Polygenic hazard scores in preclinical Alzheimer's disease

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ABSTRACT

Identifying asymptomatic older individuals at elevated risk for developing Alzheimer's disease (AD) is of clinical importance. Among 1,081 asymptomatic older adults, a recently validated polygenic hazard score (PHS) significantly predicted time to AD dementia and steeper longitudinal cognitive decline, even after controlling for *APOE* ε4 carrier status. Older individuals in the highest PHS percentiles showed the highest AD incidence rates. PHS predicted longitudinal clinical decline among older individuals with moderate to high CERAD (amyloid) and Braak (tau) scores at autopsy, even among *APOE* ε4 non-carriers. Beyond *APOE*, PHS may help identify asymptomatic individuals at highest risk for developing Alzheimer's neurodegeneration.

INTRODUCTION

There is increasing consensus that the pathobiological changes associated with late-onset Alzheimer's disease (AD) begin years if not decades before the onset of dementia symptoms.[1,2] Identification of cognitively asymptomatic older adults at elevated risk for AD dementia (i.e. those with preclinical AD) would aid in evaluation of new AD therapies.[2] Genetic information, such as presence of the ε4 allele of *apolipoprotein E* (*APOE*) can help identify individuals who are at higher risk for AD dementia.[3] Longitudinal studies have found that *APOE* ε4 status predicts decline to mild cognitive impairment (MCI) and dementia[4], and steeper cognitive decline in cognitively normal individuals[5].

Beyond *APOE* ε4 carrier status, recent genetic studies have identified numerous single nucleotide polymorphisms (SNPs), each of which is associated with a small increase in AD dementia risk.[6] Using genome-wide association (GWAS) from AD cases and controls, we have recently developed a novel 'polygenic hazard score' (PHS) for predicting age-specific risk for AD dementia that integrates 31 AD-associated SNPs (including *APOE* ε4) with US-population based AD dementia incidence rates.[7] To further evaluate the usefulness of the PHS, in this study, we prospectively evaluated whether PHS predicts rate of progression to AD dementia and cognitive decline in cognitively asymptomatic older adults and individuals with MCI.

METHODS

We evaluated longitudinal clinical and neuropsychological data (from March 2016) from the National Alzheimer's Coordinating Center (NACC).[8] Using the NACC uniform dataset, we focused on older individuals classified at baseline as cognitively normal (CN), with a Clinical Dementia Rating[9] (CDR) of 0 and available genetic information (n =1,081, Table 1). We also

evaluated older individuals classified at baseline as MCI (CDR = 0.5) with available genetic information (n = 571, Table 1). We focused on CN and MCI individuals with age of AD dementia onset < age 88 to avoid violations of Cox proportional hazards assumption as evaluated using scaled Schoenfeld residuals (total n = 1,652).

We first investigated the effects of the PHS on progression to AD dementia by using a Cox proportional hazards model, with time to event indicated by age of AD dementia onset. We resolved 'ties' using the Breslow method. We co-varied for effects of sex, *APOE* ε4 status (binarized as having at least 1 ε4 allele versus none), education and age at baseline. To prevent violating the proportional hazards assumptions, we additionally stratified baseline age by quintiles.[10]

Next, we employed a linear mixed-effects (LME) model to evaluate the relationship between PHS and longitudinal clinical decline as assessed by change in CDR-Sum of Boxes (CDR-SB) as well as by change in Logical Memory test (LMT), Wechsler Adult Intelligence Scale - Revised (WAIS-R) Digit Symbol, the Boston Naming Test (BNT), Trail-Making Tests A and B (TMTA/B), forward and backward Digit Span (f/b DST) tests. To maintain consistent directionality across all tests, we inverted the scale for Trail-Making tests such that lower scores represent decline. We co-varied for sex, *APOE* ε4 status, education, baseline age and all their respective interactions with time. We examined the main effect of PHS by comparing slopes of cognitive decline over time in the neuropsychological tests for individuals with high (~84 percentile) and low PHS (~16 percentile), defined by 1 standard deviation above or below the mean of PHS respectively.[11] We also compared goodness of fit between the LME models with and without PHS using likelihood ratio tests.

Finally, we evaluated the relationship between PHS, *APOE* and neuropathology in preclinical AD. Specifically, we conducted LME analysis assessing longitudinal change in CDR-SB in CN individuals with available neuropathology (specifically, neuritic plaque scores based on the Consortium to Establish a Registry for AD (CERAD) and neurofibrillary tangle scores assessed with Braak stages).

RESULTS

PHS significantly predicted risk of progression from CN to AD dementia (hazard ratio (HR) = 2.36, 95% confidence interval (CI) = 1.38 – 4.03, $p = 1.66\times10^{-3}$) illustrating that polygenic information beyond *APOE* ε4 can identify asymptomatic older individuals at greatest risk for developing AD dementia. Individuals in the highest PHS decile had the highest annualized AD incidence rates (Figure 1). PHS also significantly influenced risk of progression to AD dementia in MCI individuals (HR = 1.17, 95% CI = 1.02 – 1.35, $p = 2.36\times10^{-2}$). Using the combined CN and MCI cohorts (total n = 1,652) to maximize statistical power, we found that PHS significantly predicted risk of progression from CN and MCI to AD dementia (HR = 1.31, 95% CI = 1.14 – 1.51, $p = 1.82\times10^{-4}$) (Supplemental Figure 1). At 50% risk for progressing to AD dementia, the expected age for developing AD dementia is approximately 85 years for an individual with low PHS (~16 percentile); however, for an individual with high PHS (~84 percentile), the expected age of onset is approximately 78 years (Supplemental Figure 1). In all Cox models, the proportional hazard assumption was valid for all covariates.

Evaluating clinical progression and cognitive decline within the CN individuals, we found significant PHS by time interactions for CDR-SB (ß = 0.05, standard error (SE) = 0.02, p = 3.64×10^{-4}), WAIS-R (ß = -0.61, SE = 0.30, p = 4.25×10^{-2}), TMTB (ß = -2.48, SE = 0.99, p = 1.20×10^{-2}), and fDST test (ß = -0.93, SE = 0.45, p = 3.76×10^{-2}) (Supplemental Table 1), with

significantly steeper slopes for high PHS individuals for WAIS-R, TMTB, and CDR-SB (Supplemental Table 2, Figure 2). Evaluating average percentage change across all neuropsychological tests, we found that PHS predicted cognitive decline (ß = 0.84, SE = 0.30, $p = 4.50\times10^{-3}$), with high PHS individuals showing greater rates of decline (ß = -1.80, SE = 0.89, $p = 4.30\times10^{-2}$) compared to low PHS individuals (ß = -0.12, SE = 0.80, $p = 0.88$). Goodness of fit comparison using likelihood ratio tests showed that the full LME model comprising PHS and covariates resulted in a better model fit for predicting decline in CDR-SB, BNT, WAIS-R, fDST and TMTB (Supplemental Table 3). We found similar results within the MCI individuals and the combined CN and MCI cohort (Supplemental Tables 1-7, Supplemental Figure 2) illustrating that polygenic information beyond *APOE* ε4 can identify asymptomatic and mildly symptomatic individuals at highest risk for clinical and cognitive decline.

Finally, among CN individuals with moderate and frequent CERAD "C" score at autopsy, we found that PHS predicted change in CDR-SB over time (ß = 1.25, SE = 0.28, $p = 6.63\times10^{-6}$), with high PHS individuals showing a greater rate of increase (ß = 5.62, SE = 0.92, $p = 1.23\times10^{-9}$). In a reduced model without PHS, *APOE* ε4 status did not predict change in CDR-SB (ß = 0.26, SE = 0.50, $p = 0.61$). Furthermore, even in *APOE* ε4 non-carriers, PHS predicted change in CDR-SB over time (ß = 2.11, SE = 0.38, $p = 3.06\times10^{-8}$), with high PHS individuals showing a greater rate of increase (ß = 6.11, SE = 1.08, $p = 1.60\times10^{-8}$). Similarly, among CN individuals with Braak stage III – IV at autopsy, PHS predicted change in CDR-SB over time (ß = 0.93, SE = 0.24, $p = 1.11\times10^{-4}$), with high PHS individuals showing a greater rate of increase (ß = 3.98, SE = 0.79, $p = 4.45\times10^{-7}$).

DISCUSSION

Here, we show that PHS predicts time to progress to AD dementia and longitudinal cognitive decline in both preclinical AD and MCI. Among CN individuals with moderate to high CERAD and Braak scores at autopsy, we found that PHS predicted longitudinal clinical decline, even among *APOE* ε4 non-carriers. Beyond *APOE*, our findings indicate that PHS can be useful to identify asymptomatic older individuals at greatest risk for developing AD neurodegeneration.

These results illustrate the value of leveraging the polygenic architecture of the Alzheimer's disease process. Building on prior work[4,5], our findings indicate that polygenic information may be more informative than *APOE* for predicting clinical and cognitive progression in preclinical AD. Although prior studies have used polygenic risk scores in preclinical AD,[12-14] by focusing on maximizing differences between 'cases' and 'controls', this approach is clinically suboptimal for assessing an age dependent process like AD dementia where a subset of 'controls' will develop dementia over time (see Figure 1). Furthermore, given the bias for selecting diseased cases and normal controls, baseline hazard/risk estimates derived from GWAS samples cannot be applied to older individuals from the general population.[15] By employing an age-dependent, survival analysis framework and integrating AD-associated SNPs with established population-based incidence rates[16] PHS provides an accurate estimate of age of onset risk in preclinical AD.

In our neuropathology analyses, PHS predicted longitudinal clinical decline in older individuals with moderate to high amyloid or tau pathology indicating that PHS may serve as an enrichment strategy for secondary prevention trials. Congruent with recent findings that the risk of dementia among *APOE* ε4/4 is lower than previously estimated[17], among CNs with moderate to high amyloid load, we found that *APOE* did not predict clinical decline and PHS predicted change in CDR-SB even among *APOE* ε4 non-carriers. Our combined findings suggest that

beyond *APOE*, PHS may prove useful both as a risk stratification and enrichment marker to identify asymptomatic individuals most likely to develop Alzheimer's neurodegeneration.

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Conflicts of Interest Disclosures: JBB served on advisory boards for Elan, Bristol-Myers Squibb, Avanir, Novartis, Genentech, and Eli Lilly and holds stock options in CorTechs Labs, Inc. and Human Longevity, Inc. LKM holds stock in CorTechs Labs, Inc . AMD is a founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is also a member of the Scientific Advisory Board of Human Longevity, Inc. (HLI), and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

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Table 1. Cohort demographics

	CN (*n* = 1,081)	MCI (*n* = 571)
Age ± SD	71·19 (6·65)	74·70 (5·85)
Education ± SD	16·07 (2·57)	15·70 (2·91)
Sex (% Female)	719 (66·51)	291 (50·96)
APOE ε4 carriers (%)	297 (27·47)	347 (60·77)
Converted to AD dementia (%)	38 (3·52)	390 (68·30)
Baseline MMSE ± SD	29·22 (1·05)	25.67 (3·36)

MMSE: Mini–Mental State Examination

FIGURE LEGENDS

Figure 1. Annualized or cumulative incidence rates in CN individuals showing the instantaneous hazard as a function of PHS percentiles and age.

Figure 2. Differences in change over time in CDR-SB in CN individuals over time for low (-1 SD, ~16 percentile) and high (+1 SD, ~84 percentile) polygenic hazard score (PHS) individuals. Dotted lines around fitted line indicate estimated standard error.

Figure 1

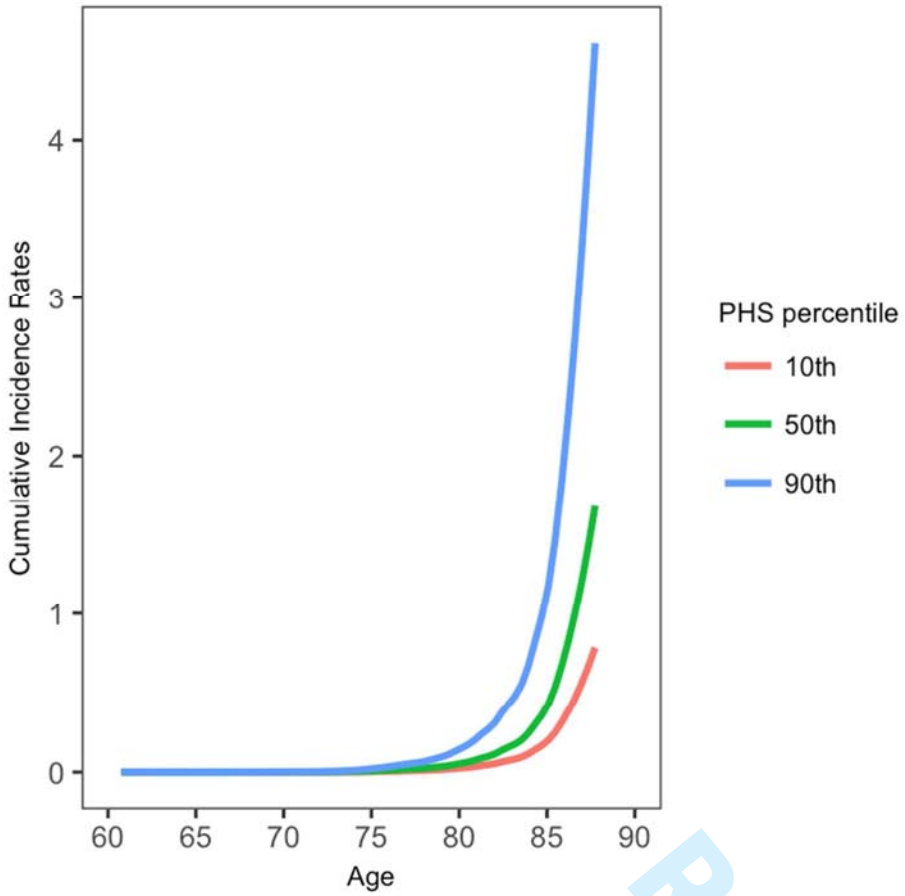
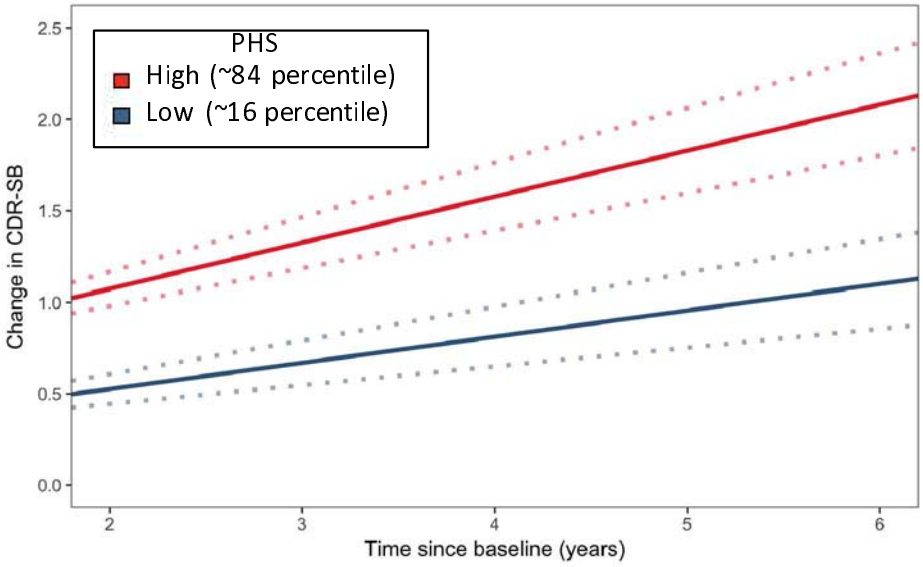


Figure 2

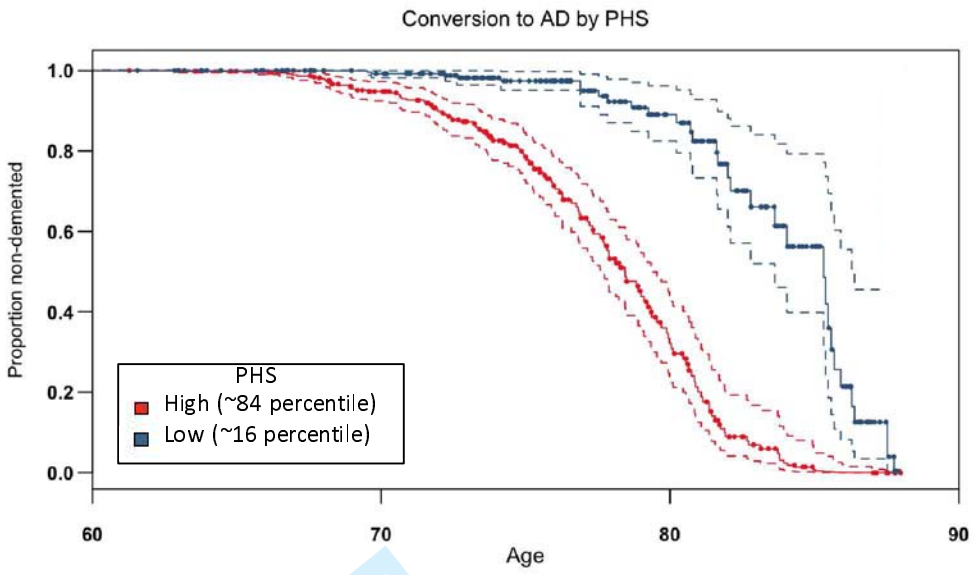


SUPPLEMENTAL FIGURE LEGENDS

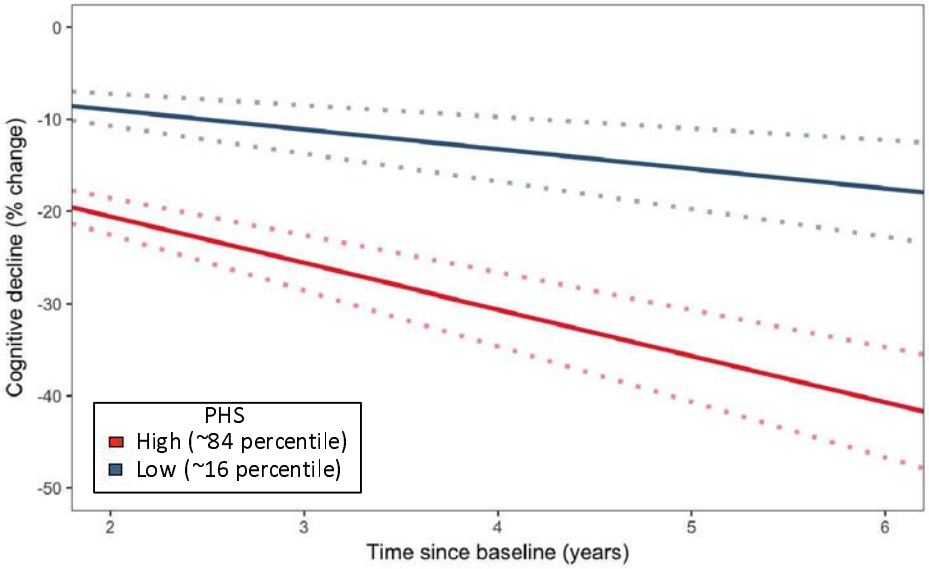
Supplemental Figure 1. Survivor plot showing progression to AD dementia for low (-1 SD, ~16 percentile) and high (+1 SD, ~84 percentile) polygenic hazard score (PHS) individuals who were CN and MCI at baseline. Dotted lines represent 95% confidence intervals.

Supplemental Figure 2. Differences in percentage change in cognitive performance in the combined CN + MCI cohort (average over all neuropsychological tests) over time for low (-1 SD, ~16 percentile) and high (+1 SD, ~84 percentile) polygenic hazard score (PHS) individuals. Dotted lines around fitted line indicate estimated standard errors.

Supplemental Figure 1



Supplemental Figure 2



Supplemental Table 1. Effects of polygenic hazard score (PHS) on longitudinal cognitive decline in CN and MCI individuals separately.

	PHS*Time (**CN**)			PHS*Time (**MCI**)		
	ß (SE)	*p*-value	*n*	ß (SE)	*p*-value	*n*
Logical Memory	0·01 (0·6)	0·99	780	-2·12 (1·73)	0.22	444
WAIS-R Digit Symbol	**-0·61 (0·30)**	**$4{\cdot}25\times10^{-2}$**	700	**-2·44 (0·88)**	**$5{\cdot}69\times10^{-3}$**	443
Boston Naming Test	-0·31 (0·17)	0.07	765	-0·85 (0·62)	0·17	474
Trail-Making Test A	-0·88 (0·73)	0.23	778	-5·08 (2·69)	0.06	477
Trail-Making Test B	**-2·48 (0·99)**	**$1{\cdot}20\times10^{-2}$**	770	**-6·50 (2·78)**	**$1{\cdot}91\times10^{-2}$**	442
Digit Span (forward)	**-0·93 (0·45)**	**$3{\cdot}76\times10^{-2}$**	780	-0·66 (0·75)	0·38	478
Digit Span (backward)	-0·22 (0·59)	0.70	781	0·10 (1·05)	0·92	477
CDR-SB	**0·05 (0·02)**	**$3{\cdot}64\times10^{-4}$**	1081	**0·27 (0·07)**	**$8{\cdot}28\times10^{-5}$**	571

WAIS-R: Wechsler Adult Intelligence Scale Revised. CDR-SB: Clinical Dementia Rating Sum of Boxes. Significant interactions are in bold.

Supplemental Table 2. Differences in rates of cognitive decline for low and high polygenic hazard score (PHS) in CN individuals.

	Low PHS (~16 percentile)		High PHS (~84 percentile)	
	ß (SE)	*p*-value	ß (SE)	*p*-value
Logical Memory	1·97 (1·61)	0·22	1·99 (1·82)	0·27
WAIS-R Digit Symbol	**-2·08 (0·82)**	**$1{\cdot}08\times10^{-2}$**	**-3·30 (0·90)**	**$2{\cdot}66\times10^{-4}$**
Boston Naming Test	-0·18 (0·46)	0·69	-0·81 (0·51)	0·11
Trail-Making Test A	-2·19 (1·95)	0·26	-3·96 (2·19)	0·07
Trail-Making Test B	-0·85 (2·62)	0·75	**-5·81 (2·96)**	**$4{\cdot}94\times10^{-2}$**
Digit Span (forward)	0·03 (1·19)	0·98	-1·82 (1·33)	0·17
Digit Span (backward)	-1·13 (1·57)	0·47	-1·58 (1·77)	0·37
CDR-CB	**0·14 (0·04)**	**$4{\cdot}28\times10^{-4}$**	**0·25 (0·05)**	**$<6{\cdot}03\times10^{-8}$**

WAIS-R: Wechsler Adult Intelligence Scale Revised. CDR-SB: Clinical Dementia Rating Sum of Boxes. Significant interactions are in bold.

Supplemental Table 3. Goodness of fit improvements for linear mixed-effects models with the addition of polygenic hazard score (PHS) in CN and MCI individuals separately using likelihood ratio tests.

	CN		**MCI**	
	$\chi^2(2)$	*p*-value	$\chi^2(2)$	*p*-value
Logical Memory	0·01	0.99	2·11	0.35
WAIS-R Digit Symbol	**7·08**	**$2{\cdot}91\times10^{-2}$**	**10·84**	**$4{\cdot}43\times10^{-4}$**
Boston Naming Test	**8·78**	**$1{\cdot}24\times10^{-2}$**	2·33	0·31
Trail-Making Test A	4·01	0.13	**7·20**	**$2{\cdot}73\times10^{-2}$**
Trail-Making Test B	**14·42**	**$7{\cdot}40\times10^{-4}$**	**8·84**	**$1{\cdot}20\times10^{-2}$**
Digit Span (forward)	**6·97**	**$3{\cdot}07\times10^{-2}$**	0·95	0·62
Digit Span (backward)	0·17	0·92	1·00	0·61
CDR-SB	**29·30**	**$4{\cdot}34\times10^{-7}$**	**22·47**	**$1{\cdot}32\times10^{-5}$**

WAIS-R: Wechsler Adult Intelligence Scale Revised. CDR-SB: Clinical Dementia Rating Sum of Boxes. Significant interactions are in bold.

Supplementary Table 4. Differences in rates of cognitive decline for low and high polygenic hazard score (PHS) in MCI individuals.

	Low PHS (~16 percentile)		High PHS (~84 percentile)	
	ß (SE)	*p*-value	ß (SE)	*p*-value
Logical Memory	-7·74 (4·30)	0·07	**-11·99 (5·32)**	**$2{\cdot}44\times10^{-2}$**
WAIS-R Digit Symbol	**-9·10 (2·19)**	**$3{\cdot}19\times10^{-5}$**	**-13·97 (2·70)**	**$2{\cdot}29\times10^{7}$**
Boston Naming Test	**-5·58 (1·50)**	**$2{\cdot}04\times10^{-4}$**	**-7·28 (1·88)**	**$1{\cdot}11\times10^{-4}$**
Trail-Making Test A	**-21·48 (6·50)**	**$9{\cdot}57\times10^{-4}$**	**-31·64 (8·14)**	**$1{\cdot}01\times10^{-4}$**
Trail-Making Test B	-11·76 (6·29)	0·06	**-24·78 (8·03)**	**$2{\cdot}02\times10^{-3}$**
Digit Span (forward)	-2·71 (1·85)	0·14	-4·04 (2·28)	0·08
Digit Span (backward)	**-6·49 (2·58)**	**$1{\cdot}19\times10^{-2}$**	**-6·27 (3·18)**	**$4{\cdot}89\times10^{-3}$**
CDR-CB	**0·72 (0·18)**	**$8{\cdot}89\times10^{-5}$**	**1·27 (0·22)**	**$1{\cdot}13\times10^{-8}$**

WAIS-R: Wechsler Adult Intelligence Scale Revised. CDR-SB: Clinical Dementia Rating Sum of Boxes. Significant interactions are in bold.

Supplementary Table 5. Effects of polygenic hazard score (PHS) on longitudinal cognitive decline in CN and MCI individuals combined.

	PHS*Time		
	ß (SE)	*p*-value	*n*
Logical Memory	**-1·51 (0·68)**	**$2{\cdot}74\times10^{-2}$**	1,224
WAIS-R Digit Symbol	**-1·53 (0·35)**	**$1{\cdot}60\times10^{-5}$**	1,143
Boston Naming Test	**-0·96 (0·24)**	**$6{\cdot}98\times10^{-5}$**	1,239
Trail-Making Test A	**-3·25 (1·00)**	**$1{\cdot}05\times10^{-3}$**	1,255
Trail-Making Test B	**-4·36 (1·04)**	**$2{\cdot}85\times10^{-5}$**	1,212
Digit Span (forward)	**-1·07 (0·39)**	**$5{\cdot}47\times10^{-3}$**	1,258
Digit Span (backward)	-0·59 (0·53)	0·26	1,258
CDR-SB	**0·22 (0·03)**	**$8{\cdot}88\times10^{-16}$**	1652

WAIS-R: Wechsler Adult Intelligence Scale Revised. CDR-SB: Clinical Dementia Rating Sum of Boxes. Significant interactions are in bold.

Supplementary Table 6. Differences in rates of cognitive decline for low and high polygenic hazard score (PHS) in CN and MCI individuals combined.

	Low PHS (~16 percentile)		High PHS (~84 percentile)	
	ß (SE)	*p*-value	ß (SE)	*p*-value
Logical Memory	-3·20 (1·80)	0·07	**-6·22 (2·06)**	**$2{\cdot}54\times10^{-3}$**
WAIS-R Digit Symbol	**-5·38 (0·94)**	**$1{\cdot}20\times10^{-8}$**	**-8·44 (1·07)**	**$2{\cdot}89\times10^{-15}$**
Boston Naming Test	**-3·02 (0·62)**	**$1{\cdot}28\times10^{-6}$**	**-4·94 (0·72)**	**$5{\cdot}01\times10^{-12}$**
Trail-Making Test A	**-10·95 (2·58)**	**$2{\cdot}12\times10^{-5}$**	**-17·46 (2·96)**	**$3{\cdot}79\times10^{-9}$**
Trail-Making Test B	**-6·08 (2·67)**	**$2{\cdot}26\times10^{-2}$**	**-14·81 (3·07)**	**$1{\cdot}46\times10^{-6}$**
Digit Span (forward)	-1·28 (1·01)	0·21	**-3·43 (1·16)**	**$3{\cdot}05\times10^{-3}$**
Digit Span (backward)	**-3·90 (1·38)**	**$4{\cdot}54\times10^{-3}$**	**-5·09 (1·56)**	**$1{\cdot}27\times10^{-3}$**
CDR-CB	**0·63 (0·07)**	**$<2\times10^{-16}$**	**1·08 (0·09)**	**$<2\times10^{-16}$**

WAIS-R: Wechsler Adult Intelligence Scale Revised. CDR-SB: Clinical Dementia Rating Sum of Boxes. Significant interactions are in bold.

Supplementary Table 7. Goodness of fit improvements for linear mixed-effects models with the addition of polygenic hazard score (PHS) in CN and MCI individuals combined using likelihood ratio tests.

	$\chi^2(2)$	*p*-value
Logical Memory	**6·85**	**$3{\cdot}26\times10^{-2}$**
WAIS-R Digit Symbol	**28·16**	**$7{\cdot}67\times10^{-7}$**
Boston Naming Test	**21·74**	**$1{\cdot}91\times10^{-5}$**
Trail-Making Test A	**21·58**	**$2{\cdot}06\times10^{-5}$**
Trail-Making Test B	**34·41**	**$3{\cdot}38\times10^{-7}$**
Digit Span (forward)	**10·78**	**$4{\cdot}57\times10^{-3}$**
Digit Span (backward)	2·78	0·25
CDR-SB	**88·33**	**$<2\times10^{-16}$**

WAIS-R: Wechsler Adult Intelligence Scale Revised. CDR-SB: Clinical Dementia Rating Sum of Boxes. Significant interactions are in bold.

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