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I. Title:

The association between APOE genotype, race and incident dementia: Analysis of 7 population-based studies

II. Abbreviated Title:

APOE and dementia

III. Select cohorts to be used in proposal:

AGES	ARIC	CHS	FHS	HAAS	MESA	REGARDS	SALSA	Whitehall II
x	x	x	x	x	x			x

IV. Writing Group:

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V. Background

APOE is an established genetic risk factor for Alzheimer's Disease and other related dementias (ADRD). APOE, specifically the APOE e4 allele, has been shown to be associated with an increased risk of mortality and dementia.[1-3] It has been suggested that the association between APOE and dementia may differ by race. One study suggests that Black individuals who carry APOE e4 experience an earlier age of dementia onset and diagnosis than White individuals who are APOE e4 carriers, however compared to non-carriers, the e4 allele has a larger impact on dementia risk in White participants.[4] Recently, it has been suggested that the APOE e2 allele may increase survival and serve as a protective factor for cognitive decline and dementia.[1,5-7] However, data are not consistent across studies.[1, 7-9] The discrepancies may be due to the rarity of the e2 allele frequency, with only 1% of the population being e2e2 carriers, making it difficult to ascertain the association between the APOE e2/e2 genotype and dementia without a large sample size. Additionally, current literature surrounding APOE e2/e2 focusing on dementia as an outcome is lacking, with larger focus on mortality and cognitive decline. Furthermore, few studies have investigated the race -specific APOE e2 effects on dementia. One meta-analysis

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suggests that the e2 allele is protective against dementia, with the strongest effect in White individuals.[10] However, other studies suggest that the protective effect of the e2 allele does not differ by race.[5,11] Therefore, it is not fully understood how race may modify the protective effect of APOE e2. Therefore, a study with long follow-up time to assess incident dementia, the ability to investigate modifiers, and a sufficiently large sample size including a diverse population is necessary to study the relationship between APOE genotype and dementia.

The role of the APOE glycoprotein is to mediate and regulate lipid transport and uptake.[1] Levels of HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides vary among the APOE alleles, with APOE e2 carriers having lower levels of LDL and total cholesterol, while APOE e4 carriers have higher levels of these lipids.[1,12] While a study showed that adjusting for LDL cholesterol does not affect mortality risk among the APOE genotypes,[1] lipid profiles among APOE status needs to examined in a larger and more diverse population.

By pooling data from 7 population-based studies, we will have a sample size sufficiently large to elucidate the association between APOE genotypes including e2e2, potential modifiers, and dementia. We will use data from the Dementia Risk Pooling Project (DRPP) which is rigorously harmonized and curated to study this question.

VI. Main Study Questions and Hypotheses

Is APOE e2 carriership protective for dementia and is this effect modified by race?

We hypothesize that APOE e2e2 will be protective for dementia, while the other genotypes will not be.

We hypothesize that the protective effect of APOE e2e2 will vary across race/ethnicity.

VII. DRPP data to be used

Demographic: Age, sex, race/ethnicity, education

Clinical: Systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, LDL cholesterol, HDL cholesterol, smoking, physical activity, diabetes status, depression, medication use, hypertension,

Genetic: APOE (all genotypes)

Outcome: Dementia (all types)

VIII. Analytic Plan

Population

We will use data from 7 large, community-based, prospective cohort studies as part of DRPP. The cohorts include: the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik), Whitehall II study, the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Honolulu-Asia Aging Study (HAAS), the Multi-Ethnic Study of Atherosclerosis (MESA), and the original Framingham Heart Study (FHS) and five of its offshoots (Offspring (FOS), New Offspring Spouse (NOS), Generation 3 (Gen 3), Omni and Omni 2). All data are centralized at Northwestern University for pooling, harmonization, and analysis.

APOE genotyping

APOE isoforms were estimated from rs7412 and rs429358 Single Nucleotide Polymorphisms (SNPs).

APOE alleles of interest are APOE e2e2, e2e3, e2e4, e3e3, e3e4, e4e4. APOE e3e3 will be considered as reference.

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Dementia incidence
The primary outcome of interest is dementia incidence (all types).

Imputation
Multiple imputation will be used to account for missing data.

Analysis plan
We will use Cox proportional hazard models to estimate the association between APOE genotypes and incident dementia, adjusting for age, sex, study, and cardiovascular risk factors (hypertension, diabetes, high cholesterol, smoking, physical activity, BMI). Follow-up time will begin at the participant's entry into the study and continue until diagnosis of dementia or censoring. Participants will be censored at the end of study, loss to follow-up, or death, whichever occurs first. Prior to analysis, the proportional hazards assumption will be assessed by visual inspection of the survival curves (log-log plots) and assessing Schoenfeld residuals.
To evaluate the association between APOE genotype and incident dementia by race, Cox proportional hazard models will be used such that the data are subset to the race of interest and hazard ratios (HR's) will be estimated with APOE e3/e3 as the comparison group in each analysis, adjusted for age, sex, cohort, cardiovascular risk factors (hypertension, diabetes, high cholesterol, smoking, physical activity, BMI), and education. Models estimating the risk of dementia among Black and White participants will be modeled with APOE genotype, while models estimating the risk of dementia among Asian participants will be modeled with combined genotypes (APOE e2 and e4 carriership). Cause-specific hazard ratios will be reported for all survival analyses, with follow-up time beginning on the date of study enrollment and censored at the end of study follow-up, loss to follow-up, or death, whichever occurred first. Because some APOE genotypes are associated with increased or decreased mortality, mortality will be considered a competing risk. A sensitivity analysis will be conducted such that Cox proportional hazard models will be used to estimate the cause-specific hazard ratios (HRs) for mortality, with follow-up time censored at the end of study follow-up, loss to follow-up, and incident dementia. This will allow a comparison of the association of APOE genotype and incidence dementia with the association of APOE genotype and dementia-free survival. Second, a sensitivity analysis was conducted using a subdistribution proportional hazards model for a competing risk assessment, as described by Fine and Grey.

We will calculate HRs for each of the cohorts as well as in the pooled cohort to evaluate heterogeneity to ensure a single cohort is not driving the association between APOE genotype and dementia.

We will adjust the associations by lipid levels (HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides) to assess if the associations can be explained by the lipid levels.

We plan to discuss the following limitations associated with conducting an analysis by race in full detail in the discussion section: 1) Use of self-reported race, 2) confounding by geography, and 3) biased measurements of cognition by race leading to the possibility that Black participants may have been differentially diagnosed with dementia at a higher rate compare with White or Asian participants.

IX. Timeline

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September 22,2023- DRPP Manuscript Proposal Approved
September 22,2023-October 22,2023- Data Analysis + interpretation
October 22,2023-December 2023- Draft paper
January 2024 -March 2024- Revisions
March/April 2024- Submit Paper

X. References

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