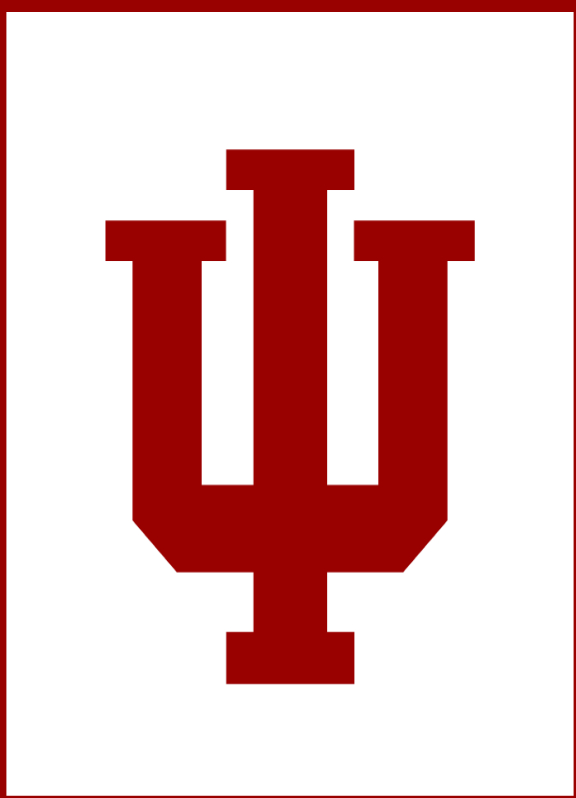




Blood-based Transcriptional Risk Scores Across Alzheimer's Disease Continuum: Relation To Imaging Biomarkers And Progression In Koreans

Shiwei Liu¹, Tamina Park¹, Dahyun Yi², Yen-Ning Huang¹, Min Soo Byun³, Paula J Bice¹, Dong Young Lee^{2,3}, Andrew J Saykin¹, Kwangsik Nho¹

¹IDemartment of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA; ²Institute of Human Behavioral Medicine, Seoul National University, Seoul, Korea; ³Department of Psychiatry, Seoul National University Hospital, Seoul, Korea

Abstract

BACKGROUND: AD causes cognitive decline and amyloid-beta (A β) accumulation. **Transcriptional risk scores (TRS)** from blood transcriptomics summarize AD-associated gene expression, understudied in diverse populations. **METHODS:** Blood RNA-Seq on **506 KBASE participants**. Causal AD genes identified via Mendelian randomization and colocalization. TRS tested against diagnosis, A β PET/MRI, cognition, and longitudinal change. **RESULTS:** Higher TRS linked to AD diagnosis, A β positivity, amyloid deposition, reduced hippocampal volume, and poorer cognition, and predicted faster memory decline and diagnostic conversion, especially in non-APOE ϵ 4 carriers. **CONCLUSION:** Blood TRS is a **noninvasive biomarker** for AD-related pathology and cognitive decline in a Korean cohort, with potential utility in Asian populations.

Background

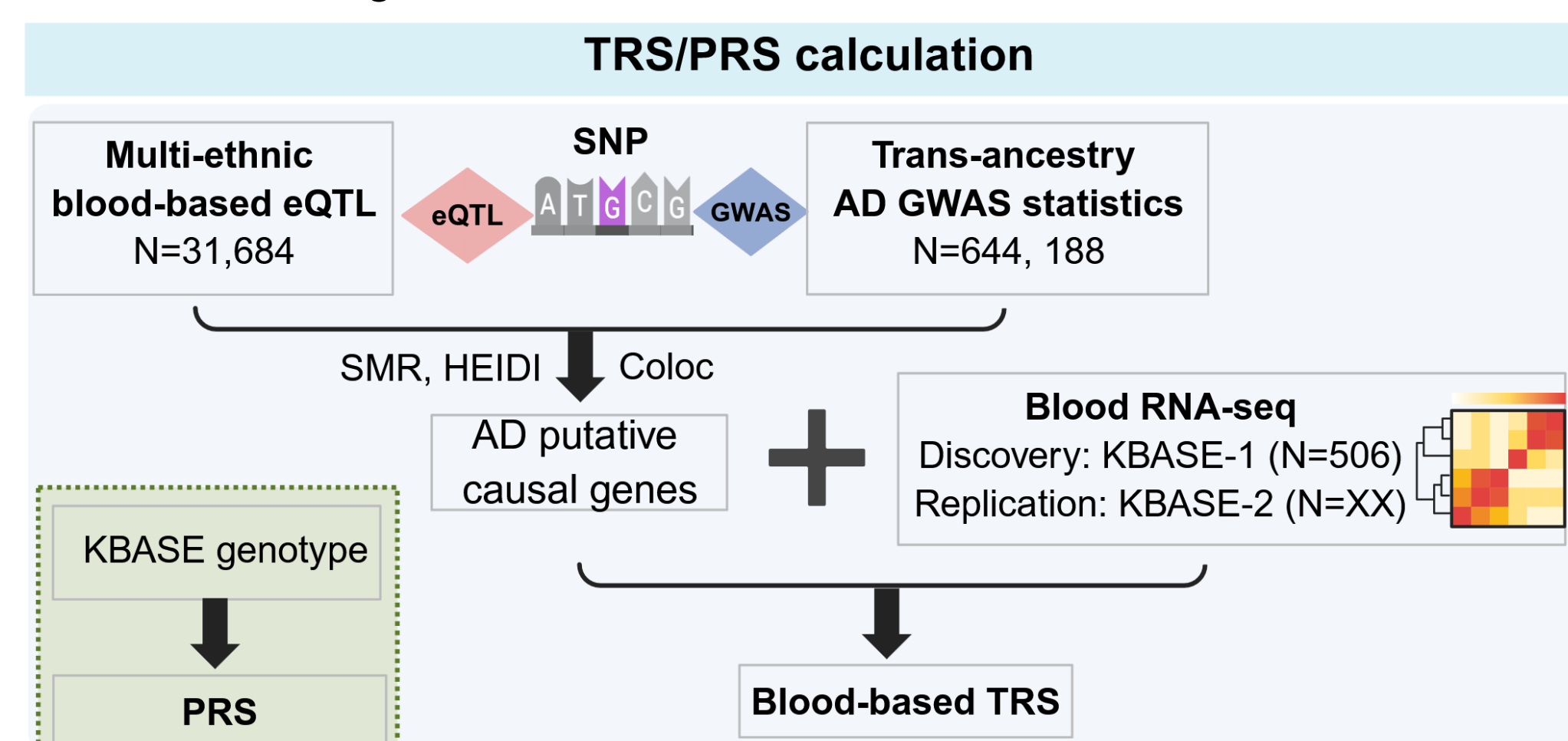
- **AD:** Progressive cognitive decline driven by A β accumulation; genetic risk acts via gene regulation.
- **TRS:** Blood transcriptomics-derived score summarizing AD-associated gene expression.
- **Gap:** TRS understudied in non-European, particularly Asian, populations.
- **Cohort (KBASE):** N=506 Korean adults (CN, MCI, AD); blood RNA-Seq, A β PET, MRI, cognitive assessments.
- **Follow-up:** Longitudinal data for cognitive change and diagnostic conversion.

Table 1. Participant characteristics.

	CN (N=274)	MCI (N=138)	AD (N=94)
Age (mean $\pm$ SD)	69.2 $\pm$ 8.34	73.6 $\pm$ 6.93	73.6 $\pm$ 7.48
Sex (F:M)	138:136	90:48	66:28
RNA integrity	7.31 $\pm$ 2.06	6.99 $\pm$ 2.05	6.22 $\pm$ 2.75
APOE ϵ 4 (-: +)	218:51	86:52	29:55
PIB SUVR	0.07 $\pm$ 0.05	0.13 $\pm$ 0.08	0.20 $\pm$ 0.09
A β pos. (-: +)	228:41	66:72	15:69

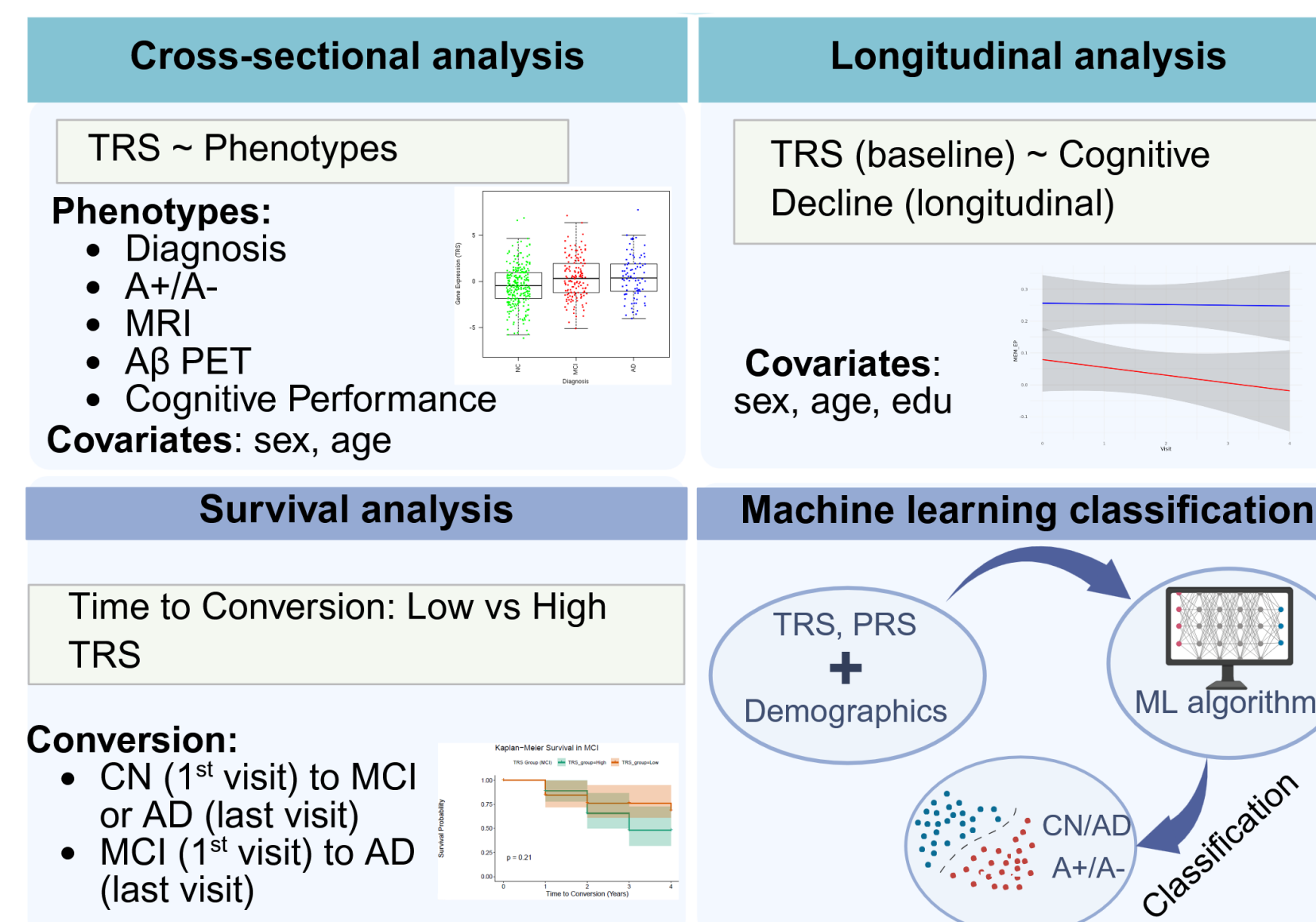
Method: TRS/PRS calculation

- Mendelian randomization (MR) and colocalization to identify putative causal AD genes regulated by AD risk variants
- Integrated trans-ancestry GWAS with multi-ethnic blood-based eQTL data to select TRS genes
- Transcriptional Risk Score (TRS) = sum of polarized expression levels of selected causal AD genes



Method: association/classification analysis

- Cross-sectional regression: TRS vs. diagnosis, A β PET/MRI, cognition
- Mixed-effects models: TRS vs. longitudinal cognitive change
- Logistic/Cox regression: TRS vs. diagnostic conversion
- ML classifier: TRS added value for A β positivity prediction



Cross-sectional analysis: TRS ~ AD phenotypes

- TRS was significantly associated with AD diagnosis and A β positivity (Fig. 1A, 1B)
- TRS associated with A β deposition on PET and hippocampal volume on MRI (Fig. 1C)
- TRS associated with domain-specific cognitive performance across multiple cognitive domains (Fig. 1C & D)

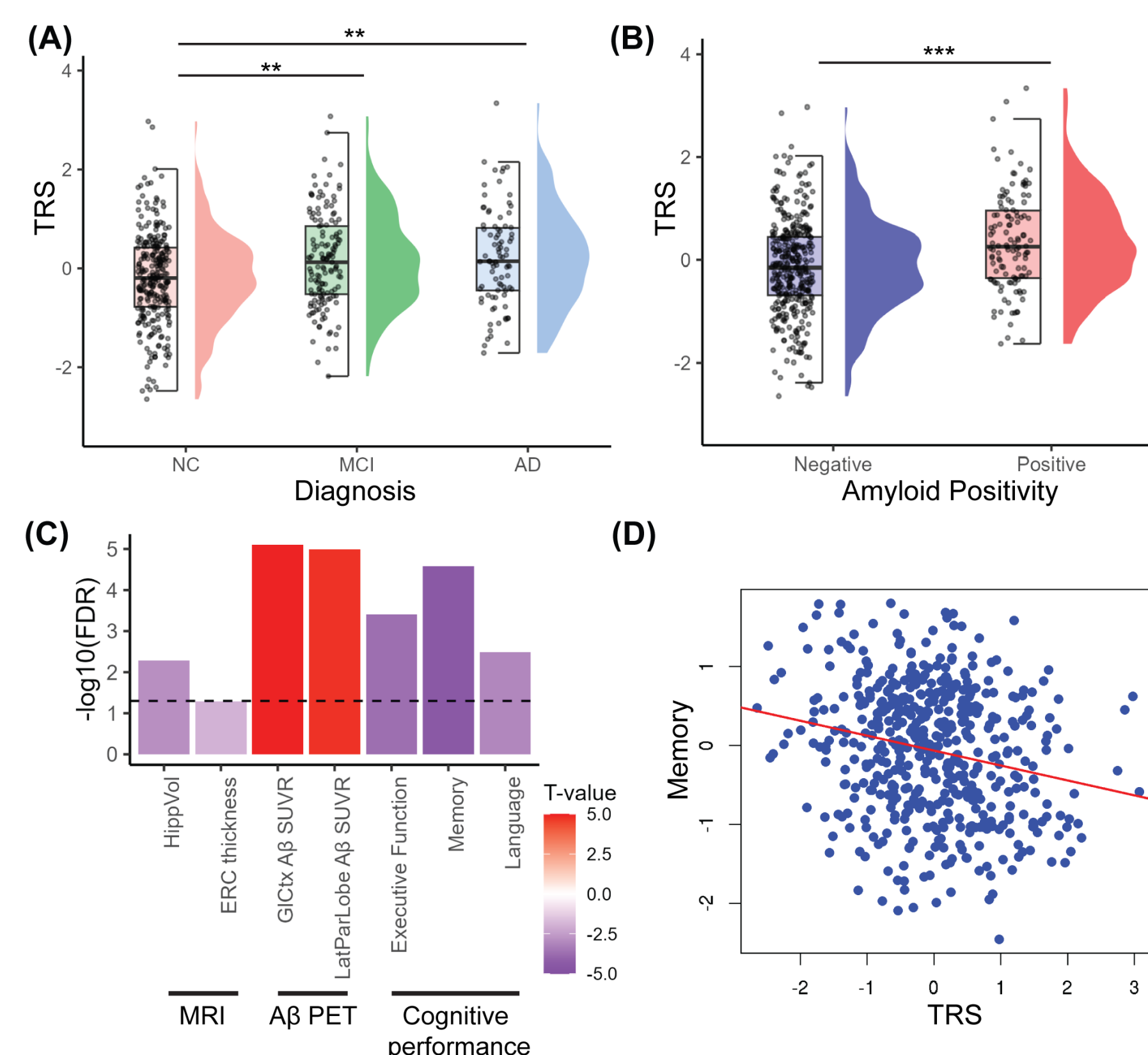


Fig. 1

References

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- Nho K et al. Blood-based gene expression and neuroimaging biomarkers in AD — KBASE cohort
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Longitudinal analysis: Associations between baseline TRS and longitudinal cognitive decline

- **Fig. 2A:** Higher baseline TRS predicted significantly greater memory decline over time (TRS $\times$ visit interaction p=0.01; p=0.003 after APOE ϵ 4 adjustment).
- **Fig. 2B:** No significant association with longitudinal language change (p=0.05), though significance was reached after APOE ϵ 4 adjustment (p=0.046).
- **Fig. 2C:** Baseline TRS was not associated with executive function decline (p=0.33), remaining nonsignificant after APOE ϵ 4 adjustment (p=0.51).

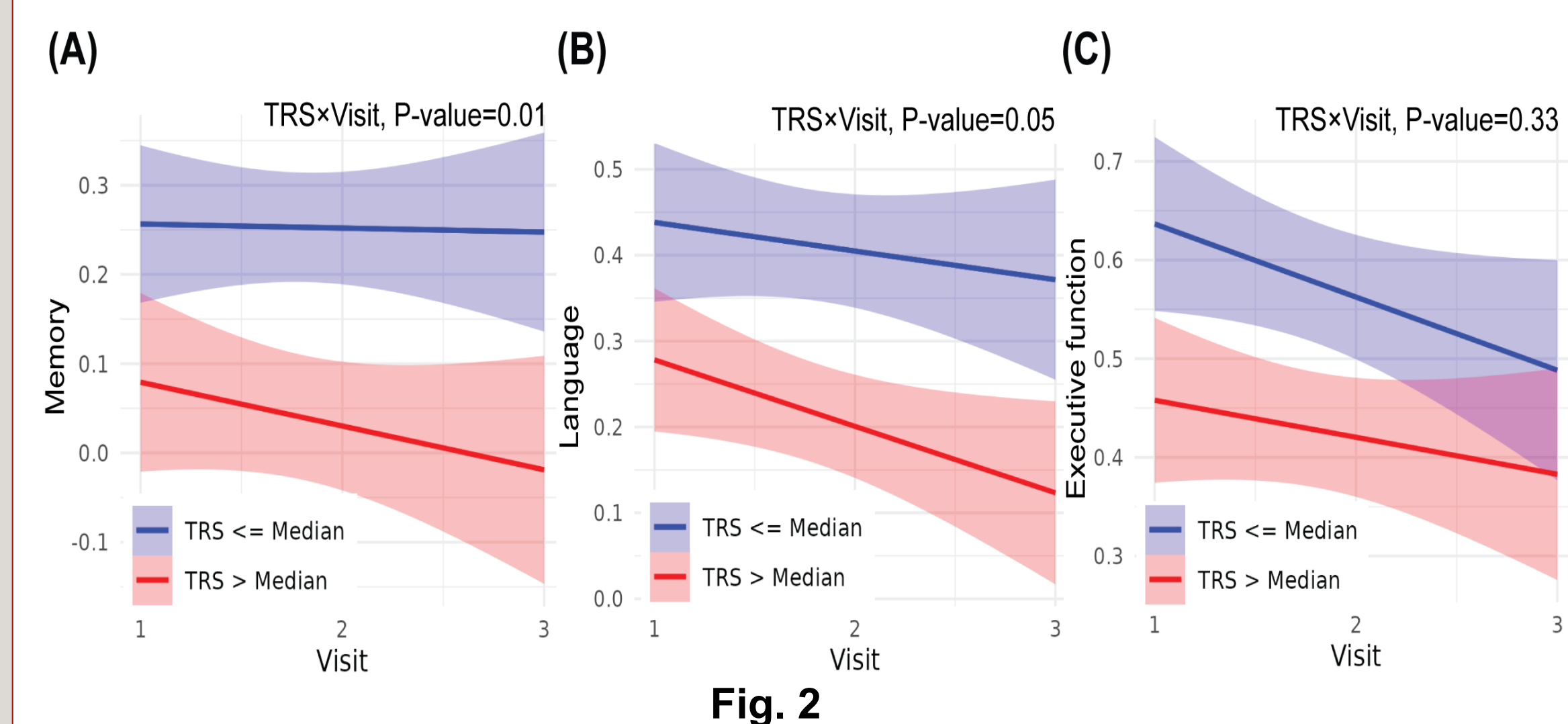


Fig. 2

Longitudinal analysis: Baseline TRS and diagnostic conversion

- **Fig. 3A:** Converters had higher baseline TRS than stable participants (p=0.021).
- **Fig. 3B:** Higher TRS associated with faster conversion (HR=1.44, p=0.014).
- **Fig. 3C:** Higher TRS predicted conversion in APOE ϵ 4- MCI (p=0.005).
- **Fig. 3D:** Higher TRS strongly linked to faster conversion in APOE ϵ 4- MCI (HR=2.40, p=0.004).

Lastly, TRS improved classification of A β positivity beyond demographic variables.

Conclusions

- Blood RNA-Seq-derived TRS is associated with AD diagnosis, amyloid pathology, brain atrophy, and cognitive decline in a Korean population
- TRS is associated with longitudinal cognitive decline and diagnostic conversion, particularly in APOE ϵ 4 non-carriers
- TRS improves A β positivity classification beyond demographic models alone
- Findings suggest TRS may serve as a complementary, noninvasive biomarker for AD diagnosis and progression in diverse (Asian) populations