Gut microbiota and iron deficiency anemia: mechanisms, microbial signatures, and dietary interactions (A narrative review)

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ABSTRACT

Background and Objectives: Iron deficiency anemia (IDA) is one of the most prevalent micronutrient disorders worldwide. Recent work suggests that dysbiosis may not simply be a consequence of low iron status but may actively contribute to impaired absorption. This narrative review synthesizes the evidence on gut microbiota patterns in IDA across age groups, examines the mechanistic links between dysbiosis and iron metabolism, and identifies the potential roles of microbiota-related dietary and therapeutic strategies. **Methods and Study Design:** This narrative review used a selective, theory-driven approach, based on targeted searches of PubMed, Scopus, and Web of Science (2005–2026), to synthesize heterogeneous human, experimental, and mechanistic evidence on gut microbiota–iron interactions in iron deficiency anemia (IDA). **Results:** Evidence suggests a bidirectional, context-dependent relationship between IDA and gut microbiota involving host iron regulation, microbial competition, metabolites, and diet. Individuals with IDA often show reduced microbial diversity, depletion of SCFA-producing taxa, and enrichment of iron-scavenging bacteria, although direct causal evidence in humans remains limited. **Conclusions:** IDA is commonly associated with recurring dysbiosis patterns characterized by reduced short-chain fatty acid-producing commensals and relative enrichment of inflammatory, iron-competitive taxa. While iron supplementation remains the cornerstone of evidence-based IDA management, the ecological effects of unabsorbed luminal iron on gut microbial communities support the concept of a potential "iron paradox," particularly in inflammatory or high-infection settings. Therefore, microbiota-targeted strategies should currently be regarded as hypothesis-generating concepts rather than established clinical interventions and require further mechanism and clinical validation.

Key Words: anemia, bioavailability, dietary intake, gut microbiota, iron deficiency anemia

INTRODUCTION

Iron deficiency anemia (IDA) remains the most prevalent micronutrient deficiency worldwide and is a major contributor to disability, affecting an estimated 1.2 billion individuals across all age groups.[1] IDA disproportionately affects vulnerable populations including infants, preschool-aged children, women of reproductive age, and pregnant women.[2,3] Although IDA is traditionally attributed to inadequate dietary iron intake, malabsorption, chronic blood loss,

and increased physiological demand,[2] these factors do not fully explain the inter-individual variability in iron status.

A systematic review reported that supplementation, fortification, and food-based interventions generally improve hemoglobin levels and reduce anemia prevalence among pregnant women and children under five; however, intervention effectiveness is strongly influenced by adherence, dietary quality, iron absorption enhancers such as vitamin C and animal protein, and educational support.[4] A recent cross-sectional study showed that among 645 female senior high school students in stunting-risk areas of Ambon, Indonesia, 19.7% had anemia, whereas only 19.5% adhered to weekly iron–folic acid (IFA) supplementation, despite more than half having previously consumed IFA tablets.[5]

Recent advances in microbiome science have revealed that disturbances in the gut microbiota may influence iron metabolism and inflammatory regulation.[6] The human gut microbiota functions as a metabolic and immunological organ that influences nutrient absorption, intestinal barrier integrity, host inflammation, and energy homeostasis.[7] Several microbial taxa contribute to iron metabolism through ferric-to-ferrous reduction, fermentation of dietary fibers into short-chain fatty acids (SCFAs) that facilitate iron absorption, and modulation of mucosal immune responses that influence hepcidin, the central regulator of systemic iron balance.[6,8] Conversely, dysbiosis, characterized by reduced microbial diversity and loss of beneficial SCFA-producing bacteria, has been linked to impaired iron uptake, heightened intestinal inflammation, altered hepcidin signaling, and increased oxidative stress.[8] However, most available human evidence remains observational and associative, and direct causal pathways linking microbiota alterations to the development of IDA have not yet been conclusively demonstrated.[9]

Recent evidence has demonstrated a bidirectional interaction between iron status and the gut microbiome. Dysbiosis may predispose individuals to iron malabsorption, while unabsorbed iron in the intestinal lumen may selectively enrich iron-dependent pathobionts and exacerbate intestinal inflammation.[10] Dietary composition further modulates this interaction because fiber, polyphenol, fat, and protein sources influence both microbial fermentation patterns and iron bioavailability.[11,12] Nevertheless, existing findings are frequently derived from small, heterogeneous cohorts and analyzed in isolation by age group, limiting cross-population comparability and synthesis.

Despite accumulating evidence, no review has comprehensively synthesized microbiota signatures associated with IDA across different age groups and populations. Moreover, most reports emphasize taxonomic descriptions without functional validation, and few

investigations have concurrently evaluated dietary exposure, microbial metabolism, inflammatory signaling, and iron absorption. Consequently, a comprehensive critical synthesis that contextualizes microbiota signatures, evaluates mechanistic plausibility, and appraises the evidentiary strength across populations is currently lacking.

This narrative review aimed to (1) assess the consistency and heterogeneity of microbiota patterns reported in individuals with IDA across populations and life stages; (2) examine mechanistic hypotheses through which gut microbes may influence iron bioavailability; and (3) appraise the methodological limitations, contextual variability, and translational uncertainties that constrain the causal interpretation of microbiota–iron interactions. By integrating microbial iron acquisition strategies, host nutritional immunity, and dietary exposure within a unified ecological framework, this review aims to advance the current understanding of the iron–microbiota–host axis in IDA.

MATERIALS AND METHODS

This article was conducted as a narrative review using a selective, theory-driven approach to critically synthesize evidence regarding gut microbiota–iron interactions in IDA. The literature search was performed using PubMed, Scopus, and Web of Science, covering studies published between 2005 and 2026. Earlier landmark references were also included when considered essential for conceptual and mechanistic understanding. The search strategy used combinations of predefined keywords including (“iron deficiency anemia” OR “iron deficiency”) AND (“gut microbiota” OR “gut microbiome” OR “intestinal microbiota”) AND (“iron metabolism” OR “iron absorption” OR “hepcidin” OR “siderophore” OR “short-chain fatty acids” OR “dietary iron”). Additional relevant studies were identified through manual screening of reference lists from eligible articles.

Studies were included if they (1) examined associations between gut microbiota and iron deficiency anemia or iron metabolism; (2) investigated microbial metabolites, inflammatory pathways, hepcidin regulation, siderophore-mediated iron competition, or dietary factors related to iron homeostasis; and (3) included human observational studies, randomized controlled trials, animal experiments, mechanistic studies, or Mendelian randomization analyses that contributed to biological or clinical interpretation. Studies were excluded if they were case reports, conference abstracts without full text, non-English publications, studies unrelated to iron–microbiota interactions, or articles lacking sufficient relevance to the conceptual framework of this review.

Study selection was guided by conceptual relevance, biological plausibility, and translational significance rather than exhaustive systematic retrieval. A narrative review approach was chosen because the current evidence base is highly heterogeneous in study design, populations, microbiome methodologies, and outcome measures, which limits the feasibility of formal quantitative synthesis. This approach allowed integration of mechanistic, experimental, and epidemiological evidence into a unified conceptual framework of the iron–microbiota–host axis. Given the narrative nature of this review, formal risk-of-bias assessment and meta-analysis were not undertaken. The inherent limitations of selective literature appraisal, including potential selection bias and heterogeneity across studies, are acknowledged.

TAXONOMIC SIGNATURES ASSOCIATED WITH IDA: PATTERNS AND INCONSISTENCIES

Across human cohorts, animal models, and Mendelian randomization (MR) analyses, IDA has been associated with recurring but context-dependent microbial patterns that reflect shifts in taxonomic composition and functional capacity (Table 1). A consistent finding across multiple human studies is the reduced abundance of SCFA-producing taxa, including *Faecalibacterium*, *Roseburia*, and *Ruminococcus*.[13–18] A reduced *Bifidobacteriaceae*/*Enterobacteriaceae* ratio, which is a commonly used indicator of microbial imbalance, has also been reported.19 These genera contribute to epithelial barrier integrity and nutrient absorption through butyrate and the production of other SCFAs, rendering their depletion biologically plausible in relation to impaired iron uptake and mucosal dysfunction.

In contrast to the loss of fermentative commensals, multiple studies have documented an enrichment of opportunistic and iron-acquisitive organisms. Pregnant women with IDA exhibited a marked expansion of Streptococcus species, accompanied by the upregulation of siderophore-related metabolites and iron transport pathways.[20] Patients with chronic renal failure and IDA showed increased *Escherichia coli* abundance,[21] and pediatric anemic participants also demonstrated overgrowth of several opportunistic taxa.[22]

Broader enrichment of mucin-degrading or pro-inflammatory taxa, including *R. gnavus*, *Hungatella*, *Parasutterella*, *Enterobacteriales*, *Veillonella*, and *Enterobacteriaceae*, has been described in diverse IDA populations.[13–18,23] The expansion of *Proteobacteria*, a phylum associated with oxidative stress and iron scavenging, has also been linked to low hematocrit

levels.[24] Overall, these findings suggest that iron-restricted or inflammatory gut conditions may favor taxa equipped with efficient iron acquisition strategies.

Animal models provide additional insights into metabolic restructuring under iron-deficient conditions. Clostridium spp. enrichment has been consistently observed in experimental IDA models and is accompanied by alterations in SCFA production and broader microbial metabolic shifts.[25,26] Given the functional heterogeneity within this genus, such enrichment may reflect adaptive ecological reorganization rather than a single pathogenic expansion.[22]

MR studies have provided causal evidence supporting this signature. Lei et al. reported that *Roseburia*, *Prevotella*, *Oscillospira*, and *Clostridia* are protective, whereas *Ruminococcus gnavus*, *Hungatella*, and *Parasutterella* increase the risk of developing IDA.[17] Similarly, Zheng et al. identified *Ruminococcus E* sp003521625 as a risk taxon and *Jiangellaceae* as a protective taxon.[18] However, some discrepancies remain. For example, *Prevotella* depletion has been observed in experimental and early-life studies;[27,28] however, MR analyses suggest a protective association.[17] This divergence suggests that the role of *Prevotella* may depend on dietary substrate availability, host metabolic context, or species-specific ecological interactions, rather than representing a uniform risk or protective factor.

Experimental models reinforce these observations: low-iron challenge mice demonstrate a loss of *Prevotellaceae* and *Porphyromonadaceae* under iron restriction,[28] whereas early-life iron deficiency studies in humans and monkeys show persistent depletion of *Prevotella* even after apparent hematologic recovery.[27] In women with IDA, reduced *Faecalibacterium* abundance was partially recovered following oral iron therapy,[16] suggesting a dynamic relationship between iron status and fermentative taxa.

Likewise, diversity metrics varied: monkeys with IDA did not show alpha diversity loss despite altered beta diversity,[29] whereas pregnant women[20] and chronic renal failure patients[21] exhibited significant diversity reductions. MR analyses have also produced discordant findings; for example, *Desulfovibrio* has been reported to be protective in MR analyses but reduced in experimental IDA models.[30] Such inconsistencies may reflect differences between genus-level aggregation and strain-specific metabolic functions, as well as variability in host species, disease etiology, and study design.

Geographic and socioeconomic contexts further modify these patterns. Studies conducted in low- and middle-income countries, including Peru and China[14,15,23], have demonstrated a more pronounced proliferation of pathobionts and a stronger depletion of beneficial taxa, possibly reflecting environmental enteropathy, infection exposure, and dietary variability. In contrast, cohorts from high-income countries[25] often show subtler compositional shifts,

potentially due to greater baseline microbiota stability.[23] Overall, the accumulated evidence suggests that IDA is associated with broad ecological tendencies, namely depletion of SCFA-producing commensals and enrichment of iron-acquisitive or inflammatory taxa, while the magnitude, direction, and diversity impact of these shifts remain influenced by host, environmental, and methodological contexts.

LIFE-COURSE PERSPECTIVE AND IRON HOMEOSTASIS

Interactions between the gut microbiota and iron metabolism vary across the life course, reflecting changes in iron requirements, physiological maturation, and environmental exposure. During infancy and early childhood, microbiota development is highly dynamic and sensitive to dietary patterns and infection challenges. Studies conducted on infants with IDA have shown increases in *Veillonella* and *Enterobacteriaceae*, along with reductions in SCFA-producing bacteria, such as *Butyricicoccus*. These alterations impair intestinal epithelial maturation and increase oxidative stress.[15,19] This indicates that in early life, when iron demands are too high to support rapid growth, even minor shifts in microbiota composition can have substantial implications for the risk of anemia. Additionally, sex-based differences should be considered when examining the risk of anemia. A study in Peru demonstrated that, among male infants with IDA, the reduced butyrate-producing taxa included *Coprococcus* and *Roseburia*, whereas in female infants with IDA, a primary reduction was observed in *Butyricicoccus*.[15]

During adolescence and early adulthood, hormonal factors and menstrual cycle regulation in females can influence iron balance. A study conducted in Korea reported that women with IDA exhibited reductions in *Faecalibacterium* and *Ruminococcaceae*, along with shifts in bacteria involved in lipid and bile acid metabolism, such as *Collinsella*.[16] Following iron supplementation, some of these protective bacterial taxa were partially recovered, indicating a dynamic interaction between iron status and microbiota composition in this population.

As pregnancy progresses, metabolic and immunological adaptations lead to substantial shifts in the gut microbial ecosystem. Reductions in SCFA-producing taxa have also been reported in women of reproductive age, a pattern indicative of low-grade inflammation and reduced iron absorption capacity.[14] These alterations may increase the risk of inflammation, affect hepcidin regulation, and impair iron uptake. The findings from this cohort study further revealed that microbiota composition shifts across trimesters. Notable differences were observed in the third trimester between women with gestational anemia and healthy controls.[14] Collectively, these observations highlight pregnancy as a critical period during

which physiological changes and dysbiosis contribute to the development or exacerbation of IDA.

In healthy adults, interactions between the gut microbiota and iron metabolism tend to be more stable, although they are influenced by dietary patterns and iron supplementation. A study on healthy adult women demonstrated that iron supplementation can modify microbiota composition, including reductions in *Bacteroides* and increases in *Clostridiales*.[23] These findings are consistent with those of previous studies conducted in high-income countries. However, the patterns observed differ from those in low-income settings, where iron supplementation induces broader alterations in microbiota composition.[19]

In older adults, an increased risk of anemia may be attributed to an age-related decline in gut microbiota diversity, increased systemic inflammation, and a higher prevalence of chronic diseases.[31] Reduced SCFA-producing bacteria and increased in pro-inflammatory taxa can further impair iron absorption and disrupt iron homeostasis, particularly in older individuals experiencing chronic inflammation or malnutrition.

BIOLOGICAL MECHANISMS LINKING IRON HOMEOSTASIS AND GUT ECOLOGY

While population-level observations provide insights into when dysbiosis occurs across the life course, understanding how these microbial shifts influence iron metabolism requires an examination of the underlying biological mechanisms linking host iron regulation to gut ecology (Figure 1).

Host iron regulation and inflammatory signaling

Systemic iron homeostasis in humans is tightly regulated through the coordinated control of intestinal absorption, recycling from senescent erythrocytes, and storage within hepatocytes and macrophages. Central to this process is hepcidin, a peptide hormone primarily synthesized by hepatocytes, which functions as the master regulator of iron trafficking. Hepcidin exerts its effects by binding to ferroportin, the only known cellular iron exporter expressed on enterocytes, macrophages, and hepatocytes, triggering its internalization and degradation, which in turn reduces dietary iron absorption and limits the release of recycled iron into the circulation.[32,33] Through this mechanism, elevated hepcidin levels suppress ferroportin-mediated iron efflux from enterocytes and macrophages, thereby promoting intracellular iron sequestration.[34]

Under physiological conditions, hepcidin expression is dynamically modulated by systemic iron requirements. Iron deficiency, hypoxia, and increased erythropoietic demand suppress

hepcidin production to facilitate greater intestinal iron uptake and mobilization of stored iron, whereas iron sufficiency and inflammatory stimuli upregulate hepcidin transcription to restrict circulating iron availability.[2] Inflammation is one of the most potent non-dietary regulators of iron metabolism. Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), activate the janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway and induce hepcidin overexpression, even in the presence of systemic iron deficiency.[35,36] Commensal and pathogenic microbes may further shape this process by activating IL-1β-driven and bone morphogenic protein/ suppressor of mother against decapentaplegic (BMP/SMAD-dependent) signaling pathways in hepatocytes, resulting in increased hepcidin production,[37] thereby linking microbial cues to systemic iron regulation.

Importantly, microbiota-induced inflammation may amplify iron sequestration by disrupting intestinal barrier integrity and enhancing microbial translocation, which triggers macrophage activation and cytokine production, reinforcing hepcidin-mediated iron retention.[26] In addition to hepatocytes, immune cells contribute to iron regulation; for instance, conventional dendritic cells locally produce hepcidin to limit iron availability during inflammatory responses.[37] Macrophages also play a dual regulatory role by controlling intracellular iron turnover through divalent metal transporter 1 (DMT1)-dependent pathways that influence both iron recycling and antimicrobial responses, such as lipocalin-2 expression, [38] highlighting the interplay between iron metabolism and host defense. This inflammatory induction of hepcidin represents a key component of nutritional immunity, in which the host restricts extracellular iron availability to deprive pathogens of an essential nutrient while simultaneously reducing iron availability for erythropoiesis.[39]

From an evolutionary perspective, this inflammatory response represents a component of nutritional immunity, wherein the host restricts iron availability to limit microbial proliferation during infection.[40] As the intestinal mucosa functions simultaneously as a primary site of iron absorption and a major immunological interface, low-grade intestinal inflammation, increased epithelial permeability, or microbial translocation may amplify hepcidin signaling and reduce iron bioavailability, independent of dietary intake.[2, 41] Observational studies reporting the associations between systemic inflammatory markers, elevated hepcidin concentrations, and impaired iron absorption suggest that mucosal immune activation may indirectly contribute to iron-restricted erythropoiesis.

To meet the high iron demands of hemoglobin synthesis, erythropoiesis and hypoxia also regulate hepcidin through coordinated Epo-dependent and independent pathways. Stress erythropoiesis stimulates the secretion of erythroferrone (ERFE) from erythroid precursors,

which suppresses hepcidin and promotes iron mobilization from storage sites.[42] Similarly, hypoxia-inducible factors (HIFs), particularly HIF-2α, enhance iron absorption by upregulating apical and basolateral transporters such as DMT1 and ferroportin in duodenal enterocytes, partly independent of systemic hepcidin levels.[43,44] These adaptive responses ensure that iron availability is prioritized during periods of increased erythropoietic demand or reduced oxygen availability.[45]

However, it is important to emphasize that most human evidence linking inflammation, hepcidin dysregulation, and iron deficiency is associative rather than causal, particularly in community-based populations without overt infections or chronic diseases. Although inflammatory signaling provides a biologically plausible pathway through which gut microbial perturbations may influence iron homeostasis, direct interventional evidence demonstrating that microbiota-driven inflammation independently induces IDA remains limited. Collectively, the hepcidin–ferroportin axis provides a critical framework for understanding how immune activation, intestinal ecology, and systemic iron distribution intersect. Integrating these host regulatory pathways with microbial competition for iron is essential for interpreting the broader iron microbiota–host axis explored in subsequent sections.

Siderophore-mediated iron competition and nutritional immunity

One of the most important yet often under-discussed mechanisms linking gut microbes and iron metabolism is microbial competition for iron through siderophore production. Siderophores are small, high-affinity, iron-chelating molecules secreted by microorganisms under iron-limited conditions to solubilize, capture, and transport ferric iron into cells, enabling growth, metabolic activity, and, in pathogens, virulence.[46,47] Siderophores influence iron homeostasis via several interconnected mechanisms involving microbial competition and host nutritional immunity.

High-affinity siderophore systems constitute a central iron acquisition strategy employed by members of the Enterobacteriaceae family and other gut pathobionts to overcome host-mediated nutritional immunity. Enterobactin, a canonical catecholate siderophore produced by *Escherichia coli*, Salmonella, and related taxa, exhibits one of the strongest known affinities for ferric iron, thereby enabling efficient iron sequestration in iron-limited environments, such as the intestinal lumen.[47–50] In response, the host deploys defense mechanisms such as lipocalin-2, which binds catecholate siderophores and restricts microbial

iron acquisition. To overcome this problem, some pathogenic bacteria produce modified siderophores such as salmochelin, which can avoid detection by the immune system.[48,51]

In addition, many pathobionts produce several types of siderophores such as enterobactin, salmochelin, aerobactin, and yersiniabactin, which enhance their competitive fitness in iron-limited environments.[52,53] Some bacteria can also use siderophores produced by other microbes (xenosiderophores), which gives them the additional advantage of competing for iron and increasing virulence.[54,55] Collectively, these strategies enhance microbial competitiveness within iron-limited intestinal ecosystems and may contribute to dysbiotic shifts observed in iron-related disorders.[56,57]

Host nutritional immunity is a key defense mechanism through which the body limits microbial growth by restricting essential nutrients, particularly iron. One of the primary components of this system is lipocalin 2 (LCN2), a host-derived protein that binds to catecholate siderophores, especially enterobactin, thereby preventing pathogenic bacteria from accessing the iron required for survival and proliferation.[50,58] In addition to directly inhibiting bacterial iron uptake, LCN2 plays an important role in maintaining the gut microbiota balance; its absence has been associated with dysbiosis and the expansion of Enterobacteriaceae populations.[59–61] Nevertheless, some pathogens can evade this defense strategy by producing modified siderophores, such as salmochelin, which are not recognized by LCN2 and can thus continue to facilitate iron acquisition.[48,51] In addition to LCN2, host mechanisms, including transferrin 1-mediated iron sequestration during infection and regulation of intracellular iron availability by DMT1 in macrophages, further contribute to limiting microbial growth and modulating the control of siderophilic pathogens.[38,62] Experimental studies further support this framework of host–microbe competition for iron, demonstrating that microbial communities can directly influence host iron transport pathways under different iron availability conditions.

Mechanistic support for this bidirectional framework was demonstrated in controlled gnotobiotic mouse models. In a recent study comparing germ-free and conventionally colonized mice fed iron-replete and iron-depleted diets, the presence of microbiota enhanced intestinal ferritin accumulation when iron was sufficient. Conversely, during iron scarcity, microbiota suppressed the expression of the duodenal iron transporter DMT1 through HIF-2α-dependent signaling, thereby limiting host iron uptake and illustrating competitive microbial behavior.[63] These findings provide rare experimental evidence that microbial communities may influence host iron transport pathways rather than being merely associated with iron status.

Collectively, integrating concepts from nutritional immunity and microbial iron competition offers a more comprehensive understanding of how iron availability shapes gut ecology. These interactions likely operate bidirectionally and in a context-dependent manner and are influenced by host inflammation, baseline microbiota composition, dietary exposure, and supplement formulation. Further human studies incorporating functional microbial profiling and controlled iron interventions are required to clarify their translational relevance.

Microbial metabolites (SCFAs), barrier function, and iron absorption

In addition to direct microbial competition for iron, the gut microbiota may indirectly influence iron homeostasis by producing bioactive metabolites that shape the intestinal microenvironment. SCFAs, primarily acetate, propionate, and butyrate, are the most abundant fermentation products derived from dietary fiber metabolism and play a key integrative role in linking gut ecology to nutrient absorption.[64,65]

SCFAs contribute to intestinal homeostasis by serving as the primary energy source for colonocytes. They also promote epithelial differentiation, tight junction assembly, mucus production, and barrier integrity. These effects reduce luminal permeability and microbial translocation, which would otherwise trigger low-grade inflammation and disrupt nutrient transport processes.[66] In addition, SCFAs exhibit immunomodulatory properties by inhibiting histone deacetylases and activating G-protein-coupled receptors (e.g., GPR41/43), which collectively dampen pro-inflammatory cytokine production. Given that inflammatory signaling is a key inducer of hepcidin, such anti-inflammatory effects provide a biologically plausible pathway that links microbial metabolites to systemic iron regulation.

Mechanistically, SCFAs may influence iron bioavailability through several complementary pathways, including enhancement of luminal iron solubility by lowering colonic pH and facilitating the reduction of ferric iron to its more absorbable ferrous form, as well as upregulation of intestinal iron transporters such as DMT1 and ferroportin under certain conditions.[6,34,67–69] However, not all microbial metabolites uniformly promote absorption; commensal-derived compounds such as reuterin and 1,3-diaminopropane may suppress iron uptake by inhibiting HIF-2α signaling, thereby reducing transporter expression and shifting iron toward intracellular storage pathways.[70–72] Furthermore, microbial metabolites regulate mucin secretion and luminal pH, generating microenvironmental conditions that can either facilitate or impede iron bioavailability, depending on host–microbe interactions and dietary context.[70]

Consistent with these mechanisms, observational studies in individuals with IDA have frequently reported a reduced abundance of SCFA-producing taxa associated with butyrate production and epithelial health, and their depletion has been linked to heightened mucosal inflammation and impaired gut barrier function.[8,16] Iron deficiency itself may also reshape microbial metabolic output; compensatory increases in SCFA production have been observed as part of a host–microbe adaptive response, with downstream effects on immune and metabolic pathways.[25] IDA has also been associated with epithelial damage, increased intestinal permeability, and increased microbial translocation, which may amplify inflammatory signaling and disrupt iron absorption dynamics.[26]

Most of the evidence connecting SCFAs to iron absorption is indirect and inferential. Human studies that directly measure SCFA concentrations along with iron absorption kinetics are scarce, and causality cannot be established from the current cross-sectional designs. Therefore, it is unclear whether reduced SCFA production contributes to impaired iron uptake, or whether iron deficiency itself alters microbial fermentation capacity through changes in diet, host physiology, or supplementation practices. These bidirectional and context-dependent relationships complicate interpretation and underscore the need for controlled interventional studies that incorporate metabolomic and functional readouts.

Iron supplementation, the iron paradox, and clinical implications

Iron supplementation is the cornerstone of the prevention and treatment strategies for IDA. In most clinical settings, iron administration effectively improves hemoglobin concentration and replenishes iron stores. However, accumulating evidence indicates that iron exposure within the gastrointestinal lumen may exert unintended ecological effects on the gut microbiota, creating translational tension between correcting systemic deficiencies and preserving intestinal homeostasis. This tension has been described as the “iron paradox,” whereby iron supplementation confers systemic hematological benefits while potentially promoting local dysbiosis and inflammation in the gut.

A central mechanism underlying this paradox is that a substantial fraction of orally administered iron remains unabsorbed, particularly in the context of inflammation, impaired mucosal function, or high-dose regimens.[73,74] Animal models have demonstrated that oral iron increases colonic iron deposition in the digesta and tissues, with luminal (cecal) iron concentrations rising up to 55-fold in fortified diets compared to those in deficient diets.[74] This unabsorbed iron acts as an exogenous nutrient source for gut microbes and reshapes the

microbial community structure.[75,76] Luminal iron may function as an ecological perturbation that selectively favors iron-dependent organisms, including siderophore-mediated uptake.[69]

Consistent with this ecological framework, multiple studies have reported that increased luminal iron levels promote the overgrowth of pathobionts, particularly members of Proteobacteria and Enterobacteriaceae. Many of these taxa possess high-affinity iron acquisition systems that allow them to outcompete iron-sparing commensals under iron-replete conditions. High-dose iron supplementation increases *Proteobacteria*, *Escherichia-Shigella*, and other pathobionts in piglets and women.[77–79] Oral iron administered after antibiotic exposure increases Bacteroides while reducing protective taxa such as *Akkermansia* and *Bilophila*.[80] High iron levels enhance *Salmonella Typhimurium* abundance and motility, and $FeSO_4$ increases virulence relative to fungal-bound iron.

In infants and children, supplementation has been associated with reductions in *Bifidobacterium* and *Lactobacillus* and concomitant increases in enteropathogens, consistent with pathogen blooms.[76] Randomized human trials have further shown that iron fortification or supplementation can increase *Enterobacteriaceae* abundance while reducing beneficial SCFA-producing taxa, sometimes accompanied by elevated fecal calprotectin levels and increased intestinal inflammation.[6,81]

In addition to microbial compositional shifts, iron overload may directly promote inflammatory and cytotoxic processes through two converging pathways. First, microbiota-driven inflammation may arise because iron-induced dysbiosis increases lipopolysaccharide production and immunostimulatory metabolites, which are correlated with intestinal iron levels and systemic iron stores.[26,79] High-iron diets lower SCFA levels and compromise immune resilience during microbiota recovery.[80]

Second, iron-mediated cytotoxicity contributes to epithelial injury. Unabsorbed ferrous and ferric ions participate in Fenton chemistry, generating reactive oxygen species that induce lipid peroxidation and epithelial damage.[82] Iron overload and inflammatory cytokines induce ferroptosis in colonic epithelial cells, aggravating colitis[83] and impairing intestinal stem cell function, goblet cell differentiation, and barrier integrity.[84] Collectively, these processes provide a mechanistic basis for how iron supplementation amplifies mucosal inflammation under certain conditions.

Beyond direct cellular damage, the clinical manifestation of the iron paradox is heavily shaped by the host's systemic environment. In low- and middle-income countries (LMICs), the iron paradox is primarily driven by a high burden of infection, undernutrition, and chronic inflammation, where anemia of inflammation (AI) frequently coexists with true iron

deficiency. Recurrent infections such as tuberculosis, malaria, and enteric diseases stimulate IL-6/STAT3–mediated hepcidin upregulation, leading to ferroportin degradation, reduced intestinal iron absorption, and sequestration of iron within macrophages despite ongoing deficiency.[85–87] This results in hypoferremia with normal or elevated ferritin, making diagnosis difficult because ferritin may reflect inflammation rather than adequate iron stores. Studies in Cameroon, for example, reported similar prevalence of AI (30.2%) and iron deficiency (34.6%) among children, highlighting the frequent coexistence of both conditions.88 In these settings, oral iron supplementation may be less effective due to hepcidin-mediated absorption blockade and may worsen infection risk and gut dysbiosis by increasing luminal iron availability for pathogens.[10,89,90]

In contrast, in high-income countries (HICs), the iron paradox is more commonly driven by obesity, metabolic syndrome, and chronic low-grade inflammation rather than infectious disease. Excess adiposity increases IL-6 and C-reactive protein (CRP), stimulating hepcidin synthesis and creating functional iron deficiency despite adequate or elevated iron stores.91 Women with obesity often present with high ferritin but low circulating iron and reduced transferrin saturation, reflecting impaired iron mobilization rather than depletion. Obesity-related iron dysregulation also contributes to insulin resistance, oxidative stress, and type 2 diabetes, linking iron metabolism to broader metabolic disease progression.[91–94] These differences show that the same biochemical presentation, low serum iron with high ferritin, may arise from different mechanisms across LMIC and HIC populations, making universal iron supplementation inappropriate and emphasizing the need for context-specific diagnosis and treatment strategies.

The iron paradox—coexistence of anemia with low serum iron but normal or high ferritin driven by inflammation—fundamentally alters how anemia must be diagnosed and treated in developing countries. The evidence shows that inflammation, infection burden, malaria, Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS), parasitic diseases, and gut dysbiosis distort standard iron biomarkers, reduce effectiveness of oral iron, and increase infection risks.[95,96] As a result, developing countries cannot rely on "iron-only" strategies; instead, treatment must integrate infection control, improved diagnostics, and context-specific supplementation.

From a translational perspective, it is essential to distinguish between established evidence-based anemia management and emerging microbiota-targeted hypotheses. Although strong evidence supports iron supplementation for correcting IDA, limited data demonstrate that deliberate manipulation of the microbiota independently improves iron absorption and anemia

outcomes. The proposed strategies, including the co-administration of prebiotics, probiotics, synbiotics, lower-dose regimens, intermittent dosing, and alternative formulations with improved bioavailability, remain promising, but largely investigational.[6,9] Most available studies are small, short-term, or rely on surrogate markers rather than on definitive clinical endpoints.

Overall, the iron paradox reframes iron supplementation not only as a nutritional intervention, but also as a potential ecological perturbation within the gut environment. Integrating host iron physiology, microbial competition, inflammatory signaling, and contextual factors may enable the development of more tailored and context-sensitive therapeutic strategies. Until stronger causal and interventional evidence is available, clinical recommendations should remain grounded in established anemia treatment guidelines, and microbiota-informed approaches should be regarded as adjunctive and hypothesis-generating rather than definitive therapeutic alternatives.

DIETARY EXPOSURE AND MICROBIAL ECOLOGY

In addition to therapeutic supplementation, habitual dietary iron intake plays an important role in shaping the gut microbial environment. Dietary iron exposure is a major determinant of gut microbial ecology, as both low- and high-iron intakes reshape microbial composition and metabolic activity. Variations in dietary iron significantly alter microbiota structure and functional output, influencing the profiles of metabolites such as SCFAs.[63,97–99] High dietary iron has been shown to selectively promote the expansion of *Proteobacteria* and *Enterobacteriaceae*, while suppressing beneficial taxa, including *Lactobacillus* and *Bifidobacterium*.[97,99] Conversely, iron deficiency reduces commensal diversity and increases susceptibility to pathogenic colonization.99 Importantly, these effects are not isolated from a broader dietary context; interactions with dietary fat content, fiber intake, and overall nutrient composition further modulate how iron availability translates into ecological shifts.[100] Thus, dietary patterns determine the luminal iron landscape, which directly influences microbial selection pressure and community structure.

Mechanistically, changes in iron intake alter microbial growth dynamics and competitive interactions in the gut ecosystem. Iron is an essential micronutrient for most bacteria, and shifts in luminal iron levels modify the taxa that can thrive under prevailing ecological conditions. Many gut microbes produce siderophores and other chelating systems to compete for iron, meaning that alterations in dietary iron intake change the competitive hierarchies among taxa.[37,50] When iron is limited, certain microbes upregulate iron acquisition strategies,

whereas iron-replete conditions may benefit taxa capable of rapidly utilizing soluble iron pools. In parallel, microbiota composition itself can influence iron valency and solubility within the intestinal environment, further shaping the species that can access iron.[37] Dietary iron also indirectly affects microbial composition through its interaction with fermentative metabolism; SCFAs, such as butyrate, increase iron solubility and facilitate enterocyte absorption,[68] whereas SCFA production lowers intestinal pH and forms soluble iron complexes that support specific microbial niches.[67] Disruption of SCFA-producing communities in low-iron states is linked to iron availability, fermentation patterns, and ecological restructuring.[25]

Dietary iron also influences microbiota–immune interactions and barrier integrity, creating feedback loops that further modulate microbial selection. Microbial shifts can activate macrophages, enhance inflammatory signaling, and stimulate hepcidin production, which reduces luminal iron availability and alters the persistence of microbes.[79] Hepcidin induced by hepatocytes and local dendritic cells restricts intestinal iron flux, selecting species adapted to low-iron environments.[37] Iron status has also been associated with changes in gut barrier function.[26] Because barrier integrity affects oxygen diffusion and nutrient gradients, these alterations indirectly restructure microbial communities. Collectively, these mechanisms illustrate that dietary iron does not act solely as a nutrient input; rather, it dynamically interacts with microbial metabolism and host immune regulation. The microbiota responds to and reshapes iron availability, generating a reciprocal feedback loop that links diet, iron chemistry, microbial ecology, and host iron homeostasis.

EVIDENCE APPRAISAL: LIMITATIONS, BIAS, AND CAUSAL INFERENCE

Understanding the causal relationships between the gut microbiota and IDA requires careful consideration of the study design. Much of the current evidence is derived from observational research, which is inherently limited in its ability to establish directionality. Observational designs, including cross-sectional, case-control, and cohort studies, are valuable for identifying associations between microbial composition and iron status; however, they are highly susceptible to confounding and reverse causation.[101,102]

For example, Dorsey et al. conducted a cross-sectional study among 49 preschool-aged anemic children in Peru and found that children who failed to respond to iron supplementation had higher relative abundance of Barnesiellaceae and Enterobacteriales, despite no significant differences in overall α- or β-diversity.[13] This suggests that specific microbial signatures, rather than overall diversity, may influence treatment response. Similarly, McClorry et al.

analyzed stool and serum samples from 95 Peruvian infants and reported reductions in butyrate-producing taxa such as *Coprococcus* and *Roseburia* in males and *Butyricicoccus* in females, accompanied by metabolic alterations suggesting oxidative stress and mitochondrial dysfunction.[15] In South Korea, Seo et al. examined 31 premenopausal women (15 IDA patients and 16 healthy controls) and found significant depletion of Faecalibacterium and *Ruminococcaceae i*n women with IDA, with partial recovery after iron treatment.[16] These studies provide important ecological and clinical insights but remain susceptible to confounding and reverse causation.

Confounding arises because the iron status is strongly influenced by diet, age, medication use, infection burden, inflammation, socioeconomic factors, and environmental exposure.[101] For instance, Long et al. reported that among pregnant women in China (24 women with gestational anemia and 54 matched controls in the first trimester; 30 women with gestational anemia and 56 controls in the third trimester), gestational anemia was associated with reduced alpha diversity and depletion of dominant butyrate-producing taxa such as *Faecalibacterium*, particularly during the third trimester.[14] In contrast, a 21-day double-blind randomized controlled trial among Australian women of reproductive age, found that iron supplementation did not significantly alter overall microbiota composition, although minor increases in *Clostridiales* and decreases in *Bacteroides* were observed.[23] These differences may reflect variation in baseline microbiota composition, environmental exposure, dietary quality, and infection burden between low- and middle-income and high-income settings. Reverse causation is also a major concern because iron deficiency may alter dietary intake, gastrointestinal physiology, immune activation, or supplementation practices, which in turn reshape the microbiota.[102] Moreover, measurement errors, exposure variability due to daily microbiome fluctuations, and selection bias further limit the inference.[101] Consequently, observational studies are best regarded as hypothesis-generating rather than causally definitive.

MR has emerged as a complementary causal inference approach to address these limitations. MR uses genetic variants, most commonly single nucleotide polymorphisms, identified through genome-wide association studies (GWASs), as instrumental variables to test whether an exposure has a causal effect on an outcome.[103,104] Because genetic variants are inherited at conception and randomly assorted during meiosis, MR is often described as mimicking a “natural randomized controlled trial,” in which genotype is not influenced by postnatal environmental or behavioral factors.[103] This design reduces confounding factors and minimizes reverse causation, which is the principal methodological limitation of

observational epidemiology.[105,106] MR has been increasingly applied in gut microbiota and disease research to explore the potential causal links between microbial taxa and health outcomes.[107]

Recent MR studies have provided stronger evidence supporting potential causal relationships between specific microbial taxa and IDA. Lei et al., using a two-sample MR design based on MiBioGen Consortium microbiome data and UK Biobank IDA outcomes, identified nine gut bacterial taxa causally associated with IDA. *Roseburia*, *Prevotella*, *Oscillospira*, *Clostridia*, and *Actinomycetaceae* were identified as protective taxa, whereas *Ruminococcus gnavus* group, *Hungatella*, and *Parasutterella* were associated with increased IDA risk.[17] Zheng et al., using a three-sample MR framework integrating FINRISK, Canadian Longitudinal Study on Aging (CLSA), Pan-UK Biobank, FinnGen, and Genetic Epidemiology Research on Adult Health and Aging (GERA) datasets, similarly reported that Jiangellaceae had a protective effect against IDA, whereas *Ruminococcus E sp003521625* increased IDA risk.[18] They further demonstrated that plasma metabolites partially mediated this relationship, suggesting a microbiota–metabolite–IDA pathway. These MR findings strengthen causal inference beyond conventional observational associations.

However, valid causal inference in MR depends on three core assumptions: (1) the selected genetic variants must be strongly associated with the exposure (relevance); (2) they must not be associated with confounders (independence); and (3) they must influence the outcome exclusively through the exposure of interest (exclusion restriction).[108,109] However, these assumptions are not always satisfied in practice. Horizontal pleiotropy, in which genetic variants affect outcomes through alternative biological pathways, can introduce bias,[108,110] and weak instruments can reduce statistical power.[111] Importantly, MR strengthens causal inference but does not definitively prove causality.[104,112]

In the context of iron–microbiota research, observational and MR approaches offer complementary strengths and limitations. Observational studies capture real-time microbial composition in relation to iron deficiency or supplementation exposure, allowing detailed characterization of dysbiosis patterns, SCFA shifts, and pathogen blooms in IDA cohorts.[105] For example, studies in Peru, China, and South Korea consistently report depletion of *Faecalibacterium*, *Roseburia*, and other butyrate-producing taxa, but differ in the magnitude of *Proteobacteria* expansion and supplementation response, reflecting important contextual variability.[13–16] MR studies, in contrast, reduce confounding from diet, socioeconomic status, and systemic inflammation because genetic variants are fixed before birth[113] and precede disease onset.[19,102] Nonetheless, microbiome GWAS resources remain limited, and genetic

instruments for many taxa are weak.[114] MR cannot capture environmentally driven changes in microbial communities, such as those induced by diet, antibiotics, or iron supplementation.[108] Moreover, MR does not capture ecological responses to luminal iron exposure, which is central to phenomena such as the iron paradox.

Overall, for iron–microbiota research, integrating both approaches is essential; observational data provide an ecological context and mechanistic richness, whereas MR offers genetically informed causal triangulation.[19] Neither design alone is sufficient to establish definitive microbiota-driven causation of IDA; however, together, they strengthen the inference when interpreted cautiously and within their respective methodological constraints.

LIMITATIONS OF CURRENT EVIDENCE AND FUTURE RESEARCH

Despite the growing interest in the relationship between the gut microbiota and IDA, the current evidence base is constrained by several methodological limitations. Most human studies examining microbiota profiles in IDA rely on cross-sectional or case-control observational designs, which limit the ability to establish temporal directionality and are inherently susceptible to confounding factors such as diet, inflammation, infection, medication use, and socioeconomic factors.[6,7] In addition, microbiome measurement approaches vary substantially across studies, including differences in sample collection, sequencing platforms, targeted 16S rRNA regions, and bioinformatics pipelines. Such methodological heterogeneity complicates direct comparisons of taxonomic findings and may partly explain the inconsistencies in the reported microbial signatures associated with iron deficiency.[115,116] Interactions between iron supplementation and the gut microbiota may also differ between high-income countries and low- and middle-income settings, where the infection burden, environmental enteric dysfunction, and dietary patterns vary considerably.[81]

Genetic causal inference approaches, such as MR, provide an important complementary framework, but also have important limitations. The validity of MR inference depends on several key assumptions.[117] However, microbiome GWASs remain relatively underpowered, and genetic instruments for many microbial taxa are weak or inconsistent across different cohorts. Furthermore, most available microbiome GWAS datasets are derived predominantly from individuals of European ancestry, which limits their generalizability to populations with the highest IDA burden, particularly in low- and middle-income settings with distinct dietary patterns and environmental exposures.[118] Finally, the lack of longitudinal studies integrating microbiome composition, microbial function, dietary intake, and iron biomarkers restricts the

ability to disentangle the causal pathways within the iron–microbiota–host axis. Therefore, future research should prioritize longitudinal and interventional studies.

In summary, this narrative review critically synthesizes evidence indicating that individuals with IDA frequently exhibit reduced microbial diversity, depletion of SCFA-producing taxa, and relative enrichment of facultative or iron-scavenging bacteria. However, these taxonomic patterns are not specific to IDA and substantially overlap with microbial signatures observed in other inflammatory and metabolic conditions. Mechanistic pathways involving hepcidin regulation, siderophore-mediated iron acquisition, and microbial metabolite production provide biologically plausible explanations for these associations. However, direct causal evidence in humans remains limited.

In conclusion, gut microbiota alterations should be viewed not as isolated determinants of IDA but as part of a broader, dynamic system that both influences and responds to iron availability. While conventional diagnosis and iron replacement remain the foundation of current clinical management, understanding this ecological interaction may help explain variability in treatment response and the "iron paradox" observed in some populations. Microbiota-informed interventions remain investigational and should not yet replace established anemia management strategies. A nuanced understanding of this system, grounded in critical appraisal and methodological rigor, is crucial for translating microbiome science into meaningful nutritional and clinical practice.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

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DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

The author(s) assert that Generative AI was employed in the composition of this paper. We recognize the utilization of AI aid, particularly ChatGPT, for enhancing the language, clarity, and conciseness of the manuscript. No artificial intelligence methods were employed for data analysis, interpretation, or the generation of scientific content. All scientific hypotheses, findings, and conclusions were formulated and validated by the author(s).

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that there is no conflict of interest.

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Table 1. Taxonomic signatures associated with iron deficiency anemia across studies

Signature Pattern	Consistently Reported In	Functional Implication
↑ Streptococcus / Enterobacteriaceae[21,26]	IDA in pregnancy, CRF, animal models	Iron-scavenging bacteria with strong siderophore systems that promote microbial competition for iron and inflammation
↓ *Faecalibacterium*[16]	Women with IDA	Major butyrate-producing taxon; supports epithelial barrier integrity and enhances iron absorption via SCFA production
↓ *Prevotella*[27,28]	Low-iron mice, early-life iron deficiency	Fiber-fermenting bacteria producing SCFAs that reduce luminal pH and improve iron solubility
↑ *Clostridium* spp.[25,26]	IDA animal models	Metabolic restructuring under iron restriction; altered SCFA production and microbial fermentation patterns
↑ Siderophore-related pathways[14,20]	Pregnant women with IDA	Enhanced microbial iron acquisition through siderophore biosynthesis and ABC transport systems
↑ *R. faecis*, *B. uniformis*[22]	Anemic low-income populations	Opportunistic fermenters associated with dysbiosis and inflammatory gut environments
Mixed *Prevotella* results[17,27,28]	Human MR vs animal models	Context-dependent role influenced by diet, host metabolism, and ecological niche
Mixed *Desulfovibrio* results[30,119]	Human MR vs in vivo models	Sulfate-reducing bacteria influencing redox balance and inflammation; functional heterogeneity across strains
Protective taxa (*Roseburia, Oscillospira*)[17]	Human MR studies	SCFA-producing and metabolically active taxa potentially supporting iron absorption
Risk-associated taxa (*R. gnavus, Hungatella, Parasutterella*)[17]	Human MR studies	Inflammatory or dysbiosis-associated bacteria linked to increased IDA susceptibility

√, The project was taken on that day.

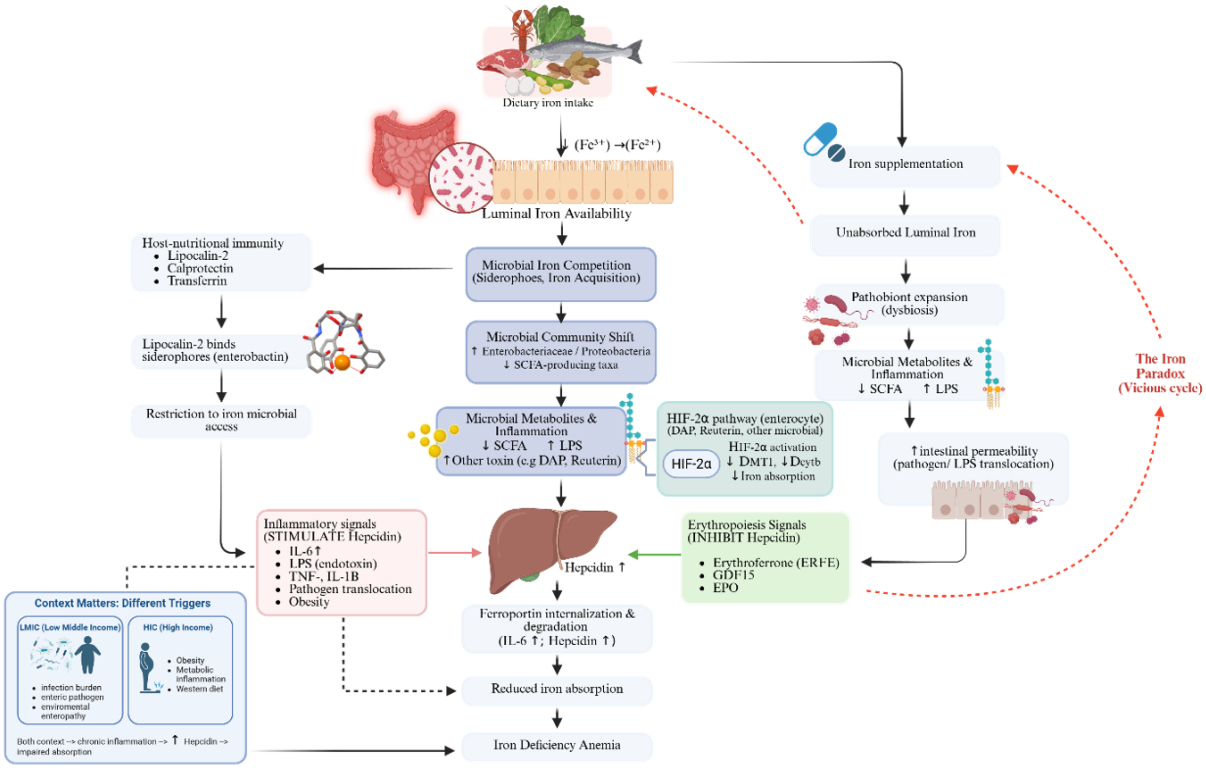

Figure 1. Conceptual model of the iron–microbiota–host axis in iron deficiency anemia.
Dietary iron and supplementation increase luminal iron, promoting dysbiosis and inflammation. Microbial metabolites and pathogen translocation activate inflammatory pathways (e.g., IL-6), stimulating hepatic hepcidin production. Hepcidin triggers ferroportin degradation, reducing iron absorption and trapping iron in storage sites. Erythropoietic signals (e.g., ERFE) counterbalance hepcidin. The resulting "iron paradox" forms a vicious cycle that perpetuates iron deficiency. Triggers differ by context: infection-driven inflammation in LMICs versus obesity-driven inflammation in HICs. (Created in https://BioRender.com).