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Nutrient Information (Invited)

# Iron

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## Iron

Each cell in the body acquires iron from the systemic circulation in a calibrated, carefully orchestrated manner for growth, development, and function [1,2]. Iron, able to shuttle electrons between ferric ($Fe^{3+}$) and ferrous ($Fe^{2+}$) forms, is an essential element for oxygen transport, storage, and utilization. Iron is required for energy production and cellular proliferation and is present in cytochromes, heme and nonheme enzymes, iron-sulfur clusters, neurotransmitters, and other iron-dependent compounds. Although all cells require iron, the majority of body iron (~80%) is present within hemoglobin in circulating red blood cells. The body carefully conserves iron, losing only very small amounts each day, and has no regulated means of excretion. Consequently, iron homeostasis depends on the following: *1*) strict control of intestinal iron absorption; *2*) efficient recycling of iron from red blood cells at the end of their life span; *3*) prompt passage of recycled iron to the erythroid marrow for effective erythropoiesis; and *4*) managed maintenance of iron stores in macrophages and hepatocytes. The transport protein *transferrin* delivers iron through plasma to cells, with each molecule bearing up to 2 $Fe^{3+}$ ions. The master regulator of iron homeostasis, hepcidin, adjusts the concentration of transferrin-bound iron in the plasma to control the amount and distribution of body iron. The principal sources of iron export into plasma are the recycling of iron from senescent erythrocytes by specialized macrophages, dietary iron absorption by duodenal enterocytes, and iron release from hepatocyte stores. Hepcidin regulates iron entry to plasma by binding to the only known iron export protein, ferroportin. Hepcidin obstructs and induces degradation of ferroportin, resulting in the retention of iron within iron-exporting cells. Each cell in the body acquires iron from plasma transferrin by expressing transferrin receptor 1 on the cell membrane. After binding, the transferrin-iron-transferrin receptor 1 complex is internalized in an endocytic vesicle, and iron is subsequently released into the cytoplasm. Within the cell, the iron is either used for synthesis of iron-requiring compounds or is safely stored within ferritin, a large spherical protein that can hold up to 4500 iron atoms, and hemosiderin, aggregates of partially digested ferritin. In healthy individuals, plasma or serum ferritin concentrations are an indicator of the amount of body iron stores. With inflammation, plasma ferritin concentrations increase with the acute phase response while hepcidin rises and plasma iron falls.

### Deficiencies

Iron deficiency develops when the supply of iron in the body cannot provide the amounts required for erythropoiesis and tissue needs [3]. In *absolute iron deficiency*, the iron supply cannot be maintained because of reduced or absent body stores. In functional iron deficiency, body iron stores are adequate, but iron mobilization is insufficient to meet the requirements because of inflammation. Absolute and functional iron deficiency may coexist. Iron deficiency, with or without anemia, may be asymptomatic or result in gastrointestinal disturbances, weakness, dizziness, fatigue, irritability, and difficulty concentrating. Iron deficiency may be associated with detrimental functional outcomes in pregnancy, cognitive performance, immune response, exercise capacity, work performance, and body temperature regulation. In infants and children, iron deficiency may result in psychomotor and cognitive abnormalities that, without treatment, can lead to learning difficulties.

### Diet recommendations

Iron requirements are based on the maintenance of equilibrium between fractional iron absorption from the diet and the amount of iron needed to replace normal basal and menstrual iron losses and to meet increased iron demand over the life cycle

*Abbreviations:* $Fe^{3+}$, ferric; $Fe^{2+}$, ferrous.

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for growth and development and for pregnancy and lactation (Table 1).

## Food sources

Dietary iron is present in food in 2 main forms, heme and nonheme. Heme iron, as a component of hemoglobin and myoglobin, is found in animal foods such as meat, fish, seafood, and poultry. Nonheme iron is present in plant-based foods and iron-fortified foods (eg, iron-fortified cereals). Heme iron absorption is approximately 25%, whereas nonheme iron is less well and more variably absorbed. A number of dietary and physiological factors influence the efficiency of dietary nonheme iron absorption. Individuals with adequate body iron stores absorb less nonheme iron than individuals with insufficient body iron stores. Dietary components that influence nonheme iron absorption include animal muscle tissue and ascorbic acid. Inhibitors of nonheme absorption include phytates, polyphenols, and calcium. Mean dietary iron absorption from Western-style diets is estimated to be around 15% to 18%.

## Clinical uses

Worldwide, iron deficiency is considered to be the most common nutritional deficiency disorder. If dietary iron intake is insufficient to meet iron requirements, body iron stores will become depleted. When a negative iron balance persists for a sufficient period of time, iron deficiency anemia develops. Because dietary iron requirements are elevated during periods of growth or when menstrual or other blood losses are high, certain groups are at greater risk of iron deficiency anemia. These include infants, young children, adolescents, women of childbearing age, and pregnant or lactating women. Short- and long-term clinical consequences of iron deficiency anemia can include developmental delay, cognitive impairment, adverse pregnancy outcomes, and impaired physical performance and quality of life. These adverse outcomes may justify oral iron supplementation when diet alone is anticipated to be insufficient to provide requirements for erythropoiesis and tissue needs and rebuild depleted body iron stores within a reasonable period of time.

**TABLE 1**
Dietary reference intakes for iron (mg/d)

| Age | EAR | | RDA | | AI | UL |
|---|---|---|---|---|---|---|
| | Men | Women | Men | Women | | |
| | | | | | 0.27 | 40 |
| 0–6 mo | | | | | | 40 |
| 7–12 mo | 6.9 | 6.9 | 11 | 11 | | 40 |
| 1–3 y | 3.0 | 3.0 | 7 | 7 | | 40 |
| 4–8 y | 4.1 | 4.1 | 10 | 10 | | 40 |
| 9–13 y | 5.9 | 5.7 | 8 | 8 | | 40 |
| 14–18 y | 7.7 | 7.9 | 11 | 15 | | 45 |
| 19–30 y | 6.0 | 8.1 | 8.0 | 18 | | 45 |
| 31–50 y | 6.0 | 8.1 | 8.0 | 18 | | 45 |
| 51–70 y | 6.0 | 5.0 | 8.0 | 8.0 | | 45 |
| >70 y | 6.0 | 5.0 | 8.0 | 8.0 | | 45 |
| Pregnant, ≤18 y | | 23 | | 27 | | 45 |
| Pregnant, 19–50 y | | 22 | | 27 | | 45 |
| Lactation, ≤18 y | | 7 | | 10 | | 45 |
| Lactation, 19–50 y | | 6.5 | | 9.0 | | 45 |

AI, adequate intake; EAR, estimated average requirement; RDA, recommended dietary allowance; UL, tolerable upper intake level.

Supplemental oral iron is available as ferrous and ferric iron, with ferrous iron salts such as ferrous sulfate, ferrous fumarate, and ferrous gluconate being absorbed better than ferric iron. When oral iron supplementation is unsuccessful, with severe iron deficiency anemia and in individuals with complex medical disorders, intravenous iron therapy is generally the treatment of choice. With the intravenous iron formulations now available, low molecular weight iron dextran, ferric gluconate, iron sucrose, ferric carboxymaltose, and ferric derisomaltose, risks of anaphylactic reactions are very low and serious adverse events are uncommon.

## Toxicity

Acute iron toxicity can produce life-threatening caustic and cellular damage after accidental or intentional overdose. Chronic iron toxicity develops with iron overload. Excess can produce chemically reactive forms of iron that damage lipids, proteins, and DNA, causing organ injury. Iron overload is the result of genetic or acquired disorders that disrupt or bypass regulatory control of absorption and recycling of iron. Hemochromatosis describes a set of heterogeneous disorders of genes involved in hepcidin and ferroportin regulation of iron homeostasis; the most common is autosomal dominant *HFE* hemochromatosis. Iron overload also develops in anemia requiring chronic transfusion, in iron-loading anemia with ineffective erythropoiesis, with some forms of chronic liver disease, and in a variety of other rare acquired and inherited disorders.

## Recent research

Iron biology, metabolism, and nutrition over the life cycle and in different health contexts remain very active areas of investigation. Substantial advances have been made in characterizing the molecular machinery underlying the control of systemic iron homeostasis, leading to ongoing development of hepcidin diagnostics and therapeutic agents. Nonetheless, our understanding of iron metabolism remains incomplete in vital areas, such as the autonomous regulation of iron in the brain, heart and other organs, the control of iron homeostasis during pregnancy and in early childhood, the pathway of intestinal heme absorption, the functions of soluble transferrin receptor and of secreted ferritin, the involvement of iron in a variety of metabolic disorders, and the biological roles of ferroptosis, a form of programmed cell death. Dietary iron intake is not directly related to body iron levels because of the wide variability in nonheme iron absorption, which complicates the derivation of Dietary Reference Intakes and has necessitated the use of dietary bioavailability algorithms to predict absorption. Novel stable isotope methods have been developed to measure long-term iron absorption and iron losses, which will aid future updates on dietary recommendations. Given the widespread prevalence of iron deficiency and anemia, a considerable and active body of research exists on strategies to resolve these consequential public health problems. A number of programs are examining iron biofortification of staple crops as this is considered to be more sustainable than food fortification. The search for more effective forms of iron for use as supplements and fortificants continues. Iron deficiency frequently exists against a backdrop of multinutrient malnutrition and of infectious diseases and inflammation. Approaches for the assessment of iron status under these conditions have been developed. Guidelines have been issued by the WHO on the

treatment of iron deficiency in countries where malaria is endemic and on the use of intermittent, instead of daily, iron supplementation. The complexity and pervasive nature of iron deficiency and anemia in a global context has prompted the publication of a comprehensive framework for accelerating anemia reduction by the WHO, targeted at a wide audience that includes policy makers, program managers, and funding organizations [4].

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## Conflicts of interest

The authors report no conflicts of interest.

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