Iron-Status Indicators

Sources and Physiological Functions

Iron functions as a component of proteins and enzymes. Almost two-thirds of the iron in the body (approximately 2.5 grams of iron) is found in hemoglobin, the protein in red blood cells that carries oxygen to tissues. About 15% is in the myoglobin of muscle tissue. The average American diet provides 10–15 milligrams (mg) of iron daily in the form of heme and nonheme iron. Heme iron is found in animal foods that originally contained hemoglobin and myoglobin, such as red meat, fish, and poultry. Nonheme iron is found in plant foods, such as lentils and beans, and in iron-enriched and iron-fortified foods. Although heme iron is absorbed better than nonheme iron, most dietary iron is nonheme iron (Miret 2003). Each day the body absorbs approximately 1–2 mg of iron to compensate for the 1–2 mg of iron that the (non-menstruating) body loses (Institute of Medicine 2001). The 2025–2030 Dietary Guidelines for Americans recommends that pregnant women talk to their healthcare professional about taking a daily prenatal vitamin containing iron (U.S. Department of Agriculture and U.S. Department of Health and Human Services 2026). For young children, women capable of becoming pregnant, and women who are pregnant, low intake of iron is of public health concern.

Health Effects

Iron moves from one organ to another through reversible binding to the transport protein, transferrin. Transferrin then forms a complex with a highly specific transferrin receptor (TfR) located on the plasma membrane surfaces of cells. Intracellular iron availability is regulated through the increased expression of cellular TfR concentration by iron-deficient cells. Ferritin is the major iron-storage compound: Its production increases in cells as iron supplies increase. Ferritin's main function is to provide a store of iron that can be used for heme synthesis when required. Although all cells can store iron, the liver, spleen, and bone marrow cells are the primary iron-storage sites in humans (Institute of Medicine 2001).

Iron deficiency and iron overload are the two major disorders of iron metabolism. Iron-deficiency anemia is the most severe consequence of iron deficiency, and it is reversible. It is linked to many adverse consequences, such as reduced physical capacity (Haas 2001) and poor pregnancy outcomes (Schorr 1994). Iron deficiency with and without anemia, however, has been linked to negative effects on cognitive development among infants and adolescents (Beard 1999; Grantham-

McGregor 2001). The global prevalence of anemia across all ages was 24.3% in 2021, down from 28.2% in 1990 (GBD 2021 Anaemia Collaborators 2023). Limitations in iron deficiency guidelines, data, and monitoring of disparities in the United States have been discussed (Jefferds 2022).

Iron overload is the accumulation of excess iron in body tissues. It is usually caused by a genetic predisposition to absorb more iron than normal. However, it can also be caused by excessive ingestion of iron supplements or multiple blood transfusions (Pietrangelo 2004). In advanced stages of iron overload disease (hemochromatosis), iron accumulates in the parenchymal cells of several organs, particularly the liver, followed by the heart and pancreas. This condition can lead to organ dysfunction and even death (Pietrangelo 2004).

Two national health goals that relate to iron deficiency reduction are part of Healthy People 2030. Objective NWS-16: Reduce iron deficiency in children aged 1 to 2 years and Objective NWS-17: Reduce iron deficiency in females aged 12 to 49 years. To provide data for these objectives, NHANES continues with periodic monitoring of iron status in the population groups of interest.

Intake Recommendations

The daily Recommended Dietary Allowance (RDA) for different age groups is as follows (Institute of Medicine 2001):

- 8 mg for adult men ages 19 years and older and postmenopausal women ages 51 and older
- 18 mg for premenopausal women ages 19–50 years
- 27 mg for pregnant women ages 14–50 years
- 10 mg for lactating women ages 14–18 years or 9 mg for ages 19–50 years
- 11 mg for boys ages 14–18 years and 15 mg for girls ages 14–18 years
- 8 mg for boys and girls ages 9–13 years
- 10 mg for children ages 4–8 years and 7 mg for children ages 1–3 years
- 11 mg for infants ages 7–12 months

The Adequate Intake (AI) for infants 0–6 months is 0.27 mg per day (Institute of Medicine 2001).

The Tolerable Upper Intake Level for adults is 45 mg per day of iron, a level based on gastrointestinal distress as an adverse effect (Institute of Medicine 2001).

Biochemical Indicators and Cutoff Values

The Biomarkers of Nutrition for Development (BOND) project published a comprehensive review of iron biology and biomarkers (Lynch 2018). Biochemical assessment of iron status generally relies on a panel of indicators that describe the adequacy of one or more of the body iron compartments: iron stores, transport iron, and functional iron. Depletion of each compartment leads to a different iron deficiency stage, namely iron depletion, iron deficiency erythropoiesis, and iron deficiency anemia (Hastka 1996).

Ferritin. Ferritin is present in the blood in very low concentrations. Serum ferritin is in equilibrium with tissue stores, and its concentration declines early in the development of iron deficiency. So, low serum ferritin concentration is a sensitive indicator of iron deficiency, but it does not necessarily reflect the severity of the depletion as it progresses (WHO 2011). Ferritin is also an acute-phase protein; acute and chronic diseases can result in increased ferritin concentration, potentially masking an iron-deficiency diagnosis (Worwood 2007). The World Health Organization (WHO) guideline on the use of ferritin to assess iron status in individuals and populations recommends concurrent measurement of two acute phase proteins (C-reactive protein [CRP] and alpha-1-acid glycoprotein [AGP]) to assess serum ferritin in areas of widespread infection or inflammation (WHO 2020). WHO suggests three approaches to account for the effect of inflammation on serum ferritin:

- Raise the ferritin cutoff value that defines deficiency (to 30 ng/mL or 70 ng/mL, depending on the age group).
- Exclude individuals with elevated concentrations of CRP or AGP.
- Use arithmetic or regression correction approaches to adjust ferritin concentrations for inflammation and then apply cutoff points recommended for healthy populations (WHO 2020).

Depending on the availability of data, one regression correction method used is the BRINDA approach (Namaste 2017). It uses linear regression to adjust ferritin concentrations by CRP only, or by CRP and AGP concentrations, on a continuous scale, and malaria infection as a dichotomous variable.

Soluble TfR (sTfR). sTfR is the truncated form of the membrane-bound TfR that is cleaved and released into the serum. The amount of sTfR is proportional to the number of membrane-bound TfR. sTfR circulates bound to transferrin, and its concentration is not strongly affected by

concurrent inflammation or infection (Beard 2007). Serum sTfR concentration increases when the iron functional pool is depleted and during activated erythropoiesis (Kuiper-Kramer 1998). It continues to do so as the severity of iron-deficient erythropoiesis increases, reflecting the increasing number of receptors on the erythroid cells of the bone marrow. The measurement of sTfR is therefore a useful tool for the diagnosis of iron deficiency or for monitoring erythropoiesis.

Body iron index. While serum ferritin is the most sensitive index of iron status when there are residual iron stores, serum sTfR is more sensitive when there is functional iron deficiency (Skikne 1990). There is a close, linear relationship between the logarithm of the sTfR to serum ferritin ratio and stored iron (body iron), expressed as mg per kg body weight (Skikne 1990). Cook et al. demonstrated that, in healthy persons, we can estimate body iron from the ratio of sTfR to serum ferritin (reported in microgram [µg]/mL for both assays) (Cook 2003).

"Body iron index" might be a more appropriate term than "total body iron" and "total body iron stores", terms that have been used before. Body iron index is in a positive balance (≥0 mg/kg) when there is residual storage iron and in a negative balance (<0 mg/kg) when there is functional iron deficiency. The latter represents a deficit in iron required to maintain a normal hemoglobin concentration. The body iron index methodology allows us to evaluate the full range of iron status of populations, but it has not yet been validated for use in children.

Transferrin saturation. Transferrin saturation and erythrocyte protoporphyrin are other iron status indicators that inform about the adequacy of iron supply provided by the transport iron compartment (Beard 2007). Transferrin saturation represents the percentage of binding sites on all transferrin molecules occupied with iron molecules. We can calculate it in different ways: ratio of serum iron to transferrin, ratio of serum iron to total iron-binding capacity (TIBC), or ratio of serum iron to the sum of serum iron and unsaturated iron-binding capacity (UIBC). The measured serum iron concentration is the fraction of ferric iron (Fe^{3+}) that circulates bound primarily to transferrin. Serum iron concentration is decreased in many people with iron deficiency anemia and in people with chronic inflammatory disorders. Elevated concentrations of serum iron occur in iron-loading disorders such as hemochromatosis. Serum iron is not, however, a good indicator of iron stores and is not a sensitive measure of iron deficiency, partly because of daily fluctuations. For enhanced utility, serum iron measurements are used in conjunction with TIBC measurements, as transferrin saturation. Normally, because only about one third of the iron-binding sites of transferrin are occupied by iron, serum transferrin has considerable reserve iron-binding capacity.

TIBC is a measurement of serum transferrin after saturation of all available binding sites with reagent iron. Concentrations of serum TIBC vary with the type of iron-metabolism disorder. For example, in iron deficiency TIBC is often increased, and in chronic inflammatory disorders, malignancies, and hemochromatosis, it is often decreased.

Erythrocyte protoporphyrin. Finally, when there is not enough iron delivery to the bone marrow to maintain the incorporation of iron into newly synthesized globin and porphyrin protein, erythrocyte protoporphyrin concentrations increase. Yet erythrocyte protoporphyrin is not useful to distinguish iron deficiency from infection and is also elevated in response to lead poisoning (Roels 1975). As a result, erythrocyte protoporphyrin measurement is most useful in settings where iron deficiency levels are common and where infections, lead poisoning, and other causes of anemia are rare. Erythrocyte protoporphyrin is a generic term for the directly measured concentration of zinc protoporphyrin (the form present in erythrocytes) or the free erythrocyte protoporphyrin concentration measured after extraction.

Cutoff values. The CDC recommended cutoff value for serum ferritin below which iron stores are considered to be depleted is ≤15 nanogram per milliliter (ng/mL) for persons ages >6 months (U.S. Centers for Disease Control and Prevention 1998; Hallberg 1993). Cutoff values recommended by the WHO are similar: <15 ng/mL for persons ages 5 years and older and <12 ng/mL for persons younger than 5 years (WHO 2011; WHO 2020). In apparently healthy individuals ages 5 years and older, serum ferritin concentrations >200 ng/mL for males and >150 ng/mL for females represent a risk of iron overload (WHO 2020). Literature reviews reevaluated ferritin cutoff values in preparation for the 2020 WHO ferritin guideline (Garcia-Casal 2018a; Garcia-Casal 2019).

No generally accepted cutoff value is available for sTfR because there are large differences among assays, so researchers are using assay-specific cutoff values. For example, the Ramco ELISA assay uses a sTfR concentration of 8.3 mg/L as the upper end of the normal range, while the Roche Tina-quant assay uses 4.4 mg/L in women of childbearing age. Using NHANES 2003–2010 data generated with the Roche Tina-quant sTfR assay, Mei et al. defined a cutoff of 6.0 mg/L for U.S. children ages 1–5 years and 5.33 mg/L for non-pregnant women ages 15–49 years (97.5th percentile in a defined healthy reference population) (Mei 2012).

Low serum iron concentrations in conjunction with elevated TIBC or transferrin concentrations, yielding less than 16% transferrin saturation, generally indicate iron deficiency anemia (U.S. Centers for Disease Control and Prevention 1998). Transferrin saturation values of more than 60%

may be indicative of hemochromatosis or iron overload (WHO 2001). The generally accepted cutoff level for erythrocyte protoporphyrin is 80 µg/dL red blood cells for people ages 5 years and older and 70 µg/dL red blood cells for children younger than age 5 years (U.S. Centers for Disease Control and Prevention 1998).

Analytical Methods

A supplement publication from the 2016 NIH "Workshop on Iron Screening and Supplementation in Iron-Replete Pregnant Women and Young Children" (Taylor 2017) summarizes the strengths, limitations, and analytical challenges of laboratory methodologies for indicators of iron status (Pfeiffer 2017). Clinical laboratories are mostly using fully automated clinical analyzers to measure the serum-based biochemical indicators. Serum ferritin, transferrin, and sTfR are measured by immunoassays (by turbidimetry or nephelometry) (Worwood 2002a; Worwood 2002b). Serum iron, TIBC, and UIBC are measured on chemistry analyzers using a colorimetric reaction with ferrine or ferrozine as a chromogen to form a color complex with iron (Beard 2007). A systematic review and meta-analysis assessing the performance and comparability of laboratory methods for ferritin concluded that most methods have comparable accuracy and performance (Garcia-Casal 2018b). International reference materials are available for most iron status indicators (Thorpe 2010). The National Institute of Standards and Technology (NIST) offers a Standard Reference Material (SRM) for iron in the form of an iron wire (SRM 937) or an iron standard solution (SRM 3126A). The WHO, through the United Kingdom National Institute of Biological Standards and Control (NIBSC), offers an international standard for ferritin (NIBSC 94/572; NIBSC 10/118) and a reference reagent for sTfR (NIBSC 07/202). The European Institute for Reference Materials and Measurements offers a reference material for transferrin (ERM-DA470). The fourth international standard for ferritin (NIBSC 10/118) has been shown to perform comparably to the third international standard (NIBSC 94/572) (Fox 2022). The sTfR reference reagent (NIBSC 07/202) has been shown to be commutable across multiple assay platforms (Lyle 2023).

Clinical laboratories typically use conventional units for iron-status indicators. Ferritin is calculated in nanograms per milliliter (ng/mL) and sTfR in milligrams per liter (mg/L). Iron, total iron-binding capacity (TIBC), and erythrocyte protoporphyrin are calculated in micrograms per deciliter (μg/dL). Conversion factors from conventional to International System of Units (SI) are as follows:

- 1 ng/mL = 2.247 picomole (pmol)/L for ferritin
- 1 mg/L = 0.085 nanomole (nmol)/L for sTfR
- 1 μg/dL = 0.179 micromole per liter (μmol/L) for iron and TIBC
- 1 μg/dL = 0.01777 μmol/L for erythrocyte protoporphyrin

Findings from NHANES

The National Health and Nutrition Examination Survey (NHANES) is the only source for nationally representative data on iron status indicators for the U.S. population (Pfeiffer 2026a). Monitoring the iron status of the U.S. population has been an important goal since the inception of NHANES in 1971. Each NHANES survey cycle has included a battery of hematologic and biochemical indicators of iron status (Looker 1995; Pfeiffer 2017). Since NHANES II (1976–1980), models that employ multiple biochemical iron status indicators have been used to define iron deficiency in the population (Pilch 1984). The ferritin model (also known as the three-indicator model), using serum ferritin, transferrin saturation, and erythrocyte protoporphyrin, was developed in 1980. It was applied to NHANES III (1988–1994) and to the first few years of the continuous NHANES survey beginning in 1999. Prevalence estimates of iron deficiency using the three-indicator model were similar in NHANES III (Looker 1997) and in NHANES 1999–2000 (Looker 2002).

Starting in 2003, NHANES limited the population of interest to children (ages 1–5 years) and women of childbearing age (ages 12–49 years). Furthermore, the measurement of serum sTfR was introduced, which allows the evaluation of iron status by the body iron index model developed by Cook *et al.* (2003). Using data for children and non-pregnant women from NHANES 2003–2006, the body iron index model showed fair to good agreement to the previously used ferritin model (Cogswell 2009). Among non-pregnant women (ages 20–49 years), the body iron index model produced lower estimates of iron deficiency prevalence (9.2% compared with 15.7%) and better predicted anemia. The body iron index model appeared to be less affected by inflammation than the ferritin model. The iron deficiency prevalence in pregnant women was 18% (body iron index model) in NHANES 1999–2006 (Mei 2011). Other researchers reported similar iron deficiency

estimates: 15.1% in toddlers ages 12–23 months (NHANES 2003–2010); 10.4% in nonpregnant females ages 15–49 years (NHANES 2007–2010); and 6.3% in pregnant females ages 12–49 years (NHANES 1999–2010) (Gupta 2017).

NHANES data have also been used to derive physiologically based cutoff values for serum ferritin for iron deficiency; these cutoff values are determined by assessing inflection points where the relationship between different iron indicators changes (e.g., association between ferritin and hemoglobin, ferritin and sTfR, or ferritin and erythrocyte protoporphyrin). Researchers derived serum ferritin cutoff values (ng/mL) of about 20 for children and 25 for nonpregnant women from NHANES 2003–2018 data (based on hemoglobin and sTfR) (Mei 2021). The trimester-specific serum ferritin cutoff values (ng/mL) for U.S. pregnant women in NHANES 2003–2018 were: 25.8 (first); 18.3 (second); and 19.0 (third) (Mei 2024). The earlier NHANES III (1988–1994) used the radioimmunoassay for serum ferritin measurements. These data also resulted in physiologically based serum ferritin cutoff values (ng/mL) that were higher than those based on expert opinion. For children, the serum ferritin cutoff values were 21.2 (based on hemoglobin) and 18.7 (based on erythrocyte protoporphyrin). For nonpregnant women, the serum ferritin cutoff values were 24.8 (based on hemoglobin) and 22.5 (based on erythrocyte protoporphyrin) (Mei 2023).

After adjusting for demographic changes over time, mean concentrations of serum ferritin did not change in children but decreased ~15% in women of reproductive age from NHANES 2003–2004 to August 2021–August 2023 (Pfeiffer 2026b). The prevalence of iron deficiency (ferritin <15 ng/mL) increased in WRA from ~12% to 17% over the same time period (Pfeiffer 2026c).

A multiple regression analysis of NHANES 2003–2006 examined the effects of sociodemographic (age, education, income, and race-ethnicity) and lifestyle (alcohol consumption, body mass index, dietary supplement use, physical activity, and smoking) variables on the variability of iron-status indicators in women of reproductive age. Together, these variables explained 4% (ferritin), 5% (body iron index), and 13% (sTfR) of the biomarker variability (Pfeiffer 2013).

After adjusting for sociodemographic and lifestyle variables, race-ethnicity retained a strong association with sTfR and body iron index. Smoking and alcohol consumption were strongly associated with all three iron-status indicators (Pfeiffer 2013). Another multiple regression analysis of NHANES 2003–2006 showed that, after controlling for demographic variables, smoking, supplement use, fasting, inflammation, and renal function, inflammation was associated with significantly higher ferritin concentrations (24.6%) and higher body iron index (0.7%), while fasting

and renal function were not associated with ferritin, sTfR, or body iron index (Haynes 2013). Pregnancy (in women ages 20–49 years) was associated with significantly lower ferritin concentrations (-33.1%) and lower body iron index (-1.4%) (Haynes 2013).

For more information about iron, see the Institute of Medicine's Dietary Reference Intake reports (Institute of Medicine 2001) and fact sheets from the National Institutes of Health, Office of Dietary Supplements (https://ods.od.nih.gov/factsheets/list-VitaminsMinerals/).

Data in the 2026 tables

Data presented are from univariate analysis that was not adjusted for demographic variables (e.g., age, sex, race and Hispanic origin) or other blood concentration determinants (e.g., dietary intake, supplement use, smoking, BMI). Data for the iron-status indicators were available from different NHANES cycles and have been generated by different methods. To allow for comparisons over time, we present method-adjusted data in tables or figures that cover a time period in which multiple methods were used. During time periods where only one method was used, we present the original method data. Table footnotes indicate whether original or adjusted method data are presented. Data from the 2019–March 2020 cycle are not included because field operations were suspended in March 2020 due to the COVID-19 pandemic and the resulting data were not considered nationally representative. NHANES resumed operations in August 2021 and the most recent cycle with publicly available data concluded in August 2023.

Iron-status indicator	NHANES cycle	Method
Serum ferritin	1999–2002	BioRad QuantImune immunoradiometric assay
	2003–2008	Roche Tina-quant immunoturbidimetric assay on Hitachi 912 analyzer
	2009–2010	Roche Tina-quant immunoturbidimetric assay on Roche E-170 analyzer
	2015–2018; Aug 2021–Aug 2023	Roche Tina-quant immunoturbidimetric assay on Roche cobas e601 analyzer
Serum sTfR	2003–2008	Roche Tina-quant immunoturbidimetric assay on Hitachi 912 analyzer
	2009–2010	Roche Tina-quant immunoturbidimetric assay on Roche Mod P analyzer
	2015–2018; Aug 2021–Aug 2023	Roche Tina-quant immunoturbidimetric assay on Roche cobas c501 analyzer
Body iron index	2003–2010; 2015–2018; Aug 2021–Aug 2023	Calculated from serum sTfR and ferritin[1]
Serum transferrin saturation	1999–2000	Calculated from serum iron and TIBC[2]
Erythrocyte protoporphyrin	1999–2000	Fluorometric method[3]

[1] Body iron index is calculated by using the following formula: body iron index (mg/kg) = -[log10 (sTfR * 1000 / ferritin) – 2.8229] / 0.1207 (Cook 2003). The sTfR concentration in this formula represents an adjusted concentration to make the Roche Tina-quant sTfR concentrations (either from the Hitachi 912 or from the Roche Mod P) equivalent to the Flowers assay (1989) used in the development of the body iron index model: Flowers sTfR = 1.5 * Roche sTfR + 0.35 mg/L (Pfeiffer 2007).

[2] Iron and TIBC data were generated by a manual colorimetric method based on the procedures of Giovaniello *et al.* (1968) during 1999–2000.

[3] Free erythrocyte protoporphyrin was measured by a modification of the method of Sassa *et al.* (1973) after acid extraction during 1999–2000.

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