

Is *APOE* $\epsilon 2$ Always a Protective Allele? Ancestry-Specific Modulation of Survival and Mortality in Admixed Brazilian Populations

Santos, G.N.¹; Rodrigues, P.H.S.¹; Passos, C.H.¹; Paco, S.L.G.¹; Ignacio, I.B.¹; Alexandria, M.A.L.S.¹; Bastos, A.O.¹; Veronezz, L.A.¹; Oliveira Neto, F.A.¹; Bardella, M.U.¹; Suemoto, C.K.^{1,3}; Leite, R.¹; Lea Grinberg^{1,4}; Meyer, D.¹; Zatz, M.¹; Naslavsky, M.S.^{1,2}
¹ University of São Paulo, São Paulo, Brazil; ² Hospital Israelita Albert Einstein, São Paulo, Brazil;
³ UT Health San Antonio, San Antonio, TX, USA; ⁴ Mayo Clinic, Jacksonville, FL, USA



BACKGROUND

The *APOE* $\epsilon 2$ allele is widely regarded as a **protective factor** against **Alzheimer's disease** and a contributor to **exceptional longevity**. However, this paradigm is largely based on European-ancestry cohorts, and its **relevance across diverse admixed populations remains unclear**. Because $\epsilon 2$ is relatively rare, its effects within different **local ancestry (LA)** backgrounds are poorly characterized. High-resolution genomic approaches are needed to determine **whether the protective effects attributed to $\epsilon 2$ are consistent across ancestral contexts**.

OBJECTIVE

To investigate whether the protective effect traditionally attributed to *APOE* $\epsilon 2$ is consistent across **different local ancestry backgrounds** in admixed Brazilian populations. By comparing survival and mortality cohorts, we evaluated whether **ancestry-specific *APOE* genotype** patterns provide evidence of **differential effects on longevity**.

STUDY DESIGN & METHODS

SABLE
(LIVING COHORT, Census-Based)
Represents **survival pressure**.

BAS
(DECEASED COHORT, Post-Mortem Biobank)
Represents **mortality pressure**.

We analyzed two large population-based sample collections from **São Paulo, Brazil**:

- BAS (Biobank for Aging Studies):** n = 716 deceased individuals (mean age 72.7 ± 12.5 years) representing the mortality group.
- SABLE (Health, Well-being and Aging Study):** n = 952 community-dwelling older adults (mean age 72.4 ± 9.5 years) representing the survival group.

APOE genotyping and **Local Ancestry Inference (LAI)** assigned African (AFR), European (EUR), or Native American (NAM) ancestry to each *APOE* haplotype, accessed by SNP Array and WGS. Hardy-Weinberg Equilibrium (HWE) was calculated and adjusted for LA using Monte Carlo simulations.

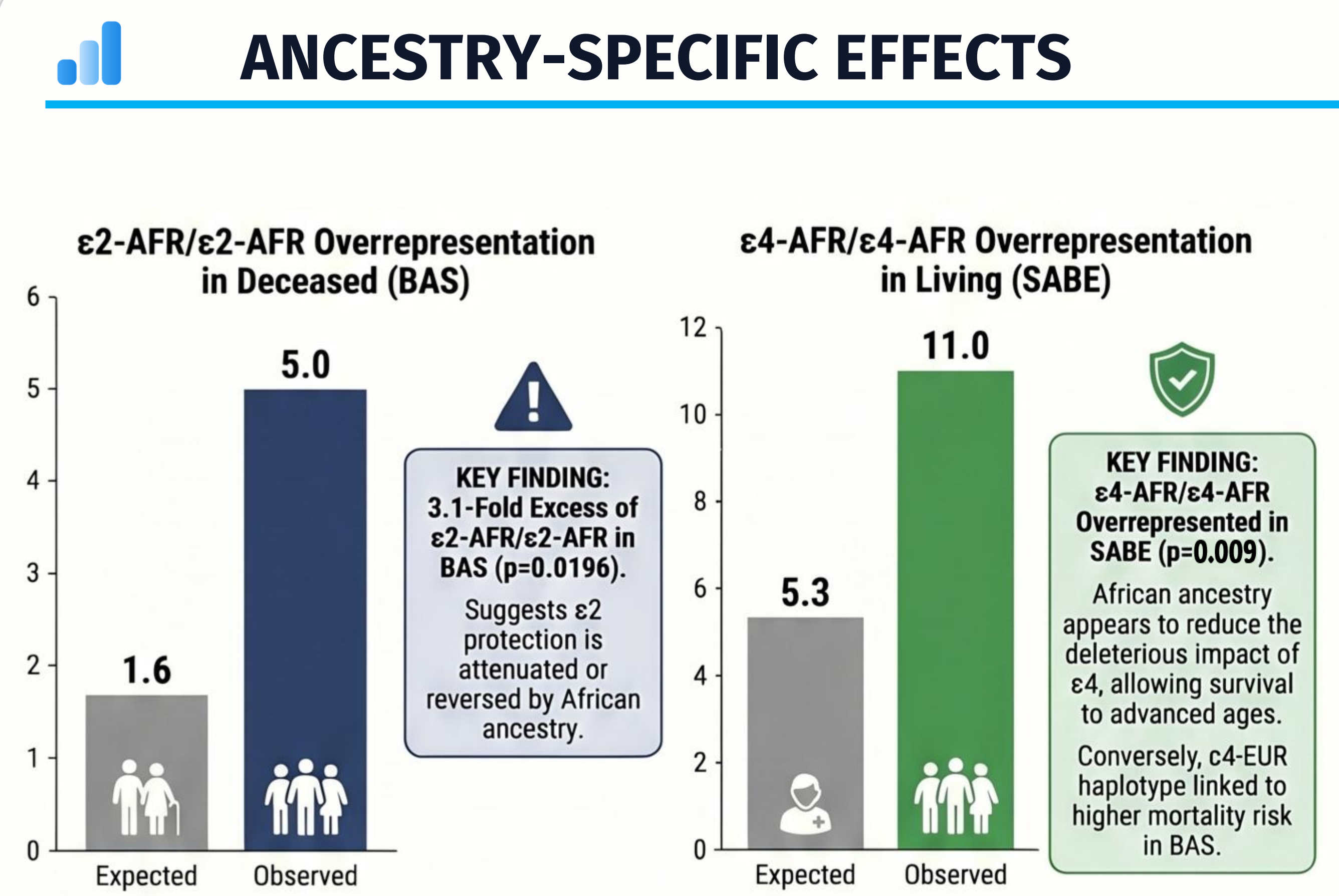


Figure1. Ancestry-Specific Deviations from Hardy-Weinberg Equilibrium (HWE). Observed vs. expected counts for *APOE*+LA genotypes using Monte Carlo simulations (10,000 permutations). (Left) The "ε2 Paradox" in the deceased cohort (BAS), showing a significant 3.1-fold excess of ε2-AFR/ε2-AFR homozygotes (Observed = 5, Expected = 1.6; p = 0.0196). (Right) The "Ancestry Buffer" in the living cohort (SABLE), showing a significant overrepresentation of ε4-AFR/ε4-AFR homozygotes (Observed = 11, Expected = 5.3; p = 0.009).

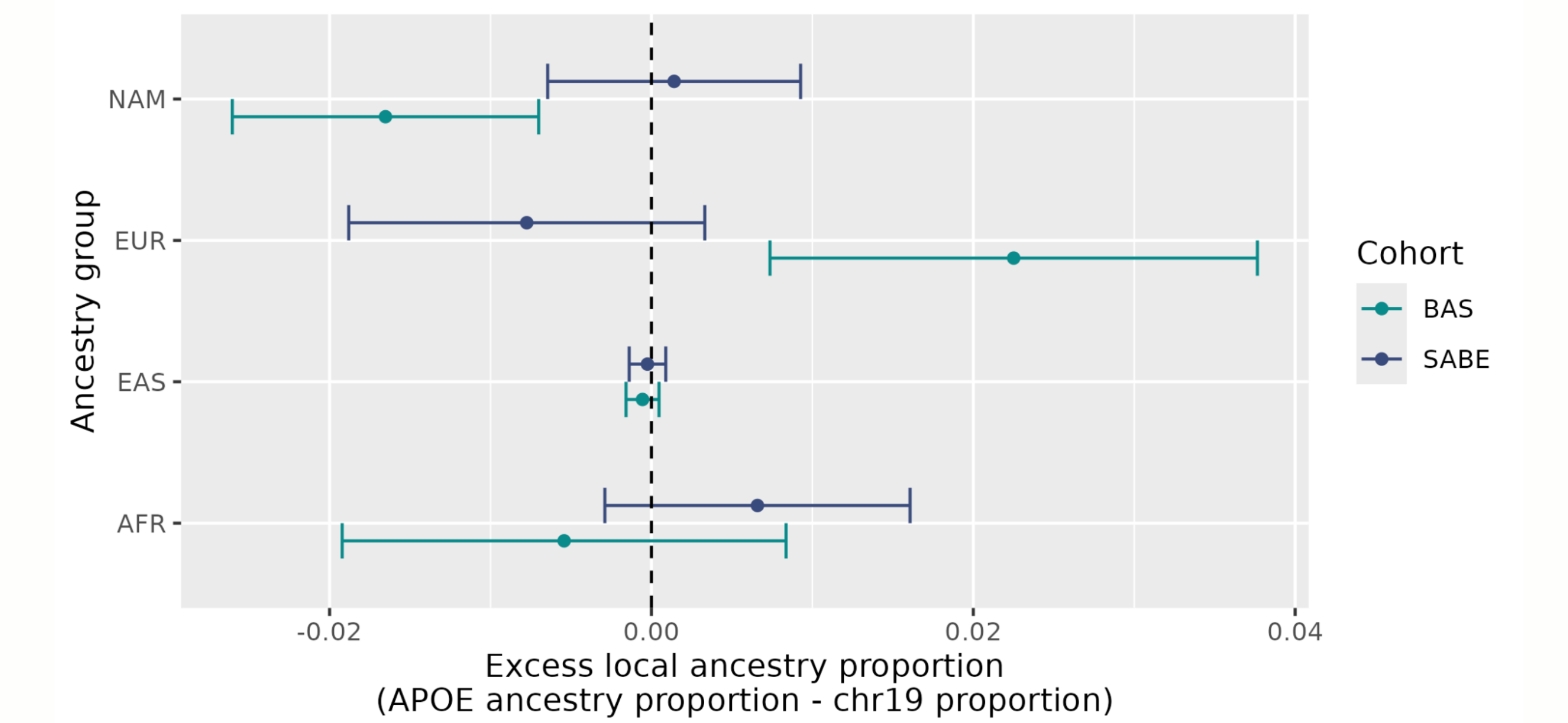


Figure2. Local Ancestry Enrichment: Comparison of local ancestry (LA) at the *APOE* locus relative to chromosome 19 background. The deceased cohort (BAS) exhibits significant European LA enrichment (+1.3%, p=0.031) and Native American depletion (-0.95%, p=0.014), while the living cohort (SABLE) remains stable

SUBJECTS CHARACTERISTICS

Metric / Variable	BAS (Deceased)	SABLE (Living)	p-value
Sample size (n)	716	952	0.081
Mean Age	72.7 yrs	72.4 yrs	0.749
African Ancestry (AFR)	30.0%	17.5%	< 0.001
European Ancestry (EUR)	63.8%	76.1%	< 0.001
ε2 Allele Frequency	6.6%	6.4%	0.831
ε2/ε2 Homozygotes	0.8%	0.1%	0.05

CONCLUSIONS

Our findings challenge the assumption that *APOE* alleles exert uniform effects across populations. Although ε2 is widely regarded as a protective variant associated with longevity, the 3.1-fold excess of ε2-AFR/ε2-AFR homozygotes observed in the mortality collection **raises the possibility that its protective effect is not uniformly expressed across ancestral backgrounds**. Conversely, the overrepresentation of ε4-AFR/ε4-AFR homozygotes among survivors suggests attenuation of the deleterious effects typically associated with ε4. Together, these observations indicate that **local ancestry may substantially modify the phenotypic impact of *APOE* alleles, challenging a “one-size-fits-all” interpretation of ε2 as a longevity allele and ε4 as a risk allele**. While not demonstrating a definitive loss of ε2-mediated protection, our results question its universality and highlight the importance of ancestry-aware approaches for understanding genetic risk and longevity in admixed populations.

ACKNOWLEDGMENTS

You can check the Preprint here!

Logos of funding and collaborating institutions: FAPESP, Instituto de Biociências, serra pilheira, CNPq, MEDICINA, USP, and genoma.