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# Targeting Body Weight Regulation with Probiotics: A Review of Randomized Trials in Obese and Overweight People Free of Co-morbidities

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## Abstract

Accumulating evidence has pointed towards a role of the gut microbiota in the pathogenesis of obesity. Also, the gut microbiota is a dynamic and modifiable community offering itself as a target for therapeutic interventions potentially improving host health. This review gives an overview on effects of clinically controlled interventions with probiotics on body weight regulation in overweight or obese individuals free of co-morbidities.

Literature search was performed through PubMed with the criteria 1) healthy overweight/obese adults without co-morbidities as study population, 2) probiotics as intervention without limits regarding dose or duration of intervention 3) healthy overweight/obese adults receiving placebo as controls, 4) body weight-related variables as the primary outcome and 5) randomized controlled trial as the study design. Methodological quality of the included studies was assessed using the Jadad score.

Seven studies from five different countries met the inclusion criteria. Three studies reported improvements in body weight-related variables after probiotic supplementation compared to that in the controls, whereas four did not find such improvements. Overall, the methodological quality of the studies was limited and ranged from three to five based on the Jadad score.

In conclusion, this review failed to identify convincing evidence of a robust effect of interventions with probiotics on body weight regulation in overweight or obese individuals free of co-morbidities. Large high quality randomized controlled trials in well-phenotyped study participants on regulated and to some extent standardized diets with mixtures of probiotics known to have master-switch roles in the gut microbiota composition and function in healthy lean individuals are needed to examine the effects of probiotics on body weight in greater detail.

**Keywords:** Probiotic; Microbes; Obesity; Weight regulation; Metabolism; Gut microbiota

**Abbreviations:** BMI: Body Mass Index; BW: Body Weight; FM: Fat Mass; LPS: Lipopolysaccharides

## Introduction

### Obesity

Obesity is defined by World Health Organization as abnormal or excessive fat accumulation that may impair health and is classified as a Body Mass Index (BMI) greater than or equal to 30 (kg/m$^2$). Obesity is widely accepted as a risk factor of several non-communicable diseases such as type 2 diabetes, cardiovascular diseases and some forms of cancers [1]. Currently, the prevalence of obesity is reaching epidemic proportions and in 2030 obesity is estimated to affect 573 million people worldwide [2]. Genetic susceptibility and environmental factors such as an unhealthy diet and lack of physical activity are known risk factors predisposing to obesity. However, lifestyle-targeted weight loss methods generally produce poor long-term results, why a growing interest in novel preventive and therapeutic tools for combatting the obesity epidemic has evolved.

### Gut microbiota: A link to obesity

The human gut microbiota refers to the billions of microbes that reside inside the gut. The gut microbiota has several health effects on the host including colonic fermentation of dietary fibres and thereby energy harvest of nutrients, synthesis of vitamins and amino acids, prevention of colonization by pathogens, modulation of gastrointestinal hormone release, effects on bidirectional neuronal signalling between the gut and the brain, and education of the immune system [3,4]. The engagement of altered gut microbiota in the pathogenesis of obesity originates from studies in rodents. A study reported that transplantation of gut microbiota from conventionally raised mice into their germ-free counterparts resulted in increased body fat and decreased insulin sensitivity [5]. Correspondingly, in another study, transplantation of gut microbiota from human twin donors discordant for obesity into germ-free mice resulted in transmission of the obesity phenotype. Cohousing, the mice harboring an obese twin's microbiota with mice containing a lean co-twin's microbiota, prevented the development of increased body mass and adiposity. Interestingly, this rescue was diet-dependent [6]. Collectively, these findings suggest an active role of an altered gut microbiota in the pathogenesis of obesity. Subsequently, obesity has been associated with decreased bacterial diversity and specific alterations in bacterial species in human studies

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[7,8]. At the molecular level it is still unsettled how the gut microbiota may contribute to obesity pathogenesis, but numerous mechanisms have been proposed (Figure 1). Three major mechanisms point to an induction of a systemic low-grade inflammatory state and a state of dysmetabolism.

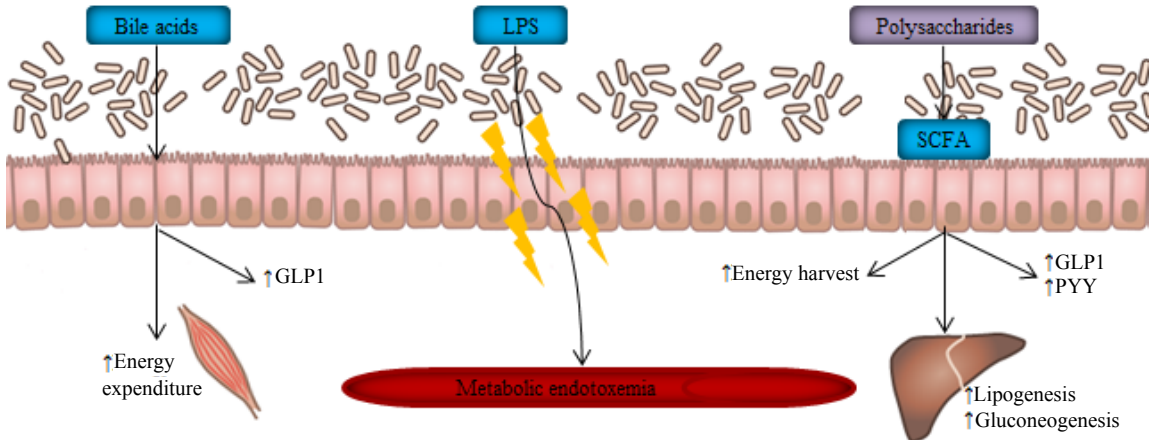
- Lipopolysaccharide (LPS), an endotoxin of gram-negative bacteria, has been suggested to affect host health by activating pro-inflammatory pathways and contribute to postprandial inflammation in humans, which is a characteristic feature of both type 2 diabetes and obesity [9]. Increased LPS concentration may occur due to increased intestinal permeability or by uptake of LPS in chylomicrons secreted from intestinal epithelial cells [9].
- De-conjugated primary bile acids can be transformed to secondary bile acids by the bacteria residing in the colon. The secondary bile acids binds to the TGR5 receptor, resulting in increased energy expenditure in muscle and secretion of Glucagon-like peptide-1 from the intestinal L-cells, a signalling pathway, which has been found to counteract metabolic dysfunction [10].
- The short chain fatty acids, butyrate, acetate and propionate, are produced through fermentation of complex polysaccharides by the colonic gut bacteria and enter the circulation. The short chain fatty acids bind to G-protein coupled receptors on intestinal epithelial cells and butyrate and propionate induce levels of the peptide hormones Glucagon-like peptide-1 and peptide YY and reduce food intake [11]. Additionally, butyrate seems to possess beneficial effect on insulin sensitivity and energy balance [12], whereas acetate and propionate mainly function as substrates for gluconeogenesis and lipogenesis in the liver [3].
- An obesity-associated gut microbiota possesses an increased capacity for energy harvest [5,13]. An increased utilization of indigestible carbohydrates such as resistant starch and dietary fibre is an additional source of energy and is estimated to increase daily caloric uptake by 5-10% [14]. However, the hypothesis is in contrast with epidemiological data, which indicate that a high dietary fibre intake protects against obesity [15].

The gut microbiota is a stable and unique personal habitat since samples obtained over time from the same individual are more similar to one another than to those obtained from different individuals [16]. Yet, it is too a dynamic community influenced by factors such as diet [17], alcohol intake [18], food additives [19], physical activity [20], smoking [21] and antibiotics [22] offering it as a target for therapeutic interventions improving host health [23].

## Probiotics

Probiotics have gained much interest over the last few years as a possible regulator of obesity and its metabolic complications due to its potential effects on gut microbial composition and function in relation to host biology [24,25].

Probiotics are defined as live microorganisms that, when administered in adequate amounts confer a health benefit on the host. Furthermore, safety and efficacy of the defined strains have to be adequately demonstrated in order to be considered as a probiotic [26]. The majority of the bacterial microorganisms investigated as probiotics belong to the genera of *Lactobacillus* and *Bifidobacterium* as well as the Nissle 1917 strain of *E. coli* [27]. Several animal studies of obesity have demonstrated major therapeutic effects of various strains of *Lactobacillus* and *Bifidobacterium* on host biology including but not limited to inhibition of diet-induced weight gain, enhanced insulin sensitivity and reduced fat accumulation in liver and white adipose tissue [28-31].




Abbreviations: GLP1: Glucagon-like peptide-1; LPS: lipopolysaccharides; PYY: peptide YY; SCFA: short chain fatty acids.

**Figure 1:** Three suggested mechanisms of how gut microbiota may affect development of obesity and related pathologies. Bacteria residing in the colon are able to convert de-conjugated primary bile acids into secondary bile acids. The secondary bile acids bind to the TGR5 receptor and activate GLP1 secretion from the intestinal L-cells, resulting in increased energy expenditure in muscle and secretion of Glucagon Like Peptide-1 (GLP1) from the intestinal L-cells, a signalling pathway, which counteracts metabolic dysfunction. Lipopolysaccharides (LPS), in chylomicrons secreted from intestinal epithelial cells or absorbed through increased intestinal permeability, induce metabolic endotoxemia by triggering secretion of pro-inflammatory cytokines. Short Chain Fatty Acids (SCFA) as butyrate, propionate and acetate are produced through fermentation of complex polysaccharides by the colonic gut bacteria and enter the circulation. The complex polysaccharides would without the gut microbiota be indigestible but due to microbial fermentation of indigestible carbohydrates the total amount of harvested energy increases. Butyrate and propionate trigger the release of the peptide hormones GLP1 and Peptide YY (PYY), possibly reducing food intake. Acetate and propionate mainly function as substrates for intestinal gluconeogenesis and hepatic lipogenesis.

Probiotics are suggested to affect obesity through an effect on the gut microbiota as well as the gut mucus and epithelium by influencing multiple mechanisms such as inhibiting pro-inflammatory pathways by reducing gut permeability thus potentially inhibiting passage of LPS [32], modification in the enterohepatic recirculation of bile acids [33] and competing with nutrients. Furthermore, probiotics is proposed to produce bacteriocins/defensins (anti-microbial substances), compete with and prevent adhesion of pathogenic bacteria and reduce luminal pH [34-36]. Rijkers et al. 2010 categorized another level by which probiotics can act; that probiotics can exert effects beyond the gut to the immune system and other organs such as the liver or the brain. Most of these effects of probiotics have been established in animal and in *in vitro* studies [35]. Yet, data from human studies on the effects of probiotic intervention on body weight (BW)-related variables overall are sparse and inconsistent [37-43].

The aim of this review is to provide an overview on effects of clinically controlled interventions with probiotics on BW regulation in overweight or obese individuals free of co-morbidities.

## Regulation of Body Weight by Probiotics

### Methods

**Criteria for study selection:** The study characteristics used as criteria for eligibility was 1) healthy overweight/obese adults without co-morbidities as study population, 2) probiotics as intervention without limits regarding dose or duration of intervention 3) healthy overweight/obese adults receiving placebo as controls, 4) BW-related variables as the primary outcome and 5) randomized controlled trial as the study design.

**Search strategy, data sources and study selection:** The collection of materials for the present review involved a literature search performed on September 14$^{th}$ 2015 through the electronic database PubMed by NBK. The search phrase used was: Probiotics AND (body mass OR fat mass OR BMI) AND (clinical trial OR RCT OR randomized controlled trial).

**Quality assessment:** The methodological quality assessment of reports of the clinical trials was performed using a three-item instrument that evaluates likelihood of bias in research reports [44]. The three items evaluated by a five-point scale are quality of randomization, quality of blinding and reasons for withdrawals or drop-out (0=worst, 5=best).

## Results

### Study selection

A total of 70 citations were identified through the search in PubMed and seven additional citations were identified by checking the references of relevant papers. Of these, 57 were discarded after reviewing the titles and abstracts. The full text of the remaining 20 articles was examined and 13 of these did not meet the inclusion criteria. Seven studies met the inclusion criteria and were included in the review. See flow chart, Figure 2.

### Study characteristics

All seven studies, published in English, were designed as randomized controlled trials, six of which were parallel designed and one cross-over designed. An overview of the study characteristics and main results are presented in Table 1. The participants were all overweight/obese adults (18-69 years) free of co-morbidities with a proportion of male participants ranging from 0 to 68%. The duration of the interventions varied between three to twelve weeks. All studies reported BW, BMI and/or a measure of fat mass (FM) as primary outcomes. One study was performed in Denmark, two studies in Japan, one in Canada, two in Korea and one in Russia. The Jadad score ranged from 3 to 5 (Table 1). Six studies received a score of 3, because they did not state the method of randomization and blinding of both participants and investigators [37-41,43], while a single study received a score of 5 [42].

### Results of individual studies

Three of the seven included studies reported significant reductions in BW-related variables [38,39,42]. In the study by Agerholm-Larsen et al. 2000, 70 participants were divided into five groups and randomized to receive either 1. Two strains of *S. thermophilus* and two strains of *L. acidophilus* ($4.5 \times 10^{10}$ CFU and $9 \times 10^{9}$ CFU), 2. Delta-acid-lactone (chemically acidified placebo), 3. Two strains of *S. thermophilus* and one strain of *L. rhamnosus* ($3.6 \times 10^{11}$ CFU and $9 \times 10^{10}$ CFU), 4. One strain of *E. faecium* and two strains of *S. thermophilus* ($2.7 \times 10^{10}$ CFU and $4.5 \times 10^{11}$ CFU) administered in 450 mL yoghurt or 5: Two placebo pills. No difference in change of BW, FM or waist-to-hip ratio in the any of the groups was reported. In the study by Kadooka et al. 2010, abdominal visceral, subcutaneous and total fat areas, BW, BMI, waist circumference, hip circumference, waist-to-hip ratio, FM, fat percentage were all reduced in the participants receiving the probiotic intervention ($1 \times 10^{11}$ *L. gasseri* in 200 g fermented milk) compared to the controls (200 g fermented milk), while lean mass did not differ (n=87). Kadooka et al. 2013 [39] intervened with the same probiotic but in different amounts. Participants (n=210) were categorized to receive either 1. $2 \times 10^{9}$ CFU *L. gasseri*, 2. $2 \times 10^{8}$ CFU *L. gasseri* or 3. Placebo, all incorporated into fermented milk. In the groups (1 and 2.) receiving the probiotic, the visceral abdominal fat area, BMI, waist circumference, hip circumference and FM decreased compared to those in the control group (3.). In the randomized controlled double-blind cross-over study by Omar et al. 2013, participants (n=28) were provided a diet containing 35% of energy as fat, 50% as carbohydrates and 15% as protein. Participants were divided into three groups and randomized to receive either 1. $1.39 \times 10^{9}$ CFU *L. amylovorus,* 2. $1.08 \times 10^{9}$ CFU *L. fermentum* or 3. Placebo incorporated into 100 g fermented yoghurt. Of note is, endpoint scans of all three phases were obtained from a smaller subgroup of subjects, reducing the number of participants with baseline and endpoint scans (1. n=12, 2. n=11 and 3. n=12). No difference in change of BW, FM or lean mass in neither of the two groups compared the control group was reported. In the study by Jung et al. 2013 [41], 57 participants were randomized to receive either $1 \times 10^{10}$ CFU *L. gasseri* or placebo in capsules, which resulted in no difference in change of BW, BMI, fat percentage, muscle mass, waist circumference, hip circumference, visceral adipose tissue, superficial adipose tissue or deep adipose tissue between the two groups. In the study by Sharafedtinov et al. 201 [41], 40 participants were on a low-calorie diet during the study. The participants were also randomized to receive either probiotic ($2.5 \times 10^{10}$ CFU *L. plantarum*) or placebo incorporated into cheese. BMI was reduced in the participants receiving the probiotics compared to the change in controls, while change in BW, muscle mass and FM did not differ between the groups. The change in waist-to-hip ratio was significantly different between the two groups; however, this was due to a greater reduction in the control group compared with that in the probiotic group. In the study by Lee et al. 2014 [43], 50 participants consumed Bofutsushosan and restricted caloric intake to 20-25 kcal/kg, change in BW, BMI, waist circumference, fat percentage and FM did not differ between the groups

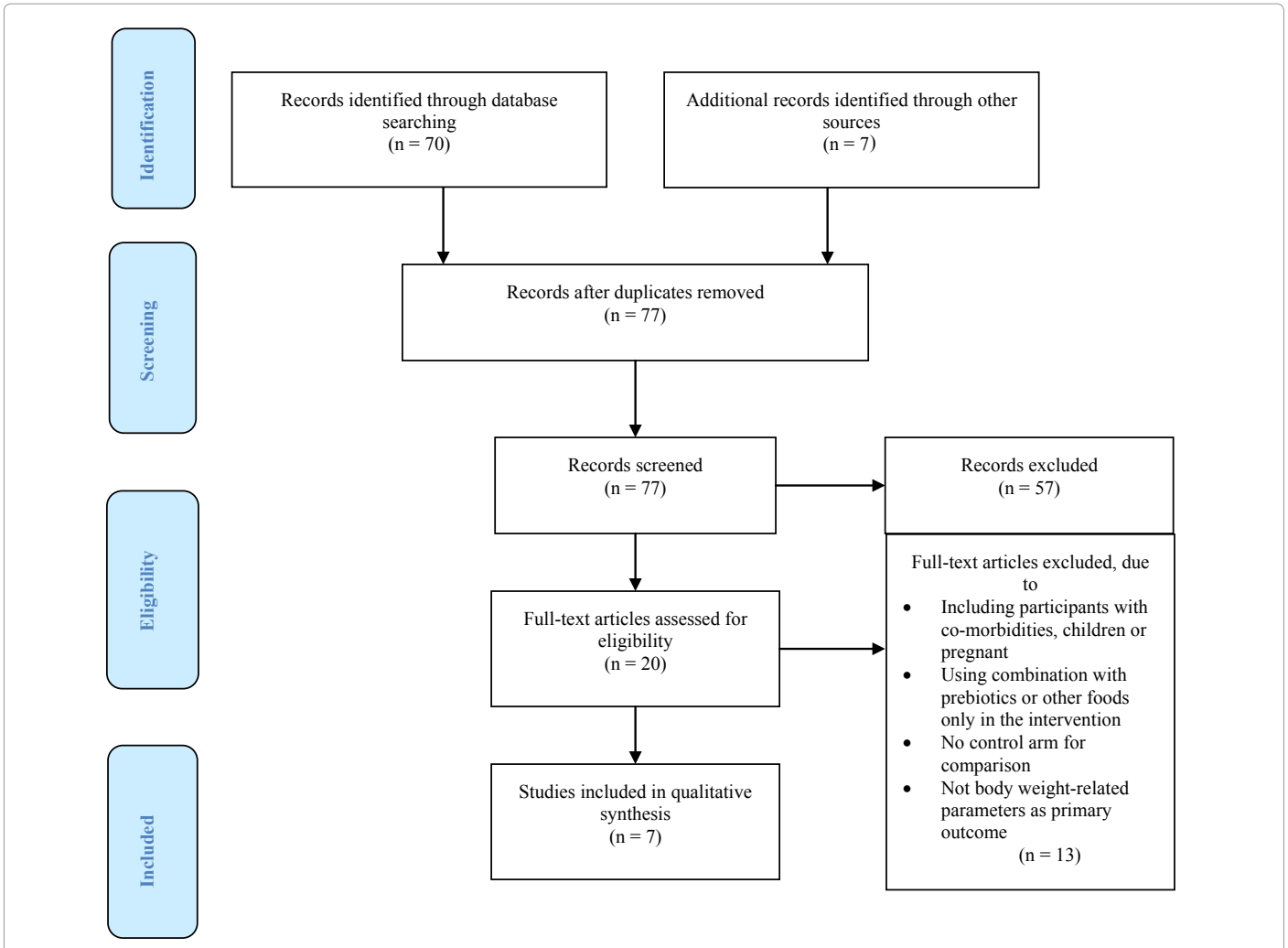



**Figure 2:** Flow chart of literature selection process.

| Study (Country) | Participants | Intervention (Dose per day) | Control | Study design (Jadad score) | Duration | Outcome |
|---|---|---|---|---|---|---|
| Agerholm-Larsen et al. 2000 [37] (Denmark) | 70 overweight/obese participants (18-55 y), ♀ (50) and ♂ (20) | 1. Two strains of S. thermophilus and two strains of L. acidophilus ($4.5 \times 10^{10}$ CFU and $9 \times 10^{9}$ CFU) in 450 mL yoghurt | 450 mL yoghurt fermented with 2. Delta-acid-lactone (chemically fermented placebo group) or 5. Two placebo pills | Double-blind RCT (3) | 8 wk | ↔BW, FM and waist-to-hip ratio |
| | | 2. Delta-acid-lactone (chemically acidified placebo) in 450 mL yoghurt | | | | |
| | | 3. Two strains of S. thermophilus and one strain of L. rhamnosus ($3.6 \times 10^{11}$ CFU and $9 \times 10^{10}$ CFU) in 450 mL yoghurt | | | | |
| | | 4. One strain of E. faecium and two strains of S. thermophilus ($2.7 \times 10^{10}$ CFU and $4.5 \times 10^{11}$ CFU) in 450 mL yoghurt | | | | |
| | | 5: Two placebo pills | | | | |
| Kadooka et al. 2010 [38] (Japan) | 87 participants with high BMI and visceral abdominal fat areas (33-63 y), ♀ (28) and ♂ (59) | L. gasseri SBT2055 ($1 \times 10^{11}$ CFU) in fermented milk | 200 g fermented milk | Double-blind RCT (3) | 12 wk | ↓Abdominal visceral, subcutaneous and total fat areas |
| | | | | | | ↓BW, BMI, waist circumference, hip circumference, waist-to-hip ratio, FM and fat percentage |
| | | | | | | ↔Lean mass |

| | | | | | | |
|---|---|---|---|---|---|---|
| Kadooka et al. 2013 [39] (Japan) | 210 participants with large visceral fat areas (35-60 y), ♀ (105) and ♂(105) | 1.L. gasseri SBT2055 (2 × $10^9$ CFU) | 200 g fermented milk | Double-blind RCT (3) | 12 wk | 1. and 2. ↓Visceral abdominal fat area, BMI, waist circumference, hip circumference and FM |
| | | 2.L. gasseri SBT2055 (2 × $10^8$ CFU) | | | | ↔Lean mass and subcutaneous fat area |
| | | 3.Placebo in 200 g fermented milk | | | | |
| Omar et al. 2013 [40] (Canada) | 28 overweight participants (46.3±2.4 y), ♀ (18) and ♂ (10) | 1.L. amylovorus (1.39 × $10^9$ CFU) | 100 g fermented yoghurt with diets of 35 E% fat, 50 E% carbohydrate, 15 E% protein | Randomized controlled double-blind cross-over (3) | 3 × 43 d with 6 wk wash-out | ↔FM, BW and lean mass |
| | | 2.L. fermentum (1.08 × $10^9$ CFU) | | | | |
| | | 3. Placebo in 100 g fermented yoghurt with diets of 35 E% fat, 50 E% carbohydrate and 15 E% protein | | | | |
| Jung et al. 2013 [41] (Korea) | 57 obese participants, (19-60 y), ♀ (35) and ♂ (22) | L. gasseri BNR17 (1 × $10^{10}$ CFU) in capsules | Placebo capsules | Double-blind RCT (3) | 12 wk | ↔BW, BMI, fat percentage, muscle mass, waist circumference, hip circumference, VAT, SAT and DAT |
| Sharafedtinov et al. 2013 [42] (Russia) | 40 obese participants with hypertension, 30-69 y, ♀ (27) and ♂(13) | L. plantarum TENSIA DSM 21380 (2.5 × $10^{10}$ CFU) in 50 g cheese with LCD | 50 g cheese with LCD | Double-blind RCT (5) | 3 wk | ↓BMI |
| | | | | | | ↔BW, muscle mass, and FM |
| | | | | | | ↑Waist-to-hip ratio |
| Lee et al. 2014 [43] (Korea) | 50 participants with higher BMI (>25 kg/m2) and waist circumference (>85 cm), 19-65 y, ♀ (64) and ♂ (0) | S. thermophiles KCTC 11870BP, L. plantarum KCTC 10782BP, L. acidophilus KCTC11906BP, L. rhamnosus KCTC 12202BP, B. lactis KCTC 11904BP, B. longum KCTC 12200BP, and B. breve KCTC 12201BP (1 × $10^9$ viable cells) In capsules with 3 g Bofutsushosan and hypocaloric diet | Placebo capsules with 3 g Bofutsushosan and hypocaloric diet | Double-blind RCT (3) | 8 wk | ↔BW, BMI, waist circumference, fat percentage and FM |

Abbreviations: ♀: Women; ♂: Men; B.: Bifidobacterium; BMI: Body Mass Index; BW: Body Weight; CFU: Colony Forming Units; d: Days; DAT: Deep Adipose Tissue; E.: Enterococcus; FM: Fat Mass; g: Gram; L: Lactobacillus; LCD: Low-Calorie Diet; RCT: Randomized Controlled Trial; S: Streptococcus, SAT: Superficial Adipose Tissue; VAT: Visceral Adipose Tissue; wk: Weeks; y: Years.

**Table 1:** Characteristics of the studies reviewed.

(intervention: 1 × $10^9$ viable cells of *S. thermophiles*, *L. plantarum*, *L. acidophilus*, *L. rhamnosus*, *B. lactis*, *B. longum*, and *B. breve* in capsules, control: placebo in capsules).

## Discussion

Overall, the evidence of effects of probiotic interventions on BW regulation in overweight or obese individuals free of co-morbidities is not convincing. Only seven eligible studies were identified from which only one received a complete Jadad score. Three out of seven studies found reductions in some BW-related variables after probiotic supplementation compared to that in the controls, whereas four did not find such improvements.

Even though the population of interest is relatively well-defined, factors such as individual susceptibilities to probiotic exposure can confound the results possibly due to the genetic make-up of the host or other environmental impacts than the probiotic itself. Yet, these confounding factors were ideally evaded in the individual studies due to randomized controlled designs. Furthermore, the included studies are very comparable with regards to outcome measures, study design and to some extent number of participants. One of the studies used a cross-over design and thereby induced a risk of carry-over effects, why this design is not recommended, when assessing effects of probiotics [45]. The quality of the studies varied and most of the studies did not mention methods of randomization and blinding, which reduces the reliability of the results. Of note is that the two largest studies found/replicated an effect of the probiotic intervention on BW-related variables. Yet, an effect was also observed in the study including less than half of the number of participants (40 individuals) and three studies including more participants did not demonstrate such an effect, suggesting that inadequate statistical power may not be an issue for the lack of an effect of probiotics in the majority of the seven studies.

The crux of the contradictory results may rely in the differences in probiotic products and the application of this in the included studies. Five studies used single-strains alone belonging to the genera of *Lactobacillus,* three studies (of which two used the same strain), found an effect of the probiotic on BW-related variables. The remaining two studies used multi-strain probiotic mixtures belonging to the genera of *Lactobacillus, Bifidobacterium*, *Streptococcus,* and *Enterococcus* and observed no effects on BW-related variables [37,43]. Even closely related microbial strains of the same genera or species may not be equally potent in terms of the impact on BW and FM. This is most likely due to different mechanisms of action. Furthermore, multiple strains in mixtures may act differently than in isolation and may be more potent due to an additive or synergistic effect of combining the stains. In contrast, the combination of probiotic strains may also result in reduced effects if the strains of interest have opposite effects and thus inhibit each other. In terms of interpretation of the results, combining the strains may impede a clear definition of the underlying mechanisms of action, since it is not possible to attribute an effect to one specific strain. This issue is not only valid in the studies, which administered multiple strains in mixtures, but also the studies in which the probiotics were incorporated into fermented milk or yoghurt [38-40]. Moreover, the concentration of the administered probiotics and

duration of treatments varied widely ($2 \times 10^8$-$4.5 \times 10^{11}$ CFU and 3-12 weeks) and are factors, which may make it problematic to observe general changes in BW as a result of a probiotic intervention. In order to assess the impact of a probiotic on host health it is important to examine the dose-response effect of probiotics. This information would help to identify the appropriate dose and duration to see an effect on the relevant response variable and add to the probability, that the observed association is causal. Selecting the right response variable may be difficult in itself and may raise questions such as which of the proposed target functions or biological responses are the most plausible and/or which one(s) are the easiest/least expensive to measure as well as what level of significance has to be observed before the effect can be considered biologically relevant. All of which can have a great impact on the results and conclusions drawn from the studies. Additionally, a conclusion on results from the included studies is hampered by the fact that compliance was only monitored in half of the included studies [37,39-41], which is an important item, when assessing the impact of an intervention. Compliance can be monitored by measuring concentration of the known component or its metabolites in blood, tissue, urine, breath or feces or in other cases by adding a marker to the food in which the probiotic is provided (e.g., fermented milk) [46]. However, in most studies, investigating the effects of probiotics, compliance is monitored by pill count and dietary reports from the study participants or by screening for the probiotic in the gut microbiota. Another potential confounder in the examined studies may be the habitual diet of study participants. One of the included studies attempted to control for this by providing diets, in which energy percentage was pre-defined [40]. Yet, diet has been shown to modulate the gut microbiota to a great extent and does not seem readily controlled for by only adjusting energy percentage in the diet. Studies on mice and humans have demonstrated that changes in diet result in rapid and major alterations of the gut microbiota composition and functionality and that various dietary regimens (such as plant-based vs. animal based, amount of dietary fibers and fat) are associated with different gut microbiota compositions [3]. Thus, the effect of the probiotics may drown in the enormous inter-individual variation in the diet and its effect on the gut microbiota. Correspondingly, the difference in the more remarkable effects of probiotics observed in animal [28-31] compared to those found in human studies may rely in the controlled setting an animal study can offer. Thus, studies in mice are advantageous due to the possibility of a well-controlled environment including but not limited to standardized diets, controlled compliance and physical activity. However, these studies cannot serve as evidence for a potential effect of probiotics in humans living in a diverse environment with a far different biology. Yet, this inconsistency in significance of results may very well emphasize the importance of the confounding effects observed in the human studies such as habitual diet, compliance and physical activity.

Even though the proposed mechanisms of action upon probiotic administration mainly rely on a shift in the gut microbiota composition (probiotics may act directly through interactions with host cells as well, as previously discussed), only few of the included studies investigated survival of the probiotics [42] and only two report changes in gut microbiota composition with specific primers [40,43]. Information of the viability of added probiotics in the intestine and impact on gut microbiota is evidently key factors, when evaluating effects of probiotics. Furthermore, it is not possible to state that specific changes in gut microbiota composition are responsible for improvements in obesity, if any. *L. gasseri* is a well-studied microorganism that improves the intestinal environment in humans and lowers adipocyte enlargement in rats [47,48] adding biological plausibility to the effect on BW-related variables observed in overweight/obese adults in Kadooka et al. 2010 [38] and Kadooka et al. 2013 [39]. Correspondingly, the authors suggest influence on inflammatory status through the gut microbiota and the intestinal epithelial cells as the mechanisms of action. A different strain from the same species *L. Gasseri* was investigated in the study by Jung et al. 2013 [41], in which no difference was observed of the probiotic effect on host metabolism compared to placebo, possibly emphasizing the specific effects of a particular strain in a given individual. In two studies gut microbiota was assessed for more than just the specific probiotic offering the opportunity to draw conclusions on the impact of probiotics on more than just survival of the particular probiotic [40,43]. However, in these studies, no effects of the probiotic intervention on the primary outcome were demonstrated.

Limitations of the present study include publication bias, which may have an impact on the results and conclusion of our review. However, half of the included studies provide null results, which may indicate that this concern is settled to some extent. Neither language bias can be ruled out since our search was exclusively based on English-language dominated sources.

## Conclusions

This review failed to identify convincing evidence of an effect of clinically controlled interventions with single stain or multiple strains probiotics on BW regulation in overweight or obese individuals free of co-morbidities. The opposing outcomes reported in the included randomized controlled trials could be due to differences in number of study participants, individual susceptibility toward the probiotic, study design, quality of studies, use of different probiotic strain vs. strains, dosage of probiotics, and duration of intervention, incompliant participants or variations in the diets of included study participants. All factors, which make it problematic to draw conclusions on any general effects of probiotics.

A logical next step to get closer to potential evidence of effects of probiotics on BW regulation in obesity is to conduct large high quality randomized controlled trials in well-phenotyped study participants on regulated and to some extent standardized diets with mixtures of probiotics known to have master-switch roles in the gut microbiota of healthy lean individuals ('next generation probiotics'), in which deeper insights into the biological pathways of the gut microbiome and its interaction with host physiology should be sought by applying state-of-the-art methods including quantitative metagenomics and host metabolomics at levels of fecal water, serum and urine.

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