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Effects of different delivering matrices of β-glucan on lipids in mildly hypercholesterolaemic individuals: a meta-analysis of randomised controlled trials

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Abstract

β-Glucan has been reported for its health benefits on blood lipids in hypercholesterolaemic individuals for years. However, people have paid little attention to the effects of β-glucan in populations with mild hypercholesterolaemia as well as the various delivering matrices. Our objective was to perform a meta-analysis to analyse the effects of β-glucan with different delivering matrices in mildly hypercholesterolaemic individuals. After conducting a comprehensive search in Web of Science, PubMed, Scopus and Cochrane Library, a total of twenty-one randomised controlled trials involving 1120 participants were identified to measure the pooled effect. The overall results indicated that consuming a dose of ≥3 g/d of β-glucan for at least 3 weeks could significantly reduce total cholesterol (TC) (−0·27 mmol/l, 95 % CI −0·33, −0·21, $P < 0·001$) and LDL-cholesterol (−0·26 mmol/l, 95% CI −0·32, −0·20, $P < 0·001$) compared with the control group in mildly hypercholesterolaemic individuals, while no significant difference was observed in TAG (−0·03 mmol/l, 95% CI −0·11, 0·06, $P = 0·521$) and HDL-cholesterol (0·01 mmol/l, 95% CI −0·03, 0·04, $P = 0·777$). There was evidence for modest unexplained heterogeneity in the meta-analysis. In conclusion, β-glucan can significantly reduce risk factors like TC and LDL-cholesterol for CVD in mildly hypercholesterolaemic individuals; furthermore, it appears that the effects of food matrices with both 'solid products' and 'liquid products' where β-glucan was incorporated into were ranked as the best way to exert its beneficial properties, while 'liquid' and 'solid' products were ranked as the second and third positions, respectively.

Key words: **β-Glucan: Total cholesterol: LDL: Hyperlipidaemia: Meta-analyses**

For decades, CVD has been accounting for the main death rate in different countries with upper-middle income or high income[1]. In Germany, about 40 % (approximately 140 000) of deaths were attributed to CVD events in 2017[2]. Evidence from clinical studies suggested that dyslipidaemia, which is mainly characterised by elevated levels of LDL-cholesterol, TAG or total cholesterol (TC), is the important predictive factor for CVD[3–5]. Generally, reducing LDL-cholesterol concentration is the primary target for individuals who have high risk of arteriosclerotic CVD in clinics, and statin is the preferred drug[6,7]. However, for patients at the early stage of dyslipidaemia, drug therapy seems not so necessary; on the other hand, dietary habits and lifestyle modification may play primary roles in reducing the risk of CVD with different kinds of mechanisms[8,9], being also consistent with American Heart Association guidelines on the management of blood cholesterol[10]. For that reason, it has been attracting researchers' attention to seek an alternative therapy like transforming the diet pattern to improve abnormal lipids.

β-Glucan, a kind of dietary fibre, can be found not only in the cell wall of certain micro-organisms but also in protists like mushrooms and grains. In fact, there are two different linkages that exist in β-glucan: mixed β-(1,6) and β-(1,3) glucosidic linkages, derive from yeast and mushrooms, which are insoluble; another one is β-(1,3/1,4)-D-linked glucose units originating from oat and wheat, which is soluble[11–13]. In general, most of the biological effects of yeast β-glucan have been focused on enhancing immunity[14,15]; on the other hand, the majority of reports about the health benefits of β-glucan obtained from grains are focused on the modulation of blood lipids, and part of mushrooms were included[16–18]. Since Groot reported the cholesterol-lowering effect of β-glucan for the first time[19], a quantity of studies with further objectives have been

Abbreviations: MW, molecular weight; TC, total cholesterol.

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performed to explore the biological efficacies of β-glucan. A recent review by Sima *et al.*[20] summarised the relationship between β-glucan and cholesterol and listed the clinical evidence in detail. Official institutions like the Food and Drug Administration (FDA) recommended individuals obtaining beneficial effects by supplementing more than 3 g oat β-glucan each day. To date, robust evidence from clinical studies and meta-analysis has confirmed the cholesterol-lowering effects of β-glucan[21–25]; of those, however, participants included in trials involved populations without any restriction on blood lipids, either in healthy individuals, hypercholesterolaemic patients or a mixture of both; in other words, effects of β-glucan on lipids in mildly hypercholesterolaemic individuals remained inconclusive. Therefore, illuminating the benefits of β-glucan for a population with marginal high cholesterol may be better to reflect its primary application value. In addition, although β-glucan with different molecular weights (MW) was assessed in trials[26], few studies have paid attention to the effects of delivering matrices where β-glucan will be incorporated into, which may execute a minor discrepancy on blood lipids to some extent.

Hence, to further investigate the potential effects of β-glucan in mildly hypercholesterolaemic individuals, we deemed it necessary to collect a quantitative synthesis of evidence and make a meta-analysis to evaluate the effect in a mildly hypercholesterolaemic population.

Methods

This meta-analysis was conducted in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[27]. In addition, there was no necessity for ethical approval since all trials included in this meta-analysis were published officially.

Literature search strategy

Potential literature was identified through a systematic and comprehensive search in June 2019 in the following four electronic databases without language restriction: Web of Science, PubMed, Scopus and Cochrane Library. We employed a combination of MESH terms and keywords for searching ('Hypercholesterolemia' or 'Hyperlipidemias' and 'beta-Glucans' or 'Glucans ' or 'β-glucan'). References in papers were viewed as well so that any relevant studies were not missed. Data extraction was performed by two independent reviewers (D. X. and H. L.). Our study was limited only to randomised controlled trials, and any disagreements were resolved either by consultation together or by the third author (H. X.).

Inclusion and exclusion criteria

To do the meta-analysis, selected studies must meet the following criteria: (1) study design has to be randomised controlled trial which evaluated the effects of β-glucan on blood lipids, (2) the level of fasting serum TC or LDL-cholesterol was between 5·0 and 8·0 mmol/l or 2·7 and 5·0 mmol/l, respectively[28], (3) inclusion of an appropriate control diet and (4) contain data with available mean change from end point to baseline and any of SD, SE or 95 % CI for blood lipids.

The exclusion criteria were listed as below: (1) research objectives were animal or cell, (2) secondary information like reviews, (3) articles without sufficient data (e.g. data were showed only by figures) or suitable control group and (4) reporting outcomes were which we have no interest.

Data extraction and methodological assessment

Detailed information of articles included in this meta-analysis was extracted as follows: first author and year, sample size (male/female), mean age, baseline of blood lipids, sources of glucan, delivering matrices, amount of glucan, duration, comparison group and study design. Besides, net mean change and standard deviation of TC, TAG, LDL-cholesterol and HDL-cholesterol in each group were also collected; for studies which did not show effective data directly, we calculated it according to the following methods: the net mean change of blood lipids was measured through subtracting the end and baseline values, we assumed the last one as the end value if there were end points more than one; for SD of the net change, formula was used as below:

$$\mathrm{SD}_{\text{net change}} = \sqrt{\mathrm{SD}(\text{baseline})^2 + \mathrm{SD}(\text{end point})^2 - 2R \times \mathrm{SD}(\text{baseline}) \times \mathrm{SD}(\text{end point})},$$

for designing a correlation coefficient R 0·5 according to Higgins *et al.*[29]. We divided the delivering matrices of β-glucan given to volunteers into three ways: incorporated into food like bread and biscuits, named 'solid products'; dissolved in drink like milk and beverages, called 'liquid products'; and the last one is a combination of both, which means volunteers consumed β-glucan derived from both 'solid products' and 'liquid products'. Also, we regarded there was a parallel number of trials when involving multiple experimental groups in a single study. It is worth noting that we had converted mg/dl into mmol/l if necessary before the meta-analysis was performed; the conversion coefficient of TC, TAG, LDL-cholesterol and HDL-cholesterol is 0·0259, 0·0113, 0·0258 and 0·0258 for 1 mg/dl, respectively.

Quality assessment was examined based on the Cochrane Risk of Bias Tool[29], and the tool mainly covers seven validity questions: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias; each item was scored by high, unclear, low risk of bias for all included studies; upon evaluating above domains for each article, a figure of overall risk of bias was derived.

Statistical analysis

First of all, we have an assumption that randomisation could balance the baseline value between groups and effective value is estimated using the inverse-variance method[30]. Heterogeneity within studies was assessed by means of the I^2 statistics, which range from 0 to 100 %. We considered I^2 of <25 and 50 % as a no obvious and a moderate heterogeneity, respectively, and an I^2 of >75 % suggests a high level of heterogeneity; based on this, a fixed effects model was applied if heterogeneity is <50 %; otherwise, the random effects model

British Journal of Nutrition

was used. In addition, we performed a sensitivity analysis and subgroup to investigate the sources of heterogeneity by omitting each study and then repeating the analysis, and the subgroup analysis was conducted by delivering matrices of β-glucan, sources of β-glucan, dose of daily intake, duration of intervention, mean age of participants, study design and controlled diets. Furthermore, a funnel plot and Egger's regression were created to explore potential publication bias, and a 'trim and fill' analysis was to further observe the stability of results if there is any asymmetry in funnel plot[31]. Finally, meta-regression with a restricted maximum likelihood method was performed to investigate association between blood lipids change and delivering matrices. All analyses were run in Stata version 12 with a 5 % level of significance.

Results

Search results and trial characteristics

A flow diagram for selected trials is shown in Fig. 1. A total of 1262 articles were identified initially with the search strategy from four databases, of which 1217 were removed after reviewing title and abstracts, including ninety-five duplications. And then, forty-five full-text trials were retrieved for further information; of those, twenty-four studies were excluded for the following reasons: ten for insufficient information, five for inappropriate control and nine for uninterested outcomes. Finally, twenty-one trials with enough data were selected in this meta-analysis.

The present meta-analysis involved 1120 participants in total, ranging from sixteen to 155 for each study, of which the ratio of male:female is 50·8 to 49·2 %. The mean age was between 10·60 and 63·36 years approximately. Sixteen trials were interventions with β-glucan derived from oat, and the remaining were from barley. The mean intervention duration of included studies was 5·95 (SD 2·13) weeks with a daily intake amount of β-glucan varing from 1·45 to 11·2 g. All trials were randomised controlled trials with six cross-over designs and fifteen were performed as parallel studies. More detailed characteristics included in the meta-analysis are summarised in Table 1. Assessments of the risk of bias in included studies are shown in Table 2.

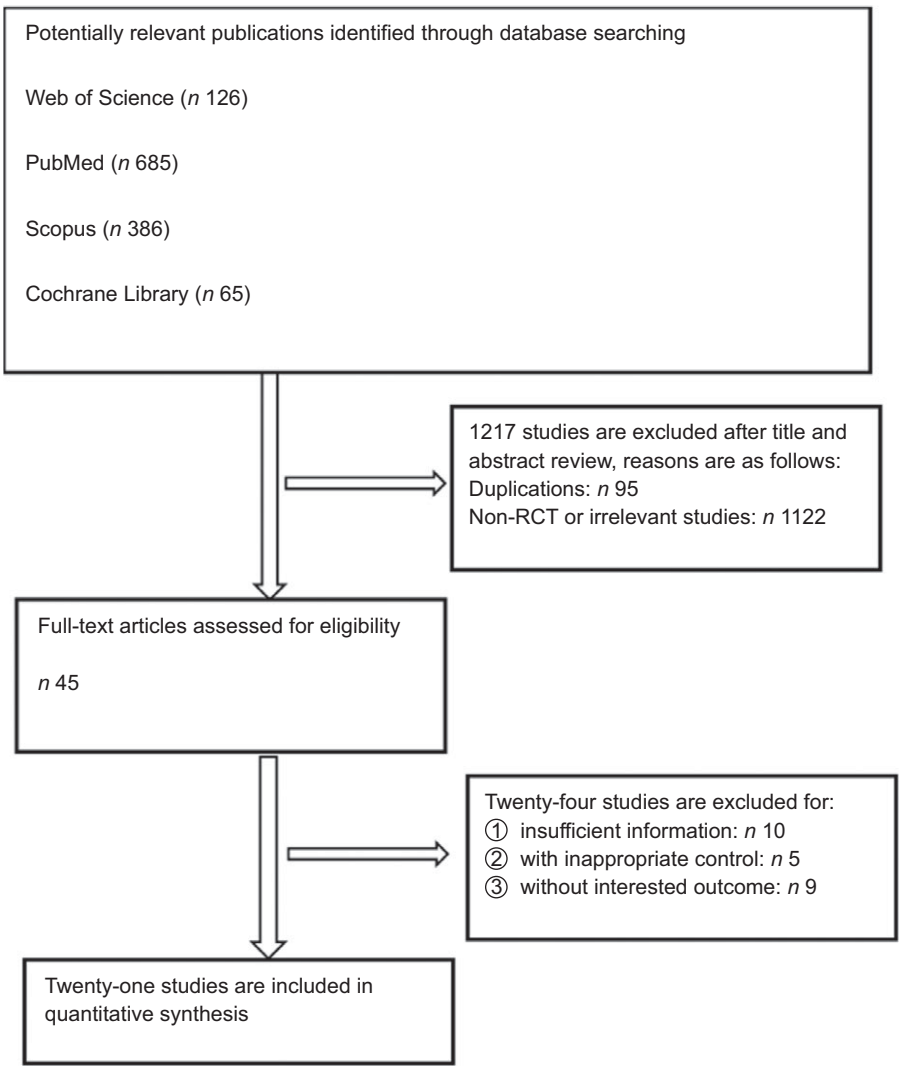

Fig. 1. Flow diagram for selected trials. RCT, randomised controlled trail.

Table 1. Characteristics of included twenty-one trials for meta-analysis
(Mean values and standard deviations)

Authors, year	Sample size	Male/ female	Age (years)		Baseline of blood lipids (mmol/l)	Sources of β-glucan	Delivering matrices	Amounts of β-glucans (g/d)	Duration (weeks)	Comparison group	Study design
			Mean	SD							
Amundsen *et al.*, 2003[32]	16	9/7	57·0	7·9	TC = 7·47 (SD 0·65)	Oat β-glucan	Solid products	5	3	Controlled diet without oat β-glucan	Single-blind, randomised cross-over
Behall *et al.*, 2004[33]	25	7/18	M = 43 F = 48·5	M = 5 F = 3·5	TC: M = 5·58 (SD 0·24) F = 5·58 (SD 0·22) LDL-cholesterol: M = 3·75 (SD 0·21) F = 3·76 (SD 0·19)	Barley β-glucan	Solid products	3; 6	5	Wheat and rice	Randomised Latin-square design
Biörklund *et al.*, 2008[34]	43	19/24	58	8·2	TC = 6·9 (SD 0·6) LDL-cholesterol = 4·3 (SD 0·6)	Oat β-glucan	Solid products	4	5	Maltodextrin and rapeseed oil	Single-blind, parallel, placebo-controlled trial
Biörklund *et al.*, 2005[35]	89	44/45	56	10	TC = 6·49 (SD 1·0) LDL-cholesterol = 4·35 (SD 0·8)	Oat/barley β-glucan	Liquid products	5; 10	5	Rice starch	Single blind, randomised, dose-controlled trial
Charlton *et al.*, 2012[36]	87	41/46	51	10·22	TC = 5–7·5	Oat β-glucan	Solid products	1·45; 3·24	6	Rice	Single-blind, parallel, randomised-controlled trial
Ferguson *et al.*, 2019[16]	72	27/45	55·07	1·41	TC = 6·57 (SD 0·11) LDL-cholesterol = 4·39 (SD 0·99)	Oat β-glucan	Solid products	3	6	Placebo without oat β-glucan	Double-blinded, randomised, placebo-controlled trial
Karmally *et al.*, 2005[37]	152	49/103	49·0	10·7	LDL-cholesterol = 3·09–4·9	Oat β-glucan	Solid products	3	6	Maize	Randomised controlled trial
Keenan *et al.*, 2007[25]	155	75/80	54·8	11·1	LDL-cholesterol = 3·09–4·9	Barley β-glucan	Both	3; 5	6	Controlled diet without barley β-glucan	Randomised, double-blind, controlled, parallel trial
Liatis *et al.*, 2009[38]	41	23/18	63·36	8·9	TC = 6·07 (SD 0·61) LDL-cholesterol = 4·12 (SD 0·63)	Oat β-glucan	Solid products	3	3	Controlled diet without oat β-glucan	Randomised, double-blind study
Lovegrove *et al.*, 2000[39]	62	31/31	56·55	9·3	TC = 6·45 (SD 0·8) LDL-cholesterol = 4·3 (SD 0·65)	Oat β-glucan	Solid products	3	8	Wheat bran	Double-blind, placebo-controlled, randomised study
Maki *et al.*, 2003[40]	18	13/5	10·6	0·5	TC = 5·0 (SD 0·15) LDL-cholesterol = 3·2 (SD 0·13)	Oat β-glucan	Solid products	3	8	Controlled diet without oat β-glucan	Randomised, double-blind, controlled, crossover design
Mårtensson *et al.*, 2005[41]	36	15/21	56	7·5	TC = 5·89 (SD 0·8) LDL-cholesterol = 3·81 (SD 0·81)	Oat β-glucan	Lipid products	3·5	5	Controlled diet without oat β-glucan	Randomised, double blind trials
McIntosh *et al.*, 1991[42]	21	21/0	44·2	7·6	TC = 6·26 (SD 0·24)	Barley β-glucan	Solid products	8	4	Wheat	Randomised, crossover design
Naumann *et al.*, 2006[43]	47	18/29	M = 56 F = 49	M = 9 F = 16	TC = 6·98 (SD 0·69) LDL-cholesterol = 4·65 (SD 0·61)	Oat β-glucan	Lipid products	5	5	Rice starch	Placebo-controlled, double-blind design
Queenan *et al.*, 2007[44]	75	25/50	44·9	2·1	TC = 6·2 (SD 0·1) LDL-cholesterol = 4·12 (SD 0·1)	Oat β-glucan	Lipid products	6	6	Dextrose	Randomised, double-blind design
Reyna-Villasmil *et al.*, 2007[45]	38	38/0	59·84	0·61	TC = 6·02 (SD 0·06)	Oat β-glucan	Solid products	6	8	Whole wheat	Randomised controlled trial
Rondanelli *et al.*, 2011[46]	24	24/0	50·3	5·3	TC = 6·44 (SD 0·55) LDL-cholesterol = 4·17 (SD 0·56)	Barley β-glucan	Solid products	6·9	8	Rice bran	Randomised, controlled, crossover design
Shimizu *et al.*, 2008[47]	39	39/0	41·5	8·5	TC = 6·23 (SD 0·63)	Barley β-glucan	Solid products	7	12	Rice	Randomised, double-blinded, placebo-controlled study
Thongoun *et al.*, 2013[48]	24	2/22	51·04	6·87	TC = 6·3 (SD 0·63) LDL-cholesterol = 4·52 (SD 0·64)	Oat β-glucan	Lipid products	3	4	Rice porridge	Randomised, crossover design
Torronen *et al.*, 1992[49]	28	28/0	25–52		TC = 6·39 (SD 0·91)	Oat β-glucan	Solid products	11·2	8	Controlled diet with little oat β-glucan	Randomised, double blind trials
Kerckhoffs *et al.*, 2003[50]	48	21/27	53	2	TC: M = 6·36 (SD 0·17) F = 5·96 (SD 0·15) LDL-cholesterol: M = 4·39 (SD 0·16) F = 3·82 (SD 0·14)	Oat β-glucan	Solid products	5·9	4	Wheat fibre	Randomised controlled experiment

TC, total cholesterol; M, male; F, female.

Table 2. Quality assessments of included studies based on the Cochrane guidelines

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Amundsen *et al.* [32]	U	U	L	L	L	L	L
Behall *et al.*[33]	U	H	H	L	L	L	L
Biörklund *et al.*[34]	U	L	L	L	L	L	L
Biörklund *et al.*[35]	U	U	H	L	L	L	L
Charlton *et al.*[36]	L	L	L	U	L	L	L
Ferguson *et al.*[16]	U	L	L	L	L	L	L
Karmally *et al.*[37]	U	H	H	L	L	L	L
Keenan *et al.*[25]	L	L	L	L	L	L	L
Liatis *et al.*[38]	L	L	L	L	L	L	L
Lovegrove *et al.*[39]	U	L	L	U	L	L	L
Maki *et al.*[40]	U	U	L	L	L	L	L
Mårtensson *et al.*[41]	U	U	L	U	L	L	L
McIntosh *et al.*[42]	U	U	H	U	L	L	L
Naumann *et al.*[43]	U	U	L	L	L	L	L
Queenan *et al.*[44]	U	U	L	L	L	L	L
Reyna-Villasmil *et al.*[45]	U	U	H	U	L	L	L
Rondanelli *et al.*[46]	L	L	L	L	L	L	L
Shimizu *et al.*[47]	U	U	L	U	L	L	L
Thongoun *et al.*[48]	U	H	H	L	L	L	L
Torronen *et al.*[49]	U	U	L	U	L	L	L
Kerckhoffs *et al.*[50]	U	U	L	L	L	L	L

U, unclear risk of bias; L, low risk of bias; H, high risk of bias.

Overall and subgroup effects of β-glucan intake on fasting serum total cholesterol concentration in mildly hypercholesterolaemic individuals

Twenty-nine studies (based on twenty-one articles) were reported to calculate the pooled effect, resulting in a significant decrease on the mean difference of TC of −0·27 mmol/l (95 % CI −0·33, −0·21, $P < 0·001$) with a random effects analysis. Although substantial evidence of heterogeneity between studies was observed with an overall analysis ($I^2 = 71·2$ %, $P < 0·001$), TC reduced more (−0·46 mmol/l, 95 % CI −0·56, −0·35, $P < 0·001$) after intaking β-glucan with 'both' ways in subgroup of delivering matrices and accompanied with a lower heterogeneity ($I^2 = 0$ %, $P = 0·461$), which is shown in Fig. 2. More detailed subgroup analysis is summarised in Table 3.

Overall and subgroup effects of β-glucan intake on fasting serum TAG concentration in mildly hypercholesterolaemic individuals

The meta-analysis consisted of twenty-one studies (including seventeen articles) demonstrated that the level of fasting serum TAG was not significantly changed by β-glucan consuming compared with control groups (weighted mean difference = −0·03 mmol/l, 95 % CI −0·11, 0·06, $P = 0·521$). There was still a serious heterogeneity before subgroup analysis ($I^2 = 87·8$ %, $P < 0·001$, Fig. 3). However, we observed a significant difference between TAG and β-glucan intake after adjusting delivering matrices and sources of β-glucan (see Table 3).

Overall and subgroup effects of β-glucan intake on fasting serum LDL-cholesterol concentration in mildly hypercholesterolaemic individuals

Results of the present study revealed that the LDL-cholesterol-lowering effect of β-glucan was significant overall with the pooled estimate of −0·26 mmol/l (95 % CI −0·32, −0·20, $P < 0·001$), which was conducted from the random effects model with heterogeneity $I^2 = 80·4$ % ($P < 0·001$). In addition, an outcome similar to TC was obtained when subgroup analysis was performed (Fig. 4). Table 3 shows the remaining results of subgroup analysis.

Overall and subgroup effects of β-glucan intake on fasting serum HDL-cholesterol concentration in mildly hypercholesterolaemic individuals

It is well known that HDL-cholesterol is regarded as a protective factor for CHD; the present meta-analysis including twenty-eight studies (based on twenty articles) was to explore the effect of β-glucan on fasting serum HDL-cholesterol concentration in mildly hypercholesterolaemic individuals. However, we did not identify any significant difference compared with control group from the random effects model (weighted mean difference = 0·01 mmol/l, 95 % CI −0·03, 0·04, $P = 0·777$), and heterogeneity of inter-study was $I^2 = 93$ %, $P < 0·001$ (Fig. 5). Nevertheless, we found several significant differences after conducting subgroup analysis by duration and controlled diets. The remaining results of subgroup analysis for HDL-cholesterol are found in Table 3.

Sensitivity analysis

Sensitivity analysis was performed to assess the stability and credibility of pooled effect through sequentially removing each eligible study and then repeating the analysis, and results suggested that it could not change the overall estimate effects of β-glucan on blood lipids in mildly hypercholesterolaemic individuals.

Subgroup analysis

The effects of β-glucan intake on blood lipids in subgroup based on volunteers' characteristics are summarised in Table 3.

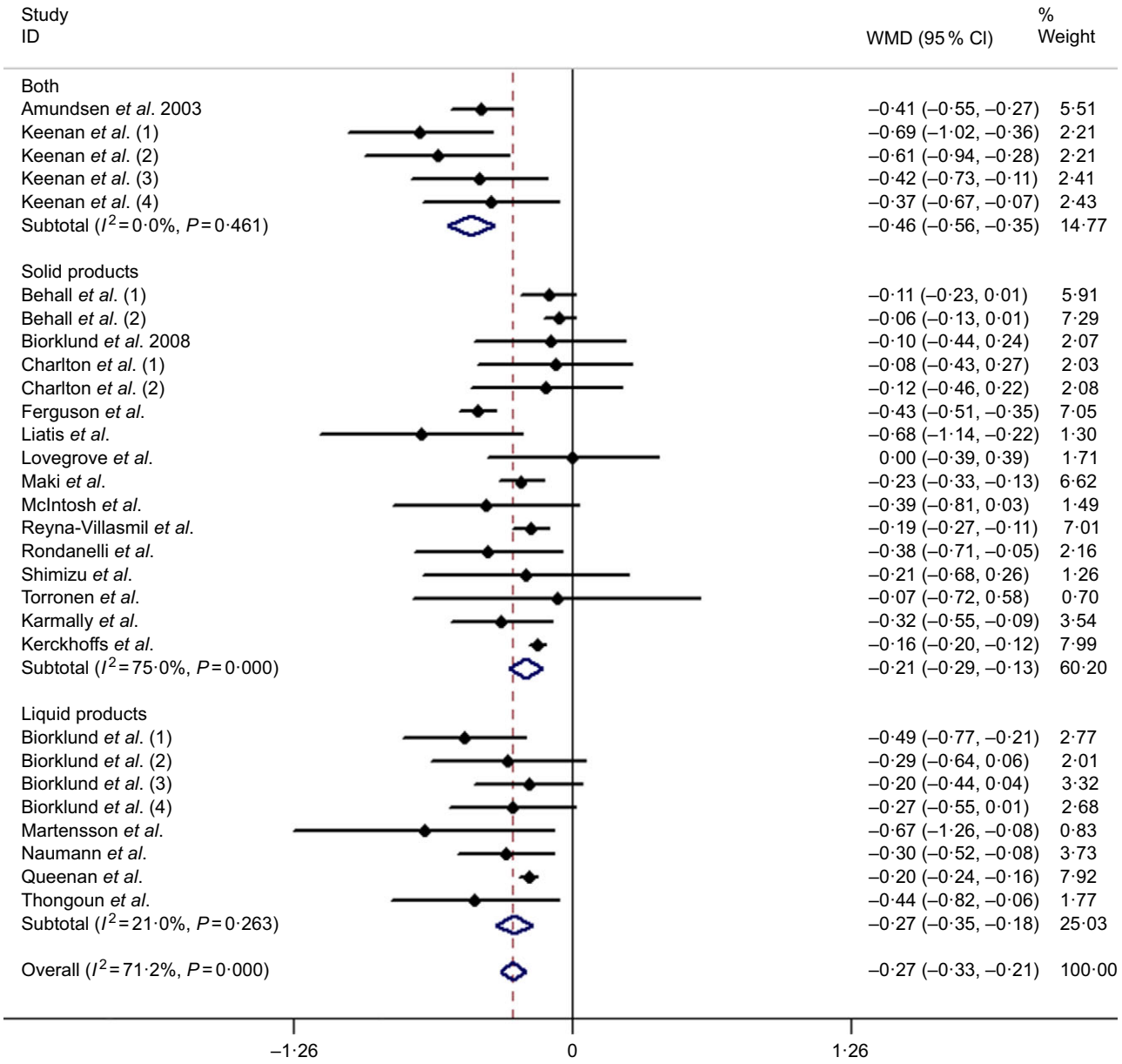

Fig. 2. Overall and subgroup effects of β-glucan intake on fasting serum total cholesterol concentration in mildly hypercholesterolaemic individuals. Weights are from random effects analysis. WMD, weighted mean difference.

Generally speaking, there was no obvious difference from the overall effects even after adjusting delivering matrices, sources of β-glucan, dosage, durations of trials, mean age of participants, study design and controlled diets for TC and LDL-cholesterol. As for TAG and HDL-cholesterol, several distinctions were observed before and after subgroup analysis.

Publication bias

Funnel plots and Egger's regression test of blood lipids were conducted to measure if there are potential publication biases, which are judged through symmetry of the funnel plots. For TAG, LDL-cholesterol and HDL-cholesterol, visual scanning of funnel plots suggested no asymmetry with Egger's regression *P* values of 0·118, 0·259 and 0·64, respectively, while we observe there is minor asymmetry for TC with Egger's regression *P* value of 0·019 (Fig. 6); consequently, we further performed the 'trim and fill' method to evaluate the robustness of the results in the presence of publication bias, and results show there is no change before and after adding the estimated missing literature, which suggesting that the results of TC are reliable.

Meta-regression

To further explore the sources of heterogeneity between studies, meta-regression was performed to assess association between blood lipids changes and delivering matrices of β-glucan. Results indicated a significant inverse relationship among mean difference and delivering matrices of β-glucan for TC (slope = −0·12, 95 % CI −2·0, −0·04, *P* = 0·004), while little

British Journal of Nutrition

Table 3. Effects of β-glucan on blood lipids by delivering forms, sources of β-glucan, dosage, duration of trials, mean age of participants, study design and controlled diets
(Mean values and 95 % confidence intervals)

Lipids	Subgroup	No. of trials	Weighted mean difference		*P*	I^2 (%)	*P* value of heterogeneity
			Mean	95 % CI			
Total cholesterol	Overall	29	−0·27	−0·33, −0·21	0·000	71·2	0·000
	Delivering matrices						
	Solid products	16	−0·21	−0·29, −0·13	0·000	75	0·000
	Liquid products	8	−0·27	−0·35, −0·18	0·000	21	0·263
	Both	5	−0·46	−0·56, −0·35	0·000	0	0·461
	Sources of β-glucan						
	From oat	18	−0·27	−0·33, −0·21	0·000	71·4	0·000
	From barley	11	−0·3	−0·43, −0·17	0·000	70·2	0·000
	Dosage						
	<5 g	13	−0·32	−0·41, −0·23	0·000	47·9	0·027
	≥5 g	16	−0·21	−0·27, −0·16	0·000	61·6	0·001
	Duration of trials						
	<5 weeks	5	−0·36	−0·56, −0·17	0·000	78·7	0·001
	≥5 weeks	24	−0·26	−0·33, −0·20	0·000	69·7	0·000
	Mean age of participants						
	<55 years	17	−0·26	−0·34, −0·18	0·000	63·7	0·000
	≥55 years	12	−0·28	−0·38, −0·19	0·000	78·7	0·000
	Study design						
	Crossover	7	−0·24	−0·37, −0·12	0·000	78	0·000
	Parallel-controlled	22	−0·29	−0·35, −0·22	0·000	68·7	0·000
	Controlled diets						
	Wheat	6	−0·14	−0·19, −0·08	0·000	45·9	0·1
	Rice or placebo	20	−0·36	−0·43, −0·29	0·000	33·4	0·074
	Others	3	−0·2	−0·24, −0·16	0·000	0	0·5
TAG	Overall	21	−0·03	−0·11, 0·06	0·521	87·8	0·000
	Consumption matrices						
	Solid products	12	−0·02	−0·08, 0·04	0·536	52	0·000
	Liquid products	8	−0·10	−0·35, 0·14	0·399	89·8	0·000
	Both	1	0·27	0·08, 0·46	0·000	~	~
	Sources of β-glucan						
	From oat	6	0·02	−0·08, 0·12	0·692	0	0·000
	From barley	15	−0·15	−0·22, −0·07	0·000	88·8	0·000
	Dosage						
	<5 g	8	−0·00	−0·15, 0·15	0·973	60·3	0·014
	≥5 g	13	−0·04	−0·15, 0·07	0·452	91·7	0·000
	Duration of trials						
	<5 weeks	5	−0·04	−0·25, 0·17	0·706	76·4	0·000
	≥5 weeks	16	−0·03	−0·14, 0·08	0·585	88·6	0·000
	Mean age of participants						
	<55 years	9	−0·08	−0·31, 0·08	0·455	79·6	0·000
	≥55 years	12	0·02	−0·04, 0·07	0·517	43	0·056
	Study design						
	Crossover	6	−0·11	−0·31, 0·08	0·249	79·6	0·020
	Parallel-controlled	15	0·01	−0·09, 0·10	0·898	87·9	0·000
	Controlled diets						
	Wheat	6	−0·03	−0·11, 0·05	0·466	74·8	0·001
	Rice or placebo	12	−0·08	−0·20, 0·05	0·216	60·9	0·003
	Others	3	0·13	−0·14, 0·39	0·352	78·3	0·010
LDL-cholesterol	Overall	29	−0·26	−0·32, −0·2	0·000	80·4	0·000
	Consumption matrices						
	Solid products	16	−0·23	−0·32, −0·15	0·000	87	0·000
	Liquid products	8	−0·25	−0·29, −0·22	0·000	0	0·780
	Both	5	−0·40	−0·48, −0·31	0·000	0	0·617
	Sources of β-glucan						
	From oat	18	−0·27	−0·35, −0·19	0·000	86·3	0·000
	From barley	11	−0·24	−0·32, −0·16	0·000	45	0·052
	Dosage						
	<5 g	13	−0·28	−0·35, −0·20	0·000	41·7	0·057
	≥5 g	16	−0·26	−0·34, −0·18	0·000	86·5	0·000
	Duration of trials						
	<5 weeks	5	−0·31	−0·51, −0·12	0·001	84·4	0·000
	≥5 weeks	24	−0·26	−0·32, −0·20	0·000	71·6	0·000
	Mean age of participants						
	<55 years	17	−0·25	−0·37, −0·13	0·000	90·7	0·000
	≥55 years	12	−0·24	−0·29, −0·19	0·000	34·8	0·078
	Study design						
	Crossover	7	−0·23	−0·31, −0·16	0·000	57·2	0·029
	Parallel-controlled	22	−0·27	−0·34, −0·19	0·000	83·6	0·000

Table 3. (*Continued*)

Lipids	Subgroup	No. of trials	Weighted mean difference		*P*	I^2 (%)	*P* value of heterogeneity
			Mean	95 % CI			
	Controlled diets						
	Wheat	6	−0·23	−0·37, −0·08	0·002	94·4	0·000
	Rice or placebo	20	−0·29	−0·35, −0·23	0·000	34	0·07
	Others	3	−0·26	−0·30, −0·22	0·000	0	0·641
HDL-cholesterol	Overall	28	0·01	−0·03, 0·04	0·777	93	0·000
	Consumption matrices						
	Solid products	15	0·02	−0·04, 0·09	0·482	96·2	0·000
	Liquid products	8	0·01	−0·02, −0·04	0·368	0	0·788
	Both	5	−0·02	−0·08, 0·04	0·519	0	0·708
	Sources of β-glucan						
	From oat	10	−0·01	−0·05, 0·03	0·629	93·5	0·000
	From barley	18	0·04	−0·01, 0·09	0·130	71	0·000
	Dosage						
	<5 g	13	−0·05	−0·06, 0·03	0·281	0	0·555
	≥5 g	15	0·03	−0·03, 0·008	0·348	96·3	0·000
	Duration of trials						
	<5 weeks	5	−0·06	−0·07, −0·04	0·000	0	0·788
	≥5 weeks	23	0·01	−0·03, 0·04	0·549	93·5	0·000
	Mean age of participants						
	<55 years	16	0·03	−0·02, 0·07	0·257	86	0·000
	≥55 years	12	−0·02	−0·09, 0·06	0·645	98·7	0·000
	Study design						
	Crossover	7	0·03	−0·04, 0·11	0·329	90·2	0·000
	Parallel-controlled	21	−0·01	−0·05, 0·04	0·773	92·4	0·000
	Controlled diets						
	Wheat	6	0·07	−0·05, 0·20	0·244	98·4	0·000
	Rice or placebo	19	−0·03	−0·04, 0·01	0·128	0	0·801
	Others	3	−0·01	−0·02, 0·00	0·017	0	0·993

significant association was observed for LDL-cholesterol, TAG and HDL-cholesterol (slope = −0·07, 95 % CI −0·14, 0·007, $P = 0·078$; slope = 0·05, 95 % CI −0·1, 0·2, $P = 0·525$ and slope = −0·03, 95 % CI −0·08, 0·03, $P = 0·311$, respectively).

Discussion

The present meta-analysis of twenty-one trials involving 1120 participants revealed the beneficial properties of β-glucan on risk factors for CVD, consuming ≥3 g/d of β-glucan for a period of time, could significantly reduce the concentrate of fasting serum TC (−0·27 mmol/l) and LDL-cholesterol (−0·26 mmol/l) in mildly hypercholesterolaemic individuals, and subgroup analysis further suggested it appears that the effects in the consumption manner of combination with 'solid products' and 'liquid products' were greater than alone of either one. However, we did not notice significant effects on TAG and HDL-cholesterol level. Different delivering matrices and controlled diets may explain some unknown heterogeneity.

The most outcomes concluded from the present meta-analysis have some similarities with previous studies. Whitehead *et al.* and Talati *et al.*[21,51] reported significant decreases of TC and LDL-cholesterol through intaking barley and oat with reductions of −0·35, −0·30 mmol/l and −0·26, −0·25 mmol/l, respectively, and it seems that barley may have more strength in improving TC concentrate compared with oat; the rationale behind this may be owing to a higher content in β-glucan in barley under the same weight[52], which in accordance with our overall and sub-analysis results. In the meta-analysis conducted by Talati *et al.*, the authors found that there was a significant decrease in TAG with barley-derived soluble fibre, which was the same with our subgroup analysis, even though inconsistent with the articles published before[53,54], and the discrepancy may be related to the meta-analysis including small-size articles since executing a flow with strict inclusion criteria. Interestingly, a recent network meta-analysis consisted of a total of 3900 individuals conducted by Hui *et al.*[55] suggested, except oat and oat bran, barley and wheat show no remarkable association with either TC or LDL-cholesterol, and then we speculate a part of healthy volunteers were included in analysis and unconventional statistical methods may attribute to the surprising conclusions to some extent. More importantly, subgroup analysis in this meta-analysis indicated that β-glucan would have a slight adverse effect on HDL-cholesterol because the no. of size of trials ≤5 weeks was relatively small. Also we were unclear about the potential effects of controlled diet itself, it is possible that some potential confounding factors generated some confusions in the meta-analysis, but maybe it is credible for mildly hypercholesterolaemic individuals. Further studies with high quality would be necessary to understand the clear mechanisms.

The bioactivity of β-glucan relies on its physical structure like MW and three-dimensional conformation, which will influence the viscosity and solubility of β-glucan in turn[56].

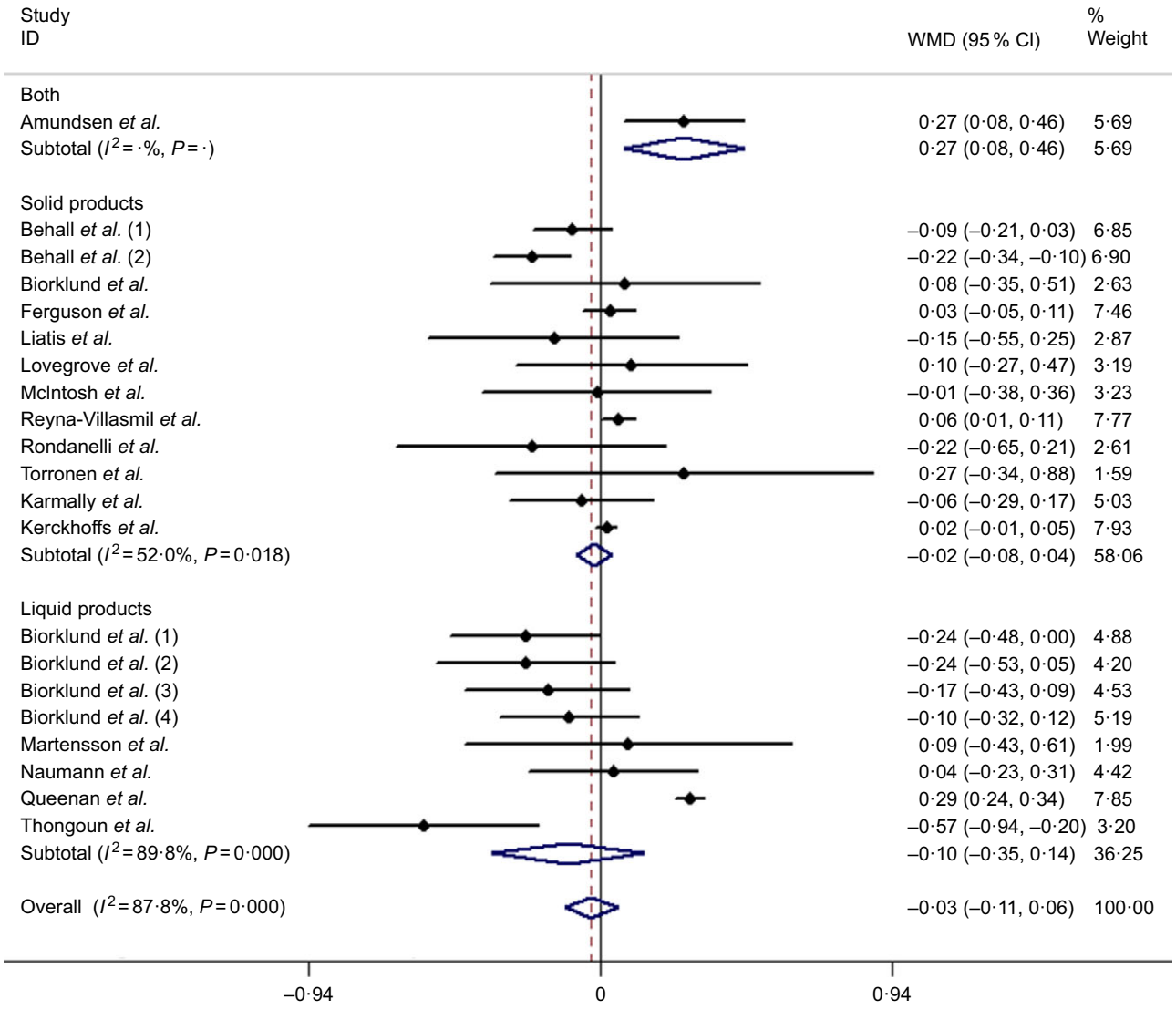

Fig. 3. Overall and subgroup effects of β-glucan intake on fasting serum TAG concentration in mildly hypercholesterolaemic individuals. Weights are from random effects analysis. WMD, weighted mean difference.

However, there were also some distinctions in the extracting and processing, including the storage condition and distribution of wholegrain as bran and endosperm[57,58]. It is reported that the cholesterol-lowering effect of β-glucan was mainly determined by its viscosity; when the high-molecular-weight β-glucan was ingested, a special microenvironment with high viscosity would be created in the small intestine, which will act as a physical barrier by preventing the absorption of cholesterol, promoting the excretion of bile acids which participate in the synthesis of cholesterol and reducing the reabsorption of bile acids existed in enterohepatic cycle[50,59–62]. Besides above physical properties of β-glucan, mechanisms involved in biomolecule metabolism with body were also reported, which included the whole process of cholesterol synthesis, metabolism and transport[63]. Furthermore, β-glucan could be fermented by the colon microbiota and gives the end products of SCFA (mainly acetic, propionic and butyric acids), of which propionic acid plays a crucial role in hypocholesterolaemic activities with suppressing the activity of hydroxy methylglutaryl coenzyme A (HMG CoA), which is a rate-limiting enzyme during endogenous cholesterol synthesis[64–66]. *In vitro*, β-glucan could also act as an inhibitor of HMG-CoA and resulting in impairment of cholesterol biosynthetic pathway[67,68]. Clinical trials and reviews suggested that supplement of β-glucan could stimulate to increase the abundance of certain beneficial gut microbiota, such as *Bifidobacterium* and *Lactobacillus*[69,70], and these bacterial genera are known to predominately contain bile salt hydrolase-positive species, which could modulate the host bile acid pool signature through deconjugation of conjugated bile acid. Unconjugated bile acids have reduced micellular activity and therefore are less effective mediators of cholesterol absorption in the host relative to conjugated bile acids[71,72]. According to Wang *et al.*'s[73] report, β-glucan could alter the gut microbiota and the changes observed were

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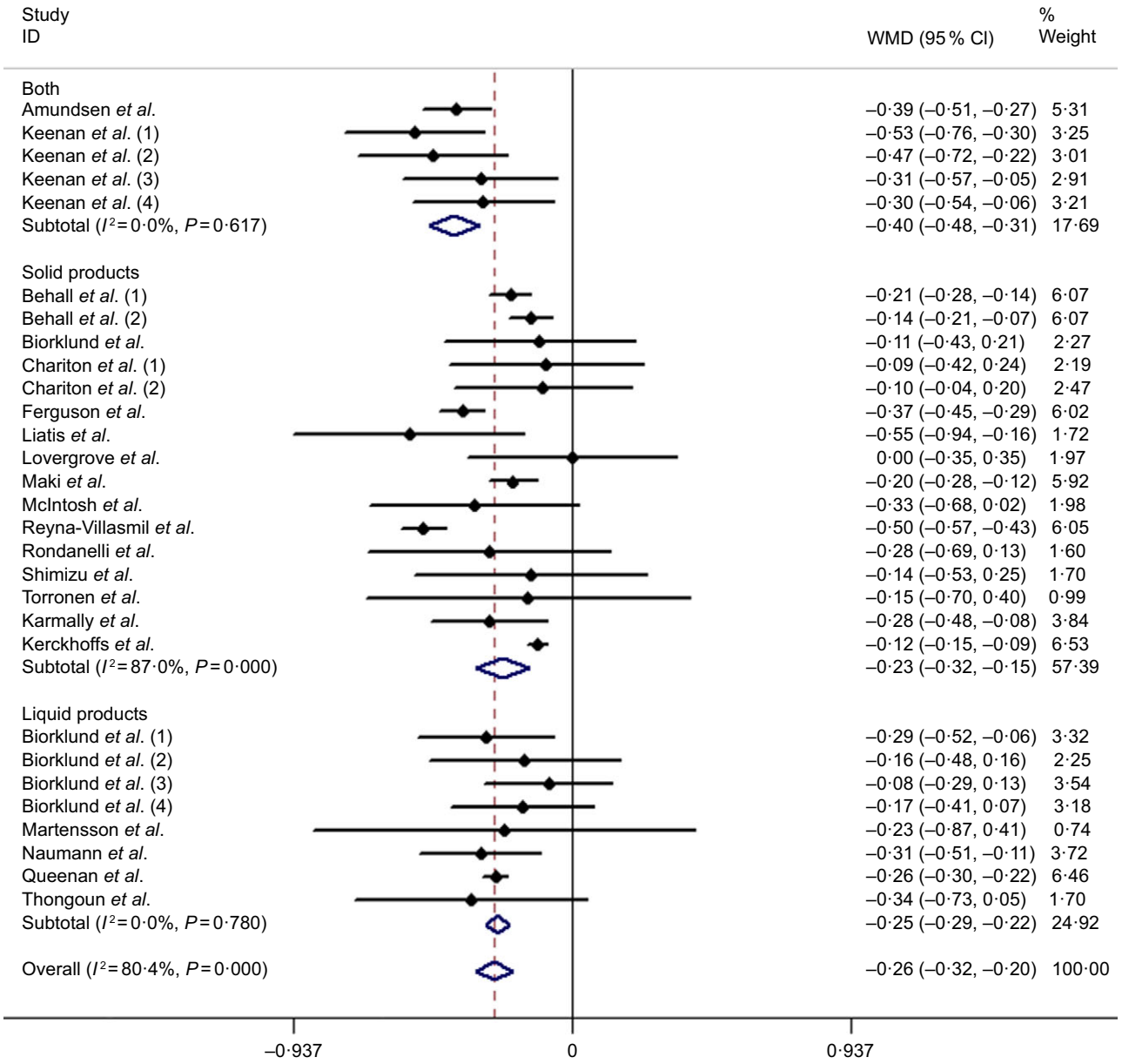

Fig. 4. Overall and subgroup effects of β-glucan intake on fasting serum LDL-cholesterol concentration in mildly hypercholesterolaemic individuals. Weights are from random effects analysis. WMD, weighted mean difference.

positively associated with an improved CVD risk factor profile. Interestingly, the delivering food where β-glucan was incorporated into may have different effects on the efficacy of β-glucan, according to Kerckhoffs, drink with oat β-glucan appeared to be somewhat more effective than food like bread and cookies enriched with oat β-glucan, since the processing could reduce its MW to some extent[74], and beverages and liquid test meal may rank the best carrier to deliver β-glucan[75]. Our subgroup analysis further supported those ideas, and liquid meal enriched with β-glucan is better than food like bread and cookies; in this way, we observed a combination of 'liquid' and 'solid' food might be the most effective way to deliver β-glucan compared with isolate food or drink, although there is a modest heterogeneity.

In addition, trials included in this meta-analysis involve a variety of controlled diets, ranging from rice, maize, dextrose and even wheat, those may have crucial impacts on overall heterogeneity, especially wheat that have a low amount of β-glucan[76], and subsequent subgroup analysis by controlled diets proved it. On the other hand, participants included in the meta-analysis were defined as mildly hypercholesterolaemic individuals. To our knowledge, this is the first meta-analysis to assess the effects of β-glucan on blood lipids in the population and have a similar result with previous studies.

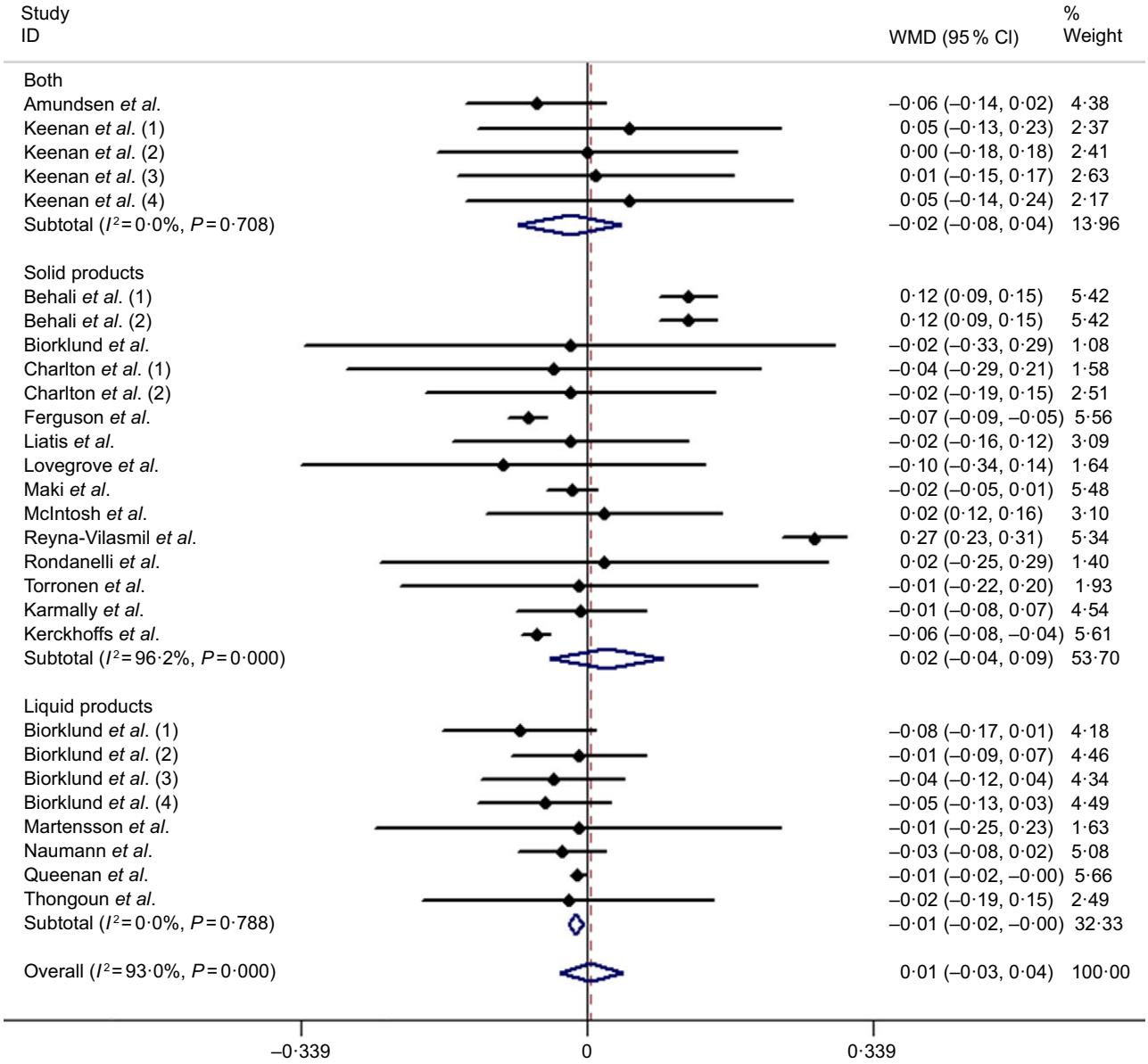

Fig. 5. Overall and subgroup effect of β-glucan intake on fasting serum HDL-cholesterol concentration in mildly hypercholesterolaemic individuals. Weights are from random effects analysis. WMD, weighted mean difference.

There are several limitations which should be taken account to the meta-analysis: first, insufficient information in some included studies which we could not find a standardised method to measure the MW of β-glucan; as a result, a detailed description on the MW of β-glucan would not be obtained, even the area where the β-glucan was extracted from was not taken into consideration; all the above conditions may make a potential confound on our results. Second, even though subgroup analysis by forms of delivering matrices and controlled diets explains most of the heterogeneity, a modest heterogeneity was still observed in the analysis, of which we consider it may be inevitable due to studies with amounts of different aspects, such as countries and races where the trials were conducted, and definitions of mild hypercholesterolaemia. Third, we still found a slight asymmetry in funnel plots for TC, although a comprehensive and systematic search was performed to avoid publication bias, since unpublished trials with negative outcomes have always existed; nevertheless, the further method of 'trim and fill' has ensured the robustness of results for TC. Consequently, a greater number of high-quality trials with appropriate control are necessary to verify these results.

We conclude that β-glucan can reduce risk factors like TC and LDL-cholesterol for CVD in mildly hypercholesterolaemic individuals significantly. Furthermore, the food matrices of delivering β-glucan with a combination of both 'liquid' and 'solid'

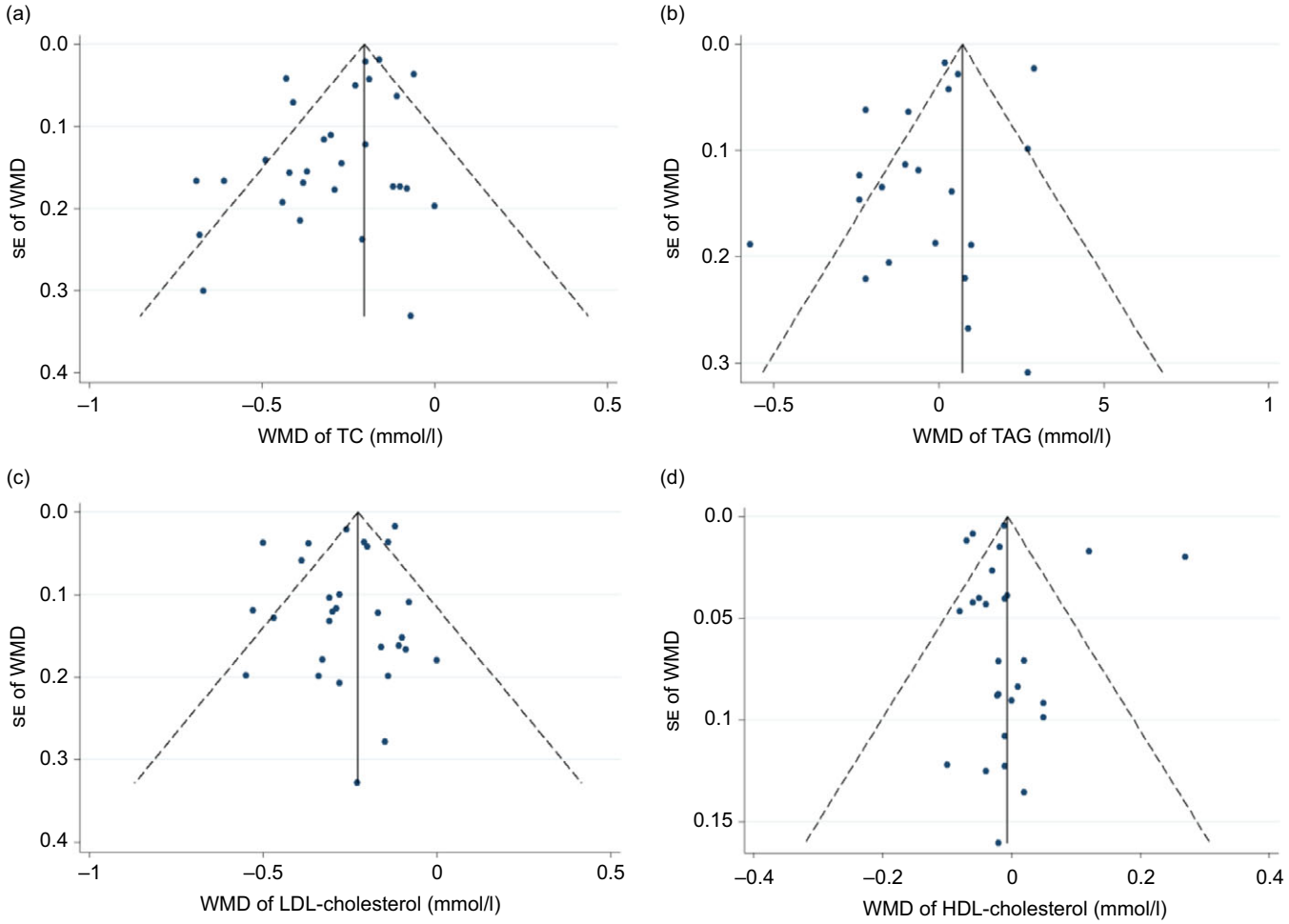

Fig. 6. Funnel plots measuring publication bias and effect of β-glucan intake for (a) total cholesterol (TC) Egger's test ($P = 0{\cdot}019$), (b) TAG Egger's test ($P = 0{\cdot}118$), (c) LDL-cholesterol Egger's test ($P = 0{\cdot}259$) and (d) HDL-cholesterol Egger's test ($P = 0{\cdot}64$) in mildly hypercholesterolaemic individuals. WMD, weighted mean difference.

products were ranked as the best way to exert its beneficial properties, while 'liquid' product was ranked as the second, following with 'solid' product.

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D. X. designed the study and wrote the paper, D. X. and H. L. searched and reviewed the relevant trials and collected the data. H. X. played a role as a consultant. D. P. helped employing search strategies. C. Y. and X. Y. performed statistical analysis. L. Y. and S. W. were responsible for the quality assessments for the studies. All authors reviewed the manuscript and approved the final manuscript.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114520001610

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