ARIC Manuscript Proposal # 951

PC Reviewed: 08/07/03	**Status: __A__**	**Priority: __2__**
SC Reviewed: 08/07/03	**Status: __A__**	**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):

Lead: **Kathryn Rose, PhD**
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Proposed writing group members:

Kathy Rose, April Perry, David Couper, Ron Klein, Richey Sharrett, Tien Wong

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 stroke [3-5], while associations with hypertension [6-11] 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 study [16-18]. 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 microvasculature [21].

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 hypertension [22-24], cerebral white matter lesions [25], stroke [26], and CHD [27]. In the ARIC Study, retinal arteriolar narrowing was associated with CHD in women but not men [27]. 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 stroke [28], central serous retinopathy [29], 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 migraines [34].

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 1variables 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 occlussions) 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 __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)?

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

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

References:

1. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA* 1992;267:64-9.
2. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002;58:885-94.
3. Mitchell P, Wang JJ, Currie J, Cumming RG, Smith W. Prevalence and vascular associations with migraine in older Australians. *Australian & New Zealand Journal of Medicine.* 1998;28:627-32.
4. Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N. Association between migraine and stroke in a large-scale epidemiological study of the United States. *Archives of Neurology.* 1997;54:362-8.
5. Buring JE, Hebert P, Romero J et al. Migraine and subsequent risk of stroke in the Physicians' Health Study. *Archives of Neurology.* 1995;52:129-34.
6. Cirillo M, Stellato D, Lombardi C, De Santo NG, Covelli V. Headache and cardiovascular risk factors: positive association with hypertension. *Headache* 1999;39:409-16.
7. Hagen K, Stovner LJ, Vatten L, Holmen J, Zwart JA, Bovim G. Blood pressure and risk of headache: a prospective study of 22 685 adults in Norway. *Journal of Neurology, Neurosurgery & Psychiatry.* 2002;72:463-6.
8. Mathew NT. Migraine and hypertension. *Cephalalgia.* 1999;19:17-9.
9. Prentice D, Heywood J. Migraine and hypertension. Is there a relationship? *Australian Family Physician.* 2001;30:461-5.
10. Rasmussen BK, Olesen J. Symptomatic and nonsymptomatic headaches in a general population. *Neurology.* 1992;42:1225-31.
11. Wiehe M, Costa Fuchs S, Moreira LB, Stoll Moraes R, Fuchs FD. Migraine is more frequent in individuals with optimal and normal blood pressure: a population-based study. *J Hypertens* 2002;20:1303-6.
12. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population--a prevalence study. *Journal of Clinical Epidemiology.* 1991;44:1147-57.
13. Leviton A, Malvea B, Graham JR. Vascular diseases, mortality, and migraine in the parents of migraine patients. *Neurology.* 1974;24:669-72.
14. Chen TC, Leviton A, Edelstein S, Ellenberg JH. Migraine and other diseases in women of reproductive age. The influence of smoking on observed associations. *Archives of Neurology.* 1987;44:1024-8.
15. Cook NR, Bensenor IM, Lotufo PA et al. Migraine and coronary heart disease in women and men. *Headache.* 2002;42:715-27.
16. Rose KM, Paton C, Folsom AR, Stang PE, Szklo M, Wijnberg L. The association between migraine headaches and angina in the Atherosclerosis Risk in Communities Study. *Circulation* 1998;97:828 (abstract).
17. Rose KM, Perry AL, Stang PE et al. The association of migraine and other headaches with coronary heart disease: The Atherosclerosis Risk in Communities Study. *Submitted to the ARIC Study for internal review.*; May 2003.
18. Stang PE, Rose KM, Perry AL, Mo JP, Ephross SA, Shahar E. The association of migraine and other headaches with ischemic stroke in the Atherosclerosis Risk in Communities Study. *Submitted to ARIC Study for internal review.*; May 2003.
19. Ruschitzka FT, Noll G, Luscher TF. The endothelium in coronary artery disease. *Cardiology.* 1997;88:3-19.
20. Collins NR, Evans DA, Funkenstein HH, Scherr PA, Ostfeld AM. Endothelial dysfunction in patients with angina and normal coronary arteriograms. In: Kaski JC, ed. *Angina pectoris with normal coronary arteries: Syndrome X*. Boston, MA: Kluwer Academic Publishers; 1994.

21. Quyyumi AA, Cannon RO, 3rd, Panza JA, Diodati JG, Epstein SE. Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation.* 1992;86:1864-71.
22. Hubbard LD, Brothers RJ, King WN et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology.* 1999;106:2269-80.
23. Sharrett AR, Hubbard LD, Cooper LS et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *American Journal of Epidemiology.* 1999;150:263-70.
24. Wong TY, Hubbard LD, Klein R et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *British Journal of Ophthalmology.* 2002;86:1007-13.
25. Wong TY, Klein R, Sharrett AR et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *Jama.* 2002;288:67-74.
26. Wong TY, Klein R, Couper DJ et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet.* 2001;358:1134-40.
27. Wong TY, Klein R, Sharrett AR et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *Jama.* 2002;287:1153-9.
28. Weintraub MI, Lambert D, Rothman AL. Migraine related to ocular stroke. *Neurology.* 1986;36:1410.
29. Proctor SJ. Hypertension, migraine, and central retinopathy. *Lancet.* 2000;355:502.
30. Coppeto JR, Lessell S, Sciarra R, Bear L. Vascular retinopathy in migraine. *Neurology.* 1986;36:267-70.
31. Newman NJ, Lessell S, Brandt EM. Bilateral central retinal artery occlusions, disk drusen, and migraine. *American Journal of Ophthalmology.* 1989;107:236-40.
32. Beversdorf D, Stommel E, Allen C, Stevens R, Lessell S. Recurrent branch retinal infarcts in association with migraine. *Headache.* 1997;37:396-9.
33. Glenn AM, Shaw PJ, Howe JW, Bates D. Complicated migraine resulting in blindness due to bilateral retinal infarction. *British Journal of Ophthalmology.* 1992;76:189-90.
34. Healey PR, Mitchell P, Smith W, Wang JJ. Optic disc hemorrhages in a population with and without signs of glaucoma. *Ophthalmology.* 1998;105:216-23.