

WHO GUIDELINE¹: USE OF FERRITIN CONCENTRATIONS TO ASSESS IRON STATUS IN INDIVIDUALS AND POPULATIONS

EXECUTIVE SUMMARY

Accurate determination of iron status is crucial for diagnostic and screening purposes in the clinical setting and to guide public health interventions at the population level. In an individual patient, diagnosis of iron deficiency or overload will help guide management, including further investigations and appropriate therapy. At the population level, determination of the magnitude and distribution of iron deficiency can help to prioritize appropriate interventions in settings in which the prevalence is regarded as a severe public health problem, or help to identify populations with hereditary conditions that predispose them to iron overload.

Ferritin is an iron-storage protein present in all cells and can be measured in serum, plasma, liver, red blood cells, and other specimens. Low ferritin concentrations suggest deficient iron stores, whereas elevated ferritin concentrations could suggest iron overload.

Purpose of the guideline

This guideline provides global, evidence-informed recommendations on the use of indicators for assessing a population's iron status and application of the use of ferritin concentrations for monitoring and evaluating iron interventions.

The recommendations in this guideline are intended for a wide audience, including health professionals, clinicians, researchers, managers of nutrition and health programmes, and public health policy-makers, their expert advisers, and technical and programme staff at government institutions and organizations involved in the design and conduct of surveys to assess micronutrient status in all settings.

This guideline aims to help WHO Member States and their partners to make evidence-informed decisions on the appropriate actions in their efforts to achieve the [Sustainable Development Goals](#),² and the global targets as put forward in the [Comprehensive implementation plan on maternal, infant and young child nutrition](#)³ and the [Global strategy for women's, children's and adolescents' health \(2016–2030\)](#).⁴

Guideline development methodology

WHO developed the present evidence-informed recommendations using the procedures outlined in the [WHO handbook for guideline development](#).⁵ The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and planning for (v) dissemination; (vi) implementation, equity and ethical considerations; and (vii) impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE)⁶ methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

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](#),⁷ from 15 to 17 September 2010, in Panama City, Panama and finalized by the guideline development group during a technical meeting held in Atlanta, United States of America from 3 to 5 March 2014. The development and finalization of the evidence-informed recommendations were done by the guideline development group in a meeting held in Geneva, Switzerland, from 15 to 17 June 2016.

¹ This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A standard guideline is produced in response to a request for guidance in relation to a change in practice, or controversy in a single clinical or policy area, and is not expected to cover the full scope of the condition or public health problem. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

² United Nations Sustainable Development Knowledge Platform. Sustainable Development Goals (<https://sustainabledevelopment.un.org/sdgs>).

³ Resolution WHA65.6. Comprehensive implementation plan on maternal, infant and young child nutrition. In: Sixty-fifth World Health Assembly, Geneva, 21–26 May 2012. Resolutions and decisions, annexes. Geneva: World Health Organization; 2012:12–13 (WHA65/2012/REC/1; http://www.who.int/nutrition/topics/WHA65.6_resolution_en.pdf).

⁴ The global strategy for women's, children's and adolescents' health (2016–2030). Survive, thrive transform. Geneva: World Health Organization; 2015 (<http://www.who.int/life-course/partners/global-strategy/global-strategy-2016-2030/en/>).

⁵ WHO handbook for guideline development, 2nd ed. Geneva: World Health Organization; 2014 (http://www.who.int/kms/handbook_2nd_ed.pdf?ua=1).

⁶ GRADE (<http://www.gradeworkinggroup.org/>).

⁷ Report: priorities in the assessment of vitamin A and iron status and in populations, Panama City, Panama, 15–17 September 2010. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/bitstream/handle/10665/75334/9789241504225_eng.pdf?sequence=1&isAllowed=y).

Available evidence

The following key questions were posed, based on the policy and programme guidance needs of Member States and their partners. The population, indicator, comparator, outcomes (PICO) format was used, when appropriate.

1. Is ferritin an adequate marker of iron stores (risk of deficiency and risk of iron overload)?
2. Is ferritin an adequate marker for assessing the impact of iron interventions?
3. How should ferritin be measured?
4. Should ferritin be measured in combination with indicator(s) of infection or inflammation?
5. What are the population prevalence ranges for determining a public health problem?

The available evidence for the five questions included: one systematic review that followed the procedures of the [Cochrane handbook for Diagnostic Test Accuracy review](#),¹ eight non-Cochrane systematic reviews, two data meta-analyses and two database analyses, as well as one non-Cochrane systematic review submitted for publication. The overall certainty of the available evidence was low to very low for the critical outcomes.²

Recommendations and remarks

To ensure that the recommendations are correctly understood and applied in practice, guideline users may want to also refer to the remarks, as well as to the evidence summary, including the considerations on implementation.

This *WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations* is an update of, and supersedes, previous recommendations in the WHO/Centers for Disease Control and Prevention (CDC) publication, [Assessing the iron status of populations](#), first published in 2004, and recommendations related to ferritin in [Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers](#) (2001).

An evidence to decision-making framework was used to lead discussion and decision-making. This included the following considerations: (i) the certainty of the evidence across outcomes critical to decision-making; (ii) the balance of benefits and harms; (iii) values and preferences related to the recommended intervention in different settings and for different stakeholders, including the populations at risk; (iv) the acceptability of the intervention among key stakeholders; (v) resource implications for programme managers; (vi) equity; and (vii) the feasibility of implementation of the intervention.

Question 1. Is ferritin an adequate marker of iron stores (risk of deficiency and risk of iron overload)?

Recommendations

- 1.1. Ferritin concentration is a good marker of iron stores and should be used to diagnose iron deficiency in otherwise apparently healthy **individuals**³ (*strong recommendation*,⁴ *low certainty of evidence*).
- 1.2. In **individuals** with infection or inflammation, a ferritin concentration below 30 µg/L in children and 70 µg/L in adults may be used to indicate iron deficiency (*conditional recommendation*,⁵ *low certainty of evidence*). In **populations** it is also possible to adjust ferritin values for infection/inflammation by applying correction factors as described for [Question 4: Should ferritin be measured in combination with indicator\(s\) of infection or inflammation?](#)

¹ Cochrane Methods Screening and Diagnostic Tests. Cochrane handbook for Diagnostic Test Accuracy (DTA) reviews (<https://methods.cochrane.org/sdt/handbook-dta-reviews>).

² According to GRADE, high-certainty evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect. Moderate-certainty evidence indicates that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low-certainty evidence indicates that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very-low-certainty evidence indicates that we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

³ 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.

⁴ A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. Implications of a strong recommendation are that most people in these settings would desire the recommended intervention and only a small proportion would not. For policy-makers, a strong recommendation indicates that the recommendation can be adopted as policy in most situations.

⁵ A conditional recommendation is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for populations are that while many people would desire the intervention, a considerable proportion would not. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of the intervention in each setting.

- 1.3. 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 (*conditional recommendation*, based on previous WHO recommendation). In adult, non-healthy **individuals**, a ferritin concentration exceeding 500 µg/L may indicate risk of iron overload (*conditional recommendation*, *very low certainty of evidence*).
- 1.4. Ferritin concentration should not be used alone to identify risk of iron overload. Patients with elevated ferritin levels should receive clinical and laboratory evaluation to establish the underlying cause (*strong recommendation*, *very low certainty of evidence*).

Rationale

The available studies were not sufficient to justify a change in current ferritin cut-off values to define iron deficiency and risk of iron overload by sex or age groups. The recommended cut-off values for ferritin concentrations to define iron deficiency, including previous recommendations and new evidence when available, are presented in [Table 1](#).

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	—	—	—

^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.

Remarks

- In the absence of inflammation, the concentration of plasma/serum ferritin is positively correlated with the size of the total body iron stores. Ferritin levels are low in iron-deficient individuals and high in iron-loaded individuals.
- In populations, ferritin testing to ascertain the prevalence of iron deficiency or to determine the risk of iron overload is usually performed along with haemoglobin testing to assess the prevalence of anaemia. Measures of inflammation (e.g. C-reactive protein [CRP] and/or α-1 acid glycoprotein [AGP]) and additional iron indices, such as soluble transferrin receptor, are commonly used.

- The physiological changes occurring in hormones, blood composition and haemodynamics, as well as in inflammatory status during pregnancy, render it difficult to establish a fixed, unique ferritin concentration to define iron deficiency, especially when comparing to an invasive gold standard test such as bone marrow biopsy.
- 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 assessment of the specific diagnosis, and the severity of the problem.
- Liver biopsies have commonly been used to report 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. Non-invasive methods such as magnetic resonance imaging and computerized tomography are widely used to assess iron content in the liver.

Question 2. Is ferritin an adequate marker for assessing the impact of iron interventions?

Recommendation

- 2.1. Ferritin concentration increases in response to iron-related interventions and may be used to monitor and assess the impact of interventions on iron status (*strong recommendation, moderate certainty of evidence*).

Remarks

- Iron interventions should be implemented in such a manner as to enable monitoring to be undertaken with the lowest number of blood draws.
- The interval following initiation of an iron intervention at which ferritin should be measured depends on the type of intervention and the amount of iron provided.
- 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.
- Knowledge of the prevalence of infection/inflammation is critical for interpretation of ferritin concentrations in population surveys and to interpret changes after iron interventions.
- The inclusion of markers to diagnose iron-related genetic disorders is valuable, especially in regions where thalassaemias and other haemoglobinopathies are common.
- Cases of iron overload should be treated at individual level, since high ferritin concentrations are not sensitive to the effects of nutrition interventions.
- More research is needed to evaluate the effect of nutrition interventions on ferritin concentration through the life-cycle, especially during pregnancy, owing to changes in concentration, especially the typical decrease in concentration in late pregnancy.

Question 3. How should ferritin be measured?

Recommendations

- 3.1. Ferritin may be measured 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. Once a method has been selected, that same method should be used for the follow-up of individuals and populations (*strong recommendation, moderate/low certainty of evidence*).
- 3.2. Use of the WHO international reference standard of ferritin is 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 (*strong recommendation, moderate certainty of evidence*).

Remarks

- The risks of radioactive contamination and the high cost of equipment are important drawbacks of radiometric assays.
- For follow-up of individuals and populations, the same method for ferritin determination should be used, 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.
- Ferritin may be measured in either serum, plasma or other biological fluids, but the same sample matrix should be used when measuring the impact of interventions in individuals and at the population level.
- International reference materials for ferritin have been developed for calibrating working standards in the routine ongoing assays performed in laboratories and also for evaluating and standardizing new tests for quantification of ferritin. 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](#)), is commercially available and recommended for use with all assays.
- 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.
- 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.

Question 4. Should ferritin be measured in combination with indicator(s) of infection or inflammation?

Recommendations

- 4.1. 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 (*strong recommendation, moderate certainty of evidence*).
- 4.2. The increase in ferritin values caused by inflammation should be accounted for in **individuals** and **populations**. One method is to raise the cut-off value that defines deficiency, to 30 µg/L or 70 µg/L, depending on the age group (see [Table 1](#)). Another method is to exclude individuals with elevated concentrations of CRP or AGP from prevalence calculations based on ferritin. Alternatively, arithmetic or regression correction approaches may be used to adjust ferritin concentrations for inflammation and apply the cut-off points recommended for healthy populations. The adjustment that best suits the country reality should be selected and used as long as those conditions prevail (*strong recommendation, moderate certainty of evidence*).

Remarks

- The need for and magnitude of infection/inflammation correction depends on the population group, geographic region and other factors.
- The application of different adjustment approaches will result in a high degree of variability in the estimated prevalence of depleted iron stores. The selected adjustment based on country conditions should be used as long as those conditions prevail.
- Determination of both CRP and AGP concentrations may be important because they reflect different phases of the acute phase response that range from acute infection to chronic inflammation.

- Possible adjustments include the following:
 - the higher ferritin cut-off adjustment approach uses a higher ferritin-concentration cut-off value for individuals with infection/inflammation, e.g. <30 µg/L;
 - the exclusion approach uses the inflammation, malaria-biomarker information, or both, to exclude individuals with elevated inflammation (as defined by a CRP concentration >5 mg/L, AGP concentration >1 g/L, or both) or individuals with malaria infection;
 - the arithmetic correction factor approach applies an arithmetic correction factor by grouping inflammation into groups, e.g. (i) reference (both CRP concentration <5 mg/L and AGP concentration <1 g/L); (ii) incubation (CRP concentration >5 mg/L and AGP concentration <1 g/L); (iii) early convalescence (both CRP concentration >5 mg/L and AGP concentration >1 g/L); and (iv) late convalescence (CRP concentration <5 mg/L and AGP concentration >1 g/L);
 - the regression correction approach uses linear regression 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.

Question 5. What are the population prevalence ranges for determining a public health problem?

Remarks

- Owing to the scarcity and dispersion of data, it was not possible to make a 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. To classify iron deficiency as severe, moderate, mild or no public health problem (measured by ferritin concentration below the recommended cut-off values), the prevalence of iron deficiency could be $\geq 40.0\%$, 20.0–39.9%, 5.0–19.9% or $\leq 4.9\%$, respectively (see [Table 2](#)).
- 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

Research gaps

Discussions between the members of the WHO guideline development group and the external resource group highlighted the limited evidence available in some knowledge areas, meriting further research, particularly in the following areas:

- studies comparing ferritin concentrations and bone marrow iron content in healthy, non-infected/non-inflamed populations of all ages;
- studies comparing ferritin and other iron status indicator concentrations and bone marrow iron content in the presence of biomarkers of inflammation, to validate the different approaches to adjusting iron status for inflammation;
- well-designed, population-based longitudinal studies to define the role of other iron indicators and their response to iron interventions, which can be used to monitor the impact of public health programmes;
- studies that clarify cut-off points for iron deficiency and the differential diagnoses when chronic or low-degree inflammation is present in older persons and conditions such as obesity or controlled diabetes;
- changes affecting ferritin concentrations during pregnancy and establishment of cut-off points by trimester;
- factors affecting ferritin levels (fasting, inflammation, infection, liver disease, comorbidities) in the general population, stratified by age, sex and physiological status, living in different settings (malaria, tuberculosis and HIV);
- studies on the utility of ferritin concentrations to diagnose the risk of iron overload and to establish cut-off values for all age groups and settings; and
- the comparability of ferritin concentrations among sample matrices: venous blood collection versus pooled capillary samples or dried serum spot samples.

Plans for updating the guideline

The WHO Secretariat will continue to follow research developments on iron deficiency, particularly on biomarkers to detect it, with emphasis on ferritin determination and cut-off values to define iron deficiency and iron overload in different settings and age groups, and on the influence of infection/inflammation on diagnosis of iron status, particularly for questions in which the certainty of evidence was found to be low or very low. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition and Food Safety will coordinate the guideline update, following the formal procedures of the [*WHO handbook for guideline development*](#).

As the guideline nears the 10-year review period, the Department of Nutrition and Food Safety at the WHO headquarters in Geneva, Switzerland, along with its internal partners, will be responsible for conducting a search for new evidence.