Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis[1–3]

David I Thurnham, Linda D McCabe, Sumanto Haldar, Frank T Wieringa, Christine A Northrop-Clewes, and George P McCabe

ABSTRACT

Background: The World Health Organization recommends serum ferritin concentrations as the best indicator of iron deficiency (ID). Unfortunately, ferritin increases with infections; hence, the prevalence of ID is underestimated.

Objective: The objective was to estimate the increase in ferritin in 32 studies of apparently healthy persons by using 2 acute-phase proteins (APPs), C-reactive protein (CRP) and α_1-acid glycoprotein (AGP), individually and in combination, and to calculate factors to remove the influence of inflammation from ferritin concentrations.

Design: We estimated the increase in ferritin associated with inflammation (ie, CRP >5 mg/L and/or AGP >1 g/L). The 32 studies comprised infants (5 studies), children (7 studies), men (4 studies), and women (16 studies) (n = 8796 subjects). In 2-group analyses (either CRP or AGP), we compared the ratios of log ferritin with or without inflammation in 30 studies. In addition, in 22 studies, the data allowed a comparison of ratios of log ferritin between 4 subgroups: reference (no elevated APP), incubation (elevated CRP only), early convalescence (both APP and CRP elevated), and late convalescence (elevated AGP only).

Results: In the 2-group analysis, inflammation increased ferritin by 49.6% (CRP) or 38.2% (AGP; both $P < 0.001$). Elevated AGP was more common than CRP in young persons than in adults. In the 4-group analysis, ferritin was 30%, 90%, and 36% (all $P < 0.001$) higher in the incubation, early convalescence, and late convalescence subgroups, respectively, with corresponding correction factors of 0.77, 0.53, and 0.75. Overall, inflammation increased ferritin by ≈30% and was associated with a 14% (CI: 7%, 21%) underestimation of ID.

Conclusions: Measures of both APP and CRP are needed to estimate the full effect of inflammation and can be used to correct ferritin concentrations. Few differences were observed between age and sex subgroups. *Am J Clin Nutr* 2010;92:546–55.

INTRODUCTION

Plasma ferritin concentrations reflect the concentration of stored iron in the liver (1), and most investigators accept that serum ferritin concentrations <12 or <15 μg/L in those younger than or older than 5 y, respectively, indicate iron deficiency (2, 3). In addition, plasma ferritin concentrations respond well in iron-intervention studies (4) and were the principal recommendation of the World Health Organization (WHO) at a meeting in 2004 to discuss the best way of assessing iron status in populations (5). However, ferritin is also a positive acute-phase protein (APP) that is elevated in the presence of infection or inflammation (6, 7). Therefore, the WHO working group recommended that ferritin measurements should be accompanied by the analysis of one or more APPs to detect the presence of infection or inflammation (5, 8). However, there is uncertainty about how APP should be used. Regression analyses of data from African American infants and Guatemalan school-age children showed that serum ferritin correlated with APP concentrations but found poor positive predictive values (9). Investigators have suggested raising ferritin thresholds to higher values in the presence of inflammation to discriminate iron deficiency (3), but others have suggested that such action is fraught with uncertainty (2). Likewise, the exclusion of results from subjects with inflammation (8, 10) could bias the results if iron-deficient persons are more prone to infection. It is also impractical if the number of persons with elevated APP in a study population is high, eg, as in The Gambia, where >90% of apparently healthy infants had elevated APP concentrations (11).

We believe that regression analysis is poorly predictive of ferritin concentrations (9) because the increase in ferritin after infection follows a different pattern than that of either C-reactive protein (CRP) or α_1-acid glycoprotein (AGP) (12). At the onset of infection, CRP rises rapidly and reaches maximum concentrations between 24 and 48 h, whereas AGP may take 4–5 d to reach a plateau (13). As the intensity of infection

[1] From the Northern Ireland Centre for Food & Health, University of Ulster, Coleraine, United Kingdom (DIT); the Statistics Department, Purdue University, West Lafayette, IN (LDM and GPM); the School of Agriculture, Food and Rural Development, Newcastle University, Newcastle, United Kingdom (SH); the UMR 204 "Prévention des Malnutritions et des Pathologies Associées" IRD Centre de Montpellier, Montpellier Cedex 5, France (FTW); and the Elsie Widdowson Laboratory, MRC Human Nutrition Research, Fulbourn Road, Cambridge, United Kingdom (CAN-C).

[2] Supported by HarvestPlus, International Food Policy Research Institute, Washington DC (provided travel funds to facilitate the above study through research agreement number 8044).

[3] Address correspondence to DI Thurnham, 46 High Street, Little Wilbraham, Cambridge CB21 5JY, United Kingdom. E-mail: di.thurnham@ulster.ac.uk.

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diminishes, CRP falls rapidly, whereas AGP remains elevated. In contrast, ferritin rises rapidly within a few hours of a trauma and remains elevated after the CRP concentrations have subsided and while AGP concentrations are still increased (14). Plasma retinol concentrations are also influenced by inflammation and to overcome the different decay times of the inflammatory protein and to avoid excluding data, we devised a way of using elevated APPs to categorize apparently healthy subjects by their inflammatory state. This method also produced correction factors to remove the influence of inflammation (15). In this article we use the same method for plasma ferritin concentrations.

METHODS

Choice of studies

The studies were initially identified by using "ferritin" and "inflammation" or "acute phase proteins" or "CRP", "α_1-antichymotrypsin"(ACT) or "AGP" or "orosomucoid" as key words to interrogate the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) with no time limit. ACT was included because it has similar characteristics on infection to CRP (13, 16). Orosomucoid is an older and alternative name for AGP. Of the initial studies identified, studies were eliminated if they did not provide data for ferritin and at least 2 APP data in apparently healthy human volunteers. An apparently healthy person was defined as someone showing no outward signs of infection. Thus, they could have parasites in their bodies or be HIV positive but outwardly show no signs of infection.

Reference lists from suitable reports were cross-checked for other studies. Our knowledge of persons who had measured APP concentrations provided us with the names of persons who had unpublished data, who agreed to let us use their data. We initially identified 39 studies, Data from 8 of these studies were no longer available, authors from 2 of the studies could not be contacted, and one unpublished study was not released. The remaining 28 studies were discussed at our first meeting, and it was decided that the study populations in some could be subdivided: eg, pregnant and nonpregnant, night blind and non–night blind, or HIV-1 positive and HIV-1 negative. Men and women in the same study were also examined separately, and there were separate groups for infants and children. We did not separate infants or children by sex because there was no available information that sex-related factors influenced iron stores until a girl reached menarche. For intervention studies, only the baseline or first available data in any study were used. This produced a list of 35 separate study groups, which were analyzed before a second meeting, during which it was decided to remove 3 of these studies [subjects with prostate-specific antigen >2 units (17), unpublished data on Zairian adolescents some of whom may have had clinical malaria and unpublished data from Papua New Guinea] because we knew too little about the subjects and whether they could be described as "apparently healthy." The results described in this article were obtained from the 32 study groups listed in **Table 1**. Note that the references are given as the source of the data. The information shown in this article may differ from those sources because we included only subjects for whom ferritin and 2 APP results were available.

Biochemical data

In all investigations, plasma or serum ferritin concentrations were measured by using the manufacturers' kits. The APPs were measured by using radial immuno-diffusion (18), immunoturbidimetry (19, 20), and enzyme-linked immunosorbent assay (21). We made no attempt to correct for differences between methods because we found no discernable difference in ferritin ratios (*see* Study methods below) computed for the different assay methods (data not shown). Thresholds used to define abnormal ferritin were <12 or <15 μg/L in those < and >5 y of age, respectively (3). Inflammation was indicated when the CRP concentration was >5 mg/L and/or the AGP concentration was >1 g/L (15).

Statistical analysis

Data from Pakistan

In one study of Pakistani preschool children (19), ferritin, AGP, and ACT data were available. As indicated above, ACT can substitute for CRP (13, 16), and inflammation was indicated when the ACT concentration was >0.6 g/L. Both CRP and ACT rise rapidly on stimulation and plateau within 24–48 h. Thus, ACT can identify the incubation group as accurately as can CRP, and ACT is reasonably good at differentiating the convalescent groups as well. The analyses were run with and without Pakistan (data not shown), and the results were qualitatively the same; therefore, Pakistan was included in both the 2- and 4-group analyses.

Study methods

We compared serum ferritin concentrations between subsets of individuals. We used natural logs of these concentrations because distributions of serum ferritin were frequently skewed. We converted the results back to the original scales to facilitate interpretation; thus, the CIs were not necessarily symmetrically distributed around the overall summary estimate. The choice of the natural log transformation enabled the geometric means to be calculated as a summary; the back-transformed difference in the means of the logs was the ratio of the geometric means of the original data. In the tables, the differences in ferritin between groups are expressed as ratios.

Data analysis

To assess the relation between the individual APPs and serum ferritin, we first conducted a 2-group meta-analysis (15) for CRP and AGP separately. Individuals were classified as having a normal CRP if the serum concentration was ≤5 mg/L and as having a high concentration if it was >5 mg/L. Similarly, we used a cutoff of 1.0 g/L for AGP. APP concentrations recorded as being below the lowest detectable level or higher than the limit of detection were classified as normal and high, respectively. We calculated the mean log ferritin value of each group and the study summary, which was the difference between the mean log ferritin concentration for the normal group and that for the high group. The 2-group analysis was done on all possible studies and separately on the groups containing the infants, children, men, and women because of the potentially large differences in plasma ferritin concentrations between these subgroups.

In the 4-group analysis, we classified individuals from each study as reference, incubating, early convalescence, or late

TABLE 1
Summaries of data used in the meta-analysis[1]

		Subjects[2]					Ferritin		CRP	AGP
Study no.	Country of study, population, exposure, reference	Total	Incubation	Early convalescence	Late convalescence	Reference	Median (IQR)	Low[3]	Median (IQR)	Median (IQR)
		n	*n*	*n*	*n*	*n (% of total)*	*μg/L*	%	*mg/L*	*g/L*
1	Europe, men treated for malaria (22)[4]	22	5	3	3	11 (50)	186 (138, 311)	0	3.56 (2.57, 5.9)	0.65 (0.47, 1.04)
2	Kenya, men, HIV+ (20)[4]	56	4	28	5	19 (34)	489 (206, 1084)	0	6.46 (1.90, 28.13)	1.05 (0.73, 1.77)
3	UK, men, dietary study (23)	30	0	0	5	25 (83)	73 (46, 107)	0	1.09 (0.56, 1.71)	0.83 (0.69, 0.95)
4	Zaire, women, not pregnant (24)[4]	172	11	27	86	48 (28)	57 (39, 84)	0.6	3.40 (2.6, 4.55)	1.21 (0.90, 1.50)
5	Guatemala, children (9)	157	1	1	22	133 (85)	52 (34, 73)	1.3	0.68 (0.34, 1.53)	0.71 (0.54, 0.90)
6	USA, Louisiana, men, no prostate cancer (17)[4]	173	26	22	30	95 (55)	195 (88, 303)	1.7	0.95 (0.001, 5.23)	0.90 (0.74, 1.06)
7	Thailand, children (25)[4]	447	15	15	32	385 (86)	39 (26, 59)	3.4	4.99 (4.99, 4.99)[5]	0.57 (0.46, 0.75)
8	Europe, women treated for malaria (22)	15	7	0	0	8 (53)	143 (86, 164)	6.7	4.86 (4.59, 5.98)	0.60 (0.56, 0.74)
9	Nepal, women (iron folate supplementation study), 32 wk gestation (26)	100	10	0	3	87 (87)	30 (21, 42)	9.0	1.06 (0.6, 2.75)	0.46 (0.35, 0.57)
10	Kenya, women, HIV+ (20)[4]	107	14	35	11	47 (44)	90 (31, 220)	10.3	3.94 (0.86, 13.18)	0.93 (0.73, 1.29)
11	Nepal, women, MM supplement study, 32 wk gestation (26)[4]	87	8	2	2	75 (86)	25 (18, 34)	10.3	1.85 (0.76, 3.61)	0.48 (0.37, 0.58)
12	USA, Detroit, 9-mo-old infants (9)[4]	293	3	9	41	240 (82)	30 (19, 49)	11.6	0.19 (0.09, 0.60)	0.65 (0.47, 0.89)
13	Indonesia, 10-mo-old infants, +iron (27, 28)[4]	162	13	26	33	90 (56)	34 (18, 53)	11.7	2.35 (0.10, 5.00)	0.90 (0.76, 1.15)
14	USA, Oklahoma, preschool children (29)	125	0	15	34	76 (61)	20 (14, 30)	16.8	1.00 (1.0, 1.0)[5]	0.91 (0.78, 1.18)
15	South Africa, women, HIV+, 6 wk postpartum (30)[4]	69	9	21	23	16 (23)	30 (17, 47)	17.4	4.00 (0.001, 23.0)	1.09 (0.97, 1.37)
16	Laos, preschool children, survey[4,6]	483	13	63	131	276 (57)	34 (15, 61)	18.2	0.59 (0.15, 2.77)	0.91 (0.72, 1.17)
17	Laos, women, survey[4,6]	831	39	29	54	709 (85)	40 (15, 78)	19.9	0.38 (0.09, 1.43)	0.70 (0.59, 0.85)
18	South Africa, women, HIV−, 6 wk postpartum (30)[4]	68	5	28	16	19 (28)	26 (14, 59)	20.6	5.00 (3.0, 10.5)	1.08 (0.95, 1.40)
19	Indonesia, women, 13–27 wk gestation[7]	164	37	3	0	124 (76)	25 (11, 40)	26.8	2.90 (1.89, 4.90)	0.49 (0.43, 0.61)
20	Indonesia, 6-mo-old infants (31)[4]	135	12	30	20	73 (54)	24 (11, 52)	28.2	2.70 (2.1, 6.7)	0.88 (0.66, 1.14)
21	PNG women[8]	21	0	0	3	18 (86)	23 (10, 34)	28.6	0.30 (0.3, 0.4)	0.76 (0.67, 0.89)
22	Indonesia, women, 6 mo postpartum (31)[4]	137	6	8	11	112 (82)	19 (10, 33)	30.7	1.90 (1.7, 2.3)	0.75 (0.64, 0.89)
23	Zaire, women, pregnant, exposed to malaria (32)[4]	206	120	31	2	53 (26)	16 (10, 35)	33.5	10.05 (5.0, 27.6)	0.64 (0.50, 0.81)
24	Indonesia, women, 36 wk gestation[7]	162	50	0	1	111 (69)	15 (8, 23)	40.7	3.55 (2.7, 6.0)	0.37 (0.29, 0.44)
25	Zambia, 6-mo-old infants, exposed to malaria[4,9]	433	5	7	94	327 (76)	13 (7, 24)	46.0	0.41 (0.16, 1.40)	0.72 (0.53, 0.97)

(Continued)

TABLE 1 (*Continued*)

Study no.	Country of study, population, exposure, reference	Subjects[2]					Ferritin		CRP	AGP
		Total	Incubation	Early convalescence	Late convalescence	Reference	Median (IQR)	Low[3]	Median (IQR)	Median (IQR)
		n	*n*	*n*	*n*	*n (% of total)*	*μg/L*	%	*mg/L*	*g/L*
26	India, children (33)	79	0	4	11	64 (81)	12 (7, 23)	49.4	0.15 (0.02, 270.47)	0.86 (0.71, 0.96)
27	Indonesia, no iron, 10-mo-old infants (27, 28)[4]	255	16	49	38	152 (60)	12 (6, 23)	49.4	1.90 (0.1, 5.1)	0.89 (0.66, 1.14)
28	Marshall Islands, preschool children (34, 35)	95	0	26	29	40 (42)	12 (5, 25)	49.5	1.75 (0.72, 5.69)	1.07 (0.87, 1.28)
29	Nepal, pregnant women (36)[4]	740	68	11	3	658 (89)	12 (6, 21)	51.4	1.07 (0.44, 2.28)	0.41 (0.34, 0.50)
30	Pakistan, survey, preschool children (19)[4,10]	2765	5	304	1403	1053 (38)	6 (2, 15)	68.9	0.39 (0.3, 0.49)	1.14 (0.85, 1.61)
31	Nepal, night-blind women (37)[4]	100	15	8	7	70 (70)	6 (5, 10)	83.0	2.06 (1.5, 4.79)	0.56 (0.36, 0.80)
32	Nepal, non–night-blind women (37)[4]	1057	9	5	4	89 (83)	6 (4, 9)	85.1	2.04 (1.45, 3.35)	0.46 (0.37, 0.66)

[1] Studies are arranged in order of increasing prevalence (%) of low ferritin concentrations. AGP, α_1-acid glycoprotein; CRP, C-reactive protein; IQR, interquartile range; PNG, Papua New Guinea; MM, multimicronutrient; +, positive; −, negative.

[2] The subjects in the studies are shown as totals and by acute-phase protein (APP) status: incubation (elevated CRP only), early convalescence (elevated CRP and AGP), late convalescence (elevated AGP only), and reference (no elevated APP).

[3] Low ferritin is defined as <12 μg/L for individuals ≤5 y of age and <15 μg/L for individuals >5 y of age. All studies were included in the 2-group analysis if APPs were elevated (ie, CRP >5 mg/L or AGP >1 g/L).

[4] Studies included in the 4-group analysis.

[5] Values indicate very little inflammation and very few abnormal values.

[6–9] Unpublished data, 2007–2008: [6]from Jacky Knowles, [7]from Frank Wieringa, [8]from Katie Tripp, [9]from S Kuvibidila.

[10] α_1-Antichymotrypsin was measured instead of CRP.

convalescence on the basis of the values for 2 APPs. In the case of Pakistan, ACT was substituted for CRP, and the analyses were run with and without this group, as described above. Individuals in the reference group were defined as having normal APPs, ie, both were less than or equal to their respective cutoff values. The incubation group was defined by a normal AGP and an elevated CRP value. The early convalescence group was defined by elevated AGP and CRP concentrations, and the late convalescence group by an elevated AGP and a normal CRP concentration. The 4-group analysis resulted in a comparison of 6 pairs of mean log ferritin concentrations. Each of these was summarized by study and then analyzed as described previously.

Within-study variance

The summary statistic (effect size) was the difference between 2 means, and the variability associated with each summary statistic was related to sample sizes. In general, studies with a large number of samples will have smaller variability than will those with a small number. To combine the summary statistics of all the studies, traditional weights were calculated based on the inverse of the within-study variance. In this way, studies with a large variance, and therefore a relatively imprecise estimate of the study summary, received less weight than a study with a smaller variance. Two additional weighting methods were also examined: weights generated that were inversely proportional to sample sizes and the same weight for each study (data not shown). In general, the overall summary statistic had the smallest variability when the inverse of the within-study variance-weighting scheme was used.

In the 4-group analysis, to avoid the difficulty of interpretation that would occur if different weights were computed for the comparison of each pair, weights were computed from the sum of the variances for the 4 groups and on the total sample size for the 4 groups. Although 6 comparisons were possible, only 3 had practical use for interpretation of plasma ferritin concentrations in cross-sectional studies, namely the comparison against the reference group. To estimate the variability of the overall summary statistic and to provide study to study variation, the random-effects model was used for all the analyses reported because it allowed for small differences between studies and enabled the generation of valid SDs.

RESULTS

Of the 32 study groups, 5 consisted of infants, 7 consisted of preschool or school children, 4 consisted of men, and 16 consisted of women (Table 1), which totaled 8796 subjects. Median ferritin concentrations ranged widely from 6 to 489 μg/L, although, in most studies (n = 28), the median was <100 μg/L. The prevalence of low ferritin concentrations similarly ranged widely from 0% to 85%. Median CRP concentrations were generally <5 mg/L, except for subjects known to be HIV-positive or exposed to malaria. Likewise, the median AGP concentration was <1 g/L, except in 5 groups: 2 of which were HIV-positive, 1 of which was nonpregnant Zairian women, and 2 of which were preschool children.

The numbers and proportions of subjects by inflammation group are shown in **Table 2**. The data are shown with and without subjects from Pakistan, where there was a high proportion of subjects with high AGP concentrations. The exclusion of subjects from Pakistan, however, still showed that the largest inflammation groups were those in late convalescence with high AGP concentrations, but this was predominantly due to results from studies in infants and children. In adult women, the highest proportion of those with inflammation was found in the incubation phase, and there was no appreciable difference between phases for the men.

For the 2-group analysis in which either CRP (n = 8745) or AGP (n = 8619) were examined separately, data from 30 study groups were used in both cases to determine the relative difference in mean ferritin concentrations in those with and without the respective elevated APP (**Table 3**). The 2 studies were excluded because there were no high CRP or AGP results, respectively. The analyses produced geometric mean ferritin concentrations that were 50% ($P < 0.001$) and 38% ($P < 0.002$) higher when CRP and AGP were elevated by inflammation, respectively (Table 3). To remove the influence of inflammation from ferritin, these differences convert to multipliers of 0.67 and 0.73 to reduce concentrations of ferritin when CRP and AGP are elevated, respectively. When different age and sex subgroups of the studies were examined separately; the increase in ferritin associated with an elevated CRP was similar in women (48%), children (59%), and infants (64%, all $P < 0.001$) but not in the men (17%; $P = 0.676$). For AGP, the increases in ferritin in the subgroups were 33% for women, 39% for men, 28% for children, and 73% for infants; however, these increases were only significant in infants ($P < 0.001$).

For the 4-group analysis in which ferritin in the reference group was compared with each of the other 3 inflammation groups, 22 studies (7848 subjects) provided complete information (Table 1). Generally speaking, study groups that were

TABLE 2
Summaries of subject numbers in all studies and inflammation groups with and without Pakistan[1]

Groups	All subjects	Acute-phase protein status			
		Incubation	Early convalescence	Late convalescence	Reference
	n	*n* (%)			
All studies	8796	526 (6)	810 (9)	2157 (25)	5303 (60)
All studies, without Pakistan	4250	521 (9)	506 (8)	754 (13)	4250 (70)
Infants	1278	49 (4)	121 (9)	226 (18)	882 (69)
Children	4151	34 (1)	428 (10)	1662 (40)	2027 (49)
Children, without Pakistan	1386	29 (2)	124 (9)	259 (19)	974 (70)
Men	281	35 (13)	53 (19)	43 (15)	150 (53)
Women	3086	408 (13)	208 (7)	226 (7)	2244 (73)

[1] Grouping of subjects by acute-phase proteins is described in Table 1.

TABLE 3
Ferritin ratios for subjects with or without inflammation as indicated by C-reactive protein (CRP) or α_1-acid glycoprotein (AGP) concentration: 2-group analysis[1]

	No. of studies	No. of participants	Ratio (95% CI)	*P*
CRP				
All studies	30[2]	8745	1.50 (1.34, 1.67)	<0.001
Infants	5	1278	1.64 (1.33, 2.03)	<0.001
Children	7	4151	1.59 (1.23, 2.06)	<0.001
Men	3	251	1.17 (0.56, 2.41)	0.676
Women	15	3065	1.48 (1.31, 1.68)	<0.001
AGP				
All studies	30[3]	8619	1.38 (1.13, 1.68)	<0.002
Infants	5	1278	1.73 (1.43, 2.09)	<0.001
Children	7	4151	1.28 (0.94, 1.74)	0.124
Men	4	281	1.39 (0.82, 2.37)	0.218
Women	14	2909	1.33 (0.98, 1.81)	0.071

[1] Values are ratios of geometric mean ferritin concentrations for the respective subgroups with and without inflammation from the 2-group analysis.
[2] Studies 3 and 21 were excluded because there were no high CRP concentrations.
[3] Studies 8 and 24 were excluded because there were no high AGP concentrations.

TABLE 4
Ferritin ratios for respective inflammation versus reference group comparisons: 4-group meta-analysis[1]

Studies compared	Ratio (95% CI)	*P*
Incubation vs reference		
All studies	1.30 (1.15, 1.47)	<0.001
Infants	1.13 (0.90, 1.41)	0.30
Children	1.56 (1.22, 1.99)	<0.001
Men	1.07 (0.79, 1.44)	0.66
Women	1.37 (1.07, 1.76)	0.01
Early convalescence vs reference		
All studies	1.90 (1.51, 2.37)	<0.001
Infants	2.09 (1.66, 2.63)	<0.001
Children	2.55 (1.37, 4.72)	0.003
Men	1.17 (0.52, 2.65)	0.706
Women	1.72 (1.27, 2.33)	<0.001
Late convalescence vs reference		
All studies	1.36 (1.19, 1.55)	<0.001
Infants	1.42 (1.14, 1.76)	<0.002
Children	1.53 (1.15, 2.04)	<0.004
Men	1.61 (0.98, 2.64)	0.058
Women	1.17 (0.96, 1.43)	0.124

[1] Values are ratios of geometric mean ferritin concentrations for the respective pairs from the 4-group analysis. There were 6 possible group comparisons, but only the 3 most important ones are shown. For the group comparisons, there were a total of 22 studies (n = 7848): 5 in infants (n = 1278), 3 in children (n = 3695), 3 in men (n = 251), and 11 in women (n = 2624).

excluded from the 4-group analysis had small sample sizes. The numbers of studies of infants, children, men, and women for the 4-group analysis were 5, 3, 3, and 11 respectively. Two studies were from areas where there was active transmission of malaria (studies 23 and 25; Table 1), and 2 were from studies with subjects previously infected with malaria (studies 1 and 8); 3 of these remained in the 4-group analysis. Three groups were HIV-1 positive (studies 1, 10, and 18; 2 female, one male), and these also remained in the 4-group analysis. Of the female groups, 4 were of pregnant women and 2 remained in the 4-group analysis. There was a very large range in the sizes of the different studies, which remained even for the 4-group analysis.

In the 4-group analysis, there were significantly higher geometric mean ferritin concentrations in the incubation (30%), early convalescence (90%), and late convalescence (36%) groups than in the reference group (all $P < 0.001$) (**Table 4**). These values converted to correction multipliers of 0.77, 0.53, and 0.75, respectively, to correct for serum ferritin values in the specific groups for inflammation. The same pattern of differences was also present in 3 of the subgroups, namely infants, children, and women, for whom ferritin concentrations were 13–56%, 72–155%, and 17–53% higher than those in the reference groups for the incubation, early convalescence, and late convalescence groups, respectively; for men, the respective values were 7%, 17%, and 61%. For infants, women, and children, ferritin was significantly higher in 7 of 9 of the subgroups comparisons ($P < 0.05$), whereas none of the differences were significant for men.

We also carried out comparisons of the ratios obtained from the 4-group analysis for different subgroups (**Table 5**), including men, women, children, infants, all adults, pregnant and nonpregnant women, HIV-positive and HIV-negative adults, persons exposed and not exposed to malaria, and groups with high and low ferritin concentrations. No significant difference emerged for any subgroup or inflammatory group comparison.

Finally we determined the effects of correcting ferritin concentrations on the prevalence of iron deficiency in the 22 studies used for the 4 group meta-analysis (**Table 6**). For each of the studies in the 4-group meta-analysis, we calculated the ratio of the prevalence of ferritin deficiency for all subjects divided by that of the reference group. We then calculated the bias by calculating the mean and the 5% and 95% CIs for this ratio (data not shown) and finally subtracted those values from 100 to determine the underestimation in prevalence of ferritin deficiency before correction. The data were then corrected by using the relevant correction factors (0.77, 0.53 and 0.75 as multipliers corresponding to values elevated by 30%, 90%, and 36%, respectively), and the calculation was repeated to determine the prevalence of ID (ferritin deficiency) after correction. We also performed similar calculations on serum ferritin concentrations before and after correction to determine the percentage overestimate of serum ferritin for all study groups in uncorrected data by comparison with the reference groups. We showed that, without correction for inflammation, the prevalence of ID using ferritin alone would be underestimated by 14% (CI: 7%, 21%) and that the underestimate was brought about by the fact that ferritin concentrations were 30% (CI: 15%, 45%) higher (Table 6). Correcting the data for inflammation by using both APPs removed the deviations; however, if only one APP was used, then ≈50% of the underestimate of ID still remained because only half of the ferritin increase was removed.

DISCUSSION

In the nutritional studies collected for these analyses, data were obtained from persons who were apparently healthy but in whom a subsequent analysis showed some covert inflammation. Most

TABLE 5
Comparison of 4-group meta-analysis results between subgroups of different ages, sexes, and other characteristics

	First subgroup			Second subgroup				
Reference versus	No. of studies	No. of subjects	Ratio (CI)[1]	No. of studies	No. of subjects	Ratio (CI)	z	P^2
	Men			Women				
Incubation	3	251	1.07 (0.79, 1.44)	11	2624	1.37 (1.07, 1.76)	−1.24	0.21
Early convalescence			1.17 (0.52, 2.65)			1.72 (1.27, 2.33)	−0.87	0.38
Late convalescence			1.61 (0.98, 2.64)			1.17 (0.96, 1.43)	1.18	0.24
	Infants			Children				
Incubation	5	1278	1.13 (0.90, 1.41)	3	3695	1.56 (1.14, 1.76)	−1.92	0.055
Early convalescence			2.09 (1.66, 2.63)			2.55 (1.14, 1.76)	−0.58	0.56
Late convalescence			1.42 (1.14, 1.76)			1.53 (1.15, 2.04)	−0.41	0.68
	Infants			Adults				
Incubation	5	1278	1.13 (0.90, 1.41)	14	2875	1.29 (1.07, 1.57)	−0.93	0.35
Early convalescence			2.09 (1.66, 2.63)			1.58 (1.16, 2.14)	1.45	0.15
Late convalescence			1.42 (1.14, 1.76)			1.26 (1.03, 1.55)	0.76	0.44
	Children			Adults				
Incubation	3	3695	1.56 (1.22, 1.99)	14	2875	1.29 (1.07, 1.57)	1.18	0.24
Early convalescence			2.55 (1.37, 4.72)			1.58 (1.16, 2.14)	1.36	0.17
Late convalescence			1.53 (1.15, 2.04)			1.26 (1.03, 1.55)	1.07	0.29
	Pregnant			Nonpregnant				
Incubation	5	1240	1.27 (0.98, 1.65)	6	1384	1.39 (1.00, 1.94)	−0.42	0.68
Early convalescence			1.48 (0.83, 2.66)			1.78 (1.25, 2.54)	−0.53	0.60
Late convalescence			1.29 (0.82, 2.03)			1.15 (0.83, 1.58)	0.41	0.68
	Malaria exposure			No malaria				
Incubation	3	661	1.02 (0.76, 1.36)	19	7187	1.35 (1.19, 1.54)	−1.73	0.08
Early convalescence			1.76 (1.20, 2.59)			1.92 (1.48, 2.48)	−0.35	0.73
Late convalescence			1.67 (1.34, 2.08)			1.31 (1.13, 1.52)	1.78	0.08
	HIV+			HIV−				
Incubation	3	232	1.39 (0.96, 2.02)	19	7616	1.29 (1.12, 1.49)	0.36	0.72
Early convalescence			2.61 (1.29, 5.27)			1.83 (1.45, 2.32)	0.93	0.35
Late convalescence			1.76 (0.88, 3.51)			1.32 (1.17, 1.50)	0.81	0.42
	Low ferritin[3]			High ferritin				
Incubation	11	5777	1.41 (1.09, 1.83)	11	2071	1.25 (1.08, 1.44)	0.80	0.43
Early convalescence			1.83 (1.46, 2.30)			1.93 (1.35, 2.75)	−0.24	0.81
Late convalescence			1.18 (1.01, 1.38)			1.46 (1.19, 1.80)	−1.63	0.10

[1] Values are ratios of the geometric mean ferritin concentrations (5% CI, 95% CI) for the respective pairs (reference vs inflammatory group) from the 4-group analysis for the specific subject groups.
[2] P values reflect differences between ratios for respective inflammation and subgroup comparisons.
[3] Studies were arbitrarily allocated to 2 groups on the basis of lower or higher mean ferritin concentrations (*see* Table 1).

persons fell into the reference group category (ie, no elevated inflammatory proteins (Table 2). In the reference group, nutritional biomarkers will be least likely to be influenced by inflammation and ferritin values will be more likely to represent the true nutritional status of the specific population groups.

In the groups with inflammation, most infants and children were in late convalescence and the fewest were in the incubation group. The latter is not surprising because the incubation period is at most 48 h (13), so the intensity of infection would have to be very high for numbers in this group to be large. In contrast, the late convalescent group may represent a much longer period if nutritional status is poor and recovery from disease is slow. In adult women, however, the situation was reversed, which suggested that convalescence was shorter than in infants and children, probably because humeral immunity was more fully developed and recovery quicker.

We analyzed 22 studies in which the reference and all 3 inflammation groups were present in infants, children, men, and

TABLE 6
Effect of correcting plasma ferritin concentrations on the prevalence of iron deficiency and plasma ferritin concentrations in the 22 studies in the 4-group meta-analysis[1]

	Prevalence of iron deficiency[2]			Serum ferritin concentration[3]		
Group	No. of studies	Before correction	After correction[4]	No. of studies	Before correction	After correction[4]
		% underestimate	*% underestimate*		*% overestimate*	*% overestimate*
All groups	19	14 (7, 21)	0 (−10, 9)	22	30 (15, 45)	5 (−3, 12)
Subgroups						
Infants	5	16 (2, 31)	5 (−14, 23)	5	26 (−9, 61)	5 (−17, 27)
Children	3	10 (−6, 27)	−2 (−14, 10)	3	16 (2, 30)	−2 (−21, 17)
Men	1	—[5]	—[5]	3	37 (−91, 165)	2 (−47, 51)
Women	10	16[5] (4, 28)	4[5] (−6, 13)	11	34 (7, 60)	7 (−6, 21)
All groups	19					
AGP only		14 (7, 21)	9 (2, 16)	22	30 (15, 45)	14 (3, 26)
CRP only	19	14 (7, 21)	5 (−3, 13)	22	30 (15, 45)	13 (5, 22)
CRP only without Pakistan	18	14 (7, 22)	5 (−3, 14)	21	31 (15, 47)	14 (4, 23)

[1] Values are means (5% CI, 95% CI) before and after correction for inflammation. AGP, α_1-acid glycoprotein; CRP, C-reactive protein.
[2] Iron deficiency defined as ferritin concentrations <12 μg/L for individuals ≤5 y of age (studies 12, 13, 16, 20, 25, 27, and 30) and <15 μg/L for individuals >5 y of age for all subjects compared with those in the reference groups and expressed as % underestimated of the number in the reference group.
[3] The higher concentrations of ferritin for each study are expressed as a percentage of that in the reference groups minus 100 for the 22 studies.
[4] Data were corrected by using both acute-phase proteins (AGP and CRP) to classify individuals into incubation, early, or late convalescence groups, and ferritin concentrations were multiplied by 0.77, 0.53, or 0.75, respectively. When data were corrected for only 1 of the 2 acute-phase proteins, the multipliers were 0.65 (CRP) or 0.72 (AGP) to correct the ferritin concentrations for the effects of inflammation.
[5] Two studies for men and one study for women could not be included in these calculations because there was no iron deficiency in the reference subgroup.

women, and we quantified the mean rise in ferritin concentrations in the incubation period (at the start of an infection but before the appearance of clinical symptoms, 30%), during early convalescence (the period immediately after clinical signs had disappeared, 90%), and during late convalescence (36%). These measurements were made on studies of apparently healthy persons but in whom there was only evidence of covert inflammation as indicated by slightly elevated CRP and/or AGP concentrations. The data clearly show that ferritin was increased by inflammation, and the increased ferritin concentration in the incubation group confirmed the report (14) that ferritin concentrations increased rapidly at the onset of inflammation.

There are often large differences in ferritin concentrations between groups with different ages and sexes. We therefore compared the increases in ferritin in the 3 inflammation subgroups in the different age and sex study groups to determine whether the increases in ferritin were influenced by high or low ferritin concentrations or by age, sex, pregnancy, HIV status, or exposure to malaria. None of these factors significantly influenced the increase in ferritin associated with the inflammatory states. Essentially, this means that at each stage in the infection cycle the increases in ferritin associated with inflammation were proportional to ferritin concentrations of the group, where there was no inflammation; ie, the reference group. This supports earlier observations that the increase in ferritin produced by inflammation was proportional to baseline concentrations (7).

The one group of studies in which there was least conformity in the effects of inflammation on ferritin was that in the men, in whom there was little increase in ferritin in both the incubation and early convalescence groups (Table 4). Studies 1, 2, and 6 (Table 1) contained the men who were included in the meta-analysis. Mean ferritin concentrations were highest in these groups, and ferritin concentrations in most individual men were >100 μg/L (data not shown). It is possible that, when baseline ferritin concentrations were very high, the inflammatory stimulus on ferritin was not as great as in persons with lower concentrations. Mean ferritin concentrations in all of the women groups in the meta-analysis were <100 μg/L. Thus, although there was no statistically significant difference in ferritin increases when men were compared with women or when those with high ferritin were compared with low ferritin, more studies are needed of men with ferritin concentrations in the same range as those of women to resolve this issue.

Two studies have recently reported that AGP was especially useful at interpreting ferritin concentrations and at assessing iron deficiency in HIV-infected Zimbabwean women (38) and Zanzibarian children prone to chronic malaria (39). We examined the results in Table 5 to determine whether the ferritin ratios in the convalescence groups of subjects exposed to malaria (studies 1, 23, and 25) or HIV positive (studies 2, 10, and 18; Table 1) were different from those studies not similarly affected. There was some evidence in the late convalescence subgroups of higher ferritin ratios in the malaria-exposed subjects (ratio: 1.67; $P = 0.08$), but, although there was a similar ferritin ratio in HIV-positive subjects (1.76), the latter was not different from ferritin ratios of the HIV-negative subjects in late convalescence ($P = 0.81$). Higher ratios in late convalescence might suggest that the relation between AGP and ferritin was particularly strong and possibly more useful than CRP to correct the influence of inflammation on plasma ferritin concentrations in persons with malaria (39). However, our 2-group meta-analyses of ferritin concentrations suggested that the increase in ferritin was greater when CRP (50%) rather than AGP (38%) was increased; therefore, we recommend strongly against the use of one APP and suggest that both CRP and AGP be used because they cover the full inflammation cycle and thus will result in unbiased estimates of prevalence.

The importance of using both APPs to correct a plasma ferritin concentration was also shown when we applied the correction factors to the data used in the meta-analysis to calculate the percentage deficit in cases of ID when compared with the percentage of cases in the reference groups. With the use of both APPs, there was an overall 14% underestimate in the prevalence of ID based on low ferritin concentration, which can be compared with the uncorrected prevalences of ID shown in Table 1. After correction with the use of both APPs, the mean underestimate was reduced to zero; however, if either AGP or CRP was used alone, an average prevalence of ID of 5% or 9%, respectively, remained (Table 6). Likewise, we showed that, on average, ferritin concentrations were 30% higher in all subjects than in the respective reference groups. However, when the overestimate was corrected for only one or the other of the 2 APPs, half the overestimate still remained. Obviously, these percentage values are averages from the studies in this meta-analysis, and the actual numbers will depend on the actual amount of inflammation in a specific study population. The values do, however, give us a measure of the effect of covert inflammation associated with both APP on serum ferritin and indicate that it is important to remove the effect of inflammation to correctly assess iron status on the basis of serum ferritin concentrations.

It is possible that the underestimate in ID is >14%. Our value is based on the difference in ferritin between all subjects and those in the reference groups. Subjects in the inflammation groups may have been deprived of iron during their illness and be more iron deficient than those in the reference group. However, this is speculation and we can only use the ferritin data that are available. The important thing is that the ferritin data are corrected for inflammation to expose a more accurate measurement of ID. This will be particularly important in intervention studies in which inflammation may differ between baseline and after intervention, both in the individuals and the numbers affected. For reasons of cost and practicality, plasma ferritin concentrations are the best biomarker of iron status (3, 5), and the WHO recommended ferritin for the purposes of describing the prevalence of ID in a population with a single number, except when inflammation was present (8). Correcting serum ferritin concentrations for inflammation enables the distinct international standards of the WHO to be used and will improve our ability to monitor the benefits of iron intervention to reduce the global prevalence of anemia.

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