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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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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; impatient 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 ± 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

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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 ± 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 $P < 0{\cdot}10$. 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 $P < 0{\cdot}05$. 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 $P < 0{\cdot}05$. 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 $P < 0{\cdot}05$ 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 RCT's 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, $I^2 \geq 50\,\%$, $P < 0{\cdot}10$), 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;

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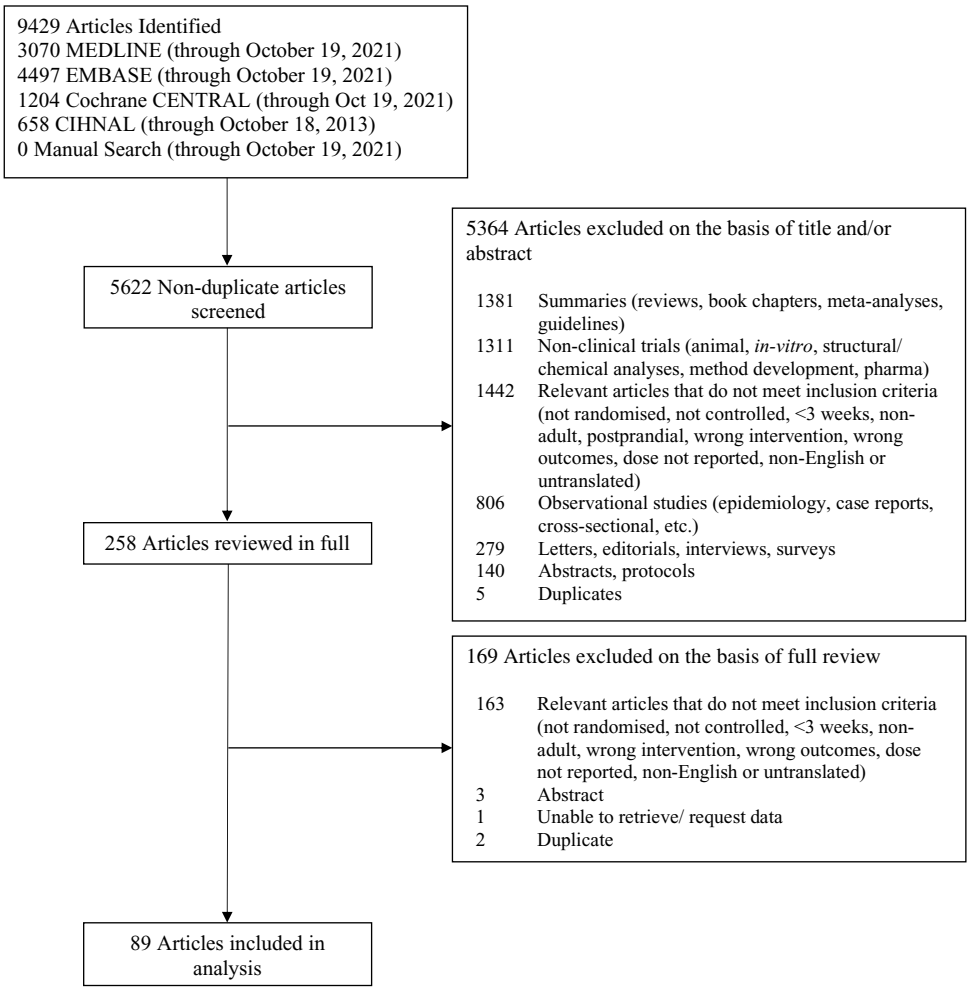

Fig. 1. Flow of literature. Summary of the number of articles that were identified and included in the meta-analysis of the effect of viscous fibre on LDL cholesterol, non-HDL cholesterol and ApoB. MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL databases were searched.

$P < 0{\cdot}01$), 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; $P < 0{\cdot}01$) followed by KJM (MD = –0·38 mmol/l; 95 % CI: –0·56, –0·21 mmol/l; $P < 0{\cdot}01$) and psyllium (MD = –0·35 mmol/l; 95 % CI: –0·42, –0·28 mmol/l; $P < 0{\cdot}01$). The lowest LDL cholesterol reduction was found with barley β-glucan (MD = –0·21 mmol/l; 95 % CI: –0·31, –0·11 mmol/l; $P < 0{\cdot}01$) and oat β-glucan (MD = –0·20 mmol/l; 95 % CI: –0·25, –0·14 mmol/l; $P < 0{\cdot}01$). The presence of substantial inter-study heterogeneity was observed in the overall analysis ($I^2 = 73$ %, $P < 0{\cdot}01$). 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 ($P < 0{\cdot}01$), with residual $I^2 = 66{\cdot}3$ % (online Supplementary Table S3). Categorical *a priori* subgroup analyses revealed a significant effect of fibre type on LDL cholesterol ($P < 0{\cdot}01$), with residual $I^2 = 62{\cdot}4$ % (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; $P = 0{\cdot}04$). 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; $P < 0{\cdot}01$) and oat β-glucan (MD = –0·33 mmol/l; 95 % CI: –0·51, –0·15 mmol/l; $P < 0{\cdot}01$). Psyllium showed a lower effect compared with barley β-glucan (MD = –0·16 mmol/l; 95 % CI: –0·28, –0·04 mmol/l; $P = 0{\cdot}01$) and oat β-glucan (MD = –0·16 mmol/l; 95 % CI: –0·25, –0·06 mmol/l; $P < 0{\cdot}01$). Significant effects were also found for disease status ($P = 0{\cdot}03$, residual $I^2 = 70{\cdot}8$ %), 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; $P < 0{\cdot}01$) and healthy individuals (MD = –0·24 mmol/l; 95 % CI: –0·46, –0·03 mmol/l; $P = 0{\cdot}03$) (online Supplementary Fig. S2). There was also a significant effect of dose $< 6{\cdot}0$ *v* $\geq 6{\cdot}0$ g/d with higher dose associated with larger reduction ($P = 0{\cdot}01$, residual $I^2 = 65{\cdot}3$ %) (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.

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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 1 low calorie	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/R1 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/R1 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.

Outcome	No. trials	N	Pooled Effect Estimates MD (95% CI)	P-value	Heterogeneity I^2	P-value
LDL-C (mmol/L)						
Konjac	5	201	−0·384 [−0·562, −0·207]	<0·001	51%	0·090
Guar Gum	11	154	−0·525 [−0·674, −0·376]	<0·001	0%	0·860
Psyllium	22	1295	−0·351 [−0·420, −0·283]	<0·001	63%	<0·001
Barley B-glucan	17	624	−0·206 [−0·306, −0·105]	<0·001	67%	<0·001
Oat B-glucan	47	2926	−0·196 [−0·250, −0·142]	<0·001	67%	<0·001
Total	102	4958	−0·261 [−0·302, −0·219]	<0·001	73%	<0·001

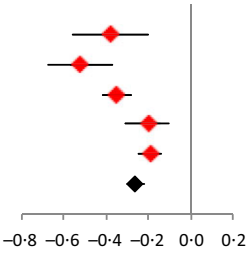

Fig. 2. Superplot of randomised controlled trials investigating the effect of viscous dietary fibres on LDL cholesterol (mmol/l). Mean differences (95 % CI) between viscous and non-viscous, cereal-type dietary fibre are generated using the generic inverse variance random-effects model. The red diamonds represent the pooled effect estimates for each fibre type, while the black diamond represents the pooled effect estimate from all fibre types. I^2 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 ($I^2 = 79$ %, $P < 0·01$). 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 $I^2 = 76·6$ % (online Supplementary Fig. S3). There was also a significant effect of BMI, with individuals under 25 kg/m^2 associated with a larger reduction ($P = 0·04$, residual $I^2 = 79·0$ %) (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 ($I^2 = 70$ %, $P < 0·01$). 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 $I^2 = 31·1$ % (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 $I^2 = 71·2$ %) (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).

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Outcome	No. trials	N	Pooled Effect Estimates MD (95% CI)	P-value	Heterogeneity I^2	P-value
Non-HDL-C (mmol/L)						
Konjac	5	201	−0·385 [−0·572, −0·197]	<0·001	51%	0·080
Guar Gum	18	297	−0·526 [−0·694, −0·358]	<0·001	21%	0·200
Psyllium	20	1257	−0·400 [−0·532, −0·267]	<0·001	84%	<0·001
Barley B-glucan	16	600	−0·266 [−0·380, −0·152]	<0·001	66%	<0·001
Oat B-glucan	46	2695	−0·292 [−0·368, −0·217]	<0·001	81%	<0·001
Pectin	1	20	0·600 [-0·106, 1·306]	0·100	-	-
Total	106	5070	−0·334 [−0·389, −0·279]	<0·001	79%	<0·001

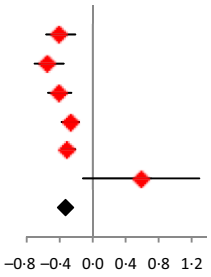

Fig. 3. Superplot of randomised controlled trials investigating the effect of viscous dietary fibres on non-HDL cholesterol (mmol/l). Mean differences (95 % CI) between viscous and non-viscous, cereal-type dietary fibre are generated using the generic inverse variance random-effects model. The red diamonds represent the pooled effect estimates for each fibre type, while the black diamond represents the pooled effect estimate from all fibre types. I^2 represents the estimated heterogeneity between individual studies.

Outcome	No. trials	N	Pooled Effect Estimates MD (95% CI)	P-value	Heterogeneity I^2	P-value
ApoB (g/L)						
Konjac	3	46	−0·130 [−0·194, −0·066]	<0·001	0%	0·600
Guar Gum	1	16	−0·090 [−0·266, 0·086]	0·320	-	-
Psyllium	9	802	−0·038 [−0·068, −0·008]	0·010	75%	<0·001
Barley B-glucan	2	77	−0·078 [−0·131, −0·025]	<0·001	0%	0·550
Oat B-glucan	9	618	−0·040 [−0·055, −0·025]	<0·001	14%	0·320
Total	24	1558	−0·044 [−0·062, −0·027]	<0·001	70%	<0·001

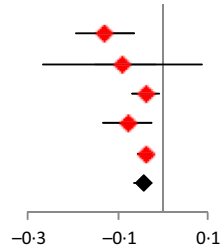

Fig. 4. Superplot of randomised controlled trials investigating the effect of viscous dietary fibres on ApoB (g/l). Mean differences (95 % CI) between viscous and non-viscous, cereal-type fibre were generated using the generic inverse variance random-effects model. The red diamonds represent the pooled effect estimates for each fibre type, while the black diamond represents the pooled effect estimate from all fibre types. I^2 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

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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

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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.

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Supplementary material

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