THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. 73, No. 3, 380–385
doi:10.1093/gerona/glw332
Advance Access publication January 20, 2017

OXFORD

Research Article

Association Between Non-Iron-Deficient Anemia and Insomnia Symptoms in Community-Dwelling Older Adults: The Baltimore Longitudinal Study of Aging

Lenis P. Chen-Edinboro,[1] Laura E. Murray-Kolb,[2] Eleanor M. Simonsick,[3] Luigi Ferrucci,[3] Richard Allen,[4] Martha E. Payne,[5] and Adam P. Spira[6,7]

[1]School of Health and Applied Human Sciences, University of North Carolina Wilmington. [2]Department of Nutritional Sciences, The Pennsylvania State University, University Park. [3]Intramural Research Program, National Institute on Aging, Baltimore, Maryland. [4]Department of Neurology, Johns Hopkins University, Baltimore, Maryland. [5]Office of Research Development, Duke University School of Medicine, Durham, North Carolina. [6]Department of Mental Health, [7]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, Maryland.

Address correspondence to Lenis Chen-Edinboro, PhD, School of Health and Applied Human Sciences, UNC Wilmington, Wilmington, NC 28403. E-mail: edinborol@uncw.edu

Received August 11, 2016; Editorial Decision Date December 11, 2016

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: Anemia is associated with poorer sleep in children, and clinically, anemia is linked to insomnia. However, the association between anemia and insomnia in older adults is understudied.

Methods: We examined the cross-sectional association between anemia and insomnia in 1,053 adults (71.4 ± 10.6 years) in the Baltimore Longitudinal Study of Aging. Participants were classified as nonanemic, non-iron-deficient anemic, or iron-deficient anemic based on hemoglobin, ferritin, transferrin saturation, and mean cell volume. Insomnia symptoms were evaluated by the Women's Health Initiative Insomnia Rating Scale (WHIIRS). A total score (range 0–20) was generated, and participants were also classified as having 0, 1, or 2+ symptoms.

Results: Overall, 10.5% of participants had non-iron-deficient anemia, 0.9% had iron-deficient anemia, and 88.5% had no anemia. Due to its low prevalence, the iron-deficient anemic group was dropped from analyses. In models adjusted for demographics, number of medical conditions, and Center for Epidemiologic Studies Depression Scale score, non-iron-deficient anemic individuals had significantly higher WHIIRS total scores, indicating greater insomnia severity, compared to those without anemia (predicted adjusted mean WHIIRS of 7.24 [95% confidence interval (CI): 6.40–8.08] vs 5.92 [95% CI: 5.65–6.19]). They also had twice the risk of reporting ≥2 insomnia symptoms (vs 0 symptoms; relative risk ratio = 2.20, 95% CI: 1.25–3.89).

Conclusions: Results suggest that individuals with non-iron-deficient anemia are more likely to experience insomnia symptoms than those who are nonanemic. These results may have implications for insomnia treatment or the identification of underlying frailty in individuals with sleep problems.

Keywords: sleep—hemoglobin—iron

Anemia, defined as low circulating hemoglobin, is associated with poor cognitive outcomes and mortality (1,2). Insomnia occurs frequently in older adults and is associated with depression and cognitive decline (3–5). An association between iron-deficient anemia and poor sleep has been identified in children (6–10) and consideration of anemia is recommended as part of the clinical assessment of insomnia patients (11).

Despite this, the research literature on the association of anemia status with insomnia in older adults is sparse. Insomnia could be a cause, a consequence, or a marker of anemia, and the nature of

this association could have important clinical implications. Although a few studies have examined anemia and sleep in adults (12–14), to our knowledge, only two have investigated anemia and insomnia in community-dwelling older adults (13,14). In the English Longitudinal Study of Ageing, older men and women in the middle tertile of insomnia symptom frequency were more likely to have anemia; both insomnia frequency and shorter sleep duration were associated with lower hemoglobin in men only (13). A second study, in older South Koreans, found insomnia prevalence to be higher in those with a lifetime history of anemia (14).

A link between anemia and insomnia in older adults could have important implications for the treatment of each condition; anemia may be a modifiable contributor to insomnia, and vice versa. Alternatively, positive findings could suggest an underlying medical morbidity, frailty, or other factor driving both anemia and insomnia. We hypothesized that community-dwelling older adults in the United States with anemia (both iron-deficient and non-iron-deficient anemia) would have more severe insomnia symptoms compared to those without anemia.

Methods

Participants

Participants were enrolled in the Baltimore Longitudinal Study of Aging (BLSA), a prospective observational study administered by the Intramural Research Program of the National Institute on Aging (15). The present study is a cross-sectional study within a continuous enrollment cohort. All data for this article were collected over a 10-year period from 2004 to 2014. Based on age, participants have study visits every 1–4 years, at which they complete cognitive, functional, and other health measures (15). Data from the most recent visit to the BLSA Clinical Research Unit in Baltimore, MD with the sleep, clinical, and medical variables of interest in this study were used. Of the 1,105 BLSA participants aged 50 and older who met these criteria, 29 were excluded because they did not fit in an anemia category (n = 29, details below), and an additional 13 were excluded because they were missing responses on one or more insomnia scale items. Although there were 1,063 individuals with either iron-deficient anemia or non-iron-deficient anemia, we ultimately dropped the 10 individuals with iron-deficient anemia from our main analyses due to the low prevalence of that condition, leaving a final sample of n = 1,053 for these analyses.

Iron Status and Anemia

Participants underwent blood draws on the morning of the first day of the clinic visit after a 10-hour overnight fast. Blood samples were processed the same day they were collected. Iron measures obtained from morning fasting samples included ferritin, a measure of iron stores (16); serum iron; total iron-binding capacity, a measure of open binding sites on the iron transport molecule transferrin (17); and transferrin saturation ([serum iron/total iron-binding capacity] × 100%) (17). Other iron-related measures included mean cell volume and hemoglobin.

We used the following cutoffs to indicate abnormal iron status: ferritin <15 μg/L per World Health Organization guidelines (18), transferrin saturation <16% (17,19), and mean cell volume <80 fL (20). For iron deficiency, we required abnormal values for at least two of these measures, an approach consistent with other studies (21). However, because low ferritin is specific to iron deficiency (22), we also categorized participants as iron-deficient anemic if they were anemic with only low ferritin, even if they had normal transferrin saturation and normal mean cell volume. Iron-deficient anemia was defined as having both anemia and iron deficiency.

Recent studies support using lower hemoglobin cutoffs for Black individuals (23,24). For non-Black individuals, we defined anemia using hemoglobin cutoffs established by the World Health Organization: <12 g/dL for women and <13 g/dL for men (25). We categorized Black women with hemoglobin <11 g/dL and Black men with hemoglobin <12 g/dL as anemic.

We categorized participants as having non-iron-deficient anemia if they had ferritin ≥15 μg/L, transferrin saturation ≥16%, mean cell volume ≥80 fL, and anemia as defined above.

Based on these cutoffs, we categorized participants as not anemic, non-iron-deficient anemic, or iron-deficient anemic. Anemia status was considered missing if a participant had a missing hemoglobin value or was determined to be anemic but had at least one of the following: (1) one or more missing iron measures; (2) low transferrin saturation but normal ferritin and normal mean cell volume; (3) low mean cell volume but normal ferritin and transferrin saturation; (4) abnormally high ferritin but abnormally low mean cell volume or transferrin saturation (ie, signs of both iron overload and deficiency).

Insomnia Symptoms

Participants completed a version of the Women's Health Initiative Insomnia Rating Scale (WHIIRS) (26) as part of the BLSA interview. They were asked to rate the frequency of several insomnia symptoms over the prior month, including "have trouble falling asleep (within 30 minutes)," "wake up several times at night," "wake up earlier than you planned to," and "have trouble getting back to sleep after you woke up too early" (26). Participants responded using a 5-point Likert-type scale (0 = "never"; 1 = "<1/week"; 2 = "1–2/week"; 3 = "3–4/week"; 4 = "5+/week") (26). Sleep quality was assessed by asking about participants' "typical night's sleep" over the past month (responses ranged from 0 = "very sound or restful" to 4 = "very restless") (26). The global WHIIRS score (ranging from 0 to 20) was created by summing all five WHIIRS items, with higher scores representing greater insomnia severity (26). We also created a categorical variable representing the number of insomnia symptoms endorsed (0 insomnia symptoms, 1 symptom, or ≥2 symptoms). Insomnia symptoms were considered present if they occurred at least three times per week or if sleep quality was rated as "restless" or "very restless."

Restless Legs Syndrome

We determined restless legs syndrome status based on questions adapted from the Cambridge-Hopkins Questionnaire validated for the diagnosis of restless legs syndrome (27). Participants were considered restless legs syndrome-negative if they responded "No" to questions about "recurrent uncomfortable feelings or sensations" in their legs and "a recurrent need to or urge to move" their legs. They were deemed restless legs syndrome-positive if they answered "Yes" to both of these questions, indicated they were more likely to have the sensations while resting, reported obtaining relief from the sensations when moving around or reported daily symptoms, and responded "Yes" or "Don't Know" to the question "Are these feelings worse at night or in the evening than at other times of the day?" Participants who did not fall into either category above were categorized as missing restless legs syndrome status.

Other Measures

Demographic variables included age, sex, race/ethnicity (non-Hispanic White; non-Hispanic Black; and other), and education.

Height and weight were measured and body mass index was calculated (BMI; kg/m^2). Smoking was classified as current or past smoker in the past 10 years versus never smoker or quit >10 years ago. Categories of alcohol consumption were 0 or <1 alcoholic beverage/week, 1–7/week, or 8+/week over the past 12 months. Participants reported whether a doctor or other health professional ever told them that they had hypertension, heart attack or myocardial infarction, angina, diabetes, cancer, kidney disease, cirrhosis, hepatitis, stroke, or a transient ischemic attack. The categories of heart attack and angina were combined to form a variable for heart-related conditions, and stroke and transient ischemic attack were combined to form a stroke/transient ischemic attack variable. Participants were classified as having 0, 1, or ≥2 chronic conditions. Participants also completed the Center for Epidemiologic Studies Depression Scale (CES-D) (28).

Statistical Analyses

We compared continuous participant characteristics by anemia status using *t*-tests or Mann–Whitney *U* tests for normally distributed and skewed variables, respectively, and categorical characteristics with chi-squared or Fisher's exact tests. To determine if continuous covariates were related to insomnia, we conducted simple linear regressions with continuous covariates as predictors and insomnia variables as the outcomes. To determine if categorical covariates were related to the WHIIRS insomnia score, we used the Kruskal–Wallis or Wilcoxon rank sum test. Known potential confounders (e.g., age, sex, depressive symptoms) were identified a priori or through their known associations with anemia and insomnia in the literature (29). We identified additional potential confounders if they differed by anemia status and were associated with the WHIIRS insomnia score at the p <.10 level.

We then fit regression models with anemia category as a predictor and WHIIRS insomnia score as the outcome. Model 1 was unadjusted. In Model 2, we adjusted for age, sex, and race/ethnicity. In Model 3, we additionally controlled for number of chronic conditions, which included hypertension, heart attack/angina, diabetes, cancer, kidney disease, cirrhosis, hepatitis, and stroke/transient ischemic attack. Finally, Model 4 added depressive symptoms in the form of CES-D score to Model 3. Restless legs syndrome may mediate the association between anemia and insomnia. Therefore, we conducted a sensitivity analysis with and without restless legs syndrome symptoms. We report adjusted mean WHIIRS values for the different anemia categories based on each of the linear models.

To examine the association between iron/anemia status and number of insomnia symptoms, we performed a multinomial logistic regression with anemia category as a predictor and 0, 1, or 2 or more insomnia symptoms as an outcome. The coefficient yielded by a multinomial logistic regression is the relative risk ratio, or RRR, which in this case represents the relative risk of having a given number of insomnia symptoms versus 0 symptoms, comparing those in a particular anemia category to those who are not anemic.

All statistical analyses were performed using Stata 12.1 (30).

Results

Overall, 10.5% of participants had non-iron-deficient anemia, 0.9% had iron-deficient anemia, and 88.5% had no anemia. Compared to the nonanemic, the non-iron-deficient anemic group was older and had lower BMI on average (Table 1). Compared to the nonanemic (in which just under half were male, 65% were White, and 36% had two or more chronic diseases), almost three-quarters of the non-iron-deficient anemic group were male, about 84% were White, and about 66% had two or more chronic diseases. There was a marginally significant association between anemia status and restless legs syndrome (p = .069): compared to 13% of the nonanemic group, 20% of the non-iron-deficient anemic group had restless legs syndrome. Of these variables that differed by anemia subcategory, race/ethnicity, number of chronic diseases, and restless legs syndrome (in sensitivity analyses) were retained as covariates due to their association with the WHIIRS insomnia measure at the p <.10 level; age, sex, and depressive symptoms were also included in the models because they are known correlates of insomnia and/or anemia (29). Due to the small sample size, we excluded the 10 individuals with iron-deficient anemia from analyses.

After adjusting for demographic variables, adjusted mean WHIIRS scores of non-iron-deficient anemic individuals (mean = 7.60, 95% confidence interval [CI]: 6.78–8.42) were significantly higher than those of nonanemic individuals (mean = 5.92, 95% CI: 5.65–6.19; Table 2), and these scores remained significantly different after further adjustment for number of chronic conditions (mean = 7.45, 95% CI: 6.61–8.30 vs mean = 5.94, 95% CI: 5.66–6.21). In addition, after further adjustment for depressive symptoms, non-iron-deficient anemic participants still had significantly higher adjusted mean WHIIRS scores than nonanemic individuals (mean = 7.24, 95% CI: 6.40–8.08 vs mean = 5.92, 95% CI: 5.65–6.19). Results of the sensitivity analysis with incremental adjustment for restless legs syndrome did not change inferences; non-iron-deficient anemic participants still had higher adjusted mean WHIIRS scores than those without anemia (mean = 7.02, 95% CI: 6.11–7.94 vs mean = 5.61, 95% CI: 5.32–5.90).

In the multinomial logistic regression, participants who were non-iron-deficient anemic were 2.75 times more likely to have ≥2 insomnia symptoms versus 0 symptoms compared to persons without anemia, adjusting for demographics (RRR = 2.75, 95% CI: 1.63–4.65, Table 3). This association was only slightly attenuated after adjustment for number of chronic diseases (RRR = 2.39, 95% CI: 1.40–4.07) and depressive symptoms (RRR = 2.20, 95% CI: 1.25–3.89). Inferences remained the same after controlling for restless legs syndrome in the sensitivity analysis.

Discussion

We found, in a sample of community-dwelling older adults aged 50 years and older, that non-iron-deficient anemia was associated with a higher likelihood and greater severity of insomnia. This finding is consistent with results from other studies of older adults, namely the link between anemia and insomnia symptom frequency observed in the English Longitudinal Study of Ageing (13), and the association between lifetime anemia history and higher insomnia risk reported in a South Korean sample (14); however, these prior studies did not measure iron status when determining anemia status.

The mechanisms that might underlie a causal association between non-iron-deficient anemia and insomnia are unclear. Jackowska et al. (13) noted the association of both anemia and insomnia to fatigue (31–33), implying that fatigue may mediate the anemia-insomnia link. Fatigue, as a symptom of anemia (31), could lead to insomnia-related complaints by reducing physical activity (34,35) or by interfering with environmental cues (eg, bright light exposure) that affect circadian rhythms and the timing of sleep (36). Of course, the other direction—in which insomnia leads to fatigue

Table 1. Demographic, Nutrition, and Health Characteristics of BLSA Sample (*n* = 1,053) by Anemia Status, *n* (%); Mean ± SD, or Median (25th %ile, 75th %ile)

Variable	Not Anemic (*n* = 941)	Non-Iron-Deficient Anemic (*n* = 112)	*p* Value
Age (median [25th %ile, 75th %ile])	70 (63, 78)	82 (75.5, 87)	<.0001
Sex			<.001
Female	506 (53.8)	29 (25.9)	
Male	435 (46.2)	83 (74.1)	
Race/ethnicity* (*n* = 1,048)			<.001
White	606 (64.7)	94 (83.9)	
Non-Hispanic Black	261 (27.9)	8 (7.1)	
Other	69 (7.4)	10 (8.9)	
Education† (*n* = 1,052)	17.0 ± 2.6	16.7 ± 2.6	.2495
Body mass index (kg/m²) (*n* = 1,050)	27.8 ± 5.0	26.3 ± 3.9	.0003
Smoking (*n* = 989)			.113
Nonsmoking	846 (95.8)	105 (99.1)	
Smoking	37 (4.2)	1 (0.9)	
Number of alcoholic drinks/wk (*n* = 1,043)			.160
0 or <1	394 (42.3)	52 (46.9)	
1–7	371 (39.8)	47 (42.3)	
8+	167 (17.9)	12 (10.8)	
Number of chronic conditions (*n* = 1,017)			<.001
0	241 (26.4)	12 (11.4)	
1	342 (37.5)	24 (22.9)	
2+	329 (36.1)	69 (65.7)	
CES-D (*n* = 989)	4 (1, 7)	4.5 (2, 7)	.2292
Restless legs syndrome (*n* = 844)			.069
Absent	659 (87.3)	71 (79.8)	
Present	96 (12.7)	18 (20.2)	
WHIIRS score	5 (3, 9)	7 (5, 10)	<.0001

Notes: CES-D = Center for Epidemiologic Studies Depression Scale; WHIIRS = Women's Health Initiative Insomnia Rating Scale. Percentages may not add up to 100 due to rounding. Total *n* = 1,053 unless otherwise indicated.

*Other category includes Hispanic, Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and two or more races. †Education values are years of school completed.

Table 2. Adjusted Mean (SE) WHIIRS Scores* by Anemia Subcategory in Older Adults Aged 50+

Women's Health Initiative Insomnia Rating Scale (WHIIRS)	Model 1 (*n* = 1,053)	Model 2 (*n* = 1,048)	Model 3 (*n* = 1,013)	Model 4 (*n* = 953)	Sensitivity Analysis (*n* = 759)
Not anemic	5.92 (0.14)	5.92 (0.14)	5.94 (0.14)	5.92 (0.14)	5.61 (0.15)
Anemic without iron deficiency	7.54 (0.40)	7.60 (0.42)	7.45 (0.43)	7.24 (0.43)	7.02 (0.47)
Difference in adjusted means† (95% CI)	1.63 (0.80–2.45)	1.68 (0.81–2.56)	1.52 (0.61–2.42)	1.32 (0.43–2.21)	1.41 (0.44–2.39)
p Value	<.001	<.001	.001	.004	.005

Notes: Model 1: unadjusted. Model 2: adjusted for age, sex, and race/ethnicity. Model 3: adjusted for covariates in Model 2 + number of chronic diseases (0, 1, 2+). Model 4: adjusted for covariates in Model 3 + Center for Epidemiologic Studies Depression Scale. Sensitivity analysis: adjusted for covariates in Model 4 + restless legs syndrome.

*Higher WHIIRS scores indicate greater insomnia severity. †Difference in average WHIIRS total scores between anemia categories. Values may be slightly different from calculated differences between the two anemia groups due to rounding.

Table 3. Association of Anemia Subtypes With Number of Insomnia Symptoms in Older Adults 50+ (Multinomial Logistic Regression)

	≥2 Insomnia Symptoms vs 0 Insomnia Symptoms				
	Model 1, RRR (95% CI), (*n* = 1,053)	Model 2, RRR (95% CI), (*n* = 1,048)	Model 3, RRR (95% CI), (*n* = 1,013)	Model 4, RRR (95% CI), (*n* = 953)	Sensitivity Analysis, RRR (95% CI), (*n* = 759)
Not anemic	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Anemic without iron deficiency	2.65 (1.62–4.32)	2.75 (1.63–4.65)	2.39 (1.40–4.07)	2.20 (1.25–3.89)	2.60 (1.36–4.97)
p Value	<.001	<.001	.001	.007	.004

Notes: RRR = relative risk ratio. Model 1: unadjusted. Model 2: adjusted for age, sex, and race/ethnicity. Model 3: adjusted for covariates in Model 2 + number of chronic diseases (0, 1, 2+). Model 4: adjusted for covariates in Model 3 + Center for Epidemiologic Studies Depression Scale. Sensitivity analysis: adjusted for covariates in Model 4 + restless legs syndrome.

by limiting restorative sleep—also is possible. In addition, a recent neuroimaging study in the BLSA linked both hemoglobin levels and anemia status to cerebral blood flow in frontotemporal and other brain regions (37), and another BLSA investigation linked shorter sleep duration to cortical thinning in frontotemporal regions (38). The overlapping brain regions in these studies may indicate a common pathway linking anemia and insomnia, but that is only speculative at this time. Finally, it is plausible that insomnia is simply a marker of the medical morbidity or frailty reflected by non-iron-deficient anemia, and that disease burden drives the association between anemia and insomnia. These possibilities all require further examination.

The nature of the association between insomnia and non-iron-deficient anemia could have important clinical implications. If insomnia contributes to anemia, or vice versa, treatment of the contributing condition may help relieve the resulting problem. If non-iron-deficient anemia reflects medical morbidity or underlying frailty as a cause of insomnia, then it may alert health practitioners to evaluate the underlying frailty or to the insomnia itself. If insomnia is a marker of non-iron-deficient anemia, then identification of both anemia and insomnia may reflect medical morbidity or frailty in the older individual that needs to be addressed. Further observational research in humans complemented by experimental work in animal models is needed to clarify these associations.

This study has several strengths. To our knowledge, it is the only study investigating the association between anemia and insomnia with a specific focus on community-dwelling U.S. older adults. Further, we considered a number of potential covariates, including restless legs syndrome in sensitivity analyses and showed the association between non-iron-deficient anemia and insomnia was independent of these covariates. However, this study also has limitations. First, the BLSA sample consists of highly educated, relatively healthy older adults, so the prevalence of iron-deficient anemia is low compared to other U.S. older adults (39). In fact, we dropped the few (n = 10) individuals with iron-deficient anemia given limited statistical power to evaluate group insomnia symptoms. Second, only 112 out of 1,053 subjects (10.6%) of the sample had non-iron-deficient anemia. Although we observed significant associations between non-iron-deficient anemia and insomnia, replication of our findings in larger samples with a greater proportion of people who have non-iron-deficient anemia is needed. Third, sleep-related variables and medical conditions were assessed by self-report as opposed to objective measures. Finally, the study's cross-sectional nature prevents us from establishing temporal relationships between anemia and insomnia. Prospective studies that include greater numbers of iron-deficient anemic individuals and that use objective sleep measures (eg, polysomnography, actigraphy) are recommended.

In conclusion, we found that, compared to nonanemic individuals, those who were anemic (non-iron-deficient) had more severe insomnia and a greater likelihood of having two or more insomnia symptoms. Additional research is needed to elucidate the nature of this association and develop appropriate clinical recommendations.

Funding

This work was supported in part by the Intramural Research Program of the National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. This work was supported by the following National Institutes of Health grants: the National Institute of Mental Health (grant number T32MH014592 to P. Zandi supporting L.C.E.); the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Building Interdisciplinary Research Careers in Women's Health (BIRCWH) K12 program (grant number HD043446 supporting M.E.P.); and the National Institute on Aging (grant number K01AG033195 to A.P.S.). The BLSA is supported by the National Institute on Aging (NIA) Intramural Research Program through Research and Development Contract HHSN-260-2004-00012C.

Acknowledgments

Special thanks to Dr. Christopher Kaufmann and Dr. Alden Gross for statistical consultation. A version of this study was presented at the Experimental Biology Conference in Boston (March 2015).

Conflict of Interest

Dr. Spira has agreed to serve as a consultant to Awarables, Inc. in support of an NIH grant.

References

1. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. *Blood*. 2006;107:3841–3846.
2. Deal JA, Carlson MC, Xue QL, Fried LP, Chaves PH. Anemia and 9-year domain-specific cognitive decline in community-dwelling older women: the Women's Health and Aging Study II. *J Am Geriatr Soc*. 2009;57:1604–1611.
3. Ancoli-Israel S, Cooke JR. Prevalence and comorbidity of insomnia and effect on functioning in elderly populations. *J Am Geriatr Soc*. 2005;53:S264–S271.
4. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord*. 2011;135:10–19.
5. Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of sleep on the risk of cognitive decline and dementia. *Curr Opin Psychiatry*. 2014;27:478–483.
6. Kordas K, Siegel EH, Olney DK, Katz J, Tielsch JM, Chwaya HM, et al. Maternal reports of sleep in 6–18 month-old infants from Nepal and Zanzibar: association with iron deficiency anemia and stunting. *Early Hum Dev*. 2008;84:389–398.
7. Peirano P, Algarín C, Garrido M, Algarín D, Lozoff B. Iron-deficiency anemia is associated with altered characteristics of sleep spindles in NREM sleep in infancy. *Neurochem Res*. 2007;32:1665–1672.
8. Kordas K, Siegel EH, Olney DK, et al. The effects of iron and/or zinc supplementation on maternal reports of sleep in infants from Nepal and Zanzibar. *J Dev Behav Pediatr*. 2009;30:131–139.
9. Peirano PD, Algarín CR, Chamorro RA, et al. Sleep alterations and iron deficiency anemia in infancy. *Sleep Med*. 2010;11:637–642.
10. Peirano PD, Algarín CR, Garrido MI, Lozoff B. Iron deficiency anemia in infancy is associated with altered temporal organization of sleep states in childhood. *Pediatr Res*. 2007;62:715–719.
11. Morin CM. *Insomnia: Psychological Assessment and Management*. New York, NY: Guilford Press; 1993:67.
12. Bixler EO, Vgontzas AN, Lin HM, Vela-Bueno A, Kales A. Insomnia in central Pennsylvania. *J Psychosom Res*. 2002;53:589–592.
13. Jackowska M, Kumari M, Steptoe A. Sleep and biomarkers in the English Longitudinal Study of Ageing: associations with C-reactive protein, fibrinogen, dehydroepiandrosterone sulfate and hemoglobin. *Psychoneuroendocrinology*. 2013;38:1484–1493.
14. Kim W-H, Kim B-S, Kim S-K, et al. Prevalence of insomnia and associated factors in a community sample of elderly individuals in South Korea. *Int Psychogeriatr*. 2013;25:1729–1737.
15. National Institute on Aging. About BLSA. Baltimore Longitudinal Study of Aging website. https://www.blsa.nih.gov/about/. Accessed July 14, 2016.
16. Cook JD, Lipschitz DA, Miles LE, Finch CA. Serum ferritin as a measure of iron stores in normal subjects. *Am J Clin Nutr*. 1974;27:681–687.

17. Gibson RS. Assessment of iron status. In: Gibson RS, ed. *Principles of Nutritional Assessment*. 2nd ed. Oxford: Oxford University Press; 2005:443–476.
18. WHO. *Serum Ferritin Concentrations for the Assessment of Iron Status and Iron Deficiency in Populations. Vitamin and Mineral Nutrition Information System*. Geneva, Switzerland: World Health Organization; 2011:1–5.
19. Lennartsson J, Bengtsson C, Hallberg L, Lundgren BK, Tibblin E. Serum iron and transferrin saturation in women with special reference to women with low transferrin saturation. The population study of women in Göteborg 1968–1969. *Scand J Haematol*. 1979;23:182–196.
20. Gibson RS. Assessment of folate and vitamin B12 status. In: Gibson RS, ed. *Principles of Nutritional Assessment*. 2nd ed. Oxford: Oxford University Press; 2005:595–640.
21. Fleming DJ, Jacques PF, Tucker KL, et al. Iron status of the free-living, elderly Framingham Heart Study cohort: an iron-replete population with a high prevalence of elevated iron stores. *Am J Clin Nutr*. 2001;73:638–646.
22. Dallman PR, Siimes MA, Stekel A. Iron deficiency in infancy and childhood. *Am J Clin Nutr*. 1980;33:86–118.
23. Lynch S. Annex 1: Indicators of the iron status of populations: red blood cell parameters. In: WHO, CDC, eds. *Assessing the Iron Status of Populations: Including Literature Reviews: Report of a Joint World Health Organization/Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level*. 2nd ed. Geneva, Switzerland: World Health Organization; 2007.
24. Nestel P; International Nutritional Anemia Consultative Group. *Adjusting Hemoglobin Values in Program Surveys*. Washington, DC: ILSI Human Nutrition Institute; 2002.
25. WHO. *Nutritional Anaemias: Report of a WHO Scientific Group*. Geneva, Switzerland: World Health Organization; 1968.
26. Levine DW, Lewis MA, Bowen DJ, et al. Reliability and validity of Women's Health Initiative Insomnia Rating Scale. *Psychol Assess*. 2003;15:137–148.
27. Allen RP, Burchell BJ, MacDonald B, Hening WA, Earley CJ. Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. *Sleep Med*. 2009;10:1097–1100.
28. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385–401.
29. Onder G, Penninx BW, Cesari M, et al. Anemia is associated with depression in older adults: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci*. 2005;60:1168–1172.
30. StataCorp. *Stata Statistical Software: Release 12*. 12.1 ed. College Station, TX: StataCorp LP; 2011.
31. Beghe C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. *The American Journal of Medicine*. 2004;116(suppl 7A):3S–10S.
32. Thomas KS, Motivala S, Olmstead R, Irwin MR. Sleep depth and fatigue: role of cellular inflammatory activation. *Brain Behav Immun*. 2011;25:53–58.
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
34. Egerton T, Chastin SF, Stensvold D, Helbostad JL. Fatigue may contribute to reduced physical activity among older people: an observational study. *J Gerontol A Biol Sci Med Sci*. 2016;71:670–676.
35. King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. Moderate-intensity exercise and self-rated quality of sleep in older adults. a randomized controlled trial. *JAMA*. 1997;277:32–37.
36. Zee PC, Attarian H, Videnovic A. Circadian rhythm abnormalities. *Continuum*. 2013;19:132–147.
37. Gottesman RF, Sojkova J, Beason-Held LL, et al. Patterns of regional cerebral blood flow associated with low hemoglobin in the Baltimore Longitudinal Study of Aging. *J Gerontol A Biol Sci Med Sci*. 2012;67:963–969.
38. Spira AP, Gonzalez CE, Venkatraman VK, et al. Sleep duration and subsequent cortical thinning in cognitively normal older adults. *Sleep*. 2016;39:1121–1128.
39. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood*. 2004;104:2263–2268.