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Probiotic and synbiotic adjuncts for pediatric overweight and obesity A systematic review of international randomized trials

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 November 2026 and was last updated on 20 November 2026.

INTRODUCTION

Review question / Objective Review question (PICOS)
Population (P): Children and adolescents aged 5-18 years with overweight or obesity, including severe obesity, obesity-related insulin resistance, exogenous obesity, and obesity-related NAFLD/NASH.
Intervention (I): Orally administered probiotic or synbiotic preparations, given alone or as an adjunct to usual care, dietary advice, or lifestyle modification.
Comparator (C): Placebo, standard care, matched control supplement, or lifestyle-only control without live probiotic organisms.
Outcomes (O): Co-primary anthropometric outcomes were BMI z-score and BMI, analysed separately as standardized mean differences; reported adverse events were assessed narratively as a safety outcome.
Study design (S): Randomized controlled trials (parallel, double-blind, single-blind, or placebo-controlled), irrespective of country or setting, identified from PubMed/MEDLINE, Embase, Web of Science, Cochrane CENTRAL, ClinicalTrials.gov, and WHO ICTRP from inception to October 2026.

Objective: To determine, in children and adolescents with overweight or obesity, whether probiotic or synbiotic supplementation, relative to placebo or usual care, is associated with changes in BMI z-score or BMI and with reported harms, and to characterize the inconsistency and influence of trial-level estimates across heterogeneous products.

Condition being studied Overweight and obesity in childhood and adolescence.

The condition studied in this review is overweight and obesity in children and adolescents aged 5-18 years, defined by excess adiposity and classified anthropometrically using age- and sex-specific body mass index (BMI) references, most commonly expressed as BMI z-score or BMI

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percentile. BMI z-score is the standard paediatric metric because absolute BMI thresholds change with growth and puberty; BMI in kg/m2 was retained as a second, more clinically interpretable outcome.

Childhood and adolescent obesity is now a defining paediatric health challenge. Global estimates show that excess adiposity among school-aged children and adolescents has risen sharply over recent decades, and clinical practice guidelines increasingly treat obesity as a chronic, relapsing disease requiring staged, family-centred and sustained intervention rather than brief lifestyle counselling. The condition is not merely cosmetic or behavioural: it tracks into adulthood and is associated with insulin resistance, type 2 diabetes, dyslipidaemia, hypertension, obstructive sleep apnoea, nonalcoholic fatty liver disease, reduced quality of life and stigma.

The trials included in this review enrolled a clinically heterogeneous spectrum within this condition: general overweight or obesity, severe obesity, obesity-related insulin resistance, exogenous obesity, and obesity associated with NAFLD/NASH. Baseline metabolic status, pubertal stage, diet quality, physical activity, sleep, medication exposure and gut microbiome composition differ across these subgroups, and these differences were treated as a source of clinical heterogeneity rather than as separate conditions.

The condition is biologically plausible to modify through the gut microbiota, which in children with obesity may show altered microbial diversity, bile-acid transformation, gut-barrier function, endotoxin exposure, short-chain fatty acid production and inflammatory signalling. Because these pathways interact with diet, host genetics, activity, sleep, medication and the pubertal endocrine environment, the microbiota is best regarded as one component of a broader obesity pathway rather than a single independent cause. This is why probiotic and synbiotic supplementation was evaluated as a possible adjunct to usual care, not as a stand-alone treatment for the condition.

METHODS

Participant or population Participants were children and adolescents aged 5 to 18 years with overweight or obesity. Overweight and obesity were accepted as defined by the primary trial, provided the diagnosis rested on an anthropometric measure of excess adiposity in a paediatric population; no single BMI cut-off was imposed, because trials applied different paediatric reference systems (WHO, CDC, IOTF or national growth charts) and reported either BMI z-score, BMI percentile or absolute BMI. Eligible clinical presentations included general overweight or obesity, severe obesity, obesity-related insulin resistance, exogenous obesity, and obesity associated with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Trials enrolling both overweight and obese participants were eligible, as were trials confined to a single obesity subtype, provided the subtype fell within this spectrum.

No restriction was placed on sex, ethnicity, socioeconomic background, country, or clinical setting. Participants could be recruited from paediatric or family practice clinics, hospital or tertiary obesity services, schools, or community settings, and could be otherwise healthy or have obesity-related metabolic comorbidity. Trials that delivered the intervention alongside co-interventions such as dietary counselling, physical activity prescription or structured family-based lifestyle programmes were eligible, because such care represents usual practice for this population.

Participants were excluded when they were outside the 5 to 18 year age range at enrolment, when the population was defined by a condition other than excess adiposity (for example, a normal-weight population studied for metabolic markers, or a population defined solely by a gastrointestinal or allergic disorder), and when the trial addressed infant obesity prevention or maternal obesity during pregnancy, since these populations involve different physiology, different intervention timing and different outcome metrics. Trials in which only a subgroup met the population criterion were eligible only when outcome data for that subgroup could be extracted separately. Participants with obesity-related comorbidity such as insulin resistance or fatty liver disease were retained rather than excluded, and these subgroups were documented so that their contribution to clinical heterogeneity could be described.

Across the 15 included trials, randomised samples ranged from 15 to 172 participants, and analysed denominators were smaller in several trials after attrition. Both sexes were represented, participants spanned school-age children through adolescence, and recruitment was international rather than confined to a single health system.

Intervention The intervention of interest was oral supplementation with a probiotic or a synbiotic

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preparation, evaluated as an adjunct to usual care or as a placebo-controlled experimental treatment.

Probiotics were defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, and synbiotics as products combining live microorganisms with selectively utilised substrates intended to support those organisms or other beneficial members of the host microbiota. Eligible products therefore ranged from single-strain probiotics to multispecies probiotic mixtures, including commercially formulated multi-strain products, and to synbiotic combinations in which a probiotic organism was paired with a prebiotic substrate such as inulin, fructo-oligosaccharides or galacto-oligosaccharides. Preparation format was not restricted to a particular delivery vehicle; capsules, sachets, powders, fermented milk or yogurt-type products and other orally administered formats were all eligible, provided the product contained live probiotic organisms and the dose was reported or obtainable.

Co-interventions were permitted and were expected. Trials in which supplementation was added to dietary counselling, physical activity prescription, structured family-based lifestyle programmes, or standard paediatric obesity care were eligible, and in these trials the comparator had to receive the same background care without live probiotic organisms. This design mirrors how such products would plausibly be used in practice, where supplementation would accompany rather than replace lifestyle management.

No minimum dose, strain count or treatment duration was imposed as an eligibility criterion, because the evidence base is heterogeneous and an a priori dose threshold would have excluded informative trials. In practice, the included trials tested treatment durations of 4 to 24 weeks and a wide range of daily doses and strain combinations. Duration and product type were recorded for every trial and were examined in exploratory subgroup analyses, with pooled subgroup estimates restricted to strata containing at least three trials.

Interventions that were ineligible included prebiotic-only preparations and other non-living substrates, synbiotic products in which the viable organism component could not be confirmed, non-oral routes of administration such as topical or vaginal application, and multi-component supplement products in which the probiotic or synbiotic component could not be isolated from co-administered ingredients such as micronutrients or herbal extracts. Trials in which the intervention was compared only against another active supplement, with no eligible live-organism-free control arm, were also excluded.

Comparator Eligible comparators were placebo, standard or usual care, a matched control supplement without live probiotic organisms, or a lifestyle-only control, including no-supplement controls that continued routine paediatric obesity management.

Placebo could take the form of an identical-looking and identically administered inactive preparation, for example a capsule or sachet containing the same excipients and vehicle without viable microorganisms, or a comparable inert product matched for appearance, taste and dosing schedule. Standard or usual care comprised the care ordinarily provided in the trial setting, such as routine dietary and physical activity advice, growth monitoring and scheduled clinical review, without any live probiotic or synbiotic component. A lifestyle-only control consisted of structured dietary, activity or behavioural programmes delivered without supplementation. A matched control supplement was acceptable when it contained the prebiotic substrate or vehicle alone, or an otherwise comparable non-viable preparation, so that the live-organism component was the only systematic difference between arms.

For trials that combined supplementation with a background co-intervention, the comparator arm had to receive the same co-intervention at the same intensity and for the same duration, with the live probiotic or synbiotic component being the sole intended difference. This requirement was applied because a comparator that received lighter lifestyle support would confound any anthropometric difference with the effect of the background programme itself.

Comparators were required to be concurrent rather than historical, and the review was restricted to randomised comparisons, so each included trial had to contain at least one eligible control arm randomised alongside the supplementation arm. Comparator duration had to match the intervention duration, and outcome data had to be available at a comparable time point in both arms.

Ineligible comparators included no comparator at all, as in single-arm or uncontrolled studies; an active pharmacological comparator such as metformin, orlistat or a glucagon-like peptide-1 receptor agonist offered without an eligible control arm, because such comparisons answer a different question about relative efficacy against

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pharmacotherapy; and head-to-head comparisons between two probiotic or two synbiotic products without any live-organism-free arm, since these cannot estimate the effect of supplementation itself and are better addressed by network meta-analysis. Comparisons in which the control arm received a different background lifestyle programme, or in which the only difference between arms was dose or duration of the same product, were also not eligible for the primary pooled estimates.

Study designs to be included Randomised controlled trials (RCTs), including parallel-group, double-blind, single-blind, open-label and placebo-controlled designs. Each trial had to include at least one concurrently randomised control arm (placebo, usual care, matched control supplement, or lifestyle-only control) and report an eligible BMI or BMI z-score outcome with analysable group-level data. Non-randomised, uncontrolled single-arm, cross-sectional, cohort and case-control studies, quasi-experimental designs, and conference abstracts or protocols without complete results were excluded.

Eligibility criteria Additional inclusion criteria:

Time frame. No restriction was placed on publication year; the boundary was the search end date, and all records identified from database inception through October 2026 were eligible. Records published after that date were not considered, and the included trials were published between 2011 and 2026.

Completeness of reporting. The record had to be a retrievable full report containing usable results. Conference abstracts, trial protocols, and registry entries without posted results were excluded, and records that could not be retrieved in full were excluded rather than assessed from secondary descriptions.

Quantitative sufficiency. The report had to provide group-level sample sizes together with means and standard deviations, or a directly analysable change estimate with variance, or summary statistics convertible to these quantities. Standard errors were converted using SD = SE x root n, and medians with interquartile ranges were converted using the method of Wan et al. Reports that reported only medians without dispersion, only percentages of change without variance, or only graphical data without numerical values were excluded as lacking analysable data.

Publication type. Primary reports of randomised trials were eligible. Narrative reviews, meta-analyses, pooled analyses, secondary or post hoc analyses of already included trials, commentaries, editorials, and other non-primary publication types were excluded, although such records were screened for additional eligible trials through citation searching.

Independence of data. Multiple reports describing the same randomised trial were linked and treated as one trial, and the same participant data were used only once in each quantitative analysis to avoid double counting.

No restriction was imposed on country, health system, or clinical setting. No language restriction was applied; non-English reports were eligible provided the required data could be extracted.

Exclusion criteria additional to the PICOS framework were therefore: irretrievable records, abstracts or protocols without complete results, reports without analysable group-level data, non-primary publication types, and duplicate or overlapping reports that could not be disentangled.

Information sources Electronic bibliographic databases. Four databases were searched: PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). Each was searched from database inception to October 2026 using a strategy that combined paediatric population, overweight or obesity, probiotic or synbiotic intervention, and randomised-design concepts.

Trial registers. Two prospectively registered trial sources were searched: ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). Registers were used both to identify completed trials and to check whether identified trials had been registered prospectively and whether registered outcomes matched those reported.

Other sources. Reference lists of all included trials and of relevant reviews were screened, and citation searching of key included trials and prior paediatric syntheses was performed to identify additional eligible trials missed by the electronic strategies. This backward and forward citation approach yielded a substantial share of the included evidence base, which is expected in a small and dispersed literature.

Yield. The searches identified 1,267 database records (PubMed/MEDLINE 312, Embase 428,

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Web of Science 351, Cochrane CENTRAL 176), 44 register records (ClinicalTrials.gov 26, WHO ICTRP 18), and 27 records through reference-list and citation searching, giving 1,338 records before deduplication. Complete database-specific search strings and per-source yields are provided in Supplementary Table S1.

Deliberate design choice. The electronic strategy was constructed to be outcome-independent: BMI and BMI z-score terms were deliberately not required in the search strings, so that trials reporting anthropometric outcomes under alternative terminology, or reporting them only in supplementary material, would not be missed. This increased screening volume but reduced the risk of an outcome-driven selection of studies.

Sources not used. No formal grey-literature search of dissertations, thesis repositories, or regulatory documents was undertaken, and conference proceedings were not hand-searched as a separate source; conference abstracts encountered through the database and citation searches were screened but were excluded unless a complete report was available. Contact with trial authors to obtain unpublished data or missing numerical results was not undertaken, and no such data were used. No restriction on language or publication year was applied to any source.

Main outcome(s) Two co-primary outcomes were specified: body mass index (BMI) z-score and BMI. Both index excess adiposity on different scales and were analysed separately rather than combined into a composite.

Timing. The outcome time point was the end of the intervention period; interventions in the included trials lasted 4 to 24 weeks, and no post-intervention follow-up time point was planned a priori. Change-from-baseline values with an analysable variance were preferred; when not reported, post-intervention values were used, and the choice was recorded for every study.

Effect measure. Because reports mixed change and post-intervention values, applied different paediatric BMI reference systems, and did not consistently provide compatible change-score variances, Hedges-corrected standardised mean differences (SMDs) were used. SMDs were reported with 95% confidence intervals, with negative values oriented to favour supplementation. Random-effects models used Paule-Mandel estimation of between-study variance with Hartung-Knapp adjustment, and I-squared, tau-squared and 95% prediction intervals were reported for each outcome.

Analysis structure. BMI z-score and BMI were synthesised in separate models, never combined. Eleven trials contributed to the BMI z-score analysis and six to the BMI analysis, two contributing to both. Exploratory subgroup analyses by product type (probiotic versus synbiotic) and treatment duration were performed for BMI z-score only, and pooled subgroup estimates were restricted to strata with at least three trials.

Safety was a secondary outcome, assessed narratively rather than by meta-analysis because adverse-event reporting across the 15 trials was too heterogeneous and incompletely standardised for pooling; arm-level event counts, serious adverse events, and withdrawals attributed to the supplement were extracted where reported. Certainty of evidence for both co-primary outcomes was rated using GRADE.

Quality assessment / Risk of bias analysis Risk of bias in the included randomised trials was assessed using the complete Cochrane Risk of Bias 2 (RoB 2) tool for randomised trials, applied to the outcome level rather than to the study as a whole.

Domains and algorithm. The standard five domains were assessed: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain was evaluated through its prescribed signalling questions, and domain-level judgements were then combined into an overall study-level judgement using the tool's standard algorithm, under an intention-to-treat effect-of-assignment perspective.

How judgements were supported. Sequence generation, allocation concealment and baseline comparability were examined for the randomisation domain; blinding of participants and personnel, co-intervention balance and any deviations from the protocol for the deviations domain; completeness of outcome data and handling of attrition for the missing-data domain; whether outcome assessors were blinded and whether the outcome was objective or standardised for the measurement domain; and availability of a protocol or registered analysis plan, together with consistency between registered and reported outcomes, for the selective-reporting

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domain. Anthropometric outcomes are objective and were generally measured with standardised equipment and procedures, which limited concern in the measurement domain, whereas deviations from intended interventions, missing outcome data and selection of reported results were the more frequent sources of concern.

Reporting of judgements. Trial-level judgements were presented as a traffic-light plot across the five domains and as a summary plot, and the results were summarised as the number of trials judged low risk, some concerns, or high risk overall. In the present evidence base, five trials were judged low risk overall, eight as some concerns, and two as high risk.

Transparency about process. The assessment was not documented as having been performed independently by two assessors, so duplicate independent RoB 2 assessment is not claimed and the judgements should be read with that limitation in mind. No alternative or supplementary quality scale, such as the Newcastle-Ottawa Scale or Jadad score, was applied, because only randomised trials were eligible and RoB 2 covers the relevant domains. Risk of bias contributed a downgrading domain to the GRADE assessment of certainty for both co-primary outcomes.

Strategy of data synthesis Data were synthesised in two separate random-effects meta-analyses, one for BMI z-score and one for BMI. The two outcomes were never pooled together, because they measure the same construct on non-comparable scales and because trial-level data were reported inconsistently across them.

Model. Between-study variance was estimated using the Paule-Mandel estimator, which does not rely on the normality assumptions of DerSimonian-Laird and performs well in sparse, heterogeneous datasets, and confidence intervals used the Hartung-Knapp adjustment, which is recommended when the number of studies is small and heterogeneity is substantial. Each pooled estimate was reported with its 95% confidence interval, I-squared, tau-squared, and a 95% prediction interval computed from the outcome-specific between-study variance and the Hartung-Knapp uncertainty. Prediction intervals were reported deliberately, because they describe the range of effects a future comparable trial might plausibly show and are more informative than the confidence interval alone when heterogeneity is high. Because the Hartung-Knapp interval can be wide with few studies, pooled estimates were interpreted as broad averages across non-equivalent products rather than as precise class effects.

Heterogeneity. Heterogeneity was quantified rather than assumed away: I-squared and tau-squared were reported for every model, and the magnitude and direction of individual trial estimates were inspected alongside the pooled value. No a priori threshold was used to abandon pooling, because the review question concerned how trial-level effects behave when the outcomes are kept separate, not whether a single average effect exists.

Subgroups. Exploratory subgroup analyses were performed by product type (probiotic versus synbiotic) and by treatment duration, for BMI z-score only. Pooled subgroup estimates were calculated only for strata containing at least three trials; strata with fewer trials were displayed without a pooled estimate. Subgroup results were labelled exploratory and were not interpreted as tests of effect modification.

Robustness. Leave-one-out analyses were run for BMI z-score, omitting each trial in turn, and influential trials were identified and reported, including a sensitivity analysis omitting the single most influential estimate and one omitting both extreme estimates. These analyses were prespecified in intent as sensitivity checks rather than as alternative primary results.

Small-study effects. Funnel plots were examined descriptively. Formal small-study-effect tests were not emphasised, because the BMI analysis contained only six trials and the BMI z-score set combined substantial heterogeneity with an extreme standardised estimate, conditions under which such tests are unreliable.

Certainty and software. Certainty of evidence was rated with GRADE for each co-primary outcome. Analyses were run in R, with study-level inputs and reproducible code supplied as supplementary files; no individual participant data were available or used.

Subgroup analysis Subgroup analyses will be restricted to the BMI z-score outcome, because the BMI evidence base comprises only six trials and cannot support stratified analysis.

Two dimensions will be examined: product type (probiotic versus synbiotic) and treatment duration (at least 12 weeks versus less than 12 weeks). A pooled subgroup estimate will be computed only for strata containing at least three trials; strata with

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fewer trials will be reported descriptively, without a pooled estimate, to avoid presenting an imprecise average as a subgroup finding.

Subgroup models will use the same specification as the primary analysis, namely Paule-Mandel estimation of between-study variance with Hartung-Knapp confidence intervals, so that subgroup and overall estimates are directly comparable and any difference between them reflects the data rather than a change of method. Heterogeneity will be reported within each stratum.

These analyses are exploratory. They will not be interpreted as tests of effect modification, and no formal interaction test will be used to claim that one product category or one duration is superior. Because trials will be grouped by product category rather than by strain, dose, viability or substrate, a stratum will still pool non-equivalent products; because subgroup membership is a trial-level attribute, participants within a trial will not be assumed to share the defining characteristic; and because duration is confounded with product type, background lifestyle programme and baseline adiposity in this literature, duration strata will not be treated as isolating a duration effect.

Results will therefore be presented as descriptive context for heterogeneity, not as guidance on which product to use or how long to continue it. Any subgroup finding that departs from the overall estimate will be reported with its stratum-level trial count, heterogeneity and prediction interval where calculable.

Sensitivity analysis Leave-one-out sensitivity analyses for BMI z-score yielded pooled standardized mean differences ranging from −0.51 to −0.15, with all 95 % confidence intervals crossing zero. Excluding the highly influential Muthukrishnan 2025 trial attenuated the pooled SMD to −0.15 (95 % CI −0.45, 0.14; I^2 = 40.8 %). Further removal of both Muthukrishnan 2025 and Kelishadi 2014 resulted in a pooled SMD of −0.08 (95 % CI −0.34, 0.18; I^2 = 14.8 %), substantially reducing heterogeneity. Influence diagnostics confirmed Muthukrishnan 2025 exerted the largest single-study impact on the overall pooled result, driven partly by its small reported standard deviations. The BMI meta-analysis contained only six trials, so formal leave-one-out exploration was limited. Funnel-plot inspection was descriptive only; quantitative testing for small-study effects was not performed due to severe heterogeneity and the outlying estimate. These sensitivity findings underline that the original pooled estimate for BMI z-score is unstable and heavily dependent on a small number of outlying trials.

Country(ies) involved China.

Keywords Probiotics; Synbiotics; Pediatric Obesity; Randomized Controlled Trials as Topic; Meta-Analysis as Topic.

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