

ARIC Manuscript Proposal #2244

PC Reviewed: 10/8/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Smoking and progression of white matter hyperintensities: The ARIC-MRI Study

b. Abbreviated Title (Length 26 characters): Smoking and WMH

2. Writing Group:

Writing group members: Jennifer Deal, Rebecca Gottesman (senior), Cliff Jack, David Knopman, Tom Mosley, Melinda Power (first), A. Richey Sharrett, others welcome

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

Completion 2 -3 months after approval.

4. Rationale:

White matter hyperintensities (WMHs) are small lesions commonly detected as incidental findings on MRI. Current understanding suggests that they reflect subclinical small vessel disease, specifically damage to areas of white matter due

to hypoperfusion, thrombosis of arterioles, or a leaky blood-brain barrier. Greater WMH volume and WMH progression is associated with subsequent increased risk of stroke, dementia and mortality, and also appears to predict decline in some domains of cognitive function that are often impaired in vascular dementia.¹

Smoking appears to be associated with cognitive decline and dementia, including Alzheimer's disease and vascular dementia.² Similarly, smoking is an established risk factor for stroke.³ Therefore, it is reasonable to hypothesize that smoking may influence cognitive decline, dementia, and stroke risk through promotion of small vessel disease.

While few studies have focused on the cross-sectional association between smoking and WMHs, studies of other risk factors for WMHs and studies surveying multiple potential risk factors often report on the smoking-WMH association. As has been noted by others, a handful of studies reporting unadjusted univariate correlations actually suggest an inverse association between smoking and WMHs.^{4,5} However, the majority actually report null (e.g.⁶) or positive associations (e.g.^{7,8}). Notably, in a prior study in ARIC, smoking was positively associated with WMH severity, with stronger associations observed among African-Americans than among European-Americans.⁹ Similar findings are reported in studies that specify smoking as a risk factor of interest. In a series of 253 Japanese patients oversampled for stroke, duration of smoking and current or former smoking were significantly positively correlated with periventricular hyperintensity grade.¹⁰ Likewise, current smoking was associated with greater periventricular WMHs among those under 65, and with greater deep WMH among those over 65 in a series of 595 Korean patients who underwent brain MRI in the outpatient setting.¹¹

Relatively few studies have assessed risk factors, including smoking, for WMH progression. Associations with progression provide stronger evidence for a causal relation, as progression is a stronger predictor of cognitive decline than baseline WMH volume and studies within-person change are less susceptible to confounding. To date all three studies of risk factors for WMH progression suggest positive findings for smoking. In the Cardiovascular Health Study, whose primarily white participants are all over age 65, baseline current smoking predicted WMH progression.¹² Similarly, in the Rotterdam Scan Study, whose participants are primarily white and over 65, baseline current cigarette smoking predicted progression of small vessel disease, as indicated by WMH progression.¹³ Finally, a prior study in ARIC noted suggestive, but not significant, positive associations between ever versus never and current versus not former/never smokers and one or more grade increase in WMH score.¹⁴

There are several limitations to the existing work on the association between WMH and smoking. First, in many of the previous studies, and in all studies of WMH progression, smoking was not the primary risk factor of interest. Instead, most considered broad swaths of risk factors in a search for independent predictors of WMHs and choice of adjustment for covariates included both potential confounders and potential intermediates. In addition, most studies considered only smoking defined as current versus non-smokers; therefore questions relating to timing of smoking cessation, smoking intensity, and other characteristics of smoking behavior remain unresolved. Second, in most studies, and in both of the studies reporting on the association between smoking and progression, the participants were primarily white and over age 65. It is unclear whether race or timing of smoking influence the observed association; in the previous work in ARIC, which considered a younger, more racially diverse group than other similar studies, the association was suggestive, but weaker.

As such, we propose to describe the relationship between smoking and white matter hyperintensity progression in the ARIC Brain MRI study. Specifically, we will assess whether smoking status predicts white matter hyperintensities and whether this association differs by black versus white race. In addition, we will determine whether the association between smoking and WMH progression varies by intensity or duration of smoking or timing of smoking or smoking cessation.

5. Main Hypothesis/Study Questions:

We hypothesize that cigarette smoking will be strongly associated with WMH progression from visit 3 to the Brain MRI study, and that this relationship will be (1) stronger in black participants than in white participants, (2) stronger with greater pack-years or duration of smoking, and (3) will attenuate with increased time since quitting smoking among former smokers.

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).

Exclusions:

No MRI at visit 3 or the Brain MRI study, missing smoking data.

Independent variables:

Smoking status (current/former/never) at visits 1,2,3,4 and Brain MRI. Pack-years and duration of smoking among ever smokers and time since smoking cessation for former smokers, both prior to visit 3 and through the Brain MRI study, derived from visit 1-4, annual follow-up questionnaires, and the Brain MRI questionnaire. We may also consider other aspects of smoking behavior in secondary analyses.

Dependent variables:

Change in WMH volume from visit 3 to the brain MRI study, computed as measured volume minus imputed volume, according to an established algorithm¹⁵, and change in WMH score using the Cardiovascular Health Study (CHS) scale¹⁶ from visit 3 to the brain MRI study.

Effect modifiers:

Gender, race, age, hypertension, diabetes.

Statistical Analyses:

For analyses using change in WMH volume, we propose to use linear regression to assess the association between our smoking variables and continuous change in WMHs and logistic regression to assess the association between smoking and the risk of being in the top quintile of progression.

For secondary analyses using change in CHS score, we propose to use ordinal logistic regression to assess the relationship between smoking and change in CHS score.

All analyses will be adjusted for age, education, race/center, and gender. We will also consider models that additionally adjust for potential intermediates, including body mass index, diabetes, hypertension, and prevalent coronary heart disease. We will use multiplicative interaction terms to assess effect modification.

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 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?
 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? 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"?
 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.csc.unc.edu/ARIC/search.php>

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)?

#1894 Retinal microvascular abnormalities predict progression of white matter disease and incident lacunar infarcts: The ARIC MRI study

#1387 Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI Study

Knopman, D. S., et al. (2011). "Vascular risk factors and longitudinal changes on brain MRI: the ARIC study." *Neurology* 76(22): 1879-1885.

Gottesman, R. F., et al. (2010). "Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort: Atherosclerosis Risk in Communities (ARIC) Study." *Stroke* 41(1): 3-8.

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number ARIC Brain MRI: 1999.01)

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.csc.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.csc.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.

References

1. DeBette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010-07-26 00:00:00 2010;341.
2. Anstey KJ, von Sanden C, Salim A, O'Keane R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol*. Aug 15 2007;166(4):367-378.
3. Peters SAE, Huxley RR, Woodward M. Smoking as a Risk Factor for Stroke in Women Compared With Men: A Systematic Review and Meta-analysis of 81 Cohorts, Including 3 980 359 Individuals and 42 401 Strokes. *Stroke*. October 1, 2013 2013;44(10):2821-2828.
4. Bots ML, Breteler MMB, Hofman A, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *The Lancet*. 5/15/ 1993;341(8855):1232-1237.
5. van Swieten JC, Kappelle LJ, Algra A, van Latum JC, Koudstaal PJ, van Gijn J. Hypodensity of the cerebral white matter in patients with transient ischemic attack or minor stroke: influence on the rate of subsequent stroke. Dutch TIA Trial Study Group. *Ann Neurol*. Aug 1992;32(2):177-183.
6. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ. Brain White Matter Hyperintensities: Relative Importance of Vascular Risk Factors in Nondemented Elderly People. *Radiology*. October 1, 2005 2005;237(1):251-257.
7. Jeerakathil T, Wolf PA, Beiser A, et al. Stroke Risk Profile Predicts White Matter Hyperintensity Volume: The Framingham Study. *Stroke*. August 1, 2004 2004;35(8):1857-1861.
8. Longstreth WT, Manolio TA, Arnold A, et al. Clinical Correlates of White Matter Findings on Cranial Magnetic Resonance Imaging of 3301 Elderly People: The Cardiovascular Health Study. *Stroke*. August 1, 1996 1996;27(8):1274-1282.
9. Liao D, Cooper L, Cai J, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. *Neuroepidemiology*. 1997;16(3):149-162.
10. Fukuda H, Kitani M. Cigarette Smoking Is Correlated With the Periventricular Hyperintensity Grade on Brain Magnetic Resonance Imaging. *Stroke*. April 1, 1996 1996;27(4):645-649.
11. Kim S, Yun C-H, Lee S-Y, Choi K-h, Kim M, Park H-K. Age-dependent association between cigarette smoking on white matter hyperintensities. *Neurological Sciences*. 2012/02/01 2012;33(1):45-51.
12. Longstreth WT, Arnold AM, Beauchamp NJ, et al. Incidence, Manifestations, and Predictors of Worsening White Matter on Serial Cranial Magnetic Resonance Imaging in the Elderly: The Cardiovascular Health Study. *Stroke*. January 1, 2005 2005;36(1):56-61.
13. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of Cerebral Small Vessel Disease in Relation to Risk Factors and Cognitive Consequences: Rotterdam Scan Study. *Stroke*. October 1, 2008 2008;39(10):2712-2719.
14. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology*. May 31 2011;76(22):1879-1885.
15. Gottesman RF, Coresh J, Catellier DJ, et al. Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort: Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. January 1, 2010 2010;41(1):3-8.
16. Manolio TA, Kronmal RA, Burke GL, et al. Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke*. Feb 1994;25(2):318-327.