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Association of genetic risk of Alzheimer's disease and cognitive function in two European populations

Biqi Wang[1]✉, Lori B. Chibnik[2,3], Seung Hoan Choi[4], Deborah Blacker[3,5], Anita L. DeStefano[4] & Honghuang Lin[1]

Although there is some evidence of an association between Alzheimer's disease polygenic risk score (AD PRS) and cognitive function, limited validations have been performed in large populations. We investigated the relationship between AD PRS and cognitive function in the UK Biobank in over 276,000 participants and further validated the association in the Alzheimer's Disease Neuroimaging Initiative (ADNI) sample. We developed the AD PRS (excluded the *APOE* variants) in the middle age UK Biobank participants (age ranged 39–72, mean age 57 years) of European ancestries by LDpred2. To validate the association of AD PRS and cognitive function internally in the UK Biobank, we linearly regressed standardized cognitive function on continuous standardized AD PRS with age at cognitive test, sex, genotyping array, first 10 principal components of genotyping, smoking, education in years, body mass index, and apolipoprotein E gene *ε4* (*APOE4*) risk allele dosages. To validate the associations externally, we ran the linear mixed effects model in the ADNI sample free of dementia (age ranged 55–91, mean age 73), including similar covariates as fixed effects and participants' IDs as the random effect. Stratification by age, *APOE4* carrier status, and cognitive status (cognitively normal or mild cognitive impairment) was also investigated. Our study validated the associations of AD PRS and cognitive function in both midlife and late-life observational cohorts. Although not all of the cognitive measures were significantly associated with AD PRS, non-verbal fluid reasoning (matrix pattern completion, β = − 0.022, *P* = 0.003), processing speed (such as symbol digit substitution, β = − 0.017, *P* = 1.08E−05), short-term memory and attention (such as pairs matching, β = − 0.014, *P* = 1.66E−10), and reaction time (β = − 0.010, *P* = 1.19E−06) were inversely associated with increasing AD PRS in the UK Biobank. Higher likelihood of cognitive impairment was also associated with higher AD PRS in the ADNI cognitive normal individuals (AD assessment scale β = 0.079, *P* = 0.02). In summary, we confirmed that poorer cognitive function was associated with a higher polygenic AD risk, and suggested the potential utility of the AD PRS in identifying those who may be at risk for further cognitive decline.

Keywords Alzheimer's disease, Polygenic risk score, Cognitive test, Cohort

Abbreviations

AD	Alzheimer's disease
PRS	Polygenic risk score
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE4	Apolipoprotein E gene ε4
SNVs	Single-nucleotide variants
GWAS	Genome-wide association studies
QC	Quality control
MAF	Minor allele frequency

[1]Department of Medicine, University of Massachusetts Chan Medical School, Worcester, MA, USA. [2]Department of Neurology, Massachusetts General Hospital, Boston, MA, USA. [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [4]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA. [5]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. ✉email: Biqi.Wang@umassmed.edu

BMI	Body mass index
ICD-10	International Classification of Disease-10
PCs	Principal components
FI	Fluid intelligence
MAT	Matrix pattern completion
TWR	Tower rearranging
MEMN	Numeric memory
MEMP	Pairs matching
SDS	Symbol digit substitution
RT	Reaction time
TMT B	Trail making test B
MMSE	Mini-Mental State Exam
ADAS	Alzheimer's Disease Assessment Scale
MoCA	Montreal Cognitive Assessment
FAQ	Functional Assessment Questionnaire
ADNI_MEM	ADNI memory summary score
ADNI_EF	ADNI executive function summary score
ADNI_LAN	ADNI language summary score
ADNI_VS	ADNI visuospatial summary score

Alzheimer's disease (AD), which accounts for 60–70% of dementia, is a common polygenic progressive neurodegenerative disorder mainly affecting people in late life. It is one of the major causes of disability and dependency[1,2]. Although some medical management can improve the quality of life for people living with AD, and new medications may be able to slow the progression of the disease to some extent, there is no effective cure for the illness[3]. Screening for AD before it is clinically detectable or during the early stages of the disease is therefore crucial. Cognitive impairment based on episodic memory or global cognitive tests is typically used to identify at-risk populations[4,5]. However, prediction of future AD risk solely based on cognitive tests is not sufficient because there is substantial baseline variation in cognitive performance and psychosocial and medical factors may contribute to cognitive decline in the absence of latent degenerative or vascular dementia pathologies[6,7].

Beyond abovementioned cognitive indicators, genetic component can also be a powerful biomarker for AD risk stratification. The overall heritability of AD is 40–70% and only a part of it captured by the single-nucleotide variants (SNVs) identified by genome-wide association studies (GWAS)[8,9]. A polygenic risk score (PRS), which represents the collective influence of many SNVs, can enhance the risk prediction of AD[10]. The exploration of AD PRS and cognitive function associations may reveal potential pathology of cognitive impairment leading to AD and may suggest the usefulness of AD PRS in identifying subtle cognitive changes in normal and/or mildly impaired populations[11–14].

Both the establishment of large AD consortia[15] and PRS methods development provide opportunities to characterize AD genetic risks, i.e., capture more genetic variability of AD. For example, recent GWAS have identified nearly one hundred AD risk loci[12,15], and one of the most widely used PRS calculation methods "LDpred2" has shown better predictive accuracy and faster computational speed in PRS estimation than the prior version "LDpred" and other PRS methods (e.g., lassosum, PRS-CS, SBayesR) in European populations[16]. New findings on AD PRS and cognitive function may arise by integrating recent PRS methods with new AD GWAS results. Thus, we will utilize the summary results from the most recent AD GWAS to examine the association of AD PRS and cognitive function in the UK Biobank. We will validate associations we identify in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods

Populations

We used the UK Biobank as the training set for the AD PRS derivation, as well as the internal testing set for the association of AD PRS and cognitive function. The UK Biobank is a large prospective cohort of over 500,000 participants with rich genetic and health information[17,18]. We initially included 339,506 unrelated middle-age participants (i.e., no kinship was found in the UK Biobank Field ID 22021) with available imputed genotypes. We then excluded 62,837 participants of non-European ancestries (Field ID 22006 not in Caucasian) and 13 individuals with prevalent AD at baseline. This left 276,656 participants in the PRS training set (Fig. 1). Those participants with cognitive tests were included as the internal testing set in the UK Biobank.

We externally validated the AD PRS and cognitive function associations in ADNI, which is a longitudinal study focusing on early detection and disease progression with multiple time-points of data collections[19]. We included 685 individuals without dementia at baseline and high quality whole genome sequencing data in the external testing set from ADNI (Fig. 1).

Genetic data

Two Affymetrix (BiLEVE Axiom array and Affymetrix UK Biobank Axiom array) genotyping arrays were utilized in the UK Biobank to code over 850,000 variants[18]. The genotype data in the UK Biobank was imputed by the UK10K and 1000 Genomes Phase 3 reference panels for over 480,000 participants who passed the sample-based quality control (QC) including heterozygosity check, less than 5% missing rate, no sex mismatch, no duplicates, and no sample mishandling. Genetic variants with minor allele frequency (MAF) < 0.0001 were filtered out before imputation.

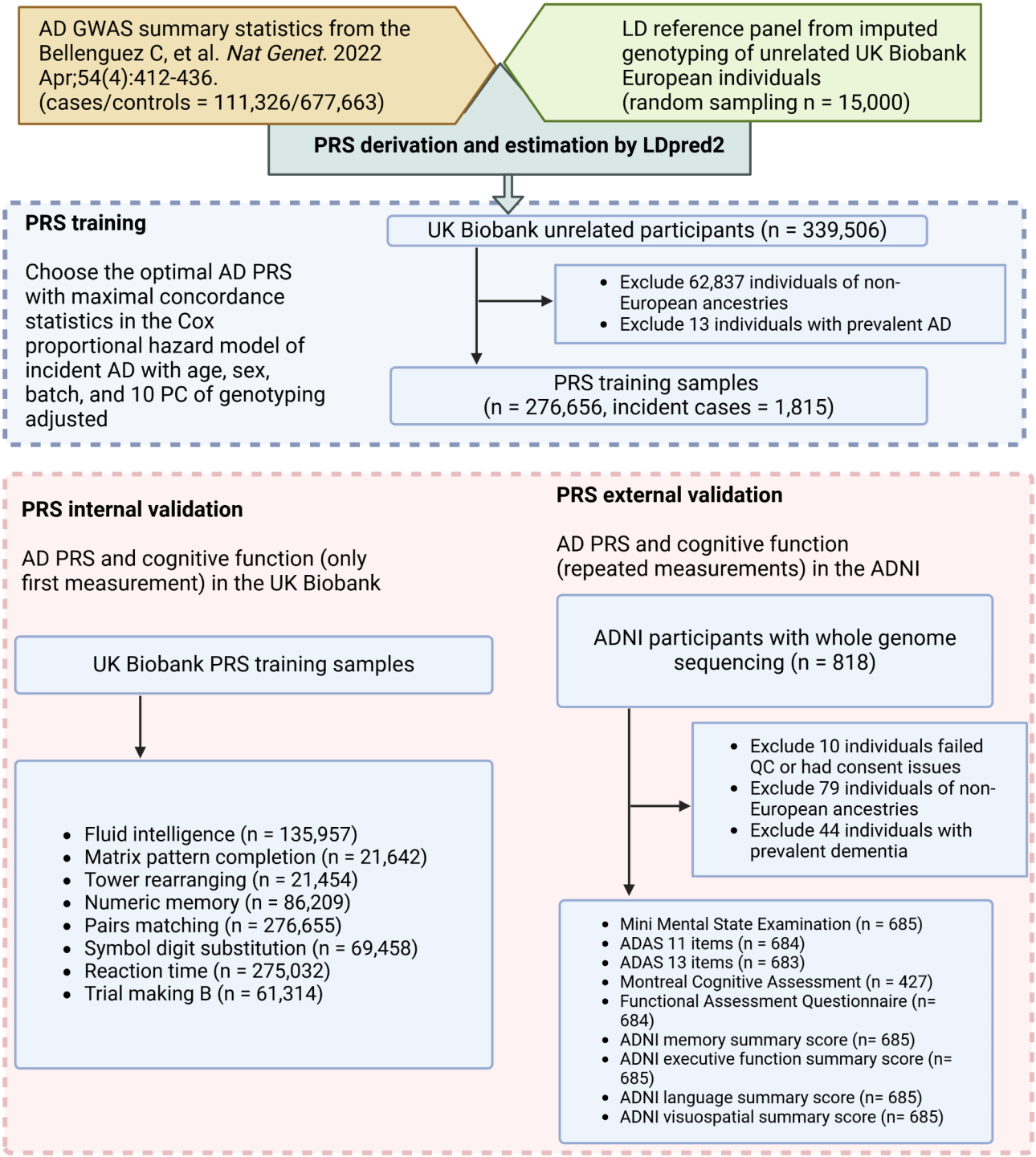

Fig. 1. Analytic framework of AD polygenic score derivation and its association with cognitive functions. Created in https://BioRender.com.

The whole genome sequencing was performed in 818 ADNI participants by Illumina's non-CLIA laboratory at roughly 30–40× coverage[20,21]. Genetic variants with Hardy-Weinberg Equilibrium < 1e−06, and missing rate < 95% were included as passed QC variants in the PRS calculation.

Polygenic risk score derivation

We used LDpred2-grid to derive the AD PRS. The GWAS summary statistics were based on the meta-analysis of over 100,000 AD or proxy AD cases with European ancestry[12]. We selected the overlapped variants among AD GWAS summary statistics, UK Biobank imputed genotype data, and HapMap3+ (with over 1,400,000 SNVs across the whole genome) to calculate the PRS. Variants within the *APOE* linkage region (Genome Build 37,

chromosome 19: 4500000–4580000) were excluded[22], leaving 1,415,926 SNVs to calculate the PRS. The LD reference panel was based on genotyping 15,000 randomly selected unrelated individuals of European ancestry in the UK Biobank. The tuning hyper-parameters in the LDpred2-grid were heritability (0.0083, 0.0248, 0.0579, 0.0827, or 0.1157), proportion of causal variants (0.0001, 0.00018, 0.00032, 0.00056, 0.001, 0.0018, 0.0032, 0.0056, 0.01, 0.018, 0.032, 0.056, 0.1, 0.18, 0.32, 0.56, 1), and modeling sparsity options (yes or no). The PRS with the highest concordance statistics (C-stats) in the prediction of incident AD was considered optimal and used in the downstream analyses.

To generate the PRS in ADNI, we used the 1,387,064 SNVs both in the ADNI whole genome sequencing data and in the optimal PRS from the UK Biobank described above (covered 98% SNVs of the UK Biobank). The ADNI PRS was then calculated as a linear combination of those variants and their shrinkage effect sizes derived from the optimal PRS from UK Biobank.

AD diagnosis

The outcome in the polygenic score calculation was incident AD in the UK Biobank. AD was coded based on the International Classification of Disease (ICD-10) diagnosis code of G30 and READ code F00 (UK Biobank Field ID 131036, and 130836)[23]. The AD diagnosis in ADNI was based on a clinical diagnosis of expert clinicians following standard research criteria[24], while mild cognitive impairment (MCI) was diagnosed based on one of the following: memory complaints, Mini-Mental State Exam (MMSE) (MCI: 24–30, dementia: 20–26), Clinical Dementia Rating score, or Logical Memory II subscale of the Wechsler Memory Scale[25,26].

We also used self-reported parental dementia as a secondary outcome to validate the AD PRS in the UK Biobank. Parental dementia status was defined based on all available visits for the reported biological parents and was missing for those who did not complete family history questionnaires: Yes was defined as either parent with a reported diagnosis, Neither as both parents without dementia.

Cognitive function

Participants in the UK Biobank completed their cognitive tests either in assessment centers or during online follow-up[27–29]. We included eight cognitive tests (Fluid intelligence (FI), Matrix pattern completion (MAT), Tower rearranging (TWR), Numeric memory (MEMN), Pairs matching (MEMP), Symbol digit substitution (SDS), Reaction time (RT), and Trail making test B (TMT B)) as the outcomes[30] in the association analysis of AD PRS and cognitive function. The scores of some tests were transformed as shown in Supplemental Table 1. For participants with multiple cycles of cognitive tests in the UK Biobank, we only used the tests on the first cycle, and higher cognitive scores meant better cognitive function.

To further validate the AD PRS and cognitive function beyond tests focused on one domain, we used general cognitive tests from ADNI. Those cognitive tests included MMSE, the Alzheimer's Disease Assessment Scale 11 (ADAS 11), Alzheimer's Disease Assessment Scale 13 (ADAS 13), Montreal Cognitive Assessment (MoCA), and Functional Assessment Questionnaire (FAQ).We also validate the associations of AD PRS with cognitive domains in memory (ADNI_MEM), executive function (ADNI_EF), language (ANDI_LAN), and visuospatial domain (ADNI_VS). Methods to calculate these domain summary scores can be found elsewhere[31,32]. In ADNI, participants were administered these tests approximately every 6 months.

Covariates

To control potential confounders in the association of AD PRS and cognitive function, we used age at testing, genotyping array, the first 10 principal components (PCs), smoking status (never, past, current), education years, body mass index (BMI), and apolipoprotein E gene *ε4* (*APOE4)* risk allele (rs429358 and rs7412) dose (0, 1, or 2) as covariates in the UK Biobank. We also used age at testing, sex, education years, first 10 PCs, ever or never smokers (i.e., whether reported a history of cigarette smoking), BMI, and number of *APOE4* alleles as covariates in ADNI.

Statistical analysis

We determined the optimal PRS in the training samples composed of unrelated European individuals from the UK Biobank. The Cox proportional hazard model with age, sex, genotyping array, and first 10 PCs adjusted was used to find the optimal AD PRS with maximal C-stats.

Each cognitive measure as well as the polygenic scores were standardized (mean 0 and standard deviation 1). To validate the association of optimal AD PRS and cognitive function internally in the UK Biobank, we linearly regressed the standardized cognitive scores on continuous standardized AD PRS with partially or fully covariates adjustments: Model 1 adjusted for age at cognitive testing, sex, genotyping array, first 10 PCs; Model 2 additionally adjusted for smoking, education in years, and BMI; Model 3 additionally adjusted for the *APOE4* risk allele dosages. We also assessed the PRS effects modified by age (less than 60 years vs. aged 60 years and above), *APOE4* carrier status, education (high school graduated or not, smoking (ever or never), and obesity (BMI > 30 or not) by adding a multiplicative interaction term into the linear models respectively.

To validate the associations externally, we ran one linear mixed effects model in ADNI with each standardized cognitive score as the dependent variable, continuous standardized AD PRS, age at cognitive testing, sex, education in years, smoking status (never vs. ever), BMI as fixed effects, and participants' ID as a random effect. To evaluate the effect of *APOE* on the PRS and cognitive associations we ran an additional mixed effects model with *APOE4* alleles as an additional fixed effect. To assess the PRS effects modified by baseline diagnosis and/or *APOE4* status we performed analysis stratified by baseline cognitive status (cognitively normal or MCI), and *APOE4* status.

Secondary analysis included using categorical AD PRS (PRS lower than 10%, 10–90%, and higher than 90%) as the independent variable to improve clinical interpretations. Logistic regressions were used to assess

the association of parental dementia—comparing one parent with dementia to both parents free of dementia, or comparing two parents with dementia to both parents free of dementia—and AD PRS in the UK Biobank. Additionally, the Cox proportional hazard model was employed to examine the PRS associations with incident dementia or incident MCI in the ADNI.

Some cognitive scores (e.g., MMSE, ADAS11, ADAS13) might not normally distributed among cognitively normal or MCI participants in the ADNI, we conducted inverse normal transformation for all the cognitive scores in ADNI and reran the abovementioned linear mixed models as sensitivity analysis.

All the analysis was conducted using R 4.2.1. Specifically, the R package *bigsnpr* was used to calculate the AD PRS[33]. We used a two-sided P value < 0.05 and Bonferroni corrections for multiple comparison (UK Biobank significance level = 0.05/8 = 6.25E−03, while ADNI significant level = 0.05/9 = 5.6E−03).

Results

Over 276,000 participants were included in the association analysis of AD PRS and cognitive function in the UK Biobank. The mean age was 57 years (SD = 8 years) and the mean education years was 14.0. Participants from ADNI were generally older with a mean age of 75 years (SD = 6 years) for the cognitively normal group and 72 years (SD = 7 years) for the MCI group. As expected, the percentage of *APOE4* carriers was higher in the MCI group (46%) compared with the cognitively normal group (28%). More detailed data on demographic characteristics of the UK Biobank and ADNI participants can be found in Tables 1 and 2, respectively.

The AD PRS was significantly associated with six of the eight cognitive measures (the exceptions were fluid intelligence and numeric memory) based on the models without *APOE4* adjustment. Two cognitive measures (tower rearranging and trail making B) attenuated to null when we additionally adjusted for *APOE4* (Table 3). The rest of the measurements (matrix pattern completion (β = − 0.022, P value = 0.003), pairs matching (β = − 0.014, P value = 1.66E−10), symbol digit substitution (β = − 0.017, P value = 1.08E−05), and reaction time (β = − 0.010, P value = 1.19E−06)) were significantly associated with AD PRS even with *APOE4* adjustment. The association directions were all negative across varied cognitive measures indicating the higher AD PRS the worse cognitive performance.

Table 4 shows the associations of cognitive function and AD PRS in cognitively normal and MCI participants separately. The MMSE, ADAS 11, ADAS 13 scores were significantly associated with AD PRS in fully adjusted models among cognitively normal individuals. Almost all the comprehensive cognitive scores (MMSE, ADAS 11, ADAS 13, MoCA), functional activity score (FAQ), as well as specific domain scores, ADNI memory summary score, ADNI executive function score, and ADNI language summary score) were significantly associated with AD PRS in the partially adjusted models among MCI individuals. Only two cognitive scores (ADAS 11 and ADAS 13) remained nominal significant (i.e., P value < 0.05) when additionally adjusted for *APOE4*. The association directions also suggested increasing AD PRS was associated with reduced cognitive performance.

The interaction analysis showed potential effects modification by age or *APOE4* status but not by education (P interaction ranged from 0.04 to 0.99), smoking status (P interaction ranged from 0.03 to 0.92), or obesity (P interaction ranged from 0.05 to 0.92) in the UK Biobank. Stratification analysis results were presented in Supplemental Tables 2 and Supplemental Table 3. The effect of AD PRS on cognitive function varied by age group (age less than 60, or 60 and above), *APOE4* carrier status, and cognitive status (normal or MCI). For example, the effect size of reaction time was larger in the older age group (β = − 0.013, P value = 5.78E−05) than in the younger group (β = − 0.008, P value = 0.004, and P interaction = 0.04). However, we observed stronger associations of AD PRS and symbol digital substitution in the younger UK Biobank population (β = − 0.020, P value = 9.75E−05) than the older ones (β= − 0.016, P value = 9.76E−03, P interaction = 3.42E−14).

The associations of categorical AD PRS (lower than 10%, 10-90%, and 90% and higher) and cognitive function were similar to the continuous AD PRS associations: the mean scores of pair matching and reaction time were lower in the high PRS group, higher in the low PRS group comparing with the middle group (Supplemental Table 4). Other categorical PRS results can be found in Supplemental Tables 5 and Supplemental Table 6.

In secondary analysis, we found positive associations of parental AD with AD PRS in the UK Biobank, the odds of both parents with AD were 2.27 times than those with parents free of AD by 1-SD PRS increment (Supplemental Table 7). For individuals with normal cognition or MCI, the future risk of incident dementia was higher by 25% with 1-SD of PRS increment (Supplemental Table 8). Sensitivity analysis showed consistent association results with or without inverse normalized transformed for those cognitive scores in the ADNI (Supplemental Table 9).

Discussion

Our study validated the associations of AD PRS and cognitive function in both midlife and late-life observational cohorts. Although not all of the cognitive measures were significantly associated with AD PRS, cognitive impairments involving processing speed (such as symbol digit substitution) and short-term memory and attention (such as pairs matching) were associated with the increment of AD PRS in the midlife population (i.e., the UK Biobank). Reduced cognitive performance (e.g., MMSE, ADAS 11, ADAS 13) was also associated with higher AD PRS in the cognitively normal but old population (i.e., the ADNI cognitively normal individuals).

Previous systematic reviews and original investigations illustrated the associations of AD PRS and cognitive measures in populations with relatively small sample sizes[22,34]. One recent study reported the associations of late-onset AD PRS and fluid intelligence or matrix completion among more than 32,000 individuals from the UK Biobank, but such associations had not been validated by external validation cohorts, nor been assessed through global cognitive function[14]. Another study from the UK Biobank also suggested that cognitive function diverged in midlife (e.g., aged 45 to 55 years) between higher and lower AD PRS groups[13].

	Overall
n	276,656
Male (%)	129,182 (46.7)
Age (years)	
Mean (SD)	57 (8)
Range	39–72
BMI (kg/m^2)	
Mean (SD)	27.4 (4.8)
Range	12–75
Education (years)	
Mean (SD)	14.0 (5.1)
Range	0–20
Smoking (%)	
Never	151,279 (54.9)
Past	96,832 (35.1)
Current	27,604 (10.0)
Incident AD (%)	1815 (0.7)
Mother with AD (%)	25,847 (9.3)
Father with AD (%)	13,458 (4.9)
APOE4 risk allele frequency, %	15.6
APOE4 risk allele (%)	
Non-carrier	196,853 (71.2)
Carrier	79,789 (28.8)
Fluid intelligence, FI	
Mean (SD)	6.13 (2.04)
Range	0–14
Matrix pattern completion, MAT	
Mean (SD)	8.03 (2.10)
Range	0–15
Tower rearranging, TWR	
Mean (SD)	9.89 (3.23)
Range	0–18
Numeric memory, MEMN	
Mean (SD)	6.83 (1.43)
Range	2–12
Pairs matching, MEMP	
Mean (SD)	12.64 (3.77)
Range	0–24
Symbol digit substitution, SDS	
Mean (SD)	19.79 (5.18)
Range	0–35
Reaction time, RT	
Mean (SD)	− 6.30 (0.19)
Range	− 7.58 to − 4
Trail making B, TMT B	
Mean (SD)	− 4.13 (0.34)
Range	− 6.62 to − 3

Table 1. Baseline characteristics of participants in the UK Biobank. Body mass index, BMI. Mean (standard deviation) and Range (minimum–maximum) for continuous variables, counts (%) for categorical variables.

Our finding of fluid intelligence and matrix pattern completion and their null associations with AD PRS were not consistent with previous UK Biobank publications[14]. The PRS was based on the AD GWAS summary statistics derived from varied studies[12,35]. The PRS improvements in prediction accuracy of "LDpred2" versus the "LDpred" might also contribute to such inconsistencies. We did not find a significant association between AD PRS and numeric memory. Although numeric memory was one of the working memory measures, its subtle changes along with aging and AD PRS increment were comparably smaller than the changes in pairs matching and symbol digit substitution. A prior study also found significant pairs matching and symbol digit differences

Baseline characters	Cognitively normal	Mild cognitive impairment
n	248	437
Age (years)		
Mean (SD)	75 (6)	72 (7)
Range	60–90	55–91
Male (%)	128 (51.6)	262 (60.0)
Education (years)		
Mean (SD)	16.4 (2.7)	16.0 (2.9)
Range	6–20	6–20
BMI (kg/m^2)		
Mean (SD)	25.7 (4.0)	26.7 (4.9)
Range	18.4–45.8	17.9–50.9
Ever smokers (%)	95 (38.3)	163 (37.3)
APOE4 risk allele frequency, %	15.3	27.4
APOE4 risk allele (%)		
Non carrier	178 (71.8)	236 (54.0)
Carrier	70 (28.2)	201 (46.0)
Mini Mental State Exam, MMSE		
Mean (SD)	29.06 (1.17)	27.93 (1.66)
Range	24–30	23–30
Alzheimer Disease Assessment Scale 11, ADAS 11		
Mean (SD)	5.81 (2.90)	9.56 (4.34)
Range	0–19	1–26
Alzheimer Disease Assessment Scale 13, ADAS 13		
Mean (SD)	9.13 (4.25)	15.35 (6.66)
Range	0–24	2–36
Montreal Cognitive Assessment, MoCA		
Mean (SD)	25.66 (2.26)	23.63 (2.99)
Range	19–30	15–30
Functional Assessment Questionnaire, FAQ		
Mean (SD)	0.17 (0.67)	2.86 (3.91)
Range	0–6	0–22
ADNI memory summary score, ADNI_MEM		
Mean (SD)	1.04 (0.56)	0.30 (0.67)
Range	− 0.3 to 3.1	− 1.5 to 2.2
ADNI executive function score, ADNI_EF		
Mean (SD)	0.82 (0.76)	0.37 (0.85)
Range	− 1.0 to 3.0	− 2.0 to 3.0
ADNI language summary score, ANDI_LAN		
Mean (SD)	0.89 (0.73)	0.32 (0.77)
Range	− 1.0 to 3.1	− 2.0 to 2.6
ADNI visuospatial summary score, ADNI_VS		
Mean (SD)	0.28 (0.57)	0.05 (0.72)
Range	− 1.6 to 0.7	− 2.5 to 0.7

Table 2. Baseline characteristics of participants in the ADNI by their cognitive status. Body mass index, BMI. Mean (standard deviation) and Range (minimum−maximum) for continuous variables, counts (%) for categorical variables.

among high and low PRS groups but not numeric memory[13]. The associations of comprehensive cognitive measures and AD PRS in the ADNI were similar to a recent ADNI-based study: the correlation of AD PRS and ADAS 13 was stronger than other comprehensive scores such as MMSE and FAQ with and without *APOE* adjustment[36].

The overlapped genes in the AD GWAS and the global cognitive function GWAS could be the biological mechanism behind the relationship between AD PRS and cognitive function[37]. Global cognitive function GWAS from more than 53,000 individuals identified four risk genes (*TOMM40*, *APOE*, *ABCG1*, and *MEF2C*), which have also been reported by the AD GWAS[37]. Other studies also suggested the AD PRS effects on executive function or memory interacted with β-amyloid (Aβ) accumulation: PRS was related to cognitive decline in Aβ + participants but not in Aβ- participants even with *APOE4* adjusted[38]. Another finding in the associations

Cognitive function	*N*	Model 1		Model 2		Model 3	
		Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
Fluid intelligence, FI	135,957	− 0.002 (0.003)	0.36	− 0.006 (0.003)	0.02	− 0.005 (0.003)	0.11
Matrix pattern completion, MAT	**21,642**	**− 0.023 (0.007)**	**5.45E-04**	**− 0.025 (0.006)**	**1.26E−04**	**− 0.022 (0.007)**	**3.01E−03**
Tower rearranging, TWR	*21,454*	*− 0.029 (0.007)*	*8.09E-06*	*− 0.030 (0.007)*	*8.11E−06*	− 0.021 (0.008)	6.70E−03
Numeric memory, MEMN	86,209	− 0.003 (0.003)	0.33	− 0.006 (0.003)	0.09	− 0.001 (0.004)	0.81
Pairs matching, MEMP	**276,655**	**− 0.017 (0.002)**	**1.78E-20**	**− 0.016 (0.002)**	**1.21E−18**	**− 0.014 (0.002)**	**1.66E−10**
Symbol digit substitution, SDS	**69,458**	**− 0.025 (0.003)**	**3.94E-13**	**− 0.027 (0.003)**	**1.22E−14**	**− 0.017 (0.004)**	**1.08E−05**
Reaction time, RT	**275,032**	**− 0.008 (0.002)**	**9.98E-06**	**− 0.009 (0.002)**	**8.98E−07**	**− 0.010 (0.002)**	**1.19E−06**
Trail making B, TMT B	*61,314*	*− 0.017 (0.004)*	*5.24E-06*	*− 0.019 (0.004)*	*2.19E−07*	− 0.010 (0.004)	0.02

Table 3. Association of 1-SD increment in AD polygenic risk score with cognitive function in the UK Biobank. Model 1: age, sex, array, 10 PC adjusted. Model 2: Model 1 + Smoking (never, past, current) + Education in years + BMI. Model 3: Model 2 + *APOE4* risk allele dosages. Cognitive function were in bold as all statistically significant (P value < 0.0062) across all the models, were in italic if only significant in some of the models.

Cognitive functions	Cognitive normal				Mild cognitive impairment			
	Model 1		Model 2		Model 1		Model 2	
	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
Mini-Mental State Exam, MMSE	*− 0.074 (0.026)*	*4.89E−03*	− 0.067 (0.030)	0.03	*− 0.218 (0.041)*	*1.46E−07*	− 0.076 (0.047)	0.10
Alzheimer Disease Assessment Scale 11	*0.089 (0.029)*	*2.63E−03*	0.079 (0.033)	0.02	*0.252 (0.041)*	*2.32E−09*	0.118 (0.047)	0.01
Alzheimer Disease Assessment Scale 13	*0.094 (0.032)*	*4.01E−03*	0.082 (0.037)	0.03	*0.254 (0.042)*	*3.67E−09*	0.109 (0.048)	0.02
Montreal Cognitive Assessment	− 0.067 (0.038)	0.08	− 0.050 (0.043)	0.24	*− 0.252 (0.047)*	*1.12E−07*	− 0.094 (0.053)	0.08
Functional Assessment Questionnaire	0.057 (0.027)	0.03	0.053 (0.030)	0.08	*0.211 (0.044)*	*1.92E−06*	0.055 (0.050)	0.27
ADNI memory summary score	− 0.084 (0.042)	0.05	− 0.073 (0.048)	0.13	*− 0.226 (0.039)*	*2.06E−08*	− 0.085 (0.045)	0.06
ADNI executive function score	− 0.061 (0.043)	0.16	− 0.049 (0.048)	0.31	− 0.106 (0.040)	7.27E−03	0.005 (0.046)	0.90
ADNI language summary score	− 0.035 (0.042)	0.41	− 0.054 (0.048)	0.26	*− 0.157 (0.040)*	*8.55E−05*	− 0.066 (0.047)	0.15
ADNI visuospatial summary score	− 0.013 (0.037)	0.73	− 0.016 (0.042)	0.70	− 0.066 (0.035)	0.06	0.023 (0.041)	0.58

Table 4. Association of 1-SD increment in AD polygenic score with cognitive function in ADNI. Mixed effects linear regression model: Model 1: age at the visit, sex, education, ever vs. never smokers, BMI, 10 PC adjusted. Model 2: Model 1 + *APOE4* risk allele dosages. Cognitive function were in bold as all statistically significant (P value < 0.0056) across all the models, were in italic if only significant in some of the models.

of AD PRS and cognitive function is the role of *APOE4* status. Typically, their associations attenuated when further adjusted for *APOE4*, and more significant PRS (already excluded *APOE* variants) and cognitive function associations appeared in the *APOE4* carriers rather than non-carriers. Another study reported the *APOE4* effects on reaction time or memory were not observed nor was an interaction with age or cardiovascular disease[39]. Characterizing a genetic predisposition to AD solely relying on *APOE* genotyping has been discouraged[40]. The modifying effect of *APOE4* on the AD PRS could potentially increase the accuracy of risk predictions for AD and early cognitive impairment[41]. Our study potentially provide evidence that the AD risk stratification models should consider both AD polygenic (e.g., AD PRS) and monogenic (e.g., *APOE4*) effects.

Although some effects modification by age and *APOE4* was found in the UK Biobank, we did not identify the effects modified by other risk factors such as education, BMI, and smoking. Previous study indicated higher educational attainment in early life may attenuate the risk for dementia, particularly among people with high genetic predisposition[42]. The average education lengths were approximately the same as 14 years across 10% lower or 90% upper PRS group in our data, and made us difficult to find the interaction between PRS and education. Further investigation in other populations or with even larger sample size, or meta-analysis of PRS and cognitive function across multiple cohorts may be warranted.

The clinical significance of AD PRS and its association with cognitive scores is extremely important as these genetic risk factors could be having an impact earlier than what was usually described since we found such associations in middle age population. Identifying individuals who were more likely to have cognitive decline could lead to more targeted preventive measures or treatment strategies depending on their PRS score. Besides the cognitive assessments, genetic information or PRS could serve as one reliable objective evaluation on AD risk stratification and treatment support, potentially in early detection of subtle cognitive impairment.

The strengths of our study include the application of the genome-wide PRS estimation, the validation of our results in an external cohort, and the robustness to multiple covariate adjustments. However, we acknowledge several limitations: the first one is the AD GWAS meta-analysis summary statistics included UK Biobank AD cases, and the AD PRS training in the UK Biobank might have overlapping samples[43]. Secondly, the diagnosis of AD were different in UK Biobank and ADNI. The AD PRS composed by the UK Biobank might not exactly

capture all the genetic predisposition of AD in ADNI, but it could somehow predict incident dementia in ADNI as showed in Supplemental Table 8. Thirdly, residual confounders such as diet, medications, comorbidities of diabetes and cardiovascular diseases might bias the association of AD PRS and cognitive functions, but our results would not significantly change given the UK Biobank was a relatively healthy population and those risk factors effect sizes contributing to cognitive function were trivial[29]. Lastly, the populations for our study were restricted to European ancestries to minimize the noise of PRS estimates among multiethnic populations. The generalizability was limited and should be further validated in populations of diverse ancestry.

Conclusions

In summary, we validated that cognitive function decrease was associated with higher polygenic AD risk and suggested the usefulness of AD PRS in identifying those who may be at risk for further cognitive decline.

Data availability

AD GWAS summary statistics were downloaded from the European Bioinformatics Institute GWAS Catalog (https://www.ebi.ac.uk/gwas/) under accession no. GCST90027158. The UK Biobank data generated and/or analyzed during current study are not publicly available for privacy reasons, but can be requested through the UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). We accessed the data under Application Number 76269. The ADNI whole genome sequencing datasets generated and/or analyzed during the current study are available in the NIAGADS Data Sharing Site (https://dss.niagads.org/sample-sets/snd10002/) with accession number snd10002.

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Author contributions

B.W. and H.L. conceived the study idea. B.W. conducted data analyses, and wrote the first draft of the manuscript. L.B.C., S.H.C., D.B., and A.L.D. reviewed the manuscript critically for important intellectual content. HL supervised the work and made significant contributions to the interpretation of the results and editing of the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

All human subjects included in this study provided informed consent. All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki. The UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. This research has been conducted using the UK Biobank Resource under Application Number 76269. The ADNI study was approved by the institutional review boards of all the participating institutions, and informed written consent was obtained from all participants at each site. One such institution is the Office for the Protection of Research Subjects at the University of Southern California. More details can be found at adni.loni.usc.edu.

Additional information

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Correspondence and requests for materials should be addressed to B.W.