ARIC Manuscript Proposal # 1134r

PC Reviewed: 03/_21__/06	**Status: _____**	**Priority: _____**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full Title: Associations of Negative Emotions with Retinal Microvascular Disease and Age-Related Maculopathy

b. Abbreviated Title (Length 26 characters): Negative Emotions and Retinal Diseases

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

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3. Timeline:

Manuscript proposal to Publication's Committee:	Jan / 2006
Data analysis completed:	June / 2006
Completed manuscript to Publication's Committee:	Oct / 2006

4. Rationale:

Negative emotional states (anger, hostility and depression) have been linked with development and progression of cardiovascular diseases[1]. Much of this research has focused on the impact of negative emotion on macrovascular disease. For example, numerous studies have shown that anger and hostility predict incident coronary heart disease [2, 3], incident stroke[4] and cardiovascular mortality[5]. Anger also appears to predict risk of hypertension[6]. 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[7], and a two-fold greater risk of incident stroke among participants aged 60 or younger[8].

Similarly, depression has also been linked to various cardiovascular risk factors and cardiovascular diseases[8, 9], including progression of carotid atherosclerosis[10-12] as well as incident stroke[13-16]. Vital exhaustion is a closely related construct and overlaps considerably with measures of depression, and has also been linked with incident cardiovascular disease[17-19]. Preliminary findings from ARIC also revealed significant associations between vital exhaustion and metabolic syndrome[20].

Although the pathophysiological basis linking these negative emotions with CVD have not been fully elucidated, several hypotheses have been proposed. First, individuals with higher levels of negative emotions tend to have poorer cardiovascular risk profiles (e.g., more likely to be smokers and to have less physical activity), although the excess cardiovascular risk associated with negative emotions persists even when studies controlled for these risk factors. Second, negative emotions may interact with other psychosocial risk factors (e.g., individuals high in hostility may engender stressful interpersonal environments and ultimately reduced social support). Finally, there is increasing evidence that negative emotions may influence CVD risk via increased sympathetic and neuroendocrine responses, resulting in alterations in the hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary axis[21].

There have been few studies on the possible impact of negative emotions on small vessel diseases. "Microvascular angina", or cardiac syndrome X, a condition caused by coronary microvascular dysfunction[22], has been linked with measures of anxiety and depression in both men[23] and women[24]. It has also been associated with trait anger and neuroticism[25]. In addition, previous meta-analysis has reported statistically significant associations of depression with diabetes complications including diabetic retinopathy (r = 0.17)[26]. However, whether negative emotions, including vital exhaustion and trait anger, also impact on retinal microvascular changes is unclear.

Furthermore, the data addressing the effect of negative emotions on age-related macular degeneration (AMD) are also scarce. A review of the recent clinical studies proposed AMD as a risk factor for depression[27]. Nevertheless, there is a lack of population-based data to support this notion. In addition, whether there are associations between AMD and other measures of negative emotions such as vital exhaustion and trait anger still remains undetermined.

In the current study, we propose to examine the association between negative emotions (trait anger and vital exhaustion) with retinal microvascular disease and AMD in the ARIC cohort.

5. Main Hypothesis/Study Questions:

We hypothesize that trait anger and vital exhaustion will be positively associated with retinal microvascular signs and AMD, independent of standard cardiovascular risk factors.

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

- **A.** Retinal microvascular variables at **Visit 3**: retinal arteriolar diameter, retinal venular diameter, arteriovenous nicking, focal arteriolar narrowing, blot hemorrhages, soft exudates (cotton wool spots), and microaneurysms
- **B.** AMD variables at **Visit 3**. Any AMD, early AMD, late AMD and specific AMD lesions (drusen, RPE de-pigmentation, any pigmentary changes)
- **C.** Vital exhaustion at **Visit 2**: the Maastricht questionnaire
- **D.** Trait anger at **Visit 2** and **Visit 4**: the Spielberger Trait Anger Scale
- **E.** Other variables:
  - i. Cardiovascular risk factors at **Visit 1, 2 and 3**: hypertension, blood pressure, diabetes, cigarette smoking, plasma total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, glucose, BMI
  - ii. Medications with known psychotropic effects

Plan of analysis

Participants with a history of stroke or TIA prior to Visit 3 or missing data will be excluded from the analysis. We will analyze the association of vital exhaustion and trait anger characteristics at Visit 2 with retinal variables at Visit 3, adjusting for potential confounders at Visit 2. In sub-group analyses, we will also (1) examine the association of trait anger at Visit 4 with retinal signs at Visit 3, and (2) adjust for confounders (systolic blood pressure, glucose, total cholesterol, triglyceride and BMI) with values that are the average of Visits 1 to 3. Limitations that this is not a pure cross-sectional analysis will be discussed in the paper.

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 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 _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 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

__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)?

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 retinal disease.

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.

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