eTable 1: Distribution of values of the five DNA methylation measures of aging within each diagnostic category in ADNI. For comparison purposes, values are standardized to mean = 0 and SD = 1. **Panel A** shows sex-adjusted means (95% confidence intervals) of values within the Cognitively Normal (CN), Mild Cognitive Impairment (MCI) and Dementia categories. **Panel B** shows results of regression analyses of DNA methylation measures of aging on diagnostic category. **Panel C** shows the same analyses, this time including white blood cell abundance estimates as covariates. Only DunedinPACE was consistently associated with diagnostic category, such that faster pace of aging was seen in the MCI and, to a greater extent, the dementia groups compared to the CN group. Analyses were conducted with baseline category = CN. All analyses included sex as a covariate in the model. To account for clustering, we report Huber-White robust standard errors.** p < .01; * p < 0.05.

	Panel A	**Panel B: sex adjusted Model**	**Panel C: Adjusted for white blood cell abundance estimates**
Independent factor level	**Sex-Adjusted Mean (95% CI)**	**Beta (Robust SE)**	**Beta (Robust SE)**
Horvath			
CN	0.03 (-0.06, 0.11)		
MCI	-0.03 (-0.10, 0.03)	-0.06 (0.08)	-0.06 (0.08)
Dementia	0.02 (-0.08, 0.13)	-0.00 (0.10)	0.01 (0.10)
Hannum			
CN	-0.02 (-0.10, 0.07)		
MCI	0.01 (-0.06, 0.08)	0.03 (0.09)	0.03 (0.08)
Dementia	-0.01 (-0.11, 0.10)	0.01 (0.10)	-0.02 (0.09)
PhenoAge			
CN	-0.07 (-0.15, 0.02)		
MCI	0.01 (-0.06, 0.08)	0.08 (0.08)	0.06 (0.07)
Dementia	0.07 (-0.03, 0.18)	0.14 (0.10)	0.08 (0.10)
GrimAge			
CN	-0.07 (-0.15, 0.01)		
MCI	0.05 (-0.02, 0.11)	0.12 (0.08)	0.12 (0.07)
Dementia	-0.01 (-0.11, 0.09)	0.07 (0.09)	0.07 (0.08)
DunedinPACE			
CN	-0.14 (-0.23, -0.06)		
MCI	0.04 (-0.02, 0.11)	0.19 (0.08)*	0.18 (0.07)*
Dementia	0.13 (0.03, 0.24)	0.28 (0.10)**	0.22 (0.10)*

eTable 2: Sensitivity analyses of associations between cognitive screening tests and DNA methylation measures of aging in ADNI. We conducted sensitivity analyses in two ways. First, as the distributions of cognitive screening scores in ADNI violate the assumption of normality, we applied transformations to the data. **Panel A** shows results using the untransformed 'native' cognitive screening score as reported in Table 3 of the manuscript. **Panel B** shows results of analyses where the cognitive screening score was Log10 transformed prior to analysis. **Panel C** shows the results of analysis where individuals were distributed into quintiles on the basis of their cognitive screening score. Data transformation had little effect on effect size estimates. Second, we conducted the association analyses described in Table 3 of the manuscript (model adjusted for sex only) with adjustment for estimates of white blood cell abundance. Across all the analyses, adjusting for white blood cell abundance estimates resulted in a slight attenuation of effect size. Both cognitive screening scores and DNA methylation measures of aging are standardized to Mean = 0, SD = 1 prior to analysis. All analyses included sex as a covariate in the model. To account for clustering, we report Huber-White robust standard errors.ADAS-Cog-13 = Alzheimer's Disease Assessment Scale; MMSE = Mini-Mental State Examination; MOCA = Montreal Cognitive Assessment; SE = Standard Error. ***p < .001; ** p < .01; * p < 0.05.

	Panel A: un-transformed cognitive screening scores		Panel B: Log-transformed cognitive screening scores		Panel C: cognitive screening scores split into quinitiles	
ADAS-Cog-13	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates
	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)
Horvath	0.00 (0.04)	0.01 (0.04)	-0.01 (0.04)	0.00 (0.03)	0.02 (0.04)	0.03 (0.03)
Hannum	0.02 (0.04)	0.01 (0.03)	0.01 (0.04)	-0.01 (0.03)	0.02 (0.04)	0.01 (0.03)
PhenoAge	0.07 (0.03)*	0.04 (0.03)	0.07 (0.03)	0.03 (0.03)	0.07 (0.03)*	0.04 (0.03)
GrimAge	0.01 (0.03)	0.01 (0.03)	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)
DunedinPACE	0.08 (0.04)*	0.05 (0.04)	0.09 (0.03)*	0.05 (0.03)	0.09 (0.03)*	0.06 (0.03)
MMSE	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates
	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)
Horvath	0.01 (0.03)	0.01 (0.03)	0.02 (0.03)	0.02 (0.03)	0.01 (0.03)	0.00 (0.03)
Hannum	-0.02 (0.04)	0.00 (0.03)	-0.04 (0.04)	-0.02 (0.04)	-0.04 (0.03)	0.00 (0.03)
PhenoAge	-0.06 (0.03)	-0.04 (0.03)	-0.05 (0.03)	-0.03 (0.03)	-0.07 (0.03)*	-0.03 (0.03)
GrimAge	0.01 (0.03)	0.02 (0.03)	0.03 (0.03)	0.04 (0.03)	-0.03 (0.03)	-0.02 (0.03)
DunedinPACE	-0.08 (0.03)*	-0.05 (0.03)	-0.08 (0.03)***	-0.06 (0.03)	-0.11 (0.03)***	-0.07 (0.03)*

MOCA	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates
	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)
Horvath	0.03 (0.03)	0.02 (0.03)	0.02 (0.03)	0.02 (0.03)	0.01 (0.04)	0.01 (0.03)
Hannum	-0.02 (0.03)	0.00 (0.03)	-0.02 (0.03)	-0.01 (0.03)	-0.06 (0.04)	-0.02 (0.03)
PhenoAge	-0.07 (0.03)*	-0.04 (0.03)	-0.07 (0.03)*	-0.04 (0.03)*	-0.07 (0.03)*	-0.02 (0.03)
GrimAge	-0.03 (0.03)	-0.02 (0.03)	-0.02 (0.03)	-0.02 (0.03)	-0.04 (0.03)	-0.03 (0.03)
DunedinPACE	-0.10 (0.04)**	-0.07 (0.04)	-0.10 (0.04)*	-0.07 (0.04)*	-0.11 (0.03)***	-0.06 (0.03)

eTable 3: Sensitivity analyses of associations between cognitive function tests and DNA methylation measures of aging in ADNI. We conducted sensitivity analyses in two ways. First, as the distribution of cognitive function scores in ADNI violates the assumption of normality, we also applied transformations to the data. **Panel A** shows results using the untransformed 'native' cognitive fucntion score as reported in Table 3 of the manuscript. **Panel B** shows results of analyses where the cognitive function score was Log10 transformed prior to analysis. **Panel C** shows the results of analysis where individuals were distributed into quintiles on the basis of their cognitive function score. Data transformation had little effect on effect size estimates. Second, we conducted the association analyses described in Table 3 of the manuscript (model adjusted for sex only) with further adjustment for estimates of white blood cell abundance. Across all the analyses, adjusting for white blood cell abumndance resulted in a slight attenuation of effect size. Both cognitive function scores and DNA methylation measures of aging are standardized to mean = 0, SD = 1 prior to analysis. All analyses included sex as a covariate in the model. To account for clustering, we report Huber-White robust standard errors. RAVLT = The Rey Auditory Verbal Learning Test; SE = Standard Error.***p < .001; **p < .01; * p < 0.05.

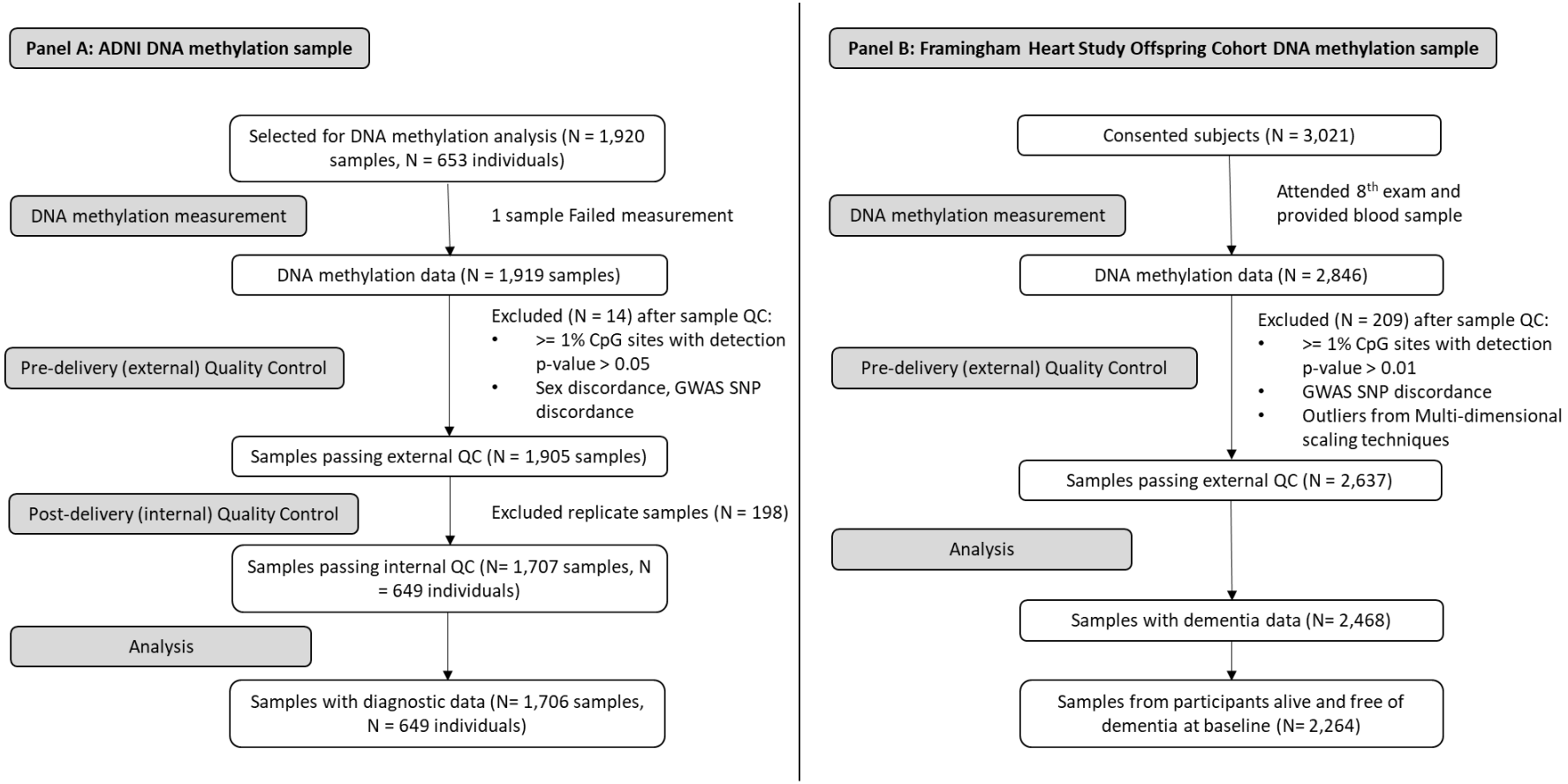
	Panel A: un-transformed cognitive function scores		Panel B: Log-transformed cognitive function scores		Panel C: cognitive function scores split into quinitiles	
RAVLT immediate recall	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates
	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)
Horvath	0.01 (0.04)	0.00 (0.03)	0.01 (0.03)	0.00 (0.03)	0.00 (0.04)	0.00 (0.03)
Hannum	-0.02 (0.04)	0.00 (0.03)	-0.02 (0.03)	0.00 (0.03)	-0.02 (0.04)	0.00 (0.03)
PhenoAge	-0.06 (0.04)	-0.02 (0.03)	-0.06 (0.03)	-0.02 (0.03)	-0.06 (0.03)	-0.02 (0.03)
GrimAge	-0.05 (0.03)	-0.04 (0.03)	-0.03 (0.03)	-0.03 (0.03)	-0.05 (0.03)	-0.04 (0.03)
DunedinPACE	-0.12 (0.04)***	-0.07 (0.03)*	-0.11 (0.04)**	-0.07 (0.04)	-0.11 (0.04)**	-0.07 (0.03)*
RAVLT percent forgotten	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates
	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)
Horvath	0.01 (0.03)	0.02 (0.03)	-0.01 (0.04)	0.00 (0.03)	0.00 (0.03)	0.01 (0.03)
Hannum	0.00 (0.03)	-0.01 (0.03)	-0.01 (0.04)	-0.03 (0.03)	-0.01 (0.04)	-0.02 (0.03)
PhenoAge	0.06 (0.03)	0.03 (0.03)	0.04 (0.04)	0.02 (0.03)	0.06 (0.03)	0.04 (0.03)
GrimAge	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)	0.02 (0.03)	0.03 (0.03)	0.03 (0.03)
DunedinPACE	0.10 (0.03)**	0.07 (0.03)*	0.09 (0.03)**	0.06 (0.03)	0.09 (0.03)**	0.07 (0.03)*

	Panel A: un-transformed cognitive function scores		Panel B: Log-transformed cognitive function scores		Panel C: cognitive function scores split into quinitiles	
Logical Memory	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates
	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)
Horvath	-0.01 (0.04)	-0.02 (0.04)	-0.02 (0.04)	-0.03 (0.04)	-0.02 (0.04)	-0.03 (0.03)
Hannum	-0.01 (0.04)	0.01 (0.03)	-0.01 (0.04)	0.00 (0.03)	-0.02 (0.04)	0.00 (0.03)
PhenoAge	-0.10 (0.04)**	-0.07 (0.03)*	-0.08 (0.03)*	-0.06 (0.03)	-0.11 (0.03)**	-0.07 (0.03)*
GrimAge	-0.03 (0.03)	-0.03 (0.03)	-0.01 (0.03)	-0.01 (0.03)	-0.04 (0.03)	-0.04 (0.03)
DunedinPACE	-0.11 (0.04)**	-0.08 (0.03)*	-0.09 (0.04)*	-0.06 (0.04)	-0.12 (0.04)***	-0.08 (0.03)*
Trail Making Test Part B	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates	Sex adjusted Model	Adjusted for white blood cell abundance estimates
	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)	Beta (Robust SE)
Horvath	-0.02 (0.03)	-0.01 (0.03)	-0.02 (0.03)	-0.01 (0.03)	-0.02 (0.04)	-0.02 (0.03)
Hannum	0.00 (0.03)	-0.01 (0.03)	0.00 (0.04)	-0.02 (0.03)	-0.01 (0.04)	-0.04 (0.03)
PhenoAge	0.03 (0.03)	0.01 (0.03)	0.04 (0.03)	0.00 (0.03)	0.03 (0.03)	0.00 (0.03)
GrimAge	0.00 (0.03)	0.00 (0.03)	0.01 (0.03)	0.01 (0.03)	0.03 (0.03)	0.02 (0.03)
DunedinPACE	0.06 (0.04)	0.04 (0.03)	0.09 (0.04)*	0.05 (0.03)	0.10 (0.04)**	0.06 (0.03)

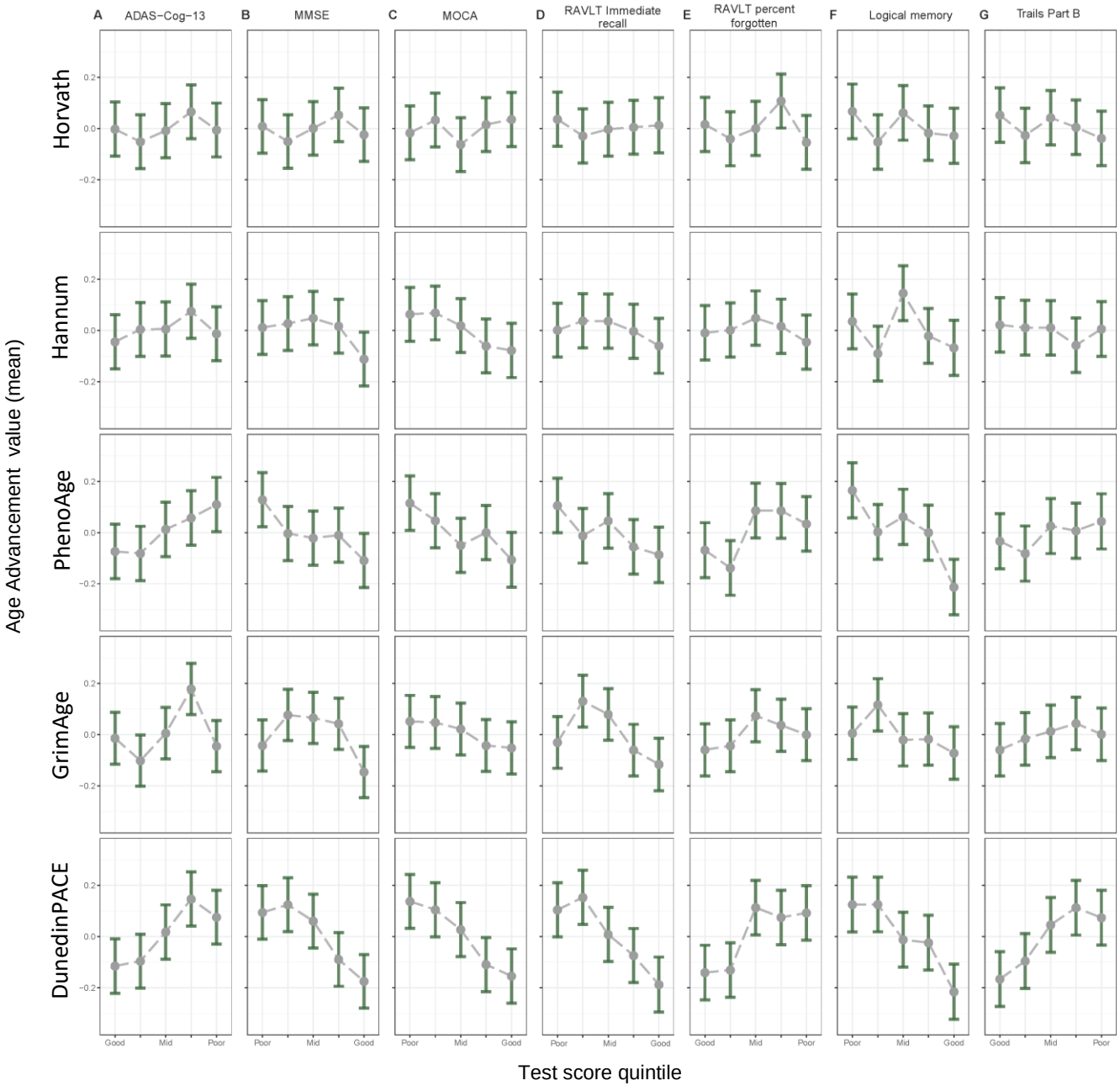
eTable 4: Mean DNA methylation Age Advancement values in DNA samples with 0 (N = 1,007), 1 (N = 571), or 2 (N = 128) *APOE ε4* alleles in the ADNI cohort. There were no significant differences in mean values across these groups for any of the measures.

Age Acceleration Measure	Number *APOE ε4* alleles	Sex-Adjusted Mean(95%CI)	*F* value	*p* value
Horvath	0	-0.02(-0.08-0.04)	1.97	0.14
	1	0.06(-0.02-0.14)		
	2	-0.13(-0.3-0.04)		
Hannum	0	0.00(-0.06-0.06)	0.84	0.43
	1	0.03(-0.05-0.11)		
	2	-0.14(-0.31-0.04)		
PhenoAge	0	-0.02(-0.08-0.04)	0.47	0.62
	1	0.03(-0.06-0.11)		
	2	0.02(-0.15-0.19)		
GrimAge	0	-0.01(-0.07-0.05)	0.34	0.71
	1	0.04(-0.04-0.11)		
	2	-0.10(-0.27-0.06)		
DunedinPACE	0	-0.01(-0.07-0.05)	0.43	0.65
	1	0.02(-0.06-0.11)		
	2	0.03(-0.14-0.20)		

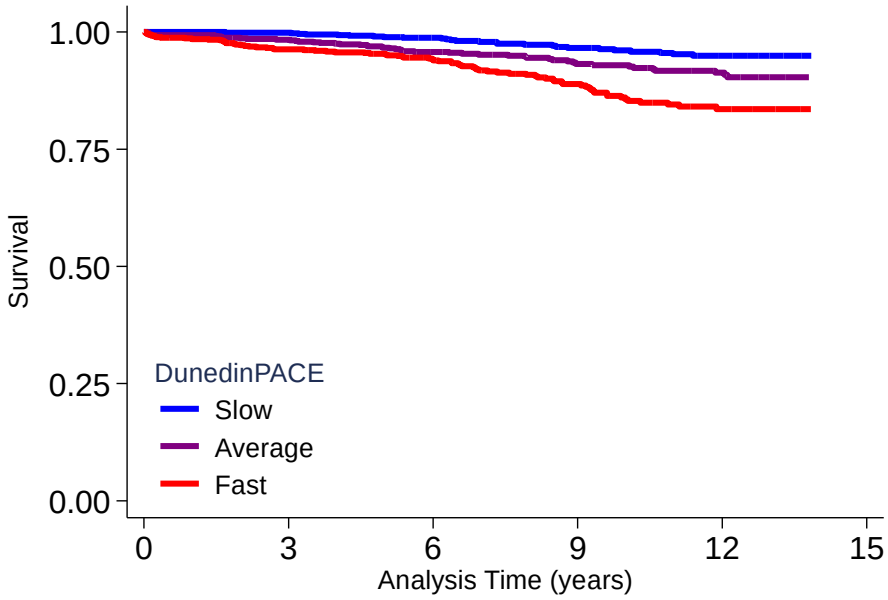
eFigure 1: Flowchart of sample selection in the ADNI **(Panel A)** and the Framingham Heart Study (FHS) Offspring Cohort (**Panel B**) studies. In the case of ADNI, the initial pool of available participants represents those selected for DNA methylation measurement by ADNI Cohort investigators and not the entire cohort. For FHS Offspring Study, the initial pool of available particpants were those who consented to DNA methylation measurement and not the entire FHS Offspring Cohort.



eFigure 2: Plots of the relationship between five DNA methylation measures of aging and cognitive screening and function tests. Panels show distribution of test scores: **Panel A** = Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog-13) 13), **B** = Mini-Mental State Examination (MMSE), **C** = Montreal Cognitive Assessment (MOCA), **D** = Rey Auditory Verbal Learning Test immediate recall, **E** = Rey Auditory Verbal Learning Test, percent forgotten, **F** = Logical Memory, **G** = Trail-making test Part B. Each row represents a different DNA methylation measure of aging: (from top to bottom) Horvath, Hannum, PhenoAge, GrimAge, DunedinPACE. Test scores (x-axis) are binned into quintiles (0-5); grey dots represent mean age advancement value and whiskers represent 95% CI. The y-axis represents values on each DNA methylation measure of aging (standardized to mean = 0, SD = 1).



eFigure 3: Association of DunedinPACE with dementia in the Framingham Heart Study Offspring Cohort. The figure plots Kaplan-Meier curves for three groups of participants: those with DunedinPACE 1 SD or more below the mean ('slow' DunedinPACE, blue line); those with DunedinPACE within 1 SD of the mean ('average' DunedinPACE, purple line); and those with DunedinPACE 1 SD or more above the mean ('fast' DunedinPACE, red line). The table below the figure details the number of participants at risk per 3-year interval and, in parentheses, the number who developed dementia during the interval.



Number At Risk (Dementia)

Slow DunedinPACE	766	(1)	734	(8)	611	(11)	396	(6)	257	(0)	0
Average DunedinPACE	750	(12)	699	(18)	553	(11)	348	(6)	205	(2)	0
Fast DunedinPACE	748	(26)	635	(13)	491	(22)	293	(15)	135	(0)	0