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MECHANISTIC INSIGHTS INTO THE EFFECTS OF PROBIOTIC SUPPLEMENTATION ON GUT-DERIVED FECAL SHORT-CHAIN FATTY ACIDS AND CENTRAL OBESITY IN OVERWEIGHT AND OBESE ADOLESCENTS: A NARRATIVE REVIEW

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ABSTRACT
Central fat distribution, rather than total body mass, drives most of the cardiometabolic risk associated with adolescent obesity. Yet, the interventions that might modulate it via the gut microbiota remain poorly characterized. Gut-derived short-chain fatty acids (SCFAs) are candidate mediators, and probiotics are candidate modulators, but the evidence in adolescence is sparse and inconsistent. The objective of the review is to synthesize the mechanistic and clinical evidence linking probiotic supplementation, fecal SCFAs, and central obesity, indexed by the waist-to-height ratio (WHtR), in overweight and obese adolescents, and to define the study-design features needed to test that link. A narrative review was conducted using PubMed, Scopus, Web of Science, and ScienceDirect as primary databases (records to July 2026), with Google Scholar as a supplementary source; every finding was verified against the primary article. Eligible records addressed gut microbiota or SCFAs, probiotic supplementation, or central adiposity/WHtR; evidence from children, adults, animal models, and *in vitro* work was used only to support mechanistic explanations.
Fecal SCFA concentration reflects only the small unabsorbed remainder of colonic production in the distal gut and is shaped by production, absorption, transit, and stool water content; it therefore indexes luminal microbial activity, not microbial synthesis or systemic exposure. SCFAs act on adiposity through GPR41/GPR43 signaling, gut-hormone secretion, hepatic and adipocyte lipid handling, and histone deacetylase inhibition, but these effects are context-dependent rather than uniformly beneficial. Adolescent probiotic trials are few and heterogeneous; based on our search, no probiotic-only trial has reduced WHtR, none have paired probiotic supplementation with fecal SCFA or metabolomic profiling alongside WHtR, and strain, dose, duration, baseline microbiota, diet, and pubertal stage all modify efficacy. The probiotic–SCFA–central obesity axis is biologically plausible but not yet validated in adolescents; its clinical benefit and causal direction remain unproven. WHtR, paired with untargeted fecal metabolomics, is proposed as the readout most likely to capture microbiota-mediated change.

KEYWORDS: Probiotics, Short-chain fatty acids, Gut microbiota, Waist-to-height ratio, Central obesity, Adolescents, Fecal metabolomics

1. INTRODUCTION

Rates of overweight and obesity among adolescents have climbed for two decades, and the sharpest increases now sit in low- and middle-income countries, moving through a rapid nutrition transition (1,2). This is not a benign trajectory. Excess fat gained during adolescence closely tracks insulin resistance, dyslipidemia, hypertension, and metabolic dysfunction-associated steatotic liver disease, and it seldom resolves on its own; the cardiometabolic abnormalities that begin in this window tend to follow the child into adulthood (3,4). The pattern belongs to the wider double burden of malnutrition, in which excess adiposity coexists with undernutrition and micronutrient deficiency within the same populations and often the same households as transitional economies shift toward energy-dense, ultra-processed foods (2,4). Adolescence is therefore a narrow, arguably time-limited window for intervention before these metabolic trajectories become fixed (3).
Where fat sits matters more than how much of it there is. BMI has remained the default screening tool because it is cheap and quick. Yet it cannot distinguish fat from lean mass or indicate where fat is deposited. This blind spot

widens during puberty, when sex hormones, skeletal growth, and muscle accretion remodel body composition independently of adiposity (3,5,6). Waist-to-height ratio (WHtR) speaks to that gap: dividing waist circumference by standing height yields a dimensionless index of central adiposity that has matched or outperformed BMI in predicting cardiometabolic outcomes in children and adolescents (6–9). It is, however, a surrogate. WHtR estimates central adiposity from an external anthropometric ratio; it does not measure visceral adipose tissue directly, and it cannot distinguish visceral from subcutaneous abdominal fat, which imaging methods such as magnetic resonance imaging or dual-energy X-ray absorptiometry can. Its height adjustment and relative independence from age and sex underpin the familiar rule that a waist below half of standing height marks low risk (8,9). Still, this single 0.5 threshold is not universal: pooled analyses place the optimal cut-off for abdominal obesity near 0.49, drifting lower, toward 0.46, in Asian, African, and South American youth, and the best cut-off varies further by age, sex, ethnicity, and whether the purpose is screening or diagnosis (5,10–12). That variation is not academic for Indonesian adolescents, in whom central fat frequently coexists with a normal or near-normal BMI, the metabolically obese normal-weight phenotype now documented in pediatric cohorts (13). Even so, WHtR is still rarely a primary outcome in adolescent obesity trials.

The story does not end with anthropometry. A growing body of work casts the gut microbiota as a functional mediator of obesity-related metabolic dysregulation, largely through short-chain fatty acids (SCFAs), acetate, propionate, and butyrate, produced by microbial fermentation of non-digestible carbohydrates; these feed into energy harvest, gut hormone secretion, appetite regulation, lipid metabolism, barrier maintenance, and inflammatory signaling (14,15). Pediatric SCFA studies disagree, with much of the discrepancy attributable to differences in diet, transit time, stool water content, and analytical methods rather than biology (14). Probiotics enter as candidate modulators of microbiota composition and, by extension, of metabolic output, barrier function, and inflammatory tone (16). In adolescents, evidence remains limited, with small sample sizes, short interventions, and wide heterogeneity in strain and dose, which is why recent systematic reviews and meta-analyses have reported conflicting findings (17,18). Few adolescent trials pair probiotic supplementation with fecal SCFA outcomes alongside WHtR, so the link between microbiota modulation and central adiposity remains largely untested in this age group. The general objective of this review is to synthesize the mechanistic and clinical evidence linking probiotic supplementation, fecal SCFAs, and central obesity, as indexed by WHtR, in overweight and obese adolescents. The specific objectives are: (i) to characterize gut microbiota dysbiosis and fecal SCFA alterations in adolescent obesity and to clarify how fecal SCFA measurements should be interpreted; (ii) to examine the mechanisms by which probiotic supplementation may modulate microbial SCFA output; (iii) to appraise the molecular pathways linking SCFAs to central adiposity, distinguishing directly demonstrated steps from hypothesized ones; (iv) to evaluate the clinical evidence on probiotic supplementation, SCFAs, and central adiposity in adolescents, keeping probiotic, synbiotic, and combined interventions separate; (v) to identify the biological, formulation, and methodological factors that modify probiotic efficacy; and (vi) to propose an integrated, testable framework and the study-design features needed to evaluate it.

2. METHODS

2.1 Search Methodology and study selection

A structured literature search was conducted between January and July 2026 for records published up to July 2026. The primary sources were PubMed, Scopus, Web of Science, and ScienceDirect, with Google Scholar used only to identify records not indexed in those databases. The reference lists of retrieved articles were hand-searched for additional sources. Every record retrieved through a supplementary route was traced to and verified against its primary published article before inclusion; AI-based literature tools were not used as sources of evidence. Search strings combined the terms “probiotic,” “gut microbiota,” “dysbiosis,” “short-chain fatty acids,” “acetate,” “propionate,” “butyrate,” “waist-to-height ratio,” “central obesity,” “overweight,” “obesity,” “adolescent,” and “children” with the Boolean operators AND and OR.

After duplicates were removed, titles and abstracts were screened against the review’s three domains, and full texts were assessed against the eligibility criteria described below. The selection process and the grounds for exclusion are shown in **Fig. 1**. Seventy-three sources were retained for qualitative synthesis: 19 mechanistic or narrative reviews, 12 WHtR validation or cut-off studies, 9 preclinical animals, ex vivo, or in vitro studies, 8 reports of 7 intervention trials in children or adolescents, 8 systematic reviews or meta-analyses, 6 epidemiological or background sources, 5 observational microbiota or metabolite studies, 4 methodological references, and 2 consensus statements. All 73 are cited in the text. Because this was a narrative rather than a systematic review, the number of records at each screening stage was not recorded prospectively, and no meta-analytic pooling was performed; the synthesis prioritized mechanistic relevance and population applicability and interpreted the evidence qualitatively.

2.2 Population, eligibility criteria, and use of non-adolescent evidence

The population of interest was adolescents, defined following the World Health Organization as individuals aged 10–19 years, with overweight or obesity defined by age- and sex-specific BMI-for-age criteria (a BMI-for-age z-score above +1 SD for overweight and above +2 SD for obesity by WHO references, or the percentile-based national or CDC criteria applied in individual studies). Records were eligible if they addressed one or more of the review’s three domains: gut microbiota or SCFAs, probiotic supplementation, and central adiposity or WHtR.

Eligible designs included randomized controlled trials (RCTs), observational and cohort studies, systematic reviews and meta-analyses, consensus statements, and preclinical or *in vitro* studies. Priority was given to peer-reviewed, English-language work published from 2013 onward and to studies enrolling children or adolescents with confirmed overweight or obesity; earlier landmark studies were retained where they remain the primary source for a pathway. Studies in adults, animal models, or *in vitro* systems were retained only where they informed the mechanistic explanation of pathways that cannot be studied directly in adolescents; such evidence is identified as mechanistic throughout and is not treated as clinical evidence in the target population.
Excluded were adult-only reports lacking mechanistic transferability, records reporting no microbiota, metabolite, or adiposity outcomes, and conference abstracts, editorials, or other non-peer-reviewed material. Trials of prebiotics, synbiotics, or fecal microbiota transplantation without a probiotic arm fell outside the primary scope; they were cited only when they provided mechanistic, methodological, or WHtR-related information, and their design is identified wherever they appear.

2.3 Appraisal of study quality

Because this is a narrative review, formal risk-of-bias scoring was not applied to every record. The pediatric and adolescent interventions that carry the review's clinical weight were appraised qualitatively for design, sample size, blinding, attrition, co-interventions, and the resulting strength of evidence, and these attributes are summarized alongside each trial in **Table 1**. The evidence for probiotics rests on small studies. Larsen et al. (VSL #3, n = 50) (19) and the trial of 19 obese Latino adolescents et al. (20) were randomized and placebo-controlled. Still, the second was underpowered: recruitment stopped early, leaving 8 participants on probiotic and 11 on placebo (19). Famouri et al. (n = 64) (21) and Sanchis-Chordà et al. (n = 48) (22) were larger and randomized. Yet each qualifies: in the former, only children with sonographic evidence of NAFLD were enrolled, and in the latter, every child received dietary advice, to which the authors attribute the fall in BMI (21,22). Joseph et al. was a pediatric before-and-after study with no control arm (23). The two synbiotic trials in children and adolescents (Atazadegan et al., n = 60; the Probesity-2 trial, n = 61) were randomized and double-masked, but both delivered a prebiotic alongside the probiotic, so neither can isolate a probiotic effect; in Probesity-2, diet and physical-activity advice went to both groups, which preserves the between-group comparison but makes the supplement's effect conditional on that background (24). Across this body of intervention evidence, small sample sizes, short durations, heterogeneous strains and doses, and frequent co-interventions place the overall certainty at low to very low, consistent with the GRADE ratings of the most rigorous syntheses (25). This appraisal frames the interpretation of every subsequent clinical claim.

3. Gut microbiota dysbiosis and fecal short-chain fatty acids in adolescent obesity

3.1 SCFA production and gut microbial ecology

Short-chain fatty acids are, at root, fermentation products: the gut microbiota break down the non-digestible carbohydrates that escape the upper gastrointestinal tract, and SCFAs are the fermentation products (15,26,27). Much of the metabolism relies on cross-feeding, with byproducts of one taxon becoming substrates for another, and the pooled output feeds back into host metabolic regulation through several signaling pathways (15,26–28). The principal producers, *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Roseburia*, and *Eubacterium*, contribute in proportions that vary with substrate and the surrounding community (26,27,29).
Acetate, propionate, and butyrate are neither produced in equal amounts nor by a single route. In the colon and feces, they occur in an approximate ratio of about 60:20:20. Still, this figure is only a general order of magnitude: the relative proportions depend on diet, fiber type along the length of the gut, transit time, and the analytical method used to measure them, so it should not be read as a fixed value (26,27). Each SCFA follows its own pathway: acetate via the Wood–Ljungdahl pathway or acetyl-CoA; propionate mainly by the succinate route, and butyrate mainly by butyryl-CoA:acetate-CoA transferase in *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and related Firmicutes (26,27), so a change in one SCFA's share reflects a shift in which taxa dominate fermentation, not a uniform rise or fall in activity. Most SCFAs never reach the stool: an estimated 90–95% are absorbed across the gut mucosa before the rectum (26,27,30), leaving fecal concentration to capture only the small unabsorbed remainder of total production.

3.2 Dysbiosis and fecal SCFAs as functional microbial outcomes

Timing matters here. Gut microbiota composition and SCFA output are still settling during a developmental window of dietary transitions, growth, and pubertal change, and disruptions to that trajectory have been linked to several pediatric conditions, including obesity among them (31). In adolescents, these gut adiposity axes may matter more than usual because host–microbiota interactions are still maturing and open to environmental modification (32,33). Obesity-associated dysbiosis in children is rarely a single, clean signature; it manifests as shifts in fermentative taxa, often with fewer SCFA-producing bacteria (14,34–36).
Fecal sampling occupies an odd place in pediatric research, chosen for reasons as much practical as scientific. Sampling the gut lumen directly is invasive and hard to justify in a healthy adolescent. In contrast, fecal material captures the same luminal activity non-invasively and repeatedly, the only realistic way to follow the microbial trajectory across an intervention (32). Its value in overweight and obesity is a functional window onto the

microbial activity, fermentation output, energy harvest, and signaling-molecule production that mechanistic models place between dysbiosis and central adiposity (16,29,37).

That window is, however, partial and indirect. Feces reflect mainly the distal colon and rectum, not the more proximal segments where much fermentation occurs, and the measured SCFA concentration is the joint product of microbial production, mucosal absorption, intestinal transit, and stool water content rather than a direct readout of total gut activity (26,27,30). Because most colonic SCFAs are absorbed before reaching the rectum, a high fecal value can indicate greater production, reduced absorption, or faster transit, and a single measurement cannot distinguish among them. Fecal SCFAs are therefore best read as functional markers of luminal microbial activity, not as proxies for systemic exposure or microbial synthesis (15,26–28,30), a distinction that matters wherever later sections treat fecal SCFA change as an intervention outcome.

3.3 Targeted SCFA measurement versus untargeted fecal metabolomics

Two analytical strategies answer different questions and should not be conflated. Targeted SCFA analysis, typically gas chromatography mass spectrometry with propyl chloroformate derivatization, quantifies a predefined panel of acetate, propionate, and butyrate and often branched-chain fatty acids, with high precision and known limits of detection (33). Untargeted metabolomics instead surveys a broad, unspecified range of metabolites, including bile acid derivatives, amino acid-related compounds, and other fermentation products, generating hypotheses rather than testing a fixed panel (38,39). The two are complementary: targeted analysis measures the SCFAs of direct mechanistic interest, while untargeted profiling widens the functional readout beyond them and can reveal metabolic changes that a three-analyte panel would miss. Where this review treats fecal metabolomics as the "missing functional link," it means untargeted profiling used *alongside*, not instead of, targeted SCFA quantification.

3.4 SCFA profiles, pediatric, and adolescent obesity

The evidence on SCFA profiles in pediatric obesity is inconsistent (14,34–36,40,41). Four studies, each approaching the question differently, show why. Li et al. compared gut microbiota and metabolite profiles between 49 obese and 50 normal-weight children aged 7–14 years using whole-genome shotgun metagenomics and serum metabolomics (34). Proteobacteria were more abundant in the obese group at the phylum level; at the genus level, *Oscillibacter* and *Alistipes* were significantly lower, butyrate fell, and caproate rose relative to normal-weight controls (34).

Kim et al.'s meta-analysis pointed the other way. Pooling seven human studies (246 obese cases, 198 non-obese controls), obesity was associated with significantly higher fecal concentrations of acetate (SMD 0.87, 95% CI 0.24–1.50), propionate (SMD 0.86, 95% CI 0.35–1.36), and butyrate (SMD 0.78, 95% CI 0.29–1.27), with no matching difference in phylum-level abundance (37). Murugesan et al. tied altered microbial SCFA production to childhood obesity through effects on energy, glucose, and lipid homeostasis (40). Holmes et al., applying an ex vivo fermentation model to fecal samples from 17 adolescents with obesity, watched SCFA output swing with the prebiotic substrate supplied, providing evidence that the method, not only population biology, shapes the apparent direction of an SCFA–obesity association (41).

Read alone, fecal concentration misleads. Kim et al.'s higher fecal acetate, propionate, and butyrate in excess adiposity (37) seem to say "more SCFA, more risk." Yet, the bacterial-level trend often runs the other way, with fewer SCFA-producing taxa a common feature of obesity-associated dysbiosis (14,34). The two coexist because fecal concentration is a net of production, absorption, and transit (26,27,34). Within this mixed picture, Joseph et al. carry particular weight: microbiota and fecal SCFA profiles measured in Malaysian schoolchildren before and after probiotic administration, one of the few pediatric datasets to read SCFA change as an intervention outcome rather than a cross-sectional descriptor (23). Comparable profiling in obese children from Northern Thailand underlines how little Southeast Asian pediatric data exists (42).

3.5 Why are the findings contradictory?

The contradiction is not in the biology; it comes from measuring the same molecule at different points on its journey. An elevated fecal SCFA value may signal beneficial microbial activity or reflect greater energy harvest, reduced absorption, faster transit, or more fermentable substrate, none of which are necessarily protective, and concentration alone cannot separate these (15,26,27,37). A second problem sits beneath the first: several apparent disagreements compare different measurements as though they were the same. Reduced SCFA-producing taxa (14) set against elevated fecal SCFA in the same populations (23,37) looks contradictory only if bacterial abundance and fecal concentration are treated as interchangeable, which they are not (26,27,34,40); that circulating, rather than fecal, SCFA tracks with insulin sensitivity and GLP-1 (30) adds a further layer. Fold in heterogeneous collection, storage, and analytical protocols (15,26–28), and much of the apparent contradiction turns out to be different studies measuring different things at different points in the pathway under different conditions.

4. Mechanisms of probiotic supplementation in modulating gut microbiota and short-chain fatty acid production

4.1 Definition and scope

Probiotics have a consensus definition: live microorganisms that confer a health benefit on the host when given in adequate amounts, formalized by the International Scientific Association for Probiotics and Prebiotics (ISAPP) to standardize terminology across a crowded field of microbiota-modulating products (16). This review focuses on probiotics, live single- or multi-strain formulations. Prebiotics (selectively fermented substrates), synbiotics (a probiotic combined with a prebiotic), and postbiotics (inanimate microbial preparations) are treated as outside its primary scope and are noted only where they inform the sparse adolescent WHtR evidence, with their class named each time. The distinction is not pedantic. These product classes act on the microbiota and on SCFA output through non-interchangeable pathways, and strain identity, formulation, and delivery matrix, not incidental details, set the biological effect (43,44).

4.2 Probiotics as modulators of microbial metabolic output

The rationale for probiotics as an SCFA-modulating intervention rests on two pathways, and they are not equal. An administered strain may contribute directly to fermentation in the colonic lumen, provided it survives gastric and biliary transit and establishes at least transient colonization (44). The more consistently reported route is indirect. Through cross-feeding, metabolic intermediates from the administered strain serve as substrates for resident taxa, thereby reshaping the downstream SCFA profile even when the probiotic itself is not a major direct producer (16,28,29,43). Markowiak-Kopeć and Śliżewska, reviewing SCFA production by the human intestinal microbiome, concluded that probiotic-induced shifts in output are frequently mediated through changes in the abundance and activity of endogenous SCFA-producing taxa (29). The corollary for reading adolescent trials: a null or modest change in the administered strain's abundance does not rule out a real shift in community-level output.

4.3 Strain specificity

One caveat applies to the rest of this review: probiotic effects are strain-specific, so this manuscript avoids the blanket claim that probiotics as a category increase SCFA production or reduce adiposity (16,43). What a trial reports depends on strain and species, dose, duration, the host's baseline microbiota, concurrent diet, and how the single- or multi-strain product is formulated and delivered (16,43). The Joseph and Larsen trials (19,23) make the point concretely: comparable populations and divergent functional outcomes are best explained by strain and formulation rather than any failure of the concept. This heterogeneity is why narrative rather than quantitative synthesis suits the current evidence.

4.4 Pediatric evidence on probiotics and SCFAs

Direct evidence linking probiotic administration to measured fecal SCFA change in children is thin, which makes the few studies that exist carry outsized weight. Joseph et al. is the anchor. The authors measured gut microbiota composition and SCFA profiles in 42 normal-weight and overweight schoolchildren in Selangor, Malaysia, before and after probiotic administration, making it one of the few trials in this age range to pair microbiota and metabolite outcomes simultaneously (23). Larsen et al. supply the instructive negative. Twelve weeks of *Lactobacillus salivarius* Ls-33 in 50 obese adolescents measurably altered fecal microbiota composition, including a significant increase in the Bacteroides-Prevotella-Porphyromonas-to-Firmicutes ratio, yet did not alter fecal SCFA concentrations (19). Put side by side, the two studies sketch a pattern that recurs throughout this review: taxonomic change and functional metabolic change need not travel together. A null SCFA result is not necessarily a null biological effect; it may mark a dissociation between compositional and functional outcomes that turn on strain, dose, or analytical sensitivity.

5. Molecular mechanisms linking short-chain fatty acids to central obesity

5.1 Receptor-mediated signaling: FFAR2 (GPR43) and FFAR3 (GPR41)

Several pathways converge on adiposity, but one is far better characterized than the rest. SCFAs signal through two G protein-coupled receptors, free fatty acid receptor 2 (FFAR2, also designated GPR43) and free fatty acid receptor 3 (FFAR3, also designated GPR41), expressed on enteroendocrine cells, adipocytes, and immune cells throughout the gut and beyond (15,26,28). The two receptors are not interchangeable, and the difference matters for how a probiotic-induced shift in fermentation should be read. FFAR2 responds most strongly to acetate and propionate and couples to both Gαi/o and Gαq, so its activation lowers cyclic AMP while raising intracellular calcium and engaging ERK1/2 and β-arrestin-2 signaling. FFAR3 is preferentially activated by propionate and butyrate, couples to Gαi/o alone, and acts largely through the Gβγ-phospholipase Cβ route (45). Together, ligand preference and receptor coupling explain why acetate-rich and butyrate-rich fermentation profiles can produce different host responses even when total SCFA output is unchanged. The ratio may matter more than the total. That bears directly on adolescent trials in which a probiotic shifts the acetate–propionate–butyrate balance while leaving the total unchanged.

Animal models tie these receptors to energy homeostasis through adipose-specific pathways. GPR43-deficient mice develop obesity on a normal diet. In contrast, mice with adipose-specific overexpression of GPR43 remain

lean even on a high-fat diet, suggesting that GPR43 acts as a sensor of excess dietary energy, directing metabolic substrates toward oxidation rather than storage (15,28). In adipose tissue, GPR43 activation suppresses insulin signaling, limits further fat accumulation, and promotes energy expenditure in other tissues (45). The picture is not uniform across preclinical models; some studies of GPR43-deficient mice on a high-fat diet report reduced rather than increased adiposity, and the directionality of the relationship between FFAR2 activation and body-fat accumulation remains contested (28). GPR41 contributes in a complementary manner to the regulation of energy expenditure, sympathetic nervous system activity, and glucose homeostasis through partially overlapping yet mechanistically distinct pathways (15,28). Gnotobiotic work makes the GPR41 route the most directly demonstrated of the two: on an identical microbiota, GPR41-deficient mice secrete less peptide YY, show altered intestinal transit, harvest less dietary energy, and remain leaner than wild-type littermates (46).

5.2 Epigenetic regulation: histone deacetylase inhibition

Butyrate's role is of a different kind. As an inhibitor of class I and class IIa histone deacetylases (HDACs), it increases histone acetylation and alters gene expression in colonocytes and immune cells, among them intestinal macrophages and dendritic cells, with downstream effects on gut barrier integrity and mucosal inflammatory tone, extending beyond receptor signaling to include epigenetic regulation (27,47). The best-characterized consequence is immunological. In murine intestinal macrophages, butyrate downregulated lipopolysaccharide-induced nitric oxide, interleukin-6, and interleukin-12 production, and the effect persisted when Toll-like receptor and G-protein-coupled receptor pathways were experimentally excluded, which localizes it to HDAC inhibition rather than to receptor-mediated signaling (48). A trial measuring only receptor-linked outcomes may therefore miss it entirely. Its dependence on high local butyrate concentration also bounds where it can plausibly operate: in the colonic mucosa, where butyrate is the preferred fuel of the colonocyte, rather than in peripheral tissues, where circulating butyrate is orders of magnitude lower (27,30).

5.3 Energy sensing and lipid handling: AMPK, PPARγ, and SREBP-1c

The clearest account of how SCFA signaling reaches lipid metabolism runs through cellular energy status rather than through receptors. SCFA oxidation raises the AMP-to-ATP ratio and activates AMP-activated protein kinase (AMPK) in the liver, skeletal muscle, and adipose tissue, shifting cells from anabolic storage toward catabolic oxidation (27,49). In mice, dietary SCFA supplementation prevented and reversed high-fat-diet-induced metabolic abnormalities by decreasing PPARγ expression and activity, raising mitochondrial uncoupling protein 2 expression and the AMP-to-ATP ratio, and stimulating oxidative metabolism in liver and adipose tissue via AMPK; both the reduction in body weight and the improvement in insulin sensitivity were absent in mice with adipose-specific PPARγ disruption, and the reduction in hepatic steatosis was absent in mice lacking hepatic PPARγ (49). Acetate acts on the same node. In high-fat-fed mice, it reduced body fat and hepatic lipid accumulation and increased hepatic expression of PPARα, acyl-CoA oxidase, carnitine palmitoyltransferase-1, and uncoupling protein 2; the same induction was reproduced in cultured hepatocytes and was abolished by knockdown of the α2 catalytic subunit of AMPK (50). PPARγ moves counterintuitively in this pathway: it is downregulated rather than induced, and that downregulation is what permits the switch from lipogenesis to oxidation (49).

Downstream of AMPK sits the lipogenic transcription program. AMPK activation restrains sterol regulatory element-binding protein 1c (SREBP-1c) and its target enzymes acetyl-CoA carboxylase and fatty acid synthase, so SCFA exposure would be expected to lower hepatic de novo lipogenesis while raising fatty acid oxidation; suppression of SREBP-1c alongside FFAR2 and FFAR3-linked enhancement of mitochondrial β-oxidation is the mechanism most often invoked for the antisteatotic effect of fermentation-derived SCFAs (51). The direction of effect is not fixed, and this is where the framework has to stay careful. Colonizing germ-free mice with a normal cecal microbiota promotes monosaccharide absorption and induces de novo hepatic lipogenesis, producing a 60% increase in body fat within 14 days despite reduced food intake (52). Acetate is itself a lipogenic substrate, so the same molecule can supply carbon for hepatic triglyceride synthesis or, through AMPK and PPARγ, restrain it, with the balance set by dose, route of delivery, and the host's metabolic state (15,27,49). A claim that probiotic-induced SCFA production reduces central fat therefore has to specify which route is invoked, at what concentration, and in which tissue.

5.4 Barrier integrity and the LPS–TLR4–NF-κB pathway

A fourth route runs through inflammation, and it is the one that points most directly at central rather than total fat. Dysbiosis loosens the epithelial barrier, and lipopolysaccharide (LPS) from Gram-negative bacteria crosses into the portal and systemic circulation, producing what has been termed metabolic endotoxemia. Four weeks of high-fat feeding in mice raised plasma LPS two- to three-fold; subcutaneous infusion of LPS alone then reproduced the weight gain, hepatic triglyceride accumulation, adipose macrophage infiltration, and fasting hyperinsulinemia of high-fat feeding, while CD14-mutant mice were largely spared (53). The endotoxin alone was sufficient. Downstream, LPS engages Toll-like receptor 4 (TLR4), activating IKKβ and JNK and freeing NF-κB to drive transcription of TNF-α, interleukin-6, and interleukin-1β; mice lacking TLR4 resist lipid-infusion-induced suppression of insulin signaling in muscle, are partly protected against diet-induced insulin resistance, and show less inflammatory gene expression in liver and adipose tissue (54). The depot matters here. Visceral adipose tissue

generates and amplifies this inflammatory tone, so its consequences surface in central fat and the metabolic profile around it rather than in total body mass (51,55).

SCFAs meet this pathway at two points. Butyrate reinforces the barrier itself: in Caco-2 monolayers, it accelerated tight-junction assembly and increased transepithelial electrical resistance via AMPK activation, and pharmacological inhibition of AMPK abolished the effect (56). That places AMPK at the junction of the lipid-handling and barrier routes; butyrate-driven tight-junction assembly is the most concrete link available between a probiotic-induced rise in colonic butyrate and a fall in endotoxin translocation. Butyrate acts again after translocation, blunting the macrophage response to LPS through the HDAC-dependent mechanism set out earlier (48). Strains that expand butyrate producers, or that strengthen mucin and tight-junction expression, would, on this account, lower endotoxin load and, with it, adipose inflammation and insulin resistance (14,29,43) Whether they do so in adolescents is unknown. No trial identified in this review measured intestinal permeability, circulating endotoxin, or NF-κB-dependent cytokines alongside fecal SCFAs and WHtR. For a study already collecting stool and anthropometric data, a permeability or endotoxin marker adds little to participant burden, and it would test a link that the framework currently leaves entirely open.

5.5 Gut hormones, hepatic lipid handling, and epigenetic regulation

Appetite is the first level. When SCFAs bind these receptors on intestinal L-cells, they trigger the secretion of GLP-1 and PYY, gut hormones that suppress appetite and slow gastric emptying (15,28), the main route by which probiotic-induced SCFA shifts are thought to influence energy intake before any change in expenditure. Propionate and acetate also support hepatic lipid metabolism, with evidence indicating reduced de novo lipogenesis and increased fatty acid oxidation, as well as modulation of hepatic glucose output (27,47).

Den Besten et al. add a caveat worth keeping in view. The individual leads are well supported by preclinical and in vitro evidence. Still, a coherent, quantitative account of actual SCFA fluxes to peripheral tissues and of the concentrations at which each pathway switches on in humans is largely missing (27). The gap is not minor because the receptor-mediated, AMPK–PPARγ, and HDAC routes described above are all concentration-dependent, and the concentrations at which they were demonstrated in rodent and cell-culture systems are not those observed in human peripheral tissue. A compartment problem sits underneath this. In a cross-sectional study of 160 adults spanning normoglycemia to impaired glucose metabolism, Müller et al. found that fasting circulating, but not fecal, concentrations of acetate, propionate, and butyrate were independently associated with fasting GLP-1, whole-body lipolysis, and peripheral insulin sensitivity measured by hyperinsulinemic-euglycemic clamp; fecal concentrations showed no such association (30). If that holds beyond one cohort, the receptor-mediated and energy-sensing pathways described above may operate mainly on the circulating SCFA pool, the fraction absorbed into systemic circulation, rather than on the luminal and excreted fraction that fecal measurement reflects.

5.6 From microbial signaling to central fat: demonstrated steps and hypothesized ones

Not every step in this pathway rests on the same evidence, and the difference should be kept in view. Two domains rest on direct animal-model evidence and together establish something specific: SCFA-receptor signaling affects host adiposity in a measurable, receptor-dependent way, independent of caloric intake. First, hepatic and adipose lipid handling, in which the germ-free colonization experiments described above provide direct causal evidence (48). Second, gut-hormone-mediated energy harvest through SCFA–GPR41 signaling, where a gnotobiotic comparison on an identical microbiota does the same (42). What matters here is not the findings themselves, which are set out earlier in this section, but that both are causal within their models and both are entirely rodent.

The remaining domains are softer: insulin sensitivity, appetite regulation via GLP-1 and PYY, and hepatic fatty acid oxidation rest on broader mechanistic literature rather than on single studies (15,27,28), while the adipose-inflammation and barrier domains, where butyrate fuels colonocytes, rest on comparatively indirect evidence (26,27).

The pathways added here do not carry equal evidential weight either. Strongest is the AMPK–PPARγ route, where tissue-specific gene deletion in mice supplies direct causal evidence: direct, but entirely rodent, and never shown in humans (49,50). HDAC inhibition has been demonstrated in cells and ex vivo tissue at luminal butyrate concentrations, whereas the effects of butyrate on peripheral tissue in adolescents remain unmeasured (44). SREBP-1c is weaker still, carried over from the AMPK literature and integrative reviews, rather than demonstrated specifically for probiotic-derived SCFAs (51). That is an inference, not a demonstration. For LPS TLR4 NF-κB, the animal work is solid, resting on infusion and gene-deletion experiments (53,54), and the adolescent evidence is simply absent. None of these steps has been tested end to end in overweight or obese adolescents. That unevenness partly explains why trials with similar strains still diverge on anthropometric results

5.7 Central adiposity as the downstream readout

Central adiposity is never just a number on a tape measure. WHtR sits downstream of metabolic and endocrine dysregulation across several organ systems, the gut included, where disrupted microbiota–host signaling raises intestinal energy harvest and shifts the metabolic phenotype, an early basis for the dysbiosis–adiposity link (55), and because these SCFA-driven effects shed visceral and abdominal fat while sparing lean mass, they show up on WHtR more directly than on BMI, which makes it the outcome best suited to microbiota-related effects that leave total body mass unchanged (8,9,55). Inflammation points the same way. Visceral rather than subcutaneous

adipose tissue is the principal site of endotoxin-driven macrophage infiltration and NF-κB-dependent cytokine release, so a reduction in endotoxin load should register on a central adiposity index before it appears in body weight (51,53). WHtR remains, as noted in the Introduction, an indirect surrogate for these depots rather than a direct measure of them.

6. Clinical evidence on probiotic supplementation, gut-derived short-chain fatty acids, and central obesity

6.1 Overview of adolescent probiotic evidence

Adolescent probiotic trials are few, and no two look alike. Clinical evidence remains sparse relative to the adult literature, and the available trials differ substantially in strain composition, dose, duration, and outcome selection (57). Their outcomes cluster into five domains: anthropometry and central adiposity, lipid profile, glycemic markers, inflammatory markers, and gut microbiota composition. No single trial reports consistently favorable findings across all five, a pattern that motivates the mechanistic framework advanced in Section 8.

6.2 Anthropometric and central-adiposity outcomes

Probiotic-only trials in adolescents have not demonstrated a reduction in central adiposity, and none report WHtR as an outcome. Larsen et al.'s twelve-week trial of *Lactobacillus salivarius* Ls-33 in 50 obese adolescents left anthropometric measures unchanged (19), and the sixteen-week VSL#3 trial, discussed in Section 2.3, reported a significant increase, rather than a decrease, in adiposity (20). Based on our search through July 2026, we did not identify any probiotic-only adolescent trial reporting WHtR as an outcome; this gap supports WHtR's use as a primary endpoint.

The only adolescent trials reporting WHtR directly used synbiotic, not probiotic, formulations. Hence, they sit outside this review's scope and are noted only because they anchor an otherwise empty evidence base. Atazadegan et al. saw a borderline within-group WHtR reduction (0.55 ± 0.05 to 0.54 ± 0.05; $P = 0.05$) over eight weeks of synbiotics, without between-group significance (24); the multispecies-synbiotic Probesity-2 trial, paired with diet and activity counseling over twelve weeks, produced significant between-group reductions in body weight, BMI, waist circumference, and WHtR (58). That both positive signals come from synbiotic, counseling-supported regimens rather than from probiotics alone is exactly what sharpens the question here: can probiotics reduce central adiposity via the SCFA pathway, and would the effect even be visible without a functional readout?

Two limits belong here, before either result is read as support for the axis. Neither synbiotic trial measured SCFAs. Whatever moved WHtR in those studies was not shown to be fermentation, and the prebiotic that makes fermentation the most plausible explanation on paper is precisely what makes that explanation unverifiable in practice. The Atazadegan result is also the kind that survives in a narrative summary and disappears under pooling. Only Probesity-2 produced a difference between arms (58,59).

One point of interpretation should be corrected here, since it bears on how much weight that result can carry. Diet and increased physical activity were prescribed to both arms, not only to the intervention arm, so the difference between them cannot be attributed to the lifestyle component. The probiotic's contribution, however, cannot be separated from the prebiotic's.

6.3 Microbiota and short-chain fatty acid outcomes

The functional picture is thinner still. Among probiotic trials, Larsen et al. assessed fecal microbiota composition in obese adolescents receiving *Lactobacillus salivarius* Ls-33. They found a significant shift in the Bacteroides-Prevotella-Porphyromonas-to-Firmicutes ratio, with no corresponding change in SCFA (19), a within-trial dissociation that echoes Section 2. Fecal SCFAs, in fact, are measured in none of the adolescent probiotic trials identified; they appear only in the pediatric probiotic study by Joseph et al. (23). That absence is the empirical basis for this review's central claim: that SCFA quantification is the missing functional link. The one adolescent WHtR-positive trial, the multispecies synbiotic Probesity-2 (20,59), profiled microbiota composition (20).Yet, being a synbiotic study, it, too, left the probiotic SCFA WHtR combination untested.

Put plainly, the SCFA WHtR relationship has never been tested in adolescents, in either direction. No study in this age group has measured fecal SCFAs and WHtR in the same participants, so there is not even a cross-sectional correlation to report, let alone an intervention effect. The trials that moved WHtR did not measure SCFAs (24,58); the trials that measured SCFAs did not report WHtR (19,23). The two literatures pass each other without meeting. The proposition therefore rests entirely on the mechanistic chain set out in Section 3, and every link in that chain was demonstrated in rodents, in cell systems, or in adults (30,46,49,52–54). The distinction deserves to be stated in its own terms. That SCFA-receptor signaling alters adiposity in mice is a validated finding. That probiotic supplementation raises fecal SCFA output in adolescents is an untested hypothesis. That a rise in fecal SCFA lowers WHtR in adolescents is a hypothesis no trial has yet put into measurable form. The 2025 Cochrane review, which searched more widely than we did, reached the same conclusion and identified no adolescent probiotic trial that paired fecal SCFA or metabolomic profiling with WHtR (18).

What would settle the question is not simply another trial. Establishing SCFAs as the mediator requires four things that no adolescent study has assembled: a demonstrated effect of the intervention on the metabolite, a demonstrated effect on WHtR, temporal ordering in which the metabolite moves first, and a mediation analysis relating the two within participants. A trial could satisfy the first two and still leave the question open, since diet, adherence, and pubertal stage move both variables independently (3,5). Larsen et al. supply the warning. A

compositional shift with no accompanying SCFA change (19) would, in a trial that measured composition and WHtR but not SCFAs, have been read as mechanistic support for the SCFA data that specifically rejects it.
One caution belongs in this section rather than in the mechanistic one, because it constrains what even a well-designed trial could conclude. Fecal SCFA is a proxy for the wrong compartment. It indexes the unabsorbed remainder of colonic production, whereas the receptor- and energy-sensing pathways that plausibly act on adipose tissue respond to the circulating pool; in adults, the two do not track together (30). A null fecal result would therefore not refute the axis, and a positive one would not confirm it. The implication is not to abandon stool, which remains the only repeatable, non-invasive window on colonic fermentation in this age group (37), but to pair it with circulating SCF wherever venous sampling is acceptable and to read the fecal measure as a marker of luminal activity rather than as a stand-in for systemic exposure.

6.4 Unexpected anthropometric findings

A sixteen-week, double-blind, placebo-controlled trial of VSL#3 in 19 obese Hispanic adolescents found a significant increase in total body adiposity (+1.7 ± 0.6% vs. −1.3 ± 0.5% with placebo, $P < 0.01$) and trunk adiposity (+3.3 ± 0.8% vs. −1.8 ± 0.8%, $P < 0.01$) in the probiotic arm, with no effect on liver fat, fibrosis, insulin, glucose, or gut microbial abundance (20).
This is best reported as an unexpected anthropometric finding rather than as evidence of harm: the sample was very small ($n = 19$), the trial was terminated early and consequently underpowered, and a single small study cannot establish an adverse effect. Even so, the direction and statistical significance of the adiposity change warrant plain reporting, not omission in favor of positive trials, and they underline how far the adolescent evidence is from supporting any uniform benefit.

6.5 Evidence from systematic reviews and meta-analyses

Recent syntheses do not converge, and the split runs deeper than "effective" versus "uncertain" (**Table 2**). Zhang et al. and Ding et al. report specific, statistically significant benefits for multi-strain and combined regimens on anthropometric and inflammatory outcomes (17,60), whereas Fahim et al.'s Cochrane review and Wu et al.'s GRADE-assessed meta-analysis find predominantly null pooled effects, softened only by very-low-certainty single-trial signals (18,25). The disagreement is not about rigor; it reflects which trials each review pooled, how strain types were grouped, and which age ranges and outcomes were counted (21,22,61–65). Blanket claims of probiotic efficacy in adolescent obesity are therefore unsupportable in either direction, and the individual-trial evidence carries more weight than pooled estimates in identifying which formulations, durations, and populations actually show a signal.
Taken together, sections 3, 4, and 5 describe a pathway that is specified at molecular resolution but tested almost nowhere. **Fig. 2** sets it out in full, from probiotic supplementation through microbiota modulation and SCFA production to receptor, epigenetic, energy-sensing, and inflammatory signaling and finally to central adiposity, as indexed by WHtR, with each step marked according to the strength of the evidence supporting it. Read alongside **Table 1**, the mismatch is plain: the mechanistic chain has eight stages, and the adolescent trials that might test it measure one or two. What determines whether a given trial can detect movement along the chain at all is the subject of Section 5.
Set side by side, the interventions themselves explain much of the disagreement **(Table 1).** Seven trials in children and adolescents have tested a probiotic or synbiotic against an obesity-related outcome, and no two used the same product. Formulations range from a single strain to a multispecies mixture and durations from eight to sixteen weeks, and three of the seven bundled a prebiotic, dietary counseling, or both so that any effect belongs to the package rather than to the organism. Two trials measured fecal SCFAs. One showed no change despite a clear compositional shift, and the other lacked a control arm. Two reported WHtR, and both were synbiotic. Most striking is the mechanism column: not one trial measured the pathway it invoked. Appetite hormones were assayed in the single trial that named them and did not move, while barrier integrity, endotoxin, and SCFA flux went unmeasured throughout. The heterogeneity is therefore not only in strain and dose but in what the trials chose to observe, and a pooled estimate across products this different describes no intervention that anyone actually administered.

7. Factors influencing the efficacy of probiotic supplementation

The heterogeneity of adolescent trial outcomes is not random noise. It is largely attributable to a set of biological, formulation, and methodological factors that determine whether a given probiotic reaches, colonizes, and metabolically engages the colonic environment and whether any resulting change is detectable in the measured outcomes. In the context of a randomized trial, these are better described as prognostic factors or effect modifiers than as confounders, since randomization is designed to balance them across arms; the concern is not confounding of the treatment effect but variation in that effect across strata, and, for co-interventions such as diet, contamination of the between-arm contrast. What matters practically is that each be measured so that it can be adjusted for or examined as an effect modifier.

7.1 Strain, dose, and duration

Strain complexity, dose, and duration together gate whether a nominally identical intervention helps, harms, or does nothing (16,43). The meta-analyses bear this out: Ding et al. found greater benefit past three months or under age twelve (60), and Zhang et al. found that multi-strain formulations outperform single-strain products anthropometrically (17). Yet the null Ls-33 result over twelve weeks (19) compared with the adiposity rise with multi-strain VSL#3 over sixteen weeks (20) shows that neither longer duration nor more strains guarantee a benefit. A trial shorter than the resident community's turnover period, or dosed below the colonization threshold, can yield a null result that reflects the design rather than biological inertness. Strain, delivered dose (CFU), and duration should be reported for every arm and treated as pre-specified effect modifiers (**Table 1**).

7.2 Baseline microbiota, pubertal stage, and other host factors

Two adolescents are rarely the same experiment. The host's baseline microbiota decides whether an administered strain can establish cross-feeding and shift community-level SCFA output (29,43), so different starting communities can produce different responses to the same product. Pubertal stage and sex add another layer, shaping adiposity distribution, insulin sensitivity, microbiota composition, and metabolite profile and confounding WHtR and SCFA outcomes if left unadjusted (3,5). Because central fat distribution and microbiota composition diverge by Tanner stage independent of chronological age, two same-age adolescents at different pubertal points are not comparable at baseline. Trials should therefore record and adjust for Tanner stage or an equivalent marker alongside sex, rather than lean on age as a proxy for development. Recent antibiotic exposure, a potent perturbation of the microbiota, should be screened for and recorded. Physical activity, which influences both adiposity and the microbiota, should be measured by questionnaire or accelerometry.

7.3 Diet and fiber as an intervention

SCFA production sits directly downstream of the substrate. Any probiotic trial that ignores dietary intake risks crediting the intervention with a change that the diet actually drove. Total energy intake, dietary fiber, resistant starch, and fermented-food consumption each shape the colonic fermentation substrate and, therefore, SCFA output, largely independent of probiotic strain (15,26,27,37). This is not an abstract worry in Indonesia. Ultra-processed foods, typically low in fermentable fiber, have risen alongside adolescent obesity in the country's cities, so baseline substrate availability is itself in flux (5). Diet should be measured at baseline and follow-up (for example, by repeated 24-hour recalls or a validated food-frequency questionnaire) so that a probiotic-driven shift in microbial output can be distinguished from one produced by concurrent dietary counseling, a real concern when healthy-living counseling reaches every participant regardless of allocation, in which case diet is a shared co-intervention rather than a between-arm difference.

7.4 Formulation, delivery, and viability

Delivery is where good strains go to waste. Probiotics act only if enough live organisms survive gastric acid, bile, and storage to reach the colon. Hence, the practically relevant variables are viability at the point of consumption, the actual dose of live organisms delivered, storage and cold-chain conditions, palatability, and adherence (44). Divergent trial outcomes may reflect differences in the delivered dose of viable organisms as much as differences in the strains themselves, an underreported source of variability (44,66).

Detailed encapsulation chemistry is beyond this review’s scope; what matters clinically is that these delivery attributes be specified and verified, since a product that is unpalatable or has lost viability during storage can produce a false negative regardless of strain.

7.5 Measurement and analytical standardization

Fecal SCFA numbers are shaped as much by how the sample was handled as by the biology underneath. Stool collection timing relative to the last meal, storage temperature, duration before freezing, and whether a stabilizing buffer was used all affect the measured concentration, as residual microbial activity continues to metabolize SCFAs in unfrozen samples (15,29,37). Standardized methods help. Propyl chloroformate derivatization, followed by gas chromatography–mass spectrometry, quantifies SCFAs and branched-chain amino acids from a single stool aliquot and has been adopted in several pediatric studies (67). Normalization is itself a choice, not a single standard. SCFA results can be expressed per gram of wet stool, per gram of dry (lyophilized) stool to correct for water content, relative to a stable internal standard, or as molar proportions (%) among the measured SCFAs; each option has trade-offs, and dry-weight or internal-standard normalization is generally preferred when stool water content varies across an intervention, at the cost of additional processing. Anthropometry needs the same discipline: a consistent waist-measurement site, fixed timing relative to respiration, duplicate readings, and population-appropriate WHtR cut-offs rather than a blanket 0.5 (5,10,12). Across collection, storage, derivatization, and analysis, this standardization is a prerequisite for between-study comparison, not a detail.

8. An integrated Framework and future direction

8.1 Proposed, testable probiotic–SCFA–central obesity axis

Read together, sections 3 to 5 point to a single testable pathway, not a scatter of associations (**Fig. 2**). The proposal is that probiotic supplementation shifts gut microbiota composition and activity, altering the colonic acetate–

propionate–butyrate pool derived from non-digestible carbohydrate (15,26,27,29); those SCFAs signal through GPR41 and GPR43 and, for butyrate, histone deacetylase inhibition, influencing gut-hormone secretion, hepatic and adipocyte lipid handling, and epigenetic regulation (15,28,46,52). If these effects favor appetite regulation, insulin sensitivity, hepatic lipid metabolism, barrier integrity, and inflammatory tone, the net result would be less central fat (15,19,21), read more sensitively than BMI or total weight (8–11). The essential qualification, carried from section 2.2, is that this is a mechanistic scaffold assembled largely from animal, adult, and *in vitro* evidence, with several steps hypothetical in adolescents; it is not a causal sequence validated end-to-end in the target population.

8.2 What's new here

No single claim here is new. Each mechanistic step has precedent in the adult and mechanistic literature; what is new is the integration of three domains usually kept apart: probiotic supplementation in adolescent obesity (57), gut-derived SCFAs as functional metabolites in pediatric populations (5,14,15,26,27,29,34,37), and WHtR as a central adiposity marker with population-specific validity (5–12). Existing adolescent trials report anthropometric or microbiota outcomes but rarely both and seldom quantify SCFA (17–20,24,58,59). Untargeted fecal metabolomics, used alongside targeted quantification as defined in Section 2, is positioned as the missing functional link (6,34,35).

8.3 WHtR and untargeted metabolomics as the readout choice

WHtR is well validated for discrimination but still underused as a primary endpoint, with most trials defaulting to BMI or BMI z-score (6). Two things recommend it. Because visceral and abdominal depots drive obesity-related metabolic dysregulation, an index that reflects them registers meaningful change more readily than one indexing total mass to height (8,9): an intervention trimming central fat while sparing lean mass, as dietary, activity, or microbiota-modulating approaches might, could move WHtR with little BMI change, so BMI alone risks a false negative (68–72), and its age-independence suits populations spanning pubertal stages, where longitudinal imaging shows depot-specific fat tracking, triglycerides, hsCRP, and leptin regardless of BMI, and BMI z-score obscuring shifts driven by pubertal stage (73). Pairing WHtR with untargeted fecal metabolomics, alongside targeted SCFA measurement, supplies the functional readout that anthropometry alone cannot. WHtR is not, however, a direct measure of visceral adipose tissue, and where feasible it should be complemented by body-composition assessment, imaging, and cardiometabolic biomarkers.

8.4 Research gaps

The gaps form a consistent set. Trials rarely use WHtR as a primary or co-primary endpoint (5–12). Few pairs of fecal SCFA measurements with an anthropometric outcome. Where SCFA data exist, they often dissociate from composition, as in Larsen et al. (40). Based on our search, untargeted fecal metabolomics has been applied in no adolescent probiotic trials (38,39). Geography is the third gap: trials cluster in Iran, Turkey, the United States, and Europe, with none from Southeast Asia despite its rapid nutrition transition and lower WHtR cut-offs (5,6,42). Addressing these gaps calls for trials that combine WHtR as a primary or co-primary endpoint, fecal SCFA quantification paired with untargeted metabolomics, standardized adjustments for diet and pubertal stage, and recruitment from underrepresented populations. This review is written independently of any single trial. The authors are conducting a randomized trial in Indonesian adolescents that incorporates these design features; it is mentioned here only for transparency, and the arguments above stand on the published literature rather than on that ongoing work.

9. DISCUSSION

The most useful thing this literature offers is not a verdict on whether probiotics work in adolescents. Still, a diagnosis of why the question remains hard reveals two dominant measurement problems that dominate. First, fecal SCFA concentration does not report what mechanistic models assume: most colonic SCFA is absorbed before the rectum (26,27,30), and the systemic metabolic effects of SCFAs on appetite, insulin sensitivity, and lipid handling track circulating rather than fecal concentrations (26), so a fecal value marks the unabsorbed luminal remainder, not microbial synthesis or systemic exposure (30). Much of the apparent contradiction dissolves once that distinction holds and bacterial abundance and fecal concentration are kept separate (14,34,37). Second, composition and function dissociate. Larsen et al. reported an altered microbiota with no corresponding SCFA shift (23), and the same dissociation appeared wherever this review found the two measured together, so trials (19) measuring composition alone cannot tell whether an intervention altered the metabolic output that sits between microbiota and central adiposity. Pairing composition with a functional readout, extending beyond the three principal SCFAs via untargeted metabolomics (38,39), is the single change most likely to move the field from association toward mechanism.

A third problem is not one of measurement. The optimal WHtR cut-off is lower in Asian than in European youth, at about 0.46 versus 0.50 (5,6,12). Central fat often coexists with a normal BMI in Indonesian adolescents (5), and no adolescent probiotic trial with an adiposity endpoint has been run in a Southeast Asian population (18,39,54), the one Southeast Asian probiotic study identified, Joseph et al., enrolled Malaysian schoolchildren in a before-and-after design with no control arm and no adiposity outcome (23), findings from Iranian, Turkish,

American, and European cohorts cannot be assumed to transfer (38,42,57). Against the divided systematic reviews (17,18,25,60), individual-trial and mechanistic evidence have more traction than pooled estimates, which average across strain, dose, formulation, and population differences that determine whether a probiotic works at all. The framework in section 8 makes no claim of a reliable effect; it specifies the conditions under which the claim could be tested.

This narrative review indicates that the probiotic–SCFA–central obesity axis is biologically plausible but remains insufficiently validated in overweight and obese adolescents. Evidence supports several components of the pathway: probiotics may alter gut microbial composition and metabolic activity (16,29,43); SCFAs may influence appetite regulation, glucose and lipid metabolism, gut barrier integrity, and inflammatory signaling (15,26–28); and WHtR is a clinically relevant marker of central adiposity in this age group (6,8,9). However, no adolescent probiotic trial identified in this review has evaluated the entire pathway by simultaneously measuring probiotic exposure, functional microbial metabolites, and changes in WHtR (18,55). The available evidence, therefore, supports a mechanistic hypothesis rather than a confirmed causal sequence.

A major interpretive challenge concerns the meaning of fecal SCFA concentrations. Because most SCFAs produced in the colon are absorbed before reaching the rectum, fecal measurements represent only the residual balance of microbial production, mucosal absorption, intestinal transit, substrate availability, and stool water content (26,27,30). Higher fecal SCFA concentrations should therefore not automatically be interpreted as greater microbial production or a more favorable metabolic response. They may reflect increased fermentation, reduced absorption, faster intestinal transit, or a combination of these processes. This distinction may explain why pediatric studies have reported both higher and lower fecal SCFA concentrations in association with obesity (14,34,37). It also emphasizes that fecal SCFA concentration, circulating SCFA exposure, and the abundance of SCFA-producing bacteria are related but non-interchangeable measures (26,27,30,34).

The available studies further demonstrate that microbiota composition and metabolic function do not necessarily change in parallel. Larsen et al., for example, reported changes in microbial composition without corresponding changes in fecal SCFAs (19). This finding suggests that taxonomic shifts alone cannot establish whether an intervention has altered the metabolic output that may link the microbiota to central adiposity. Conversely, metabolic activity may change without major, detectable alterations in relative bacterial abundance due to shifts in microbial gene expression, substrate utilization, cross-feeding, or community-level functions (29). Future studies should therefore combine microbiota profiling with functional measurements. Targeted SCFA analysis can quantify prespecified metabolites, whereas untargeted fecal metabolomics (67) may identify broader changes in bile acids, amino acid-related compounds, branched-chain fatty acids, and other microbial products relevant to obesity (38,39).

The clinical evidence does not currently support a uniform beneficial effect of probiotics on adolescent adiposity. Probiotic-only trials have not shown a between-group reduction in central adiposity. Larsen et al. left anthropometric measures unchanged (19), and one small trial reported an increase in total and trunk adiposity (20). Famouri et al. reported a fall in waist circumference in the probiotic group but as a within-group change, alongside unchanged weight, BMI, and BMI z-score, and in a population selected for sonographic non-alcoholic fatty liver disease (21). In contrast, some systematic reviews have reported improvements in selected anthropometric, inflammatory, or metabolic outcomes, particularly with multi-strain products or longer interventions (17,60). Others, by contrast, have concluded that the evidence is uncertain or of low certainty (18,25). These differences likely reflect substantial heterogeneity in probiotic strain, dose, formulation, intervention duration, participant age, baseline metabolic status, co-interventions, and outcome selection (16,43). Probiotics should therefore not be regarded as a single homogeneous intervention, and findings from one strain or formulation should not be generalized to other products.

Diet is a particularly important determinant of SCFA production and may substantially modify probiotic effects. Microbial fermentation depends on the availability of non-digestible carbohydrates, resistant starch, and dietary fiber (15,26,27,37). A probiotic strain may have limited functional effects when the host diet provides insufficient fermentable substrate. Conversely, changes in fiber intake during an intervention may alter SCFA profiles independently of probiotic supplementation. Dietary intake should therefore be assessed at baseline and during follow-up, including total energy, fiber quantity and type, resistant starch, fermented foods, and ultra-processed food consumption (5). Where healthy-living counseling is provided to both intervention and control groups, its potential contribution to changes in diet, microbial metabolism, and adiposity should also be considered.

Host characteristics may further influence intervention response. Puberty is accompanied by major changes in sex hormones, insulin sensitivity, lean mass, fat distribution, and potentially gut microbiota composition (3,5,73). Chronological age alone may therefore be an inadequate indicator of biological maturity. Pubertal stage and sex should be recorded and considered in stratification or adjusted analyses. Baseline microbiota composition, habitual diet, recent antibiotic exposure, gastrointestinal conditions, adherence, and metabolic phenotype may also distinguish responders from non-responders (29,43). Future trials may consequently need to examine heterogeneity of treatment effects rather than relying only on average intervention effects.

The WHtR may be particularly useful as an anthropometric endpoint in this field. BMI remains important for obesity classification, but it cannot distinguish fat mass from lean mass or identify the distribution of adiposity (6,8,9). A microbiota-modulating intervention could theoretically reduce abdominal fat or improve metabolic function without producing a substantial change in total body weight. Such effects may be better captured by

WHtR or waist circumference than by BMI alone (8,9,68,69). Nevertheless, WHtR is not a direct measure of visceral adipose tissue and should, where feasible, be complemented by body-composition assessment, imaging, and cardiometabolic biomarkers. Population-specific interpretation is also important because the optimal WHtR threshold may differ across ethnic and geographic populations (5,10,12).

The geographical concentration of existing studies limits the generalizability of current findings. Most adolescent probiotic trials have been conducted outside Southeast Asia, despite regional differences in habitual diet, gut microbiota, environmental exposures, body composition, and cardiometabolic risk (42,57). Asian adolescents may develop central adiposity and metabolic abnormalities at lower BMI or WHtR values than some Western populations (5,10,12). Findings from Iranian, Turkish, European, or North American cohorts should therefore not be assumed to apply directly to Indonesian adolescents (5). Mechanistically integrated studies in Southeast Asian populations are needed both to evaluate the proposed pathway and to assess the relevance of population-specific anthropometric thresholds. This regional and methodological gap is a central rationale for the research proposed below.

10. STRENGTHS AND LIMITATIONS OF THE REVIEW

This review has several strengths. It integrates evidence from microbiology, metabolomics, nutrition, endocrinology, and pediatric obesity rather than evaluating probiotic efficacy solely through body weight or BMI. It also distinguishes microbial composition from metabolic function and emphasizes the limitations of interpreting fecal SCFAs as direct measures of microbial production or systemic exposure. In addition, it highlights WHtR as a practical marker of central adiposity and draws attention to the underrepresentation of Southeast Asian adolescents.

Several limitations should also be acknowledged. As a narrative review, study selection and interpretation were not based on a fully systematic screening process or formal risk-of-bias assessment, and publication bias cannot be excluded. Small sample sizes and substantial heterogeneity in probiotic products, intervention duration, analytical methods, and outcomes limited the available clinical literature. Some proposed biological pathways were derived primarily from animal, in vitro, or adult studies and may not translate directly to adolescents (30,46,52). Furthermore, fecal metabolite concentrations provide only a partial representation of microbial metabolism and cannot determine metabolite flux or systemic exposure (30,43).

Future randomized trials should use well-characterized, strain-specific probiotic formulations with verified viability throughout storage and the intervention period (43,44,66). WHtR and other measures of central adiposity should be prespecified, and waist measurements should be standardized. Microbiota profiling should be combined with targeted SCFA analysis and broader metabolomics (38,39,67), ideally complemented by circulating metabolites and relevant metabolic biomarkers (30). Dietary intake, pubertal stage, antibiotic exposure, adherence, and baseline microbiota should also be assessed. Mediation analyses could then evaluate whether changes in microbial function precede or statistically explain changes in central adiposity.

Overall, the evidence does not yet establish that probiotic supplementation reduces central obesity in adolescents through SCFA-mediated mechanisms. Rather, it identifies a coherent but incompletely tested pathway and clarifies the methodological requirements for evaluating it. The priority is therefore not merely to conduct more probiotic trials, but to undertake mechanistically integrated, strain-specific studies that link microbial changes to clinically meaningful improvements in central adiposity and metabolic health.

11. FUTURE PERSPECTIVE

11.1 Multi-omics integration

Taxonomic change without functional change runs through this review, and it is a measurement problem. The three layers answer different questions: metagenomics reports which genes are present, metabolomics what was produced, and metatranscriptomics which genes were being transcribed. Larsen et al. found a compositional shift with no change in fecal SCFA (19). With only two layers, a community that failed to respond cannot be distinguished from one that responded without altering its output. The transcriptional layer separates them. Li et al. paired shotgun metagenomics with serum metabolomics in children with obesity (34), and Therdtatha et al. combined microbiome and fecal metabolite profiling in Thai schoolchildren (42). Neither was a probiotic trial. No study has yet stacked the layers within a single intervention, with untargeted profiling generating hypotheses and targeted panels testing them (21,38,39).

11.2 Personalized probiotic selection

The question is whether a response to a given strain can be predicted before allocation rather than explained afterward. Holmes et al. applied an ex vivo fermentation model to stool from adolescents with obesity and found that SCFA output varied with the supplied substrate and the donor's own community (41). Before randomization, such an assay would turn the baseline microbiota from a post hoc explanation into a stratification variable. Sequencing has been proposed as a basis for individualized selection in pediatric obesity (14); no trial has yet acted on such a prediction.

11.3 Precision nutrition

Precision nutrition here means measuring intake well enough to model it, then designing the supplement around the diet rather than around the organism alone. A strain given to an adolescent eating little fermentable carbohydrate is working without raw material, so a null result reflects the diet as much as the product (15,20,21,31).

11.4 Biomarker-guided strategies

A biomarker-guided trial must prespecify three things: which analyte, which compartment, and which threshold. None is settled. Fecal SCFA indexes luminal activity. In adults, it was the circulating pool, not the fecal one, that tracked insulin sensitivity, lipolysis, and GLP-1 (30), so the compartment decides what a null result means. Untargeted metabolomics widens the readout beyond three analytes (21,38,39) but generates hypotheses rather than testing them; a validated, targeted protocol makes the output interpretable (21). The threshold is anthropometric. In Asian, African, and South American youth, the optimal WHtR cut-off lies closer to 0.46–0.49 than to 0.5 (5,10–12), so a single global threshold would misclassify the population of interest.

11.5 Longitudinal designs

Adolescence is not a static background. Microbiota composition and SCFA output are still settling during this window (31–33), and adipose depots track differently across pubertal stages, independent of BMI (73). The trials in **Table 1** ran for eight to sixteen weeks, possibly less than the turnover time of the resident community and certainly less than the interval over which central adiposity shifts. Longitudinal cohorts with repeated sampling would establish the developmental trajectory against which an effect must be judged and supply the temporal ordering that mediation requires (section 6.3). Follow-up beyond the intervention would show whether any microbiota effect outlasts the supplement.

11.6 Translational priority

These five share one shift. The question is not whether probiotics work, but for whom, how, and for how long. The Cochrane verdict of very low certainty across all outcomes (18) describes what happens when heterogeneous products meet heterogeneous readouts in trials too short for the endpoint to move. In Southeast Asia, where no trial has been conducted despite a rapid nutrition transition and lower cutoffs (42,49), the opportunity lies in properly designing the first one.

12. CONCLUSION

The probiotic–SCFA–central obesity axis is biologically plausible but remains unconfirmed in adolescents. Current evidence does not establish probiotics as an effective strategy for reducing central adiposity. Future strain-specific trials should integrate WHtR with functional microbiota and metabolomic outcomes to determine whether microbial changes translate into meaningful metabolic and anthropometric benefits.

ABBREVIATION

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMPK, AMP-activated protein kinase; BMI, body mass index; CI, confidence interval; CFU, colony-forming units; CRP, C-reactive protein; FFAR, free fatty acid receptor; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; FMT, fecal microbiota transplantation; GC-MS, gas chromatography–mass spectrometry; GLP-1, glucagon-like peptide-1; GPR41, G-protein-coupled receptor 41; GPR43, G-protein-coupled receptor 43; HDAC, histone deacetylase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; ISAPP, International Scientific Association for Probiotics and Prebiotics; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MD, mean difference; NAFLD, non-alcoholic fatty liver disease; OW/OB, overweight or obese; PYY, peptide YY; RCT, randomized controlled trial; SCFA, short-chain fatty acid; SMD, standardized mean difference; SREBP-1c, sterol regulatory element-binding protein 1c; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; WHtR, waist-to-height ratio.

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AUTHORS CONTRIBUTIONS

M.M. conceptualized the review, designed and conducted the literature search, appraised the evidence, and drafted and revised the manuscript. F.F., D.O., and R.A. contributed to the interpretation of the evidence. F.F. and R.A. supervised the review and critically reviewed, edited, and revised the manuscript for important intellectual content. R.A. provided final oversight of the version submitted for publication. All authors read and approved the final manuscript and agree to be accountable for its content.

CONFLICT OF INTERESTS
None declares.

AI USE STATEMENT
The author used an AI-assisted tool for language editing and reference formatting during manuscript preparation. AI tools were not used to generate scientific content, to conduct the literature search as a source of evidence, or to interpret data. The author reviewed and edited all output, verified every citation and factual claim against the primary sources, and takes full responsibility for the final content.

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TABELS

Table 1: Probiotic and synbiotic interventions in pediatric and adolescent obesity, compared by formulation, dose, duration, SCFA measurement, clinical outcome, and the mechanism the authors invoked.

Trial (ref)	Population and design	Strain or species	Duration	Dose and regimen as reported	Main clinical outcome	Mechanism
Larsen et al. (19)	50 obese adolescents; randomized, double-blind, placebo-controlled	*Lactobacillus salivarius* Ls-33 ATCC SD5208 single strain (probiotic)	12 wk	A daily dose of one capsule (10^{10} CFU per capsule)	• *Bacteroides–Prevotella–Porphyromonas* to *Firmicutes* ratio significantly increased ($p \leq 0.05$); • cell numbers of individual taxa unchanged; • no effect on metabolic syndrome in the parent trial **Fecal SCFA measured by gas chromatography and unchanged**	Compositional shift proposed to alter fermentation; not tested. The clearest demonstration that taxonomic and functional change can dissociate

Trial (ref)	Population and design	Strain or species	Duration	Dose and regimen as reported	Main clinical outcome	Mechanism
Jones et al. (20)	19 obese Hispanic/Latino adolescents (8 probiotic, 11 placebo); terminated early	VSL#3 multi-strain (probiotic powder) mixture of eight strains of live, freeze-dried lactic acid bacteria: *streptococcus thermophilus, bifidobacterium breve, bifidobacterium longum, bifidobacterium infantis, lactobacillus acidophilus, lactobacillus plantarum, lactobacillus paracasei, and lactobacillus delbrueckii* subsp. *Bulgaricus* (Sigma-Tau Pharmaceuticals, Product: VMS003DL)	16 wk	• Three sachets daily; • CFU per sachet not recoverable • Each sachet contains 450 billion lyophilized lactic acid bacteria	• Total adiposity increased (+1.7 ± 0.6% vs −1.3 ± 0.5%, $p < 0.01$) and trunk adiposity increased (+3.3 ± 0.8% vs −1.8 ± 0.8%, $p < 0.01$); • no effect on liver fat or fibrosis, insulin, glucose, gut microbial abundance or gut hormones **Fecal SCFA not measured**	Appetite regulation via gut hormones was the stated hypothesis; the hormones were measured and did not change, so the proposed mechanism was not supported
Joseph et al. 2019 (23)	42 normal-weight and overweight schoolchildren, Selangor, Malaysia; pre–post, no control arm	LcS-fermented probiotic drink composed of fructose, maltitol, skimmed milk powder, glucose and permitted flavoring in an 80-ml bottle (probiotic)	1st phase: 4 wk 2nd phase: 4 wk	probiotic drinks contained at least 3.0×10^{10} colony-forming units of LcS	Microbiota composition and SCFA profiles reported before and after administration; the absence of a control group prevents causal inference **Fecal SCFA measured, the only pediatric dataset pairing microbiota with SCFA across a probiotic intervention**	Cross-feeding of resident SCFA producers; inferred from paired profiling rather than tested

Trial (ref)	Population and design	Strain or species	Duration	Dose and regimen as reported	Main clinical outcome	Mechanism
Famouri et al. 2017 (21)	64 obese children and adolescents with sonographic NAFLD; randomized, triple-blind	*Lactobacillus acidophilus* ATCC B3208, *Bifidobacterium lactis* DSMZ 32269, *B. bifidum* ATCC SD6576, *Lacticaseibacillus rhamnosus* DSMZ 21690 (four strains)	12 wk	Single capsule; per-strain • *Lactobacillus acidophilus* ATCC B3208 ($3x10^9$ CFU), • *Bifidobacterium lactis* DSMZ 32269 ($6x10^9$ CFU), • *B. bifidum* ATCC SD6576 ($2x10^9$ CFU), • *Lacticaseibacillus rhamnosus* DSMZ 21690 ($2x10^9$ CFU)	• ALT fell 32.8 → 23.1 U/L (P = 0.02) and AST 32.2 → 24.3 U/L (P = 0.02); • cholesterol, LDL-C, triglycerides and waist circumference fell; • weight, BMI and BMI z-score unchanged; • normal liver sonography in 53.1% vs 16.5% **Fecal SCFA not measured**	Hepatic lipid handling and gut barrier function; inferred from biochemistry, with no mechanistic measurement
Sanchis-Chordà et al. 2019 (22)	48 obese, insulin-resistant children aged 10–15 y; all received dietary advice	*Bifidobacterium pseudocatenulatum* CECT 7765 single strain (probiotic)	13 wk	Daily capsule; $10^{-9–10}$ CFU	• hsCRP fell (P = 0.026) and MCP-1 fell (P = 0.032); • HDL-C rose (P = 0.035) and omentin-1 rose (P = 0.023); • Rikenellaceae and Alistipes increased; BMI fell in all children, which the authors attribute to the dietary advice **Fecal SCFA not measured**	Anti-inflammatory action on the endotoxin–cytokine axis; the inflammatory readouts moved, but no barrier, endotoxin or SCFA measure was taken
Atazadegan et al. 2023 (24)	60 overweight or obese children and adolescents aged 8–18 y; randomized, double-blind	*Lactobacillus coagulans* SC-208 and *L. indicus* HU36, with fructo-oligosaccharide two strains (symbiotic)	8 wk	Two capsules daily; total and per-strain ($6x10^9$ CFU),	• WHtR fell within the synbiotic group (0.55 ± 0.05 → 0.54 ± 0.05, P = 0.05); • no significant between-group difference in WHtR or in any other anthropometric or body-composition measure	Prebiotic-driven fermentation; the prebiotic component means any SCFA effect cannot be attributed to the strains

Trial (ref)	Population and design	Strain or species	Duration	Dose and regimen as reported	Main clinical outcome	Mechanism
					Fecal SCFA not measured	
Kilic Yildirim et al.-Probesity-2 (58,59)	61 children with exogenous obesity; randomized, double-blind; all received standard diet and increased physical activity	Multi-strain synbiotic supplement (probiotic mixture including *Lactobacillus acidophilus, Lacticaseibacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Enterococcus faecium* and *fructo-oligosaccharides*) (*Probesity-2, symbiotic)*	12 wk	One sachet daily; 4.3 × 10^8 CFU per strain, once daily a synbiotic supplement	Between-group reductions in body weight ($P < 0.01$), BMI ($P < 0.05$), waist circumference ($P < 0.05$) and waist-to-height ratio ($P < 0.05$); no difference in glucose, lipids or NAFLD prevalence **Fecal SCFA not measured; microbiota profiled in the companion report (48)**	Combined prebiotic and probiotic effect; the design cannot separate the probiotic contribution from the prebiotic. Diet and activity were prescribed to both arms and do not confound the between-group comparison

Note: Trials are ordered by publication year within probiotic and synbiotic classes. The mechanism column records the pathway proposed in each report, not a measured pathway; no trial in this table quantified the mechanism it invoked. Dose is reported as in the primary study. Where a colony-forming unit exponent could not be recovered from the indexed record, the cell is marked for verification against the full text rather than estimated.

Table 2: Recent systematic reviews and meta-analyses of probiotic, prebiotic, and synbiotic supplementation in overweight or obese children and adolescents. The four syntheses do not converge; the disagreement reflects differences in pooled trials, strain grouping, and included age ranges.

Review (ref)	Design & scope	Significant effects	No effect/null	Certainty	Overall conclusion	Main reason it differs from the others
Zhang et al. (17)	Bayesian network meta-analysis; 15 RCTs, 820 participants; OW/OB children & adolescents	Multi-strain probiotics: ↓ BMI (MD −2.13 kg/m²), ↓ waist circumference (−1.34 cm), ↓ total cholesterol, triglycerides, leptin, and hs-CRP. Synbiotics: ↓ BMI z-score, ↓ LDL	Synbiotics: small ↑ fasting glucose	Moderate–low	Multi-strain and combined regimens improve anthropometric and inflammatory outcomes	The network approach ranks multi-strain and combined regimens separately, surfacing benefits that pairwise pooling dilutes
Fahim et al. (18)	Cochrane systematic review; 17 RCTs, 838 participants; 0–19 y (10–19 y analyzed separately)	Single-trial signals (0–19 y): prebiotics ↓ BMI & weight; synbiotics ↓ systolic BP; SCFAs ↓ waist circumference & BMI	Adolescents 10–19 y: probiotics & FMT little-to-no effect on BMI, weight, waist circumference, body fat, blood pressure	Very low	Little to no effect in adolescents; positive signals rest on single trials of <60 participants	Analyses adolescents separately and applies strict GRADE, so small-trial signals are downgraded

Review (ref)	Design & scope	Significant effects	No effect/null	Certainty	Overall conclusion	Main reason it differs from the others
Ding et al. (60)	Systematic review & meta-analysis; 16 RCTs, 763 participants; OW/OB children & adolescents	↓ BMI z-score, ↓ CRP, ↓ TNF-α; greater benefit when treatment >3 months or participants <12 y	No effect in participants with NAFLD	Not reported	Supplementation reduces adiposity and inflammation, with duration- and age-dependent benefit	Pools probiotics and synbiotics together and includes younger children, amplifying an age/duration effect
Wu et al. (25)	GRADE-assessed meta-analysis; RCTs; OW/OB children & adolescents	Probiotics alone: ↓ fasting blood glucose ($P < 0.001$)	No pooled effect on weight, BMI, BMI z-score, insulin, HOMA-IR, lipid parameters	GRADE-assessed	Supplementation "cannot improve cardiometabolic risk factors" overall	Focuses on cardiometabolic endpoints under GRADE, so most anthropometric signals fail to reach certainty

FIGURES

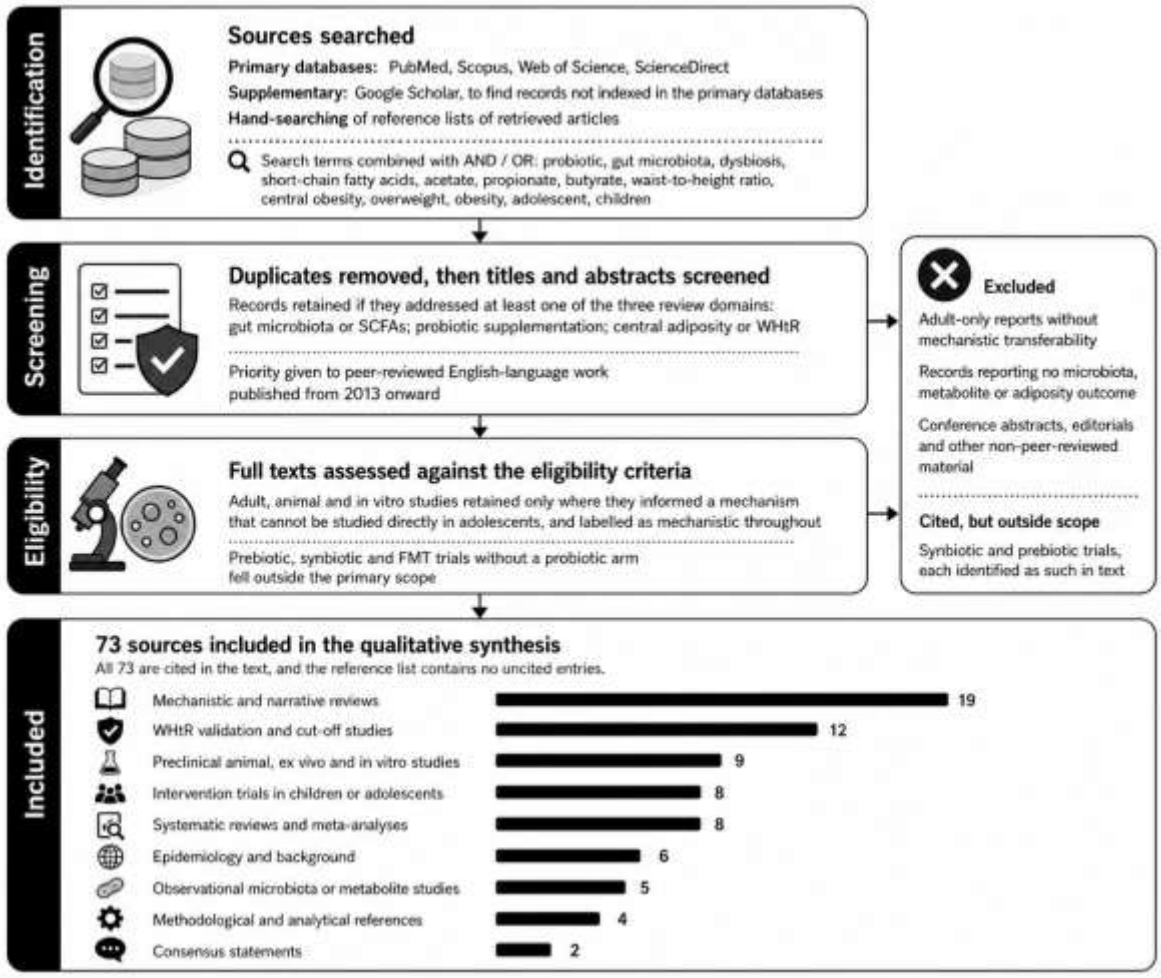


Figure 1. Search Methodology.
Study selection and composition of the evidence base. Searches were conducted between January and July 2026 for records published through July 2026 across four primary databases, with Google Scholar as a supplementary source and hand-searching of reference lists. Records were screened against the review's three domains, and full texts were assessed against the eligibility criteria, with exclusions on the grounds shown. Seventy-three sources

were retained for qualitative synthesis, classified here by evidence type; all 73 are cited in the text, and the reference list contains no uncited entries. Because the review was conducted as a narrative rather than a systematic review, the number of records at each screening stage was not recorded prospectively, and the figure reports the sources, criteria, and composition of the evidence, rather than stage-wise counts. FMT, fecal microbiota transplantation; SCFA, short-chain fatty acid; WHtR, waist-to-height ratio.

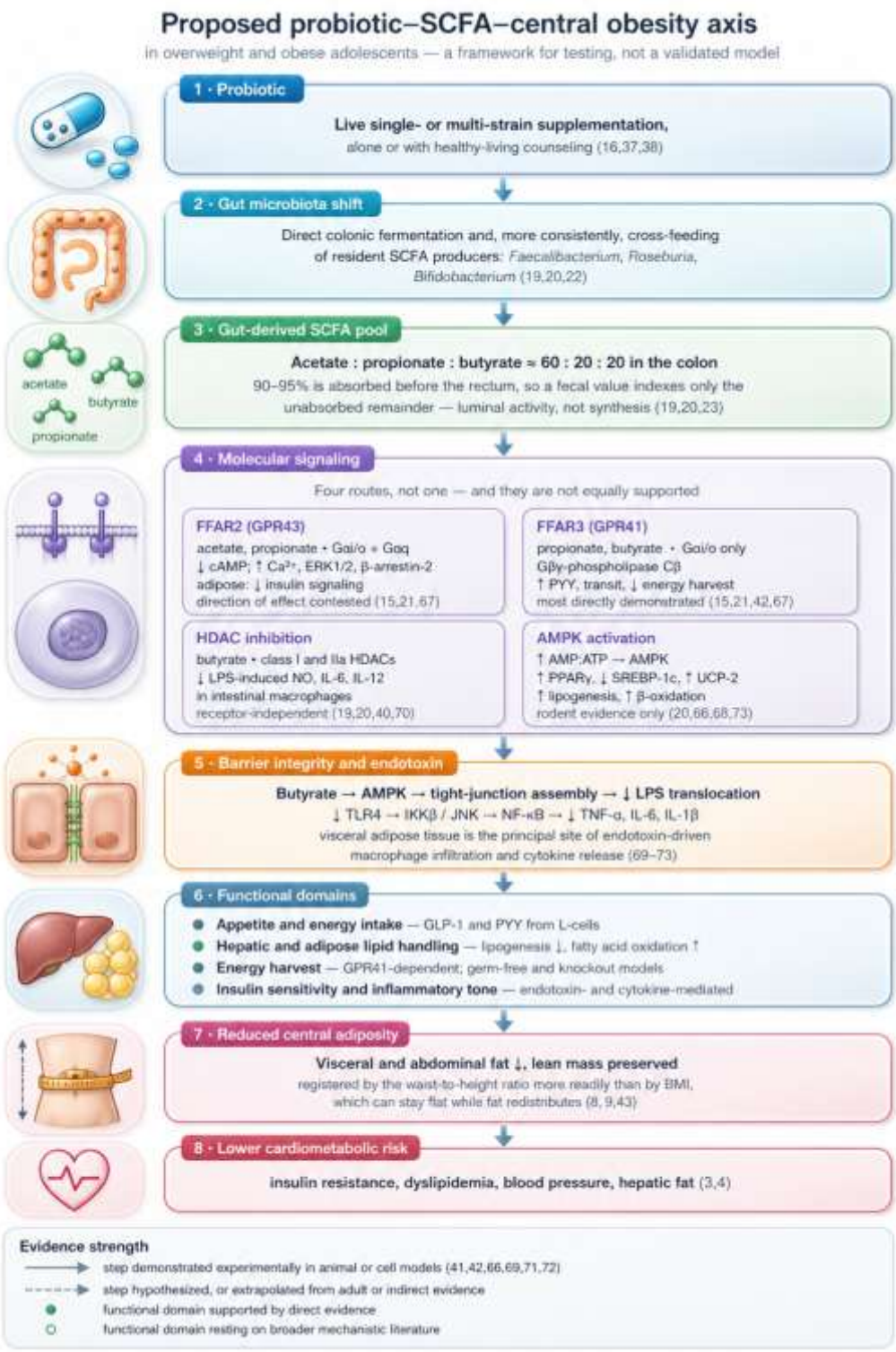
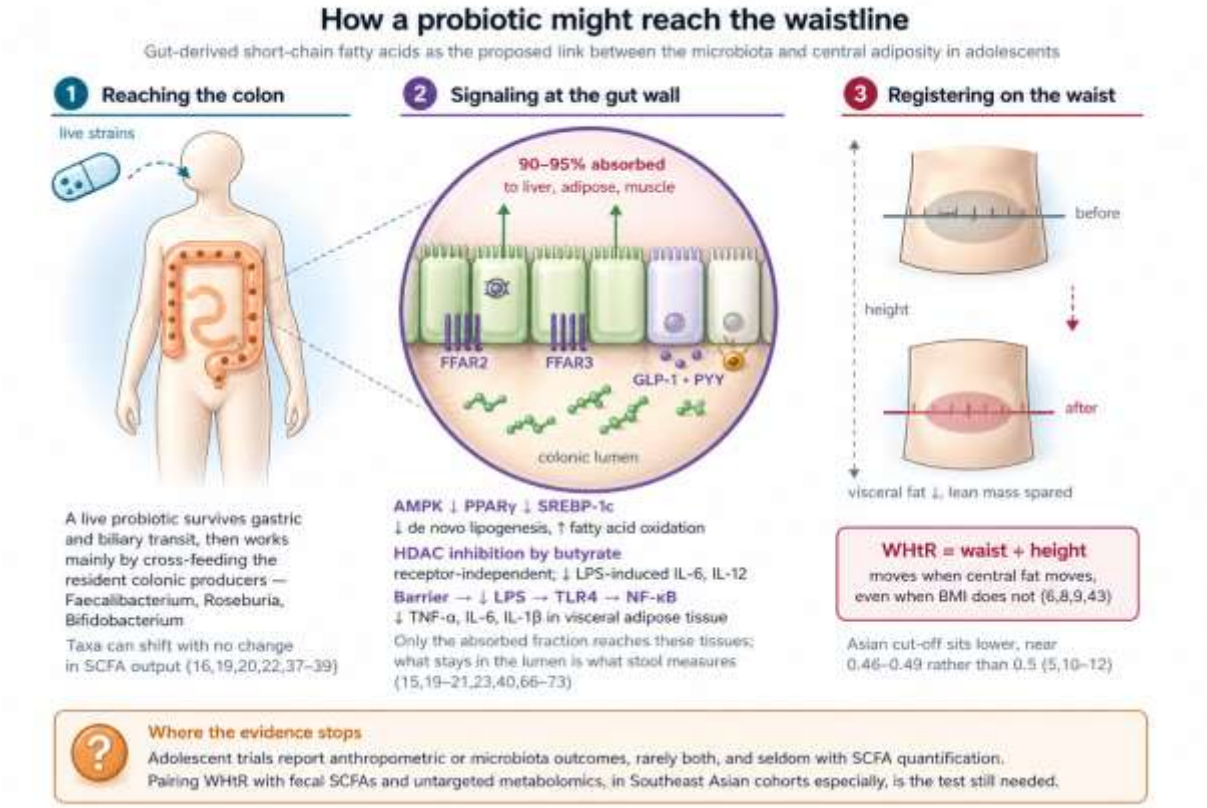


Figure 2. Proposed probiotic–SCFA–central obesity axis in overweight and obese adolescents.
Probiotic supplementation shifts the composition and metabolic activity of the gut microbiota, largely by cross-feeding resident short-chain fatty acid (SCFA) producers (stages 1–2). The resulting colonic acetate–propionate–butyrate pool is almost entirely absorbed before the rectum, so fecal SCFA concentration indexes luminal

microbial activity rather than microbial synthesis or systemic exposure (stage 3). Four molecular routes then carry the signal (stage 4). FFAR2 (GPR43) and FFAR3 (GPR41) differ in ligand preference and G-protein coupling; histone deacetylase inhibition by butyrate operates independently of both receptors; and AMP-activated protein kinase activation lowers PPARγ and SREBP-1c, shifting the cell from lipogenesis toward oxidation. AMPK also drives tight junction assembly, thereby reducing lipopolysaccharide translocation and downstream TLR4–NF-κB signaling (stage 5). These routes converge on appetite, hepatic and adipose lipid handling, energy harvest, insulin sensitivity, and inflammatory tone (stage 6), which together would reduce visceral and abdominal fat while sparing lean mass and change the waist-to-height ratio registers more readily than BMI (stages 7–8).
Solid arrows mark steps demonstrated experimentally in animal or cell models; dashed arrows mark steps that are hypothesized or extrapolated from adult or indirect evidence. In stage 6, filled circles mark domains with direct evidence and open circles those supported by broader mechanistic literature. No step in the chain has been tested end to end in overweight or obese adolescents, and the figure should be read as a framework for testing rather than as a validated causal model.

Graphical Abstract



A probiotic can shift the resident microbiota toward short-chain fatty acid (SCFA) producers, primarily through cross-feeding rather than direct fermentation. The acetate, propionate, and butyrate released act via FFAR2 and FFAR3, via histone deacetylase inhibition, and via AMPK-dependent suppression of PPARγ and SREBP-1c. At the same time, butyrate-driven tight-junction assembly limits lipopolysaccharide translocation and downstream TLR4–NF-κB signaling. Together, these would trim visceral and abdominal fat while sparing lean mass, a shift the waist-to-height ratio registers more readily than the body mass index does. Fecal SCFA is only a partial readout: it captures the fraction of colonic production that escapes absorption, not what the microbes synthesize or what reaches the circulation. Adolescent trials to date report anthropometric or microbiota outcomes, rarely both, and seldom with SCFA quantification. Pairing WHtR with fecal SCFAs and untargeted metabolomics, especially in Southeast Asian cohorts, where the cut-off is lower at roughly 0.46 to 0.49, is the test the field still needs.