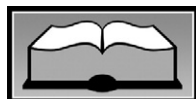


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# Nutrient Intake and Anemia Risk in the Women's Health Initiative Observational Study

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## ABSTRACT

**Background** Nutrient-related anemia among postmenopausal women is preventable; recent data on prevalence are limited.

**Objective** To investigate the association between nutrient intakes and anemia prevalence, in relation to both incidence and persistence, in a longitudinal sample of postmenopausal women. We hypothesized that anemia prevalence, incidence, and persistence would be greater among women reporting lower intake of vitamin B-12, folate, and iron.

**Design** Prospective cohort analysis.

**Participants/setting** The observational cohort of the Women's Health Initiative, including 93,676 postmenopausal women, aged 50 to 79 years, who were recruited across the United States at 40 clinical study sites. Women were enrolled between 1993 and 1998; data collection for these analyses continued through 2000.

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**Main outcome measures** Anemia was defined as a blood hemoglobin concentration of <12.0 g/dL (120.0 g/L). Persistent anemia was defined as anemia present at each measurement time point. Diet was assessed by food frequency questionnaire for iron, folate, B-12, red meat, and cold breakfast cereal; inadequacies were based on dietary reference intakes for women older than age 50 years.

**Statistical analysis** Descriptive statistics (mean±standard deviation) were used to characterize the population demographics, anemia rates, and diet. Unconditional logistic regression was used to investigate associations between diet and incident and persistent anemia. Associations are presented as odds ratio and 95% confidence intervals.

**Results** Anemia was identified in 3,979 (5.5%) of the cohort. Inadequate intakes of multiple anemia-associated nutrients were less frequent in non-Hispanic whites (7.4%) than other race/ethnic groups (inadequacies demonstrated in 14.6% to 16.3% of the sample). Age, body mass index, and smoking were associated with anemia. Women with anemia reported lower intakes of energy, protein, folate, vitamin B-12, iron, vitamin C, and red meat. Multiple (more than a single nutrient) dietary deficiencies were associated with a 21% greater risk of persistent anemia (odds ratio 1.21, 95% confidence interval 1.05 to 1.41) and three deficiencies resulted in a 44% increase in risk for persistent anemia (odds ratio 1.44, 95% confidence interval 1.20 to 1.73).

**Conclusions** Inadequate nutrient intake, a modifiable condition, is associated with greater risk for anemia in postmenopausal women participating in the Observational Study of the Women's Health Initiative. Efforts to identify and update incidence estimates for anemia-associated nutrient deficiencies in aging women should be undertaken.

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**A**nemia is a relatively common health problem in the older population of the United States and is associated with increased mortality (1) and more frequent hospitalization (2). The World Health Organization defines anemia as a hemoglobin concentration of <13.0 g/dL (130 g/L) in men, and <12.0 g/dL (120 g/L) in women (3). Using this criteria and the third National Health and Nutrition Examination Survey (NHANES) dataset, researchers found anemia to be present in >10% of those aged 65 and older; this prevalence parallels that seen in other aging adults (1,4-7).

Nutritional anemia includes those associated with prolonged inadequate intake of folate, vitamin B-12, iron, protein, and vitamin C (8,9). Elderly women may be at an increased risk for inadequate micronutrient intake (10). Inadequate nutrient intake is commonly the result of health symptoms such as poor dentition (reduced red meat consumption resulting in reduced iron and vitamin B-12 intake), reduced appetite (resulting in general reduction in all nutrients) and reduced tolerance of milk products (a moderate source of vitamin B-12). In addition, a loss of intrinsic factor with aging is a well-characterized indirect cause of nutritional anemia.

Anemia of nutritional etiology is generally, but not always (as may be in the case in individuals with obesity with underlying inflammation and alterations in iron metabolism) (11), responsive to diet modification. Achieving adequacy in intake of anemia-associated nutrients could either reduce risk for or correct prevalence and severity of nutritional anemia. Further, correction of anemia would in turn reduce or eliminate the associated morbidity (12,13).

In addition to anemia of nutritional etiology, non-nutritional anemia is common in aging women. This includes anemia associated with inflammation in which elevated pro-inflammatory cytokines decrease iron bioavailability, thus inhibiting the hematopoietic response (14,15). Chronic illnesses and anemia of unknown etiology (16,17), as well as blood loss (18), are also thought to be other primary causes of microcytic anemia in aging populations.

A better understanding of the dietary factors associated with anemia in an ethnically diverse population of postmenopausal women is an important first step for supporting preventive and therapeutic approaches. The Women's Health Initiative Observational Study (WHI-OS) cohort affords an important opportunity to re-examine anemia in aging women with a focus on potential dietary etiologies for reduced hemoglobin concentrations. Further, the sample population provides specific information across diverse ethnicities and races. Baseline dietary intake data are available for the 93,676 WHI-OS participants in order to evaluate these associations. The primary objective of this article is to update available evidence investigating the association between self-reported nutrient intakes and anemia prevalence; secondarily, we prospectively investigated the risk of incident and persistent anemia associated with dietary intake. The hypothesis for this investigation was that the prevalence, incidence, and persistence of anemia would be greater among postmenopausal women reporting low vitamin B-12, folate, or iron intake at the time of study enrollment, relative to women with adequate intake of

these nutrients (as defined by Dietary Reference Intakes), after controlling for confounding factors. Further, it was hypothesized that a greater number of dietary inadequacies of these nutrients would be associated with a greater risk for incident and persistent anemia at Year 3 of the study.

## METHODS

### Study Population

This study includes postmenopausal women enrolled in the WHI-OS. This observational cohort was recruited across 40 clinical research sites nationally from 1993-1997 (19). The majority of women were recruited through mail or newspaper advertisements, although a wide range of recruitment approaches were employed. Each recruitment site obtained Institutional Review Board approval and all participants provided written informed consent. The consent process was completed between the participant and local study coordinator during an on-site clinic visit. The WHI-OS population evolved from the screening cohort of women found to be either ineligible or uninterested in the clinical trials portion of WHI in addition to women recruited explicitly for the WHI-OS. At the time of enrollment, women ranged in age from 50 to 79 years. Women were excluded from participation if they had a medical condition with <3 years life expectancy, if they were currently enrolled in another intervention trial, or if health habits or diagnosis diminished the women's ability to provide informed consent or study data (eg alcoholism or dementia). Given the well-documented associations between non-nutrient-deficiency anemia and certain chronic diseases (20-24), participants with a history of myocardial infarction, congestive heart failure, rheumatoid arthritis, lupus, and any cancer were excluded from these analyses. Exclusion for renal disease was not necessary because no participants with renal disease were enrolled in the WHI. Participants lacking baseline hemoglobin data were also excluded.

Participants without baseline dietary data and those reporting extreme energy intakes were identified and excluded using a two-part scheme: all extreme outliers (those reporting <300 kcal or >7,000 kcal daily) were excluded; moderate outliers were excluded when their reported energy intakes changed by more than 50% between baseline and Year 3 (those reporting 300 to 499.99 kcal with >50% change, or 5,000 to 7,000 kcal with >50% change). Cut-off points were based on natural breaks in the data, as determined by visual inspection of energy distribution plots.

This prospective analysis required the availability of Year 3 hemoglobin data. To ensure consistency between analyses and simplicity of design, the same WHI-OS participants were included in the cross-sectional analysis of baseline dietary intake and anemia prevalence.

### Anemia Assessment

In this study, anemia was defined according to the World Health Organization definition as a baseline hemoglobin concentration <12.0 g/dL (<120.0 g/L) (3). Incident anemia (newly diagnosed) was defined by a reduction in hemoglobin from values  $\geq 12.0$  g/dL ( $\geq 120.0$  g/L) at base-

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