Estimates of Iron Sufficiency in the US Population

By James D. Cook, Barry S. Skikne, Sean R. Lynch, and Molly E. Reusser

Traditionally the iron status of a population is assessed by estimating the prevalence of iron deficiency anemia. This approach is inadequate in countries where the diet is heavily fortified with iron because it conveys no information about the iron-replete segment of the population. In the present study iron status of a US adult population was evaluated using data collected in the second National Health and Nutrition Examination Survey (NHANES II). Body iron was estimated in each of 2,829 individuals from measurements of hemoglobin concentration, serum ferritin, transferrin saturation, and erythrocyte protoporphyrin. When individuals between 18 and 64 years of age were divided on the basis of sex and menstrual status, body iron reserves were normally distributed and averaged 309 mg in women 18 to 44 years, 608 mg in women 45 to 64 years, and 776 mg in men 18 to 64 years. The dispersion of storage iron in these groups was similar, with standard deviations of 346, 372, and 313 mg, respectively. The prevalence of iron deficiency anemia was surprisingly low, ranging from only 0.2% in adult men to 2.6% and 1.9% in pre- and postmenopausal women, respectively. Epidemiologic methods that examine iron status in the entire population assume importance in light of evidence that in certain segments of the US population, iron deficiency anemia is now less common than the homozygous state for hereditary hemochromatosis.

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THE IRON STATUS of a population is presently assessed by determining the proportion of individuals with laboratory values outside a predefined cutoff level. This approach is flawed by the extensive overlap in laboratory values between normal and iron-deficient individuals. With hemoglobin measurements, for example, the number of normal individuals with values below the accepted cutoff level commonly exceeds the number with true iron deficiency anemia even when the prevalence of iron deficiency is high.[1,2] A more important limitation with current epidemiologic methods is that they reflect only the prevalence of iron deficiency and ignore the iron-replete segment of the population. This is a concern in the United States, where iron is liberally consumed in supplements and fortified foods and where the heterozygote frequency for hemochromatosis is now estimated to exceed 10%.[3]

Several iron measurements are available for detecting varying degrees of iron lack.[4] In clinical practice these laboratory indices are commonly integrated to estimate body iron stores in an individual patient. In the present study this principle was used to estimate body iron in a random sample of the US population. The data base consisted of 2,829 adult subjects examined as part of the second National Health and Nutrition Examination Survey (NHANES II). The results indicate a low prevalence of iron deficiency and a broad distribution of body iron reserves.

MATERIALS AND METHODS

NHANES II. This survey was based on a stratified probability cluster sample of households from 64 separate geographic locations throughout the United States.[5,6] A total of 27,803 subjects aged 6

months to 72 years were identified of whom 20,322 were examined over a four-year period beginning in early 1976. A weighting procedure based on selection probabilities, adjustments for nonresponse, and poststratification adjustments was applied to each observation.[7] Each person was then considered to represent a certain number of individuals in the total US population. The data used for the present analysis were kindly provided by Cliff Johnson, National Center for Health Statistics. Estimates of the prevalence of iron deficiency anemia based on NHANES II have been published recently.[5,8]

Subsample selection. Because of the central importance of serum ferritin levels in estimating iron status, the analysis was limited to individuals in whom this measurement was available. Of the original 27,803 subjects sampled in NHANES II, serum ferritin measurements were performed in 5,157. Approximately one third of these were selected because of an abnormal red cell count, hemoglobin, hematocrit, mean corpuscular volume, or white cell count.[5] The objective was to include all persons with laboratory data suggestive of iron deficiency anemia. The remainder were selected randomly from the hematologically normal NHANES II population. Although the combined sample included a disproportionately high number of anemic individuals, the results can be extrapolated to the population by applying the weighting procedure.

To obtain relatively homogeneous subsets with regard to iron status, the present study was limited to adults between the ages of 18 and 65 years. Blacks were excluded to eliminate the effect of racial differences in hemoglobin concentration.[9,10] No persons were excluded because of abnormal laboratory values. Males between 18 and 64 years of age were analyzed as a single group (1,335), whereas because of the effect of menopause on iron status, women were divided into those below 45 years of age (937) and those 45 and above (557).

Laboratory measurements. Iron status was estimated from serum ferritin, erythrocyte protoporphyrin, transferrin saturation, and blood hemoglobin levels.[5,11] Erythrocyte protoporphyrin was analyzed fluorometrically in 10 μL whole blood using a modification of the extraction method of Sassa et al.[12] The results were converted to μg/dL packed red blood cells using the hematocrit determination. Serum iron was measured by the automated Technicon AA11-25 method and total iron-binding capacity (TIBC) was measured by the same technique after removing excess saturating iron with magnesium carbonate. Transferrin saturation was calculated by expressing the serum iron as a percent of the TIBC.

Serum ferritin determinations were performed at the University of Kansas Medical Center using a two-site immunoradiometric assay.[13] Ferritin protein was standardized against bovine serum albumin (BSA) using the Lowry technique.[14] Standards from a

single batch of recrystallized human ferritin were diluted to 1,000 μg/L in buffered 5% BSA and stored at −20 °C. All assays were performed in triplicate at an initial dilution of 1:20. Samples with values <20 μg/L or >200 μg/L were reassayed at dilutions of 1:10 or 1:100, respectively, with diluted standards containing equivalent concentrations of normal rabbit serum. Quality control over the five-year span of the project was achieved by performing measurements at the beginning, midpoint, and end of each assay on an aliquotted pool of normal serum stored at −70 °C. At the conclusion of the survey ferritin measurements in each assay were adjusted to the overall average for this quality control.

Criteria of iron deficiency. Iron deficiency was defined using multiple criteria[5,15] as abnormal values for at least two of the following iron parameters: serum ferritin, transferrin saturation, and erythrocyte protoporphyrin. Serum iron was used in place of transferrin saturation in approximately 10% of sampled individuals in whom TIBC values were not available. Cutoff levels for these measurements are listed in Table 1. Iron deficiency anemia was considered present when, in addition, the hemoglobin concentration fell below the listed cutoff levels (Table 1).

Estimates of body iron. For this purpose body iron is divided into a storage compartment and a functional compartment comprising circulating hemoglobin and all nonstorage tissues. Body iron is expressed in relation to the storage compartment.[16] A positive value represents the amount of iron that could be removed from the body without inducing a deficit in the functional compartment. A negative value denotes iron deficiency and represents the amount of iron that must be returned to the body before iron stores can accumulate.

To calculate iron stores, individuals were divided into three levels of iron status on the basis of the initial laboratory measurements. In those with iron deficiency anemia (abnormal hemoglobin and at least two abnormal iron parameters), iron stores were calculated as follows:

$$\text{iron stores (mg)} = -15 \times (\text{mean HB} - \text{observed HB}) \quad [A]$$

where mean hemoglobin (HB) is 140 g/L in women and 150 g/L in men. This calculation is based on the assumption that the deficit in body iron with anemia is inversely proportional to the hemoglobin concentration, that the mean hemoglobin concentration in normal men and women is 20 g/L higher than the cutoff level for anemia, and that 10 g/L circulating hemoglobin corresponds to 150 mg body iron. This algorithm was used in 8.5% of premenopausal women and 3.7% of postmenopausal women.

The formula used to calculate iron stores in those without iron deficiency anemia depended on the serum ferritin level. When this was less than 12 ug/L, serum ferritin, transferrin saturation, and erythrocyte protoporphyrin were weighted about equally in estimating the storage iron deficit. An index with values ranging from 0 to 5 was used as follows:

$$\text{iron stores (mg)} = -80 \times \text{index} \quad [B]$$

To calculate this index a value of 1 was given for each of the

Table 1. Criteria of Iron Deficiency

	Abnormal Value
Serum ferritin (μg/L)	<12
Transferrin saturation (%)	<16
Serum iron* (μg/dl)	<50
Erthrocyte protoporphyrin (μg/dL RBC)	>70
Hemoglobin concentration (g/L)	
Men	<130
Women	<120

*Used only when transferrin saturation was not available.

following: serum ferritin below 9 μg/L, transferrin saturation below 16%, transferrin saturation below 10%, erythrocyte protoporphyrin above 70 μg/dL RBC, and erythrocyte protoporphyrin above 100 μg/dL RBC.

In the remaining individuals with normal serum ferritin levels, iron stores were calculated as follows:

$$\text{iron stores (mg)} = 400 \times (\log \text{SF} - \log 12) \quad [C]$$

where log is the natural logarithm and SF is serum ferritin in μg/L. This formula is derived from quantitative phlebotomy studies indicating that 1 μg serum ferritin is equivalent to approximately 8 to 10 mg storage iron.[17-19] A log transformation was employed because of evidence that the removal of storage iron by phlebotomy in normal subjects with high iron stores produces a greater fall in the serum ferritin level than in those with low stores.[20] In subjects with borderline iron deficiency (serum ferritin 12 to 30 μg/L), algorithms B and C were both applied. Formula B was not used at higher serum ferritin levels because a low transferrin saturation or elevated erythrocyte protoporphyrin value was considered in this situation to more likely reflect chronic inflammation rather than iron deficiency.[21] Algorithm B was used alone in 17.2% of premenopausal women and 5.3% of postmenopausal women, and was used in conjunction with algorithm C in a further 7.5% and 4.0% of these groups, respectively. Formula C was used exclusively in more than 95% of men.

RESULTS

Measurements of iron status in the three study groups are shown in Table 2. Values for erythrocyte protoporphyrin and transferrin saturation were similar in all groups, whereas serum ferritin levels differed markedly. The median ferritin of 27 μg/L in premenopausal women increased sharply to 63 μg/L in women over 45 years of age, but remained lower than the median of 92 μg/L observed in men. These values agree well with previous surveys in North America. For example, median values of 25 μg/L in premenopausal women and 94 μg/L in men were reported in the United States,[15] and geometric means of 23 μg/L and 93 μg/L, respectively, in a Canadian study.[22]

As anticipated, there was a striking difference in body iron in the three groups with mean values of 309 mg in premenopausal women, 608 mg in postmenopausal women, and 776 mg in men. The differences were even more dramatic at the lower end of the frequency distribution curve as reflected by fifth percentile values of −195 mg, −80 mg, and 242 mg iron, respectively. On the other hand, the upper end of the frequency distribution in postmenopausal women approached that of men with differences of less than 100 mg at the 90th and 95th percentiles. Interestingly, the width of the frequency distribution as reflected in the standard deviation was similar in the three groups with values between 313 mg, and 372 mg.

The cumulative frequency distribution of body iron approached a Gaussian distribution (Fig 1). In menstruating women a slight deviation from linearity occurred from 0 mg to 200 mg, whereas in postmenopausal women the points were slightly curvilinear, implying a mixture of two or more discrete populations. This became more apparent when the frequency distributions were plotted as histograms (Fig 2). Whereas the distribution in premenopausal women was

Table 2. Measurements of Iron Status and Estimated Iron Stores In Adults 18 to 64 Years

Measurement*	N	Mean	SD	Percentile						
				5	10	20	50	80	90	95
Female, 18 to 44 yr										
HB (g/L)	937	133	10	117	121	126	133	142	146	149
SF (μg/L)	937	37(24)†	38	3	7	11	27	57	82	108
EP (μg/dl)	937	55	20	37	40	43	52	64	74	83
TS (%)	860	27	12	11	14	18	25	37	42	47
ST (mg)	937	309	346	−195	−115	−73	324	623	770	879
Female, 45 to 64 yr										
HB	557	137	11	119	124	128	136	146	152	156
SF	557	78(56)†	68	11	18	27	63	116	152	193
EP	557	56	24	34	38	42	51	65	75	89
TS	503	26	9	14	15	19	25	32	36	43
ST	557	608	372	−80	108	324	663	907	1016	1110
Male, 18 to 64 yr										
HB	1335	152	11	135	139	143	152	161	166	170
SF	1335	113(85)†	94	22	32	46	92	157	207	299
EP	1335	50	27	34	37	40	46	56	63	70
TS	1335	30	10	16	18	21	28	37	43	47
ST	1335	776	313	242	370	537	801	1026	1135	1264

*HB, hemoglobin; SF, serum ferritin; EP, erythrocyte protoporphyrin; TS, transferrin saturation; ST, iron stores.

†Geometric means given in parentheses.

roughly symmetrical, it was negatively skewed in postmenopausal women. Because iron stores are known to expand following menopause, postmenopausal women were separated into smaller age groups (Fig 3). In women 45 to 49 years of age the distribution of iron stores was quite broad, whereas in the 50- to 54-year age range the distribution was bimodal. In women between 55 and 59 years the histogram approached a normal distribution, indicating that nearly a decade is required following menopause to achieve a homogeneous population in regard to iron status.

Various methods for estimating the prevalence of iron deficiency are compared in Table 3. The prevalence of iron deficiency anemia is appreciably higher when using a single criterion (abnormal hemoglobin) than when based on either multiple criteria or iron stores less than −300 mg, the latter

two agreeing well. For example, in premenopausal women the estimated prevalence by these three techniques is 7.5%, 2.3%, and 2.6%, respectively. It should be noted that prevalence estimates expressed as a percentage in this table are lower than when calculated from the listed number of subjects because of the weighting procedure. For example, 60 of 937 or 6.4% of women between 18 and 44 years had iron stores below −300 mg as compared to a prevalence after weighting of 2.6%.

Similar comparisons were made for the prevalence of iron deficiency. Using a single criterion in younger women, the prevalence was substantially higher when based on serum
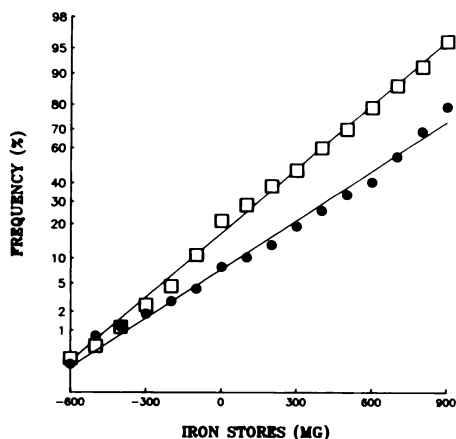

Fig 1. Cumulative frequency distributions of iron stores in women 18 to 44 (□) and 45 to 64 (●) years of age.
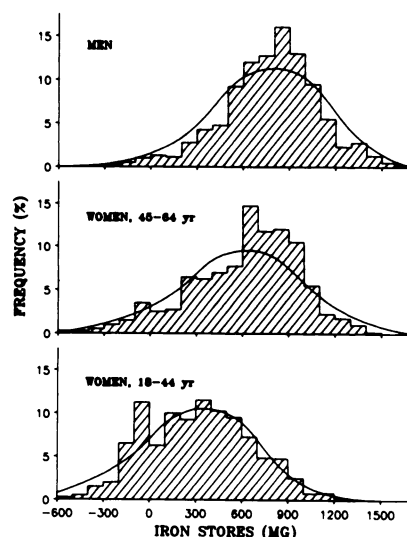

Fig 2. Histograms of the frequency distribution of body iron stores in adult men and women.
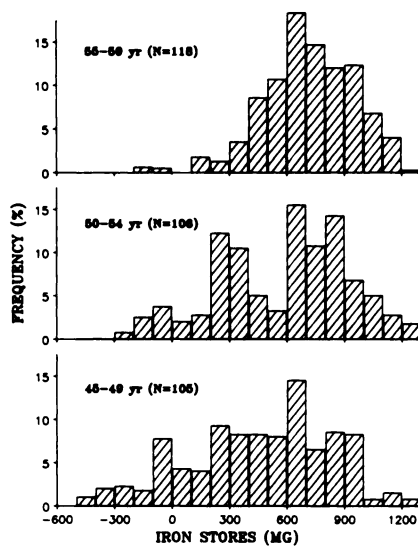
Fig 3. Frequency distributions of body iron stores in post-menopausal women.

ferritin levels (21.3%) than when based on transferrin saturation (14.5%) or erythrocyte protoporphyrin (12.1%). This difference is not unexpected because storage iron depletion as reflected by serum ferritin occurs prior to the onset of iron-deficient erythropoiesis as measured by transferrin saturation or erythrocyte protoporphyrin. It is interesting, however, that this pattern was reversed in both postmenopausal women and in men in whom the prevalence of mild iron deficiency was distinctly lower when determined by serum ferritin levels. This supports the suggestion that other disorders such as chronic inflammation or infection contribute to abnormal transferrin saturation or erythrocyte protoporphyrin levels in these population segments.[8]

When iron deficiency was defined by multiple criteria, the prevalence fell to 10% in premenopausal women and to only 4.1% and 0.7% in postmenopausal women and men, respectively. These values agree closely with the prevalence of iron

deficiency defined as iron stores less than −100 mg; prevalence levels of 11.1%, 4.0%, and 0.8%, respectively, were observed. Interestingly, the prevalence increases almost two-fold (22.3%, 7.6%, and 1.8%) if a cutoff level of 0 mg rather than −100 mg iron stores is used. Taken together these results indicate that the calculation of iron stores can be used to estimate the prevalence of iron deficiency with or without anemia, as well as to characterize the iron status of the entire population.

One possible advantage of estimating iron stores in each individual is to improve the precision and reliability of population surveys. To evaluate this, groups of 50 women were selected randomly by computer from the total sample of 937 premenopausal women. In each of these samples the prevalence of iron deficiency anemia was estimated using a single criterion (abnormal hemoglobin), multiple criteria, or body iron stores less than −300 mg. The latter was determined by calculating the mean and standard deviation for body iron in each sample and determining the proportion of the population with iron stores less than −300 mg from tables of the normal distribution. When 10 such samples were drawn the prevalence based only on hemoglobin ranged widely from 14% to 42% (Fig 4). The estimated prevalence averaged only 4.5% when using multiple criteria with a range of 0% to 8%. The most consistent estimate of prevalence was obtained by calculating iron stores, with values ranging from only 3.3% to 7.5%. Weighting factors were not applied in this study.

DISCUSSION

Three separate computations were used to calculate body iron in the present report depending on whether laboratory measurements indicated iron deficiency anemia, iron deficiency, or residual iron stores. The calculation in anemic individuals (formula A) is relatively straightforward because the deficit in body iron is clearly related to hemoglobin concentration once the level has fallen below the cutoff level for anemia. This calculation might be further refined by using a formula based on body weight rather than assuming a

Table 3. Prevalence of Iron Deficiency in Adults Living in the US Measured by Various Criteria

	Women 18 to 44 yr		Women 45 to 64 yr		Men 18 to 64 yr	
	N	%	N	%	N	%
Iron Deficiency Anemia						
Single criterion	151	7.5	73	5.2	113	2.2
Multiple criteria	55	2.3	21	1.4	14	0.2
Storage estimate	60	2.6	24	1.9	16	0.2
Iron Deficiency						
Single Criterion*						
SF	213	21.3	45	5.9	38	1.6
TS	171	14.5	79	10.8	105	5.0
EP	147	12.1	92	12.3	75	4.2
Multiple Criteria	124	10.0	40	4.1	27	0.7
Storage Estimate						
Below 0 mg	226	22.3	56	7.6	45	1.8
Below −100 mg	129	11.1	38	4.0	30	0.8

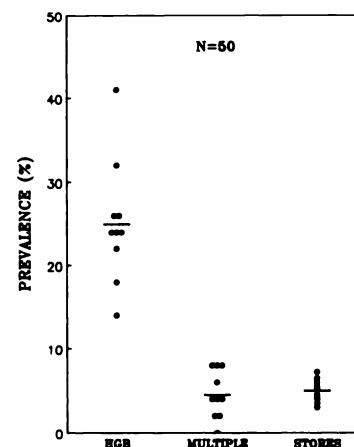*SF, serum ferritin; TS, transferrin saturation; EP, erythrocyte protoporphyrin.

Fig 4. Comparison of methods for estimating the prevalence of iron deficiency anemia in 10 groups of 50 premenopausal women selected randomly from the NHANES II sample.

fixed value of 15 mg iron for each 1 g/L difference in circulating hemoglobin. Expression on a body weight basis will obviously be required if this approach is used in infants and children and may be useful when comparing iron status in populations with appreciable differences in mean body weight. The number of anemic individuals in the present study was too small to fully evaluate alternate computational methods.

The estimation of body iron in iron-replete individuals is based on evidence that the serum ferritin concentration correlates closely with body stores as measured either by quantitative phlebotomy or indirectly by nonheme marrow iron concentration or iron absorption.[4] However, the precise quantitative relationship between body iron reserves and serum ferritin has been examined by phlebotomy in only a limited number of subjects. From these studies a linear relationship using a conversion factor of 8 to 10 mg body iron for each μg/L serum ferritin has often been used. However, based on the widely accepted normal range of 12 to 300 μg/L serum ferritin, this would predict that roughly 2.5% of normal individuals have iron stores in excess of 3 g, a figure that seems rather high. Since there is no clearcut evidence that body iron stores are highly skewed in a normal population, we have used a conservative calculation based on a log transformation for serum ferritin although this may underestimate iron stores at high serum ferritin levels. Additional studies are needed to establish the precise relationship between body iron and serum ferritin, especially in the high normal range. Techniques such as magnetic susceptometry may assist in this effort.[23]

The greatest uncertainty exists in estimating body iron in individuals with mild iron deficiency. A scoring system (formula C) was used to relate the degree of abnormality in transferrin saturation, erythrocyte protoporphyrin, and serum ferritin to the deficit in body iron. More sophisticated approaches such as multiple regression analysis might be developed by monitoring the changes in these iron parameters during the gradual induction or alleviation of mild iron deficiency. Further refinements in this calculation might also be developed by studying populations with a higher prevalence of mild iron deficiency. It should be noted that by using a combination of iron parameters, precise cutoff levels for transferrin saturation, erythrocyte protoporphyrin, and serum ferritin are less critical than when using any one of these alone. We observed that 10% to 20% changes in cutoff levels for calculating the index (in formula B) had little effect on calculated iron stores.

One important problem in assessing the iron status of a population is in distinguishing chronic inflammation from iron deficiency. Chronic inflammation assumes greater importance in the elderly and in poorer socioeconomic seg-

ments of a population. Clinically, inflammation can be recognized by a low transferrin saturation or elevated erythrocyte protoporphyrin in combination with a high serum ferritin level. It is of interest that the serum ferritin was disproportionately elevated relative to transferrin saturation or erythrocyte protoporphyrin in men and postmenopausal women, suggesting an influence of chronic inflammation in this age group. This effect might be eliminated by excluding individuals from the analysis who have an abnormal transferrin saturation and erythrocyte protoporphyrin but a serum ferritin greater than 50 μg/L.[19] There were too few individuals in the present study (7 out of 2,829) to detect the effect on the frequency distributions.

The ability to estimate iron stores on an individual basis offers certain advantages in survey work. Existing methods are based on the proportion of individuals with one or more abnormal laboratory measurements, an approach that requires large surveys, particularly if the prevalence of iron deficiency is low. Another advantage in estimating iron stores individually is to reduce the time required to plan, conduct, and analyze population surveys, which in the case of NHANES II was nearly a decade. A single technologist can perform the battery of measurements required to estimate iron stores in 20 to 30 individuals daily. This would permit population studies of iron status to be analyzed on an ongoing basis and reduce both the cost and time to conduct them. In addition, individual estimates of body iron provide a measure of variability in iron status and a method of identifying factors that affect iron nutrition in smaller subsets of a population such as method of contraception, intake of iron supplements, socioeconomic status, and bioavailability of dietary iron.

One of the most important advantages in estimating body iron stores is that it defines iron status in the entire population. This has assumed added importance in light of the apparent reduction in the prevalence of iron deficiency between the original HANES conducted in 1973 and NHANES II completed in 1980.[5] Increased consumption of heavily fortified foods and iron supplements have undoubtedly contributed to this improvement. Careful monitoring of the iron status in this country is justified in light of the relatively high frequency of the iron-loading gene which has been reported.[3,24] Although once thought to be a rare disorder, the homozygous state for hereditary hemochromatosis is now believed to occur in approximately 0.5% of this population. This is appreciably higher than the prevalence of iron deficiency anemia observed in adult males in NHANES II. Epidemiologic techniques that are sensitive to changes in the iron-replete as well as iron-deficient segments of the population could assist in drafting regulatory policies relating to iron fortification and supplementation.

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