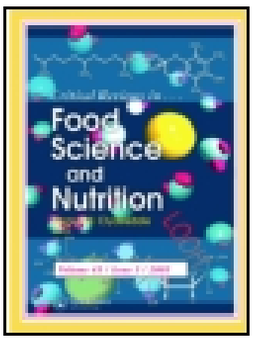

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REVIEW

Does infant formula containing synbiotics support adequate growth in infants? A meta-analysis and systematic review of randomized controlled trials

Parisa Janmohammadi[a], Zeinab Nourmohammadi[b], Siavash Fazelian[c], Atieh Mirzababaei[d], Shahab Alizadeh[a], Mahtab Zarei[b], Elnaz Daneshzad[e], and Kurosh Djafarian[a]

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ABSTRACT

In recent years, several studies have shown that formulas that contain synbiotics, i.e. composed prebiotics and probiotics have been proposed to have a beneficial effect on anthropometric indices. However, the results are inconsistent thus this meta-analysis was performed to assess this effect. PubMed/MEDLINE, Web of Science, SCOPUS, and Embase were systematically searched up to May-2020. Weight gain, length gain, head circumstance gain, weight-for-age z scores, and length-for-age z scores were considered as the outcomes. Weighted mean differences (WMD) with the 95% CI were applied for estimating the combined effect size. Subgroup analysis was performed to specify the source of heterogeneity among studies. Consumption of formulas containing synbiotics did not affect growth significantly in healthy infants (weight gain (WMD = 2.06, 95% CI: − 4.08 to 8.21; p = 0.51), length gain (WMD = − 0.05, 95% CI: − 0.70 to 0.60; p = 0.88), head circumstance (WMD = − 0.28, 95% CI: − 0.66 to 0.11; p = 0.15), on weight-for-age z-scores (WMD = − 0.05, 95% CI: − 0.23 to 0.13; p = 0.57) and length-for-age z-scores (WMD = − 0.16, 95% CI: − 0.50 to 0.19; p = 0.37)). The main results indicate a non-significant increase in infant's growth following synbiotics supplementation of infant formula. Further large-scale studies are warranted to confirm present findings.

KEYWORDS

Growth; infant; prebiotics; probiotics; synbiotics

Introduction

Breastfeeding is the preferred source of nutrition for all term newborn infants and has been proven to provide a range of short-term and long-term benefits for support growth and development in early life (Dieterich et al. 2013). Human milk contains bioactive components that beneficially affect intestinal health, gut microbial colonization, and immune systems (Jost et al. 2015; Garcia et al. 2013). When breastfeeding is not possible or contraindicated for an infant to be fed breast milk, infant formula is used formulas. All formulas intended for infants must be secure and appropriate to meet the nutritional requirements and advance growth of infants born at term (Hernell et al. 2015; Lönnerdal 2014). In recent years, several studies have shown that fermented infant milk formulae beneficially affect the gastrointestinal (GI) function (Roy et al. 2004; Thibault, Aubert-Jacquin, and Goulet 2004; Mullié et al. 2004; Vandenplas et al. 2017). Fermented formulae can decrease the frequency and severity of gut pain (Roy et al. 2004), decrease the severity of diarrhea (Thibault, Aubert-Jacquin, and Goulet 2004), and motivate the presence of intestinal bifidobacteria in term infants (Mullié et al. 2004). The gut microbiota plays an influential role in inflammation and enteropathy, which may be connected to growth faltering. The gut microbiota affects the somatotropic axis via regulation of IGF-1 and growth hormone production, thereby affecting growth. Modifying the microbiota through interventions such as diet, antibiotics, probiotics, prebiotics, synbiotics or fecal microbiota transplantation to promote healthy growth and development (Robertson et al. 2019; Gaufin, Tobin, and Aldrovandi 2018).

Fermentation processes using food-grade microorganisms produce bioactive combinations, which are also known as postbiotics (Patel and Denning 2013; Aguilar-Toalá et al. 2018). Probiotics are live microorganisms considered to have beneficial health effects (Stanton et al. 2001; Cummings, Macfarlane, and Macfarlane 2003; Rastall et al. 2005). The important impact of probiotics is to stabilize the intestinal microflora. Stable consumption of probiotics has been observed to decrease the incidence of different diseases; hospitalized children and those who do not use milk or are living in a deprived situation are vulnerable to illness (Cummings, Macfarlane, and Macfarlane 2003). Prebiotics

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are non-digestible food ingredients that selectively motive the growth of intestinal bacteria that affect health positively (Gibson and Roberfroid 1995).

Consumption of prebiotic- and probiotic-enriched formulas have been increased in the past decade years. It has been offered that these formulas could decrease the incidence of infectious diseases and eczema (Vouloumanou et al. 2009; Rautava, Salminen, and Isolauri 2008; Kukkonen et al. 2008). Several clinical studies in which the formula of infants was supplemented with probiotics offer that probiotics could decrease the incidence of diseases, preventing GI disorder, prevent the onset of allergy, and be useful in the treatment of skin disease (Isolauri et al. 2000; Kalliomäki et al. 2007; Szajewska and Mrukowicz 2001; Saavedra et al. 1994). The beneficial effects of prebiotics are multifaceted; in addition to increasing growth of indigenous bacteria, prebiotics are fermented in the large intestine, producing short-chain fatty acids (SCFAs). These make an acidic environment that prevents the growth of potentially pathogenic bacteria (Gibson and Roberfroid 1995) as well as an energy source for the gut epithelium (Cummings and Macfarlane 1991). Further, it has also been offered that SCFAs aid the absorption of iron, calcium, magnesium (Sako, Matsumoto, and Tanaka 1999; Chonan, Takahashi, and Watanuki 2001). Newly, formulas have been suggested that contain synbiotics, i.e. composed prebiotics and probiotics have been proposed to have a synergistic effect by both ensuring survival of delivered probiotics and motiving the growth of selected indigenous bacteria than probiotics or prebiotics alone (Gibson and Roberfroid 1995; Kukkonen et al. 2008; Collins and Gibson 1999). Synbiotics formulas have been shown to play a role in both the prevention and treatment of allergies in infants (Grüber et al. 2010; van der Aa et al. 2011). Although, clinical studies indicating the effects of feeding synbiotics on infants are rare. According to the Cochrane review of Osborn and Sinn (2013), the overall level of evidence to substantiate a preventive effect of prebiotics on allergy in healthy and/or high-risk populations is currently insufficient, possibly because of considerable heterogeneity, e.g. type of prebiotic intervention. Vandenplas et al (Vandenplas, Zakharova, and Dmitrieva 2015) reported that prebiotics are safe and since most studies suggest a trend of beneficial effect. Positive clinical results have led to the increasing of food supplements and infant formula including prebiotic and probiotic ingredients. This systematic review and meta-analysis of clinical trial studies aimed to determine the effect of infant formula containing synbiotics to support adequate growth in infants.

Method

Search strategy

This systematic review and meta-analysis was performed by following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane handbook for systematic reviews of intervention protocols (Moher et al. 2015; Higgins and Green 2009).

To avoid missing any possible pertinent articles two independent reviewers (PJ and ZN) searched PubMed/MEDLINE, Web of Science, SCOPUS, and Embase from inception until May 2020 with no restrictions regarding age, sex, year of publication, or the duration of the study. We considered randomized controlled trials (RCTs) that measured the effects of synbiotics supplementation on infant's growth.

Keywords were searched through [tiab] and [Mesh] tags and the following search terms were used in the current study: terms related to synbiotics ("probiotics","probiotic"," prebiotics","prebiotic","synbiotics","symbiotics","synbiotic","Lactobacillus","Bifidobacterium","oligosaccharide", "GOS", "FOS", "Fructo oligosaccharide","Galacto oligosaccharide","Fructo-oligosaccharides"," Galactooligosaccharides","GOS/FOS", "lcGOS"[tiab] OR "scFOS"[tiab] OR "lcGOS/scFOS", "inulin"), terms related to infants (infant", "infant formula", "neonate", "newborn", "baby", "premature", "preterm", "term", "full term infant") and terms related to growth ("growth", "weight", "length", "head circumference", "anthropometry"). Hand-search of the references list of RCTs and previous related reviews was performed to include other potentially eligible trials. A bibliographical database was created using EndNote X7, which was used to store and manage the references.

Selection criteria

The review's population, intervention, comparison, outcome (PICO) items defined the search strategy: Participants (P) included infants; Intervention (I) examined the effects of infant formula containing synbiotics; Comparisons (C) addressed synbiotics intervention versus control groups; Outcomes (O) following anthropometric growth markers: weight, length/height, head circumference in both treatment and control groups.

Studies were excluded if they: 1) used pro-/prebiotics in control group 2) reported duplicate data; 3) were reviews, conference papers, letters, editorial articles, or case reports, and 6) insufficient information.

Quality assessment

The Cochrane Collaboration's risk of bias tool (following these domains: allocation concealment, random sequence generation, Journal Pre-proof blinding of participants and personnel, incomplete outcome data, blinding of outcome assessment, selective reporting, and other probable sources of biases) (Cumpston et al. 2019) was used by the same two reviewers independently to evaluate the methodological quality and risk of bias of the included RCTs; and any disagreement was resolved by consensus.

Data extraction

The two investigators independently conducted study selection by screening the titles and/or abstracts of studies. Articles that did not appear to meet the inclusion criteria were discarded. For each RCT that fulfilled the inclusion

criteria, the following information (authors, country, publication year, age, gender, the number of participants, the health status of the study population, follow-up period, means and standard deviations (SD) of outcome variables, the gestational age, birth weight, delivery type, characteristics of prebiotic, probiotic, and synbiotic species) was collected and were abstracted into a data table (Table 1).

Statistical analysis

Treatment effect was evaluated by the mean difference in the endpoint values of outcome measures between the treatment and the control group. If the change from baseline values were not available, we calculated the mean change from baseline to follow-up for each intervention and control group. SEs and confidence intervals (CIs) were converted to SD for the analyses. We performed random-effects meta-analysis to estimate the pooled weighted mean difference (WMD) and 95% confidence interval (CI) and was calculated based on the means and corresponding SDs of the anthropometric growth markers (weight, length/height, head circumference) for both intervention and control groups. To identify potential sources of heterogeneity, sensitivity analysis, and predefined subgroup analysis were conducted; subgroup analysis was performed based on background disease and gender. Publication bias was evaluated by funnel plot analysis and Egger's statistical test (Egger et al. 1997). Heterogeneity among the studies was evaluated by the I^2 statistics. The heterogeneity was considered significant if $I^2 >$ 50% ($p < 0.1$). All statistical tests for current the meta-analysis were performed with STATA (version 14.0; Stata Corporation, College Station, TX). For all statistical analyses, p-value <.05 was considered statistically significant.

Results

Study characteristics

A total of 2145 studies were identified in the initial search. After removing 592 duplicate articles, 1554 were excluded after scanning the titles/abstracts because they were irrelevant to the present meta-analysis. After carefully screening the remaining 29 full-texts, we also excluded 20 more studies because they did not report relevant variables or enough data, had an appropriate control group or had an inappropriate intervention. The flow chart of study selection is presented in Figure 1. Finally, 11 trials (Kukkonen et al. 2008; Rodriguez-Herrera et al. 2019; Vlieger et al. 2009) with a total of 1554 participants were included in the meta-analysis. Data obtained included 9 studies with 14 data sets on weight gain (Kukkonen et al. 2008; Rodriguez-Herrera et al. 2019; Chouraqui et al. 2008), 8 studies with 12 data sets on length gain (Kukkonen et al. 2008; Abrahamse-Berkeveld et al. 2016; Puccio et al. 2007), 7 studies with 11 data sets on the head circumference (Rodriguez-Herrera et al. 2019; Abrahamse-Berkeveld et al. 2016; Gil-Campos et al. 2012; Chouraqui et al. 2008; Puccio et al. 2007), 2 studies on weight-for-age z scores (Abrahamse-Berkeveld et al. 2016; Vlieger et al. 2009), and 2 studies on length-for-age z-scores (Abrahamse-Berkeveld et al. 2016; Vlieger et al. 2009). The duration of interventions ranged from 4 to 52 weeks with a birth weight ranging from 2700 to 3595 g. The total number of participants included in each study ranged from 32 to 900 people. The majority of studies were performed on healthy subjects, while 2 studies were carried out on infants with allergy (Kukkonen et al. 2008; Ahanchian et al. 2014) and 1 study was reported on healthy infants born to the human immunodeficiency viruses (HIV)+ mothers (Cooper et al. 2016). Additionally, regarding the gender of participants, 2 articles reported males and females separately (Chouraqui et al. 2008; Puccio et al. 2007) and other studies reported the results for the combination of both genders. Formulas containing synbiotics in the included studies consisted of various pre-and probiotics including a mixture of bovine milk-derived oligosaccharides (BMOS) or galacto (GOS) -and fructo-oligosaccharides (FOS) as prebiotics and the probiotic from the strains of *Bifidobacterium, Lactobacillu, Propionibacterium freudenreichii, and Streptococcus.* The characteristics of the included studies in the meta-analysis are presented in Table 1.

Risk of biases within studies

The majority of studies were categorized as having a low risk of bias in the randomization and blinding with unclear risk of bias in the selective reporting and other sources of bias due to insufficient reporting. Details on the authors' judgment and rationale for risk of bias can be found in Tables 2 and 3.

Findings from Meta-Analysis

Synbiotics and weight gain

Among the included studies examining weight gain as an outcome, administration of formulas enriched in synbiotics, compared with routine formulas, had no significant effect on weight gain in the overall analysis (WMD = 2.06, 95% CI: − 4.08 to 8.21; p = 0.51) and subgroups of males (WMD = 0.92, 95% CI: − 1.29 to 3.12; p = 0.41) and females (WMD = 0.90, 95% CI: − 1.39 to 3.19; p = 0.44), with a significant heterogeneity across studies (I^2 = 99.4%, p<0.001) (Figure 2). In the subgroup analysis by background disease (Supplemental Figure 1), consumption of formulas containing synbiotics also did not affect weight gain significantly in healthy infants, however, was related to a significant increase in weight gain among infants with allergy based on 2 analyzed studies (WMD = 15.01, 95% CI: 8.51 to 21.52; p< 0.001). Meta-regression analysis found no significant association between follow-up duration (coefficient: − 0.03, SE: 0.11, P value= 0.78) and effect of formulas containing synbiotics on the weight gain of infants.

Synbiotics and length gain

Figure 3 demonstrates the overall and subgroup analysis by gender for the effect of formulas containing synbiotics on

Table 1. Characteristics of the included studies.

Author/ Year	Country	Background Disease	Birth weight (g)	Birth height (cm)	Types of Delivery	Case (n)	Control (n)	Duration (week)	Probiotic type	Prebiotic type	Case outcome (mean + SD)	Control outcome (mean + SD)	Initiation age	Gender
Abrahamse-Berkeveld et al. (2016)	Germany	Healthy	3450	53·2	V/C	45	57	13	Bifidobacterium breve M-16V	scGOS/lcFOS	Weight gain[a]: 28.7(6.4) Head circumstance gain[b] :15.64(0.43) Length gain[c]: 33.45(5.64) weight-for-age z scores[d]: length-for-age z scores[e]:	Weight gain: 29.8(6) Head circumstance gain:16.51(0.43) Length gain: 35.63(6.95) weight-for-age z scores: length-for-age z scores	>35d	M/F*
Chouraqui et al. (2008)	France	Healthy	3400	50	V/C	28	25	17	Bifidobacteriumlongum (BL999) +Lactobacillusrhamnosus (LPR)	GOS/scFOS	Weight gain: 31.5(5.9) Head circumstance gain:17.9(2.3) Length gain: 33.1(3.7)	Weight gain:30.9(6.1) Head circumstance gain:18.4(2.3) Length gain: 32.6(3.6)	>2wks	F
Chouraqui et al. (2008)	France	Healthy	3400	50	V/C	28	25	17	Bifidobacteriumlongum (BL999) +Lactobacillus paracasei (ST11)	GOS/scFOS	Weight gain: 32.1(5.9) Head circumstance gain:18.3(2.3) Length gain: 34.2(3.6)	Weight gain:30.9(6.1) Head circumstance gain:18.4(2.3) Length gain: 32.6(3.6)	>2wks	F
Chouraqui et al. (2008)	France	Healthy	3400	50	V/C	26	28	17	Bifidobacteriumlongum (BL999) +Lactobacillusrhamnosus (LPR)	GOS/scFOS	Weight gain: 27.5(6) Head circumstance gain:16.2(2.3) Length gain: 31.7(3.6)	Weight gain: 26.9(6) Head circumstance gain:16.7(2.4) Length gain: 31.2(3.7)	>2wks	M
Chouraqui et al. (2008)	France	Healthy	3400	50	V/C	32	28	17	Bifidobacteriumlongum (BL999) +Lactobacillus paracasei (ST11)	GOS/scFOS	Weight gain:28.1(6) Head circumstance gain:16.6(2.4) Length gain: 32.7(3.8)	Weight gain:26.9(6) Head circumstance gain:16.7(2.4) Length gain: 31.2(3.7)	>2wks	M
Cooper et al. (2016)	South Afr	motherHIV+	3090	50.2	V	93	86	52	Bifidobacterium animalis subsp	BMOS	Weight gain:28.1(7.71)	Weight gain: 28.2(7.41)	>3d	M/F
Cooper et al. (2016)	South Afr	motherHIV+	3130	50.3	C	72	72	52	Bifidobacterium animalis subsp	BMOS	Weight gain:29.6(7.64)	Weight gain:29.6(7.64)	>3d	M/F
Gil-Campos et al. (2012)	Spain	Healthy	3200	ND	V/C	61	60	21	Lactobacillus fermentum	GOS	Weight gain:24.8(39.83) Head circumstance gain:0.43(0.78) Length gain: 29.2(71.17)	Weight gain:25.3(46.47) Head circumstance gain:0.421(0.77) Length gain: 27.3(45.625)	>120d	M/F
Meli et al. (2014)	Italy	Healthy	3300	49.5	V/C	56	63	17	Bifidobacteriumlongum (BL999)+ Lactobacillusrhamnosus (LPR)	BMOS	Weight gain: 30.5(6.3) Head circumstance gain: 16.73(2.73) Length gain: 31.94(5.78)	Weight gain:30.3(6.4) Head circumstance gain:17.33(3.04) Length gain: 32.54(5.17)	14days	M/F
Picaud et al. (2010)	France	Healthy	3000	50	V/C	422	349	ND	Bifidobacterium longum+ Streptococcus thermophilus	FOS	Weight gain:18.3(8.7) Length gain:20.42(9.56)	Weight gain:16.9(7.5) Length gain: 19.55(10.86)	150days	M/F
Puccio et al. (2007)	Italy	Healthy	ND	ND	V/C	42	55	16	Bifidobacteriumlongum (BL999)	GOS/FOS	Weight gain: 35.5(4.4) Head circumstance gain:17.4(2.9) Length gain: 35.5(4.4)	Weight gain:35.5(4.1) Head circumstance gain:17.9(2.7) Length gain: 35.5(4.1)	>14d	M/F
Puccio et al. (2007)	Italy	Healthy	ND	ND	V/C	42	55	16	Bifidobacteriumlongum (BL999)	GOS/FOS	Weight gain:35.5(4.4) Head circumstance gain:15.5(3) Lg:32.2(4.6)	Weight gain:35.5(4.1) Head circumstance gain:16(2.8) Lg:32.2(4.3)	>14d	M/F
Rodriguez-Herrera et al. (2019)	Italy	Healthy	3200	50	V/C	94	105	17	Bifidobacteriumbreve C50+ Streptococcusthermophilus 065	scGOS/lcFOS	Weight gain:28.3(7.4) Head circumstance gain:17.03(3.95)	Weight gain: 30.1(6.6) Head circumstance gain:16.42(3.65)	>28d	M/F
Vlieger et al. (2009)	Netherla	Healthy	3500	50	V/C	41	38	6month	Lactobacillus paracasei ssp. Paracasei+ Bifidobacterium animalis ssp. lactis	GOS	weight-for-age z scores: length-for-age z scores	weight-for-age z scores: length-for-age z scores	>7d	M/F

Kukkonen et al. (2008)	Finland	Allergy	3595	50.5	V/C	456	446	25	Lactobacillus rhamnosus GG and LC705+ Bifidobacterium breve Bb99+ Propionibacterium freudenreichii ssp shermanii	GOS	Weight gain: 25.3(2.76) Length gain: 27.6(6.6)	Weight gain: 8.09(0.95) Length gain: 29.6(8)	Birth	M/F
Ahanchian et al. (2014)	Iran	Allergy	ND	ND	V/C	16	16	4	Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus	FOS	Weight gain: 25(15) Head circumstance gain:0.02(0.01) Length gain: 0.02(0.01)	Weight gain:15(10) Head circumstance gain:0.02(0.01) Length gain: 0.03(0.02)	1–12 months	M/F

Note: Mean ± SD were reported for the intervention and control group.
[a]Value: g/day, [b]Value: mm/month, [c]Value: g/week, [e]Value: cm/week
Abbreviations: M, Male; F, Female; scGOS, short-chain Galacto-oligosaccharides; lcFOS, long-chain Fructo-oligosaccharides; V, Vaginal; C, Cesarean; BMOS, mixture of bovine milk-derived oligosaccharides

length gain. Compared with placebo, supplementation of formulas with synbiotics had no significant effect on length gain in the overall analysis (WMD = − 0.05, 95% CI: − 0.70 to 0.60; p = 0.88) and in males and females using the random-effects model (I^2= 59.2%, P = 0.005). No significant formulas containing synbiotics affect one the health status of infants was also observed in the subgroup analysis (Supplemental Figure 2). Meta-regression analysis showed that the duration of intervention was not associated with the treatment effects of formulas containing synbiotics on length gain (coefficient: −0.06, SE: 0.06, P value= 0.32).

Synbiotics and head circumference

Figure 4 shows the impact of formulas containing synbiotics on head circumference. The pooled analysis revealed no significant effect of synbiotics supplementation on the head circumference in the overall analysis (WMD = − 0.28, 95% CI: − 0.66 to 0.11; p = 0.15) and in males and females. Because of remarkable evidence for heterogeneity, the random-effects model was used for analysis (I^2= 90.8%, p< 0.001). No significant impact of synbiotics supplementation on the health status of infants was also identified in the subgroup analysis (Supplemental Figure 3). Meta-regression analysis showed that the effect of formulas containing synbiotics on head circumference was not modified by the duration of the intervention (coefficient: − 0.001, SE: 0.03, P value= 0.97).

Synbiotics and weight-for-age and length-for-age z-scores

Figure 5 demonstrates the effect of formulas containing synbiotics on weight-for-age and length-for-age z-scores. Compared with placebo, supplementation of formulas with synbiotics had no significant effect on weight-for-age z-scores (WMD = − 0.05, 95% CI: − 0.23 to 0.13; p = 0.57) and length-for-age z-scores (WMD = − 0.16, 95% CI: − 0.50 to 0.19; p = 0.37).

Publication bias

Egger's test suggested no significant asymmetry for the effect estimation on length gain (P = 0.88) and head circumference (P = 0.21), but there was significant evidence for publication bias in studies investigating the impact of formulas containing synbiotics on weight gain (p< 0.001) (Supplemental Figure 4).

Discussion

Normal growth has been identified as an important indicator for the measurement of adequate nutrition intake (Mugambi et al. 2012) and the healthy development of an infant (de Onís et al. 1993). Administration of food and drugs considers the rate of weight gain is the most important information in the clinical evaluation of an infant's health status. Recently, there is a trend in the consumption of prebiotics, probiotics, or synbiotics for weight gain because of their beneficial effects on macronutrient and

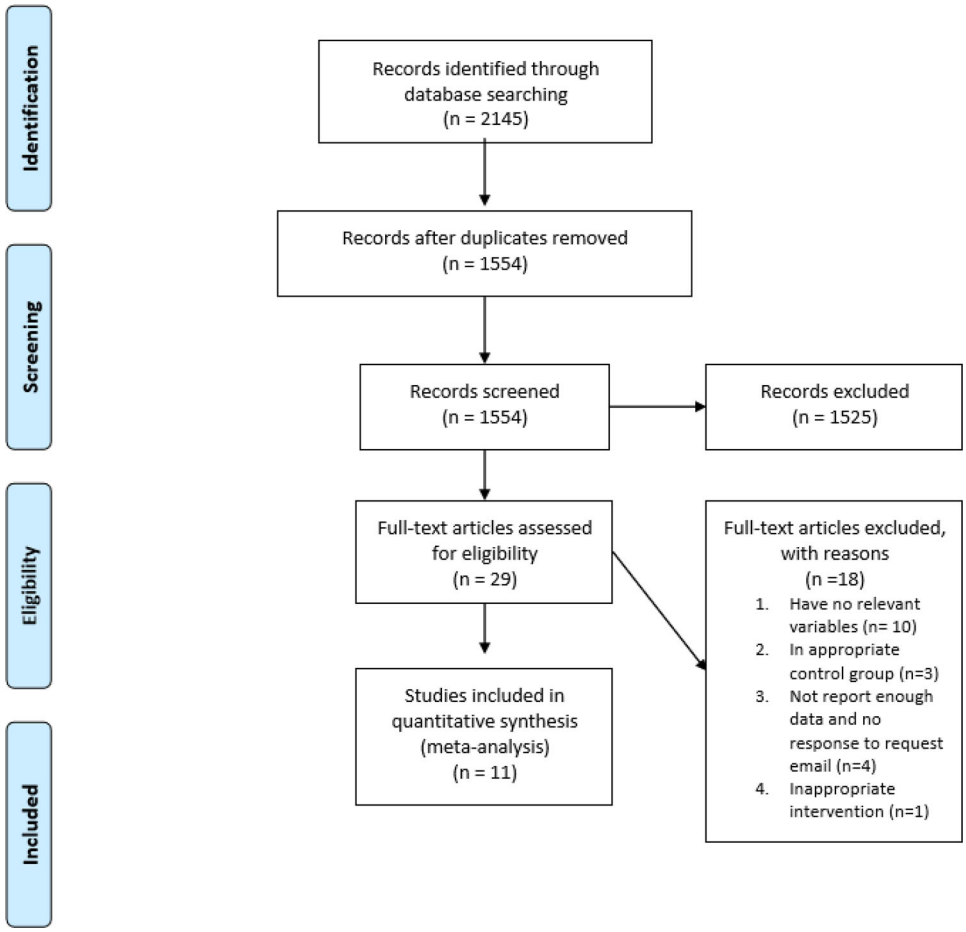

Figure 1. Flow chart of the process of the study selection.

Table 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Vlieger et al. (2009)	Rodriguez-Herrera et al. (2019)	Puccio et al. (2007)	Picaud et al. (2010)	Meli et al. (2014)	Kukkonen et al. (2008)	Gil-Campos et al. (2012)	Cooper et al. (2016)	Chouraqui et al. (2008)	Ahanchian et al. (2014)	Abrahamse-Berkeveld et al. (2016)	
+	+	+	−	+	+	+	+	+	+	+	Random sequence generation (selection bias)
+	+	+	−	+	+	+	+	+		+	Allocation concealment (selection bias)
+	+	+	−	+	+	+	+	+	+	+	Blinding of participants and personnel (performance bias)
+	+	+	−	+	+	+	+	+	+	+	Blinding of outcome assessment (detection bias)
	+	+		+	+	+	+	+	+	+	Incomplete outcome data (attrition bias)
+		+			+		+	+	+	+	Selective reporting (reporting bias)
											Other bias

micronutrient absorption (Scholz-Ahrens et al. 2007) and health benefit to the host. Furthermore, different gut microbiota may influence caloric intake, intestinal absorption, and energy balance (Jumpertz et al. 2011). Synbiotics (the combination of prebiotics and probiotics) have been considered in the management of malnutrition with promising results on mortality (Kerac et al. 2009). It has been realized that prebiotics in the synbiotics mixture improves the probiotic bacteria survival and stimulates the activity of the host's endogenous bacteria (Rautava, Salminen, and Isolauri 2008, Samarzija et al. 2009, Ouwehand and Vesterlund 2003).

In the present meta-analysis of clinical trial studies, we investigated the efficacy of infant formula containing synbiotics on supporting adequate growth in infants. Our meta-analysis involving 11 trials with 3034 infants demonstrated

Table 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

	Low of Risk of bias	High risk of bias	Unclear risk of bias
Other bias	0	0	100
Selective reporting (reporting bias)	47.394		52.606
Incomplete outcome data (attrition bias)	75.645		24.355
Blinding of Outcome data (Detection bias)	95.012	7	
Blinding of Participants and personnel (performance bias)	95.012	7	
Allocation Concealment (selection Bias)	87.926	7.074	7
Random Sequence generation (selection Bias)	98.409	7.591	
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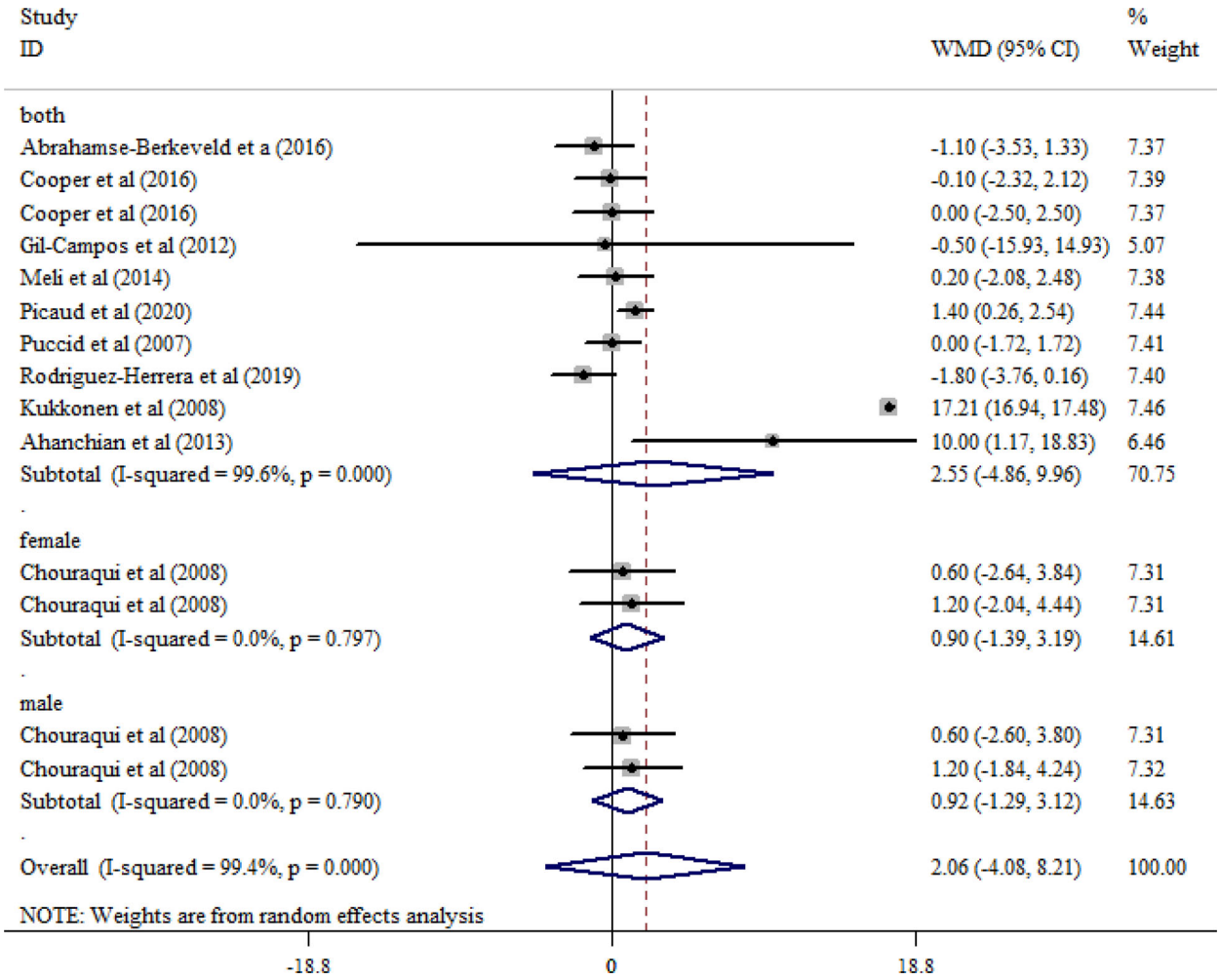

Figure 2. Overall and subgroup analysis by gender for the effect of formulas containing synbiotics on weight gain.

no significant association between supplementation of synbiotics containing formula and weight gain.

In line with our study, a systematic review conducted by Mugambi et al. investigated the growth effect of probiotics, prebiotics, and synbiotics separately with 25 trials, which revealed that consumption of synbiotics and probiotics have not any significant effect on growth parameters but surprisingly prebiotics formula significantly increased weight gain compared to control group (Mugambi et al. 2012). Also, no difference was seen in anthropometric measures between healthy term infants received probiotics and prebiotics formula and control group (Chouraqui et al. 2008). Like another study that did not confirm any significant effect of probiotics on weight, height, and head circumference of 126 infants aged 0–6 months (Vlieger et al. 2009).

On the other hand, in several studies, it is shown that probiotics have a positive effect on weight gain, while in the other studies, caused weight loss; Ahanchian et al. study showed that combinations of seven probiotics with fructo-oligosaccharides increase weight and other growth indices (Ahanchian et al. 2014); the same result was seen in the Saran et al. study that evaluated the effect of probiotics (Lactobacillus acidophilus) for failure to treat (FTT) children in India (Saran, Gopalan, and Krishna 2002).

Some evidences showed the mechanism beneath the growth regulation of probiotics; probiotics increase or

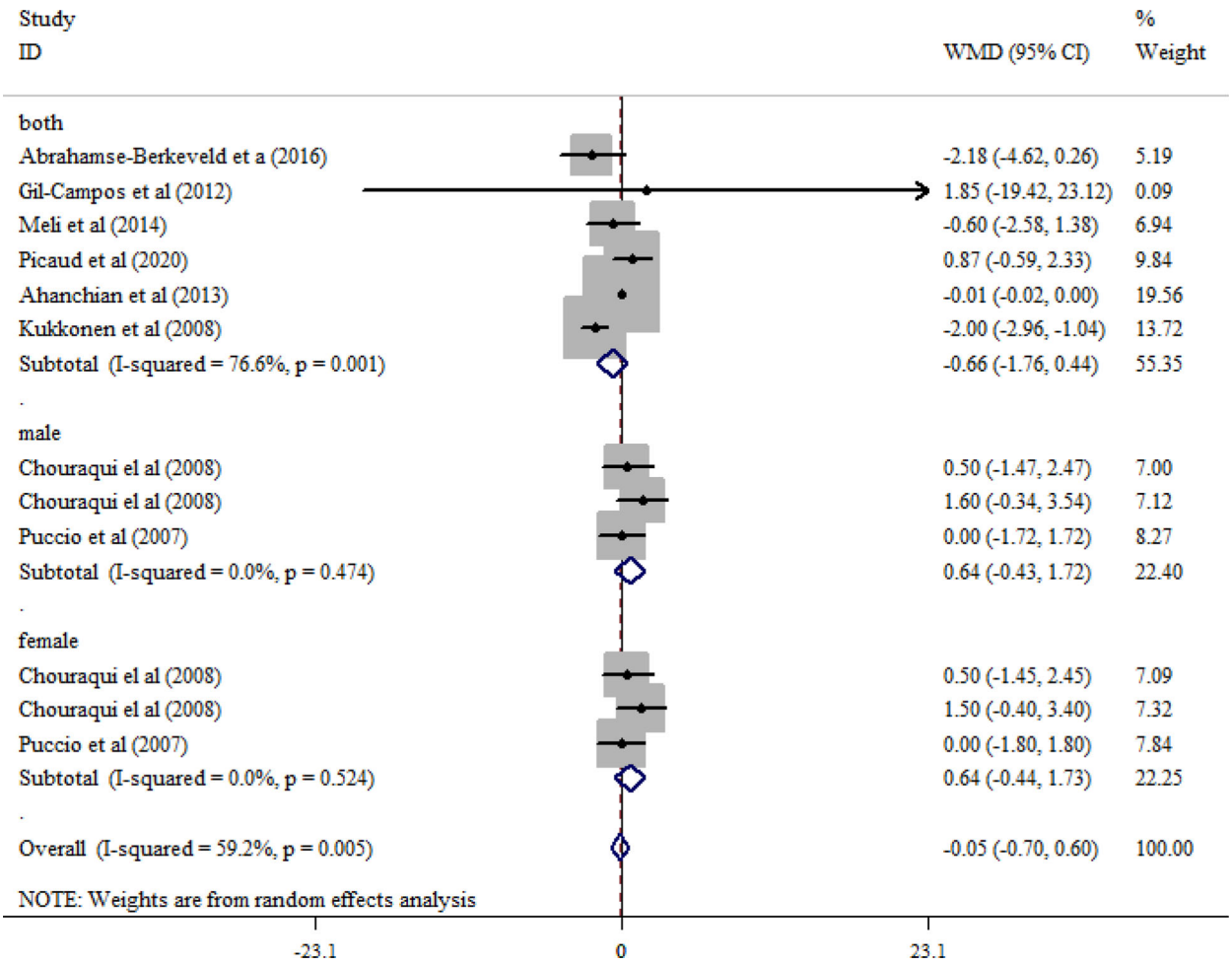

Figure 3. Overall and subgroup analysis by gender for the effect of formulas containing synbiotics on length gain.

decrease gene expression in human small bowel mucosa of more than 300 different genes including many involved in cell growth and apoptosis, such as MAP kinase, caspases-3, −6 and −8 (Banasaz et al. 2002). Moreover, increasing the proliferation of villus cell by probiotics leads to increase absorption of nutrient and promote growth (Di Caro et al. 2005). The other possible mechanism for better growth may by through ghrelin – a potent growth hormone stimulator from the stomach. (Dixit et al. 2004)

To our knowledge, therapeutic effects of synbiotics on weight gain greatly depend on the type of the probiotic species and strains, single-strain, or multi-strain. A comparative meta-analysis by Million et al. showed that different Lactobacillus species are associated with different effects on weight in humans and animals that are host-specific (Million et al. 2012); several documents reported a relationship between the diversity of the intestinal microbiota and weight gain in very low birth weight (VLBW) infants (Lyra et al. 2010; Surono et al. 2011; Jacquot et al. 2011). So we suppose that the insignificant results in the present meta-analysis may be due to heterogeneity in species of probiotics. A recent study by Million et al. showed that 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 (Million et al. 2012).

In the current study, secondary analyses of subgroups showed a significant increase in weight gain among unhealthy infants with allergy; although the result of the analysis was significant, it should be considered that only 2 studies with same positive result conducted in infants with allergy and it was expected that pooling of these 2 studies in current meta-analysis lead to a significant result. On the other hand, in the sub-analysis of other studies that included vulnerable infants, like infants born with HIV (Steenhout, Rochat, and Hager 2009), VLBW (Kitajima et al. 1997) and infants with infection and diarrhea (Yang et al. 2019) probiotics had the improving effect of growth. These data showed that more investigation in unhealthy infants with various results is needed. In our meta-analysis, there was no difference between study groups in head circumference and length. Since the change in head circumference and length needs more prolonged usage of synbiotics formula and some studies had a short duration, it may be the reason for not observing the difference between study groups. In Meta-regression analysis we found no significant association between follow-up duration and growth; because most of the studies had partially the same duration as each other; relatively similarity of follow up duration in most of these included studies may influence the result of Meta-regression analysis to be insignificant; although one study by Cooper

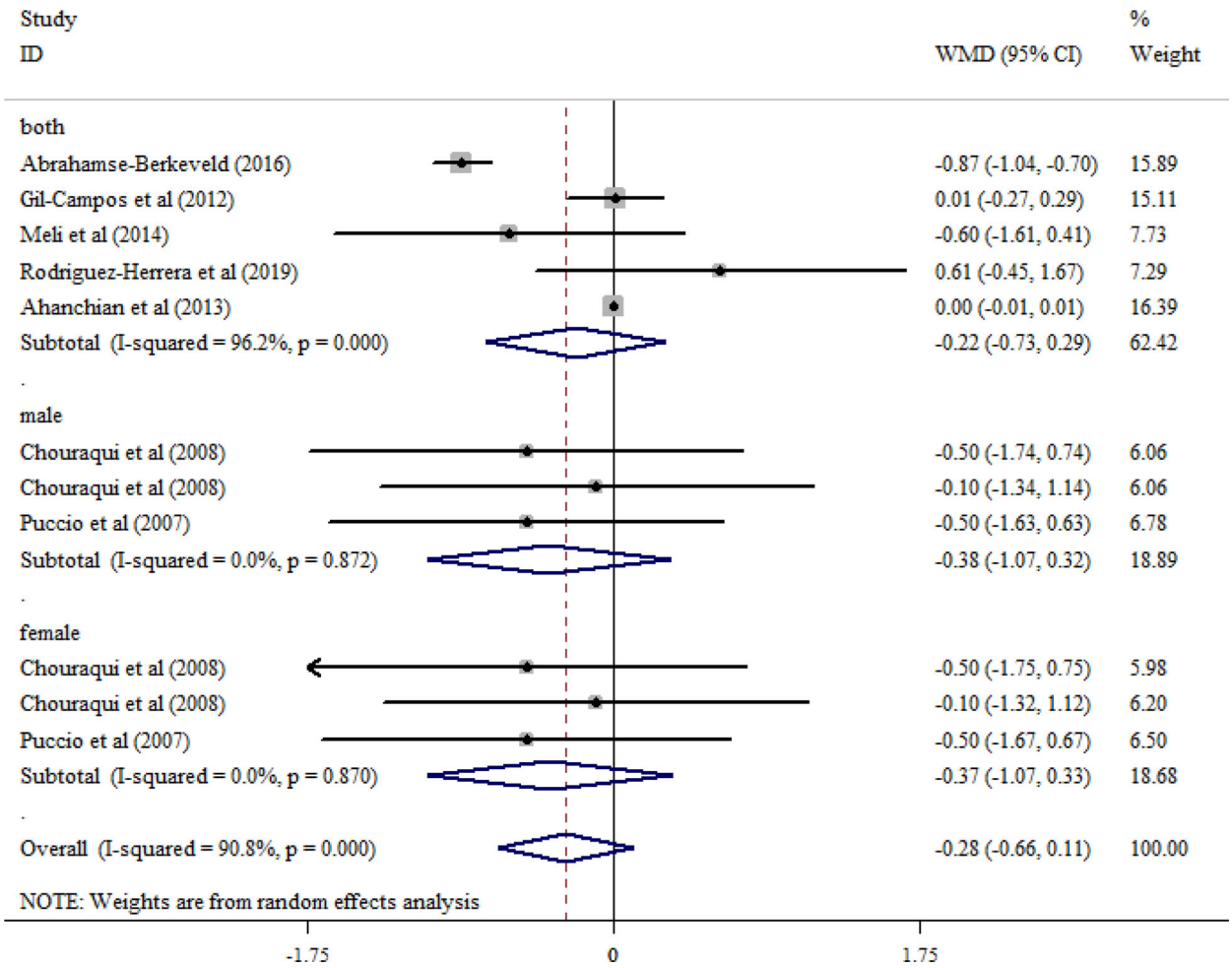

Figure 4. Overall and subgroup analysis by gender for the effect of formulas containing synbiotics on head circumference.

et al. had a longer follow up (52 weeks) (Cooper et al. 2016). The major strength of this study is subgroup analysis and assessment of unhealthy infants which let us clarify the need for conducting more studies about the effect of synbiotics on the growth status of unhealthy infants. Furthermore, we had a large sample size of 3034 which lead to acceptable statistical analysis. To assess the quality of evidence in this review, we used Cochrane Collaboration's risk of bias tool (Cumpston et al. 2019). The validity of the meta-analysis is also always limited by the quality of the included trials. However, the funnel plot asymmetry revealed that there was bias in studies investigation of the impact of formulas containing synbiotics on weight gain and no other outcomes, the trials included in this meta-analysis were, on the whole, of good quality.

Certain limitations should be considered when interpreting the results of this meta-analysis. Oligosaccharides dosage widely varied in included studies which can greatly imply heterogeneity in data and affect the result to be insignificant; with the same dose, each strain may contribute significantly to the different clinical outcomes of growth. Moreover the probiotics to prebiotics ratio is important which was not resembling in the included studies and can highly affect the response to the intervention. Moreover, a limited number of studies analyzed the effects of synbiotics formula supplementation on growth and more limited not separated by genders made interpreting the effects of synbiotics supplementation of infant formula on clinical outcomes more difficult. Majority of the studies had short treatment duration ranging from 28 days to 13 months and all the studies had small sample sizes. Therefore, we were unable to evaluate the long-term effect of supplementation in this analysis especially the synbiotics effects on length.

More well-designed long term follows up clinical trials that use the same treatment regimens (same probiotics strains, treatment duration, and dosage) are required. Moreover, clinical trials on unhealthy infants like infants with an allergy should be conducted to establish the efficacy of formula containing synbiotics in healthy and unhealthy infant's growth.

In conclusion, there is not enough evidence to state that the use of synbiotics, improve clinical outcomes of growth in infants. Therefore this review does not support the routine supplementation of infant formula with synbiotics for growth induction. More well-design long term clinical trials that use the same probiotics strains, dosage and same treatment duration are needed to state that synbiotics are superior to probiotics or prebiotics

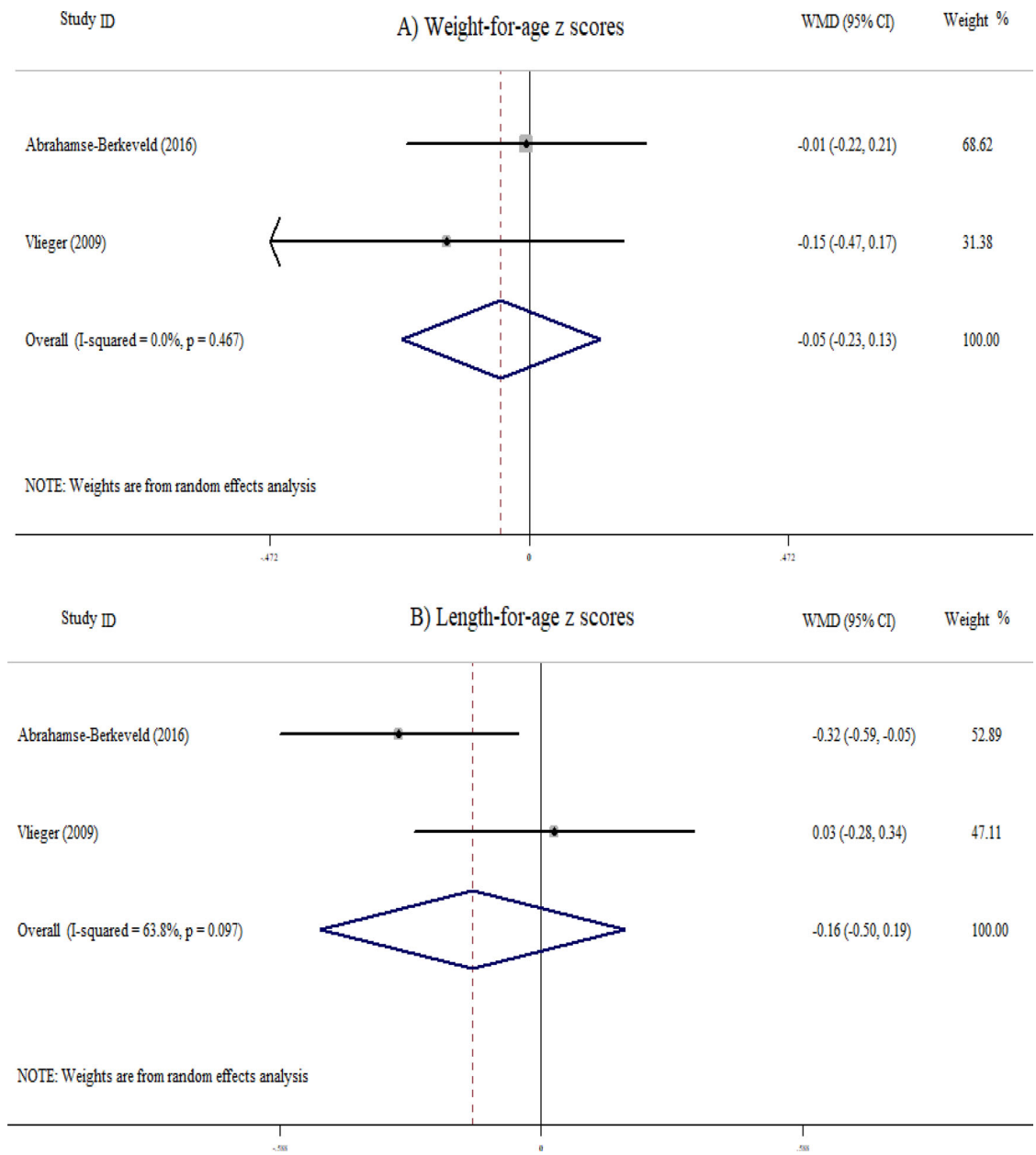

Figure 5. Overall and subgroup analysis by gender for the effect of formulas containing synbiotics on weight-for-age z scores (A) and length-for-age z scores (B).

Dislcosure statement

There is no conflict of interest.

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