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Efficacy of prebiotic, probiotic and synbiotic administration in improving growth in children aged 0–59 months living in low- and middle-income countries: a systematic review and meta-analysis

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Abstract

Background Poor growth is one of the major obstacles to human development, affecting millions of children under the age of 5 years, particularly those living in low- and middle-income countries (LMICs). The objective of this review was to evaluate the efficacy of administering pre-, pro- or synbiotics on the growth of children aged 0–59 months living in LMICs.

Methods Google scholar, Pubmed, clinical trial.org and Science Direct databases were searched in April 2023 for randomised controlled trials of pre-, pro- or synbiotics that evaluated growth in under fives in LMICs. The primary outcome were weight and height gain. Secondary outcomes were head circumference, body mass index gain and Z score. Random-effects meta-analysis was used to calculate mean differences for continuous outcomes. Grading of Recommendations Assessment, Development and Evaluation criteria was used to assess certainty of the evidence.

Results Eight trials involving 1375 children under 5 years of age were identified. Meta-analysis of 6 RCTs ($n=991$ children) revealed a significant difference in favor of the experimental group ($n=579$) compared the control group ($n=412$) for weight gain: (MD = 0.33 kg, 95% CI 0.11 to 0.55); low-certainty evidence. Sub-group analysis revealed that pre-, pro, or synbiotics may be more effective in malnourished that healthy children ($p=0.003$). Meta-analysis of height gain for 4 RCTs ($n=845$) found that there was no significant difference between the experimental group ($n=496$) and the control group ($n=349$) (MD = 0.31 cm; 95% CI -0.36 to 0.98); low-certainty evidence. In sub-group analysis, prebiotics had a greater impact on height gain than synbiotics ($p=0.03$). In the only study reporting an increase in head circumference ($n=32$ children), this was not improved by the administration of synbiotics. However, administration of synbiotics to undernourished children significantly improved BMI gain.

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Conclusion The evidence for the administration of pre-, pro- or synbiotics on the growth of children in LMICs is weak. Administration of pre-, pro- or synbiotics may improve weight gain in both healthy and malnourished children. Prebiotics and synbiotics had a significant effect on weight gain. Further research is needed due to the small number of studies, short duration of administration and small sample size.

Keywords Prebiotics, Probiotics, Synbiotics, Children, Growth, LMIC

Background

Child growth consists of an increase in size, weight, surface area and volume of various organs, tissues and regions of the body [1]. Growth serves as summary of indicators of health, nutrition and well-being, especially for infants and young children [2]. It enables the child's general state of health to be assessed and the adequacy of total energy intake to be determined [2]. Monitoring growth and the promotion of optimal nutrition are essential elements of the health care provided to all children [3]. The consequences of poor nutrition in the early years include weakened immunity, cognitive impairment and poor ponderal and linear growth [4] and these outcomes are common in many low- and middle-income countries (LMICs) [5].

In children living in LMICs exposed to poor hygiene and sanitation, invasion of the gut by pathogenic microbes, can lead to a subclinical enteropathy called "environmental enteric dysfunction" (EED) that contributes to undernutrition, and stunting [6]. EED can already be present at 6–12 weeks of age[7, 8]. Dietary supplementation with probiotics, prebiotics, or synbiotics used alongside breastfeeding may be a pragmatic and safe way to strengthen the resilience of the developing gut microbiota against adverse environmental factors [9]. Through improved gut health and better digestion and absorption of nutrients, these interventions can contribute to optimal physical and cognitive development. Several efforts in multiple fields have been made to improve growth, including the administration of pre-, pro- and synbiotics [10]. A prebiotic is a substrate used selectively by host microorganisms, typically bifidobacteria and lactobacilli in the gut, conferring a health benefit [11]. Probiotics are live microorganisms which, when administered in adequate amounts confer a health benefit on the host [12]. The Lactobacillus and *Bifidobacterium* species are most commonly used as probiotics, but some *E. coli* and Bacillus species and the yeast *Saccharomyces cerevisiae* are also used as probiotics [13]. Probiotics are consumed in the form of fermented food and dairy products, and can be added to infant and toddler formula [14]. A synbiotic is a mixture comprising live microorganisms and one or more prebiotics [15]. The beneficial effects of prebiotics and probiotics taken separately may be enhanced if they are combined [16].

The potential health benefits imparted by pre-, pro- or synbiotics have been the subject of extensive research in the past few decades. These 'functional foods' have been demonstrated to modify and reinstate after antibiotic exposure the pre-existing intestinal flora [17]. Prebiotics are important for the development of the intestinal microbiota and the metabolic and immunological systems of the young child, which may have health consequences later in life. Indeed, mixtures of certain prebiotics, such as short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides, when added to infant formula have been shown to increase bifidobacteria and lactobacilli in the infant's gut to levels observed in breastfed infants [11]. Studies have evaluated the effects of probiotics on a large number of gastrointestinal disorders, including inflammatory bowel disease and irritable bowel syndrome[18]. The feasibility, safety and acceptability of synbiotic administration in newborns at the community level, including those who are exclusively breastfed, were confirmed in a study of more than 4,500 newborns in rural areas of India, where a synbiotic reduced neonatal sepsis[18].

In a systematic review that assessed the use of probiotics during a key period of a child's growth, between birth and 59 months, Catania et al. showed that there was no evidence that probiotics had a clinically significant effect on growth outcomes in children from high-income countries. Data from LMICs showed that there may be a small beneficial effect on weight and height gain; however, the certainty of the evidence was assessed to be low and moderate, respectively, for these endpoints [19]. The review by Heuven et al. reported in 2021 [20] examined the effect of pre-, pro or synbiotic on the growth of children aged 6 to 59 months living in LMICs and also the effect of these interventions on the intestinal microbiota of children.

In addition Catania et al. excluded trials on prebiotics and those that included undernourished children as participants[19]. The literature search in the Heuven et al. review was limited to trials published in English and the review did not include head circumference as an outcome[20]. Our review addresses these research gaps and includes the results of recent trials to provide current evidence on the effects of pre-, pro- and synbiotic supplementation focusing exclusively on growth parameters

in children aged 0–59 months living in low- and middle-income countries. Children in this age group and in these countries are particularly vulnerable and are the most affected by stunting due to poor hygiene and sanitation conditions. Given the great interest in modifying the gut microbiota in early life to promote growth, our systematic review will identify the most effective interventions and provide healthcare professionals with evidence-based recommendations.

The objective of this review was to evaluate the effectiveness of pre-, pro- and synbiotics on the growth of children aged 0–59 months living in LMICs including recently-published studies.

Methods

We conducted a systematic review and reported our results according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Figure 1 shows the PRISMA flow diagram (PRISMA diagram). We developed a team consensus on the study questions and methods before the start of the study and

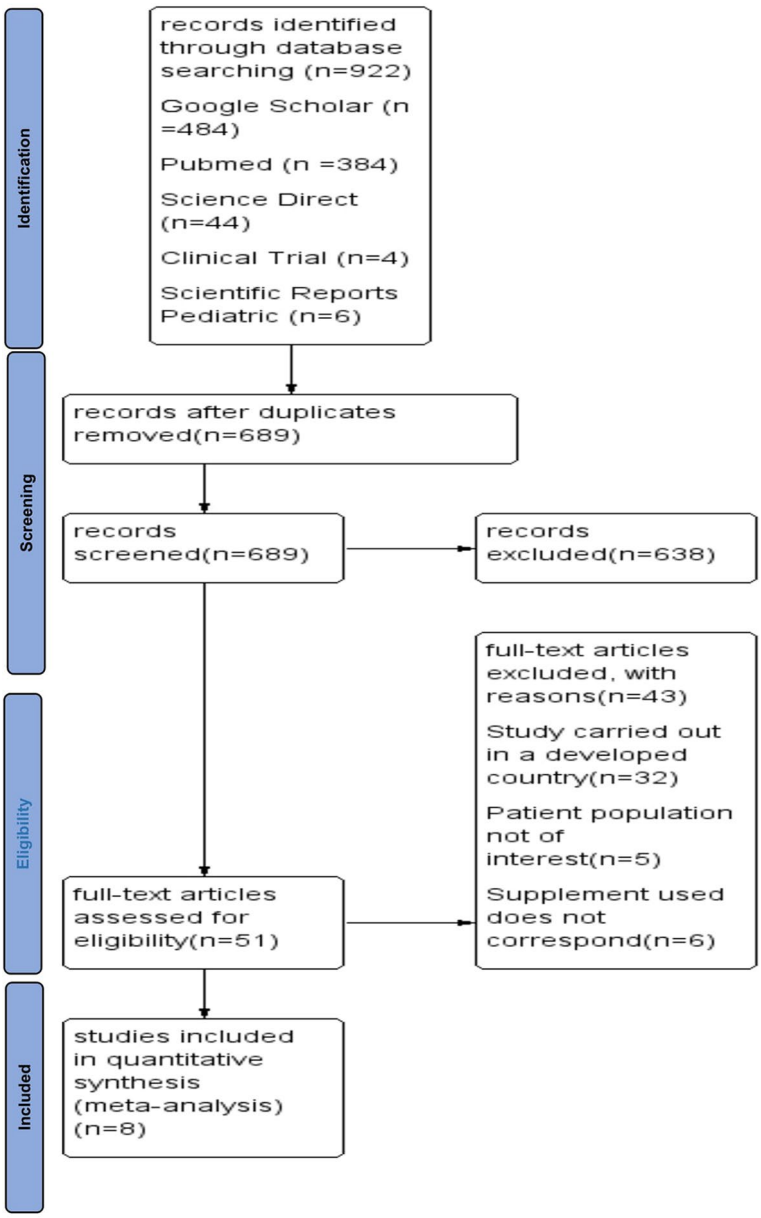

Fig. 1 PRISMA diagram

registered the protocol on PROSPERO http://www.crd.york.ac.uk/prospero/ (CRD42022343138).

Inclusion and exclusion criteria

We included single-blind and double-blind randomised controlled trials (RCTs) undertaken in children aged 0–59 months living in LMICs (based on the WHO classification) [21] who received either a pre-, pro- or a synbiotic. We included studies with a suitable comparison group, such as a standard care group, a placebo group or a no intervention group. We included studies of both malnourished and healthy children. Studies were included regardless of dose, dosage form or strain of pre-, pro- or synbiotic. We did not restrict publication dates and there were no language restrictions. We excluded studies on children born prematurely, suffering from necrotising enterocolitis or with congenital anomalies. We also excluded studies conducted in HICs [21].

Research strategy

We searched Google Scholar, Pubmed, clinical trial.org and ScienceDirect. The terms "prebiotics", "probiotics" and "synbiotics" were combined with the terms "child" and "growth" in order to identify relevant studies. The Boolean method used the following keywords: 1) "probiotic or synbiotic or prebiotic" AND "children or babies or infants" AND "growth" And "Randomized controlled trials", 2) "probiotic dietary supplements or synbiotic dietary supplements or prebiotic dietary supplements" AND "children or babies or infants" AND "growth" AND "Non-randomised clinical trials". The initial search strategy in PubMed was as follows: (((((probiotics) OR (prebiotic) OR (synbiotics) AND children) AND growth) AND randomized clinical trials); ((((probiotics) OR (prebiotic) OR (synbiotics) AND children) AND growth) AND clinical trials). This search strategy was modified to search other electronic databases. Table 1: Search strategy for each database (supplementary file).

We also searched for grey literature in the databases of the World Health Organisation (WHO), the United Nations Children's Fund (UNICEF), the World Food Programme (WFP), Action Against Hunger (ACF) the Emergency Nutrition Network (ENN), the Global Nutrition Cluster, and the United Nations Standing Committee on Nutrition and the United Nations Office for the Coordination of Humanitarian Affairs (OCHA). Finally, we examined the bibliographic references of the selected articles in order to identify other relevant articles that could be included in the review.

Data extraction and selection process

The articles identified were exported to a Zotero 6.0.36 and duplicates removed. Two reviewers (MK and MD) screened titles and abstracts using Rayyan software https://rayyan.ai/cite [22]. In the event of disagreement between the reviewers, the arbitration of a third reviewer (DS) has been requested. The first step in selecting the studies was to examine the title and abstract to check whether the article met the selection criteria. If the title was not accompanied with an abstract, the full text was examined and assessed. At the end of this process, all the qualified studies were moved on to the second stape, which consisted of examining the full text of the selected articles to check whether they meet the predefined selection criteria.

Full-text articles from potentially eligible studies meeting the selection criteria were obtained. Two reviewers (MK, MD) extracted data independently using a pretested data extraction form. We extracted data for study design, study setting (hospital or community, country) participant inclusion and exclusion criteria, participant characteristics for intervention and comparison groups (age, nutritional status) and intervention characteristics (type, strain, form, duration, frequency, dose). Mean ± SD differences between study arms for anthropometric outcomes were extracted. The assessors (MK, MD) checked the data and resolved any differences through discussion. One reviewer (MK) entered the data into Review Manager (RevMan 5) and the other (MD) validated the data. The reviewers were not blind to the authors, journals, country of publication, results and conclusions of the articles. We contacted some authors to request missing information but did not receive any responses.

Assessment of quality of evidence

Quality assessment of each included study was carried out independently by two researchers (MK and MD) using the revised Cochrane Risk of Bias 2 (RoB 2) tool for randomised studies, [23]. Each study was judged to be either low, of concern, or at high risk of bias. The certainty of the overall evidence of the effect of pre-, pro- or synbiotic on an outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method [24].

Outcome measures

The two primary outcomes were growth during the intervention period, measured by weight gain and length/height gain. Secondary outcomes were head circumference gain, body mass index gain (BMI) and Z score for weight, height attained at end of intervention.

Statistical analysis

The data were presented and analysed using RevMan Version 5.4 and STATA 15. Analysis was limited to available cases when data were missing. The potential impact

of missing data on the results is discussed. The mean difference (MD; with 95% confidence interval [CI]) between the treatment and control groups was selected because outcomes were reported as continuous variables. Heterogeneity was quantified by I^2 and interpreted as the percentage of total variation between studies attributable to heterogeneity rather than chance. A value of 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity [25].

The analyses were based on the random effects model since the studies were clinically heterogeneous in terms of different contexts (e.g. participant characteristics, countries), doses and strains of synbiotics and probiotics or types of prebiotics, durations of treatment and other factors. The source of statistical heterogeneity was explored to assess whether the intervention effects were significantly different for the following subgroups: intervention type (pre-, pro- or synbiotic), participant health status (healthy versus undernutrition) and duration of supplementation. These different interventions may have different effects on the gut. For example, prebiotics may have a specific role in blocking pathogen binding to mucous attachment sites[12]. However, all three interventions aim to change the gut microbiota and increase potentially beneficial bacteria. On this basis, and given the multiple potential mechanisms involved[26], we have combined the interventions for the purposes of this analysis. Heterogeneity among included studies was also investigated by a sensitivity analysis that accounted for the results of the risk of bias assessment. For studies that used two experimental groups and a control group, we combined the results of the experimental groups for comparison with the control group. If the standard error (SE) is reported we will use the generic inverse variance method in RevMan to calculate the treatment effect.

Results

Study selection

The literature search identified 922 articles. During title and abstract selection, 233 duplicate records were removed, resulting in 689 articles, of which 638 did not meet the inclusion criteria. Full-text screening of the remaining 51 studies resulted in the exclusion of 43 studies as 32 were conducted in high income countries (HICs), 5 did not have a study population of interest and 6 did not use an appropriate intervention (Table 1:Studies excluded after reading the full text; Supplementary file). This resulted in the inclusion of 8 studies [27–34] with a total of 1375 participants (741 in the experimental group and 634 in the control group). Figure 1 shows the (PRISMA diagram).

Risk of bias assessment

Using the Cochrane Risk of Bias 2 (RoB 2) tool [23], the majority of studies had a low risk of bias. The exceptions were Nuzhat et al. and Ahanchian et al. [29, 34] which was assessed to be at high risk for the generation of the randomisation sequence and blinding of participants and personnel for Nuzhat (Fig. 2: Risk of bias for the 8 RCTs (RoB 2) tool).

Characteristics of the included studies

The characteristics of the studies are described (as above). The studies were undertaken in various countries, 3 studies (37.5%) were carried out in Iran[29, 30, 32], 1 (12.5%) in Indonesia[28], and 1 (12.5%) in each of Pakistan[33], Bangladesh[34], India[27], and China[31] (Fig. 3: Geographical distribution of included articles: Supplementary file). Five (62.5%) studies were carried out on healthy children[27–31] and three (37.5%) on malnourished children[32–34]. Three studies (37.5%) evaluated a synbiotic [27, 29, 32], two (25%) prebiotics [30, 33], and one (12.5%) probiotics [28]. One (12.5%), probiotic and synbiotic [34] and one (12.5%) evaluated both prebiotics and synbiotic [31]. Six studies were double-blind RCTs [27–29, 31–33]; one was a triple-blind RCT [30] and one was a single-blind RCT [34].

Four studies (50%) used a single probiotic strain [27, 28, 31, 34], either *Lactobacillus, Bifidobacterium, Streptococcus* or *Enterococcus*. Two trials (25%) used a mixture of probiotics including 2 to 7 strains [29, 32]. Dosage varied for both *Bifidobacterium* and *Lactobacillus* from 10^9 colony forming units (CFU) to 10^6 CFU/day. Doses for *Enterococcus was* 2.31×10^8 CFU/day and for *Streptococcus* 10^6 CFU/day. Two studies (25%) evaluated only prebiotics: galacto-oligosaccharides, fructo-oligosaccharides, Lacto-N-neotetraose-LNnT and polydextroses [30, 33]. The duration of intervention varied markedly from 1 to 16 months.

Main outcome indicators

Growth parameters

Weight gain

The effect of pre-, pro and synbiotic administration on weight was reported in all 8 RCTs [27–34] ($n = 1375$ children).

The effect of pre-, pro- or synbiotic supplementation on weight gain was reported in six RCTs[27–29, 31, 32, 34] ($n = 991$). Weight gain was reported over periods varying from 1 to 16 months. Three RCTs [27–29] reported weight gain in kg and three RCTs [31, 32, 34] in g; we converted to kg to harmonize the results. Meta-analysis showed there was a significant difference for weight gain in favor of the experimental ($n = 579$) compared to the control group ($n = 412$): [MD = 0.33 kg, 95% CI (0.11

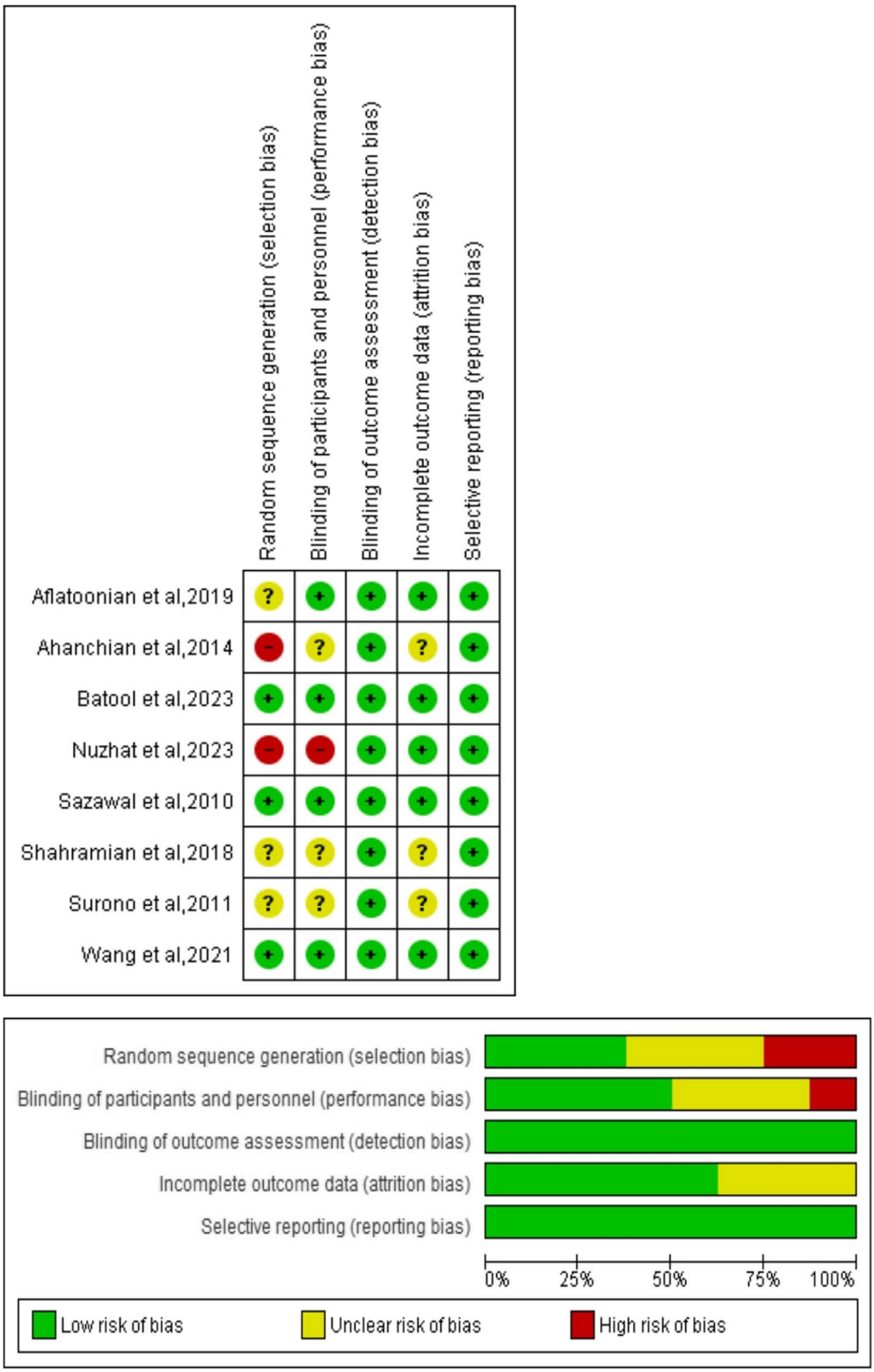

Fig. 2 Risk of bias for the 8 RCTs (RoB 2) tool [23]

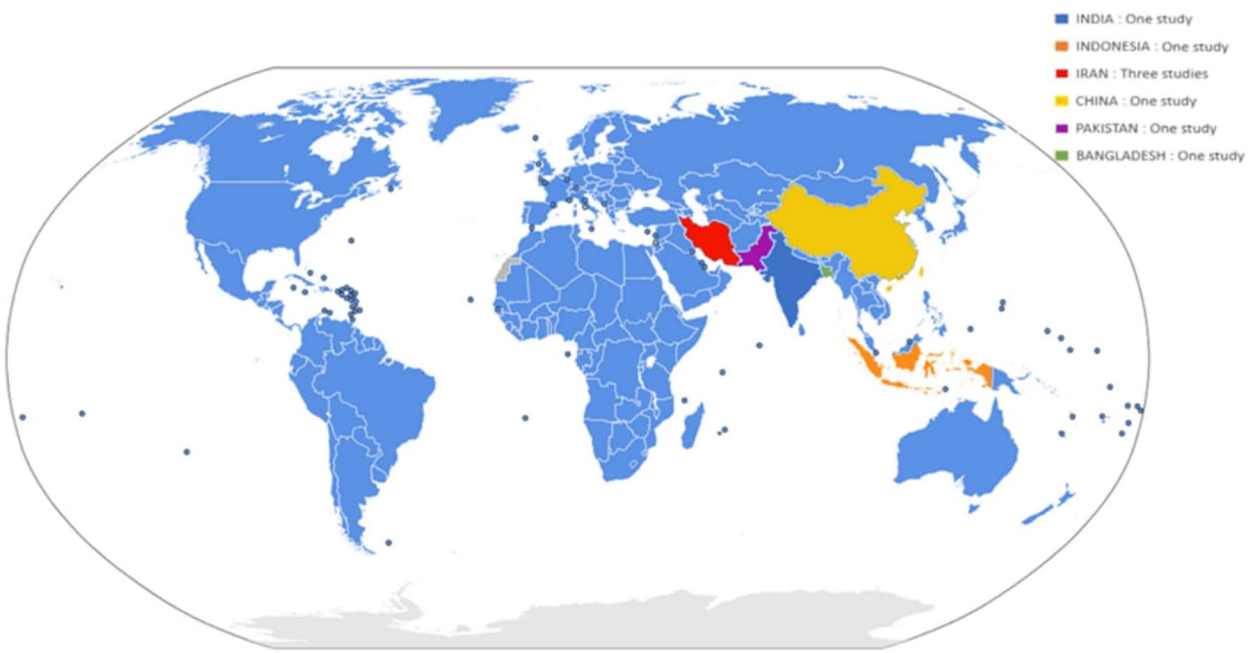

Fig. 3 Geographical distribution of included studies

to 0.55)]. Heterogeneity between trials was considerable ($P<0.01$, $I^2=98\%$) and may be due to differences in the population studied, duration of treatment or nutritional status (Fig. 4A). The certainty of the evidence was reduced to low due to clinical heterogeneity. An analysis of heterogeneity using subgroup analysis based on intervention type yielded the following results:

Weight gain by type of intervention

We grouped together the studies that used probiotics 2 RCTs [28, 34], prebiotics 1 RCTs [31] and synbiotics 3 RCTs [27, 29, 32] to carry out sub-group analysis.

Weight gain for probiotics administration

In the subgroup analysis for probiotic supplementation (2 RCTs, $n=123$), There was no significant difference between the experimental group ($n=60$) and the control group ($n=63$): (MD 0.93 kg, 95% CI −0.31 to 2.16; heterogeneity between trials was considerable ($P<0.01$, $I^2=95\%$).This heterogeneity was not explained by type of intervention (test for sub-group differences; $p=0.16$) (Fig. 4B).

Weight gain for prebiotics administration

In the subgroup analysis for prebiotic supplementation (1 RCTs, $n=153$), there was a significant difference for weight gain in favor of the experimental group ($n=97$) compared to the control ($n=56$): [MD = 0.08 kg, 95% CI (0.06 to 0.10)] (Fig. 4B).

Weight gain for synbiotic administration

In the subgroup analysis for synbiotic supplementation (2 RCTs, $n=794$), there was a significant difference for weight gain in favor of the experimental group ($n=422$) compared to the control ($n=372$): [MD = 0,23 kg, 95% CI 0.01 to 0.46]. The heterogeneity among trials was considerable ($P<0.01$, $I^2=98\%$). This heterogeneity was not explained by type of intervention (test for sub-group differences; $p=0.16$) (Fig. 4B).

Weight gain by nutritional status

Four RCTs [27–29, 31] investigated the effects of pre-, pro or synbiotic supplementation on the weight of healthy children, including 855 children. There was a significant difference for weight gain in favor of the experimental group ($n=498$) compared to the control ($n=357$): (MD 0.07 kg, 95% CI 0.04 to 0.11; heterogeneity between trials was not significant ($P=0.34$, $I^2=11\%$) (Fig. 4C).

Two RCTs [32, 34] investigated the effects of a prebiotic and a multi-strain probiotic on the weight of malnourished children, including 136 children. There was a significant difference for weight gain in favor of the experimental group ($n=81$) compared to the control ($n=55$): (MD 0.74 kg, 95% CI 0.30 to 1.18). The heterogeneity among trials was considerable ($P<0.01$, $I^2=91\%$). This heterogeneity could be explained by nutritional status (test of differences between subgroups; $p=0.003$) (Fig: 4C).

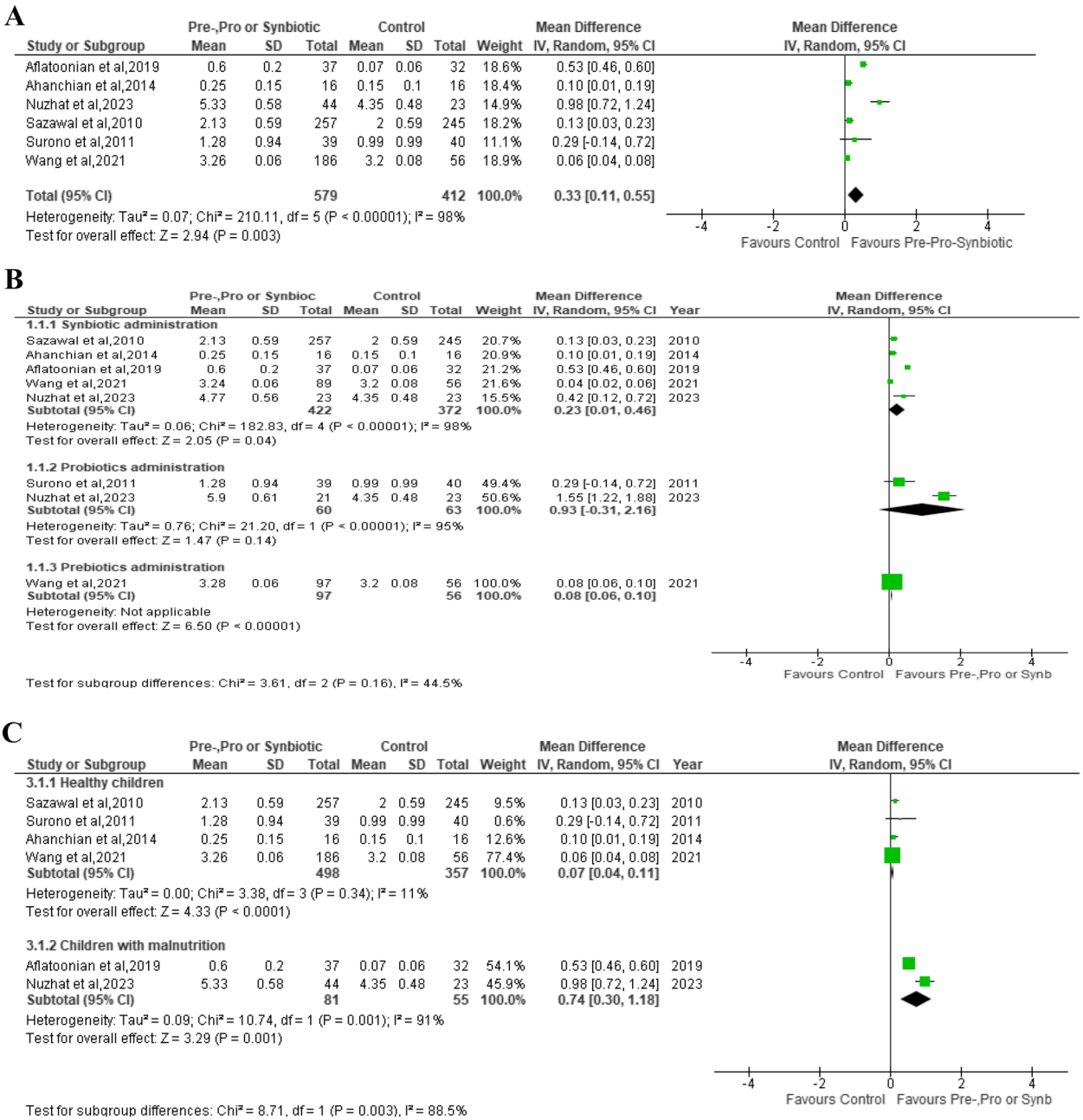

Fig. 4 **A** Effect of prebiotic, probiotic and synbiotic on the weight gain (kg) of children living LMICs. **B** Effect of prebiotic, probiotic and synbiotic on the weight gain (kg) of children by intervention. **C** Effect of prebiotic, probiotic and synbiotic on the weight gain (kg) of children by nutritional status

Weight gain by the duration of supplementation

Five RCTs[28, 29, 31, 32, 34] reported the effects of the administration of pre-, pro or synbiotic for a treatment duration between 1 and 4 months. Subgroup analysis showed significant difference in weight gain in favor of the experimental group ($n=322$) compared to the control ($n=167$): (MD 0.38 kg, 95% CI 0.11 to 0.65; heterogeneity between trials was considerable high ($P<0.01$, $I^2=98\%$). This heterogeneity could be explained by duration of supplementation (test of differences between subgroups; $p=0.01$) (Fig: 4D supplementary file). One RCT[27] reported the effects of the administration of pre-, pro or synbiotic for a treatment duration between 12 and 16 months. Subgroup analysis showed significant

difference in weight gain in favor of the experimental group ($n=257$) compared to the control ($n=245$): [MD 0.13 kg, 95% CI 0.03 to 0.23] (Fig: 4D supplementary file).

One RCT studied the effects of prebiotic administration in children with SAM [33]. They reported weight gain in terms of mean difference (MD) and 95% CI. They also reported the corresponding standard error (SE). The mean difference and standard error were used to calculate the treatment effect (using the generic inverse variance method in RevMan). Therefore, they showed that prebiotic supplementation increased weight: (MD 0.73 kg, 95% CI 0.63 to 0.83, $n=204$).

In addition, a RCT [30] conducted in Iran studied the effectiveness of prebiotics in healthy children. In this study there is an experimental group which is compared to a control group and a breastfed group. A calculated treatment effect showed that, prebiotic administration did not significantly increase weight gain compared to the control and breastfed-groups analysed separately: (MD 1.0 kg, 95% CI −0.16 to 2.16, $n=120$).

A sensitivity analysis excluding the two studies with a high risk of bias did not alter the magnitude, direction or statistical significance of the weight gain results (supplementary file Fig: 7).

Height gain

The effect of pre-,pro or synbiotic administration on height gain was studied in four RCTs [27, 29, 31, 32] ($n=845$). There was no significant difference in height gain between the experimental ($n=496$) and control groups ($n=349$) (MD = 0.31 cm; 95% CI −0.36 to 0.98). The heterogeneity among trials was considerable ($P<0.01$, $I^2=100\%$) and may be due to differences in the population studied, duration of treatment or nutritional status (Fig. 5A). The certainty of the evidence was reduced due to clinical heterogeneity. An analysis of heterogeneity using subgroup analysis based on intervention type yielded the following results:

Height gain by type of supplement

Four RCTs [27, 29, 31, 32] reported the effects of synbiotic administration on children's height. Subgroup analysis did not show a significant difference in height gain between the experimental group ($n=399$) and the control group ($n=349$), (MD = 0.31 cm; 95% CI −0.36 to 0.97). The heterogeneity among trials was considerable ($P<0.01$, $I^2=100\%$). This heterogeneity could be explained by type of intervention (test of differences between subgroups; $p=0.03$) (Fig: 5B). One RCTs [31] using prebiotics reported results on children's height. There was a significant difference for height gain in favor of the experimental group ($n=97$) compared to the control ($n=56$): (MD = 1.01 cm; 95% CI 0.94 to 1.08) (Fig. 5B).

Height gain by nutritional status

Three RCTs [27, 29, 31] reported the effects of administration with pre-, pro or synbiotics on the height of healthy children. Subgroup analysis did not show a significant difference in height gain between the experimental group ($n=459$) and the control group ($n=317$), (MD = 0.39 cm; 95% CI −0.38 to 1.17). The heterogeneity between trials was considerable ($P<0.01$, $I^2=100\%$). This heterogeneity was not explained by type nutritional status (test for sub-group differences; $p=0.43$) (Fig: 5C). One RCT [32] reported the effects of supplementation synbiotics on the heigth of malnourished children. Subgroup analysis did not show a significant difference in height between the experimental group ($n=37$) and the placebo group ($n=32$), (MD = 0.04 cm; 95% CI −0.36 to 0.44) (Fig: 5C).

Height gain by duration of supplementation

Three RCTs [29, 31, 32] reported the effects of the administration of pre-, pro or synbiotic for a treatment duration between 1 and 4 months. Subgroup analysis showed significant difference in height gain in favor of the experimental group ($n=239$) compared to the control ($n=104$): (MD 0.14 cm, 95% CI 0.11 to 0.17; heterogeneity between trials was considerable high ($P<0.01$, I2 = 100%). This heterogeneity was not explained by duration of supplementation (test of differences between subgroups; $p=0.57$) (Fig: 5D supplementary file). One RCT [27] reported the effects of the administration of pre-, pro or synbiotic for a treatment duration between 12 and 16 months. Subgroup analysis did not show a significant difference in height gain in favor of the experimental group ($n=257$) compared to the control ($n=245$): [MD 0.21 cm, 95% CI −0.03 to 0.45] (Fig: 5D supplementary file).

A sensitivity analysis excluding the two studies with a high risk of bias did not alter the magnitude, direction or statistical significance of the height gain results (supplementary file Fig: 8).

Secondary outcome indicators

Head circumference gain

The effect of pre-,pro or synbiotic administration on height gain was studied in Two RCTs [29, 31] ($n=274$). There was no significant difference in head circumference gain between the experimental ($n=202$) and control groups ($n=72$): (MD 0.00, 95% CI: −0.00 to 0.01); heterogeneity between trials was not significant ($P=0.27$, I2 = 16%) (Fig. 6:).

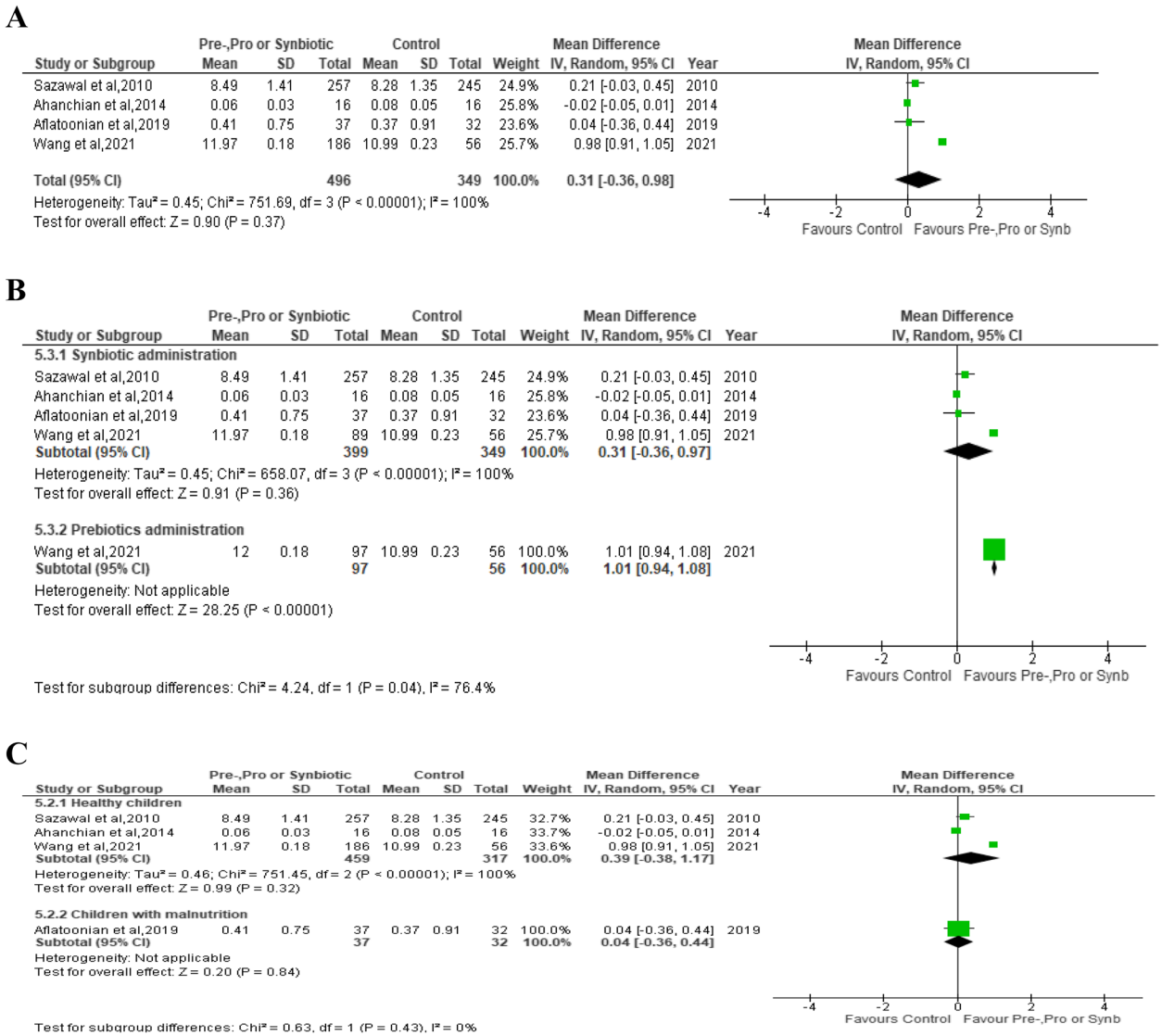

Fig. 5 **A** Effect of prebiotic, probiotic and synbiotic on the height gain (cm) of children living in LMICs. **B** Effect of prebiotic, probiotic and synbiotic on the height gain (cm) of children by intervention. **C** Effect of prebiotic, probiotic and synbiotic on the height gain (cm) of children by nutritional status

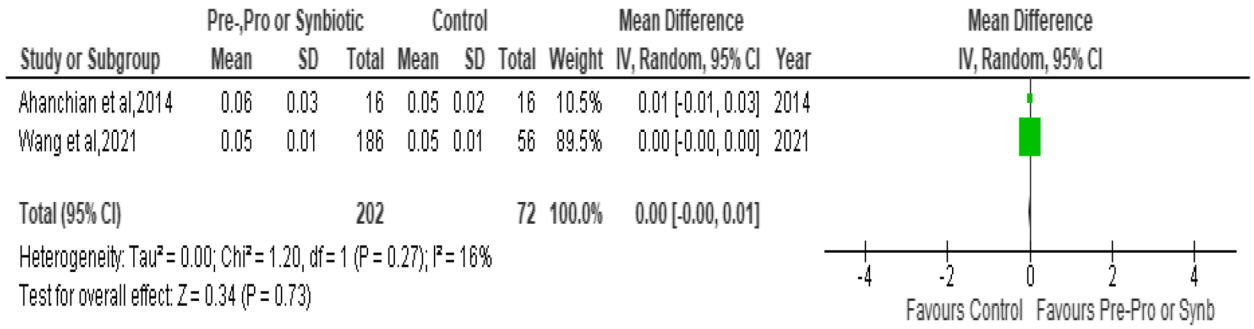

Fig. 6 Effect of prebiotic, probiotic and synbiotic administration on the head circumference gain (cm) of children

Attained body mass index (BMI) gain

One RCT[32] of synbiotic supplementation in children with mild to moderate malnutrition reported a gain in body mass index. A calculated treatment effect showed that synbiotics successfully increased body mass index gain compared to controls (MD 0.37 kg/m^2, 95% CI: 0.16 to 0.58, $n=69$).

We were unable to do the funnel plot or the egger test for the results presented. With only 6 articles included in the meta-analysis, it is difficult to draw meaningful conclusions about asymmetry. It is therefore likely that any asymmetry is not clearly visible and gives a false impression of absence of bias[35].

Other presentations of growth results

Only 3 RCTs [27, 31, 34] provided interpretable information on Z scores with different estimates that precluded combining in a forest plot. Nuzhat et al. [34] showed in a linear mixed effects model, the mean weight-for-age z-score was 0.57 ($P=0.018$) higher in the probiotic group than in the control group at the end of the intervention. The change in length-for-age z-score (LAZ), although not statistically significant, tended to be higher in children in the probiotic ($\beta=0.25$) and synbiotic ($\beta=0.26$) groups than in children in the control group in a multivariable linear analysis. Sazawal et al. [27] showed that there was no significant difference in change between pre-, probiotic group and control group for weight-for-age ($P=0.12$), length-for-age ($P=0.55$), and weight-for-height z-score ($P=0.09$). Wang et al. [31] reported that mean z-scores for weight- for-age, height-for-age, head circumference-for-age and BMI-for-age in both pre-, synbiotic and control groups were all within or very close to the mean WHO growth standards of ± 0.5 for age.

Discussion

This systematic review identified eight trials that randomised 1375 children. Studies varied in terms of enrollment criteria, sample size, interventions, and treatment duration. The evidence reviewed revealed that, overall, administration of prebiotics, probiotics or synbiotics have a significant effect on growth in children aged 0–5 years living in LMICs. However, in subgroup analysis, there was a significant effect on the weight of healthy and malnourished children (Fig. 4C), and a significant effect on weight for pre-or synbiotic supplementation (Fig. 4B). However, we were unable to perform a meta-analysis for the total 8 RCTs. Indeed, differences in the reporting of results between studies hampered the inclusion of data in the meta-analysis. Future studies should report results consistently, for example, weight gain could be reported as mean (SD) kg/month to facilitate meta-analysis.

Our systematic review, which synthesizes the effect of the administration of prebiotics, probiotics and synbiotics on the growth of children, was initially focussed on children living in Africa, but the literature search did not allow us to identify sufficient studies for a meta-analysis. Therefore, also we extended the scope to include all LMICs, more studies should be carried out in Africa as the effects of modulating the gut microbiome may differ between geographies.

We used the GRADE approach to assess the overall certainty of the evidence for the effect of prebiotics, probiotics and synbiotics on the selected primary and secondary outcomes (Table 4 supplementary file). The GRADE method generates evidence scores for each outcome and takes into account factors such as study type, risk of bias, inconsistency of results, indirectness of evidence, imprecision of summary estimate and publication bias [18]. All of the included studies were randomized controlled trials. Overall, the majority of studies did not have.

a high risk of bias, so we did not adjust the overall assessment of the certainty of the evidence for risk of bias. However, we adjusted the level of certainty due to clinical heterogeneity resulting from the evaluation of many different prebiotics, probiotics and synbiotics for all outcomes assessed. The number of studies that contributed data varied among the outcomes. We downgraded the evidence for imprecision where the number of included studies was small and the confidence interval for the estimates of effect included a null effect.

Previous reviews have shown that pre-, pro- or synbiotic administration may have a small effect on growth in children living in low- and middle-income countries. Catania et al. reviewed 25 studies (8417 healthy children aged 0–59 months) in LMICs and reported that probiotics may have a small effect on weight (SMD: 0.26, 95% CI: 0.11–0.42, degree of certainty = low) and height (SMD 0.16, 95% CI: 0.06–0.25, degree of certainty = moderate) [19]. Similarly, Onubi et al. provided a narrative review with one study of healthy children and four studies of malnourished children aged 0–59 months in LMICs[36]. The study on healthy children reported a beneficial effect of probiotics with a significant difference in weight gain (0.93 g/day; $p=0.025$) and weight-for-age (0,09 g/day; $p=0.036$) between the intervention group and the control group[36]. The four studies on undernourished children found an improvement in weight in the probiotic group compared with the control group[36]. However, mean differences were not reported in any of the studies[36]. Heuven et al. (20 studied) observed a beneficial effect of the administration of probiotics on the growth of children aged 6 to 59 months living in LMICs (11

studies including 5776 children), and synbiotics (4 studies including 1098 children), especially in malnourished children, prebiotics (6 studies including 1207 children) had no effect[20]. However, no summary standardised mean difference is calculated in this review due to the heterogeneity and small number of studies[20]. Mugambi did not distinguish between LMICs and HICs and showed that the administration of synbiotics (3 studies including 475 children) and probiotics (10 studies including 933 children) had no significant effect on the growth of children[14]. On the other hand, the addition of prebiotics (12 studies including 1563 children) to infant formula had a significant effect on weight gain, but had no significant effect on length and head circumference[14]. Reviews by Catania et al. and Onubi et al. also studied the effects of probiotic supplementation on growth in children living in HICs[19, 36]. For Catania et al. (51 studies; 10,832 children) there was evidence of moderate certainty that probiotics had no clinically significant effect on weight compared with the control group (SMD: 0.01, 95% CI: −0.04–0.05, $p=0.78$, I 2=7%)[19]. Onubi et al., in their narrative (7 studies; 1159 children) summary also found no significant effect on growth[36]. The results observed between HICs and LMICs, may differ because of differences in the intestinal microbiome due to marked differences in diet and exposure to poor sanitation and hygiene conditions between the two contexts.

The findings of these previous reviews of studies undertaken in LMICs are consistent with our results. Indeed, we found that the administration of pre-, pro- and synbiotics improved weight gain in both healthy and malnourished children. In sub-group analysis, probiotics had no effect on growth parameters, prebiotics and synbiotics had a significant effect on weight gain. We also observed that for studies with short treatment durations (1 to 4 months), the administration of pre-, pro- or synbiotics had a significant effect on weight and height gain. Only one study administered the pre-, pro- or synbiotic for more than 4 months, so the effects of longer-term administration could not be reliably assessed. These significant results can be explained by the fact that, pre-, pro- and synbiotics can improve growth through improved gut health via multiple mechanisms[26]. These include improving colonisation against intestinal pathogens and innate and adaptive immunity. In addition, improving mucus production and strengthening mucosal tight junctions can reduce intestinal permeability and therefore reduce systemic inflammation that inhibits the growth hormone axis[26].

This systematic review has limitations because the majority of studies had short treatment durations with five (62.5%) studies administering the interventions for less than 3 months. In addition, sample sizes were relatively small for some studies, which raises questions about their statistical power to observe differences between intervention groups.

Given that the studies included were often heterogeneous, small with insufficient power to identify the relevant effects on growth, and that the follow-up periods of the trials were short, the results of this review must be interpreted with caution. Much research remains to be done to assess the effectiveness of prebiotic, probiotic and synbiotic administration on the growth of children living in LMICs. Well-designed RCTs with long-term follow-up and larger sample sizes are needed in order to assess reliably the effect of prebiotics, probiotics or synbiotic administration on growth.

Table 3: Rating the quality of evidence;(supplementary file) *Explanations: a: Downgraded one level for considerable heterogeneity; b: Downgraded one level due to missing data.

Conclusion

Although our analysis indicates that administration of pre-, pro- or synbiotics may improve weight gain, in both healthy and malnourished children. The evidence base is weak and these results should be intrepreted with caution. Further and larger clinical trials are needed to confirm these findings.

Abbreviations

B lactis	Bifidobacterium lactis Bb12
BMI	Body mass index
CI	Confidence interval
MD	Mean difference
RCT	Randomized controlled trial
CFU	Colony Forming Unit
LMICs	Low- and middle-income countries

Supplementary Information

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Supplementary Material 1

Authors' contributions

MK and MD: funding acquisition, drafted and revised the manuscript. MK, MD, and SA: data analysis.MK, MD, DS, SA: data interpretation. DS, SA, and BF: Supervision and revised the manuscript. AD and NSD: Revised the manuscript. All authors read and approved the final manuscript.

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Data Availability

Data are provided in the manuscript or in the supplementary information files.

Declarations

Ethics approval and consent to participate
Ethical clearance was not required as this is a systematic review of literature, and anonymized data was used.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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