Hemoglobin level in older persons and incident Alzheimer disease

Prospective cohort analysis

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ABSTRACT

Objective: To test the hypothesis that level of hemoglobin is associated with incident Alzheimer disease (AD).

Methods: A total of 881 community-dwelling older persons participating in the Rush Memory and Aging Project without dementia and a measure of hemoglobin level underwent annual cognitive assessments and clinical evaluations for AD.

Results: During an average of 3.3 years of follow-up, 113 persons developed AD. In a Cox proportional hazards model adjusted for age, sex, and education, there was a nonlinear relationship between baseline level of hemoglobin such that higher and lower levels of hemoglobin were associated with AD risk (hazard ratio [HR] for the quadratic of hemoglobin 1.06, 95% confidence interval [CI] 1.01–1.11). Findings were unchanged after controlling for multiple covariates. When compared to participants with clinically normal hemoglobin (n = 717), participants with anemia (n = 154) had a 60% increased hazard for developing AD (95% CI 1.02–2.52), as did participants with clinically high hemoglobin (n = 10, HR 3.39, 95% CI 1.25–9.20). Linear mixed-effects models showed that lower and higher hemoglobin levels were associated with a greater rate of global cognitive decline (parameter estimate for quadratic of hemoglobin = −0.008, SE −0.002, $p < 0.001$). Compared to participants with clinically normal hemoglobin, participants with anemia had a −0.061 z score unit annual decline in global cognitive function (SE 0.012, $p < 0.001$), as did participants with clinically high hemoglobin (−0.090 unit/year, SE 0.038, $p = 0.018$).

Conclusions: In older persons without dementia, both lower and higher hemoglobin levels are associated with an increased hazard for developing AD and more rapid cognitive decline. ***Neurology***® **2011; 77:219–226**

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; **FEV1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **HR** = hazard ratio; **MCI** = mild cognitive impairment.

Alzheimer disease (AD) is the leading cause of dementia in older persons, but its underlying biology is poorly understood. AD affects about 5.3 million persons in the United States[1] and is anticipated to affect 13.5 million individuals by 2050.[2] Prevention of AD requires identifying risk factors for the development of AD, especially factors amenable to intervention. Hemoglobin abnormalities are common in the elderly[3,4] and have been associated with increased mortality.[5] Some cross-sectional studies have found relations between anemia and a lower level of cognition,[6,7] and we previously reported that both lower and higher hemoglobin levels are associated with worse performance on cognitive tests.[8] Currently, it is unclear whether hemoglobin level is related to developing AD. A historical cohort study found that older persons with anemia were not more likely to develop AD[9] while another prospective cohort study pointed to anemia having a higher hazard for incident dementia, including AD.[10] A recent

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meta-analysis highlighted the lack of studies examining the effects of high hemoglobin levels and AD.[11]

In this study, we examined the relationship of hemoglobin levels to incident AD utilizing data from almost 900 community-dwelling persons with hemoglobin assessment and annual detailed clinical evaluations for up to 5 years in the Rush Memory and Aging Project.[12] A complementary analysis was conducted to examine the relation of hemoglobin level to the annual rate of cognitive decline.

METHODS

Participants. All participants were older, community-dwelling individuals who agreed as part of the Memory and Aging Project to annual clinical evaluations and brain donation at the time of death.[12] They come from more than 40 groups in the Chicago, IL, vicinity.

The Memory and Aging Project began in 1997, is still ongoing with rolling enrollment, and has an overall follow-up rate of about 95% of survivors. Because of the rolling admission and mortality, the length of follow-up and number of examinations varies across participants. Blood collection was started in February 2003. To maintain the temporal relation between hemoglobin measures and dementia assessments, the first evaluation of hemoglobin level and the associated cognitive testing and clinical evaluation defined "baseline" for this report. All subsequent clinical evaluations and cognitive testing available for each participant were used to estimate the hazard for incident AD and the rate of change in cognition, respectively. Inclusion in these analyses required a valid hemoglobin level, absence of dementia at the visit associated with the hemoglobin measurement, and one or more follow-up clinical evaluations to determine incident AD.

Standard protocol approval, registration, and patient consents. The study was approved by the Institutional Review Board of Rush University Medical Center. Written informed consent was obtained from all study participants.

Assessment of cognitive function and AD diagnosis. Participants underwent a uniform structured clinical evaluation that included a medical history, neurologic examination, and cognitive performance testing. Clinical diagnoses were made using a multistep process.[13] A battery of 21 cognitive function tests was administered in an approximately 1-hour session. After cognitive test data were reviewed by an experienced neuropsychologist who determined if cognitive impairment was present, participants were evaluated in person by an experienced clinician who used all available current year cognitive and clinical testing results to diagnose dementia and AD using the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[14] Mild cognitive impairment (MCI) was defined as having impairment on cognitive evaluation but not meeting AD diagnostic criteria.[15] Using the mean and SD from the baseline evaluation of all participants, raw scores from 19 individual cognitive tests were converted to *z* scores which were averaged to construct a global cognitive function summary score along with 5 specific cognitive domain scores for episodic memory, semantic memory, working memory, visuospatial ability, and perceptual speed.[16] A summary score was considered as missing if less than half of its component raw test scores were available. All follow-up evaluations were performed by examiners blinded to data collected in prior years.

Measurement of hemoglobin. Phlebotomists and nurses skilled in venipuncture collected blood in a 2-mL EDTA tube. Complete blood count analyses were performed using a Beckman/Coulter LH750 automated processor (Quest Laboratories, Wood Dale, IL).[8] Clinically low hemoglobin (anemia) was defined as having a hemoglobin level less than 12 g/dL for women and less than 13 g/dL for men.[17] Clinically high hemoglobin was defined as having a hemoglobin level greater than 15.5 g/dL for women and greater than 17.5 g/dL for men.

Comorbidities and other covariates. Individuals were asked for demographic information including date of birth, sex, and highest number of years of education completed. Mean corpuscular volume and red cell distribution width were determined using a Beckman/Coulter LH750 automated processor.[8] Body mass index was calculated by dividing the measured weight converted to kilograms by the square of the measured height expressed in meters. Glomerular filtration rate was calculated using the 4-variable formula derived from the Modification of Diet in Renal Disease Study.[18] The number of chronic medical conditions at study baseline was determined based on self-report for cancer, congestive heart failure, coronary artery disease, head injury, hip fracture, smoking, and thyroid disease; self-report along with review of medications for diabetes and hypertension; and self-report along with clinician assessment for depression, Parkinson disease, and stroke. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) raw scores were averaged from 2 trials with a hand-held spirometer and converted to *z* scores.[19,20] Physical activity was based on self-report on the number of hours of physical activities engaged in during the 2 weeks prior to the evaluation.[21,22] Current frequency of participation in cognitively stimulating activities was assessed with a structured, 9-item questionnaire.[21] Depressive symptoms experienced in the previous week were assessed using a 10-item version of the Center for Epidemiologic Studies Depression Scale.[23] Social network size was the number of children, family, and friends seen at least once per month.[24] *APOE* genotype was determined by high throughput sequencing of codon 112 (position 3937) and codon 158 (position 4075) of exon 4 of the *APOE* gene on chromosome 19 (Agencourt Bioscience Corporation, Beverly, MA).[25]

Statistical analysis. We compared the bivariate associations of baseline hemoglobin levels with demographic variables and other covariates. We divided the cohort into those who did and who did not develop AD during the course of the study and compared their baseline demographic and covariate measures. Discrete time Cox proportional hazards models[26] were used to examine the hazard for developing AD associated with baseline hemoglobin. Previous cross-sectional analyses in this cohort[8] showed a nonlinear relationship between hemoglobin and cognitive function. Therefore, our core model for these analyses included both linear and quadratic terms for hemoglobin, together with terms adjusting for age, sex, and education. Then, we replaced the hemoglobin terms with terms comparing the hazard for developing incident AD for participants with anemia or clinically high hemoglobin as compared to participants with clinically normal hemoglobin levels. To examine if the relationship of hemoglobin levels to incident AD was modified by demographic variables, our core model was repeated 3 times with interactions for linear and quadratic terms for hemoglobin and age, sex, and

education, respectively. Next, we repeated the core model adding several covariates which might affect the association of baseline hemoglobin with developing AD. We added each covariate individually into the core model (result not shown) and then all the covariates together in the same model. In a sensitivity analysis, we repeated our core model after excluding individuals with MCI. We conducted a complementary set of analyses using mixed-effects, repeated measures models[27] to examine the relationship of hemoglobin to decline in cognitive function over time, the clinical hallmark of AD, and to control for baseline cognitive function. We included random person-specific intercepts and slopes, with coefficients for linear and quadratic terms in hemoglobin levels as well as with their interactions with time in study. Terms for age, sex, and education were included in all models along with their interactions with time in study. We repeated the mixed effects model 5 times with each specific cognitive domain as the outcome. Model assumptions of normality, independence, and constant variance of errors were adequately met. Analyses were carried out in SAS®, version 9.1.8 (SAS Institute Inc., Cary, NC).

RESULTS As of October 2008, 1,059 participants had a valid baseline hemoglobin level. Of these participants, 96 had clinical dementia and 39 were not eligible for follow-up examination (10 persons died prior to their first follow-up and 29 had not yet reached their first follow-up). Of the 924 participants who were eligible for follow-up examination, 43 had missing follow-up data, yielding a participation rate of >95%. The remaining 881 participants had an average 3.3 years of follow-up (SD 1.4 years, range 1–5 years), 75% were female, the mean age was 80.6 (SD 7.4) years, and the mean education level was 14.4 (SD 3.0) years.

Descriptive properties of hemoglobin. Baseline hemoglobin level was symmetrically distributed with a mean of 13.3 g/dL (SD 1.3, range 8.7–18.0, skewness = −0.22). Hemoglobin levels were weakly correlated with age ($r = -0.078$, $p = 0.02$) and education level ($r = 0.128$, $p < 0.001$). Hemoglobin levels were higher in men than women (13.9 g/dL [SD 1.4] vs 13.2 g/dL [SD 1.2] [$t(df = 335] = 7.36$, $p < 0.001$). Hemoglobin level was correlated with mean corpuscular volume ($r = 0.234$, $p < 0.001$), red cell distribution width ($r = -0.276$, $p < 0.001$), estimated glomerular filtration rates ($r = 0.217$, $p < 0.001$), and pulmonary function tests measured by forced expiratory volume ($r = 0.246$, $p < 0.001$) and vital capacity ($r = 0.233$, $p < 0.001$). Hemoglobin levels had a weak correlation with report of chronic medical conditions ($r = -0.095$, $p = 0.01$). Baseline characteristics for participants with clinically low, normal, and high hemoglobin levels are shown in table e-1 on the *Neurology*® Web site at www.neurology.org.

Hemoglobin and incident AD. Over an average of 3.3 years of follow-up, 113 participants developed AD. At baseline, individuals who developed AD were older and had lower Mini-Mental State Examination

Table 1 Baseline participant characteristics by development of Alzheimer disease

Characteristics	Developed AD (n = 113)	Did not develop AD (n = 768)	p Value
Age, y, mean (SD)	85.9 (6.3)	80.0 (7.4)	<0.001
Women, n (%)	78 (69.0)	580 (75.5)	0.16
Education, y, mean (SD)	14.3 (2.9)	14.4 (3.0)	0.56
Mini-Mental State Examination score, out of 30,[a] mean (SD)	25.9 (2.6)	28.2 (1.8)	<0.001
Hemoglobin, g/dL, mean (SD)	13.2 (1.5)	13.4 (1.3)	0.42
Mean corpuscular volume, μL, mean (SD)	92.2 (5.4)	92.1 (5.1)	0.83
Red cell distribution width, mean (SD)	13.9 (1.1)	14.0 (1.2)	0.58
Body mass index, kg/m^2, mean (SD)	26.2 (4.3)	27.5 (5.4)	0.01
Glomerular filtration rate, mg/mL/1.73 m^2, mean (SD)	55.7 (16.8)	59.1 (15.8)	0.05
No. of chronic medical conditions, out of 12,[b] mean (SD)	1.4 (1.4)	1.5 (1.3)	0.55
Forced expiratory volume, L in 1 s, mean (SD)	1.6 (0.5)	1.6 (0.6)	0.37
Forced vital capacity, L, mean (SD)	2.0 (0.6)	1.9 (0.5)	0.73
Physical activity, h/wk, mean (SD)	3.2 (3.8)	3.2 (3.6)	0.91
Cognitive activity, frequency/wk, mean (SD)	2.8 (0.8)	3.2 (0.7)	<0.001
Depressive symptoms, out of 10, mean (SD)	1.7 (2.1)	1.2 (1.7)	0.003
Social network contacts, no. seen at least once per month, mean (SD)	5.3 (4.3)	6.5 (5.9)	0.03
Number with *APOE* ε4 allele (% of available genotypes)	29 (25.9)	151 (21.0)	0.27

Abbreviation: AD = Alzheimer disease.
[a] The Mini-Mental State Examination score has a maximum value of 30 with higher scores indicating better performance.
[b] Chronic medical conditions determined by report of cancer, congestive heart failure, coronary artery disease, depression, diabetes, head injury, hip fracture, hypertension, smoking, stroke, Parkinson disease, and thyroid disease.

Table 2 Relationship of baseline hemoglobin with incident Alzheimer disease

Variable	Model A,[a] hazard ratio (95% CI)	Model B,[b] hazard ratio (95% CI)
Age (per year)	1.10 (1.06–1.14)	1.12 (1.08–1.16)
Male sex	1.49 (0.95–2.35)	1.14 (0.63–2.09)
Education (per year)	0.98 (0.91–1.05)	1.02 (0.95–1.09)
Hemoglobin	0.20 (0.06–0.74)	0.17 (0.04–0.79)
Hemoglobin × hemoglobin[c]	1.06 (1.01–1.11)	1.07 (1.01–1.13)

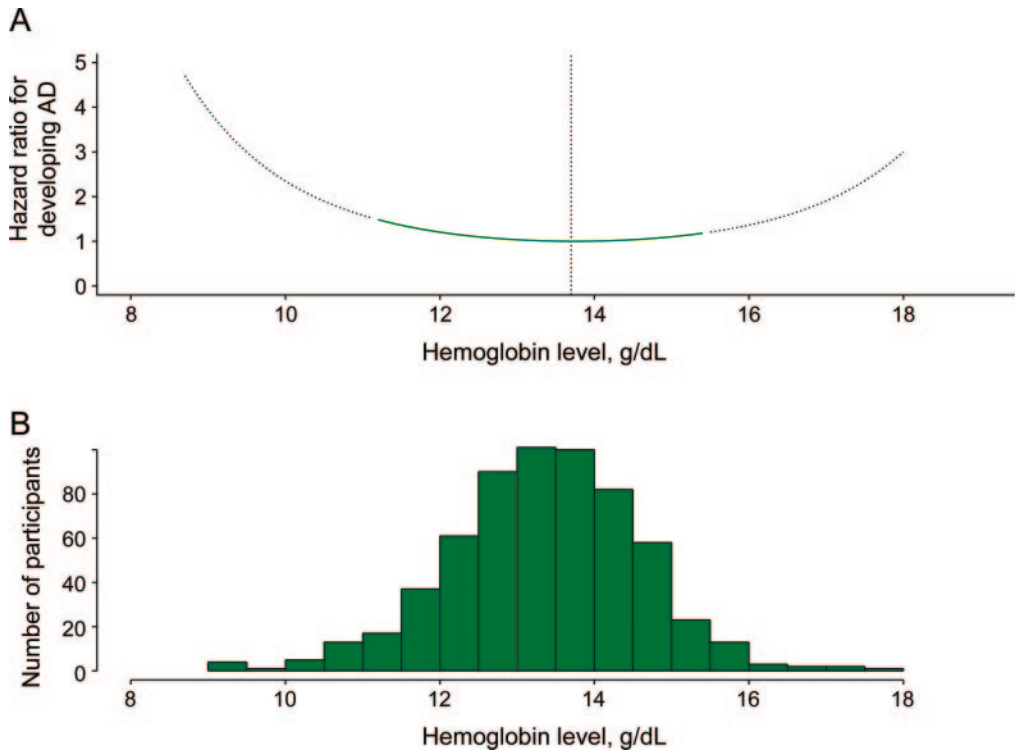
Abbreviation: CI = confidence interval.
[a] From proportional hazards model adjusted for age, sex, and education.
[b] From proportional hazards model which included all the terms in model A as well as terms for the following covariates: linear and nonlinear terms for mean corpuscular volume, red cell distribution width, linear and nonlinear terms for body mass index, estimated glomerular filtration rate, forced expiratory volume, forced vital capacity, number of 12 common chronic conditions reported, physical activity, cognitive activity, depressive symptoms, social networks, and the presence of an *APOE* ϵ4 allele.
[c] The effect of a 1 g/dL difference in hemoglobin.

scores, lower body mass index, lower cognitive activity, more depressive symptoms, and lower social network contacts as compared to individuals who did not (table 1).

Using a Cox proportional hazards model adjusted for age, sex, and education, both linear and quadratic terms for hemoglobin were associated with incident AD (table 2, model A). As shown in figure 1, the incident AD hazard ratios (HRs) increased with hemoglobin levels lower or higher than 13.7 g/dL. In a model comparing the hazard for developing AD for participants with anemia or clinically high hemoglobin to participants with clinically normal hemoglobin, anemia was associated with a 60% increased hazard ratio (95% CI 1.02–2.52). Having a clinically high hemoglobin level also was associated with an increased hazard for developing AD (HR 3.39; 95% CI 1.25–9.20).

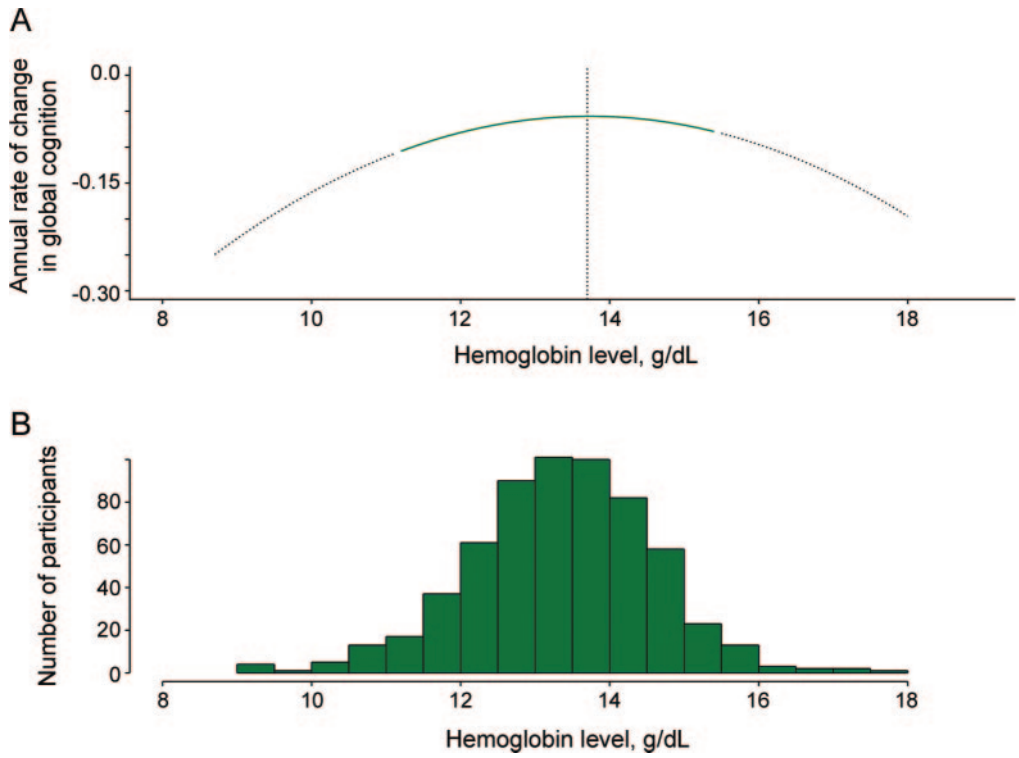
When we repeated the core model to determine if the association between baseline hemoglobin level and incident AD varied by demographic variables, no interactions were found (results not shown). When we repeated the core model by adding terms for covariates potentially associated with hemoglobin levels (linear and quadratic terms for mean corpuscular volume, red cell distribution width, linear and quadratic terms for body mass index, glomerular filtration rate, common chronic medical conditions, and pulmonary function measures) and potentially associated with cognitive function (physical activity, cognitive activity, depressive symptoms, social net-

Figure 1 Hazard ratio for incident Alzheimer disease (AD) as a function of baseline hemoglobin level



(A) The curve is generated from a proportional hazards model with age, sex, education, and linear and quadratic terms for hemoglobin. Reference hazard ratio was for the hemoglobin level associated with the lowest hazard ratio (13.7 g/dL). (B) The distribution of hemoglobin for the cohort depicts data available for interpreting the relationship of baseline level to risk of AD.

Figure 2 Rate of annual cognitive decline as a function of baseline hemoglobin level



(A) The curve is generated from a mixed-effects model with time, age, sex, education, linear and quadratic terms for hemoglobin, and each term's interaction with time. Y-axis shows the annual rate of change in cognition with a more negative value associated with a more rapid rate of decline. Lowest annual rate of cognitive decline was associated with hemoglobin of 13.7 g/dL. (B) The distribution of hemoglobin for the cohort depicts data available for interpreting the relationship of baseline level to annual rate of cognitive decline.

works, and presence of an *APOE* ϵ4 allele), the association between baseline hemoglobin and incident AD was unchanged (table 2, model B). When we repeated the core model excluding participants with MCI, the HR for developing AD was unchanged but no longer significant (HR for quadratic of hemoglobin 1.08; 95% CI 0.99–1.17).

Hemoglobin and rate of change in cognition. To ensure that our findings were not an artifact of diagnostic classification and to control for baseline global cognitive function, we examined the relation of hemoglobin level with rate of cognitive decline. Baseline global cognition *z* scores ranged from −1.81 to 1.43, with higher scores indicating better function. Linear mixed-effects models adjusted for age, sex, education, and baseline level of cognition showed that lower and higher hemoglobin levels were associated with a greater annual rate of global cognitive decline (parameter estimate for quadratic of hemoglobin = −0.008, SE −0.002, $p < 0.001$). The lowest rate of decline was associated with a hemoglobin level of 13.7 g/dL (figure 2). Compared to participants with clinically normal hemoglobin, participants with anemia had a more rapid cognitive decline (parameter estimate = −0.061, SE 0.012, $p < 0.001$) as did participants with clinically high hemoglobin (parameter estimate = −0.090, SE 0.038, $p = 0.018$). Since baseline age was associated with cognitive decline in this model, having anemia can be contextualized as being associated with an equivalent rate of cognitive decline associated with a participant approximately being 12 years older (anemia × time, −0.061 = age × time, −0.005 × 12 years). Having clinically high hemoglobin was associated with an equivalent rate of cognitive decline for a participant approximately being 18 years older. Hemoglobin was nonlinearly associated with all specific cognitive domains except visuospatial ability (table 3).

DISCUSSION In nearly 900 older persons without dementia examined annually for up to 5 years, low and high hemoglobin levels were associated with incident AD. Our complementary finding that low and high hemoglobin levels were associated with the rate of cognitive decline in analyses that controlled for baseline level of cognition suggests that the association of hemoglobin with incident AD is not likely the result of diagnostic misclassification. The results point to the possibility of common pathophysiologic processes between he-

Table 3 Relationship of baseline hemoglobin with decline in specific cognitive domains[a]

	Cognitive domain parameter estimate (SE, *p* value)				
Variable	**Episodic memory**	**Semantic memory**	**Perceptual speed**	**Visuospatial ability**	**Working memory**
Time	−1.273 (0.358, <0.001)	−1.691 (0.339, <0.001)	−1.299 (0.369, <0.001)	−0.658 (0.451, 0.115)	−1.441 (0.364, <0.001)
Hemoglobin[b]	0.287 (0.200, 0.151)	0.397 (0.182, 0.030)	0.733 (0.223, 0.001)	0.142 (0.219, 0.517)	0.168 (0.214, 0.434)
Hemoglobin × time	0.175 (0.054, 0.001)	0.236 (0.051, <0.001)	0.173 (0.056, 0.002)	0.088 (0.068, 0.20)	0.200 (0.055, <0.001)
Hemoglobin × hemoglobin	−0.011 (0.008, 0.153)	−0.015 (0.007, 0.036)	−0.026 (0.008, 0.002)	−0.003 (0.008, 0.74)	−0.006 (0.008, 0.46)
Hemoglobin × hemoglobin × time	−0.006 (0.002, 0.002)	−0.008 (0.002, <0.001)	−0.006 (0.002, 0.003)	−0.003 (0.003, 0.21)	−0.007 (0.002, <0.001)

[a] From mixed-effects model adjusted for age, sex, and education, and terms for the interaction with time in study.
[b] The effect of a 1 g/dL difference in hemoglobin.

moglobin abnormalities and brain dysfunction in elders.

A novel feature of this study is the ability to examine the effects of the entire range of hemoglobin levels on hazard of developing AD. To our knowledge, prior studies only examined clinically low hemoglobin levels (anemia) and found mixed results. A retrospective cohort study of persons over age 65 with anemia found no increased hazard for AD over 5 years of follow-up[9] while a prospective study in an older Swedish cohort found that anemia was associated with a 2-fold increased hazard for developing AD over 3 years.[10] Our work is consistent with the prior prospective cohort finding with anemia. The current study extends prior work in 2 important ways. First, by measuring the full range of hemoglobin, the current study found that each unit of hemoglobin lower and higher than 13.7 g/dL was nonlinearly associated with an increased risk of incident AD. Second, the current study found that there is also a nonlinear relationship between hemoglobin and the rate of cognitive decline, consistent with our prior cross-sectional data.[8] As hemoglobin is frequently measured in current clinical practice, these results may have important translational consequences for identifying older persons at increased risk for developing AD and cognitive decline in our aging population.

The mechanisms linking hemoglobin levels to incident AD and cognitive decline are not understood. The association of hemoglobin levels and AD may be due to both being markers for frailty in older persons. Low hemoglobin level may be a marker for ischemia associated with cerebrovascular disease, hypoxia-associated changes in hypoxia inducible factor and erythropoietin levels, or oxidative stress–associated changes in heme regulation. Our finding that hemoglobin levels are associated with cognitive decline in other domains than episodic memory hints at a potential vascular cause. In older, community-dwelling persons, anemia has been associated with increased risk of white matter disease progression on neuroimaging.[28] Second, chronic kidney disease (associated with low hemoglobin levels) could result in cerebral hypoxia. Initial studies mainly in animal models point to chronic kidney disease[29] being associated with decreased production of hypoxia inducible factor, which may reduce erythropoietin production. As erythropoietin receptors have been localized in the brain[30] and seem to have a neuroprotective effect in animal models of stroke or hypoxia,[31,32] lower erythropoietin levels may increase the risk of neuronal degeneration in certain cognitive pathways. Finally, greater red cell fragility in conditions associated with lower hemoglobin levels may lead to brain astroglia having to process more heme molecules crossing the blood–brain barrier. Heme may upregulate the production of hemo-oxygenase-1 resulting in increased sterol dysregulation and oxidative stress damage, especially in individuals already with subclinical AD pathology.[33] Our finding of high hemoglobin levels being associated with AD and cognitive decline warrant further investigation given the limited number of cases with clinically high hemoglobin levels. High hemoglobin levels may be associated with cognitive decline via ischemic and hypoxic mechanisms. Polycythemia vera has been associated with an increased risk of cerebral thrombosis.[34] In limited studies, chronic obstructive pulmonary disease (associated with high hemoglobin levels) has been associated with cognitive decline in older persons[35] and with decreased frontal and parietal lobe perfusion on brain imaging.[36] Further studies are needed to determine the biologic basis for the association between hemoglobin, cognitive decline, and AD in elders.

Strengths of our study include detailed annual cognitive and clinical evaluations on a large, community-based cohort. We also were able to adjust for some important comorbidities associated with hemoglobin levels and AD. Our study has limitations. Although we were able to find an association between hemoglobin and incident AD, our study design limits our ability to determine whether hemo-

globin alone causes AD or whether hemoglobin levels and AD may share a common cause. Also, due to the multiple risk factors that may be associated with both hemoglobin levels and AD, we were not able to adjust for other factors that may be associated with both items including but not limited to macronutrient and micronutrient deficiencies.

Our findings suggest that low hemoglobin levels may need to be considered as a potential contributing factor to the development of AD in older persons. Before tests of specific interventions in the elderly to correct hemoglobin abnormalities on reducing the hazard of developing AD are initiated, further confirmation of the relationship between hemoglobin and AD will be needed from other longitudinal cohort studies.

AUTHOR CONTRIBUTIONS

Dr. Shah: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Buchman: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. Dr. Wilson: drafting/revising the manuscript, analysis or interpretation of data. Dr. Leurgans: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Dr. Bennett: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding.

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DISCLOSURE

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