

Genetic Resilience and Resistance in Alzheimer's Disease Diagnosis and Pathology

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Objective: Some individuals avoid Alzheimer's disease (AD) pathology as they age, or retain cognition despite substantial pathology, suggesting mechanisms of resistance or resilience to neurodegeneration. Educational attainment (EA) is associated with reduced risk of cognitive decline, although the underlying mechanisms remain unclear. We investigated whether genome-wide polygenic scores (GPS) based on cognitive and non-cognitive components of EA, reflecting intelligence and behavioral/social traits, respectively, show differential associations with AD diagnosis and neuropathology.

Methods: Associations between GPS for cognitive and non-cognitive components of EA and AD outcomes were examined across four cohorts: two cohorts included living participants with biomarker assessments (BioHermes-1, $n = 770$; Alzheimer's Disease Neuroimaging Initiative [ADNI], $n = 1,361$), and two included postmortem neuropathological evaluations (Religious Orders Study and Rush Memory and Aging Project [ROSMAP], $n = 841$; Brain for Dementia Research [BDR], $n = 511$). Outcomes included clinical diagnosis, amyloid status, plasma neurodegenerative biomarkers, and neuropathological measurements.

Results: We found a significant negative association between cognitive EA GPS and clinical diagnosis of AD across all four cohorts and with Braak stage in ROSMAP and BDR cohorts. In contrast, the GPS for non-cognitive component of EA showed no significant association with AD diagnosis, neurodegenerative plasma biomarkers or amyloid positron emission tomography (PET) status and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores.

Interpretation: These results suggest a brain maintenance mechanism that supports the brain's ability to resist to changes in neuronal integrity. This indicates that interventions focused on increasing EA solely by additional years of schooling are unlikely to affect AD incidence, whereas alternative approaches targeting the cognitive component of EA (intelligence) may offer greater potential for prevention.

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide.¹ Although amyloid- β plaques and neurofibrillary τ tangles define AD neuropathology,² individuals vary in how pathology translates into cognitive decline.³

Some remain cognitively intact despite substantial neuropathological burden, whereas others exhibit significant decline with comparable levels of pathology.⁴ This dissociation between pathology and clinical expression underpins the concepts of resilience and/or resistance, which, although distinct in their focus, are not mutually exclusive.^{5,6} Arenaza-Urquijo and Vemuri⁵ proposed resistance and resilience as parallel, but operationally distinct processes in the context of preclinical AD. Resistance is conceptualized as the brain's ability to avoid or reduce the development of AD pathology itself, whereas resilience refers to the brain's ability to maintain cognitive function despite the presence of AD-related pathological changes, reflecting an ability to tolerate or adapt to neurodegeneration.⁵ Brain maintenance, brain reserve, and cognitive reserve are more specific, operational constructs proposed to define and investigate how those broad concepts can be studied and measured.⁶ Brain maintenance refers to the relative preservation of neural structure and biological integrity over time,^{7,8} whereas cognitive reserve is mostly shaped by lifelong exposures such as EA and occupational complexity.^{9–11} Brain reserve referring to the “neurobiological capital” (larger brain volume, number of neurons, and synapses) that allows individuals to maintain cognitive function despite brain aging and pathology.¹² It is important to note that the above-discussed concepts are often interrelated, and their definitions continue to be refined with emerging evidence.

Evidence from Mendelian randomization (MR) studies indicate that higher cognitive ability confers protection against AD, independently of education,¹³ and only the cognitive component of educational attainment (EA), intelligence, is independently causally associated with AD risk.^{9,14} Most of those genetic findings to date are based on MR approach that rely on genome-wide summary statistics, typically focusing on genome-wide significant loci and clinically defined AD phenotypes, which may be heterogeneous and susceptible to misclassification. Consequently, these methods may not fully capture the complex genetic architecture underlying these traits. Nevertheless, accumulating evidence suggests that genetic factors related to cognitive ability may play a key role in mediating the relationship between underlying neuropathology and its clinical manifestation.

Polygenic scores (GPS) provide a complementary approach to MR, offering greater statistical power and

often being more suitable for analyses in samples of small to moderate size.¹⁵ In this study, we used genome-wide association studies (GWAS) summary statistics of cognitive (intelligence) and non-cognitive components derived from GWAS of EA.¹⁶ We constructed GPS for both components (cognitive [COG-GPS] and non-cognitive [NONCOG-GPS]) and tested their associations in four independent cohorts.

We hypothesized that COG-GPS is associated with a reduced risk of clinical AD diagnosis. We examined the extent to which the two components of EA-related GPS (COG-GPS and NONCOG-GPS) are associated with clinical AD diagnosis, mild cognitive impairment (MCI), AD-related plasma biomarkers, and neuropathological measures indicative of resistance. These aims were addressed using data from four cohorts. First, the BioHermes-1 and Alzheimer's Disease Neuroimaging Initiative (ADNI) cohorts represent living clinical populations, characterized by standardized cognitive assessments, plasma biomarkers of amyloid and neurodegeneration, and amyloid positron emission tomography (PET) imaging. Second, two cohorts with available clinical assessments and post-mortem measures of Braak stage, reflecting τ pathology, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, reflecting neuritic plaque burden.

Methods

Cohort Description

BioHermes-1 study was supported by the Global Alzheimer's Platform Foundation to evaluate the ability of several blood and digital biomarkers to detect the presence of brain amyloid. This study contains clinical status (healthy, MCI, and mild AD), various cognitive tests, has several measurements of blood biomarkers related to neurodegeneration (A β 40, A β 42, NFL, GFAP, p-tau217, and the A β 42/A β 40 ratio), amyloid PET scans, and genetic data. More details on the participants and study design can be found in Morh et al.¹⁷

All data have been accessed and processed on the Alzheimer's Disease Data Initiative (ADDI) platform (<https://addi-portal.alzheimersdata.org/>). The original dataset contained 1,005 individuals. After quality control (QC), 191 AD cases, 246 MCI, and 332 controls remained for further analysis with both genetic biomarker data available. Demographic and clinical characteristics are presented in Table 1 and Table S1, while biomarker distributions are summarized in Table S2.

ADNI

ADNI is a longitudinal study that was developed for the early detection of AD with the use of clinical, genetic, and

TABLE 1. Demographics, based on Clinical Status in BioHermes-1, ADNI, RMM, and BDR Cohorts

Cohort	Status	N	Gender	Age	PET amyloid	APOE ε4 freq
BioHermes-1	AD	192	96:96	74.7 [6.03]	115:66:11	7.8/37/55.2
	MCI	246	125:121	72.7 [6.7]	89:147:0	3.2/35.4/61.4
	Controls	332	127:205	70.7 [6.5]	66:250:16	3.6/28.6/67.8
ADNI	AD	503	300:203	79.3 [7.8]	138:27:338	16.1/48.7/35.2
	MCI	408	250:158	79.7 [7.8]	100:122:19	8.1/31.6/60.3
	Controls	450	215:235	79.4 [7.2]	49:112:289	2.5/25.3/72.2
ROSMAP	AD	474	147:327	87.8 [3.5]	NA	2.7/32.9/64.4
	Controls	367	126:241	85.4 [5.1]	NA	1.1/13.3/85.6
BDR	AD	351	184:167	83.1 [8.5]	NA	12.9/57.6/29.5
	Controls	162	73:91	85.7 [9.7]	NA	1.2/31.5/67.3

Status corresponds to AD, MCI, or control classification. Gender (M:F) represents the number of males and females. Age is reported as mean $\pm$ standard deviation. Amyloid PET status is coded as 1 = positive, 0 = negative, and NA = not available. APOE ε4 carrier status was defined as the allele dosage, coded as 2/1/0. According to the number of ε4 present.

AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; BDR = Brain for Dementia Research; MCI = mild cognitive impairment; N = the number of individuals; PET = positron emission tomography; ROSMAP = Religious Orders Study and Rush Memory and Aging Project.

imaging data.¹⁸ The data were collected from participants between ages 55 and 90 years. Initially, participants were followed for 2 to 3 years with repeated imaging scans and psychometric measurements (ADNI1). The study was extended with the addition of new participants (ADNI-GO, ADNI2, ADNI3, and ADNI4). All participants provided written consent. More information can be found at <http://adni.loni.usc.edu/>. The ADNI samples were genotyped in three phases: ADNI1 (n = 757), ADNI2-GO (n = 432), and ADNI3 (n = 327), followed by imputation and standard QC procedures. After QC, 503 AD cases, 408 MCI, and 450 controls (last point of assessment available at 2026) remained for analysis. Demographic and clinical characteristics are presented in Table 1 and Table S1. Plasma biomarkers (n = 530) and amyloid PET imaging data (n = 202) were available for subsets of individuals, see Table S3.

Religious Orders Study and the Rush Memory and Aging Project

Religious Orders Study and the Rush Memory and Aging Project (ROSMAP) data^{19,20} ongoing longitudinal clinical-pathologic cohort studies of aging and AD. The dataset was downloaded from Accelerating Medicines Partnership in AD Knowledge Portal (<https://www.synapse.org>) following all terms and condition to use the data (project number syn68739308). All participants enrolled without known

dementia and agreed to detailed clinical evaluation and brain donation at death. The study was approved by an institutional review board of Rush University Medical Center. Each participant signed informed and repository consents and an Anatomic Gift Act. After applying all exclusion criteria, QC procedures, and restricting to individuals to clinically definition of AD status, the dataset comprised 474 AD cases and 367 controls, Table 1 and Table S1.

Brains for Dementia Research

Brains for Dementia Research (BDR)^{21,22} is an initiative that has recruited participants across five United Kingdom (UK) brain banks to help to investigate the mechanistic pathways of dementia by studying phenotypic data collected during their lives and their donated brain tissue after death. Data collection followed standardized brain donation procedures and included longitudinal clinical, psychometric, in vivo, and ex vivo assessments. After QC, we retained 351 AD cases and 162 controls based on clinical diagnosis, see Table 1 and Table S1.

Genetic Data and GPS

QC analyses were performed separately for each cohort using PLINK²³ (see Supporting Information for full details and thresholds). Briefly, in the imputed datasets, SNPs were excluded if they had poor imputation quality (INFO $\leq$ 0.7). Across all cohorts, SNPs were additionally

excluded if they were non-biallelic, duplicated by name, or located on non-autosomal chromosomes. Samples were removed because of excess heterozygosity, high missingness (low call rate), relatedness, or non-European ancestry, as determined by clustering with the 1,000 Genomes Project reference populations using the first two principal components (PCs).²⁴ Additional SNP-level filtering was applied based on minor allele frequency (MAF) >0.05 and deviation from Hardy–Weinberg equilibrium (HWE) $p < 1e-6$. After all exclusions, principal components were recomputed and used in subsequent analyses for each cohort.

We used two sets of discovery GWAS summary statistics²⁵ derived with genomic structural equation modeling (Genomic-SEM),²⁶ originally applied to educational attainment and cognitive performance GWAS.²⁷ This approach enables the derivation of non-cognitive GWAS by “subtracting” the genetic influence of cognitive performance from the association of each SNP with EA. Specifically, we used summary statistics representing (1) cognitive ability (COG-GPS; $n = 257,700$) and (2) non-cognitive skills (NONCOG-GPS; $n = 510,795$). By construction, these two GWAS are genetically independent with ($r_g = 0$).²⁸

We used GPS calculation approach with continuous shrinkage (PRS-CS)²⁹ that uses a high-dimensional Bayesian regression framework with the 1,000 Genomes reference panel and does not depend on p -value threshold or clumping parameters. European panel was used with the automated optimization of global shrinkage parameter. To account for population structure, we used the first five PCs derived from the genetic data using PLINK. All GPS were adjusted for PCs and standardized.

Statistical Analysis

In each cohort, GPS derived from the cognitive and non-cognitive components of EA, were tested for association with AD versus control and amyloid PET pathology in the BioHermes-1 and ADNI cohorts using logistic regression models. In additional analyses, we also examined MCI versus controls and AD versus MCI diagnostic contrasts and further evaluated the associations of these GPS with plasma biomarkers of neurodegeneration, including A β 40, A β 42, p-tau217, NFL, and GFAP and the A β 42/A β 40 ratio³⁰ using linear regression. In the ROSMAP and BDR cohorts, we additionally tested associations with neuropathological measures (Braak and CERAD scores) using linear regression models. All biomarker and neuropathological measures analyses were adjusted for age and sex.

We report p -values without correction for multiple testing, as we have tested two primary associations:

(1) COG-GPS and (2) NONCOG-GPS with clinical AD diagnosis. Additional analyses were conducted to support and interpret the primary findings, including tests of associations with biomarkers and neuropathological measures. For replication, these analyses were performed across independent cohorts.

Results

Demographics

Demographics for BioHermes-1, ADNI, ROSMAP, and BDR are presented in Table 1. Briefly, in the BioHermes-1 cohort, sex distribution differed slightly with more females among controls, and AD cases were older than MCI and controls. Of the 192 AD cases, 66 individuals (34%) were amyloid-negative based on PET imaging. Conversely, among the 332 controls, 66 participants (20%) were amyloid-positive. In ADNI, there was a higher proportion of males among cases and MCI compared to controls, and the age at the last assessment was similar between AD cases, MCI, and controls, at approximately 79 years.

In the ROSMAP cohort, there was a difference in sex distribution with a higher proportion of females among AD cases and controls, whereas no sex difference was observed in the BDR cohort. Regarding age at death, controls in the ROSMAP cohort were younger than AD cases. In contrast, in the BDR cohort, controls were older than AD cases.

Primary Analyses: Association of Cognitive and Non-cognitive GPS with Clinical Diagnosis

Table 2 presents the results of association of clinical status of AD with cognitive and non-cognitive GPS across all four cohorts. The GPS based on the cognitive component (COG-GPS) was negatively significantly associated with AD diagnosis in BioHermes-1, ADNI, ROSMAP, and BDR ($p < 0.05$), with comparable effect sizes (in range of $\beta = -0.17$ to -0.22) observed across cohorts, indicating a consistent relationship. In contrast, the GPS derived from the non-cognitive component (NONCOG-GPS) showed no significant association in any of the cohorts.

In additional analyses, we investigated the association of COG-GPS with diagnostic status in AD versus MCI and MCI versus control comparisons. Although the direction of effect was consistent across analyses, with mean COG-GPS values highest in controls, intermediate in MCI, and lowest in AD, statistical significance was reached only in the ADNI cohort for the MCI versus control comparison ($\beta = -0.19$, $p = 0.004$). As before NONCOG-GPS showed no significant association in any of the analyses, Table S4.

TABLE 2. Performance of Logistic Regression Models for examining AD, MCI, and Controls Classification using COG-GPS and NONCOG-GPS Across BioHermes-1, ADNI, ROSMAP, and BDR Cohorts

	BioHermes-1		ADNI		ROSMAP		BDR	
N-AD cases/N-controls	192/332		503/450		474/367		351/162	
Generic predictors	β [SE]	p	β [SE]	p	β [SE]	p	β [SE]	p
COG-GPS	-0.22 [0.09]	0.01	-0.2 [0.06]	1.8e-3	-0.17 [0.07]	0.017	-0.22 [0.1]	0.018
NONCOG-GPS	-0.009 [0.09]	0.91	0.04 [0.06]	0.5	0.1 [0.07]	0.13	-0.11 [0.1]	0.26

AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; BDR = Brain for Dementia Research; COG-GPS = cognitive genome-wide polygenic scores; MCI = Mild Cognitive Impairment; NONCOG-GPS = non-cognitive genome-wide polygenic scores; ROSMAP = Religious Orders Study and Rush Memory and Aging Project.

Secondary Analyses: Association of Cognitive and Non-cognitive GPS with Neurodegenerative Markers

To refine the above findings, we examined the relationships between COG-GPS and NONCOG-GPS and biomarkers of AD pathology in the BioHermes-1 and ADNI cohorts. Specifically, we assessed both GPS components with plasma levels of A β 40, A β 42, p-tau217, NFL, and GFAP, as well as the A β 42/A β 40 ratio. In addition, we evaluated associations with amyloid PET status. Results from analyses conducted in the primary analysis set, comprising individuals with AD and controls, are presented in Table 3, whereas results including all diagnostic groups (AD, MCI, and controls) are provided in Table S5.

In both cohorts and in all the analyses, neither the COG-GPS nor the NONCOG-GPS showed significant association with any plasma biomarker or with amyloid PET status.

Next, we investigated the relationships between both GPS components and neuropathological burden as measured by Braak stage and CERAD score in ROSMAP and BDR cohorts (see Table 4).

In both cohorts, COG-GPS showed a significant negative association with Braak stage in the ROSMAP and BDR cohorts (Beta = -0.13 and -0.17, $p < 0.05$, respectively), indicating a consistent inverse relationship between the cognitive genetic component and τ -related neuropathology. Again, NONCOG-GPS was not associated with Braak or CERAD stage in either cohort, suggesting that the observed genetic effects are specific to τ pathology rather than amyloid plaque burden.

Discussion

In this study, we aimed to dissect the role of educational attainment in AD development, focusing on its cognitive and non-cognitive components using GPS. We analyzed four independent cohorts: two cohorts of living

individuals (BioHermes-1 and ADNI) and two with available postmortem neuropathological measurements (ROSMAP and BDR). Our primary analysis demonstrated a consistent inverse association between COG-GPS and clinical AD diagnosis across all cohorts, with MCI representing an intermediate state while exhibiting the same direction of effect. NONCOG-GPS was not associated with outcomes in any dataset. These findings are consistent with previous MR studies^{9,13,14} and suggest that the association between higher educational attainment and lower AD risk is largely driven by intelligence, rather than reflecting an independent protective effect of, for example, extended duration of schooling.

The lack of association between COG-GPS and plasma biomarkers of neurodegeneration or amyloid PET deposition in BioHermes-1 and ADNI suggests that genetic contributions to differences in intelligence do not appear to influence amyloid accumulation. In addition, in the BDR and ROSMAP cohorts, COG-GPS was significantly associated with Braak stage, while showing no association with CERAD score. This pattern points toward a selective relationship based on τ pathology rather than amyloid plaque burden. Although the lack of association between COG-GPS and p-tau217 in living cohorts may seem counterintuitive, this biomarker has consistently been shown to effectively distinguish individuals with and without A β pathology²⁸ and is generally regarded as a marker of amyloid plaque burden²⁹ and has been reported to correlate positively with APOE, as both primarily reflect amyloid deposition.³⁰ In brain tissue, Braak stage reflects the anatomical progression and cumulative burden of neurofibrillary tangles, which are composed of aggregated, hyperphosphorylated τ and are often considered a late-stage manifestation of τ pathology. In contrast, p-tau217 reflects soluble phosphorylated τ changes that are more closely linked to amyloid-associated τ dysregulation and earlier AD processes. Overall, this pattern

TABLE 3. Linear Regression Analyses Examining Associations of Plasma Biomarkers and Amyloid PET, with COG-GPS and NONCOG-GPS in BioHeremer-1 and ADNI Cohorts for AD and Controls

	COG-GPS		NONCOG-GPS	
	β [SE]	<i>p</i>	β [SE]	<i>p</i>
BioHemres-1				
A β 40	−0.04 [0.04]	0.26	0.02 [0.04]	0.66
A β 42	−0.04 [0.04]	0.33	0.05 [0.04]	0.17
A β 42/A β 40	0.013 [0.04]	0.75	0.07 [0.04]	0.11
p-tau217	−0.07 [0.05]	0.15	−0.037 [0.05]	0.48
GFAP	−0.02 [0.04]	0.57	−0.04 [0.04]	0.32
NFL	−0.031 [0.04]	0.79	−0.017 [0.04]	0.68
Amyloid PET	−0.07 [0.09]	0.4	−0.13 [0.1]	0.16
ADNI				
A β 40	−0.006 [0.05]	0.9	−0.01 [0.05]	0.84
A β 42	0.03 [0.05]	0.56	−0.02 [0.05]	0.71
A β 42/A β 40	0.067 [0.05]	0.21	0.06 [0.05]	0.28
p-tau217	−0.028 [0.05]	0.54	−0.03 [0.05]	0.54
GFAP	−0.036 [0.05]	0.48	−0.05 [0.05]	0.36
NFL	−0.06 [0.05]	0.22	−0.036 [0.05]	0.46
Amyloid PET	−0.03 [0.02]	0.11	−0.006 [0.02]	0.79

ADNI = Alzheimer's Disease Neuroimaging Initiative; COG-GPS = cognitive genome-wide polygenic scores; NONCOG-GPS = non-cognitive genome-wide polygenic scores; PET = positron emission tomography.

TABLE 4. Linear Regression Analyses Examining Associations of Braak and CERAD Scores with COG-GPS and NONCOG-GPS in ROSMAP and BDR Cohorts

Genetic predictors	ROSMAP				BDR (n = 488)			
	Braak (n = 841)		CERAD (n = 841)		Braak (n = 490)		CERAD (n = 446)	
	β [SE]	<i>p</i>	β [SE]	<i>p</i>	β [SE]	<i>p</i>	β [SE]	<i>p</i>
COG-GPS	−0.13 [0.04]	1.9e−3	−0.01 [0.04]	0.71	−0.17 [0.08]	0.04	−0.08 [0.06]	0.13
NONCOG-GPS	0.03 [0.04]	0.38	0.008 [0.04]	0.82	−0.1 [0.08]	0.25	−0.07 [0.06]	0.19

BDR = Brain for Dementia Research; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; COG-GPS = cognitive genome-wide polygenic scores; NONCOG-GPS = non-cognitive genome-wide polygenic scores; ROSMAP = Religious Orders Study and Rush Memory and Aging Project.

of resistance to aggregation of τ and decreased risk of developing clinical AD could be explained by the brain maintenance mechanism in living individuals.

These findings can be interpreted alongside evolving models of AD pathogenesis that extend beyond the classical amyloid cascade hypothesis. Rather than a simple

neuron-centric, linear sequence from amyloid- β (A β) deposition to dementia, AD likely involves a prolonged and complex phase during which different brain cell types interact through dynamic feedback loops.³¹ Disease progression may, therefore, occur across multiple stages, including A β aggregation, the transition to τ pathology,

and eventual neuronal loss, with potential windows for compensatory responses. This perspective is further supported by prior work demonstrating that genetic risk for AD is partly distinct from genetic susceptibility to amyloid deposition,³² highlighting the multifaceted nature of disease mechanisms.

Our study has limitations. First, the sample sizes are limited. Although such a sample would clearly be insufficient for a GWAS, even relatively small samples can provide adequate statistical power for GPS analyses as statistical power in GPS analyses depends strongly on the proportion of variance explained by GPS, which is primarily determined by the size of the discovery GWAS rather than the size of the test sample. As aggregates of many small genetic effects, the COG-GPS capture a meaningful proportion of the variance in genetic liability to AD,¹⁴ thereby providing sufficient power even in modestly sized samples. Additionally, the consistency of findings across several independent cohorts further strengthens confidence that the results are unlikely to reflect type I error. Crucially, because our primary conclusions do not rely on interpreting null associations, they are unlikely to be attributable to type II error resulting from limited statistical power. Second, because of the absence of detailed clinical history and other potential confounders, such as lifestyle, deprivation index, etc., we have not investigated whether the effects of the genetic liability to intelligence on AD manifestation might be explained by exposure to other dementia risk factors, and therefore, we cannot confidently exclude a role for these exposures. Finally, we note that we conducted secondary analyses as exploratory investigations to help interpret the main findings.

Together, our findings suggest a genetic skeleton underneath certain stages of disease pathogenesis where genetic contributions to differences in intelligence do not influence amyloid accumulation, but may instead contribute the brain's capacity to resist τ -related neurodegeneration. Notably, this is the first study to examine how these genetic components relate to both plasma biomarkers of neurodegeneration and neuropathological measures, providing a complementary perspective on the interplay between AD pathology and cognition. The association of GPS based on the cognitive component of educational attainment with clinical AD diagnosis and AD neuropathology appear to point toward an underlying genetic basis for cognitive resilience, particularly brain maintenance.

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Author Contributions

G.L., V.E.P., K.M., and T.Q. contributed to the conception and design of the study; G.L., K.M., L.H., and K.B. contributed to the acquisition and analysis of data; G.L., J.S.S., and V.E.P. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

Following Demange et al, 2021 publication, the summary statistics for NONCog and Cog (excluding 23andMe) were publicly available on GWAS catalog with accession nos. GCST90011874 and GCST90011875, respectively. BioHermes-1 can be requested and accessed through the ADDI platform: globalalzplatform.org/2025/08/05/dementia-help-accelerating-alzheimers-research-the-bio-hermes-001-dataset-is-now-publicly-available/. ADNI data are shared through the LONI Image and Data Archive (IDA), a secure research data repository: adni.loni.usc.edu/data-samples/adni-data/#AccessData. ROSMAP data can be requested through www.radc.rush.edu. Brains for Dementia Research (BDR) data are available on request through www.brainsfordementiaresearch.org/apply/.

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