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Polygenic hazard score predicts synaptic and axonal degeneration and cognitive decline in Alzheimer's disease continuum

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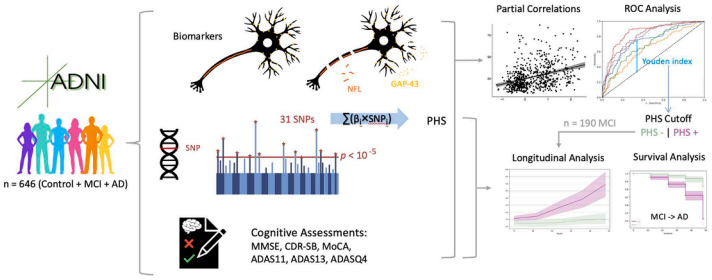
HIGHLIGHTS

- PHS shows high diagnostic accuracy in distinguishing AD, MCI, and healthy controls.
- PHS can predict cognitive decline and progression of MCI to AD.
- PHS impacts the relationship between neurodegenerative biomarkers and cognitive decline.

GRAPHICAL ABSTRACT



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[2] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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ABSTRACT

Background: Growth associated protein-43 (GAP-43) and neurofilaments light (NFL) are biomarkers of synaptic and axonal injury, and are associated with cognitive decline in Alzheimer's disease (AD) contiuum. We investigated whether Polygenic Hazard Score (PHS) is associated with specific biomarkers and cognitive measures, and if it can predict the relationship between GAP-43, NFL, and cognitive decline in AD.

Method: We enrolled 646 subjects: 93 with AD, 350 with mild cognitive impairment (MCI), and 203 cognitively normal controls. Variables included GAP-43, plasma NFL, and PHS. A PHS of 0.21 or higher was considered high risk while a PHS below this threshold was considered low risk. A subsample of 190 patients with MCI with four years of follow-up cognitive assessments were selected for longitudinal analysis . We assessed the association of the PHS with AD biomarkers and cognitive measures, as well as the predictive power of PHS on cognitive decline and the conversion of MCI to AD.

Results: PHS showed high diagnostic accuracy in distinguishing AD, MCI, and controls. At each follow-up point, high risk MCI patients showed higher level of cognitive impairment compared to the low risk group. GAP-43 correlated with all follow-up cognitive tests in high risk MCI patients which was not detected in low risk MCI patients. Moreover, high risk MCI patients progressed to dementia more rapidly compared to low risk patients.

Conclusion: PHS can predict cognitive decline and impacts the relationship between neurodegenerative biomarkers and cognitive impairment in AD contiuum. Categorizing patients based on PHS can improve the prediction of cognitive outcomes and disease progression.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is the primary cause of dementia among elderly individuals (Salvadores et al., 2020). The primary pathological mechanisms initiate many years before the onset of clinical dementia symptoms and involve the build-up of amyloid beta protein (Aβ), leading to the formation of plaques, which is then followed by the aggregation of hyperphosphorylated tau protein (P-tau) into neurofibrillary tangles (Öhman et al., 2021). Accordingly, it is essential to identify patients as soon as possible and offer them prompt management (Jack et al., 2018). Using a comprehensive panel of AD-associated biomarkers can dramatically improve the accuracy of early AD diagnosis and accelerate the process (Olsson et al., 2016, Planche et al., 2023). Higher levels of P-tau and lower Aβ levels is commonly reported in AD (Friedrich et al., 2010, Hansson et al., 2017), as Aβ causes amyloid plaques in the brain, whereas P-tau causes neurofibrillary tangles. Tau aggregation in cerebrospinal fluid (CSF), serving as early pathological biomarkers of AD, are associated with cognitive decline in individuals. The most prominent association between AD biomarkers and cognitive decline is observed in memory and other cognitive domains, such as executive function and visuospatial abilities (Öhman et al., 2021).

Axonal and synaptic degeneration biomarkers are also suggested as biomarkers for AD. Synaptic markers found in CSF are potential candidates for use as neurodegeneration biomarkers. It is not yet clear when synaptic dysfunction first manifests over the course of the disease. However, synapse degradation and loss are fundamental aspects of AD pathophysiology (Janelidze et al., 2016). Recent research found elevated levels of synaptic biomarkers in the CSF of individuals with AD and prodromal AD (Citron et al., 1994, Portelius et al., 2015). These markers include neurogranin, growth-associated protein 43 (GAP-43), synaptosomal-associated protein 25, and synaptotagmin proteins (Milà-Alomà et al., 2020, Skene et al., 1986), where the presynaptic protein GAP-43, also known as neuromodulin, is intimately linked to synaptic plasticity, axonal guidance, and neurite outgrowth (Milà-Alomà et al., 2020, Skene et al., 1986). Synaptic loss is evident even in the early stage of AD, known as mild cognitive impairment (MCI) and is associated with cognitive decline measures (Pereira and al., 2021, Zhang et al., 2018). Additionally, studies have linked tau pathology and amyloid abnormalities with elevated CSF levels of GAP-43 in patients with MCI and AD, showing the GAP-43 effects on cognition assessment in AD patients (Citron et al., 1994, Hulo et al., 2002, McGrowder et al., 2021, Sandelius et al., 2019). Furthermore, neurofilament light chain (NFL), as a quantitative indicator of ongoing axonal injury, indicates the occurrence of ongoing neuroinflammatory and neurodegenerative processes, hence its excessive levels may provide a prognostic value in various neurological disorders (Gaetani et al., 2019, Kuhle et al., 2019). NFL concentrations have been found to increase in CSF and blood among central nervous system (CNS) and peripheral nervous system (PNS) arising diseases indicating axonal damage or degeneration (Olsson et al., 2019).

Despite extensive research on fluid biomarkers of AD, affected individuals still manifest differential trajectories despite similar baseline biomarker burden. This could be linked to the substantial role of genetic susceptibility in the age of onset and course of AD. The Polygenic Risk Score (PRS) combines the impact of numerous genetic variants to create a unified measure for forecasting disease risk and has been recognized as a recent trend in AD research. While PRS has demonstrated predictive efficacy in various intricate conditions, it falls short in considering the age of onset, which is particularly crucial in neurodegenerative diseases like AD. Addressing this gap, the recent introduction of the Polygenic Hazard Score (PHS) surpasses this limitation by estimating an individual's age-specific risk of developing AD (Desikan et al., 2017). This assessment of immediate risk for AD proves to be valuable supplementary information, potentially enhancing the tracking of disease advancement and enabling timely interventions. The conceptual difference between PHS and PRS is that PRS employs odds ratios from case-control analyses, while PHS uses single nucleotide polymorphism (SNP) level effect size estimates from survival analysis (Cox proportional hazards model). The second distinction is that effect sizes for PRS were derived univariately, while hazard ratios for PHS were determined using a multivariate technique (Altmann et al., 2020). PHS has exhibited marginally superior predictive abilities compared to relying solely on APOE ε4 status (Vacher et al., 2022).

Despite current research on AD, early and accurate diagnosis of AD remains a challenge. This study investigates the potential of combining neurodegenerative biomarkers with PHS for a more robust prediction of cognitive decline in the AD spectrum than looking at these factors separately. We investigated whether PHS is associated with specific biomarkers and cognitive measures, and if it can impact the relationship between levels of GAP-43 and NFL, markers of synaptic and axonal dysfunction, and cognitive decline in AD stages. We assumed that individuals with a higher PHS, indicative of increased genetic risk, will exhibit a stronger association between these biomarkers and cognitive decline. This could ultimately result in a more comprehensive approach leading to early identification and treatment planning for AD.

2. Material and methods

2.1. ADNI database

Data were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, a longitudinal study initiated in 2004 with the leadership of Dr. Michael W. Weiner as a public-private partnership. ADNI's goal is early diagnosis of AD and tracking of AD with the test of clinical trials through functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), blood biological markers, and tests of CSF. ADNI's website is available for more information (https://adni.loni.usc.edu/).

2.2. Participants and classification criteria

All participants with available cognitive assessments, CSF GAP-43, plasma NFL, and PHS were extracted from the ADNI database. MCI patients (cognitively normal subjects (CN) and AD subjects were omitted due to the small size of the sample) with four years of follow-up were selected for subgroup longitudinal analysis. Due to high missing data points, we considered the AD biomarkers at only baseline timepoint, though cognitive tests data obtained for four years of follow-up.

CN subjects, as categorized by the ADNI, were healthy individuals matched by age to the MCI group with no significant impairment in cognitive functions or activities of daily living. Inclusion criteria for CN subjects included a mini-mental state examination (MMSE) score of 24–30, a clinical dementia rating sum of boxes (CDR) score of 0, and delayed recall scores from logical memory II (Wechsler memory scale-revised) of $\geq$ 9 for 16 years of education, $\geq$ 5 for 8–15 years of education, and $\geq$ 3 for 0–7 years of education (Petersen et al., 2010). A diagnosis of MCI was made based on having an MMSE score of 24–30, a CDR score of 0.5 with a memory box score of 0.5 or greater, and delayed recall scores from Logical Memory II of $\leq$8 for 16 years of education, $\leq$4 for 8–15 years of education, and $\leq$ 2 for 0–7 years of education. Additionally, individuals must exhibit largely intact general cognition and functional performance and must not qualify for a diagnosis of dementia (Petersen et al., 2010). Lastly, a diagnosis of AD required an MMSE score ranging from 20 to 26. They should have a CDR score of 0.5 or 1, and their memory performance, based on the Logical Memory II subscale, must be below specific cutoff scores: $\leq$8 for 16 years of education, $\leq$4 for 8–15 years of education, and $\leq$2 for 0–7 years of education. Additionally, they must have a diagnosis of mild AD and meet the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD (Petersen et al., 2010).

According to ADNI (https://adni.loni.usc.edu/), exclusion criteria for subjects included the use of antidepressant medications with anticholinergic properties, regular use of narcotic agents exceeding two doses per week within four weeks of screening, and the use of neuroleptic medications or other drugs with anticholinergic properties within four weeks of screening. Additionally, the use of antiparkinsonian medications within four weeks of screening, participation in any other investigational drug studies within four weeks of screening, and the initiation or discontinuation of diuretic drugs within four weeks prior to screening were also grounds for exclusion. For subjects with MCI, cholinesterase inhibitors and memantine were permitted if the dose had been stable for four weeks prior to screening (Petersen et al., 2010). Similarly, estrogen, estrogen-like compounds, and vitamin E were allowed if the dose had been stable for four weeks prior to screening. Participants were required to report any medication changes to the site investigators once enrolled in the study (Petersen et al., 2010).

2.3. Cognitive assessments

The CDR-SB scale, Montreal cognitive assessment (MoCA), MMSE, and the Alzheimer's disease assessment scale (ADAS) were utilized for a comprehensive neuropsychological evaluation.

The CDR is a rating system for patients with senile dementia of AD type, introduced in 1982 with later revisions (Hughes et al., 1982, Berg, 1988). CDR evaluates each participant based on interviewing both the subject and their caregiver (informant), combined with the clinician's professional judgment. It assesses six cognitive and behavioral domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal care. There are two sets of questions: one directed at the informant, covering the subject's memory problems, judgment, community affairs, home life, hobbies, and personal care, and another directed at the subject, focusing on memory, orientation, and judgment and problem-solving abilities The CDR uses a scale from 0 to 3, where 0 indicates no dementia, 0.5 suggests questionable dementia, 1 corresponds to mild cognitive impairment (MCI), 2 indicates moderate cognitive impairment, and 3 represents severe cognitive impairment (Morris et al., 1997). CDR-SB is a summation of each individual score for each category of CDR.

The MoCA was developed in 2005 as a screening tool for mild dementia in the community and academic settings and was more sensitive than MMSE to detect MCI (sensitivity 100 vs. 78 %, specificity 87 vs. 100 %) (Nasreddine et al., 2005). Throughout these years, it has been used worldwide as a recognized cognitive test for the general population. MoCA measures cognitive domains such as visuospatial/executive, naming, orientation, memory and recall, language, abstraction, and attention. The highest possible score is 30, with those with 12 years of education receiving an extra point to account for educational differences. Cut-off scores determine the severity of cognitive impairment: scores 18–25, 10–17, and less than 10 represent mild, moderate, and severe impairment, respectively.

MMSE is 30-item assessment of global cognitive status and is regularly applied for testing dementia, cognitive impairment, and questioning about cognitive areas and assessing them, for instance, memory, attention, orientation, language, and visual construction (Bernard & Goldman, 2010). The orientation tests included graded questions to orientation to time and place and accounted for 10 points. The memory registration asked the subjects to remember three unrelated items, and then the memory recall asked them to repeat the items later. Then, the serial calculation was tested for degree of attention by subtraction 7 from 100 with five repeats. Finally, the language tasks included naming, repeating, following 3-stage orders, reading, writing, and copying design. Its total score ranged from 0 (worst) to 30 (best) points (Folstein et al., 1975).

The ADAS is frequently used in pre-dementia research studies, although it was initially designed for studies on dementia (Kueper et al., 2018). The ADAS was developed to assess cognitive and non-cognitive dysfunction in patients with mild to severe AD. The ADAS takes 45 minutes to administer completely, and the total score on this tool ranges from 0 to 150, with higher scores indicating poorer performance. The ADAS consists of two subscales; however, the non-cognitive subscale (ADAS-Noncog) will not be discussed further because it is employed less frequently (Rosen et al., 1984). Word recall and word recognition account for most of the ADAS-11 scores in pre-dementia populations, and age may affect scores in older adults with CN (Kueper et al., 2018). In addition, the modified 13-item ADAS scale (Mohs et al., 1997) includes all of the original ADAS items, a number cancellation exercise, and a delayed free recall task for a total of 85 points. Higher scores denote greater severity, precisely similar to the original version. According to Mohs et al. (Mohs et al., 1997), these additional items aim to broaden the scope of symptom severity and the number of cognitive domains without significantly increasing the duration of administration (Mohs et al., 1997).

2.4. GAP and NFL measurements

CSF GAP-43 was measured using ELISA technology, employing an in-house ELISA method previously described in detail (Sandelius et al.,

2019). The ELISA was developed by combining the mouse monoclonal GAP-43 antibody NM4 (coating antibody) from Fujirebio, Ghent, Belgium, and a polyclonal GAP-43 antibody (detector antibody) from ABB-135, Nordic Biosite, Täby, Sweden, both of which recognize the C-terminal of GAP-43. Board-certified laboratory technicians conducted the analyses, with values reported in pg/mL. The assay range is 312-20, 000 pg/mL, with a total of 1268 data points collected. Quality control (QC) samples comprised leftover CSF samples from the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, Sweden. During the clinical evaluation study, the repeatability CV% for QC1 and QC2 was 5.5 % versus 11 %, and the inter-assay CV% was 6.9 % versus 15.6 %.

This study also incorporated the axonal NFL protein examination in plasma from ADNI-1 samples. Plasma NFL was measured using the Single Molecule array (Simoa) technique. This assay employs a combination of monoclonal antibodies and purified bovine NFL as a calibrator. All samples were measured in duplicate, except for one due to technical issues. Intra-assay and interassay coefficients of variation were 11.7–12.1 % for QC samples with clinically relevant low and high concentrations (17.9 and 257 pg/mL, respectively) (Mielke et al., 2019). The validated measurement range was 6.7–1,620 pg/mL. The analytical sensitivity of the assay was less than 1.0 pg/mL, and no sample had NFL levels below the limit of detection (LOD). For more detailed information, see https://adni.loni.usc.edu/.

2.5. Polygenic hazard score

The PHS was used to quantify age-specific genetic risk for AD (Desikan et al., 2017). The PHS used in the current study was calculated for each participant as the vector product of that individual's genotype for examining the relationship between genetic predisposition and neurodegenerative processes in cognitive impairment by determining a cut-off value for the PHS. The PHS was calculated for all participants as described in detail by Desikan et al. (2017). Briefly, using genotype data from 17,008 AD cases and 37,154 controls from the International Genomics of Alzheimer's Project (IGAP Stage 1) drawn from four different consortia across North America and Europe (including the United States of America, England, France, Holland, and Iceland), they identified AD-associated SNPs with a significance threshold of $p < 10^{-5}$ (Naj et al., 2021). These SNPs were integrated into a Cox proportional hazard model using genotype data from 6,409 AD patients and 9,386 older controls from Phase 1 of the Alzheimer's Disease Genetics Consortium (ADGC). This approach gave each participant a PHS, allowing estimates of instantaneous risk for developing AD based on genotype and age. To derive these estimates, Desikan et al. combined population-based incidence rates with genotype-derived PHS for each individual and tested replication in multiple independent cohorts, including ADGC Phase 2, National Institute on Aging Alzheimer's Disease Center (NIA ADC), and ADNI, encompassing a total of 20,680 participants (Desikan et al., 2017). Specifically, 31 AD-associated SNPs were selected through a stepwise Cox proportional hazards model, adjusting for baseline allele frequencies with European genotypes from the 1000 Genomes Project. These SNPs include ε2 allele, ε4 allele, and others such as rs4266886 and rs61822977. The method was further validated using an ADGC-independent sample of 692 older controls and participants with MCI or AD from ADNI-1, illustrating the utility of the genotype-derived PHS in estimating cumulative incidence rates for AD development based on genotype and age.

2.6. Statistical analysis

Statistical analyses were conducted using R (version 4.1.2). The Shapiro–Wilk normality test was used to assess normality. Due to deviation from the normal distribution, non-parametric tests were employed for further analysis. Categorical variables were analyzed using the Chi-square test, and continuous variables were evaluated using the Kruskal–Wallis test. Post hoc analyses coupled with the Bonferroni correction for multiple comparisons were performed for continuous variables. The median and interquartile range (IQR) were used to summarize continuous variables. To evaluate the diagnostic accuracy of each biomarker, receiver operating characteristic (ROC) curve analyses were employed to calculate the area under the curve (AUC) with 95 % confidence intervals (CIs). The Youden index was utilized to determine the cut-off point for PHS and the obtained score was applied in the subsequent analyses. Youden index identifies the point on the ROC curve that maximizes the difference between true positive rate (sensitivity) and false positive rate (1-specificity), thus providing an optimal balance between sensitivity and specificity. The threshold corresponding to the maximum Youden Index was selected as the optimal cut-off point through the following formula:

$$J_{max} = \max_{PHS}\{\text{sensitivity(PHS)} - \text{specificity(PHS)} - 1\}.$$

The partial correlation test was employed to examine correlations between baseline CSF GAP-43 or plasma NFL levels and CSF core AD biomarkers (including CSF Aβ42, T-tau, and P-tau) and cognitive tests (including MMSE, CDR-SB, MoCA, ADAS11, and ADAS13). The effect of age, gender, education, and *APOE* ε4 status (carrier or noncarrier) were controlled in all partial correlation tests. For the longitudinal cognitive assessments, a specific approach was implemented to handle missing data. Participants with two or more missing cognitive test scores were excluded from the analysis. For cases with a single missing test score, the missing value was imputed using the mean of the scores from the previous and following years. This method affected only 2.3 % of the data, ensuring that the overall dataset remained robust and reliable. Furthermore, for each longitudinal timepoint, we applied the Mann-Whitney test to compare cognitive scores between the high risk(+) and low risk(-) PHS groups. The p-adjusted value (P_{adj}) calculated using the Bonferroni method was applied to correct for multiple testing and is reported as P_{adj}. Finally, the predictive role of PHS in the MCI to AD conversion was assessed using the Cox proportional hazard model with the Logrank method. Hazard ratios with 95 % CIs were calculated to determine the magnitude of the effect.

2.7. Data and code availability

Data used to prepare this manuscript were obtained from the ADNI database (http://adni.loni.usc.edu) and are freely available after registration. Python and R scripts to analyse the data and to produce the results presented here are available at https://github.com/MEFarhadieh/PHS2AD.

3. Results

3.1. Characteristics of participants

A total of 646 subjects including 93 AD, 350 MCI, and 203 CN were included (Supplementary Figure 1). Table 1a depicts demographics, biomarkers, and cognitive assessments of all participants in each group. Significant age differences among the three groups were detected ($p < 0.001$). PHS showed substantial differences between CN, MCI, and AD ($p < 0.001$). AD biomarkers including CSF T-tau, CSF P-tau, CSF GAP-43, plasma NFL were significantly higher in the AD group compared to MCI and CN groups ($p < 0.001$) and in MCI compared to CN ($P_{adj} < 0.05$), except for GAP-43 and NFL in the MCI group compared to CN. As expected, the CN and MCI groups showed lower level of cognitive impairment than the AD group ($p < 0.001$). Table 1b represents longitudinal four-year follow-up data of selected 190 MCI patients. There were no significant differences in demographics, biomarkers, and cognitive measurements across the four time points.

Table 1a
Demographics, biomarkers, and cognitive assessments across study groups.

Characteristic	CN (n = 203)	MCI (n = 350)	AD (n = 93)	*p* value
Age	73 (68, 78)	71 (66, 77)	74 (69, 79)	0.002 [a,b]
Sex				0.012
Female	112 (55 %)	156 (45 %)	36 (39 %)	
Male	91 (45 %)	194 (55 %)	57 (61 %)	
Education	16 (16, 18)	16 (14, 18)	16 (14, 18)	0.005 [c]
APOE ε4 [T]				<0.001
0	146 (72 %)	178 (51 %)	29 (31 %)	
1	51 (25 %)	134 (38 %)	43 (46 %)	
2	6 (3.0 %)	38 (11 %)	21 (23 %)	
PHS	-0.14 (-0.38, 0.47)	0.27 (-0.24, 1.01)	0.79 (0.11, 1.27)	<0.001 [a,b,c]
CSF Aβ42	1,336 (872, 1,700)	900 (679, 1,371)	624 (490, 787)	<0.001 [a,b,c]
CSF T-tau	216 (179, 300)	248 (187, 330)	354 (276, 451)	<0.001 [a,b,c]
CSF P-tau	20 (16, 27)	23 (17, 33)	34 (27, 46)	<0.001 [a,b,c]
GAP-43	4,387 (3,189, 6,286)	4,387 (3,258, 6,244)	5,864 (4,082, 8,543)	<0.001 [b,c]
Plasma NFL	32 (25, 42)	35 (26, 46)	42 (33, 57)	<0.001 [b,c]
MMSE	29 (29, 30)	28 (27, 29)	23 (21, 25)	<0.001 [a,b,c]
CDR-SB	0.00 (0.00, 0.00)	1.50 (1.00, 2.00)	4.50 (3.50, 5.50)	<0.001 [a,b,c]
ADAS11	6 (3, 7)	9 (6, 12)	19 (16, 24)	<0.001 [a,b,c]
ADAS13	9 (6, 12)	14 (10, 19)	30 (24, 36)	<0.001 [a,b,c]
MoCA	26 (24, 28)	23 (21, 25)	19 (14, 20)	<0.001 [a,b,c]

Measurements were expressed by median (IQR); and number (%).
[a] = significant difference between CN and MCI
[b] = significant difference between MCI and AD
[c] = significant difference between CN and AD.
[T] : Number of alleles are presented for *APOE* ε4.
Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; PHS, polygenic hazard score; CSF, cerebrospinal fluid; Aβ, amyloid-β; T-tau, total tau; P-tau, plasma phosphorylated tau; GAP-43, growth-associated Protein 43; NFL, neurofilament light chain; MMSE, mini-mental state examination; CDR-SB, clinical dementia rating scale sum of boxes; ADAS, Alzheimer's disease assessment scale; MoCA, Montreal cognitive assessment.

3.2. Diagnostic ability of PHS, GAP-43, NFL, and CSF biomarkers

ROC analyses were conducted, and AUCs were calculated to evaluate the diagnostic accuracy of PHS and AD biomarkers. Biomarkers showed high diagnostic accuracy in distinguishing AD from MCI and CN, but limited effectiveness in differentiating between MCI and CN (Table 2 and Fig. 1). PHS also demonstrated a similar performance with relatively high AUCs in the comparisons (AUC > 0.6, p < 0.001). Moreover, based on Youden's method, best cut-off points between CN, MCI, and AD were determined for PHS, and we considered a PHS of 0.21 or higher as high risk and a PHS below this threshold as low risk.

3.3. GAP-43 and NFL levels correlate with AD biomarkers and cognitive assessments in the baseline

Partial correlation was used to assess the correlation of GAP-43 and NFL with other biomarkers and cognitive assessments controlling for potential confounding variables (Table 3). Our analyses demonstrated that CSF T-tau and P-tau were significantly and positively correlated with GAP-43 in all three groups. Additionally, in the CN group, there was also a significant positive correlation between CSF Aβ42 and GAP-43 (P_{adj} values= 0.001).Furthermore, only ADAS11 and ADAS13 in MCI group showed a significant positive correlation with plasma NFL (P_{adj} values < 0.05).

In the next step, the abovementioned correlations were explored in subjects with low risk and high risk PHS in each diagnostic group. As shown in **Supplementary Table 1**, the correlation between GAP-43 with CSF T-tau and CSF P-tau in the six subgroups was significant and positive. Interstingly, in the high risk MCI group, GAP-43 was correlated with cognitive measures, whereas this correlation was not detected in the low risk group. The NFL biomarker showed no statistically significant correlations across these groups. .

3.4. Correlations of baseline GAP-43 and NFL with four-year cognitive tests among the MCI group

A total of 190 MCI subjects were selected for the four-year analyses. According to Table 4, baseline CSF GAP-43 had a significant negative correlation with baseline MMSE (r_s= -0.24, P_{adj} value= 0.003), while a positive correlation with baseline ADAS13 was observed (r_s= 0.22, P_{adj} value= 0.008). During the first and second years of follow-up, GAP-43 exhibited significant correlations with cognitive assessments, except for CDR-SB. In the third and fourth years, however, GAP-43 showed

Table 1b
Demographics, biomarker features, and cognitive assessments of the selected MCI patients during the four-year follow-up.

Characteristic	Baseline (n= 190)	12 months (n= 190)	24 months (n= 190)	36 months (n= 190)	48 months (n= 190)	*p* value
Age	70 (7)	71 (7)	72 (7)	73 (7)	74 (7)	<0.001
Sex						1
Female	85 / 190 (45 %)	85 / 190 (45 %)	85 / 190 (45 %)	85 / 190 (45 %)	85 / 190 (45 %)	
Male	105 / 190 (55 %)	105 / 190 (55 %)	105 / 190 (55 %)	105 / 190 (55 %)	105 / 190 (55 %)	
Education	16 (3)	16 (3)	16 (3)	16 (3)	16 (3)	1
APOE ε4						1
0	96 / 190 (51 %)	96 / 190 (51 %)	96 / 190 (51 %)	96 / 190 (51 %)	96 / 190 (51 %)	
1	72 / 190 (38 %)	72 / 190 (38 %)	72 / 190 (38 %)	72 / 190 (38 %)	72 / 190 (38 %)	
2	22 / 190 (12 %)	22 / 190 (12 %)	22 / 190 (12 %)	22 / 190 (12 %)	22 / 190 (12 %)	
PHS	0.45 (0.80)	0.45 (0.80)	0.45 (0.80)	0.45 (0.80)	0.45 (0.80)	1
MMSE	28 (2)	28 (2)	27 (3)	27 (4)	26 (4)	0.065
CDR-SB	1.40 (0.88)	1.47 (1.22)	1.84 (1.80)	2.22 (2.60)	2.78 (3.62)	0.2
ADAS11	9 (4)	9 (5)	9 (6)	10 (7)	12 (10)	0.2
ADAS13	14 (6)	14 (8)	15 (9)	16 (10)	18 (13)	0.2
MoCA	23 (3)	24 (3)	24 (4)	23 (4)	23 (5)	0.4

Measurement values were expressed by Median (IQR); and number (%).
[T]: Number of alleles are presented for *APOE* ε4.
Abbreviations: MCI, mild cognitive impairment; PHS, polygenic hazard score; CSF, cerebrospinal fluid; Aβ, amyloid-β; T-tau, total tau; P-tau, plasma phosphorylated tau; MMSE, mini-mental state examination; CDR-SB, clinical dementia rating scale sum of boxes; ADAS, Alzheimer's disease assessment scale; MoCA, Montreal cognitive assessment.

Table 2
ROC analyses of biomarkers and PHS.

ROC analysis	Variable	AUC	CI Low	CI Up	*p* value
CN vs AD	PHS	0.747	0.687	0.807	8.73E-12
	GAP-43	0.655	0.586	0.722	1.83E-05
	NFL	0.699	0.639	0.757	3.83E-08
	Aβ42	0.839	0.784	0.890	4.23E-21
	T-tau	0.802	0.749	0.852	7.65E-17
	P-tau	0.827	0.779	0.874	1.70E-19
CN vs MCI	PHS	0.636	0.583	0.680	8.69E-08
	GAP-43	0.507	0.457	0.555	7.73E-01
	NFL	0.547	0.497	0.597	6.52E-02
	Aβ42	0.654	0.608	0.700	1.19E-09
	T-tau	0.567	0.517	0.613	8.12E-03
	P-tau	0.580	0.531	0.627	1.62E-03
MCI vs AD	PHS	0.612	0.549	0.673	9.36E-04
	GAP-43	0.645	0.579	0.705	1.76E-05
	NFL	0.647	0.591	0.705	1.23E-05
	Aβ42	0.736	0.673	0.790	2.25E-12
	T-tau	0.722	0.667	0.773	4.54E-11
	P-tau	0.729	0.677	0.778	1.05E-11
CN vs AD&MCI	PHS	0.612	0.549	0.673	9.36E-04
	GAP-43	0.645	0.579	0.705	1.76E-05
	NFL	0.647	0.591	0.705	1.23E-05
	Aβ42	0.736	0.673	0.790	2.25E-12
	T-tau	0.722	0.667	0.773	4.54E-11
	P-tau	0.729	0.677	0.778	1.05E-11
AD vs CN&MCI	PHS	0.612	0.549	0.673	9.36E-04
	GAP-43	0.645	0.579	0.705	1.76E-05
	NFL	0.647	0.591	0.705	1.23E-05
	Aβ42	0.736	0.673	0.790	2.25E-12
	T-tau	0.722	0.667	0.773	4.54E-11
	P-tau	0.729	0.677	0.778	1.05E-11

Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; ROC, receiver operating characteristic; AUC, area under the curve; CI Low, lower confidence interval 95 %; CI Up, upper confidence interval 95 %; PHS: polygenic hazard score; GAP-43, growth-associated Protein 43; NFL, neurofilament light chain; Aβ, amyloid-β; T-tau, total tau; P-tau, plasma phosphorylated tau.

significant correlationswith all assessments. A similar pattern was also observed for baseline plasma NFL.

Supplementary Table 2 represents the abovementioned analyses in two subgroups of the selected MCI subjects based on PHS status. At each stage, GAP-43 was significantly correlated with cognitive measures in high risk MCI subjects. In contrast, no correlation between GAP-43 and cognitive measures was observed during either time period. However, this pattern did not hold for NFL correlations, as NFL showed significant correlations with cognitive assessments in both high risk and low risk groups.

3.5. Longitudinal cognitive test analysis based on PHS status

To evaluate the impact of PHS on cognitive decline during the follow-up, cognitive assessments were compared between high risk and low risk PHS groups at each time point (**Supplementary Table 3**, Fig. 2). As depicted in Figure 2, ADAS and CDR-SB scores were higher in the high risk group, whereas MMSE and MoCA scores were lower, indicating more pronounced cognitive decline in individuals with high risk PHS.

3.6. Ability of PHS to predict future cognitive impairment

The potential of PHS to predict conversion from MCI to AD was explored by performing the Cox proportional hazard model. The subjects with high risk PHS progressed to dementia more rapidly compared to the low risk group (Hazard ratio= 4.661, $p < 0.001$; Fig. 3).

4. Discussion

We investigated the role of PHS in predicting the associations between markers of neurodegeneration (GAP-43 and NFL) and cognitive decline in patients with MCI or AD. Axonal degeneration results from tau dissociation from microtubules, which can be detected indirectly using the NFL biomarker (Mattsson et al., 2017). Contrary to expectations, this study revealed no correlation between CSF Tau, P-Tau, and NFL. This result confirms recent findings that NFL, at least in the early stages of the disease, is not the most reliable predictor of amyloid and tau deposition (Pereira and al., 2021). While our use of plasma NFL measurements instead of CSF levels could be a contributing factor (Aschenbrenner et al., 2020), future explorations should consider alternative factors. This observation may also be attributed to the NFL or to the fact that these pathologies are distinct, and the early signs of cognitive

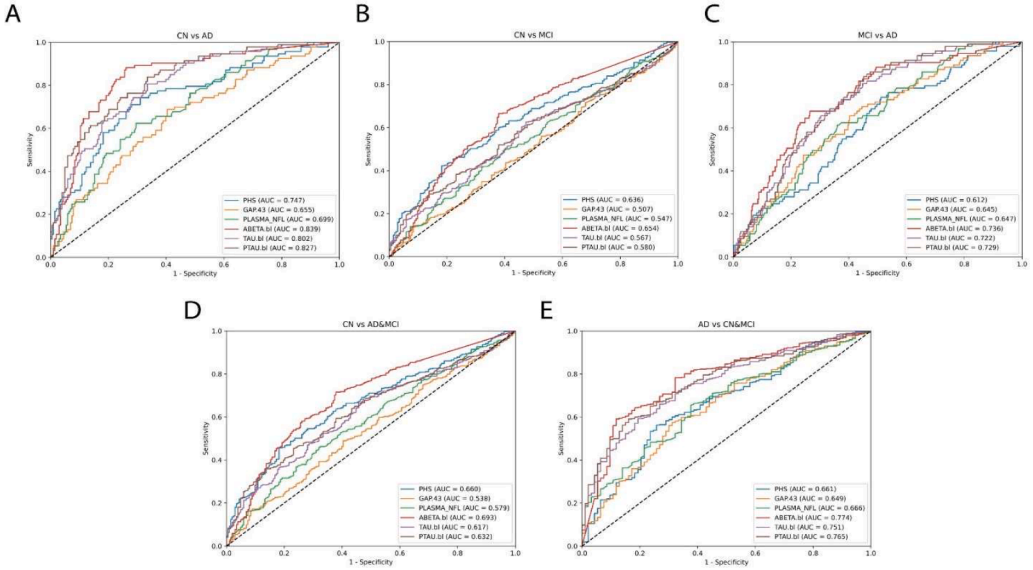

Fig. 1. ROC analyses for the diagnostic accuracy of biomarkers and PHS. (**A**) CN versus AD, (**B**) CN versus MCI, (**C**) MCI versus AD, (**D**) CN versus MCI with AD, and (**E**) AD versus CN with MCI.
Abbreviations: PHS, polygenic hazard score; CN, cognitive normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; ROC, receiver operating characteristic; AUC, area under the curve; GAP-43, growth-associated protein 43; NFL, neurofilament light chain; ABETA, amyloid amyloid-β; P-tau, plasma phosphorylated TAU.

Table 3
Correlations of GAP-43 and NFL levels with other biomarkers and cognitive tests at the baseline.

Variable	CN_r_s	CN_p	CN_p_{adj}	MCI_r_s	MCI_p	MCI_p_{adj}	AD_r_s	AD_p	AD_p_{adj}
GAP-43									
Aβ42	0.283	<0.001	0.002	0.095	0.079	1.000	0.243	0.022	0.651
T-tau	0.763	<0.001	<0.001	0.814	<0.001	<0.001	0.658	<0.001	<0.001
P-tau	0.768	<0.001	<0.001	0.793	<0.001	<0.001	0.630	<0.001	<0.001
NFL	-0.011	0.878	1.000	0.013	0.813	1.000	-0.020	0.851	1.000
MMSE	0.020	0.774	1.000	-0.150	0.005	0.155	0.007	0.951	1.000
CDR-SB	0.018	0.806	1.000	0.062	0.252	1.000	0.017	0.874	1.000
ADAS11	-0.066	0.356	1.000	0.099	0.067	1.000	0.006	0.957	1.000
ADAS13	-0.063	0.378	1.000	0.141	0.009	0.262	-0.031	0.771	1.000
MoCA	0.182	0.010	0.305	-0.103	0.055	1.000	0.029	0.790	1.000
	NFL								
Aβ42	-0.202	0.004	0.125	-0.088	0.101	1.000	0.061	0.570	1.000
T-tau	0.072	0.313	1.000	0.062	0.250	1.000	0.063	0.557	1.000
P-tau	0.077	0.277	1.000	0.055	0.311	1.000	0.027	0.801	1.000
GAP-43	-0.011	0.878	1.000	0.013	0.813	1.000	-0.020	0.851	1.000
MMSE	-0.031	0.666	1.000	-0.095	0.078	1.000	-0.035	0.744	1.000
CDR-SB	0.015	0.836	1.000	0.101	0.060	1.000	0.019	0.863	1.000
ADAS11	0.044	0.537	1.000	0.180	0.001	0.023	0.188	0.078	1.000
ADAS13	0.085	0.233	1.000	0.213	0.000	0.002	0.149	0.162	1.000
ADASQ4	0.024	0.739	1.000	0.208	0.000	0.003	-0.075	0.485	1.000
MoCA	-0.081	0.253	1.000	-0.094	0.082	1.000	-0.009	0.933	1.000

rs= r value of the Spearman partial correlation test.
Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; Aβ, amyloid-β; T-tau, total tau; P-tau, plasma phosphorylated tau; GAP-43, growth-associated protein 43; NFL, neurofilament light chain; MMSE, mini-mental state examination; CDR-SB, clinical dementia rating scale sum of boxes; ADAS, Alzheimer's disease assessment scale; MoCA, Montreal cognitive assessment.

dysfunction detected by the NFL may not be caused by axonal damage (Das et al., 2023). Further investigation into the dynamic relationship of these biomarkers through AD progression could shed light on this matter. On the other hand, we found significant positive correlations between CSF GAP-43 and CSF T-tau, and P-tau in the CN, MCI, and AD groups. The findings are consistent with previous studies, showing tau phosphorylation to be crucial in synaptic dysfunction as measured by GAP-43 (Mattsson et al., 2017). Previous studies have demonstrated that synaptic loss predominates other changes in the progression of AD (Pereira & al., 2021). Therefore, this particular correlation between synaptic loss and tau pathology can be used as a marker for the early diagnosis of AD, since it does not increase in other types of dementia (Aschenbrenner et al., 2020).

Correlations of baseline GAP-43 or NFL levels with cognitive tests were assessed longitudinally. MCI patients with elevated baseline GAP-43 or NFL levels showed more cognitive changes at the four-year follow-up. For instance, GAP-43 and MMSE showed a weak and negative relationship in the MCI group, which is consistent with some studies (Sandelius et al., 2019, Abed et al., 2023), but inconsistent with others (Das et al., 2023, Zhu et al., 2022). This finding can be explained by the fact that GAP-43 in AD patients reaches a fixed level after the disease's early stages and does not change significantly over time (Sandelius et al., 2019). However, further studies are needed to validate such results. These findings suggest that these two biomarkers are important as diagnostic tools and in predicting disease progression. A limitation of this study is the lack of analysis of follow-up biomarker data due to data unavailability. Accordingly, the relationship between baseline biomarker levels and cognitive decline over time was investigated. This study could not establish a causal relationship between elevated GAP-43 or NFL and subsequent cognitive decline. Still, it does suggest that synaptic and axonal degeneration at baseline may play a role in cognitive decline over four years. These findings are supported by previous results indicating that the goal of AD biomarker discovery has shifted from simply confirming clinical diagnosis to identifying individuals at high risk of cognitive decline (Donohue et al., 2017, Fagan et al., 2007, Soldan et al., 2016).

We also investigated the correlation between Plasma NFL and cognitive tests in PHS+ and PHS- participants at different time points. According to previous studies, plasma NFL is a prognostic marker of cognitive decline (Sandelius et al., 2019, Abed et al., 2023, Zhu et al., 2022, Donohue et al., 2017, Fagan et al., 2007). The findings showed significant correlations between Plasma NFL and mental tests, such as MMSE, CDR-SB, ADAS11, ADAS13, ADASQ4, and MoCA, primarily among PHS+ participants, as some were also reported in previous research (Alagaratnam et al., 2021). These results suggest that axonal degeneration, as indicated by elevated Plasma NFL levels, is accompanied by cognitive decline in individuals with a higher polygenic risk of dementia. On the other hand, correlations between Plasma NFL and cognitive tests were less pronounced or non-significant in PHS- individuals, indicating the crucial role of genetic susceptibility. Regarding GAP-43, results also showed significant positive correlations between GAP-43 and various cognitive tests over four years, including ADAS11, ADAS13, ADASQ4, MMSE, and MoCA among PHS+ participants. Consistent with some previous studies, these results suggest that higher levels of synaptic degeneration, as indicated by elevated GAP-43 levels, are linked to long-term cognitive decline and impairment in patients with a higher polygenic risk of dementia (Qiang and al., 2022, Selkoe, 2002, Terry et al., 1991). These correlations, observed at various times, suggest important longitudinal evidence supporting the fact that synaptic degeneration contributes to cognitive decline in this high-risk subgroup. However, In PHS- individuals over four years, no significant correlations were found between GAP-43 and cognitive variables, indicating a less pronounced association between synaptic degeneration (GAP-43) and cognitive decline compared to PHS+ participants. The findings of differential correlations between GAP-43 or Plasma NFL and cognitive tests in PHS+ and PHS- subgroups, highlight the potential role of genetic risk in influencing the relationship between neurodegenerative biomarkers and cognitive decline. In line with the current study, prior research revealed that individuals with a higher PHS exhibited a more pronounced cognitive decline, surpassing the rate of decline observed in individuals with a lower PHS (Tan et al., 2017).

Given the high proportion of missing biomarker data over the four-year period (77.5 % missing data) and the absence of any participant with complete annual biomarker evaluation, longitudinal analysis of biomarkers was not feasible. In contrast, sufficient annual data over the four-year period were available for cognitive tests. Hence, we were not able to fully capture the dynamic changes in biomarkers over time and only used longitudinal cognitive assessments for temporal transitions in

Table 4
Correlations of baseline GAP-43 and NFL levels with cognitive tests in theMCI subgroup during follow-ups.

GAP-43 baseline						
		MMSE	CDR-SB	ADAS11	ADAS13	MoCA
Baseline	r_s	-0.244	0.099	0.144	0.225	-0.165
	p	0.0006	0.169	0.046	0.001	0.022
	p_{adj}	0.003	0.849	0.232	0.008	0.111
Year one (12 months)	r_s	-0.191	0.149	0.280	0.262	-0.222
	p	0.008	0.040	9.11E-05	0.0002	0.002
	p_{adj}	0.040	0.202	0.0004	0.001	0.010
Year two (24 months)	r_s	-0.215	0.162	0.364	0.358	-0.250
	p	0.003	0.025	3.20E-07	6.04E-07	0.0005
	p_{adj}	0.015	0.127	1.60E-06	3.02E-06	0.002
Year three (36 months)	r_s	-0.225	0.211	0.339	0.325	-0.238
	p	0.001	0.003	2.23E-06	6.23E-06	0.001
	p_{adj}	0.009	0.018	1.12E-05	3.12E-05	0.005
Year four (48 months)	r_s	-0.273	0.264	0.261	0.257	-0.299
	p	0.0001	0.0002	0.0003	0.0004	5.43E-05
	p_{adj}	0.0009	0.001	0.001	0.002	0.0002
Plasma NFL Baseline						
		MMSE	CDR-SB	ADAS11	ADAS13	MoCA
Basline	r_s	-0.242	0.063	0.165	0.224	-0.242
	p	0.0007	0.383	0.022	0.001	0.0007
	p_{adj}	0.003	1	0.113	0.009	0.003
Year one (12 months)	r_s	-0.271	0.140	0.225	0.294	-0.203
	p	0.0001	0.055	0.001	3.86E-05	0.004
	p_{adj}	0.0007	0.275	0.008	0.0001	0.024
Year two (24 months)	r_s	-0.214	0.231	0.312	0.329	-0.275
	p	0.003	0.001	1.44E-05	5.00E-06	0.0001
	p_{adj}	0.016	0.006	7.21E-05	2.50E-05	0.0007
Year three (36 months)	r_s	-0.348	0.287	0.376	0.403	-0.342
	p	1.13E-06	6.72E-05	1.26E-07	1.27E-08	2.25E-06
	p_{adj}	5.66E-06	0.0003	6.32E-07	6.33E-08	1.13E-05
Year four (48 months)	r_s	-0.371	0.335	0.339	0.383	-0.381
	p	2.65E-07	3.07E-06	2.90E-06	1.11E-07	1.69E-07
	p_{adj}	1.32E-06	1.53E-05	1.45E-05	5.57E-07	8.43E-07

rs= r value of the Spearman partial correlation test.
Abbreviations: MCI, mild cognitive impairment; GAP-43, Growth-associated Protein 43; NFL, neurofilament light chain; MMSE, mini-mental state examination; CDR-SB, clinical dementia rating scale sum of boxes; ADAS, Alzheimer's disease assessment scale; MoCA, Montreal cognitive assessment.

this study. Having complete longitudinal biomarker data would have provided valuable insights into their relationship with PHS over the time. Moreover, the lack of sufficient data to perform survival analysis for predicting the transition from the control group to AD and MCI was evident. Longer-term studies, extending over 10 years or more, are necessary to provide more accurate information on the predictive performance of the PHS. Similar to most AD research, this study faced significant challenges in achieving ethnically and racially diverse representation in calculating the PHS and in the ADNI cohort. The fact that the selected SNPs were based on the genomic profiles of individuals predominantly of non-Hispanic white and East Asian descent compared to other races may pose challenges in applying the PHS to other ethnic groups. Future research efforts focusing on AD in populations from Africa, South America, and West Asia will be crucial to addressing and potentially mitigating these challenges.

It was observed that PHS strongly predicted clinical progression to AD by analyzing the time to AD diagnosis and the decline in clinical scores. PHS represented as a valuable predictor of cognitive decline in people with MCI, as well as the progression from MCI to AD. Modeling PHS can help determine the best time to start treatment based on individual risk profiles, and it can improve clinical trials by including individuals at a higher risk of developing AD (Motazedi et al., 2022). Previous studies support the use of PHS as a biomarker for predicting the onset age of dementia and AD. Desikan et al. discovered a relationship between PHS and increased volume loss in brain areas associated with AD, as well as a person's polygenic profile influencing the risk of developing AD at a certain age (Desikan et al., 2017). Including PHS in the predictive models improves the accuracy of results by Kauppi et al. regarding estimating the risk of disease progression. This indicates that PHS provides valuable additional information beyond what MRI biomarkers alone can provide (Kauppi et al., 2018). Tan et al. demonstrated that PHS was associated with post-mortem amyloid load, neurofibrillart tangles, Lewy body, and cerebrovascular pathology, validating and indicating their potential utility in identifying individuals at higher risk of developing multi-etiological dementia in addition to APOE (Tan and al., 2019). Despite the effects of APOE ε4, PHS is still valid in MCI and preclinical AD therapeutic trials for identifying biomarker-positive individuals at the highest risk of short-term clinical progression (Tan et al., 2018). Wang et al. examined the decline in verbal memory among people with AD. They represented the first evidence demonstrating the impact of PHS status and APOE ε4 allele on those cognitive measures and interactions with follow-up visits (Wang et al., 2023). Additionally, in AD-susceptible brain regions, including the default mode network (DMN), executive control network (ECN), and visuospatial network, PHS is linked to functional impairments, gray matter atrophy, and amyloid accumulation (Li et al., 2021). In MCI patients, PHS-based stratification using a sensitive combined outcome measure can thus improve trial efficiency, reduce participant burden, and reduce costs. The study's focus on PHS's ability to predict cognitive decline and conversion to AD aligns with recent researches advocating for personalized risk assessment tools to guide early interventions and therapeutic strategies. The identified cut-off points for PHS contribute to the ongoing discourse on defining thresholds for effective risk prediction. The use of monoclonal antibodies (mAbs) in the treatment of AD has shown considerable promise, particularly in targeting and reducing amyloid-beta plaques, which are a key pathological feature of AD (Leggins et al., 2023). Despite this, several significant limitations and challenges persist with these therapies. Monoclonal antibodies such as aducanumab, donanemab, and lecanemab have demonstrated efficacy in reducing amyloid plaques; however, translating these reductions into meaningful clinical benefits, such as cognitive improvement, has been inconsistent and generally modest (Heidebrink & Paulson, 2024, Söderberg et al., 2023). Additionally, mAb treatments are associated with adverse side effects, high costs, accessibility issues, uncertain long-term outcomes, and variability in patient responses depending on genetic factors and the stage of the disease. In this context, PHS calculations become particularly valuable. By assessing the genetic risk of patients, clinicians can personalize monitoring strategies, ensuring that individuals at higher genetic risk are closely observed for any changes in cognitive function or biomarker levels during treatment. Utilizing PHS in clinical trials can enhance the selection of participants who are more likely to benefit from the therapy, thereby improving the overall efficiency and effectiveness of the trials. It also aids in stratifying patients based on their genetic risk, allowing for more precise analysis of treatment outcomes (Zhou et al., 2021). Furthermore, the integration of PHS and lifestyle modifications represents a promising approach to the prevention of AD, especially for those with a genetic predisposition. This strategy parallels the management of other multifactorial diseases, such as type 2 diabetes and cardiovascular diseases, where genetic risk is mitigated through lifestyle interventions. By identifying individuals at genetic risk and implementing targeted lifestyle changes, it is possible to mitigate the risk and potentially delay or prevent the onset of AD (Kivipelto et al., 2018, Lourida et al., 2019).

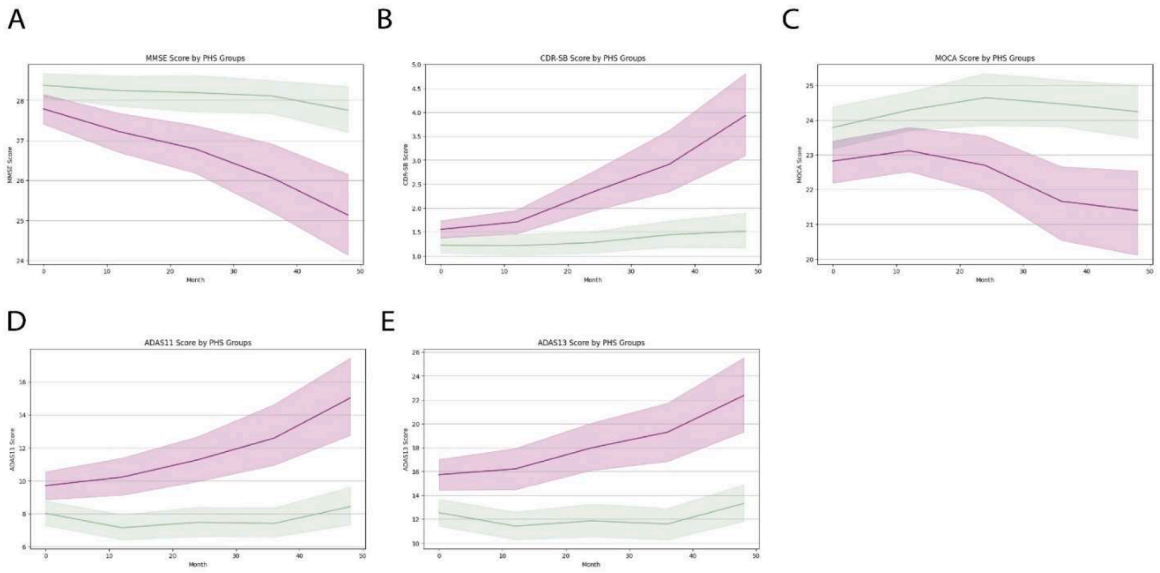

Fig. 2. Cognitive decline in patients with MCI over 48-month follow-up based on (**A**) MMSE, (**B**) CDR-SB, (**C**) MoCA, (**D**) ADAS11, and (**E**) ADAS13. Green indicates the low risk PHS group and purple indicates the high risk PHS group. The 95 % confidence are also demonstrated (shaded with corresponding colors).
Abbreviations: PHS, polygenic hazard score; MCI, mild cognitive impairment; MMSE, mini-mental state examination; CDR-SB,cClinical dementia rating scale sum of boxes; MoCA, Montreal cognitive assessment; ADAS, Alzheimer's disease assessment scale.

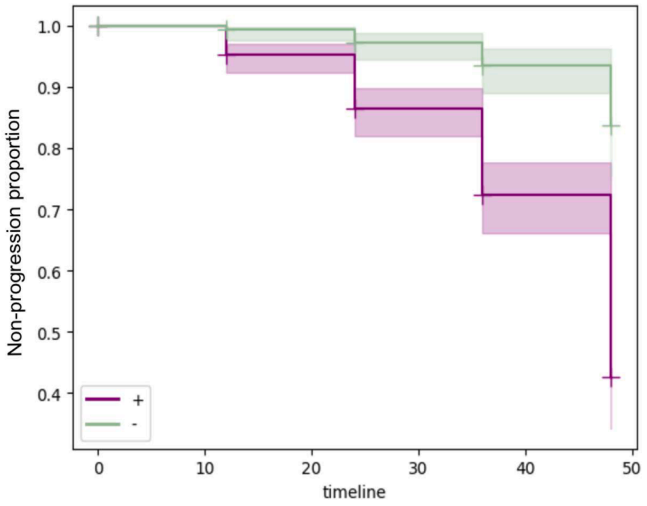

Fig. 3. PHS as a predictor of conversion from MCI to AD. PHS was analyzed as categorical variables in the Cox proportional hazard model. The 95 % confidence intervals of Kaplan–Meier curve is also demonstrated (shaded with corresponding colors).
Abbreviations: PHS, polygenic hazard score; MCI, mild cognitive impairment; AD, Alzheimer's disease.

Continued research and personalized intervention strategies will be essential in maximizing the benefits of this approach. The focus of future research should be the validation of these observed correlations between GAP-43, NFL, and cognitive decline in larger populations while accounting for follow-up periods. A valuable topic of investigation could also include the exact process that causes cognitive decline due to biomarker levels, which can be explored through interventional studies. Finally, considering PHS as a robust genetic prediction aid, exploring the potential of combining established biomarkers of cognitive decline with GAP-43 and NFL measurements could be a starting point for a powerful personalized tool for the early detection of AD.

5. Conclusion

Our results showed how differences in the overall adjusted genetic susceptibility to AD can account for part of the differences in the predictive potential of synaptic and axonal degeneration for cognitive decline in individuals in the AD dementia continuum. Considering genetic predispositions can improve the prediction of cognitive outcome and AD progression, which could ultimately result in earlier identification and treatment planning for AD. Further studies are warranted to specify the influence of genetic susceptibility on the neurodegerative biomarkers and cognitive decline.

Data availability

The data supporting the findings of this study are openly available in ADNI at https://adni.loni.usc.edu/.

CRediT authorship contribution statement

Mohammad-Erfan Farhadieh: Writing – original draft, Formal analysis, Data curation. **Mehrdad Mozafar:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Saameh Sanaaee:** Writing – original draft. **Parastoo Sodeifi:** Writing – original draft. **Kiana Kousha:** Writing – original draft. **Yeganeh Zare:** Writing – original draft. **Shahab Zare:** Writing – original draft. **Nooshin Maleki Rad:** Writing – original draft. **Faezeh Jamshidi-Goharrizi:** Writing – original draft. **Mohammad Allahverdloo:** Writing – original draft. **Arman Rahimi:** Writing – original draft. **Mohammad Sadeghi:** Supervision. **Mahan Shafie:** Supervision, Writing – review & editing. **Mahsa Mayeli:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

Authors have no competing interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2024.105576.

References

Abed, S. S., et al. (2023). Plasma tau and neurofilament light chain as biomarkers of Alzheimer's disease and their relation to cognitive functions. *Journal of Medicine and Life, 16*(2), 284–289.

Alagaratnam, J., et al. (2021). Correlation between CSF and blood neurofilament light chain protein: a systematic review and meta-analysis. *BMJ Neurology Open, 3*(1), Article e000143.

Altmann, A., et al. (2020). A comprehensive analysis of methods for assessing polygenic burden on Alzheimer's disease pathology and risk beyond APOE. *Brain Communications, 2*(1), fcz047.

Aschenbrenner, A. J., et al. (2020). Neurofilament light predicts decline in attention but not episodic memory in preclinical Alzheimer's disease. *Journal of Alzheimer's Disease : JAD, 74*(4), 1119–1129.

Berg, L. (1988). Clinical Dementia Rating (CDR). *Psychopharmacology Bulletin, 24*(4), 637–639.

Bernard, B. A., & Goldman, J. G. (2010). MMSE - Mini-Mental State ExaminationK. Kompoliti, & L. V. Metman (Eds.), MMSE - Mini-Mental State Examination. *Encyclopedia of Movement Disorders*, 187–189. Editors.

Citron, M., et al. (1994). Excessive production of amyloid beta-protein by peripheral cells of symptomatic and presymptomatic patients carrying the Swedish familial Alzheimer disease mutation. *Proceedings of the National Academy of Sciences U S A,, 91*(25), 11993–11997.

Das, S., et al. (2023). Synaptic biomarkers in the cerebrospinal fluid associate differentially with classical neuronal biomarkers in patients with Alzheimer's disease and frontotemporal dementia. *Alzheimer's Research & Therapy, 15*(1), 62.

Desikan, R. S., et al. (2017). Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. *PLoS Medicine, 14*(3), Article e1002258.

Donohue, M. C., et al. (2017). Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA, 317*(22), 2305–2316.

Fagan, A. M., et al. (2007). Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Archives of Neurology, 64*(3), 343–349.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189–198.

Friedrich, R. P., et al. (2010). Mechanism of amyloid plaque formation suggests an intracellular basis of Abeta pathogenicity. *Proceedings of the National Academy of Sciences U S A,, 107*(5), 1942–1947.

Gaetani, L., et al. (2019). Neurofilament light chain as a biomarker in neurological disorders. *Journal of Neurology, Neurosurgery, and Psychiatry, 90*(8), 870–881.

Hansson, O., et al. (2017). Blood-based NfL: A biomarker for differential diagnosis of parkinsonian disorder. *Neurology, 88*(10), 930–937.

Heidebrink, J. L., & Paulson, H. L. (2024). Lessons learned from approval of Aducanumab for Alzheimer's Disease. *Annual Review of Medicine, 75*(1), 99–111.

Hughes, C. P., et al. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry : The Journal of Mental Science, 140*, 566–572.

Hulo, S., et al. (2002). A point mutant of GAP-43 induces enhanced short-term and long-term hippocampal plasticity. *The European Journal of Neuroscience, 15*(12), 1976–1982.

Jack, C. R., Jr., et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association, 14*(4), 535–562.

Janelidze, S., et al. (2016). Plasma β-amyloid in Alzheimer's disease and vascular disease. *Scientific Reports, 6*, 26801.

Kauppi, K., et al. (2018). Combining polygenic hazard score with volumetric MRI and cognitive measures improves prediction of progression from mild cognitive impairment to Alzheimer's disease. *Frontiers in Neuroscience, 12*, 260.

Kivipelto, M., Mangialasche, F., & Ngandu, T. (2018). Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nature Reviews Neurology, 14*(11), 653–666.

Kueper, J. K., Speechley, M., & Montero-Odasso, M. (2018). The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and responsiveness in pre-dementia populations. A narrative review. *Journal of Alzheimer's disease : JAD, 63*(2), 423–444.

Kuhle, J., et al. (2019). Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. *Neurology, 92*(10), e1007–e1015.

Leggins, B., et al. (2023). Perceptions about dementia clinical trials. *Alzheimer's & Dementia, 19*, Article e074906.

Li, K., et al. (2021). Polygenic hazard score associated multimodal brain networks along the Alzheimer's disease continuum. *Frontiers in Aging Neuroscience, 13*, Article 725246.

Lourida, I., et al. (2019). Association of lifestyle and genetic risk with incidence of dementia. *JAMA, 322*(5), 430–437.

Mattsson, N., et al. (2017). Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. *JAMA Neurology, 74*(5), 557–566.

McGrowder, D. A., et al. (2021). Cerebrospinal fluid biomarkers of Alzheimer's disease: Current evidence and future perspectives. *Brain Sciences, 11*(2).

Mielke, M. M., et al. (2019). Plasma and CSF neurofilament light: Relation to longitudinal neuroimaging and cognitive measures. *Neurology, 93*(3), e252–e260.

Milà-Alomà, M., et al. (2020). Amyloid beta, tau, synaptic, neurodegeneration, and glial biomarkers in the preclinical stage of the Alzheimer's continuum. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 16*(10), 1358–1371.

Mohs, R. C., et al. (1997). Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Disease and Associated Disorders, 11*(Suppl 2), S13–S21.

Morris, J. C., et al. (1997). Clinical dementia rating training and reliability in multicenter studies: the Alzheimer's Disease Cooperative Study experience. *Neurology, 48*(6), 1508–1510.

Motazedi, E., et al. (2022). Using polygenic hazard scores to predict age at onset of Alzheimer's disease in nordic populations. *Journal of Alzheimer's Disease : JAD, 88*(4), 1533–1544.

Naj, A.C., et al., *Genome-wide meta-analysis of late-onset Alzheimer's disease using rare variant imputation in 65,602 Subjects identifies novel rare variant locus NCK2: The international genomics of Alzheimer's project (IGAP).* medRxiv, 2021: p. 2021.03.14.21253553.

Nasreddine, Z. S., et al. (2005). The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695–699.

Öhman, F., et al. (2021). Current advances in digital cognitive assessment for preclinical Alzheimer's disease. *Alzheimer's & Dementia (Amsterdam, Netherlands), 13*(1), e12217.

Olsson, B., et al. (2016). CSF and blood biomarkers for the diagnosis of Alzheimer's disease: A systematic review and meta-analysis. *The Lancet Neurology, 15*(7), 673–684.

Olsson, B., et al. (2019). Association of cerebrospinal fluid neurofilament light protein levels with cognition in patients with dementia, motor neuron disease, and movement disorders. *JAMA Neurology, 76*(3), 318–325.

Pereira, J. B., et al. (2021). Untangling the association of amyloid-β and tau with synaptic and axonal loss in Alzheimer's disease. *Brain : A Journal of Neurology, 144*(1), 310–324.

Petersen, R. C., et al. (2010). Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. *Neurology, 74*(3), 201–209.

Planche, V., et al. (2023). Validity and performance of blood biomarkers for Alzheimer disease to predict dementia risk in a large clinic-based cohort. *Neurology, 100*(5), e473–e484.

Portelius, E., et al. (2015). Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. *Brain: A Journal of Neurology, 138*(Pt 11), 3373–3385.
Qiang, Q., et al. (2022). CSF GAP-43 as a biomarker of synaptic dysfunction is associated with tau pathology in Alzheimer's disease. *Scientific Reports, 12*(1), 17392.
Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. *The American Journal of Psychiatry, 141*(11), 1356–1364.
Salvadores, N., Gerónimo-Olvera, C., & Court, F. A. (2020). Axonal degeneration in AD: The contribution of Aβ and Tau. *Frontiers in Aging Neuroscience, 12*, Article 581767.
Sandelius, Å., et al. (2019). Elevated CSF GAP-43 is Alzheimer's disease specific and associated with tau and amyloid pathology. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association, 15*(1), 55–64.
Selkoe, D. J. (2002). Alzheimer's disease is a synaptic failure. *Science (New York, N.Y.), 298*(5594), 789–791.
Skene, J. H., et al. (1986). A protein induced during nerve growth (GAP-43) is a major component of growth-cone membranes. *Science (New York, N.Y.), 233*(4765), 783–786.
Söderberg, L., et al. (2023). Lecanemab, aducanumab, and gantenerumab—binding profiles to different forms of amyloid-beta might explain efficacy and side effects in clinical trials for Alzheimer's disease. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics, 20*(1), 195–206.
Soldan, A., et al. (2016). Hypothetical preclinical Alzheimer disease groups and longitudinal cognitive change. *JAMA Neurology, 73*(6), 698–705.
Tan, C. H., et al. (2017). Polygenic hazard scores in preclinical Alzheimer disease. *Annals of Neurology, 82*(3), 484–488.
Tan, C. H., et al. (2018). Polygenic hazard score: An enrichment marker for Alzheimer's associated amyloid and tau deposition. *Acta Neuropathologica, 135*(1), 85–93.
Tan, C. H., et al. (2019). Polygenic hazard score, amyloid deposition and Alzheimer's neurodegeneration. *Brain : A Journal of Neurology, 142*(2), 460–470.
Terry, R. D., et al. (1991). Physical basis of cognitive alterations in Alzheimer's disease: Synapse loss is the major correlate of cognitive impairment. *Annals of Neurology, 30*(4), 572–580.
Vacher, M., et al. (2022). Assessment of a polygenic hazard score for the onset of pre-clinical Alzheimer's disease. *BMC Genomics, 23*(1), 401.
Wang, K., et al. (2023). Linear mixed model analysis of polygenic hazard score on verbal memory decline in Alzheimer's disease. *Nursing Research, 72*(1), 66–73.
Zhang, H., et al. (2018). Cerebrospinal fluid synaptosomal-associated protein 25 is a key player in synaptic degeneration in mild cognitive impairment and Alzheimer's disease. *Alzheimer's Research & Therapy, 10*(1), 80.
Zhou, X., et al. (2021). Polygenic score models for Alzheimer's disease: from research to clinical applications. *Frontiers in Neuroscience, 15*, Article 650220.
Zhu, Y., et al. (2022). Association of CSF GAP-43 and APOE ε4 with cognition in mild cognitive impairment and Alzheimer's disease. *Cells, 12*(1).