Published in final edited form as:

J Am Geriatr Soc. 2014 May ; 62(5): 972–973. doi:10.1111/jgs.12810.

LOWER HEMOGLOBIN IS ASSOCIATED WITH POORER COGNITIVE PERFORMANCE AND SMALLER BRAIN VOLUME IN OLDER ADULTS

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To the Editor

Anemia, a condition defined by abnormally low hemoglobin (Hb) levels, is a potential risk factor for cognitive impairment and dementia¹ that is not only common but also increases in prevalence with older age. One in 10 adults aged 50 and older meets criteria for anemia. This proportion doubles for those aged 85 and older.² Anemia is of particular concern for elderly African Americans, who have lower Hb on average and a prevalence of anemia two

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Jonassaint: study concept and design, analysis and interpretation of data, preparation of manuscript. Varma, Chuang, Harris: study concept and design, acquisition of subjects and data, analysis and interpretation of data, preparation of manuscript. Polinder-Bos, Yasar: study concept and design, revising of manuscript for important intellectual content. Carlson: study principal investigator and lead, study concept and design, interpretation of data and analyses, preparation of manuscript. All authors approved the submitted version of this manuscript.

to three times as great as that of their white counterparts, a disparity that socioeconomic status, health behaviors, nutrition, or other chronic diseases do not account for.³

In a sample of predominantly black, urban-dwelling older adults, the association was investigated between Hb levels and cognitive performance and brain volumetric measures. It was hypothesized that lower Hb would be associated with poorer cognitive function and smaller brain volume, independent of comorbidities related to anemia.

Information was collected on blood and cognitive tests and brain magnetic resonance imaging (MRI) at baseline between 2006 and 2009 in older adults from the Brain Health Study (BHS),⁴ a substudy within the Baltimore Experience Corps Trial (BECT). The study design and eligibility criteria for the BECT have been described elsewhere.⁵ At the baseline visit, a research nurse measured body mass index (BMI; kg/m²) and collected nonfasting blood samples for a number of assays, including Hb, white blood cell count (WBC), mean corpuscular volume (MCV), glycosylated Hb (HbA1c), total bilirubin, and creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Participants completed tests of processing speed, working memory and executive functioning, verbal learning, and memory. Processing speed was measured using the paper-and-pencil versions of the Trail-Making Test Part A (TMT-A);⁶ the Pattern Comparison task;⁷ and the Color “X” condition of a computer-administered, modified version of the Stroop Color–Word Task.⁸ Working memory was measured using the Digit Span Forward and Backward tasks.⁹ Verbal learning and memory were measured using the Rey Auditory Verbal Learning Test (RAVLT).¹⁰ Executive functioning was measured using the Trail-Making Test Part B (TMT-B)⁶ and the Color–Word (e.g., “red” printed in blue ink) condition of the computer-administered Stroop task.⁸ Neuroimaging data were collected (3.0T scanner; Phillips, Best, the Netherlands) with Magnetization Prepared Rapid Gradient Echo and T1-weighted MRI acquisition. Brain volumetric measurements are reported in cm³ and include total intracranial volume (ICV) and cortical gray matter and white matter adjusted for ICV.

More than half of the 196 participants (85% female, 93% black) were obese (BMI >30.0 kg/m²), and 67% reported being hypertensive. Mean Hb level was 12.99 g/dL (range 9.8–16.9 g/dL).

In multivariable regression models that included age, sex, education, hypertension, BMI, HbA1c, eGFR, and depressive symptoms, lower Hb was associated with slower processing speed (pattern comparison and TMT-A) and working memory (Digit Span Task) but not executive functioning (Stroop and TMT-B), verbal learning, or memory (RAVLT). For MRI measures, lower Hb was associated with smaller ICV and gray matter volume; the direction of effect was similar for white matter volume (Table 1). Although cross-sectional, these results may indicate that the effect of low hemoglobin is evident in brain and behavior.

The current study has some important implications for research on cognition in older adults. Several studies have found an association between anemia, or lower Hb, and cognitive function in healthy older adults, but to the knowledge of the authors of the current study, this

is the first to examine the associations between anemia and specific cognitive domains in a predominately black population. Research findings on anemia from majority populations may not be generalizable to racial and ethnic minority groups. In addition, the association between lower Hb and cognitive functioning may be specific to working memory and processing speed; studies that have not specifically measured these domains may not have detected an effect. Finally, an association was found between low Hb and smaller brain volume, providing a potential mechanism to explain the greater risk of dementia in individuals with anemia.¹¹ The overall negative effect of low Hb on brain outcomes in these data supports the notion that chronic hypoxia accelerates cognitive decline and increases the risk of brain disease.¹²

Acknowledgments

Funded by the Johns Hopkins Claude D. Pepper Center, the Johns Hopkins Neurobehavioral Research Unit, a supplement to National Institute on Aging Grant P01-AG027735-03, a gift from S.D. Bechtel, and the Alzheimer's Drug Discovery Foundation.

Sponsor's Role: None.

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Table 1

Multivariable Regression Analyses for Associations Between Hemoglobin Level and Cognitive Domains
Brain Volumetric Measures (cm³) After Adjustment for Potential Confounders

Outcome	Coefficient ^a (95% Confidence Interval)	Correlation Coefficient	P-Value
Cognitive test			
Trail-Making Test Part A	-2.94 (-5.45 to -0.43)	-0.25	.02
Trail-Making Test Part B-A	-8.77 (-19.55-2.01)	-0.17	.11
Digit span			
Forward	0.40 (0.12-0.68)	0.30	.006
Backward	0.69 (0.30-1.09)	0.36	.001
Total	1.09 (0.50-1.69)	0.38	<.001
Pattern comparison	0.90 (0.09-1.72)	0.23	.03
Stroop task			
Color 'X' condition ^b	-20.92 (-57.11-15.26)	-0.13	.25
Color-word condition	0.01 (-0.02-0.04)	0.05	.64
Rey Auditory Verbal Learning Test			
Trial 1-5 total	0.92 (-0.40-2.24)	0.15	.17
Long delay	0.06 (-0.45-0.58)	0.03	.80
Brain volume ^c			
Intracranial	19.93 (-5.76-45.63)	0.18	.07
White matter	3.58 (-3.02-10.20)	0.13	.28
Gray matter	5.31 (-0.80-10.70)	0.22	.05

Analyses were adjusted for age, sex, education, hypertension, body mass index, glycosylated hemoglobin, estimated glomerular filtration rate, and depressive symptoms.

^aThe effect of a 1-g/dL difference in hemoglobin.

^bLack of an association with the Stroop Color "X" condition may have been due to lack of participant facility with the color-coded keypad used for testing.

^cStructural volumes adjusted for intracranial volume.