1.a. **Full Title**: Negative Emotions and Subclinical Cerebrovascular Disease

b. **Abbreviated Title (Length 26 characters)**: Negative emotions and CbVD

2. **Writing Group (list individual with lead responsibility first):**

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3. **Timeline:**

   Manuscript proposal to Publication's Committee: September / 2004
   Data analysis completed:   October / 2004
   Completed manuscript to Publication's Committee:  January / 2004

4. **Rationale:**

   Negative emotional states have been associated with the development and progression of cardiovascular disease (CVD; Smith & Ruiz, 2002). Much of this research has focused on anger and hostility or depression and depressive symptoms.

   The initial literature on the role of anger and hostility in CVD risk was somewhat inconsistent; however, a meta-analytic review of 45 studies published in 1996 concluded that hostility is independently related to coronary heart disease (CHD) (Miller et al., 1996). A number of more recent studies have documented consistent associations between hostility or anger and anger coping styles and incident CVD. In the Normative Aging Study, hostility predicted 3-year incident CHD (Niaura et al., 2002) and anger predicted incident CVD over 7 years (Kawachi, Sparrow, Spiro, Vokonas & Weiss, 1996). Data from the Kuopio Ischemic Heart Disease Study indicated that hostility predicted increased risk of myocardial infarction and CV mortality (Everson et al., 1997) and anger coping styles predicted greater risk of hypertension (Everson et al., 1998). In the ARIC cohort, Williams and colleagues found that high trait anger was associated with a 2.7-times greater risk of CHD morbidity and death in normotensives (Williams, Nieto, Sanford et al., 2000).
Depression has also been linked to cardiovascular risk factors, morbidity, and mortality. Following myocardial infarction (MI), depression has been associated with risk of recurrence and mortality (Frasure-Smith, Lesperance, & Talajic, 1993; Frasure-Smith, Lesperance, & Talajic, 1995). Depression also has been associated with excess CHD morbidity and mortality in several prospective studies (Kubzansky & Kawachi, 2000). A related construct, hopelessness, has been associated with incident MI, progression of carotid atherosclerosis, and CHD mortality (Everson et al., 1996; Everson, Kaplan, Goldberg, Salonen, & Salonen, 1997; Stern, Dhanda & Hazuda, 2001). Vital exhaustion is a closely related construct and overlaps considerably with measures of depression. Vital exhaustion has been related to incident MI (Appels & Mulder, 1989), recurrence of cardiac events (Kop et al., 1994), and severity of coronary artery disease (Kop, Appels, Mendes de Leon, de Swart, & Bar, 1993). Preliminary findings from ARIC also revealed significant associations between vital exhaustion and metabolic syndrome (Mosley, Andrew, Dubbert, Wyatt, & McGovern, 1998).

Mechanisms linking negative emotions and CVD are not fully understood. Individuals with higher levels of negative emotions tend to have poorer behavioral risk profiles (e.g., greater smoking, higher alcohol use, less physical activity). However, this association does not adequately explain excess CVD risk, which persists in most studies after controlling for these risk factors. Negative emotions may interact with other psychosocial risk factors. For example, individuals high in hostility may engender stressful interpersonal environments and ultimately reduced social support. The most direct pathway whereby negative emotions may influence CVD risk is through sympathetic activation involving elevated cardiovascular and neuroendocrine responses, with alterations in the hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary axis (Musselman, Evans, & Nemeroff, 1998).

Less is known about the role of negative emotional states in cerebrovascular disease (CbVD). Based on findings linking negative emotions to CVD risk as well as to behavioral and biological risk factors for CVD, a relationship is plausible. Several studies have identified a positive association between depressive symptoms and increased stroke risk or mortality. In the Alameda County Study, a high level of depressive symptoms predicted a 50% excess risk of stroke mortality 29 years later in adjusted analyses (Everson et al., 1998). Similarly, in the NHANES I Epidemiologic Follow-up Survey depressive symptoms were associated with a 73% excess risk of stroke over 16-22 years of follow-up (Jonas et al., 2000). Depressive symptoms were related to an 83% greater risk of stroke over 8 years among those 70 or older in a community study of the elderly in Australia (Simons et al., 1998) and predicted 2.7-fold greater risk of ischemic stroke in a sample of 900 middle-aged and elderly rural Japanese over 10 years of follow-up (Ohira et al., 2001). Depression, diagnosed via structured interview, predicted a 2.6-fold greater risk of stroke over 13 years in the Baltimore site of the Epidemiologic Catchment Area Study (Larson et al., 2001).

Anger also has been related to stroke risk. In a population-based sample of Finnish men, Everson et al. (1999) found that high levels of expressed anger predicted a 6.9-fold increased risk of stroke in those with a history of CHD (Everson, Kaplan, Goldberg, Lakka, Sivenius & Salonen, 1999). Trait anger was associated with a two-fold greater risk of incident stroke in adjusted analyses in ARIC among participants aged 60 or younger (Williams, Nieto, Sanford, Couper, & Tyroler, 2002).
Advances in brain imaging have made it possible to identify pathologic changes in brain parenchyma well before clinical symptoms become apparent. Subclinical markers of CbVD were found to be quite prevalent in ARIC, and because they are less likely to be affected by diagnostic or referral bias compared to clinical end points, are well-suited to elucidate risk factors and possible mechanisms underlying clinical CbVD.

A recent study found that silent CbVD, as measured by MRI, was independently associated with stress-induced blood pressure reactivity (Waldstein et al., 2004). Blood pressure reactivity to stress has been associated with increased stroke risk (Everson et al., 2001) and negative emotions (Smith & Ruiz, 2002).

In the current study, we propose to examine the association between negative emotions and MRI-defined subclinical CbVD in the ARIC cohort. Specifically, we will examine the association of trait anger and vital exhaustion with prevalent infarct-like lesions (ILLs) and white matter hyperintensities (WMHs).

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

We hypothesize that trait anger and vital exhaustion will be positively associated with ILLs and WMHs, independent of risk factors for stroke.

6. **Data (variables, time window, source, inclusions/exclusions):**

The primary dependent variables of interest are ILLs (>3mm, present/absent) and WMLs (> grade 3, present/absent). A series of linear regression models will be fit, adjusting for potential confounder variables and stroke risk factors (described in Framingham and ARIC) in successive models. Model 1 will adjust for demographic variables (age, sex, race/center, years of education, and income). Model 2 will add behavioral risk factors (smoking, alcohol consumption, and BMI). Model 3 will add biological risk factors (hx of CHD, LVH, HTN, antihypertensive medication, diabetes, plasma fibrinogen, creatinine, von Willebrand factor). In secondary analyses, we will examine associations with subscale factors for both measures (i.e., score composed of DSM-4 depression items only vs. vital exhaustion total score; and angry-temperament and anger-reaction subscale scores vs. anger total score).

Participants with a history of stroke or TIA prior to Visit 3 will be excluded from the analysis.

Exclusions:
1. Missing Visit 2 trait anger or vital exhaustion.
2. History of stroke or TIA prior to Visit 3.
3. Race not black or white, or blacks from Minn. or Washington

Other variables:
Medications with known psychotropic effects

7.a. **Will the data be used for non-CVD analysis in this manuscript?**  _XX_ No
b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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 ___XX__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ___ 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html
___XX___ 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)?

ARIC MS #666, Williams et al. (Stroke, 2002) demonstrated an association between trait anger and incident stroke risk.

We are aware of no ARIC manuscripts or proposals related to negative emotions and MRI-defined lesions.

11. 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


