

Genetic Modifiers Of *APOE*- ϵ 4 Provide Insight Into Amyloid Resilience

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Key Takeaway: Genome-wide analyses identified multiple loci associated with amyloid burden in an *APOE* ϵ 4-dependent manner, supporting the presence of genetic modifiers that may contribute to heterogeneity in *APOE* ϵ 4-associated amyloid pathology.

INTRODUCTION

Background

- APOE* ϵ 4 is the strongest common genetic risk factor for Alzheimer's disease (AD) and is strongly associated with cerebral amyloid accumulation.
- APOE* ϵ 4 is **neither necessary nor sufficient** for AD onset, and substantial heterogeneity exists among carriers in both amyloid burden and downstream clinical outcomes.
- One possible explanation for this heterogeneity is the presence of genetic modifiers that alter the biological effects of *APOE* ϵ 4.
- Identifying such modifiers may improve our understanding of amyloid resilience and reveal pathways relevant to disease heterogeneity.

Objective

To identify genetic variants that modify the relationship between *APOE* and Amyloid burden.

Phenotype

- Harmonized amyloid burden measured as Centiloid values

METHODS

Sample

- Primary analytic sample included **5,069** European-ancestry participants with amyloid PET and genomic data.
- Analyses included **2,076 *APOE* ϵ 4 carriers** and **2,993 non-carriers**.
- Participants were 60–85 years old at amyloid PET acquisition.
- APOE* ϵ 2 carriers were excluded from the primary analysis.
- Amyloid burden was measured using harmonized Centiloid values.

Analysis

- Cohort-specific genome-wide association analyses were performed for amyloid Centiloid values.
- Stratified analyses were performed separately among *APOE* ϵ 4 carriers and non-carriers.
- Models included age at amyloid PET, sex, and the first five European ancestry principal components as covariates.
- Cohort-level summary statistics were meta-analyzed using fixed-effects inverse-variance weighting in GWAMA.
- Functional annotation was performed using FUMA, including MAGMA gene-based analyses and eQTL annotation.

RESULTS

Figure 1. Genome-wide analyses

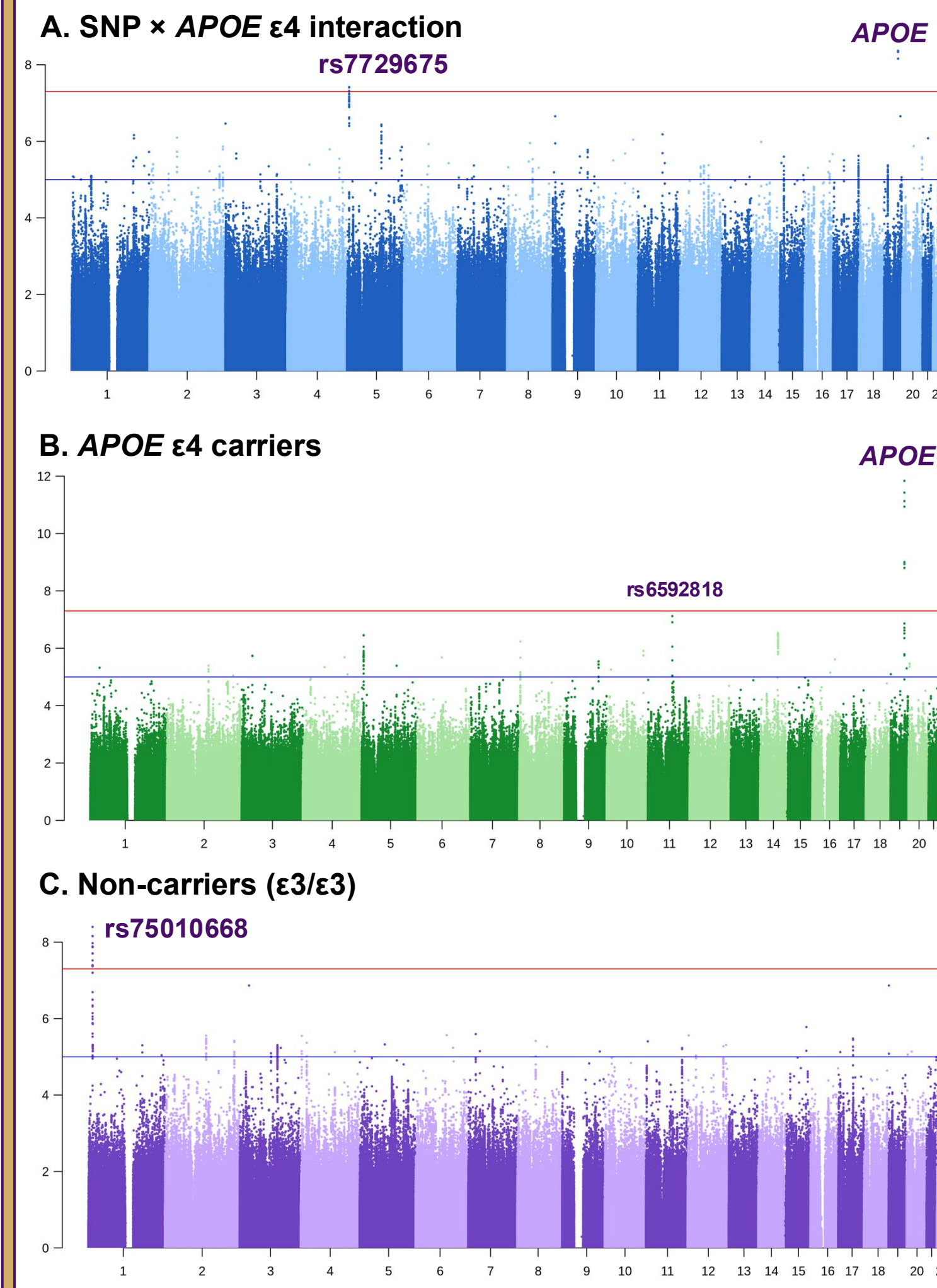


Figure 2. Regional association plot of the Chr5 Locus

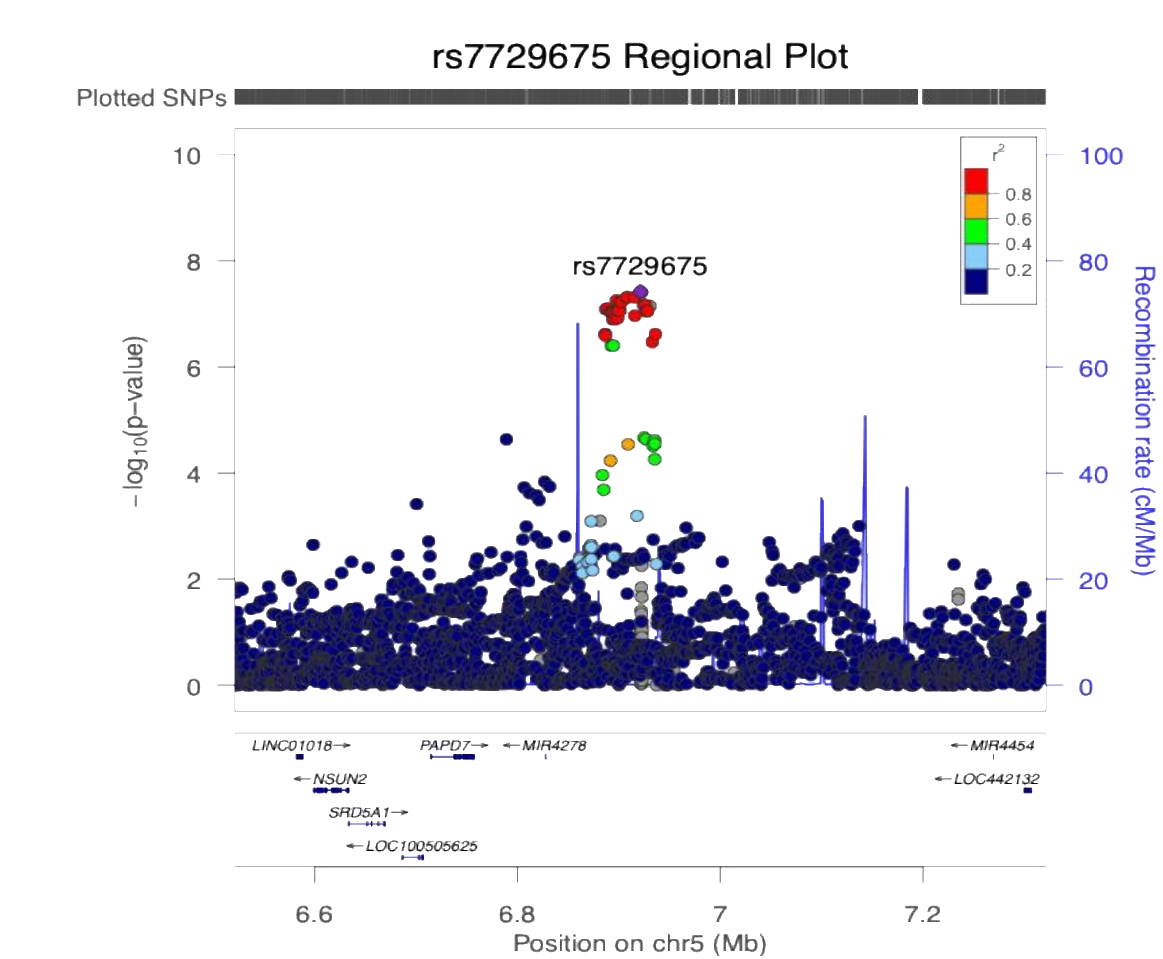


Figure 3. rs7729675 genotype effects by *APOE* status

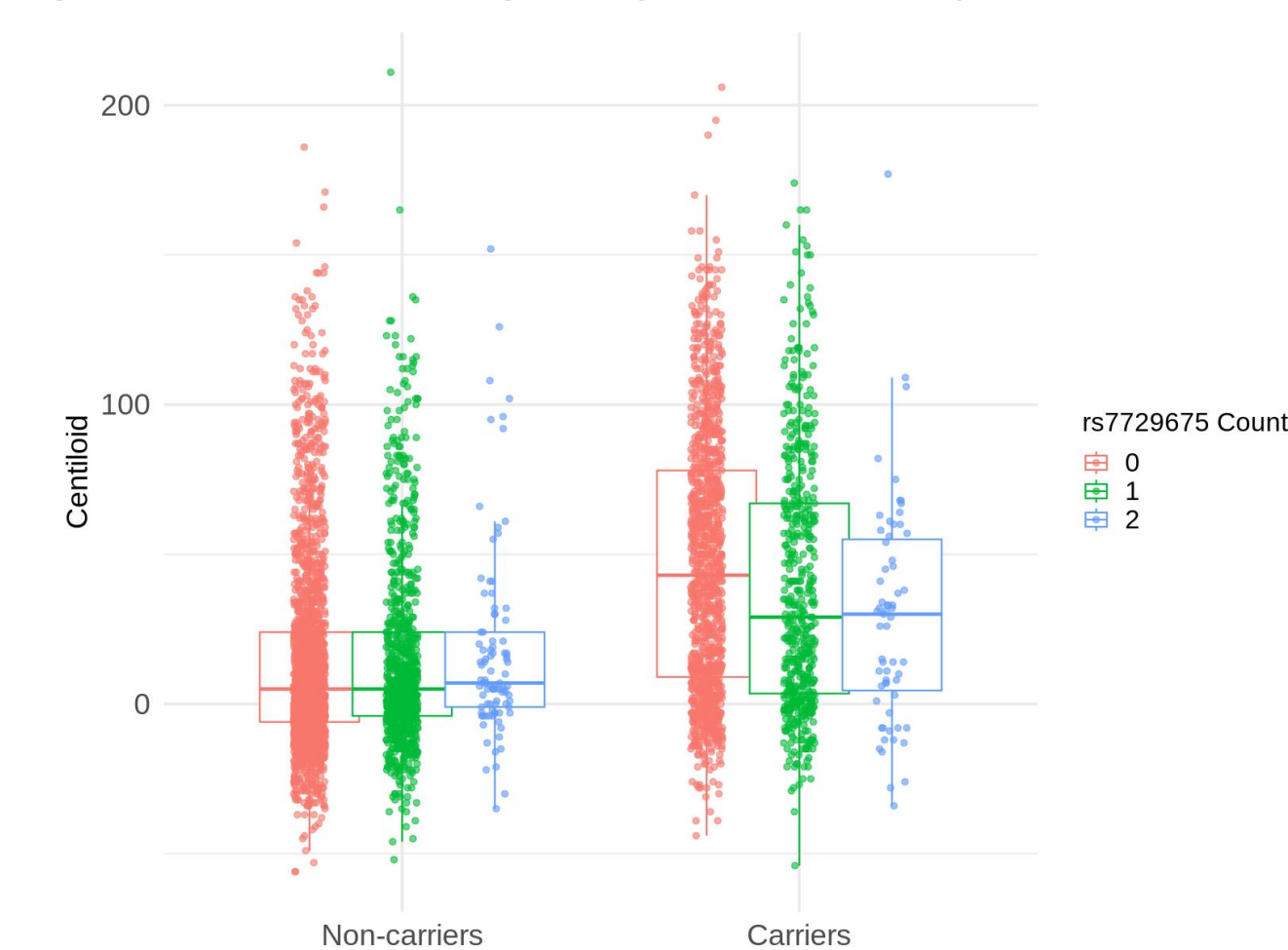
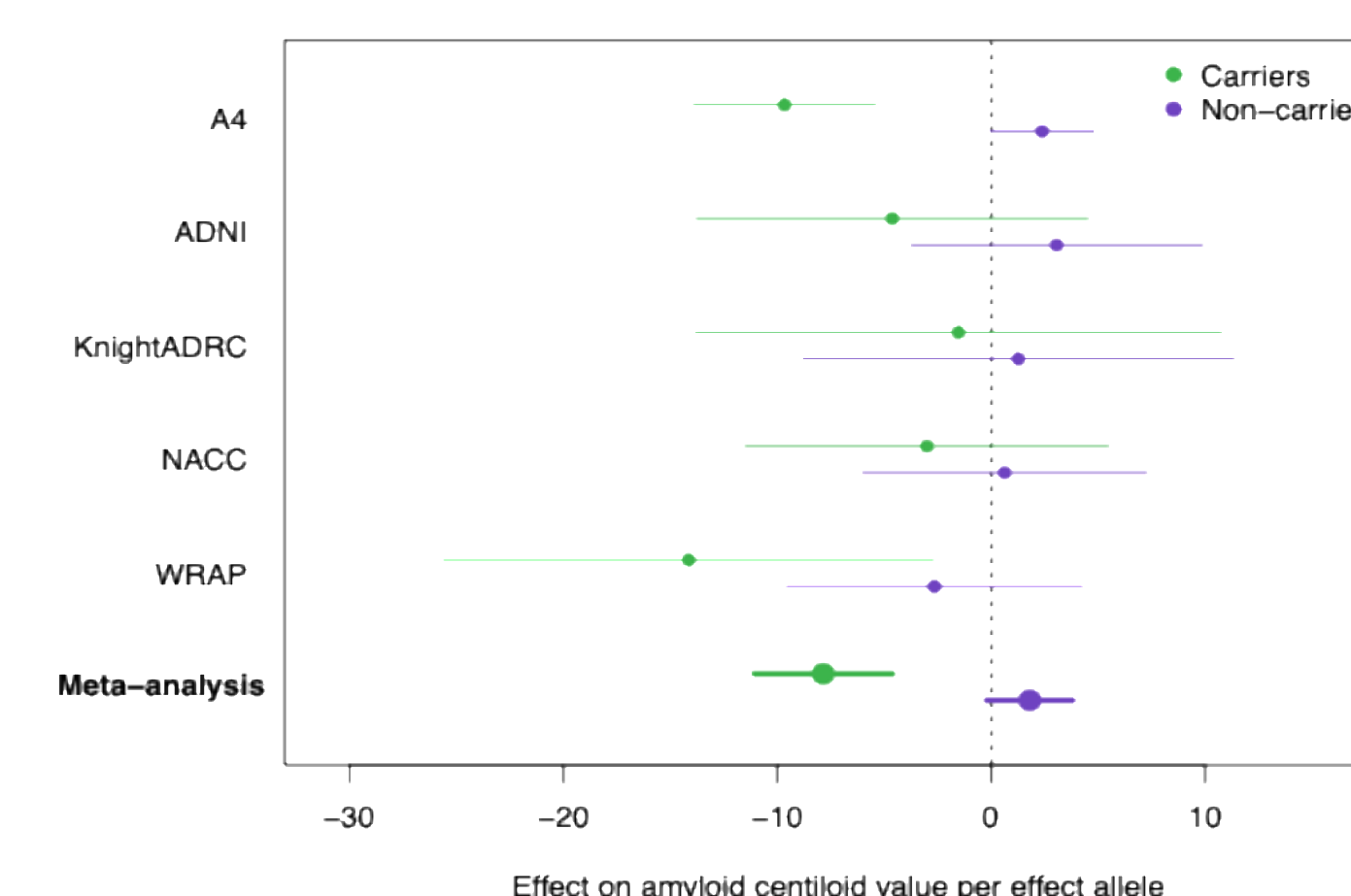


Figure 4. Effect of rs7729675 by cohort



CONCLUSIONS

- A genome-wide significant SNP $\times$ *APOE* ϵ 4 interaction identified a chromosome 5 locus led by **rs7729675** ($\beta_{\text{Carriers}} = -7.9$, $P = 1.90 \times 10^{-6}$; $\beta_{\text{Noncarriers}} = 1.8$, $P = 0.07$), supporting an *APOE*-dependent genetic effect on amyloid burden. The minor allele was associated with lower Centiloid values in *APOE* ϵ 4 carriers, with minimal association in non-carriers.
- Functional annotation prioritized **LINC02196**, **NSUN2**, and **FASTKD3** at this locus. eQTL resources linked the signal to reduced *LINC02196* expression, and SEA-AD data showed *LINC02196* enrichment in layer 5 intratelencephalic neurons.
- No non-*APOE* locus reached genome-wide significance in the *APOE* ϵ 4 carrier GWAS, although follow-up gene-based analyses highlighted **FKSG61** and **NOXRED1** on chromosome 14.
- A genome-wide significant chromosome 1 locus was identified in non-carriers ($\beta_{\text{Carriers}} = 1.12$, $P = 0.7$; $\beta_{\text{Noncarriers}} = 15.4$, $P = 3.99 \times 10^{-9}$), near **KAZN**, with **PDPN** implicated by eQTL annotation.
- These findings suggest that genetic modifiers contribute to heterogeneity in *APOE* ϵ 4-associated amyloid pathology, but additional replication and functional work are needed.

DISCOVERY COHORTS



REPLICATION COHORTS

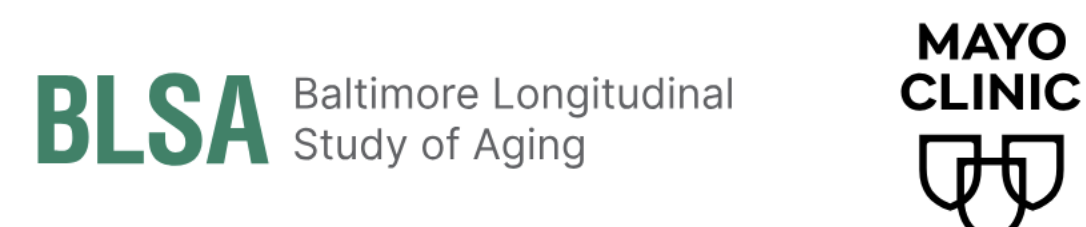


Table 1 Characteristics of the primary analytic sample according to *APOE* ϵ 4 carrier status

Characteristic	Total	<i>APOE</i> ϵ 4 carriers	Non-carriers
<i>n</i>	5,069	2,076	2,993
Age at amyloid PET, years	72.6 $\pm$ 5.8	72 $\pm$ 5.6	73 $\pm$ 5.8
Female, <i>n</i> (%)	2,895 (57.1%)	1,167 (56.2%)	1,728 (57.7%)
Education, years	16.6 $\pm$ 2.7	16.6 $\pm$ 2.7	16.6 $\pm$ 2.6
Centiloid value	13 [-2, 54]	43 [9, 79]	5 [-5, 24]
Cognitively unimpaired, <i>n</i> (%)	3,589 (70.8%)	1,334 (64.3%)	2,255 (75.3%)
Mild cognitive impairment, <i>n</i> (%)	513 (10.1%)	233 (11.2%)	280 (9.4%)
Alzheimer's disease dementia, <i>n</i> (%)	347 (6.8%)	242 (11.7%)	105 (3.5%)
Diagnosis unavailable, <i>n</i> (%)	620 (12.2%)	267 (12.9%)	353 (11.8%)
ϵ 3/ ϵ 3, <i>n</i> (%)	2,993 (59%)	0 (0%)	2,993 (100%)
ϵ 3/ ϵ 4, <i>n</i> (%)	1,787 (35.3%)	1,787 (86.1%)	0 (0%)
ϵ 4/ ϵ 4, <i>n</i> (%)	289 (5.7%)	289 (13.9%)	0 (0%)

Data are presented as mean $\pm$ SD, median [IQR], or *n* (%). *APOE* ϵ 2 carriers were excluded from the primary analytic sample.

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Questions or collaborations?
Please reach out!

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