ARIC Manuscript Proposal # 1604

PC Reviewed: 2/9/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association between hemoglobin and cerebral structure and function

b. Abbreviated Title (Length 26 characters): **Hemoglobin and the brain**

2. Writing Group:

Writing group members: Rebecca F. Gottesman, Thomas Mosley, Richey Sharrett, Josef Coresh, Elizabeth Selvin, Brad Astor; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __RG___ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: We anticipate that the analysis will be performed in the coming 3-6 months, with an abstract to be submitted in Spring or Summer 2010 for either the American Neurological Association meeting or the International Stroke Conference; the manuscript will be written and submitted soon after.

4. Rationale: Chronically impaired perfusion to the brain has multiple potential causes, including hypotension and hypoxia. Anemia is another potential mechanism of

inadequate cerebral oxygenation, which may lead to impaired cerebral perfusion and cerebral function. The purpose of this study is to evaluate associations between hemoglobin level and 1) cognitive performance and 2) extent of white matter disease of the brain in a community-based population.

The response of the brain to anemia is one of vasodilation, in an attempt to compensate for this decrease in hemoglobin. Eventually, as hemoglobin falls, this compensation fails and cerebral blood flow is inadequate, sometimes leading to ischemia.[1] In patients undergoing cardiac surgery, lower perioperative hemoglobin levels are associated with higher risk of postoperative stroke.[2] Patients who present with strokes and are anemic have higher mortality than persons who are not anemic.[3] In my own studies, hemoglobin level was associated with worse cognitive performance (hemispatial neglect, particularly), among persons with right-hemispheric stroke (Gottesman, Bahrainwala, and Hillis; accepted as poster presentation for International Stroke Conference, February 2010), independent of size of the infarct (by MRI) (see figure). A similar pattern was found not only for presence of neglect, an indication of right-hemispheric dysfunction, but for severity of neglect. The increased probability of neglect at higher hemoglobin levels may represent hemoconcentration and hypovolemia, which could be associated with worse cognitive performance.

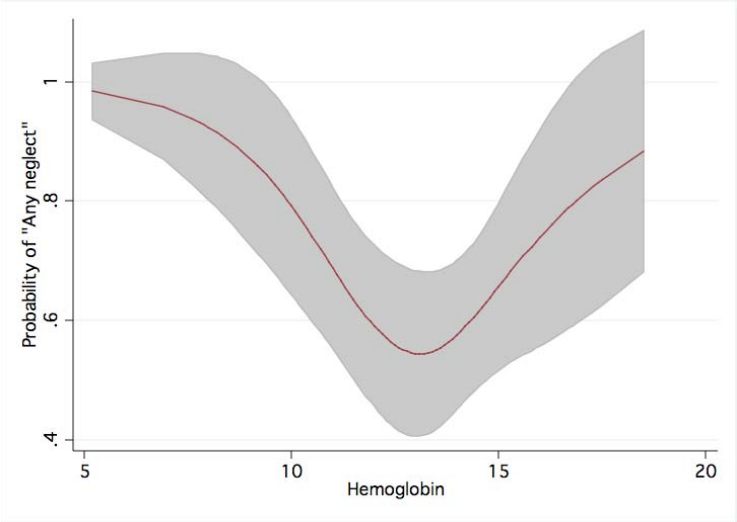

Figure. Probability of hemispatial neglect based on level of hemoglobin (g/dL). Graph shows cubic spline with 95% confidence bands.

In the Rush Memory and Aging project, a similar cross-sectional association was described between hemoglobin level and cognition, with worst performance at extreme values.[4] This U-shaped relationship is not dissimilar to that described for associations between blood pressure and cognitive performance.[5, 6]

Anemia has been identified as a risk factor for dementia in a small meta-analysis of existing data (only 3 studies, of which only 2 could be combined); hazard ratio of 1.94 for risk of dementia with anemia (defined as hemoglobin<13.6 g/dL for men, and <12.6 g/dL for women).[7]

One of the potential consequences to the brain of hypoperfusion is injury to the white matter tracts,[8] which may be apparent in the form of white matter disease, although most investigation in this area is on the role of hypotension. Among 1805 individuals 65 to 75 years of age, both increase in diastolic blood pressure (DBP) and *decrease* in DBP were associated with an increase in severity of periventricular white matter disease.[9] Similarly, in the Rotterdam study, individuals with a drop of DBP of at least 10 mm Hg over 20 years had a relative risk of 2.2 (95% CI 1.0, 5.2) for the presence of subcortical white matter lesions.[10] Animal studies have also supported a role for hypoperfusion in the development of white matter lesions.[11] Mouse models of cerebral hypoperfusion (via carotid artery occlusion) demonstrate delayed ischemic lesions in the white matter and hippocampus.[12, 13]

In the Cardiovascular Health Study, presence of anemia was associated with progression of white matter disease of the brain, but only among individuals with hypertension.[14] It is still unknown, however, whether these associations exist across a wide range of hemoglobin values (and not only in the anemic range), and whether a similar U-shaped relationship exists, with larger volumes of white matter disease at the extreme value of hemoglobin.

5. Main Hypothesis/Study Questions:

1. Level of hemoglobin is associated with cognitive function, with worst cognitive performance at *highest* and *lowest* levels of hemoglobin, independent of other confounders.

a. Hemoglobin levels (from visit 1 and 2) will have a U-shaped association with: 1) cognitive scores on each of the cognitive tests administered at visit 2; 2) cognitive scores from the ARIC-BRAIN MRI visit; and 3) with change in cognitive score from visit 2 to the BRAIN visit. In particular, we would anticipate stronger associations with the digit symbol substitution test (DSST) and verbal fluency test, and with changes in these tests, than with performance on the delayed word recall test, which is less affected in subcortical dementias.c. Cross-sectional associations (visit 2 hemoglobin associated with visit 2 performance)) will be stronger than longitudinal associations (visit 1 hemoglobin predicting later performance), perhaps due to transient alterations in cerebral blood flow and cerebral function.

2. Level of hemoglobin is associated with extent of a) white matter disease, with largest volume of white matter disease at extreme values of hemoglobin, and b) radiographic infarcts.

a. Similar to #1, we will analyze associations from hemoglobin measured at visit 1, as well as from visits 3 and the BRAIN visit, each, with 1) visit 3 white matter category, 2) the follow up Brain MRI visit white matter disease volume, 3) progression of white matter disease volume (using a technique I have published previously, from ARIC, calculating estimated visit 3 white matter volume and subtracting this from the measured Brain MRI visit[15]), and, for hypothesis 2b, with visit 3 presence/ absence of lacunar infarcts and Brain MRI visit presence/ absence of lacunar infarcts.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: prospective cohort study.

Exposure: Hemoglobin level (in g/dL) will be the primary exposure of interest, and will be primarily analyzed as a continuous variable. Anemia, defined by hemoglobin (below 13 g/dL in men and below 13 g/dL in men, consistent with the WHO definition of anemia), will also be analyzed as an exposure, as a dichotomous variable.

Outcomes:

Hypothesis 1: Cognitive score for DSST, Word Fluency, and Delayed word recall tests, each, and change in score from Visit 2 to the visit 4 and BRAIN MRI visits. In addition, we will look at score on the additional cognitive tests performed in the ARIC-BRAIN MRI visit.

For hypothesis 2, outcomes of interest are: 1) visit 3 white matter category; 2) BRAIN visit white matter volume; and 3) change in estimated white matter volume from visit 3 to the BRAIN MRI visit.

Other Variables of interest: Hemoglobin from visits 1 and 2, ARIC-BRAIN, also white matter grade from visit 3, standardized white matter volume from BRAIN visit, and estimated change (calculated in previous published study, see above). Also, sex, age, race, smoking, history of hypertension, h/o MI, h/o diabetes, education level, total and HDL cholesterol, h/o CHD, stroke.

Inclusion/ exclusion: ARIC participants from the BRAIN MRI cohort will be included who are not missing data on hemoglobin or hematocrit. For hypothesis #1, we will exclude individuals missing cognitive testing results, and for hypothesis #2, we will exclude individuals missing MRI white matter category/ volume results.

Statistical analysis: We will use linear regression to model the association of hemoglobin levels with cognitive performance after adjustment for covariates of interest. Cognitive scores will be analyzed as raw scores and also as age-, sex-, race-, and education-adjusted Z-scores. We will model hemoglobin both linearly and using a cubic spline, as well as a quadratic term. For white matter disease, we will employ linear regression models in a similar analysis with hemoglobin as a predictor, and also logistic regression looking at top quintile of volume of white matter disease and top quintile of white matter disease progression as the outcome. Analysis of cognitive change (from visit 3 to the BRAIN MRI visit) will be performed using generalized estimating equations using tests measured on as many as four occasions when available.

Limitations:

The primary limitation is the possibility of unmeasured confounders in an association between hemoglobin level and cognition and white matter disease. Lower hemoglobin is often an indicator of chronic disease, and may represent another chronic condition which could also be responsible for neurodegeneration. In addition, socio-economic status could be another important confounder. Another possible limitation is the staggered chronology of the hemoglobin levels and MRI and cognitive data. The hemoglobin levels are from visits 1 and 2, but cognition was measured in visit 2 and the BRAIN MRI visit, with MRI data from visits 3 and BRAIN MRI. This will not allow for analysis of cross-sectional associations between brain MRI and hemoglobin levels. We will explore whether hemoglobin measurements from visits 3,4, and the BRAIN MRI visits are possible.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X___ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____Yes ____No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

_____ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to
contact lead authors of these proposals for comments on the new proposal or collaboration)? #863, #952;

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* _1999.01 (ARIC BRAIN)_____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References

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