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Review

Microbiota manipulation for weight change

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ABSTRACT

Manipulation of the intestinal microbiota has been linked to weight changes and obesity. To explore the influence of specific agents that alter the intestinal flora on weight in different patient groups we conducted a meta-analysis of randomized controlled trials (RCTs) reporting on the effects of probiotics, prebiotics, synbiotics, and antibiotics on weight. We searched the Pubmed and Cochrane Library databases for trials on adults, children, and infants evaluating the effects of these substances on weight. Our primary outcome was weight change from baseline. Standardized mean differences (SMDs) with 95% confidence intervals were calculated.

We identified and included 13 adult, 17 children, and 23 infant RCTs. Effects were opposite among adults and children, showing weight loss among adults (SMD −0.54 [−0.83, −0.25)) and minor weight gains among children (SMD 0.20 [0.04, 0.36]) and infants (SMD 0.30 [−0.01, 0.62]) taking mainly *Lactobacillus* probiotic supplements. Heterogeneity was substantial in the adult and infant analyses and could not be explained by intervention or patient characteristics. Azithromycin administration in children with pulmonary disease was associated with weight gain (SMD 0.39 [0.24, 0.54]), without heterogeneity. A high risk of selective reporting and attrition bias was detected across the studies, making it difficult to draw firm conclusions. Overall, our meta-analysis suggests that there may be a role for probiotics in promoting weight loss in adults and weight gain in children, however additional studies are needed. Though we cannot recommend antibiotic administration for weight manipulation, its use provides advantageous weight gain in children with cystic fibrosis and bronchiectasis.

Contents

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1. Background

The rising prevalence of obesity among children and adults and its harmful associations are of increasing global concern [1,2]. Attempts to understand the etiology of this growing problem have highlighted the combined influences of environmental, genetic, and hormonal factors on weight gain and obesity [3–11]. Newer studies have also implicated the microbial gut composition in contributing to this epidemic [12–15]. Some of the first experiments exploring the relationship between the gut microbiota and obesity found that germ-free mice, which are leaner than conventional mice, display increases in body fat, intestinal monosaccharide absorption, and production of liver triglycerides upon introduction of cecum-derived feces from conventional donor mice [14]. Subsequent research in humans and mice revealed that gut microbial communities influence caloric intake, intestinal absorption, and energy balance and that these features are transmissible though microbiota transplantation [16,17]. This sparked the beginning of deeper investigations to further unveil the relationship between the gut microbiota and obesity.

More recent studies have since observed a reduction in species diversity in the microbiota of obese compared to lean individuals [17,18]. Additional experiments implicated specific microbial species in relation to weight gain or loss. Historically, higher proportions of *Bacteroidetes* species relative to *Firmicutes* species have been correlated with a leaner status in humans [17]. Nowadays, identification of microbiota at the species and strain level allow for finer associations between bacteria and weight. Although the diversity on the species level was profound among the subjects in this study, the results were still representative as these two divisions made up over 90% of the microbiota [17]. Pro-, pre-, synbiotics, and antibiotics have also been reported to change microbiota composition [19,20]. As a result, these supplements have been hypothesized to help treat obesity and malnourishment clinically by triggering changes in the microbial community [21,22]. Studies employing certain probiotic regimens in adults to combat obesity have indeed found them to promote weight loss in diet-induced obesity [23] and to enable prevention and treatment of obesity [24]. Furthermore, the combined use of prebiotics with probiotics containing species that are associated with leaner hosts has been proclaimed to augment these effects by enhancing the nourishment and activity of the microbiota [19,20,25].

Simultaneous to investigation of their potential use in weight loss, pre-, pro-, and synbiotics have been utilized to induce weight gain in neonates and malnourished children [26–28]. Some randomized control trials have succeeded in promoting growth and improving nutritional status of infants by introducing probiotic supplements into formula [28,29], whereas many have shown no effect [27,30–32]. Antibiotic use has also been proposed to induce weight changes through its effects on microbiota [33]. Studies in animals, children, and adults have correlated the use of certain classes of antibiotics, including macrolides and tetracyclines, with weight gain and obesity [33]. However the question remains as to whether these effects are due to improved health status in these patients or the result of changes in the gut microbiota.

This meta-analysis aims to review the evidence available on the effects of microbiota manipulation using microbes (probiotics) or drugs that affect the microbial communities of the gut (prebiotics and antibiotics). Thus, we plan to include only randomized controlled trials (RCTs) assessing the effects of these additives on body mass index (BMI) and weight change in neonates, children, and adults of normal, obese, or underweight status. The effects are likely heterogeneous and depend on the type of additive, the duration of its administration and the host. Conclusions from this study can provide insight into the potential clinical use or implications of utilizing agents that affect the microbiota.

2. Methods

We compiled RCTs that explored the effects of microbes (probiotics) or other substances that influence the microbiota (prebiotics, synbiotics, antibiotics) on BMI or weight.

2.1. Study inclusion and exclusion criteria

Types of studies: We included RCTs and cross-over RCTs if they reported outcomes at the end of the first cross-over period.

Types of participants: Adults (18 years and above), children (2–18 years), and infants (1 month to two years of age) with normal, obese or lean weight at baseline were included. Subjects with inflammatory bowel disease, colitis, *Clostridium difficile* infection, diarrhea and other disturbances of the gastrointestinal tract at baseline that might mask the effects of microbiota modulation were excluded. Pregnant women, preterm babies and neonates were also excluded as the effects are likely to differ in these patient groups. In studies that recruited infants from birth, we included those that continued the intervention for the minimal defined duration from 1 month of age. In addition, subjects with HIV were excluded following studies suggesting that these individuals experience greater effects of probiotics/synbiotics than uninfected controls [34,35].

Types of interventions: Interventions that affects the GI microbiota composition, including any antibiotic, probiotic, prebiotic or symbiotic were included. Studies in which the probiotic bacterial species was not defined to the level of the bacterial species or the prebiotic or antibiotics contents were not clearly described were excluded. Only trials comparing intervention vs. placebo and that had an intervention period of 14 days or longer were included with the assumption that shorter durations would not affect weight in the long-term. Inhaled interventions were excluded. Comparisons between different interventions, doses or administration schedules were excluded. If multiple interventions (e.g. different doses or

different combinations of probiotics) were assessed in the study, the intervention with the highest dose and smallest number of probiotics species was used for comparison to controls.

Types of outcome measures: We included only trials that reported on one of the primary outcomes quantitatively. Our primary outcomes were weight/BMI change from baseline and absolute end weight/BMI. If age or weight-adjusted values were reported for children, those were extracted as well. All weight outcomes were taken at the end of intervention and extracted by intention to treat preferentially. Secondary outcomes included weight at end of follow-up, fasting glucose, triglyceride, HDL, and LDL blood levels at the end of the intervention period.

2.2. Search methods for identification of studies

Pubmed and the Cochrane library were searched with the following search string: (prebiotic OR symbiotic OR probiotic OR antibiotic) AND (weight OR obese OR obesity OR malnutrition OR kwashiorkor OR malnourished OR body-mass). Filters were applied in order to limit the searches to RCTs.

2.3. Assessment of risk of bias in included studies

Risk of bias was assessed for each study based on the following variables: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data. Items were classified to low, high or indeterminate risk of bias based on definitions of the Cochrane Handbook [36]. If the number of subjects randomized was equal to the number analyzed for the primary outcome of weight, the study was defined as low-risk, whereas all other studies were regarded as high-risk with respect to the incomplete outcome data parameter.

2.4. Data extraction and analysis

Two independent reviewers piloted the process of applying inclusion/exclusion definitions and data extraction. A single reviewer performed all data extraction (TD). Differences in data extraction and unclear data were resolved by reviewer discussion. Review Manager 5.3 was used to calculate the standardized mean difference (SMD) with a 95% confidence interval for weight change from baseline and absolute end weight at both end of treatment (EOT) and end of follow-up (EOF) time points (if applicable). When uniform measures of weight were reported we calculated the absolute mean differences. The analysis was stratified by age (adults, children, and infants) and then by intervention (probiotics, prebiotics, synbiotics and antibiotics). Heterogeneity was assessed using a χ^2 test and the I-squared test for inconsistency. I-squared values greater than 50% were considered to be indicative of

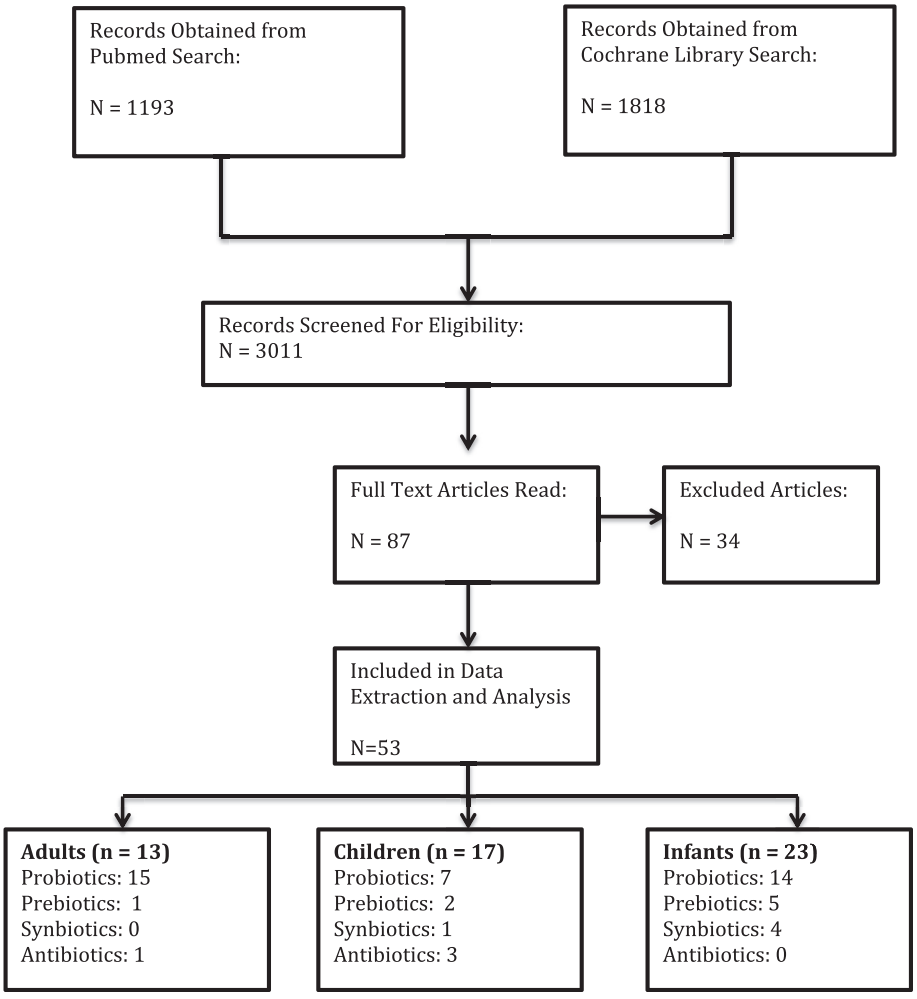

Fig. 1. Summary of study search results.

substantial inconsistency. Meta-analysis was performed using a fixed effect model unless heterogeneity could not be explained, in which case a random effects model was used.

3. Results

The PubMed and Cochrane library searches resulted in 1818 and 1193 articles respectively. A total of 87 potentially eligible studies were evaluated, 53 of which were included contributing to 63 different analyses [1,28,29,31,36–87]. Thirty-four studies were excluded from the analysis for the following reasons: quantitative data on primary outcome was not provided (n = 7), subjects did not match the inclusion criteria (10 preterm infants, 1 HIV, 3 pregnant women, 1 acute malnutrition), intervention duration was too short (n = 1), intervention involved inhaled antibiotics (n = 1), study was not an RCT (n = 3), intervention was not clearly defined (n = 2), and publication was not accessible (n = 5). Amongst included studies, 17 were conducted in adults, 13 in children, and 23 in infants. The search results are summarized in Fig. 1.

Adequate allocation generation and concealment methods were described in 54% and 43% of studies, respectively (Fig. 2). However, most (87%) were double blinded. Outcome assessors were unblinded in most studies and the risk of attrition bias was high. The study was registered in a public trial registry before inception in 22/53 studies (42%) and among those registered the primary outcome reported in the final publication was similarly defined in the trial registry in 7 (32%), indicating a high risk of bias related to selective reporting.

3.1. Adults

Of the adult studies, 15 examined probiotics, 1 prebiotics, 0 synbiotics and 1 antibiotics.

3.2. Probiotics vs. placebo

The meta-analysis of 14 studies assessing the influence of probiotics on weight changes in adults revealed that administration of probiotics resulted in significant weight loss (SMD −0.54 [95% CI −0.83, −0.25]) compared to controls at the EOT time point (Table 2). The heterogeneity of the pooled studies was significant ($p < 0.001$; $I^2 = 73\%$), Fig. 3. Heterogeneity resulted from different degrees of weight loss rather than opposing directions of effects and there was no clear factor associated with the heterogeneity, including the type of probiotic, intervention duration and baseline population. Both the studies leaning toward weight loss in the intervention group as well as those showing no difference involved primarily obese subjects in their 30 s to 40 s, assessed an intervention period of 8–12 weeks and used various *Lactobacillus* species. Doria 2013, which assessed *Lactobacillus* strains in obese women for 13 weeks, was a strong outlier favoring a greater reduction in weight with the intervention; excluding it maintained the weight-loss effect (SMD −0.43 [−0.67, −0.20]), but heterogeneity persisted ($p = 0.005$, $I^2 = 58\%$). In eight studies reporting uniformly on BMI, the absolute mean difference was −0.43 [−0.54, −0.33], without heterogeneity ($p = 0.77$, $I^2 = 0\%$). Eight studies reported absolute weight at end of therapy and showed no significant difference between the probiotic and control groups with no heterogeneity (SMD −0.04 [−0.25, 0.17]; $p = 0.83$; $I^2 = 0\%$).

3.3. Other interventions

In the single study assessing the effect of prebiotics (inulin type fructans), the standard mean difference at EOT was −0.52 [−1.25, 0.21], indicating no significant difference between groups. One study on the influence of clarithromycin on absolute end weight in adults revealed a small but significant increase in the weight of the intervention group relative to the controls (SMD 0.13 [0.02, 0.23] or mean difference of 0.6 Kg [0.12, 1.08]).

3.4. Children

The studies conducted in children included 7 on probiotics, 2 on prebiotics, 1 on synbiotics, and 4 on antibiotics (Table 1).

3.5. Probiotics vs. placebo

A total of five studies assessed the effect of probiotics (mainly *Lactobacillus* sp.) on weight change in children at EOT (Table 2). Meta-analysis demonstrated a significant increase in weight compared to the controls (SMD 0.20 [0.04, 0.36]) with no heterogeneity ($p = 0.72$; $I^2 = 0\%$), Fig. 3. Analysis of the effects of probiotics on absolute end weight revealed no difference between the experimental and control groups (SMD −0.28 [−0.73, 0.17]) with significant heterogeneity ($p = 0.05$; 62%). The heterogeneity may be attributable to two studies involving obese/overweight children around the age of 10 that tended toward lower absolute end weights with probiotics versus two studies involving children of pre-school age of lean or normal weight that showed no effect.

3.6. Antibiotics vs. placebo

A meta-analysis of four studies in children evaluating the effects of azithromycin on weight changes at EOT revealed a significant increase in weight in the intervention group relative to the control (SMD 0.39 [0.24, 0.54]) with no heterogeneity ($p = 0.60$; $I^2 = 0\%$), Fig. 4. All studies were conducted in children with cystic fibrosis or bronchiectasis and azithromycin was administered for 6 months–2 years. Weight assessment was a secondary outcome. Each study reported a different weight measure (BMI Z scores, weight for age Z

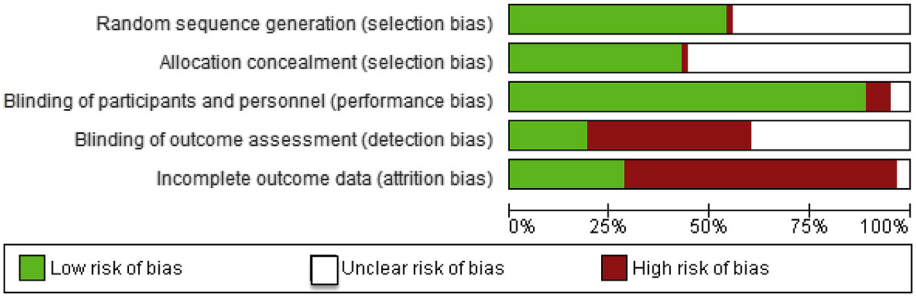

Fig. 2. Assessment of risk of bias.

Table 1
Study characteristics.

Study Id	Intervention	Intervention duration (weeks)	Recruitment start date	Recruitment end date	Country	Age (mean yrs ± SD for adults) intervention/ placebo	Obesity trait	Baseline condition	Number randomized(intervention/ placebo)
Adults									
Probiotics vs. Placebo									
Agerholm-Larsen 2000 [38]	Yoghurt + Streptococcus thermophilus + Lactobacillus acidophilus control	8	NS	NS	Denmark	38.6 ± 2.1 39.4 ± 2.1	Obese	25.0 < BMI < 37.5 kg = m2	16 14
Chang 2011 [39]	Yogurt + Streptococcus thermophilus, Lactobacillus acidophilus and Bifidobacterium infantis, Bifidobacteria control	8	August 2009	December 2009	Korea	36.45 ± 9.92 37.16 ± 8.89	Normal	Healthy volunteers between 20 and 65yr olds and BMI between 18 and 30	53 48
Doria 2013 [40]	7.5×10^8 Lactobacillus Casei + 7.5×10^8 Lactobacillus acidophilus	13	NS	NS	Italy	40.3 ± 8.2 42.5 ± 7.5	Obese	Obese Women	20 20
Fathi 2015 [41]	Low-fat dairy products commercial Kefir drink: Lactobacillus kefiri, Saccharomyces cerevisiae, Saccharomyces unisporus, Saccharomyces exiguous, and Kluyveromyces marxianus control	8	December 2013	April 2014	Iran	35.2 ± 5.5 36.5 ± 5.5	Obese	Premenopausal Women	25 25
Hariri 2015 [42]	Soy milk containing Lactobacillus planetarium A7 control	26	June 2005	June 2005	USA	48.6 41.2	Obese	Pre-gastric bypass surgery	22 22
Hulston 2015 [43]	Yakult light + *Lactobacillus caseii* control	4	NS	NS	UK	25 ± 5.7 24 ± 6.0	Normal	Healthy, physically active (exercise 3 + times per day for 30 min ea time) BMI 18.5 −24.9	8 9
Jung 2013 [44]	Capsules with 10^10 cfu of *Lactobacillus gasseri* BNR17 control	12	NS	NS	Korea	Between 19 and 60	Obese	BMI >23 kg/m^2 and fasting glucose >100 mg/dL	31 31
Kadooka 2010 [46]	Fermented milk + LG2055 (*Lactobacillus gasseri SBT2055)* (200 g/ day)	12	August 2008	December 2008	Japan	48.3 ± 9.3 49.2 ± 9.1	Obese	Healthy adults with obese tendencies (BMI 24.2 to 30.7, abdominal visceral fat between 81.2 and 178.5)	43 44
Kadooka 2013 [45]	100 g of mixture of 10^7 cfu/g LG2055 cells + Fermented Milk prepared with lactic acid bacteria starter cultures (Streptococcus thermophilus and Lactobacillus delbrueckii ssp. Bulgaricus) 2× daily control	12	July 2011	January 2012	Japan	47.2 ± 7.4 47.4 ± 7.0	Unspecified	High visceral fat	71 70
Lee 2014 [47]	Bofutsushosan herbal extracts (Tsumura & Co, Japan) 3 g per administration) + probiotics (One capsule of Duolac 7 included 5 billion viable cells of Streptococcus thermophiles (KCTC 11870BP), Lactobacillus plantarum (KCTC 10782BP), Lactobacillus acidophilus (KCTC 11906BP), Lactobacillus rhamnosus (KCTC 12202BP), Bifidobacterium lactis (KCTC 11904BP), Bifidobacterium longum (KCTC 12200BP), and Bifidobacterium breve (KCTC 12201BP)). BTS and probiotics	8	February 2011	November 2011	Korea	19–65	Overweight/ Obese	Healthy with BMI (>25 kg/ m2) and waist circumference (>85 cm)	25 25

	were co-administered in capsule form 2×/day control								
Sanchez 2013 [82]	2 capsules/day of LPR formulation (10 mg of a Lactobacillus rhamnosus (LPR) powder providing 1·62 × 10^8 cfu, 300 mg of a mix of oligofructose and inulin (70:30, v/v) and 3 mg of magnesium stearate) control	24	January 2010	May 2012	Canada	35 ± 7.9 37 ± 7.9	Overweight/ Obese	BMI between 29 and 41 kg/ m2; without associated co-morbidities	62 63
Savard 2011 [80]	Yoptimal-10 (1010 cfu/100 g of Bifidobacterium animalis subsp. lactis (BB-12), 109 cfu/100 g of Lactobacillus acidophilus (LA-5) and 40 mg of green tea extract) control	4	August 2008	May 2009	Canada	29.6 ± 11.3 35.4 ± 12.9	Lean or normal	Healthy adults body mass index (BMI)b35 kg/m2	20 20
Woodard 2009 [81]	Puritan's Pride® probiotic supplement with each pill containing 2.4 billion live cells of Lactobacillus species. Taken daily control	26	June 2005	June 2005	USA	48.6 41.2	Obese	Obese and scheduled for gastric bypass surgery	22 22
Zarrati 2014 [79]	Low Calorie Diet + Probiotic Yogurt (200 g/day yogurt with S. thermophilus and L. bulgaricus. starter strains, enriched by Lactobacillus acidophilus La5, Bifidobacterium BB12, and Lactobacillus casei DN001 108 colony forming units/g). 1 × 107 colony-forming units/mL of each probiotic strain.	8	August 2011	August 2012	Iran	36 ± 8.4 36 ± 9.7	Obese/ Overweight	healthy	25 25
Sharafedtinov 2013 [49]	50 g/day of probiotic cheese containing L. plantarum TENSIA control	3	Nov 2010	March 2011	Russia	52.0 ± 10.9 51.7 ± 12.1	Obese	Metabolic syndrome (hypertension and obesity without other chronic diseases that need treatment)	25 15
Antibiotics vs. Placebo									
Lane 2011 [48]	H. pylori eradication therapy (ranitidine bismuth citrate 400 mg and clarithromycin)500 mg twice daily for 2 weeks) Control	2	May 1996	May 2006	UK	48.4 ± 8.0 48.6 ± 8.0	Unspecified	Adults positive for *H. pylori* using the 13C-labelled urea breath test (UBT)	787 771
Prebiotic vs. Placebo									
Dewulf 2013 [78]	16 g/d (8 g twice a day) ITF prebiotics (inulin/oligofructose 50/50 mix; n = 15) Control	13	May 2008	May 2011		47 ± 9 48 ± 8	Obese	Body mass index (BMI) > 30 kg/m2	23 21
children									
Probiotic vs. Placebo									
Agustina 2012 [83] and Agustina 2013 [84]	180 mL low lactose milk with a regular calcium (440 mg/d) with 5 × 108 CFU/ d Lactobacillus reuteri DSM 17938 (reuteri; n = 124)	26	August 2007	September 2008		58.9 ± 15.1 58.9 ± 14.2	Unspecified	Healthy	124 126
De Micco 2011 [86]	12 billion CFU/day lactobacillus rhamnosus strain GG control	8	NS	NS	Italy		Obese	Obesity related liver disease	10 10
Mitra 2014 [87]	Infant formulas containing probiotics Lactobacillus reuteri (L. reuteri DSM 17938)	26	NS	NS	India	<2weeks	unspecified	Healthy, term	92 95
Silva 2008 [28]	Lactobacillus acidophilus (10^8 colony-forming units per milli-liter) + fermented milk beverage fortified with iron amino acid chelate (3 mg iron per 80 mL)	14	NS	NS	Brazil	2–5yrs	Unspecified	Preschool children with a usually low–bioavailable-iron diet intake	109 81
Surono 2011 [51]	1 mg lyophilized E. faecium IS-27526 (2.31 10^8 cfu/day) in 125 ml	13	NS	NS	Indonesia	33 months	Lean/ Normal	Healthy pre-school children who lived in Teluk Naga sub	39 40

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Table 1 (*continued*)

Study Id	Intervention	Intervention duration (weeks)	Recruitment start date	Recruitment end date	Country	Age (mean yrs ± SD for adults) intervention/ placebo	Obesity trait	Baseline condition	Number randomized(intervention/ placebo)
	commercial UHT low fat milk (daily) control							District, Tangerang, Banten Province, Indonesia	
Alisi 2014 [52]	VSL#3 1–2 sachet/day: mixture of eight probiotic strains (Streptococcus thermophilus, bifidobacteria [B. breve, B. infantis, B. longum], Lactobacillus acidophilus, L. plantarum, L. paracasei, and L. delbrueckii subsp. bulgaricus)	17	August 2012	May 2013	Italy	10 [9–12] 11 [10–12] yrs. Median (IQR)	Obese	Obese children with biopsy proven NAFLD	24 24
Antibiotic vs. Placebo									
Clement 2006 [50]	Oral azithromycin three times a week for 12 months	52	NS	NS	fRANCE	10.9 ± 3.5 11.1 ± 3.2	Unspecified	Cystic fibrosis age 6–21 years	42 42
Saiman 2010 [53]	250 mg (weight 18–35.9 kg) or 500 mg (weight ≥36 kg) of azithromycin 3 days per week (Monday, Wednesday, and Friday) control	24	February 2007	November 2009	USA/Canada	10.7 ± 3.25 10.6 ± 3.10	Unspecified	Cystic fibrosis (FEV1) of at least 50% predicted	131 132
Saiman 2003 [54]	250 mg of oral Azithromycin 3 d/week for subjects <40 kg and 500 mg for subjects >40 kg		December 2000	May 2002	USA	20.2 ± 7.9 20.6 ± 8.6	Unspecified	CF over age 6 with pseudomonas infection for 1 year or more and FEV1 of 30% or more	
Valery 2013 [55]	30 mg/kg Azithromycin (once per week)	104	November 2008	December 2010	Australia, Mauri, Pacific Islands	3.99 ± 2.14 4.22 ± 2.30	Unspecified	Bronchiectasis or chronic suppurative lung disease	44 41
Prebiotic vs. Placebo									
Liber 2014 [31]	Oligofructose. Children aged 7–12 years: 8 g/day, children aged 12–18 years: 15 g/day. Taken 2×/day for 12 weeks control	12	January 2012	December 2013	Poland	12.3 ± 2.9 12.4 ± 2.7	Obese	Healthy children ages 7–18years that are overweight or obese	48 49
Abrams 2007 [56]	Prebiotic (8 g/d of a prebiotic co–spray dried 1:1 mixture of oligofructose (average degree of polymerization, DPav = 4) and long-chain inulin (Dpav = 25)., ITF (Beneo Synergy1, Orafti, Tienen Belgium) control	52	NS	NS	USA	11.8 ± 0.2 11.4 ± 0.2	Normal/ Lean	Non-obese healthy 9–13 yr olds with Tanner stage 2–3 and girls had to be premenarchal	48 49
Synbiotic vs. Placebo									
Safavi 2013 [57]	Probiotic capsules (Protexin company, London, Englhmel and) containing a combination of viable freeze-dried Lactobacillus Casei, Lactobacillus Rhamnosus, Streptococcus Thermophilus, Bifidobacterium Breve, Lactobacillus Acidophilus, Bifidobacterium Longum and Lactobacillus Bulgaricus of human origin with prebiotics (frocto oligosaccharides), Vitamin E, Vitamin A and Vitamin C. Each capsule contained 2.0108 colony-forming units (CFU) daily. Taken 1× daily control	8	March 2011	November 2011	Iran	10.75 ± 2.49 10.09 ± 1.93	Obese	Healthy	29 27
Infants									
Probiotics vs. Placebo									
Dupont 2010 [77]	Formula that is a-lactalbumin enriched and probiotics supplemented	Formula that is a-lactalbumin enriched and probiotics	NS	NS	France	52.5 50.3	Unspecified	Infants born at term, aged 3 weeks–3 months, weaned,	30 32

	(Lactobacillus rhamnosus, Bifidobacterium infantis), reduced in protein and lactose content, and thickened with corn starch control	supplemented (Lactobacillus rhamnosus, Bifidobacterium infantis), reduced in protein and lactose content, and thickened with corn starch						with normal growth and with more than 3 weeks of crying periods, at least 3 h per day, 3 days per week	
Gibson 2009 [58]	Probiotic Formula containing Bifidobacterium lactis and LC-PUFA (long chain-poly unsaturated fatty acids), fish oil DHA and AA (arachadonic acid) control	30	August 2003	May 2005	Australia		Normal	Healthy term newborns <10d old with birth weight of 2.5–4.0 kg	72 70
Gil-Campos 2012 [85] + Maldonado-Lobón 2015 [36]	Infant formula with a nutritional composition in accordance with current EU regulations, supplemented with galactooligosaccharides (GOS) (0.3 g/100 mL) plus Lactobacilus fermentum CECT5716 at a concentration dose of 107E7 cfu/g	22	May 2009	September 2010	Spain	48.6	Unspecified	Healthy	66 71
Hol 2008 [59] +Dupont 2015 [60]	Lactobacillus casei CRL431 (Lactobacillus paracasei subspecies paracasei) and Bifidobacterium lactis Bb-12 (B animalis subspecies lactis; 107 colony-forming units/g formula for each of the probiotic bacteria used) supplemented to Friso 1 Allergy Care control	26	March 2004	May 2007	Netherlands	4.3 ± 1.2 months 4.15 ± 1.5 months	Unspecified	Infants less than 6 months with Cow's Milk Protein Allergy (CMPA)	59 60
Inostroza 2014 [37]	Experimental (EXPL) formula with 1.65 g of protein/100 kcal (62.8 kcal/100 mL) and containing probiotics (2×10^{7} cfu/g of formula of *Lactobacillus* PR and *B. Lactis* control	39	October 2007	December 2014	Chile	3 m	infants of overweight mothers (body mass index [BMI] > 25 kg/m2)	Normal	86 86
Nopchinda 2012 [61]	Bb12 (Bifidobacterium Bp12) control	26	NS	NS	Thailand	6–36 months	Unspecified	Healthy	51 43
Puccio 2007 [62]	Formula with 2 × 107 colony-forming units of B. longum BL999 (BAA-999, designation BB536, ATCC, Morinaga, Japan) and 4 g/L of a mixture of a GOS and a FOS (90% and 10%).control	17	NS	NS	Italy	<14d	Normal	Healthy	69 69
Savino 2010 [63]	L reuteri DSM 17938 (10^{8} colony-forming units).Control	3	March 2008	August 2009	Italy	32.5 [21] 28.5 [21] Mean interquartile range, days	Unspecified	Exclusively breastfed colicky infants, diagnosed according to modified Wessel's criteria	25 25
Vajro 2011 [64]	Oral *Lactobacillus* GG (12billion CFU/day) control	8	NS	NS	Italy	10.7 ± 2.1 yrs	Obese	Obese children (BMI) > 95th percentile for age and sex with obesity related liver disease (persisting hypertransaminasemia and ultrasonographic (US) bright liver)	10 10
Velaphi 2008 [64]	Chemically Acidified Formula With Probiotics	26	March 2003	August 2003	South Africa	<1 week	Normal	Healthy, normal birth weight, term infants <1 week born to HIV + mothers who decided on exclusive formula-feeding for 4 mo	53 51

(*continued on next page*)

Table 1 (*continued*)

Study Id	Intervention	Intervention duration (weeks)	Recruitment start date	Recruitment end date	Country	Age (mean yrs ± SD for adults) intervention/ placebo	Obesity trait	Baseline condition	Number randomized(intervention/ placebo)
Vendt 2006 [65]	Control formula + L. rhamnosus GG (LGG, ATCC 53103) at 10^7colony-forming units per gram (CFU g)1)	26	February 2002	December 2002	Estonia	37.4 ± 10.3 days 42.2 ± 10. Days	Unspecified	Healthy	60 60
Vlieger 2009 [66]	standard formula below + 107 CFU B. animalis ssp. Lactis/g (also known as Bifidobacterium Bb-12), Paracasei ssp. Paracasei/g (L. casei CRL-431) control	13	November 2004	January 2007	Netherlands	<7 days old	Unspecified	Term,healthy	69 64
West 2008 [68] + Chorell 2013 [67]	Cereal + 1 × 10^8 cfu Lactobacillus paracasei ssp. Paracasei F19 (LF19) per serving (1serving/day) control	39	August 2000	November 2003	Sweeden	40.2 ± 1.2 weeks 39.9 ± 1.3 weeks	Unspecified	Healthy	89 90
Urban 2008 [69]	Probiotics (Bifidobacterium lactis) + Biologically acidified whey adapted formula control	17	February 2000	May 2002	South Africa	<7 days old	Normal	Infants born to HIV-infected women who had elected not to breast-feed	Male 17, Female 12 Male 15, Female 13
Prebiotics vs. Placebo									
Cooper 2010 [70]	chemically acidified whey starter formula with prebiotics only. Prebiotic was a blend of short-chain and long chain fructo-oligosaccharides (70:30) with a total of 2 g per litre when reconstituted to liquid form. Control	26	September 2001	December 2002	South Africa	<7d	Normal	Newborn infants born to consenting HIV-positive women who had previously decided not to breast feed	50 50
Fanaro 2005 [1]	0.2 g/dL acidic oligosaccharides 0.6 g/dL neutral oligosaccharides (mixture of galacto- and fructo-oligosaccharides, which are the prebiotics) control	6	NS	NS	Italy	3.4 days 2.9 days	Unspecified	Healthy, term	15 16
Piemontese 2011 [71]	Prebiotic non-hydrolysed cow's milk based formula + neutral short chain galacto-oligosaccharides and long chain fructo-oligosaccharides, ratio 9:1 and specific pectin acidic-oligosaccharides (15 wt%), was added. Total oligosaccharides was 8 g/L with 6.8 g/L neutral and 1.2 g/L pectin acidic-oligosaccharides) control	52	July 2005	December 2006	Netherlands	30days 32 days	Normal	Healthy, term	414 416
Schmelzel 2003 [72]	Galactooligosac- charides (GOS) 90% and fructooligosaccharides (FOS) 10%, fat, partially hydrolyzed whey protein, and starch	12	NS	NS	Germany	7 ± 5 days 7 ± 5 days	Normal	Healthy, term	76 78
Ziegler 2007 [73]	PGL8 group (control formula supplemented with 8 g/L of a prebiotic blend containing PDX, GOS, and LOS, 50:33:17 ratio) Conrol	15	June 2004	October 2004	USA	14 days	Unspecified	Healthy, term	76 74
Synbiotics vs. Placebo									
Ahanchian 2014 [74]	1 billion Colony Forming Units (CFU) of ProtexinR Restore: a mixture of Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus and FOS (Protexin		February 2009	December 2010	Iran	6 ± 2.4 months 5.5 ± 2.8 months	Unspecified	Infants with cow's milk protein allergy	21 24

	healthcare, Somerset, UK), in the form of freeze dried powder control								
Firmansyah 2011 [29]	Control milk: cow's milk based and contained protein, carbohydrate, fat, vitamins, and minerals in amounts sufficient for normal growth of toddlers aged 12–24 months as supplementary food control	52	NS	NS	Indonesia	377 ± 6.4 days 377 ± 6.8 days	Normal	Healthy	199 194
Rozé 2011 [75]	Lactobacillus rhamnosus LCS- 742 and Bifidobacterium longum subsp infantis M63) and by the addition of prebiotics: 96% galacto-oligosaccharides and 4% short-chain fructo-oligosaccharides. This formula was also enriched with bovine a-lactalbumin, using a native whey protein concentrate with high a-lactalbumin concentration (34% of soluble proteins) obtained using careful fractionation techniques (ultrafiltration).Control	26	February 2007	March 2008	France	<3 Days	Unspecified	Healthy term infants in first 3 days of life that were exclusively fed formula	48 49
Sazawal 2010 [76]	Probiotic and prebiotic milk containing 1.9 × 10^7 colony-forming units per day of probiotic B lactis HN019 and 2.4 g/day of prebiotic oligosaccharides milk. Control	52	April 2010	April 2004	Indonesia	22.2 ± 6.4 months 22.9 ± 6.8 months	Unspecified	Children 1–3 years old, likely to remain in the area, not experiencing severe malnutrition, and nonallergic to milk were invited to participate in the study	312 312

Table 2
Standard mean differences for the primary outcome at EOT.

Weight change from baseline					Absolute end weight			
Intervention type	SMD	95% CI	I^2	p-value for I^2	Standard mean difference	95% Confidence interval	I^2 value	p-value for I^2
Adults								
Probiotic	−0.54	[−0.83, −0.25]	73	<0.001	−0.04	[−0.25,0.17]	0	0.83
Prebiotic	−0.52	[−1.25, 0.21]	NA	NA	NA	NA	NA	NA
Synbiotic	NA	NA	NA	NA	NA	NA	NA	NA
Antibiotic	NA	NA	NA	NA	0.13	[0.02, 0.23]	NA	NA
Children								
Probiotic	0.20	[0.04, 0.36]	0	0.72	−0.28	[−0.73, 0.17]	62	0.05
Prebiotic	0.00	[−0.44, 0.44]	NA	NA	−0.40	[−-0.73,−0.07]	0	0.48
Synbiotic	1.38	[0.79,1.97]	NA	NA	0.09	[−0.43, 0.62]	NA	NA
Antibiotic	0.39	[0.24, 0.54]	0	0.88	NA	NA	NA	NA
Infants								
Probiotic	0.30	[−0.01, 0.62]	86	<0.001	−0.01	[−0.58, 0.55]	91	<0.001
Prebiotic	0.48	[−0.13, 1.08]	91	<0.001	NA	NA	NA	NA
Synbiotic	0.44	[−0.27, 1.14]	73	0.05	0.28	[−0.15,0.71]	NA	NA
Antibiotic	NA	NA	NA	NA	NA	NA	NA	NA

NA = not applicable; SMD = Standard mean difference; CI = Confidence interval; EOT = End of treatment.

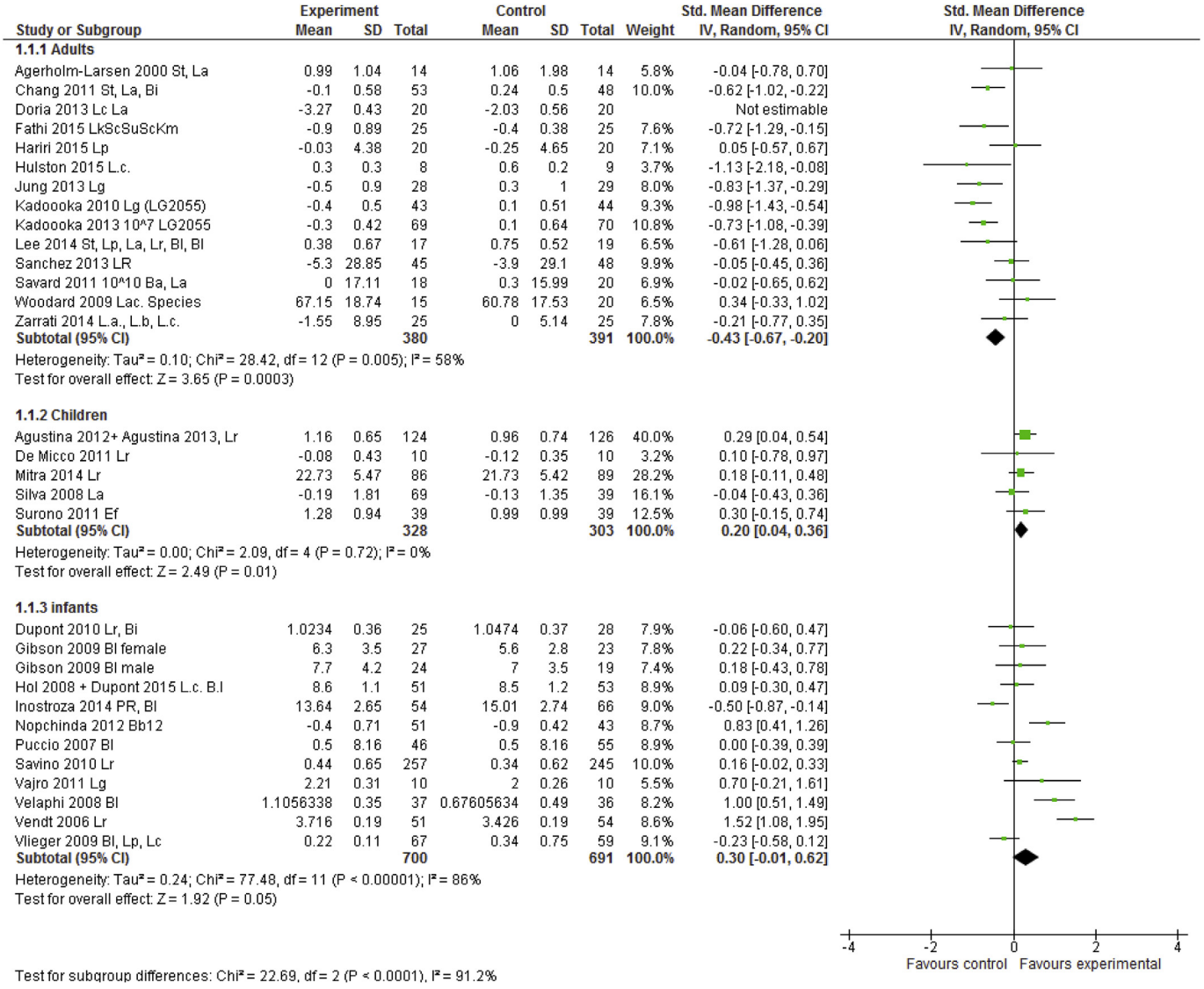

Fig. 3. Probiotics vs. placebo or no treatment: SMD of weight change from baseline. La – Lactobacillus acidophilus, Lr – Lactobacillus rhamnosus, Ls – Lactobacillus species, Lp–Lactobacillus planetarium, Lc – Lactobacillus casei, Ba – Bifidobacterium animalis, Bb – Bifidobacterium BB12, Bla – Bifidobacterium lactis, Blo – Bifidobacterium longum, St – Streptococcus thermophiles, Bi – Bifidobacterium infantis, Lk – Lactobacillus kefiri, Sc – Saccharomyces cerevisiae, Su – Saccharomyces unisporus, Se – Saccharomyces exiguous, Km – Kluyveromyces marxianus, Lg – Lactobacillus gasseri.

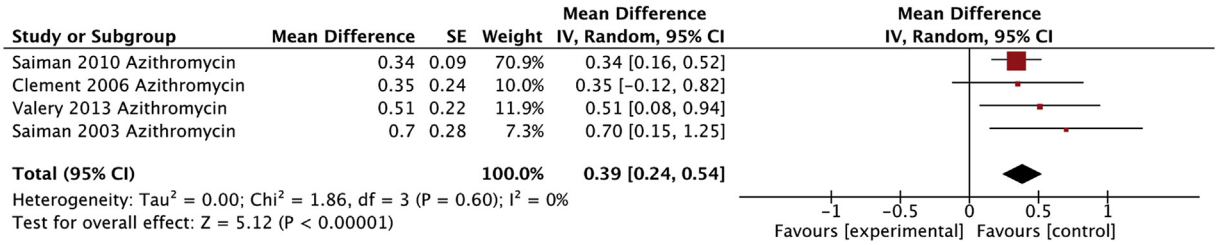

Fig. 4. SMD of weight change from baseline in Antibiotics vs. Placebo Children.

score, absolute Kg or BMI).

3.7. Other comparisons

One study (Liber 2014) assessing the prebiotic oligofructose in obese children showed no difference in weight change between the oligofructose and placebo groups at 12 weeks EOT (SMD 0.00 [−0.44, 0.44]). A meta-analysis of Liber 2014 and Abrams 2007 [31,56], both of which used oligofrutose prebiotics, showed a significant reduction in absolute end weight in the intervention group (SMD −0.4 [−0.73, −0.07]) with no detectable heterogeneity ($p = 0.48$; $I^2 = 0\%$). Liber 2014 also reported a reduction in absolute end weight at the 12 week post intervention EOF time point (SMD = −0.60; 95% CI [−1.16, −0.03]), which is consistent with the EOT results. Two studies were identified that reported on the effect of synbiotics on weight in children. One of the studies ([57]) provided values for both weight change from baseline and absolute end weight at EOT. The analysis of weight change from baseline revealed a significant weight gain in experimental subjects compared to control (SMD 1.38 [0.79, 1.97]) but no difference in absolute end weight (SMD 0.09 [−0.43, 0.62]).

3.8. Infants

In infants, 14 trials examined probiotics, 5 prebiotics and 4 assessed synbiotics.

3.9. Probiotics vs. placebo

Twelve studies demonstrated an increase in weight in response to probiotic administration with borderline significance (SMD 0.30 [−0.01, 0.62]), but with significant heterogeneity ($I^2 = 86\%$, $p < 0.001$) at EOT (Fig. 3). There were no apparent distinctions between studies that leaned toward weight gain versus those showing no effect. Six studies reported on absolute end weight. There was no difference between the intervention and control groups (SMD −0.01 [−0.58, 0.55]) at EOT and the heterogeneity was substantial $p < 0.001$; $I^2 = 91\%$) without apparent cause. Two studies, one of which was further separated into male and female groups, provided comparisons for the weight change at the EOF to probiotic treatment. There was no difference between the intervention and control groups (SMD 0.12 [−0.62, 0.86]) and the meta-analysis was again heterogeneous ($p = 0.02$; $I^2 = 76\%$). Consistent with the above data, a meta-analysis on two studies in infants reporting absolute end weights at EOF showed no difference between control and intervention groups (SMD 0.16 [−0.50, 0.82]) with persistent heterogeneity ($p = 0.05$); $I^2 = 75\%$).

3.10. Prebiotics vs. placebo

No difference in weight was seen in the intervention treatment vs. control at EOT (SMD 0.48 [−0.13, 1.08], 4 trials). There was substantial heterogeneity ($p < 0.001$; $I^2 = 91\%$) with no clear underlying reason.

3.11. Synbiotics vs. placebo

A meta-analysis on two studies revealed no difference between the intervention and control groups (SMD 0.44 [−0.27, 1.14]) at EOT, with significant heterogeneity ($p = 0.05$, $I^2 = 73\%$), perhaps due to the different bacterial species used by the studies. EOF for one of these records was consistent with EOT in that the synbiotic intervention showed a small but significant weight gain relative to the control (SMD 0.10 [0.01, 0.19]).

4. Discussion

In this meta-analysis, we explored the impact of chemicals that alter the microbiota composition on weight change in adults, children, and infants. We found evidence of minor weight loss in adults and weight gains in children and infants ingesting probiotic supplements. More specifically, in obese adults 2.7×10^{10} cfu/day of *Lactobacilli* probiotic administration for 2–3 months was associated with significant weight loss (SMD −0.54 [−0.83, −0.25]). In BMI the absolute difference was −0.43 [−0.54, −0.33]. The minor weight gain observed in children was in relation to probiotic supplements (mainly *Lactobacillus* species) taken between 2 and 6.5 months. Among infants, consumption of probiotic enriched formulas for 3 weeks–10 months was associated with borderline significant weight gain (SMD 0.30 [−0.01, 0.62]). An increase in weight was observed among children with cystic fibrosis and bronchiectasis treated with azithromycin between six months and two years (SMD 0.39 [0.24, 0.54]). This result was consistent with the single antibiotic study on adults that revealed a small but significant increase in weight (SMD 0.13 [0.02, 0.23]) with clarithromycin. In all analyses, differences detected in change of weight from baseline were not observed in comparisons of absolute end weight. We consider the change from baseline effect to be more accurate as some of the smaller studies began with intervention groups that were of different baseline BMIs.

Systematic reviews on pro-, pre-, syn- and antibiotics have implicated these agents in promoting weight changes in individuals of all ages and varying baseline conditions [88–91]. A recent meta-analysis of RCTs on early antibiotic exposure (from 1 month to 12 years of age) in relation to obesity concluded that antibiotics increase growth (weight and height) in children of low and middle-income countries [92]. These results are consistent with our findings in children with pulmonary disease taking azithromycin, despite the differing baseline conditions between our analyses. Also in accordance with our results, a recent Cochrane review observed greater weight gains in children with cystic fibrosis who were administered azithromycin [93]. Although studies on malnourished children in developing countries have found antibiotic use to improve weight outcomes [94–96], severely

undernourished children often have accompanying infections [96] and whether the weight gain in these patients associated with antibiotic exposure is primarily due to microbiota changes or alleviation of infection and inflammation remains uncertain. Kwashiorkor or acute severe malnutrition may be confounders, as alternations in the gut microbiome have been found to underlie these syndromes and antibiotics may act just by restoring gut flora to a healthy state potentially explaining the weight gain [97,98]. Observational studies on long term antibiotic use for endocarditis that reported weight gains associated with antibiotic exposure also found alterations in the microbiota [99,100], some of which correlate with increased levels of species that have been implicated in weight gain and obesity [100]. The mechanism behind the increased weight seen in children with chronic respiratory illness following antibiotic exposure could be due to a combination of the health benefits associated with infection reduction as well as alterations to the microbiota, which were not explored in these studies [50,53–55].

Probiotics and prebiotics have been shown to alter the intestinal flora, mainly by increasing the relative amounts of mostly *Lactobacillus* and *Bifidobacterium* species [90,101,102]. A number of studies have linked increased levels of certain *Lactobacillus* species [103,104] as well as other species to weight gain and obesity [104–107]. Recent meta-analyses evaluating the influence of probiotics, prebiotics and synbiotics on weight, however, have found difficulties drawing conclusions from the available data due to the scarcity and low quality of the studies [88–90]. A recent meta-analysis in individuals of mixed ages found probiotics to have no effect, but suggested that no conclusion could be made due to the poor quality of the trials [89]. Our analysis was stratified by age and we found opposing effects of weight gain in children and infants and weight loss in adults. The mechanism behind the weight loss seen in adults likely relates to the reduction of inflammation and strengthened intestinal epithelial barrier that has been observed to accompany probiotic administration [21,108–110]. *Lactobacillus* probiotics that are associated with weight loss, have been shown to change the intestinal microbial composition in mice by increasing the levels of host *Bifidobacteria*, ultimately resulting in anti-inflammatory effects [101,111]. This same study implicated certain *Lactobacillus* species in promoting weight loss by inducing expression of metabolic enzymes and hormones involved in fatty acid oxidation [101,111]. As all of the included studies on adults administered probiotics involved *Lactobacillus*, the weight loss seen in adults taking probiotics may be due to anti-inflammatory effects, improved intestinal barrier integrity, and increased metabolic activity associated with changes to the intestinal flora.

The primary limitation of our meta-analyses is the diversity of probiotic interventions employed by the different studies, each with a different impact on the microbiota. This is important, as different species of the same genus of bacteria have been implicated in promoting opposing effects on weight. For instance, *Lactobacillus acidophilus* administration has been linked to weight gain, whereas *Lactobacillus gasseri*, has been linked to weight loss in humans and animals [107]. Indeed, the heterogeneity of the probiotic studies in our review was substantial, likely due to the different species used in each study and the range of intervention durations. Categorizing the studies by probiotic genus in most cases did not reduce the heterogeneity nor did grouping by intervention duration. As this field is still relatively new and expanding exponentially, combining results from future studies might allow more detailed analyses by patient and intervention characteristics and will perhaps clarify some of these ambiguities. Our search did not target unpublished trials and we could have missed RCTs that did not report on weight measures in the abstract. The major strength of this review is the inclusion of RCTs only, limiting the overall bias of the combined studies. However, risk of bias assessment revealed potential residual bias. Less than half of the trials were registered under a public registry and only about 1/3 of those studies reported on their pre-defined primary outcomes. This might reflect selective reporting bias among the trials, as it is possible that unfavorable results obtained from originally defined outcomes were discarded. Even among trials which were pre-registered with primary outcome, the follow up duration did not match the initially proposed time points, perhaps indicating that extensive exposure or follow-up time was necessary to observe an effect on weight. We have no information on whether blinding was kept when analyzing weight-related outcomes. A recent systematic review reported that industry-funded RCTs on pro, pre, synbiotics were more likely to report positive conclusions on weight gain than non-industry-funded trials [88]. Our analysis highlights the “wishful” and opposing trends observed in different patient groups with probiotics (weight gain in children and infants, weight loss in obese adults) and raises the suspicion of bias. We stress the importance avoiding attrition bias and selective reporting in future RCTs. Improving the quality of reporting in RCTs on the subject of weight and microbiota-altering agents will allow for more accurate evidence-based conclusions and practical applications.

Taken together, this meta-analysis provides insight into the effects and potential weight implications that accompany the use of probiotics and antibiotics. Though probiotics had heterogeneous effects across the different comparisons, our meta-analysis in adults suggests that these products might be useful for weight loss. Our results in children with cystic fibrosis and bronchiectasis suggest that antibiotic therapy in infected people has an advantageous outcome in terms of weight gain, but as the mechanism remains to be unveiled, we cannot recommend antibiotic administration for the purpose of weight manipulation.

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Conflict of interest

All authors, none declared.

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