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The effect of probiotic and synbiotic supplementation on appetite-regulating hormones and desire to eat: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Recent studies have demonstrated the effect of probiotics, prebiotics, and synbiotics on adiponectin and leptin levels; however, those findings remain contested. The present study aimed to explore the impact of probiotics/synbiotics on appetite-regulating hormones and the desire to eat.

Methods: A systematic review was conducted by searching the Medline (PubMed) and Scopus databases from inception to December 2021, using relevant keywords and MeSH terms, and appropriate randomized controlled trials (RCTs) were extracted. The standardized mean differences (SMD) and 95% confidence intervals (95%CIs) were calculated as part of the meta-analysis using a random-effect model to determine the mean effect sizes. Analysis of Galbraith plots and the Cochrane Chi-squared test were conducted to examine heterogeneity.

Results: Meta-analysis of data from a total of 26 RCTs (n = 1536) showed a significant decrease in serum/plasma leptin concentration following probiotic/synbiotic supplementation (SMD: −0.38, 95%CI= −0.638, −0.124); P-value= 0.004; I^2= 69.4%; P heterogeneity < 0.001). The leptin level decrease from probiotic/synbiotic supplementation was higher in patients with NAFLD than those with overweight/obesity or type 2 diabetes mellitus/metabolic syndrome/ prediabetes. Probiotic/synbiotic supplementation was associated with a trending increase in adiponectin levels, stronger in patients with type 2 diabetes mellitus, metabolic syndrome, and prediabetes (SMD: 0.25, 95%CI= 0.04, 0.46) μg/mL; P-value= 0.021; I^2 = 16.8%; P heterogeneity= 0.30). Additionally, supplementation with probiotic/synbiotic was linked to a slight increase in desire to eat (SMD: 0.34, 95%CI= 0.03, 0.66) P-value = 0.030; I^2 = 39.4%; P heterogeneity= 0.16).

Conclusion: Our meta-analysis indicates a favorable impact of probiotic/synbiotic supplementation on regulating leptin and adiponectin secretion.

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1. Introduction

The human gut harbors a variety of bacteria shown to contribute significantly to health and disease [1,2]. The gut microbiota can affect the host's immune and metabolic processes, inflammation levels, and homeostasis [3,4]. It is the primary source of several vital metabolites, especially short-chain fatty acids (SCFAs), hydrogen sulfide (H_2S), indoles, trimethylamine, and vitamins K and B. In addition, the intestinal microbiota is essential in regulating bile acid, steroid, and cholesterol metabolism processes [5,6]. As an additional feature, the microbiome also contributes significantly to maintaining host homeostasis, controlling immune response and hormone function [5,6]. Dysbiosis is understood as a shift in the balance between an abundance of nonpathogenic (commensal) and pathogenic microorganisms, often associated with reduced overall diversity of the microbial community in the gut [5–9]. Recent reports have connected the alteration of gut microbiota to elevated intestinal permeability, endotoxemia, inflammation, and the onset and/or progression of chronic diseases, metabolic and immunologic dysfunction, and inflammation, such as seen in obesity, type 2 diabetes mellitus (T2DM), hepatic and gastrointestinal diseases, metabolic syndrome (MetSyn), hypertension, and cardiovascular diseases [5–11].

Probiotics are living microorganisms with nonpathogenic, advantageous traits for the host, including the ability to stimulate the immune system [7,8]. Synbiotics are probiotic supplements that contain prebiotic components such as an oligosaccharide mixture that support the growth and survival of these nonpathogenic microorganisms [12]. There is evidence that the health benefits of probiotics and synbiotics are driven by increased intestinal bacterial diversity and the release of numerous metabolites with antibacterial, anti-inflammatory, and immunomodulatory effects [12,13]. Studies have shown that altering the microbiome with probiotics and synbiotics can improve glucose sensitivity, reduce the production of pro-inflammatory mediators, and lower body fat by decreasing gut permeability and reducing endotoxemia [12,14–16].

Adiponectin and leptin are members of the adipokines secreted by white adipose tissue involved in inflammation and glucose homeostasis. Adiponectin seems to have insulin-sensitizing and anti-inflammatory properties that decrease obesity and T2DM. Leptin levels directly associate with adipocyte stores and decrease satiety. However, during obesity, this suppression is disturbed, which leads to an increased risk of obesity and T2DM. [17–20]. Current evidence reveals the effects of probiotics and synbiotics on various satiety-related factors, including leptin and adiponectin. However, there is still considerable uncertainty about the relative efficacy and duration of the effects of these supplements. Probiotics affect adipokine concentrations by altering the gut microbiota [14,21]. Synbiotic consumption has been shown to affect adiponectin levels [22]. In a previous systematic review that used meta-analysis to determine the effects of probiotics, prebiotics, or synbiotics on adiponectin and leptin levels in adults, adiponectin and leptin levels in the probiotics groups did not differ significantly from those of the control groups [21]. Even though probiotics are associated with several health benefits, the study did not find combined effects on adiponectin and leptin specifically. Yet, the meta-analysis was conducted on limited trials in which only a few qualified assessments were conducted, and the probiotic doses and strains used varied widely. Second, the included studies were limited by sample size and lack of control for comorbidities as well as age and other lifestyle characteristics [21]. The central aim of our systematic review and meta-analysis was therefore, to investigate the efficacy of probiotic and synbiotic supplementation on appetite and its regulating hormones, however the probable mechanistic pathways which can be evident mainly from in vitro and experimental studies, are not explore in the current analysis.

2. Methods

2.1. Search strategy

Using free-text terms, MeSH terms, and systematic literature searches in the Medline (PubMed) and Scopus databases, relevant publications were found from the beginning (1972) to December 5, 2021. Our initial search included only studies on humans published in English. We performed manual searches and cross-reference tracking to identify other relevant publications. The search terms used are described in Supplementary File 1. The keywords used are likewise described in Supplementary File 1. Two researchers (MN and ZGh) examined each publication individually and performed data extraction and quality assessment. Discussions were held with third parties (AK and MMR) to resolve any divergences until a consensus was reached.

The present report on our systematic review and meta-analysis was written and structured according to the PRISMA 2020 statement: an updated guideline for reporting systematic reviews [23]. The study protocol was previously prepared and is available in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) under registration number CRD42022334123 (Supplementary File 2).

2.2. Study selection

The PICOS criteria (Participants, Intervention, Comparison, Outcomes, Study design) were used to outline the research question as displayed in Table 1. Randomized controlled studies were selected that aimed to investigate the impacts of pro- or synbiotic consumption in the forms of foods or supplements on plasma and serum concentrations of at least one of the key appetite-regulating hormones and neurotransmitters (leptin, adiponectin, amylin, cholecystokinin, corticotropin-releasing factor, dopamine, ghrelin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, GLP-2, glucagon, oxyntomodulin, pancreatic polypeptide, peptide YY, gastrin, or neuropeptide-Y, serotonin) or and scores for appetite (defined as "desire to eat" score) based on visual analog scale or other specific measures applied in the trials. Studies were eligible to be included only if the baseline/end of the study values or changes in these factors throughout the trials in both intervention and control groups were reported (Table 1). Of these outcome measures, only leptin, adiponectin, and desire to eat were reported in enough studies for their meta-analysis to be robust. So the analysis was taken further for these three parameters specifically.

We excluded RCTs involving bariatric surgery or with subjects who were in severe stages of illness, acute infectious, inflammatory diseases (e.g., critically ill patients, hemodialysis patients, patients with severe neurological dysfunction, spinal cord injury, HIV/AIDS, etc.), as well as subjects who suffered from gestational diabetes, RCTs involving children, adolescents, or pregnant and lactating women. Furthermore, RCTs were excluded if the duration of probiotic/synbiotic intervention was less than six weeks, trials lacked a control group or used an experimental

Table 1
PICOS criteria for inclusion of studies.

Parameter	Criterion
Population	All adult subjects (healthy and unhealthy aged more than 18 years old)
Intervention	Probiotics (single strain or multi-strain) or synbiotic foods or supplements in form of a capsule, powder, sachet, tablet, liquid vial, milk, yogurt, drink, or soy milk, administered for at least six weeks
Comparison	Placebo supplements.
Outcomes	Plasma/serum levels of at least of the key appetite-regulating hormones and neurotransmitters (leptin, adiponectin, amylin, cholecystokinin, corticotropin-releasing factor, dopamine, ghrelin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, GLP-2, glucagon, oxyntomodulin, pancreatic polypeptide, peptide YY, gastrin, neuropeptide-Y, serotonin)
Study design	Parallel randomized, controlled trials.

or uncontrolled study design, and publications did not contain sufficient data for estimating changes in the variables of interest throughout the trial. We excluded studies in which dietary supplements were administered in combination with certain drugs or the form of enteral nutrition or breast milk. Finally, case series, book chapters, observational or experimental research, and review publications were excluded from the present meta-analysis. We used a two-step process to verify that the articles were appropriate for the study. First, a list of related publications was generated by MN, NSh, and ZGh, reviewing the titles, abstracts, and keywords of the selected articles. Second, two researchers (MN and ZGh) individually reviewed the full texts and performed data extraction for the final analysis and quality assessments of the included RCTs. In case of disagreement, affiliated researchers (AK and MMR) were consulted until a consensus was reached.

2.3. Data extraction

A selection of eligible trials for the final meta-analysis followed the data collected by MN, ZGh, MMR, and AK. For this, the researchers assessed details on publication (i.e., first author name, year of publication, and geographic region), main trial features (i.e., design, the studied subjects' health status and main demographic characteristics, type of intervention (probiotic or synbiotic), type of supplements applied (fortified foods, fermented products, supplements, etc.), the bacterial strains, dosage, trial duration, body mass index (BMI), and sample size of the subjects in the intervention and control arms), and the mean and standard deviations (SD) of serum or plasma levels of the variables of interest at baseline and end of the trial (or mean and SD of changes). For RCTs that assessed outcomes of interest at multiple time points, only the most recent time point was included in the meta-analysis. Each arm in which an independent intervention was implemented compared with the control group was considered a separate study for multi-arm studies. However, to avoid each subject studied being represented more than once in the meta-analysis, the sample size of the controls was divided by two in these cases.

2.4. Risk of bias assessment

The Cochrane Risk of Bias Tool for Randomized Controlled Trials was used to evaluate the risk of bias in the selected RCTs [24]. Multiple aspects of potential bias are considered in this systematic framework, such as: random sequence generation, allocation concealment, participant and researcher blinding, inadequate outcome data, blinding of outcome evaluator, and selective reporting of the studied variables. Two review authors (MN and ZGh) independently assessed the included publications and classified them as either unclear, low risk of bias, or high risk of bias. The classification was based on guidelines published by the Cochrane Collaboration. In case of disagreement, the affiliated investigator (AK) was consulted. After that, each RCT was finally classified as being of poor, fair, or good quality.

2.5. Statistical analysis

The present meta-analysis was performed using the STATA 16 software (StataCorp LC, Texas, USA). After data extraction, the reported "desire to eat" scores were encoded according to a visual analog scale (scored from 1 to 10). The units denoting serum/plasma levels of adiponectin and leptin were all coded in μg/mL and ng/mL, respectively. When the required baseline and end-of-study mean data were not available for the outcomes of interest, the associated SDs of the means in each arm studied were estimated instead using the method below:

SD_{change} = square root ($SD^{2}_{baseline} + SD_{final}{}^{2} - (2 \times r \times SD_{baseline} \times SD_{final})$), assuming a correlation coefficient (r) ≅ 0·8·

In the Zarrati et al., 2014 [21], Kazemi et al., 2019 [22], and Tonucci et al., 2016 [23] trials, the required data on the mean (SD) of before-after differences in leptin, desire to eat, and adiponectin levels, respectively, were estimated from the plots applying the Web Plot Digitizer software.

The outcome variable in each studied group was determined by subtracting the mean values before and at the end of the study. The mean differences between the groups were approximated by dividing these values by the mean (SD) of the changes between the groups. The heterogeneity was evaluated using the Cochrane Chi-squared test and visualized with Galbraith plots. An I^2 statistic of ≥ 50% (Cochrane Chi-squared) was considered to indicate significant heterogeneity. Mixed effect models were used for the final meta-analysis to determine the mean effect sizes under consideration of heterogeneity and trial features (i.e., age, sex, health conditions of the studied subjects, etc.). Effect sizes are presented as standardized mean differences (SMD). The 95% confidence intervals (95% CIs) are shown as forest plots (Figs. 2–4). The threshold for statistical significance (P value) was equal to 0.05.

2.5.1. Subgroup analyses

Five main subgroups were defined as follows: based on the health status of study participants (subdivided into studies including patients with overweight or obesity, non-alcoholic fatty liver disease (NAFLD), T2DM, MetSyn, or prediabetes, versus other conditions (e.g., healthy subjects, major depression, hypothyroidism)); based on the type of intervention (subdivided into supplementation with probiotics or synbiotics); based on the duration of follow-up (subdivided into shorter than 12 weeks or longer), based on the total dose of bacteria prescribed (subdivided into low dose (less than 1 ×10^10 CFU/day) vs high dose (more than 1 ×10^10 CFU/day)), and the form of intervention (subdivided into dietary supplements in the form of capsules/tablets/powder/pouches/drink vs fermented products containing probiotic bacteria), as well as according to the risk of bias assessment findings (or quality of included RCTs, subdivided into high risk of bias and low risk of bias studies).

2.5.2. Meta-regression

A random-effects meta-regression was performed to explore the associations of age and BMI as potential moderators and approximated net changes in the score for the desire to eat and adipokines (adiponectin and leptin) by applying the unrestricted maximum likelihood method.

2.5.3. Publication bias

Egger's weighted regression tests and visual inspection of funnel plot asymmetry were applied to approximate the potential risk for publication bias. A non-parametric random effect trim-and-fill (the Duval & Tweedie "trim and fill") method was considered in case of finding any potential risk for publication bias to take into account the influence of this bias [25] (Supplementary file 3).

2.5.4. Sensitivity/influence analysis

A leave-one-out sensitivity analysis was applied to explore the impact of each analyzed trial in estimating the overall effect size. A sensitivity analysis was additionally run to corroborate the influences of risk of bias on the observed findings by excluding the RCTs ranked as at high risk of bias (Supplementary File 4).

2.5.5. Certainty of evidence

The certainty of evidence was rated using the approach Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [26] (Supplementary file 7). RCTs start with high quality of evidence and may be downgraded according to the risk of bias, inconsistency (substantial heterogeneity without any probable explanations, $I^2 > 50\%$; $p < 0.05$), indirectness (the presence of any plausible cause that lower generalizability of the study findings), imprecision (95% CI for effect size are wide or sample size of lower than 400), and the evidence showing publication bias. According to the GRADE approach, the

certainty of evidence was ranked as high, moderate, low, and very low.

3. Results

Of the 908 records found during the literature search, 903 were considered for an initial assessment by scanning the titles and abstracts. Then, 316 publications were identified as potentially relevant papers and considered for the full-text evaluation (Fig. 1). Finally, 26 publications (one of them had two arms [27]) met the requirements for inclusion in the meta-analysis after thoroughly reviewing the retrieved articles. Fig. 1 shows the search process for the current meta-analysis.

3.1. Characteristics of included studies

In total, the 26 eligible RCTs included 1536 patients who were randomized into the intervention (n total=776, mean age=47.79 years, mean BMI=28.52 kg/m^2, received probiotics or synbiotics supplements in the form of capsules/tablet/powder) or control (n total=760, mean age=47.56 years, mean BMI=28.82 kg/m2, received placebo) groups.

All of the included articles were parallel, randomized, placebo-controlled trials published between 2002 and 2021, of which ten trials were conducted in Iran [22,28–36], four in Japan [37–40], two in Italy [41,42], Brazil [43,44], Sweden [27,74], and the United States [45,46], respectively. The remaining studies were each conducted in one of the following countries: Saudi Arabia [47], India [48], Canada [49], and Poland [50].

Probiotics supplements (containing mainly the bacterial genera *Lactobacillus* and *Bifidobacterium*) were administered in 22 study arms of the included studies. Synbiotic supplements (primarily consisting of a probiotic in addition to inulin or fructooligosaccharide) were prescribed in five study arms. As in the study by Mobini et al. [27], two intervention arms were compared, high dose and low dose versus placebo; each was here considered a separate study when conducting the meta-analysis. The duration of treatment with probiotics/synbiotics varied from study to study, ranging from thirty days to one year. None of the trials reported any serious adverse events due to the use of synbiotics/probiotics.

Table 2 shows the demographics and trial characteristics of the

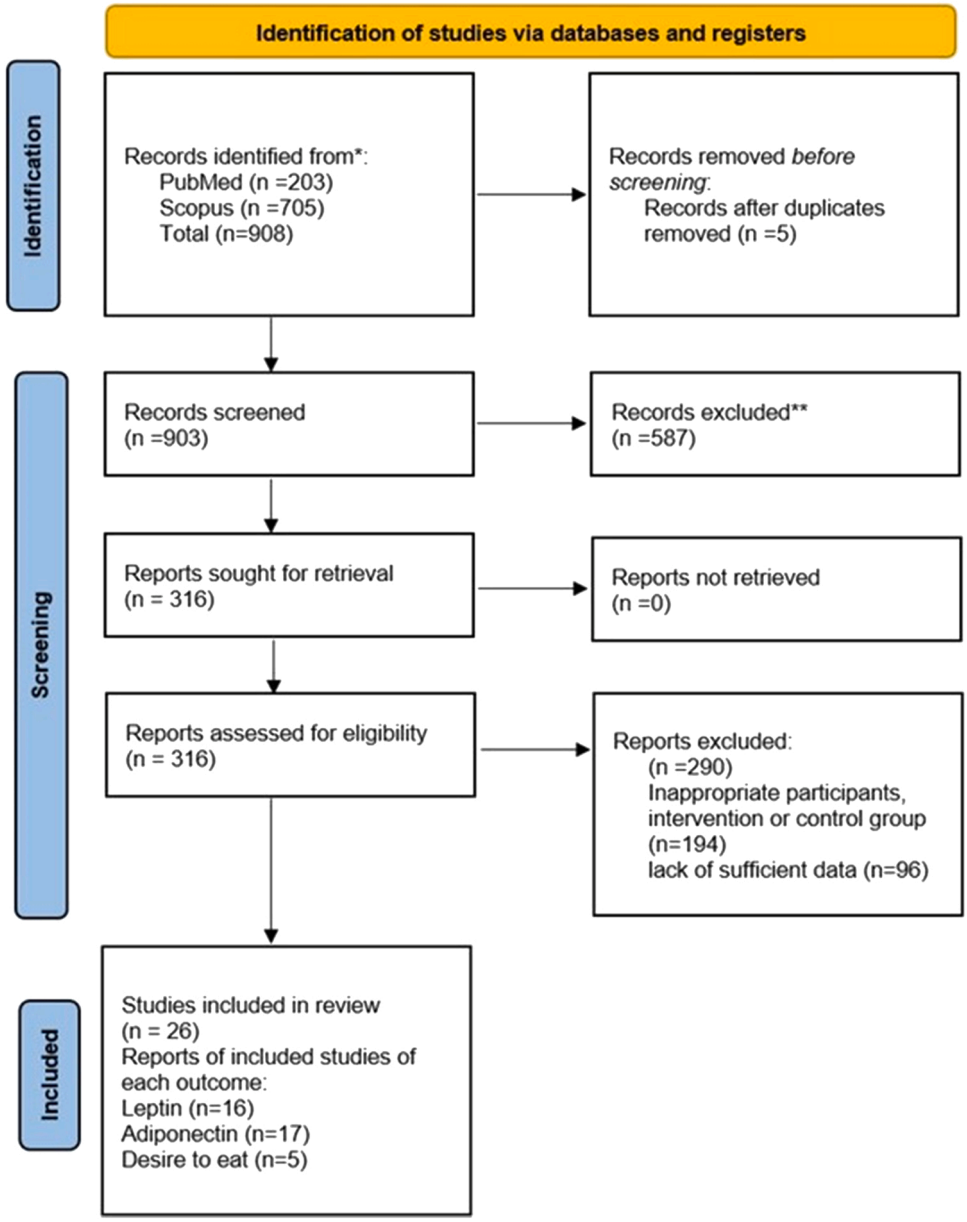

Fig. 1. Meta-analysis flow diagram.

Table 2
Included studies characteristics.

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
Naruszewicz et al. 2002 [74]	Sweden	randomized, double-blind, placebo-controlled study	other	F/M	Drink /Probiotic	L. plantarum 299 v	400 cc	400 * 5 * 10^7 high dose	6 weeks	42.3/41.8	18/18	24.8/25.8
McMullen et al. 2006[45]	United States	randomized, single-blind, placebo-controlled study	healthy	M	Capsules /Probiotic	Lactobacillus acidophilus, Bifidobacterium longum, 10–15 mg fructooligosaccharide	3	3 * 10^9 low dose	2 months	26/25	20/11	24.4/23.2
Kadooka et al. 2010[37]	Japan	randomized, double-blind, placebo-controlled study	overweight/ obesity	F/M	Milk /Probiotic	Streptococcus thermophilus, Lactobacillus delbrueckii ssp. Bulgaricus, Lactobacillus gasseri SBT2055	2	2 * 5 * 10^10 high dose	12 weeks	48.3/49.2	43/44	27.5/27.2
Sanchez et al. 2014[49]	Canada	randomized, double-blind, placebo-controlled study	overweight/ obesity	F/M	Capsules /Probiotic	Lactobacillus rhamnosus CGMCC1.3724, oligofructose and inulin	2	2 * 1.6 * 10^8 low dose	24 weeks	35/37	62/63	33.8/33.3
Zarrati et al. 2014[28]	Iran	randomized, double-blind, placebo-controlled study	overweight/ obesity	F/M	Yogurt /Probiotic	Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus acidophilus La5, Bifidobacterium BB12, and Lactobacillus casei DN001	1	10 ^ 8 low dose	8 weeks	36/36	25/25	33.8/33.9
Nabavi et al. 2015[29]	Iran	randomized, double-blind, placebo-controlled study	NAFLD	F/M	Yogurt /Probiotic	Lactobacillus bulgaricus, Streptococcus thermophilus, B. lactis Bb12, L. acidophilus La5	1	15.9 * 10^6 low dose	8 weeks	42.8/44.05	36/36	30.1/31.4
Ekhlasi et al. 2016[30]	Iran	randomized, double-blind, placebo-controlled study	NAFLD	F/M	Capsules /Synbiotic	Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus bulgaricus, fructooligosaccharide	2	2 * 7 * 2 × 10^8 low dose	8 weeks	/	15/15	27.28/27.84
Tonucci et al. 2016[43]	Brazil	randomized, double-blind, placebo-controlled study	T2DM	F/M	Milk /Probiotic	Lactobacillus acidophilus La-5, Bifidobacterium animalis subsp lactis BB-12	1	2 * 10^9 low dose	6 weeks	51.8/50.95	23/22	27.49/27.94
Behrouz et al. 2017[31]	Iran	randomized, double-blind, placebo-controlled study	NAFLD	F/M	Capsules /Probiotic	Lac tobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium breve	2	2 * 5 * 10^9 high dose	12 weeks	38.5/38.43	30/30	29.56/31.9
Sato et al. 2017 [38]	Japan	randomized, double-blind,	T2DM	F/M	Milk /Probiotic	Lactobacillus casei		4 × 10^10 high dose	16 weeks	64/65	34/34	24.2/24.6

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Table 2 (*continued*)

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
		placebo-controlled study										
Mobini et al. 2017[27]	Sweden	randomized, double-blind, placebo-controlled study	T2DM	F/M	Powder/ Sachet /Probiotic	Lactobacillus reuteri DSM 17938		10^8 low dose	12 weeks	66/65	15/8	30.6/30.7
Mobini et al. 2017[27]	Sweden	randomized, double-blind, placebo-controlled study	T2DM	F/M	Powder/ Sachet Probiotic	Lactobacillus reuteri DSM 17938		10^10 high dose	12 weeks	64/65	14/7	32.3/30.7
Feizollahzadeh et al. 2017 [32]	Iran	randomized, double-blind, placebo-controlled study	T2DM	F/M	Soy Milk /Probiotic	lactobacillus planetarum A7	1	2 * 10^7 low dose	8 weeks	56.9/53.6	20/20	26.68/26.58
Gomes et al. 2017[44]	Brazil	randomized, double-blind, placebo-controlled study	overweight/ obesity	F	Powder/ Sachet /Probiotic	Lactobacillus acidophilus LA-14, Lactobacillus casei LC-11, Lactococcus lactis LL-23, Bifidobacterium bifidum BB-06, Bifidobacterium lactis BL-4	4	2 * 10^10 high dose	8 weeks	/	21/22	31.7/33.34
Sabico et al. 2019[47]	Saudi Arabia	randomized, double-blind, placebo-controlled study	T2DM	F/M	Powder/ Sachet /Probiotic	Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19, L. lactis W58.	2	2 * 2.5 * 10^9 low dose	6-month	48/46.6	31/30	29.4/30.1
Duseja et al. 2019[48]	India	randomized, double-blind, placebo-controlled study	NAFLD	F/M	Capsules /Probiotic	Lactobacillus paracasei DSM 24733, Lactobacillus plantarum DSM 24730, Lactobacillus acidoph ilus DSM 24735 and Lactobacillus delbrueckii subsp. bulgar icus DSM 24734, Bifidobacterium longum DSM 24736, Bifidobacterium infantis DSM 24737, Bifidobacterium breve DSM 24732, Streptococcus thermophilus DSM 24731	2	675 billion low dose	1 year	38/33	19/20	26/27
Smith-Ryan et al. 2019 [46]	United States	randomized, double-blind, placebo-controlled study	healthy	F	Powder/ Sachet /Probiotic	Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, L.	2	2 * 2.5 * 10^9 low dose	6 weeks	30.5/30.2	12/18	25.1/24.3

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Table 2 (*continued*)

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
						casei W56, Lactobacillus salivarius W24, Lactococcus lactis (W19 and W58)						
Kazemi et al. 2019[33]	Iran	randomized, double-blind, placebo-controlled study	other	F/M	Powder/ Sachet /Probiotic	Lactobacillus helveticus R0052, Bifidobacterium longum R0175	1	$\geq 10 * 10^{9}$ high dose	8 weeks	36.2/36	28/26	26.2/26.6
Vafa et al. 2020 [34]	Iran	randomized, double-blind, placebo-controlled study	overweight/ obesity	F	Capsules /Synbiotic	Lactobacillus ca sei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophiles, 38.5 mg fructoligosaccharides.	1	10^{9} low dose	10 weeks	53.8/52.39	44/44	30.93/30.88
Toshimitsu et al. 2020 [39]	Japan	randomized, double-blind, placebo-controlled study	prediabetes	F/M	Yogurt /Probiotic	Lactobacillus plantarum OLL2712		$> 5 \times 10^{9}$ high dose	12 weeks	50.6/51.2	62/64	24.7/24.9
Narmaki et al. 2020[35]	Iran	randomized, double-blind, placebo-controlled study	overweight/ obesity	F	Capsules /Probiotic	Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium longum, Lactobacillus rhamnosus, Lactobacillus reuteri	2	$2 * 9.2 * 10^{9}$ low dose	12 weeks	35.2/33.9	31/31	34.5/34.3
Talebi et al. 2020[36]	Iran	randomized, double-blind, placebo-controlled study	other	F/M	Capsules /Synbiotic	Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Strepto coccus thermophilus, 40 mg fructooligosaccharide	1	$527 * 10^{8}$ low dose	8 weeks	42.4/43.96	29/27	26.88/27.1
Cicero et al. 2021[41]	Italy	randomized, double-blind, placebo-controlled study	metabolic syndrome	F/M	Liquid vial /Synbiotic	Lactobacillus plantarum PBS067, Lactobacillus acidophilus PBS066, Lactobacillus reuteri PBS072, prebiotic fibers, inulin, fructooligosaccharides	1	6×10^{9} low dose	60 days	72/71	30/30	27.4/27.3
Toshimitsu et al. 2021 [40]	Japan	randomized, double-blind, placebo-controlled study	overweight/ obesity	F/M	Yogurt/ Probiotic	Lactobacillus plantarum OLL2712		$> 5 \times 10^{9}$ low dose	12 weeks	45.5/44.7	46/46	27.4/27.5
Raji Lahiji et al. 2021[22]	Iran	randomized, triple-blind, placebo-	overweight/ obesity	F	Capsules /Synbiotic	Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus,	1	$7 * 10^{9}$ low dose	8 weeks	56.6/58.31	36/36	29.6/30

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Table 2 (*continued*)

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
		controlled study				Bifidobacterium breve, Bifidobacterium longum, and Streptococcus thermophiles, 35 mg fructoligosaccharides						
Rondanelli et al. 2021 [42]	Italy	randomized, double-blind, placebo-controlled study	overweight/ obesity	F/M	Capsules /Probiotic	Saccharomyces cerevisiae variant boulardii, strain DBVPG 6763, 500 IU SOD	2	2 * 5.0 × 10^9 high dose	60-Day	57.3/50.31	12/13	34.6/35.04
Folwarski et al. 2021[50]	Poland	randomized, placebo-controlled study	other	F/M	Capsules /Probiotic	Lactobacillus rhamnosus GG	1	6 * 10^6 low dose	30 days	57.3/66.5	20/20	23/24.8

T2DM: type 2 diabetes mellitus NAFLD: non alcoholic fatty live disease

included studies. Of the 26 selected studies, seven RCTs were related to patients with prediabetes or T2DM, nine RCTs were related to overweight or obese subjects, four were performed in NAFLD, one in MetSyn, four were related to other conditions, and two were conducted in healthy participants.

3.2. Quality assessment

Of the 26 included RCTs, eight were rated as good quality (overall low risk of bias), eleven were ranked as fair quality, and seven were rated as poor quality (overall high risk of bias). Although the majority of included RCTs addressed most of the bias-causing factors, several studies did not provide sufficient details on the procedures used to generate allocation concealment. The quality assessment of the included studies based on the Cochrane Risk of Bias Tool for Randomized Controlled Trials is shown in Table 3.

3.3. Quantitative data synthesis

3.3.1. Adiponectin

Mixed effect meta-analysis of data from 17 RCTs with 18 effect sizes indicated a trend towards an increase in serum/plasma adiponectin concentration after receiving probiotic/synbiotic supplements but could not conclude significance (SMD (95% CI) = 0.25 (−0.04, 0.53); P-value= 0.090; I^2 (%) = 80.6; P heterogeneity < 0.001) (Table 4, Fig. 2). The certainty of this finding is moderate (Supplementary file 7). Neither the health condition of the studied participants, probiotics daily dosage, the form of intervention, intervention duration, nor RCT quality form significant sources of heterogeneity.

The subgroup of RCTs on patients with T2DM, MetSyn, and prediabetes evidenced a significant increase in serum/plasma levels of adiponectin (SMD (95%CI) = 0.25 (0.04, 0.46) μg/mL; P-value= 0.021; I^2 (%)= 16.8; P heterogeneity= 0.297). However, changes in adiponectin levels between other subgroups did not differ significantly (Table 4), Supplementary File 5, Supplementary Figure 5a-e).

Meta-regression for BMI and age also did not reach significance (Table 5) (Supplementary File 6, Supplementary Figure 10 (a-b).

3.3.2. Leptin

Random-effect meta-analysis of data from 16 RCTs with 17 effect sizes indicated a significant decrease in serum/plasma leptin concentration after receiving probiotic/synbiotic supplements with high heterogeneity (SMD (95%CI) = −0.38 (−0.64, −0.12); P-value= 0.004; I^2 (%)= 69.4; P heterogeneity < 0.001) (Table 4, Fig. 3). The certainty of this finding is moderate (Supplementary file 7). According to the conducted subgroup analysis, the study population's health condition is the only significant source of heterogeneity.

Subgroup analysis revealed significant differences in efficacy due to the health conditions of participants such that RCTs on patients with NAFLD showed the highest significant decrease in serum/plasma levels of leptin, though with high heterogeneity (SMD (95%CI)= −1.15 (−1.72, −0.59) ng/mL; P-value < 0.001; I^2 (%)= 69.4; P heterogeneity= 0.020). There were no significant differences in serum/plasma levels of leptin in other subgroups (Table 4), Supplementary File 5, Supplementary Figures 6 a to e). However, it seems that using dietary supplements may significantly reduce serum/plasma levels of leptin with high heterogeneity (SMD (95%CI)= −0.36 (−0.66, −0.06) ng/mL; P-value= 0.018; I^2 (%)= 71.7; P heterogeneity= 0.001). Further, follow-up duration for 12 weeks or more was associated with a significant decrease in serum/plasma leptin levels by the intervention with high heterogeneity (SMD (95%CI) = −0.53 (−1, −0.07) ng/mL; P-value= 0.023, I^2 (%)= 77.5; P heterogeneity< 0.001, respectively). Additionally, considering the total daily dosage of the probiotic bacteria, leptin decrease under the intervention reached significance specifically in the subgroup administering a low dose probiotic (SMD (95%CI)= −0.23 (−0.42, −0.04) ng/mL; P-value= 0.020, I^2 (%)= 28.5; P

Table 3
Quality assessment of the studies using the Cochrane Risk of Bias Tool for Randomized controlled trials.

	Quality	Random sequence generation	Allocation concealment	Selective reporting bias	Blinding of participants	Incomplete outcome data	Outcome assessor blinding	Other bias
Naruszewicz et al. 2002[74]	Fair	L	H	L	L	L	U	L
McMullen et al. 2006 [45]	Poor	L	H	L	H	H	H	L
Kadooka et al. 2010 [37]	Poor	L	H	U	L	L	L	H
Sanchez et al. 2014 [49]	Fair	L	L	L	L	L	H	U
Zarrati et al. 2014[28]	Fair	L	L	U	L	L	L	L
Nabavi et al. 2015[29]	Good	L	L	L	L	L	L	L
Ekhlasi et al. 2016[30]	Fair	L	H	L	L	L	L	U
Tonucci et al. 2016 [43]	Good	L	L	L	L	L	L	L
Behrouz et al. 2017 [31]	Poor	L	H	L	L	L	H	L
Sato et al. 2017[38]	Poor	L	H	L	H	H	L	U
Mobini et al. 2017[27]	Fair	L	H	L	L	L	L	U
Mobini et al. 2017[27]	Fair	L	H	L	L	L	L	U
Feizollahzadeh et al. 2017[32]	Poor	L	H	H	L	L	L	L
Gomes et al. 2017[44]	Poor	L	H	H	L	L	H	L
Sabico et al. 2019[47]	Fair	L	L	L	L	L	H	U
Duseja et al. 2019[48]	Good	L	L	L	L	L	L	L
Smith-Ryan et al. 2019 [46]	Fair	L	L	H	L	L	L	L
Kazemi et al. 2019[33]	Fair	L	L	L	L	L	H	L
Vafa et al. 2020[34]	Good	L	L	L	L	L	L	L
Toshimitsu et al. 2020 [39]	Good	L	L	L	L	L	L	L
Narmaki et al. 2020 [35]	Good	L	L	L	L	L	L	U
Talebi et al. 2020[36]	Fair	L	H	L	L	L	L	L
Cicero et al. 2021[41]	Fair	L	L	L	L	L	L	H
Toshimitsu et al. 2021 [40]	Good	L	L	L	L	L	L	L
Raji Lahiji et al. 2021 [22]	Good	L	L	L	L	L	L	L
Rondanelli et al. 2021 [42]	Fair	L	H	L	L	L	L	U
Folwarski et al. 2021 [50]	Poor	L	H	L	H	H	L	U

Low risk of bias (L, possible bias unlikely to seriously alter the trial findings).
High risk of bias (H, possible bias that seriously weakens confidence in the trial findings).
Unclear risk of bias (U, possible bias that raises some doubt about the trial findings).

heterogeneity= 0.174). Likewise, in the subgroup of RCTs with a high risk of bias, significant reductions in leptin levels with high heterogeneity (SMD (95%CI)= −0.34 (−0.63, −0.05) ng/mL; P-value= 0.023 I^2 (%)= 65.1; P heterogeneity= 0.001 ng/mL) (Table 4), Supplementary File 5, Supplementary Figures 6.a to e) was observed, likely due to higher number of studies thus reaching statistical power.

Meta-regression for BMI and age did not reach significance (Table 5, Supplementary File 6, Supplementary Figure 10a-b).

3.3.3. Desire to eat

Probiotic/synbiotic supplementation was associated with a significantly higher desire to eat with a moderate certainty (SMD (95%CI) = 0.34 (0.03, 0.66) P-value = 0.030, I^2 (%) = 39.4; P heterogeneity = 0.159) (Fig. 4, and Supplementary file)). With only five RCTs testing this outcome, subgroup analysis was not feasible.

Meta-regression for BMI and age did not reach significance (Table 5) (Supplementary File 6, Supplementary Figure 11a-b.

3.3.4. Publication bias

Visual inspection of the funnel plot of the study precision (inverse SEM) by effect size (mean changes) did not confirm any major asymmetry in the effect sizes estimated according to the enrolled RCTs. Similarly, Egger's linear regression test results showed no evidence of potential publication bias for the effects of pro- and synbiotic administration on leptin, adiponectin, or appetite scores (Supplementary File 3, Supplementary Figure 1a-c).

3.3.5. Influence/Sensitivity analysis

The summary SMD on leptin, adiponectin, and desire to eat was robust and remained unchanged when each study was sequentially removed from the main analysis (Supplementary File 4, Supplementary Figure 2–4).

4. Discussion

In the present meta-analysis of a total of 26 clinical trials, 17 of them reported data on adiponectin, 16 of them reported data on leptin, and five of them reported data on the desire to eat. It was revealed that probiotic/synbiotic supplementation resulted in a significant decrease in serum leptin levels. The heterogeneity regarding the impact of probiotic/synbiotic administration on serum/plasma leptin concentrations was 69.4% which may represent substantial heterogeneity, so subgroup analysis was conducted. Subgroup analysis revealed significant difference regarding targeted health conditions, and leptin level decreases was larger in NAFLD patients than in other clinical indications. Although the degree of leptin decrease did not significantly differ based on either

Table 4
Subgroup analysis according to included trials studied subjects' health condition, type of intervention, follow-up duration, the total daily dose of probiotics bacteria, and form of intervention.

	n	SMD (95%CI)*	P value	I^2 (%)	P heterogeneity	P between
Adiponectin						
All included trials	18	0.25 (−0.04, 0.53)	0.090	80.6	**< 0.001**	
Health conditions[¥]						
Overweight/obesity	6	0.45 (−0.30, 1.20)	0.239	92.7	**< 0.001**	0.242
NAFLD	3	-0.15 (−0.61, 0.31)	0.527	56.0	0.103	
T2DM/ MetSyn/ Prediabetes	8	0.251 (0.038, 0.464)	0.021	16.8	0.297	
Form of intervention						
Dietary supplements	7	-0.001 (−0.23, 0.23)	0.994	40.1	0.124	0.117
Probiotic food	11	0.419 (−0.06, 0.89)	0.083	85.6	**< 0.001**	
Follow up duration						
< 12 weeks	8	0.44 (−0.24, 1.12)	0.201	90.1	**< 0.001**	0.348
≥ 12 weeks	10	0.11 (−0.09, 0.30)	0.277	33.6	0.139	
Probiotics daily dosage						
Low dose	10	0.42 (−0.08, 0.93)	0.101	0.0	0.912	0.150
High dose	8	0.03 (−0.15, 0.21)	0.761	88.8	**< 0.001**	
Quality of included RCTs						
High risk of bias	12	0.13 (−0.06, 0.32)	0.178	25.1	0.197	0.396
Low risk of bias	6	0.47 (−0.29, 1.22)	0.228	93.0	**< 0.001**	
Leptin						
All included trials	17	-0.38 (−0.64, −0.12)	0.004	69.4	**< 0.001**	
Health conditions						
Overweight/obesity	5	-0.06 (−0.27, 0.15)	0.555	0.0	0.684	0.005
NAFLD	4	-1.15 (−1.72, −0.59)	< 0.001	69.4	0.020	
T2DM/ MetSyn/ Prediabetes	4	-0.25 (−0.56, 0.06)	0.119	0.00	0.838	
Healthy subjects or other conditions	4	-0.22 (−0.84, 0.41)	0.500	71.2	0.015	
Form of intervention						
Dietary supplements	14	-0.36 (−0.66, −0.06)	0.018	71.7	0.001	0.690
Probiotic food	3	-0.49 (−1.036, 0.066)	0.085	64.6	0.059	
Follow up duration						
< 12 weeks	10	-0.27 (−0.57, 0.03)	0.082	61.0	0.006	0.346
≥ 12 weeks	7	-0.534 (−1.00, −0.07)	0.023	77.5	< 0.001	
Probiotics daily dosage						
Low dose	11	-0.23 (−0.42, −0.04)	0.020	28.5	0.174	0.259
High dose	6	-0.65 (−1.35, 0.05)	0.070	84.1	< 0.001	
Quality of included RCTs						
High risk of bias	13	-0.34 (−0.63, −0.05)	0.023	65.1	0.001	0.572
Low risk of bias	4	-0.53 (−1.16, 0.09)	0.094	83.2	< 0.001	

NAFLD: non alcoholic fatty live disease; MetSyn: metabolic syndrome; T2DM: type 2 diabetes mellitus
*Standardized mean differences (SMD); 95% confidence interval (95%CI).
[¥]For adiponectin, only one study was included as an "other disorders subgroup".

form of intervention, the total dose of bacteria administered, follow-up duration, or the quality of RCTs, a trend toward a more prominent leptin decrease was revealed when probiotic/synbiotic supplementation was administered in the form of dietary supplements, for ≥ 12 weeks and in low dose daily dosage. Moreover, in the pooled analysis, adiponectin elevation did not reach significance. The heterogeneity regarding the impact of probiotic/synbiotic administration on serum/plasma adiponectin was 80.6%, considered substantial, so subgroup analysis was conducted. The subgroup of RCTs conducted in patients with T2DM, MetSyn, and prediabetes did so, implying potentially stronger indications under those conditions. However, future follow-up meta-analyses may challenge this view when more studies are available. Further,

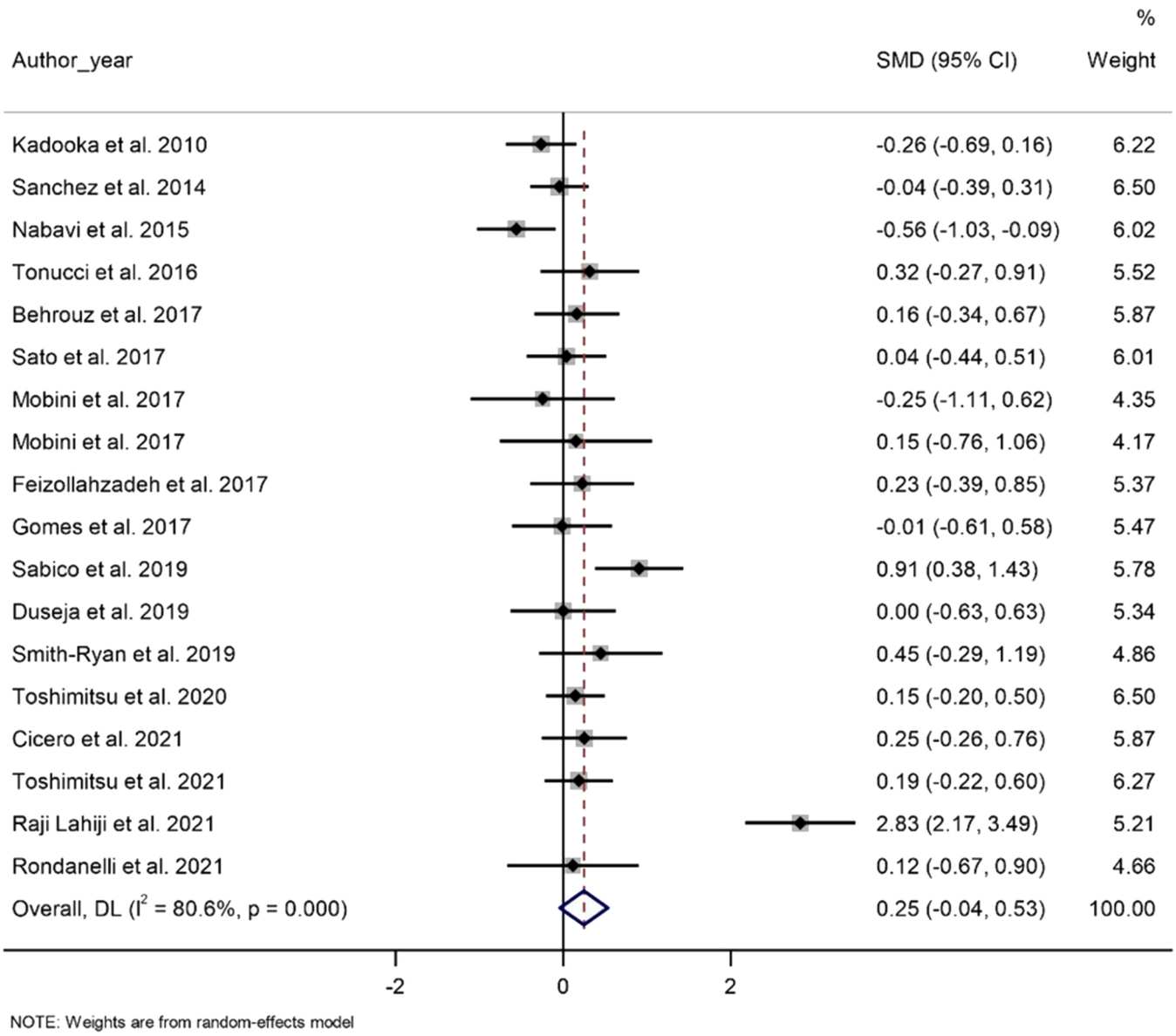

Fig. 2. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of probiotic/synbiotic administration on serum/plasma adiponectin.

Table 5
Meta-regression analysis for potential moderators*.

	Coefficient (95%CI)	P value	Residual heterogeneity: I2 (%)	R-squared (%)
Adiponectin				
Age	0.008 (−0.026, 0.042)	0.618	82.20	-5.56
BMI	-0.005 (−.125, 0.115)	0.93	81.71	-8.14
Leptin				
Age	0.006 (−.017,.030)	0.58	69.27	-8.65
BMI	0.039 (−0.048, 0.12)	0.34	69.79	-1.78
Desire to eat score				
Age	0.020 (−0.03, 0.07)	0.25	21.67	51.48
BMI	-0.035 (−0.16, 0.09)	0.43	36.75	14.15

* Age and body mass index (BMI).

significant increment was noted in the desire to eat among the subjects who received the probiotic/synbiotic supplements compared to those receiving placebo. Moderate heterogeneity was reported regarding the desire to eat (39.4%). Aside from this, number and granularity of available studies permitted no subgroup analysis.

In the RCTs covered by the current study, the desire to eat was investigated by a subjective method [33,42,50]. Using the subjective appetite rating by visual analog scales (VAS), Kazemi et al. investigated the effect of probiotic and prebiotic supplementation on patients with the major depressive disorder who suffer from reduced appetite and body weight. The results showed promising effects of probiotic supplementation on appetite enhancement in these patients [33]. Rondanelli et al. investigated the impact of probiotic supplementation on the desire to eat using Eating Motivation VAS in obese patients but found no statistically significant effects [42]. Using postoperative appetite VAS, Folwarski et al. showed that postoperative *Lactobacillus rhamnosus* GG supplementation increased appetite [50]. Therefore, it can be speculated that probiotics may affect patients' appetite based on the baseline appetite status and the reason for appetite impairment [33].

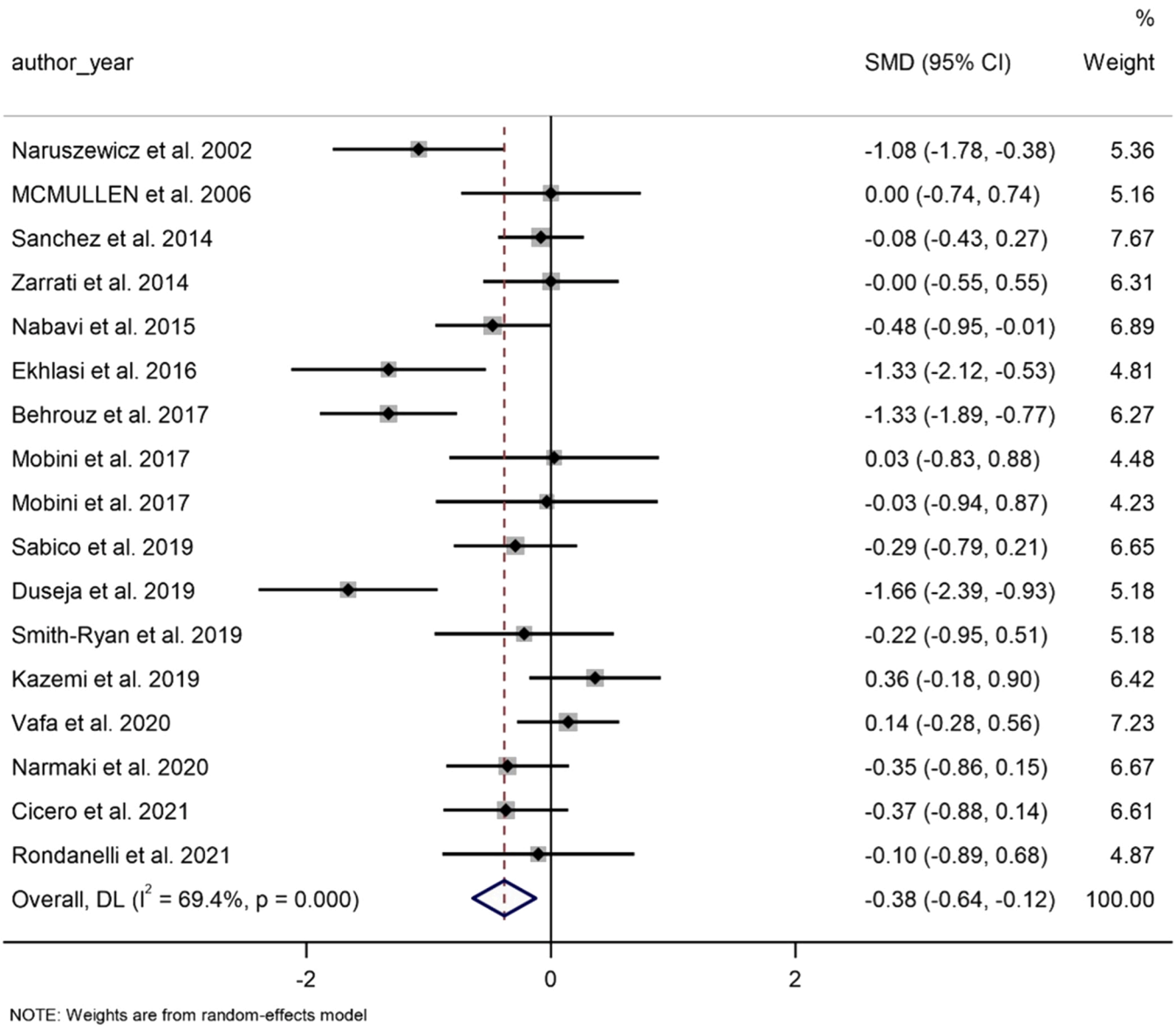

Fig. 3. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of probiotic/synbiotic administration on serum/plasma leptin concentrations.

Additionally, it can be postulated that the observed role of probiotic/synbiotic supplements in increasing appetite in this present meta-analysis study may suggest these supplements as a complementary treatment to stimulate the desire for food intake in anorexia patients and cancer patients with cachexic conditions. Nevertheless, it should also be taken in mind that assessing the desire to eat by such subjective measures might have limitations making these results less reliable than those investigating satiety and hunger-regulating hormones in the serum/plasma samples.

In the only recent systematic review and meta-analysis on probiotics, prebiotics, or synbiotics examining the effects on adiponectin and leptin levels in adults, the probiotic group did not differ significantly from those in the control group. Despite the health benefits of probiotics, no effect on adiponectin and leptin was found in the study above [21].

Both animal and human studies have reported a significant decrease in serum leptin levels after probiotic/synbiotic supplementation [31,48,51]. For example, according to animal studies, probiotic supplementation in form of *Bifidobacterium spp.* and *Lactobacillus plantarum* reduced leptin levels [52,53]. Besides, as shown by Ekhlasi et al., synbiotics supplementation effectively lowered leptin levels [30].

Probiotics may decrease leptin levels in the blood, but the exact mechanism is still unclear. Possible mechanisms include regulating leptin expression in the brain, reducing leptin release by adipocytes, and indirectly activating the peroxisome proliferator-activated receptor (PPAR), which reduces energy intake and leads to a reduction in fat mass. Subsequently, this effect decreases tissue resistance to insulin, and lowers blood leptin concentrations [54]. Fermentation of prebiotic components in synbiotic results in propionic acid production, which is shown to reduce leptin concentrations through ligand-activated PPAR [54]. Additionally, probiotic bacteria such as *Lactobacillus* and *Bifidobacterium* decrease the hydrolysis of conjugated hormone in the colon, which lowers enterohepatic circulation of leptin [54]. The effect of probiotics on body weight reduction leading to lower leptin levels was demonstrated previously [51,55,56]. According to Xie et al., rats treated with *L. plantarum* 9–41-A lost much more weight than the control group and had fewer fat cells in their liver and less adipose tissue mass [57]. Adipocytes in the mesenteric white adipose tissue were also smaller in rats treated with *L. plantarum* 9–41-A-than in the control group.

According to a previous study, certain bacteria can prevent host weight gain [58–60]. Lean Zucker rats receiving *L. gasseri* SBT2055 also

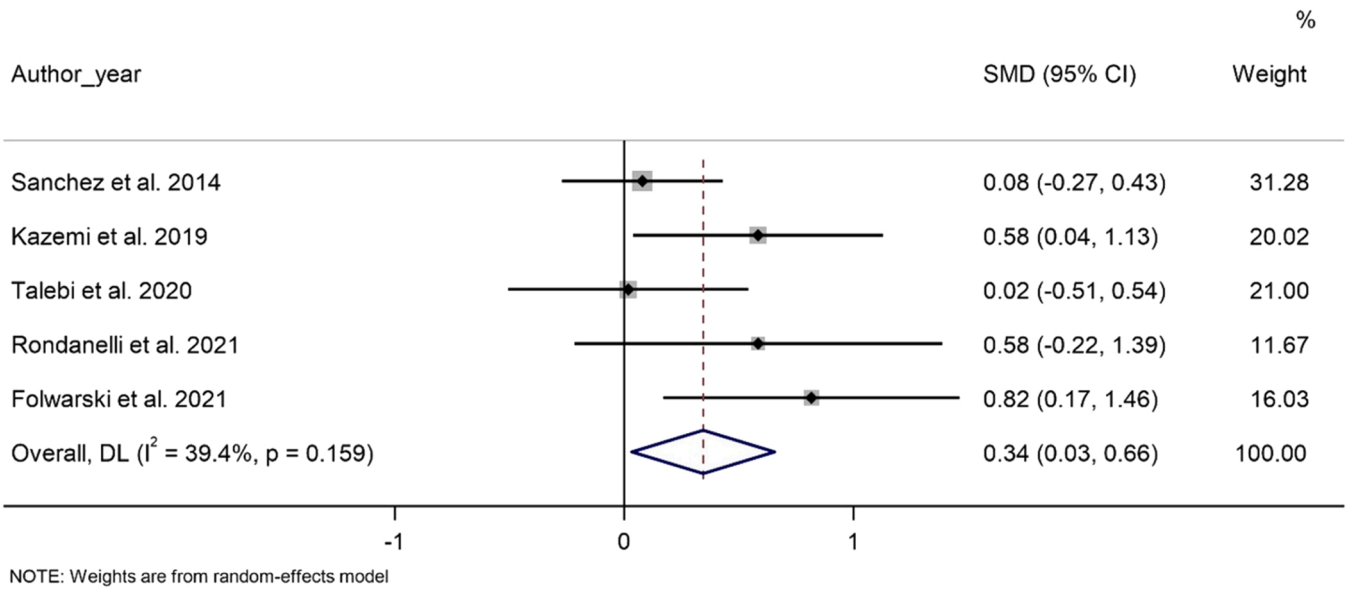

Fig. 4. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of probiotic/synbiotic administration on the "desire to eat" score.

had low leptin levels, resulting in smaller adipocytes and less fat mass. This suggests that *L. gasseri* can control adipocyte size through a mechanism to suppress hypertrophy. This is likely due to reducing fat absorption in the intestine, shown by measuring the amount of fat in feces [58]. Previous research has demonstrated that certain probiotic strains can reduce fat storage in the tissues of obese persons by inhibiting fat absorption [55].

Furthermore, in the paraventricular nucleus of the hypothalamus, leptin alters oxytocin levels and activates oxytocin neurons. On the other hand, increased oxytocin levels, could enhance leptin sensitivity and modulate leptin resistance state, a common condition observed in overweight/obese individuals [61]. Interestingly, some probiotic bacterial strains such as *L. reuteri* has been demonstrated to increase oxytocin gene expression [62]. This effect could subsequently lead to improving the body weight homeostasis regulation [61].

Furthermore, the increased level of leptin due to obesity acts as a pro-inflammatory adipokine [63], and interventions providing anti-inflammatory properties may have significant effects [64,65]. The anti-inflammatory effect of probiotics is shown previously in [66,67], and probiotics such as *Lactobacillus* are postulated to perform their role through regulating leptin gene expression because leptin increases the production of specific cytokines, such as TNF-alpha [52,68,34].

According to the findings of the present meta-analysis, there was a trending elevation in adiponectin levels due to probiotic/synbiotic supplementation, though it was not statistically significant. Probiotic supplementation has been linked to increased adiponectin production in several previous animal studies [69,70]. In mice with induced diabetes, a *Bifidobacterium* species increased adiponectin mRNA expression [69]. In addition, probiotic therapy in mice significantly increased adiponectin synthesis in white adipose tissue [70]. *L. rhamnosus* GG, administered orally to mice for 13 weeks, increased insulin sensitivity by increasing adiponectin production and activating AMP-activated protein kinase (AMPK) signaling pathway [70]. Besides, from the included studies, Behrouz et al. have shown that adiponectin levels increased more in the probiotic and prebiotic groups than in the placebo group. However, this value was not statistically significant, possibly due to the influence of lifestyle interventions in each group [71]. According to Kadooka et al., supplementation with *L. gasseri SBT 2055* significantly increased serum adiponectin in obese patients [37]. Similar findings were reported by Raji Lahiji et al., where synbiotic treatment significantly increased adiponectin levels compared to placebo [22]. As noted above, adiponectin is an insulin-sensitizing adipokine with anti-inflammatory, anti-atherogenic, and anti-diabetic effects that decreases obesity and T2DM [17,18]. Studies suggest that prebiotic and probiotic effects on adipokine concentrations are mediated by changes in the microbiota, although the exact processes involved remain unclear [14]. Adiponectin secretion may benefit from the synthesis of SCFAs during the fermentation of prebiotic fiber [72]. Taken together, there are multiple credible mechanistic pathways underlying the influence of probiotic/synbiotic supplementation on appetite, which we here have shown, suggesting directions for future work.

5. Strengths and limitations

In the current systematic review and meta-analysis, we aimed to investigate the effectiveness of probiotic and synbiotic supplementation on appetite-regulating hormones and the desire to eat. To the best of our knowledge, the last study on changes in adiponectin and leptin levels following probiotic administration was conducted three years ago [21]. Several large studies have been conducted since then, prompting us to carry out the current study. Besides, in this study, the effectiveness of probiotic/synbiotic supplementation on the desire to eat was investigated for the first time in meta-analysis. Finally, the findings of this study are based on a moderate certainty of evidence.

However, our work has some limitations. Lifestyle factors, including diet, dietary supplements, drugs, and weight loss programs, are essential confounders affecting the results we could not consider when conducting this meta-analysis. Furthermore, as each probiotic strain may perform a unique role in the various health conditions [73], pooling the effects of different types of synbiotics and probiotics containing various strains together constitutes a limitation of the present meta-analysis. Only publications written in English were included in the current analysis, which may also increase publication bias risk. In addition, included studies are limited with regards to coverage of duration of intervention [29–32,42] with regards to sample size [27,30,31,33,35,38,42,46–48,50] and lack data on the bacterial load of stool [22,31–33,41] as well as sometimes on baseline microbiome [41], as well as use of medications affecting the gut microbiota [27]. All of these can be rectified if further funding is allotted to this field. The probable mechanistic pathways are not explored in the current analysis and can be evident mainly from in vitro and experimental studies.

6. Conclusion

In the present meta-analysis of a total of 26 clinical trials, including 17 clinical trials on adiponectin, 16 clinical trials on leptin, and five clinical trials on the desire to eat, it was revealed that probiotic/synbiotic supplementation significantly reduced serum leptin levels, in particular among patients with NAFLD, as well as increasing an operationalized subjective measure of appetite, compared to placebo. A trending (yet non-significant) elevation in adiponectin levels was also observed in the overall pooled analysis. However, future studies on health conditions and indicators may allow such conclusions to be drawn even more widely. These results already suggest a broad potential for probiotic and synbiotic interventions in various health conditions where appetite and nutrition (whether overeating or undereating) are salient, alone or in combination with other nutritional, pharmaceutical or biotic approaches.

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CRediT authorship contribution statement

The authors' responsibilities were as follows- Z.Gh., M.N., S.K.F. and U.L.: designed the study; Z.Gh., M.N., N.Sh., and M.M.R.: performed literature search and screening; M.N., Z.Gh, and N.Sh.: performed data extraction; M.N., Z.Gh., A.K., and M.M.R: conducted quality assessment; Z.Gh., A.K. and S.K.F.: performed and revised the meta-analysis process, M.N., Z.Gh., and T.U.P: wrote the initial draft, U.L., T.U.P. and S.K.F.: reviewed the draft, modified the text, and prepared the final draft; S.K.F. and Z.Gh.: had primary responsibility for content; and all authors: read and approved the final manuscript.

Conflict of interest

Authors declare that there is no conflict of interest.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106614.

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