# Associations between Serum C-reactive Protein and Serum Zinc, Ferritin, and Copper in Guatemalan School Children

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## Abstract

Inflammation affects trace nutrient concentrations, but research on copper and particularly in children is limited. We assessed associations between serum C-reactive protein (CRP) and zinc, iron, copper, and other biomarkers (alkaline phosphatase, hemoglobin, and albumin), in 634 healthy 6- to 11-year-old Guatemalan schoolchildren. CRP was measured by a standardized, high-

sensitive method. For significant associations with CRP, we stratified nutrient concentrations across categories of CRP and compared concentrations above and below several CRP cutoff points (0.5, 1, 3, 5, and 10 mg/L), and then adjusted values using correction factors (ratios of geometric means of the nutrients in the low and high groups). Prevalence of serum zinc (<65 μg/dL0, ferritin (<15 μg/L), and copper (<90 μg/dL) deficiency were 21%, 2.1%, and 23.8%, respectively. Median (25th and 75th percentiles) CRP was 0.56 (0.26 and 1.54) mg/L. CRP concentration was positively associated with ferritin and copper concentrations ($r$=0.23 and 0.29, respectively; $P$<0.0001) but not with zinc and other bio-markers ($P$>0.05). Regardless of CRP cutoffs, high (> cutoff) vs. low ( cutoff) CRP levels had higher ferritin and copper concentrations and lower prevalence of copper deficiency of <90 μg/dL ($P$<0.05). Adjustment for inflammation had the greatest influence on recalculated prevalence for the CRP 0.5 mg/L cutoff. The low ferritin prevalence hardly changed (from 2.1% to 2.5%) while the low copper prevalence changed appreciably (from 23.8% to 31.2%). In conclusion, CRP was positively associated with ferritin and copper but not with zinc concentrations. Adjustment for inflammation had little effect on low ferritin prevalence, low to begin with, and a large impact on low copper prevalence. High-sensitive CRP methods and the use of very low CRP cutoffs may be more accurate than traditional CRP methods in the adjustment of serum copper concentrations for inflammation in healthy school children.

## Keywords

Inflammation; C-reactive protein; School children; Ferritin; Zinc; Copper

## Introduction

Inflammation induces transient changes in concentrations of zinc, iron, and copper status [1, 2]. Even apparently healthy children may have elevated inflammatory biomarkers [3, 4]. The impact of inflammation on serum ferritin is very strong and has been consistently demonstrated in many studies; in fact, serum ferritin is recognized as an acute phase protein (APP) of the inflammation process [5–8]. The influence of inflammation on serum zinc and copper concentrations may be weaker [9]. Some studies found significant associations between inflammation and serum zinc concentrations in community-based populations while other studies reported no association [5, 10]. Some studies investigated the association between inflammation and serum copper concentration in hospitalized patients and adult volunteers [11–14]; but, to our knowledge, no study has assessed this association in apparently healthy children.

Approaches to the study of inflammation vary. The WHO/CDC recommends the measurement of at least one APP, such as C-reactive protein (CRP), alpha-1-acid glyco-protein (AGP), and alpha-1-antichymotrypsin, together with serum ferritin [15]. Several community-based studies measured CRP alone with different cutoff points [8]. Traditional methods can detect only CRP concentrations of >3 mg/L [16]. Most studies consider CRP of >10 mg/L as inflamed [5, 6], based on the fact that 99% of healthy adults have CRP of <10 mg/L [17]. Thurnham et al. suggested using the CRP cutoff of 5 mg/L because CRP values of >5 to 10 mg/L probably indicate mild inflammation [18]. The American Heart Association defines the risk of inflammation on cardiovascular diseases as average (CRP, 1 to 3 mg/L) and high (CRP, >3 mg/L) [19]. Abraham et al. demonstrated that inflammation may influence nutrient concentrations at levels as low as CRP (>0.6 mg/L; 75th percentile) [7]. The 60th and 75th percentiles of healthy US children and young adults were 0.5 and 1 mg/L, respectively [20]. Therefore, the use of lower CRP cutoffs may yield a better reference group of healthy individuals and improve the adjustment of nutrient concentrations

for inflammation. However, traditional methods can detect only CRP concentrations of >3 mg/L [16]

This paper aims to investigate associations between serum CRP and biomarkers of zinc, iron, and copper, and to assess effects of inflammation on nutrient concentrations and prevalence of low status where the associations are significant. We measured CRP concentration using a high-sensitive method with a detection limit as low as 0.1 mg/L [21], which permits the use of a wide range of CRP cutoffs to adjust for inflammation and to assess the magnitude of bias on specific nutrient biomarkers.

## Materials and Methods

### Study Design and Population

We analyzed data collected from school-aged children in a low-income community in Guatemala City, Guatemala in 2006 [22]. The study was a collaborative effort between the Hubert Department of Global Health at the Rollins School of Public Health, Emory University, Atlanta, GA, and the Institute of Nutrition of Central America and Panama (INCAP), Guatemala City. The study protocol was reviewed and approved by the ethics committees of both institutions.

We recruited children in grades 1–4 (6–11 years old) from five public schools in San José la Comunidad, a low-income area in Guatemala City, Guatemala. Exclusion criteria included any known severe illness affecting zinc status (e.g., sickle cell disease, cystic fibrosis, renal or liver disease, severe burns, or acrodermatitis enteropathica) [23], and other severe or chronic illness (e.g. cancer, diabetes, or seizures). Parental informed consent and child assent were obtained before data collection.

### Data Collection Procedures

Data were collected from February to April 2006. Blood samples were obtained between 9 a.m. and noon, approximately 2 h after eating. Following standard procedures, a nurse drew 7 mL of venous blood into trace element-free Vacutainers (Becton Dickinson, Franklin Lakes, NJ). One drop of blood was used to measure hemoglobin concentration with the use of the HemoCue® B-Hemoglobin machine (Hemocue Inc., Mission Viejo, CA). The remaining blood was quickly centrifuged at 2,500×g for 10 min at room temperature, aliquoted, refrigerated at the school, frozen in trace element-free cryogenic vials at −20° C at the INCAP in Guatemala City, then shipped in liquid nitrogen, stored at −70°C, and analyzed at the National Institute of Public Health (INSP) laboratories, Cuernavaca, Mexico.

Serum C-reactive protein was measured by a high-sensitive laser nephelometry with an antiserum specific for CRP (Behring Nephelometer 100 Analyzer, Behring Laboratories, Messer Grisheim Gmbh, Frankfurt, Germany). Serum zinc and copper concentrations were assessed with flame atomic absorption chromatography, using graphite furnace (Analyzer 300, Perkin Elmer Co Norwalk, CT, USA). Serum ferritin concentration was measured by an automated immune assay (Dade Behring Inc, Newark, DE 19714, USA). Serum alkaline phosphatase is a zinc-containing enzyme and thus, its activity is a functional indicator of zinc status; serum alkaline phosphatase activity was measured by the hydrolysis of $p$-nitrophenyl phosphate at 37°C (CE Human, Bisbaden, Germany). A substantial portion of plasma zinc is in albumin and thus this protein is a potential biomarker for zinc; serum albumin concentration was analyzed by a colorimetric method using kits from Human Gesellschah fur Biochemica und Diagnostica, Wiesbaden, Germany, using a spectrophotometer Prestige 24i (Tokyo Boeki Medical System, Tokyo, Japan). The accuracy of the determination was assessed by using certified material from the US National Institute of Standard and Technology and the UK National Institute of Biological Standard and

Control. Precision was assessed through duplicate measurements on 20% of the sample. The between-assay coefficients of variation for serum CRP, zinc, ferritin, copper, albumin, and alkaline phosphatase were 5.29%, 4.77%, 1.54%, 6.34%, 4.80%, and 3.43%, respectively.

### Definitions of Categorical Variables

Continuous variables were categorized using study-specific cutoffs or conventional definitions. Serum CRP concentrations were categorized into six intervals using cutoff points: 0.5, 1, 3, 5, and 10 mg/L. The values were based on previously suggested CRP cutoffs and the range of CRP values in normal healthy US children and young adults [5, 7, 18–20]. Low serum zinc level was defined as serum zinc concentration of <65 μg/dL [24–26]. Low serum ferritin level was defined as serum ferritin concentration of <15 μg/L as suggested by the WHO for the assessment of iron deficiency in children >5 years of age [15]. Low serum copper level was defined as serum copper concentration of <90 μg/L [27]. Anemia was defined as hemoglobin values <115 mg/L [15].

### Statistical Analyses

Only data from children with complete measurements for serum CRP and key outcome variables (i.e., serum zinc, ferritin, and copper concentrations) were analyzed. We assessed normality using the Kolmogorov–Smirnov test. Serum CRP and ferritin were not normally distributed. Continuous variables were reported as means (standard deviations) and medians with interquartile ranges (25th and 75th quartiles) for normal and non-normal distributions, respectively. Categorized variables were described as frequencies (percent). We assessed correlations between serum CRP and nutrient concentrations using Spearman's correlation coefficients. Significant correlations (i.e., serum CRP–ferritin concentrations and serum CRP–copper concentrations) were further explored. First, we stratified nutrient concentrations across categories of CRP levels (i.e., 0–0.5, >0.5–1, >1–3, >3–5, >5–10, and >10 mg/L). Global differences in nutrient concentrations among all levels were assessed by Kruskall-Wallis tests. Pairwise differences in concentrations between the CRP 0–0.5 mg/L levels and higher CRP levels were assessed by Wilcoxon tests. Next, for each CRP cutoff of 0.5, 1, 3, 5, and 10 mg/L, we defined a high CRP level and a low CRP level ( CRP cutoff vs. > CRP cutoff) and assessed differences in specific nutrient concentrations and the prevalence of low nutrient levels by Wilcoxon tests for continuous variables and Fisher's exact-tests for binary variables. Finally, we adjusted the specific nutrient concentrations using correction factors based on each CRP cutoffs, which are ratios of geometric means of the nutrients in the reference group to those in the elevated group [18]. We then calculated the averages of nutrient concentrations and their low nutrient prevalence using correction factors and compared them with those before adjustment or after exclusion of cases with CRP of >10 mg/L.

SAS version 9.2 (SAS institute) was used for all analyses. We used $P<0.05$ as the criterion of statistical significance. The resulting sample of 634 children allowed us to detect a correlation as low as 0.11 between CRP and any nutrient indicator, given a type-1 error α of 0.05, a power of 0.80, using POWER procedure in SAS 9.2 version.

## Results

### Characteristics of the Study Population

Six hundred and thirty-four children had complete data on serum CRP, zinc, ferritin, and copper and were included in the analysis. Half of the children (51%) were males and the mean (SD) age was 9.0 (1.2) years (Table 1). The prevalence of stunting was 15% (*n*=96), and the prevalence of serum zinc (<65 μg/dL), ferritin (<15 μg/dL), and copper (<90 μg/dL) was 21.0%, 2.1%, and 23.8%, respectively. Only two (0.3%) children had hemoglobin of

<11.5 g/dL, and none had serum albumin of <3.5 g/dL. The median (25th and 75th quartiles) serum CRP was 0.57 (0.26 and 1.59) mg/L. There were 17 (2.7%) and 47 (7.4%) children with CRP concentrations of <10 and <5 mg/L, respectively.

### Association between serum CRP concentration and biochemical concentrations

Serum CRP concentration was not associated with serum zinc, alkaline phosphatase, albumin, and hemoglobin concentrations ($P$>0.05) (Table 2). Serum CRP concentration, however, was associated with serum ferritin and copper concentrations ($r$=0.23 and 0.29, respectively, both $P$<0.0001).

### Associations Between Serum Ferritin and Copper Concentrations with CRP Levels

Stratified by CRP intervals, ferritin and copper concentrations gradually increased from the lowest to the highest CRP intervals (Table 3). Concentrations varied across CRP intervals ($P$<0.0001); higher CRP intervals had ferritin and copper concentrations higher than the lowest CRP interval (0–0.5 mg/L). Categorized into low and high CRP levels ( cutoff vs. > cutoff), high CRP levels had increased ferritin and copper concentrations compared with low CRP levels for any CRP cutoff from 0.5 to 10 mg/L ($P$<0.001) (Table 4).

Similar analyses using the prevalence of serum copper (<90 µg/dL) as the outcome also showed significant differences between high and low CRP levels ($P$<0.05), except for CRP of 10 mg/L (Table 5). However, there were no significant differences when the outcome was low serum ferritin prevalence of <15 µg/L ($P$>0.05).

### Adjustment of Ferritin and Copper Measurements by Correction Factors

We compared the medians and prevalence of serum ferritin and copper before and after adjustment for inflammation using different adjustment methods and CRP cutoffs (Table 6). Before any adjustment, the median concentrations of serum ferritin and copper were 47.4 µg/L and 101 µg/dL, respectively; the prevalence of ferritin (<15 µg/L) and copper (<90 µg/dL) were 2.1% and 23.8%, respectively. Exclusion of cases with extreme CRP values of >10 mg/L resulted in small changes (medians, 46.6 µg/L and 100.8 µg/dL and prevalence, 2.1% and 24.2%, respectively, for ferritin and copper). Adjustment by correction factors had a larger impact compared with the exclusion method; lower CRP cutoffs resulted in greater changes than higher CRP ones. The changes were maximal with the CRP 0.5 mg/L cutoff. Overall, adjustment for inflammation was negligible on iron status (low ferritin prevalence changed from 2.1% to 2.5%) but was substantial for copper status (low copper prevalence changed from 23.8% to 32.1%).

## Discussion

### Low Prevalence of Inflammation

In this sample of Guatemalan school children, only 2.7% and 7.4% of the children had elevated CRP concentrations of >10 and >5 mg/L, respectively. This may reflect a low risk of acute infections in this sample of apparently healthy 6- to 11-year-old urban children. Previous studies about inflammation recruited participants from populations at very high risk of infections. For example, some studies indicated 14.6% of Indonesian infants, 13.9% of Bangladeshi 3- to 7-year-old children, 23% of Peruvian 11- to 19-month-old children, and 50% of HIV-1 seropositive Kenyan adults with CRP of >10 mg/L [5, 28, 29]. These studies demonstrate an important effect of inflammation on average concentrations or prevalence of nutrient status, particularly serum ferritin [5, 6, 30].

## Problems with the Assessment of Serum CRP–Nutrient Associations

Even with high prevalence of elevated CRP levels, these studies have not detected significant linear associations (i.e., Pearson or Spearman's correlations) between serum CRP concentration and any trace nutrient concentrations [5, 6, 29, 30]. Few studies investigated the association between serum CRP concentration and nutrient concentrations [31]. One study reported non-significant correlations between serum CRP concentrations and ferritin or zinc concentrations in a sample of children with a very high prevalence of CRP of >10 mg/L (72%) [31]. Most studies investigated the associations between high CRP levels (e.g., >5 and >10 mg/L), not serum CRP concentrations, and the concentrations of serum zinc, ferritin, or copper [5, 6, 12, 18].

Lack of evidence for significant linear associations between serum CRP concentration and trace nutrient concentrations may be due to poor measurement of CRP concentrations. Two recent studies that reported significant correlations between plasma CRP and nutrient concentrations in infants and children used high-sensitive CRP methods [32, 33]. Traditional methods have low sensitivity and can detect only CRP concentrations of >3 mg/L [16]. Therefore, using a high-sensitive CRP method which can measure CRP concentration as low as 0.1 mg/L [34], one can test associations between CRP and nutrient biomarkers with greater precision.

## Associations of CRP with Nutrient Concentrations

In general, our findings agree with previous studies [6, 35, 36]. We found a null association between serum CRP and zinc concentrations. In apparently healthy children, previous studies observed that serum zinc concentrations were not different in young Peruvian children with signs, compared with no signs, of clinical infections [6]; in Guatemalan children with elevated white blood cells or sedimentation rate, compared with healthy children [35]; and in Zimbabwean school children with high CRP levels, compared with low CRP levels [36]. There was no association between serum CRP and zinc concentrations in low-income US children, although 72% had elevated CRP (>10 mg/L) [31]. Previous studies consistently observed high ferritin concentrations among apparently healthy children and adults with high CRP levels [5–7, 37]. Two studies reported significant correlations between plasma CRP and ferritin concentrations in infants and children [32, 33]. The positive association between serum CRP levels and copper concentrations has been demonstrated in many human populations, such as hospitalized patients [13, 14], adult volunteers [9, 38], healthy adults [11, 12], and children with clinical signs of infection [6]. However, the present study is the first to investigate the effect of inflammation on serum copper using high-sensitive CRP methods and to show a positive association between serum CRP and copper concentrations in apparently healthy children. However, serum copper is not a sensitive biomarker for copper status in marginal copper deficiency [39–41],

While studies measuring serum CRP by traditional CRP assay methods observed differences in ferritin concentrations between binary CRP levels dichotomized by CRP cutoffs of 10, 5, or 3 mg/L [5, 18, 28, 37], we observed significant differences in serum ferritin concentrations and copper concentrations between high CRP levels and low CRP levels, as low as 0.5 mg/L. In addition, we observed significant differences in low copper prevalence, but not in low ferritin prevalence between CRP levels, probably due to high prevalence of low copper levels in children (23.8% before adjustments) but very low prevalence of low ferritin levels (only 2.1% before adjustment). Therefore, in this population, only the prevalence of low copper needed adjustment.

### Implications

Our findings may have important implications for the assessments of iron and copper status. The use of low CRP cutoffs (e.g., 0.5 mg/L) may increase the ability to adjust for inflammation in apparent healthy children, especially when CRP is used as the only biomarker for inflammation. Thurnham et al. performed a meta-analysis to adjust ferritin concentrations for inflammation using 32 studies among children and adults ($n$=8,796 individuals) [18]. The authors suggested that compared with the reference subgroup with normal CRP and AGP (i.e., CRP of 5 mg and/or AGP of 1 g/L), the prevalence of iron deficiency was underestimated by 14% with no adjustment, 5% with adjustment for CRP of >5 mg/L, and 9% with adjustment for AGP of >1 g/L [18]. The results suggested that "the increase in ferritin was greater when CRP rather than AGP was increased" [18]. The use of lower CRP cutoffs (e.g., 0.5 mg/L) to define reference CRP subgroups can improve the estimation of prevalence of low ferritin levels. Because low reference CRP subgroups may not be "completely normal" with some individuals with inflammation, the ferritin concentrations in the reference subgroups may be elevated and therefore, the true prevalence of iron deficiency may still be underestimated.

### Limitations

This study is limited by the use of CRP as the single biomarker of inflammation, which is less sensitive in detecting inflammation in chronic infections [1]. Adjustment using only CRP may provide lower precision compared with using both CRP and AGP.

### Conclusions

CRP concentration was not associated with biomarker concentrations of zinc status (i.e., serum zinc, ALP, and albumin), but was related with serum ferritin and copper concentrations in apparently healthy school children. High CRP levels, defined by low cutoff points as low as 0.5 mg/L, can influence ferritin and copper concentrations. With very low risk of iron deficiency in the participants, the adjustment for inflammation had little influence on the prevalence of iron deficiency. The adjustment had a strong impact on the prevalence of low copper levels. High-sensitive CRP methods and the use of very low CRP cutoffs may be more accurate than traditional CRP methods in the adjustment of serum copper concentrations for inflammation in healthy school children. Further studies are required to compare the accuracy of using low CRP cutoffs with other methods, combining several APPs in the adjustment for inflammation

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**Table 1**

Demographic, nutritional, and biochemical characteristics of school children in Guatemala 2006 (*n*=634)

| Age (year) | 9.0 (1.2) |
|---|---|
| Gender | |
|    Boy | 322 (50.8%) |
|    Girl | 312 (49.2%) |
| Height-for-age Z-score | −0.64 (−1.25, 0.07) |
| Serum CRP (mg/L) | 0.56 (0.26, 1.54) |
|    CRP (<10 mg/L) | 17 (2.7%) |
|    CRP (<5 mg/L) | 47(7.4%) |
| Serum zinc (µg/dL) | 74.5 (66.5, 83.5) |
|    Zinc (<65 µg/dL) | 133 (21.0%) |
| Serum ferritin (µg/L) | 47.37 (33.84, 63.05) |
|    Ferritin (<15 µg/L) | 13 (2.1%) |
| Serum copper (µg/dL) | 101.04 (90.98, 110.81) |
|    Copper (<90 µg/dL) | 151 (23.8%) |
| Serum alkaline phosphatase (IU/L) | 555.5 (469.0, 625.7) |
| Serum albumin (g/L) | 58.9 (56.7, 61.8) |
| Hemoglobin (g/L) | 137.5 (132.5, 143.0) |

Values are mean (SD), median (25th and 75th), or number (%)

**Table 2**

Spearman's correlations between serum C-reactive protein and biochemical variables ($n$=634)

| Pair of variables | Spearman's coefficient | P |
|---|---|---|
| CRP–zinc | 0.05 | 0.23 |
| CRP–ferritin | 0.23 | <0.0001 |
| CRP–copper | 0.29 | <0.0001 |
| CRP–alkaline phosphatase | 0.03 | 0.5 |
| CRP–albumin | −0.01 | 0.77 |
| CRP–hemoglobin | 0 | 1 |

**Table 3**

Serum ferritin and copper concentrations within CRP intervals ($n$=634)

| CRP intervals | Number | Ferritin (μg/L) | Copper (μg/dL) |
|---|---|---|---|
| 0–0.5 mg/L | 285 | 44.5 (31.7, 57.4)[a] | 96.4 (86.8, 105.6)[a] |
| >0.5–1 mg/L | 137 | 44.9 (32.8, 64.0) | 103.4 (92.5, 113.1)[***] |
| >1–3 mg/L | 116 | 49.2 (34.9, 67.6)[*] | 104.0 (95.4, 113.4)[***] |
| >3–5 mg/L | 49 | 51.0 (40.6, 66.8)[**] | 105.0 (93.5, 112.4)[***] |
| >5–10 mg/L | 30 | 56.3 (40.4, 98.1)[***] | 106.9 (98.3, 113.1)[***] |
| >10 mg/L | 17 | 81.1 (62.7, 100.4)[***] | 111.2 (104.2, 119.0)[***] |
| $P^b$ | | <0.0001 | <0.0001 |

Values are median (25th and 75th percentiles)

[*] $P$<0.05;

[**] $P$<0.01;

[***] $P$<0.0001 ($P$ values by two-sample Wilcoxon tests)

[a] Reference group for pairwise comparison of ferritin and copper concentrations

[b] $P$ values by Kruskal–Wallis for global comparisons

**Table 4**

Serum ferritin and copper concentrations within groups defined by binary CRP levels (*n*=634)

| CRP levels | Low level | | High level | | $p^a$ |
|---|---|---|---|---|---|
| | *n* | Median (25th and 75th) | *n* | Median (25th and 75th) | |
| Ferritin (μg/L) | | | | | |
| 0.5 vs. >0.5 | 285 | 44.5 (31.7, 57.4) | 349 | 49.9 (36.4, 70.6) | <0.0001 |
| 1 vs. >1 | 422 | 44.6 (31.9, 59.9) | 212 | 51.8 (39.3, 73.0) | <0.0001 |
| 3 vs. >3 | 538 | 45.7 (32.5, 60.7) | 96 | 58.3 (42.0, 77.2) | <0.0001 |
| 5 vs. >5 | 587 | 46.5 (33.0, 61.4) | 47 | 64.1 (43.5, 100.4) | <0.0001 |
| 10 vs. >10 | 617 | 46.6 (33.3, 61.9) | 17 | 81.1 (62.7, 100.4) | <0.0001 |
| Copper (μg/dL) | | | | | |
| 0.5 vs. >0.5 | 285 | 96.4 (86.8, 105.6) | 349 | 104.8 (94.7, 113.2) | <0.0001 |
| 1 vs. >1 | 422 | 98.9 (88.1, 107.6) | 212 | 106.2 (95.6, 113.4) | <0.0001 |
| 3 vs. >3 | 538 | 100.3 (89.7, 109.4) | 96 | 107.4 (95.9, 113.7) | 0.0002 |
| 5 vs. >5 | 587 | 100.7 (90.1, 109.8) | 47 | 108.4 (98.3, 114.1) | 0.0003 |
| 10 vs. >10 | 617 | 100.8 (90.3, 110.1) | 17 | 111.2 (104.2, 119.0) | 0.004 |

[a] *P* values by Wilcoxon test for pairwise comparisons

**Table 5**

Prevalence of low serum ferritin and copper levels within groups defined by binary CRP levels (*n*=634)

| CRP levels (mg/L) | Low CRP leve | | High CRP level | | *p*[a] |
|---|---|---|---|---|---|
| | *n* total | *n* (%) | *n* total | *n* (%) | |
| Ferritin (<15 µg/L) | | | | | |
| 0.5 vs. >0.5 | 285 | 6 (2.1) | 349 | 7 (2.0) | 1 |
| 1 vs. >1 | 422 | 12 (2.8) | 212 | 1 (0.5) | 0.07 |
| 3 vs. >3 | 538 | 13 (2.4) | 96 | 0 (0) | 0.23 |
| 5 vs. >5 | 587 | 15 (2.2) | 47 | 0 (0) | 0.36 |
| Copper (<90 µg/dL) | | | | | |
| 10 vs. >10 | 617 | 13 (2.1) | 17 | 0 (0) | 0.7 |
| 0.5 vs. >0.5 | 285 | 96 (33.7) | 349 | 55 (15.8) | <0.0001 |
| 1 vs. >1 | 422 | 121 (28.7) | 212 | 30 (14.2) | <0.0001 |
| 3 vs. >3 | 538 | 137 (25.5) | 96 | 14 (14.6) | 0.02 |
| 5 vs. >5 | 587 | 146 (24.9) | 47 | 5 (10.6) | 0.03 |
| 10 vs. >10 | 617 | 149 (24.2) | 17 | 2 (11.8) | 0.39 |

[a] *P* values by Fisher exact tests

**Table 6**

Concentrations of serum ferritin and copper and the prevalence of their low levels before and after adjustment (*n*=634)

| | Ferritin (μg/L) | | | | Copper (μg/dL) | | | |
|---|---|---|---|---|---|---|---|---|
| | CF[a] | Median | GMC[b] | <15 μg/L (%) | CF[a] | Median | GMC[b] | <90 μg/dL (%) |
| Adjustment using CRP cutoff[a] | | | | | | | | |
| 0.5 mg/L | 0.85 | 43.0 | 42.4 | 2.5 | 0.93 | 97.0 | 95.7 | 31.2 |
| 1 mg/L | 0.82 | 43.8 | 43.4 | 2.4 | 0.94 | 99.1 | 97.6 | 27.3 |
| 3 mg/L | 0.74 | 45.3 | 44.4 | 2.2 | 0.95 | 100.5 | 98.7 | 25.1 |
| 5 mg/L | 0.67 | 46.4 | 45.1 | 2.1 | 0.93 | 100.7 | 99.0 | 24.6 |
| 10 mg/L | 0.54 | 46.5 | 45.7 | 2.1 | 0.91 | 100.9 | 99.3 | 24.1 |
| Excluding CRP (>10 mg/L) | | 46.6 | 45.7 | 2.1 | | 100.8 | 99.3 | 24.2 |
| No adjustment | | 47.4 | 46.9 | 2.1 | | 101.0 | 99.5 | 23.8 |

[a] Adjustment by multiplying the measures in higher CRP levels with correction factor (CF=ratio of the geometric means of lower CRP level by higher CRP level) for each CRP cutoff

[b] Geometric mean concentration