

Polygenic risk scores for LATE-neuropathologic change: Implications for clinical utility

Jung-Min Pyun¹, Young Ho Park^{1†}, Lincoln M.P. Shade², David W. Fardo², SangYun Kim¹, and Kwangsik Nho^{3,4†}, for the Alzheimer's Disease Neuroimaging Initiative

¹Department of Neurology, Seoul National University Bundang Hospital and Seoul National University College of Medicine, Republic of Korea, ²Department of Biostatistics, College of Public Health, University of Kentucky, USA, ³Department of Radiology and Imaging Sciences, and the Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, USA, ⁴Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, USA

ADNI

This work was funded by a grant from the Alzheimer's Association (AACSFD-24-1310485).

Background

Limbic-predominant age-related TDP-43 encephalopathy (LATE) exhibits clinical features resembling Alzheimer's disease (AD) and frequently occurs as a co-pathology, yet there are fewer biomarkers for LATE relative to AD.

Methods

We calculated polygenic risk scores for LATE-neuropathologic change (LATE-PRS) in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants aged ≥ 75 years, stratified by amyloid PET positivity status. We performed two logistic regression analyses to evaluate associations of LATE-PRS with LATE pathology (N=99): **Model 1** (age, sex, *APOE* $\epsilon 4$) and **Model 2** (Model 1+ ADNC). We performed linear mixed effects analysis of LATE-PRS with (N=538) longitudinal changes in cognition (N=538) in cognitively impaired participants (MCI and dementia).

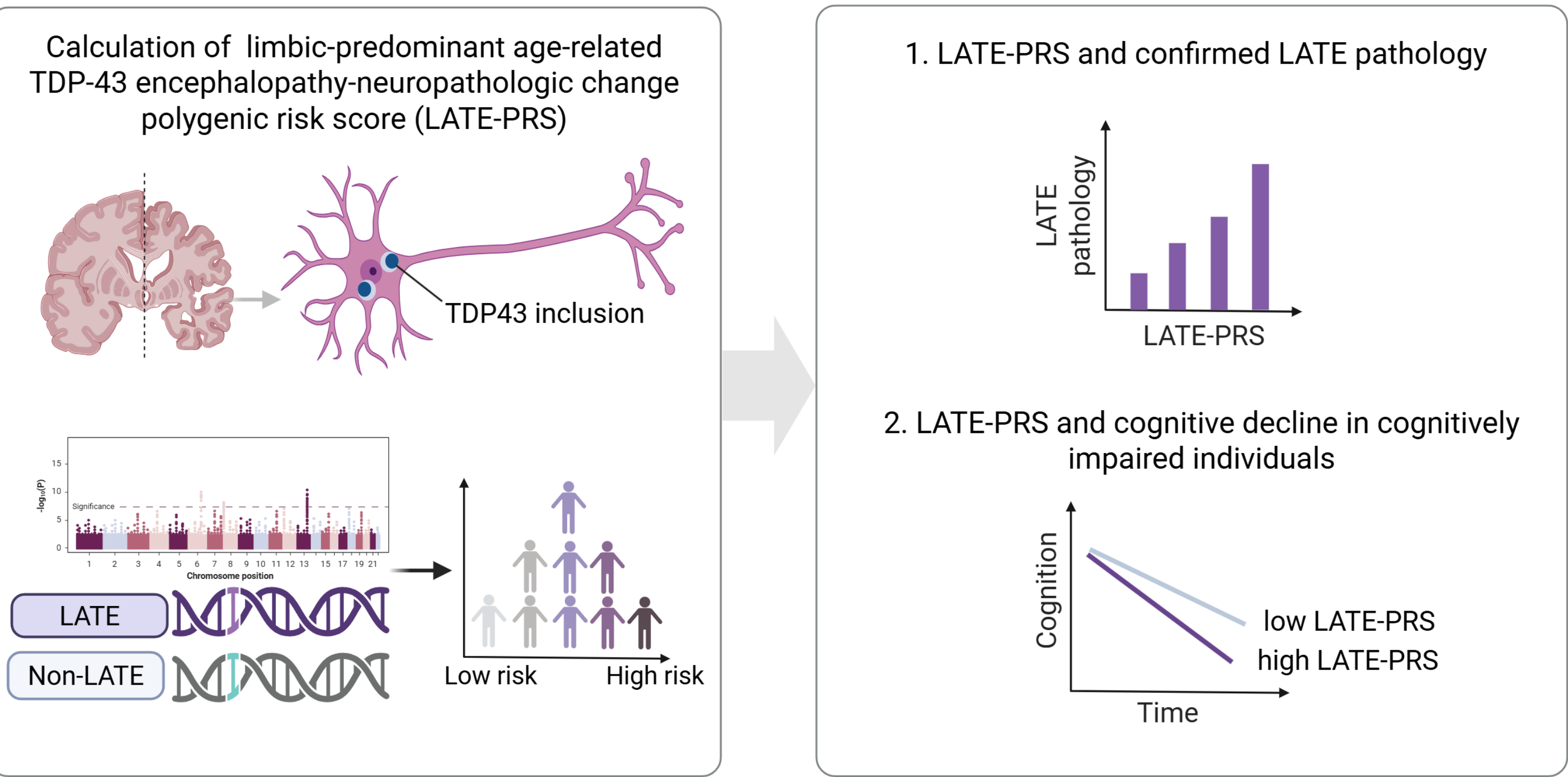


Figure 1. Analysis overview of the study.

Results

A total of 99 individuals (50 LATE-positive, 49 LATE-negative) were included in the LATE-PRS–pathology analysis (**Table 1a**) and 538 participants aged ≥ 75 years (amyloid PET–: 207; amyloid PET+: 331) in the longitudinal cognitive analysis (**Table 1b**).

Abbreviation: ADNI, Alzheimer's Disease Neuroimaging Initiative; ADNC, Alzheimer's disease neuropathologic change; ADNI EF, composite scores for executive functioning; ADNI MEM, composite scores for memory; CDR SOB, clinical dementia rating sum of boxes; CU, cognitively unimpaired; LATE, limbic-predominant age-related TDP-43 encephalopathy; MCI, mild cognitive impairment; PET, positron emission tomography; PRS, polygenic risk score.

Table 1a	Non-LATE (N = 49)	LATE (N = 50)	p-value
Age of death, years	82.3 $\pm$ 6.8	84.7 $\pm$ 6.7	0.081
Male (%)	36 (73.4)	36 (72.0)	1.000
<i>APOE</i> $\epsilon 4$ carrier (%)	29 (59.1)	27 (54.0)	0.751
LATE-PRS	-0.18 $\pm$ 0.75	0.34 $\pm$ 0.99	0.004
ADNC	2.3 $\pm$ 1.0	2.4 $\pm$ 0.8	0.781
Table 1b	Negative amyloid PET (N = 207)	Positive amyloid PET (N = 331)	p-value
Age, year	80.47 $\pm$ 4.58	80.31 $\pm$ 4.12	0.659
Male (%)	128 (61.8)	203 (61.3)	0.979
Education, year	16.64 $\pm$ 2.50	15.90 $\pm$ 2.89	0.002
<i>APOE</i> $\epsilon 4$ carrier status (%)	24 (11.6)	186 (56.1)	< 0.001
LATE-PRS	0.14 $\pm$ 0.97	-0.07 $\pm$ 1.01	0.020
Diagnosis (%), CU	110 (53.1)	91 (27.4)	< 0.001
MCI	74 (35.7)	148 (44.7)	
Dementia	23 (11.1)	92 (27.7)	< 0.001
CDR SOB	1.08 $\pm$ 1.78	2.17 $\pm$ 2.43	
ADNI MEM	0.51 $\pm$ 1.86	0.00 $\pm$ 0.86	< 0.001
ADNI EF	0.42 $\pm$ 0.94	-0.13 $\pm$ 0.92	< 0.001

Table 1. Demographics of study participants stratified by LATE pathology status and amyloid PET positivity status

The proportion of LATE pathology increased across LATE-PRS quartiles (Q1: 36% to Q4: 75%) (**Figure 2**). LATE-PRS was significantly associated with LATE pathology both before (OR = 2.192, p = 0.004) and after (OR = 2.292, p = 0.002) adjustment for ADNC (**Table 2**).

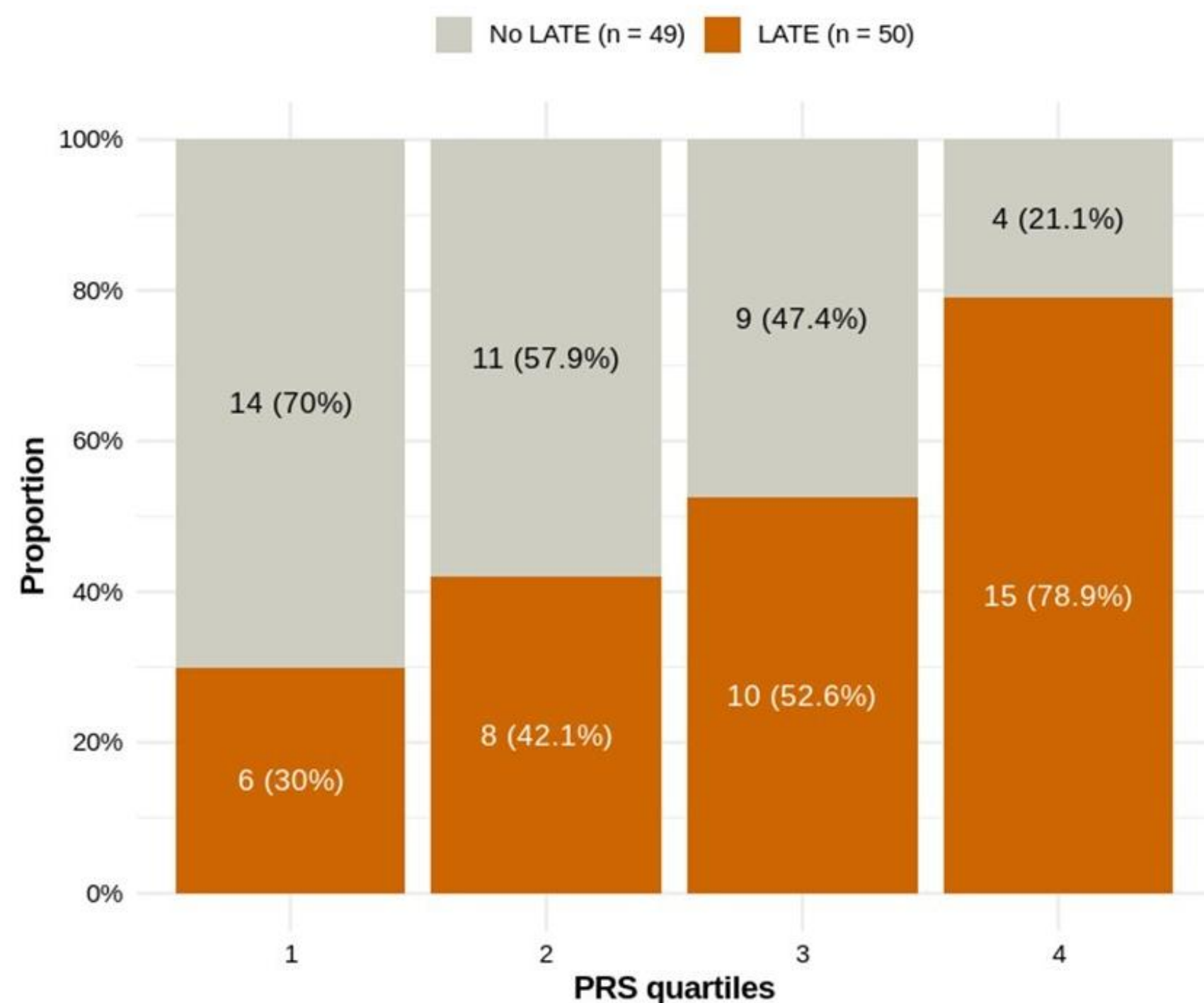


Figure 2. Distribution of LATE pathology according to LATE-PRS quartiles

	Model 1		Model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
LATE-PRS	2.192 (1.033-3.899)	0.004	2.292 (1.370-4.114)	0.002
Age	1.070 (1.004-1.144)	0.039	1.080 (1.012-1.161)	0.024
Male	0.844 (0.321-2.188)	0.727	0.896 (0.340-2.342)	0.823
<i>APOE</i> $\epsilon 4$ carrier status	1.228 (0.513-3.005)	0.646	0.889 (0.321-2.457)	0.820
ADNC	NA	NA	1.429 (0.835-2.524)	0.200

Table 2. Association of LATE-PRS with LATE pathology

In the longitudinal analysis, higher LATE-PRS was significantly associated with faster cognitive decline rates of composite score for executive function (ADNI EF; β = -0.002, p = 0.041) in amyloid PET-negative individuals (**Figure 3**). The association between LATE-PRS and longitudinal changes in composite scores for memory (ADNI MEM) was marginal (β = -1.577, p = 0.071). In amyloid PET-positive individuals, LATE-PRS was significantly associated with longitudinal changes in ADNI MEM (β = -0.002, p < 0.001) and ADNI EF (β = -0.001, p < 0.001).

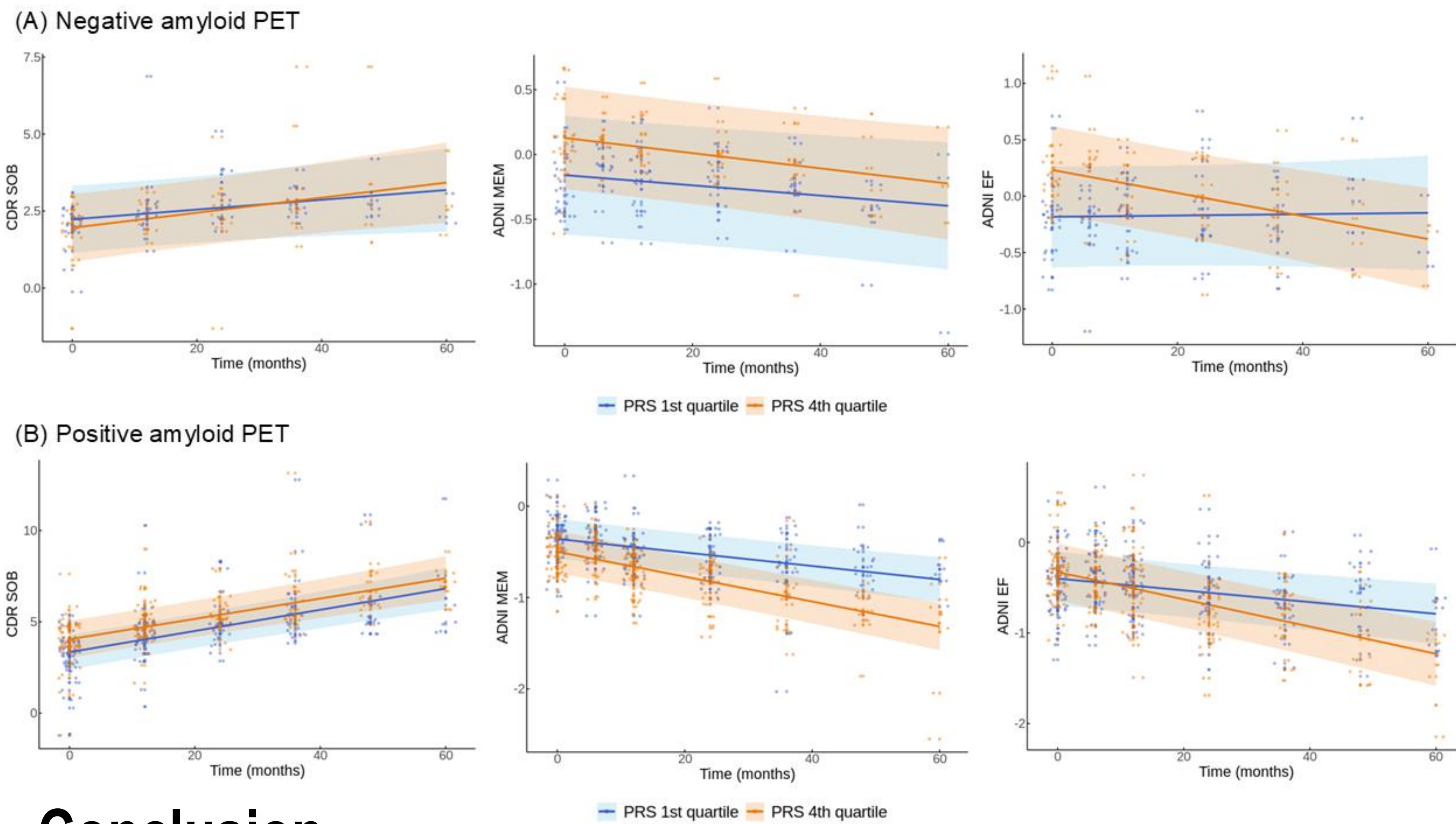


Figure 3. Longitudinal changes in cognition between the 1st and 4th LATE-PRS quartiles stratified by amyloid PET positivity status

Conclusion

LATE-PRS may serve as a potential biomarker for LATE risk and cognitive progression.