1. **Full Title:** The Association of Hemoglobin A1c with Depressive Symptoms in Persons with and without Diabetes

b. **Abbreviated Title (Length 26 characters):** Depression and Glycemia

2. **Writing Group:**
   Writing group members: Lisa Wyman; Sherita H. Golden; Kunihiro Matsushita; Elizabeth Selvin; others welcome

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

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3. **Timeline:** All data are available and we anticipate submitting this manuscript for ARIC review by August/September 2009.
4. **Rationale:**

While depression has been linked to many physical illnesses, evidence is growing of a particularly strong association with type 2 diabetes. Numerous studies have demonstrated an association between depression and diabetes, most indicating that depression is a major risk factor for the development of incident diabetes (1-5). There is also evidence that depression may worsen the course of illness through accelerating the development of diabetes complications (1,2). A recent meta-analysis of 13 publications by Mezuk et al. (3), suggested a robust association between depression and the incidence of type 2 diabetes, but a relatively weaker relationship between prevalent diabetes and incident depression. However, a stronger relation between prevalent treated type 2 diabetes and incident depressive symptoms was observed in the Multi-ethnic Study of Atherosclerosis cohort (4).

There is evidence that depression is associated with abnormalities in metabolic pathways which could contribute to insulin resistance. These include increased counter-regulatory hormone release and action, alterations in glucose transport function, and inflammatory activation (1). Previous cross-sectional studies have demonstrated higher levels of insulin resistance in individuals with depression compared to those without depression (5). In general, it appears that depression is associated with poor metabolic control in individuals with diabetes and that poor metabolic control may in turn exacerbate concurrent depression (6).

Nonetheless, little is known about the relationship between glycemia-- as measured by hemoglobin A1c (HbA1c) levels-- and depression. At least one study showed that depression was associated with higher HbA1c levels in individuals with type 2 diabetes (7), while other findings suggest no association between depression and HbA1c levels (8,9). To our knowledge, no previous study has investigated the association between hemoglobin A1c and depression in individuals without diabetes.

The ARIC study provides a unique opportunity to follow-up on previous work linking depressive symptoms and diabetes among study participants (10) by specifically examining the relationship between HbA1c levels and depressive symptoms in both individuals with and without diagnosed diabetes.

5. **Main Hypothesis/Study Questions:**

Hypothesis 1: Among those individuals with diagnosed diabetes, individuals with self-reported depressive symptoms will have higher levels of HbA1c (poorer glucose control) as compared to individuals not self-reporting depressive symptoms even after adjustment for potential confounding factors and accounting for diabetes medication use.

Hypothesis 2: HbA1c will be positively and independently associated with self-reported depressive symptoms in individuals without a diagnosis of diabetes.

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).**
Inclusion: The study population will include all individuals at the second ARIC examination who have a valid HbA1c measurement and who completed Part B (Vital Exhaustion Questionnaire) of the Health and Life Questionnaire. The second ARIC examination is the only visit for which HbA1c was measurement and the Vital Exhaustion Questionnaire was assessed.

**Depressive symptoms**
Self-reported depressive symptoms will be measured using the 21-item Vital Exhaustion Questionnaire (Part B of the Health and Life Questionnaire) administered at visit 2 (1990-1992) of the study. The correlation of depression (measured by the Beck Depression Inventory) and vital exhaustion has been found to be 0.6 (11). Previous diabetes analyses in ARIC (10) have also used the Vital Exhaustion Questionnaire to measure depressive symptoms as well as assess associations with outcomes such as obesity (12) and stroke (13).

**HbA1c**
HbA1c was previously measured from ARIC Visit 2 stored whole blood samples as part of ARIC Ancillary Studies #2003.5 and #2006.15. As of January 2009, HbA1c measurements are available on all participants who attended the ARIC Visit 2 who had a stored whole blood specimen available for measurement (N=14,069)

**Covariates**
Covariates of interest include age, sex, race/center, education level, total caloric intake, glucose, income, marital status, smoking, body mass index, physical activity score, waist circumference, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, alcohol use, presence of major medical comorbidities, and systolic blood pressure. Other variables of interest include insulin (Visit 1 only) and diabetes and anti-depressant medication use at Visit 2.

**Analysis Plan**

**Hypothesis 1: HbA1c and self-reported depressive symptoms in persons with diagnosed diabetes**
We will use linear and logistic regression models to investigate the possible independent association between depressive symptoms and HbA1c levels after adjusting for relevant confounding variables. We will analyze depressive symptom scores both continuously as well as in quartiles. We will analyze HbA1c as a continuous variable, in quartiles, and using clinically relevant cutpoints of <7, 7-8, and >8% in persons with diagnosed diabetes. Sensitivity and subgroup analyses will be performed to account for individual with and without diabetes medication use (oral medications and insulin)—diabetes medication use is associated with higher HbA1c levels in ARIC participants with diagnosed diabetes.

**Hypothesis 2: HbA1c and self-reported depressive symptoms in persons without diagnosed diabetes**
We will use linear and logistic regression models to investigate the possible independent association between HbA1c levels and depressive symptoms and after adjusting for relevant confounding variables. We will analyze depressive symptom scores both continuously as well as in quartiles. We will analyze HbA1c as a continuous variable, in quartiles, and using clinically relevant cutpoints of <5, 5-<5.5, 5.5-6.0, and >6.5% in persons without diagnosed diabetes. Stratified analyses will be conducted to assess whether any observed association is present across the spectrum of glucose impairment, comparing individuals with normal fasting glucose levels <100 mg/dl, with impaired fasting glucose (fasting glucose 100-<126 mg/dl), and undiagnosed diabetes (fasting glucose ≥126 mg/dl). Sensitivity and subgroup analyses will be conducted examining the association between HbA1c levels and depressive symptoms in normal weight individuals and in individuals without the metabolic syndrome or impaired glucose metabolism.

Limitations

There are several recognized limitations to this study. First, while vital exhaustion scores have been strongly correlated with more recognized measures of depression such as the Beck Depression Inventory, vital exhaustion remains a little used measure of depressive symptoms, especially in the United States. Ideally, data would be available from more commonly used measures of depression symptoms such as the CES-D. Second, this study is cross-sectional in nature and thus causality and temporality cannot be established even if significant associations are found. Third, vital exhaustion scores and HbA1c levels are available as single measurements only. Fourth, despite rigorous measurement of important risk factors for diabetes and depression, residual confounding remains a concern as in all observational studies. Lower socioeconomic status, for instance, remains a known risk factor for depression which may be inadequately measured by even education level and income combined.


11) Kopp MS, Falger PR, Appels A, Szedmak S. Depressive symptomatology and vital exhaustion are differently related to behavioral risk factors for coronary artery disease. Psychosom Med. 1998; 60; 752-758.


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

_____ X _____ 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)?


Manuscript Number: 565 Anger-Vital Exhaustion and Metabolic Syndrome. Mosely T.

Manuscript Number: 625 Does Vital Exhaustion Increase CVD Risk? Williams J.

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* #2003.5, #2006.15)

_____ 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.