

ARIC Manuscript Proposal # 951

PC Reviewed: 08/07/03

SC Reviewed: 08/07/03

Status: A

Status: A

Priority: 2

Priority: 2

1.a. Full Title:

Migraine Headaches and Retinal Microvascular Abnormalities

b. Abbreviated Title (Length 26 characters):

Migraine and Retinal Disease

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

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Proposed writing group members:

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3. Timeline:

Summer 2003: Data Analysis

Early Fall 2003: Submission of Abstract to Scientific Meeting

Late Fall 2003: Draft Manuscript

4. Rationale:

Migraine headaches affect approximately 17% of females and 6% of males in the United States^{1,2}. While the pathophysiologic mechanisms underlying migraine have not been elucidated, there is evidence of underlying vascular dysfunction. Migraine has been consistently associated with an increased risk of stroke³⁻⁵, while associations with hypertension⁶⁻¹¹ and CHD^{3, 12-15} have been inconclusive. This may in part reflect differences in characteristics of the populations studied or methodological issues such as relying on self-report of outcomes or not differentiating migraines by presence or absence of aura symptoms.

Several members of the proposed writing group (KR, AP) have investigated the association between migraine and other headaches lasting four or more hours and CVD-related outcomes in the ARIC study¹⁶⁻¹⁸. In the investigation of headache and ischemic stroke, migraine with aura and other headaches with aura were associated with an increased occurrence of verified ischemic stroke. Conversely, migraine and other headaches without aura were not associated with an increased occurrence of ischemic stroke. In the investigation of headache with Rose Angina, participants with a history of migraine with aura and other headaches with aura were more likely to report a history of Rose Angina. More modest but significant associations were seen for migraine and other

headaches without aura. In contrast, no association was found between migraine and other headaches, regardless of aura status, with CHD events.

Several explanations for the lack of consistency in the findings for angina and CHD have been postulated. It has been hypothesized that persons with one type of pain may have a greater propensity to report other types of pain. However, additional analysis contrasting angina, exertional chest pain, and non-exertional chest pain showed a strong association between migraine with aura and exertional chest pain, but not non-exertional chest pain. This finding suggests explanations other than a greater propensity to report pain are possible. While functional and structural changes associated with atherosclerosis are thought to lead to the ischemia resulting in exertional angina, dysfunction of endothelial vascular tone^{19, 20} may also play a role and may be specific to the microvasculature²¹.

Similarly, retinal microvascular abnormalities, which are hypothesized to result from the cumulative effect of elevated blood pressure, may also be related to vascular endothelial dysfunction although the etiology is not completely understood. Retinal microvascular abnormalities have been associated with an increased risk of hypertension²²⁻²⁴, cerebral white matter lesions²⁵, stroke²⁶, and CHD²⁷. In the ARIC Study, retinal arteriolar narrowing was associated with CHD in women but not men²⁷. This is of particular interest for migraine research, since microvascular dysfunction is a plausible explanation for the association observed between migraines and angina but not CHD. Interestingly, microvascular disease and migraine are both more common among women than men and the ARIC study offers a unique opportunity to investigate the association between migraine (with and without aura) and microvascular abnormalities. There have been case-reports linking ocular stroke²⁸, central serous retinopathy²⁹, retinal vascular occlusions^{30, 31} and retinal infarctions^{32, 33} with migraines. One population-based study reported an increased prevalence of optic disc hemorrhages among those with a history of migraines³⁴.

The aim of this proposal is to evaluate the association between lifetime headache history (migraine with aura, migraine without aura, other headaches with aura, and other headaches without aura) and retinal microvascular abnormalities among African-American and white middle-aged men and women.

5. Main Hypothesis/Study Questions:

1. Is a lifetime history of migraine associated with retinal microvascular characteristics (i.e., generalized arteriolar narrowing, focal narrowing, arteriovenous nicking, retinopathy, and retinal vein occlusions)?
 - a. If so, does this association vary by aura status?
2. Is a lifetime history of non-migrainous headaches, headaches lasting at least four hours but not satisfying all migraine criteria, associated with retinal microvascular characteristics (e.g., generalized arteriolar narrowing, focal narrowing, arteriovenous nicking, retinopathy, and retinal vein occlusions)?
 - a. If so, does this association vary by aura status?
3. Do associations, if extant, persist after controlling for risk factors associated with retinal disease (diabetes, hypertension, etc.)?

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

Participants will be limited to those who participated in the 3rd follow-up examination, as this is when headache history was ascertained and retinal photographs were taken. We will exclude those with a race other than black or white as well as black participants residing in Washington County or Minneapolis. Participants missing key exposure and outcome data will be excluded.

The following Visit 1 variables will be included in this analysis: age, gender, race, education and occupation and fibrinogen (as it is not available at visit 3 on all participants). Remaining variables will include those ascertained at Visit 3. They include: smoking status, alcohol consumption, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, use of antihypertensive medication(s), diabetes status, glucose, history of CHD, history of stroke, total serum cholesterol, HDL cholesterol, LDL cholesterol, body mass index, waist-to-hip ratio, physical activity index, variables derived from retinal photographs (arteriovenous nicking, focal arteriolar narrowing, generalized arteriolar narrowing (retinal arteriole-to-venule ratio (AVR), retinopathy, and retinal vein occlusions) and headache history variables. So that we can also ascertain longer-term blood pressure and glucose levels we also plan to include blood pressure and diabetes-related variables from visits 1 and 2 (e.g., diabetes and hypertension status, glucose levels, SBP, DBP, and MAP).

7.a. Will the data be used for non-CVD analysis in this manuscript? ☐ Yes ☒ 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 ☒ 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/csc/ARIC/stdy/studymem.html>

☒ 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)?

Migraine headaches: MS 363, MS 400, MS 400-A

Retinal microvascular disease: MS 234, MS 337, MS 383, MS 735, MS 753, MS 776

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