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Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals

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2 Sackler Faculty of Medicine, Tel-Aviv University’ Tel-Aviv, Israel
3 Rabin Medical Center, Bellinson Hospital, Petah-Tiqva, Israel

Abstract

Background: Obesity is associated with alteration of the gut microbiota. In order to clarify the effect of Lactobacillus-containing probiotics (LCP) on weight we performed a meta-analysis of clinical studies and experimental models. We intended to assess effects by Lactobacillus species.

Methods: A broad search with no date or language restriction was performed. We included randomized controlled trials (RCTs) and comparative clinical studies in humans and animals or experimental models assessing the effect of Lactobacillus-containing probiotics on weight. We primarily attempted to extract and use change from baseline values. Data were extracted independently by two authors. Results were pooled by host and by Lactobacillus species and are summarized in a meta-analysis of standardized difference in means (SMDs).

Results: We identified and included 17 RCTs in humans, 51 studies on farm animals and 14 experimental models. Lactobacillus acidophilus administration resulted in significant weight gain in humans and in animals (SMD 0.15; 95% confidence intervals 0.05–0.25). Results were consistent in humans and animals. Lactobacillus fermentum and Lactobacillus ingluviei were associated with weight gain in animals. Lactobacillus plantarum was associated with weight loss in animals and Lactobacillus gasseri was associated with weight loss both in obese humans and in animals.

Conclusions: Different Lactobacillus species are associated with different weight change that are host-specific. Further studies are needed to clarify the role of Lactobacillus species in the human energy harvest and weight regulation. Attention should be drawn to the potential effects of commonly marketed lactobacillus-containing probiotics on weight gain.

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1. Introduction

The prevalence of obesity is increasing steadily among adults, adolescents and children and is now considered a worldwide epidemic [1]. The causes driving the obesity appear to be complex and include environmental, genetic, neural and endocrine factors [2] but infectious agents have also been proposed [3]. More recently obesity was associated with a specific profile of the bacterial gut microbiota [4] and was shown to be a transmissible phenotype by microbiota transplantation [5]. First studies on obesity reported a decrease in the Bacteroidetes/Firmicutes ratio [4] and a decrease in the archae Methanobrevibacter smithii [6]. Since these pioneering studies, significant associations were found between the increase of some bacterial groups and human obesity (Lactobacillus [7], Staphylococcus aureus [8–10], Escherichia coli [10] and Faecalibacterium prausnitzii [11]). Conversely, other bacterial groups have been associated with lean status, mainly belonging to the Bifidobacterium genus [6,8–11]. We found recently that different Lactobacillus species may have a paradoxical effect with higher levels of Lactobacillus reuteri and lower levels of Lactobacillus plantarum and paracasei in obese gut microbiota [12]. In contrast, symbiotics (the combination of prebiotics and probiotics) have been proposed in the management of malnutrition with promising results on mortality [13].

As many probiotic strains of Lactobacillus and Bifidobacterium are marketed in products for human consumption, altering the intestinal flora [14], we hypothesized that widespread ingestion of probiotics may promote obesity by altering the intestinal flora [15]. However, this remains controversial [16]. On the other hand, manipulation of the gut microbiota by probiotics has been used for
growth promotion in farm animals for at least 30 years [17]. Indeed, *Lactobacillus acidophilus*, *L. plantarum*, *Lactobacillus casei*, *Lactobacillus fermentum*, *L. reuteri* are the most commonly used *Lactobacillus* spp. in agriculture [18]. All these data strongly suggest that *Lactobacillus* containing probiotics (LCP) may impact the weight regulation in humans and animals.

Many studies have reported the effects of *Lactobacillus* containing probiotics (LCP) on weight but according to recent data [12], this effect is at least species dependent. To our knowledge, no meta-analysis has been performed to confirm this difference among *Lactobacillus* containing probiotics. For this purpose, we pooled data from animal and human studies to obtain sufficient power to detect a significant effect at the species level.

2. Methods

2.1. Data sources


2.2. Study selection and data extraction

We retrieved the full text of studies including *Lactobacillus*-containing probiotics and looked for weight assessment as primary or secondary outcome. Inclusion was limited to experimental studies and randomized controlled trials in farm animals, experimental models and healthy humans. Authors were contacted when published data were incomplete. Exclusion criteria included hosts with underlying diseases (except for obesity) or pregnant women, probiotics given only to the mother, symbiotics (probiotics associated with prebiotics), other nutrients given exclusively to the intervention group, non-direct fed microbials (probiotics in silage), non viable probiotic administration, recombinant probiotics, hosts challenged prior to probiotic administration by viruses or bacteria, hosts with diarrhoea or colitis, before-after intervention studies, inappropriate control group (prebiotics, probiotics or antibiotics administration – traditional yogurt including *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* was accepted as control intervention), unavailable statistical data and double publications. Data were extracted independently by two authors (MM, EA).

2.3. Risk of bias assessment and outcome measures

The Jadad score [21] was used for the assessment of bias in evaluating human trials to determine studies to exclude and allowing sensitivity analysis based on this quality score. In animals, all studies were included except those with major methodological concerns, and a score was calculated with one point for each of these terms: dropouts mentioned, dropouts < 10%, outcome expressed as a weight difference (and not weight at the end) and absence of other risk of bias. Studies with a score > 2 were considered at low risk for bias.

The primary outcome was the effect on weight. Weight change from baseline, weight at the end of the study, daily weight change, weight/age ratio, delta-BMI (Body Mass Index) and weight percentile were considered as outcome measures. We primarily attempted to extract and use change from baseline values.

2.4. Statistical analysis and heterogeneity investigation

We used RevMan v5.1 [22] to carry out meta-analysis of the standardized difference in means (SMD) with 95% confidence interval for weight change after probiotics administration. When means were available and the *p*-value was described as > 0.05 (or “not significant”), a two-tailed *p*-value of 0.9 was attributed in order to increase the sensitivity of this pioneering work in this area. Each trial could contribute more than one comparison but comparisons were pooled for each study only if experimental conditions were similar. Heterogeneity was assessed by the *I*-squared value, 50% being considered as substantial. Summary measures were determined by a random effect model assuming significant clinical heterogeneity regardless of the *I*-squared value. We primarily investigated heterogeneity by stratifying results by *Lactobacillus* species including comparisons with only one *Lactobacillus* species in the probiotic product. In addition, subgroup analyses were planned a priori to discern weight changes by host category; overweight/obese animals or humans; and very low weight birth (VLWB) newborns. The effect of studies’ risk of bias was assessed through sensitivity analysis. Funnel plot was used to identify outliers subsequently excluded and to assess small studies and publication bias. Classic fail-safe *N*, Egger’s test for asymmetry were also used to assess small studies bias and Duval and Tweedie’s Trim and Fill adjustment with random effects model was used to provide an estimate of the unbiased effect size. A standardized difference in means > 0.10 was considered clinically relevant as it correspond to a 1 kg weight difference for a 70 kg man based on data from a sample of 5000 healthy human individuals [23].

3. Results

The search yielded 200 studies of which 118 were excluded because of probiotic or host group definitions, study design or missing outcome data (Fig. 1). 82 studies, involving 153 comparisons, were included in the quantitative synthesis. Included human studies involved 15 double-blind randomized controlled trials and two open-labelled randomized trials (Table 1). Included animal studies involved 14 studies on experimental models and 51 on farm animals. After exclusion of two studies with high risk of bias (weight significantly different at baseline, open label design), LCPs were not associated with significant weight change in human adults (SMD = 0.18; 95%CI (−0.43–0.79)), infants (SMD = 0.004; 95%CI (−0.20–0.21)), or preterm newborn infants (SMD = −0.10; 95%CI (−0.32–0.12)). Meta-analysis of all comparisons in healthy humans and animals (134 comparisons, overweight and VLWB newborns excluded) resulted in weight gain but significant heterogeneity (SMD = 0.15; 95%CI (0.12–0.18); *p* < 0.001; *I*² = 85%) and thus we proceeded directly to the subgroup analyses, primarily assessing effects by species.

3.1. *Lactobacillus acidophilus*

The meta-analysis of 13 studies and 18 comparisons including 3307 subjects (879 humans) on *L. acidophilus* administration showed a significant weight gain effect (SMD = 0.15; 95%CI (0.05–0.25); *p* = 0.005; *I*² = 42%) (Fig. 2). Using classic fail-safe *N*, 34 unpublished studies would have been necessary to bring *p*-value > 0.05, Duval and Tweedie’s trim and fill did not change this result, and Egger’s asymmetry test was not significant (two-tailed *p*-value = 0.66) making this summary effect robust and publication bias unlikely. Direction of effect favouring weight gain was consistent in humans and animals. A sensitivity analysis including only studies with a quality score > 2 reduced heterogeneity and found a consistent and significant result (*I*² = 28%,
p = 0.005). The difference (SMD = 0.15) was clinically relevant as it corresponds to a weight gain of 1.5 kg for a 70 kg man.

3.2. Lactobacillus fermentum

The meta-analysis of 3 studies and 12 comparisons including 598 chicks, pigs and ducks but no humans on L. fermentum found a significant weight increase (SMD = 0.81; 95%CI (0.12–1.50); p = 0.02; $I^2 = 90\%$). After exclusion of one outlier, 34 unpublished studies would have been necessary to bring a p-value to > 0.05 using classic fail-safe N, Duval and Tweedie’s trim and fill one study but found a consistent result (SMD = 0.53; 95% CI (0.18–0.87)) and Egger’s asymmetry test was not significant (two-tailed p-value = 0.28) making this summary effect robust. All these studies have a quality score > 2.

3.3. Lactobacillus ingluviei

The meta-analysis of three studies and 11 comparisons including 198 chicks, ducks and mice on one L. ingluviei strain isolated from an ostrich found a significant weight increase effect (SMD = 0.97; 95%CI (0.49–1.45); p < 0.001; $I^2 = 59\%$). After exclusion of one outlier [24], 27 unpublished studies would have been necessary to bring a p-value > 0.05 using classic fail-safe N, Egger’s asymmetry test was not significant (p = 0.59) and Duval and Tweedie’s trim and fill gave a similar significant result (SMD = 0.76; 95% CI (0.48–1.03)). All these studies had a quality score > 2. No human trials included L. ingluviei.

3.4. Lactobacillus plantarum

Pooled analysis of three studies, three comparisons including 335 lean chicks, rats and mice on L. plantarum showed a weight loss effect direction but result was not significant (Fig. 3a). However, L. plantarum was associated with significant weight loss effect in overweight/obese animals in four studies and five comparisons including 64 mice and rats (SMD = −1.33; 95%CI (−2.50 to −0.16); $p = 0.03$; $I^2 = 74\%$) (Fig. 3b). No human studies included L. plantarum. Small studies bias was unlikely because 19 unpublished studies would have been necessary to bring the p-value to > 0.05, Duval and Tweedie’s trim and fill did not change this result and Egger’s asymmetry test was not significant (two-tailed p-value = 0.52). All these comparisons in experimental animals had a medium to low risk of bias.

3.5. Lactobacillus gasseri

L. gasseri was associated with a trend for weight loss in lean animals in three studies and four comparisons including 48 pigs and rats (p = 0.09) (Fig. 3a). In obese animals and humans (Fig. 3b), three studies and three comparisons including 87 humans and 36 rats found an anti-obesity effect (SMD = −0.67; 95%CI (−1.17 to −0.16); p = 0.009; $I^2 = 29\%$). Using classic fail-safe N, six unpublished studies would have been necessary to bring the p-value to > 0.05, Duval and Tweedie’s trim and fill did not change this result and Egger’s asymmetry test was not significant (two-tailed p-value = 0.88) making this summary effect robust and small studies bias unlikely. This effect was consistent between humans and animals. Two L. gasseri strains (SBT2055 [25–27] and BNR17 [28]) have a significant anti-obesity effects in individual studies. All these studies had a medium to low risk of bias. In obese individuals, the difference (SMD = −0.57) was clinically relevant since it correspond to a weight loss of 6 kg in humans.

3.6. Other species

Other species (L. reuteri, L. casei, Lactobacillus rhamnosus and Lactobacillus sporogenes) were not associated with significant and consistent effects. Only L. delbrueckii was significantly associated with weight gain (five comparisons; $I^2 = 0\%$; SMD = 0.39; 95%CI (0.06–0.71); p = 0.02) but this effect was summarized from only two different studies in chicks and rats.

4. Discussion

4.1. Significant impact of Lactobacillus-containing probiotics on weight

In this meta-analysis, we showed that some Lactobacillus species were significantly associated with weight modifications in human and animals: L. acidophilus, L. ingluviei, L. fermentum were linked to weight gain whereas L. gasseri and L. plantarum were linked to weight loss or an anti-obesity effect. The latter effect seemed particularly evident in overweight or obese individuals. Wide variation in response was explained by probiotic species and host. Stratification only by probiotic species revealed significant and consistent results. In a second step, we showed that the host was a covariate explaining part of the heterogeneity found for a specific probiotic species (Table A.2). The differences found were clinically relevant as they correspond to a weight change that ranged from 1.5 kg gain in lean for L. acidophilus or 6 kg loss in overweight for L. gasseri based on the statistics of a population of >600 healthy men with an average weight of 70 kg (standard deviation of 9.8 kg) [23].

4.2. Lactobacillus species associated with weight gain

With the results of our meta-analysis, bacteria candidates for increasing energy efficiency in humans are L. acidophilus and L. fermentum. To our knowledge, L. ingluviei was not identified in the human digestive microbiota but only in the intestinal tract of pigeons, chickens and ostrich and is not contained in probiotics.
Table 1
Characteristics of included human studies.

<table>
<thead>
<tr>
<th>Study source</th>
<th>Location; period of inclusion; mono or multicentric; study design; risk of bias (Jadad score)</th>
<th>Subjects included; age and sex; sample size (subjects enrolled, dropped out, used); no of treated /control subjects</th>
<th>Exclusion criteria</th>
<th>Probiotic (dose); duration of treatment</th>
<th>Outcomes (primary in first); weight change assessment (unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactobacillus probiotics in infants (&lt;2 years)</strong></td>
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<tr>
<td>Chouraqui et al., 2008</td>
<td>France; 2004–2005; multicentric (n = 5); prospective, double-blind, reference controlled, parallel-group, randomized trial; low (5)</td>
<td>Full term, singletons, exclusively formula fed healthy infants, with weight between 2500 and 4500 g; &lt; 15 d of age (284, 57, 227) – 2/4 groups using prebiotics were excluded from this meta-analysis; two comparisons: boys: 29/25; girls: 30/28</td>
<td>Major deformities or cardiovascular, GI, renal, neurologic, or metabolic illnesses, intensive care for ≥ 3 days, mother with diabetes, parents having difficulties complying the feeding regimen</td>
<td><em>B. longum</em> BL999 (1.3 × 10^8 cfu per 100 ml of reconstituted formula) and <em>L. rhamnosus</em> LPR (6.45 × 10^8 cfu per 100 ml of reconstituted formula) in powdered starter formula; 4 months</td>
<td>Weight gain; daily weight gain on 4 months (g/d)</td>
</tr>
<tr>
<td>Maldonado et al., 2010</td>
<td>Spain; period of inclusion not mentioned; monocentric; prospective, double-blind, placebo controlled, randomized trial; medium (3)</td>
<td>Healthy breast-fed infants fed exclusively with formula at the moment of recruitment, sixth month of life; boys 39, girls 41; (80, 0, 80); treated/control: 40/40</td>
<td>Frequent gastrointestinal disorders (frequent diarrheal, constipation episodes, gastroesophageal reflux), gastrointestinal surgery, cow’s milk protein allergy, metabolic disease (diabetes or lactose intolerance), antibiotic treatment during the trial or within the preceding 3 wk</td>
<td><em>L. salivarius</em> CECT5713 (2 × 10^8 cfu/g) on formula; 6 months</td>
<td>Multiple outcomes: antibiotic susceptibility of the strain, AEs, growth parameters, intestinal microbiota; weight gain on 6 months (g)</td>
</tr>
<tr>
<td>Robinson et al., 1952</td>
<td>USA; period of inclusion not mentioned; two centers; prospective, randomized trial (no mentioned blinding); high (1)</td>
<td>~800 enrolled newborns, number of dropped out not mentioned; four groups (treated/control): Completely bottle fed (124/123), partially breast fed infants (79/89), completely bottle fed with folic acid (134/129), partially breast fed with folic acid (60/83) – sex ratio not mentioned</td>
<td>Infants who were obviously ill in the hospital, who had congenital irregularities or those found to have been ill and that did not gain at least 16 ounces during the first month</td>
<td><em>L. acidophilus</em> ATCC4962 and ATCC4963 (&gt;5 × 10^8 cfu), 1 ml to each quart of formula; from birth until hospital discharge (1–6 days)</td>
<td>Weight gain; weight gain at one month*</td>
</tr>
<tr>
<td>Scalabrin et al., 2009</td>
<td>USA; 2006–2007; multicentric; prospective, double-blind, randomized trial; low (4)</td>
<td>Healthy term infants (birth weight ≥ 2500 g) enrolled at 14 d of age, solely formula fed; M/F = 94/94; (188, 55, 133) – one group using different casein formula was excluded; treated/control: 63/70</td>
<td>Underlying disease or congenital malformation, formula intolerance, weight at 14 d of age ≤ 98% of birth weight, large for gestational age born from a mother diabetic at childbirth, immunodeficiency, fever, antibiotic within 7 d, systemic steroid since birth, LGG-suppl diet since birth, diarhoea within 24 h</td>
<td>Extensively hydrolysed casein formula supplemented or not with <em>L. rhamnosus</em> strain GG (10^8 cfu/g of formula powder); 120 days</td>
<td>Growth and tolerance; weight gain (g/d) on 120 d</td>
</tr>
<tr>
<td>Vendt et al., 2006</td>
<td>Finland; 2002; multicentric; prospective, double-blind, randomized trial; medium (3)</td>
<td>Healthy infants from 0 to 2 months on formula at least half of their daily feedings; M/F = 60/60; (120, 15, 105); treated/control: 51/54</td>
<td>Not mentioned (reasons for discontinuation: colic pain, cow’s milk protein intolerance, constipation, diarhoea, excessive breastfeeding)</td>
<td><em>L. rhamnosus</em> strain GG ATCC53103 (1 × 10^10 cfu); till the age of 6 months</td>
<td>Growth and fecal flora on 6 months</td>
</tr>
<tr>
<td>Weizman et al., 2006</td>
<td>Israel; 2006; monocentric; prospective, double-blind, randomized trial; low (4)</td>
<td>Full term healthy infants aged 3–65 days solely formula fed; M/F = 26/13; (39; 7; 32); treated/control: 16/17.</td>
<td>&lt;36 wks gestation, birth weight &lt; 2500 g, congenital anomalies, chronic disease, failure to thrive (weight loss of &gt; 2 percentiles), allergy or atopic disease and recent (less</td>
<td><em>L. reuteri</em> ATCC55730 (BioGAIA AB, Sweden) (1 × 10^8 cfu); 4 weeks</td>
<td>Growth parameters, daily characteristics of feeding, stooling and behaviour and side effects.</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Study source</th>
<th>Location; period of inclusion; mono or multicentric; study design; risk of bias (Jadad score)</th>
<th>Subjects included; age and sex; sample size (subjects enrolled, dropped out, used); no of treated /control subjects</th>
<th>Exclusion criteria</th>
<th>Probiotic (dose); duration of treatment</th>
<th>Outcomes (primary in first); weight change assessment (unit)</th>
</tr>
</thead>
</table>
| **Lactobacillus probiotics in lean adults**  
De Roos et al., 1999  
The Netherlands; period of inclusion not mentioned; monocentric; prospective, double-blind, randomized trial; medium (3) | Healthy adults between 18 and 65 years; BMI 24 ± 3, at least 50% of the enrolled volunteers had serum cholesterol levels over 5 mmol/L, M/F = 22/56; (85,7,78); treated/control: 39/39 | Heart disease, diabetes, liver or kidney disease, medications known to affect blood lipid metabolism, serum total cholesterol concentration higher than 8 mmol/L or a triglyceride concentration higher than 4 mmol/L | L. acidophilus L-1 (5 × 10⁹ to 3 × 10¹⁰ cfu/d) | Lipid profile and body weight change; weight change difference (kg) |
| **Lactobacillus probiotics in overweight/obese adults**  
Agerholm-Larsen et al., 2000  
Denmark; period of inclusion not mentioned; monocentric; prospective, double-blind, randomized trial; low (4) | Healthy weight-stable overweight and obese (25 < BMI < 37.5 kg/m²); mean 38 years, M/F = 4/12, 5/9 and 4/10; (73,3,70); treated L. acidophilus 16L, rhamnosus 14/14 | Diabetes, kidney or liver disease, high blood pressure, pregnancy, breastfeeding, elite athlete, chronic ethylism | 2 strains of L. acidophilus (2 × 10⁹/ml) and 1 strain of S. thermophilus (10 × 10⁹/ml); 2 strains of S. thermophilus (8 × 10⁹/ml) and 1 strain of L. rhamnosus (2 × 10⁹/ml) | Lipid profile and body weight; weight change (kg) |
| **Lactobacillus probiotics in overweight/obese adults**  
Kadooka et al., 2010  
Japan; 2008; multicentric (n = 10); prospective, double-blind, randomized trial; medium (3) | Healthy adults with body mass index (BMI) between 24.2 and 30.7 kg/m², abdominal visceral fat area between 81.2 and 178.5 cm² aged 33–63 years, M/F = 59/28; (87,3,87); treated/control: 43/44 | Serious disorders, including internal organ diseases, diabetes and hypersensitivity to dairy products. | L. gasseri SBT2055 (5 × 10¹⁰ cfu/100 g)–200 g/day; 12 weeks | Abdominal adiposity and body weight; weight change (kg) |
| Woodard et al., 2009  
USA; 2006–2007; monocentric; prospective, double-blind, randomized trial; low (3) | Morbidly obese patients undergoing Roux-en-Y gastric bypass (RYGB) (BMI = 45 kg/m²); Age 40–50 yrs, M/F = 5/36; (44, 8, 35); treated/control: 15/20 | No exclusion criteria mentioned | Puritan’s Pride® (2.4 × 10⁸ cfu/pill) one pill a day – characterization of the Lactobacillus strains; 6 months | Bacterial overgrowth, weight loss, quality of life; percent excess weight loss (%) |

a  g calculated from ounce, ×28.35.  
b  Data given by the authors under request – in this study, weight of treated group was significantly lower at baseline.
marketed for humans. The L. ingluviei comparisons included in this analysis involved only one strain, isolated from an ostrich gut, showing an astonishing weight gain effect both in farm animals and experimental models [24,29]. One candidate for the transmission of the obese phenotype, L. acidophilus, is widely present in many products for human consumption as the "acidophilus milk," traditionally consumed in the United States or in other formulations such as freeze-dried products sold without any regulation on the internet. The consumption of this species is particularly prevalent in the United States [30] where the prevalence of obesity is particularly important.

4.3. Lactobacillus species associated with anti-obesity effect

On the other hand, many bacteria appear to be protective against obesity. In our study, a strong species dependent anti-obesity effect was observed with two species having a significant anti-obesity effect: L. gasseri and L. plantarum (Fig. 3b). This anti-obesity effect was consistent with absence of significant weight gain effect in lean individuals (Fig. 3a). A recent study confirmed our results showing a 6-months weight-loss effect of L. plantarum DSM 15313 in high-energy-dense diet rats when administered to mother and offspring [31]. This anti-obesity effect could be an important adjunct in the treatment of obesity, since, apart from surgery, no medical treatment can support efficiently the fight against obesity to date.

4.4. Limitations

However, the paucity of data in individual hosts impelling us to the pool animal and human data limits the generalization of these

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>SMD (95% CI)</th>
<th>Weight loss</th>
<th>Weight gain</th>
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<tbody>
<tr>
<td>Lactobacillus acidophilus</td>
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<tr>
<td>Abdulrahim 1999</td>
<td>10.4%</td>
<td>0.23 [0.00, 0.46]</td>
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<tr>
<td>Abe 1995</td>
<td>9.4%</td>
<td>0.47 [0.22, 0.72]</td>
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<tr>
<td>Abu-Tarboush 1996</td>
<td>1.0%</td>
<td>0.06 [-0.92, 1.04]</td>
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<tr>
<td>Bernardeau 2002</td>
<td>3.2%</td>
<td>0.74 [0.22, 1.27]</td>
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<tr>
<td>Brashears 2003</td>
<td>9.2%</td>
<td>0.02 [-0.23, 0.28]</td>
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<tr>
<td>Cruywagen 1996</td>
<td>2.4%</td>
<td>-0.27 [-0.90, 0.35]</td>
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<tr>
<td>de Roos 1999 (humans)</td>
<td>4.2%</td>
<td>0.17 [-0.28, 0.61]</td>
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<tr>
<td>Elam 2003</td>
<td>14.3%</td>
<td>0.01 [-0.15, 0.17]</td>
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<tr>
<td>Harper 1983</td>
<td>10.5%</td>
<td>-0.01 [-0.24, 0.21]</td>
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<tr>
<td>Jin 2000</td>
<td>5.8%</td>
<td>0.22 [-0.14, 0.58]</td>
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<tr>
<td>Nakaniishi 1993</td>
<td>1.6%</td>
<td>0.05 [-0.72, 0.82]</td>
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<tr>
<td>Peterson 2007</td>
<td>12.6%</td>
<td>0.07 [-0.11, 0.26]</td>
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<tr>
<td>Robinson 1952 (humans)</td>
<td>15.5%</td>
<td>0.18 [0.04, 0.32]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.15 [0.05, 0.25]</td>
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Heterogeneity: P = 0.06 ; I² = 42%
Test for overall effect: Z = 2.83 (P = 0.005)

Lactobacillus fermentum

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>SMD (95% CI)</th>
<th>Weight loss</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan 2007</td>
<td>0.9%</td>
<td>20.59 [13.42, 27.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weis 2010a</td>
<td>26.7%</td>
<td>0.27 [0.01, 0.52]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weis 2010b</td>
<td>25.6%</td>
<td>0.98 [0.60, 1.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weis 2010c</td>
<td>20.7%</td>
<td>0.98 [0.22, 1.75]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu 2008</td>
<td>26.1%</td>
<td>0.39 [0.06, 0.71]</td>
<td></td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.81 [0.12, 1.50]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: P < 0.00001 ; I² = 90%
Test for overall effect: Z = 2.31 (P = 0.02)

Lactobacillus ingluviei

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>SMD (95% CI)</th>
<th>Weight loss</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelakis 2010a</td>
<td>17.2%</td>
<td>1.06 [0.27, 1.89]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angelakis 2010b</td>
<td>17.8%</td>
<td>0.79 [0.00, 1.58]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angelakis 2011a</td>
<td>25.2%</td>
<td>0.67 [0.17, 1.17]</td>
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</tr>
<tr>
<td>Angelakis 2011b</td>
<td>21.9%</td>
<td>0.55 [-0.07, 1.17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khan 2007</td>
<td>17.8%</td>
<td>1.99 [1.20, 2.78]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.97 [0.49, 1.45]</td>
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</tr>
</tbody>
</table>

Heterogeneity: P = 0.05; I² = 59%
Test for overall effect: Z = 4.00 (P < 0.00001)

Fig. 2. Forest plot of three Lactobacillus species associated with weight gain in humans and animals (a) L. acidophilus, (b) L. fermentum, (c) L. ingluviei (strain isolated from an ostrich [24]). A weight gain effect is represented by a deviation of the square (standardized difference in the means) to the right. The length of the horizontal line represents the 95% confidence interval and the diamond represents the summarized effect. Substantial heterogeneity was cancelled after sensitivity analysis for L. acidophilus. L. acidophilus and L. fermentum, when administered in overweight/obese humans or animals didn’t have a significant anti-obesity effect (data not shown).
Moreover, effect size and standard deviation are probably very different in experimental models and in the general human population. Only few clinical studies have been conducted to test a weight gain effect assessing only one *Lactobacillus* species because, unlike animal studies, this effect was generally not sought in humans. *L. acidophilus* increased weight gain both in bottle-fed and breast-fed newborns but this effect was stronger in bottle-fed newborns [32], *L. gasseri* SBT2055 resulted in significant weight loss in human adults with obese tendencies [27].

### 4.5. Conflict of interest in nutrition and obesity research

Finally, it is possible that the design and/or interpretation of the results of each individual study had been affected by a conflict of interest of each team. It has recently been shown that published papers in nutrition and obesity research in which the authors were funded by industry were more likely than other papers to contain results or an interpretation that favored the industry or company that was producing the product or service that was being studied [33]. Furthermore, while a comprehensive search was performed using several strategies, we cannot be sure that all studies examining the effects of LCPs on weight have been identified.

### 4.6. Perspectives

In the next future, new double-blind randomized human trials should assess long-term growth in newborn infants receiving *Lactobacillus*-containing probiotics. A critical point is to stratify according to the initial weight [34]. For species associated here with a significant weight change and used for human consumption as

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**Fig. 3.** Forest plot of three *Lactobacillus* species associated with an anti-obesity effect in humans and animals. *Lactobacillus plantarum* and *L. gasseri* and weight changes in (a) lean (b) and overweight/obese humans and animals. Weight loss effect is represented by a deviation of the square (standardized difference in the means) to the left. The length of the horizontal line represents the 95% confidence interval and the diamond represents the summarized effect. Anti-obesity effect was consistent for these two species.
L. acidophilus, L. fermentum, L. plantarum and L. gasseri, trials evaluating weight gain as a primary outcome measure will be needed. The long-term evaluation to at least 3–5 years of age will be critical to identify a difference that could have been undetected by shorter studies [35]. According to the register ClinicalTrials.gov, at least one current study is testing the average weight gain as a primary endpoint among newborns receiving a probiotic containing L. fermentum (trial number NCT01346644). This bacterium has been associated with obesity in our study. In addition, case–control studies comparing obese and lean children according to their consumption of Lactobacillus-containing probiotics in the first weeks of life should be carried out.

5. Conclusion

Food is a source of bacteria and viruses and changes in patterns of food consumption result in differences in human gut flora among different groups of people [36,37]. As a result, it is necessary to further investigate the effects of routinely adding high amounts of bacteria in food [38]. Our systematic analysis found that the manipulation of the gut microbiota by L. acidophilus, L. ingluviei or L. fermentum results in weight gain whereas specific strains of L. gasseri and L. plantarum used as food supplements presented an anti-obesity effect. Only two studies including these species were available in humans, one showing a significant weight gain effect of L. acidophilus in newborns whereas L. gasseri was found to have a significant anti-obesity effect in the first and only well-designed study to date assessing the impact of Lactobacillus-containing probiotics on overweight humans. L. acidophilus and L. gasseri were associated with the same effect direction both in animals and humans. L. fermentum and L. ingluviei were associated with an astonishing weight gain effect in ducks, chicks and mice but have never been studied in humans. Next-generation human probiotic species should contain Lactobacillus spp. that are not associated with weight gain in humans. Of note, on 24 August 2007, the FDA issued regulations that require current good manufacturing practice for dietary supplements to be phased in over the next few years [39]. These regulations should focus on weight assessment outcome according to probiotic species and strains. Finally, selection of specific Lactobacillus containing probiotics could take part in the future management of the two major health problems in the 21st century, malnutrition and obesity.

Competing interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no authors have support from probiotics companies for the submitted work; (2) no authors have relationships with probiotics companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have not financial relationships that may be relevant to the submitted work; and (4) no authors have non-financial interests that may be relevant to the submitted work.

Contributors

DR conceived and designed the study, MM & EA extracted the data, MM, FA, MP, LL analysed the data, MM, EA and DR wrote the manuscript, MP & LL revised the paper. MM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and is guarantor. MM and EA contributed equally to this work.

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Ethical approval

Not required.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.micpath.2012.05.007.

References

Glossary

**Probiotics**: Probiotics are defined as “Live microorganisms which when administered in adequate amounts confer a health benefit on the host.” According to FAO/WHO.

**Obesity**: According to the WHO, Obesity is defined by a BMI > 30 kg/m² and a massive expansion of fat, and is associated with a significant increase in morbidity and mortality.

**Lactobacillus**: Lactobacillus is a genus of Gram-positive facultative anaerobic or microaerophilic rod-shaped bacteria. They are a major part of the lactic acid bacteria group, named as such because most of its members convert lactose and other sugars to lactic acid. In humans they are present in the vagina and the gastrointestinal tract. They are largely present in food products for human and animal consumption as probiotics.

**Meta-analysis with random effect model**: A meta-analysis combines the results of several studies by identification of a common measure of effect size, of which a weighted average might be calculated. A random effect model assumes that heterogeneity is due at least in part to the different experimental conditions between individual studies.