SUPPLEMENTARY MATERIAL

S1.1 Neuropsychological Evaluation

The following neuropsychological tests were used in the neuropsychological assessment, assessing five different cognitive domains (memory, language, executive function, attention, and visual-spatial ability). The Mini Mental State Examination [1] was used as a screening test, followed by the Greek Verbal Learning Test [2], the Medical College of Georgia Complex Figure Test (copy condition, recognition, immediate and delayed recall, and recognition) [3], a semantic and phonological verbal fluency test [4], subtests of the Greek version of the Boston Diagnostic Aphasia Examination short form and selected items from the Complex Ideational Material Subtest [5], the Greek Trail Making Test [6], a graphical sequence task and, an abbreviated form of Benton's Judgment of Line Orientation [7], as well as the Clock Drawing Test [8], and a Greek multiple choice vocabulary test [9].

S1.2 Genotype Imputation in HELIAD

Variants included in the removal marker list by Illumina were excluded, and only variants for which the full-length probes aligned uniquely on GRCh38 genome without mismatches were kept. Variant intensity quality control (QC) was conducted for all autosomal variants according to established thresholds, and sex-check was performed using chromosome X variants [10]. Subsequently, sample QC was performed using the PLINK v1.9 software. Samples with a missingness rate of more than 5%, sex inconsistencies, or with a heterozygosity rate deviating more than six standard deviations (SD) from the mean, were excluded. To identify population outliers, Principal Component Analysis (PCA) using the 1000 Genome Project phase 3 reference panel was performed, and the combined dataset was projected onto two dimensions, using the flashPCA2 software [11]. To control for cryptic relatedness, one individual from each pair of samples with a kinship coefficient of more than 0.125 (cut-off for second-degree relatives) was excluded. Furthermore, variants with a missingness rate of more than 5% in at least one genotyping center, or with a significant differential missingness test ($p < 10^{-10}$), were excluded. The Hardy-Weinberg equilibrium test ($p < 5*10^{-6}$) was performed only in controls, and for each genotyping center/country separately.

To improve imputation accuracy, imputed variant frequencies were compared against two reference panels, the population of the Haplotype Reference Consortium v1.1 (HRC) [12], excluding samples from the 1000 Genome Project, and the Genome Aggregation Database v3 (gnomAD) [13], using the chi-square test. Variants with a $x^2 > 3{,}000$ in both HRC and gnomAD, or with a $x^2 > 3{,}000$ in one reference panel and not present in the other, were excluded. Finally, genome-wide association studies (GWAS) were performed between controls across genotyping centers to assess for potential frequency differences between genotyping centers, using the SNPTEST software [14], under an additive model and adjusting for associated principal components. Variants with a significant Likelihood Ratio Test at $p < 10^{-5}$ were excluded. Finally, ambiguous variants with a minor allele frequency (MAF) of ≤5% were removed, and only one copy of any duplicated variants was retained, prioritizing the one with the lowest missingness rate.

Samples and variants satisfying the aforementioned QC metrics were imputed on the Michigan Imputation Server (v1.2.4) [15], using the TOPMed Freeze 5 reference panel. Phasing and imputation were performed using the EAGLE v2.4 and Minimac4 v4-1.0.2 software,

respectively. Apolipoprotein E isoforms were determined by the coding SNPs rs429358 and rs7412 genotypes, using the SNP array data.

S1.3 Polygenic Risk Score Calculation

The analysis involved the calculation of risk scores for 5.611.082 single-nucleotide polymorphisms (SNPs) meeting the specific previously described quality criteria using the PRSice software version 1.25 (PRSice_v1.25, http://prsice.info/ accessed on 19 June 2022).
To ensure that only independent markers were included in the PRS computation, SNP clumping for linkage disequilibrium (LD) was performed, using the default PRSice settings for clumping (rc2 of 0.1 and wc of 250 kb). SNPs within the APOE gene region (defined as 1 Mb up-and downstream of the APOE gene (chromosome 19: 44.4–46.5 Mb)) were excluded, and the APOE genotype was included as a predictor in the analyses. Additionally, SNP clumping for linkage disequilibrium (LD) was performed using specific parameters.

In particular, a risk score was calculated for each SNP by multiplying the risk allele number (0, 1, and 2) with the corresponding effect size (beta coefficient) reported in the GWAS summary data. Each participant was assigned a set of polygenic risk scores (PRS) based on their individual SNP-risk scores, calculated for SNPs achieving genome-wide significance at 10 pre-defined GWAS p-value thresholds (i.e., 5 × 10−8, 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5).

S1.4 Polygenic Risk Score Thresholds

As each PRS threshold comprises a distinct set of SNPs, we used logistic regression models with aMCI/AD as outcome and the different thresholds as the primary predictors. To control for potential cryptic relatedness between subjects [16] as well as unexpected genotyping errors [17], models were adjusted the first two principal components of genetic ancestry (PC1, PC2 derived from the PCA command in PLINK version 1.9) and APOE ε4 genotype. We computed the area under the curve (AUC) for each of the 10 distinct thresholds (P_T). The PRSs with the best classification accuracy area under the curve, which were $p_T<10^{-4}$ for PRS $A\beta_{42}$ consisting of 57 SNPs and $p_T<0.3$ for PRS WMH, consisting of 64331 SNPs, were considered to exhibit superior discriminatory ability between presence and absence of WMH pathology as well as $A\beta_{42}$ positivity, and were, therefore, used as the measure of genetic predisposition in subsequent analyses (**Tables S1 and S2**).

Table S1: Number of SNPs included at each PRS $A\beta_{42}$ calculated at different GWAS P-value thresholds. AUC area together with p value of each PRS derived from a logistic regression with outcome aMCI/AD status, adjusted for APOE e4 genotype, PC1 and PC2.

p_T [1] $A\beta_{42}$	SNPs [2] (N)	AUC [3]	OR [4]	P-value
5×10^{-5}	30	0.534	1.155	0.214
10^{-4}	*57*	0.576	1.339	**0.041**
10^{-3}	546	0.460	1.040	0.763
5×10^{-2}	13957	0.474	1.059	0.665

10^{-2}	3879	0.472	1.052	0.686
0.1	23399	0.538	1.169	0.191
0.2	38349	0.516	1.117	0.386
0.3	49846	0.515	1.115	0.393
0.4	59148	0.523	1.144	0.281
0.5	66573	0.525	1.145	0.277

[1] p-value threshold, [2] single nucleotide polymorphism, [3] area under curve, [4] odds ratio
Bold letters indicate statistical significance (p <0.05).

Table S2: Number of SNPs included at each PRS WMH calculated at different GWAS P-value thresholds. AUC area together with p value of each PRS derived from a logistic regression with outcome aMCI/AD status, adjusted for APOE e4 genotype, PC1 and PC2.

p_T [1] WMH	SNPs [2] (N)	AUC [3]	OR [4]	P-value
5×10^{-8}	30	0.545	1.197	0.109
10^{-4}	298	0.498	1.090	0.432
10^{-3}	1307	0.510	1.126	0.372
10^{-2}	6500	0.530	1.153	0.203
5×10^{-2}	20149	0.536	1.160	0.192
0.1	32222	0.547	1.215	0.106
0.2	50504	0.549	1.242	0.090
0.3	64331	0.558	1.320	**0.005**
0.4	75199	0.545	1.184	0.112
0.5	83820	0.543	1.175	0.130

[1] p-value threshold, [2] single nucleotide polymorphism, [3] area under curve, [4] odds ratio
Bold letters indicate statistical significance (p <0.05).

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