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Etiology and Pathophysiology

Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: a systematic review and meta-analysis of randomized controlled trials

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Summary

A systematic review and meta-analysis of randomized controlled trials was conducted to examine the effects of probiotic supplementation on body weight, body mass index (BMI), fat mass and fat percentage in subjects with overweight (BMI 25–29.9 kg m^{-2}) or obesity (BMI ≥30 kg m^{-2}). MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched for studies published between 1946 and September 2016. A meta-analysis, using a random effects model, was performed to calculate the weighted mean difference between the intervention and control groups. Of 800 studies identified through the literature search, 15 were finally included. The studies comprised a total of 957 subjects (63% women), with the mean BMI being 27.6 kg m^{-2} and the duration of the interventions ranging from 3 to 12 weeks. Administration of probiotics resulted in a significantly larger reduction in body weight (weighted mean difference [95% confidence interval]; −0.60 [−1.19, −0.01] kg, I^2 = 49%), BMI (−0.27 [−0.45, −0.08] kg m^{-2}, I^2 = 57%) and fat percentage (−0.60 [−1.20, −0.01] %, I^2 = 19%), compared with placebo; however, the effect sizes were small. The effect of probiotics on fat mass was non-significant (−0.42 [−1.08, 0.23] kg, I^2 = 84%).

Keywords: Meta-analysis, obesity, probiotics, systematic review.

Abbreviations: **BMI**, body mass index; **CFU**, colony forming units; **CI**, confidence interval; **SD**, standard deviation; **WMD**, weighted mean difference.

Introduction

The prevalence of obesity has reached epidemic proportions over the last few decades. In 2013, 36.9% of adult (age ≥20 years) men and 29.8% of women were considered overweight (body mass index [BMI] 25–29.9 kg m^{-2}) or obese (BMI ≥30 kg m^{-2}) (1), and recent trend analyses show that the number of subjects who are overweight or obese is continuing to rise worldwide (2). Because of the multifaceted nature of obesity, there is no single or simple solution to combat this growing epidemic. Novel, and most likely individualized interventions, may thus be necessary to effectively prevent and treat overweight and obesity.

Animal and human studies demonstrate that the trillions of bacteria in the gut, the gut microbiota, are associated with energy homeostasis (3,4). The gut bacteria ferment otherwise indigestible carbohydrates, synthesize short chain fatty acids and amino acids and may thereby, possibly, contribute to the energy supplied to the host (5,6), although it is unclear whether this process is of clinical significance in man.

Then again, by-products from the bacterial fermentation process might also lower appetite and increase satiety (7),

and by modulation of bile acid metabolism (8), the microbiota may suppress diet-induced obesity through increased energy expenditure (9). Also, the gut bacteria may manipulate an individual's taste and dietary preferences (reviewed in (10)).

Interestingly, obesity, as compared with normal weight, is associated with a disease-specific dysbiotic shift in the faecal microbiota and also a lower bacterial richness (11). Energy-restriction and weight loss, on the other hand, is associated with an increased bacterial richness (12). The altered microbiota in the gut of subjects with obesity seems to be more efficient at harvesting energy from the diet (13) and may possibly contribute to further weight gain. Consequently, the gut microbiota is a potential modifiable target for prevention and/or treatment of obesity.

Oral administration of viable strains of bacteria (probiotics) has been proposed as a way of manipulating the gut ecosystem to favour weight reduction or decrease weight gain; however, the mechanisms by which probiotic supplementation may influence the gut microbiota are largely unknown (14). A few studies indicate that probiotics may exert an effect on the function of different bacterial species in the gut (15,16), but there is currently no clear evidence of compositional alterations of the faecal microbiota in response to probiotic supplementation (17). Several recent studies have, however, found probiotic supplementation to promote both weight gain and weight loss (18,19).

Two recent reviews concluded that consumption of probiotics slightly reduces body weight and BMI in adults. However, first, the independent effects of probiotics on body weight and BMI could not be determined as the intervention groups in many of the included trials also received prebiotics. Second, the previous reviews did not focus on populations where weight loss is favourable, i.e. subjects/populations with overweight or obesity. Finally, to the best of our knowledge, no systematic review has been undertaken to examine the effects of probiotic supplementation on fat mass or fat percentage.

Objectives

This systematic review and meta-analysis seeks to examine, through the results available from randomized controlled trials, the independent effects of probiotic supplementation on body weight, BMI, fat mass and fat percentage in subjects with overweight or obesity.

Methods

Protocol and registration

This systematic review has been registered in PROSPERO (CRD42016052609) and the protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016052609.

Eligibility criteria

We included randomized controlled trials of adults (18 years or older) with overweight (BMI 25–29.9 kg m^{-2}), obesity (BMI ≥30 kg m^{-2}) or mean BMI ≥25 kg m^{-2}. Studies including subjects with gastrointestinal disorders or patients who had undergone gastrointestinal surgery were excluded, as were studies of patients with medical conditions in which weight loss is contraindicated or studies including pregnant women.

All probiotics species, whether administered through capsules or added to foods, were accepted. Studies where the probiotic bacterial species were not clearly defined were excluded. Also excluded were studies with multiple intervention components (e.g. prebiotics in addition to probiotics) where the independent effects of probiotics on outcomes were not estimated. In cases of multiple interventions (different doses of probiotics and/or different species of probiotics), the highest dose and largest number of probiotic species were compared with control. Studies with both short-term and longer-term follow-up, of any length, were included. In studies where effect sizes were reported multiple times during follow-up, the effect size after the longest follow-up was used. We included studies comparing intervention with placebo or no probiotic supplementation, and the outcomes of interest were change in, or baseline and final value of, body weight, BMI (kg /m^{-2}), fat mass (kg) and/or fat percentage.

Information sources and search strategy

The search was performed in cooperation with health science librarians with expertise in systematic review searching, using medical subject headings and text words related to probiotics, BMI, body weight, fat mass (see Table S1 for complete search strategy) on 1 September 2016. We searched MEDLINE, EMBASE, as well as the Cochrane Central Register of Controlled Trials. The electronic database search was supplemented by searching for trial protocols through ClinicalTrials.gov. Also, additional studies were searched for in references of retrieved articles.

The literature search was restricted to English language and human subjects. Articles published ahead electronically, ahead-of-print, were evaluated, but protocols not leading to any publication were not included, and unpublished data were not obtained. There was no restriction on publication dates. The search strategy was subsequently peer reviewed by a second librarian.

Data collection

The literature search results were uploaded to http://www.covidence.org, which is an internet-based review program that facilitates review literature screening and collaboration among reviewers.

Two members of the review team (H. B. and L. K. J.) independently screened the titles and abstracts, yielded by the search, against the inclusion criteria, with full reports for all titles meeting the inclusion criteria thereafter obtained. The reviewers resolved uncertainty and disagreement by discussion with a senior author (J. H.), with whom the final decision rested.

Data extraction

The following data were extracted from each study; Authors, publication year, trial registration number, study design and duration, method of analysis, study population characteristics (number of subjects, % women, mean BMI or BMI range and age range), number of probiotic species, how probiotics were administered and the daily dose, number of subjects in intervention and control group, change in or baseline and final values of body weight, BMI, fat mass and fat percentage and whether body weight, BMI, fat mass or fat percentage were the primary outcomes of the trial.

Risk of bias within individual studies

Risk of bias within the individual studies was independently evaluated by two reviewers (H. B. and J. H.) using the Cochrane collaborations tool, where the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases (e.g. lack of a priori sample size calculation or an author's financial interest) were judged as high, low or unclear (20). The reviewers resolved uncertainty and disagreement by discussion and consensus.

Statistical analysis

The mean change (standard deviation) in body weight, BMI, fat mass and fat percentage from baseline was used to calculate the mean difference (95% confidence interval [CI]) between the intervention group and the control group. When not provided by the study authors, we calculated the standard deviation of the mean change in body weight, BMI, fat mass and fat percentage using the formula in the succeeding text (21). The correlation coefficient of the formula was imputed using data from included studies reporting both baseline, final values and changes from baseline of body weight and BMI. Our estimated value of 0.90 indicated that the correlation between baseline and final values of body weight and BMI was very high.

$$SD_{Change} = \sqrt{SD^2_{Baseline} + SD^2_{Final} - (2 \times 0.9 \times SD_{Baseline} \times SD_{Final})}$$

Results from all the individual studies were used to calculate a weighted mean difference (WMD) using a random effects model. Between-study heterogeneity was assessed using Cochrane Q-test, and the magnitude of heterogeneity was evaluated by the I^2 statistics. I^2 values of 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively (22). To investigate possible sources of heterogeneity, we performed sensitivity analyses and subgroup analyses using both study-level and patient-level characteristics. Study level characteristics were dichotomized (according to the different within-study risks of bias) into low risk and unclear/high risk. As the test for between-group heterogeneity is likely to be invalid when moderate to high heterogeneity is observed in one or more subgroups, we ran a meta-regression (random effects) to enable calculation of the proportion of between-study variance explained by each patient-level or study-level characteristic. The between-study variation accounted for by the different covariates was estimated by comparing tau^2 in the meta-regression analysis when the covariate was included to when the covariate was omitted from the meta-regression analysis. Sensitivity analyses were also performed by omitting one study at a time from the meta-analysis, thereby assessing its effect on the WMD (influential analysis).

Publication bias was assessed by visual inspection of funnel plots and the Egger's test. However, tests for publication bias were not performed when there were fewer than 10 studies with the same endpoint as the power of the test would be too low to distinguish chance from real asymmetry.

Statistical analyses were performed using Review manager 5.3 and STATA/MP 14.2. P values <0.05 were considered statistically significant.

Results

Study selection

The literature search identified 800 unique citations whereof 774 were excluded because of irrelevant content or non-English language (Fig. 1). Of the 26 articles which were full text screened, a total of 11 articles did not meet the criteria of inclusion either because the independent effects of probiotics on outcomes were not possible to estimate (23–30), the probiotic species were not defined (31) or the patients had undergone gastric bypass (32) or lacked sufficient information on the outcomes of interest (33). Finally, 15 articles were included in the systematic review and meta-analysis (34–48).

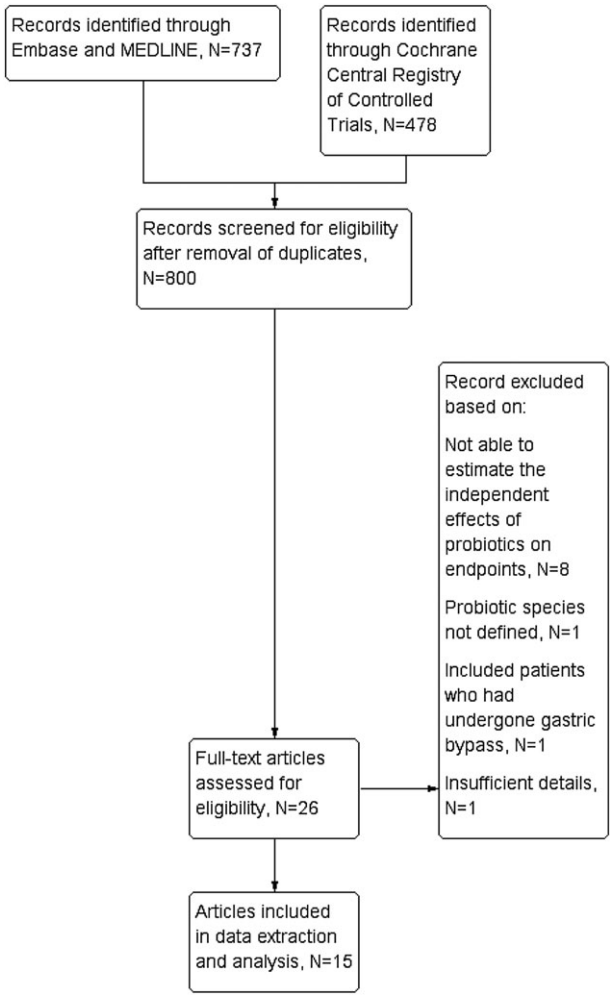

Figure 1 Flow diagram for study selection.

Study characteristics

General characteristics of the 15 studies included in this systematic review are presented in Table 1. The 15 studies comprised a total of 957 subjects (63% women), with a mean BMI of 27.6 kg m^{-2} and age between 18 and 75 years. Two-thirds (n = 10) of the studies included generally healthy subjects, whereas the remaining studies included subjects with arterial hypertension (n = 1), non-alcoholic fatty liver disease (n = 1), hypercholesterolemia (n = 1), type 2 diabetes mellitus (n = 1) and high fasting glucose (≥100 mg dL^{-1}) (n = 1). Eight of the studies included only overweight and obese subjects (34,35,37,41–43,45,47), whereas the remaining studies did not state that they excluded normal weight subjects, but the mean BMI was above 25 kg m^{-2}, and most often closer to 30 kg m^{-2}, in all included studies.

Two-thirds (n = 10) of the studies included one single species of probiotics, while the remaining studies (n = 5) included two or multiple species of probiotics. Probiotics were supplemented in food such as yoghurt (n = 5), fermented milk (n = 2), cheese (n = 1), soy milk (n = 1) and capsules (n = 5) or powder (n = 1). The control groups in all trials received either similar food without probiotics or placebo capsules. Also, in one study, both cases and controls were supplemented with an anti-obesity herb (Bofutsushosan) in addition to probiotics/placebo (42). The daily doses of probiotics varied between 1.0×10^9 and 4.8×10^{11} colony forming units (CFU), and the duration of the trials ranged from 3 to 12 weeks (median: 8 weeks).

The majority of the studies reported changes, or baseline and final values, of body weight (n = 13), BMI (n = 13) or both (n = 10), whereas 7 and 5 studies reported changes or baseline and final values of fat mass and fat percentage, respectively. Changes in body weight, BMI, fat mass/fat percentage or related outcomes such as changes in abdominal fat mass were the primary outcomes in 9 of the included studies (35–37,39,40,42–45).

Risk of bias within studies

Risk of bias within the individual studies is shown in Fig. 2. All 15 studies were randomized, and the majority (n = 11) described the method of randomization. Methods of allocation concealment were only properly described in 20% (n = 3) of the included studies, but almost all (n = 14) studies were double blinded (participants and study-personnel). None of the studies stated that outcome assessment was blinded, but we believe that the outcome measurement is not likely to be influenced by lack of blinding (49). Studies regarded as having low risk of bias in terms of incomplete outcome date (n = 10) include those with no drop outs, those where data were analysed according to the intention to treat principle or where reasons for exclusions were provided, as well as studies where the number of drop-outs were evenly distributed between the intervention and control groups. Importantly, less than half (n = 6) of the trials were preregistered in a clinical trial registry, which might have caused reporting bias. Studies defined as having high risk of other biases included those which were funded by companies with marked interests or were researched by authors with vested financial interests (n = 4), as well as those lacking a priori sample size calculation (n = 9).

Results of individual studies according to different endpoints

Body weight

The meta-analysis of the 13 studies examining the effects of probiotics on body weight revealed that administration of probiotics resulted in a significantly larger weight loss (WMD [95% CI] −0.60 [−1.19, −0.01] kg) compared with placebo, and the heterogeneity between the studies was moderate (p = 0.02, I^2 = 49.1%) (Fig. 3).

Table 1 Characteristics of studies examining the effects of probiotic supplementation on body weight, BMI, fat mass and fat percentage

Authors (year)	Trial registration number	Study design (duration)	ITT	Study population characteristics *n* (% women) Mean BMI (range) Age-range	Intervention (total daily dose)	Control	No. intervention/ no. control	Outcome(s) (body weight or related endpoints were primary endpoints; yes/no)
Agerholm-Larsen *et al.* (2000) (48)	–	Randomized, double blind, controlled (8 weeks)	No	Healthy weight stable subjects *n* = 70 (71%) 30.0 (>25.0 < 37.5) kg m^{-2} 18–55 years	Yoghurt with *Enterococcus faecium* and *Streptococcus termophilus* (4.8×10^{11} CFU)	Yoghurt	Intervention group (*n* = 16) Control group (*n* = 14)	Body weight and fat mass (no)
Chung *et al.* (2016) (32)	Clinical Research Information Service of Korea KCT0000452 (Korean language)	Randomized, double blind, controlled (12 weeks)	No	Overweight and obese adults *n* = 37 (46%) 28.5 (25.0–35.0) kg m^{-2} 25–65 years	Capsules with *Lactobacillus* JBD301 (1×10^9 CFU)	Capsules	Intervention group (*n* = 18) Control group (*n* = 19)	Body weight (yes)
Hariri *et al.* (2015) (33)	Iranian Registry of Clinical Trials, identifier: IRCT201405265062N8	Randomized, double blind, controlled (8 weeks)	No	Patients with type 2 diabetes *n* = 40 (53%) 26.6 (?)kg m^{-2} 35–68 years	Soy milk with *Lactobacillus planetarium* A7 (4×10^9 CFU)	Soy milk	Intervention group (*n* = 20) Control group (*n* = 20)	Body weight and BMI (yes)
Higashikawa *et al.* (2016) (34)	–	Randomized, double blind, controlled (12 weeks)	Yes	Healthy volunteers *n* = 41 (63%) 27.1 (25.0–30.0) kg m^{-2} 20–70 years	Probiotic powder with *Pediococcus pentosaceus* LP28 (1×10^{11} CFU)	Placebo powder	Intervention group (*n* = 21) Control group (*n* = 20)	BMI, body fat percentage and body fat mass (yes)
Jones *et al.* (2012) (35)	ClinicalTrials.gov (NCT ID: NCT0118579)	Randomized, double blind, controlled (6 weeks)	No	Hypercholestremic subjects *n* = 120 (64%) 26.1 (22.0–32.0) kg m^{-2} 20–75 years	Yoghurt with *Lactobacillus reuteri* NCIMB 30242 (2×10^{10} CFU)	Yoghurt	Intervention group (*n* = 59) Control group (*n* = 61)	Body weight and BMI (no)
Jung *et al.* (2013) (45)	–	Randomized, double blind, controlled (12 weeks)	Yes	Volunteers with blood glucose ≥100 mg/dL *n* = 57 (61%) 29.1 (?)kg m^{-2} 19–60 years	Capsules with Lactobacillus gasseri BNR17 capsules (6×10^{10} CFU)	Capsules	Intervention group (*n* = 28) Control group (*n* = 29)	Body weight, BMI and body fat (no)
Kadooka (2010) (49)	–	Randomized, double blind, controlled (12 weeks)	No	Generally healthy adults *n* = 87 (32%) 27.4 (24.2–30.7) kg m^{-2} 33–63 years	Fermented milk with *Lactobacillus gasseri* SBT2055(LG2055) (1×10^{11} CFU)	Fermented milk	Intervention group *n* = 43 Control group *n* = 44	Body weight, BMI, fat percentage and fat mass (yes)
Kadooka (2013) (37)	–	Randomized, double blind, controlled (12 weeks)	No	Healthy adults with large visceral fat areas *n* = 139 (50%) 27.4 (?) kg m^{-2}	Fermented milk with *Lactobacillus gasseri* SBT2055 (LG2055) (1.6×10^{10} CFU)	Fermented milk	Intervention group *n* = 69 Control group *n* = 70	BMI (yes)

(*Continues*)

Table 1 (Continued)

Authors (year)	Trial registration number	Study design (duration)	ITT	Study population characteristics *n* (% women) Mean BMI (range) Age-range	Intervention (total daily dose)	Control	No. intervention/ no. control	Outcome(s) (body weight or related endpoints were primary endpoints; yes/no)
				35–60 years				
Lee (2014) (39)	Clinical Research Information Service (KCT0000386)	Randomized, double blind, controlled (8 weeks)	No	Overweight or obese women *n* = 50 (100%) 28.4 (25.0–?) kg m^{-2} 19–65 years	Capsules with *Streptococcus thermophiles*, *Lactobacillus plantarum*, *Lactobacillus acidophilus, Lactobacillus rhamnosus*, *Bifidobacterium lactis*, *Bifidobacterium longum* and *Bifidobacterium breve* (1×10^{10} CFU) Bofutsushosan (herbal anti-obesity medicine)	Capsules and Bofutushosan	Intervention group *n* = 25 Control group *n* = 25	Body weight, BMI, fat percentage and fat mass (yes)
Madjd (2016) (40)	http://www.irct.ir IRCT201402177754N8	Randomized, single blind, controlled (12 weeks)	Yes	Healthy, overweight or obese pre-menopausal women *n* = 89 (100%) 32.1 (27.0–40.0) kg m^{-2} 18–50 years	Yoghurt with *Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12 with a total of minimum (4×10^{9} CFU)	Low fat yoghurt	Intervention group *n* = 44 Control group *n* = 45	Body weight and BMI (yes)
Minami *et al.* (2015) (41)	–	Randomized, double blind, controlled (12 weeks)	No	Adult volunteers *n* = 44 (61%) 27.4 (24.0–30.0) kg m^{-2} 40–69 years	Capsules with *Bifidobacterium breve* B-3 (5×10^{10} CFU)	Capsules	Intervention group *n* = 19 Control group *n* = 25	Body weight, BMI, fat percentage and fat mass (yes)
Nabavi *et al.* (2014) (38)	–	Randomized, double blind, controlled (8 weeks)	No	Patients with NAFLD *n* = 72 (54%) 30.8 (25–40) kg m^{-2} 23–63 years	Yoghurt with *Bifidobacterium lactis* Bb12 and *Lactobacillus* La5 (2.5×10^{9} CFU)	Yoghurt	Intervention group *n* = 36 Control group *n* = 36	Body weight and BMI (no)
Sharafedtinov *et al.* (2013) (42)	Current Controlled Trials ISRCTN76271778	Randomized, double blind, controlled (3 weeks)	No	Patients with obesity and arterial hypertension *n* = 40 (68%) 37.0 (30.0–?) kg m^{-2} 30–69 years	Probiotic cheese with *Lactobacillus plantarum* TENSIA ($1 \times 10^{10.4}$ CFU)	Cheese	Intervention group *n* = 25 Control group *n* = 15	Body weight, BMI and fat mass (yes)
Simon *et al.* (2015) (43)	ClinicalTrials.gov NCT01250106	Randomized, double blind, controlled (4 weeks)	No	Generally healthy subjects *n* = 21 (48%) 29.2 (19.0–45) kg m^{-2} 40–65 years	Capsules with *Lactobacillus reuteri* SD5865 (2×10^{10} CFU)	Capsules	Intervention group *n* = 11 Control group *n* = 10	Body weight, fat percentage (no)

(*Continues*)

Table 1 (Continued)

Authors (year)	Trial registration number	Study design (duration)	ITT	Study population characteristics *n* (% women) Mean BMI (range) Age-range	Intervention (total daily dose)	Control	No. intervention/ no. control	Outcome(s) (body weight or related endpoints were primary endpoints; yes/no)
Zarrati (2014) (44)	–	Randomized, double blind, controlled (8 weeks)	No	Overweight and obese subjects *n* = 50 (68%) 33.9 (25.0–40.0) kg m^{-2} 20–50 years	Yoghurt with *Lactobacillus acidophilus* LA5, *Bifidobacterium lactis* BB12 and *Lactobacillus casei* DN001 (6×10^9 CFU)	Yoghurt	Intervention group *n* = 25 Control group *n* = 25	Body weight, BMI (no)

BMI, body mass index; CFU, colony forming units; ITT, intention to treat.

Figure 2 Risk of within-study bias. [Colour figure can be viewed at wileyonlinelibrary.com]

The effect of probiotic supplementation on body weight loss was reduced when restricting the analyses to studies which only included subjects who were clearly defined with overweight or obesity (WMD [95% CI]; −0.25 [−1.06, 0.56] kg), subjects who were generally healthy (−0.40 [−1.31, 0.50] kg) or to studies where body weight or related outcomes were primary endpoints (−0.40 [−1.50, 0.66] kg) (Table 2). The covariates 'number of probiotic species' and

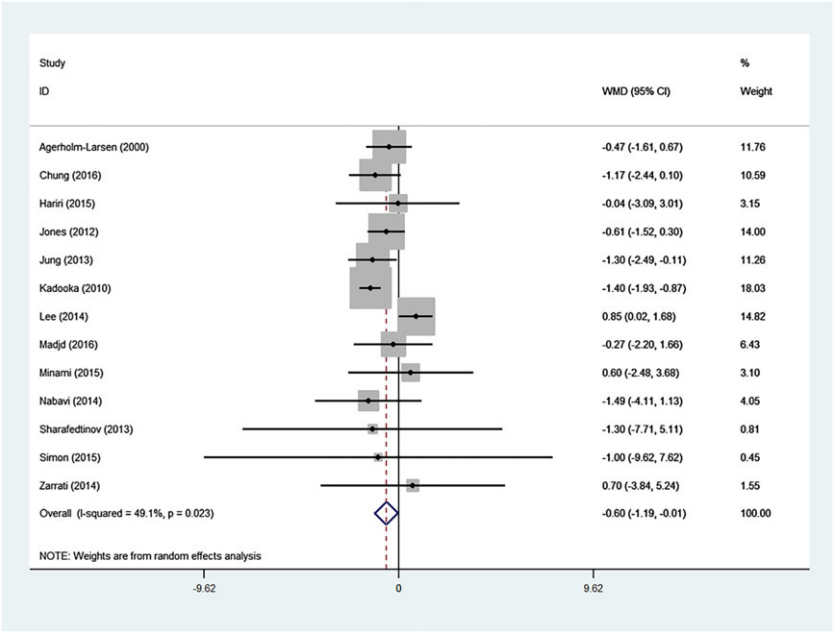

Figure 3 The effect of probiotic supplementation on body weight. CI, confidence interval; WMD, weighted mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

'intervention duration' individually explained 74.1% and 62.2% of between-study heterogeneity, respectively.

In the study by Lee *et al*., the reduction in body weight was larger in the control group than in the intervention group. Consequently, by removing the study by Lee *et al*. from the meta-analysis, the effect of probiotic supplementation on body weight increased (−1.05 [−1.42, −0.69] kg) (Table S2). Similarly, when this study was excluded, the effect of probiotic supplementation on body weight increased when restricting the analyses to studies where subjects were clearly defined with overweight or obesity (−0.73 [−1.46, −0.01] kg), generally healthy (−1.28 [−1.56, −0.70] kg) and among studies where body weight or related outcomes were primary endpoints (−1.23 [−1.69, −0.77] kg). When the study by Lee *et al*. was excluded from the analyses, no heterogeneity (I^2 = 0%, p = 0.83) between the studies, or significant differences between subgroups, were observed.

There was no indication of publication bias as the funnel plot (Fig. S1) was satisfactory, and the Egger's test indicated that there was no small-study effect (p = 0.48).

Body mass index

A total of 13 studies examined the effects of probiotic supplementation on BMI. Administration of probiotics was associated with significantly larger reduction in BMI (WMD [95% CI]; −0.27 [−0.45, −0.08] kg m^{-2}] compared with placebo (Fig. 4), with a moderate heterogeneity ($p < 0.01$, I^2 = 56.8%) between the studies.

Sensitivity analyses showed that the effect of probiotic supplementation on BMI was reduced when the meta-analyses were restricted to studies that only included subjects who were clearly defined with overweight or obesity (WMD [95% CI]; −0.14 [−0.45, 0.18] kg m^{-2}) and subjects who were generally healthy (−0.21 [−0.45, 0.03] kg m^{-2}) or to studies where body weight or related outcomes were primary endpoints (−0.21 [−0.44, 0.02] kg m^{-2}) (Table 3). The covariates 'number of probiotic species', 'intervention duration' and 'reporting bias' each explained 100%, 70.0% and 64.1% of between-study heterogeneity, respectively.

The study by Lee *et al*. had a substantial influence on the overall WMD, and the effect of probiotic supplementation on BMI increased when this study was removed from the analysis (−0.39 [−0.50, −0.29] kg m^{-2}) (Table S3). Similarly, the effect of probiotic supplementation on BMI among studies where subjects were clearly defined with overweight or obesity (−0.32 [−0,56, −0.07] kg m^{-2}), where subjects were generally healthy (−0.40 [−0.51, −0.28] kg m^{-2}] and among studies where body weight or related outcomes were primary endpoints (−0.39 [−0.51, −0.27] kg m^{-2}] increased when the study by Lee *et al*. was excluded from the analyses. Also, by removing this single study, no heterogeneity (I^2 = 0%, p = 0.58) between the studies, or significant differences between subgroups, were observed.

There was no indication of publication bias as the funnel plot was satisfactory (Fig. S2), and the Egger's test indicated no small-study effect (p = 0.34).

Table 2 Sensitivity and subgroup analyses performed according to patient-level and study-level characteristics (body weight)

	Number of studies	Weighted mean difference (95% CI)	Adjusted R^2 *
Sensitivity analyses			
Overweight and obese individuals only	7	−0.25 (−1.06, 0.56)	
Generally healthy subjects only	8	−0.40 (−1.31, 0.50)	
Studies with body weight or related outcome as primary outcome	7	−0.40 (−1.50, 0.66)	
Subgroup analyses			
Number of probiotic species			74.1% ($p = 0.03$)
Single	8	−1.16 (−1.56, −0.77)	
Multiple	5	0.07 (−0.77, 0.90)	
Duration of intervention			62.2% ($p = 0.05$)
≤8 weeks	6	−0.08 (−0.68, 0.53)	
>8 weeks	7	−1.26 (−1.70, −0.83)	
Method of administration			2.74% ($p = 0.46$)
Food	8	−1.04 (−1.44, −0.64)	
Capsules or powder	5	−0.36 (−1.61, 0.90)	
Random sequence generation (selection bias)			−12.8% ($p = 0.59$)
Low risk	9	−0.81 (−1.36, −0.25)	
High or unclear risk	4	−0.36 (−1.84, 1.12)	
Allocation concealment (selection bias)			−9.72% ($p = 0.67$)
Low risk	2	−1.01 (−2.17, 0.14)	
High or unclear risk	11	−0.54 (−1.24, 0.17)	
Blinding of participants and personell (performance bias)			−9.0% ($p = 0.78$)
Low risk	12	−0.62 (−1.25, 0.01)	
High or unclear risk	1	−0.27 (−2.20, 1.66)	
Incomplete outcome asessement (attrition bias)			−28.7% ($p = 0.19$)
Low risk	8	−1.05 (−1.43, −0.67)	
High or unclear risk	5	−0.09 (−1.63, 1.44)	
Selective reporting (reporting bias)			34.5% ($p = 0.17$)
Low risk	7	−0.22 (−0.98, 0.55)	
High or unclear risk	6	−1.20 (−1.63, −0.77)	
Other bias			−10.4% ($p = 0.64$)
Low risk	3	−1.02 (−2.03, 0.00)	
High or unclear risk	10	−0.53 (−1.22, 0.17)	

*Heterogeneity explained by the covariate.
CI, confidence interval.

Fat mass and fat percentage

The overall estimate of the seven studies reporting changes in fat mass showed a larger reduction in fat mass in the intervention groups compared with the control groups, but the difference was non-significant (WMD [95% CI]; −0.42 [−1.08, 0.23] kg), and between-study heterogeneity was high ($p < 0.001$, $I^2 = 83.6\%$) (Fig. 5).

Because of the low number of studies examining the effect of probiotics on fat mass, subgroup analyses or meta-regression were not performed with regards to these endpoints. However, the studies by Agerholm-Larsen *et al.* and Lee *et al.* were the only studies reporting either increased amounts of fat mass or lower reduction in fat mass in the intervention group compared with the control group, and by excluding these studies, there was no heterogeneity ($p = 0.77$, $I^2 = 0\%$), and the estimated effect of probiotic supplementation on fat mass increased (WMD [95% CI]; −0.97 [−1.28, −0.66] kg).

Five studies reported on changes in fat percentage, and the pooled estimate showed a significantly larger reduction in fat percentage in the intervention groups compared with the control groups (WMD [95% CI]; −0.60 [−1.20, −0.01] %), with low heterogeneity ($p = 0.30$, $I^2 = 18.7\%$) between the studies (Fig. 6).

Discussion

Summary of evidence

The current systematic review and meta-analysis have examined the effect of probiotic supplementation on body weight, BMI, fat mass and fat percentage in overweight or obese subjects. A total of 15 randomized controlled trials were included, whereof 13 studies reported on changes in body weight, 13 studies reported on changes in BMI and 7 and 5 studies reported on changes in fat mass and fat percentage, respectively. The estimates showed that probiotic supplementation significantly reduced body weight (WMD [95% CI]; −0.60 [−1.19, −0.01] kg), BMI (−0.27 [−0.45, −0.08] kg m^{-2}) and fat percentage (−0.60 [−1.20, −0.01] %), but the effects

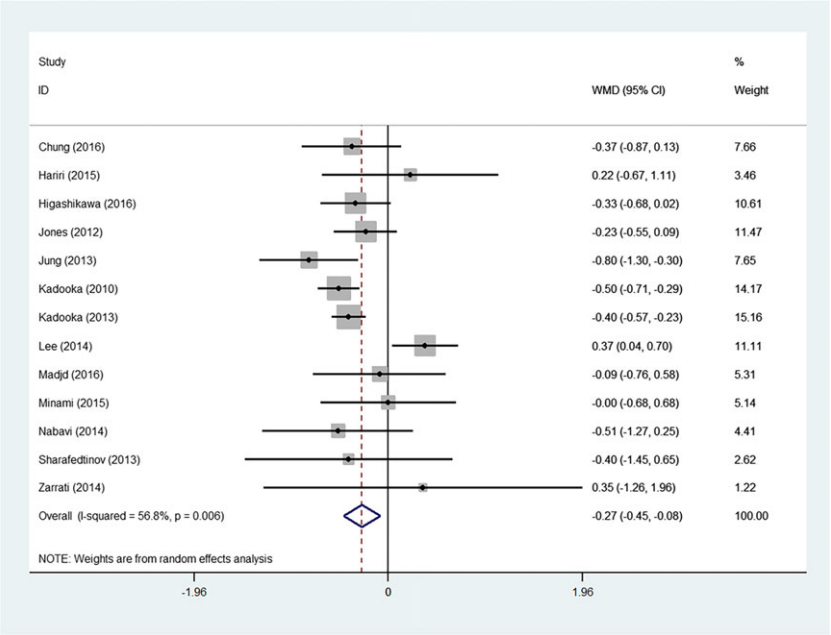

Figure 4 The effect of probiotic supplementation on BMI. CI, confidence interval; WMD, weighted mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

sizes were small. Probiotic supplementation also reduced body fat mass, albeit not significantly (−0.42 [−1.08, 0.23] kg).

Strengths and limitations

The present review was based on a broad literature search performed in cooperation with an expert librarian, and it is therefore unlikely that important trials were overlooked.

The meta-analyses examining the effects of probiotics on body weight and BMI included an adequate number of studies, while the number of studies included in the meta-analyses of the effects of probiotics on body fat mass and percentage were low, thus meaning that the latter results should be interpreted with caution. The results are, however, strengthened in that fat mass, and percentage had been estimated using a similar method in all trials (bioelectrical impedance). A few studies included more than one probiotic intervention, and we chose to include the intervention groups who received the highest daily dose over the longest time period as we considered these groups more likely to experience an effect on body weight and related outcomes.

Most studies had low risk of selection, performance and attrition bias. However, less than half of the trials were preregistered in a clinical trial registry and were thus judged as having unclear risk of reporting bias, while 12 studies were either funded by companies with marked interests, researched by authors with vested financial interests or lacked a priori sample size calculation and were regarded as having high risk of other biases. The majority of the studies were of small size, and as only six trials had performed a priori sample size calculations with body weight, BMI, fat mass or fat percentage as primary endpoints, it is likely that a number of the included studies were underpowered. Also, because of small sample sizes, the baseline values of the intervention and control groups were not always comparable despite being randomized. To account for this, we estimated the mean change from baseline, where these values were not reported, and included these values, in place of post-intervention values, in the meta-analyses.

The study by Lee *et al*. was found to be the main source of heterogeneity. Lee *et al*. reported greater reductions in body weight and BMI in the control group than in the intervention group. Consequently, when this study was excluded from the meta-analyses, the WMD increased (i.e. greater reductions in body weight and BMI in the intervention groups compared with the control groups). This study was the only study that included another intervention (the anti-obesity herb Bofutsushosan) in addition to probiotics, but we chose to include the study in the screening process as both the intervention group and the control group received the herb. However, we cannot exclude the possibility of an interaction effect between the herb and the probiotic supplement. Also, the study by Lee *et al*. differed from the remaining studies in that the intervention group received seven different species of probiotics, while the other studies included between one and three species. Whether the anti-obesity herb, the large number of different probiotic species or another variable not accounted for, was the source of heterogeneity is not known.

Table 3 Sensitivity and subgroup analyses performed according to patient-level and study-level characteristics (BMI)

	Number of studies	Weighted mean difference (95% CI)	Adjusted R^2 *
Sensitivity analyses			
Overweight and obese individuals only	7	−0.14 (−0.45, 0.18)	
Generally healthy subjects only	8	−0.21 (−0.45, 0.03)	
Studies with body weight or related outcome as primary outcome	9	−0.21 (−0.44, 0.02)	
Subgroup analyses			
Number of probiotic species			100% ($p < 0.01$)
Single	9	−0.40 (−0.51, −0.29)	
Multiple	4	0.06 (−0.38, 0.50)	
Duration of intervention			70.0% (p = 0.03)
≤8 weeks	6	0.03 (−0.38, 0.32)	
>8 weeks	7	−0.40 (−0.51, −0.29)	
Method of administration			−16.2% ($p = 0.99$)
Food	8	−0.39 (−0.50, −0.27)	
Capsules or powder	5	−0.22 (−0.64, 0.21)	
Random sequence generation (selection bias)			−17.8% ($p = 0.85$)
Low risk	9	−0.30 (−0.48,-0.12)	
High or unclear risk	4	−0.24 (−0.58, 0.11)	
Allocation concealment (selection bias)			−3.09 (p = 0.58)
Low risk	2	−0.04 (−0.72, 0.68)	
High or unclear risk	11	−0.28 (−0.48, −0.09)	
Blinding of participants and personell (performance bias)			−8.03 ($p = 0.68$)
Low risk	12	−0.28 (−0.47, −0.08)	
High or unclear risk	1	−0.09 (−0.76, 0.58)	
Incomplete outcome asessement (attrition bias)			19.8% ($p = 0.28$)
Low risk	8	−0.38 (−0.49, −0.27)	
High or unclear risk	5	−0.13 (−0.71, 0.46)	
Selective reporting (reporting bias)			64.1% (p = 0.03)
Low risk	6	−0.05 (−0.35, 0.25)	
High or unclear risk	7	−0.43 (−0.55, −0.32)	
Other bias			−2.13% ($p = 0.27$)
Low risk	3	−0.45 (−0.74, −0.16)	
High or unclear risk	10	−0.19 (−0.43, 0.05)	

*Heterogeneity explained by the covariate.
BMI, body mass index; CI, confidence interval.

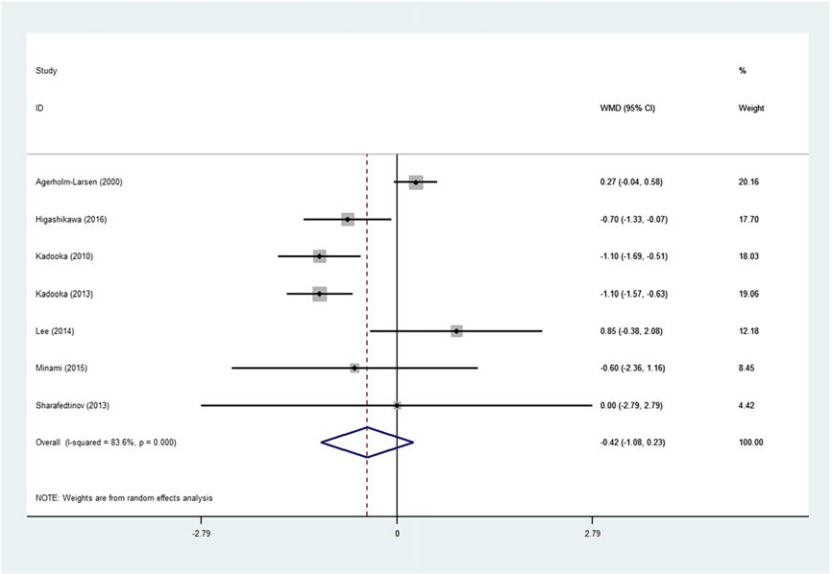

Figure 5 The effect of probiotic supplementation on body fat mass. CI, confidence interval; WMD, weighted mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

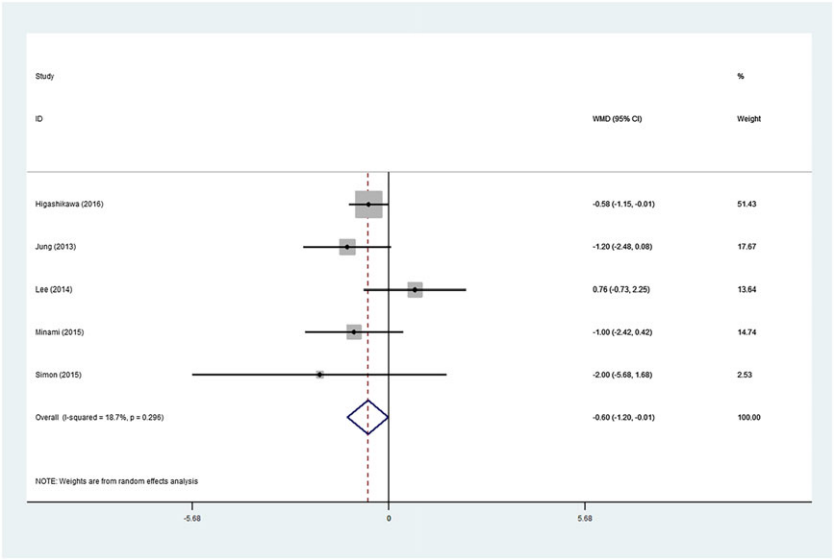

Figure 6 The effect of probiotic supplementation on body fat percentage. CI, confidence interval; WMD, weighted mean difference. [Colour figure can be viewed at wileyonlinelibrary.com]

All but three studies included probiotics from the *Lactobacillus* genus in their interventions, and subgroup analyses showed that the effect sizes did not differ between studies that supplemented with *Lactobacillus* and those who did not (data not shown). Because of a large number of studies including multiple genera and species of probiotics, we did not perform further subgroup analyses. A limitation of this study is thus that the estimates have low specificity with regard to the effects of different genera/species of probiotics on body weight, BMI, fat mass and fat percentage. Further, there were no large variations in the supplemented daily doses of probiotics, and consequently, subgroup analyses with regard to daily dose of probiotics were not performed.

Agreements and disagreements with other studies or reviews

In accordance with our findings, previous reviews have found probiotics to reduce body weight in adults, and the reported effect sizes were small (19,50). However, to the best of our knowledge, this is the first of recent reviews including only overweight/obese adults or populations. Also, no previous systematic review has, to our knowledge, examined the effects of probiotics on body fat mass and fat percentage. One recent review examined the effect of probiotics on body weight in infants, children and adults and found probiotics to increase weight in infants and children, while having the opposite effect among adults (50). These findings raise suspicions of reporting bias where only favourable results are reported. Hence, as the present study only included subjects where weight loss is favourable, we cannot exclude the possibility of selective reporting.

A synergistic effect between probiotics and prebiotics is not unlikely; therefore, in order to minimize between-study heterogeneity, only studies where the independent effects of probiotics on body weight, BMI, fat mass and fat percentage could be determined were included. Prior reviews have included interventions with both probiotic and prebiotics, and to our knowledge, no other review has been undertaken to examine the independent effects of probiotics on body weight and the related outcomes.

Conclusions

Our meta-analysis showed that short-term (≤12 weeks) probiotic supplementation reduced body weight, BMI and fat percentage, but the effect sizes were small. Overall, the risk of bias within included studies was low, but, importantly, a number of trials were not registered and/or lacked a priori sample size calculation and were thus regarded as having unclear or high risk of reporting and other biases. Accordingly, further long-term studies are required to examine the effects of probiotic supplementation on various measures on body weight.

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Conflict of interest statement

No conflict of interest was declared.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. https://doi.org/10.1111/obr.12626

Table S1 Search strategy
Table S2 Results of the influential analysis from the random effects model examining the effect of probiotic supplementation on body weight. **Note:** The table shows how the WMD is altered when one study at a time is excluded from the meta-analysis
Table S3 Results of the influential analysis from the random effects model examining the effect of probiotic supplementation on BMI. **Note:** The table shows how the WMD is altered when one study at a time is excluded from the meta-analysis
Figure S1 Funnel plot of studies examining the effect of probiotic supplementation on body weight. **Abbreviations:** se(WMD), standard error of the weighted mean difference; WMD weighted mean difference
Figure S2 Funnel plot of studies examining the effect of probiotic supplementation on BMI. **Abbreviations:** se(WMD), standard error of the weighted mean difference; WMD weighted mean difference

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