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Meta-analyses

Do probiotics, prebiotics and synbiotics affect adiponectin and leptin in adults? A systematic review and meta-analysis of clinical trials

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SUMMARY

Background & aims: Human studies have reported controversial findings regarding the health promoting effects of probiotic, prebiotic and synbiotic on adiponectin and leptin levels. This systematic review and meta-analysis was conducted to understand the effect of probiotics, prebiotics or synbiotics on adiponectin and leptin levels in adults.
Methods: Electronic searches were performed in PubMed, Scopus, Web of Science, Cochrane Library and Google scholar up to February 11, 2018 without any restriction. Controlled clinical trials, in any age of adults, which reported the effect of probiotic, prebiotic and synbiotic on serum level of adiponectin and leptin were included. As leptin and adiponectin were reported in different units across the studies, Hedges's adjusted g was used to calculate effect size. A random-effects model was used to pool calculated effect sizes.
Results: Of 12 eligible studies, 10 publications focused on probiotics, and only 3 studies reported the effect of prebiotics ($n = 2$) or synbiotics ($n = 1$) on leptin and adiponectin. There were no significant changes in adiponectin (Hedges' $g = -0.04$; 95% CI: −0.27, 0.19) and leptin (Hedges' $g = -0.30$; 95% CI: −0.86, 0.26) in probiotic group compared with controls. Subgroup analyses ranged in heterogeneity from 0% to 93%, but no subgroup showed an effect of probiotics on adiponectin or leptin.
Conclusion: There were limited studies regarding the effect of prebiotic and synbiotic on adiponectin and leptin. Although previous studies reported several health promoting effects of probiotics, we could not find any pooled effect on adiponectin and leptin.

1. Introduction

White adipose tissue (WAT) is a metabolic endocrine organ which secretes several hormones including adiponectin and leptin [1]. In addition to the central role of lipid storage, WAT is involved in a wide range of metabolic and physiological processes, including energy balance, inflammation and glucose homeostasis [2]. Adiponectin and leptin are the most well-known protein hormones secreted by WAT [3]. Adiponectin is an insulin-sensitizing protein which has anti-inflammatory, anti-atherogenic, and anti-diabetic affects [4]. In contrast to the other adipokines, circulating concentrations of adiponectin decline in obesity and diabetes [5]. Moreover, weight reduction elevates plasma concentrations of adiponectin [6]. Leptin is a product of the *OB* gene which affects energy homeostasis via decreasing food consumption, acting on lipogenesis and fatty acid oxidation [7]. Serum concentrations of leptin increase in obesity and type 2 diabetes and decrease during fasting [3]. The expression of leptin depends on energy stores and WAT depots [8].

Gut microbiota have a critical role in the pathogenesis of various metabolic diseases [9] and beneficial modulation of the intestinal microbiome is a potential strategy that could be considered as a complementary therapeutic option to improve host health [10,11]. In this approach, probiotics, prebiotics and synbiotics have attracted a great deal of attention. Probiotics are live micro-organisms

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which improve intestinal microbial balance in the host [12]. The term prebiotic, according to the recently updated definition, refers to a substrate that is selectively utilized by host microorganisms conferring a health benefit [13]. The combination of probiotics and prebiotics, referred to as synbiotics, has a synergistic effect on survival and growth of the probiotic bacteria [12].

Evidence suggests that probiotics and prebiotics supplementation may have beneficial effects on lipid metabolism, insulin resistance and inflammatory mediators by alteration in the form and/or function of gut microbiota [14]. Animal studies showed a positive effect of probiotics and prebiotics on circulating levels of adipokines, especially adiponectin and leptin [15,16]. However, results of recent human trials in participants with non-alcoholic fatty liver disease and type 2 diabetes mellitus have shown mixed results [17,18]. Therefore, the present study was conducted to systematically identify and quantify the effect of probiotic, prebiotic and synbiotic supplementation on adiponectin and leptin levels in adult human subjects.

2. Material and methods

2.1. Search strategy

We conducted a meta-analysis based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [19]. The electronic search for the current systematic review and meta-analysis was performed up to February 11, 2018 in PubMed, Scopus, Web of Science, Cochrane Library and Google scholar. Above mentioned databases were searched utilizing Boolean operator tools, specifically using the following terms: (probiotic OR prebiotic OR synbiotic OR Bifidobacter OR Lactobacilli), in combination with (adipokines OR adiponectin OR leptin OR adipocytokines). No restrictions on language or publication date were imposed. An additional manual search was followed by reference lists of selected studies to detect other relevant trials.

2.2. Inclusion and exclusion criteria

Relevant articles were included if they: (1) were in adults; (2) examined the effects of probiotics/prebiotic/synbiotic on adiponectin and/or leptin; (3) applied a clinical trial design; and (4) provided sufficient information regarding serum adiponectin and leptin levels in both treatment and control groups. Studies were excluded if they: (1) used a mixture of probiotic/prebiotic/synbiotic with other substance; (2) were uncontrolled studies; (3) reported duplicate data; (4) included pregnant or lactating women, or (5) were reviews, letters, editorial articles, or case reports. If multiple publications reported the same or overlapping data, the publication with the largest sample size was used.

2.3. Quality assessment and data extraction

The Jadad Scale [20] was applied to appraise the methodological quality of included studies. This 5-point tool consists of key domains covering randomization and allocation concealment (0–2 points), blinding (0–2 points), and withdrawal or drop-out rate (1 point). Studies with scores of $\geq$3 and <3 were defined as high and low-quality studies, respectively. H.M, A.M and A.R extracted the following required data: first author's name, publication year, location of studies, research design, body mass index, number and age of subjects, sample size, duration of intervention, dose and type of intervention in experimental and comparison group. Also, we extracted mean and standard deviation (SD) of adiponectin and leptin at baseline and after the intervention.

2.4. Statistical analysis

To calculate overall effect size for each study, the following steps were undertaken: 1) Baseline value in treatment group, baseline value in placebo group, endpoint in treatment group and endpoint value in placebo group were extracted. If baseline values were not reported in a study, only endpoint values were used; 2) Change ±SD from baseline was calculated for the placebo group and treatment group, separately; 3) Mean difference between changes from baseline in treatment group vs. changes from baseline in placebo group was calculated and used as overall effect size. As leptin and adiponectin were reported in different units across the studies, Hedges's adjusted *g* was used to calculate effect size. A random-effects model was used to pool calculated effect sizes. The I^2-squared test to explore the heterogeneity, where an $I^2 > 75\%$ is considered high heterogeneity and an $I^2 < 25\%$ is considered low heterogeneity. When the I^2-value was $\geq 50\%$ and the *P*-value was ≤ 0.10, subgroup analysis was performed based on number of used strain, duration of study and participant baseline body mass index (BMI) to detect potential causes of heterogeneity. Heterogeneity between subgroups was evaluated using a fixed-effect model. Sensitivity analysis was performed by omitting one study at a time, to detect any significant changes in the results obtained. We used Begg's rank correlation test and Egger's regression asymmetry test to evaluate publication bias. Statistical analysis was performed using STATA 11 software (StataCorp, College Station, Texas, USA).

3. Results

3.1. Search result and systematic review

The search process is illustrated in Fig. 1. In total, 442 records were identified in a combined search of electronic databases. Of the 125 unduplicated papers, 113 were excluded because they were animal studies ($n = 14$), not relevant to the topic ($n = 94$), methodological article ($n = 1$) or conducted in children ($n = 2$) or lactating women ($n = 1$). Also, one study was excluded that used probiotics in combination with other interventions. Finally, 12 eligible articles were included in the present systematic review [17,18,21–30]. All included studies were double blinded except for the trial by McMullen et al. [24]. Three were conducted in type 2 diabetes patients [18,25,27], three studies enrolled subjects with non-alcoholic fatty liver disease [17,21,30] and the subjects in four studies were overweight and obese adults [22,26,28,29]. The mean age of participants ranged from 18 to 66 years. The duration of intervention ranged from 6 to 24 weeks and the quality of all eligible studies was high (Jadad score $\geq$ 3).

Most included studies focused on probiotics ($n = 10$) [17,18,22–25,27–30] and only 3 studies reported the effect of prebiotics ($n = 2$) or synbiotics ($n = 1$) on leptin and adiponectin [17,21,26]. All the studies reported that probiotic and prebiotic supplementation had no effect on adiponectin [17,18,22,23,25–27,29,30]. Studies reporting the effect of probiotics, prebiotics and synbiotics supplementation on leptin had mixed results, i.e., four studies reported no effect [24,25,29,30], and three observed a reduction in leptin concentration [17,21,28] (see Table 1).

3.2. Meta-analysis

Eight studies evaluated the effect of probiotic supplementation on changes in adiponectin concentration [17,18,22,23,25,27,29,30]. There were no significant changes in adiponectin in probiotic group compared with controls (Hedges' $g = -0.04$; 95% CI: -0.27, 0.19, Fig. 2) and heterogeneity for this outcome was moderate

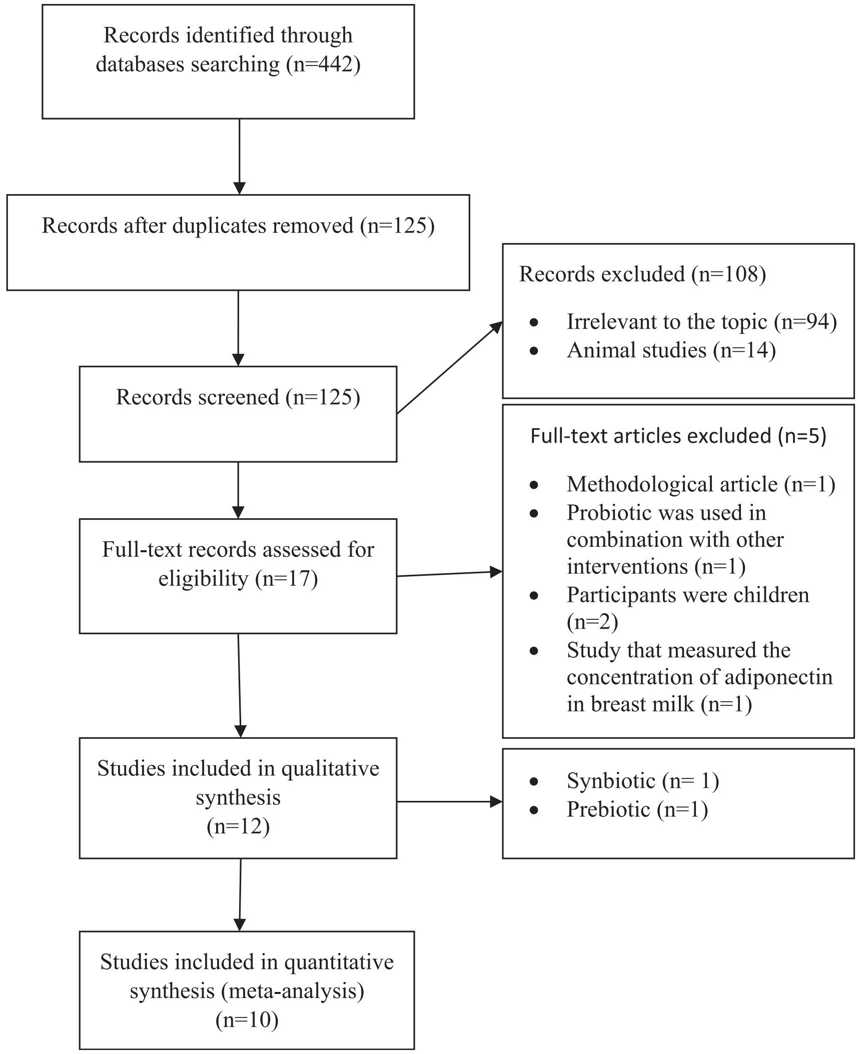

Fig. 1. Flow chart of the process of the study selection.

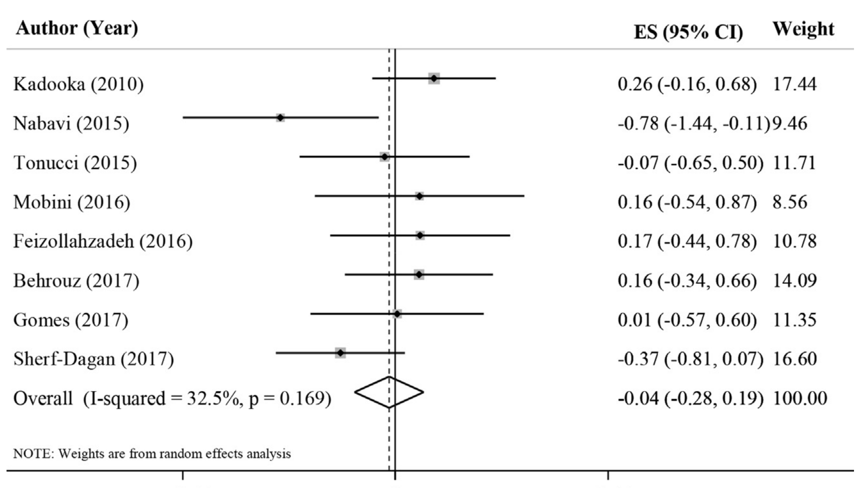

Fig. 2. Forest plot of the effect of probiotic supplementation on adiponectin in randomized clinical trials of adults.

Table 1
Characteristics of the studies included in the systematic review and meta-analysis.

Author (location; year) (ref)	RCT design (blinding)	No. (M/F)	Participants characteristics	Mean age (years)	Baseline BMI (kg/m^2)	Duration (wks)	Jadad score[a]	Intervention/dose	Main result	
									Adiponectin	Leptin
McMullen et al. (USA; 2006) [24]	Parallel (single)	39 (39/0)	Prostate cancer	18–37	<30	8 weeks	3	*Lactobacillus acidophilus* and *Bifidobacterium longum*/1 × 10^9 CFU	–	↔
Kadooka et al. (Japan; 2010) [23]	Parallel (double)	87 (59/28)	Healthy adults	48.3 ± 9.3 49.2 ± 9.1	<30	12 weeks	3	*Lactobacillus gasseri*/1 × 10^{11} CFU	↔	–
Zarrati et al. (Iran; 2014) [28]	Parallel (double)	50 (ND)	Obese adults	20–50	>30	8 weeks	4	*Lactobacillus acidophilus*, *Bifidobacterium*, and *Lactobacillus casei*/1 × 10^8 CFU	–	↓
Tonucci et al. (Brazil; 2015) [27]	Parallel (double)	45 (26/19)	Type 2 diabetes	51.8 ± 6.64 50.95 ± 7.20	<30	6 weeks	5	*Lactobacillus acidophilus* and *Bifidobacterium animalis*/1 × 10^9 CFU	↔	
Nabavi et al.[b] (Iran; 2015) [30]	Parallel (double)	72 (35/37)	NAFLD	42.75 ± 8.72 44.05 ± 8.14	>30	8 weeks	4	*B. lactis* Bb12 and *L. acidophilus* La5/6.46 × 10^6 and 4.97 × 10^6 CFU	↓	↔
Ekhlasi et al. (Iran; 2016) [21]	Parallel (double)	30 (ND)	NAFLD	25–64	<30	8 weeks	5	A synbiotic capsule contains *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Lactobacillus bulgaricus*/2 × 10^8 CFU + fructooligosaccharide	–	↓
Mobini et al. (Sweden; 2016) [25]	Parallel (double)	30 (23/7)	Type 2 diabetes	66 ± 6 65 ± 5	>30	12 weeks	4	*L. reuteri*/1 × 10^8 CFU	↔	↔
								L. reuteri/1×10^{10} CFU	↔	↔
Feizollahzadeh et al. (Iran; 2016) [18]	Parallel (double)	40 (19/21)	Type 2 diabetes	56.90 ± 1.81 53.6 ± 1.6	<30	8 weeks	3	*Lactobacillus planetarum*/2 × 10^7 CFU	↔	–
Gomes et al. (Brazil; 2017) [22]	Parallel (double)	43 (0/43)	Obese adults	20–59	>30	8 weeks	5	*Lactobacillus acidophilus*, casei; *Lactococcus lactis*, *Bifidobacterium bifidum* and lactis/2 × 10^{10} CFU	↔	–
Behrouz et al. (Iran; 2017) [17]	Parallel (double)	60 (43/17)	NAFLD	38.46 ± 7.11 38.43 ± 10.09	<30	12 weeks	5	*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Bifidobacterium breve*/5 × 10^9 CFU	↔	↓
								Oligofructose/16 g/d	↔	↓
Sherf-Dagan et al. (Israel; 2017) [29]	Parallel (double)	80 (34/46)	Morbidly obese adults	42.1 ± 9.0 44.2 ± 9.4	>30	24 weeks	5	11 different species of patented probiotics bacteria/2.5 × 10^9 CFU	↔	↔
Parnell et al. (Canada; 2017) [26]	Parallel (double)	37 (ND)	Obese adults	41.9 ± 12.7 38.6 ± 13.0	>30	12 weeks	3	Oligofructose/21 g/d	↔	–

Values are expressed as mean ± SD.
CFU: colony-forming units; M: Male; F: Female; NAFLD: nonalcoholic fatty liver disease.
[a] ≥3 = high-quality and <3 = low-quality.
[b] Results converted from median (IQR) to mean ± SD.

Table 2
Subgroup analysis to assess the effect of probiotic supplementation on serum adiponectin and leptin levels.

	Categorized by	Subgroups (number of effect size)	Effect size[a] (95% CI)	I^2 (%)	*P* for heterogeneity	*P* for between subgroup heterogeneity
Adiponectin	Number of used strain	Single (3)	0.219 (−0.091, 0.529)	0.0	0.955	0.043
		Multi (5)	−0.190 (−0.491, 0.112)	35.1	0.188	
	Duration of study	>8 weeks (4)	0.037 (−0.278, 0.352)	37.8	0.185	0.397
		≤8 weeks (4)	−0.147 (−0.532, 0.238)	37.9	0.185	
	Participant baseline BMI	>30 kg/m^2 (5)	−0.165 (−0.412, 0.082)	42.2	0.651	0.108
		≤30 kg/m^2 (3)	0.152 (−0.144, 0.447)	0.0	0.140	
Leptin[b]	Duration of study	>8 weeks (3)	−0.373 (−1.36, 0.615)	89.4	<0.001	0.811
		≤8 weeks (3)	−0.223 (−0.981, 0.535)	75.7	0.016	
	Participant baseline BMI	>30 kg/m^2 (4)	−0.299 (−0.862, 0.264)	63.6	0.041	0.053
		≤30 kg/m^2 (2)	−0.417 (−2.200, 1.366)	93.4	<0.001	

BMI: body mass index.
[a] Calculated by random effects model.
[b] Subgroup analysis by number strains was not completed for leptin due to lack of studies in each subgroup.

($I^2 = 32.5\%$; $P = 0.16$). Subgroup analysis was conducted according to number of used strains, duration of study and participant baseline BMI (Table 2). Results of subgroup analysis based on number of used strain showed that probiotic supplementation had no significant effect on adiponectin in both "single strain" (Hedges' $g = 0.219$; 95% CI: −0.091, 0.529) and "multiple strain" (Hedges' $g = -190$; 95% CI: −0.491, 0.112) subgroups, with significant between subgroup heterogeneity ($P = 0.043$). Other subgroup analysis also showed that probiotic supplementation had no significant effect on adiponectin, with no significant heterogeneity.

The effect of probiotic supplementation on changes in leptin concentration was assessed in six clinical trials [17,24,25,28–30]. There were no significant changes in leptin after probiotic supplementation in comparison with controls (Hedges' $g = -0.30$; 95% CI: −0.86, 0.26, Fig. 3). We observed significant heterogeneity ($I^2 = 81.6$; $P < 0.001$). Although subgroup analysis was conducted according to duration of study and participant baseline BMI (Table 2), observed heterogeneity was not explained by these two variables. Sensitivity analysis for adiponectin and leptin showed that overall estimates were not influenced by elimination of any study. There was no evidence of publication bias for studies examining the effect of probiotic supplementation on adiponectin ($P = 0.45$, Begg's test and $P = 0.65$, Egger's test) and leptin ($P = 0.85$, Begg's test and $P = 0.81$, Egger's test).

4. Discussion

To the best of our knowledge, the present systematic review and meta-analysis is the first study that evaluated the effects of probiotics, prebiotic and synbiotic supplementation on circulating adipokine and leptin concentrations. The pooled analysis of 10 RCTs showed that probiotics supplementation had no significant effect on serum leptin and adiponectin. Subgroup analyses based on number of strains used, study duration and participants' baseline BMI showed that probiotic supplementation had no effect on circulating levels of adiponectin and leptin.

This meta-analysis found that adiponectin concentration was not significantly affected by supplementation with probiotics. Adiponectin is secreted abundantly by adipose tissue, circulates at relatively high concentrations (between 5 g/mL and 30 g/mL [31]) and is involved in regulating glucose and lipid metabolism. Interestingly, 2015 [32] and 2017 [33] meta-analyses showed that probiotics significantly improved lipid metabolism and blood lipid profiles, as measured by cholesterol-related outcomes. Though low adiponectin has been shown to be detrimental to blood cholesterol and triglyceride profiles [34], results of the current meta-analysis suggests that the reported effects of probiotics on blood lipids [32,33] may be through mechanisms not related to adiponectin. However, differences between the current analysis and previous work [32,33] may be due to differences in populations, probiotic dose or strain. In the current analysis, populations including healthy individuals as well as those with multiple different disease types, which may increase the heterogeneity of results. Further, the large inter-study variation in dose may also increase heterogeneity of outcomes, with probiotic dose ranged from 5×10^6 CFU to 1×10^{11} CFU. Also, in the subgroup analysis of the current study, number of strains, BMI or study duration did not affect adiponectin. Though there was not a subgroup analysis focusing on strain-specific or species-specific effects, no study using lactobacillus saw an effect on adiponectin, as previous work has shown with blood lipid outcomes [33] Lastly, one study in this meta-analysis showed a significant decrease in adiponectin [30]. It is unclear what caused these results and if results are related to low probiotic dose, disease state of participants or lifestyle variables.

Similar to results for adiponectin, leptin concentrations were not significantly affected by probiotic supplementation. Leptin is recognized as an anti-obesity hormone which regulates food intake and energy expenditure. Recent meta-analyses have highlighted that probiotic supplementation may have a small but significant effect to decrease weight and fat mass [35]. Without an effect on leptin, the current analysis is suggestive of probiotics affecting body weight regulation through mechanisms not related to leptin. It is possible that probiotic supplementation does not affect leptin due to opposing physiologic effects. Some probiotics strains, like Lactobacilli and Bifidobacteria, possess low β-glucuronidase activity, acting to decrease enterohepatic circulation of leptin by reducing the hydrolysis of conjugated hormone in the intestine [24]. Potentially acting in opposition, generation of short chain fatty acids during fiber fermentation in the large intestine by probiotics has been suggested to positively effect leptin release [36]. Similar to adiponectin, heterogeneity may be affecting results due to diversity of populations, probiotic dose and strain. Further, subgroup analyses did not show any subgroups having a significantly effect on leptin. Two studies showed that probiotic supplementation significantly reduced leptin concentration [17,30], which may be an artifact of weight loss or may be related to the specific disease state (non-alcoholic fatty liver disease (NAFLD)).

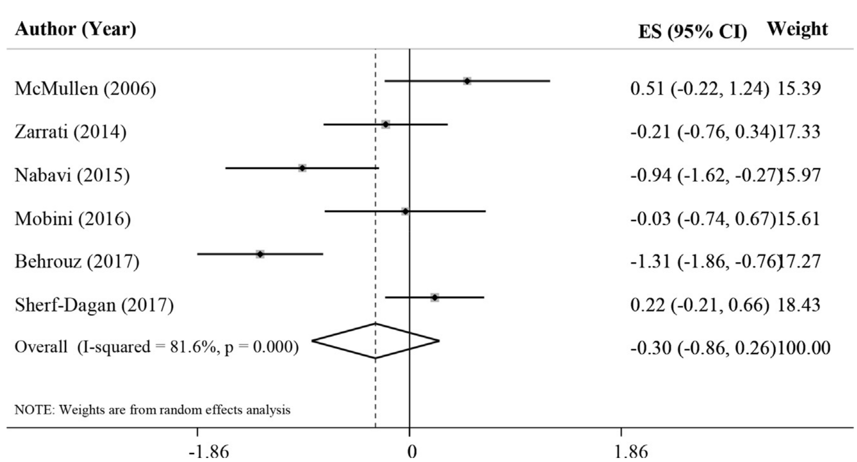

Fig. 3. Forest plot of the effect of probiotic supplementation on leptin in randomized clinical trials of adults.

There were few studies investigating the effect of prebiotics or synbiotics on adiponectin and leptin concentrations. Thus, meta-analyses were not possible, leaving it unclear how prebiotics or synbiotics affect adiponectin and leptin. Both prebiotics and synbiotics have been shown to have multiple beneficial health effects through the manipulation of gut microbiota [37,38]. However, similar to probiotics, the only two study in this systematic review using prebiotics or synbiotics with adiponectin as an outcome, saw no effect of 16 g/day or 20 g/day of oligofructose. Conversely results for leptin showed that oligofructose [17] and a symbiotic supplement [21] both significantly lowered leptin. This effect on leptin may be an artifact of weight loss in participants with NAFLD. Additionally, due to small sample sizes of studies and populations only including people with NAFLD, it is challenging to draw conclusions about the effect of prebiotics or synbiotics on leptin.

This systematic review and meta-analysis has some limitations that must be acknowledged. First, the number of eligible studies was small and qualified trials were performed in small sample sizes. Second, analyzed studies used vastly different doses and strains of probiotics. Included trials were also heterogeneous in terms of disease states of populations, age, country of origin and other lifestyle factors. Further, usual dietary intakes were not checked in terms of possible prebiotic and probiotics consumption through the normal dietary patterns of participants. Due to few available studies, meta-analyses of the effects of prebiotics or synbiotics on adiponectin and leptin were not possible. As this was only an analysis of studies in adults, it is unclear how probiotics, prebiotics and synbiotics affect adiponectin and leptin in children.

5. Conclusion

This meta-analysis did not show any significant effects of probiotics on circulating adiponectin and leptin concentrations. Due to the small number of studies that investigated the effects of prebiotics or synbiotics, it is unclear if these modulate adiponectin and leptin. Future trials are needed that compare the effect of prebiotics, probiotics and synbiotics on adipokine concentrations.

Conflicts of interest

There is no conflict of interest.

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