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Effects of probiotic supplementation on the regulation of blood lipid levels in overweight or obese subjects: a meta-analysis†

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Background: Obesity is a risk factor for many deadly diseases. Meanwhile, the prevalence of obesity has been continuously increasing in many countries. Probiotics are defined as live microorganisms that confer health benefits on hosts. Probiotic supplementation could reduce body weight, body mass index (BMI) and fat percentage. However, it is unclear whether supplementation with probiotics is beneficial to lower blood lipid levels for obese or overweight people. *Methods*: In this study, a comprehensive search across multiple databases was performed to identify studies that focused on the effects of probiotics on blood lipid levels in overweight or obese subjects. The meta-analysis included studies that compared the variations in blood lipid (total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride (TG)) concentrations between overweight and obese subjects who were supplemented with probiotics *versus* the controls who were not supplemented with probiotics. *Results*: Our findings indicated that probiotic supplementation in obese or overweight people was associated with significantly larger reductions in TC and LDL levels compared to a lack of probiotic supplementation in the control subjects. However, there was no significant difference in the variations between HDL and TG concentrations. *Conclusion*: Probiotic supplementation reduced TC and LDL concentrations in obese or overweight people. Additional data from large clinical trials are required to confirm the efficacy and safety of probiotics in the regulation of blood lipid levels in obese or overweight people.

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1. Introduction

Obesity is a pathological state marked by the accumulation of excess body mass in the abdominal region as a result of disequilibrium between energy intake and its consumption,[1] and it is a risk factor for many deadly diseases, particularly diabetes, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD) and some forms of cancer.[2–4] In 2015, 107.7 million (98.7–118.4 million) children and 603.7 million (588.2–619.8 million) adults were obese worldwide. The overall prevalence of obesity in children and adults was 5.0% and 12.0%, respectively. The prevalence of obesity has doubled since 1980 in more than 70 countries and has continuously increased in most other countries.[5]

Probiotics are defined as live microorganisms that confer health benefits on hosts when consumed in appropriate amounts in food.[6] This term also refers to some yeasts and bacteria that are used as dietary supplements or additives in certain foods. Previous studies have indicated that probiotics were associated with reducing episodes of diarrhea, malabsorption and dysbiosis.[7–9] Probiotic treatment may reduce liver fat, aspartate aminotransferase (AST) level, and glycemic and inflammatory indices in patients with NAFLD.[10,11] In addition, probiotics could be an effective option to improve immune function by enhancing natural killer (NK) cell function and interferon (IFN)-γ concentration.[12] The use of probiotics also improves the clinical and laboratory profiles of evaluated patients with chronic pancreatitis, favoring the best clinical outcome.[13] Moreover, probiotics can effectively prevent colorectal cancer by the alteration of the intestinal microflora, the inactivation of carcinogenic compounds, and the inhibition of tyrosine kinase signaling pathways and other processes.[14]

Abnormal levels of blood lipids (total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride (TG)) associated with overweight or obesity are

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major risk factors for cardiovascular disease.[15] Overweight and obese people had higher short chain fatty acids (SCFAs) that were correlated with the development of obesity.[16] Meanwhile, intestinal microflora have a suppressive effect on adenosine monophosphate kinase (AMPK) activity, thus affecting fatty acid oxidation and metabolism.[1] What's more, probiotics such as lactic acid bacteria could change the gut microbiota community.[17] Therefore, probiotics could provide anti-obesity effects in animal models and humans by the regulation of the intestinal microflora.[1] Several studies reported that probiotics significantly reduced the TC and LDL levels and improved the HDL concentration.[18–20] However, Wong VW found that the use of probiotics was not associated with changes in the body mass index (BMI), waist circumference, glucose and lipid levels.[10] The role of probiotics in the blood lipid level of obese or overweight people remains controversial. Therefore, we performed a meta-analysis of all relevant randomized control trials (RCTs) with the main focus on the efficacy of probiotics on the blood lipid levels of obese or overweight people.

2. Materials and methods

2.1. Sources and methods of data retrieval

We performed a comprehensive literature search that included studies from 1970 to September 2018; the electronic databases included PubMed, Medline, Web of Science, Cochrane Library and Google Scholar. We analyzed the variations in TC, LDL, HDL and TG concentrations in the blood lipids of obese or overweight people in response to supplementation with probiotics. The following terms were used for the literature search: probiotics, overweight, obesity, cholesterol, triglyceride, high density lipoprotein, HDL, low density lipoprotein, LDL, and blood lipids. The term 'OR' was used as the set operator to combine different sets of results. The literature search was restricted to the English language and human subjects. Location, age, probiotics and other confounding factors were also considered.

2.2. Inclusion criteria

The articles included in this meta-analysis matched the following six criteria: (1) overweight or obesity was defined according to local standards; (2) studies included an intervention group and a control group; (3) the results included quantitative data with specific values; (4) the supplementation groups and the controls had not received probiotic supplementation regularly or efficiently in the past; (5) we excluded subjects who were pregnant or breast feeding; had renal or hepatic dysfunction, heart disease, hypertension, diabetes mellitus, any metabolic disorder, or acute gastrointestinal disorders; or were taking medicines or functional food that may affect the body weight or body fat; and (6) we excluded studies that did not provide initial data, animal studies, *in vitro* studies, reviews and conference papers. Two investigators independently reviewed the literature, extracted all potentially eligible studies and resolved uncertainty and disagreement by discussion (Fig. 1).

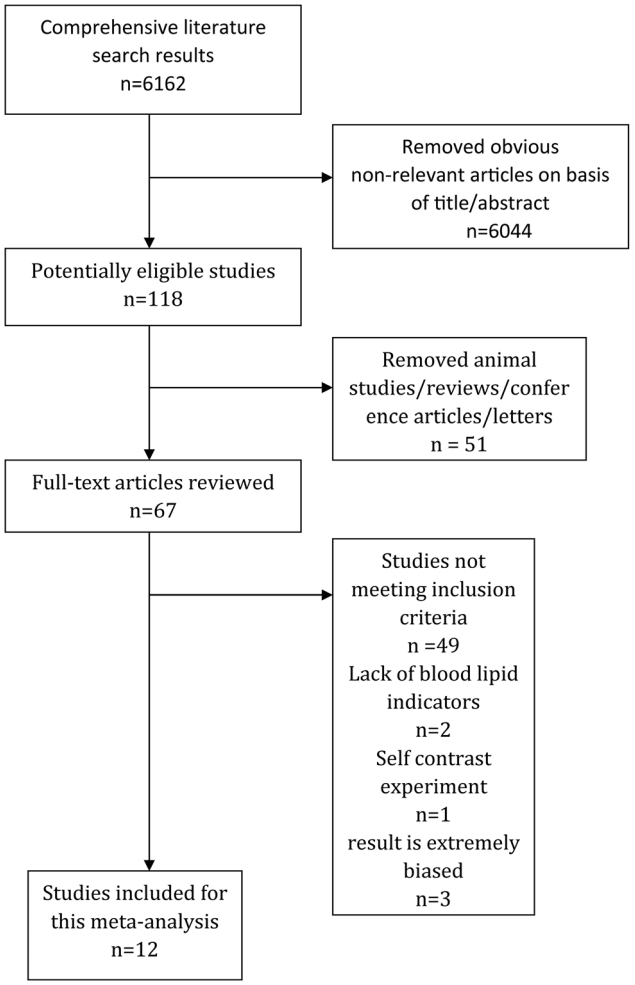

Fig. 1 Flow diagram of the literature search and selection.

2.3. Data abstraction

We reviewed all of the relevant studies and extracted the following data: (1) lead author, nationality, publication year, probiotics, subjects of studies, numbers of patients and controls, mean age and the BMI of the supplementation groups and controls, and gender of the supplementation groups and controls; and (2) the changes in the TC, LDL, HDL and TG concentrations in the supplementation groups and controls.

2.4. Risk of bias within individual studies

Two investigators used the Cochrane Collaboration (RevMan Version 5.3) software to evaluate the risk of bias (including the risks of selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases) within the individual studies independently and resolved inconsistencies by discussion and consensus.[21]

2.5. Statistical analysis

Statistical analysis was conducted using the statistical software RevMan version 5.3 and Stata (version 12.0, StataCorp LLC, College Station, TX, USA). The mean change (standard devi-

ation) in TC, LDL, HDL and TG levels from the baseline was used to calculate the mean difference (95% confidence interval [CI]) between the intervention group and the control group. When it was not provided by the study's authors, we calculated the standard deviation in the mean change in the inflammatory markers using the formula in the Cochrane handbook.[22] The correlation coefficient of the equation was imputed using the data from the included studies reporting the baseline and endpoint values and the variations. Our estimated value of 0.88 indicated that the correlation between the baseline and final values of TC, LDL, HDL and TG was high.

$$SD_{Change} = \sqrt{SD_{Baseline}^2 + SD_{Final}^2 - (2 \times 0.88 \times SD_{Baseline} \times SD_{Final})}$$

We combined the weighted mean difference (WMD) for studies that listed the mean and standard deviation values for the variations in the TC, LDL, HDL and TG concentrations in the intervention and control groups. The fixed effects model and the random effects model were used to determine the WMD and 95% confidence intervals (CIs) and to evaluate the differences in the variations in the blood lipid concentrations between the probiotic supplementation group and the controls.

Cochran's Q statistic and the I^2 statistic were used to assess the statistical heterogeneity in the meta-analysis.[23] If the data were homogeneous ($p > 0.05$), a fixed effect model meta-analysis was performed; if the data were heterogeneous ($p \leq 0.05$), a random effects model meta-analysis was performed. In the Q test, $p < 0.05$ was considered significant for heterogeneity, and the I^2 value was used to evaluate the degree of heterogeneity. I^2 values of 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively.[24] Heterogeneity was analyzed *via* sensitivity analysis. Subgroup analyses were performed based on the object (adults, children/adolescents, and women), region (Asia, Europe and others), number of probiotics (single and multiple) and probiotic species (*Lactobacillus* (L), *Lactobacillus* + *Streptococcus* (L + S) and *Lactobacillus* + *Streptococcus* + *Bifidobacterium* (L + S + B)).

3. Results

Our study identified 6162 related references, but only 12 papers met our inclusion criteria. These 12 articles included a total of 767 samples, with 391 treatments and 376 controls.[25–36] The detailed results are shown in Table 1 and Table S1.† Five of these studies were conducted in Asia,[25–27,29,30] five were conducted in Europe,[28,31–33,36] one in Oceania,[35] and one in America.[34] The subjects were adults in seven papers,[25–28,34–36] children or adolescents in three papers,[29–31] and women in two papers.[32,33] Five studies included one single species of probiotics,[26–28,31,34] while the remaining studies ($n = 7$) included two or multiple species of probiotics.[25,29,30,32,33,35,36] Seven of the studies reported changes and the baseline and final values of TC, LDL, HDL and TG,[26–28,30–32,36] whereas five studies reported changes or the baseline and final values of TC, LDL, HDL and TG.[25,29,33–35] The basic characteristics of the patients are presented in Table 1. One of the studies was excluded in the analysis of triglycerides because of heterogeneity (after excluding this study,[26] the heterogeneity changed from 82.9% ($p < 0.001$) to 17.0% ($p = 0.151$)). Additionally, one study was also excluded in the analysis of LDL (after excluding this study,[25] the heterogeneity changed from 61.6% ($p = 0.002$) to 36.9% ($p = 0.096$)).

The risk of bias within individual studies is shown in Fig. 2. All 12 studies were randomized and had complete outcome data.[25–36] Methods of allocation concealment were properly described in 9 studies,[25,26,28,31–36] and only one study had neither a double-blind setup (for participants and study personnel) nor a blinded outcome assessment.[30] Nine trials were preregistered in a clinical trial registry, which might have controlled reporting bias efficiently.[25,28–35] Moreover, two studies were funded by institutions, and the institutions may have been involved;[28,34] therefore, the studies were considered to have other potential bias. Simultaneously, we use the GRADE system to classify the quality of evidence for different outcomes. We are confident that the true effect lies close to that of the estimate of the effect (Table 2).

We conducted a meta-analysis of the TC, LDL, HDL and TG concentrations in 391 treatment and 376 control subjects. The group that was administered probiotics was associated with a significantly larger reduction in TC levels (WMD = −3.04 mg dL^{-1}, 95% CI = −4.88, −1.21 mg dL^{-1}, I^2 = 45.9%, p = 0.036; Fig. 3(A)) compared with the control group. Statistically significant differences in the variations in LDL concentrations were observed between the supplementation group and the control group (WMD = −2.28 mg dL^{-1}, 95% CI = −3.60, −0.96 mg dL^{-1}, I^2 = 36.9%, p = 0.096; Fig. 3(B)). However, there were no statistically significant differences in the variations in HDL concentrations between the supplementation group and the control group (WMD = −0.26 mg dL^{-1}, 95% CI = −2.39, 1.87 mg dL^{-1}, I^2 = 95.5%, $p < 0.001$; Fig. 3(C)). Additionally, an analysis of the results of these studies indicated that there were no significant differences between the supplementation group and the control group in terms of the variations in TG concentrations (WMD = −0.86 mg dL^{-1}, 95% CI = −2.54, 0.83 mg dL^{-1}, I^2 = 17.0%, p = 0.277; Fig. 3(D)).

Subgroup analysis was performed according to the object, region and probiotics intervention. Some details are presented in Table 3. Studies were divided into three areas: Asia, Europe and others (America and Oceania) according to the geographical study area. The studies in all three areas showed that the TC, LDL and TG variations in the supplementation group were not significantly different from those in the control group (Fig. 4(A), (B), and (D)). Additionally, in the subgroup meta-analysis of the variations in HDL concentrations, the studies in Asia and Europe did not demonstrate differences between the probiotic and control groups (Fig. 4(C)).

The included articles were divided into two groups according to the probiotics as follows: single probiotic group and multiple probiotic group. In the multiple probiotic group, the intervention group showed a larger reduction in the variations

Table 1 Studies showing the variations of blood lipid concentrations in probiotics and controls

Author	Region	Year	Probiotics	Intervention dose	Subjects	*n*		Age		Gender (male/female)	
						Study	Control	Supplementation groups	Control	Supplementation groups	Control
Higashikawa *et al.*[26]	Japan	2015	*Pediococcus pentosaceus* LP28	10^{11} CFU d^{-1}	Adult	21	20	52.50 ± 11.80	52.80 ± 11.60	8/13	7/13
Rajkumar *et al.*[25]	India	2014	VSL#3	112.5×10^{9} CFU d^{-1}	Adult	15	15	—	—	—	—
Jung *et al.*[27]	Korea	2013	*Lactobacillus gasseri* BNR17	6×10^{10} CFU d^{-1}	Adult	28	29	—	—	13/15	9/20
Stenman *et al.*[28]	Finland	2016	*Bifidobacterium animalis* ssp. *lactis* 420(B420)	10^{10} CFU d^{-1}	Adult	48	56	50.60 ± 10.60	49.90 ± 8.50	9/39	12/44
Safavi *et al.*[29]	Iran	2013	Probiotic mixture①	2.0×10^{8} CFU d^{-1}	Children/adolescents	29	27	10.75 ± 2.49	10.09 ± 1.93	—	—
Ipar *et al.*[30]	Turkey	2015	Probiotic mixture②	25.4×10^{8} CFU d^{-1}	Children/adolescents	42	35	—	—	—	—
Gobel *et al.*[31]	Denmark	2012	*L salivarius* Ls-33 ATCC SD5208	10^{10} CFU d^{-1}	Children/adolescents	27	23	12.90 ± 1.00	13.40 ± 1.10	11/16	11/12
Szulińska *et al.*[32]	Poland	2018	Probiotic mixture②	10^{10} CFU d^{-1}	Women	23	24	55.16 ± 6.87	58.72 ± 7.25	23/0	24/0
Madjd *et al.*[33]	UK	2016	Probiotic mixture④	10^{7} CFU d^{-1}	Women	44	45	32.20 ± 6.94	31.78 ± 6.81	44/0	45/0
Sanchez *et al.*[34]	Canada	2013	*Lactobacillus rhamnosus* CGMCC1.3724 (LPR)	3.24×10^{8} CFU d^{-1}	Adult	45	48	35.00 ± 10.00	37.00 ± 10.00	24/38	24/39
Ivey *et al.*[35]	Australia	2015	Probiotic mixture⑤	3.0×10^{9} CFU d^{-1}	Adult	39	40	65.00 ± 7.00	65.00 ± 8.00	23/16	23/17
Agerholm-Larsen *et al*(1).[36]	Denmark	2000	Probiotic mixture⑥	6×10^{7} CFU d^{-1}	Adult	16	14	38.60 ± 2.10	39.40 ± 2.10	12/4	9/5
Agerholm-Larsen *et al*(2).[36]	Denmark	2000	Probiotic mixture⑦	18×10^{8} CFU d^{-1}	Adult	14	14	37.90 ± 2.40	39.40 ± 2.10	10/4	9/5

Author	BMI		Supplementation groups				Controls			
	Supplementation groups	Control	TC	LDL	HDL	TG	TC	LDL	HDL	TG
Higashikawa *et al.*[26]	26.84 ± 0.25	27.37 ± 0.32	−4.10 ± 5.00	−3.60 ± 3.90	−3.00 ± 1.20	65.00 ± 41.50	−3.10 ± 4.00	1.70 ± 3.30	−1.20 ± 1.10	−3.90 ± 7.20
Rajkumar *et al.*[25]	—	—	−9.04 ± 2.85	−8.30 ± 2.33	5.33 ± 0.54	−7.57 ± 8.57	0.11 ± 6.82	0.37 ± 6.95	−0.44 ± 1.40	0.85 ± 25.73
Jung *et al.*[27]	28.60 ± 2.20	29.60 ± 3.60	5.00 ± 16.70	4.00 ± 20.70	−0.70 ± 9.90	19.20 ± 60.80	1.20 ± 20.20	3.10 ± 18.60	−3.90 ± 9.90	7.30 ± 61.80
Stenman *et al.*[28]	31.50 ± 2.20	31.20 ± 2.20	2.71 ± 20.88	1.16 ± 17.79	−1.55 ± 7.35	16.82 ± 46.04	1.93 ± 25.13	1.55 ± 18.56	0.39 ± 8.51	0.89 ± 35.42
Safavi *et al.*[29]	1.79 ± 0.50[a]	1.67 ± 0.39[a]	−3.87 ± 1.12	−1.16 ± 0.77	0.39 ± 2.51	−1.77 ± 3.81	0.39 ± 2.32	0.39 ± 0.46	0.00 ± 2.61	0.00 ± 3.45
Ipar *et al.*[30]	27.20 ± 4.50	26.30 ± 3.90	−8.40 ± 13.76	−6.00 ± 12.77	−2.80 ± 4.27	−7.80 ± 24.42	−14.10 ± 37.45	−4.10 ± 22.58	2.70 ± 5.67	−14.80 ± 28.05
Gobel *et al.*[31]	2.60 ± 0.50[a]	2.60 ± 0.40[a]	−8.12 ± 13.53	−6.19 ± 11.37	−1.16 ± 3.83	−5.31 ± 34.09	−3.48 ± 12.14	−1.93 ± 10.01	−1.16 ± 4.10	−6.20 ± 28.33
Szulińska *et al.*[32]	36.57 ± 5.95	36.10 ± 4.37	−16.00 ± 29.24	−4.76 ± 12.21	2.20 ± 7.01	−11.64 ± 39.43	−5.52 ± 27.52	−2.64 ± 14.55	3.16 ± 7.70	−6.04 ± 31.46
Madjd *et al.*[33]	32.14 ± 3.20	32.05 ± 3.94	−13.92 ± 11.37	−13.92 ± 11.21	2.71 ± 3.71	−15.05 ± 13.99	−11.60 ± 11.64	−11.60 ± 11.37	2.32 ± 3.33	−15.05 ± 13.02
Sanchez *et al.*[34]	33.80 ± 3.30	33.30 ± 3.20	−7.73 ± 19.34	−7.73 ± 15.47	0.00 ± 7.73	0.00 ± 26.56	−3.87 ± 19.34	−3.87 ± 15.47	3.87 ± 7.73	−8.85 ± 26.56
Ivey *et al.*[35]	31.00 ± 4.00	31.00 ± 4.00	−1.93 ± 21.04	−1.55 ± 17.05	−0.77 ± 6.38	0.89 ± 34.53	−0.39 ± 20.96	0.00 ± 17.98	0.77 ± 6.59	−5.31 ± 33.91
Agerholm-Larsen *et al*(1).[36]	30.00 ± 0.70	30.00 ± 0.90	1.93 ± 4.25	4.64 ± 0.39	−0.77 ± 1.16	−0.89 ± 7.97	2.32 ± 6.57	4.25 ± 4.25	−2.32 ± 3.48	−0.89 ± 24.79
Agerholm-Larsen *et al*(2).[36]	30.20 ± 0.70	30.00 ± 0.90	−1.16 ± 7.73	−0.39 ± 7.35	−1.55 ± 1.93	3.54 ± 21.25	2.32 ± 6.57	4.25 ± 4.25	−2.32 ± 3.48	−0.89 ± 24.79

①*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum* and *Lactobacillus bulgaricus*. ②*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and *Enterococcus faecium*. ③*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, and *Lactococcus lactis* W58. ④*Streptococcus thermophiles*, *Lactobacillus bulgaricus*, *Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12. ⑤*Lactobacillus acidophilus* La5 and *Bifidobacterium animalis* subsp. *lactis* Bb12. ⑥*Streptococcus thermophilus* and *Lactobacillus acidophilus*. ⑦*Streptococcus thermophilus* and *Lactobacillus rhamnosus*. [a] *Z* score for the BMI.

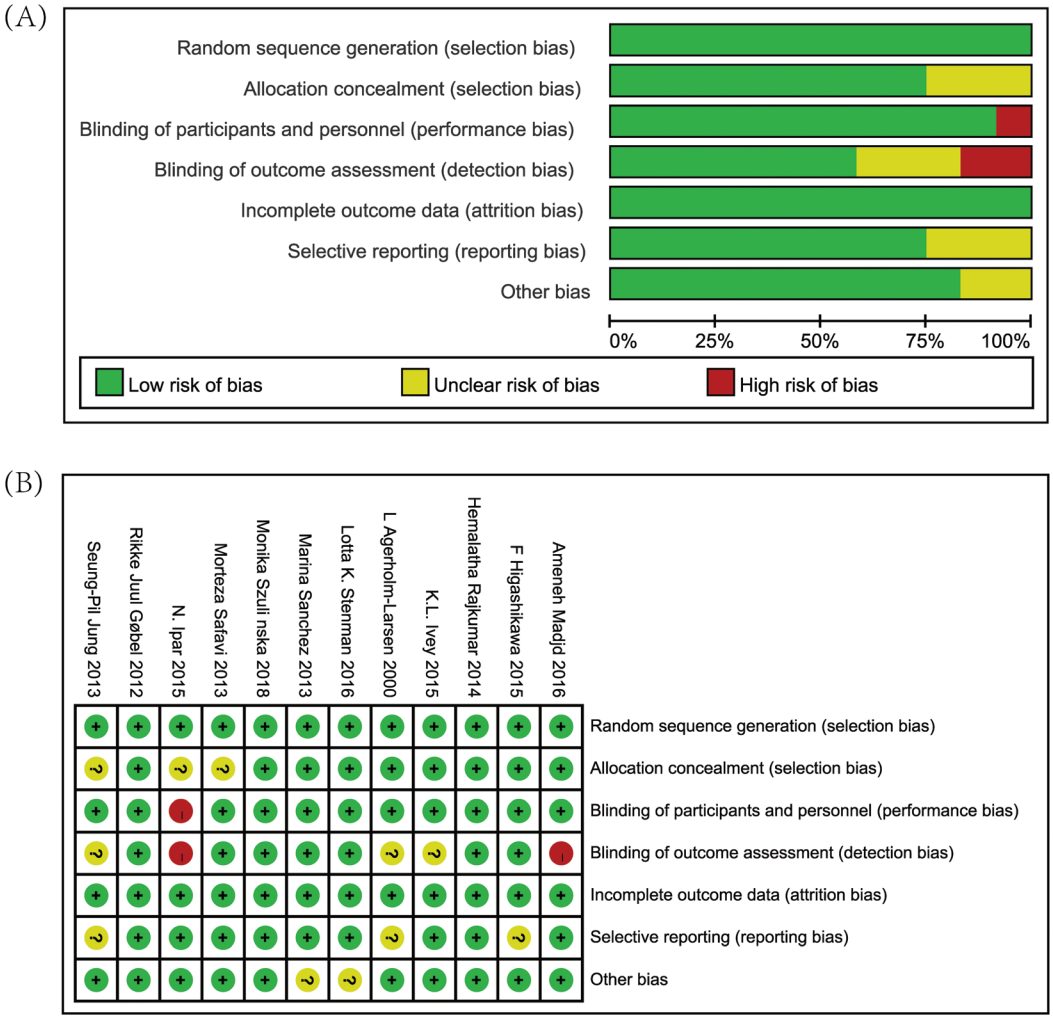

Fig. 2 Risk of within-study bias.

Table 2 Summary of the findings (SoF) with the GRADE system

Probiotic supplementation compared to no probiotic intervention for regulating blood lipid levels
Population: Overweight or obese subjects
Settings: Five studies were conducted in Asia, five studies were conducted in Europe, and the other studies were conducted in Oceania and America
Intervention: Probiotic supplementation
Comparison: No probiotic intervention

Outcome[a]	WMD (95% CI)[b]	No. of participants (studies)	Quality of the evidence comments (GRADE)
TC level	−3.04 (−4.88, −1.21) mgdL^{-1}	767 (12RCTs)	⊕⊕⊕⊕High
LDL level	−2.28 (−3.60, −0.96) mg dL^{-1}	737 (11RCTs)	⊕⊕⊕⊕High
HDL level	−0.26 (−2.39, 1.87) mg dL^{-1}	767 (12RCTs)	⊕⊕⊕○Moderate[c]
TG level	−0.86 (−2.54, 0.83) mg dL^{-1}	726 (11RCTs)	⊕⊕⊕⊕High

GRADE working group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

[a] All subjects were followed up, ranging from 6 weeks to 6 months. [b] Results for the variations in the treatments compared with the controls. [c] Downgraded by one level due to high heterogeneity. WMD: weight mean deviation; CI: confidence interval; RCT: randomized controlled trial.

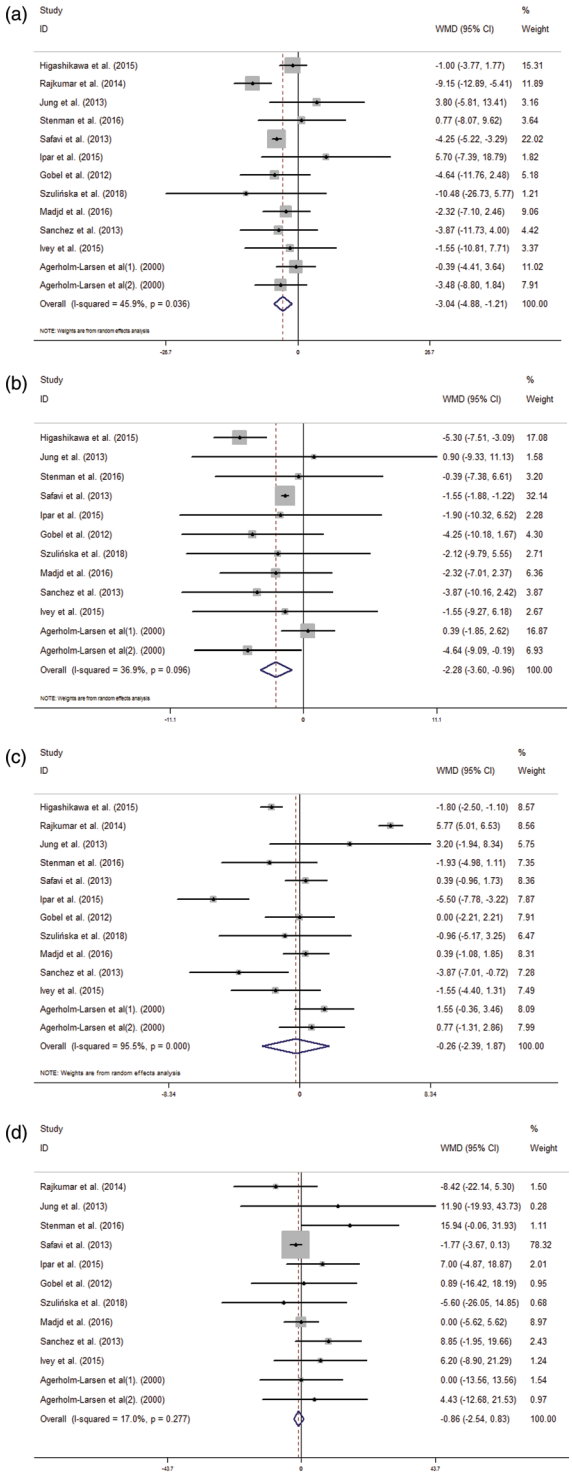

Fig. 3 (A) Forest plot of the variations in TC concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. (B) Forest plot of the variations in LDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. (C) Forest plot of the variations in HDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. (D) Forest plot of the variations in TG concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown.

in TC concentrations than the control group (Fig. 5(A)). The meta-analysis that included the variations in LDL concentrations showed that the administration of probiotics was associated with a significantly larger reduction in both the single probiotic group and the multiple probiotic group compared with that in the control group (Fig. 5(B)). The subgroup analysis that included the variations in HDL concentrations showed an overall nonsignificant effect between the single probiotic group and the multiple probiotic group (Fig. 5(C)). Moreover, the intervention group showed an increment in the variations in TG concentrations compared with the control group in the single probiotic group (Fig. 5(D)).

We divided the studies into three subgroups (adults, children/adolescents, and women) according to the subjects. The administration of probiotics was associated with a significantly larger reduction of TC and LDL concentrations in children/adolescents compared with that in the control group (Fig. 6(A) and (B)). Additionally, the subgroup analysis showed that there were no significant differences among adults, children/adolescents, and women between the probiotic and control groups in terms of the variations in HDL and TG concentrations (Fig. 6(C) and (D)).

The included articles were divided into three groups according to the probiotic species as follows: L, L + S and L + S + B (other probiotic species groups only had one study, so we could not analyse them *via* subgroup analysis). The intervention group showed a larger reduction in the variations in TC and LDL concentrations than the control group in the *Lactobacillus* + *Streptococcus* + *Bifidobacterium* group (Fig. 7(A) and (B)). However, the subgroup analysis showed that there were no significant differences among the three groups between the probiotic and control groups in terms of the variations in HDL and TG concentrations (Fig. 7(C) and (D)).

4. Discussion

Abnormal levels of blood lipids, particularly higher concentrations of TC and LDL, are major determining factors for cardiovascular disease. Additionally, the LDL or TC levels have an independent predictive effect on the risk of arteriosclerotic cardiovascular disease (ASCVD).[15,37] It has been reported that probiotic supplementation could reduce body weight, BMI and fat percentage.[38] However, it is unclear whether supplementation with probiotics is required or indeed beneficial to reduce blood lipid levels in obese or overweight people. This meta-analysis found that obese or overweight participants receiving probiotic supplementation had significantly larger reductions in TC and LDL concentrations than the control subjects. Although the specific mechanism of the effect of probiotics on TC and LDL has not yet been elucidated, several possible mechanisms have been proposed. Probiotics can bind cholesterol to reduce cholesterol absorption in the intestine.[39] Additionally, probiotics could reduce the enterohepatic circulation of bile salts, prompting the liver to mobilize more cholesterol to re-synthesize bile salts, thus reducing the cholesterol

Table 3 Subgroup analyses were performed based on the object, region and intervention

	Number of studies				Weighted mean difference (95% CI)				Heterogeneity (I^2)			
	TC	LDL	HDL	TG	TC	LDL	HDL	TG	TC	LDL	HDL	TG
Region												
Asia	5	4	5	4	−3.25 (−6.61, 0.12)	−2.80 (−5.71, 0.11)	0.34 (−3.88, 4.55)	−1.63 (−3.49, 0.23)	76.0%	73.0%	98.4%	18.6%
Europe	5	5	5	5	−2.09 (−4.46, 0.29)	−1.44 (−3.32, 0.44)	0.39 (−0.48, 1.25)	1.34 (−3.13, 5.80)	0.0%	10.4%	0.0%	0.0%
Other areas	2	2	2	2	−2.90 (−8.89, 3.10)	−2.94 (−7.82, 1.94)	−2.61 (−4.88, −0.34)	7.95 (−0.83, 16.74)	0.0%	0.0%	12.7%	0.0%
Number of probiotics												
Single	5	5	5	4	−1.23 (−3.52, 1.06)	−4.52 (−6.38, −2.66)	−1.38 (−2.83, 0.07)	9.10 (1.38, 16.81)	0.0%	0.0%	47.9%	0.0%
Multiple	7	6	7	7	−3.82 (−6.14, −1.50)	−1.53 (−1.85, −1.20)	0.21 (−2.53, 2.94)	−1.36 (−3.08, 0.37)	49.8%	0.0%	95.3%	0.0%
Probiotic species												
L	3	3	3	3	−2.38 (−7.14, 2.39)	−3.32 (−7.30, 0.65)	−0.60 (−4.05, 2.84)	7.02 (−1.78, 15.83)	5.4%	0.0%	69.1%	0.0%
L + S	1	1	1	1	−1.51 (−4.72, 1.70)	−1.74 (−6.61, 3.12)	1.19 (−0.21, 2.60)	1.71 (−8.92, 12.34)	0.0%	74.5%	0.0%	0.0%
L + S + B	5	4	5	5	−4.85 (−8.13,−1.57)	−1.55 (−1.88,−1.22)	0.12 (−3.80, 4.05)	−1.54 (−3.30, 0.22)	59.3%	0.0%	97.0%	0.0%
Subjects												
Adults	7	6	7	6	−2.52 (−5.49, 0.46)	−2.51 (−5.15, 0.13)	0.27 (−2.87, 3.42)	4.61 (−0.98, 10.20)	58.1%	58.5%	96.9%	10.1%
Children/ adolescents	3	3	3	3	−4.02 (−6.21, −1.83)	−1.56 (−1.89, −1.23)	−1.63 (−5.12, 1.86)	−1.52 (−3.39, 0.34)	10.1%	0.0%	89.9%	5.7%
Women	2	2	2	2	−2.97 (−7.56, 1.62)	−2.26 (−6.27, 1.74)	0.24 (−1.14, 1.63)	−0.39 (−5.81, 5.02)	0.0%	0.0%	0.0%	0.0%

L: *Lactobacillus*. L + S: *Lactobacillus* + *Streptococcus*. L + S + B: *Lactobacillus* + *Streptococcus* + *Bifidobacterium*.

levels.[40–42] The meta-analysis implies a stronger effect of probiotics on TC and LDL than on the TG and HDL levels, and it has been suggested that probiotics can promote the excretion of cholesterol and bile acid *via* the alteration of the pathways of cholesterol esters and lipoprotein transporters, without affecting the synthesis of hepatic cholesterol.[41,43] Therefore, the administration of probiotics may reduce the risk of ASCVD and other cardiovascular diseases in obese or overweight people.

According to the results of the subgroup meta-analysis of the variations in TC and LDL concentrations, the administration of probiotics was associated with a significantly larger reduction in their concentration in children/adolescents compared with that in the controls. At present, intestinal microflora are known to regulate blood lipid levels in two different ways. One is through the regulation of bile acid metabolism, thus affecting subsequent metabolic processes and leading to changes in blood lipid levels.[44] The other one is the production of SCFAs from indigestible polysaccharides. SCFAs such as acetate, butyrate and propionate are produced by the bacterial fermentation function as energy substrates, as well as regulators of satiety and food intake. SCFAs are also involved in the regulation of energy metabolism and insulin sensitivity in peripheral tissues by the activation of the G-protein-coupled receptors GPR41 and GPR43 on the intestinal epithelial cells.[45] The understanding of intestinal microflora in children is in its infancy; multiple endogenous and exogenous factors can influence the intestinal microflora in children, thus influencing blood lipid levels in children.[46] Probiotics are a mainstay of treatment directed at the modification of the intestinal microflora.[47] Therefore, probiotic supplementation may be more conducive to the recovery of the intestinal microflora balance in children and thus may play a role in the regulation of blood lipid levels in children.

According to the results of the meta-analysis, probiotic supplementation in obese or overweight people was associated with a significantly larger reduction in TC and LDL concentrations compared to that in the control subjects. However, when a subgroup analysis was performed according to the subjects of the studies, there were no significant differences between the probiotic and control groups in women. This result may be due to the small sample size and limited studies.

We found that the multiple probiotic groups showed a larger reduction in the variations in TC concentrations compared with the control group. However, the variations in the TC concentrations in the single probiotic group were not significantly different from those in the control group. Previous studies have found that multiple strain probiotics appear to be more feasible and effective than single strain probiotics for the prevention of necrotizing enterocolitis (NEC) and the reduction of mortality in preterm very low birth weight (PVLBW) neonates.[48] Our study also indicated that the L + S + B group showed a larger reduction in the variations in TC and LDL concentrations compared with the control group. In some findings, the intervention of lactobacilli and bifidobacteria was negatively correlated with obesity and could provide anti-obesity effects.[49–52] What's more, studies have proved that VSL#3, a freeze-dried pharmaceutical probiotic preparation containing all three strains of *Lactobacillus*, *Bifidobacterium* and *Streptococcus*, could attenuate obesity and diabetes *via* the modulation of the intestinal microflora, as well as the improvement of NAFLD.[53,54] Therefore, we considered that in the regulation of blood lipid levels, multiple strain probiotics appear to be more effective than single strain probiotics. Simultaneously, there was an increment in the variations in the TG concentrations in the single probiotic group. This

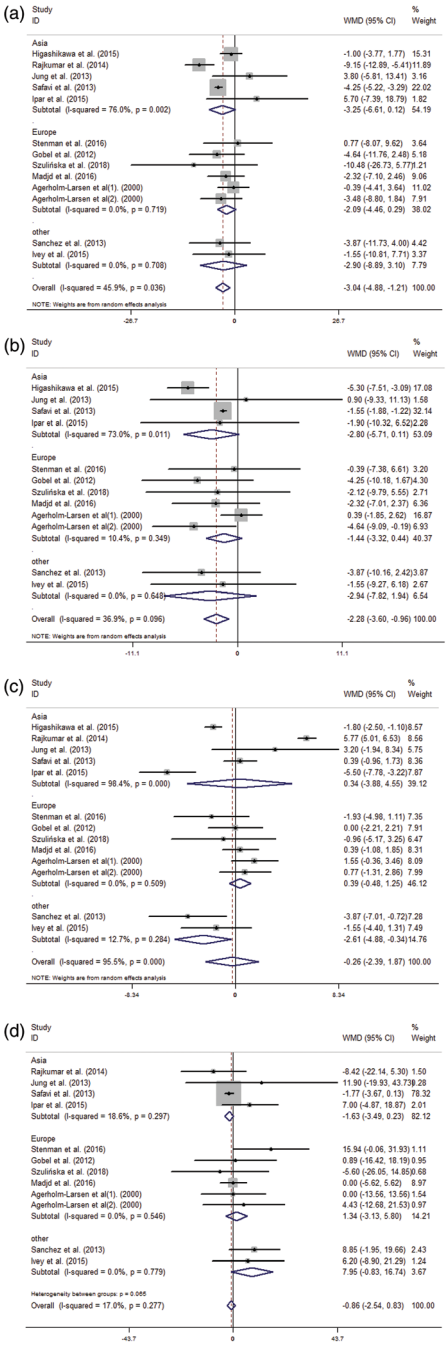

Fig. 4 (A) Forest plot of the variations in TC concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies from Asia, Europe and others. (B) Forest plot of the variations in LDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies from Asia, Europe and others. (C) Forest plot of the variations in HDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies from Asia, Europe and others. (D) Forest plot of the variations in TG concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies from Asia, Europe and others.

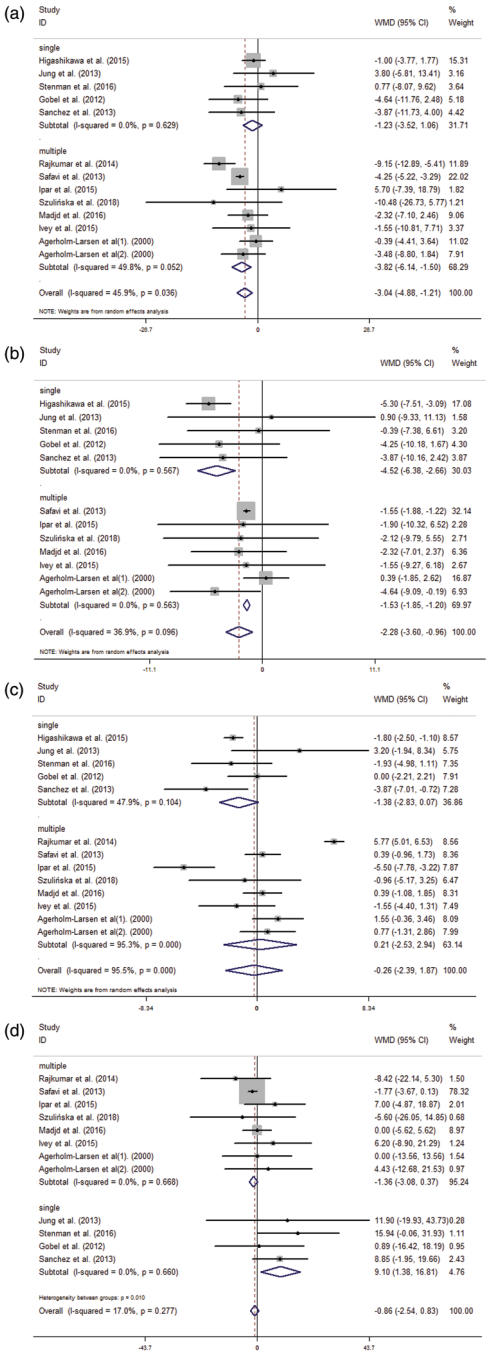

Fig. 5 (A) Forest plot of the variations in TC concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with single and multiple probiotic groups. (B) Forest plot of the variations in LDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with single and multiple probiotic groups. (C) Forest plot of the variations in HDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with single and multiple probiotic groups. (D) Forest plot of the variations in TG concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with single and multiple probiotic groups.

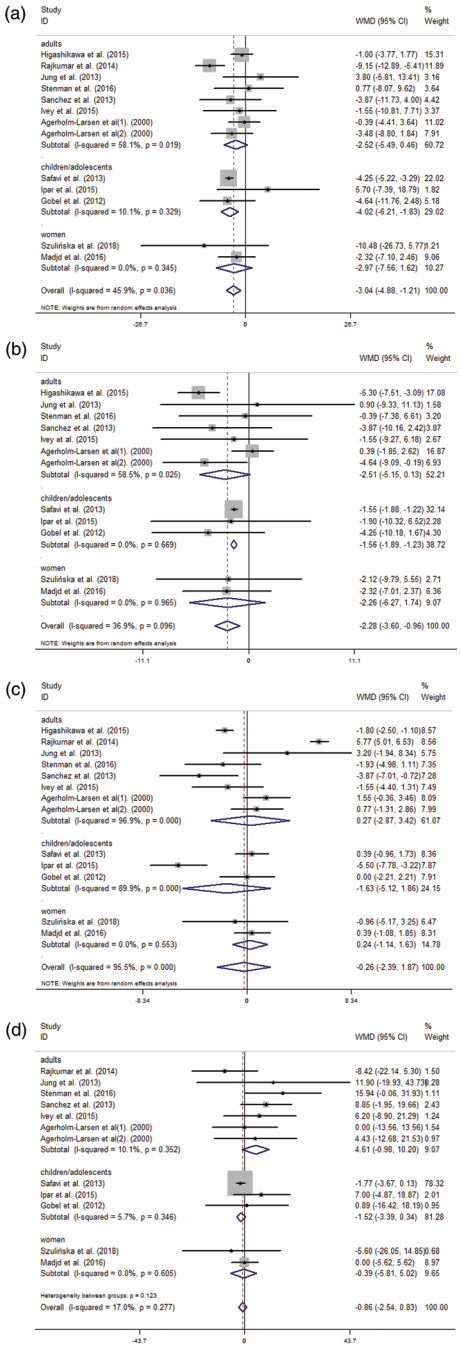

Fig. 6 (A) Forest plot of the variations in TC concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with adults, children/adolescents and women. (B) Forest plot of the variations in LDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with adults, children/adolescents and women. (C) Forest plot of the variations in HDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with adults, children/adolescents and women. (D) Forest plot of the variations in TG concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with adults, children/adolescents and women.

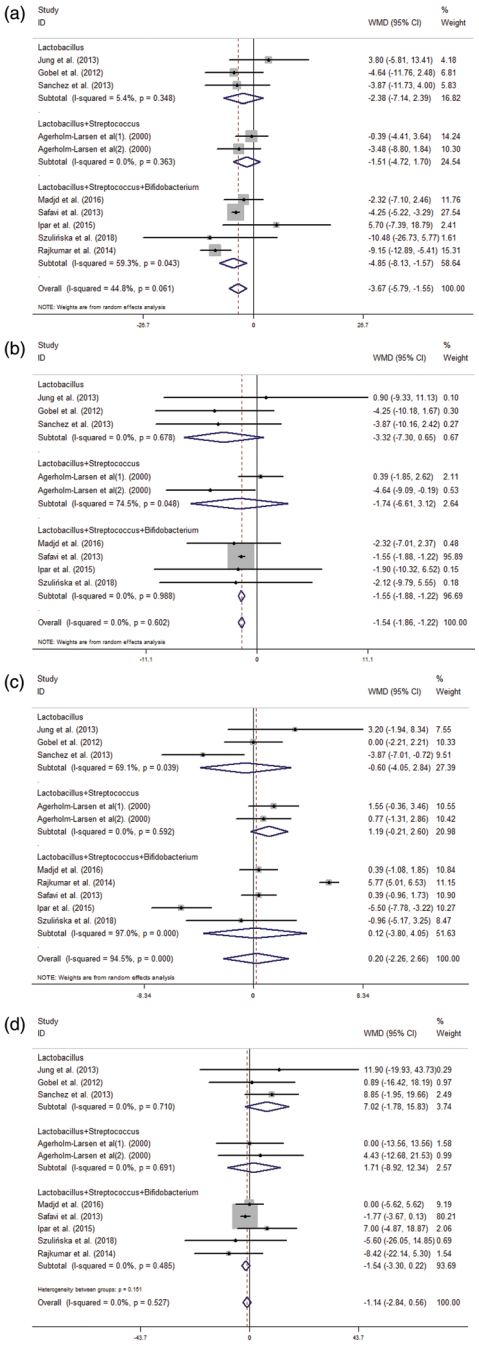

Fig. 7 (A) Forest plot of the variations in TC concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with L, L + S and L + S + B. (B) Forest plot of the variations in LDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with L, L + S and L + S + B. (C) Forest plot of the variations in HDL concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with L, L + S and L + S + B. (D) Forest plot of the variations in TG concentrations in the probiotics *vs.* control groups; weighted mean differences with 95% confidence interval and weight percentage are shown. Subtotals are for the studies with L, L + S and L + S + B.

result could be due to the small sample size and limited studies because wider confidence intervals were observed. Consequently, follow-up clinical trials and a supporting mechanistic theory are still needed.

According to the results of the meta-analysis, a large degree of heterogeneity was observed for the variations in HDL concentrations. We therefore performed an analysis to identify the source of heterogeneity, and the heterogeneity was lower in the European group when grouped by geographical study area. Therefore, we considered that different geographical study areas may be the sources of heterogeneity in the associated studies. A large degree of heterogeneity was observed in the Asian group, which may be a result of the thousands of ethnic groups in Asia, accounting for approximately 80% of the world's total. The physiological and biochemical levels among different Asian races may be different. This hypothesis requires additional data from large clinical trials on Asian populations.

This study has some limitations. A few studies included more than one probiotic intervention, and we chose to include the intervention groups that received the highest daily dose over the longest time period, as we considered these groups more likely to experience an effect on the blood lipid levels and related outcomes. This meta-analysis included only quantitative results with specific values, and studies with qualitative results were not included. Most importantly, there were fewer studies from Asia, possibly because there are more races in Asia and large differences between races, and we found that the heterogeneity was higher in the Asian group when a subgroup analysis was conducted according to the geographical study area. The effect of probiotics on the variations in HDL concentrations in this meta-analysis should be interpreted with caution. Because this is a meta-analysis of randomized controlled trials, the quality of this study is affected by the quality of data from the original publications. Although randomized trials are considered valid compared to other studies, true intervention effects could be biased by limited methodological quality.[15]

5. Conclusion

In summary, this meta-analysis found that probiotic supplementation could improve lipid metabolism, particularly by reducing TC and LDL concentrations in obese or overweight people. Considering several limitations observed in this meta-analysis and previous clinical trials, additional data from large clinical trials are required to confirm the efficacy and safety of probiotics for the regulation of blood lipid levels in obese or overweight people.

Author contributions

BL, WC and SY designed the study; SY, ZT and ML performed the study; SY and ZT analyzed the data and drafted the manuscript; SY and ML participated in amending the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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