# Micronutrient (iron, selenium, vitamin D) supplementation and the gut microbiome

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**Purpose of review**
Deficiencies in micronutrients persist as widespread global challenges, where supplementation remains a crucial therapeutic approach. This review aims to elucidate the intricate relationships between micronutrient supplementation – specifically iron, selenium (Se), and vitamin D (Vit D) – and gut microbiota composition, investigating their collective impact on host health and disease susceptibility.

**Recent findings**
Maintaining balanced iron levels is essential for gut microbiota equilibrium and host health, as both iron deficiency and excess disrupt gut bacterial balance, affecting colon health. Se supplementation can restore and improve the gut microbial balance, influencing health outcomes not only in the gut but also in areas such as neuroprotection in the brain, testicular health, and metabolic syndrome. Clinical and experimental models demonstrate that Vit D modulates the gut microbiome, enhancing anti-inflammatory effects, supporting metabolic health, and potentially reducing the risk of gut-related behavioral changes and diseases.

**Summary**
Findings of this review emphasize that balanced iron levels are essential for maintaining a healthy gut microbiota composition and underscore the beneficial effects of Se and Vit D in modulating the gut microbiome. The interactions between micronutrients and the gut microbiome are complex but may have a broad spectrum of health outcomes.

**Keywords**
iron, microbiota, micronutrient supplementation, selenium, vitamin D

## INTRODUCTION

Micronutrient deficiencies continue to be significant global health issues. The global vitamin and mineral supplement market value is projected to rise from US$ 58.8 billion in 2024 to US$ 99.7 billion by 2034. Iron, selenium (Se), and vitamin D (Vit D) are essential or probably essential micronutrients that play pivotal roles in human health. Deficiencies in these nutrients can cause not only micronutrient deficiencies but also have significant health consequences on diverse diseases such as metabolic diseases, infections, or cancer. While supplementation can correct micronutrient deficiencies, the impact on the gut microbial composition and the interaction between micronutrients and the microbiome on health outcomes remains largely unknown. This review focuses on peer-reviewed research articles related to the effects of iron, Se, and Vit D on the gut microbiome in human ($n = 11$ studies) and animal ($n = 29$ studies) models, published in the last 18 months (between August 2022 and February 2024).

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## KEY POINTS

- Iron status shapes the gut microbiota, with both deficiency and excess impacting bacterial balance. *Faecalibacterium*, a major butyrate-producing genus, is sensitive to host iron status. *Dubosiella*, known for its anti-inflammatory properties, is identified as a marker microbiota in both iron deficiency and overload.
- Excess iron may promote the growth of pathogenic bacteria like *Enterobacteriaceae*. This shift towards pathogen growth can lead to increased inflammation, potentially exacerbating conditions like colitis and altering lipid metabolism.
- Beneficial effects of Se supplementation include an increase in the abundance of *Lactobacillus* as well as reduced gut wall permeability, reduction of intestinal and systemic inflammation in association with a decrease in circulating lipopolysaccharide levels.
- Beneficial effects of Vit D supplementation are partially due to the modulation of gut microbiota composition, including an increase in the abundance of *Lactobacillus*, which is known for its positive effects on gut health and immune regulation.

## IRON

Iron is an essential trace element for all living organisms. Accumulating evidence suggests that the host's iron status may shape the gut commensal bacterial community, with both iron deficiency (ID) and iron excess impacting the composition and diversity of the gut microbiota. ID or iron deficiency anemia (IDA) may trigger gut dysbiosis by altering the ratio of *Firmicutes* to *Bacteroidetes* [1–3] or decreasing beneficial gut bacteria, such as *Lachnospiraceae* and *Ruminococcaceae*, which did not recover after iron replenish [4▪▪]. *Bacteroidetes* are iron dependent but have adaptation mechanisms that allow them to survive, but iron deprivation may restructure the *Bacteroides* genus [4▪▪]. *Firmicutes* and its major member, *Faecalibacterium*, are the most sensitive to the host's iron status, being decreased when iron is deprived and recovered after iron supplementation [4▪▪]. *Faecalibacterium* produces a large amount of butyrate, and its reduction, together with an increase in *Enterobacteriaceae*, is linked to colon inflammation and adverse human health outcomes [5▪]. By pairing human and in vitro community experiments, Celies *et al*. suggest that iron deprivation may lead to irreversible changes in the bacterial community structure [4▪▪].

Iron supplementation remains the standard treatment method for IDA, but the prescribed iron dosage varies substantially depending on the underlying causes of IDA. Studies have suggested that the effects of iron supplementation on the gut microbiota may not be uniform and vary according to participant characteristics (e.g., diet, inflammation) or the type of iron administration (e.g., dosage, chemical structure, route of administration). Animal studies show a dosage response to ferric citrate supplementation (1.25%, 2.5%, 5%) on the richness and diversity of the gut microbiota, with high ferric citrate (5%) causing leaky bowel and colonic mucosa damage [6]. Additionally, the type of iron compound may also affect gut bacteria differently; intravenous ferric carboxymaltose increased *Proteobacteria*, while ferric derisomaltose increased *Clostridia*, members of *Firmicutes* [2]. Both oral and intravenous iron supplementation restore normal gut microbiota composition in IDA women or diet-induced ID mice [1,2]. However, in anemic hemodialysis patients, intravenous iron may be more preferable than oral iron, as the intravenous iron administration increased α-diversity, but oral iron decreased the richness of the gut bacterial community [7▪].

Excess iron can be toxic, and to limit its toxicity, iron absorption rate tends to be low. The unabsorbed iron passes to the colon, where it is available for both commensals and enteropathogens. Iron supplementation may benefit the growth of enteropathogens such as *Enterobacteriaceae* and its members, including *Salmonella, Shigella*, and *Escherichia coli* [4▪▪,8]. In an S. Typhimurium-induced enterocolitis mouse model, iron-fortified diets (300 ppm) shift the microbiota towards pathogen growth and promote a more severe enterocolitis [9]. In contrast, an iron-deficient diet (<6 ppm) ameliorates the enteric infection, possibly by reshaping the gut microbiome [9]. Mice fed with a high-iron diet (1.25 g $FeSO_4$/kg diet) exhibited altered lipid metabolism and gut microbiota, with a relative reduction in the abundance of beneficial bacteria (*Akkermansia*, *Bifidobacterium*, and *Lactobacillus*) but an increase in pathogenic bacteria (*Romboutsia* and *Erysipelatoclostridium*) [10]. Gu *et al*. dissected mechanisms underlying iron-mediated colitis (5000 mg $FeSO_4$/kg diet) [11▪▪]. The authors suggested that iron overload decreased the abundance of beneficial bacteria (e.g., *Akkermansia*, *Alistipes*, and *Dubosiella*), leading to a reduction of anti-inflammatory metabolites (e.g., α-tocopherol) in the colon. Excess iron, in turn, causes lipid peroxidation and activation of ferroptosis, closely associated with *Alistipes* and *Bacteroides* [11▪▪]. A similar suppressive effect of a high iron diet (1000 mg carbonyl iron/kg diet) on *Akkermansia* was observed in mice with a colorectal cancer model, where supplementation with *Akkermansia muciniphila* successfully attenuated the tumorigenic effect induced by excess iron [12].

In summary, both iron deficiency and excess can drastically affect gut microbiota balance, influencing host health and disease susceptibility. Consequently, a well balanced iron status is crucial to ensure gut microbiota balance and overall health, illustrating the intricate interplay between diet, microbiome, and intestinal health.

## SELENIUM

Recent studies have revealed a tight relationship between Se metabolism and the gut microbiota. Specifically, Se supplementation in mice has been shown to mitigate alterations in gut metabolomics induced by microbiota depletion. This mitigation may be mediated by an Se-induced increase in the relative abundance of *Lactobacillus*, *Intestinimonas*, *Butyricicoccus*, *Ruminococcaceae_UCG014*, and certain other bacterial taxa [13▪▪]. These changes were associated with the level of intestinal metabolites. Similarly, Se-induced patterns of the gut microbiome were shown to correlate significantly with brain selenoprotein expression and brain metabolomics [14▪], thus supporting the role of the gut microbiota in shaping brain metabolism through Se treatment. In addition, the modulation of gut microbiota, with an increase in the abundance of *Lactobacillus* and certain other taxa, significantly contributed to changes in testicular selenoprotein content following Se supplementation [15]. This is generally in agreement with the positive effect of Se-induced gut microbiota shaping on the improvement of semen quality [16]. Moreover, the less pronounced induction of selenoprotein expression in the brain [14▪] and testes [15] in microbiota-depleted mice following Se supplementation clearly supports the role of gut microbiota in Se metabolism [17]. Conversely, Se deficiency also affected the gut microbiota with the most profound decrease in *L. reuteri* abundance, as well as impaired gut barrier function and increased systemic lipopolysaccharide (LPS) levels, all contributing to hepatic inflammation [18].

A number of studies have demonstrated that improvements in the gut microbiome may contribute to the anti-inflammatory effect of Se. Specifically, the administration of selenopeptides from Se-enriched *Cordyceps militaris* significantly improved the gut microbiota in LPS-exposed mice by increasing the relative abundance of *Lactobacillus* and *Alistipes*, while decreasing *Akkermansia* and *Bacteroides* populations. This contributed to reduced intestinal mucosa and brain oxidative stress and inflammation [19▪▪]. Correspondingly, treatment with Se-enriched *Bifidobacterium* restored the abundance of *Lactobacillus* and other taxa, reduced gut wall permeability, and proinflammatory cytokine production in mice with irritable bowel syndrome, resulting in neurobehavioral improvements [20▪]. In addition to the increase in the *Firmicutes/Bacteroidetes* ratio, the relative abundance of *Lactobacillus* and *Lachnospiraceae_NK4A136_group*, and the improvement of intestinal short-chain fatty acids production were shown to contribute to reduced intestinal inflammation, oxidative stress, and barrier dysfunction in mice with dextran sodium sulfate-induced colitis treated with selenium-containing soybean peptides [21▪▪]. Moreover, Se enrichment potentiated the protective effect of a probiotic treatment on gut dysbiosis, resulting in the attenuation of colitis, hepatic inflammation [22], as well as intestinal endoplasmic reticulum stress [23].

The shaping of the gut microbiota may also mediate the effects of Se supplementation in metabolic syndrome. Specifically, the administration of sweet corn cob selenium polysaccharide alleviated hyperglycemia in streptozotocin-induced diabetic mice through the down-regulation of the LPS/IκBα/NF-κB pathway and the improvement of gut microbiota with an enrichment of *Lactobacillus* and *Roseburia*, among others [24]. Furthermore, the hypolipidemic effect of Se-enriched kiwifruit in HFD-fed mice was associated with an increase in the relative abundance of *Parabacteroides*, *Bacteroides*, and *Allobaculum*, as well as the improvement of vitamin absorption, purine, and pyrimidine metabolism [25]. Finally, Se deficiency was shown to alter the gut microbiota response to a high-fat diet [26].

It is assumed that the neuroprotective effects of Se compounds are also mediated by the gut microbiota. Specifically, resveratrol-loaded selenium/chitosan nano-flowers in a rat model of Alzheimer's disease may be mediated by an increase in the relative abundance of the Bacteroidetes phylum, as well as *Desulfovibrio*, *Candidatus_Saccharimonas*, *Roseburia*, *Lachnospiraceae_UCG-006*, and *Alloprevotella* [27]. Moreover, the modulation of gut microbiota by Se supplementation in mice exposed to a chemical cocktail containing heavy metals (As, Hg, Cd), diclofenac, and flumequine contributed to the shaping of brain metabolomics [28].

## VITAMIN D

Vit D metabolism has been shown to be closely linked to the functioning of gut microbiota [29]. This relationship is confirmed by observations from a Vit D deficiency model, which results in autistic-like behaviors characterized by an increased relative abundance of *Akkermansia* and *Turicibacter*, and a reduced abundance of *Allobaculum* and *Fusicatenibacter*. Meanwhile,

the abundance of *Phascolarctobacterium*, *Parabacteroides*, and *Parasutterella* was inversely associated with social play behaviour [30▪▪]. Additionally, early-life Vit D deficiency, resulting in impaired glucose tolerance, was shown to increase the relative abundance of *Desulfovibrio*, *Roseburia*, *Ruminiclostridium*, *Lachnoclostridium*, *A2*, *GCA-900066575*, *Peptococcus*, *Lachnospiraceae_FCS020_group*, and *Bilophila*, while reducing that of *Blautia*, also affecting the gut metabolome [31].

Recent studies demonstrated the role of gut microbiota in the protective effects of Vit D in experimental models of metabolic syndrome (MetS). Specifically, in animals fed a high-fat diet (HFD), Vit D supplementation significantly reduced body weight gain, dyslipidemia, and systemic inflammation, mediated by a reduction in circulating lipopolysaccharide (LPS) levels due to improved gut microbiota biodiversity. This included an increased relative abundance of *Bacteroidetes, Proteobacteria, Desulfovibrio, Dehalobacterium, Odoribacter*, and *Parabacteroides*, as well as a decrease in *Firmicutes* and *Ruminococcus* populations [32▪▪]. Correspondingly, in a HFD-induced fatty liver disease model, Vit D supplementation mitigated hepatic lipid accumulation, improved the α-diversity index, reduced the *Firmicutes/Bacteroidetes* ratio, and increased the relative abundance of *Prevotella*, which was associated with amino acid and sphingolipid metabolism. This suggests that the systemic effects of Vit D on nonalcoholic fatty liver disease (NAFLD) may be mediated through the modulation of gut microbiota [33▪]. Moreover, the prevention of HFD-induced alterations in gut microbiota by Vit D supplementation was also associated with improved liver metabolomics and bile acid metabolism, altogether contributing to the mitigation of metabolically associated fatty liver disease (MAFLD) [34]. The interplay between altered gut microbiota and bile acid metabolism was also shown to modify MetS risk in Chinese adults [35].

The anti-inflammatory effect of Vit D supplementation was also tightly associated with modulation of gut microbiota. Specifically, in a model of LPS-induced systemic inflammation, the oral administration of Vit D reversed the LPS treatment's effects on gut microbiota [36]. Correspondingly, Vit D supplementation significantly reduced the symptoms of preeclampsia in pregnant LPS-exposed rats through the down-regulation of the TLR4/MYD88/NF-κB signaling pathway and the improvement of gut microbiota biodiversity and the relative abundance of beneficial intestinal microbiota [37].

In clinical studies, Vit D supplementation has been shown to prevent an increase in the relative abundance of the potentially hazardous *Desulfovibrio* [38] and *Haemophilus* [39] in pregnant women and infants, respectively. Correspondingly, higher circulating Vit D levels in diabetic patients were associated with a reduced relative abundance of *Escherichia* spp. and *Pseudomonas* spp., and a concomitant enrichment of butyrate-producing *Eubacterium* spp. [40▪]. A similar effect, characterized by a reduced relative abundance of *Streptococcus* and *Dialister*, with an enrichment of *Eubacterium* and *Lactobacillus*, was observed in NAFLD patients supplemented with fish oil and Vit D [41▪▪]. The intramuscular administration of Vit D3 in patients with *Clostridioides* difficile infections significantly increased the relative abundance of beneficial *Bifidobacteriaceae* and *Christensenellaceae* and reduced populations of *Proteobacteria* compared to nonsupplemented controls in the recovery period [42].

## α-Diversity

A meta-analysis was performed on the differences in α-diversity and the abundance of microbial taxa among groups using random-effects models. A total of 30 studies ($n = 41$ study arms for Chao, $n = 50$ study arms for Shannon) provided data for α-diversity. The pooled estimates indicated a moderately significant reduction in gut microbiome richness in diseased compared with nondiseased groups [Chao: SMD: −1.63 (−2.59, −0.67), $I^2$: 87%, Shannon: SMD: −1.32 (−2.04, −0.60), $I^2$: 81%] (Fig. 1a and b). Micronutrient supplementation significantly increased the richness and diversity of the gut bacterial community in animal studies [Chao: SMD: 0.90 (0.41, 1.40), $I^2$: 76%, Shannon: SMD: 1.15 (0.63, 1.67), $I^2$: 81%] (Fig. 1c and d). However, a nonsignificant adverse effect was observed in human studies.

## CONCLUSION

The host's micronutrient status may shape the composition and functionality of the gut microbiome. However, progress in identifying key microbial markers driven by micronutrient status for predicting human disease remains unsatisfactory. This is largely due to variations in host responses, chemical structures of supplement, routes of administration, and the techniques used to detect the microbiome. Nonetheless, maintaining an optimal balance of micronutrients is crucial, as deficiencies or excesses may lead to adverse effects on the gut microbiome. This underscores the importance of personalized nutrition and intervention strategies. Further research is needed to fully understand these interactions and to optimize supplementation recommendations for different populations, considering the intricate relationships between micronutrient, the gut microbiota, and overall human health.

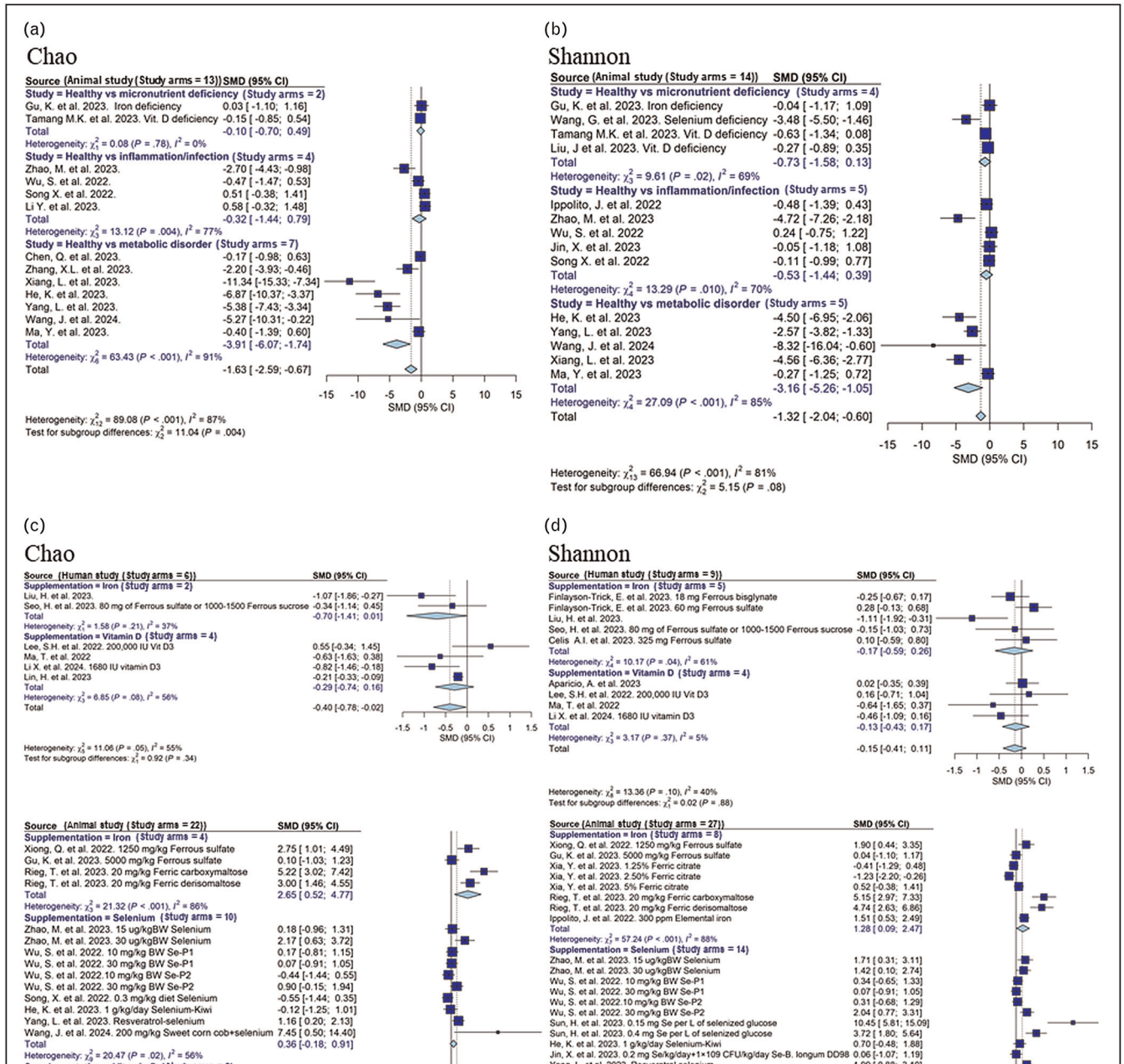


**FIGURE 1.** A forest plot of α-diversity, stratified by disease (a, b) and micronutrient supplementation (c, d), in both human and animal models. α-diversity was indicated by the Chao index, which measures species richness, and the Shannon index, which measures both species richness and evenness. (a, b) Compares diseases (categorized as micronutrient deficiency, inflammation or infection, and metabolic disorder) with nondiseases. (c, d) Compares those with micronutrient supplementation (iron, selenium, vitamin D) to those without. The effect size was calculated as the standardized mean difference (SMD). The pooled effects with 95% confidence intervals (CIs) were calculated using random-effects models based on the DerSimonian and Laird method.

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## Conflicts of interest

*There are no conflicts of interest.*

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