ARIC Manuscript Proposal # 3163

PC Reviewed: 5/8/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Migraines and risk of Dementia and Mild Cognitive Impairment in the Atherosclerosis Risk in Communities (ARIC) Neuro-cognitive Study (NCS)

b. Abbreviated Title (Length 26 characters): Migraine and Dementia

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

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3. Timeline:

Begin analysis following ARIC committee approval

4. Rationale:

Migraine headache is a complex neurological disorder characterized by throbbing, severe, and typically unilateral pain in the head. [1] Among those 12 and older in the United States, prevalence is about 6.5% in men and 18.2% in women and has remained stable over time. [2][3]

Migraine prevalence peaks between the ages of 30 and 39 for both men and women before falling to reach its lowest prevalence in those 60 and older. [4] For both sexes, prevalence is significantly higher in whites than African Americans and among those with low versus high income. [4] It is a heritable disorder with relatives of migraineurs at three times the risk of the disorder compared to those without relatives with migraines. [5]

Approximately 64% of migraines are without aura, 18% with aura, and 13% of individuals experience both. [1] Migraine is associated with autonomic, sensory, affective, and cognitive symptoms including nausea, vomiting, sensitivity to light, sound, and movement, depression and irritability, attention deficit, and transient amnesia. [1][6] This constellation of early migraine symptoms, also known as prodromes, can vary substantially between individuals.
Prodromes can precede migraine headache by several hours and are explained by two main hypotheses. [6] The first theorizes that hypothalamic neurons respond to changes in brain homeostasis by activating meningeal nociceptors that alter the balance of parasympathetic and sympathetic activity in the meninges toward predominance of parasympathetic activity. [6] The second theory proposes that hypothalamic and brainstem neurons that respond to brain homeostasis lower the threshold for transmission of nociceptive trigeminovascular signals from the thalamus to the cortex. [6] This can alter the amount of brain activity required to manage emotional and physiological stress, making migraineurs more susceptible to external and internal stressors. [6] Both theories identify neuronal hyperexcitablity as well as alterations to the brain structure and function, resultant from the repetitive state of headache, as essential features of migraine progression. [6][7][8]

There is an important distinction between migraine with and without aura, and evidence suggests the two subtypes of migraine may be separate disorders. [8] Aura is characterized by

fully reversible neurologic dysfunction related to visual, sensory, speech/language, motor, brainstem, or retinal symptoms that proceed or accompany headache. [9] Onset is usually gradual with a duration of 5-60 minutes, and visual aura is the most commonly reported with prevalence estimates as high as 99%. [9] Aura is distinct from prodromes and caused by cortical spreading depression (CSD). [9] Evidence suggests that CSD involves a wave of hyper-excitation followed by suppression of cortical neurons and glia. [8][6] This process is associated with disruption of ionic flow and leads to an increase and subsequent decrease of cerebral blood flow. [9] As with prodromes, it is unknown what triggers CSD associated with aura. [9]

The mechanisms of the headache stage of migraine are better characterized than prodromes and aura. The initial "vascular hypothesis" proposed that migraines were a vasospastic disorder that started with meningeal blood vessel constriction followed by dilation, activating the surrounding trigeminal sensory nerves and causing pain. [10][11] However, vasodilation alone does not fully explain prodromes that can accompany headache, and current hypotheses focus primarily on neural activation with vascular changes as a secondary factor. [10] It is hypothesized that migraine headache is caused by activation of the trigeminovascular system via dilation of meningeal blood vessels that mechanically activate surrounding trigeminal sensory nerve fibers. [8][12] Activation of these fibers triggers release of the vasoactive neurotransmitter calcitonin gene-related peptide (CGRP). [8][12] Signals spread via CGRP to the pain matrix of the brain, the thalamus, followed by the brainstem and spinal cord regions causing headache. [8][12] As migraine progresses, areas of the brain that receive pain impulses may become sensitized, leading to perpetuation of CGRP release, worsening of pain, and increased sensitivity to stimuli. [8][12][13] Concentration of CGRP is elevated in migraine patients, and the

neurotransmitter has been a target for intervention using selective CGRP receptor antagonists. [12][13]

While current hypotheses deemphasize the importance of vasodilation in migraine, there is still a clear vascular component, which has led research to test the connection between migraine, stroke, and cognitive decline. Several studies have found an association between migraine and ischemic stroke, particularly in women; a meta-analysis reported a pooled relative risk of 1.7 and 95% confidence interval of 1.3 to 2.3. [14] Further, as reviewed in the journal *Neurology*, history of migraine is associated with increased risk of white matter abnormalities, subclinical infarct-like lesions, and volumetric changes in the brain. [15] Stroke, white matter hyperintensities, silent infarcts, and volumetric changes in the brain are associated with cognitive impairment suggesting that migraine may be a risk factor for cognitive decline and dementia. [16] Studies have found a modest association between history of migraine and cognitive decline in older adults; however, few studies have looked at migraine and risk of developing dementia and mild cognitive impairment (MCI). [16][17]

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the association between self-reported history of migraine with risk of dementia between visit 3 (1993-1995) and visit 6 (2016-2017)

Hypothesis 1: We hypothesize ARIC participants who report a history of migraine will be at increased risk of dementia

Hypothesis 2: We hypothesize ARIC participants who report a history of migraine with aura will be at increased risk of dementia compared to those who experience migraine without aura, severe headache, or no headache.

Aim 2: Evaluate the association between self-reported history of migraine with risk of dementia with cerebrovascular disease etiology compared to non-cerebrovascular disease-related dementia

Hypothesis 1: We hypothesize that the association between migraine and dementia will be stronger in those with dementia with a cerebrovascular disease etiology compared to non-cerebrovascular disease etiology.

Aim 3: Determine whether there is effect modification on the association between migraine and dementia and MCI by sex.

Hypothesis 1: We hypothesize that the association between migraine and dementia will be stronger in women compared to men based previous study findings and the higher prevalence of migraines in women than men

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).

Study Design: Prospective Cohort Study: baseline visit 3 (1993–1995) through visit 6 (2016–2017)

Exclusions: Participants will be excluded if they are missing self-report of migraine, prevalent stroke at visit 3, prevalent dementia (identified via ICD codes) at visit 3, non-white or African American participants and African Americans in MD and MN

Exposure:

Migraine headache assessed via self-report at visit 3 will be used as the exposure of interest. Migraine will be defined as self-report of the following symptoms: 1) headache lasting 4 or more hours, 2) headache with throbbing, pounding, or pulsating pain, 3) symptoms of nausea, vomiting, or sensitivity to light or sound, and 4) one or more years with history of headaches. Participants will be identified as having migraines with aura if they meet the previous criteria as well as report occurrence of visual aura (e.g. spots, jagged lives, etc.). [17] Those who report headache lasting more than four hours, but no other symptoms will be defined as suffering from severe, non-migraine headache, and participants that deny having a headache lasting 4 or more hours will be defined as having no severe headache or migraine. [17]

Outcome:

We will use dementia and MCI outcomes identified using the three levels of diagnostic certainty as identified in the ARIC database. The first level, involved adjudicated outcomes from visits 5 and 6 NCS evaluations including evidence of cognitive decline based on assessments from earlier visits. [18] A standardized definition for dementia and MCI was used for level 1

classification to generate computer algorithmic diagnoses; a panel of physicians and neuropsychologists reviewed each case of suspected cognitive impairment as well as a random sample of cognitively normal participants, and the final diagnosis included changes to the algorithmic diagnoses made by the panel. [18]

Level 2 dementia and MCI includes cases identified in level 1 as well as participants who did not attend ARIC-NCS, but were identified through telephone interview for cognitive status (TICS) or informant telephone interview of suspect cases (based on hospital or death certificate codes) using a modified version of the Clinical Dementia Rating (CDR). [18] Finally, level 3 includes levels 1 and 2 as well as participants only identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia, but lacking informant interviews. [18] Cases occurring after visit 5 were also identified using surveillance based on interviews with the Six Item Screener and, when indicated, the ID8 with an informant.

Separate analyses will be run using two definitions of dementia and MCI outcomes. The first definition will include all incident dementia cases available in ARIC (level 3 criteria). The second definition will only include adjudicated dementia and MCI cases, which were identified at ARIC visits 5 and 6 and include information on etiology at visit 5 (level 1 criteria).

Covariates from visit 1: age, sex, race (MS-blacks, NC-whites, NC-blacks, MN-whites, and MD-whites), APOE ε4, income, and education

Covariates from visit 3: body mass index (BMI), smoking status, hypertension, diabetes, prevalent coronary heart disease (CHD), drinking status, HDL cholesterol, and total cholesterol

Data Analysis:

For all analyses, we will follow the most recent ARIC NCS analysis working group recommendations. We will first address aim 1, evaluate the association between self-reported history of migraine with risk of dementia using all dementia and MCI cases (level 3). MCI cases prevalent at visit 5 and 6 will also be examined. For Aim 1, hypothesis 1, Poisson regression will be used to calculate incidence rates of dementia and MCI stratified by headache subtype (migraine with aura, migraine without aura, severe headache, and no migraine or severe headache) and sex between visits 3 and 6 (1993-2017). Cox regression with a competing risk of non-dementia related death will then be used to assess hazard of incident dementia and MCI in relation to migraine over the same follow-up period. For Aim 1, Hypothesis 2, Cox regression with a competing risk of non-dementia related death will be used to assess hazard of dementia and MCI in relation to headache subtype with those identified as having "no migraine or severe headache" as the reference.

Following analysis with all dementia cases, we will repeat the analysis using adjudicated cases from visits 5 and 6 (level 1 cases). For Aim 1, hypothesis 1, relative risk regression will be used to assess the association between migraine and adjudicated dementia and MCI cases using inverse probability weighting to account for death or failure to attend visits 5 or 6. For Aim 1, hypothesis 2, we will use relative risk regression to assess the association between headache subtype and adjudicated dementia and MCI with inverse probability weights. Relative risk regressions will be conducted using generalized linear models with a Poisson distribution and a log link.

For aim 2, we will evaluate the association between self-reported history of migraine with risk of dementia and MCI with primary or secondary cerebrovascular disease etiology compared

to dementia cases without cerebrovascular disease etiology. Etiology data is only available for adjudicated dementia and MCI cases, so this analysis will only include level 1 cases. To address Aim 2, hypothesis 1, relative risk regression will be used assess the association between migraine and each subtype of adjudicated dementia and MCI in two separate models.

Finally, to address Aim 3, determine whether there is effect modification on the association between migraine and dementia and MCI by sex, we will use both outcome criteria. Using level 3 cases, we will we run a Cox regression with a competing risk for dementia-related death to assess hazard of dementia and MCI in relation to migraine including a sex by migraine interaction term. Using level 1 cases, we will run a relative risk regression to assess the risk of adjudicated dementia and MCI with a sex by migraine interaction term. For both analyses, sex-specific models will be run and presented if the sex by migraine interaction term is statistically significant.

For all analyses, models will be adjusted for baseline covariates (from visits 1 and 3):

Model 1: age, sex, race, APOE ε4, income, and education

Model 2: plus BMI, smoking status, hypertension, diabetes, prevalent CHD, drinking status, HDL cholesterol, and total cholesterol.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ Yes ____ 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? _X___ Yes ____ No

(This file ICTDER 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? __X__ 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ 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)?

To our knowledge, there are no related manuscripts.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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