

Are all fibres created equal with respect to lipid lowering? Comparing the effect of viscous dietary fibre to non-viscous fibre from cereal sources: a systematic review and meta-analysis of randomised controlled trials

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(Submitted 20 January 2022 – Final revision received 5 July 2022 – Accepted 18 July 2022 – First published online 5 August 2022)

Abstract

Although compelling evidence from observational studies supports a positive association between consumption of cereal fibre and CVD risk reduction, randomised controlled trials (RCT) often target viscous fibre type as the prospective contributor to lipid lowering to reduce CVD risk. The objective of our study is to compare the lipids-lowering effects of viscous dietary fibre to non-viscous, cereal-type fibre in clinical studies. RCT that evaluated the effect of viscous dietary fibre compared with non-viscous, cereal fibre on LDL cholesterol and alternative lipid markers, with a duration of ≥ 3 weeks, in adults with or without hypercholesterolaemia were included. Medline, EMBASE, CINAHL and the Cochrane Central Register were searched through October 19, 2021. Data were extracted and assessed by two independent reviewers. The generic inverse variance method with random effects model was utilised to pool the data which were expressed as mean differences (MD) with 95 % CI. Eighty-nine trials met eligibility criteria (n 4755). MD for the effect of viscous dietary fibre compared with non-viscous cereal fibre were LDL cholesterol (MD = -0.26 mmol/l; 95 % CI: -0.30 , -0.22 mmol/l; $P < 0.01$), non-HDL cholesterol (MD = -0.33 mmol/l; 95 % CI: -0.39 , -0.28 mmol/l; $P < 0.01$) and Apo-B (MD = -0.04 g/l; 95 % CI: -0.06 , -0.03 g/l; $P < 0.01$). Viscous dietary fibre reduces LDL cholesterol and alternative lipid markers relative to the fibre from cereal sources, hence may be a preferred type of fibre-based dietary intervention targeting CVD risk reduction.

Key words: Fibre: Viscous dietary fibre: Cholesterol: Lipids: CVD

Over the past 50 years, evidence has continuously supported the role of diets high in fibre and whole grain in the prevention of CHD often attributed to cholesterol lowering. As such, dietary fibre has been instituted as one of the key features of healthy dietary pattern recommendations^(1,2).

The general consensus on the lipid-lowering effects is built upon data from both cohort study observations and smaller scale feeding trials spanning a broad umbrella of fibre-rich foods and functional supplements^(3–6). Due to the great variation in physicochemical properties of fibre sources, developing definitions that adequately classify fibre types, while predicting physiological responses such as lipid lowering,

has been challenging^(7–9). Classification according to solubility remains common⁽⁸⁾, but grading fibres according to its gel-forming capability may be more relevant for functional implications⁽¹⁰⁾. Major CVD and lipid management guidelines, nonetheless, largely continue to generalise recommendations to total dietary fibre as a single entity, upwards to impractical quantities of 40 g/d, with few attempts to emphasise any selection of fibre by type to optimise benefit^(2,11,12).

While some convincing data has emerged from randomised controlled trials (RCT) that used viscous soluble fibres, thus contributing to several fibre-based health claims^(13,14), not all agree⁽¹⁵⁾. Viscous fibre is found in the diet in oats and barley as β -glucan,

Abbreviations: KJM, konjac-glucomannan; MD, mean difference; RCT, randomised controlled trial.

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certain legumes (ex. guar), citrus fruits (ex. pectin) and in supplements such as psyllium husk or konjac-glucomannan (KJM). Differences in fibre efficacy have been attributed to the difference in rheological properties and the ability to increase the viscosity of the intestinal content, thus binding to bile acids to stimulate excretion and *de novo* synthesis^(16–19).

Non-viscous or non-gelling structural fibres such as wheat bran cellulose, hemicelluloses (i.e. arbinoxylans) or lignins are a counterpart to viscous fibre, consumed mostly in the western diet as part of cereal crops and whole grains. Much of the debate resides in regards to cardio-protection offered from these types of grain fibres, in part due to disparity between consistent observational evidence⁽²⁰⁾ and, on the contrary, inconsistent RCT data on major CVD risk factors including lipids⁽²¹⁾, making this topic a highly controversial issue in nutrition. Although certain assumptions prevail that non-gelling insoluble cereal fibres may not be metabolically inactive, several novel mechanisms supporting the cardiometabolic relevance of insoluble fibre have also emerged^(22–24).

It is therefore of significant clinical interest to systematically characterise how administration of viscous fibre compares to the non-viscous cereal fibre sources on lipid targets within a randomised controlled setting. The objective of this study, therefore, is to summarise and quantify the available evidence for the effect of viscous fibres compared with the effect of non-viscous fibre types, on LDL cholesterol as well as novel lipid markers non-HDL cholesterol and ApoB, using high-quality data from RCT compared with diets containing non-viscous types of fibre including cereal grain.

Methods

Protocol and registration

The Cochrane Handbook for Systematic Reviews of Interventions⁽²⁵⁾ was applied in conducting this systematic review and meta-analysis and results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines⁽²⁶⁾ (online Supplementary Table S1). The study protocol is available at clinicaltrials.gov (NCT02068248).

Search strategy and data sources

MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched using the strategy presented in Supplementary Table S2. The database search was supplemented with a manual search of references. Searches were performed with the most recent update on October 19, 2021.

Study eligibility

Included trials are RCT that investigated the effect of major viscous fibre sources including: barley β -glucan, oat β -glucan, KJM, psyllium, guar gum and pectin, compared with an insoluble fibre (i.e. non-viscous cereal fibre sources of wheat, rice, maize or isolates) in adults with and without hypercholesterolaemia for ≥ 3 weeks duration on LDL cholesterol, non-HDL

cholesterol and ApoB. Studies that did not report non-HDL cholesterol but provided sufficient information to calculate the lipid marker were also considered. Included trials must also have reported the dose of dietary fibre or provide enough information to be computable. In multi-arm trials, we selected the groups most relevant to our research question. In publications with duplicate populations, we selected the most recent publication. Only trials written in English or translated to English by the authors were considered.

Data extraction and quality assessment

Independent reviewers extracted data from eligible studies using a standardised pro forma. Relevant data included information on study design (crossover or parallel), sample size, duration, subject characteristics (sex, age, BMI, disease status), background diet, energy balance, dose of fibre, comparator, study setting (country; inpatient or outpatient) and funding source. If the soluble fibre content of psyllium was not reported, it was considered to be 70 % soluble dietary fibre. If the β -glucan content was not reported, whole barley and barley soluble fibre were considered to be 4.75 % and 93.8 % β -glucan, respectively⁽²⁷⁾. Oat bran, whole oats and oat soluble fibre was considered to be 6.9 %, 5.0 %, and 92.5 % β -glucan, respectively^(28–30). Baseline and end data, or changes from baseline data for LDL cholesterol, non-HDL cholesterol and ApoB for both control and intervention groups were extracted as means \pm SE or were computed according to standard formulas outlined in the Cochrane Handbook⁽²⁵⁾. In multi-arm trials, the SE (mean difference (MD)) was adjusted to take into account multiple comparisons extracted per control group⁽²⁵⁾. Authors were contacted for additional information when necessary.

The risk of bias in each included study was assessed using the Cochrane Risk of Bias tool⁽²⁵⁾. The domains assessed included sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. A 'high risk' of bias was assigned to studies that contained methodological flaws that were likely to affect the results. A 'low risk' was assigned if the flaw was deemed inconsequential, and an 'unclear risk' was assigned to studies where insufficient information was provided to assess risk of bias. Any discrepancies in the extracted data or the risk of bias assessments were resolved by discussion until an agreement was reached between co-extractors.

Data management and statistical analysis

Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA version 14 (StataCorp) were used to analyse data. Plot Digitizer version 2.6.8 (<http://plotdigitizer.sourceforge.net/>) was used to estimate effect sizes when data was presented through graphs. The difference between the change from baseline of the control and the intervention arms was calculated for each study and used as the MD between interventions for LDL cholesterol, non-HDL cholesterol and ApoB. If change from baseline values was not provided and could not be calculated, the difference between end-of-treatment values was used. In studies that did not directly report non-HDL cholesterol, it was calculated by obtaining the difference





between total cholesterol and HDL cholesterol. The standard deviations of the calculated non-HDL cholesterol values were estimated with the equation: $SD = \sqrt{(SD^2_{\text{total cholesterol}} + SD^2_{\text{HDL cholesterol}})}$ ^(31,32). Paired analyses were conducted for all cross-over trials, and a conservative correlation coefficient of 0.50 was used to compute the SE of the MD⁽³³⁾. The MD \pm SE from each study was pooled for each lipid outcome by using the generic inverse-variance method with DerSimonian and Laird random-effects model. Pooled results are expressed as MD with 95 % CI. A two-sided *P*-value of < 0.05 was set as the level of significance. For all lipid outcomes, the primary analysis was further divided into subgroups by fibre type.

The presence of heterogeneity between studies was tested using the Cochran Q-statistic and the degree of heterogeneity was quantified by the I^2 statistic with a significance level of $P < 0.10$. An $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity⁽²⁵⁾. Sources of heterogeneity were investigated through subgroup and leave-one-out sensitivity analyses. When ≥ 10 trials were available for an outcome, subgroup analyses of categorical and continuous variables that were determined *a priori* were conducted for baseline values including, BMI, dose, duration, study design, energy balance, fibre type, disease status, funding and background diet. Meta-regression analyses were performed to estimate the influence of subgroup effects, with a significance level set at $P < 0.05$. Leave-one-out sensitivity analyses involved individually removing each trial from the meta-analysis and recalculating the overall effect size and heterogeneity to assess the influence of each single trial on the overall pooled result.

Dose-response analyses were performed using linear (continuous) and non-linear (cubic spline) meta-regression with significance at $P < 0.05$. If ≥ 10 trials were available, publication bias was assessed through visual inspection of funnel plots for asymmetry and verified through Egger's and Begg's tests, where $P < 0.05$ was considered evidence for small study effects. If publication bias was suspected, Duval and Tweedie 'trim and fill' method was used to estimate the effect size after imputing 'missing' study data⁽³⁴⁾.

Grading the evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used to assess the overall certainty of the available evidence^(35–47). The certainty of evidence for each outcome was assessed as either 'very low', 'low', 'moderate', or 'high' from two independent reviewers. Evidence from RCTs received a default grade of 'high' quality, however it can be downgraded on the basis of pre-specified criteria: risk of bias (assessed through the Cochrane Risk of Bias tool), inconsistency (substantial unexplained inter-study heterogeneity, $I^2 \geq 50\%$, $P < 0.10$), indirectness (presence of factors that limit the generalisability of results), imprecision (95 % CI for effect estimates are wide and cross a minimally important difference for benefit or harm and criteria for the optimal information size are not met) and publication bias (assessed through visual inspection of a funnel plot and statistical tests for asymmetry (Egger's and Begg's test)).

Results

Search results

The search strategy is presented in Fig. 1. The search yielded a total of 9429 publications, of which 258 were reviewed in full and 89 (*n* 4755) were included in the final analysis. Of these, eighty studies reported on LDL cholesterol (*n* 4579) and 22 studies reported ApoB (*n* 1536). Non-HDL cholesterol was not directly reported in any of the included studies, however eighty-four studies provided sufficient information to calculate it (*n* 4537).

Trial characteristics

Characteristics of included studies are summarised in Table 1^(10,24,48–134). The majority of the studies (45 %) were set in North America (twenty-seven in the USA, twelve in Canada and one in Mexico), 33 % of the studies were conducted in Europe (ten in Finland, seven in the UK, three in Netherlands, three in Sweden, one each in Italy, Greece, Slovenia and Norway and one each across Spain and Netherlands and UK and Germany), 11 % of the studies were conducted in Asia (three in Japan, three in Iran and one each in China, Thailand, Taiwan and Pakistan), 7 % in Australia, 2 % in New Zealand, and 2 % in South America (one in Brazil and one in Venezuela). Of all RCT, 35 (39 %) used a cross-over design and 54 (61 %) used a parallel design. Participants were generally middle aged (mean age = 50.8 years) and overweight (average BMI = 26.9), with an approximately even distribution of sexes (1812 males, 1815 females). The majority of studies were conducted in individuals with hypercholesterolaemia (70 %), whereas the remaining were conducted in individuals with type 2 diabetes mellitus (16 %), healthy (8 %) or overweight (2 %), and 1 % each with metabolic syndrome, type 1 diabetes mellitus, ulcerative colitis and polycystic ovary syndrome. The median dose of viscous fibres across all outcomes was 7.0 g/d, with KJM of 15.0 g/d, guar gum 15.0 g/d, psyllium 7.1 g/d, barley β -glucan 5.3 g/d, oat β -glucan 3.1 g/d and pectin 12.0 g/d, with the treatment duration ranging from 3 to 52 weeks. The median dose of non-viscous fibres was 10.2 g/d (30 trials did not report dose). In more than half of the trials, 63 % of participants followed their normal habitual (unmodified) diet. Of the trials that used a background diet, 29 % used a healthy diet (NCEP diet, AHA diet, etc), 6 % used a low-fat diet and 1 % each used a low-calorie diet, low-fibre diet or high-fat diet.

Using the Cochrane Risk of Bias tool (online Supplementary Fig. S1), the majority of trials were determined to have an unclear risk of bias in random sequence generation and allocation concealment methodology, and a low risk of bias in attrition (incomplete outcome data), selective reporting bias and performance (blinding of participants and personnel). Funding for trials included industry (33 %), agency (24 %), agency industry (20 %), none (1 %) or funding source was not reported (22 %).

Effect on LDL cholesterol

Figure 2 shows the effect of viscous fibres on LDL cholesterol. Pooled effect of eighty studies, including 102 comparisons (*n* 4958) showed a significant effect of viscous fibres on LDL cholesterol (MD = -0.26 mmol/l; 95 % CI: -0.30 , -0.22 mmol/l;

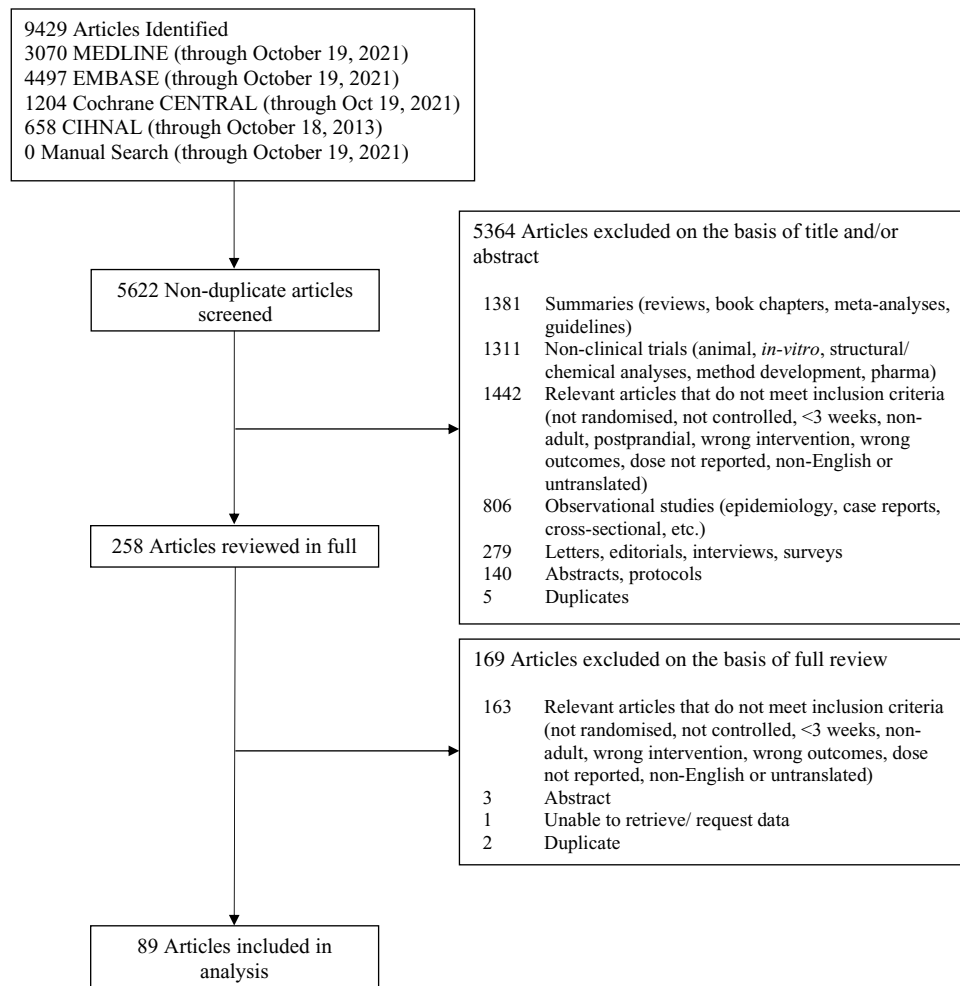


Fig. 1. Flow of literature. Summary of the number of articles that were identified and included in the meta-analysis of the effect of viscous fibre on LDL cholesterol, non-HDL cholesterol and ApoB. MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL databases were searched.

$P < 0.01$), compared with non-viscous control. In individual subgroups by fibre type, guar gum demonstrated a numerically greatest reduction on LDL cholesterol (MD = -0.53 mmol/l; 95 % CI: -0.67 , -0.38 mmol/l; $P < 0.01$) followed by KJM (MD = -0.38 mmol/l; 95 % CI: -0.56 , -0.21 mmol/l; $P < 0.01$) and psyllium (MD = -0.35 mmol/l; 95 % CI: -0.42 , -0.28 mmol/l; $P < 0.01$). The lowest LDL cholesterol reduction was found with barley β -glucan (MD = -0.21 mmol/l; 95 % CI: -0.31 , -0.11 mmol/l; $P < 0.01$) and oat β -glucan (MD = -0.20 mmol/l; 95 % CI: -0.25 , -0.14 mmol/l; $P < 0.01$). The presence of substantial inter-study heterogeneity was observed in the overall analysis ($I^2 = 73\%$, $P < 0.01$). Leave-one-out sensitivity analysis did not alter the heterogeneity observed or the significance, direction and size of the pooled effect. Continuous *a priori* subgroup analyses suggested that LDL cholesterol was significantly modified by dose with every subsequent increase in dose (g/d) being associated with an LDL cholesterol reduction of -0.01 ($P < 0.01$), with residual $I^2 = 66.3\%$ (online Supplementary Table S3). Categorical *a priori* subgroup analyses revealed a significant effect of fibre type on LDL cholesterol ($P < 0.01$), with residual $I^2 = 62.4\%$ (online

Supplementary Fig. S2). KJM showed a greater reduction compared with oat β -glucan (MD = -0.19 mmol/l; 95 % CI: -0.37 , -0.01 mmol/l; $P = 0.04$). Guar gum showed a greater lowering effect compared with both barley β -glucan (MD = -0.33 mmol/l; 95 % CI: -0.52 , -0.14 mmol/l; $P < 0.01$) and oat β -glucan (MD = -0.33 mmol/l; 95 % CI: -0.51 , -0.15 mmol/l; $P < 0.01$). Psyllium showed a lower effect compared with barley β -glucan (MD = -0.16 mmol/l; 95 % CI: -0.28 , -0.04 mmol/l; $P = 0.01$) and oat β -glucan (MD = -0.16 mmol/l; 95 % CI: -0.25 , -0.06 mmol/l; $P < 0.01$). Significant effects were also found for disease status ($P = 0.03$, residual $I^2 = 70.8\%$), where individuals with T2DM showed greater reductions in LDL-cholesterol than individuals with hypercholesterolaemia (MD = -0.24 mmol/l; 95 % CI: -0.41 , -0.08 mmol/l; $P < 0.01$) and healthy individuals (MD = -0.24 mmol/l; 95 % CI: -0.46 , -0.03 mmol/l; $P = 0.03$) (online Supplementary Fig. S2). There was also a significant effect of dose < 6.0 v ≥ 6.0 g/d with higher dose associated with larger reduction ($P = 0.01$, residual $I^2 = 65.3\%$) (online Supplementary Fig. S2). Further *a priori* subgroup analyses found no effect on BMI, duration, study design, energy balance, baseline LDL cholesterol, comparator, funding and background diet.

Table 1. Summary of included trials

Fibre type	No. of trials*	Participants†	Population (no. of trials)	Mean age (years)	Range	Mean BMI (kg/m ²)	Range	Median Duration	Blinding	Average dose (g/d)	Range	Comparator (no. of trials)	Background diet	Funding source	Setting
Barley β -glucan ^(48–59)	126C, 6P	512 236M: 135F	9 HC, 1 healthy, 1 OW1 MetS	50.9	41.4–63.4	26.6	24.8–30.0	4.5 weeks (4–12)	5 DB, 3 SB, 4 NB	5.7	1.4–12.3	8 Wheat, 3 rice, 1 cellulose	5 healthy, 7 usual	2 A, 2 I, 5 A-I, 3 N/R	6 NA, 3 Europe, 2 Asia, 1 Australia
Oat β -glucan ^(24,60–94,134)	37 12C, 25P	2513 990M: 1095F	31 HC, 3 healthy, 2 T2DM, 1 UC	52.1	26.1–66.2	26.9	23.5–32.1	6 weeks (3–24)	17 DB, 4 SB, 15 NB, 1 N/R	4.6	1.3–13.4	25 Wheat, 3 rice, 5 maize, 2 starch, 2 cereal	11 healthy, 1 low fat, 24 usual, 1 other	6 A, 14 I, 4 A-I, 13 N/R	17 NA, 2 SA, 9 Europe, 4 Asia, 4 Australia, 1 NZ
KJM ^(10,95–97,132)	5 3C, 2P	201 47M: 54F	1 healthy, 1 OW, 3 T2DM	45.0	35.0–55.0	26.3	23.8–28.0	3 weeks (3–52)	4 DB, 1 N/R	12.9	3.9–17.5	3 Wheat, 2 rice	2 healthy, 2 usual	5 I	4 NA, 1 Asia
Psyllium ^(10,85,98–114,133)	20 4C, 16P	1277 546M: 481F	17 HC, 1 healthy, 1 T2DM, 1 PCOS	48.7	27.5–55.8	26.1	23.8–31.7	8 weeks (3–52)	12 DB, 3 SB, 5 N/R	7.6	1.7–10.7	5 Wheat, 1 rice, 13 cellulose, 1 cereal	7 healthy, 1 low fat, 11 usual, 1 other	7 A, 6 I, 1 A-I, 5 N/R, 1 none	14 NA, 2 Europe, 3 Asia, 1 Australia
Guar Gum ^(115–130)	16 11C, 5P	281 51M: 47F	6 HC, 1 healthy, 8 T2DM, 1 T1DM	50.4	27.0–62.0	27.7	23.3–31.0	13 weeks (3–26)	13 DB, 1 SB, 2 N/R	17.9	7.6–31.7	15 Wheat, 1 cereal	1 healthy, 2 low fat, 13 usual	5 A, 3 I, 8 A-I	1 NA, 15 Europe
Pectin ⁽¹³¹⁾	1P	20 6M: 14F	1 healthy	29.6		N/R		4 weeks	1 N/R	12.0		1 cellulose	1 usual	1 A	1 NZ
Total	89 35C, 54P	4755 1812M: 1815F	62 HC, 7 healthy, 2 OW, 14 T2DM, 1 T1DM, 1 MetS, 1 UC, 1 PCOS	50.8	26.1–66.2	26.9	23.3–32.1	6 weeks (3–52)	51 DB, 11 SB, 19 NB, 8 N/R	8.4	1.3–31.7	52 Wheat, 10 rice, 15 cellulose, 5 maize, 1 starch, 6 cereal	26 healthy, 4 low fat, 56 usual, 1 low calorie, 2 other	21 A, 29 I, 18 A-I, 20 N/R, 1 none	40 NA, 2 SA, 29 Europe, 10 Asia, 6 Australia, 2 NZ

A, agency; A-I, agency-industry; C, crossover; DB, double blind; HC, hypercholesterolaemia; I, industry; MetS, metabolic syndrome; NA, North America; NB, no blinding; N/R, not reported; NZ, New Zealand; OW, overweight; P, parallel; PCOS, polycystic ovary syndrome; SA, South America; SB, single blind; T1DM, type 2 diabetes mellitus; T2DM, type 2 diabetes mellitus; UC, ulcerative colitis.

* The total values do not add up to the sum of each fibre type because some studies investigated multiple fibre types.

† The number of male and female participants do not equal the total number of participants because some studies did not specify the sex of the subject.

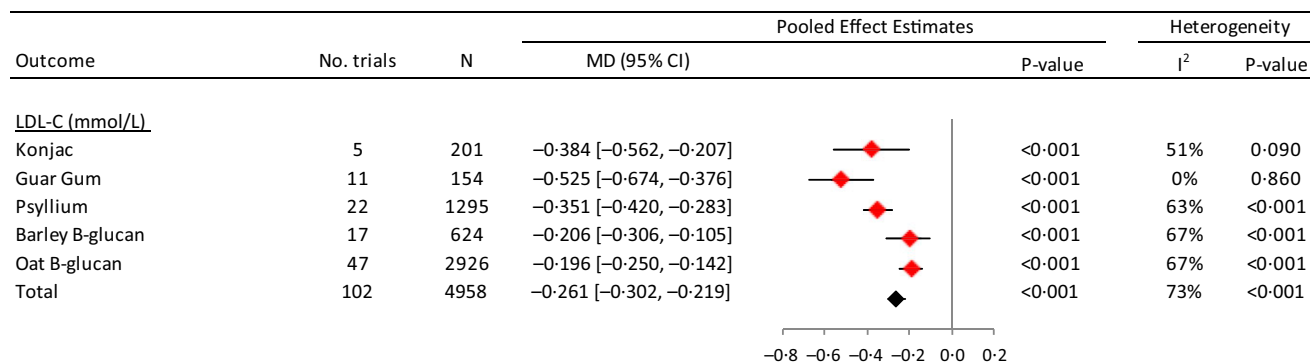


Fig. 2. Superplot of randomised controlled trials investigating the effect of viscous dietary fibres on LDL cholesterol (mmol/l). Mean differences (95 % CI) between viscous and non-viscous, cereal-type dietary fibre are generated using the generic inverse variance random-effects model. The red diamonds represent the pooled effect estimates for each fibre type, while the black diamond represents the pooled effect estimate from all fibre types. I² represents the estimated heterogeneity between individual studies.

Effect on non-HDL cholesterol

Figure 3 shows the effect of viscous fibres on non-HDL cholesterol. Pooled effects of eighty-four studies, including 106 comparisons (*n* 5070) showed a significant effect of viscous fibres on non-HDL cholesterol (MD = -0.33 mmol/l; 95 % CI: -0.39, -0.28 mmol/l; *P* < 0.01), compared with control. Substantial inter-study heterogeneity was observed in the overall analysis (I² = 79 %, *P* < 0.01). Sensitivity analysis by systematic removal of individual trials did not alter the heterogeneity or pooled effect. Continuous *a priori* subgroup analyses were not significant (online Supplementary Table S3). However, categorical *a priori* subgroup analyses revealed a significant effect of fibre type on non-HDL cholesterol (*P* = 0.03), with residual I² = 76.6 % (online Supplementary Fig. S3). There was also a significant effect of BMI, with individuals under 25 kg/m² associated with a larger reduction (*P* = 0.04, residual I² = 79.0 %) (online Supplementary Fig. S3). Further *a priori* subgroup analyses found no effect on dose, duration, study design, energy balance, baseline non-HDL cholesterol, comparator, disease status, funding and background diet.

Effect on ApoB

Figure 4 shows the effect of viscous fibres on ApoB. Pooled effects of twenty-two studies, including twenty-four comparisons (*n* 1558) showed a significant effect of viscous fibres on ApoB (MD = -0.04 g/l; 95 % CI: -0.06, -0.03 g/l; *P* < 0.01), compared with control. Substantial inter-study heterogeneity was observed in the overall analysis (I² = 70 %, *P* < 0.01). Sensitivity analysis by systematic removal of individual trials did not alter the heterogeneity or pooled effect. Continuous *a priori* subgroup analyses were not significant (online Supplementary Table S3). However, categorical *a priori* subgroup analyses revealed that the ApoB lowering effects of viscous fibre were modified by background diet (*P* < 0.01), with residual I² = 31.1 % (online Supplementary Fig. S4). Significant effects were found between healthy and low-fat diets (MD = -0.08 g/l; 95 % CI: -0.13, -0.03 g/l; *P* < 0.01), healthy and standard diets (MD = -0.04 g/l; 95 % CI: -0.07, -0.00 g/l; *P* = 0.04), healthy and other (MD = -0.08 g/l; 95 % CI: -0.14, -0.03 g/l;

P < 0.01), low-fat and standard diet (MD = 0.04 g/l; 95 % CI: 0.00, 0.09 g/l; *P* = 0.04) and standard diet and other (MD = -0.05 g/l; 95 % CI: -0.10, -0.00 g/l; *P* = 0.05). There was also a significant effect of study design, with cross-over studies showing greater reductions (*P* = 0.04, residual I² = 71.2 %) (online Supplementary Fig. S4). Further *a priori* subgroup analyses found no effect on dose, BMI, duration, energy balance, baseline ApoB, fibre type, comparator, disease status and funding.

Publication bias

Visual inspection of contour enhanced funnel plots (online Supplementary Fig. S5) showed signs of publication bias for LDL cholesterol, non-HDL cholesterol and ApoB. This was supported by Egger's and Begg's test for both LDL cholesterol (*P* < 0.01; *P* < 0.01, respectively) and non-HDL cholesterol (*P* = 0.04; *P* < 0.01, respectively), but only Egger's test for ApoB (*P* = 0.01, *P* = 0.36). The Duval and Tweedie 'Trim and Fill' method did not change the direction or significance of the pooled effect estimate for any outcome (online Supplementary Fig. S6).

Dose response

The dose-response analysis revealed a significant linear association between increasing dose of viscous fibre and lowering of LDL cholesterol compared with non-viscous control (*P* = 0.01) (online Supplementary Fig. S7). There was no evidence of a linear or non-linear association between increasing dose of viscous dietary fibre and non-HDL cholesterol and ApoB (online Supplementary Fig. S7). Linear and non-linear dose response for guar gum, barley β-glucan and oat β-glucan showed no significant association between increasing dose of fibre and LDL cholesterol (online Supplementary Fig. S8). Psyllium showed a linear dose response suggesting a greater reduction in LDL-cholesterol with lower doses (*P* = 0.05) (online Supplementary Fig. S8). A dose-response analysis could not be conducted on KJM due to insufficient number of studies. Non-linear dose-response analysis conducted at the median threshold for individual fibre type on LDL cholesterol also showed no significant association (online Supplementary Fig. S9).

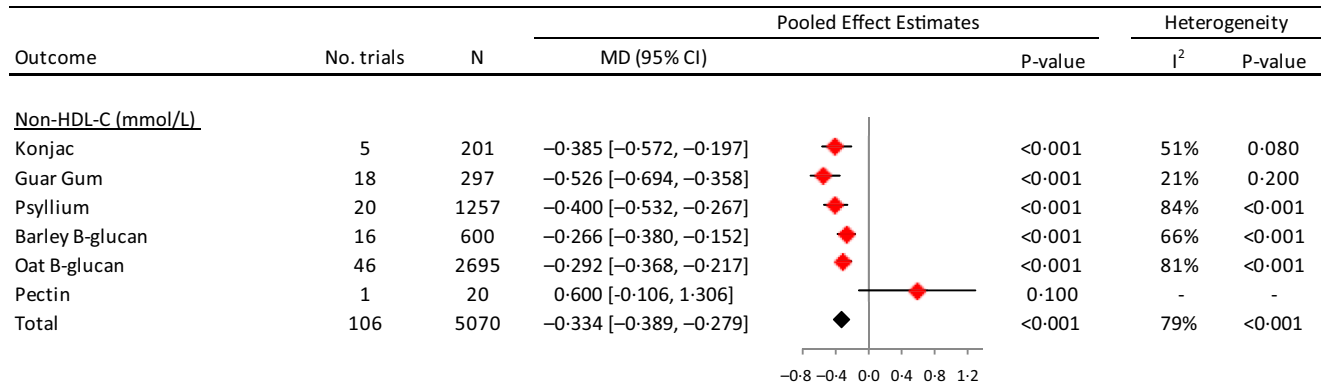


Fig. 3. Superplot of randomised controlled trials investigating the effect of viscous dietary fibres on non-HDL cholesterol (mmol/l). Mean differences (95% CI) between viscous and non-viscous, cereal-type dietary fibre are generated using the generic inverse variance random-effects model. The red diamonds represent the pooled effect estimates for each fibre type, while the black diamond represents the pooled effect estimate from all fibre types. I² represents the estimated heterogeneity between individual studies.

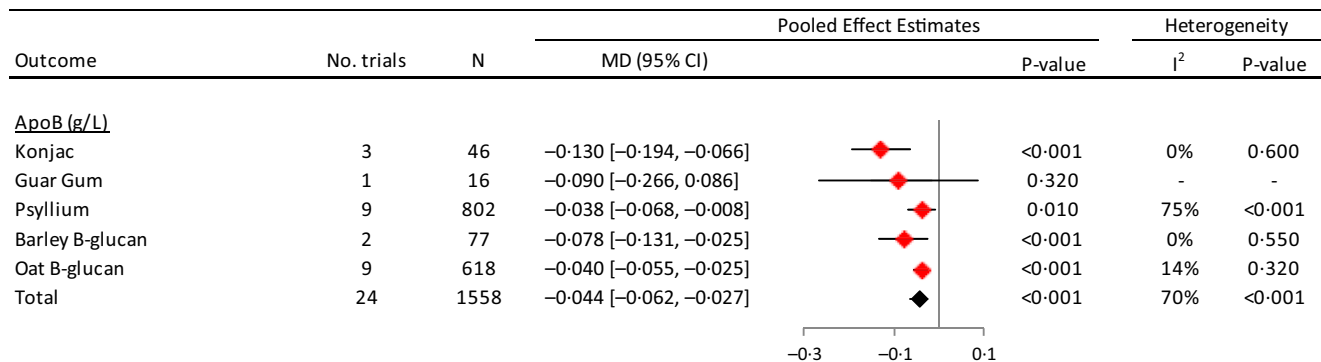


Fig. 4. Superplot of randomised controlled trials investigating the effect of viscous dietary fibres on ApoB (g/l). Mean differences (95% CI) between viscous and non-viscous, cereal-type fibre were generated using the generic inverse variance random-effects model. The red diamonds represent the pooled effect estimates for each fibre type, while the black diamond represents the pooled effect estimate from all fibre types. I² represents the estimated heterogeneity between individual studies.

GRADE assessment

Supplementary Table S4 shows the GRADE assessment of the overall certainty of the evidence for the effect of viscous fibres compared with non-viscous fibres on cholesterol. The evidence for LDL cholesterol and non-HDL cholesterol was downgraded for inconsistency and the evidence for ApoB was downgraded for imprecision and thus all outcomes were graded as moderate quality.

Discussion

Summary

The present systematic review and meta-analysis includes data from 89 RCT (*n* 4755) to provide a comparative effect of viscous dietary fibres *v* non-viscous, cereal fibre-type counterparts in adults with or without hypercholesterolaemia on LDL cholesterol, non-HDL cholesterol and ApoB. Based on our pooled analysis of trials providing a median quantity of 7.0 g/d of viscous fibre, consumed within a median duration of 6 weeks, viscous fibre lowered LDL cholesterol (MD = -0.26 mmol/l; 95% CI: -0.30, -0.22 mmol/l), non-HDL cholesterol (MD = -0.33 mmol/l; 95% CI: -0.39, -0.28 mmol/l) and ApoB (MD = -0.04 g/l; 95% CI:

-0.06, -0.03 g/l), beyond the effect of comparator insoluble cereal fibre sources, in a dose-dependent manner. The analysis suggests a benefit regardless of BMI or duration of intake. Evidence from lipid outcomes were graded as moderate.

Viscosity has been recognised as a physicochemical property of dietary fibre that is postulated to exert a metabolic benefit through decreased nutrient kinetics in the gut, demonstrated to lower postprandial blood glucose, blood pressure and improve diabetes management in addition to its lipid-lowering effects^(135,136). Therefore, the physical classification of fibres by viscosity is relevant to distinguish clinical effects of dietary fibres. Wood *et al.* (1994) had shown early on that acid hydrolysis processing debilitated the beneficial effects of oat β -glucans that resulted in reductions of viscosity⁽¹³⁷⁾. Our group later showed that the property of viscosity, rather than quantity of dietary fibre predicts lipid lowering⁽¹⁰⁾. Within our sub-analysis of individual viscous dietary fibres, it appears that the generally more viscous fibres, such as KJM and guar gum, have generated larger differences in LDL cholesterol than the less viscous, but broadly recommended β -glucan.

Conversely, insoluble, non-viscous fibres are the principal components of cereal fibres and whole grains. This type of structural plant fibre, especially wheat and corn sources, have

typically been quantified to depict fibre intake from food frequency questionnaires in large prospective cohorts that conferred cardiometabolic benefits, paralleled by low dietary intake and inadequate documentation of other functional fibre sources and supplements. In comparison, data from RCT on the effect of cereal-type non viscous fibres are scarce and largely without effect^(138,139). In one of the earlier trials comparing 3-month supplementation of non-viscous wheat bran fibre to control, Jenkins *et al.* (2002) did not demonstrate a difference on blood lipids^(21,140). Similarly, administration of rye and whole wheat cereals relative to refined cereals failed to modify lipid markers in metabolic syndrome⁽¹⁴¹⁾. More recently, the OptiFit trial did not find a difference in cardiometabolic outcomes following 1-year intake of 7.5 g/d insoluble cereal fibre supplement⁽¹⁴²⁾. Nonetheless, there are data that in some studies, where 26 g/d of wheat bran improved the blood lipid profile in healthy individuals⁽¹⁴³⁾. It is unclear whether perhaps longer duration of non-viscous fibres intake is needed for a metabolic benefit or whether the beneficial effect from observational evidence is a result of the displacement of foods supplying saturated fat or refined carbohydrates.

The findings of this study provide a clearer lens on the current knowledge on dietary fibre, suggesting that the degree of lipid lowering varies between two major fibre classes. Each of the dietary fibres for which data was available, including konjac, guar gum, psyllium and oat and barley β -glucan, independently demonstrated significant LDL cholesterol lowering relative to the non-viscous fibres. The presence of a biological gradient of a dose-response relationship further supports the proposed association.

The data here build on a broader report of over 25 years ago that hinted at a 0.057 mmol/l reduction in LDL cholesterol per gram of fibre for major soluble dietary fibres relative to any placebo control, but precludes direct comparison to current analysis⁽¹⁴⁴⁾.

A dose of 5–10 g of viscous fibre has been previously projected to confer a ~5 % reduction in LDL cholesterol. In the current analysis, doses above a median dose of ~6 g of viscous dietary fibre demonstrate a clinically relevant further 8 % reduction in both LDL cholesterol (–0.32 mmol/l) and non-HDL cholesterol (–0.40 mmol/l) compared with non-viscous fibre. Thus, selecting a dietary pattern rich in viscous fibre foods such as oats, beans, fruits and vegetables such as apples, oranges, okra, eggplant or Brussel sprouts, may offer greater reductions in blood lipids compared with selecting non-viscous fibre types. Consuming a 3/4 cup serving of oat bran, one medium orange and 1/2 cup of cooked Brussel sprouts per day, for example, would be sufficient to reach clinically meaningful doses of viscous fibre⁽¹⁴⁵⁾. Additionally, choosing a small quantity of about 1 tablespoon per day of isolated viscous fibre sources such as those studied here may also offer health benefits. This has a strong practical application that should be considered in dietary recommendations, given the presently advocated amounts of total dietary fibre of > 30 g/d, which may be unrealistic in light of current average population intake being about half as much.

In comparison, other well-established and recommended dietary strategies associated with lipid lowering have produced more subtle differences in LDL cholesterol such as a diet rich in nuts (MD = –0.12 mmol/l) or soy protein (WMD = –0.12

mmol/l), low fat diet (MD = –0.11 mmol/l), DASH diet (MD = –0.1 mmol/l) or a Mediterranean diet (MD = –0.07 mmol/l)^(146–150).

At present, the Canadian Cardiovascular Society has recognised the application of viscous fibres to a dietary portfolio including other cholesterol-lowering foods⁽²⁾. Similarly, the 2019 European SC/EAS guidelines and the 2016 Chinese guidelines place particular emphasis on viscous fibre use in the context of the hypercholesterolaemic reductions⁽¹¹⁾. However, this shift towards physiological differentiation of fibre types has not been reflected in other lipid-lowering guidelines to date^(151,152).

Strengths

This is the first meta-analysis to our knowledge to comprehensively quantify the effect of non-HDL cholesterol and Apo-B of fibres. While LDL cholesterol remains the primary treatment target, these markers are part of the major lipid guidelines to guide therapy as alternate and plausibly more eminent targets for CVD risk reduction^(2,153). A further strength of the present study includes the largest number of RCT on dietary fibre to date, with findings generalisable to both healthy and hypercholesterolaemic individuals. The study population included a wide range of participants from several different countries with variations in background diet and CVD risk. Balancing the strengths and limitations, the overall evidence was graded as moderate-quality for LDL cholesterol, non-HDL cholesterol and ApoB.

Limitations

Limitations to this meta-analysis should be acknowledged. First, our pooled analyses for LDL and non-HDL cholesterol were subject to high heterogeneity which remained largely unexplained after *a priori* subgroup analyses and sensitivity analyses downgrading the certainty of evidence. However, this may have been inevitable due to a sizable study number with a range of fibre types, doses, levels of background therapy and conditions included in the analysis which partially explained some inconsistency. Second, the median duration of trial is < 2 months. Longer intake studies are needed to demonstrate whether the benefit of non-viscous fibres remains. Third, the difference between end-of-treatment values were used when change from baseline values were not provided or could not be calculated. Lastly, due to recent inclusion of alternate lipid targets into clinical practice guidelines, few studies reported ApoB while non-HDL cholesterol was indirectly assessed.

Conclusions

In summary, this systematic review and meta-analysis presents a comprehensive synthesis of evidence to date of the therapeutic dose-dependent effects of viscous dietary fibres in the reduction of primary and alternative lipid markers relative to cereal-type fibres. Choosing a dietary pattern rich in viscous fibres or an addition of approximately a tablespoon per day of isolated viscous fibres may be utilised as an effective dietary means to reduce LDL cholesterol and the alternative lipid profile in adults with and without hypercholesterolaemia. Nevertheless, limitations raised by GRADE should be considered. Future research





should directly examine ApoB endpoints relevant to guidelines and expand evidence on common fibres to corroborate the proposed relationship. These data at present make a convincing case to support emerging recommendations to improve strategies that focally increase viscous dietary fibre intake for CVD risk lowering.

Acknowledgments

The authors thank Teruko Kishibe, Information Specialist, Scotiabank Health Sciences Library at St. Michael's Hospital, for her help in the development of search terms used.

The authors' responsibilities were as follows — E. J., A. K., A. J. and V. V.: designed the research; M. N., Y. K., H. V. T. H., E. J. and A. Z.: conducted the research; M. N., Y. K., R. K., T. A. K., D. L., J. L. S.: performed or assisted in performing the statistical analysis of the data; E. J., M. N. and A. K.: wrote the manuscript draft; V. V., E. J. and J. L. S.: had primary responsibility for the final content; and all authors: contributed to the critical revision of the manuscript for important intellectual content and approved the final manuscript.

V.V. previously held the Canadian (2 410 556) and American (7 326 404) patents on the medical use of viscous fibre blend for reducing blood glucose for treatment of diabetes, increasing insulin sensitivity, and reducing systolic blood pressure and blood lipids. A.J. is part owner of INQUIS Clinical Research (formally Glycemic Index Laboratories, Inc.), a contract research organisation. J.L.S. has received research support from the Canadian Foundation for Innovation, Ontario Re-search Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of Health Research (CIHR), Diabetes Canada, American Society for Nutrition (ASN), International Nut and Dried Fruit Council (INC) Foundation, National Honey Board (the USA. Department of Agriculture [USDA] honey 'Checkoff' program), Institute for the Advancement of Food and Nutrition Sciences (IAFNS), Pulse Canada, Quaker Oats Center of Excellence, The United Soybean Board (the USDA soy 'Checkoff' program), The Tate and Lyle Nutritional Re-search Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), The Plant Protein Fund at the University of Toronto (a fund which has received contributions from IFF), and The Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received food donations to support randomised controlled trials from the Almond Board of California, California Walnut Commission, Peanut Institute, Barilla, Unilever/Upfield, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, WhiteWave Foods/Danone, Nutrartis and Dairy Farmers of Canada. He has received travel support, speaker fees and/or honoraria from ASN, Danone, Dairy Farmers of Canada, FoodMinds LLC, Nestlé, Abbott, General Mills, Nutrition Communications, International Food Information Council (IFIC), Calorie Control Council, International Sweeteners Association and International Glutamate Technical Committee. He has or has had consulting

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None of the sponsors had a role in any aspect of the current study, including design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review and approval of the manuscript or decision to publish.

Supplementary material

For supplementary material accompanying this paper visit <https://doi.org/10.1017/S0007114522002355>

References

1. U.S. Department of Health and Human Services & U.S. Department of Agriculture (2015) 2015–2020 Dietary Guidelines for Americans 8th Edition. <http://health.gov/dietaryguidelines/2015/guidelines/> (accessed July 2020).
2. Anderson TJ, Gregoire J, Pearson GJ, *et al.* (2016) 2016 Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* **32**, 1263–1282.
3. Aller R, de Luis DA, Izaola O, *et al.* (2004) Effect of soluble fiber intake in lipid and glucose levels in healthy subjects: a randomized clinical trial. *Diabetes Res Clin Pract* **65**, 7–11.
4. Hunninghake DB, Miller VT, LaRosa JC, *et al.* (1994) Long-term treatment of hypercholesterolemia with dietary fiber. *Am J Med* **97**, 504–508.
5. Jenkins DJ, Kendall CW, Vuksan V, *et al.* (2002) Soluble fiber intake at a dose approved by the US Food and Drug Administration for a claim of health benefits: serum lipid risk factors for cardiovascular disease assessed in a randomized controlled crossover trial. *Am J Clin Nutr* **75**, 834–839.
6. Cicero AFG, Fogacci F, Stoian AP, *et al.* (2021) Nutraceuticals in the management of dyslipidemia: which, when, and for whom? Could nutraceuticals help low-risk individuals with non-optimal lipid levels? *Curr Atheroscler Rep* **23**, 57.
7. Jones JM (2014) CODEX-aligned dietary fiber definitions help to bridge the 'fiber gap'. *Nutr J* **13**, 34.



8. Mudgil D & Barak S (2013) Composition properties and health benefits of indigestible carbohydrate polymers as dietary fiber: a review. *Int J Biol Macromol* **61**, 1–6.
9. Williams BA, Mikkelsen D, Flanagan BM, *et al.* (2019) 'Dietary fibre': moving beyond the 'soluble/insoluble' classification for monogastric nutrition, with an emphasis on humans and pigs. *J Anim Sci Biotechnol* **10**, 45.
10. Vuksan V, Jenkins AL, Rogovik AL, *et al.* (2011) Viscosity rather than quantity of dietary fibre predicts cholesterol-lowering effect in healthy individuals. *Br J Nutr* **106**, 1349–1352.
11. Task Force Members, ESC Committee for Practice Guidelines (CPG) & ESC National Cardiac Societies (2019) ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis* **290**, 140–205.
12. Nerenberg KA, Zarnke KB, Leung AA, *et al.* (2018) Hypertension Canada's 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children. *Can J Cardiol* **34**, 506–525.
13. US Food and Drug Administration (2019) CFR—Code of Federal Regulations Title 21— Food and Drugs Chapter I— Food and Drug Administration Department of Health and Human Services Subchapter B—Food for Human Consumption. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=101.81> (accessed July 2020).
14. EFSA Panel on Dietetic Products Nutrition and Allergies (2010) Scientific Opinion on the substantiation of health claims related to konjac mannan (glucomannan) and reduction of body weight (ID 854, 1556, 3725), reduction of post-prandial glycaemic responses (ID 1559), maintenance of normal blood glucose concentrations (ID 835, 3724), maintenance of normal (fasting) blood concentrations of triglycerides (ID 3217), maintenance of normal blood cholesterol concentrations (ID 3100, 3217), maintenance of normal bowel function (ID 834, 1557, 3901) and decreasing potentially pathogenic gastro-intestinal microorganisms (ID 1558) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J* **8**, 1798.
15. Swain JF, Rouse IL, Curley CB, *et al.* (1990) Comparison of the effects of oat bran and low-fiber wheat on serum lipoprotein levels and blood pressure. *N Engl J Med* **322**, 147–152.
16. Barsanti L, Passarelli V, Evangelista V, *et al.* Chemistry, physico-chemistry and applications linked to biological activities of beta-glucans. *Nat Prod Rep* **28**, 457–466.
17. Dikeman CL & Fahey GC (2006) Viscosity as related to dietary fiber: a review. *Crit Rev Food Sci Nutr* **46**, 649–663.
18. Marounek M, Volek Z, Synytsya A, *et al.* (2007) Effect of pectin and amidated pectin on cholesterol homeostasis and cecal metabolism in rats fed a high-cholesterol diet. *Physiol Res* **56**, 433–442.
19. Wong JM & Jenkins DJ (2007) Carbohydrate digestibility and metabolic effects. *J Nutr* **137**, 2539s–2546s.
20. Veronese N, Solmi M, Caruso MG, *et al.* (2018) Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. *Am J Clin Nutr* **107**, 436–444.
21. Jenkins DJ, Kendall CW, Augustin LS, *et al.* (2002) Effect of wheat bran on glycemic control and risk factors for cardiovascular disease in type 2 diabetes. *Diabetes Care* **25**, 1522–1528.
22. Weickert MO & Pfeiffer AF (2008) Metabolic effects of dietary fiber consumption and prevention of diabetes. *J Nutr* **138**, 439–442.
23. Weickert MO & Pfeiffer AFH (2018) Impact of dietary fiber consumption on insulin resistance and the prevention of type 2 diabetes. *J Nutr* **148**, 7–12.
24. Reynolds H, Quiter E & Hunninghake D (2000) Whole grain oat cereal lowers serum lipids. *Top Clin Nutrition* **15**, 74–83.
25. Higgins JP, Thomas J & Chandler J (editors) (2011) Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). www.handbook.cochrane.org (accessed July 2020).
26. Page MJ, McKenzie JE, Bossuyt PM, *et al.* (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71.
27. Limberger-Bayer VM, de Francisco A, Chan A, *et al.* (2014) Barley beta-glucans extraction and partial characterization. *Food Chem* **154**, 84–89.
28. Chen WJ & Anderson JW (1981) Soluble and insoluble plant fiber in selected cereals and vegetables. *Am J Clin Nutr* **34**, 1077–1082.
29. Anderson JW & Bridges SR (1988) Dietary fiber content of selected foods. *Am J Clin Nutr* **47**, 440–447.
30. Whitehead A, Beck EJ, Tosh S, *et al.* (2014) Cholesterol-lowering effects of oat beta-glucan: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* **100**, 1413–1421.
31. Borenstein M, Hedges LV, Higgins JPT, *et al.* (2009) *Introduction to Meta-Analysis*, 2nd ed. Chichester: John Wiley & Sons, Ltd.
32. Harvard University (2007) A Summary of Error Propagation. Cambridge, MA: Harvard University. https://sites.fas.harvard.edu/~scphys/nsta/error_propagation.pdf (accessed April 2021).
33. Elbourne DR, Altman DG, Higgins JP, *et al.* (2002) Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* **31**, 140–149.
34. Duval S & Tweedie R (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455–463.
35. Balshem H, Helfand M, Schunemann HJ, *et al.* (2011) GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* **64**, 401–406.
36. Guyatt G, Oxman AD, Akl EA, *et al.* (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* **64**, 383–394.
37. Guyatt GH, Oxman AD, Kunz R, *et al.* (2011) GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* **64**, 395–400.
38. Guyatt GH, Oxman AD, Kunz R, *et al.* (2011) GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol* **64**, 1283–1293.
39. Guyatt GH, Oxman AD, Kunz R, *et al.* (2011) GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol* **64**, 1303–1310.
40. Guyatt GH, Oxman AD, Kunz R, *et al.* (2011) GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol* **64**, 1294–1302.
41. Guyatt GH, Oxman AD, Montori V, *et al.* (2011) GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* **64**, 1277–1282.
42. Guyatt GH, Oxman AD, Sultan S, *et al.* (2011) GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol* **64**, 1311–1316.
43. Guyatt GH, Oxman AD, Vist G, *et al.* (2011) GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* **64**, 407–415.
44. Brunetti M, Shemilt I, Pregno S, *et al.* (2013) GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol* **66**, 140–150.
45. Guyatt G, Oxman AD, Sultan S, *et al.* (2013) GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol* **66**, 151–157.



46. Guyatt GH, Oxman AD, Santesso N, *et al.* (2013) GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *J Clin Epidemiol* **66**, 158–172.
47. Guyatt GH, Thorlund K, Oxman AD, *et al.* (2013) GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* **66**, 173–183.
48. Aoe S, Ichinose Y, Kohyama N, *et al.* (2017) Effects of high beta-glucan barley on visceral fat obesity in Japanese individuals: a randomized, double-blind study. *Nutrition* **42**, 1–6.
49. Behall KM, Scholfield DJ & Hallfrisch J (2004) Diets containing barley significantly reduce lipids in mildly hypercholesterolemic men and women. *Am J Clin Nutr* **80**, 1185–1193.
50. Behall KM, Scholfield DJ & Hallfrisch J (2004) Lipids significantly reduced by diets containing barley in moderately hypercholesterolemic men. *J Am Coll Nutr* **23**, 55–62.
51. Ezatagha A (2007) *The Effect of Barley Beta-Glucan Concentrate of LDL-Cholesterol and Other Risk Factors for Cardiovascular Disease (Thesis)*. Toronto: University of Toronto.
52. Lupton JR, Robinson MC & Morin JL (1994) Cholesterol-lowering effect of barley bran flour and oil. *J Am Diet Assoc* **94**, 65–70.
53. McIntosh GH, Whyte J, McArthur R, *et al.* (1991) Barley and wheat foods: influence on plasma cholesterol concentrations in hypercholesterolemic men. *Am J Clin Nutr* **53**, 1205–1209.
54. Newman RK, Lewis SE, Newman CW, *et al.* (1989) Hypocholesterolemic effect of barley foods on healthy men. *Nutr Rep Int* **39**, 749–760.
55. Rondanelli M, Opizzi A, Monteferrario F, *et al.* (2011) Beta-glucan- or rice bran-enriched foods: a comparative crossover clinical trial on lipidic pattern in mildly hypercholesterolemic men. *Eur J Clin Nutr* **65**, 864–871.
56. Shimizu C, Kihara M, Aoe S, *et al.* (2008) Effect of high beta-glucan barley on serum cholesterol concentrations and visceral fat area in Japanese men—a randomized, double-blinded, placebo-controlled trial. *Plant Foods Hum Nutr* **63**, 21–25.
57. Sundberg B (2008) Cholesterol lowering effects of a barley fibre flake product. *Agro Food Ind Hi-Tech* **19**, 14–17.
58. Velikonja A, Lipoglavsek L, Zorec M, *et al.* (2019) Alterations in gut microbiota composition and metabolic parameters after dietary intervention with barley beta glucans in patients with high risk for metabolic syndrome development. *Anaerobe* **55**, 67–77.
59. Wang Y, Harding SV, Eck P, *et al.* (2016) High-molecular-weight beta-glucan decreases serum cholesterol differentially based on the CYP7A1 rs3808607 polymorphism in mildly hypercholesterolemic adults. *J Nutr* **146**, 720–727.
60. Anderson JW, Gilinsky NH, Deakins DA, *et al.* (1991) Lipid responses of hypercholesterolemic men to oat-bran and wheat-bran intake. *Am J Clin Nutr* **54**, 678–683.
61. Bremer JM, Scott RS & Lintott CJ (1991) Oat bran and cholesterol reduction: evidence against specific effect. *Aust NZ J Med* **21**, 422–426.
62. Charlton KE, Tapsell LC, Batterham MJ, *et al.* (2012) Effect of 6 weeks' consumption of beta-glucan-rich oat products on cholesterol levels in mildly hypercholesterolaemic overweight adults. *Br J Nutr* **107**, 1037–1047.
63. Connolly ML, Tzounis X, Tuohy KM, *et al.* (2016) Hypocholesterolemic and prebiotic effects of a whole-grain oat-based granola breakfast cereal in a cardio-metabolic 'At Risk' population. *Front Microbiol* **7**, 1675.
64. Davidson MH, Dugan LD, Burns JH, *et al.* (1991) The hypocholesterolemic effects of beta-glucan in oatmeal and oat bran. A dose-controlled study. *JAMA* **265**, 1833–1839.
65. Davy BM, Davy KP, Ho RC, *et al.* (2002) High-fiber oat cereal compared with wheat cereal consumption favorably alters LDL-cholesterol subclass and particle numbers in middle-aged and older men. *Am J Clin Nutr* **76**, 351–358.
66. Gerhardt AL & Gallo NB (1998) Full-fat rice bran and oat bran similarly reduce hypercholesterolemia in humans. *J Nutr* **128**, 865–869.
67. Gold KV & Davidson DM (1988) Oat bran as a cholesterol-reducing dietary adjunct in a young, healthy population. *West J Med* **148**, 299–302.
68. Johnston L, Reynolds HR, Hunninghake DB, *et al.* (1998) Cholesterol lower benefits of a whole grain oat ready-to-eat cereal. *Nutr Clin Care* **1**, 6–12.
69. Kabir M, Oppert JM, Vidal H, *et al.* (2002) Four-week low-glycemic index breakfast with a modest amount of soluble fibers in type 2 diabetic men. *Metabolism* **51**, 819–826.
70. Karmally W, Montez MG, Palmas W, *et al.* (2005) Cholesterol-lowering benefits of oat-containing cereal in Hispanic americans. *J Am Diet Assoc* **105**, 967–970.
71. Kerckhoffs DA, Hornstra G & Mensink RP (2003) Cholesterol-lowering effect of beta-glucan from oat bran in mildly hypercholesterolemic subjects may decrease when beta-glucan is incorporated into bread and cookies. *Am J Clin Nutr* **78**, 221–227.
72. Kestin M, Moss R, Clifton PM, *et al.* (1990) Comparative effects of three cereal brans on plasma lipids, blood pressure, and glucose metabolism in mildly hypercholesterolemic men. *Am J Clin Nutr* **52**, 661–666.
73. Lepre F & Crane S (1992) Effect of oatbran on mild hyperlipidaemia. *Med J Aust* **157**, 305–308.
74. Liao MY, Shen YC, Chiu HF, *et al.* (2019) Down-regulation of partial substitution for staple food by oat noodles on blood lipid levels: a randomized, double-blind, clinical trial. *J Food Drug Anal* **27**, 93–100.
75. Liatis S, Tsapogas P, Chala E, *et al.* (2009) The consumption of bread enriched with betaglucan reduces LDL-cholesterol and improves insulin resistance in patients with type 2 diabetes. *Diabetes Metab* **35**, 115–120.
76. Lovegrove JA, Clohessy A, Milon H, *et al.* (2000) Modest doses of beta-glucan do not reduce concentrations of potentially atherogenic lipoproteins. *Am J Clin Nutr* **72**, 49–55.
77. Maki KC, Beiseigel JM, Jonnalagadda SS, *et al.* (2010) 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 Am Diet Assoc* **110**, 205–214.
78. Momenzadeh A, Heidari R, Sadeghi M, *et al.* (2014) Effects of oat and wheat bread consumption on lipid profile, blood sugar, and endothelial function in hypercholesterolemic patients: a randomized controlled clinical trial. *ARYA Atheroscler* **10**, 259–265.
79. Noakes M, Clifton PM, Nestel PJ, *et al.* (1996) Effect of high-amylose starch and oat bran on metabolic variables and bowel function in subjects with hypertriglyceridemia. *Am J Clin Nutr* **64**, 944–951.
80. Onning G, Wallmark A, Persson M, *et al.* (1999) Consumption of oat milk for 5 weeks lowers serum cholesterol and LDL cholesterol in free-living men with moderate hypercholesterolemia. *Ann Nutr Metab* **43**, 301–309.
81. Panahi S (2006) *The Effect of Oat Beta-Glucan on Glycemia and Blood Lipid Risk Factors for Cardiovascular Disease, Thesis*. Toronto: University of Toronto.
82. Pick ME, Hawrysh ZJ, Gee MI, *et al.* (1996) Oat bran concentrate bread products improve long-term control of diabetes: a pilot study. *J Am Diet Assoc* **96**, 1254–1261.



83. Pins JJ, Geleva D, Keenan JM, *et al.* (2002) Do whole-grain oat cereals reduce the need for antihypertensive medications and improve blood pressure control? *J Fam Pract* **51**, 353–359.
84. Reyna-Villasmil N, Bermudez-Pirela V, Mengual-Moreno E, *et al.* (2007) Oat-derived beta-glucan significantly improves HDLC and diminishes LDLC and non-HDL cholesterol in overweight individuals with mild hypercholesterolemia. *Am J Ther* **14**, 203–212.
85. Romero AL, Romero JE, Galaviz S, *et al.* (1998) Cookies enriched with psyllium or oat bran lower plasma LDL cholesterol in normal and hypercholesterolemic men from Northern Mexico. *J Am Coll Nutr* **17**, 601–608.
86. de Souza SR, de Oliveira GM, Luiz RR, *et al.* (2016) Effects of oat bran and nutrition counseling on the lipid and glucose profile and anthropometric parameters of hypercholesterolemia patients. *Nutr Hosp* **33**, 123–30.
87. Theuwissen E & Mensink RP (2007) Simultaneous intake of beta-glucan and plant stanol esters affects lipid metabolism in slightly hypercholesterolemic subjects. *J Nutr* **137**, 583–588.
88. Thongoun P, Pavadhgul P, Bumrungpert A, *et al.* (2013) Effect of oat consumption on lipid profiles in hypercholesterolemic adults. *J Med Assoc Thai* **5**, S25–32.
89. Turnbull WH & Leeds AR (1987) Reduction of total and LDL-cholesterol in plasma by rolled oats. *J Clin Nutr Gastroenterol* **2**, 177–181.
90. Uusitupa MI, Ruuskanen E, Mäkinen E, *et al.* (1992) A controlled study on the effect of beta-glucan-rich oat bran on serum lipids in hypercholesterolemic subjects: relation to apolipoprotein E phenotype. *J Am Coll Nutr* **11**, 651–659.
91. Van Hom L, Liu K, Gerber J, *et al.* (2001) Oats and soy in lipid-lowering diets for women with hypercholesterolemia: is there synergy? *J Am Diet Assoc* **101**, 1319–1325.
92. Whyte JL, McArthur R, Topping D, *et al.* (1992) Oat bran lowers plasma cholesterol levels in mildly hypercholesterolemic men. *J Am Diet Assoc* **92**, 446–449.
93. Wolever TM, Tosh SM, Gibbs AL, *et al.* (2010) Physicochemical properties of oat beta-glucan influence its ability to reduce serum LDL cholesterol in humans: a randomized clinical trial. *Am J Clin Nutr* **92**, 723–732.
94. Zhang J, Li L, Song P, *et al.* (2012) Randomized controlled trial of oatmeal consumption *v.* noodle consumption on blood lipids of urban Chinese adults with hypercholesterolemia. *Nutr J* **11**, 54.
95. Reimer RA, Yamaguchi H, Eller LK, *et al.* (2013) Changes in visceral adiposity and serum cholesterol with a novel viscous polysaccharide in Japanese adults with abdominal obesity. *Obesity* **21**, E379–87.
96. Vuksan V, Jenkins DJ, Spadafora P, *et al.* (1999) Konjac-mannan (glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. A randomized controlled metabolic trial. *Diabetes Care* **22**, 913–919.
97. Vuksan V, Sievenpiper JL, Owen R, *et al.* (2000) Beneficial effects of viscous dietary fiber from Konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. *Diabetes Care* **23**, 9–14.
98. Anderson JW, Davidson MH, Blonde L, *et al.* (2000) Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am J Clin Nutr* **71**, 1433–1438.
99. Anderson JW, Floore TL, Geil PB, *et al.* (1991) Hypocholesterolemic effects of different bulk-forming hydrophilic fibers as adjuncts to dietary therapy in mild to moderate hypercholesterolemia. *Arch Intern Med* **151**, 1597–1602.
100. Anderson JW, Riddell-Mason S, Gustafson NJ, *et al.* (1992) Cholesterol-lowering effects of psyllium-enriched cereal as an adjunct to a prudent diet in the treatment of mild to moderate hypercholesterolemia. *Am J Clin Nutr* **56**, 93–98.
101. Anderson JW, Zettwoch N, Feldman T, *et al.* (1988) Cholesterol-lowering effects of psyllium hydrophilic mucilloid for hypercholesterolemic men. *Arch Intern Med* **148**, 292–296.
102. Asghar J & Bashir A (2011) Single blind and placebo controlled research study of effects of Ispaghula on serum lipids. *Pak J Med Health Sci* **5**, 654–657.
103. Bell LP, Hectorne K, Reynolds H, *et al.* (1989) Cholesterol-lowering effects of psyllium hydrophilic mucilloid. Adjunct therapy to a prudent diet for patients with mild to moderate hypercholesterolemia. *JAMA* **261**, 3419–3423.
104. Everson GT, Daggy BP, McKinley C, *et al.* (1992) Effects of psyllium hydrophilic mucilloid on LDL-cholesterol and bile acid synthesis in hypercholesterolemic men. *J Lipid Res* **33**, 1183–1192.
105. Flannery J & Raulerson A (2000) Hypercholesterolemia: a look at low-cost treatment and treatment adherence. *J Am Acad Nurse Pract* **12**, 462–466.
106. Jenkins DJ, Wolever TM, Vidgen E, *et al.* (1997) Effect of psyllium in hypercholesterolemia at two monounsaturated fatty acid intakes. *Am J Clin Nutr* **65**, 1524–1533.
107. Levin EG, Miller VT, Muesing RA, *et al.* (1990) Comparison of psyllium hydrophilic mucilloid and cellulose as adjuncts to a prudent diet in the treatment of mild to moderate hypercholesterolemia. *Arch Intern Med* **150**, 1822–1827.
108. Maciejko JJ, Brazg R, Shah A, *et al.* (1994) Psyllium for the reduction of cholestyramine-associated gastrointestinal symptoms in the treatment of primary hypercholesterolemia. *Arch Fam Med* **3**, 955–960.
109. Pal S, Ho S, Gahler RJ, *et al.* (2017) Effect on insulin, glucose and lipids in overweight/obese Australian adults of 12 months consumption of two different fibre supplements in a randomised trial. *Nutrients* **9**, 91.
110. Sola R, Bruckert E, Valls RM, *et al.* (2010) Soluble fibre (*Plantago ovata* husk) reduces plasma low-density lipoprotein (LDL) cholesterol, triglycerides, insulin, oxidised LDL and systolic blood pressure in hypercholesterolaemic patients: a randomised trial. *Atherosclerosis* **211**, 630–637.
111. Spence JD, Huff MW, Heidenheim P, *et al.* (1995) Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. *Ann Intern Med* **123**, 493–499.
112. Sprecher DL, Harris BV, Goldberg AC, *et al.* (1993) Efficacy of psyllium in reducing serum cholesterol levels in hypercholesterolemic patients on high- or low-fat diets. *Ann Intern Med* **119**, 545–554.
113. Summerbell CD, Manley P, *et al.* (1994) The effects of psyllium on blood lipids in hypercholesterolaemic subjects. *J Hum Nutr Diet* **7**, 147–151.
114. Ziai SA, Larijani B, Akhoondzadeh S, *et al.* (2005) Psyllium decreased serum glucose and glycosylated hemoglobin significantly in diabetic outpatients. *J Ethnopharmacol* **102**, 202–207.
115. Aro A, Uusitupa M, Voutilainen E, *et al.* (1981) Improved diabetic control and hypocholesterolaemic effect induced by long-term dietary supplementation with guar gum in type 2 (insulin-independent) diabetes. *Diabetologia* **21**, 29–33.
116. Aro A, Uusitupa M, Voutilainen E, *et al.* (1984) Effects of guar gum in male subjects with hypercholesterolemia. *Am J Clin Nutr* **39**, 911–916.
117. Blake DE, Hamblett CJ, Frost PG, *et al.* (1997) Wheat bread supplemented with depolymerized guar gum reduces the



- plasma cholesterol concentration in hypercholesterolemic human subjects. *Am J Clin Nutr* **65**, 107–113.
118. Fuessl HS, Williams G, Adrian TE, *et al.* (1987) Guar sprinkled on food: effect on glycaemic control, plasma lipids and gut hormones in non-insulin dependent diabetic patients. *Diabet Med* **4**, 463–468.
 119. Makkonen M, Simpanen AL, Saarikoski S, *et al.* (1993) Endocrine and metabolic effects of guar gum in menopausal women. *Gynecol Endocrinol* **7**, 135–141.
 120. McIvor ME, Cummings CC, Van Duyn MA, *et al.* (1986) Long-term effects of guar gum on blood lipids. *Atherosclerosis* **60**, 7–13.
 121. Peterson DB, Ellis PR, Baylis JM, *et al.* (1987) Low dose guar in a novel food product: improved metabolic control in non-insulin-dependent diabetes. *Diabetes Med* **4**, 111–115.
 122. Sels JP, Postmes TJ, Nieman F, *et al.* (1993) Effects of guar bread in type 1 and type 2 diabetes mellitus. *Eur J Intern Med* **4**, 193–200.
 123. Tuomilehto J, Karttunen P, Vinni S, *et al.* (1983) A double-blind evaluation of guar gum in patients with dyslipidaemia. *Hum Nutr Clin Nutr* **37**, 109–116.
 124. Tuomilehto J, Voutilainen E, Huttunen J, *et al.* (1980) Effect of guar gum on body weight and serum lipids in hypercholesterolemic females. *Acta Med Scand* **208**, 45–48.
 125. Turner PR, Tuomilehto J, Happonen P, *et al.* (1990) Metabolic studies on the hypolipidaemic effect of guar gum. *Atherosclerosis* **81**, 145–150.
 126. Uusitupa M, Siitonen O, Savolainen K, *et al.* (1989) Metabolic and nutritional effects of long-term use of guar gum in the treatment of noninsulin-dependent diabetes of poor metabolic control. *Am J Clin Nutr* **49**, 345–351.
 127. Uusitupa M, Sodervik H, Silvasti M, *et al.* (1990) Effects of a gel forming dietary fiber, guar gum, on the absorption of glibenclamide and metabolic control and serum lipids in patients with non-insulin-dependent (type 2) diabetes. *Int J Clin Pharmacol Ther Toxicol* **28**, 153–157.
 128. Uusitupa M, Tuomilehto J, Karttunen P, *et al.* (1984) Long term effects of guar gum on metabolic control, serum cholesterol and blood pressure levels in type 2 (non-insulin-dependent) diabetic patients with high blood pressure. *Ann Clin Res* **43**, 126–131.
 129. Vaaler S, Hanssen KF, Dahl-Jorgensen K, *et al.* (1986) Diabetic control is improved by guar gum and wheat bran supplementation. *Diabetes Med* **3**, 230–233.
 130. Vuorinen-Markkola H, Sinisalo M & Koivisto VA (1992) Guar gum in insulin-dependent diabetes: effects on glycemic control and serum lipoproteins. *Am J Clin Nutr* **56**, 1056–1060.
 131. Hillman LC, Peters SG, Fisher CA, *et al.* (1985) The effects of the fiber components pectin, cellulose and lignin on serum cholesterol levels. *Am J Clin Nutr* **42**, 207–213.
 132. Reimer RA, Wharton S, Green TJ, *et al.* (2021) Effect of a functional fibre supplement on glycemic control when added to a year-long medically supervised weight management program in adults with type 2 diabetes. *Eur J Nutr* **60**, 1237–1251.
 133. Pourbehi F, Ayremlou P, Mehdizadeh A, *et al.* (2018) Effect of psyllium supplementation on insulin resistance and lipid profile in non-diabetic women with polycystic ovary syndrome: a randomized placebo-controlled trial. *Int J Women's Health Reprod Sci* **8**, 184–191.
 134. Nyman M, Nguyen TD, Wikman O, *et al.* (2020) Oat bran increased fecal butyrate and prevented gastrointestinal symptoms in patients with quiescent ulcerative colitis—randomized controlled trial. *Crohn's & Colitis* **360** **2**, otaa005.
 135. Jovanovski E, Khayyat R, Zurbau A, *et al.* (2019) Should viscous fiber supplements be considered in diabetes control? Results from a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care* **42**, 755–766.
 136. Khan K, Jovanovski E, Ho HVT, *et al.* (2018) The effect of viscous soluble fiber on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis* **28**, 3–13.
 137. Wood PJ, Braaten JT, Scott FW, *et al.* (1994) Effect of dose and modification of viscous properties of oat gum on plasma glucose and insulin following an oral glucose load. *Br J Nutr* **72**, 731–743.
 138. Truswell AS (2002) Cereal grains and coronary heart disease. *Eur J Clin Nutr* **56**, 1–14.
 139. Jenkins DJ, Kendall CW, Vuksan V, *et al.* (1999) Effect of wheat bran on serum lipids: influence of particle size and wheat protein. *J Am Coll Nutr* **18**, 159–165.
 140. Jenkins DJ, Kendall CW, McKeown-Eyssen G, *et al.* (2008) Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. *JAMA* **300**, 2742–2753.
 141. Giacco R, Lappi J, Costabile G, *et al.* (2013) Effects of rye and whole wheat *v.* refined cereal foods on metabolic risk factors: a randomised controlled two-centre intervention study. *Clin Nutr* **32**, 941–949.
 142. Honsek C, Kabisch S, Kemper M, *et al.* (2018) Fibre supplementation for the prevention of type 2 diabetes and improvement of glucose metabolism: the randomised controlled Optimal Fibre Trial (OptiFiT). *Diabetologia* **61**, 1295–1305.
 143. Munoz JM, Sandstead HH, Jacob RA, *et al.* (1979) Effects of some cereal brans and textured vegetable protein on plasma lipids. *Am J Clin Nutr* **32**, 580–592.
 144. Brown L, Rosner B, Willett WW, *et al.* (1999) Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* **69**, 30–42.
 145. Dieticians of Canada (2012) Food Sources of Soluble Fibre. <https://carleton.ca/healthy-workplace/wp-content/uploads/soluble-fibre.pdf> (accessed April 2021).
 146. Del Gobbo LC, Falk MC, Feldman R, *et al.* (2015) Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am J Clin Nutr* **102**, 1347–1356.
 147. Lu M, Wan Y, Yang B, *et al.* (2018) Effects of low-fat compared with high-fat diet on cardiometabolic indicators in people with overweight and obesity without overt metabolic disturbance: a systematic review and meta-analysis of randomised controlled trials. *Br J Nutr* **119**, 96–108.
 148. Rees K, Hartley L, Flowers N, *et al.* (2013) 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* **2013**, Cd009825.
 149. Siervo M, Lara J, Chowdhury S, *et al.* (2015) Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. *Br J Nutr* **113**, 1–15.
 150. Blanco Mejia S, Messina M, Li SS, *et al.* (2019) A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. *J Nutr* **149**, 968–981.
 151. Grundy SM, Stone NJ, Bailey AL, *et al.* (2019) 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **139**, e1082–e143.
 152. Kinoshita M, Yokote K, Arai H, *et al.* (2018) Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. *J Atheroscler Thromb* **25**, 846–884.
 153. Lepor NE & Vogel RE (2001) Summary of the third report of the National Cholesterol Education Program Adult Treatment Panel III. *Rev Cardiovasc Med* **2**, 160–165.