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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.

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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Anemia 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 ≥12.0 g/dL (≥120.0 g/L) at base-

line to values <12.0 g/dL (<120.0 g/L) at Year 3. Women were alternately categorized as having persistent anemia (hemoglobin <12.0 g/dL [<120.0 g/L] at baseline and Year 3) or resolved anemia in cases where hemoglobin increased to >12.0 g/dL (>120.0 g/L) from a baseline value <12.0 g/dL (<120.0 g/L). Women could also be categorized as not having anemia (incident or persistent). Hemoglobin concentrations were assessed as part of the complete blood count measured at baseline and again at the 3-year clinic visit from 12-hour fasting blood samples.

Dietary Intake

Dietary intake was collected from study participants at baseline and Year 3 using a food frequency questionnaire (FFQ) developed and validated by the Fred Hutchinson Cancer Research Center. This questionnaire was specifically designed for the WHI to include foods representative of the national food supply (25) and to capture regional and ethnic food selections. The questionnaire includes 122 food lines and asks respondents to indicate the portion consumed as well as the frequency of consumption using a Likert-type scale referencing food intake patterns over the previous 3-month period. Nutrient intake was derived from a Fred Hutchinson Cancer Research Center-designed specialty software program that utilizes the Nutrition Data System for Research food and nutrient database (26). A validation study suggested that the energy-adjusted anemia-associated nutrient intake correlations between FFQ and 8-day food records collected from WHI study participants were 0.2 for vitamin B-12, 0.5 for folate, 0.3 for vitamin C, and 0.6 for iron (26). WHI-OS participants completed the FFQ at baseline during the screening period and each questionnaire was reviewed for completeness by the WHI site coordinator before being forwarded to the WHI Coordinating Center for analysis. It is important to note that the baseline FFQ data were collected between 1993 and 1998 and reflect folic acid intake before the mandatory fortification date; data were analyzed using annual US Department of Agriculture database estimates for folic acid and folate as well as other nutrients.

Dietary exposure variables of interest included vitamin B-12, folate, iron, vitamin C, animal protein intake, vegetable protein intake, red meat intake, and fortified cereal intake (iron, folic acid). Dietary inadequacy was defined as below Dietary Reference Intakes for individual nutrients based on intake recommendations for women older than age 50 years. Use of supplemental nutrients including multivitamins, B-complex vitamins, and individual nutrient supplementation including iron, vitamin B-12 and folic acid were also evaluated. In addition to evaluating individual nutrient intake, analyses were performed for combined nutrient inadequacies. In these models, each intake for an individual nutrient below the Recommended Dietary Allowance was summed to determine the association between quantity of individual nutrient inadequacy and anemia.

Statistical Analysis

Baseline characteristics of the study participants are presented as mean±standard deviation or frequencies (%) by anemia group. To compare women with baseline anemia vs those without baseline anemia, t tests and χ^2 tests were conducted for continuous and categorical variables, respectively. Adjusted and unadjusted mean nutrient intakes were calculated by anemia status; adjusted means were calculated using linear prediction, and means were adjusted for age category (50 to 59, 60 to 69, and 70 to 79 years), ethnicity, smoking status (nonsmoker, former smoker, or current smoker) and income category (<$10,000, $10,000 to $19,999, $20,000 to $34,999, $35,000 to $49,999, $50,000 to $74,999, $75,000 to $99,999, $100,000 to $149,999, and ≥$150,000).

Unconditional logistic regression was used to investigate the association of inadequate nutrient intake, servings of selected food groups, and the number of anemia-associated dietary micronutrient inadequacies at baseline with both incident and persistent anemia. In investigating the association between the anemia-associated dietary micronutrient inadequacies, the data were assessed two ways: first, the number of inadequacies was treated as a categorical variable to allow for nonlinearity in the association with anemia; second, the number of inadequacies was treated as a continuous variable to test for trend if the categorical analysis suggested a possible linear association. Both crude and adjusted logistic regression models were conducted: adjusted models included indicator variables for category of age (50 to 59, 60 to 69, and 70 to 79 years), race/ethnicity (American Indian or Alaskan native, Asian or Pacific islander, black or African American, Hispanic/Latino, white [non-Hispanic], and other), smoking status (nonsmoker, former smoker, or current smoker) and income (<$10,000, $10,000 to $19,999, $20,000 to $34,999, $35,000 to $49,999, $50,000 to $74,999, $75,000 to $99,999, $100,000 to $149,999, and ≥$150,000) as well as body mass index (BMI; calculated as kg/m^2) as a continuous variable. Confounders were selected a priori based on plausibility and previous literature and included BMI, age range, race/ethnicity, smoking, and income.

For each of the five anemia-related nutrients (ie, folate, iron, vitamin B-12, vitamin C, and protein), multiplicative interaction terms between race/ethnicity and nutrient inadequacy were created to assess if the association between anemia and a given nutrient varies by race/ethnicity. Specifically we used the likelihood ratio test to determine whether the addition of this interaction term significantly improved any of the adjusted models. Because this required testing for an interaction with ethnicity in five separate models (one for each of the anemia-related nutrients), the Bonferroni adjustment was used to account for multiple comparisons; thus, the level of significance required in any model was equal to α/n, where α was set to .05 and n=5, the number of tests. All analyses were performed with Stata statistical software (version 10.1 [2007] and 11.1 [2009], Statacorp, College Station, TX).

RESULTS

Of the 93,676 women enrolled in the WHI-OS, 18,733 were excluded from the analytical cohort due to previous diagnosis of chronic disease, 1,484 were excluded due to extreme energy reporting, and 626 were excluded due to missing hemoglobin or baseline diet data. Of the 72,833

Table 1. Demographic characteristics of Women's Health Initiative Observational Study participants by anemia status

	No Anemia		Anemia[a]	
Variable	**n**	**%**	**n**	**%**
Total	68,854	94.5	3,979	5.5
Age at screening*	63.2	7.3	63.5	7.6
Education**				
Some high school or less (≤11 y)	3,098	4.5	265	6.7
High school diploma or equivalent	11,013	16.1	672	17.0
College or vocational school	54,220	79.3	3,016	76.3
Family income*				
<$10,000	2,336	3.5	236	6.2
$10,000-$34,999	21,447	32.6	1,296	34.3
$35,000-$99,999	32,596	49.5	1,745	46.1
>$100,000	7,451	11.3	369	9.8
Don't know	2,008	3.0	137	3.6
Ethnicity**				
American Indian or Alaskan native	270	0.4	20	0.5
Asian or pacific islander	2,124	3.1	94	2.4
Black or African American	4,533	6.6	880	22.2
Hispanic/Latino	2,638	3.8	156	3.9
White not of Hispanic origin	58,342	85.0	2,759	69.6
Other	760	1.1	56	1.4
Body mass index	27.1	5.7	27.0	6.2
Body mass index category**				
Underweight (<18.5)	794	1.2	54	1.4
Normal (18.5-24.9)	27,622	40.6	1,725	43.8
Overweight (25.0-29.9)	23,393	34.4	1,229	31.2
Obesity I (30.0-34.9)	10,398	15.3	537	13.6
Obesity II (35.0-39.9)	3,687	5.4	215	5.5
Extreme obesity III (≥40)	2164	3.2	178	4.5
Height**	161.8	6.7	161.0	6.8
Weight***	71.3	16.4	70.4	17.2
Smoking status**				
Never smoked	34,915	51.4	2,115	54.1
Past smoker	28,781	42.4	1,649	42.1
Current smoker	4,217	6.2	149	3.8
	← *mean±standard deviation* →			
Hemoglobin (g/dL)**	13.6±0.9		11.3±1.0	
Hematocrit (%)**	40.3±3.0		34.5±3.0	
White blood cell (×10^9 cells)	6.2±12.3		5.9±15.4	

[a]Anemia defined by World Health Organization definition of hemoglobin <12.0 g/dL. To convert g/dL hemoglobin to g/L, multiply g/dL by 10.0. To convert g/L hemoglobin to g/dL, multiply g/L by 0.1. Hemoglobin of 12.0 g/dL=120.0 g/L.
*$P<0.05$.
**$P<0.001$.
***$P<0.01$.

women in the analytical cohort, 3,979 cases of baseline anemia were identified representing 5.5% of the WHI-OS study population (Table 1). Anemia was higher in women of advanced age (>63.5 years) and current smokers and inversely associated with education, income, and body weight (Table 1). BMI showed a U-shaped association with anemia risk. Race/ethnicity also was associated with anemia, with 16.3% of the 5,413 African Americans having hemoglobin <12.0 g/dL (<120.0 g/L) and rates of 5.6%, 4.5%, and 4.2% in Hispanic/Latino, non-Hispanic whites, and Asians, respectively. Hemoglobin concentrations were normally distributed across the population.

Table 2 shows the average dietary intake at baseline among WHI-OS women categorized by anemia status. As shown, lower reported intake of most nutrients was demonstrated for women diagnosed with either incident or persistent anemia. Higher mean dietary intakes of energy, protein, folate, vitamin B-12, iron, and vitamin C as well as red meat were reported in women without anemia as compared to those with anemia. Supplemental iron and vitamin B-12 were greater in women with anemia. Multivitamin use was not different by anemia group.

Given that poor diets may be associated with multiple nutrient deficiencies and that inadequacies in dietary intake may present differently across racial/ethnic groups, frequency of multiple deficiencies for iron, folate and vitamin B-12 by race/ethnicity were also evaluated (Table 3). At baseline, the majority of WHI-OS women demonstrate intake of anemia-associated nutrients at levels meeting requirements of nutritional adequacy. However, non-Hispanic whites were less likely to report multiple inadequacies compared to other racial/ethnic groups. Only 7.4% of non-Hispanic whites reported inadequacies in all three nutrients while 15.2% of Native Americans/Alaskans, 14.6% Asian/Pacific Islanders, 15.3% of African Americans, and 16.3% of Hispanic/Latinos reported all three nutrient inadequacies.

The odds ratios (ORs) for incident and persistent anemia in relation to dietary inadequacies in intake of folate, iron, vitamin B-12, vitamin C, and protein are presented in Table 4. Inadequate intakes of each of the evaluated nutrients at baseline were associated with increased risk of both incident and persistent anemia, with the associations tending to be stronger with persistent anemia than with incident anemia. An evaluation of anemia risk in relation to red meat (as an indicator of heme iron) vs fortified cold breakfast cereals (as a source of nonheme iron and/or folic acid) showed that greater red meat consumption was marginally associated with lower risk of persistent anemia (OR 0.89; 95% confidence interval [CI] 0.79 to 1.01) whereas fortified cold breakfast cereal was not (Table 5). These associations were attenuated when adjusted for covariates.

Modeling the association of the total number of inadequate nutrient intakes including iron, folate, and vitamin B-12 at baseline with anemia suggests that a single nutrient inadequacy is associated with a significant increase in risk (Table 6). Tests for trends detected significantly increased risk of baseline, incident, and persistent anemia with additional baseline dietary deficiency. Specifically, any dietary deficiency at baseline was associated with an 18% greater risk of baseline anemia (dietary deficiency OR 1.18; 95% CI 1.08 to 1.29); a 10% (OR 1.10;

Table 2. Reported baseline nutrient intakes using food frequency questionnaire data in Women's Health Initiative Observational Study women, according to anemia[a] status; adjusted for body mass index, age, ethnicity, smoking status, and income

Dietary variable	No anemia	Incident anemia[b]	Persistent anemia[c]
	← *mean± standard deviation* →		
Dietary energy (kcal)*	1,546.7±580.4	1,517.0±581.4	1,473.3±584.8
Dietary total carbohydrate (g)*	201.3±77.0	197.1±77.2	192.3±77.6
Dietary protein (g)*	65.3±26.6	63.7±26.6	61.2±26.8
Ratio of animal to vegetable protein**	2.4±1.2	2.4±1.2	2.4±1.2
Dietary folate equivalents (μg)*	487.9±206.2	478.6±206.6	470.1±207.8
Dietary iron (mg)*	12.4±5.3	12.1±5.3	11.8±5.4
Dietary vitamin B-12 (μg)*	5.7±3.3	5.5±3.3	5.4±3.3
Dietary vitamin C (mg)*	104.6±56.0	101.8±56.1	98.3±56.4
Supplemental folic acid (μg)	207.8±259.2	206.8±259.7	205.4±261.2
Supplemental iron (mg)*	8.6±21.2	11.4±21.3	11.9±21.4
Supplemental vitamin B12 (μg)***	16.9±75.5	19.1±75.6	22.4±76.1
Supplemental vitamin C (mg)	330.8±658.7	310.6±659.9	324.4±663.7
Total dietary folate equivalents**	602.2±252.4	592.3±252.9	583.1±254.3
Total iron at baseline*	21.0±21.9	23.5±21.9	23.7±22.0
Total vitamin B-12 at baseline**	22.5±75.5	24.6±75.7	27.7±76.1
Total vitamin C	435.4±663.4	412.4±664.6	422.6±668.4
Cold cereal, medium servings/d	0.4±0.4	0.4±0.4	0.4±0.4
Red meat, medium servings/d*	0.6±0.5	0.6±0.5	0.6±0.5
	n **%**	**n** **%**	**n** **%**
Multivitamin without minerals			
Yes	2,244 4.2	116 4.3	60 4.2
No	51,419 95.8	2,605 95.7	1,374 95.8
Multivitamin with minerals			
Yes	20,835 38.8	1,059 38.9	522 36.4
No	32,828 61.2	1,662 61.1	912 36.4
Cold cereal, fortified			
Yes	7,022 15.1	400 14.7	193 15.9
No	39,516 84.9	2,321 85.3	1,016 84.1

[a]Anemia defined by World Health Organization definition of hemoglobin <12.0 g/dL. To convert g/dL hemoglobin to g/L, multiply g/dL by 10.0. To convert g/L hemoglobin to g/dL, multiply g/L by 0.1. Hemoglobin of 12.0 g/dL=120.0 g/L.
[b]Incident anemia (newly diagnosed) is defined by a reduction in hemoglobin from values ≥12.0 g/dL at baseline to values <12.0 g/dL at Year 3.
[c]Persistent anemia is defined as hemoglobin <12.0 g/dL at baseline and Year 3.
*$P<0.001$.
**$P<0.05$.
***$P<0.01$.

Table 3. Racial and ethnic differences in the number and percent of the sample population of the Women's Health Initiative Observational Study (n=72,632) reporting dietary nutrient inadequacies of folate, iron, and vitamin B-12

No. of nutrient inadequacies	American Indian or Native Alaska		Asian or Pacific Islander		Black or African American		Hispanic/ Latino		White (Not Hispanic)		Other		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	144	49.79	1,169	52.7	2,338	43.2	1,324	47.4	37,653	53.1	433	53.1	43,061	59.3
1	54	18.6	345	15.6	1,128	20.8	506	18.1	10,701	17.5	152	18.6	12,886	17.7
2	48	16.6	380	17.1	1,120	20.7	508	18.2	8,250	13.5	124	15.2	10,430	14.4
3	44	15.2	324	14.6	827	15.3	456	16.3	4,497	7.4	107	13.1	6,255	8.6
Total	290		2,218		5,413		2,784		61,101		816		72,632	

NOTE: Information from this table is available online at www.adajournal.org as part of a PowerPoint presentation.

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for incident and persistent anemia, relative to no anemia[a] (n=53,663), associated with inadequate of dietary intake of select nutrients as reported by food frequency questionnaire completed at baseline by participants in the Women's Health Initiative Observational Study

	Incident Anemia[b] (n=2,721)		Persistent Anemia[c] (n=1,434)	
Nutrient	**Crude**	**Adjusted[d]**	**Crude**	**Adjusted[d]**
	← *OR (95% CI)* →			
Dietary folate equivalents <400 μg	1.20 (1.11-1.30)	1.12 (1.03-1.21)	1.46 (1.32-1.63)	1.26 (1.13-1.41)
Dietary iron <8 mg	1.23 (1.13-1.35)	1.13 (1.02-1.24)	1.56 (1.38-1.75)	1.32 (1.16-1.49)
Dietary vitamin B-12 <2.4 μg	1.25 (1.12-1.40)	1.16 (1.03-1.30)	1.56 (1.35-1.80)	1.28 (1.10-1.49)
Dietary vitamin C <75 mg	1.08 (0.99-1.17)	1.09 (1.00-1.19)	1.24 (1.12-1.39)	1.25 (1.11-1.40)
Dietary protein <0.8 g/kg	1.18 (1.10-1.28)	1.07 (0.98-1.16)	1.43 (1.29-1.59)	1.22 (1.08-1.36)
Dietary protein <0.8 g/kg (energy adjusted)	1.12 (1.02-1.24)	0.99 (0.89-1.11)	1.21 (1.06-1.39)	1.05 (0.90-1.22)

[a]No anemia as defined by World Health Organization definition of hemoglobin ≥12.0 g/dL. To convert g/dL hemoglobin to g/L, multiply g/dL by 10.0. To convert g/L hemoglobin to g/dL, multiply g/L by 0.1. Hemoglobin of 12.0 g/dL=120.0 g/L.
[b]Incident anemia (newly diagnosed) is defined by a reduction in hemoglobin from values ≥12.0 g/dL at baseline to values <12.0 g/dL at Year 3.
[c]Persistent anemia is defined as hemoglobin <12.0 g/dL at baseline and Year 3.
[d]Adjusted for body mass index, age range, race/ethnicity, smoking status, and income.
NOTE: Information from this table is available online at www.adajournal.org as part of a PowerPoint presentation.

Table 5. Odds ratios (ORs) and 95% confidence intervals (CIs) for incident and persistent anemia, relative to no anemia[a] (n=53,663), in participants in the Women's Health Initiative Observational Study associated with each additional serving of selected food groups

	Incident Anemia[b] (n=2,721)		Persistent Anemia[c] (n=1,434)	
Food group	**Crude**	**Adjusted[d]**	**Crude**	**Adjusted[d]**
	← *OR (95% CI)* →			
Red meat	0.95 (0.88-1.03)	0.98 (0.90-1.06)	0.82 (0.73-0.92)	0.89 (0.79-1.01)
Fortified cold cereal	0.95 (0.85-1.07)	0.97 (0.86-1.09)	1.04 (0.89-1.21)	1.07 (0.91-1.26)

[a]No anemia as defined by World Health Organization definition of hemoglobin ≥12.0 g/dL. To convert g/dL hemoglobin to g/L, multiply g/dL by 10.0. To convert g/L hemoglobin to g/dL, multiply g/L by 0.1. Hemoglobin of 12.0 g/dL=120.0 g/L.
[b]Incident anemia (newly diagnosed) is defined by a reduction in hemoglobin from values ≥12.0 g/dL at baseline to values <12.0 g/dL at Year 3.
[c]Persistent anemia is defined as hemoglobin <12.0 g/dL at baseline and Year 3.
[d]Adjusted for body mass index, age range, race/ethnicity, smoking status, and income.

95% CI 0.99 to 1.22) greater risk of incident anemia and a 21% (OR 1.21; 95% CI 1.05 to 1.41) greater risk of persistent anemia, respectively. Total nutrient deficiencies were also associated with increased anemia risk, most substantially in relation to the demonstrated 34% increased risk for persistent anemia (OR 1.34; 95% CI 1.14 to 1.56), a risk elevation that reached 56% when three deficiencies were present (OR 1.56; 95% CI 1.25 to 1.95).

Discussion

This study of diet and anemia represents one of the largest assessments of anemia and dietary intake among postmenopausal women. The findings demonstrate that anemia-associated nutrient inadequacies are not uncommon in postmenopausal women regardless of race/ethnicity and that select racial groups, such as African Americans, are at an elevated risk for diet-associated anemia as compared to non-Hispanic whites. These data also suggest that inadequacy in several nutrients, compared to a single nutrient inadequacy, is associated with greater persistence of anemia in older women. Among eligible WHI-OS participants, 5.5% presented on enrollment with hemoglobin values <12.0 g/dL (<120.0 g/L) a prevalence rate well below the 10.2% reported in a nationally representative sample of older women from NHANES III as well as rates reported in similar population samples, including the Framingham cohort (4,27,28). One important difference across samples is that the WHI-OS sample included women as young as age 50 years; however, when anemia prevalence was evaluated only for those women older than age 65 years, the estimate only increased to 5.64%. Nevertheless, WHI-OS is not a random sample of the aging female population in the United States. The lower prevalence of anemia may partially reflect a nutritionally replete population of postmenopausal women. Baseline estimates of dietary intake in the WHI-OS sample averaged at the time of study enrollment 12 mg iron, 486 μg folate (suggesting adequate intake even before mandate for folic acid fortification of grain products in 1998), and 5.6 μg vitamin B-12 daily; intakes above the Estimated Average Requirements of 6 mg, 320 μg, and 2.0 μg daily, respectively, for these anemia-associated nutrients. This suggests that fewer women demonstrated low hemoglobin concentrations

Table 6. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for incident[b] and persistent[c] anemia, relative to no anemia[d], associated with the number of anemia-associated dietary micronutrient inadequacies at baseline (folate, vitamin B-12, vitamin C, iron, and protein) among participants in the Women's Health Initiative Observational Study

Deficiency	Baseline anemia[d]	Incident anemia[b]	Persistent anemia[c]
	← OR (95% CI) →		
No. of deficiencies of dietary intake			
1	1.18 (1.08, 1.29)	1.10 (0.99, 1.22)	1.21 (1.05, 1.41)
2	1.19 (1.09, 1.31)	1.09 (0.96, 1.22)	1.32 (1.13, 1.53)
3	1.27 (1.13, 1.42)	1.24 (1.08, 1.43)	1.44 (1.20, 1.73)
No. of deficiencies of total intake			
1	1.23 (1.12, 1.35)	1.09 (0.97, 1.23)	1.34 (1.14, 1.56)
2	1.17 (1.04, 1.31)	1.09 (0.94, 1.25)	1.39 (1.16, 1.66)
3	1.28 (1.11, 1.48)	1.14 (0.94, 1.37)	1.56 (1.25, 1.95)

[a]Adjusted for body mass index, age, income, smoking status, and race/ethnicity.
[b]Incident anemia defined as hemoglobin <12 g/dL at baseline assessment. To convert g/dL hemoglobin to g/L, multiply g/dL by 10.0. To convert g/L hemoglobin to g/dL, multiply g/L by 0.1. Hemoglobin of 12.0 g/dL=120.0 g/L.
[c]Persistent anemia defined as hemoglobin <12.0 g/dL at baseline and Year 3 assessments.
[d]No anemia as defined by World Health Organization definition of hemoglobin ≥12.0 g/dL; anemia defined as hemoglobin >12.0 g/dL.
NOTE: Information from this table is available online at www.adajournal.org as part of a PowerPoint presentation.

than would have been expected based on cross-sectional diet reports at baseline.

An additional explanation for the lower rates of anemia in this sample may be that WHI-OS was a sample of free-living older women in contrast to other studies among institutionalized or home-bound elderly wherein anemia prevalence is reportedly as high as 39.6% (17,29,30). Women with renal disease were excluded from enrollment in WHI-OS and women with chronic diseases were excluded from the analytical cohort. There is the possibility that as the population aged, renal dysfunction may have contributed to new cases (31). Further, data regarding gastrointestinal diagnoses (eg, irritable bowel syndrome) and/or medication use that might alter nutrient absorption (ie, proton pump inhibitors, histamine 2 blockers) are not available to evaluate as potential confounders. Consistent with data from other population samples, this analysis indicates that anemia prevalence is higher among women of lower income and smokers (32,33).

The association between BMI and anemia is less frequently described in the literature, although a multiethnic cohort study among adults residing in New York City demonstrated an inverse association between BMI and circulating iron in Hispanic/Latino, but not non-Hispanic, women (34). These findings demonstrated a U-shaped association between BMI and low hemoglobin. This may suggest that nutrient inadequacies contribute to anemia rates among women with lower BMI (<25) whereas increased hepcidin concentrations that are more common in obese women, particularly in extreme obesity (11), could impair iron absorption resulting in anemia when BMI is >30. In support of this interpretation, a study of 50 obese women in Spain demonstrated a significant association between BMI and soluble transferrin receptor (35). Small sample size in these subgroups and lack of objective measures of iron regulatory proteins makes our interpretation of these findings somewhat speculative.

Few studies have explored racial/ethnic differences in anemia prevalence. This sample, which is enriched for minority postmenopausal women, found a higher prevalence of anemia in African Americans and, to a somewhat lesser extent, in Hispanic women. NHANES III reported a 28% prevalence of anemia among African-American women, compared to only 8.7% in non-Hispanic whites (4). In addition, anemia was found in 11.5% of older Hispanic women enrolled in the Massachusetts Hispanic Elders Study compared to 7.3% in non-Hispanic white women (36). Our data also suggest that multiple anemia-associated nutrient inadequacies (three nutrients or more) are more common in African American (15.3%) and Hispanic/Latinos (16.3%) than non-Hispanic white (7.4%) women, suggesting that diet quality may be one factor contributing to risk. Earlier evidence suggests that lower dietary intake alone does not explain the totality of racial differences in hemoglobin levels (37). Genetic differences in sickle cell and thalassemia traits likely account for some of the variance (38). This suggests that hemoglobin alone may have limited value in evaluating anemia in multiracial/ethnic populations.

Inadequate intake of dietary iron, vitamin B-12, and folate were each associated with approximately 10% to 20% elevated risk for incident anemia among WHI-OS study participants and the odds increased for persistent anemia to 21%. Persistent anemia was also associated with inadequate intake of vitamin C (OR 1.25, 95% CI 1.11 to 1.40) and protein (OR 1.22, 95% CI 1.08 to 1.36), suggesting that among women with persistent anemia a diet pattern of low overall nutrient density is likely. There was no indication that supplemental multivitamin or multivitamin-mineral use was protective against anemia. Anemia was diagnosed in 7.3% of women taking multinutrient supplements and 7.2% of those not taking these supplements. In addition, the levels of supplemental B-12 or supplemental iron were higher in women demonstrating incident or persistent anemia as compared to women with no anemia. This finding suggests that dietary supplementation for the treatment of anemia may have been a confounder in our analysis. As no specific data regarding clinical diagnosis and treatment of

nutritional anemia are available for this cohort, it is only assumed that among women taking these supplements the demonstrated low hemoglobin concentrations reflect either a new diagnosis under treatment or a lack of response to supplementation. Also, women previously diagnosed with anemia may have been prescribed supplementation before enrolling in the WHI study. If supplementation corrected a previous inadequacy this would mask our ability to detect these associations using postenrollment data. It is clear from this analysis (Table 6) that in WHI-OS the risk for persistent anemia is incrementally higher for people with an increased number of inadequate dietary intakes of the selected nutrients. These findings are important and suggest that individual nutrient inadequacies leading to nutritional anemia frequently do not occur in isolation. Therefore, reducing the likelihood and/or severity of diet-associated anemia should include evaluation of the overall diet. It is possible that among postmenopausal women presenting with hemoglobin concentrations <12.0 g/dL (<120.0 g/L), enhanced access to nutrient-dense foods that target iron, B-12, and/or folate intake may be required to correct nutritional anemia. This is supported by the findings that multivitamin-mineral use was not associated with lower rates of anemia.

This study does have some inherent limitations. First, anemia risk was evaluated in relation to self-reported dietary intake using an FFQ. It is known that these instruments are associated with significant measurement error (39), although more so in relation to energy and macronutrient intake than the micronutrients evaluated here. The dietary data reflect a food supply before folic acid fortification and thus current anemia rates may be lower. Further, the definition of anemia was based on cut-off points for hemoglobin concentrations alone (3). Although these values do correlate with other measures of anemia status, serum ferritin is the more generally accepted clinical measure of iron-deficiency anemia (40) and macrocytic anemias are better diagnosed using soluble or red blood cell folate and/or serum vitamin B-12 levels. A more complete assessment of anemia also would include additional blood biomarkers, such as mean corpuscular volume, mean corpuscular hemoglobin concentration, red blood cell count, serum folate, and serum vitamin B-12 and ferritin as well as serum transferrin receptor and hepcidin. C-reactive protein and other inflammatory indexes would also be included to rule out non-nutritional causes of anemia common in elderly people. These measures are currently not available for the entire WHI-OS study population. Further, current literature suggests that anemia cut-offs should be adjusted in older people and based on the association between blood biomarkers of anemia and comorbidities such as falls and hospitalizations (2,6). This study is also an observational study of a nonrepresentative US sample and as such has inherent limitations, including lack of generalizability and the inability to determine whether improving the diet in relation to enhancement of intake of select micronutrients would result in correction of low hemoglobin concentrations.

There are several important strengths to this research. This is the first study of this size to investigate the associations between dietary intake and anemia in a prospective sample of aging, postmenopausal women. The study participants have provided extensive demographic and clinical data resulting in a robust characterization of enrollees and an opportunity to control for confounding factors. The multiethnic enrollment serves as a notable strength of this study in that few studies provide such diversity in describing anemia–diet associations. Repeated measures of hemoglobin allow for a prospective assessment of new-onset anemia and an opportunity to exclude acute anemia likely associated with nondietary etiologies such as inflammation, new onset disease, extreme obesity, or infection.

CONCLUSIONS

This study suggests that inadequate nutrient intakes are a significant risk factor for anemia in this population of older women and use of multivitamin-mineral supplements is not associated with lower rates of anemia. The study cannot ascertain whether nutrient repletion in the setting of non-nutritional causes of anemia (eg, blood loss, inflammation, or select medication use) would alter risk given the lack of specific data in these areas. Yet, overall mortality is increased in relation to a diagnosis of anemia (1,41), and anemia, particularly iron deficiency, has been associated with reduced capacity for physical work and physical inactivity (42-44), injury related to falls (45), and hospitalizations (2), making this an important health care concern in aging populations. Efforts to identify anemia that may be responsive to modifiable factors such as diet to improve health outcomes are needed. Additional efforts to regularly evaluate postmenopausal women for anemia should be considered and should be accompanied by an assessment of dietary intake to determine adequacy of intake of anemia-associated nutrients, including iron, vitamin B-12, and folate. Although anemia is often treated with supplemental nutrients, as designated by a more comprehensive biochemical assessment, nutrition therapy to improve overall nutrient density and quality of the diet should also be a clinical focus.

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