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The association of biomarkers of iron status with mortality in US adults

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Abstract *Background and Aims:* Elevated iron biomarkers are associated with diabetes and other cardiometabolic abnormalities in the general population. It is unclear whether they are associated with an increased risk of all-cause or cause-specific mortality. The purpose of the current analysis was to evaluate the association of ferritin and transferrin saturation levels with all-cause, cardiovascular, and cancer mortality in the general US adult population.
Methods and Results: A prospective cohort study was conducted with 12,258 adults participating in the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of the US population. Study participants were recruited in 1988–1994 and followed through December 31, 2006 for all-cause, cardiovascular disease, and cancer mortality. The multivariable-adjusted hazard ratios (95% confidence interval) for all-cause mortality comparing the fourth versus the second quartiles of ferritin and transferrin saturation were 1.09 (0.82–1.44; p-trend across quartiles = 0.92) and 1.08 (0.82–1.43; p-trend across quartiles = 0.62), respectively, for men, 1.43 (0.63–3.23; p-trend across quartiles = 0.31) and 1.48 (0.70–3.11; p-trend across quartiles = 0.60), respectively, for premenopausal women, and 1.03 (0.79–1.34; p-trend across quartiles = 0.95) and 1.17 (0.92–1.49; p-trend across quartiles = 0.63), respectively, for postmenopausal women. Quartile of ferritin and transferrin saturation also showed no association between biomarkers of iron status and mortality.
Conclusions: In a large nationally representative sample of US adults, within the spectrum of normal iron metabolism, ferritin and transferrin saturation were not associated with risk of

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mortality among people who were not taking iron supplements and did not have a baseline history of cardiovascular disease or cancer.

Introduction

Iron has a catalytic role in the generation of highly reactive oxygen species, such as hydroxyl radical, through Fenton and Haber—Weiss reactions [1]. As a result, elevated iron levels, below the levels found in genetic hemochromatosis, may have a role in a variety of disease processes. Body iron stores can be estimated using serum ferritin and previous studies have found that elevated ferritin levels, below the levels found in genetic hemochromatosis, are associated with diabetes, metabolic syndrome, hypertension, dyslipidemia, elevated fasting insulin and glucose, and abdominal adiposity [2—4]. The association of ferritin and other biomarkers of iron metabolism with mortality, however, remains controversial. Few studies are available investigating the association between iron biomarkers and mortality, and those studies are particularly limited in their ability to investigate this association in non-white populations [5—7].

The purpose of the current analysis was to evaluate the association of ferritin and transferrin saturation levels with all-cause, cardiovascular, and cancer mortality in the general US adult population. To do so, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) Mortality Study, a cohort study based on a nationally representative sample of US adults with ferritin and transferrin saturation measured in 1988—1994 and followed for mortality through December 31, 2006.

Methods

Study population

NHANES III was a stratified, multistage probability survey designed to be representative of the civilian non-institutionalized US population [8]. Overall, 18,825 adults ≥20 years of age completed the NHANES III interview and examination. We excluded 859 participants who were taking iron supplements, 227 pregnant women, 34 participants with likely hemochromatosis (serum iron >190 ug/dL for men and >175 ug/dL for women, serum ferritin >300 ng/mL for men and >200 ng/mL for women, and transferrin saturation >60%), 1347 participants with a self-reported history of cardiovascular disease at baseline, 588 participants with a self-reported history of cancer at baseline, 126 participants ≥90 years of age, 21 participants missing follow-up information, 2156 participants missing data for ferritin, 37 missing data for transferrin saturation, 210 missing data for income, 73 missing data for education, 507 missing data for alcohol use, 20 missing data for body mass index, 19 missing data for blood pressure, 32 missing data for diabetes, 55 missing data for total cholesterol, 87 missing data for HDL-cholesterol, and 169 missing data for estimated glomerular filtration rate. A total of 12 258 NHANES III participants were thus available for the current analyses.

All participants gave written informed consent. The National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board approved the protocol for NHANES III.

Baseline data collection

Baseline data for NHANES III were collected during an in-home interview and a subsequent visit to a mobile examination center. A detailed description of all data collection methods is available elsewhere [8]. During the in-home interview, a standardized questionnaire was used to collect demographic and health-related information including age, race-ethnicity, and sex. Additional questionnaire data collected included education, household income, smoking status, alcohol consumption, menopause status (women who reported not menstruating in the previous 12 months were considered postmenopausal), and use of vitamin C supplementation, aspirin, antihypertensive, lipid lowering medication, or hormone replacement therapy (among postmenopausal women).

Weight and height were measured and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. We averaged all blood pressure measurements including three measurements during the in-home interview and three additional measurements during the visit to the mobile examination center. Plasma glucose was measured using an enzymatic reaction and we defined diabetes mellitus as fasting plasma glucose ≥126 mg/dL, non-fasting plasma glucose ≥200 mg/dL, and/or a self-reported history of diabetes with concurrent use of antidiabetes medication. Total cholesterol was quantified enzymatically. High density lipoprotein (HDL) cholesterol was measured after other lipoproteins were precipitated with a polyanion/divalent cation mixture. C-reactive protein (CRP) was measured using latex-enhanced nephelometry, a low-sensitivity assay. Serum creatinine was measured using a kinetic rate Jaffe method. We determined estimated glomerular filtration rate (eGFR) using the Modification of Diet and Renal Disease equation after aligning serum creatinine concentrations with the assay used in the development of the equation [9,10].

Ferritin was measured by a single-incubation two-site immunoradiometric assay (Bio-Rad Laboratories, Hercules, CA). The limit of detection was 3 ng/mL and participants with a concentration below the limit of detection ($n = 6$) were assigned a value of 2 ng/mL. The inter-assay coefficient of variation ranged from 2.2% to 12.1%. Serum iron and total iron-binding capacity were measured by a modification of the automated AAII-25 colorimetric methods using an Alpkem rapid flow analysis system (Alpkem, Inc, Clackamas, OR). The limits of detection for iron and total iron-binding capacity were 3 ug/dL and 1 ug/dL, respectively. There were no participants with iron or total iron-binding capacity below the limits of detection. The inter-assay coefficients of variation ranged from 2.0% to