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The Iron–Gut Microbiome Axis in Adolescent Girls:Global Evidence, Mechanisms, and Therapeutic Strategies to Combat Anemia

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ABSTRACT

Background and Aims: Anemia remains one of the most pervasive nutritional disorders worldwide, affecting approximately 1.92 billion individuals in 2021 and contributing to nearly 52 million years lived with disability (YLDs) [1]. Among vulnerable populations, adolescent girls bear a disproportionate burden due to the combined physiological demands of rapid growth, expanding blood volume, and the onset of menstruation, compounded by chronically inadequate dietary iron intake in low- and middle-income countries (LMICs). Emerging evidence over the past five years has significantly advanced our understanding of anemia pathophysiology, positioning the gut microbiome as a critical determinant of iron homeostasis and absorption.

Methods: This narrative evidence synthesis integrates findings from the Global Burden of Disease Study 2021, WHO surveillance reports (2025), and recent systematic reviews, randomized controlled trials (RCTs), and two-sample Mendelian randomization (MR) studies published between January 2021 and April 2025. Databases including PubMed, Embase, Cochrane Library, and Web of Science were systematically explored. Priority was given to studies examining interactions between iron metabolism, gut microbiota, hepcidin regulation, and adolescent or reproductive-age female populations. Evidence from probiotic, prebiotic, and synbiotic interventions, along with dietary iron bioavailability studies, was appraised using GRADE-informed criteria.

Results: Despite a modest decline in global anemia prevalence from 28.2% in 1990 to 24.3% in 2021, the absolute burden has increased from 1.50 to 1.92 billion cases due to demographic expansion in high-risk regions. Dietary iron deficiency accounts for 66.2% of anemia-related YLDs, disproportionately affecting women. Mechanistic studies demonstrate that iron deficiency anemia (IDA) disrupts gut microbial balance by reducing beneficial genera such as *Lactobacillus* and *Bifidobacterium* while promoting pathogenic taxa including *Streptococcus* and *Clostridium*. This dysbiosis elevates hepcidin via IL-6/BMP-SMAD signaling, impairing iron absorption and reinforcing a vicious cycle of deficiency. MR analyses further confirm causal links between specific microbial taxa and IDA risk. Importantly, RCTs indicate that microbiome-targeted interventions and optimized alternate-day iron dosing significantly improve hematological outcomes.

Conclusions: In conclusion, adolescent anemia should be reframed as a gut–iron axis disorder rather than a condition driven solely by dietary insufficiency. Integrated strategies combining iron supplementation with microbiome modulation offer a more effective and sustainable approach. Targeting this critical developmental window may yield long-term benefits for hematological health, reproductive outcomes, and intergenerational nutrition.

Keywords: *Iron deficiency anemia; Adolescent girls; Gut microbiome; Hepcidin; Probiotics; Prebiotics; Global burden of disease; Lactobacillus; Short-chain fatty acids; Iron bioavailability; Mendelian randomisation*

Introduction

Iron deficiency anemia (IDA) is the world's most prevalent micronutrient disorder, yet it has remained stubbornly resistant to resolution through conventional supplementation approaches. Decades of large-scale ferrous sulfate distribution programmes have yielded partial and geographically uneven reductions in anemia burden, prompting scientific and public health communities to interrogate whether the prevailing paradigm of 'more iron' is mech-

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anistically sufficient [2]. The Global Burden of Disease (GBD) Study 2021, published in The Lancet Haematology, provides the most rigorous contemporary epidemiological verdict: despite a relative decline in age-standardised prevalence rates since 1990, 1.92 billion prevalent cases of anemia were recorded in 2021 — an absolute increase attributable to demographic expansion in high-prevalence settings — and the condition generated 52 million YLDs in that year alone [1]. These figures confirm that anemia remains not merely a residual problem of nutritional transition but an active, growing global crisis.

Among all affected demographic groups, adolescent girls occupy a position of exceptional biological vulnerability and, simultaneously, of exceptional strategic importance. The World Health Organization defines adolescence as the period from ages 10 to 19 years, during which physiological, neurological, and reproductive development occurs in a compressed timeframe unparalleled in postnatal life [3]. During these years, skeletal mass may double, blood volume expands substantially, and the onset of menstruation introduces a sustained monthly iron drain that must be continuously replenished from dietary and stored iron reserves [2]. Iron requirements during peak pubertal growth increase to 10–20 mg/day — substantially exceeding the approximately 1–2 mg of elemental iron that can be absorbed from a typical bioavailable dietary intake under normal gut conditions [4]. In LMIC settings, where plant-based diets with high phytate and polyphenol content predominate and animal-source food access is limited, this physiological demand is chronically unmet [5].

The convergence of these biological realities with dietary inadequacy creates conditions of profound susceptibility to IDA. What is now emerging from the mechanistic literature, however, is that this vulnerability is not simply a problem of dietary iron supply: it is co-generated by the gut microbiome. Over the period 2021–2025, a body of evidence has accumulated from Mendelian randomisation analyses, murine model experiments, and human clinical trials that the gut microbial ecology is simultaneously a cause and a casualty of iron deficiency [6,7,8,9]. This bidirectional axis — in which IDA depletes the beneficial microbial taxa that directly facilitate iron absorption, which further deepens iron deficiency — has transformed the conceptual model of adolescent anemia and opened a therapeutically consequential new frontier.

The gut microbiome is also characterised by heightened plasticity during adolescence relative to the adult period, rendering it more responsive to dietary and pharmacological manipulation [10]. The adolescent gut microbiome undergoes profound compositional reorganisation under the influence of pubertal hormones, dietary transitions, stress, and antibiotic exposures — simultaneously creating vulnerability to dysbiosis and an opportunity for targeted intervention with durable effects [11]. An adolescent girl whose gut microbial ecology is optimised for iron absorption enters her reproductive years — and, critically, her first pregnancy — with a decisive biological advantage over her iron-depleted counterpart.

This review synthesises the global literature from 2021 to 2025 across three interlocking domains: (1) the epidemiology and clinical consequences of anemia in adolescent girls; (2) the mechanistic architecture of the iron–gut microbiome axis, incorporating causal evidence from Mendelian randomisation and molecular pathway analyses; and (3) the emerging evidence base for gut-centred therapeutic strategies, including probiotics, prebiotics, and pharmacodynamically optimised iron dosing. Our aim is to provide clinicians, public health nutritionists, and translational researchers with an integrated, evidence-grounded framework for addressing one of the most consequential — and most tractable — nutritional challenges of our time.

Global Epidemiology of Anemia: A 2021 Landscape

Prevalence Trends and the Absolute–Relative Divergence

The GBD Study 2021 provides the most methodologically rigorous characterisation of global anemia burden to date, employing Bayesian spatiotemporal modelling across 204 countries and territories [1]. Global anemia prevalence across all ages declined from 28.2% in 1990 to 24.3% in 2021 — a meaningful relative improvement sustained over three decades. However, the absolute case burden increased from approximately 1.50 billion to 1.92 billion cases over the same period, a divergence explained by the amplifying effect of population growth in high-prevalence LMICs. This discordance between relative and absolute metrics is not a statistical artefact: it represents a critical public health message that progress on age-standardised per-capita rates has not translated into fewer people suffering.

The cause-specific decomposition of GBD 2021 data is equally instructive. Dietary iron deficiency was identified as the leading cause of anemia YLDs, accounting for 66.2% of total cases, with 825 million women and 444 million men affected globally [1]. This confirms that IDA is the primary aetiological driver at the population level; however, the GBD data simultaneously challenges the assumption that iron delivery alone will resolve the problem. Fewer than half of anemic individuals in clinical settings demonstrate adequate haematological response to iron supplementa-

tion when underlying malabsorption, inflammatory, parasitic, helminthic, or haemoglobinopathy-driven causes are not concurrently addressed [2]. This provides direct epidemiological motivation for the gut-microbiome-centred approach developed in this review.

Regional heterogeneity in anemia burden is profound and epidemiologically instructive. Western sub-Saharan Africa records prevalences approaching 47%, nearly eight times that of Western Europe, and the proportion of cases attributable to IDA specifically varies with local infection burden, dietary patterns, water quality, and sanitation infrastructure [1,5]. Table 1 summarises regional burden data with associated YLD estimates and Socio-demographic Index (SDI) classifications.

Table 1. Global and regional anemia burden, 2021.

Region	Anemia Prevalence (%)	IDA Proportion (approx.)	YLDs (millions)	SDI Category
Global (all ages)	24.3	66.2%*	52.0	—
South Asia	35.7	~70%	~18.0	Low-middle
Western sub-Saharan Africa	47.4	~65%	~14.0	Low
Central sub-Saharan Africa	35.7	~60%	~8.5	Low
North America	6.8	~45%	~1.2	High
Western Europe	6.0	~42%	~1.0	High
Australasia	5.7	~38%	~0.3	High

*YLD = years lived with disability; SDI = Socio-demographic Index. *66.2% of total anemia YLDs attributable to dietary iron deficiency (825 million women, 444 million men). Source: Gardner et al. (2023); Kassebaum et al. (2016).*

Adolescent Girls: A Population of Exceptional Vulnerability

Adolescent girls constitute the most intensively affected sub-population within the women-of-reproductive-age cohort, for reasons that are simultaneously biological, dietary, and social. From a physiological standpoint, the adolescent years are characterised by iron requirements of 10–20 mg per day during peak pubertal growth phases — substantially exceeding the roughly 1–2 mg of elemental iron that a typical bioavailable dietary intake delivers under conditions of normal gut absorptive function [2,4]. The onset of menarche adds an additional average iron loss of 0.5–1.0 mg per day through menstrual blood, rising considerably for the estimated 20–30% of adolescent girls who experience heavy menstrual bleeding (HMB), a figure that translates to 1.5–2.0 mg/day of additional iron drain in affected individuals [12,13].

Epidemiological data confirm the severity of this burden. WHO and UNICEF surveillance estimates that anemia affects approximately 30% of non-pregnant women aged 15–49 globally [3], but this aggregate figure underestimates the burden among younger adolescents, who face more acute growth-related iron demands without the dietary autonomy available to adults. Data from India's Comprehensive National Nutrition Survey (CNNS 2016–18) and the fifth National Family Health Survey (NFHS-5, 2019–21) document anemia prevalence of 59.1% among adolescent girls aged 15–19 years (Ministry of Health and Family Welfare, 2021), with burden concentrated in rural, low-income, and educationally marginalised households. Cross-sectional hospital-based data from AIIMS Patna recorded an overall anemia prevalence of 47.9% among adolescent girls aged 10–19, with iron deficiency confirmed in 17.8% via serum ferritin assessment — a figure that likely underestimates true population burden owing to clinic-attendance selection bias [14]. In the United States, representing a high-income comparator, documented iron deficiency in 21.9% and IDA in 5.8% of females aged 12–21, confirming that adolescent IDA is a globally distributed, not exclusively LMIC, phenomenon [15].

The clinical consequences of adolescent IDA extend substantially beyond fatigue and pallor. Cognitive impairment, diminished academic performance, reduced immune competence, and impaired cardiorespiratory fitness have all been documented in iron-deficient adolescents [2,16]. Perhaps most consequentially from a public health investment perspective, adolescent anemia is a direct antecedent of maternal anemia — itself estimated to contribute to 22% of global maternal mortality [17] — and of adverse pregnancy outcomes including low birth weight, preterm delivery, and impaired neonatal neurodevelopment [18]. The intergenerational reach of adolescent IDA makes it among the highest-leverage points in global nutritional investment; a dollar spent reducing anemia in adolescent girls potentially breaks a multigenerational cycle of deficiency [19].

The Bidirectional Iron–Gut Microbiome Axis: Mechanistic Framework

Architecture of Iron Absorption and the Colonic Iron Ecology

Dietary iron exists in two principal physicochemical forms: haem iron — present in animal-source foods, with frac-

tional absorption rates of 15–35% — and non-haem iron — present in plant foods, with absorption typically ranging from 2–15% depending on the dietary matrix, host iron status, and gastrointestinal milieu [4]. The primary anatomical site of iron absorption is the proximal small intestine — specifically the duodenum and proximal jejunum — where ferric iron (Fe^{3+}) is reduced to the more soluble ferrous form (Fe^{2+}) by duodenal cytochrome b (DCYTB) and taken up across the apical membrane via the divalent metal transporter 1 (DMT1, SLC11A2) [4]. Within the enterocyte, ferrous iron is either stored bound to ferritin or exported basolaterally into the circulation via ferroportin (SLC40A1), the sole known cellular iron exporter.

Of critical mechanistic importance for understanding the microbiome's role: only approximately 10% of ingested dietary iron is absorbed in the small intestine under conditions of adequate iron status [20]. The remaining ~90% transits to the large intestine — a fact that has been underappreciated in conventional IDA treatment frameworks but is central to the microbiome axis developed here. Luminal iron in the colon becomes a substrate for, and battleground between, commensal microbiota, opportunistic pathobionts, and host immune defences. The colonic microbial community is not a passive conduit but an active arena of iron ecology, and its composition profoundly influences both how much iron the host ultimately assimilates and whether the residual luminal iron fuels beneficial or pathogenic microbial growth [8,9].

Iron homeostasis at the systemic level is governed by hepcidin (HAMP), a 25-amino-acid antimicrobial peptide produced by hepatocytes that functions as the master regulator of iron efflux [21]. Hepcidin binds to the basolateral iron exporter ferroportin on duodenal enterocytes, hepatocytes, and reticuloendothelial macrophages, inducing its internalisation and lysosomal degradation, thereby blocking iron entry into the circulation. Elevated hepcidin — induced by iron excess, infection, or systemic inflammation — effectively locks absorbed iron within enterocytes, from which it is shed with normal intestinal epithelial cell turnover rather than entering the erythropoietic pool [4,21].

Microbial Depletion and Pathobiont Expansion in Iron Deficiency Anemia

The mechanistic relationship between IDA and gut dysbiosis is now well-characterised through both observational and experimental evidence. Iron-deficient intestinal environments consistently reduce the relative abundance of beneficial low-iron-requiring taxa — principally Lactobacillus and Bifidobacterium species — that are exquisitely sensitive to changes in luminal iron bioavailability [8,22]. This depletion is biologically significant and self-amplifying: Lactobacillus species are among the primary microbial producers of lactic acid in the intestinal lumen, and lactic acid directly lowers luminal pH, enhancing the solubility of ferric iron and facilitating its reduction to the absorbable ferrous form [22]. Their depletion in IDA therefore creates a positive feedback loop of worsening iron malabsorption, independent of dietary supply.

Conversely, unabsorbed luminal iron — whether from dietary sources or from the majority fraction of unabsorbed supplemental iron — preferentially fuels the growth of iron-requiring pathobionts including Streptococcus spp., Enterococcus spp., Escherichia coli, and Clostridium spp. [22,23] These organisms generate mucosal inflammation through pathogen-associated molecular pattern (PAMP)-mediated toll-like receptor activation, which triggers inflammatory cytokine release — particularly IL-6 and TNF-α — that drives hepatic hepcidin production via the BMP/SMAD signalling pathway and JAK-STAT cascade [4,21]. Elevated circulating hepcidin then suppresses ferroportin-mediated iron export, creating a dysbiosis–inflammation–hepcidin–malabsorption circuit that is simultaneously mechanistically tractable and clinically underappreciated. Table 2 maps the specific microbial actors, their mechanistic effects on iron metabolism, and clinical implications.

Table 2. Key microbial taxa and metabolites in the iron–gut microbiome axis: mechanisms and clinical significance.

Microbial Taxon / Mediator	Mechanism of Action	Effect on Iron Status	Clinical Implication
Lactobacillus spp.	Lactic acid production lowers luminal pH; catalyses Fe(III)→Fe(II) reduction; suppresses hepcidin-inducing inflammation	Protective; enhances non-haem iron bioavailability	Depleted in IDA; probiotic restoration improves iron absorption [24]
Bifidobacterium longum	Ferments prebiotic substrates to SCFAs (acetate, butyrate); anti-inflammatory; competes with iron-scavenging pathobionts	Protective; reduces IL-6-mediated hepcidin induction	Evidence-based probiotic candidate for IDA adjunct therapy [25]
Short-chain fatty acids (SCFAs)	Lower colonic pH; enhance iron solubility and absorptive surface; exert anti-inflammatory effects; upregulate DMT1 and ferroportin gene expression epigenetically	Increases iron absorption by 10–40%; reduces hepcidin indirectly	Primary biochemical target of prebiotic supplementation [26]

Desulfovibrio spp.	Compete for luminal iron; produce hydrogen sulphide; promote pathogenic iron sequestration	Increased in IDA; perpetuates iron-deficiency cycle	Potential biomarker of gut dysbiosis in IDA [14]
Streptococcus / Clostridia	Proliferate with excess luminal iron from unabsorbed supplements; trigger mucosal inflammation via PAMP-TLR signalling	Increased with high-dose daily iron; elevates hepcidin	Pharmacological rationale for low-dose alternate-day iron dosing [27]
Hepcidin (hepatic peptide)	Binds ferroportin on enterocytes and macrophages → internalisation → blocks iron export; circadian nadir in morning fasting state	Elevated by dysbiosis-driven inflammation; creates functional iron deficiency	Central molecular target; dysbiosis treatment reduces hepcidin; morning dosing exploits nadir [4]
GOS/FOS prebiotics	Selectively feed Lactobacillus/Bifidobacterium; generate butyrate and propionate; reduce phytate via microbial phytase; enhance DMT1 expression	Increase iron absorption; attenuate pathobiont-driven inflammation	Improved iron bioavailability in RCTs; protective of microbiome during supplementation [26]

GOS = galacto-oligosaccharides; FOS = fructo-oligosaccharides; SCFA = short-chain fatty acids; IDA = iron deficiency anemia; DMT1 = divalent metal transporter 1; PAMP = pathogen-associated molecular pattern; TLR = toll-like receptor.

Causal Evidence from Mendelian Randomisation

Observational associations between gut microbiota composition and IDA are susceptible to confounding by shared dietary determinants and reverse causation (i.e., IDA altering gut composition), methodological limitations that have historically constrained causal inference from this body of literature. The deployment of two-sample Mendelian randomisation (MR) has substantially strengthened the causal case in recent years by using germline genetic variants as instrumental variables — exploiting Mendel's second law to estimate causal effects immune to post-conception confounders [28].

The landmark 2025 two-sample MR study by Lei et al. used GWAS data from the MiBioGen Consortium (n = 18,340 individuals across 18 cohorts) as genetic instrument sources and IDA outcome data from the UK Biobank (484,598 participants including 2,941 IDA cases) as the target dataset [6]. Using inverse-variance weighted (IVW) analysis as the primary estimator, supplemented by MR-Egger, weighted median, and weighted mode sensitivity analyses to assess pleiotropy and robustness, the study identified nine genus-level gut microbial taxa with statistically significant causal associations with IDA risk. This represents, to our knowledge, the first methodologically rigorous genetic confirmation that the gut microbiome exerts a directionally causal influence on IDA susceptibility — not merely correlational co-occurrence.

Complementary bidirectional MR analysis demonstrated the reverse causal pathway: IDA causally alters gut microbiota composition and metabolic profiles, including reductions in protective SCFA-producing taxa and dysregulation of tryptophan–serotonin metabolic pathways that modulate hepcidin expression and intestinal inflammatory tone [7]. Together, these MR datasets establish, for the first time with genetic rigour, that the iron–microbiome relationship is genuinely bidirectional and causally operative across both directions of the axis — not an epiphenomenon of shared nutritional deprivation.

The Hepcidin–Ferroportin Pathway: The Molecular Chokepoint

Hepcidin is the mechanistic fulcrum of the iron–microbiome–anemia triad [4,21]. Under conditions of gut dysbiosis, the elevated mucosal permeability that accompanies depletion of barrier-protective commensals (particularly butyrate-producing anaerobes) allows translocation of microbial products — lipopolysaccharide (LPS), flagellin, and peptidoglycan — into the portal circulation. These microbial antigens, together with locally produced inflammatory cytokines (principally IL-6, TNF-α, and IL-1β), drive hepatic hepcidin production via BMP6/SMAD1/5/8 signalling and IL-6/JAK2/STAT3 cascade activation [21]. Elevated circulating hepcidin binds the extracellular loop of ferroportin on duodenal enterocytes and reticuloendothelial macrophages, triggering its ubiquitination, internalisation, and lysosomal degradation [4]. The functional consequence is iron sequestration within cells — a state of 'functional iron deficiency' that is haematologically indistinguishable from dietary iron deficiency by standard haemoglobin assessment but is mechanistically distinct and unresponsive to dietary iron augmentation.

This distinction carries profound clinical implications for adolescent girls in high-infection-burden environments. In settings where enteric infections, Helicobacter pylori colonisation, helminth infestation, or subclinical gut inflammation are prevalent, hepcidin-mediated iron sequestration may coexist with, or even exceed in magnitude, inadequate dietary iron intake — rendering conventional supplementation strategies partially or wholly ineffective [2,23]. Treatment of the underlying gut dysbiosis

and inflammatory milieu — through probiotic or prebiotic co-intervention, antiparasitic treatment, or anti-inflammatory dietary modification — represents the mechanistically rational clinical strategy in such cases, rather than escalation of iron dose, which may paradoxically worsen the pathobiont-mediated inflammatory cycle.

Gut-Centred Therapeutic Strategies: Mechanisms and Evidence

Probiotics: Mechanisms of Action and Clinical Evidence

Lactobacillus acidophilus and Bifidobacterium longum have accumulated the most substantial and mechanistically coherent evidence base as probiotic candidates for IDA adjunct therapy. Their mechanisms of action are multiple and directly aligned with the iron–microbiome axis described in Section 3. Lactic acid produced by Lactobacillus species lowers luminal pH, enhancing the solubility and absorptive potential of ferric iron [24]. Specific strains of Lactobacillus fermentum have been demonstrated to secrete molecules that directly catalyse the $Fe^{3+} \rightarrow Fe^{2+}$ reduction reaction, functioning as biological iron reductases in the intestinal milieu [22]. Bifidobacterium species contribute to SCFA production — particularly acetate and butyrate — that suppresses the IL-6 signalling cascade driving hepcidin elevation, directly attenuating the functional iron deficiency mechanism [4,25].

The experimental mechanistic data are corroborated by clinical RCT evidence. A 2024 RCT in adolescent girls study demonstrated that multi-strain probiotic supplementation (L. acidophilus and B. longum) over 8 weeks produced statistically significant improvements in haemoglobin concentration and serum ferritin levels compared with iron supplementation alone ($p < 0.05$), while the probiotic group reported substantially fewer gastrointestinal adverse effects [29]. This trial is particularly significant as it enrolled the target population — adolescent girls — that is underrepresented in most probiotic-IDA research. The 2024 systematic review and meta-analysis by Hu et al., pooling RCT data from six databases through November 2024 ($k = 14$ RCTs), confirmed that probiotic, prebiotic, and synbiotic supplementation was associated with statistically significant increases in serum iron (standardised mean difference [SMD]: 0.42, 95% CI: 0.18–0.66) and serum ferritin (SMD: 0.38, 95% CI: 0.14–0.62) across heterogeneous anemic populations (Hu et al., 2024). Apte et al. (2025), in a complementary systematic review and meta-analysis of 29 RCTs in children and women of reproductive age, documented modest but consistent ferritin gains, with more limited effects on haemoglobin in women of reproductive age specifically — a finding that underscores the need for longer intervention durations and adolescent-specific trial designs.

Prebiotics: Mechanisms and the Iron Absorption Paradox

Prebiotic dietary fibres — principally galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), and inulin-type fructans — represent a mechanistically distinct but complementary gut-centred strategy. Unlike probiotics, which introduce exogenous microorganisms, prebiotics selectively feed and amplify resident beneficial taxa, primarily Lactobacillus and Bifidobacterium, whose iron-metabolising properties are detailed in Section 3 and 4.1 [23,26].

The 2024 Kenyan infant RCT by Mikulic et al. — representing among the highest-quality RCT evidence available in this domain — demonstrated that the addition of 7.5 g GOS/FOS to iron-fortified cereal significantly increased fractional iron absorption (assessed by stable isotope methodology: $^{57}Fe/^{58}Fe$ dual isotope) compared with iron-fortified cereal alone (geometric mean iron absorption: 12.1% vs 8.9%, $p = 0.03$), while simultaneously attenuating pathobiont proliferation (reduction in Streptococcus and Escherichia-Shigella relative abundance) and gut inflammatory markers (faecal calprotectin) typically associated with iron supplementation in African children [26]. This trial provides direct evidence that prebiotics can resolve what has been called the 'central paradox' of iron supplementation in gut microbiome-compromised populations: they protect the gut microbiome from the dysbiotic effects of excess luminal iron while simultaneously enhancing absorption efficiency.

The mechanistic basis of prebiotic-mediated iron enhancement is multifactorial. Fermentation of GOS/FOS by colonic Lactobacillus and Bifidobacterium generates SCFAs — predominantly butyrate, propionate, and acetate — that lower colonic pH, increase iron solubility and luminal absorptive surface area, exert anti-inflammatory effects that reduce hepcidin expression, and upregulate the expression of intestinal iron transporter genes (DMT1, ferroportin) through histone deacetylase inhibition and epigenetic mechanisms [8,26]. Inulin-type fructans have additionally been demonstrated to reduce phytate content through microbial phytase activity, relieving a major inhibitor of iron absorption in plant-based dietary contexts typical of LMIC adolescent populations [30]. This phytase-mediated phytate degradation is particularly relevant for adolescent girls in South Asia and sub-Saharan Africa whose staple

dietary patterns — cereal and legume-based — are inherently high in this iron absorption antagonist.

Pharmacodynamically Optimised Iron Dosing: Exploiting the Hepcidin Circadian Rhythm

The characterisation of hepcidin's 24-hour circadian rhythm — with plasma concentrations nadir in the early morning fasting state and peak in the early afternoon — has generated a precision-medicine approach to iron dosing that maximises absorption while minimising the adverse microbiome effects of excess luminal iron [31]. Iron absorption studies in iron-depleted non-anaemic women demonstrated that a single morning dose of oral iron (>60 mg elemental) upregulates hepcidin for approximately 24 hours, during which time iron absorption capacity is substantially impaired — a phenomenon termed the 'hepcidin rebound' effect [31]. This finding has direct and clinically actionable consequence: twice-daily iron dosing produces less total absorbed iron than equivalent single morning dosing, because the second dose is administered during the post-first-dose hepcidin elevation window.

The landmark Lancet Haematology RCT by Stoffel and colleagues demonstrated that alternate-day iron dosing in iron-depleted women resulted in significantly higher fractional iron absorption per dose compared with consecutive daily dosing, because each alternate-day dose was administered at the hepcidin nadir preceding the subsequent dose [27,31]. The study provide a comprehensive practical translation of this evidence for adolescent-specific clinical practice: a single dose of 60–120 mg elemental iron (as ferrous sulfate or ferrous gluconate), administered in the morning in a fasted state with a vitamin C-containing fluid, on alternate days, represents the pharmacodynamically optimised regimen — superior to the traditional twice-daily dosing that has historically driven gastrointestinal adverse effects and poor adherence in adolescent supplementation programmes [27]. Adherence, rather than dose, is the primary determinant of supplementation effectiveness in real-world adolescent settings [32].

The quantitative impact of common dietary inhibitors on iron absorption warrants explicit communication in adolescent counselling. A 2023 cross-over study documented that co-ingestion of iron with coffee reduced fractional iron absorption by 54%, and co-ingestion with a standard breakfast by 66% — providing the most precise contemporary estimates of the magnitude of these inhibitory effects and directly informing the morning fasting supplementation recommendation [8,33]. Polyphenols in black tea suppress iron absorption by 60–90% when consumed simultaneously, reinforcing the practical guideline to separate tea consumption from iron dosing by a minimum of one hour.

Dietary Quality as a Microbiome-Mediated Iron Modulator

Beyond discrete supplement interventions, dietary quality itself functions as a continuous microbiome modulator with iron-metabolic consequences. Traditional fermented foods — including yogurt, kefir, idli, dosa, kimchi, miso, and fermented legumes — deliver live microorganisms that transiently colonise the intestinal lumen, producing lactic acid and SCFAs while competing with pathobionts for luminal iron [34]. Randomised dietary intervention trials in South Asian settings have demonstrated that regular fermented food consumption improves gut microbiome alpha-diversity scores and is associated with reduced inflammatory marker concentrations (plasma CRP, faecal calprotectin) compared with non-fermented dietary controls [35]. Observational data associate higher fermented food intake with reduced anemia prevalence in adolescent girls, though adequately powered RCTs in this specific population remain limited.

Dietary patterns characterised by high intake of diverse plant fibre substrates — legumes, oats, garlic, onion, leeks, asparagus, and Jerusalem artichokes, which are natural GOS/FOS and inulin substrates — support colonic SCFA production and the iron-absorptive advantages this confers [26,30]. The anti-inflammatory properties of a plant-diverse, fibre-rich diet additionally reduce the chronic low-grade gut inflammation that drives hepcidin elevation, creating a dietary pattern-level mechanism of iron absorption optimisation [11]. Vitamin C (ascorbic acid), present in amla, guava, citrus, capsicum, tomato, and green leafy vegetables, is a potent facilitator of non-haem iron absorption, both through its reducing action on Fe^{3+} and through chelation of iron into absorbable complexes that resist inhibition by phytate and polyphenols [33]. Randomised trials have demonstrated vitamin C co-ingestion increases non-haem iron absorption by 2–3-fold — a dietary synergy with potentially transformative impact on iron status in adolescent girls with predominantly plant-based diets.

Adolescence as the Strategic Intervention Window

The concept of sensitive periods in biological development — defined as windows of heightened environmental plasticity during which exposures exert disproportionate and lasting effects — is well-established in the nutritional and neurodevelopmental sciences for the first 1,000 days of life[17,19].

Table 3. Summary of key clinical and mechanistic studies on gut-centred interventions for iron deficiency anemia (2021–2025).

Intervention	Study Design	Population	Duration	**Key Finding**	**Reference**
GOS/FOS + iron-fortified cereal	RCT (n=191); stable isotope method	Kenyan infants	3 weeks	↑ Fractional iron absorption (12.1% vs 8.9%, p=0.03); ↓ gut pathobiont abundance; ↓ faecal calprotectin	[26]
Probiotics/ prebiotics ± iron	Systematic review + meta-analysis (29 RCTs)	Children & WRA	Variable	Modest ferritin gains (SMD~0.3); limited Hb effect in WRA; stronger effects in children	[36]
Probiotics/ prebiotics/ synbiotics	Meta-analysis (RCTs to Nov 2024)	Anemic individuals (mixed)	4–24 weeks	Significant ↑ serum iron (SMD 0.42); ↑ ferritin (SMD 0.38); improved Hb; well tolerated	[25]
L. acidophilus + B. longum	RCT in adolescent girls	Girls aged 12–18 yrs, n=NR	8 weeks	↑ Hb and serum ferritin vs iron alone ($p<0.05$); fewer GI adverse effects in probiotic group	[29]
Alternate-day low-dose iron	RCT (iron-depleted WRA)	WRA, n~40 per arm	2–4 weeks	↑ Fractional absorption per dose vs daily dosing; hepcidin nadir mechanism confirmed	[27,31]
Gut microbiome → IDA (MR)	2-sample Mendelian randomisation	484,598 UK Biobank; MiBioGen n=18,340	Genetic instruments	9 genus-level microbiota causally associated with IDA risk (IVW primary; 3 sensitivity analyses)	[6]
IDA → microbiome (bidirectional MR)	2-sample Mendelian randomisation	UK Biobank + MiBioGen	Genetic instruments	IDA causally reduces SCFA-producing taxa; dysregulates tryptophan-hepcidin metabolic pathway	[7]

RCT = randomised controlled trial; MR = Mendelian randomisation; Hb = haemoglobin; WRA = women of reproductive age; GOS = galacto-oligosaccharides; FOS = fructo-oligosaccharides; SCFA = short-chain fatty acids; IVW = inverse-variance weighted; SMD = standardised mean difference. GI = gastrointestinal. NR = not reported.

The emerging evidence suggests that adolescence constitutes a second window of comparably significant plasticity for nutritional and microbiome programming, with consequences that extend across the reproductive lifespan [11,37]. The adolescent gut microbiome is compositionally less stable and more responsive to dietary manipulation than the adult microbiome [10]. During the adolescent transition, the microbiome undergoes rapid compositional reorganisation under hormonal influence — oestrogen and progesterone have been shown to modulate microbial composition independently of dietary changes — as well as under the influence of dietary transitions, psychosocial stress, sleep disruption, and antibiotic exposures [38]. This plasticity is simultaneously a vulnerability and an opportunity: adolescent microbiomes are readily dysbiosed by iron-heavy supplementation regimens, ultra-processed dietary patterns, and antibiotic exposure, but they are also capable of more durable compositional improvement in response to prebiotic or probiotic intervention than adult microbiomes [37]. Interventions introduced during adolescence may establish compositional trajectories of iron absorption competence that persist into adulthood and critically, into the first pregnancy.

The intergenerational dimension of adolescent anemia and gut health constitutes perhaps the most compelling public health argument for targeting this population with priority investment. An adolescent girl who enters her first pregnancy with replete iron stores, a diverse gut microbiome with high SCFA-producing capacity, and established fermented-food dietary habits is biologically advantaged in multiple dimensions: she will achieve more effective placental iron transfer for fetal brain development [18], her birth microbiome seeding of the neonate will be compositionally richer [39], and her breastmilk will contain appropriate immune-modulatory and iron-supporting oligosaccharide concentrations [40]. Conversely, adolescent IDA perpetuates across generations through a well-characterised cycle: maternal anemia during pregnancy predicts intrauterine growth restriction, low birth weight, neonatal iron deficiency, and developmental delays that compound into the next generation's nutritional vulnerability [17,18]. It was estimated that breaking this intergenerational cycle through targeted adolescent nutritional interventions represents among the highest economic returns in global health investment[19].

Research Gaps and Future Directions

One of the most significant research gaps identified in recent literature is the inadequate representation of adolescent girls in microbiome-related anemia studies. Most investigations conducted during the past decade have predominantly focused on infants, pregnant women, or adult populations, while adolescent girls remain comparatively understudied despite their high vulnerability to iron deficiency due to rapid growth and menstrual blood loss. Furthermore, the influence of puberty-associated hormonal changes on gut microbial diversity and iron metabolism has not been sufficiently explored. Current evidence provides limited insight into how menstrual cycles, reproductive maturation, and adolescent dietary behaviors influence the gut microbiome and iron absorption mechanisms. Consequently, there is an urgent need for large-scale, age-specific cohort studies involving adolescent girls from diverse ethnic and geographical backgrounds to better understand the microbiome dynamics unique to this stage of life [41].

Another major limitation in current literature is the predominance of cross-sectional and observational studies. Although numerous studies have demonstrated associations between gut dysbiosis and iron deficiency anemia, causality remains poorly established. Existing evidence cannot conclusively determine whether microbial imbalance contributes to iron deficiency or whether iron deficiency itself leads to alterations in gut microbial ecology. Most studies merely report correlations without examining the temporal sequence of microbiome alterations and anemia progression. Therefore, future investigations should prioritize longitudinal cohort studies, mechanistic experiments, and randomized controlled trials capable of establishing causal relationships between gut microbiota and iron metabolism [42].

The mechanistic understanding of the Iron–Gut Microbiome Axis also remains incomplete. Emerging evidence suggests that gut microbiota may influence iron homeostasis through several pathways, including hepcidin regulation, inflammatory cytokine production, microbial siderophore activity, intestinal barrier modulation, and short-chain fatty acid synthesis. However, the precise molecular mechanisms underlying these interactions are still insufficiently understood. There is limited information regarding how microbial metabolites regulate ferroportin expression, intestinal iron transporters, and systemic inflammatory signaling pathways. Additionally, the role of specific bacterial taxa in promoting or inhibiting iron absorption has not been fully characterized. Advanced multi-omics approaches integrating metagenomics, metabolomics, transcriptomics, proteomics, and immunological profiling are therefore necessary to elucidate the complex host–microbe interactions governing iron metabolism [43].

Recent literature has also highlighted concerns regarding the adverse effects of conventional oral iron supplementation on gut microbial ecology. Although iron supplementation remains the cornerstone of anemia management programs globally, several studies have reported that high-dose oral iron therapy may induce gastrointestinal discomfort, oxidative stress, intestinal inflammation, and dysbiosis characterized by increased abundance of pathogenic Enterobacteriaceae and reduced populations of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* [44]. Despite the widespread implementation of iron-folic acid supplementation programs, limited evidence exists regarding the long-term microbiome consequences of chronic iron therapy among adolescent girls. Furthermore, few studies have investigated whether lower-dose iron formulations or alternative delivery systems may improve iron status without disrupting microbial balance. Consequently, future research should focus on developing microbiome-friendly iron supplementation strategies that maximize efficacy while minimizing gastrointestinal and microbial adverse effects.

Another important research gap is the lack of personalized nutrition approaches in anemia management. Current public health interventions generally employ uniform supplementation protocols without considering individual variability in microbiome composition, inflammatory status, dietary patterns, or genetic predisposition. However, emerging evidence suggests that the gut microbiome may significantly influence individual responsiveness to iron therapy, thereby highlighting the potential importance of precision nutrition approaches. Personalized interventions integrating microbiome profiling, dietary assessment, and biomarker analysis may provide more effective and targeted strategies for anemia prevention and treatment [45]. Nevertheless, such approaches remain largely unexplored in adolescent populations, particularly in resource-limited settings.

Limited clinical evidence regarding probiotics and synbiotics also represents a significant gap in current literature. Several recent studies have demonstrated that probiotic strains such as *Lactobacillus plantarum*, *Lactobacillus reuteri*, and *Bifidobacterium* species may enhance iron absorption, improve intestinal barrier function, and reduce inflammation, thereby supporting better iron metabolism [46]. However, findings remain inconsistent due to variations in probiotic strains, dosage, treatment duration, and study populations. There is currently no consensus regarding the most effective probiotic formulations for anemia management. Moreover, very few clinical trials have spe-

cifically targeted adolescent girls. Future randomized controlled trials are therefore required to evaluate the efficacy, safety, and long-term benefits of probiotic and synbiotic therapies in improving iron status among adolescents.

Another underexplored area involves the role of dietary patterns, traditional foods, and functional foods in modulating the Iron–Gut Microbiome Axis. Very few studies have investigated how millet-based diets, fermented foods, prebiotic fibers, and indigenous dietary practices influence gut microbial diversity and iron bioavailability. Traditional fermented foods and functional food products may offer sustainable, culturally acceptable, and low-cost strategies for improving both gut health and iron status, particularly in LMICs where adherence to pharmaceutical supplementation programs may be limited. Future research should therefore focus on developing food-based interventions, nutraceuticals, probiotic beverages, and fortified functional foods targeting both iron deficiency and microbial dysbiosis.

Current literature is also limited by inadequate integration of advanced multi-omics technologies. Most existing studies rely primarily on hematological indicators such as hemoglobin and ferritin levels alongside basic microbial sequencing techniques. Such approaches provide only partial insight into the complex interactions between host physiology, immune responses, microbial metabolites, and nutrient metabolism. Future investigations should adopt systems biology approaches integrating microbiomics, metabolomics, nutrigenomics, epigenomics, and immunomics to identify novel biomarkers, therapeutic targets, and predictive microbial signatures associated with anemia susceptibility and treatment response.

Geographical disparities in research output constitute another major concern. Although the burden of anemia is highest in South Asia and Sub-Saharan Africa, most microbiome-based studies have been conducted in high-income countries. Consequently, region-specific determinants such as parasitic infections, environmental enteropathy, sanitation conditions, food insecurity, and dietary inhibitors of iron absorption remain insufficiently investigated. There is a pressing need for community-based research in LMICs, especially in countries such as India, where adolescent anemia prevalence remains alarmingly high [47]. Such studies are essential for developing context-specific, culturally appropriate intervention strategies.

From a translational perspective, current evidence on the Iron–Gut Microbiome Axis has not yet been adequately incorporated into public health nutrition policies and anemia control programs. Existing national interventions primarily focus on iron-folic acid supplementation without addressing gut microbial health, dietary quality, or functional food approaches. Future public health programs should therefore adopt microbiome-sensitive strategies incorporating dietary diversification, gut health education, probiotic supplementation, sanitation improvement, and school-based nutrition interventions targeting adolescent girls.

Future Directions

Future research on the Iron–Gut Microbiome Axis is expected to increasingly focus on precision microbiome-based therapies capable of integrating microbiome profiling, inflammatory biomarkers, dietary assessment, and iron status evaluation to develop individualized interventions. Emerging technologies such as artificial intelligence (AI), machine learning, and predictive microbiome analytics may revolutionize anemia management by enabling personalized dietary recommendations, digital nutritional monitoring, and early risk prediction models. AI-assisted approaches may further facilitate the identification of microbial biomarkers associated with treatment responsiveness and disease susceptibility.

The development of next-generation therapeutics also represents a promising future direction in this field. Novel interventions involving probiotics, synbiotics, postbiotics, and nano-iron delivery systems may improve iron bioavailability while minimizing gastrointestinal side effects and microbial dysbiosis. Additionally, microbiota-targeted iron formulations capable of selectively enhancing beneficial bacterial growth may emerge as innovative therapeutic options for sustainable anemia management.

Functional foods and nutraceutical innovations are also expected to gain increasing importance in future research. Iron-fortified fermented foods, millet-based products, probiotic beverages, and microbiome-enhancing nutraceuticals may provide sustainable and culturally acceptable alternatives to conventional supplementation programs. Such interventions may be particularly beneficial in resource-constrained settings where adherence to pharmaceutical supplementation remains low.

Future investigations should also prioritize multi-omics and systems biology approaches integrating metagenomics, metabolomics, transcriptomics, proteomics, and immunological analyses. These advanced methodologies may facilitate a more comprehensive understanding of host–microbe interactions and identify novel therapeutic targets for anemia prevention and management.

Clinical Practice Recommendations for Adolescent Girls (Evidence-Informed)

1. Screening: Assess haemoglobin AND serum ferritin at menarche and annually thereafter. Haemoglobin alone is

insensitive for detecting iron depletion prior to anaemia onset. Pair haematological screening with dietary assessment for iron inhibitors (phytate, polyphenols, tea, coffee) and iron enhancers (vitamin C, fermented foods). Clinical threshold: serum ferritin <15 μg/L indicates iron depletion; <12 μg/L confirms iron deficiency.

2. Baseline Gut Health Assessment: Where clinically and logistically feasible, assess for Helicobacter pylori (13C-urea breath test or stool antigen), intestinal helminth burden (stool microscopy or coproantigen assay), and symptoms suggestive of gut dysbiosis (altered bowel frequency, bloating, abdominal pain) before initiating supplementation. Elevated hepcidin with normal ferritin may indicate functional iron deficiency from gut inflammation.

3. Optimised Iron Dosing: Prescribe morning fasting administration of 60–120 mg elemental iron (ferrous sulfate 200 mg or ferrous gluconate 300 mg) with vitamin C-containing fluid (150 mL fresh citrus juice or 250 mg ascorbic acid supplement). Consider alternate-day dosing to exploit hepcidin pharmacodynamics and reduce gastrointestinal adverse effects. Advise separation of tea, coffee, and calcium-rich foods by ≥60 minutes from iron dose.

4. Synbiotic Co-Administration: Co-prescribe evidence-based probiotic strains (Lactobacillus acidophilus NCFM, Bifidobacterium longum BB536 or equivalent validated strains) taken at a separate meal from iron (to avoid pH-mediated interference). Consider fermented dairy foods (plain yogurt, kefir) as accessible, affordable dietary vehicles for probiotic delivery in food-insecure settings.

5. Prebiotic Dietary Enrichment: Promote regular consumption of galacto-oligosaccharide-rich foods (legumes, chickpeas, lentils) and inulin/FOS sources (garlic, onion, leek, asparagus, oats, banana) to support endogenous SCFA production and hepcidin suppression. Emphasise vitamin C co-ingestion at iron-rich meals (amla, guava, citrus, tomato, capsicum).

6. Monitoring and Response Evaluation: Reassess haemoglobin and serum ferritin at 8–12 weeks. Assess subjective GI tolerance using a validated scale; adverse effects disproportionate to dose should prompt consideration of alternate-day or lower-dose regimens. Where available, serum hepcidin can guide treatment personalisation: persistently elevated hepcidin despite supplementation indicates ongoing gut inflammation requiring microbiome-targeted intervention rather than iron dose escalation.

Conclusion

Adolescent anemia is not a simple deficiency of dietary iron. It is a complex, ecosystem-level disorder in which the gut microbiome — through its regulation of iron absorption efficiency, hepcidin signalling tone, and intestinal inflammatory state — functions as a proximal and modifiable determinant of iron status. The GBD Study 2021 has confirmed that 1.92 billion people remain anaemic globally, with adolescent girls in South Asia and sub-Saharan Africa bearing a wholly disproportionate burden [1]. The iron–microbiome science of 2021–2025 has established, with causal rigour from Mendelian randomisation analyses [6,7], that this burden is actively maintained by bidirectional feedback between IDA and gut dysbiosis — a feedback loop that conventional iron-only supplementation protocols cannot resolve.

The therapeutic implications are clear and clinically actionable. Iron supplementation, while necessary, is mechanistically insufficient when prescribed in isolation from gut microbiome status [2,8]. A gut-centred model — integrating probiotic co-administration (L. acidophilus, B. longum), prebiotic dietary enrichment (GOS, FOS, inulin-rich whole foods), alternate-day morning iron dosing exploiting hepcidin circadian pharmacodynamics, and dietary patterns that deliver vitamin C and diverse fermentable fibre — offers a mechanistically superior and clinically practical framework for adolescent anaemia management, supported by emerging RCT and meta-analytic evidence [25,29,26,27].

Adolescence is a critical and time-limited window. The gut microbiome is plastic, the iron demands are physiologically acute, and the intergenerational stakes — extending to maternal anemia, neonatal neurodevelopment, and next-generation nutritional vulnerability — are profound [18,19]. The field now possesses the mechanistic framework, epidemiological evidence base, and nascent clinical trial data to act. Translating these insights into programme design modifications, clinical guideline updates, and the accessible nutritional education that adolescent girls deserve is the proximate challenge. It is also, given the evidence presented here, an achievable one.

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Author Contributions

All authors contributed to conceptualisation, literature curation, critical appraisal, and manuscript preparation. All authors reviewed and approved the final submitted version.

Data Availability

No new data were generated or analysed for this review. All data sources are cited within the manuscript and are publicly available through the referenced databases.

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