ARIC Manuscript Proposal # 3281

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1.a. Full Title: The relationship of *APOE* ε4 to the relative times and hazards of dementia

b. Abbreviated Title (Length 26 characters): ***APOE* ε4 and time vs risk to dementia**

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3. Timeline: Manuscript will be completed in 6 months

4. Rationale:

With the aging of the population, there is increasing effort to understand risk factors for dementia and how families and societies may better anticipate the onset of dementia. One area of interest has been on genetic factors and risk of dementia and pathologic change. A review by Livingston in 2017 estimates that 7% of incident dementia cases globally are due to the *APOE* ε4 allele in particular.[1] Carriers of the ε*4* allele (homozygous or heterozygous) are at increased risk of MCI or dementia, and the ε2 allele confers a protective effect. What is unclear is if this greater risk is due to an earlier onset of cognitive decline in those with ε4 or an overall greater risk for dementia in those with an ε4 allele compared to no ε4 alleles.

Comparisons of time to dementia by allele status suggests dementia onset at younger ages for carriers of the ε4 allele, especially for persons who are homozygous for ε4.[2-8] A case-control study in Norway found the average onset of late life Alzheimer's disease was 78.4 years in those without ε4 compared to 72.9 years in those homozygous for ε4.[2] A systematic review conducted by Liu found a similar but wider age range with age of onset of 84 years in those without an ε4 allele and 68 years for ε4/ ε4.[4] In a study by Albert et al, there was modest evidence indicating carriers of the ε4 allele progress towards cognitive decline at a more rapid rate during the preclinical phase of disease compared to non-carriers[12] with similar results found for a more rapid decline in memory in other studies around the world.[4,13-14]

The effect of *APOE* on risk of dementia varies by sex and ethnic background. A meta-analysis by Farrer found that the odds ratio for Alzheimer's disease in Caucasians was significantly higher compared to African Americans (2.7-3.2 for ε4 heterozygotes in whites and 12.5-14.9 for ε4 homozygotes in whites, compared to 1.1 and 5.7 in blacks, respectively).[5] While this finding has been replicated in other studies, the possible influence of selection or sampling bias is acknowledged and cannot be excluded.[5,8-9] Risk of conversion to Alzheimer's disease is greater in females with an ε4 allele compared to men with an ε4 allele.[5,10-11]

Current literature supports the known increased risk of dementia with the presence of the ε4 allele as indicated above. Additionally, some studies, although fewer, have additionally evaluated time to dementia based on allele status. To our knowledge, an analysis by Van Der Lee in 2018 is the only study to have evaluated both overall risk and time to dementia. The authors assessed how an overall genetic risk score (including *APOE*) impacts the cumulative incidence of Alzheimer's Disease accounting for mortality as a competing risk using the Fine and Gray method.[15] Results support an 18-29 year difference in age at onset of Alzheimer disease or 18-23 year difference for dementia in those who have a high genetic risk score compared to a low risk score.[16] However, this method makes the strong assumption that the sub hazards within the two outcomes are proportional.

More broadly, these studies have assessed overall risk of dementia or analyzed age of onset of dementia without accounting for death as a competing risk. In this study, we will assess overall risk of dementia by *APOE* ε4 carrier status in ARIC participants using longitudinal follow-up from Visit 1 through Visit 6 and assess for differences in hazard of dementia as well as to time to dementia for carriers vs non-carriers as well as sex differences while accounting for the competing risk of death. We will do so using a novel methodologic approach for this research question[17], which allows us to simultaneously estimate the proportion of individuals who experience the primary outcome of dementia as well as the competing risk of death, and estimate the time distribution of each outcome by *APOE* ε4 status. To our knowledge, this is the first study to comprehensively evaluate how *APOE* impacts the overall risk of dementia for an individual, separately accounting for risk of dementia and time to dementia as well as death.

APOE ε4 genotype as a risk factor for dementia has been described in the ARIC cohort. In a paper by Bressler et al the presence of an *APOE* ε4 allele was associated with early change in cognitive test scores when present alongside certain SNPs.[18] Gottesman et al. found that *APOE* (at least one ε4 allele vs no ε4 alleles) was associated with a 1.98 (95% CI 1.78-2.21) increased risk of Level 3 dementia over time using Cox and discrete time analysis and a complimentary log-log link. Additionally, a sensitivity analysis for stroke and death as a competing risk was performed using the Fine and Gray method[19] finding certain covariate associations were attenuated but remained significant. Our study will build upon current ARIC literature[18-22] by allowing for additional analysis of time to dementia by separation of the overall risk of dementia (not dependent on time) from the relative time to dementia by *APOE* status with variable assumptions of the hazards or relative times. Additionally, our study aims to further understand how death may act as a competing risk for dementia by evaluating how *APOE* ε4 alters the proportion of individuals who experience dementia or death as well as the time to each outcome.

5. Main Hypothesis/Study Questions:

To determine if elevated dementia risk among those who are carriers of the *APOE* ε4 allele is attributable to an overall increased risk of dementia, earlier onset of dementia, or both.

- *Individuals with one or more ε4 alleles will have a shorter time to dementia compared to those with no ε4 alleles.*

- *The overall risk of dementia for those with one or more ε4 alleles is higher compared to those without an ε4 allele, with a greater risk demonstrated in women.*

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 Population: Our study sample originates from the full cohort of 15,792 participants and incorporates data from Visit 1 through Visit 6. Participants will be excluded if they are missing *APOE* ε4 status (n=419), were non-white race due to the attenuation of the ε4 and dementia association in non-white race (n=4,175), or missing both visits 5 and visits 6 due to the extensive

time gap in data (n=1,871). This yields a final sample of 8,956 participants. Of those participants remaining, 2,504 were an ε4 carrier and 6,452 had no *APOE* ε4 allele.

Outcomes: Our primary outcome of interest is a diagnosis of dementia and time to dementia diagnosis using the adjudicated Level 3 dementia diagnosis, which was ascertained utilizing several sources. First, 3-test cognitive batteries were performed at Visit 2and Visit 4. A comprehensive neuropsychological exam was completed at Visits 5 and 6 for all participants alive and able to attend. An algorithm for diagnosis of the longitudinal cognitive data and neuropsychological evaluation was used and confirmed by an expert panel. If participants did not attend Visit 5 or Visit 6, diagnosis was based on the Modified Telephone Interview for Cognitive-Status- Modified (TICS) with the participant, a modified Clinical Dementia Rating (CDR) with a family member or informant confirming hospital discharge codes or death certificate codes of dementia, or by hospital or death certificate dementia codes alone For those with a dementia diagnosis in hospital date of diagnosis was set as 6 months prior to the hospital visit date.

Time to death and date of death will be collected via hospital records, death certificates, and proxy/family interview.

Exposure: *APOE* status will be dichotomized (due to small limited participants who are homozygous for ε4) as ε4 carrier (one or more ε4 alleles) compared to no ε4 alleles.

Additional Independent variables: Basic demographic information was collected at Visit 1, including birthdate for calculating age at study visit, age at dementia diagnosis, and age at death (in years), sex, and education (highest grade or year of school completed). Education will be categorized according to standardized ARIC algorithms as less than high school, high school, or greater than high school.

Statistical Analysis: A series of time to event regression analyses will be performed to describe time and frequency of dementia occurrence with a competing risk of death. Age will be used as the time scale to account for age as a strong confounder, and the time origin will be set at age 60 years. Time to dementia will be calculated as time to diagnosis from age 60. Late entries are considered as those who enter after age 60 and began follow-up at the age of entry into ARIC. Kaplan Meier and basic Cox proportional hazard models will be run to assess proportionality of time to dementia and time to death by *APOE* status. We will model the relative time and relative hazard functions for dementia using generalized gamma distributions and stratify by sex to investigate potential differences.

To account for competing risk of death in time to dementia we will use a mixture of generalized gamma method[17] to ascertain the proportion of dementia and death events by *APOE* status as well as relative times for both outcomes (dementia and death). We will do this using the *stcrmix* command in STATA which uses maximum likelihoods to fit a competing risk model with the specification of two competing risk events and a third category of unknown or unobserved events which specifies the latest possible time a person may be expected to experience one or the other of the events (termed upper censoring). This method is an alternative to the Fine and Gray method to assess relative times and competing risk, which uses a mixture of distributions in a

parametric model to describe the frequency, and timing for individuals to reach each event type (dementia or death).

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 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? __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/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)?

MP# 924 Blair. Apolipoprotein E genotype, cardiovascular risk factors, and cognitive decline in a middle-aged cohort: the Atherosclerosis Risk in Communities Study

MP# 1771 Knopman D et al. Fourteen-year longitudinal study of vascular risk factors, *APOE* genotype, and cognition: The ARIC MRI Study.

MP# 2466 Gottesman R et al. The ARIC-PET amyloid imaging study, Brain amyloid differences by age, race, sex, and *APOE*.

MP# 2120c Gottesman R et al. Incidence of Dementia and its relationship to midlife vascular risk factors in ARIC.

MP# 1704 Bressler J. et al. Genetic variants identified in genome-wide association studies of dementia and cognitive change in middle age: The Atherosclerosis Risk in Communities (ARIC) study

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 https://www2.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.

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