**ARIC Manuscript Proposal #3581**

| | | |
|---|---|---|
| **PC Reviewed: 3/10/20** | **Status: _____** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: The Moderating Influence of Education and Lifestyle on Genetic Risk for Dementia

**b. Abbreviated Title (Length 26 characters)**: Genes, Environment, and Dementia

**2. Writing Group**: Mark Lee, BA; Pamela Lutsey, PhD; Kristen M. George, PhD; Michael Griswold, PhD; Tim Hughes PhD; Jeannette Simino, PhD

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


**First author**: Mark Lee
Address: 909 Social Sciences Building
267 19th Ave S,
Minneapolis, MN 55455
Phone: 763-229-7001
E-mail: leex6611@umn.edu

**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).
Name: Pamela Lutsey
Address: 1300 S 2nd St
300 West Bank Office Building
Minneapolis, MN 55454
Phone: 612-624-5812
E-mail: lutsey@umn.edu


**3. Timeline**:

Data analysis will begin after approval.

**4. Rationale**:

The APOE ε4 allele is a significant genetic risk factor for Alzheimer's disease and related dementia [1-3]. However, this relationship is not deterministic. Many APOE ε4 carriers live to

old age without developing dementia, and nongenetic factors can alter how this allele is expressed [4].

Dementia onset is delayed among people with higher education [5] and good cardiovascular health measured by the American Heart Association's Life's Simple 7 [6]. However, previous research has yielded mixed conclusions regarding two questions: (1) Do the education and lifestyle gradients in dementia risk persist across groups stratified by genetic risk for the disease? (2) Does genetic risk *magnify* or *diminish* the influence of education and lifestyle factors on dementia onset?

*Education*. In an early study of education, genes, and dementia in an American sample, researchers found that among 865 adults aged 70-79 years at baseline, carrying an APOE ε4 allele *diminished* the protective effect of education on dementia risk [7]. A study of 932 adults from Sweden aged 75 and older at baseline followed over nine years showed opposite results: the education gradient in dementia risk was *magnified* among APOE ε4 carriers compared with non-carriers [8]. By contrast, no interaction effect was observed in two other studies of Scandinavian participants aged 65 and older where the education gradient in dementia risk was observed across APOE genotype groups, but genetic risk did not alter the magnitude of this gradient [9-10].

*Lifestyle.* Behavioral characteristics including diet, physical activity, alcohol consumption, and smoking have also been examined as moderators of genetic risk for dementia. A study of 1,646 Canadians aged 65 and older at baseline followed for five years found that exercise significantly reduced risk of dementia among APOE ε4 non-carriers, but it had no effect among those with high genetic risk for the disease [11]. This same interaction effect between physical activity, genetic risk, and dementia was observed in a study of 3,375 Americans aged 65 and older [12]. Contradicting this, a study of 1,284 individuals from Finland showed that the relationship between mid-life (mean age 50) lifestyle risks (including diet, physical activity, alcohol consumption, and smoking) and late-life (mean age 71) dementia was *magnified* among APOE ε4 carriers compared with non-carriers [13]. Several other prospective aging studies have shown that lifestyle and genetic risks for dementia operate independently of each other [14-16].

Currently, the evidence regarding the joint influence of APOE genotype, education, and lifestyle on dementia risk is quite mixed. Many of these studies rely on sample sizes around 1,000 participants. This may make them underpowered to identify statistically significant interaction effects. Previous studies also tend to have a limited follow-up time (10 years or less), which forces them to only consider how environmental factors in late life influence dementia risk.

From a public health and policy perspective it would be valuable to show that modifiable factors – such as higher education and a beneficial lifestyle – are associated with lower risk of dementia even among individuals who have a genetic predisposition. However, whether there is effect modification is also of interest. This study will examine these potential environmental modifiers by (a) describing the education and lifestyle gradient in dementia within categories of genetic risk and (b) testing for a gene-environment interaction effect to explore whether genetic risk magnifies or diminishes the associations of education and lifestyle on dementia risk.

The ARIC-NCS panel contains sufficient data to answer these questions. Compared to previous studies that have examined gene-environment effects on dementia, ARIC-NCS has a relatively large sample (N=15,792) and a long follow-up period (approximately 28 years). The large sample size makes it possible to test for significant interaction effects, while the long term follow up means that mid-life characteristics can be used to predict later-life dementia (important given the long natural history of dementia). ARIC data have already been used to estimate the moderating effect of mid-life lifestyle factors on genetic risk for coronary artery disease [17], indicating that the current study design is feasible. Furthermore, the primary exposure variables in this study (education, lifestyle, and APOE genotype) independently show the expected relationship to dementia in the ARIC panel [18].

## 5. Main Hypothesis/Study Questions:

H1 (Preliminary Main Effects Analyses): Fewer copies of APOE ε4, higher education, and meeting more American Heart Association Life's Simple 7 (LS7) factors will each be significantly associated with lower risk of dementia.

H2 (Genetic Risk-Stratified Analyses): Beneficial effects of higher education and meeting more LS7 factors will be associated with lower risk of incident dementia, across all APOE ε4 categories.

H3 (Exploratory Interaction Analyses):

- H3a: The association between education and dementia will be stronger among APOE ε4 carriers than non-carriers.
- H3b: The association between LS7 and dementia will be stronger among APOE ε4 carriers than non-carriers.

## 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:** This study will use prospective cohort data from ARIC-NCS Visit 1 (1987-1989) through Visit 7 (2018-2019).

**Inclusion/exclusion:** Include all participants who have consented to use their genetic data for and non-CVD research. Exclude participants with missing baseline education or LS7 data or APOE genotype.

**Outcome:** Incident dementia from baseline through visit 7 (as determined according to current ARIC NCS analysis recommendations).

**Exposure variables:**

- Visit 1: Education (< high school, high school diploma or equivalent, some college or more)
- Visit 1: LS7 factors will be scored as ideal (2), intermediate (1), or poor (0). These will be summed to create an index ranging from poorest lifestyle (0) to ideal lifestyle (14). As has been done previously in ARIC [19-20], participants will be categorized as having a poor (0-4), average (5-9), or ideal (10-14) overall lifestyle. The LS7 factors are listed in Table 1.

Table 1. Life's Simple 7 indicators in ARIC adapted from Folsom et al. 2011 [21]

| Factor | Poor (0) | Intermediate (1) | Ideal (2) |
|---|---|---|---|
| Smoking | current smoker | quit in last 12 months | never or quit >12 months ago |
| Body mass index | ≥30 kg/m$^2$ | 25-29.9 kg/m$^2$ | <25 kg/m$^2$ |
| Physical activity | None | 1-149 min/week of moderate OR 1-74 min/week of vigorous OR 1-149 min/week of moderate and vigorous | ≥150 min/week of moderate OR ≥75 min/week of vigorous OR ≥150 min/week of moderate and vigorous |
| Diet<br>• ≥4.5 servings/day of fruits and vegetables<br>• ≥2 3- to 5-oz servings/week of fish<br>• ≥3 servings/day of whole grains<br>• <1,500 mg/day of sodium<br>• ≤4 glasses/week of sugar-sweetened beverages | 0-1 components | 2-3 components | 4-5 components |
| Total cholesterol | ≥240 mg/dL | <200 mg/dL treated OR 200-239 mg/dL | <200 mg/dL untreated |
| Blood pressure | SBP ≥140 mm Hg OR DBP ≥90 mm Hg | SBP <120 mm Hg and DBP <80 Hg treated OR SBP 120-139 OR DBP 80-89 mm Hg | SBP <120 mm Hg and DBP <80 mm Hg untreated |
| Fasting serum glucose | ≥126 mg/dL | <100 mg/dL treated OR 100-125 mg/dL | <100 mg/dL untreated |

- Visit 2: APOE genotype (2 copies of ε4 allele, 1 copy of ε4, no copies of ε4)

**Covariates:** Models will adjust for age, sex, and race measured at Visit 1.

**Statistical analysis:** This study will use Cox proportional hazard models to estimate the effect of the exposure variables on dementia risk with a competing risk of death. For the first hypothesis, a model will estimate the main effects of APOE genotype, education, and LS7 factors on dementia risk in the whole sample. For the second hypothesis, the sample will be stratified by APOE genotype, then models will estimate the effect of education and LS7 on dementia risk within each group. For the third hypothesis, we will use cross-product terms to assess the multiplicative interaction between education and APOE genotype, and LS7 and APOE genotype, respectively. All models will adjust for age, race, and sex. We will also explore interactions by race and sex. The proportional hazards assumption will be tested by including cross-product terms in the models.

**Methodological challenges:** The sample size of APOE ε4/ ε4 carriers may be too small to estimate precise effects of education and LS7 for this group. If so, we may stratify the genetic risk into broader categories, such as any APOE ε4 versus none. Also, we may use a genetic risk score for dementia instead of only APOE genotype. We are in the midst of calculating this score for another ARIC project (Kristen George, 1st author): if the score substantially improves prediction we will use it, however if improvements are modest we will use APOE due to its easier interpretability.

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X_ No**

**b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No**
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.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)?**

#1898 – Life's Simple 7s of neurocognitive health
#3281 – The relationship of APOE ε4 to the relative times and hazards of dementia

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

**11.b. If yes, is the proposal**

**_X_ A. primarily the result of an ancillary study (list number* _2008.06____)**

**___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

**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.

**References:**

[1] Henderson AS, Easteal S, Jorm AF, Mackinnon AJ, Korten AE, Christensen H, et al. (1995) Apolipoprotein E allele ε4, dementia, and cognitive decline in a population sample. *Lancet* 346: 1387-1390.
[2] Feshens EJ, Havekes LM, Kalmijn S, de Knijff P, Launer L, Kromhout D (1994) Apolipoprotein e4 allele and cognitive decline in elderly men. *BMJ* 309: 1202-1205.
[3] Myers RH, Schaefer EJ, Wilson PWF, D'Agostino R, Ordovas JM, Espino A, et al. (1996) Apolipoprotein E e4 association with dementia in a population-based study: the Framingham study. *Neurology* 46:673-677.
[4] Laws SM, Hone E, Gandy S, Martins RN. (2003) Expanding the association between the APOE gene and the risk of Alzheimer's disease: possible roles for APOE promoter polymorphisms and alterations in APOE transcription. *Journal of Neurochemistry* 84: 1215-1236.
[5] Stern Y, Gulrand B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. (1994) Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 271(13): 1004-1010.
[6] Sabia S, Fayosse A, Dumurgier J, Schnitzler A, Empana J-P, Ebmeier KP, et al. (2019) Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *BMJ* 366: I4414

[7] Seeman TE, Huang M, Bretsky P, Crimmins E, Launer L, Guralnik JM. (2005) Education and APOE ε4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *Journals of Gerontology: Series B* 60(2): P74-P83.
[8] Ferrari C, Xu W-L, Wang H-X, Winblad B, Sorbi S, Qiu C, et al. (2013) How can elderly apolipoprotein E ε4 carriers remain free from dementia? *Neurobiology of Aging* 34(1): 13-21.
[9] Ngandu T, von Struass E, Helkala E, Winblad B, Nissinen A, Tuomilehto J, et al. (2008) Education and dementia: what lies behind the association? *Neurology* 69: 1442-1450.
[10] Wang H-X, Gustafson DR, Kivipelto M, Pedersen NL, Skoog I, Winblad B, et al. (2012) Education halves the risk of dementia due to apolipoprotein ε4 allele: a collaborative study from the Swedish Brain Power initiative. *Neurobiology of Aging* 33(5): 1007.e1-1007.e7.
[11] Fenesi B, Fang H, Kovacevic A, Oremus M, Raina P, Heisz JJ. (2017) Physical exercise moderates the relationship of apolipoprotein E (APOE) genotype and dementia risk: a population-based study. *Journal of Alzheimer's Disease* 56(1): 297-303.
[12] Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, et al. (2005) Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology* 161(7): 639-651.
[13] Kivipelto M, Rovio S, Ngandu T, Kareholt I, Eskelinen M, Winblad B, et al. (2008) Apolipoprotein E ε4 magnifies lifestyle risks for dementia: a population-based study. *Journal of Cellular and Molecular Medicine* 12(6b): 2762-2771.
[14] Luck T, Riedel-Heller SG, Luppa M, Wiese B, Kohler M, Jessen F, et al. (2014) Apolipoprotein E ε4 genotype and a physically active lifestyle in late life: analysis of gene-environment interaction for the risk of dementia and Alzheimer's disease dementia. *Psychological Medicine* 44(6): 1319-1329.
[15] Meng X and D'Arcy C. (2013) Apolipoprotein E gene, environmental risk factors, and their interactions in dementia among seniors. *International Journal of Geriatric Psychiatry* 28(10): 1005-1014.
[16] Strand BH, Rosness TA, Engedal K, Magnus P, Bergem ALM, Schirmer H, et al. (2015) Interaction of apolipoprotein E genotypes, lifestyle factors and future risk of dementia-related mortality: The Cohort of Norway (CONOR). *Dementia and Geriatric Cognitive Disorders* 40: 137-147.
[17] Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. (2016) Genetic risk, adherence to a healthy lifestyle, and coronary disease. *New England Journal of Medicine* 375: 2349-2358.
[18] Gottesman RF, Albert MS, Alonso A. (2017) Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurology* 74(10): 1246-1254.
[19] Garg PK, O'Neal WT, Chen LY, Loehr LR, Sotoodehnia N, Soliman EZ, and Alonso A. (2018) American Heart Association's Life Simple 7 and risk of atrial fibrillation in a population without known cardiovascular disease: The ARIC (Atherosclerosis Risk in Communities) study. *Journal of the American Heart Association* 7(8): e008424.
[20] Oyenuga AO, Folsom AR, Lutsey PL, and Tang W. (2019) Association of Life's Simple 7 with reduced clinically manifest abdominal aortic aneurysm: The ARIC study. *Vascular Medicine* 24(3): 224-229.
[21] Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, and Rosamond WD. (2011) Community prevalence of ideal cardiovascular health, by the American Heart Association

definition, and relationship with cardiovascular disease incidence. *Journal of the American College of Cardiology* 57(16): 1690-1696.