in plants. It is well documented that the ingestion of dietary fiber has drastically dropped as a result of major changes in human eating habits related to industrialization [3,4]. Dietary fiber intake has been inversely linked with inflammation [5,6], insulin resistance [7], risk for cardiovascular disease [8,9], certain cancers [10,11], and overall mortality [12]. High fiber intake has also been associated with increased satiety [13] and improved body weight management [14].

Viscous fibers, such as β-glucan found in oats and barley, have been specifically linked with improved markers of cardiovascular disease [15]. Mechanisms of action as to how these fibers help reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) [16] include reducing the reabsorption of intestinal bile acids [17,18], and changing the colonic bacterial metabolism [19]. Furthermore, these fibers promote a reduced absorption of cholesterol by thickening the contents of the intestinal tract and delaying migration of nutrients to the intestinal walls [20]; where viscosity of the fiber determines its effectiveness in reducing absorption [15]. Oats, as a source of β-glucan, have been studied extensively and have consistently shown promising results related to improved lipid profiles [21,22].

Although the benefits of intrinsic or endogenous dietary fiber present in whole plant foods are well established, the health effects of dietary fibers extracted from whole foods (so called isolated or purified fibers) when used as supplements or in foods that do not naturally contain such fibers have been questioned [23,24]. For example, the three-dimensional (3D)

matrix of the plant cell wall in which the fiber is organized in whole foods confers additional benefits such as affecting the digestibility of other nutrients contained within the cells. In contrast, purified fibers may have a reduction in the micronutrients and phytochemicals present in whole plant foods. Isolated β-glucan supplements could potentially fill the gap regarding the lack of dietary fiber in modern society's eating habits [25]. Important reviews and meta-analysis have been done along the last three decades but, without exception they have pooled oats and isolated β-glucan together in their analysis [21,22,26–29]. Recently, a review had the intention to conduct sub-analyses based on intervention type (oat or OβGREs [oat beta-glucan-rich extracts]), but due to the limited number of studies included, this was not possible [30]. To fulfill this role, it is necessary to validate and understand whether isolated β-glucan also provides benefits to health. Oats, instead of other β-glucan sources, have been chosen in this review due to its worldwide consumption when compared to other β-glucan sources like barley and shiitake and reishi mushrooms [31]. The aim of this systematic review and meta-analysis was, therefore, to evaluate the impact of oat ingestion and isolated β-glucan on lipidaemia.

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Materials & Methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [32] was used in this review as a reporting guideline. This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD42021249983.

Search strategy

The databases EMBASE, PubMed, Web of science and CINHAL were searched, from the earliest indexed year available online to January 2022. A combination of Medical Subject

Heading (MeSH) terms and keywords were used for the searches in the databases. The search strategy used was as follows: ("lipid profile" OR "dyslipidaemia" OR "cholesterol") AND ("oat meal", OR "oatmeal" OR "oats" OR "*Avena sativa"* OR "beta-glucan" OR "β-glucan") Titles and abstracts of the studies identified through the computerized searches were sent to the online application Rayyan [33] for further screening. Reference lists from the original articles were also screened for additional articles that potentially could be included.

Study selection criteria

Human intervention trials published in English were included. Specifically, randomized controlled trials (RCTs), including both parallel-arm and crossover designs, were eligible if carried out in men and/or women (≥18 years of age), who either had normal or high total cholesterol levels, defined as <5.18 mmol/L or ≥5.18 mmol/L, respectively. Studies were required to have evaluated at least three of the four parameters of the lipid profile: TC, LDL, high-density lipoprotein cholesterol (HDL), and triglycerides (TG). Studies performed in populations with genetic syndromes (e.g., Down syndrome) or infectious diseases were excluded, as well as those with subjects on medications usually prescribed for hypercholesterolemia, such as statins.

Only single (participants blinded) or double-blinded studies that compared oat or isolated β-glucan with a placebo/control group were considered for this review. Intervention duration was required to be ≥2 weeks and, in the case of crossover designs, washout periods were required to be ≥2 weeks. Studies that had multiple-component interventions or that incorporated other active products that could not be separated from oats or isolated β-glucan were excluded. In studies with more than two intervention arms, of which two or more arms were eligible for inclusion, only the eligible arms were included. For studies with more than

two intervention arms, the results were taken for each arm and computed individually, comparing each intervention with the placebo/control group.

Through the initial search, titles and abstracts were evaluated independently by two of the reviewers (ACMJ and RMS) using the eligibility criteria regarding study design, population, type of intervention, and outcome. Full texts of the selected articles were examined independently by the same reviewers and disagreements were settled by consensus or by a third party (JFM). Authors of the reviewed publications were contacted by email when studies did not provide enough information. Unfortunately, several data requests were not responded to and, thus, these articles were not included in this review and meta-analysis.

Data extraction

All of the selected studies were independently reviewed and tabulated in a spreadsheet by ACMJ and RMS and later compared to eliminate discrepancies. Data was extracted on study design, population characteristics [sex, age (years), body mass index (BMI)], duration, type of blinding, washout period (for crossover studies), sample size, product used in the intervention (oats or isolated β-glucan), product used as control/placebo (corn starch, rice or wheat flour, corn flakes, etc.), intervention and control product presentation (noodles, porridge, powder, drink, bread, snacks etc.), consumed intervention and control amounts (grams per day), consumed fiber amount in the study, gastrointestinal side effects, and lipid profile data (TC, HDL, LDL and TG).

Risk of bias and study quality assessment

The Cochrane risk-of-bias tool (RoB 2) [34] was used to assess each study in the following aspects: a) randomization process; b) deviations from the intended interventions; c) missing outcome data; d) measurement of the outcome; e) selection of the reported results for RCTs

with parallel-arm groups and crossovers. For crossover RCTs, period and carryover effects were also included. Articles were classified as low risk, some concerns, or high risk of bias according to the tool's algorithms. Study quality assessment was done through the PEDro scale [35]. The studies were scored zero to ten according to the scale's criteria, with higher scores indicating better quality studies. Studies scoring nine or ten on the PEDro scale were considered methodologically to be of "excellent" quality, studies scoring from six to eight were of "good" quality, studies scoring four or five were of "fair" quality, and studies scoring below four were of "poor" quality [36]. All of the selected studies were evaluated jointly by ACMJ and RMS.

Statistical analysis

The available data from the included studies allowed us to conduct between-group meta-analyses using continuous data and random-effects models [37] to compare the effects of (i) oat interventions versus control groups from the parallel-arm included studies; (ii) Isolated β-glucan supplements included in food interventions versus control groups from the parallel-arm included studies; (iii) oat interventions versus control groups from the crossover included studies; and (iv) isolated β-glucan interventions versus control groups from the crossover included studies on lipid profile (TC, HDL, LDL, and TG). Parallel-arm and crossover studies were not combined in the meta-analyses since crossover studies may present carryover effects depending on the washout period, potentially interfering with the treatment effect [38,39].

Standardized mean differences (SMD) with 95% confidence intervals (95%CIs) were used to measure the effects of oat and isolated β-glucan as the included studies presented a considerable methodological heterogeneity (e.g., different interventions characteristics). The random-effects model analysis was performed considering the expectation that different interventions effects are not truly identical between studies [40]. The assessment of clinical

relevance was made using three categories: small effect (SMD < 0.5); medium effect (SMD from 0.5 to 0.8); large effect (SMD > 0.8) [41].

Mean difference and its standard deviation of TC, HDL, LDL, and TG for oat interventions and control groups, as well as for isolated β-glucan interventions and control groups, were imputed into the Review Manager software (RevMan, version 5.4) [40]. As most of the included studies did not report the mean difference for lipid profile variables, we calculated the value as post-intervention mean value minus baseline mean value. Furthermore, as most of the included studies (n = 15) [42–56] did not report the standard deviation of mean difference of the lipid profile outcomes (TC, HDL, LDL, and TG), the following equation (1) was used to estimate the standard deviation of mean difference [57]:

$$SD_{meandifference} = \sqrt{\left(SD|pre - test|2 + SD_{post-test}{}^{2}\right) - \left(2r \times SD_{pre-test} \times SD_{post-test}\right)}$$

(1)

For this equation, we estimated the within-participant pre-post correlation coefficients (r) for each outcome in each one of 11 included studies [58–68], which reported pre, post and change variability. After that, we averaged the r values for each outcome separated by each intervention group (oat/isolated β-glucan or control group). Thus, it was obtained the following r values: (i) for TC, r = 0.83 (oat/isolated β-glucan) and r = 0.80 (control group) [58–60,62–68]; (ii) for HDL, r = 0.88 (oat/isolated β-glucan) and r = 0.91 (control group) [59,60,62–68]; (iii) for LDL, r = 0.77 (oat/isolated β-glucan) and r = 0.78 (control group) [58,59,68,60–67]; and (iv) for TG, r = 0.82 (oat/isolated β-glucan) and r = 0.76 (control group) [58–60,63,64,66–68]. These calculations are recommended when continuous data are missing to perform meta-analysis of change scores [41].

The statistical heterogeneity of the treatment effect among studies was assessed using Tau squared (τ^2), *Q* statistic (the significance level was set $p < 0.10$) [40], and the

inconsistency I^2 test. The I^2 statistic estimates the degree of heterogeneity in effects among a set of studies between 0 and 100%, in which values above 30%, 50%, and 75% were considered indicative of moderate, substantial, and high heterogeneity, respectively [40]. Publication bias was visually assessed using funnel plots by plotting the SMD of each trial against its standard error. As recommended by Higgins and Thomas [40], "Egger's regression test" was not performed to assess asymmetry of the funnel plot because all between-groups meta-analyses involved less than 10 original studies. To improve our results, we conducted several sensitivity analyses (the one study removed method) to consider the influence of each study on the overall results, as well as to consider the influence of each study applying two or more oat or isolated β-glucan interventions. Moreover, a pre-planned subgroup analysis was conducted to test whether the participant's health status (non-hypercholesterolaemic or hypercholesterolaemic participants) influenced the outcomes. However, the included studies did not allow for pre-planned subgroup analyses to test whether participants' age (adults or older adults), sex (male or female), menopausal status (yes or no), and if equivalent or different amounts of total fiber intake in the intervention and control groups would influence the outcomes. All statistical analyses were performed in the Review Manager software (RevMan, version 5.4) [40]. A 2-tailed significance level was set at $p < 0.05$ for all analyses.

Results

Included studies

Our initial search retrieved 1643 records: 527 through CINAHL, 617 through EMBASE, 389 through PUBMED, and 110 through Web of Science. Two extra additional records were added through reviewing the reference lists of the retrieved articles, bringing the total to 1645 articles. After the removal of duplicates, 811 records were screened based on their title and/or abstract. A total of 49 full-text articles were assessed for eligibility. In our first assessment, 16 articles were excluded due to the following reasons: (i) insufficient data (n = 8); (ii)

combination of active products (n = 2); (iii) no control groups (n = 2); (iv) no washout period (n = 2); (v) no randomization (n = 1); and (vi) lack of blinding (n = 1). Another seven studies were excluded as they did not report information on change overtime (mean difference and its standard deviation) or pre- and post-intervention data (mean values and standard deviations) on lipid profile outcomes (TC, LDL, HDL, and TG) for intervention and control groups, and missing data could not be obtained from the authors [69–75]. In total, 28 studies were included in this systematic review and meta-analysis (Figure 1).

Nine parallel-arm/oat studies were included in the analysis for TC, HDL, LDL and TG [45,47,51–56,61], seven crossover/oat studies were included in the analysis for TC, HDL, LDL and TG [42,43,46,50,66–68], nine parallel-arm/isolated β-glucan studies were included in the analysis for TC, HDL and LDL [48,58–60,62–64,76,77], eight parallel-arm/isolated β-glucan studies were included in the analysis for TG [48,58–60,63,64,76,77], three crossover/isolated β-glucan studies were included in the analysis for TC, HDL and LDL [44,49,65], and two crossover/isolated β-glucan studies were included in the analysis for TG [44,49].

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Participant characteristics

Most of the studies were conducted with hypercholesterolaemic individuals [42,43,52,54–56,58–63,44,67,76,77,45–51] except for four studies that included non-hypercholesterolaemic individuals [64–66,68] and one that had both non-hypercholesterolaemic and hypercholesterolaemic individuals [53]. The non-hypercholesterolaemic subjects were younger than those with hypercholesterolaemia, as seen in Table 1. The mean age and BMI of the participants were 49.73 (±9.68) years and 26.17 (±2.15) kg/m^2, respectively (Table 1).

Intervention characteristics

The interventions ranged from 14 [46,66] to 84 [76] days in length (Table 1). The number of participants ranged from 12 [43] to 191 [77] individuals. Half of the crossover studies had a 14-day washout period [43,44,46,65,68], the other half had washout periods >14 days [42,49,50,66,67]. The quantity of β-glucan ingested for all of the studies (oats and isolated β-glucan) ranged from 1.2 g/day [51] to 11.2 g/day [45]. Only 15 of the 28 studies included in this review reported the total amount of fiber ingested by the intervention and control groups and, of these 15 studies, nine reported no difference between groups regarding total fiber ingestion [43,44,47,50,55,58,59,62,76].

Lipid profile assessment

Almost half of the included studies did not mention or report precisely the information regarding the method used for the lipid profile assessment [46,49,63,67,53–56,58,60–62]. Of the remaining studies, 14 of them reported having used enzymatic methods of analysis [42,43,64,68,76,77,44,45,47,48,50–52,59] and two studies reported a combination of enzymatic and colorimetric methods [65,66]. For the majority of the studies that properly reported the methods used for lipid assessment, LDL was calculated using Friedewald's formula. Nevertheless, a few of them simply mentioned that LDL was determined by "calculation" or "subtraction" [43,45] and others did not specify how LDL was calculated [48,50,65,66,68].

Study quality and risk of bias assessment

All the included studies were rated at least "good" regarding their quality, as shown in Table 2. According to the tool used to evaluate Risk of Bias, 19 studies were classified as "high-risk" and nine studies as "some concern". Among different areas evaluated, randomization

procedures or lack of information about it were the most concerning area. The results for the assessment of study quality and risk of bias are presented in Table 2.

Oat interventions versus control groups

Parallel-arm studies

The meta-analysis on the effects of oat interventions versus control groups in the parallel-arm studies found a significant difference for changes in TC (SMD: -0.61, 95% CI: -0.84; -0.39, $p < 0.00001$) and LDL (SMD: -0.51, 95%CI: -0.71; -0.31, $p < 0.00001$), favoring oat interventions, with evidence of significant heterogeneity for TC ($\tau^2 = 0.09$, $I^2 = 46\%$, $p = 0.03$) and LDL ($\tau^2 = 0.06$, $I^2 = 36\%$, $p = 0.08$) (Figures 2A and C, respectively). However, there was no significant difference, between groups for changes in HDL (SMD: -0.06, 95%CI: -0.21; 0.10, $p = 0.49$) and TG (SMD: 0.02, 95%CI: -0.14; 0.17, $p = 0.83$), with no evidence of heterogeneity for HDL ($\tau^2 = 0.00$, $I^2 = 0\%$, $p = 0.97$) and TG ($\tau^2 = 0.00$, $I^2 = 0\%$, $p = 0.84$) (Figures 2B and D, respectively).

Crossover studies

Oat interventions with a crossover design showed positive effects on TC (SMD: -0.70, 95%CI: -1.07; -0.34, $p = 0.0002$) and LDL (SMD: -0.38, 95%CI: -0.60; -0.15, $p = 0.001$) compared to the control groups, with evidence of significant heterogeneity for TC ($\tau^2 = 0.15$, $I^2 = 61\%$, $p = 0.02$, Figure 3A) but not for LDL ($\tau^2 = 0.01$, $I^2 = 10\%$, $p = 0.36$) (Figure 3C). However, there was no difference between groups for changes on HDL (SMD: -0.09, 95%CI: -0.39; 0.21, $p = 0.57$) and TG (SMD: -0.21,95%CI: -0.46; 0.04, $p = 0.11$), with evidence of moderate heterogeneity for HDL ($\tau^2 = 0.08$, $I^2 = 47\%$, $p = 0.08$, Figure 3B) but not for TG ($\tau^2 = 0.00$, $I^2 = 0\%$, $p = 0.71$, Figure 3D).

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β-glucan interventions versus control groups

Parallel-arm studies

In random-effects analyses of parallel-arm studies, significant differential effects of isolated β-glucan interventions versus control groups were observed for TC (SMD: -0.73; 95%CI: -1.01; -0.45, $p < 0.00001$), LDL (SMD: -0.58; 95%CI: -0.85; -0.32, $p < 0.0001$) and TG (SMD: -0.30, 95%CI: -0.49; -0.12, $p < 0.0001$), with evidence of significant heterogeneity for TC ($\tau^2 = 0.18$; $I^2 = 70\%$; $p < 0.0001$, Figure 4A) and LDL ($\tau^2 = 0.16$; $I^2 = 68\%$; $p = 0.0002$, Figure 4C) but not for TG ($\tau^2 = 0.03$; $I^2 = 31\%$; $p = 0.14$, Figure 4D). However, there were no significant differences between groups for changes in HDL (SMD: -0.04; 95%CI: -0.18; 0.10, $p = 0.60$), with no evidence of significant heterogeneity for HDL ($\tau^2 = 0.00$; $I^2 = 0\%$; $p = 0.71$, Figure 4B).

Crossover studies

The supplementation of isolated β-glucan in crossover studies lowered TC (SMD: -0.71; 95%CI: -1.39; -0.03, $p = 0.04$) and increased TG concentrations (SMD: 0.32; 95%CI: 0.07; 0.57, $p = 0.01$) compared to control group (Figure 5), with evidence of significant heterogeneity for the TC analysis ($\tau^2 = 0.29$; $I^2 = 83\%$; $p = 0.003$, Figure 5A) and no evidence of significant heterogeneity for the TG analysis (Figure 5D). There was no significant difference between groups for changes in HDL (SMD: -0.01; 95%CI: -0.25; 0.23, $p = 0.94$) and LDL (SMD: -0.74; 95%CI: -1.55; 0.07, $p = 0.07$), with no evidence of significant heterogeneity for the HDL analysis ($\tau^2 = 0.00$; $I^2 = 0\%$; $p = 0.66$, Figure 5B) and evidence of significant heterogeneity for the LDL analysis ($\tau^2 = 0.45$; $I^2 = 88\%$; $p = 0.0002$, Figure 5C).

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Sensitivity analyses

Sensitivity analyses showed that the significant effect ($p < 0.05$) of the oat interventions on TC and LDL remained even after removing each one of the included studies, independently of the study design. The same occurred with isolated β-glucan interventions on TC, LDL and TG in parallel-arm studies. However, the positive effect of isolated β-glucan interventions on TC was not sustained after removing Cicero et al.[49] (SMD: -0.34, 95%CI: -0.72; 0.05, $p = 0.09$; heterogeneity: $\tau^2 = 0.00$, $I^2 = 0\%$, $p = 0.39$) or Ibrügger et al.[65], which were both crossover studies (SMD: -0.73, 95%CI: -1.67; 0.20, $p = 0.13$, heterogeneity: $\tau^2 = 0.42$, $I^2 = 91\%$, $p = 0.0007$). No sensitivity analysis was performed for the crossover studies assessing the effects of isolated β-glucan on TG since only two studies [44,49] were included in the meta-analysis. Additionally, a sensitivity analysis was performed removing all arms (≥ 2 interventions groups) of the parallel-arm studies composed by two or more arms [48,51,60,61], and a significant effect ($p < 0.05$) of oat and isolated β-glucan interventions remained for TC and LDL. However, a sensitivity analysis showed that a significant effect ($p < 0.05$) of isolated β-glucan intervention on TG did not remain after removing all arms of the Keenan et al.[48] study (SMD: -0.24, 95%CI: -0.49; 0.01, $p = 0.06$, heterogeneity: $\tau^2 = 0.05$, $I^2 = 41\%$, $p = 0.10$).

Publication bias

Visual analyses of the funnel plots for all oat and isolated β-glucan interventions versus control groups from either parallel-arm or crossover studies determined no indication of publication bias (Figures S1, S2, and S3, respectively). However, it was not possible to perform a visual analysis involving isolated β-glucan interventions versus control groups in crossover studies since only three studies were included in this study (Figure S4). Furthermore, as reported in the methods, “Egger’s regression test” was not performed to

assess asymmetry of the funnel plot because all between-groups meta-analyses involved less than 10 original studies.

Subgroup meta-analysis

The available data allowed us to conduct only one of pre-planned subgroup analyses as the selected studies did not allow for further analysis (**Table 3**). Subgroup analysis from oat interventions in the crossover studies showed a significant effect on TC and LDL only in hypercholesterolaemic participants. However, a test for subgroups differences (non-hypercholesterolaemic vs. hypercholesterolaemic participants) found no significant subgroup differences ($p > 0.05$) for all outcomes (TC, LDL, HDL, and TG; see **Table 3**).

Discussion

The results of the current meta-analysis corroborate with other reviews regarding the benefits of oats and β-glucan on lipid profiles [21,22,26–28,78]. However, to our knowledge, this is the first meta-analysis that separately investigated the impact of oats and isolated β-glucan on lipid profiles. This approach was not conducted before, as previous reviews pooled oats and isolated β-glucan together in their analysis [21,22,26,28–30], preventing knowing whether both provide positive effects on lipid profile.

Our findings showed that isolated β-glucan improved lipid profiles, specifically TC and LDL concentrations, similarly to oats, suggesting that it is the main bioactive compound in oats. HDL cholesterol did not seem to be affected by oat or isolated β-glucan ingestion, suggesting that the mechanisms that reduce TC and LDL, mentioned previously, are different from the ones that would affect HDL. HDL can be reduced due to several factors, such as weight gain and excess saturated fat and calorie intake, while other factors can increase HDL levels, such as increased physical activity and unsaturated fat consumption [79,80]. These

changes occur due to adaptations in lipid metabolism, which increases the enzymatic activity of lipoprotein lipase, favors greater degradation of TG-rich lipoproteins, and thus causes less formation of atherogenic LDL and increases serum concentrations of the nascent HDL. Furthermore, an increase in lecithin-cholesterol-acyl-transferase and a decrease in the activity of hepatic lipase will increase the formation of HDL2-cholesterol subfractions [81]. It appears that oat and isolated β-glucan interventions are not involved with the above-mentioned mechanisms and consequently would not modify HDL levels.

The impact of oat or isolated β-glucan on TG is unclear. The parallel-arm and crossover oat groups in this meta-analysis showed no consistent improvements in TG. For the isolated β-glucan studies, TG was decreased in the parallel-arm studies, but the opposite was found in the crossover studies, as seen in Figures 4 and 5, respectively. Mechanisms of changes in the concentration of TG are linked to carbohydrates. The increase in the availability of glucose in serum, resulting from the absorption of carbohydrates, stimulates the secretion of insulin and, as a result, the synthesis of fatty acids in the liver is increased [82]. The mixed results found in this and other meta-analyses regarding TG [22,26,28,78] may be related to the fact that oats and isolated β-glucan were frequently administered through day-to-day processed foods which have sugar and other types of refined flour in their recipes. This also reinforces the fact that controlled feeding studies should be carried out to address this inconsistency regarding the effects on TG. Further, the contradictory results in the parallel-arm and crossover isolated β-glucan studies may be due to the fact that only two studies [44,49] were included in this analysis.

Considering that this review evaluated the impact of β-glucan (in oats and isolated), a viscous type of fiber, on the lipid profile, it could be judged appropriate to have other types of fiber (not β-glucan) ingested in similar amounts in the control groups of the included studies to verify if viscosity is the most important factor in cholesterol-lowering effect as seen in the

literature [15]. Nevertheless, we did not have enough studies that matched total fiber intake between intervention and control groups and, therefore, could not evaluate if the results were exclusively influenced by oat/isolated β-glucan supplementation or if other types of fiber in the background diet would have a similar impact on lipidemia. For the limited studies that did match total fiber intake between the intervention and control groups (n=9), five of them reported no significant difference in TC and LDL [43,55,59,62,76]. Therefore, future studies should match total fiber intake between groups so that the impact of β-glucan can be clearly distinguished from other types of dietary fibers.

Another aspect that also seems important to consider when analysing the impact of oat/isolated β-glucan on lipid profiles is the type and quantity of fat present in a person's diet. In this present review, none of the studies were rigorously controlled feeding trials and, therefore, did not consider background fat intake that may affect lipid profiles. Grajeta [83] found that rats fed diets containing polyunsaturated fat compared with diets containing saturated fat had different responses regarding the impact that amaranth and oat bran had on blood serum and liver lipids. Therefore, reducing saturated fat intake may be, in combination with increased viscous fiber intake from oats or isolated β-glucan, the most effective way to improve dyslipidaemia. In future studies, the amount and type of fat in the diet should be evaluated and considered accordingly.

Additionally, different oat cooking procedures, processing methods, and molecular weights would modify the viscosity and impact in cholesterol concentrations differently. Boiled oats, for instance, seem to impact the lipid profile in a greater way than brewed oats [84] and less processed oats appear to be more effective than processed oat products in improving lipidaemia [85]. Higher molecular weight is associated with increased viscosity and greater reduction in LDL [86]. It is also known that the process used to treat oats affects

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its molecular weight, and the highest viscosities were observed as a consequence of dry processes in comparison to the ones that exhibit enzymatic activity [87].

It is important to mention that the intervention time for the crossover studies (30.10 [± 13.63] days) was significantly shorter ($p < 0.001$) than the intervention time for the parallel-arm studies (46.67 [± 14.80] days). Therefore, that potentially could have interfered in the magnitude of the results found in the two distinct types of studies.

This review was able to evaluate separately the results obtained from oats and isolated β-glucan regarding its impact on the lipid profile, which allowed us to discern the potential for use of purified β-glucan as supplements or to enrich food products with fiber in human nutrition and health. However, the clinical evidence for the health effects of fiber supplements remains inconsistent [88] differently of foods naturally rich in fiber. So, it has been questioned whether purified (isolated) forms of fiber maintain their physiological effects once removed from the three-dimensional plant cell wall matrix [23,24]. Our findings here support the notion that purified, isolated forms of β-glucan, if used as supplements or added to foods, maintain their physiological effects on the lipid profile.

This review is not without limitations. Some of the included studies did not mention the method by which the lipid concentrations were obtained, which also limits the proper evaluation of the obtained results. Additionally, there was no complete dietary and physical activity evaluation in most of the articles, and no studies directly compared oats and isolated β-glucan, which would have allowed for a more thorough evaluation of the two types of interventions. A number of studies included in this review were classified as “high risk of bias”, which reinforces the need for more robust randomized controlled trials to advance human nutrition science [89]. Here 100% of the studies were classified as having some concerns or a high risk of bias, and the main reason can be attributed to the lack of details in the randomization process. This may be related to the RoB 2, which is relatively new, and

most studies predate the creation of the tool. Therefore, it is possible that there are good studies, but that did not follow the specific criteria proposed by RoB 2. Additionally, there are different tools that can be used to assess the risk of bias, and this would be related to discrepancies in the evaluations of the studies. Thus, a single instrument would be more adequate to avoid different risk of bias assessments. Finally, the tools used to assist in study design could differ from those that assess their quality when included in a systematic review or meta-analysis. This is a concern for researchers and should be rethought by guidelines.

Overall, the present systematic review and meta-analysis showed that oat interventions decreased TC and LDL concentrations. Moreover, isolated β-glucan interventions from parallel-arm studies decreased TC, LDL, and TG concentrations. Collectively, our findings show that both oat and isolated β-glucan interventions can improve lipid profiles and should be incorporated into one's regular eating habits. β-glucan supplements would be a potential tool to reduce the 'fiber gap' found in industrialized countries with low fiber intake, although the overall public health message should always focus on improving dietary quality as a whole. Future high quality and low risk of bias RCTs directly comparing oat versus isolated β-glucan interventions on lipid profiles would provide a more thorough evaluation of these two types of interventions and further inform clinical practice for cardiovascular disease prevention and treatment.

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Acknowledgements

The authors would like to thank Dr Larissa Vaz for the consulting regarding the databases research used in this review. We also thank "*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*" (CAPES) for the scholarship provided to ACMJ, and "*Conselho Nacional de Desenvolvimento Científico e Tecnológico"* (CNPq) for the financial support given to JFM (305082/2019-1).

Sources of Support: None.

Conflict of interest

The authors report there are no competing interests to declare.

Author contributions

ACMJ, RMS, RBV, JW and JFM were responsible for the project conception and design research; ACMJ and RMS conduct research, extraction, and data recording. RBV performed statistical analysis; ACMJ, RMS, RBV and JFM analyzed the data and interpreted the results; ACMJ, RMS and RBV prepared figures and tables; ACMJ, RMS and RBV had primary responsibility for final content; AMA, CP, JW and JFM edited, revised, and approved the final version of manuscript.

Data availability statement

The data set associated to this paper is available upon request.

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Table 1. Characteristics of the participants and interventions of the included studies.

Study (year)	Type of study	n (M/W)	Health status	n	Age (years)	BMI (kg/m²)	B-glucan (g/day)	Total fiber intake (g/day)		#days	Products used
								EXP	Control		
Oat											
Charlton *et*	Parallel-	87	HCh	EXP-OH:	52.43	26.74 (2.95)	3.24	NR	NR	42	Porridge and
al. (2012)	arm	(41/46)		30	(10.46)	27.28 (5.33)	1.45	NR	NR	42	cereal bars with
				EXP-OL:	51.93 (9.87)	27.74 (3.88)					oats or corn and
				26	49.75						rice flakes and
				Control: 31	(10.42)						wheat
Davidson *et*	Parallel-	140	HCh	EXP-OB28:	51.6 (NR)	24.6 (NR)	2.0	17.8	14.0	42	Powder to be
al. (1991)	arm	(80/60)		23	52.6 (NR)	24.8 (NR)	4.0	(NR)	(NR)	42	used as hot
				EXP-OB56:	54.8 (NR)	25.0 (NR)	6.0	22.6	14.0	42	cereal, muffins or
				20	51.1 (NR)	26.2 (NR)	1.2	(NR)	(NR)	42	shake with oats
				EXP-OB84:	55.0 (NR)	26.1 (NR)	2.4	25.9	14.0	42	or wheat flour

				21	51.0 (NR)	25.2 (NR)	3.6	(NR)	(NR)	42	
				EXP-OM28: 20	53.1 (NR)	25.8 (NR)		17.2 (NR)	14.0 (NR)		
				EXP-OM56: 21				15.3 (NR)	14.0 (NR)		
				EXP-OM84: 20				20.4 (NR)	14.0 (NR)		
				Control: 15							
Gerhardt and Gallo (1998)	Parallel-arm	44 (23/21)	HCh	EXP-OB: 13 Control-RB: 14	51.7 (1.5)	W: 25.82 (NR) M: 23.05 (NR)	6.72*	NR	NR	42	Powder to be mixed with food using oats or rice starch and rice bran
Liao *et al.* (2019)	Parallel-arm	74 (NR)	HCh and Non-	EXP: 37 Control: 37	38 to 76	23.38 (0.62) 23.66 (0.69)	3.12	NR	NR	70	Noodles made with oats or wheat

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			HCh								
Lovegrove *et al.* (2000)	Parallel-arm	62 (31/31)	HCh	EXP: 31 Control: 31	56.3 (9.4) 56.8 (9.2)	26.0 (3.2) 25.8 (3.7)	3.0	NR	NR	56	Cereal with oats or wheat bran
Martensson *et al.* (2005)	Parallel-arm	56 (24/32)	HCh	EXP: 20 Control: 18	55 (9)	25.3 (3.3)	3.0	No difference between groups but values NR		35	Fermented beverage made with oats or dairy
Reynolds *et al.* (2000)	Parallel-arm	43 (21/22)	HCh	EXP: 22 Control: 21	51.6 (NR)	23.8(0.7) 25.0(0.5)	2.7	25.5 (1.5)	16.8 (1.1)	28	Cereal with oats or corn flakes
Torronen *et al.* (1992)	Parallel-arm	28 (28/0)	HCh	EXP: 13 Control: 15	40 (NR) 42 (NR)	NR	11.2	39.7 (7.2)	23.1 (6.8)	56	Bread made with oats or wheat flour
Uusitupa *et al.* (1992)	Parallel-arm	36 (20/16)	HCh	EXP: 20 Control: 16	50 (6) 45 (9)	26.3 (3.3) 26.7 (2.5)	10.3	20.9 (7.6)	19.0 (6.4)	56	Powder to be added to juices, yogurt, porridge or desserts, from oats or wheat

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											bran
Amundsen *et al.* (2003)	Crossover	16 (9/7)	HCh	EXP: 16 Control: 16	57.09 (7.9)	25.49 (1.9)	5.1	28.0 (NR)	24.3 (NR)	21	Cereal, cake, bread, muffin, pasta, and apple juice with oats or wheat and rye
Bremer *et al.* (1991)	Crossover	12 (5/7)	HCh	EXP: 12 Control: 12	53 (10)	NR	3.6*	32.2 (10.3)	34.1 (11.1)	28	Bread with oats or wheat bran
Connolly *et al.* (2016)	Crossover	30 (11/19)	HCh	EXP: 30 Control: 30	42 (NR)	26.4 (5.7)	1.3	18.8 (4.41)	18.2 (5.39)	42	Granola cereal with oats or without oats
Kristensen and Bügel (2011)	Crossover	24 (NR)	Non-HCh	EXP: 24 Control: 24	25.2 (2.7)	24.9 (2.9)	8.2*	26	16	14	Bread with oats or without oats
Önning *et al.* (1999)	Crossover	52 (52/0)	HCh	EXP: 52 Control: 52	62.9 (5.9) 62.2 (5.1)	27 (NR)	3.8	NR	NR	35	Vegetable milk from oats or

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											rice
Swain *et al.* (1990)	Crossover	20 (4/16)	Non-HCh	EXP: 20 Control: 20	30 (NR)	NR	8.0*	38.9 (8.5)	18.4 (10.4)	42	Ready to eat entrees and muffins with oats or wheat flour
Trinidad *et al.* (2004)	Crossover	21 (4/17)	HCh	EXP: 21 Control: 21	M: 50 (3) W: 48 (1)	M: 25 (2) W: 25 (1)	4.7*	NR	NR	14	Cereal with oats or corn flakes
β-glucan											
Biörklund *et al.* (2005)	Parallel-arm	89 (44/45)	HCh	EXP-Oat-5: 19 EXP-Oat-10: 15 Control: 20	56 (10)	25.2 (3.3)	5.0 10.0	NR NR	NR NR	35 35	Beverage with β-glucan or rice starch
Biörklund *et al.* (2008)	Parallel-arm	43 (19/24)	HCh	EXP: 22 Control: 21	58.8 (8.2)	25.0 (3.1)	4.0	18.7 (5.7)	17.4 (5.9)	35	Soup with β-glucan or without β-glucan

Cugnet-Anceau *et al.* (2010)	Parallel-arm	53 (32/21)	HCh	EXP: 19 Control: 24	61.9 (9.1) 61.8 (7.5)	30,48 (4.08) 29.02 (4.05)	3.5	19.7 (5.3)	22.3 (12.0)	56	Soup with β-glucan or without β-glucan
Ferguson *et al.* (2019)	Parallel-arm	36 (16/20)	HCh	EXP: 18 Control: 18	56.39 (2.88) 54.78 (2.81)	27.81 (0.67) 28.49 (1.04)	3.0	30.35 (NR)	27.24 (NR)	42	Biscuits with β-glucan or without β-glucan
Keenan *et al.* (2007)	Parallel-arm	155 (75/80)	HCh	EXP-3HMW: 32 EXP-3LMW: 31 EXP-5HMW: 32 EXP-5LMW: 30 Control: 30	53.9 (10.2) 55 (10.1) 58.6 (10.6) 52.8 (11.9) 52.8 (11.9)	29.6 (5.9) 28.1 (4.3) 28.9 (6.7) 28.9 (5.3) 30.8 (4.0)	3.0 3.0 5.0 5.0	NR NR NR NR	NR NR NR NR	42 42 42 42	Beverage and cereal with β-glucan or without β-glucan
Morales *et*	Parallel-	52	HCh	EXP: 28	50.8 (10)	26.01 (3)	3.5	25.2	16.3	56	Soup with β-

al. (2021)	arm	(14/38)		Control: 24		24.54 (3.09)		(7.0)	(4.8)		glucan or without β-glucan
Naumann *et al.* (2006)	Parallel-arm	47 (18/29)	Non-HCh	EXP: 25 Control: 12	M: 56 (9) W: 49 (16)	M: 26 (2) W: 23 (3)	5.0	NR	NR	35	Fruit beverage with β-glucan or rice starch
Pino *et al.* (2021)	Parallel-arm	37 (9/28)	HCh	EXP: 20 Control: 17	EXP: 49.3 (6.75) Control: 52.8 (3.45)	EXP: 33.2 (5.16) Control: 34.2 (7.04)	5.0	22.1 (11.8)	21.4 (6.9)	84	Powder to be mixed with water or milk with β-glucan or microcrystalline cellulose
Wolever *et al.* (2021)	Parallel-arm	191 (72/119)	HCh	EXP: 96 Control: 95	47.6 (11.4)	27.9 (4.6)	3.0	26.1 (0.9)	21.1 (1.0)	28	Powder to be mixed with water containing β-glucan or rice
Cicero *et al.*	Crossover	83	HCh	EXP: 83	52.3 (4.4)	NR	3.0	NR	NR	56	Cereal with β-

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(2020)		(35/48)		Control: 83							glucan or without β-glucan
Ibrugger *et al.* (2013)	Crossover	13 (6/7)	Non-HCh	EXP: 13 Control: 13	22.9 (2.1)	22.8 (2.3)	3.3	23.2 (2.7)	26.6 (2.8)	21	Yogurt and beverage with β-glucan or without β-glucan
Theuwissen and Mensink (2007)	Crossover	42 (20/22)	HCh	EXP: 40 Control: 40	M: 54 (10) W: 51 (12)	M: 26 (2) W: 24 (3)	5.0	22.41 (5.81)	22.68 (6.48)	28	Muesli with β-glucan or wheat bran

Data presented as mean (standard deviation). BMI: body mass index; Control: control group; EXP: experimental group; M: men; NA: not applicable; NR: not reported; HCh: hypercholesterolemic (total cholesterol > 5.18 mmol/L); W: women; *0.08 g of B-glucan per gram of oat bran.

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Table 2. Study quality and risk of bias of the included studies.

Articles	Intervention	Study type	Study quality[1]	Risk of bias[2]
Charlton *et al.* (2012)	Oat	Parallel-arm	Good	High Risk
Davidson *et al.* (1991)	Oat	Parallel-arm	Good	High Risk
Gerhardt and Gallo (1998)	Oat	Parallel-arm	Good	High Risk
Liao *et al.* (2019)	Oat	Parallel-arm	Good	High Risk
Lovegrove *et al.* (2000)	Oat	Parallel-arm	Good	High Risk
Martensson *et al.* (2005)	Oat	Parallel-arm	Good	Some concerns
Reynolds *et al.* (2000)	Oat	Parallel-arm	Good	High Risk
Torronen *et al.* (1992)	Oat	Parallel-arm	Good	Some concerns
Uusitupa *et al.* (1992)	Oat	Parallel-arm	Good	Some concerns
Amundsen *et al.* (2003)	Oat	Crossover	Good	High Risk
Bremer *et al.* (1991)	Oat	Crossover	Good	High Risk
Connolly *et al.* (2016)	Oat	Crossover	Good	Some concerns
Kristensen and Bügel	Oat	Crossover	Excellent	Some concerns

(2011)				
Önning *et al.* (1999)	Oat	Crossover	Good	High Risk
Swain *et al.* (1990)	Oat	Crossover	Good	High Risk
Trinidad *et al.* (2004)	Oat	Crossover	Good	High Risk
Biörklund *et al.* (2005)	β-glucan	Parallel-arm	Good	Some concerns
Biörklund *et al.* (2008)	β-glucan	Parallel-arm	Good	Some concerns
Cugnet-Anceau *et al.* (2010)	β-glucan	Parallel-arm	Good	High Risk
Ferguson *et al.* (2019)	β-glucan	Parallel-arm	Excellent	High Risk
Keenan *et al.* (2007)	β-glucan	Parallel-arm	Good	High Risk
Morales *et al.* (2021)	β-glucan	Parallel-arm	Good	High Risk
Naumann *et al.* (2006)	β-glucan	Parallel-arm	Excellent	Some concerns
Pino *et al.* (2021)	β-glucan	Parallel-arm	Good	High Risk
Wolever *et al.* (2021)	β-glucan	Parallel-arm	Excellent	High Risk
Cicero *et al.* (2020)	β-glucan	Crossover	Excellent	High Risk
Ibrugger *et al.* (2013)	β-glucan	Crossover	Good	High Risk
Theuwissen and Mensink	β-glucan	Crossover	Good	Some concerns

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(2007)

Assessed by PEDro Scale; [2]Assessed by The Cochrane risk-of-bias tool (RoB 2).

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Table 3. Summary of subgroup analyses.

Outcomes		**Non-HCh (n=2)**	***p***	**HCh (n=5)**	***p***	***p*¥**
TC	SMD (95%CI)	-0.41 (-1.09; 0.28)	0.25	-0.82 (-1.26; -0.38)	**0.0002**	
	Heterogeneity	$\tau^2 = 0.15$, $I^2 = 61\%$	0.11	$\tau^2 = 0.15$, $I^2 = 62\%$	**0.03**	0.32
HDL	SMD (95%CI)	0.09 (-1.12; 1.30)	0.88	-0.17 (-0.41; 0.08)	0.18	
	Heterogeneity	$\tau^2 = 0.66$, $I^2 = 87\%$	**0.005**	$\tau^2 = 0.00$, $I^2 = 0\%$	0.58	0.68
LDL	SMD (95%CI)	-0.19 (-0.60; 0.23)	0.39	-0.45 (-0.75; -0.15)	**0.004**	
	Heterogeneity	$\tau^2 = 0.00$, $I^2 = 0\%$	0.74	$\tau^2 = 0.03$, $I^2 = 26\%$	0.25	0.32
TG	SMD (CI95%)	-0.29 (-0.72; 0.13)	0.17	-0.22 (-0.46; 0.02)	0.08	
	Heterogeneity	$\tau^2 = 0.00$, $I^2 = 0\%$	0.57	$\tau^2 = 0.00$, $I^2 = 0\%$	0.61	0.76

SMD: standardized mean difference; CI: confidence interval; TC: total cholesterol; HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; TG: triglycerides; HCh: hypercholesterolemic participants; non-HCh: non-hypercholesterolemic participants; τ^2: absolute heterogeneity; I^2: heterogeneity in percentual; ¥Test for subgroups differences.

Figure legends

Figure 1. Diagram flow of outcomes of review.

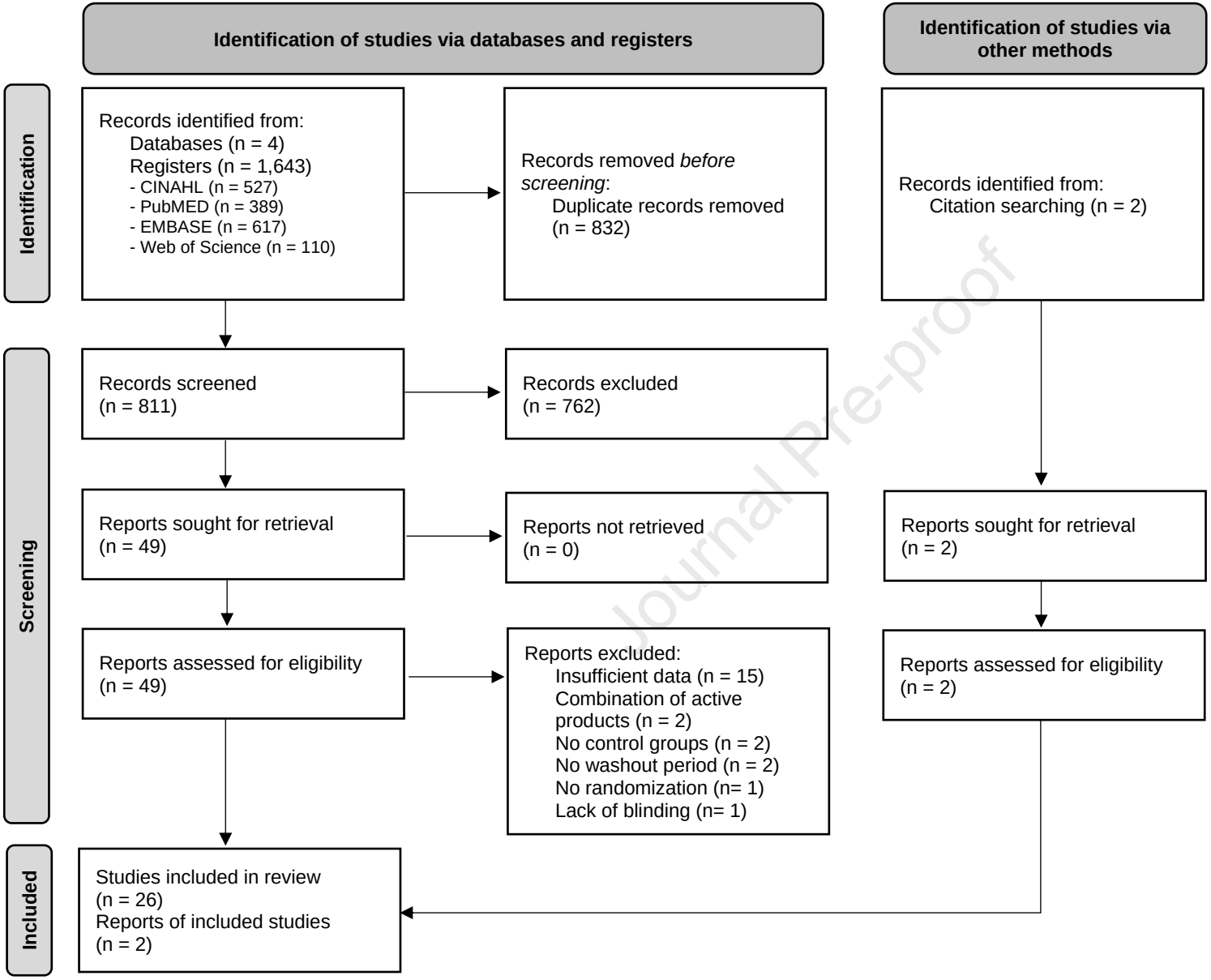
Figure 2. Main effects of oat interventions versus control groups from parallel-arm on the lipid profile (A) total cholesterol, (B) high density lipoprotein cholesterol, (C) low density lipoprotein cholesterol, and (D) triglycerides.

Figure 3. Main effects of oat interventions versus control groups from crossover studies on the lipid profile (A) total cholesterol, (B) high density lipoprotein cholesterol, (C) low density lipoprotein cholesterol, and (D) triglycerides.

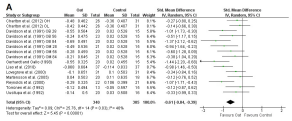
Figure 4. Main effects of isolated β-glucan interventions versus control groups from parallel-arm on the lipid profile (A) total cholesterol, (B) high density lipoprotein cholesterol, (C) low density lipoprotein cholesterol, and (D) triglycerides.

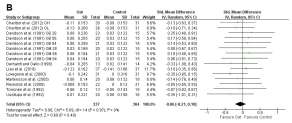
Figure 5. Main effects of isolated β-glucan interventions versus control groups from crossover studies on the lipid profile (A) total cholesterol, (B) high density lipoprotein cholesterol, (C) low density lipoprotein cholesterol, and (D) triglycerides.

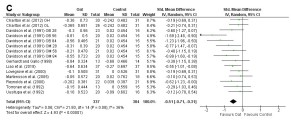
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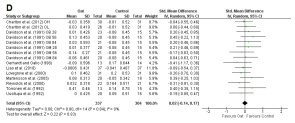


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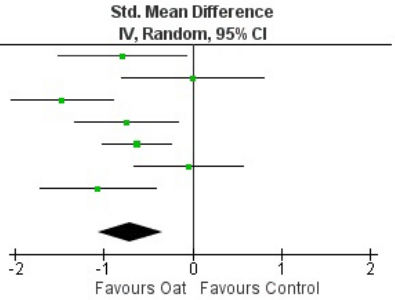


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A

Study or Subgroup	Favours Oat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amundsen et al. (2003)	-0.71	0.426	16	-0.3	0.575	16	12.4%	-0.79 [-1.51, -0.07]
Bremer et al. (1991)	-0.3	0.703	12	-0.3	0.717	12	11.2%	0.00 [-0.80, 0.80]
Connolly et al. (2016)	-0.52	0.592	30	0.49	0.752	30	15.1%	-1.47 [-2.05, -0.90]
Kristensen and Bügel (2011)	-0.59	0.54	24	-0.16	0.59	24	14.8%	-0.75 [-1.33, -0.16]
Önning et al. (1999)	-0.17	0.59	52	0.19	0.54	52	18.7%	-0.63 [-1.03, -0.24]
Swain et al. (1990)	-0.36	0.406	20	-0.34	0.406	20	14.2%	-0.05 [-0.67, 0.57]
Trinidad et al. (2004)	-0.647	0.667	21	0.104	0.714	21	13.6%	-1.07 [-1.72, -0.42]
Total (95% CI)			**175**			**175**	**100.0%**	**-0.70 [-1.07, -0.34]**

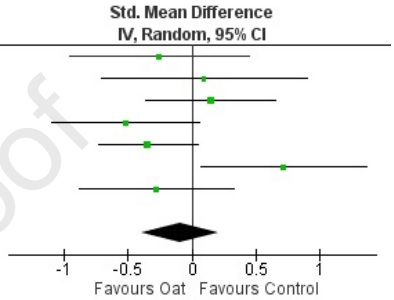
Heterogeneity: Tau² = 0.15; Chi² = 15.54, df = 6 (P = 0.02); I² = 61%
Test for overall effect: Z = 3.76 (P = 0.0002)



B

Study or Subgroup	Oat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amundsen et al. (2003)	-0.21	0.249	16	-0.15	0.213	16	11.7%	-0.25 [-0.95, 0.44]
Bremer et al. (1991)	0.1	0.087	12	0.09	0.115	12	9.8%	0.09 [-0.71, 0.90]
Connolly et al. (2016)	0.02	0.216	30	-0.01	0.181	30	16.6%	0.15 [-0.36, 0.66]
Kristensen and Bügel (2011)	-0.15	0.1	24	-0.08	0.16	24	14.6%	-0.52 [-1.09, 0.06]
Önning et al. (1999)	-0.07	0.46	52	0.05	0.17	52	20.6%	-0.34 [-0.73, 0.04]
Swain et al. (1990)	0.01	0.118	20	-0.08	0.1282	20	12.9%	0.72 [0.07, 1.36]
Trinidad et al. (2004)	-0.129	0.286	21	-0.054	0.249	21	13.8%	-0.27 [-0.88, 0.33]
Total (95% CI)			**175**			**175**	**100.0%**	**-0.09 [-0.39, 0.21]**

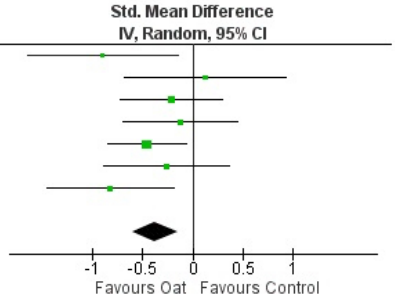
Heterogeneity: Tau² = 0.08; Chi² = 11.36, df = 6 (P = 0.08); I² = 47%
Test for overall effect: Z = 0.56 (P = 0.57)



C

Study or Subgroup	Oat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amundsen et al. (2003)	-0.4	0.364	15	-0.01	0.478	15	8.6%	-0.89 [-1.65, -0.14]
Bremer et al. (1991)	-0.3	0.741	12	-0.4	0.789	12	7.7%	0.13 [-0.67, 0.93]
Connolly et al. (2016)	-0.3	3.966	30	0.31	0.55	30	17.7%	-0.21 [-0.72, 0.29]
Kristensen and Bügel (2011)	-0.35	0.52	24	-0.29	0.45	24	14.6%	-0.12 [-0.69, 0.44]
Önning et al. (1999)	-0.21	0.45	51	0.04	0.62	51	27.3%	-0.46 [-0.85, -0.06]
Swain et al. (1990)	-0.27	0.299	20	-0.19	0.299	20	12.3%	-0.26 [-0.88, 0.36]
Trinidad et al. (2004)	-0.351	0.368	21	0.033	0.539	21	11.9%	-0.82 [-1.45, -0.18]
Total (95% CI)			**173**			**173**	**100.0%**	**-0.38 [-0.60, -0.15]**

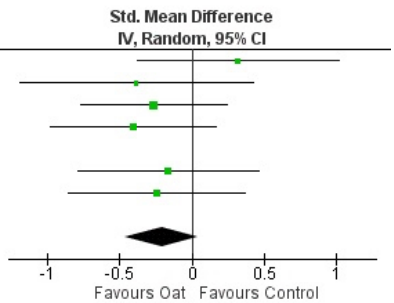
Heterogeneity: Tau² = 0.01; Chi² = 6.64, df = 6 (P = 0.36); I² = 10%
Test for overall effect: Z = 3.24 (P = 0.001)



D

Study or Subgroup	Oat Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amundsen et al. (2003)	-0.2	0.574	16	-0.47	1.006	16	13.0%	0.32 [-0.38, 1.02]
Bremer et al. (1991)	-0.2	0.541	12	0	0.462	12	9.7%	-0.38 [-1.19, 0.43]
Connolly et al. (2016)	-0.08	0.362	30	0.08	0.762	30	24.5%	-0.26 [-0.77, 0.24]
Kristensen and Bügel (2011)	-0.19	0.34	24	-0.08	0.16	24	19.3%	-0.41 [-0.98, 0.16]
Önning et al. (1999)	0.1	0.58	52	0.29	0.63	52		Not estimable
Swain et al. (1990)	-0.5	0.908	20	-0.35	0.908	20	16.4%	-0.16 [-0.78, 0.46]
Trinidad et al. (2004)	-0.599	0.476	21	-0.4629	0.611	21	17.1%	-0.24 [-0.85, 0.36]
Total (95% CI)			**123**			**123**	**100.0%**	**-0.21 [-0.46, 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 5 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.61 (P = 0.11)

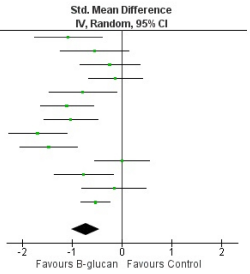


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A

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Björklund et al. (2005) Oat-10	-0.32	0.39	19	0.17	0.49	20	6.8%	-1.08 [-1.76, -0.40]
Björklund et al. (2005) Oat-5	-0.12	0.54	15	0.17	0.49	20	6.8%	-0.55 [-1.24, 0.13]
Björklund et al. (2008)	-0.18	0.38	22	-0.09	0.34	21	7.5%	-0.24 [-0.85, 0.36]
Cugnet-Anceau et al. (2010)	-0.06	0.52	29	0.01	0.52	24	8.0%	-0.13 [-0.67, 0.41]
Ferguson et al. (2019)	-0.41	0.51	18	0.02	0.55	18	6.8%	-0.79 [-1.47, -0.11]
Keenan et al. (2007) 3HMW	-0.494	0.338	32	-0.07	0.416	30	8.0%	-1.11 [-1.65, -0.57]
Keenan et al. (2007) 3LMW	-0.462	0.334	31	-0.07	0.416	30	8.0%	-1.03 [-1.56, -0.49]
Keenan et al. (2007) 5HMW	-0.755	0.382	32	-0.07	0.416	30	7.6%	-1.70 [-2.28, -1.11]
Keenan et al. (2007) 5LMW	-0.683	0.406	30	-0.07	0.416	30	7.7%	-1.47 [-2.05, -0.90]
Morales et al. (2021)	0.02	0.72	28	0.02	0.68	24	8.0%	0.00 [-0.55, 0.55]
Naumann et al. (2006)	-0.19	0.39	25	0.11	0.37	22	7.5%	-0.77 [-1.37, -0.18]
Pino et al. (2021)	-0.248	1.477	20	0.003	1.673	17	7.1%	-0.16 [-0.80, 0.49]
Wolever et al. (2021)	-0.22	0.441	96	0.04	0.529	95	10.2%	-0.53 [-0.82, -0.24]
Total (95% CI)			**397**			**381**	**100.0%**	**-0.73 [-1.01, -0.45]**

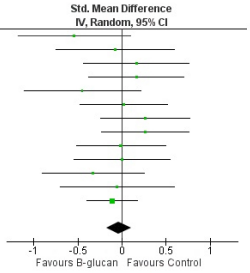
Heterogeneity: Tau² = 0.18; Chi² = 39.98, df = 12 (P < 0.0001); I² = 70%
Test for overall effect: Z = 5.13 (P < 0.00001)



B

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Björklund et al. (2005) Oat-10	-0.01	0.15	19	0.07	0.14	20	4.9%	-0.54 [-1.18, 0.10]
Björklund et al. (2005) Oat-5	0.06	0.1	15	0.07	0.14	20	4.4%	-0.08 [-0.75, 0.59]
Björklund et al. (2008)	-0.03	0.217	22	-0.07	0.26	21	5.6%	0.16 [-0.43, 0.76]
Cugnet-Anceau et al. (2010)	0.05	0.1	29	0.03	0.14	24	6.8%	0.16 [-0.38, 0.71]
Ferguson et al. (2019)	-0.03	0.13	18	0.04	0.17	18	4.5%	-0.45 [-1.11, 0.21]
Keenan et al. (2007) 3HMW	-0.013	0.14	32	-0.016	0.151	30	8.0%	0.02 [-0.48, 0.52]
Keenan et al. (2007) 3LMW	0.031	0.197	31	-0.016	0.151	30	7.8%	0.26 [-0.24, 0.77]
Keenan et al. (2007) 5HMW	0.028	0.176	32	-0.016	0.151	30	8.0%	0.26 [-0.24, 0.76]
Keenan et al. (2007) 5LMW	-0.018	0.171	30	-0.016	0.151	30	7.8%	-0.01 [-0.52, 0.49]
Morales et al. (2021)	-0.03	0.2	28	-0.03	0.2	24	6.7%	0.00 [-0.55, 0.55]
Naumann et al. (2006)	0.03	0.08	25	0.06	0.1	22	6.0%	-0.33 [-0.91, 0.25]
Pino et al. (2021)	0.045	0.234	20	0.059	0.266	17	4.8%	-0.05 [-0.70, 0.59]
Wolever et al. (2021)	-0.01	0.194	96	0.01	0.161	95	24.7%	-0.11 [-0.40, 0.17]
Total (95% CI)			**397**			**381**	**100.0%**	**-0.04 [-0.18, 0.10]**

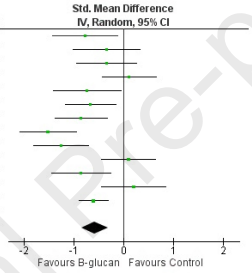
Heterogeneity: Tau² = 0.00; Chi² = 8.95, df = 12 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)



C

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Björklund et al. (2005) Oat-10	-0.24	0.35	19	0.05	0.38	20	6.9%	-0.78 [-1.43, -0.12]
Björklund et al. (2005) Oat-5	-0.11	0.54	15	0.05	0.38	20	6.7%	-0.34 [-1.02, 0.33]
Björklund et al. (2008)	-0.16	0.36	22	-0.05	0.27	21	7.4%	-0.34 [-0.94, 0.26]
Cugnet-Anceau et al. (2010)	-0.05	0.38	29	-0.1	0.51	24	7.9%	0.11 [-0.43, 0.65]
Ferguson et al. (2019)	-0.42	0.47	18	-0.05	0.51	18	6.7%	-0.74 [-1.42, -0.06]
Keenan et al. (2007) 3HMW	-0.362	0.516	32	-0.047	0.412	30	8.2%	-0.66 [-1.18, -0.15]
Keenan et al. (2007) 3LMW	-0.347	0.263	31	-0.047	0.412	30	8.1%	-0.86 [-1.39, -0.33]
Keenan et al. (2007) 5HMW	-0.582	0.273	32	-0.047	0.412	30	7.7%	-1.52 [-2.09, -0.95]
Keenan et al. (2007) 5LMW	-0.525	0.333	30	-0.047	0.412	30	7.8%	-1.26 [-1.82, -0.70]
Morales et al. (2021)	0.08	0.65	28	0.01	0.73	24	7.9%	0.10 [-0.45, 0.65]
Naumann et al. (2006)	-0.21	0.37	25	0.1	0.34	22	7.4%	-0.86 [-1.46, -0.25]
Pino et al. (2021)	0.141	0.967	20	-0.03	0.613	17	7.0%	0.20 [-0.45, 0.85]
Wolever et al. (2021)	-0.22	0.439	96	0.03	0.384	95	10.3%	-0.60 [-0.89, -0.31]
Total (95% CI)			**397**			**381**	**100.0%**	**-0.58 [-0.85, -0.32]**

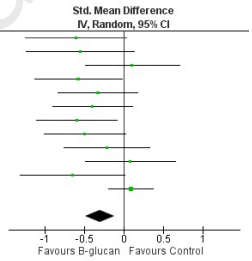
Heterogeneity: Tau² = 0.16; Chi² = 37.68, df = 12 (P = 0.0002); I² = 68%
Test for overall effect: Z = 4.27 (P < 0.0001)



D

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Björklund et al. (2005) Oat-10	-0.14	0.37	19	0.1	0.4	20	6.2%	-0.61 [-1.25, 0.03]
Björklund et al. (2005) Oat-5	-0.14	0.45	15	0.1	0.4	20	5.7%	-0.56 [-1.24, 0.13]
Björklund et al. (2008)	0	0.44	22	-0.05	0.505	21	7.0%	0.10 [-0.49, 0.70]
Cugnet-Anceau et al. (2010)	-0.12	0.38	29	0.12	0.44	24	7.8%	-0.58 [-1.13, -0.03]
Keenan et al. (2007) 3HMW	-0.14	0.605	32	0.0555	0.562	30	9.0%	-0.33 [-0.83, 0.17]
Keenan et al. (2007) 3LMW	-0.14	0.4	31	0.0555	0.562	30	8.8%	-0.40 [-0.90, 0.11]
Keenan et al. (2007) 5HMW	-0.28	0.55	32	0.0555	0.562	30	8.8%	-0.60 [-1.11, -0.09]
Keenan et al. (2007) 5LMW	-0.24	0.61	30	0.0555	0.562	30	8.7%	-0.50 [-1.01, 0.02]
Morales et al. (2021)	-0.11	0.74	28	0.03	0.48	24	8.0%	-0.22 [-0.76, 0.33]
Naumann et al. (2006)	-0.07	0.48	25	-0.11	0.47	22	7.4%	0.08 [-0.49, 0.66]
Pino et al. (2021)	-0.848	1.716	20	0.25	1.558	17	5.9%	-0.65 [-1.32, 0.01]
Wolever et al. (2021)	0.03	0.452	96	-0.01	0.45	95	16.7%	0.09 [-0.20, 0.37]
Total (95% CI)			**379**			**363**	**100.0%**	**-0.30 [-0.49, -0.12]**

Heterogeneity: Tau² = 0.03; Chi² = 15.92, df = 11 (P = 0.14); I² = 31%
Test for overall effect: Z = 3.26 (P = 0.001)

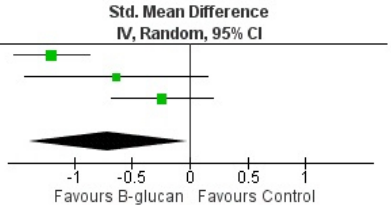


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A

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cicero et al. (2020)	-0.52	0.381	83	0	0.478	83	37.9%	-1.20 [-1.53, -0.87]
Ibrugger et al. (2013)	-0.29	0.288	13	-0.02	0.505	13	26.6%	-0.64 [-1.43, 0.16]
Theuwissen and Mensink (2007)	-0.24	0.595	40	-0.09	0.627	40	35.5%	-0.24 [-0.68, 0.20]
Total (95% CI)			**136**			**136**	**100.0%**	**-0.71 [-1.39, -0.03]**

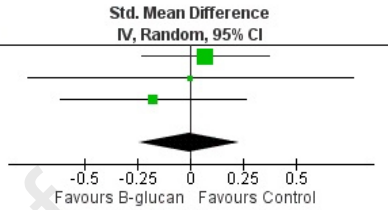
Heterogeneity: Tau² = 0.29; Chi² = 11.80, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 2.04 (P = 0.04)



B

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cicero et al. (2020)	0.01	0.158	83	0	0.12	83	61.1%	0.07 [-0.23, 0.38]
Ibrugger et al. (2013)	-0.05	0.108	13	-0.05	0.1082	13	9.6%	0.00 [-0.77, 0.77]
Theuwissen and Mensink (2007)	-0.03	0.251	40	0.01	0.192	40	29.3%	-0.18 [-0.62, 0.26]
Total (95% CI)			**136**			**136**	**100.0%**	**-0.01 [-0.25, 0.23]**

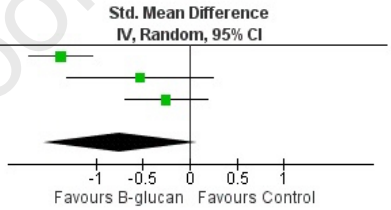
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)



C

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cicero et al. (2020)	-0.59	0.435	83	0.04	0.47	83	36.4%	-1.38 [-1.72, -1.05]
Ibrugger et al. (2013)	-0.24	0.325	13	-0.04	0.397	13	28.6%	-0.53 [-1.32, 0.25]
Theuwissen and Mensink (2007)	-0.21	0.624	40	-0.05	0.619	40	34.9%	-0.25 [-0.70, 0.19]
Total (95% CI)			**136**			**136**	**100.0%**	**-0.75 [-1.56, 0.07]**

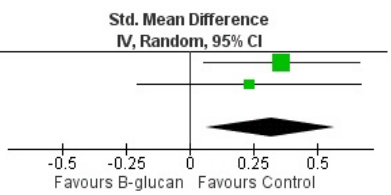
Heterogeneity: Tau² = 0.45; Chi² = 16.90, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.79 (P = 0.07)



D

Study or Subgroup	B-glucan Mean	B-glucan SD	B-glucan Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cicero et al. (2020)	0.13	0.638	83	-0.08	0.52	83	67.3%	0.36 [0.05, 0.67]
Theuwissen and Mensink (2007)	0.13	0.795	40	-0.04	0.646	40	32.7%	0.23 [-0.21, 0.67]
Total (95% CI)			**123**			**123**	**100.0%**	**0.32 [0.07, 0.57]**

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)



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