ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

Nutrición Hospitalaria

Revisión

The effect of probiotics on serum lipid levels in non-obese healthy adults with hyperlipidemia: a systematic review and meta-analysis of randomized controlled trials

El efecto de los probióticos sobre los niveles de lípidos séricos en adultos sanos no obesos con hiperlipidemia: revisión sistemática y metaanálisis de ensayos controlados y aleatorizados

Kaiwen Sun, Zhenzhu Liu, Hongyan Wang

Department of Cardiovascular Medicine. The Second Hospital of Dalian Medical University. Dalian Medical University. Dalian, Liaoning. People's Republic of China

Abstract

Introduction: probiotics might have a potential effect to manage serum lipid levels as nutraceuticals.

Objective: this systematic review was conducted to explore whether probiotics have an efficient result in non-obese healthy adults with hyperlipidemia.

Methods: PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science were searched for randomized controlled trials (from their commencement to January 2021). This meta-analysis was performed by Review Manager 5.3 and STATA 15.1. Changes in serum lipid levels after the intervention were used to evaluate the effect of the probiotics, which were expressed as the weighted mean difference (WMD) with a 95 % confidence interval (CI).

Results: a total of 16 studies, which could be regarded as 21 independent trials with 1429 participants, were included in this meta-analysis following our inclusion criteria. It could be observed that probiotics could significantly lower total cholesterol (TC) (WMD: -0.34 mmol/L, 95 % CI: -0.45 to -0.23 mmol/L; $p < 0.001$, $I^2 = 73.9$ %) and low-density lipoprotein cholesterol (LDL-C) (WMD: -0.26 mmol/L, 95 % CI: -0.36 to -0.17 mmol/L; $p < 0.001$, $I^2 = 79.0$ %) levels in non-obese healthy adults with hyperlipidemia, while no significant effect between the probiotic intervention and control groups was observed on high-density lipoprotein cholesterol (HDL-C) (WMD: 0.00 mmol/L, 95 % CI: -0.02 to 0.02 mmol/L; $p = 0.001$, $I^2 = 56.6$ %) and triglyceride (TG) (WMD: -0.08 mmol/L, 95 % CI: -0.18 to 0.01 mmol/L; $p = 0.003$, $I^2 = 52.4$ %) levels.

Conclusion: this systematic review showed that probiotics may provide a promising way to reduce serum lipid levels in non-obese healthy adults with hyperlipidemia, but their specific effect still needs more clinical experiments to be proven.

Keywords:

Hyperlipidemia. Non-obese healthy adult. Probiotics. Serum lipids.

Received: 10/05/2021 • Accepted: 30/10/2021

The protocol was registered at PROSPERO (registration number: CRD42020176302).

Author contributions: all authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Kaiwen Sun and Zhenzhu Liu. The disagreements were solved by Hongyan Wang. The first draft of the manuscript was written by Kaiwen Sun and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements: this research was supported by the Second Hospital of Dalian Medical University. The assistance of the staff is gratefully acknowledged.

Sun K, Liu Z, Wang H. The effect of probiotics on serum lipid levels in non-obese healthy adults with hyperlipidemia: a systematic review and meta-analysis of randomized controlled trials. Nutr Hosp 2022;39(1):157-170

DOI: http://dx.doi.org/10.20960/nh.03688

Correspondence:

Hongyan Wang. Department of Cardiovascular Medicine. The Second Hospital of Dalian Medical University. Dalian Medical University. 467 Zhongshan Rd, Shahekou district. Dalian, Liaoning. People's Republic of China
e-mail: 2577223926@qq.com

Resumen

Introducción: los probióticos podrían tener efecto para controlar los niveles de lípidos séricos como nutracéuticos.

Objetivo: esta revisión sistemática se realizó para explorar si los probióticos tienen un resultado eficiente en adultos sanos no obesos con hiperlipidemia.

Métodos: se realizaron búsquedas de ensayos controlados aleatorios en PubMed, Embase, el Registro Cochrane Central de Ensayos Controlados y Web of Science (desde su inicio hasta enero de 2021). Este metanálisis fue realizado mediante Review Manager 5.3 y STATA 15.1. Los cambios de los niveles de lípidos séricos después de la intervención se utilizaron para evaluar el efecto de los probióticos, que se expresaron como la diferencia de medias ponderada (DMP) con un intervalo de confianza (IC) del 95 %.

Resultados: en este metaanálisis se incluyeron un total de 16 estudios, que podrían considerarse 21 ensayos independientes con 1429 participantes, siguiendo nuestros criterios de inclusión. Se pudo observar que los probióticos podían reducir significativamente el colesterol total (CT) (DMP: -0,34 mmol/L, IC del 95 %: -0,45 a -0,23 mmol/L; $p < 0,001$, $I^2 = 73,9$ %) y el colesterol de lipoproteínas de baja densidad (C-LDL) (DMP: -0,26 mmol/L, IC del 95 %: -0,36 a -0,17 mmol/L; $p < 0,001$, $I^2 = 79,0$ %) en los adultos sanos no obesos con hiperlipidemia, mientras que no hubo efectos significativos entre los grupos de intervención y de control en el colesterol de lipoproteínas de alta densidad (HDL-C) (DMP: 0,00 mmol/L, IC del 95 %: -0,02 a 0,02 mmol/L; $p = 0,001$, $I^2 = 56,6$ %) y los triglicéridos (TG) (DMP: -0,08 mmol/L, IC del 95 %: -0,18 a 0,01 mmol/L; $p = 0,003$, $I^2 = 52,4$ %).

Conclusión: esta revisión sistemática manifestó que los probióticos podrían suponer una forma prometedora de reducir los niveles de lípidos séricos en los adultos sanos no obesos con hiperlipidemia, pero se necesitan más experimentos clínicos para demostrar su efecto específico.

Palabras clave:

Hiperlipidemia. Adulto sano no obeso. Probióticos. Lípidos séricos.

INTRODUCTION

Hyperlipidemia indicates abnormally elevated levels of lipids or lipoproteins due to abnormal fat metabolism or function, and the diagnostic standard of hyperlipidemia has been illustrated in the related guidelines (1,2). Hyperlipidemia can have a direct impact on the structure and function of vessels and the heart, leading to various cardiovascular complications (3,4). Obesity refers to excessive total and/or local fat content and abnormal distribution caused by genetic and environmental factors, and a link has been found with hyperlipidemia by lipid biomarkers according to previous research (5-7), which might provide a new idea to treat serum lipid levels in these obese individuals. There is likewise some people with other diseases that affect serum lipid levels, such as diabetes, hypothyroidism, Cushing's disease, and so on. For these kinds of patients, their primary disease may be treated to maintain serum lipid levels at a normal range (8). However, for non-obese healthy people with hyperlipidemia, which means that none of the situations above is applicable, the cause of their rising levels of serum lipids and how to control their serum lipids appropriately needs further exploration. At present, statins have a high effect in lowering LDL-C and are widely used in the clinical setting. Although statins are generally well tolerated, they are linked to numerous adverse effects like gastrointestinal events, respiratory infections, headaches, and muscle-related symptoms, including bilateral muscle pain, weakness, and inflammation. A long-term application will cause liver dysfunction, etc. It is also found that there is an increased risk of glioma with statin use according to a recent study (9). For those with hyperlipidemia who are unable to tolerate statins and those who have potential indications for non-pharmacological treatment of hyperlipidemia, it is critical to find a safe and effective way to lower serum lipid levels.

In recent years, people are more and more interested in using nutraceuticals to manage serum lipid levels. As one of the nutraceuticals, probiotics are a type of living microorganism that comes from the host and promotes the health of the host with safety and rarely side effects. Probiotics can adjust the microbial community in the intestinal tract, regulating the immune system and improving the anti-oxidative system by producing microbial components and metabolites (10-12). With the advantage of probiotics, there are numerous clinical trials (13-28) assessing the use of probiotics for the treatment of hyperlipidemia. Some systematic reviews (29-33) have supported their hyperlipidemia role built on randomized controlled trials, though their results have some limitations. For example, the studies they included in their reviews are often evaluating other primary diseases, making their results less rigorous. One of the systematic reviews (33) showed the role of probiotics in obese or overweight patients with hyperlipidemia, and the rest did not consider the factor of obesity, so there are no special reviews showing the effect of probiotics in non-obese patients, which means a further evaluation needs to be carried out. A large number of studies can potentially be missed if literature searches are restricted to English-only sources; interventions are not serious in some of the trials included before, such as the use of soy bean, which could also lower serum lipid levels by bioactive peptides probably according to previous research (10,34,35). As a consequence, it will influence

the facticity of the results. Besides, the intervention measures or subjects are relatively limited.

Therefore, a systematic review and meta-analysis was conducted to evaluate the effect of probiotics on non-obese healthy adults with hyperlipidemia.

MATERIALS AND METHODS

PROTOCOL

This meta-analysis followed the Preferred Reporting Items for Systematic Meta-Analysis (PRISMA) statement (36). The protocol was registered at PROSPERO (registration number: CRD42020176302).

SEARCH STRATEGY

Several electronic databases were searched for available research studies by the authors: PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science. All of the databases above were systematically searched from their commencement to January 2021 for relevant literature. A manual search of references of the included articles and reviews was performed for additional omitted studies. The specific search strategies were as follows:

((((“Hyperlipidemias”[Mesh]) OR ((((((((((((((((((Hypercholesterolemia[Title/Abstract]) OR Hyperlipemia[Title/Abstract]) OR Hyperlipemias[Title/Abstract]) OR Hyperlipidemia[Title/Abstract]) OR Lipidemia[Title/Abstract]) OR Lipidemias[Title/Abstract]) OR Lipemia[Title/Abstract]) OR Lipemias[Title/Abstract]) OR Cholesterol[Title/Abstract]) OR Triglycerides[Title/Abstract]) OR TGs[Title/Abstract]) OR HDL-cholesterol[Title/Abstract]) OR HDL-C[Title/Abstract]) OR LDL-cholesterol[Title/Abstract]) OR LDL-C[Title/Abstract]) OR lipid profile[Title/Abstract]) OR plasma lipids[Title/Abstract]) OR serum lipids[Title/Abstract])))) AND ((“Probiotics”[Mesh]) OR ((((((((((probiotic[Title/Abstract]) OR culturelle[Title/Abstract]) OR lactobacillus[Title/Abstract]) OR bifidobacterium[Title/Abstract]) OR enterococcus[Title/Abstract]) OR streptococcus[Title/Abstract]) OR clostridium butyricum[Title/Abstract]) OR bacillus[Title/Abstract]) OR yogurt[Title/Abstract]) OR yoghurt[Title/Abstract]) OR fermented milk[Title/Abstract])))) AND (((randomized controlled trial[Publication Type]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]).

SELECTION CRITERIA

The references retrieved were evaluated by two independent investigators (Sun and Liu) by scanning the title and abstract according to the inclusion criteria, and then screening again by reading the full text. If there were any disagreements, they would be resolved by consensus and asking the third party (Wang) to resolve the disagreements, or by contacting the original author of the article if necessary. The inclusion criteria and the exclusion criteria are shown in table I.

DATA EXTRACTION

The following data were collected and organized from the eligible studies by two independent investigators (Sun and Liu): the name of the first author; publication year; country; study design; characteristics of enrolled subjects (number, age, gender, race and BMI); interventions including strain, dose, form of probiotics, and duration; and baseline TC levels.

Table I. The inclusion criteria and exclusion criteria

The inclusion criteria	The exclusion criteria
Body mass index (BMI) < 30 kg/m^2	Obesity (BMI ≥ 30 kg/m^2)
No other disease except hyperlipidemia	Participants with any other diseases, like diabetes, coronary disease, etc.
Fasting serum TC levels ≥ 5.2 mmol/L or fasting serum LDL-C levels ≥ 3.4 mmol/L or fasting serum TG levels ≥ 2.3 mmol/L or fasting serum HDL-C < 1.0 mmol/L according to the guideline (2)	Fasting serum lipids did not meet the criteria on the left or the subject had taken other lipid-lowering drugs recently
Experiment groups: probiotic products	Treated by other ways affecting serum lipid
Control groups: placebo	Without a control group
Outcomes: change in TC, LDL-C, HDL-C and TG levels	No specific results
A randomized controlled trial	Not a randomized controlled trial
All above 18 years of age	Pregnant women, children, infants, etc.

QUALITY ASSESSMENT

The quality of the included studies and the risk of bias were assessed by two independent investigators (Sun and Liu) according to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0, which contains seven criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. These seven criteria were rated as "low risk", "unclear risk", or "high risk" depending on the characteristics of each criterion reported in the study.

STATISTICAL METHODS

The effect of the probiotics on serum lipid levels was measured by the weighted mean difference (WMD) between the intervention and the control groups at follow-up. Before the meta-analysis was performed, the lipid levels in mg/dL and mg/L were all converted into mmol/L, and standard errors or confidence intervals (CIs) were converted to standard deviation (SD) for the analyses. The changes in serum TC, LDL-C, HDL-C and TG of subjects in each group in the selected references were extracted and expressed in the form of mean ± SD (x ± s). As several included studies did not offer the net changes in SD of serum lipids from baseline values, we calculated the SD change by the following formula (1):

$$\text{SD change} = \sqrt{[(\text{SD pre-treatment})^2 + (\text{SD post-treatment})^2 - (2 * \text{coefficient} * \text{SD pre-treatment} * \text{SD post-treatment})]}$$

The coefficient was taken as 0.5 according to other eligible studies that provided the SD at baseline, final SD, and SD change.

This meta-analysis was performed using the STATA 15.1 software (Stata Corp., College Station, TX). The heterogeneity of the studies was evaluated by Cochran's Q statistic and I^2 test. Studies were considered homogeneous if the p-value of the Q-test was > 0.1 or the I^2 value was < 50 %; else they would be considered heterogeneous. We chose a random effects model to analyze data.

To further explore the other factors which could influence the results, a series of subgroup analyses was performed by Review Manager 5.3 (Cochrane Collaboration, 2014), including baseline serum lipid levels, age, intervention duration, strain, form of probiotics, type of strains, and study type, with $p < 0.05$ considered statistically significant. The sensitivity analysis was done by using the leave-one-out method to examine the impact of each study on the results.

Publication bias was evaluated using funnel plots and statistically assessed by Egger's regression test as performed by the STATA 15.1 software (Stata Corp., College Station, TX). If the funnel was asymmetric, or the Egger's test p-value was < 0.05, publication bias would be considered to exist.

RESULTS

DESCRIPTION OF STUDIES

A total of 2103 studies were retrieved on the basis of the search terms and search strategies described above. There were 1285 studies to be screened by titles and abstracts since 818 studies were removed because of repetition. Of the 1285 studies, 51 studies remained to be read full-text for further exclusion. Finally, 16 studies (13-28) were selected with the inclusion criteria (Fig. 1). Of the 16 studies, 5 studies (13,17,18,20,23) which applied more than one intervention duration were regarded as multiple independent trials. Thus, a total of 21 independent trials with 1429 participants were included in this meta-analysis. All the participants included in the trials met the diagnostic conditions of hyperlipidemia. The characteristics of each study are shown in table II.

QUALITY ASSESSMENT

The Cochrane Risk of Bias tool was used to assess the methodological quality of the included studies, which are presented in figure 2 and figure 3.

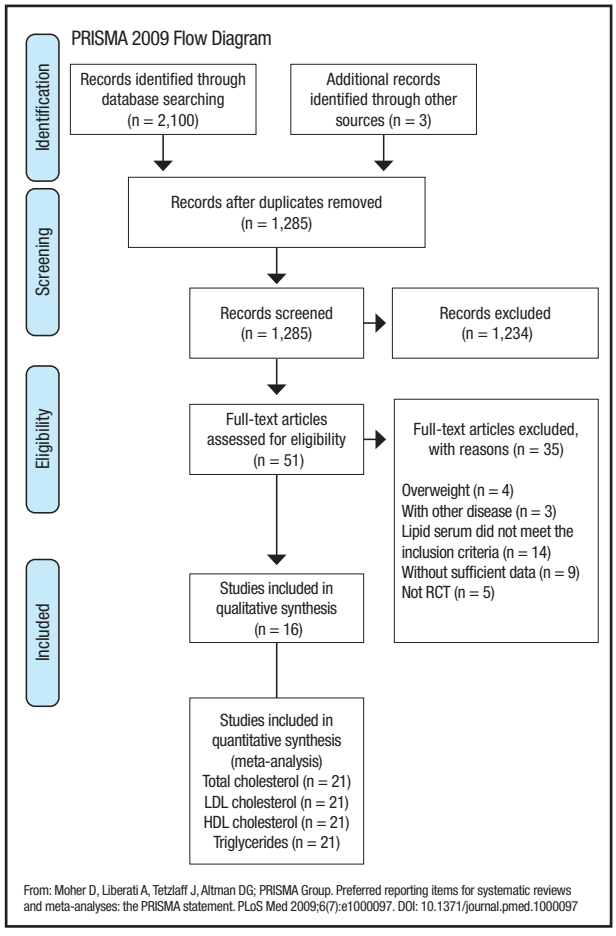

Figure 1.
Study selection process.

Table II. The characteristics of each study

The name of the first author	Publication years	Country	Study design	Subject number	Subject age (years)	Subject gender (M/F)	Subject race	Subject BMI (kg/m^2)	Intervention strain	Intervention dose	Intervention form	Intervention duration (weeks)	Baseline TC (mmol/L)
Agerbaek	1995	Denmark	RCT, DB, P	57	44.0	57/0	Western	24.2	*E. faecium* *S. thermophilus*	200 mL/d	Fermented milk	a = 3, b = 6	5.98
Ahn	2015	Korea	RCT, DB, P	92	53.4	30/62	Asian	24.8	*L. curvatus* HY7601 *L. plantarum* KY1032	2 g/d	Capsule	12	5.32
Ataie-Jafari	2009	Iran	RCT, SB C	14	50.5	4/10	Asian	26.1	*L. acidophilus* *B. lactis*	300 g/d	Yogurt	6	5.68
Bertolami	1999	Brazil	RCT, DB, C	32	55.7	11/21	Western	< 30	*E. faecium* *S. thermophilus*	200 g/d	Fermented milk	8	6.41
Fuentes	2012	Spain	RCT, DB, P	60	18-65	NM	Western	26.0	*L. plantarum* (CECT 7527 7528 7529)	1.2 x 10^9 CFU daily	Capsule	a = 6, b = 12	6.45
Fuentes	2016	Spain	RCT, DB, P	60	51.8	34/26	Western	26.2	*L. plantarum* (CECT 7527 7528 7529)	1.28-3.01 x 10^9 CFU daily	Capsule	a = 6, b = 12	6.45
Hatakka	2008	Finland	RCT, DB, C	38	42.0	38/0	Western	24.9	*L. rhamnosus* LC 705 *P. freudenreichii* JS	2.0 x 10^{10} CFU twice a day	Capsule	4	6.20
Jones	2012	Canada	RCT, DB, P	127	49.1	55/72	Western	27.2	*L. reuteri* NCIMB 30242	2.0 x 10^9 CFU twice a day	Capsule	a = 6, b = 9	6.13
Lewis	2005	United Kingdom	RCT, DB, C	79	47.0	28/51	Western	27.8	*L. acidophilus*	3.0 x 10^{10} CFU 3 times a Day	Capsule	6	6.63
Naruszewicz	2002	Sweden	RCT, DB, P	36	42.3	18/18	Western	25.3	*L. plantarum* 299v	5.0 x 10^7 CFU/mL 400 mL/d	drinking	6	5.55
Ooi	2010	Malaysia	RCT, DB, P	32	34.2	18/14	Asian	23.0	*L. acidophilus* CHO-220	4 capsule a day	Capsule	a = 6, b = 12	5.70

(Continues on next page)

Table II (Cont.). The characteristics of each study

The name of the first author	Publication years	Country	Study design	Subject number	Subject age (years)	Subject gender (M/F)	Subject race	Subject BMI (kg/m²)	Intervention strain	Intervention dose	Intervention form	Intervention duration (weeks)	Baseline TC (mmol/L)
Park	2020	Korea	RCT, DB, P	70	48.3	24/46	Asian	26.1	*L. plantarum* Q180	2 capsule a day	Capsule	12	5.20
Rerksuppaphol	2015	Thailand	RCT, DB, P	64	49.3	22/42	Asian	26.2	*L. acidophilus* *B. bifidum*	10^9 CFU 3 times a day	Capsule	6	6.04
Simons	2006	Australia	RCT, DB, P	44	51.4	16/28	Western	25.8	L. fermentum	2 x 10^9 CFU 2 capsules twice a day	Capsule	10	6.25
Tan	2017	China	RCT, SB, P	93	56.1	24/69	Asian	25.5	*L. paracasei* N1115	NM	Capsule	12	5.76
Xiao	2003	Japan	RCT, SB, P	32	43.9	32/0	Asian	< 30	*B. longum* strain BL1	300 mL/d	Yogurt	4	6.32

RCT: randomized controlled trial; DB: double blind; SB: single blind; P: parallel design; C: crossover design; NM: not mentioned; E.: Enterococcus; *S.:* Streptococcus; *L.:* Lactobacillus; *B.:* Bifidobacterium; *P.:* Propionibacterium; *CFU: colony forming units.*

Most of the 16 studies were of low risk and high quality. In the generation of random sequence, 4 studies (14,23,26,27) did not describe specific methods, while 6 studies (13,15,17,21,23,28) did not specifically describe allocation concealment; with regards to the blinding method, there were 13 double-blind studies [13,14,16-26] involving researchers and subjects, and 3 single-blind studies [15,27,28]. In the description of the outcome, 7 studies (15,16,18,20,25,26) used a blinding method, 1 (28) did not use any, and the rest failed to explain this. In terms of follow-up bias and reporting bias, all studies provided comprehensive information on follow-up or exclusion, while 5 studies (15,19-21,28) did not fully explain the selective reporting of research results, and 1 study (27) had reporting bias. For other biases, 3 articles (13,14,23) did not mention any.

EFFECT OF THE PROBIOTICS ON SERUM LIPID LEVELS

A total of 21 independent studies with 1429 subjects for changes in TC, LDL-C, HDL-C and TG were selected in this meta-analysis. It could be observed that probiotics could significantly lower TC (WMD: -0.34 mmol/L, 95 % CI: -0.45 to -0.23 mmol/L) and LDL-C (WMD: -0.26 mmol/L, 95 % CI: -0.36 to -0.17 mmol/L) levels in non-obese healthy adults with hyperlipidemia, while no significant effect between the probiotic intervention and control groups was observed on HDL-C (WMD: 0.00 mmol/L, 95 % CI: -0.02 to 0.02 mmol/L) and TG (WMD: -0.08 mmol/L, 95 % CI: -0.18 to 0.01 mmol/L) levels.

As regards heterogeneity, it was shown that TC and LDL-C had a higher heterogeneity ($p < 0.001$, $I^2 = 73.9$ % and $p < 0.001$, $I^2 = 79.0$ %), while HDL-C and TG had moderate heterogeneity ($p = 0.001$, $I^2 = 56.6$ % and $p = 0.003$, $I^2 = 52.4$ %). The detailed description results are shown in the forest map below (Figs. 4 to 7).

SUBGROUP AND SENSITIVITY ANALYSIS

Subgroup analyses were performed to evaluate the effect on baseline serum lipid levels, age, intervention duration and strains, form of probiotics, type of strains, and study type. It could be observed that the probiotics could significantly lower serum lipid levels in the TC and LDL-C groups when added in the yogurt or fermented milk, and the types of strain were *Enterococcus* and *Streptococcus*. It was also seen in the LDL-C group that probiotics could lower LDL-C levels when concentration is 3.4-4.1 mmol/L, and might be more effective on younger people (< 50 years old), with longer duration of treatment (> 6 weeks) and with *Lactobacillus* plus *Bifidobacterium* and *Enterococcus* plus *Streptococcus*. For the TG group, the heterogeneity might originate from intervention duration, the form of probiotics, and the type of strains. The detailed description results are shown below (Tables III to VI).

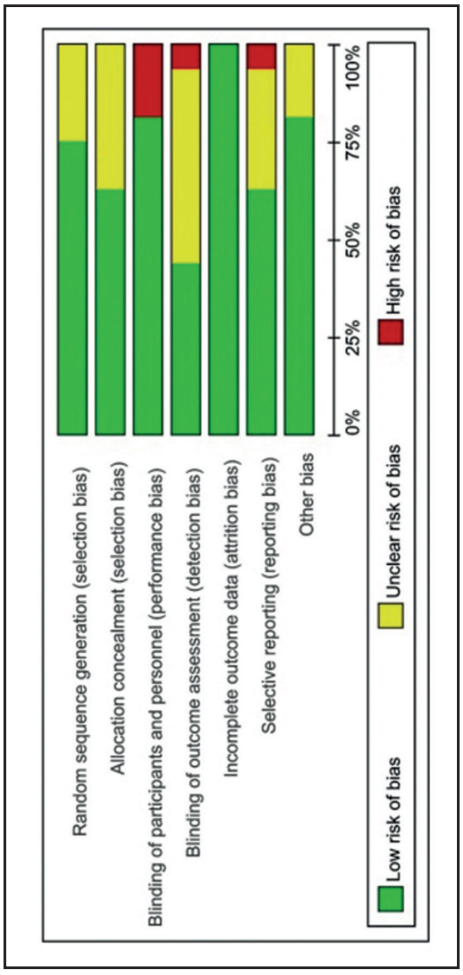

Figure 2.

Risk-of-bias graph showing the authors' judgements about each risk-of-bias item presented as percentages across all the included studies.

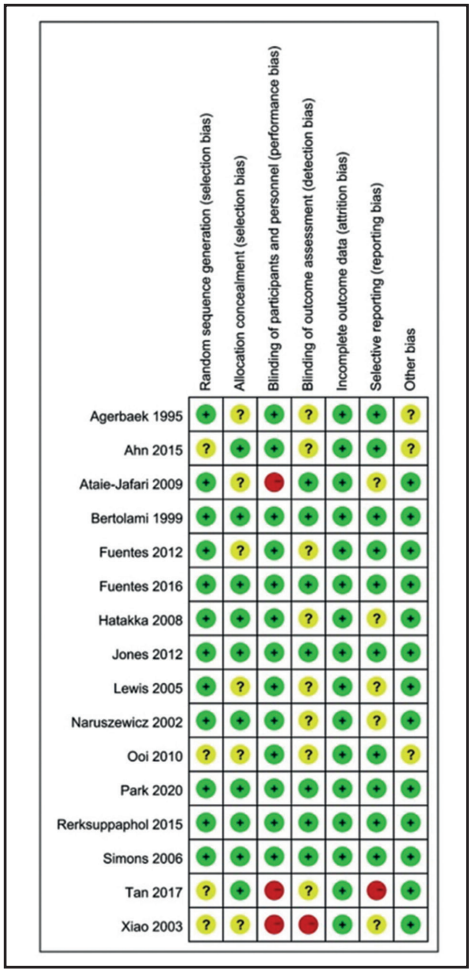

Figure 3.

Risk of bias summary showing the authors' judgements about each risk-of-bias item for each included study.

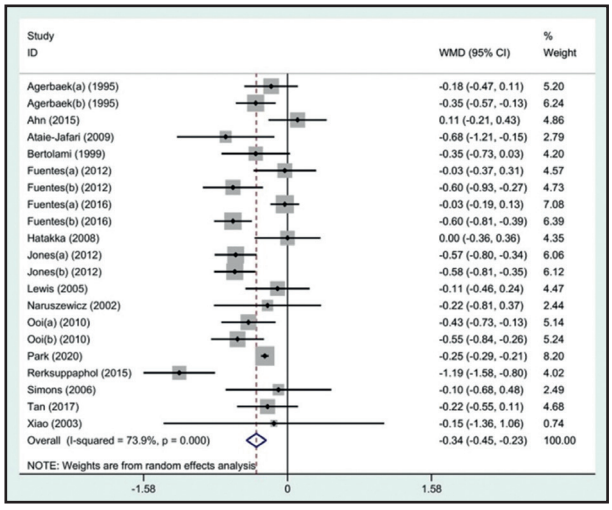

Figure 4.

Meta-analysis of the effects of probiotics compared to control changes in TC.

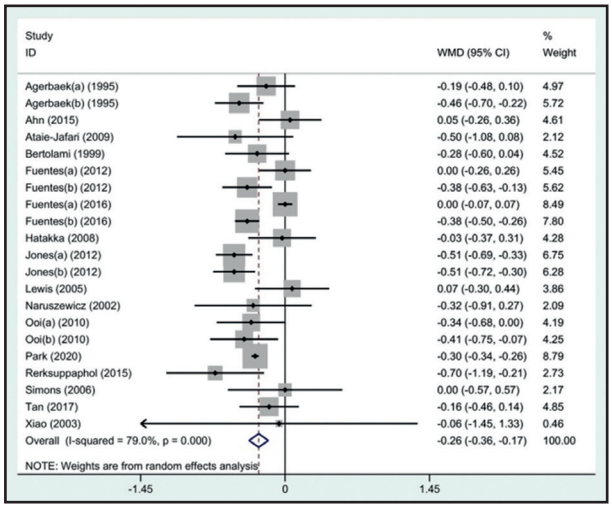

Figure 5.

Meta-analysis of the effects of probiotics compared to control changes in LDL-C.

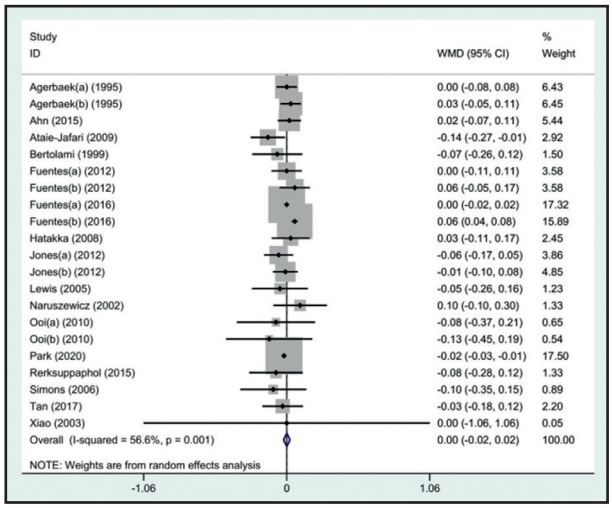

Figure 6.

Meta-analysis of the effects of probiotics compared to control changes in HDL-C.

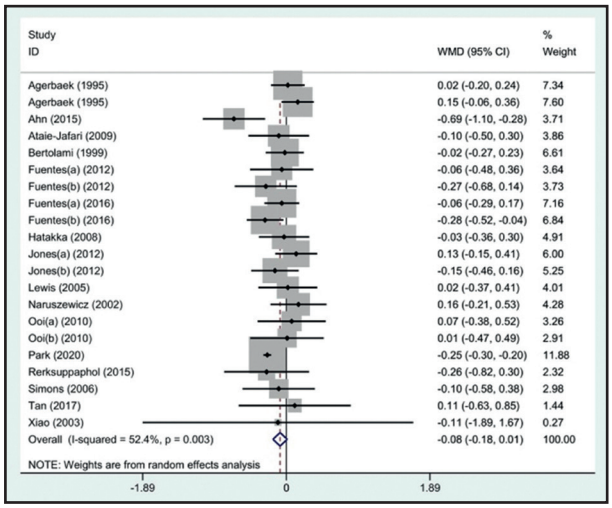

Figure 7.

Meta-analysis of the effects of probiotics compared to control changes in TG.

Table III. The subgroup analysis of TC

	Group	Number of study	Weighted mean difference (95 % CI) mmol/L	p value	I^2 %
Baseline serum lipid levels	5.2-6.2 mmol/L	12	-0.41 (-0.56, -0.26)	< 0.00001	77
	≥ 6.2 mmol/L	9	-0.24 (-0.44, -0.03)	0.02	71
Age	< 50 years old ≥ 50 years old	12 7	-0.40 (-0.54, -0.25) -0.26 (-0.50, -0.01)	< 0.00001 0.04	75 77
Intervention duration	≤ 6 weeks	12	-0.33 (-0.52, -0.14)	0.0008	76
	> 6 weeks	9	-0.37 (-0.53, -0.21)	< 0.00001	74
Intervention strains	Single strain	14	-0.35 (-0.47, -0.22)	< 0.00001	71
	Multiple strain	7	-0.36 (-0.65, -0.07)	0.02	81
Form of probiotics	Capsule	15	-0.35 (-0.48, -0.21)	< 0.00001	81
	Yogurt/Fermented milk	5 1	-0.33 (-0.48, -0.18) -0.22 (-0.81, 0.37)	< 0.0001 0.46	0 NA
Type of strain	*Lactobacillus*	14	-0.32 (-0.44, -0.20)	< 0.00001	74
	Bifidobacterium	1	-0.15 (-1.36, 1.06)	0.81	NA
	Lactobacillus and *Bifidobacterium*	2	-0.97 (-1.46, -0.47)	0.0001	56
	Lactobacillus and *Propionibacterium*	1	0.00 (-0.36, 0.36)	1.00	NA
	Enterococcus and *Streptococcus*	3	-0.30 (-0.46, -0.14)	0.0002	0
Study type	Crossover study	4	-0.24 (-0.5, 0.02)	0.07	41
	Parallel study	17	-0.36 (-0.48, -0.24)	< 0.00001	78

NA = not available.

Table IV. The subgroup analysis of LDL-C

	Group	Number of study	Weighted mean difference (95 % CI) mmol/L	p value	I^2 %
Baseline serum lipid levels	< 3.4 mmol/L	2	-0.16 (-0.50, 0.17)	0.35	79
	3.4-4.1 mmol/L	7	-0.28 (-0.44, -0.12)	0.0007	0
	≥ 4.1 mmol/L	12	-0.28 (-0.43, -0.12)	0.0004	85
Age	< 50 years old	12	-0.35 (-0.45, -0.25)	< 0.00001	45
	≥ 50 years old	7	-0.17 (-0.36, 0.02)	0.08	81
Intervention duration	≤ 6 weeks	12	-0.24 (-0.41, -0.07)	0.005	77
	> 6 weeks	9	-0.32 (-0.40, -0.23)	< 0.00001	38
Intervention strains	Single strain	14	-0.26 (-0.38, -0.15)	< 0.00001	84
	Multiple strain	7	-0.27 (-0.45, -0.08)	0.005	51
Form of probiotics	Capsule	15	-0.25 (-0.36, -0.13)	< 0.0001	85
	Yogurt/Fermented milk	5	-0.34 (-0.49, -0.19)	< 0.0001	0
		1	-0.32 (-0.91, 0.27)	0.28	NA
Type of strain	*Lactobacillus*	14	-0.25 (-0.36, -0.13)	< 0.00001	85
	Bifidobacterium	1	-0.06 (-1.45, 1.33)	0.93	NA
	Lactobacillus and *Bifidobacterium*	2	-0.62 (-0.99, -0.24)	0.001	0
	Lactobacillus and *Propionibacterium*	1	-0.03 (-0.37, 0.31)	0.86	NA
	Enterococcus and *Streptococcus*	3	-0.33 (-0.49, -0.16)	< 0.0001	5
Study type	Crossover study	4	-0.14 (-0.36, 0.07)	0.2	22
	Parallel study	16	-0.28 (-0.39, -0.18)	< 0.00001	82

Table V. The subgroup analysis of HDL-C

	Group	Number of study	Weighted mean difference (95 % CI) mmol/L	p value	I^2 %
Age	< 50 years old	12	-0.02 (-0.03, -0.00)	0.007	0
	≥ 50 years old	7	-0.00 (-0.05, 0.04)	0.97	77
Intervention duration	≤ 6 weeks	12	-0.00 (-0.02, 0.01)	0.81	0
	> 6 weeks	9	0.01 (-0.04, 0.05)	0.81	79
Intervention strains	Single strain	14	0.00 (-0.02, 0.03)	0.78	67
	Multiple strain	7	-0.01 (-0.05, 0.04)	0.75	10
Form of probiotics	Capsule	15	0.00 (-0.02, 0.03)	0.81	64
	Yogurt/Fermented milk	5	-0.02 (-0.08, 0.04)	0.50	27
		1	0.10 (-0.10, 0.30)	0.32	NA

(Continues on next page)

Table V (Cont.). The subgroup analysis of HDL-C

	Group	Number of study	Weighted mean difference (95 % CI) mmol/L	p value	I^2 %
Type of strain	*Lactobacillus*	14	0.01 (-0.02, 0.03)	0.71	67
	Bifidobacterium	1	0.00 (-1.06, 1.06)	1.00	NA
	Lactobacillus and *Bifidobacterium*	2	-0.12 (-0.23, -0.01)	0.03	0
	Lactobacillus and *Propionibacterium*	1	0.03 (-0.11, 0.17)	0.68	NA
	Enterococcus and *Streptococcus*	3	0.01 (-0.04, 0.06)	0.75	0
Study type	Crossover study	4	-0.06 (-0.14, 0.02)	0.12	2
	Parallel study	17	0.01 (-0.02, 0.03)	0.60	60

Table VI. The subgroup analysis of TG

	Group	Number of study	Weighted mean difference (95 % CI) mmol/L	p value	I^2 %
Baseline lipid serum levels	< 1.7 mmol/L	13	-0.01 (-0.14, 0.11)	0.83	64
	1.7-2.3 mmol/L	7	-0.15 (-0.28, -0.03)	0.02	0
	≥ 2.3 mmol/L	1	-0.69 (-1.10, -0.28)	0.001	NA
Age	< 50 years old	12	-0.02 (-0.16, 0.12)	0.80	65
	≥ 50 years old	7	-0.17 (-0.33, -0.01)	0.04	40
Intervention duration	≤ 6 weeks	12	0.03 (-0.06, 0.12)	0.49	0
	> 6 weeks	9	-0.22 (-0.32, -0.12)	< 0.0001	23
Intervention strains	Single strain	14	-0.11 (-0.21, -0.01)	0.04	33
	Multiple strain	7	-0.08 (-0.26, 0.10)	0.37	56
Form of probiotics	Capsule	15	-0.15 (-0.24, -0.05)	0.004	36
	Yogurt/Fermented milk	5	0.04 (-0.08, 0.17)	0.50	0
		1	0.16 (-0.21, 0.53)	0.40	NA
Type of strain	*Lactobacillus*	14	-0.12 (-0.24, -0.01)	0.03	47
	Bifidobacterium	1	-0.11 (-1.89, 1.67)	0.90	NA
	Lactobacillus and *Bifidobacterium*	2	-0.15 (-0.48, 0.17)	0.35	0
	Lactobacillus and *Propionibacterium*	1	-0.03 (-0.36, 0.30)	0.86	NA
	Enterococcus and *Streptococcus*	3	0.06 (-0.07, 0.19)	0.38	0
Study type	Crossover study	4	-0.03 (-0.19, 0.13)	0.73	0
	Parallel study	17	-0.09 (-0.20, 0.02)	0.10	58

In order to explore the impact of each study on the stability of the combined results, a sensitivity analysis was conducted by using the one-study-removed approach. It showed that there was no significant change in heterogeneity and the combined effect size (CES) after combination of each trial in the TC group, which indicated the results were robust enough. For the LDL-C group, however, when the first period of Fuentes et al. (18) was removed, heterogeneity could decline greatly (I^2 from 79 % to 45 %), while the CES did not change widely (WMD: 95 % CI from -0.26 [-0.36, -0.17] to -0.30 [-0.38, -0.23]). For the HDL-C group, there were two independent trials which could make a difference in the results. Both heterogeneity and CES changed when the second period of Fuentes et al. (18) was removed (I^2 from 57 % to 0 %, WMD 95 % CI from 0.00 [-0.02, 0.02] to -0.01 [-0.02, -0.00]); heterogeneity changed but the CES was kept consistent when Park et al. (24) was removed (I^2 from 57 % to 42 %, WMD 95 % CI from 0.00 [-0.02, 0.02] to 0.00 [-0.02, 0.03]). For the TG group, four independent trials could make the results unstable. The second period of Agerbaek et al. (13) and the first period of Jones et al. (20) had an effect on both heterogeneity and CES when removed (for Agerbaek et al. [13], I^2 from 52 % to 41 %, WMD 95 % CI from -0.08 [-0.18, 0.01] to -0.11 [-0.19, -0.02]; for Jones et al. [20], I^2 from 52 % to 49 %, WMD 95 % CI from -0.08 [-0.18, 0.01] to -0.10 [-0.19, -0.00]), while Ahn et al. (14) and Park et al. (24) only changed heterogeneity when removed (for Ahn et al. [14], I^2 from 52 % to 47 %, WMD 95 % CI from -0.08 [-0.18, 0.01] to -0.06 [-0.15, 0.03]; for Park et al. [24], I^2 from 52 % to 15 %, WMD 95 % CI from -0.08 [-0.18, 0.01] to -0.05 [-0.14, 0.03]). From that we found the heterogeneity of LDL-C might originate from Fuentes et al. (18), and the results of the HDL-C group and TG group were unstable.

PUBLICATION BIAS

Funnel plots (Figs. 8 to 11) and Egger's regression tests were performed to detect publication bias on the results of TC, LDL-C, HDL-C and TG. The first three funnel plots were visually symmetrical. Egger's linear regression tests indicated no significant publication bias for TC, LDL-C, HDL-C with a p-value equal to 0.259, 0.985 and 0.706. However, the TG group did show a publication bias, and it still existed after we used Duval and Tweedie's "trim and fill" method.

DISCUSSION

This meta-analysis included 16 (13-28) studies, which could be divided into 21 independent trials, and all studies included met the inclusion criteria. The results indicated that probiotics had a positive effect on the levels of LDL-C (-0.26 mmol/L) in non-obese healthy adults with hyperlipidemia. We performed a subgroup analysis, which showed that probiotics could significantly lower serum lipid levels in the TC and LDL-C groups when added to yogurt or fermented milk, and the types of strain were *Enterococcus* and *Streptococcus*. It also showed in the LDL-C group that probiotics could lower LDL-C levels when concentration is 3.4-4.1 mmol/L, and might be more effective on younger people (< 50 years old), with a longer duration of treatment (> 6 weeks) and with *Lactobacillus* plus *Bifidobacterium* and *Enterococcus* plus *Streptococcus*. As a result, these data indicated that probiotics could provide a promising way on serum lipid level in non-obese healthy adults with hyperlipidemia.

There had been studies (29-33) on the effect of probiotics in patients with hyperlipidemia before, but most of the studies did not consider the impact of obesity, which is a disorder of metabolism that can affect serum lipid. In addition, Pourrajab et al. (31) only used yogurt without considering a capsule. As a result, to our knowledge, this is the first meta-analysis aiming at non-obese healthy people with hyperlipidemia, and the results might be different when compared with the studies before. We observed that probiotics could lower LDL-C levels, which is different from the study by Deng et al. (29), whose results showed that probiotics could also modulate HDL-C levels without considering their impact on obesity. For heterogeneity, we found that

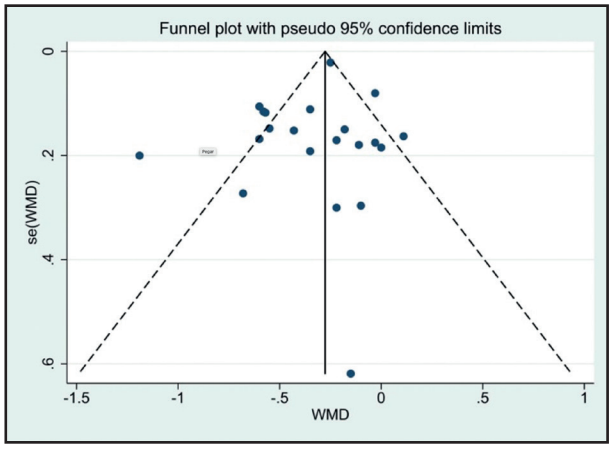

Figure 8.
The results of funnel plots for TC.

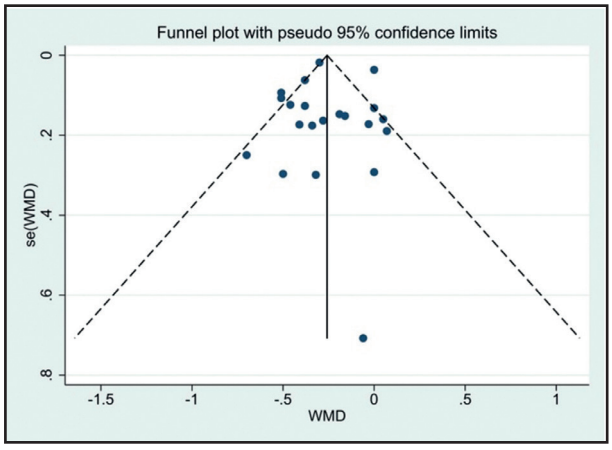

Figure 9.
The results of funnel plots for LDL-C.

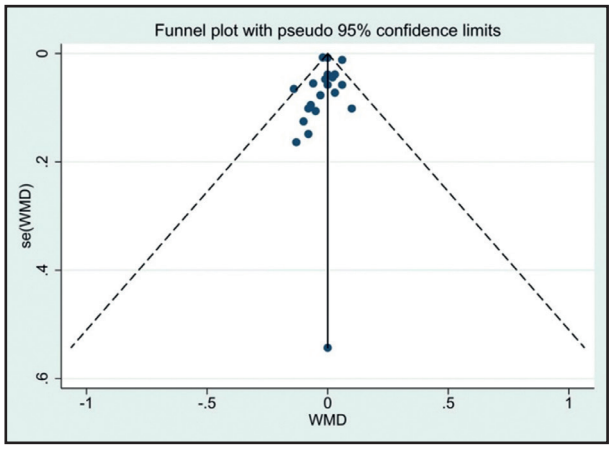

Figure 10.
The results of funnel plots for HDL-C.

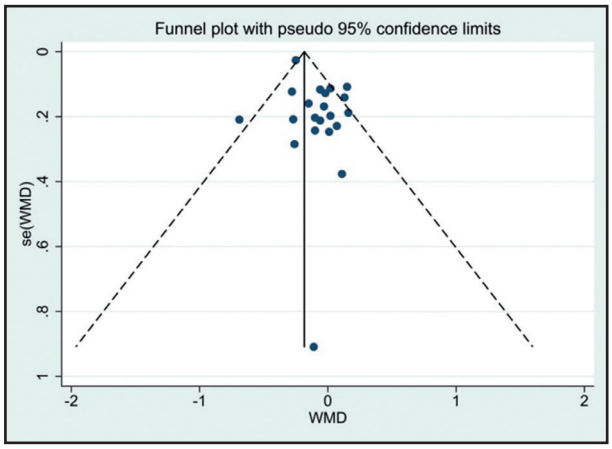

Figure 11.
The results of funnel plots for TG.

there was larger heterogeneity in the TC and LDL-C groups, while there was moderate heterogeneity in the HDL-C and TG groups. To identify the source of heterogeneity, we did a subgroup analysis including baseline serum lipid levels, age, intervention duration and strains, form of probiotics, type of strain, and study type on the four groups.

We found that intervention duration, form of probiotics, and type of strain might drive the heterogeneity found in the TG group since said heterogeneity declined to less than 50 % in each group of the three subgroups. Longer intervention duration (> 6 weeks), probiotics in capsules, and *Lactobacillus* were shown to be more effective for lower concentrations of TG. For the LDL-C group, we observed that baseline serum lipid levels had a certain impact on the results for serum lipid levels of 3.4-4.1 mmol/L, and the same situation also occurred in the form of probiotics with yogurt or fermented milk, which might need more experiments to verify. The results also showed that the probiotics taken by people less than 50 years old had a stronger effect on the LDL-C group. We speculated that it might be related to the change of intestinal flora, since the intestinal flora in younger subjects was more active, which further affected the absorption and effect of probiotics. As for intervention duration, using probiotics for a longer time (> 6 weeks) might be more effective according to the results. *Lactobacillus* plus *Bifidobacterium* and *Enterococcus* plus *Streptococcus* showed a significant effect of lowering LDL-C levels. For single *Lactobacillus*, which is a kind of traditional probiotic strain, we observed that it might also have a positive effect of lowering LDL-C and TC levels, though it showed a higher heterogeneity in subgroup analyses, which needed a larger sample size to prove its specific effect. The design type of the study could also affect the results in all four groups. Subgroup analyses found that crossover studies had no effect on serum lipid levels, which might be explained as a methodological limitation, for the washout period of each study was different, and there was no guarantee that the impact of the previous intervention could be completely eliminated.

So far, there have been many researches on the mechanism of probiotics in reducing the serum lipid. Most of them are focused on cholesterol, which can be divided into three categories: 1) inhibiting the synthesis of cholesterol. Probiotics can produce non digestible carbohydrates, improve the level of short chain fatty acids, and block the synthesis of liver cholesterol. Probiotics can also inhibit cholesterol synthesis-related enzymes to reduce serum cholesterol concentration; 2) regulate cholesterol absorption and transport. Probiotics can not only combine cholesterol, but also transform cholesterol into other substances to mitigate its absorption in the intestine. Meanwhile, probiotics can also block the transport of cholesterol through coprecipitation or inhibition of transporters; 3) promote cholesterol decomposition. After cholesterol is converted into bile acid, probiotics will produce the bile hydrolytic enzyme to hydrolyze conjugated bile acid into free bile acid, which is therefore difficult to absorb by the small intestine and is discharged from the body. Probiotics can also increase the activity of cholesterol decomposing enzymes to increase cholesterol excretion (37-40). In animal experiments, probiotics can activate the transcription of related genes, promote the absorption of cholesterol, inhibit the process of fatty transformation, and promote the decomposition, absorption, and utilization of fatty acids (41). At present, the research at the genetic level is still uncertain and needs more experiments to be supported.

Compared with the previous meta-analyses (29-33), our study contains the following advantages: first, our study excludes the influence of other diseases, especially obesity factors, which are often ignored in these previous studies (29-32). So the results are more accurate and suitable for those who are healthy and non-obese with high serum lipid levels. Second, we have no time and language restrictions in retrieving articles, and the retrieval strategy is more comprehensive, covering all relevant articles as much as possible. Third, in the article screening process, our standards are stricter. Some studies adopted interventions which included other components that might affect serum lipids. These

kinds of studies are excluded, and research designs that were not rigorous were also excluded, so the articles included are more accurate, high-quality and low-bias.

There are also some limitations in our study: First, there still remains a large heterogeneity in the results of TC, LDL-C and HDL-C, although a subgroup analysis was carried out, and the cause of heterogeneity remained to be found. In the sensitivity analysis it was found that Fuentes et al. (18) had a great influence on heterogeneity in the LDL group, and this may be the source of heterogeneity. However, the cause of heterogeneity was not found in the TC group. And the results of the HDL-C group and TG group were unstable, which means there were potential and important bias factors related to the intervention measures. Second, there still remained a publication bias in the TG group. We tried to use the "trim and fill" method, but the publication bias remained. It may be caused by heterogeneity or small sample size in this meta-analysis. Third, several studies have adopted a cross design, which may be more rigorous than the parallel design. However, it cannot fully guarantee that the washout period is sufficient, which may have an impact on the results. Finally, in some experiments, the sample size is not large enough so the results may be accidental, which requires a larger sample size to prove.

CONCLUSION

This systematic review and meta-analysis of randomized controlled trials showed that probiotics may provide a promising way to reduce serum lipid levels in non-obese healthy adults with hyperlipidemia. However, the specific effect still needs more clinical experiments to be proven. Also, the safety and adverse reactions of probiotics are worth considering.

REFERENCES

1. Campara MT, Sijaric-Voloder S, Denislic M, Tupkovic E, Vranic JD, Alajbegovic A. Hyperlipidemia as a risk factor for persons in specific professions. Mater Sociomed 2014;26(1):17-20. DOI: 10.5455/msm.2014.26.17-20
2. Committee of Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (2016). Chinese guidelines on prevention and treatment of dyslipidemia in adults. Chin Circ J 31(10):937-53.
3. Yao YS, Li TD, Zeng ZH. Mechanisms underlying direct actions of hyperlipidemia on myocardium: an updated review. Lipids Health Dis 2020;19(1):23. DOI: 10.1186/s12944-019-1171-8
4. Karr S. Epidemiology and management of hyperlipidemia. The American journal of managed care 2017;23(9 Suppl):S139-48.
5. Fava MC, Agius R, Fava S. Obesity and cardio-metabolic health. British J Hosp Med (London) 2019;80(8):466-71. DOI: 10.12968/hmed.2019.80.8.466
6. Pasanta D, Chancharunee S, Tungjai M, Kim HJ, Kothan S. Effects of obesity on the lipid and metabolite profiles of young adults by serum (1) H-NMR spectroscopy. Peer J 2019;7:e7137. DOI: 10.7717/peerj.7137
7. Vekic J, Zeljkovic A, Stefanovic A, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V. Obesity and dyslipidemia. Metabolism 2019;92:71-81. DOI: 10.1016/j.metabol.2018.11.005
8. Buldak L, Marek B, Kajdaniuk D, Urbanek A, Janyga S, Bołdys A, et al. Endocrine diseases as causes of secondary hyperlipidemia. Endokrynol Pol 2019;70(6):511-9. DOI: 10.5603/EP.a2019.0041
9. Cote DJ, Rosner BA, Smith-Warner SA, Egan KM, Stampfer MJ. Statin use, hyperlipidemia, and risk of glioma. Eur J Epidemiol 2019;34(11):997-1011. DOI: 10.1007/s10654-019-00565-8
10. Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. Nutr Rev 2017;75(9):731-67. DOI: 10.1093/nutrit/nux047
11. Tang C, Lu Z. Health promoting activities of probiotics. J Food Biochem 2019;43(8):e12944. DOI: 10.1111/jfbc.12944
12. Tanner G, Matthews K, Roeder H, Konopasek M, Bussard A, Gregory T. Current and future uses of probiotics. JAAPA 2018;31(5):29-33. DOI: 10.1097/01.JAA.0000532117.21250.0f
13. Agerbaek M, Gerdes L, Richelsen B. Hypocholesterolaemic effect of a new fermented milk product in healthy middle-aged men. Eur J Clin Nutr 1995;49(5):346-52.
14. Ahn HY, Kim M, Ahn YT, Sim J-H, Choi I-D, Lee S-H, et al. The triglyceride-lowering effect of supplementation with dual probiotic strains, Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032: Reduction of fasting plasma lysophosphatidylcholines in nondiabetic and hypertriglyceridemic subjects. Nutr Metab Cardiovasc Dis 2015;25(8):724-33. DOI: 10.1016/j.numecd.2015.05.002
15. Ataie-Jafari A, Larijani B, Alavi Majd H, Tahbaz F. Cholesterol-lowering effect of probiotic yogurt in comparison with ordinary yogurt in mildly to moderately hypercholesterolemic subjects. Ann Nutr Metab 2009;54(1):22-7. DOI: 10.1159/000203284
16. Bertolami M, Faludi A, Batlouni M. Evaluation of the effects of a new fermented milk product (Gaio) on primary hypercholesterolemia. Eur J Clin Nutr 1999;53(2):97-101. DOI: 10.1038/sj.ejcn.1600683
17. Fuentes MC, Lajo T, Carrion JM, Cune J. Cholesterol-lowering efficacy of Lactobacillus plantarum CECT 7527, 7528 and 7529 in hypercholesterolaemic adults. Br J Nutr 2013;109(10):1866-72. DOI: 10.1017/S000711451200373X
18. Fuentes MC, Lajo T, Carrión JM, Cune J. A randomized clinical trial evaluating a proprietary mixture of Lactobacillus plantarum strains for lowering cholesterol. Med J Nutrition Metab 2016;9(2):125-35. DOI: 10.3233/mnm-160065
19. Hatakka K, Mutanen M, Holma R, Saxelin M, Korpela R. Lactobacillus rhamnosus LC705 together with Propionibacterium freudenreichii ssp shermanii JS administered in capsules is ineffective in lowering serum lipids. J Am Coll Nutr 2008;27(4):441-7. DOI: 10.1080/07315724.2008.10719723
20. Jones ML, Martoni CJ, Prakash S. Cholesterol lowering and inhibition of sterol absorption by Lactobacillus reuteri NCIMB 30242: a randomized controlled trial. Eur J Clin Nutr 2012;66(11):1234-41. DOI: 10.1038/ejcn.2012.126
21. Lewis SJ, Burmeister S. A double-blind placebo-controlled study of the effects of Lactobacillus acidophilus on plasma lipids. Eur J Clin Nutr 2005;59(6):776-80. DOI: 10.1038/sj.ejcn.1602139
22. Naruszewicz M, Johansson ML, Zapolska-Downar D, Bukowska H. Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. Am J Clin Nutr 2002;76:1249-55. DOI: 10.1093/ajcn/76.6.1249
23. Ooi LG, Ahmad R, Yuen KH, Liong MT. Lactobacillus acidophilus CHO-220 and inulin reduced plasma total cholesterol and low-density lipoprotein cholesterol via alteration of lipid transporters. J Dairy Sci 2010;93(11):5048-58. DOI: 10.3168/jds.2010-3311
24. Park YE, Kim MS, Shim KW, Kim Y-I, Chu J, Kim B-K, et al. Effects of Lactobacillus plantarum Q180 on Postprandial Lipid Levels and Intestinal Environment: A Double-Blind, Randomized, Placebo-Controlled, Parallel Trial. Nutrients 2020;12(1):255. DOI: 10.3390/nu12010255
25. Rerksuppaphol S, Rerksuppaphol L. A Randomized Double-blind Controlled Trial of Lactobacillus acidophilus Plus Bifidobacterium bifidum versus Placebo in Patients with Hypercholesterolemia. J Clin Diagn Res 2015;9(3):KC01-04. DOI: 10.7860/jcdr/2015/11867.5728
26. Simons LA, Amansec SG, Conway P. Effect of Lactobacillus fermentum on serum lipids in subjects with elevated serum cholesterol. Nutr Metab Cardiovasc Dis 2006;16(8):531-5. DOI: 10.1016/j.numecd.2005.10.009
27. Tan S, Zhao A, Zheng Y, Wang P, Zhang Y. Effects of Lactobacillus paracasei N1115 on intestinal microbiota and serum lipid of dyslipidemias. FASEB J 2017;31(1 Supplement):45-6.
28. Xiao JZ, Kondo S, Takahashi N, Miyaji K, Oshida K, Hiramatsu A, et al. Effects of milk products fermented by Bifidobacterium longum on blood lipids in rats and healthy adult male volunteers. Journal of dairy science 2003;86(7):2452-61. DOI: 10.3168/jds.S0022-0302(03)73839-9
29. Deng X, Ma J, Song M, Jin Y, Ji C, Ge W, et al. Effects of products designed to modulate the gut microbiota on hyperlipidaemia. Eur J Nutr 2019;58(7):2713-29. DOI: 10.1007/s00394-018-1821-z
30. Mo R, Zhang X, Yang Y. Effect of probiotics on lipid profiles in hypercholesterolaemic adults: A meta-analysis of randomized controlled trials. Med Clin (Barc) 2019;152(12):473-81. DOI: 10.1016/j.medcle.2018.09.013
31. Pourrajab B, Fatahi S, Dehnad A, Varkaneh HK, Shidfar F. The impact of probiotic yogurt consumption on lipid profiles in subjects with mild to moderate hypercholesterolemia: A systematic review and meta-analysis of ran-

domized controlled trials. Nutr Metab Cardiovasc Dis 2020;30(1):11-22. DOI: 10.1016/j.numecd.2019.10.001
32. Shimizu M, Hashiguchi M, Shiga T, Tamura H, Mochizuki M. Meta-Analysis: Effects of Probiotic Supplementation on Lipid Profiles in Normal to Mildly Hypercholesterolemic Individuals. PLoS One 2015;10(10):e0139795. DOI: 10.1371/journal.pone.0139795
33. Yan S, Tian Z, Li M, Li B, Cui W. Effects of probiotic supplementation on the regulation of blood lipid levels in overweight or obese subjects: a meta-analysis. Food Funct 2019;10(3):1747-59. DOI: 10.1039/c8fo02163e
34. Potter SM. Soy protein and serum lipids. Curr Opin Lipidol 1996;7(4):260-4. DOI: 10.1097/00041433-199608000-00013
35. Jayachandran M, Xu B. An insight into the health benefits of fermented soy products. Food Chem 2019;271:362-71. DOI: 10.1016/j.foodchem.2018.07.158
36. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62(10):1006-12. DOI: 10.1371/journal.pmed.1000097
37. Astrup A. Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. Am J Clin Nutr 2014;99 (5 Suppl):1235S-42S. DOI: 10.3945/ajcn.113.073015
38. Choi SB, Lew LC, Yeo SK, Parvathy SN, Liong MT. Probiotics and the BSH-related cholesterol lowering mechanism: a Jekyll and Hyde scenario. Crit Rev Biotechnol 2015;35(3):392-401. DOI: 10.3109/07388551.2014.889077
39. Kumar M, Nagpal R, Kumar R, Hemalatha R, Verma V, Kumaret A, et al. Cholesterol-lowering probiotics as potential biotherapeutics for metabolic diseases. Exp Diabetes Res 2012;2012:902917. DOI: 10.1155/2012/902917
40. Reis SA, Conceicao LL, Rosa DD, Siqueira NP, Peluzio MCG. Mechanisms responsible for the hypocholesterolaemic effect of regular consumption of probiotics. Nutr Res Rev 2017;30(1):36-49. DOI: 10.1017/S0954422416000226
41. Wa Y, Yin B, He Y, Xi W, Huang Y, Wang C, et al. Effects of Single Probiotic- and Combined Probiotic-Fermented Milk on Lipid Metabolism in Hyperlipidemic Rats. Front Microbiol 2019;10:1312. DOI: 10.3389/fmicb.2019.01312