



SERUM FERRITIN CONCENTRATIONS FOR THE ASSESSMENT OF IRON STATUS IN INDIVIDUALS AND POPULATIONS: TECHNICAL BRIEF



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BACKGROUND

Ferritin is the primary iron-storage protein and is critical to iron homeostasis (1). The ferritin molecule is an intracellular hollow protein shell, composed of 24 subunits surrounding an iron core that may contain as many as 4000–4500 iron atoms. In the body, small amounts of ferritin are secreted into the blood circulation. In the absence of inflammation, the concentration of serum (or plasma) ferritin is positively correlated with the size of the total body iron stores (1, 2).

To determine its usefulness to detect low iron reserves or iron deficiency, the concentration of ferritin can be compared to iron contained in the bone marrow (3). The absence of stainable iron on a good quality bone marrow aspirate is diagnostic of iron deficiency. Although bone marrow is the appropriate tissue to assess iron deposits, aspirations or biopsies are invasive and costly procedures that are not free of methodological difficulties (4). For these reasons, they have been largely replaced by other determinations such as ferritin, serum iron and total iron-binding capacity to diagnose iron deficiency (5).

On the other side of the spectrum, liver biopsies have commonly been used to detect iron overload, because the liver is the dominant iron-storage organ; liver iron concentration correlates closely with the total iron balance; and the liver is the only organ in which the iron concentration is elevated in all forms of systemic iron overload (6). Non-invasive methods such as magnetic resonance imaging (MRI) are useful in the diagnosis and quantitation of iron overload. An advantage of MRI over other methods is that it includes a low variability between measures and can detect the iron load in the liver, heart and endocrine tissues (7, 8). Ferritin concentrations may also be used to indicate risk of iron overload.

Normal ferritin concentrations vary by age and sex and, in the absence of inflammation or liver disease, a low ferritin concentration indicates iron deficiency and a high ferritin concentration suggests risk of iron overload.

Ferritin concentrations are raised in inflammation (with or without infection), liver disease, obesity and some rare haematological conditions. Inflammation can distort the interpretation of ferritin concentrations and obscure the diagnosis of iron deficiency and be misleading in the diagnosis of iron overload (9). Clinical or biochemical assessment for concomitant inflammation is therefore essential to apply optimal adjustments of ferritin measures to account for inflammation (10).

SCOPE AND PURPOSE

This technical brief aims to provide summarized information about the use of serum ferritin for assessing iron status in individuals and populations. It is a compilation of the current World Health Organization (WHO) recommendations on the topic, and summarizes the cut-off values for describing iron stores and the chronology of their establishment. It also includes considerations for assessment of risk of iron overload. This technical brief is an update of a previous version (11), and supersedes previous recommendations of the WHO/Centers for Disease Control and Prevention (CDC) publication, *Assessing the iron status of populations*, first published in 2004) (12), and recommendations related to ferritin in *Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers* (2001) (13).

This document aims to guide WHO Member States and their partners on the appropriate use of indicators for assessing iron status in individuals and populations. Such assessments allow evaluation of progress towards international goals to reduce iron deficiency and provide data on which to base programmes for the prevention and control of iron deficiency and anaemia in all populations.

DESCRIPTION OF TECHNICAL CONSULTATIONS AND GUIDELINE DEVELOPMENT MEETINGS

The WHO guidelines and technical meetings related to the development of ferritin cut-off values to assess iron deficiency and risk of iron overload include those listed next.

Preventing and controlling anaemia through primary health care: a guide for health administrators and programme managers (14), a consultation held in Quito, Ecuador in May 1987 by the International Nutritional Anemia Consultative Group concluded that at all ages a serum ferritin value of less than 10–12 µg/L was indicative of a depletion of iron stores.

Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers (13), published in 2001, is based on a consultation organized by WHO, the United Nations Children's Fund and the United Nations University, held in Geneva, Switzerland, from 6 to 10 December 1993.

During this meeting, the cut-off values developed in 1987 were revised. Separate cut-off values were provided for individuals under 5 years of age and 5 years of age or older, for males and females, and for individuals under 5 years of age with concurrent infection. The thresholds for adults were derived largely from the clinical literature, specifically from studies examining the highest ferritin concentration among patients with microcytic iron deficiency anaemia who

also either showed a therapeutic response to iron or had no stainable iron in their bone marrow (15).

Assessing the iron status of populations (12) is the report of a joint WHO and CDC technical consultation held in Geneva, Switzerland, from 6 to 8 April 2004. The objectives of the consultation were to review currently available indicators for assessing the iron status, and to select the best indicators to assess the iron status of populations and to evaluate the impact of interventions to control iron deficiency in populations. This consultation was preceded by a short WHO/CDC working group meeting held in January 2004 to review the literature on indicators of iron status and to select indicators for discussion by the consultation.

The *WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations* (16), published in 2020, provides global, evidence-informed recommendations on the use of ferritin concentrations for assessing a population's iron status and its application for monitoring and evaluating iron interventions. The initial scoping of the guideline and the prioritization of the outcomes was done during a meeting on *Priorities in the assessment of vitamin A and iron status in populations*, held in Panama City, Panama, from 15 to 17 September 2010 (17) and finalized by the guideline development group during a technical meeting held in Atlanta, United States of America, from 3 to 5 March 2014. Various technical consultations took place from 2010 to 2015, as described in the final document (16). Recommendations were finalized by the guideline development group in a meeting held in Geneva, Switzerland, from 15 to 17 June 2016.

RECOMMENDATIONS

Ferritin as an adequate marker of iron stores (risk of deficiency and risk of iron overload)

Ferritin concentration was confirmed to be a good marker of iron stores and should be used to diagnose iron deficiency in otherwise apparently healthy individuals. However, because ferritin concentrations are raised in those with inflammation or infection, alternative cut-off values are needed to indicate iron deficiency in these individuals (see **Table 1**) (16); or ferritin values should be adjusted by applying correction factors for inflammation/infection in population studies (see *Measuring ferritin in combination with indicator(s) of infection or inflammation*). Measures of inflammation may include C-reactive protein (CRP) and/or α-1 acid glycoprotein (AGP).

Ferritin may be elevated due to iron overload or other causes, including liver disease, obesity, inflammation and malignancy. In cases of risk of iron overload, ferritin concentration only indicates the possibility of iron overload and the need for further clinical or laboratory evaluation to establish the underlying cause and the severity of the problem. Therefore,

Table 1. Recommended cut-off values to define iron deficiency and risk of iron overload in apparently healthy and non-healthy individuals by age group

	Serum ferritin (µg/L) ^{a,b}			
	Iron deficiency		Risk of iron overload	
	Apparently healthy individuals ^c	Individuals with infection or inflammation	Apparently healthy individuals	Non-healthy individuals
Infants and young children (0–23 months)	<12	<30	—	—
Children under 5 years (24–59 months)	<12	<30	—	—
Children (5 to less than 10 years)	<15	<70	>150 females >200 males	>500 ^d
Adolescents (10 to less than 20 years)	<15	<70	>150 females >200 males	>500
Adults (20–59 years)	<15	<70	>150 females >200 males	>500
Older persons (60+ years)	<15	<70	>150 females >200 males	>500
Pregnant women	<15 (first trimester) ^e	—	—	—

Source: WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/331505>) (16).

^a From previous WHO recommendations and new evidence.

^b Markers of inflammation should be assessed along with the ferritin concentration, and ferritin adjusted as necessary.

^c For the purposes of this guideline, an apparently healthy individual is defined as an individual with physical well-being for their age and physiological status, without detectable diseases or infirmities.

^d In adult, non-healthy populations, a ferritin concentration exceeding 500 µg/L may indicate risk of iron overload or other disease. This cut-off value indicates the need for further clinical and laboratory evaluation to establish the diagnosis and underlying cause of the ferritin levels.

^e There are several physiological changes occurring in pregnancy that may contribute to the variation in thresholds of iron deficiency in pregnancy as defined by serum ferritin, including a physiological rise in acute phase proteins secondary to pregnancy; second trimester plasma volume expansion; and changes in inflammatory measures in the final trimester of pregnancy.

ferritin concentration should not be used alone to identify risk of iron overload. A ferritin concentration exceeding 150 µg/L in menstruating women and 200 µg/L in men and non-menstruating women who are otherwise healthy may indicate a risk of iron overload. In adult, non-healthy individuals, a ferritin concentration exceeding 500 µg/L may indicate risk of iron overload. Iron deficiency, iron overload and other associated conditions are included in the *International Classification of Diseases (ICD-11)* (18).

Ferritin as an adequate marker for assessing the impact of iron interventions

Iron interventions and programmes should be implemented in such a manner as to enable their monitoring. Ferritin concentration increases in response to iron-related interventions and may be used to monitor and assess the impact of interventions on iron status. As noted, knowledge of the presence of infection/inflammation is critical for interpretation of ferritin concentrations and for interpretation of any changes after iron interventions. The inclusion of markers to diagnose iron-related genetic disorders is also valuable, especially in regions where thalassaemias and other haemoglobinopathies are common.

Comprehensive planning, monitoring and evaluation of all simultaneous interventions that increase iron intake and/or utilization and/or reduce iron losses are required to account for the total amount of iron being received by populations that would result in ferritin changes in cases of iron deficiency, and to avoid risk of iron overload.

Methods for assessing ferritin concentrations in blood

Ferritin may be measured in either serum, plasma or other biological fluids, using radiometric, nonradiometric and agglutination assays. One method does not appear to be superior to another and all methods are acceptable if a commutable material traceable to the WHO international reference standard is used to calibrate the assay. A WHO international standard of ferritin from the National Institute for Biological Standards and Control, WHO International Laboratory for Biological Standards, United Kingdom of Great Britain and Northern Ireland ([NIBSC code 94/572](https://www.nibsc.org/Products/Reference-standards/WHO-international-standard-for-ferritin)) (19), is commercially available and recommended for calibration of all commercial kits and in regular laboratory practice, especially when following up individual cases, for population surveys or to measure the impact of public health interventions. The international standard is used to ensure the comparability of

human serum ferritin immunoassay test results across laboratories. The WHO Expert Committee on Biological Standardization has endorsed a proposal (WHO/BS/2018.2342) (20) to develop a Fourth WHO International Standard for ferritin (21). It is important that reference materials are commutable and traceable to the WHO reference standard, so the results are equivalent among procedures and to avoid calibration bias.

Once a method has been selected, the same sample matrix and method should be used for the follow-up of individuals and populations, to minimize variability. It is also important to control other sources of error in laboratory testing related to handling of samples; transport and storage conditions; the use of manual versus automated procedures; and differences in equipment performance and those inherent to the operator.

Quality controls should be included with every run, or at least daily, on instruments measuring ferritin. The inclusion of quality controls of low, medium and high ferritin concentrations is desirable. Laboratories performing ferritin determinations for patient care or for public health assessments should participate in external quality assurance programmes. Ferritin in serum or plasma is also included in the general in vitro diagnostic test category for use in clinical laboratories to diagnose iron deficiency and overload. Health-care facilities assessing ferritin are expected to have trained laboratory technologists, specialists with expertise and the appropriate laboratory infrastructure and equipment (22).

Measuring ferritin in combination with indicator(s) of infection or inflammation

In areas of widespread infection or inflammation, serum ferritin should be assessed with the concurrent measurement of two acute phase response proteins, CRP and AGP. The increase in ferritin values caused by inflammation should be accounted for in individuals and populations. Possible adjustments include the following:

- using a linear regression correction approach to adjust ferritin concentrations by the CRP and AGP concentrations on a continuous scale, and malaria infection as a dichotomous variable. The adjusted ferritin equation is calculated by subtracting the influence of CRP, AGP and malaria as follows:

$$\text{Ferritin}_{\text{adjusted}} = \text{ferritin}_{\text{unadjusted}} - \beta_1(\text{CRP}_{\text{obs}} - \text{CRP}_{\text{ref}}) - \beta_2(\text{AGP}_{\text{obs}} - \text{AGP}_{\text{ref}}) - \beta_3 \text{ malaria}$$

where β_1 is the CRP regression coefficient, β_2 is the AGP regression coefficient, β_3 malaria is the malaria regression coefficient, obs is the observed value, and ref is the external reference value generated to define low inflammation.

The application of different adjustment approaches will result in a high degree of variability in the estimated prevalence of depleted iron stores. The adjustment that best suits the country reality should be selected and used as long as those conditions prevail.

Population prevalence ranges for determining iron deficiency as a public health problem

Owing to the scarcity and dispersion of data, it has not been possible to make an evidence-based recommendation for population prevalence ranges to define the magnitude of iron deficiency as a public health problem using ferritin concentrations. The population prevalence ranges established for determining the magnitude of anaemia as a public health problem could be suitable as a guide to determine the prevalence ranges for defining the severity of iron deficiency as a public health problem based on adjusted ferritin concentrations (see **Table 2**) (16).

Initiating iron interventions in populations with a mild, moderate and/or severe prevalence of iron deficiency could help prevent anaemia, as well as adverse consequences of iron deficiency without anaemia.

Table 2. Population prevalence ranges to define the magnitude of iron deficiency as a public health problem using ferritin concentrations

Magnitude of the public health problem	Prevalence range (%)
High	≥40.0
Moderate	20.0–39.9
Mild	5.0–19.9
No public health problem	≤4.9

Source: WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/331505>) (16).

PLANS FOR UPDATE

The WHO Department of Nutrition and Food Safety is responsible for reviewing this document and will update it as needed, following the high-quality and rigour of WHO norms and standards. This summary aims to simplify the information for the end-user.

WHO REPOSITORY FOR FERRITIN DATA

WHO manages a micronutrient database as part of the Vitamin and Mineral Nutrition Information System (VMNIS), containing over 40 micronutrient indicators assessing nutrition status, including serum and plasma ferritin in population-based surveys at the national, regional (within country) or first administrative level. These data serve to produce global and regional estimates to better understand the magnitude and distribution of iron-related risks and to evaluate public health programmes addressing iron deficiency or risk of iron overload. For more information, see <https://www.who.int/vmnis/database/en/> (23).

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SUGGESTED CITATION

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