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# Relation of Hemoglobin to Level of Cognitive Function in Older Persons

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**Key Words**
Hemoglobin · Anemia · Cognition · Elderly · Gender · Cross-sectional study

**Abstract**
***Background:*** While decreased hemoglobin concentration is common in the elderly, the relationship of the entire range of hemoglobin concentrations with cognitive function is not well understood. ***Methods:*** Cross-sectional analyses were conducted utilizing data from community-dwelling, older persons participating in the Rush Memory and Aging Project. Proximate to first available hemoglobin measurement, 21 cognitive tests were administered to measure global cognitive function along with semantic memory, episodic memory, working memory, perceptual speed and visuospatial abilities. ***Results:*** For 793 participants without clinical dementia, stroke or Parkinson's disease, the mean age was 81.0 years (SD = 7.2); 595 (75%) were women, and 94% were white. The mean hemoglobin concentration was 13.3 g/dl (SD = 1.3). 17% of the cohort had anemia. Using linear regression models adjusted for age, education, gender, body mass index, mean corpuscular volume and glomerular filtration rate, both low and high hemoglobin levels were associated with lower global cognitive function (parameter estimate = −0.015, SE = 0.007, p = 0.019). Low and high hemoglobin levels were associated with worse performance on semantic memory (parameter estimate = −0.201, SE = 0.008, p = 0.010) and perceptual speed (parameter estimate = −0.030, SE = 0.010, p = 0.004), but not the other specific cognitive functions. ***Conclusions:*** Low and high hemoglobin concentrations in older persons are associated with a lower level of cognitive function in old age, particularly in semantic memory and perceptual speed.


## Introduction

Low hemoglobin, or anemia, is common in the elderly [1]. In the USA, it is estimated that 10.2% of community-dwelling men and 11% of women over the age of 65 have anemia, although the cause of anemia is unknown in over a third of the cases [2]. Recent studies have highlighted the relationship between anemia and disability [3] and mortality [4, 5]. Cross-sectional studies in older community-dwelling populations have revealed an association between low hemoglobin and cognitive function [5, 6]. While low hemoglobin is recognized as a clinically important measure in older persons, high hemoglobin levels have also been associated with mortality [7]. However, the association of the entire range of hemoglobin concentrations with cognitive function is not well understood.

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In this study, we set out to examine the cross-sectional association of low and high hemoglobin levels to global and specific cognitive function by using a continuous, nonlinear representation of hemoglobin. We utilized data from the Rush Memory and Aging Project, a longitudinal study of aging and Alzheimer's disease in community-dwelling elders. During the study, a complete blood count was done to assess hemoglobin status. The relationship of hemoglobin levels to the results of cognitive tests done proximate to blood collection was examined.

## Materials and 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, as previously described [8]. They come from about 40 groups in the Chicago, Illinois, vicinity (see Acknowledgments). The study was approved by the Institutional Review Board of the Rush University Medical Center. The Memory and Aging Project began in 1997 and is still ongoing with rolling enrollment. As of July 3, 2006, 1,101 individuals had signed consent to participate in the Memory and Aging Project. Blood specimen collection for complete blood counts began in 2003. We identified 949 participants who had blood work collected and nonmissing, proximate cognitive data as our initial cohort. Of these, 156 participants were not included in the analysis secondary to a diagnosis of stroke, dementia or Parkinson's disease. Among the 793 included in all analyses, individuals had their first hemoglobin level measured between February 11, 2003, and July 3, 2006. Cognitive testing was conducted within an average of 11 days (SD = 22) of the hemoglobin level measurement.

*Assessment of Cognitive Function*

A battery of 21 cognitive function tests was administered in an approximately 1-hour session. The Mini-Mental State Examination [9] was used to describe the cohort but not in analyses, and Complex Ideational Material [10] was used only for diagnostic classification. The remaining 19 tests represented 5 domains of cognition. Seven tests assessed episodic memory: Word List Memory, Word List Recall and Word List Recognition [11]; immediate and delayed recall of story A from the Logical Memory subtest of the Revised Wechsler Memory Scale [12], and immediate and delayed recall of the East Boston Story [13]. Three tests assessed semantic memory: Verbal Fluency [11], a 15-item version of the Boston Naming Test [14], and a 15-item reading test [15]. There were 3 tests of working memory: Digits Forward and Digits Backward from the Revised Wechsler Memory Scale [12] and Digit Ordering [16]. Four tests assessed perceptual speed: the oral version of the Symbol Digit Modalities Test, Number Comparison [17] and two indices from a modified version of the Stroop Neuropsychological Screening Test [18]. Finally, there were 2 tests of visuospatial ability: items from Judgment of Line Orientation [19] and Standard Progressive Matrices [20]. A greater score on each of these tests represented a better performance.

To minimize floor and ceiling artifacts and other sources of measurement error, summary measures were created for semantic memory, episodic memory, working memory, perceptual speed and visuospatial ability. All the summary measures were constructed by converting the raw scores from the individual tests to z-scores, using the mean and standard deviation from the baseline evaluation of all participants, and averaging the z-scores. Therefore, the summary measures had a mean of 0; however, their standard deviations were not equal to 1. Similarly, a summary measure for global cognition was created by converting the raw scores of all 19 tests into z-scores and averaging the z-scores. A summary score was treated as missing if less than half of the component tests had valid scores. Higher (more positive) z-scores represent better performance while lower (more negative z-scores) represented worse cognitive performance. Further information on the individual tests and the derivation of the cognitive measures is published elsewhere [21].

*Measurement of Hemoglobin*

A standard procedure was used to collect blood samples. Using sterile technique, phlebotomists and nurses skilled in venipuncture collected the blood specimen in a 2-ml EDTA tube. Specimens were transferred to Quest Laboratories (Wood Dale, Ill., USA) for a complete blood count analysis using a Beckman/Coulter LH750 automated processor. Using World Health Organization criteria, anemia was defined as having a hemoglobin level less than 13 g/dl for men and less than 12 g/dl for women [22].

*Covariates*

Individuals were asked for demographic information including date of birth, highest number of years of education completed, gender and race. Lifetime occupation was coded according to perceived prestige [23] and was converted to z-scores, using a method described in a previous publication [24]. Body mass index was calculated by dividing the measured weight converted to kilograms by the square of the measured height expressed in meters. Mean corpuscular volume was determined from impedance-based measures of individual red blood cell volumes using a Beckman/Coulter LH750 automated processor. We calculated glomerular filtration rate using the 4-variable formula derived from the Modification of Diet in Renal Disease Study [25], where serum creatinine was determined using an Olympus AU4500 instrument at Quest Laboratories. Serum creatinine levels were not recalibrated to be traceable by isotope dilution mass spectrometry.

*Statistical Analysis*

A regression model was developed to estimate the linear and quadratic relation of each 1 g/dl of hemoglobin with global cognitive function. Age, education and gender were added as demographic covariates. The variables for age, education and hemoglobin were centered on their respective means. The model was also adjusted for additional variables including a linear and quadratic term for body mass index, a linear and quadratic term for mean corpuscular volume, and glomerular filtration rate.

In secondary analyses, we repeated our model to address 3 issues. First, we replaced the terms for hemoglobin and hemoglobin squared with anemia as a categorical predictor (hemoglobin $<12$ g/dl for women and $<13$ g/dl for men). Then, we examined the effect of occupation by repeating the model with a term for lifetime occupational prestige. Third, to examine the effects of race, the model was repeated with a term for black race added as a covariate.

**Table 1.** Characteristics of participants excluded and included in the cohort

| Variable | Excluded participants (n = 156) | Included participants (n = 793) | Included men (n = 198) | Included women (n = 595) |
|---|---|---|---|---|
| Age, years | 83.2 ± 7.1* | 81.0 ± 7.2 | 81.5 ± 6.5 | 80.9 ± 7.4 |
| Education, years | 14.4 ± 3.1 | 14.5 ± 3.0 | 15.3 ± 3.4 | 14.2 ± 2.7 |
| Mini-Mental State Examination score[a] | 23.6 ± 6.6* | 27.9 ± 2.1 | 27.5 ± 2.4 | 28.0 ± 1.9 |
| Hemoglobin, g/dl | 13.0 ± 1.5* | 13.3 ± 1.3 | 13.9 ± 1.5 | 13.2 ± 1.2 |
| Body mass index | 25.9 ± 4.8* | 27.4 ± 5.3 | 26.7 ± 4.0 | 27.6 ± 5.8 |
| Mean corpuscular volume, μl | 92.0 ± 5.5 | 92.2 ± 5.2 | 93.1 ± 5.8 | 91.9 ± 5.0 |
| Creatinine, mg/dl | 1.2 ± 0.3* | 1.1 ± 0.6 | 1.3 ± 0.5 | 1.1 ± 0.6 |
| Blood urea nitrogen, mg/dl | 22.3 ± 8.0* | 20.6 ± 8.3 | 21.3 ± 7.0 | 20.4 ± 8.7 |
| Glomerular filtration rate, mg/ml/1.73 $m^2$ | 54.8 ± 16.6* | 58.2 ± 15.4 | 62.7 ± 16.1 | 56.7 ± 14.9 |

* $p < 0.05$ for difference between excluded cohort and included cohort.
[a] The Mini-Mental State Examination score has a maximum value of 30 with higher scores indicating better performance.

To examine whether hemoglobin was associated with specific components of cognitive function, the adjusted model described for global cognitive function was repeated with semantic memory, episodic memory, working memory, perceptual speed and visuospatial ability, as the respective outcomes. Next, we repeated all the models replacing the terms for hemoglobin and hemoglobin squared with anemia as a categorical predictor (hemoglobin <12 g/dl for women and <13 g/dl for men).

To determine whether the relationship of hemoglobin to cognitive function was influenced by gender, we repeated the adjusted linear regression models for global and specific cognitive outcomes by adding the interaction of each hemoglobin term with gender. For the dichotomous gender variable, the reference group was defined to be men. We also constructed models stratified by gender for the linear and quadratic terms of hemoglobin that were adjusted for age, education, mean corpuscular volume, body mass index and glomerular filtration rate. To see if age affected the relationship between gender, hemoglobin and global cognition, we repeated our initial model with additional terms for the interaction of each hemoglobin variable with gender, age, and the combination of gender and age. We did not find a significant interaction between hemoglobin, gender and age (results not reported).

All models were validated graphically and analytically. Model assumptions of normality, independence and constant variance of errors were adequately met. Analyses were carried out in SAS®, version 8 (SAS Institute Inc., Cary, N.C., USA). Given multiple comparisons with the models examining specific components of cognitive function, we utilized a p value of less than 0.01 rather than 0.05 as a more stringent criterion for statistical significance.

## Results

The characteristics of Memory and Aging Project participants with a hemoglobin measurement and proximate cognitive testing are shown in table 1. The 156 individuals who did not meet inclusion criteria (due to diagnosis of stroke, Parkinson's disease or dementia) had lower hemoglobin levels and Mini-Mental State Examination scores than the 793 individuals in the cohort. They were also older, had a lower body mass index and had worse kidney function. Education level, mean corpuscular volume, gender and race did not differ between the two groups.

Of the 793 individuals in the cohort, the mean hemoglobin level was 13.3 g/dl (SD = 1.3, range = 8.7–18.0). The cohort was 94% white. In women (75% of the cohort), the mean hemoglobin was 13.2 g/dl (SD = 1.2). In men, the mean hemoglobin was 13.9 g/dl (SD = 1.5). Anemia was present in 14% of the women and 26% of the men. Only 3.5% of the participants were on iron replacement therapy. The mean body mass index was in the overweight category. The mean glomerular filtration rate of 58.2 mg/ml/1.73 $m^2$ (SD = 15.4) was in the moderate (stage 3) chronic kidney disease level by national guidelines [26]. Age was negatively correlated with hemoglobin ($p = 0.03$). Education level was positively associated with hemoglobin ($p < 0.001$). Being a woman was correlated with lower hemoglobin ($p < 0.001$).

*Hemoglobin and Cognition*

In order to determine the association between hemoglobin and cognitive function, a regression model was developed with global cognitive function as the outcome. In addition to adjustments for age, education and gender, we examined other covariates. Because hemoglobin level is associated with body mass index [27] and decreased renal function [28], we determined the effects of these covari-

**Table 2.** The relationship of high and low hemoglobin, gender, and global and specific cognitive functions

| Cognitive outcome | Parameter estimate | |
|---|---|---|
| | model A (hemoglobin × hemoglobin) | model B (hemoglobin × hemoglobin × gender) |
| Global cognition | –0.015 (0.007, 0.019) | –0.035 (0.015, 0.019) |
| Semantic memory | –0.021 (0.008, 0.010) | –0.051 (0.019, 0.007) |
| Episodic memory | –0.014 (0.009, 0.108) | –0.031 (0.020, 0.119) |
| Working memory | –0.006 (0.010, 0.566) | –0.039 (0.022, 0.086) |
| Perceptual speed | –0.030 (0.010, 0.004) | –0.037 (0.024, 0.116) |
| Visuospatial ability | 0.001 (0.010, 0.905) | –0.023 (0.023, 0.328) |

In parentheses, standard errors and p values are indicated. Model A: from a linear regression model including terms for age, education level, gender, body mass index, body mass index squared, mean corpuscular volume, mean corpuscular volume squared, glomerular filtration rate, hemoglobin and hemoglobin squared. Model B: model A with the addition of terms for the interaction of each hemoglobin variable with gender. 'Hemoglobin' represents an increment of 1 g/dl.

ates by adding terms for linear and quadratic body mass index and calculated glomerular filtration rate based on the 4-variable Modification of Diet in Renal Disease equation. Also, we added a linear and quadratic term for mean corpuscular volume in an attempt to adjust for the effects of microcytosis and macrocytosis. We included terms for hemoglobin and hemoglobin squared to allow for nonlinearity in hemoglobin's association with cognitive function. As shown in model A of table 2, each unit increment in hemoglobin squared was associated with lower cognitive function (parameter estimate = –0.15, SE = 0.007, p = 0.019) for the outcome of global cognition, indicating that both low and high levels of hemoglobin were associated with lower cognitive function.

In secondary analyses, when we repeated the models using a dichotomous variable for anemia rather than the continuous measures of hemoglobin and hemoglobin squared, the relationship between anemia and global cognition was not quite significant (parameter estimate = –0.090, SE = 0.047, p value = 0.054). As other socioeconomic variables than education may influence the relationship between hemoglobin and cognition, we used the lifetime occupational data on 707 of the 793 participants to adjust for occupation. In this analysis, the association between hemoglobin squared and global cognition was unchanged (parameter estimate = –0.015, SE = 0.001, p = 0.025). As race may influence the relationship of hemoglobin to cognition [5], the model was repeated adjusting for black race. No significant difference in the association of hemoglobin squared to cognition was noted (results not shown).

Cognition is not a unitary construct but is composed of dissociable cognitive systems. To see if hemoglobin was associated with some cognitive abilities but not others, separate regression models were conducted with semantic memory, episodic memory, working memory, perceptual speed and visuospatial ability as the outcomes. As shown in model A of table 2, hemoglobin squared was associated with worse semantic memory (p = 0.010) and perceptual speed (p = 0.004).

*Hemoglobin, Gender and Cognition*

As our initial descriptive analyses showed that being a woman was associated with a lower hemoglobin level and since WHO criteria for anemia are gender specific, we considered the possibility that the relationship between hemoglobin and cognitive function might be modified by gender. Therefore, we repeated our global cognitive model with additional terms for the interaction of gender with hemoglobin and hemoglobin squared. As shown in model B of table 2, the association of hemoglobin squared with worse global cognition was greater in women compared to men (parameter estimate = –0.035, SE = 0.015, p = 0.019). In models with specific cognitive systems, this interaction was evident only in semantic memory (model B, table 2).

To further investigate these gender differences, we created gender-stratified linear regression models adjusted for age, education, body mass index, mean corpuscular volume and glomerular filtration rate. As shown in table 3, hemoglobin squared was significantly associated with worse global cognition, semantic memory and per-

**Table 3.** The relationship of high and low hemoglobin and global and specific cognitive functions stratified by gender

| Cognitive outcome | Parameter estimate | |
|---|---|---|
| | women (n = 595) (hemoglobin × hemoglobin) | men (n = 198) (hemoglobin × hemoglobin) |
| Global cognition | –0.028 (0.009, 0.001) | 0.008 (0.014, 0.560) |
| Semantic memory | –0.038 (0.011, 0.001) | 0.008 (0.015, 0.598) |
| Episodic memory | –0.028 (0.012, 0.019) | 0.006 (0.018, 0.732) |
| Working memory | –0.020 (0.013, 0.122) | 0.025 (0.020, 0.221) |
| Perceptual speed | –0.044 (0.014, 0.002) | –0.005 (0.020, 0.812) |
| Visuospatial ability | –0.005 (0.014, 0.703) | 0.013 (0.019, 0.500) |

In parentheses, standard errors and p values are indicated. From a linear regression model including terms for age, education level, body mass index, body mass index squared, mean corpuscular volume, mean corpuscular volume squared, glomerular filtration rate, hemoglobin and hemoglobin squared. 'Hemoglobin' represents an increment of 1 g/dl.



ceptual speed in women (n = 595). By contrast, hemoglobin was not associated with cognition in men (n = 198). The association of hemoglobin and global cognitive function in women is illustrated in figure 1. The best-fit curve describing the association between hemoglobin and global cognitive function in women is an inverted U-shaped curve with a maximum global cognitive function corresponding to a hemoglobin level of 13.4 g/dl (for an 81-year old woman with 14 years of education).

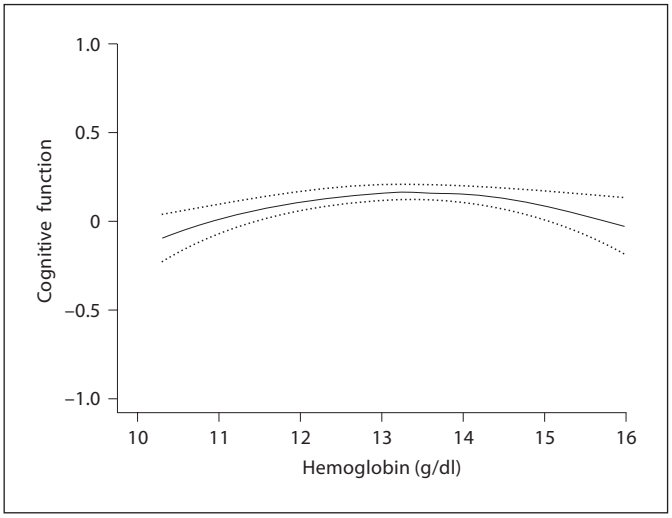


**Fig. 1.** The association of global cognition as a function of hemoglobin in women (n = 595). Using the best-fit quadratic, the association of hemoglobin with 95% confidence intervals and global cognitive function was measured by the arithmetic mean of the z-scores for 19 individual tests in a neuropsychological battery (mean = 0, SD = 0.53).

## Discussion

In this cohort of nearly 800 older persons, we examined the association of hemoglobin concentrations with global and specific measures of cognitive function. Our results suggest that both low and high hemoglobin concentrations are associated with worse cognition.

Other studies in community-dwelling, older cohorts show that anemia is associated with worse cognition [5, 6]. Our work is consistent with the findings; however, a dichotomous anemia variable as defined by the World Health Organization does not fully capture the effects of the entire range of hemoglobin levels on cognition in older persons. The results of this study show that high hemoglobin along with low hemoglobin is associated with worse global cognition. Therefore, utilizing a continuous, nonlinear measure may be a better way to characterize the relationship between hemoglobin and cognitive function.

A novel feature of this study is the availability of previously established measures of different cognitive systems. We found that hemoglobin was related to semantic memory and perceptual speed but not to episodic memory, working memory or visuospatial ability. The basis of this differential effect is uncertain. Both the semantic memory and perceptual speed composite measure include tests of executive function (i.e. verbal fluency, Stroop Neuropsychological Screening Test). Therefore, our find-

ings are consistent with a previous study that found anemia to be associated with low performance on the Trail Making Test [6].

An unexpected finding in this study was that gender influenced the association of hemoglobin to cognition. Why women are more affected by hemoglobin compared to men is not clearly understood. Our lack of a finding with men must be interpreted with caution as our power to find a relationship between hemoglobin and cognition in men was limited. Further studies in older, community-dwelling cohorts with a larger sample of men will be needed to understand the effect of gender on the relationship between hemoglobin levels and cognition.

The mechanisms linking hemoglobin levels to worse global cognition are not understood and will require further exploration. Low and high hemoglobin may be markers for the presence of conditions such as ischemia (via cerebrovascular disease), hypoxia (via hypoxia-inducible factor and erythropoietin levels) and/or oxidative stress (via iron dysregulation). Anemia significantly increased the risk of stroke in middle-aged, community-dwelling individuals with chronic kidney disease [29], and polycythemia vera, a condition associated with increased red blood cell mass, has been associated with an increased risk for cerebral thrombosis [30]. Second, chronic kidney disease (associated with low hemoglobin levels) and pulmonary disease (associated with high hemoglobin levels) could result in cerebral hypoxia. Hypoxia due to pulmonary disease has been associated with decreased cognitive function in some [31, 32] but not all [33] case-control studies. Initial studies mainly in animal models point to chronic kidney disease [34] and pulmonary disease due to smoking [35] being associated with decreased production of hypoxia-inducible factor, which in turn, may reduce the production of erythropoietin. As erythropoietin receptors have been localized in the brain and seem to have a neuroprotective effect in animal models of stroke or hypoxia [36, 37], lower erythropoietin levels may increase the risk of neuronal degeneration in certain cognitive pathways. Finally, iron dysregulation has been associated with increased brain oxidative stress [38]. Iron supplementation is frequently used as a medical therapy in low hemoglobin environments, and total iron content could be elevated in high hemoglobin conditions. In our analysis, we were unable to test this hypothesis as a small percentage of the cohort was on iron supplementation and as we did not have iron level measures.

The strengths of our study include the ability to conduct systematic, detailed cognitive testing and to analyze the association of concurrent hemoglobin measures and cognition in a large, community-dwelling cohort. We were also able to adjust for important comorbidities and confounders, including renal function and body mass index.

Our study has limitations. First, the cross-sectional design of our study does not prove a cause-effect relationship between hemoglobin and cognitive function. Second, although we were able to find an association between hemoglobin and global cognition, we were unable to fully examine whether the relationship was due to increased blood loss, impaired red blood cell production, and/or increased red blood cell destruction (in the case of low hemoglobin levels) or increased red cell production (in the case of high hemoglobin levels). Also, we were not able to adequately correct for important confounders including inflammatory markers (such as C-reactive protein), direct measures of kidney function (such as cystatin C) and measures of nutritional status (such as albumin). Third, the demographics of our population (majority white with a high education level) and the Memory and Aging Project being a volunteer (rather than a geographically defined) cohort limit application of the findings to a broader elderly population.

Most importantly, our work suggests that hemoglobin levels (both low and high) may need to be considered as a potential contributing factor in older individuals being evaluated for cognitive impairment. The ability to translate a unit change in the cognition measures into terms that are useful for clinical practice will require further investigation.


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