For healthcare professional use only

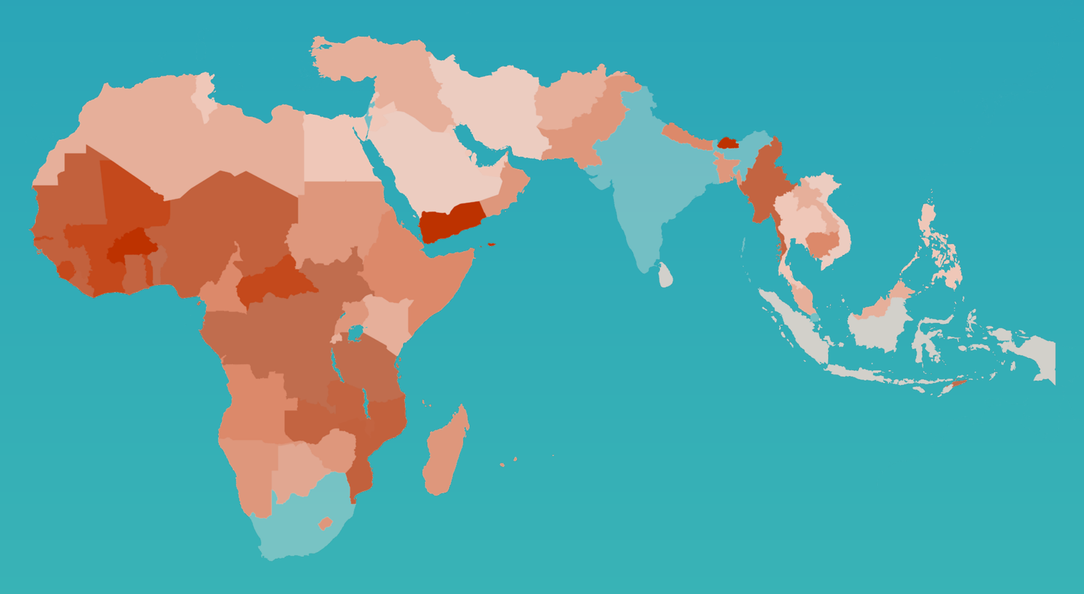
Danone Nutricia Campus

The role of dietary iron fortification in managing iron deficiency and iron deficiency anemia in early life

Iron deficiency (ID) is the most common micronutrient deficiency worldwide, with infants and children being particularly at risk.[1]

ID is the most common cause of nutritional anemia among children. Globally, ID is the cause of anemia in 42% of anemic children ≤5 years old.[2]

High prevalence of iron deficiency anemia (IDA) among children aged 6–59 months in India, South-East Asia and Africa[3]



ID/IDA in early life can have serious developmental consequences. Children with ID/IDA typically have[4,5]:

- POOR COGNITIVE DEVELOPMENT
- MOTOR SKILLS DYSFUNCTION
- HIGH RISK OF INFECTIONS

Strategies to prevent ID and IDA in early life include[6]:

Iron supplementation (administration in higher dosage for severe ID/IDA)

Dietary modification or fortification

Oral iron supplementation, although a common strategy in managing ID, is associated with several gastrointestinal effects[7]:

Diarrhea — Constipation — Nausea

→ **Non-compliance and potential treatment failure**

Dietary fortification is a potent long-term strategy for preventing ID/IDA, particularly in infants with low tolerability to oral iron supplementation.

Clinical evidence supporting dietary fortification:

A randomized, double-blind controlled trial in children aged 1 to 3 years[8] → Young-child formula (YCF) fortified with iron and vitamin D / Non-fortified cow's milk → **60%** reduction in the probability of ID with YCF

Guideline recommendations in dietary fortification for ID[9]:

According to **ESPGHAN, formula-fed infants** up to 6 months of age should receive:

Iron-fortified **infant formula**, with an **iron content of 4 to 8 mg/L** (0.6-1.2 mg/kg/day)

Follow-on formula should also be iron-fortified **between 3.6 and 14 mg/L**

Dietary iron is present as:

	Heme iron[10-12]	Non-heme iron[10,11]
Sources	Meat, fish	Cereals, legumes
Iron form	Hemoglobin, myoglobin	Both ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms

Iron bioavailability (percentage or a fraction of iron intake) depends on the chemical form of iron in the small intestine.

Bioavailability according to iron form:

The bioavailability of **heme iron** (25%) is greater than that of non-heme iron (<5–20%).

Absorption of **non-heme iron** is dependent on the iron salt form.

The reduction of Fe^{3+} to Fe^{2+} is facilitated by reducing agents such as ascorbic acid present in the intestine.

Absorption rate of iron salt form

$Fe^{2+} > Fe^{3+}$

Chronic diseases or infections can lead to suboptimal iron absorption despite fortification or supplementation[14]

Iron supplements may adversely impact the infant gut microbiome and cause the accumulation of infectious pathogens, leading to intestinal inflammation[15–17]

Dietary iron is poorly absorbed, resulting in adverse impact on the gut microbiome.[15,16]

Dietary iron

Gut microbiota dysbiosis

Proliferation of harmful bacteria (*Escherichia coli* and *Salmonella spp.*)

Increased risk of infections

Dietary fortification with vitamin C is known to enhance iron absorption and bioavailability as well[18]

While the optimal iron to vitamin C molar ratio is 1:4,[19] even a 1:2 ratio can enhance iron absorption.

VITAMIN C

100 mg/L ascorbic acid (molar ratio of iron to ascorbic acid 1:2)

\+

Iron-fortified cow's milk

~2-fold increase in iron absorption[15]

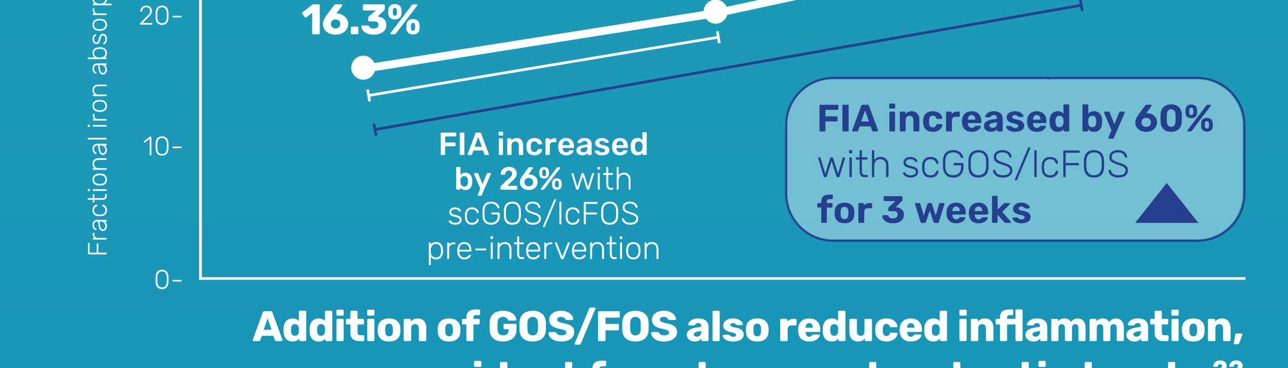
Addition of vitamin C-rich foods, such as citrus fruits to infant diet has been recommended by WHO, in order to enhance iron absorption.[20]

Prebiotics can promote iron bioavailability and balanced gut microbiome development

Prebiotics are substrates for selective utilization by host microorganisms.[17,21]

3-week randomized controlled study in Kenyan infants, who were fed a daily meal containing iron, vitamin C, with or without prebiotics [galacto-oligosaccharides/fructo-oligosaccharides (GOS/FOS)][22]

Addition of GOS/FOS increases iron absorption by 60%, after 3 weeks of intervention[22]



Addition of GOS/FOS also reduced inflammation, as evident from lower calprotectin levels.[22]

Conclusion

Iron-rich infant formulas are critical in combating ID in early life and preventing IDA. However, the benefits of these formulas can be further enhanced by fortification with vitamin C and with prebiotics (GOS/FOS). In addition to increasing iron absorption and bioavailability, prebiotics reduce the impact of gut microbiome dysbiosis resulting from iron supplementation or fortification.

References:

1. Han X, et al. eClinicalMedicine 2022;44:101299.
2. Mbunga BK, et al. Nutrients. 2021;13(3):1010.
3. World Bank. Prevalence of anemia among children (% of children ages 6-59 months). World Health Organization, Global Health Observatory Data Repository/World Health Statistics. 2019. https://data.worldbank.org/indicator/SH.ANM.CHLD.ZS?type=shaded&view=map. Accessed 1 April 2024.
4. World Health Organization. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015. https://iris.who.int/bitstream/handle/10665/177094/9789241564960_eng.pdf?sequence=1. Accessed 5 April 2024.
5. Mourad S, et al. N Am J Med Sci. 2010;2(10):461–466.
6. Bailey RL, et al. Ann Nutr Metab 2015;66(Suppl 2):22–33.
7. Amrousy DE, et al. Pediatr Res 2022;92(3):762–766.
8. Akkermans MD, et al. Am J Clin Nutr 2017;105(2):391–399.
9. Domellöf M, et al. J Pediatr Gastroenterol Nutr 2014;58(10):119–129.
10. Hertrampf E, et al. Congress Int. Soc. Hematol.; 1978, Paris, France.
11. Zimmermann MB, et al. Am J Clin Nutr. 2005;81(1):115–21.
12. Martínez-Torres C, Layrisse, M. Am J Clin Nutr. 1971;24(5):531–40.
13. Barber SA, et al. Br Med J (Clin Res Ed), 290(6470):743 –744.
14. Camaschella C. Blood 2019;133:30–39.
15. McMillen SA, et al. Nutrients 2022 ;14(20) :4380.
16. Georgieff MK, et al. Annu Rev Nutr 2019;39:121–146.
17. Rusu IG, et al. Nutrients 2020 ;12(7) :1993.
18. Lynch SR, et al. J Nutr. 2003;133(9):2978S-84S.
19. Zimmermann, MB, Hurrell RF. Lancet. 2007;370(9586):511-20.
20. World Health Organization. Nutritional Anaemias: Tools for Effective Prevention and Control. 2017. https://iris.who.int/bitstream/handle/10665/259425/9789241513067-eng.pdf?sequence=1&isAllowed=y. Accessed 5 April 2024.
21. Zakrzewska Z, et al. Microorganisms 2022;10:1330.
22. Mikulic N, et al. Am J Clin Nutr. 2024;119(2):456-469.

Danone Nutricia Campus