

RESEARCH ARTICLE

Genetic risk for Alzheimer's disease, cognition, and mild behavioral impairment in healthy older adults

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Abstract

Background: The neuropsychiatric syndrome mild behavioral impairment (MBI) describes an at-risk state for dementia and may be a useful screening tool for sample enrichment. We hypothesized that stratifying a cognitively normal sample on MBI status would enhance the association between genetic risk for Alzheimer's disease (AD) and cognition.

Methods: Data from 4458 participants over age 50 without dementia was analyzed. A cognitive composite score was constructed and the MBI Checklist was used to stratify those with MBI and those without. Polygenic scores for AD were generated using summary statistics from the IGAP study.

Results: AD genetic risk was associated with worse cognition in the MBI group but not in the no MBI group (MBI: $\beta = -0.09$, 95% confidence interval: -0.13 to -0.03 , $P = 0.002$, $R^2 = 0.003$). The strongest association was in those with more severe MBI aged ≥ 65 .

Conclusions: MBI is an important feature of aging; screening on MBI may be a useful sample enrichment strategy for clinical research.

KEYWORDS

Alzheimer's disease, cognition, mild behavioral impairment, neuropsychiatric symptoms, polygenic score

1 | BACKGROUND

Worldwide, the number of people with dementia is expected to rise to 150 million by 2050. Recent years have been marked by a number of high-profile failures of disease-modifying therapies and it is now widely recognized that identification of people in the very earliest stages of disease is a key priority for clinical trials of new treatments, and ultimately for clinical practice.¹ Genetic predictors of cognitive decline and dementia have been the subject of considerable focus in recent years. These predictors include not only apolipoprotein E (APOE) sta-

tus but also polygenic risk scores (PRS). PRS are the sum of Alzheimer's disease (AD) risk alleles carried by an individual weighted by effect size, and therefore capture more genetic risk than APOE alone. The ultimate goal of this work is the identification of a low-cost early marker of neurodegenerative disease. As an important first step, numerous studies have shown that AD genomic markers predict AD and mild cognitive impairment (MCI) case/control status, as well as progression to AD among MCI cases.²⁻⁷ However, the association between AD genetic risk and objectively measured cognition in non-dementia samples is less consistent.⁸⁻¹⁵ There are a number of methodological differences

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that likely explain these discrepancies, including the sensitivity of cognitive outcome measures and the number of risk alleles included in PRS calculation. One additional challenge is the complex etiology of cognition in older adults, which is not solely accounted for by genetic risk for neurodegeneration or neuropsychological profile. Because of the ease and low cost of genetic analysis, and promising initial findings, it is logical to explore additional strategies that may enhance sensitivity in older samples.

Previous research has shown that the association between APOE $\epsilon 4$ and cognition is strongest in older adults, one possible implication being that there are more people in older samples whose cognitive profile is linked to early neurodegeneration.¹⁴ One study found that stratification based on amyloid beta ($A\beta$)-positive positron emission tomography (PET) scans unmasked an association between AD PRS and poorer memory and executive function.¹² That neuropathological markers of AD moderate the association between AD genetic risk and neuropsychological measures is not surprising, but does offer proof of principle of sample enrichment, informing our study. To add value to a genetic screen, such sample enrichment should be low cost and scalable to large populations. There is evidence that later-life emergent neuropsychiatric symptoms (NPS), described by the validated syndrome mild behavioral impairment (MBI), may represent such a screening tool. MBI is a neurobehavioral syndrome proposed by an Alzheimer's Association consensus group to describe a risk state for cognitive decline and dementia to facilitate earlier dementia detection.¹⁶ The MBI syndrome covers late-life-emergent apathy, mood/anxiety symptoms, impulse dyscontrol, social inappropriateness, and psychotic symptoms, and is common and easily measured in the general population.¹⁷ Moreover, MBI is associated with progressive cognitive decline in individuals without significant cognitive impairment, a shorter time to dementia, and has recently been shown to associate with dementia biomarkers including PET amyloid, tau, and neurofilament light in cognitively normal samples.^{18–26} On the basis of this evidence, MBI is an attractive candidate tool to enrich samples with individuals at greater risk of dementia, but to our knowledge no studies have explored how stratification on MBI influences the relationship between genetic risk for AD and cognition. In this study we aimed to elucidate whether stratifying a cognitively normal sample on the presence of MBI symptoms affected the association between genetic risk for AD and general cognitive ability. We hypothesized AD genetic risk would be associated with poorer cognition and that this relationship would be strongest among people with MBI symptoms.

2 | METHODS

2.1 | Participants

All participants were drawn from the PROTECT study (Research Ethics Committee reference number 13/LO/1578). PROTECT is a UK-based online participant registry that tracks the cognitive health of older adults. Inclusion criteria for enrolling in PROTECT are (1) ≥ 50 years old, (2) no diagnosis of dementia, and (3) access to a computer and

RESEARCH IN CONTEXT

- 1. Systematic review:** we reviewed the literature using a PubMed and Google Scholar search. There is increasing evidence from clinical risk and biomarker studies that mild behavioral impairment (MBI) represents an at-risk state for dementia and may be the first manifestation of neurodegenerative disease. It is therefore possible that MBI screening could represent a useful sample enrichment strategy for clinical studies and possibly trials. We tested this hypothesis by examining the relationship between genetic risk for Alzheimer's disease (AD) and cognition in people with MBI and in those without.
- 2. Interpretation:** We show for the first time that stratification on MBI symptoms led to an enhanced signal between genetic risk for AD and cognition in a cognitively normal sample.
- 3. Future directions:** We propose that screening on MBI symptoms may be a novel strategy for enriching samples for individuals at risk of dementia. Our findings and study design provide a framework for further investigation of this application of MBI assessment.

internet. The sample used in this study is a subset of PROTECT study participants who also provided a saliva sample for genotyping, completed cognitive testing, and had a proxy informant available to complete the MBI Checklist (MBI-C; further detail is presented below). Specifically, genome-wide genotype data for 9146 PROTECT participants was available for analysis in this study. Of these, clinical data required for this analysis from self-report and proxy informant was available from 4458 people. The difference in numbers providing DNA and those with required clinical data is due to the MBI-C being completed by proxy informant, and nomination of a proxy is optional. Written informed consent was obtained from all participants and proxy informants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki 1975, as revised in 2008.

The following demographic data, which are routinely collected during PROTECT, were used in this analysis as covariates: age, sex, education level (school until 16, school until 18, vocational qualification, undergraduate degree, post-graduate degree, and doctoral degree) and employment status (full time, part time, self-employed, retired, and unemployed).

2.2 | Assessment of cognition

Cognitive performance was assessed via a battery of four tests (Table 1). Individual performance across cognitive tests is known to be

TABLE 1 Description of the cognitive battery used

Test	Description	Cognitive domain
Paired associates learning	A series of objects appear in the cells on screen. The participant is instructed to remember the cell in which the object appears. When an object appears at the bottom center, the participant is instructed to click on the cell in which they recall seeing that object.	Visual working memory, learning
Digit span	Using a ratchet-style approach in which each successful trial is followed by a new sequence that is 1 digit longer than the last and each unsuccessful trial is followed by a new sequence that is 1 digit shorter than the last.	Working memory
Self-ordered search	A series of boxes are present on the screen; one of the boxes will contain a diamond. The participant selects each box until they locate the diamond. The diamond is then placed in another box and again the participant must locate it, but they must be careful not to select the box in which the diamond was previously found.	Executive function, spatial working memory
Verbal reasoning	A sentence is displayed at the bottom of the screen while a square and a circle are displayed above. The participant needs to respond true or false as to whether the sentence correctly describes the configuration of the circle and square.	Verbal reasoning

correlated, and for this study we analyzed a general cognitive composite based on factor analysis of the battery. This latent construct is a well-documented feature of cognition.²⁷ To capture general cognitive ability in this sample, a composite score was calculated by computing the first unrotated principal component of the cognitive battery. The variance in total cognitive test score explained by the first principal component was 48.7% and the factor loadings were 0.53 (paired associated learning), 0.5 (digit span), 0.46 (self-ordered search), and 0.50 (verbal reasoning). This finding is comparable to recent reports in an analysis of more than 300,000 individuals across multiple cohorts.²⁸ In the present study, higher cognitive composite score was associated with a lower likelihood of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score >3.3, which indicates a negative change in cognition over 10 years via a questionnaire observed by a proxy informant (odds ratio [OR] = 0.84, 95% confidence interval [CI]: 0.78–0.91 $P < 0.001$, controlling for age, sex, and education). It was also associated with greater impairment in instrumental activities of daily living (IADL) as measured by the Minimum Data Set–Home Care IADL scale ($\beta = 0.156$, 95% CI: 0.06–0.25 $P = 0.001$), providing validation that the cognitive construct is meaningful in the context of our sample.^{29,30}

2.3 | Assessment of neuropsychiatric symptoms in the MBI framework

Neuropsychiatric symptoms were operationalized in the MBI framework using the MBI-C. The MBI-C is a validated tool designed specifically for capturing MBI symptoms and, in this study, was completed by a proxy informant who knew the participant well for at least 10 years.^{17,31–33} The scale consists of 34 questions covering the full range of MBI domains (apathy, mood/anxiety symptoms, impulse dyscontrol, social inappropriateness, and psychotic symptoms). Each question is rated on a scale of 0 (not present) to 3 (severe). The MBI-

C mandates that a symptom must be present for at least 6 months and represent a change from longstanding behavior to be rated as present. This approach facilitates differentiation of MBI symptoms from transient neuropsychiatric symptoms, and reactive conditions due to medical and environmental precipitants and life stressors to better reflect the new onset symptomatology seen in neurodegenerative disease.³⁴ In this study, participants were classified as having any symptoms of MBI (MBI-C total score >0) or having no MBI symptoms (MBI-C total score = 0) due to the strong positive skew of the MBI-C data (i.e., $\approx 50\%$ of respondents can be expected to score zero).¹⁷ Any participants with the following medical conditions were excluded (all derived from self-report responses to the question “Have you ever been diagnosed with one or more of the following even if you don’t have it currently?”): mild cognitive impairment ($n = 11$), stroke ($n = 72$), Parkinson’s disease ($n = 11$). This was done to minimize confounding associated with potential dementia syndromes and to better reflect the Alzheimer’s Association MBI diagnostic criteria stipulation that symptoms cannot be better explained by a pre-existing medical or psychiatric condition.¹⁶ Self-reported lifetime history of psychiatric diagnoses was also recorded (depression, mania/bipolar/manic depression, anxiety/generalized anxiety disorder, panic attacks, eating disorders, autism/Asperger’s/autistic spectrum disorder, attention deficit disorder, schizophrenia/other psychotic illnesses, personality disorders, and social anxiety/phobia, $n = 1515$). In addition to lifetime self-reported diagnosis we also captured current depressive symptom status using the Patient Health Questionnaire 9 (PHQ-9); here we dichotomized participants into who scored ≥ 10 on the PHQ-9 ($n = 128$) and those scoring < 10 , which has good sensitivity and specificity for a current major depressive episode.³⁵

The binary coding of the MBI-C is supported by recent data showing that in cognitively normal people, a score >0 on the MBI-C (i.e., the presence of any symptoms of any severity) was associated with worse cognitive performance (both at baseline and over 1 year) on

a range of tests, with a score of >8 being associated with the worst performance.¹⁹

2.4 | Genotyping, genetic data quality control, and AD polygenic risk score calculation

Saliva samples were collected by post and DNA extract by the National Institute for Health Research South London and the Maudsley National Health Service Biomedical Research Centre. Genotyping was done using the Illumina Global Screening Array with custom content (including directly genotyped single nucleotide polymorphisms [SNPs], rs429358 and rs7412, to determine APOE status). The total numbers of participants in the combined genotyped data for the whole PROTECT study was 9146. Genotype quality control (QC) was performed on all of these individuals but only those with MBI and cognitive data were included in the association analysis. Iterative filtering for call rate at 98% completeness (for individuals and SNPs) resulted in the exclusion of 84 samples, after which 9062 remained. In the filtered data relatedness was estimated using KING 2.2.3, followed by extraction of a list of individuals that contained no pairs of individuals with a first-, second-, or third-degree relationship.³⁶ Variants with Hardy-Weinberg equilibrium P -value < 0.00001 were excluded. Individuals whose sex estimated in plink did not match that reported by the study participants were excluded. Principal components (PCs) were calculated for the unrelated subset of the data using EIGENSOFT 6.1.4 after pruning using a window size of 1500 bases per 150 kb and an r -squared of 0.2.^{37,38} Variants in high linkage disequilibrium regions and non-autosomal regions were also excluded. K-means clustering (assuming four distinct clusters) was used on the first two derived PCs to define a cluster of European ancestry individuals. PCs were then recalculated for the cluster of individuals of European ancestry, with outlier individuals removed by EIGENSOFT if exceeding a sigma threshold of 30. Finally, individuals with excess heterozygosity (unusual patterns of genome-wide heterogeneity) calculated using the `ibc` function in plink v1.90 were excluded.³⁹ The total number of individuals excluded when removing those that were either related, of non-European ancestry, of mismatched sex, outliers in the PC calculation, or detected to have excess heterozygosity was 790 given an original sample size of 9062 participants.

International Genomics of Alzheimer's Project (IGAP) AD genome-wide association study (GWAS) summary statistics were used to calculate PRS using PRSice v2.2.12.^{40,41} Directly genotyped data was used for the PRS calculation and the total number of variants available after QC was 630,180.

Previous data suggest a wide range of inclusion thresholds for AD PRS calculation, from only genome-wide significant SNPs to many thousands of SNPs.^{2,3,8-15} In this study, we opted for two AD GWAS SNP inclusion thresholds (P_T). The first, 5×10^{-8} (22 SNPs after clumping), was chosen because it was the most strongly associated with a family history of AD (defined as self-reported number of parents with AD) in this sample ($\beta = 0.05$, 95% CI: 0.03–0.06, $P < 0.001$) and the second was all IGAP SNPs (i.e., $P_T = 1$, 83,540 SNPs after clumping).

2.5 | Statistical analysis

PRS were standardized to a mean of 0 and standard deviation of 1 before analysis. Regression coefficients thus represent unit increase in cognitive composite score per one standard deviation increase in PRS. The association between AD genetic risk and cognition was first tested by linear regression in the whole sample at both P_T . The sample was then stratified by MBI status and the dependent variable of cognitive composite was analyzed by linear regression with AD PRS and age, sex, education level, employment status (dummy coded), lifetime history of psychiatric diagnosis, PHQ-9 grouping (≥ 10 and < 10), and the first six ancestry PCs as covariates. The inclusion of psychiatric history and PHQ-9 grouping, thus, allows us to be more confident that findings are the result of MBI specifically and not confounded by MBI-C measurements capturing concurrent psychiatric disorders. Subsequent identical models were run that also controlled for APOE $\epsilon 4$ status to assess the independent effect of non-APOE SNPs in the PRS. The proportion of variance explained by the PRS was represented by R^2 of the model with only covariates subtracted from the R^2 of the full model. Regression assumptions were checked by examining residual plots and checking for outliers. Given that the two AD PRS are not independent, and a Bonferroni correction would therefore be overly conservative, a family-wise error rate of 0.025 was applied (to reflect tests on the two MBI symptom groups). All statistical analysis was performed in R version 3.4.2.

3 | RESULTS

3.1 | Participant characteristics

After medical history exclusions, data from 4458 participants were available for analysis. Participant characteristics by MBI group are shown in Table 2. There was no difference in age, sex, or education level between the MBI and no MBI strata but, as expected, the MBI group did have a lower cognitive score. There was a slightly higher proportion of retired people among those in the no-symptom group compared to the MBI symptoms group (60% vs. 56%) and more people with a history of psychiatric conditions or PHQ-9 ≥ 10 also had MBI symptoms.

3.2 | Relationship between AD PRS, cognition and MBI

In the whole sample analysis adjusting for covariates, AD PRS at $P_T = 1$ was associated with a lower mean cognitive composite score ($\beta = -0.07$, 95% CI: -0.11 to -0.03, $P < 0.001$, $R^2 = 0.002$) and modestly at the more conservative PRS at $P_T = 5 \times 10^{-8}$ ($\beta = -0.04$, 95% CI: -0.8–0.00, $P = 0.03$, $R^2 = 0.001$). Accordingly, the rest of the analysis was only conducted on AD PRS at $P_T = 1$.

A plot of the relationship between adjusted mean cognitive composite score and AD PRS adjusted for covariates is shown in Figure 1. In the

TABLE 2 Participant characteristics by MBI group

	MBI group				P
	No symptoms (MBI-C = 0)		MBI symptoms (MBI-C >0)		
N (%)	1865	42	2593	58	
Age (mean, sd)	63.6	6.7	63.5	7.2	0.9
Sex (n, %)					
Female	1423	76	1999	77	0.78
Male	442	24	594	23	
Education level (n, %)					
Secondary education	202	11	335	13	0.14
Post-secondary education	201	11	324	12	
Vocational qualification	364	20	475	18	
Undergraduate degree	690	37	922	36	
Post graduate degree	328	18	442	17	
Doctoral degree	80	4	95	4	
Employment status (n, %)					
Full time	263	14	390	15	0.003
Part time	262	14	427	16	
Self-employed	202	11	248	10	
Retired	1110	60	1458	56	
Unemployed	28	2	70	3	
Life-time history of any psychiatric diagnosis					
No	1356	73	1587	61	≤0.001
Yes	509	27	1006	39	
PHQ-9					
≤10	1850	99	2480	96	≤0.001
≥10	15	1	113	4	
Cognitive composite (mean, sd)	0.14	1.4	-0.06	1.4	<0.001

Note: Cognitive composite is the first unrotated principal component derived from scores on paired associates learning, digit span, self-ordered search, and verbal reasoning.

Abbreviations: MBI, mild behavioral impairment; MBI-C, mild behavioral impairment Checklist; PHQ-9; Patient Health Questionnaire 9; sd, standard deviation.

analysis stratified by MBI symptoms after adjusting for covariates, the association between AD genetic risk and cognition persisted but only in those with MBI symptoms ($\beta = -0.09$, 95% CI: -0.13 to -0.03 , $P = 0.002$, $R^2 = 0.003$, Table 3). In those with no MBI symptoms there was no association between AD genetic risk and cognition (Table 3). Controlling for APOE did not change the direction of associations, though there was a decrease in proportion of variance explained (whole sample: $\beta = -0.06$, 95% CI: -0.10 to -0.02 , $P = 0.003$, $R^2 = 0.002$; MBI symptoms: $\beta = -0.07$, 95% CI: -0.12 to -0.02 , $P = 0.01$, $R^2 = 0.002$).

3.3 | Sensitivity analyses

This analysis was conducted post hoc so should be considered exploratory. In our primary analysis we adopted a binary coding for MBI symptoms (none vs. any) because of evidence that even individuals with

low-level symptoms have an increased risk of cognitive decline. There are no accepted cut points on the MBI-C in cognitively normal community samples so we examined the association between AD PRS, cognitive impairment, and MBI using an MBI-C cut point of ≥ 6 ($n = 979$). The association observed in the main analysis was sustained for those with MBI symptoms at this more conservative MBI-C cut point ($\beta = -0.10$, 95% CI: -0.18 to -0.02 , $P = 0.01$, $R^2 = 0.005$, Table 3). To illustrate this relationship, adjusted mean cognitive composite score by AD PRS stratified by MBI-C using the higher threshold split is plotted in Figure 2. Finally, because of prior evidence showing that AD PRS is a stronger predictor of cognition in older people we examined the same relationship in those aged 65 or over ($n = 369$).⁴² This analysis is plotted in Figure 3 and shows a further strengthening of the relationship between AD PRS and cognition in those with an MBI-C score ≥ 6 , with proportion of variance explained rising from 0.005 to 0.02 ($\beta = -0.20$, 95% CI: -0.34 to -0.06 , $P = 0.005$, $R^2 = 0.02$, Table 3). The increase in

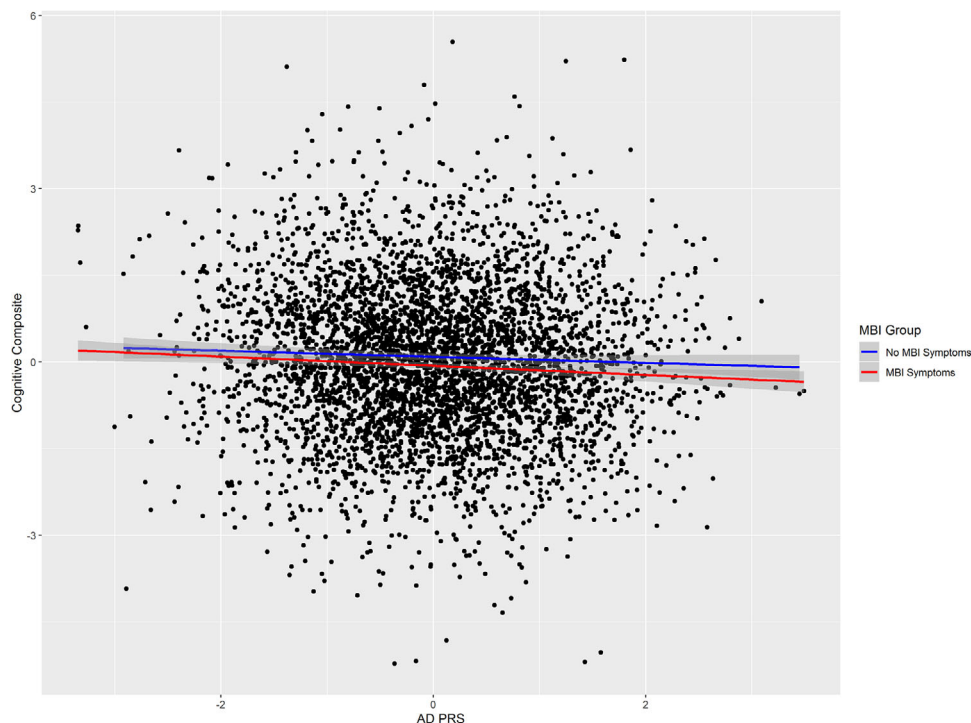


FIGURE 1 Relationship between Alzheimer's disease (AD) polygenic risk score (PRS) and cognitive composite. Fitted lines are adjusted linear regression of PRS on cognitive composite for no mild behavioral impairment (MBI) symptoms and MBI symptom groups (shaded area is 95% confidence interval)

TABLE 3 Results of linear regression of AD PRS on cognitive composite at $P_T = 1$ (83,540 SNPs)

Group	β	L 95% CI	U 95% CI	P	R^2
Whole sample	-0.07	-0.11	-0.03	<0.001	0.002
MBI symptoms (MBI-C > 0)	-0.09	-0.13	-0.03	0.002	0.003
No MBI symptoms (MBI-C = 0)	-0.05	-0.11	0.01	0.09	0.001
Sensitivity analysis					
MBI symptoms (MBI-C ≥ 6)	-0.10	-0.18	-0.02	0.02	0.005
MBI symptoms (MBI-C ≥ 6), aged ≥ 65	-0.20	-0.34	-0.06	0.005	0.02

Notes: Analysis controlled for age, sex, education, employment status, lifetime psychiatric diagnosis, PHQ-9 group, and the first six ancestry principal components.

Beta coefficients represent unit of increase in cognitive composite score per 1 standard deviation increase in PRS.

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; MBI, mild behavioral impairment; PHQ-9; Patient Health Questionnaire 9; PRS, polygenic risk scores; SNP, single nucleotide polymorphism.

variance explained was not simply attributable to the older age cutoff; the R^2 in all participants aged ≥ 65 was comparable to all that of all participants with MBI-C ≥ 6 ($\beta = -0.08$, 95% CI: -0.14 to -0.02 , $P = 0.009$, $R^2 = 0.004$).

4 | DISCUSSION

To our knowledge these findings are the first demonstration that sample stratification on neuropsychiatric symptoms (here assessed in the MBI framework) may identify a subset of the cognitively normal population in which a stronger relationship between genetic risk for AD

and cognition exists. As such our findings point to MBI-C screening as a potential sample enrichment tool as well as suggesting potential confounding by unmeasured neuropsychiatric symptoms in studies of AD genetic risk in cognitively normal samples. The association was present in our study using a PRS based on all available SNPs from AD GWAS ($P_T = 1$); was present even after controlling for psychiatric diagnoses and PHQ-9 score; and remained after controlling for *APOE* status, albeit with a diminished variance explained. As expected, we conclude that *APOE* is driving some of the signal observed in this study, consistent with previous reports, but that non-*APOE* SNPs also play a role in late-life cognition. More broadly, our findings from this sample, which is independent from previous reports, support a role for AD

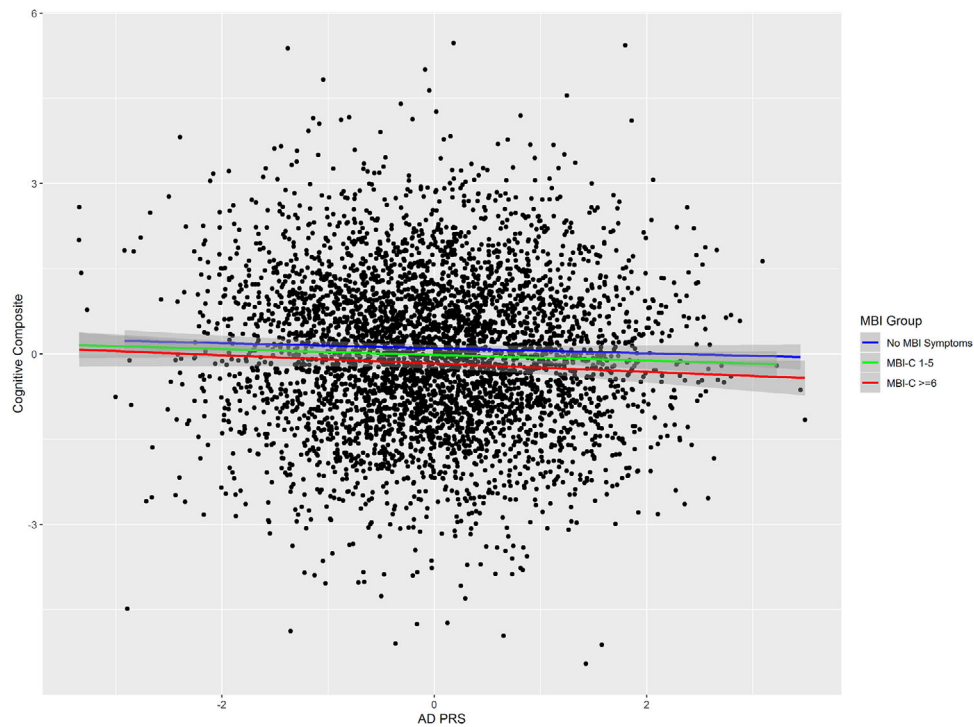


FIGURE 2 Relationship between Alzheimer's disease (AD) polygenic risk scores (PRS) and cognitive composite. Fitted lines are adjusted linear regression of PRS on cognitive composite for no mild behavioral impairment (MBI) symptoms, MBI Checklist (MBI-C) 1–6, and MBI-C ≥ 6 groups (shaded area is 95% confidence interval)

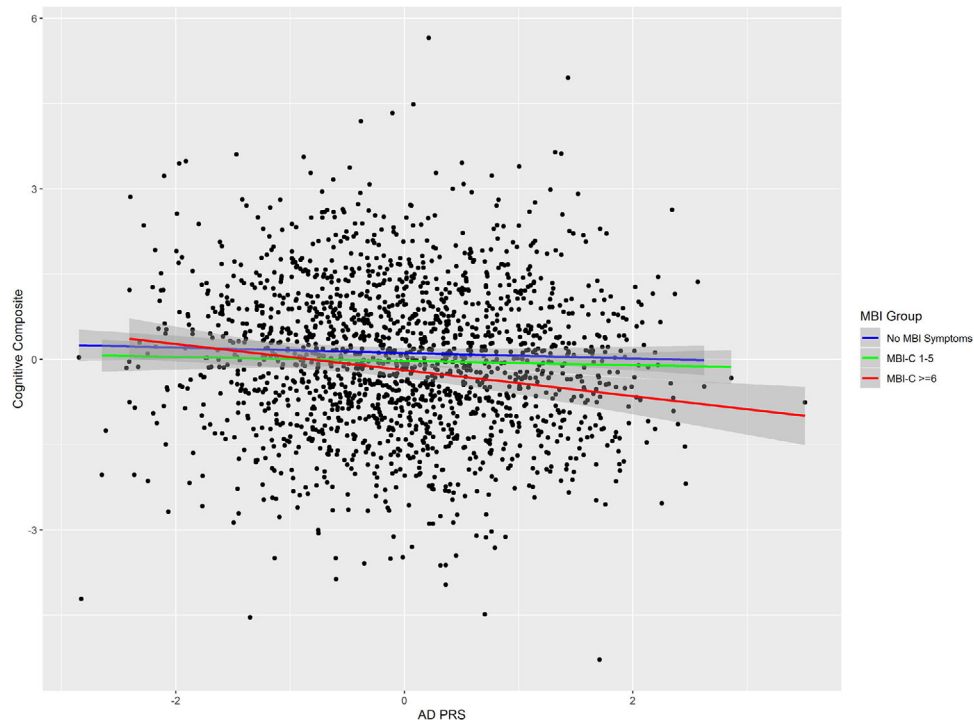


FIGURE 3 Relationship between Alzheimer's disease (AD) polygenic risk scores (PRS) and cognitive composite in the subset of the sample aged ≥ 65 . Fitted lines are adjusted linear regression of PRS on cognitive composite for no mild behavioral impairment (MBI) symptoms, MBI Checklist (MBI-C) 1–6, and MBI-C ≥ 6 groups (shaded area is 95% confidence interval)

genetic risk, beyond *APOE*, in cognition among older adults without dementia, an important finding as there is not unanimity in previous literature.^{8–11,13–15}

A recent well-phenotyped large study of older adults found that an AD PRS that included all SNPs ($P_T = 1$) was not associated with cognition in adults but *APOE* was.¹⁴ Genetic risk for AD has been shown to be pleiotropic but it is notable that a previous study found the effect of *APOE* $\epsilon 4$ on cognition to be stronger in older adults relative to earlier in life.^{14,42} Older samples are more likely to contain a larger proportion of individuals in prodromal or preclinical disease so a stronger effect of AD PRS could be reasonably expected. Similarly, we propose that stratifying on MBI, even among cognitively normal older adults, has the same effect and defines a cognitive phenotype that is “closer” to AD. This, in turn, would create better power to detect associations with those AD SNPs with smaller effect sizes, thus explaining the discrepancy between our finding and this other recent work.

The notion that MBI (i.e., late-life neuropsychiatric symptoms) may be an early marker of dementia is somewhat counterintuitive for a group of diseases that are primarily conceptualized as cognitive disorders. This cognocentric approach does not necessarily reflect the history of AD. Auguste D., the index patient described by Alois Alzheimer, presented to hospital with emotional dysregulation and suspiciousness, followed by cognitive decline.^{34,43–45} Several longitudinal studies support MBI emerging in advance of cognitive symptoms or increasing risk of incident cognitive decline and dementia.^{18,20,21,46,47} The distinction between MBI and other neuropsychiatric symptoms as risk factors versus early markers has been a topic of recent debate.^{48,49} However, new data in cognitively normal people showing that MBI symptoms are associated with higher $A\beta$ burden,²³ tau deposition,²⁶ and faster accumulation of neurofilament light⁵⁰ support the view of MBI as an early clinical marker. The implication is therefore that stratification on MBI symptoms enriches samples for individuals with preclinical or prodromal disease, creating a more etiologically homogenous sample; this hypothesis is strengthened by our post hoc analysis showing evidence of a stronger association in those with more severe MBI symptoms who are aged 65 or over. Deeper phenotyping including imaging and longitudinal follow-up with detailed neuropsychology and clinical outcomes will be required to confirm this hypothesis, which could have important implications for clinical trials in which cohort heterogeneity has been identified as a major concern.⁵¹

The operationalization of MBI is worth some discussion. A key strength of this study is the controlling of pre-existing psychiatric conditions and use of the specific MBI-C tool, which has been validated in cognitively normal samples,¹⁷ both of which provide more confidence that our findings are due to later-life emergent mild NPS rather than longstanding clinically significant psychiatric diagnoses. However, establishing appropriate cut points on the MBI-C is a matter of ongoing research. Our findings, including our post hoc analysis, and those of others suggest that relatively mild symptoms are important to consider and that the likely optimal cut point on the MBI-C for case ascertainment would lie somewhere between 2 and 8. This is supported by previous research showing that low-level symptoms of MBI as well as more severe symptoms are associated with cognitive decline in cogni-

tively normal individuals.¹⁹ Relating to this, a limitation to our study is the proxy completion of MBI-C via remote questionnaire completion, which could have led to some misclassifications, although raters in this study were required to have known the participant for at least 10 years. Other limitations include the over-representation of women and more highly educated people in our sample and, as with most genetic studies, these results may not be generalizable to non-European ancestry populations. We note our sample size is relatively small compared to much of the wider genetic literature and replication in independent cohorts is needed. In particular, we would not rule out an effect of AD PRS in the no MBI symptom group, but our data would suggest that this effect is weaker. The lack of association could be due to power as the MBI symptoms group was larger. However, it is worth noting that in our sensitivity analysis using a more stringent cut point ($\text{MBI-C} \geq 6$) there were 925 people in the MBI group, approximately half that of the no-symptoms group. At present we are not aware of any other large cohort studies that use the MBI-C; however, we would argue that our findings, along with the practical advantages of the MBI-C (it is freely available and quick to complete) provide a strong case for the wider adoption of the scale, which will allow important follow-up work to take place.

In summary, this study lends further support to the growing evidence base that later life emergent neuropsychiatric symptoms describe an at-risk state for incident cognitive decline and dementia, and can be the index manifestation of dementia for some. Our findings also support the case for using MBI as a sample enrichment tool for biomarker studies and clinical trials targeting at-risk individuals. The enrichment approach is inexpensive, simple, and scalable, and can decrease cost and improve enrolment efficiency of dementia clinical trials. Deeper phenotyping of these groups including neuroimaging and longitudinal monitoring of clinical outcomes is now essential.

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CONFLICTS OF INTEREST

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