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REVIEW

Effects of synbiotic consumption on lipid profile: a systematic review and meta-analysis of randomized controlled clinical trials

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Abstract

Background and aims Existing evidence on the possible effects of synbiotics on lipid profile is inconclusive. The aim of the present systematic review was to clarify the effects of synbiotics consumption on lipid profile.

Methods A systematic literature search of online databases PubMed, Scopus, ISI Web of science, Cochrane's library and Google Scholar was conducted up to January 2019. Randomized controlled trials (RCTs) investigating the effects of synbiotics on lipid profile in adults were included. The overall effect was presented as weighted mean difference (WMD) and 95% confidence interval (CI) in a random-effects meta-analysis model.

Results A total of 23 RCTs with 1338 participants were included. Synbiotic consumption resulted in a significant decrease in plasma concentrations of total cholesterol (WMD = − 10.17 mg/dL; 95% CI − 15.74 to − 4.60; $p < 0.001$), triglyceride (WMD = − 14.30 mg/dL; 95% CI − 25.32 to − 3.28; $p = 0.01$), low-density lipoprotein cholesterol (WMD = − 8.32 mg/dL; 95% CI − 13.21 to − 3.43; $p < 0.001$), and an increase in plasma high-density lipoprotein cholesterol (WMD = 1.3 mg/dL; 95% CI 0.03 to 2.56; $p = 0.04$) levels compared to control (placebo supplements/control foods/conventional products). The effects are more pronounced when synbiotics supplements are consumed for > 8 weeks.

Conclusion Synbiotic supplements may be beneficial to improve lipid profile, especially when they are consumed for > 8 weeks.

Keywords Synbiotics · Lipid profile · Cholesterol · Triglyceride · Meta-analysis

Introduction

Cardiovascular disease (CVD) is a multifactorial disorder with a high mortality rate. It has been expected that by 2030, CVD will remain the leading causes of death affecting approximately 23.3 millions of people worldwide [1]. Dyslipidemia, defined by the presence of one or more abnormal serum lipid concentrations [total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], is one of the main risk factors of CVD [2]. Therefore, the prevention and management of dyslipidemia have gained increasing attention over the past decades. Currently, various treatment options that target each aspect of the dyslipidemia pathogenesis have been explored and advocated, but recent guidelines encourage combination therapy for the management of multiple lipid abnormalities [3–5]. As a result, many dietary constituents and supplements are proposed to benefit lipid profile and control dyslipidemia.

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In recent years, gut dysbiosis (the imbalance of beneficial and pathogenic bacteria of the gut flora) has been linked with obesity, diabetes, metabolic syndrome and dyslipidemia through excess energy production, disturbance of host energy metabolism and pro-inflammatory signals [6–8]. Therefore, improving the balance of gut microbial flora can play a significant role in human health [9, 10]. Probiotics and prebiotics are proposed as dietary constituents to improve gut dysbiosis. Probiotic are live microorganisms that when administered in adequate amounts can have health benefits for the host [11]. On the other hand, prebiotics are characterized as non-digestible but fermentable food ingredients (mostly dietary fibers) that positively affect the host by motivating the growth and/or activity of one or a limited number of desired bacteria in the gut [12]. A mixture of the probiotics and prebiotics, called synbiotics, may have a synergic effect to improve the endurance of the bacteria passing the upper part of the gastrointestinal tract and enhancing their effects in the large bowel [13]. Therefore, many interventions have employed these dietary constituents to investigate their effects on lipid profile. However, the results of these studies are inconclusive. Therefore, the current study aims to investigate the effects of synbiotic consumption on lipid profile, including TC, TG, LDL-C and HDL-C in adults using systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods

Search strategy

Present systematic review and meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statements [14]. The electronic databases PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Scopus (https://www.scopus.com), ISI Web of Science (https://www.webofscience.com), Google Scholar (https://scholar.google.com) and Cochrane library (https://www.cochranelibrary.com) were systematically searched for relevant articles published before January 2019. Two reviewers (A.H and E.Gh) independently searched the aforementioned databases to identify RCTs on the effects of synbiotic consumption on lipid profile, using the following MeSH and text keywords: (”probiotics” OR “synbiotics” OR “symbiotics” OR “Fermented Foods” OR “Lactobacillus” OR “Bifidobacterium”) AND (“lipid” OR “cholesterol” OR” chol” OR “hypercholesterolemia” OR “triglyceride” OR “hypertriglyceridemia” OR “TG” OR “lipoprotein” OR “hyperlipoproteinemia” OR “LDL” OR “LDL-C” OR “HDL” OR “HDL-C”). No restrictions on language, publication time, and study design were considered. Also, all references of previous relevant meta-analyses, systematic reviews, and selected RCTs were manually reviewed to detect any additional trials that had not been captured via online database searches.

Study selection

Before the screening process, all publications identified through the literature search were exported to the Endnote X8 software (Thomson Reuters, New York) and checked for duplicated publications. Next, the title, abstract and full text of potential studies were reviewed for eligible studies. The eligibility criteria were: (1) original human RCTs either with parallel or crossover design; (2) which used synbiotic (supplement or food) for intervention; and (3) assessed the effect of synbiotic on at least one of the lipid parameters, including TC, TG, LDL-C, and HDL-C. Studies were excluded if they: (1) administrated synbiotic in combination with any other drugs, minerals, or botanicals (unless a separate arm controlled the effect of the mixed substance); (2) included participants younger than 18 years of age, or pregnant or lactating women; (3) had an intervention duration < 2 weeks; (4) reported duplicate data (in this case, the one with complete follow-up and outcome measures was included); or (5) were not peer-reviewed articles (protocol or conference proceeding). The study selection process was undertaken independently by two investigators (A.H and M.P) to minimize potential error. If there was a disagreement, it was resolved by consensus or involving a third researcher.

Data extraction

Eligible RCTs were reviewed independently by two authors (A.H and M.P), and the following data were collected using the standardized extraction forms to guarantee accuracy and consistency: first author’s name, publication year, location of studies, participant characteristics (including mean age, baseline body mass index (BMI), gender, and health status), the design of the study, duration of intervention, dose and type of intervention in experimental and comparison groups, probiotics strains, and mean and standard deviation (SD) of outcome measures at baseline, post-intervention and if possible their change from the baseline. Corresponding authors were contacted by email in case of any missing information.

Quality assessment

Quality assessment of included RCTs was performed by two reviewers (A.H and E.Gh) individually using Cochrane Collaboration Risk of Bias tool [15]. The items used for each included study assessment were the following ones: sequence generation, allocation concealment, blinding, outcome assessment, drop-outs and incomplete outcome data, selective outcome reporting and other potential sources of

bias. Disagreements between reviewers were resolved by involving a third author.

Statistical analysis

The statistical analyses were performed using STATA statistical program version 11.2 (Stata Corporation, College Station, TX, USA). Prior to the calculation of the effect size, the concentration of all outcomes (TC, TG, LDL-C, HDL-C) was converted to mg/dL. If there was a standard error (SE) for variation of mean in a study, SD was calculated by the following formula: $SE \times \sqrt{n}$. Effect sizes for the meta-analysis were defined as the weighted mean difference (WMD; measurement at end trial minus the measurement at baseline) and 95% confidence interval (CI). When SD of difference was missing, it was imputed following the method of Follmann et al. [16] using a correlation coefficient of 0.5. All meta-analyses were done using the random effects model which takes the between-study variability into account. The I^2 index was evaluated to assess heterogeneity. Low, moderate and high heterogeneity were defined as I^2 index < 40, 40–75 and > 75%, respectively [17]. Subgroup analyses based on the baseline BMI (overweight or obese), duration of the intervention (≤ 8 weeks or ˃8 weeks), source of the synbiotic (food or supplement), geographical population, number bacteria strains (single or multi), and type of prebiotic substrate were done to check the sources of heterogeneity. Sensitivity analyses were conducted to assess the influence of individual RCTs on the overall meta-analysis results, using leave-one-out method. Publication bias was assessed using Egger's and Begg's statistics. A p-value < 0.05 was considered statistically significant.

Results

Studies characteristics

Figure 1 presents the PRISMA flow chart of study selection. Overall, 23 studies [1, 10, 18–38] with a total of 1338 participants were included in this meta-analysis. Table 1 outlines the main characteristics of included studies. Included trials were conducted between 2012 and 2018. All studies followed a parallel design except two [18, 25] that used a cross-over design. Of the 23 trials, 15 were conducted in Iran [10, 18–22, 24, 27, 30–32, 34–36, 38], 4 in Brazil [1, 23, 28, 37], and 4 in Italy [26], UK [25], Canada [33] and Chile [29]. Men and women were included in all trials, except two studies [28, 32] that included only women and one study that examined men [1]. Gender was not reported in one study [23]. Participants were in the age range of 27 and 71 years. Based on the average BMI of participants at baseline, all trials included overweight and obese subjects (BMI > 25 kg/m^2). The total daily dose of probiotic consumption varied between 2×10^{11} [25] to 1×10^7 [18] colony-forming units (CFU), and the duration of administration varied between 4 to 28 weeks. Fifteen studies [1, 10, 19–22, 24, 27, 28, 30–32, 35, 36, 38] used a combination of more than two strains, and eight studies [18, 23, 25, 26, 29, 33, 34, 37] used a single species of probiotics. Synbiotics were delivered via capsules in 17 trials [10, 19, 21–27, 29–33, 35, 36, 38] and in six studies [1, 18, 20, 28, 34, 37] food was used as a vehicle for delivering synbiotics. Control group consumed placebo capsules or control food. In 7 studies [20, 22, 23, 26, 27, 30, 33] participants adhered to a special diet or dietary/physical activity advice, but no specific recommendation or requirement was reported in other trials

Study quality and risk of bias findings

Table 2 presents the results of risk of bias assessment of included studies. The criteria "random sequence generation", "incomplete outcome data" and "blinding of participants and personnel" were rated as low risk of bias in all trials. Some trials had unclear risk of bias in the criteria "allocation concealment" [1, 18, 20, 22, 23, 27, 29, 34, 37] and "blinding of outcome assessment" [23, 24, 26, 28, 29, 37]. Most of the studies showed low/unclear risk of bias based on 'other sources of bias'. The weakest criteria assessed was the 'selective reporting' with two trials [19, 24] evaluated as high risk of bias and twenty-one [1, 10, 18, 20–23, 25–38] as unclear risk of bias.

The effects of synbiotic consumption on TC

The effect of synbiotics consumption on TC was examined in 23 trials [1, 10, 18–38]. Overall, meta-analysis showed that synbiotics significantly decrease TC (WMD = − 10.17 mg/dL; 95% CI: − 15.74 to − 4.60; $p < 0.001$) with high heterogeneity ($I^2 = 67.0\%$, $p < 0.001$) (Fig. 2). Subgroup analysis suggested a more pronounced reduction in TC in studies with duration > 8 weeks (WMD = − 12.15 mg/dL; 95% CI − 18.56 to − 5.74; $I^2 = 43.9\%$). But the reduction in trials with duration ≤ 8 weeks was not significant (WMD = − 7.89 mg/dL; 95% CI − 17.80 to 2.02; $I^2 = 80.1\%$). Subgroup analysis of synbiotics supplements resulted in a significant reduction in TC (WMD = − 9.61 mg/dL; 95% CI − 15.28 to − 3.94; $I^2 = 57.0\%$); however, the effect was not significant when food was used to deliver synbiotics (WMD = − 13.68 mg/dL; 95% CI − 29.99 to 2.64; $I^2 = 67.0\%$). Also, subgroup analysis based on geographical population suggested a significant reduction in TC only in the subgroup of Iranian studies (WMD = − 11.57 mg/dL, 95% CI − 18.73 to − 4.41) with a significant subgroup difference. Using multi strains of probiotics (WMD = -13.84 mg/dL, 95% CI − 20.66 to − 7.01) and fructooligosaccharide

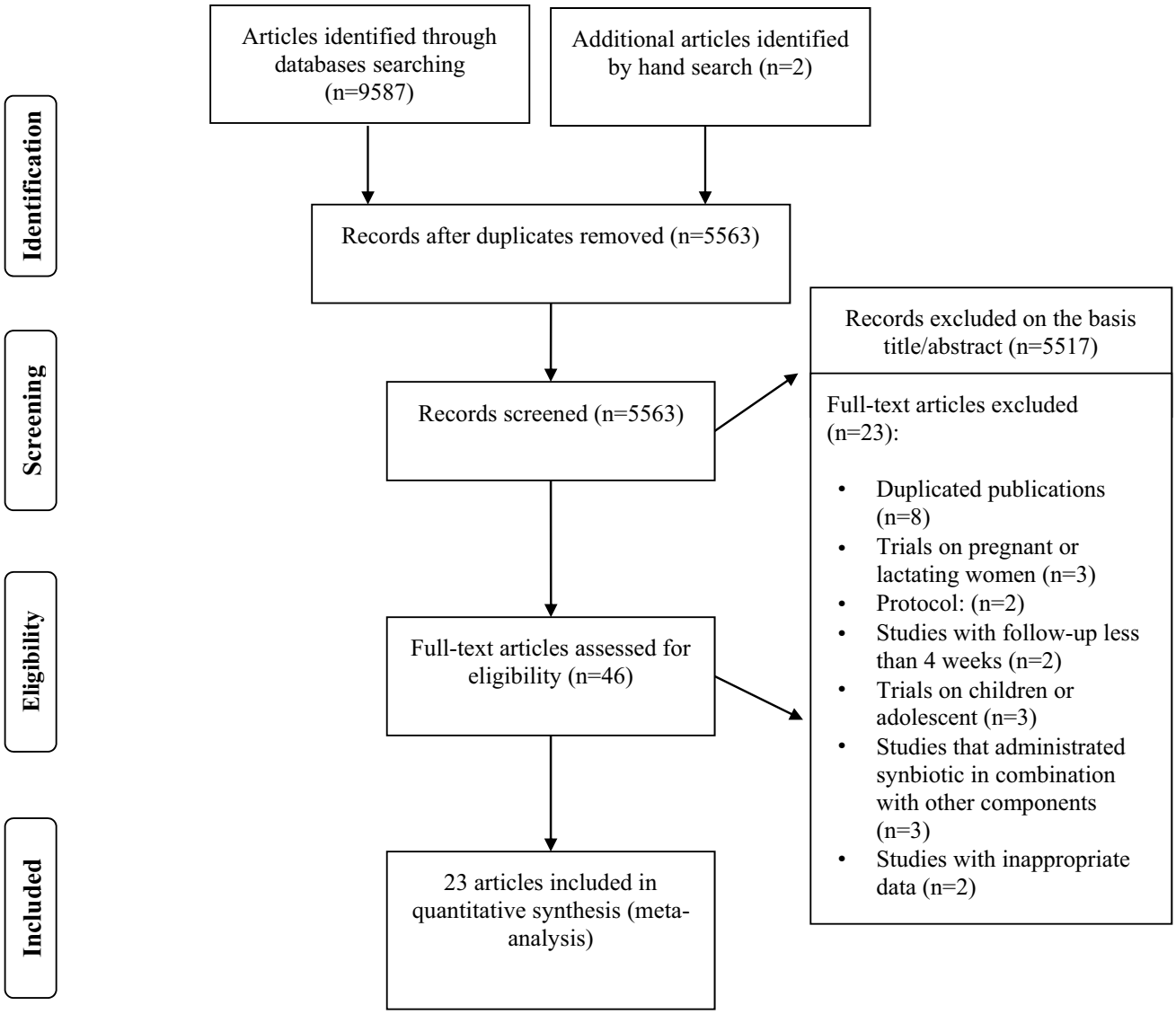

Fig. 1 PRISMA flow diagram of study selection process

prebiotics (WMD = − 14.36 mg/dL, 95% CI − 20.39 to − 8.33) resulted in a significant reduction is TC compared to their counterparts (Table 3). Meta-analysis results were not sensitive to individual studies. No evidence of publication bias was also observed ($p = 0.32$, Begg's test and $p = 0.41$, Egger's test).

The effects of synbiotic consumption on TG

Twenty-three trials reported on the effect of the synbiotics consumption on TG [1, 10, 18–38]. Synbiotics significantly reduced TG (WMD = − 14.30 mg/dL; 95% CI − 25.32 to − 3.28; $p = 0.01$) compared to placebo (Fig. 3). A high heterogeneity between the effect sizes of the included studies was observed ($I^2 = 73.8\%$, $p < 0.001$). To investigate the source of heterogeneity, subgroup analyses were performed. Subgroup analysis of synbiotics source showed a significant reduction in TG levels when synbiotic was consumed as supplement (WMD = − 13.25 mg/dL; 95% CI − 21.01 to − 5.50) with a lower heterogeneity ($I^2 = 31.2\%$). However, no meaningful effect of synbiotic consumption on TG levels was observed in the subgroup of food. Subgroup analysis of intervention duration ˃ 8 weeks also resulted in a significant reduction in TG (WMD = -21.89 mg/dL; 95% CI − 35.02 to − 8.76; $I^2 = 66.0\%$), while the effect was not significant in the shorter duration subgroup. The reduction in TG was only observed in the subgroup of overweight participants (WMD = − 10.61 mg/dL; 95% CI − 21.0 to − 0.21; $I^2 = 57.3\%$) with no meaningful reduction observed in the subgroup of obese individuals. The

Table 1 Characteristics of included trials

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Malaguarnera (2012)	Italy	33 M/33F	NASH	46	27	Parallel (Yes)	24	Synbiotic capsule (Bifidobacterium longum + fructooligosaccharide) + lifestyle modification	1	Placebo capsule + lifestyle modification	TC, TG, LDL-C, HDL-C
Moroti (2012)	Brazil	20F	T2DM	55	28	Parallel (Yes)	4	Synbiotic shake (1×10^8 CFU of Lactobacillus acidophilus, Bifidobacterium bifidum + 2 g fructooligosaccharide)	2	Placebo shake	TC, TG, HDL-C
Macfarlane (2013)	UK	21 M/22F	Elderly	71	26	Cross-over (Yes)	4	Synbiotic capsule (2×10^{11} CFU of Bifidobacterium longum + 6 g mixture of inulin and oligofructose)	1	Placebo capsule	TC, TG, LDL-C, HDL-C
Eslamparast (2014)	Iran	15 M/23F	Metabolic syndrome	46	31	Parallel (Yes)	28	Synbiotic capsule (2×10^8 CFU of Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus + 250 mg fructooligosaccharide) + lifestyle modification	7	Placebo capsule + lifestyle modification	TC, TG, LDL-C, HDL-C
Peña (2014)	Chile	5 M/33F	Obese	34	36	Parallel (Yes)	6	Synbiotic capsule (10^{10} CFU of Bifidobacterium lactis + 8 g oligofructose)	1	Placebo capsule	TC, TG, LDL-C, HDL-C
Asemi (2014)	Iran	19 M/43F	T2DM	53	29	Cross-over (Yes)	6	Synbiotic food (1×10^7 CFU of Lactobacillus sporogenes + 0.04 g inulin)	1	Control food	TC, TG, LDL-C, HDL-C

Table 1 (continued)

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Sanchez (2014)	Canada	48 M/77F	Obese	36	33	Parallel (Yes)	12	Synbiotic capsule (1.6×10^8 CFU of Lactobacillus rhamnosus + 300 mg mixture of inulin and oligofructose) + lifestyle modification	1	Placebo capsule + lifestyle modification	TC, TG, LDL-C, HDL-C
Shakeri (2104)	Iran	15 M/63F	T2DM	53	30	Parallel (Yes)	8	Synbiotic bread (1×10^8 CFU of Lactobacillus sporogenes + 0.07 g inulin)	1	control bread	TC, TG, LDL-C, HDL-C
Bedani (2015)	Brazil	36 M	Healthy	45	28	Parallel (Yes)	8	Synbiotic soy-based product (Lactobacillus acidophilus, Bifidobacterium animalis subsp. lactis, and Streptococcus thermophilus)	3	Soy-based product	TC, TG, HDL-C
Ferolla (2016)	Brazil	50.NR	NASH	57	32	Parallel (NO)	12	Synbiotic capsule (1×10^8 CFU of Lactobacillus reuteri + 4 g inulin) + lifestyle modification	1	Placebo capsule + lifestyle modification	TC, TG, LDL-C, HDL-C
Zamani (2017)	Iran	8 M/46F	Rheumatoid arthritis	49	29	Parallel (Yes)	8	Synbiotic capsule (2×10^9 CFU of Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum + 0.8 g inulin)	3	Placebo capsule	TC, TG, LDL-C, HDL-C
Asgharian (2017)	Iran	19 M/55F	NAFLD	46	29	Parallel (Yes)	8	Synbiotic capsule (Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus + fructooligosaccharide)	7	Placebo capsule	TC, TG, LDL-C, HDL-C

Table 1 (continued)

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Tajabadi-Ebrahimi (2017)	Iran	22 M/38F	T2DM	64	31	Parallel (Yes)	12	Synbiotic capsule (2×10^9 CFU of Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum + 0.8 g inulin)	3	Placebo capsule	TC, TG, LDL-C, HDL-C
Ekhlasi (2017)	Iran	27 M/9F	NAFLD	57	27	Parallel (Yes)	8	Synbiotic capsule (2×10^8 CFU of *Lactobacillus casei*, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus + fructooligosaccharide)	7	Placebo capsule	TC, TG, LDL-C, HDL-C
Sadat Ebrahimi (2017)	Iran	42 M/28F	T2DM	58	28	Parallel (Yes)	9	Synbiotic capsule (Lactobacillus family, Bifidobacterium family, Streptococus thermophilus + fructooligosaccharide)	3	Placebo capsule	TC, TG, LDL-C, HDL-C
Mofidi (2017)	Iran	23 M/19F	NAFLD	54	23	Parallel (Yes)	28	Synbiotic capsule (4×10^8 CFU + 125 mg fructooligosaccharide) + lifestyle modification	7	Placebo capsule + lifestyle modification	TC, TG, LDL-C, HDL-C
Javadi (2018)	Iran	14 M/13F	NAFLD	42	30	Parallel (Yes)	12	Synbiotic capsule (2×10^7 CFU of Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus + 10 g inulin)	2	Placebo capsule	TC, TG, LDL-C, HDL-C

Table 1 (continued)

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Samimi (2018)	Iran	60F	PCOS	27	27	Parallel (Yes)	12	Synbiotic capsule (2×10^9 CFU of Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum + 0.8 g inulin)	3	Placebo capsule	TC, TG, LDL-C, HDL-C
Xavier-Santos (2018)	Brazil	23 M/22F	Metabolic syndrome	48	32	Parallel (Yes)	8	Synbiotic diet (1×10^9 CFU of Lactobacillus acidophilus + 4 g mixture of inulin and fructooligosaccharide)	1	Control diet	TC, TG, LDL-C, HDL-C
Sayari (2018)	Iran	56 M/84F	NAFLD	43	29	Parallel (Yes)	16	Synbiotic capsule (1×10^9 CFU of Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus + fructooligosaccharide) + sitagliptin tablet	7	Placebo capsule + sitagliptin tablet	TC, TG, LDL-C, HDL-C
Bakhshimoghaddam (2018)	Iran	34 M/34F	NAFLD	40	31	Parallel (Yes)	24	Synbiotic yogurt (1×10^8 CFU of Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus and Bifidobacterium longum + 1.5 g inulin) + lifestyle modification	4	Conventional yogurt + lifestyle modification	TC, TG, LDL-C, HDL-C
Soleimani (2018)	Iran	42 M/18F	T2DM	62	26	Parallel (Yes)	12	Synbiotic capsule (2×10^9 CFU of Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum + 0.8 g inulin)	3	Placebo capsule	TC, TG, LDL-C, HDL-C

Table 1 (continued)

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Rabiei (2018)	Iran	13 M/33F	Metabolic syndrome	59	32	Parallel (Yes)	12	Synbiotic capsule (2×10^8 CFU of Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus + fructooligosaccharide) + weight loss	7	Placebo capsule + weight loss	TC, TG, LDL-C, HDL-C

M, male; F, female; RCT, randomized controlled trial; NAFLD, Non-alcoholic Fatty Liver Disease; NASH, Nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; PCOS, polycystic ovary syndrome; NR: not reported; TC, total cholestrol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

subgroup analysis based on geographical population reported a significant TG reduction only in the subgroup of Iranian studies (WMD = − 19.57 mg/dL, 95% CI − 31.22 to − 7.91), multi strains of probiotics (WMD = − 19.58 mg/dL, 95% CI − 30.84 to − 8.32) and inulin prebiotics (WMD = − 23.03 mg/dL, 95% CI − 40.61 to − 5.44) compared to their counterparts (Table 3). Excluding individual studies did not result in a significant change in the overall meta-analysis results. No evidence of publication bias was also observed ($p = 0.54$, Begg's test and $p = 0.11$, Egger's test).

The effects of synbiotic consumption on LDL-C

The meta-analysis of twenty-one trials [10, 18–27, 29–38] for the mean difference in LDL-C suggested synbiotics consumption significantly reduce LDL-C (WMD = − 8.32 mg/dL; 95% CI − 13.21 to − 3.43; $p < 0.001$) (Fig. 4). Substantial heterogeneity was observed ($I^2 = 70.4\%$, $p < 0.001$). Source of heterogeneity was explored in subgroup analyses. Reduction of LDL-C observed in overweight subgroup (WMD = − 9.04 mg/dL; 95% CI − 16.36 to − 1.72; $I^2 = 78.0\%$) was more pronounced than obese counterparts (WMD = − 7.13 mg/dL; 95% CI − 12.92 to − 1.35; $I^2 = 42.0\%$). A significant reduction in LDL-C was only observed in the longer duration (˃8 weeks) of intervention (WMD = − 10.50 mg/dL; 95% CI − 17.28 to − 3.72; $I^2 = 61.0\%$), with no meaningful reduction in shorter intervention duration. Also, the subgroup analysis of synbiotics source suggested a significant reduction in LDL-C when synbiotic supplement was consumed (WMD = − 8.66 mg/dL; 95% CI − 14.05 to − 3.27; $I^2 = 69.1\%$), with no significant reduction in the food subgroup. Reduction in LDL-C was significant in the subgroup of Iranian population (WMD = − 9.07 mg/dL; 95% CI − 15.24 to − 2.91), multi-strain of bacteria (WMD = − 10.72 mg/dL; 95% CI − 17.06 to − 4.38), and fructooligosaccharide prebiotics (WMD = -8.79 mg/dL; 95% CI − 15.26 to − 2.33) compared to their counterparts (Table 3). Overall meta-analysis result for LDL-C was not sensitive to individual studies. No evidence of publication bias was also observed ($p = 0.67$, Begg's test and $p = 0.35$, Egger's test).

The effects of synbiotic consumption on HDL-C

The effect of the synbiotics consumption on HDL-C was reported in 23 clinical trials [1, 10, 18–38]. Synbiotics consumption significantly increased HDL-C level (WMD = 1.3 mg/dL; 95% CI, 0.03 to 2.56; $p = 0.04$) compared to control (Fig. 5). A moderate heterogeneity was observed ($I^2 = 43.0\%$, $p < = 0.01$). Subgroup analysis of intervention duration suggested a significant increase in serum HDL-C when intervention duration was longer

Table 2 Risk of bias assessment for included randomized controlled clinical trails

First author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Score	Overall quality
Malaguarnera (2012)	+	+	+	?	+	?	+	5	Good
Moroti (2012)	+	+	+	?	+	?	+	5	Good
Macfarlane (2013)	+	+	+	+	+	?	+	6	Good
Eslamparast (2014)	+	?	+	+	+	?	+	5	Good
Peña (2014)	+	?	+	?	+	?	+	4	Good
Asemi (2014)	+	?	+	+	+	?	+	5	Good
Sanchez (2014)	+	+	+	+	+	?	+	6	Good
Shakeri (2104)	+	?	+	+	+	?	+	5	Good
Bedani (2015)	+	?	+	+	+	?	+	5	Good
Ferolla (2016)	+	?	+	?	+	?	+	4	Good
Zamani (2017)	+	+	+	+	+	?	+	6	Good
Asgharian (2017)	+	+	+	+	+	–	+	6	Good
Tajabadi-Ebrahimi (2017)	+	+	+	+	+	?	+	6	Good
Ekhlasi (2017)	+	+	+	+	+	?	+	6	Good
Sadat Ebrahimi (2017)	+	+	+	+	+	?	+	6	Good
Mofidi (2017)	+	?	+	+	+	?	+	5	Good
Javadi (2018)	+	+	+	?	+	-	+	5	Good
Samimi (2018)	+	+	+	+	+	?	+	6	Good
Xavier-Santos (2018)	+	?	+	?	+	?	+	4	Good
Sayari (2018)	+	+	+	+	+	?	+	6	Good
Bakhshimoghaddam (2018)	+	?	+	+	+	?	+	5	Good
Soleimani (2018)	+	+	+	+	+	?	+	6	Good
Rabiei (2018)	+	+	+	+	+	?	?	5	Good

Based on cochrane collaboration risk of bias tool

than 8 weeks (WMD = 1.81 mg/dL; 95% CI 0.26 to 3.35; $I^2 = 37.0\%$), with no meaningful effect in shorter duration of intervention. Subgroup analysis based on participant's body weight status, source of synbiotics, geographic location, bacteria strains or prebiotics types did not result in meaningful differences (Table 3). Findings from the sensitivity analysis revealed that the exclusion of Eslamparast et al. [22] (WMD = 0.78 mg/dL; 95% CI − 0.17 to 1.7), Mofidi et al. [27] (WMD = 1.2 mg/dL; 95% CI − 0.13 to 2.53), Javadi et al. [24] (WMD = 1.17 mg/dL; 95% CI − 0.10 to 2.44), Shakeri et al. [34] (WMD = 1.04 mg/dL; 95% CI − 0.20 to 2.29), Sadat Ebrahimi et al. [31] (WMD = 1.27 mg/dL; 95% CI − 0.09 to 2.64), Asemi et al. [18] (WMD = 1.20 mg/dL; 95% CI − 0.07 to 2.48), and Sayari et al. [10] (WMD = 1.33 mg/dL; 95% CI − 0.11 to 2.77) studies from the analysis changed the overall effect. No evidence of publication bias was also observed ($p = 0.44$, Begg's test and $p = 0.70$, Egger's test).

Discussion

This systematic review and meta-analysis present evidence that synbiotics consumption may benefit lipid profile and improve dyslipidemia. The subgroup analyses of this study suggested a greater improvement in lipid profile may be

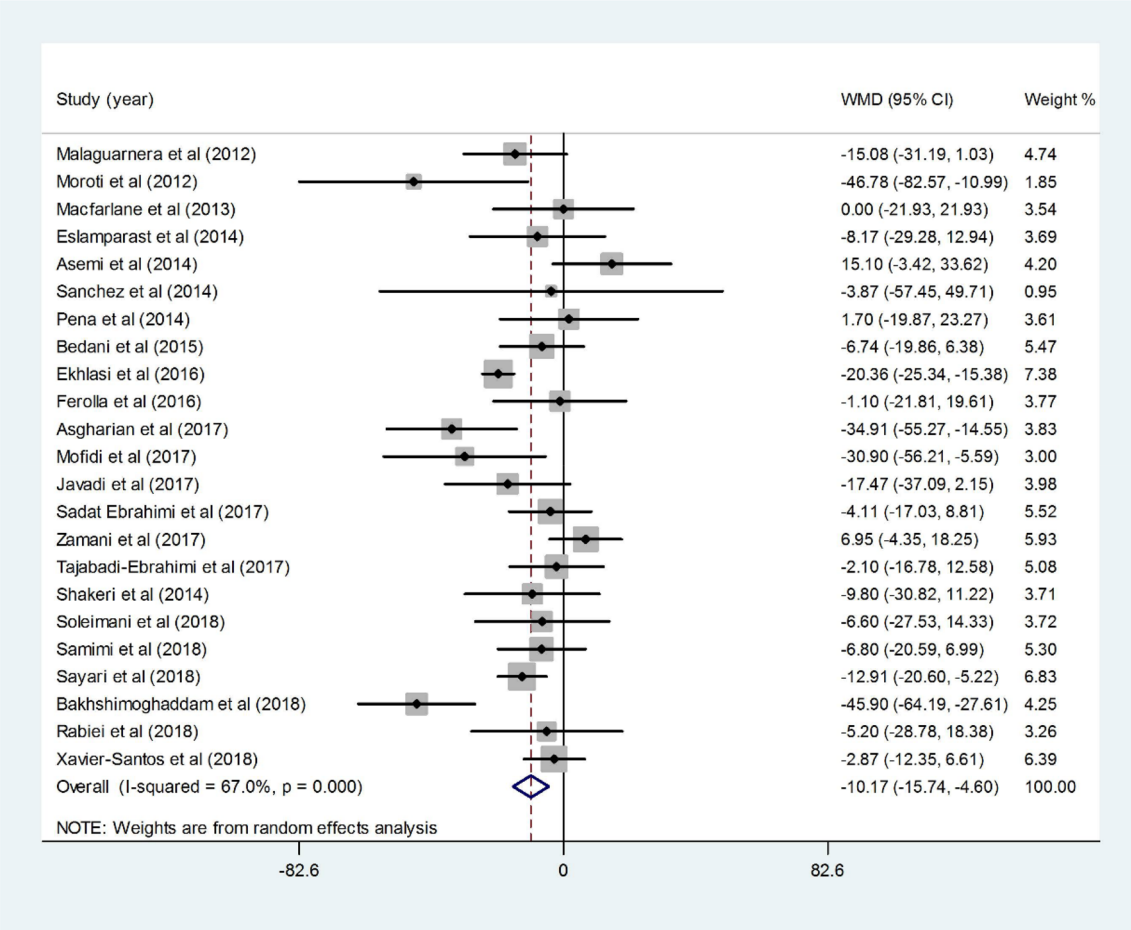

Fig. 2 Forest plot of the effect of synbiotic consumptation on TC. The dashed vertical line represents the overall meta-analysis effect. The straight vertical line represents the line of no effect. The results on the left of the no effect line favor the synbiotics over control

expected when synbiotics are consumed in supplement forms for more than 8 weeks.

Due to the synergic effect of probiotics and prebiotics in synbiotic supplements and foods, they may have greater potential in modulating the gut microbiota than either probiotics or prebiotics alone. It has been suggested that synbiotic supplementation may improve lipid metabolism, insulin resistance, inflammatory mediators and liver enzymes markers by improving gut microbiota [39]. The combination of probiotics and prebiotics may enhance the survival of bacteria passing the upper part of the gastrointestinal tract and reaching large bowel, where they may colonies and change the balance of gut flora [13]. The more pronounced effect observed on lipid profile from synbiotics supplements compared to synbiotic foods can also be explained by the potentially better survival rate of live cultures in the gastrointestinal tract in a form of supplement compared to food due to the extra protection provided by supplementation.

The mechanism of the effect of synbiotic on lipid profile has remained largely unknown. Probiotics may improve serum lipid profile via their immunomodulatory properties [40]. Probiotics may reduce inflammatory cytokines and Toll-like receptor 4 (TLR4) activation which may explain their beneficial impact on serum lipid profile [41]. TLR4 is a transmembrane protein which when activated can lead to inflammatory cytokines production. These inflammatory cytokines are responsible for activation of the innate immune system [42]. Activation of the innate immune system through TLR4 is involved in the pathogenesis of insulin resistance, diabetes, and atherosclerosis [43]. Also, probiotics are able to integrate cholesterol in their cellular membrane [44] or convert cholesterol into coprostanol [45] leading to a reduction in cholesterol absorption and serum TC levels. In addition, some probiotics can produce hydrolases which reduce cholesterol absorption via higher bile salt excretion [46, 47]. Also, probiotics can produce short-chain fatty acids (SCFA) such as propionate and butyrate

Table 3 Subgroup analysis to assess the effect of synbiotic consumption on lipid parameters

Sub-grouped by	No. of trials	Effect size[a]	95% CI	I^2 (%)	P for heterogeneity	P for between subgroup heterogeneity
TC						
Duration of intervention						0.94
> 8 weeks	13	− 12.15	− 18.56, − 5.74	43.9	0.04	
≤ 8 weeks	10	− 7.89	− 17.80, 2.02	80.1	< 0.001	
Participants' BMI status						0.15
Overweight	13	− 10.44	− 17.71, − 3.17	72.9	< 0.001	
Obese	10	− 9.80	− 18.95, − 0.66	55.9	0.01	
Source of the synbiotic						0.24
Supplement	17	− 9.61	− 15.28, − 3.94	57.0	< 0.001	
Food	6	− 13.68	− 29.99, 2.64	82.2	< 0.001	
Geographical population						0.02
Iranian	15	− 11.57	− 18.73, − 4.41	74.0	< 0.001	
Other	8	− 6.34	− 13.51, 0.84	21.3	0.26	
Number of used strain						< 0.001
Multi	15	− 13.84	− 20.66, − 7.01	71.2	< 0.001	
Single	8	− 2.44	− 8.98, 4.10	7.6	0.37	
Type of prebiotic substrate						< 0.001
Fructooligosaccharide	12	− 14.36	− 20.39, − 8.33	45.9	0.04	
Inulin	9	− 7.09	− 18.08, 3.89	73.5	< 0.001	
Both	2	− 2.42	− 11.12, 6.29	0.0	0.81	
TG						
Duration of intervention						< 0.001
> 8 weeks	13	− 21.89	− 35.02, − 8.76	66.0	< 0.001	
≤ 8 weeks	10	− 4.38	− 22.16, 13.40	76.1	< 0.001	
Participants' BMI status						0.38
Overweight	13	− 10.61	− 21.00, − 0.21	57.3	< 0.001	
Obese	10	− 21.68	− 47.25, 3.88	83.6	< 0.001	
Source of the synbiotic						0.17
Supplement	17	− 13.25	− 21.01, − 5.50	31.2	0.1	
Food	6	− 21.98	− 61.77, 17.81	90.9	< 0.001	
Geographical population						< 0.001
Iranian	15	− 19.57	− 31.22, − 7.91	70.4	< 0.001	
Other	8	− 0.56	− 21.94, 20.82	63.7	0.01	
Number of used strain						< 0.001
Multi	15	− 19.58	− 30.84, − 8.32	66.8	< 0.001	
Single	8	− 2.08	− 25.39, 21.24	73.3	< 0.001	
Type of prebiotic substrate						< 0.001
Fructooligosaccharide	12	− 12.67	− 25.70, 0.41	57.7	< 0.001	
Inulin	9	− 23.03	− 40.61, − 5.44	73.5	< 0.001	
Both	2	21.28	− 7.90, 34.66	0.0	0.53	
LDL-C						
Duration of intervention						0.15
> 8 weeks	13	− 10.50	− 17.28, − 3.72	61.0	< 0.001	
≤ 8 weeks	8	− 5.53	− 13.06, 2.00	79.9	< 0.001	
Participants' BMI status						< 0.001
Overweight	11	− 9.04	− 16.36, − 1.72	78.0	< 0.001	

Table 3 (continued)

Sub-grouped by	No. of trials	Effect size[a]	95% CI	I^2 (%)	P for heterogeneity	P for between subgroup heterogeneity
Obese	10	− 7.13	− 12.92, − 1.35	42.0	0.07	
Source of the synbiotic						0.13
Supplement	17	− 8.66	− 14.05, − 3.27	69.1	< 0.001	
Food	4	− 7.29	− 20.58, 6.01	78.1	< 0.001	
Geographical population						0.01
Iranian	15	− 9.07	− 15.24, − 2.91	72.2	< 0.001	
Other	6	− 6.42	− 14.47, 1.63	63.5	0.02	
Number of used strain						< 0.001
Multi	14	− 10.72	− 17.06, − 4.38	70.5	< 0.001	
Single	7	− 4.38	− 11.12, 2.35	57.0	0.03	
Type of prebiotic substrate						0.54
Fructooligosaccharide	11	− 8.79	− 15.26, − 2.33	73.8	< 0.001	
Inulin	9	− 8.32	− 17.11, 0.47	71.8	< 0.001	
Both	1	3.10	− 20.26, 26.46	73.4		
HDL-C						
Duration of intervention						0.09
> 8 weeks	13	1.81	0.26, 3.35	37.0	0.08	
≤ 8 weeks	10	0.71	− 1.42, 2.84	46.4	0.05	
Participants' BMI status						0.16
Overweight	13	0.82	− 0.19, 1.82	0.0	0.4	
Obese	10	2.00	− 0.72, 4.71	63.6	< 0.001	
Source of the synbiotic						0.67
Supplement	17	1.25	− 0.18, 2.67	39.2	0.05	
Food	6	1.78	− 1.28, 4.85	58.7	0.03	
Geographical population						0.05
Iranian	15	1.68	0.16, 3.21	53.6	< 0.001	
Other	8	− 0.52	− 2.46, 1.42	0.0	0.62	
Number of used strain						0.77
Multi	15	1.25	− 0.25, 2.74	50.6	0.01	
Single	8	1.64	− 1.25, 4.53	39.9	0.12	
Type of prebiotic substrate						0.10
Fructooligosaccharide	12	1.66	− 0.5, 3.47	53.3	0.01	
Inulin	9	1.32	− 0.61, 3.26	21.5	0.2	
Both	2	− 1.62	− 4.40, 1.16	0.0	0.54	

TC, total cholestrol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

[a]Calculated by Random-effects model

which are product of prebiotics fermentation [48]. SCFA prevent hydroxymethylglutaryl CoA reductase (HMG-CoA reductase) activation, which is a rate-limiting enzyme in the pathway of cholesterol synthesis, leading to lower cholesterol metabolism and better lipid metabolism [49].

Another possible mechanism of the effect of synbiotics on lipid profile is by reducing inflammation and insulin resistance, the storage of triglycerides in the liver, de novo lipogenesis driving by carbohydrate-responsive element-binding protein (ChREBP)/ sterol regulatory element-binding protein (SREBP), and very low-density lipoprotein (VLDL) secretion. Synbiotics promote the secretion of fasting-induced adipose factor (FIAF), which in turn restrains endothelial lipoprotein lipase (LPL), which is responsible for releasing triglycerides from circulating chylomicrons and VLDL. Increased serum FIAF levels also lead to the

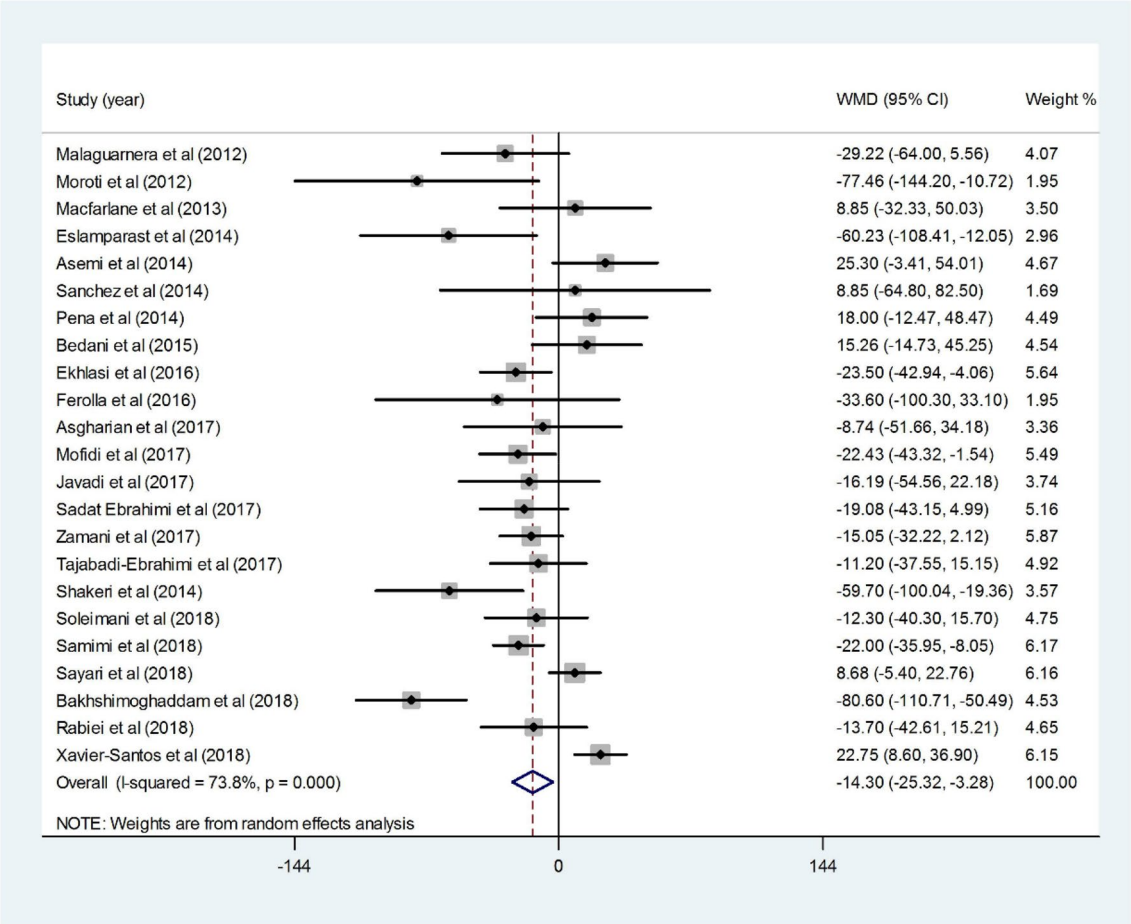

Fig. 3 Forest plot of the effect of synbiotic consumptation on TG. The dashed vertical line represents the overall meta-analysis effect. The straight vertical line represents the line of no effect. The results on the left of the no effect line favor the synbiotics over control

deactivation of hepatic lipogenic enzymes by ChREBP and SREBP-1c, resulting in a reduction of triglyceride storage in adipocytes and liver [50]. Synbiotics may also increase circulating levels of glucagon-like peptide-1 (GLP-1). GLP-1 is involved in many metabolic pathways, including the stimulation of glucose-dependent insulin secretion, blockade of postprandial glucagon release, and induction of pancreatic beta-cell proliferation [51, 52]. Literature suggests that GLP-1 directly hinders triglyceride absorption from the gut, potentially by inhibiting gastric lipases [53].

The effect of synbiotics in increasing blood HDL-C level observed in this study has important implications for CVD prevention and management. This systematic review only focused on HDL-C levels (HDL quantity) and not on the protein-to-lipid ratio in HDL-C particles (HDL-C functionality)—which is as important as HDL-C level in CVD protection [54]. However, even a small 10 mg/L increase in HDL-C may reduce the risk of CVD by 2–3% [55]. Therefore, the 1.3 mg/dL (13 mg/L) increase observed in HDL-C in this study has great clinical and public health implications.

To our knowledge, the present study is first to clarify the effect of synbiotics on lipid profile using a systematic review and meta-analysis. However, there are some limitations in this study that should be taken into account when interpreting the results. First, a significant heterogeneity was detected

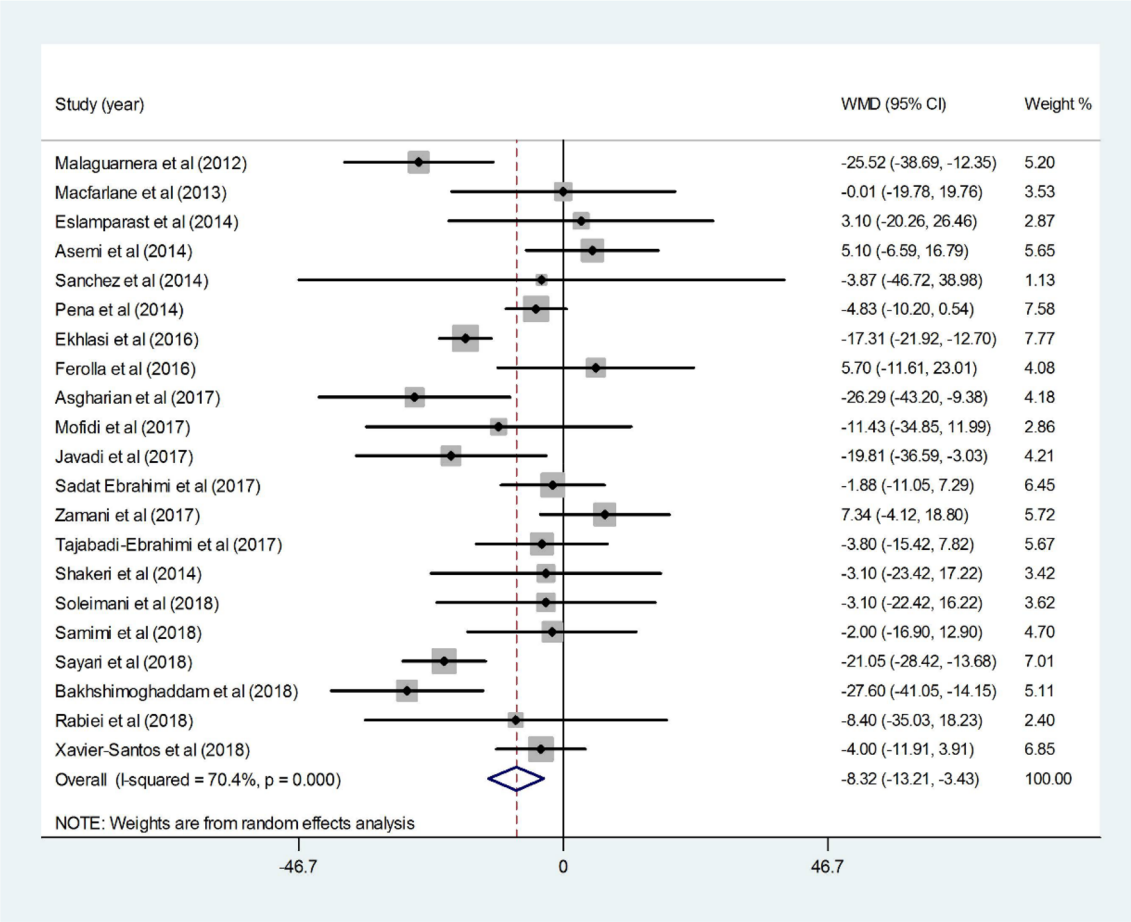

Fig. 4 Forest plot of the effect of synbiotic consumptation on LDL-C. The dashed vertical line represents the overall meta-analysis effect. The straight vertical line represents the line of no effect. The results on the left of the no effect line favor the synbiotics over control

between included studies. While the source of heterogeneity has been explored, other factors such as the dosage of synbiotic used, the health status of included population, baseline age of participants, and study conditions may influence the heterogeneity. Second, most of the included studies were conducted in Iran and Brazil. Therefore, it is difficult to generalize the results to the rest of the populations.

Conclusion

Overall this systematic review and meta-analysis suggested that synbiotics consumption may be beneficial in reducing blood TC, TG, LDL-C and increasing HDL-C levels. Also, the magnitude of effect is greater when synbiotics are administered in supplement form for more than 8 weeks. Future interventions with different synbiotics dose, bacteria strains and prebiotics types are required to explore the effect and possible mechanism of the influence of synbiotics on lipid profile.

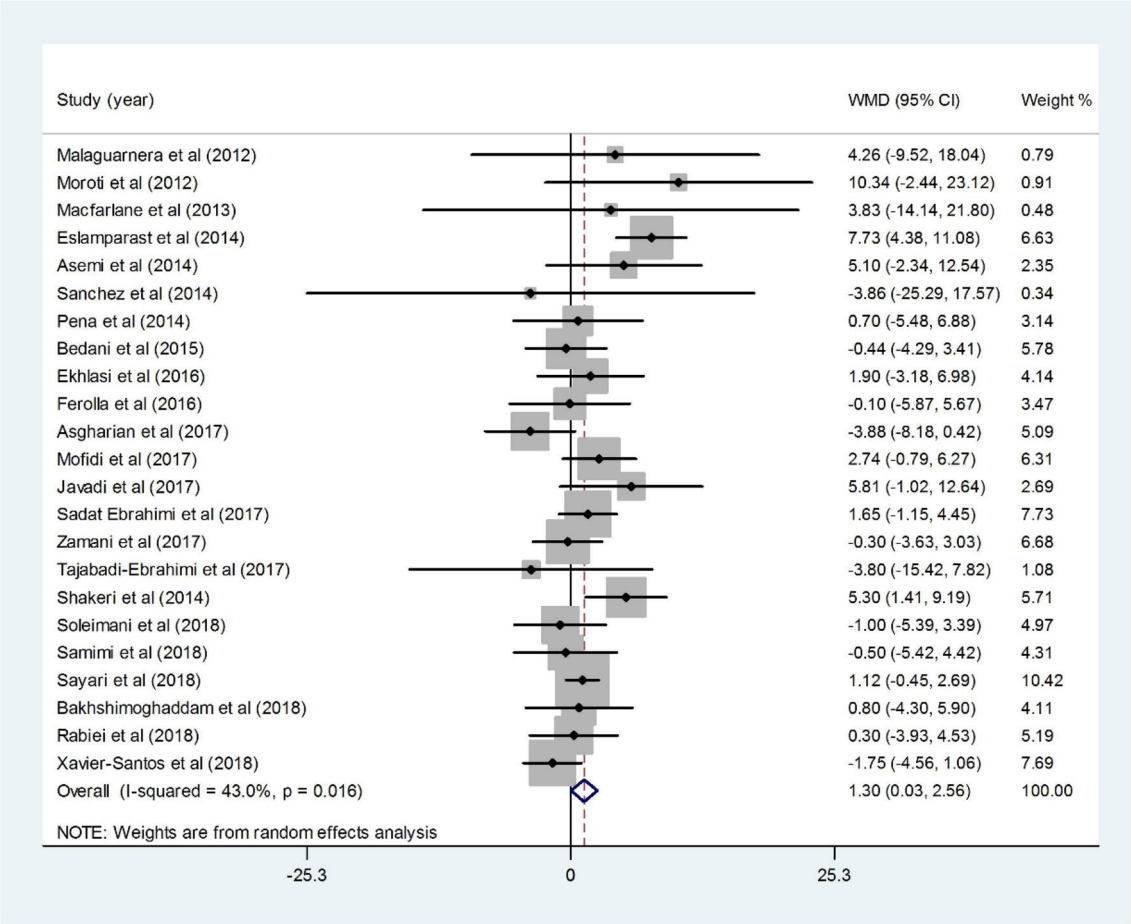

Fig. 5 Forest plot of the effect of synbiotic consumption on HDL-C. The dashed vertical line represents the overall meta-analysis effect. The straight vertical line represents the line of no effect. The results on the left of the no effect line favor the synbiotics over control

Author contribution AH and AA contributed to the conception of research. AH, MP and EG searched databases, screened articles and extracted data. AH and MP performed statistical analysis; and all authors contributed to the writing and revision of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Bedani R, Rossi EA, Cavallini DCU, Pinto RA, Vendramini RC, Augusto EM, Abdalla DSP, Saad SMI (2015) Influence of daily consumption of synbiotic soy-based product supplemented with okara soybean by-product on risk factors for cardiovascular diseases. Food Res Int 73:142–148
2. Goff DC, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY, Psaty BM (2006) Dyslipidemia prevalence, treatment, and control in the multi-ethnic study of atherosclerosis (MESA). Circulation 113(5):647–656. https://doi.org/10.1161/CIRCULATIONAHA.105.552737
3. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW (2007) Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 115(1):114–126
4. National Institutes of Health (2001) Third report of the national cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III), vol 285. National Institutes of Health, Bethesda, MD, pp 2486–2497
5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA (2019) Corrigendum to "2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk". Atherosclerosis 290(2019):140–205
6. Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ (2015) Dysbiosis of the gut microbiota in disease. Microbial Ecol Health Dis 26(1):26191
7. Chang C, Lin H (2016) Dysbiosis in gastrointestinal disorders. Best Pract Res Clin Gastroenterol 30(1):3–15

8. Gérard P (2016) Gut microbiota and obesity. Cell Mol Life Sci 73(1):147–162
9. Targher G, Day CP, Bonora E (2010) Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 363(14):1341–1350
10. Sayari S, Neishaboori H, Jameshorani M (2018) Combined effects of synbiotic and sitagliptin versus sitagliptin alone in patients with nonalcoholic fatty liver disease. Clin Mol Hepatol 24(3):331
11. Hotel ACP, Cordoba A (2001) Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Prevention 5(1):1–10
12. Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid MB (2004) Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev 17(2):259–275
13. De Vrese M, Schrezenmeir AJ (2008) Probiotics, prebiotics, and synbiotics. In: Food biotechnology. Springer, Berlin, Heidelberg, pp 1–66
14. Moher D, Liberati A, Tetzlaff J, Altman DG (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8(5):336–341
15. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
16. Follmann D, Elliott P, Suh I, Cutler J (1992) Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol 45(7):769–773
17. Green S. Higgins J (2005) Cochrane handbook for systematic reviews of interventions. Version
18. Asemi Z, Khorrami-Rad A, Alizadeh S-A, Shakeri H, Esmaillzadeh A (2014) Effects of synbiotic food consumption on metabolic status of diabetic patients: a double-blind randomized cross-over controlled clinical trial. Clin Nutr 33(2):198–203
19. Asgharian A, Mohammadi V, Gholi Z, Esmaillzade A, Feizi A, Askari G (2017) The effect of synbiotic supplementation on body composition and lipid profile in patients with NAFLD: a randomized, double blind, placebo-controlled clinical trial study. Iranian Red Crescent Med J 19(4):e42902
20. Bakhshimoghaddam F, Shateri K, Sina M, Hashemian M, Alizadeh M (2018) Daily consumption of synbiotic yogurt decreases liver steatosis in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. J Nutr 148(8):1276–1284
21. Ekhlasi G, Kolahdouz Mohammadi R, Agah S, Zarrati M, Hosseini AF, Arabshahi SS, Shidfar F (2016) Do symbiotic and Vitamin E supplementation have favorite effects in non-alcoholic fatty liver disease? A randomized, double-blind, placebo-controlled trial. J Res Med Sci 21:106. https://doi.org/10.4103/1735-1995.193178
22. Eslamparast T, Zamani F, Hekmatdoost A, Sharafkhah M, Eghtesad S, Malekzadeh R, Poustchi H (2014) Effects of synbiotic supplementation on insulin resistance in subjects with the metabolic syndrome: a randomised, double-blind, placebo-controlled pilot study. Br J Nutr 112(3):438–445
23. Ferolla SM, Couto CA, Costa-Silva L, Armiliato GN, Pereira CA, Martins FS, Ferrari MdLA, Vilela EG, Torres HO, Cunha AS (2016) Beneficial effect of synbiotic supplementation on hepatic steatosis and anthropometric parameters, but not on gut permeability in a population with nonalcoholic steatohepatitis. Nutrients 8(7):397
24. Javadi L, Ghavami M, Khoshbaten M, Safaiyan A, Barzegari A, Gargari BP (2017) The potential role of probiotics or/and prebiotic on serum lipid profile and insulin resistance in alcoholic fatty liver disease: a double blind randomized clinical trial. Crescent J Med Biol Sci 4:131–138
25. Macfarlane S, Cleary S, Bahrami B, Reynolds N, Macfarlane G (2013) Synbiotic consumption changes the metabolism and composition of the gut microbiota in older people and modifies inflammatory processes: a randomised, double-blind, placebo-controlled crossover study. Aliment Pharmacol Ther 38(7):804–816
26. Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, Mastrojeni S, Malaguarnera G, Mistretta A, Volti GL (2012) Bifidobacterium longum with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. Dig Dis Sci 57(2):545–553
27. Mofidi F, Poustchi H, Yari Z, Nourinayyer B, Merat S, Sharafkhah M, Malekzadeh R, Hekmatdoost A (2017) Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. Br J Nutr 117(5):662–668
28. Moroti C, Magri LFS, de Rezende CM, Cavallini DC, Sivieri K (2012) Effect of the consumption of a new symbiotic shake on glycemia and cholesterol levels in elderly people with type 2 diabetes mellitus. Lipids Health Dis 11(1):29
29. Peña F, Mizgier ML, Morales P, Rios I, Carrasco-Pozo C, Diaz E, Brunser O, Gotteland M (2014) Effect of the synbiotic (B. animalis spp. lactis Bb12+ oligofructose) in obese subjects. A randomized, double-blind, controlled clinical trial. J Food Nutr Res 2:491–498
30. Rabiei S, Hedayati M, Rashidkhani B, Saadat N, Shakerhossini R (2019) The effects of synbiotic supplementation on body mass index, metabolic and inflammatory biomarkers, and appetite in patients with metabolic syndrome: a Triple-Blind randomized controlled trial. J Dietary Suppl 16(3):294–306
31. Sadat Ebrahimi Z, Nasli-Esfahani E, Nadjarzade A, Mozaffari-khosravi H (2017) Effect of symbiotic supplementation on glycemic control, lipid profiles and microalbuminuria in patients with non-obese type 2 diabetes: a randomized, double-blind, clinical trial. J Diabetes Metab Disord 16(1):23
32. Samimi M, Dadkhah A, Kashani HH, Tajabadi-Ebrahimi M, Hosseini ES, Asemi Z (2019) The effects of synbiotic supplementation on metabolic status in women with polycystic ovary syndrome: a randomized double-blind clinical trial. Probiotics Antimicrob Proteins 11(4):1355–61
33. Sanchez M, Darimont C, Drapeau V, Emady-Azar S, Lepage M, Rezzonico E, Ngom-Bru C, Berger B, Philippe L, Ammon-Zuffrey C (2014) Effect of Lactobacillus rhamnosus CGMCC1. 3724 supplementation on weight loss and maintenance in obese men and women. Br J Nutr 111(8):1507–1519
34. Shakeri H, Hadaegh H, Abedi F, Tajabadi-Ebrahimi M, Mazroii N, Ghandi Y, Asemi Z (2014) Consumption of synbiotic bread decreases triacylglycerol and VLDL levels while increasing HDL levels in serum from patients with type-2 diabetes. Lipids 49(7):695–701
35. Soleimani A, Motamedzadeh A, Mojarrad MZ, Bahmani F, Amirani E, Ostadmohammadi V, Tajabadi-Ebrahimi M, Asemi Z (2019) The effects of synbiotic supplementation on metabolic status in diabetic patients undergoing hemodialysis: a randomized, double-Blinded, placebo-controlled trial. Probiot Antimicrob Proteins 11(4):1248–56
36. Tajabadi-Ebrahimi M, Sharifi N, Farrokhian A, Raygan F, Karamali F, Razzaghi R, Taheri S, Asemi Z (2017) A randomized controlled clinical trial investigating the effect of synbiotic administration on markers of insulin metabolism and lipid profiles in overweight type 2 diabetic patients with coronary heart disease. Exp Clin Endocrinol Diabetes 125(01):21–27
37. Xavier-Santos D, Lima ED, Simão ANC, Bedani R, Saad SMI (2018) Effect of the consumption of a synbiotic diet mousse containing *Lactobacillus acidophilus* La-5 by individuals with metabolic syndrome: a randomized controlled trial. J Funct Foods 41:55–61

38. Zamani B, Farshbaf S, Golkar HR, Bahmani F, Asemi Z (2017) Synbiotic supplementation and the effects on clinical and metabolic responses in patients with rheumatoid arthritis: a randomised, double-blind, placebo-controlled trial. Br J Nutr 117(8):1095–1102
39. Mohammadi H, Miraghajani M, Ghaedi E (2018) Efficacy of synbiotic supplementation in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of clinical trials: Synbiotic supplementation and NAFLD AU - Hadi. Crit Rev Food Sci Nutr. https://doi.org/10.1080/10408398.2018.1458021
40. Konstantinov SR, Smidt H, de Vos WM, Bruijns SC, Singh SK, Valence F, Molle D, Lortal S, Altermann E, Klaenhammer TR, Van Kooyk Y (2008) S layer protein A of Lactobacillus acidophilus NCFM regulates immature dendritic cell and T cell functions. Proc Natl Acad Sci 105(49):19474–19479
41. Ouwehand AC, Tiihonen K, Saarinen M, Putaala H, Rautonen N (2008) Influence of a combination of *Lactobacillus acidophilus* NCFM and lactitol on healthy elderly: intestinal and immune parameters. Br J Nutr 101(3):367–375
42. Brubaker SW, Bonham KS, Zanoni I, Kagan JC (2015) Innate immune pattern recognition: a cell biological perspective. Annu Rev Immunol 33:257–290. https://doi.org/10.1146/annurev-immunol-032414-112240
43. Dasu MR, Devaraj S, Park S, Jialal I (2010) Increased toll-like receptor (TLR) activation and TLR ligands in recently diagnosed type 2 diabetic subjects. Diabetes Care 33(4):861–868
44. Kimoto H, Ohmomo S, Okamoto T (2002) Cholesterol removal from media by *Lactococci*. J Dairy Sci 85(12):3182–3188
45. Lye H-S, Rusul G, Liong M-T (2010) Removal of cholesterol by lactobacilli via incorporation and conversion to coprostanol. J Dairy Sci 93(4):1383–1392
46. Begley M, Hill C, Gahan CG (2006) Bile salt hydrolase activity in probiotics. Appl Environ Microbiol 72(3):1729–1738
47. Patel AK, Singhania RR, Pandey A, Chincholkar SB (2010) Probiotic bile salt hydrolase: current developments and perspectives. Appl Biochem Biotechnol 162(1):166–180
48. De Preter V, Vanhoutte T, Huys G, Swings J, De Vuyst L, Rutgeerts P, Verbeke K (2007) Effects of Lactobacillus casei Shirota, Bifidobacterium breve, and oligofructose-enriched inulin on colonic nitrogen-protein metabolism in healthy humans. Am J Physiol Gastrointestinal Liver Physiol 292(1):G358–G368
49. Zhuang G, Liu X-M, Zhang Q-X, Tian F-W, Zhang H, Zhang H-P, Chen W (2012) Research advances with regards to clinical outcome and potential mechanisms of the cholesterol-lowering effects of probiotics. Clin Lipidol 7(5):501–507
50. Leung C, Rivera L, Furness JB, Angus PW (2016) The role of the gut microbiota in NAFLD. Nat Rev Gastroenterol Hepatol 13(7):412
51. Lee J, Hong S-W, Rhee E-J, Lee W-Y (2012) GLP-1 receptor agonist and non-alcoholic fatty liver disease. Diabetes Metab J 36(4):262–267
52. Campbell JE, Drucker DJ (2013) Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 17(6):819–837
53. Wojdemann M, Wettergren A, Sternby B, Holst JJ, Larsen S, Rehfeld JF, Olsen O (1998) Inhibition of human gastric lipase secretion by glucagon-like peptide-1. Dig Dis Sci 43(4):799–805
54. Ganjali S, Blesso CN, Banach M, Pirro M, Majeed M, Sahebkar A (2017) Effects of curcumin on HDL functionality. Pharmacol Res 119:208–218
55. Ali KM, Wonnerth A, Huber K, Wojta J (2012) Cardiovascular disease risk reduction by raising HDL cholesterol–current therapies and future opportunities. Br J Pharmacol 167(6):1177–1194