

INTRODUCTION

The *RELN*^{H3447R} (*RELN-COLBOS*) is a rare genetic variant found in one man carrying the *PSEN1*^{E280A} variant in the Colombian kindred of autosomal dominant Alzheimer's disease (ADAD) (1)

- The *RELN-COLBOS* carrier showed 20-year delayed onset of clinical symptoms
- Despite high amyloid- β (A β) burden, tau pathology and glucose metabolism remained preserved

OBJECTIVES

To perform a descriptive analysis of imaging and plasma biomarker profiles in the 12 heterozygous *RELN-COLBOS* carriers identified in the Colombian ADAD kindred, specifically:

- 1) Dual *RELN-COLBOS/PSEN1*^{E280A} carriers compared to typical *PSEN1*^{E280A} carriers across ADAD
- 2) *RELN-COLBOS* carriers compared to non-carriers across the healthy adult lifespan

METHODS

Colombian ADAD kindred

Neuropsychological Assessments

- Cognitive status (Functional Assessment Staging Tool)
- Global cognition (Mini-Mental State Examination)
- Delayed recall (CERAD Word List Learning)

Imaging Biomarkers

- Neocortical PiB-PET (amyloid- β)
- Entorhinal FTP-PET (tau)
- Precuneus FDG-PET (glucose metabolism)
- Hippocampal volume (normalized by TIV)
- WM hyperintensities (normalized by WM volume)

Plasma Biomarkers

- SIMOA HDx platform (Neuro-4-plex, Quanterix)
- Plasma A β 42/40 ratio, GFAP and NfL

Aim 1)

	Dual <i>RELN-COLBOS</i> / <i>PSEN1</i> ^{E280A} carriers N = 2		Typical <i>PSEN1</i> ^{E280A} carriers N = 106
Age (years)	46	71	31 (29, 37)
Female sex (n)	F	M	67 (63%)
Education (years)	11	5	11 (9, 13)
Cognitively impaired (n)	CI	CI	10 (9%)
MMSE score	25	23	28 (27, 29)
Delayed recall	1	2	7 (5, 8)

Aim 2)

	<i>RELN-COLBOS</i> Carriers N = 10	Non- Carriers N = 108
Age (years)	78 (59, 93)	35 (31, 39)
Female sex (n)	8 (80%)	67 (62%)
Education (years)	5 (3, 6)	11 (8, 15)
Cognitively impaired (n)	6 (60%)	0 (0%)
MMSE score	22 (19, 24)	29 (28, 29)
Delayed recall	5 (0, 8)	7 (6, 9)

*Mean and standard error data from older-age external cohorts were used to compare plasma biomarkers measured with the same assays (2-4).

CONCLUSIONS

- Carriers of both *RELN-COLBOS* and *PSEN1*^{E280A} variants show **distinct phenotypes suggestive of differential, possibly sex-modulated, resilience** to AD pathology
- RELN-COLBOS*-only carriers exhibit relatively **small age-related increases in GFAP**, but overall protective effects on brain aging are unclear. Smaller-than-expected effects may be **confounded by sex differences**, considering 8 in 10 *RELN-COLBOS* carriers were female.
- Larger, longitudinal and age-matched studies are needed to elucidate the mechanisms through which *RELN-COLBOS* confers protection, in order to **inform novel therapeutic** avenues to enhance resilience against AD and **promote healthy brain aging**

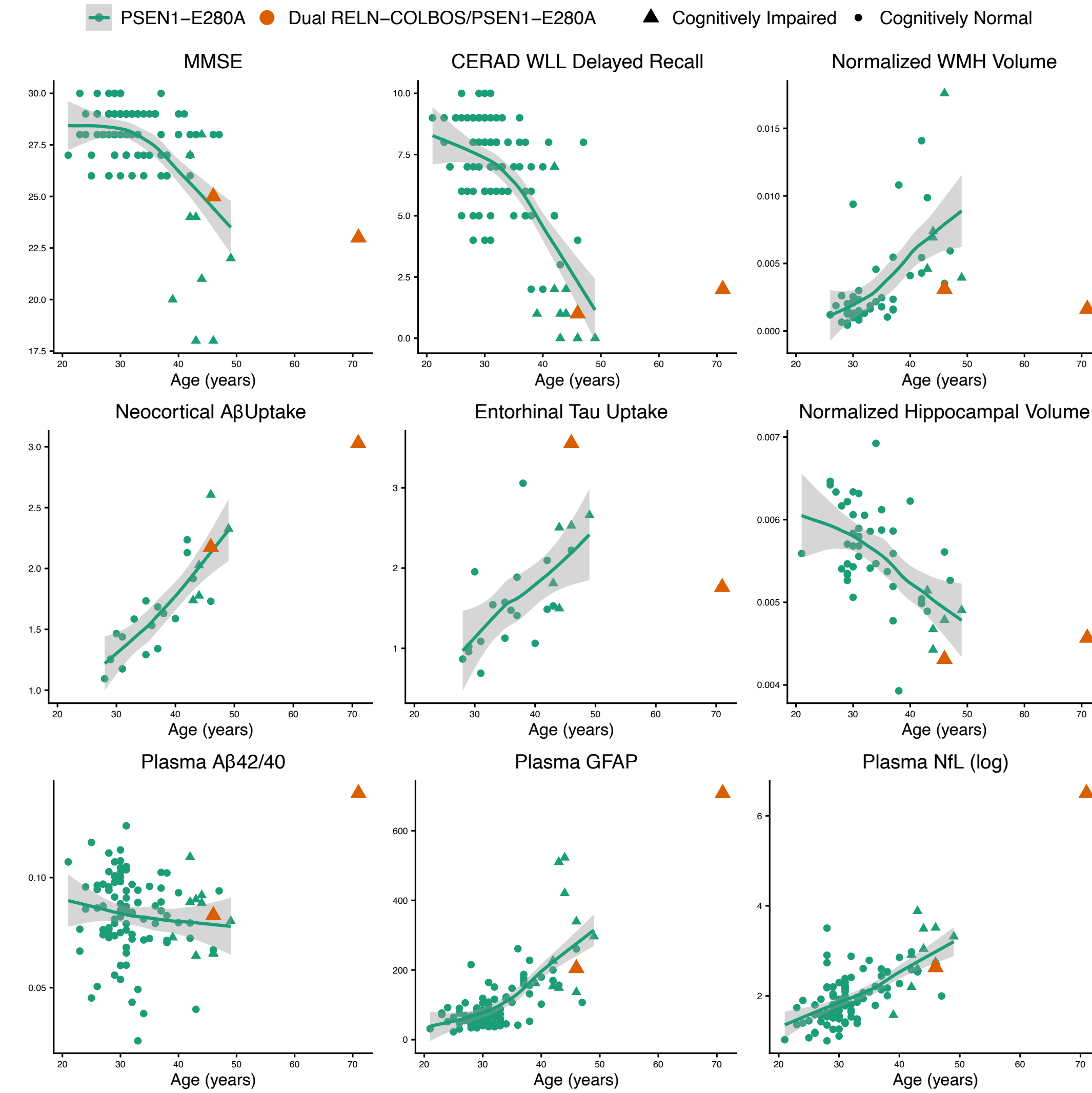
The *RELN-COLBOS* variant may be protective against pathologic changes in ADAD but its effects on the disease-free adult lifespan remain unclear and may be modulated by sex.

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References: (1) Lopera et al. Nat Med 29, 1243 (2023); (2) Stevenson-Hoare et al. Brain 146, 690 (2022); (3) Chatterjee et al. Alzheimers Dement 19, 1117 (2023); (4) Liang et al. Aging Clin Exp Res 37, 105 (2025); (5) Dark et al. Alzheimers Res Ther 16, 94 (2024)

RESULTS

Dual *RELN-COLBOS/PSEN1*^{E280A} vs typical *PSEN1*^{E280A} carriers (ADAD)



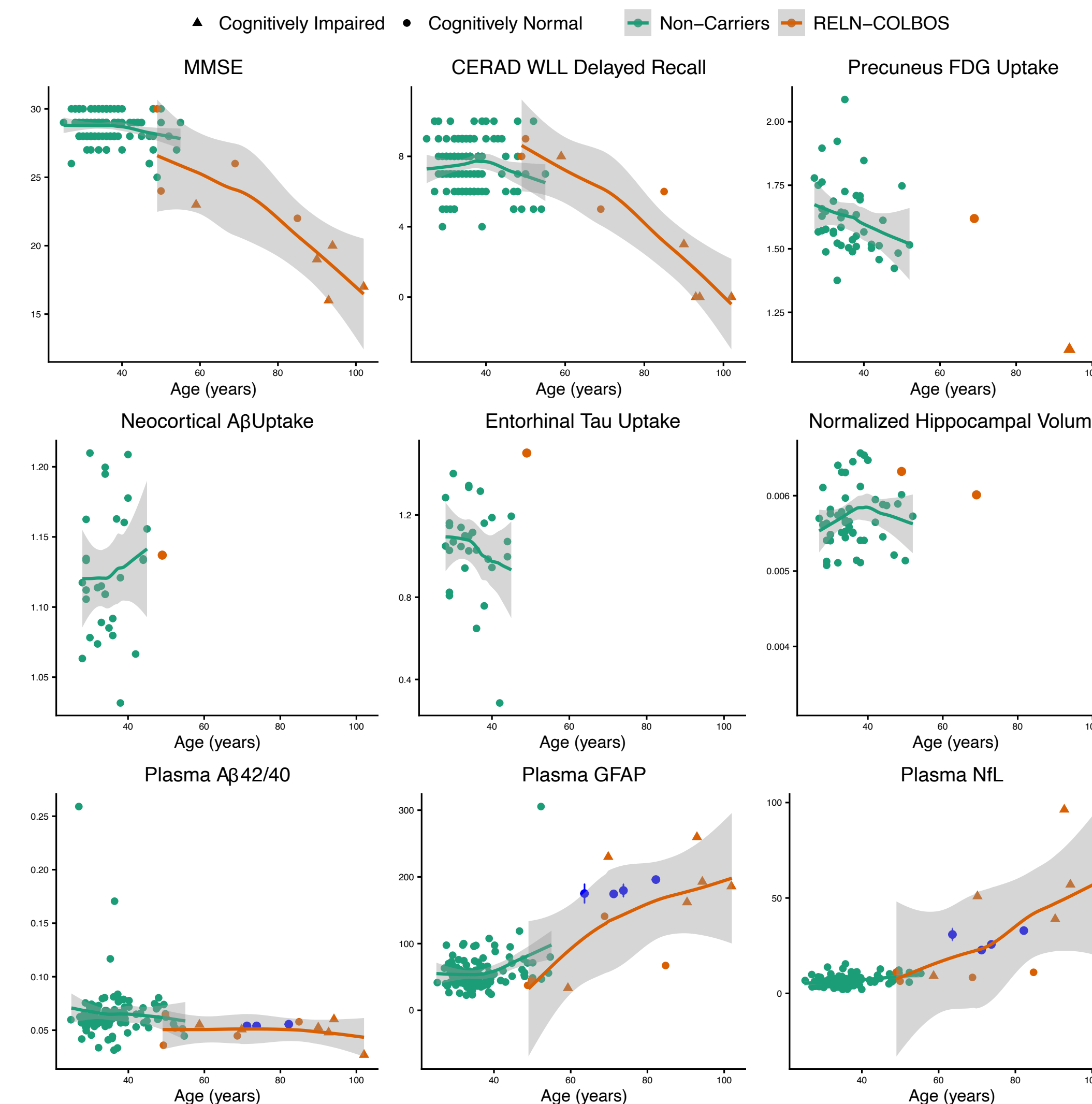
71M landmark case:

- High A β burden but limited tau pathology and neurodegeneration.**
- Plasma biomarkers, including A β 42/40, were higher than in typical *PSEN1*^{E280A} carriers.

41F case:

- Similar cognitive function and A β burden, but greater tau pathology** compared to age-matched typical *PSEN1*^{E280A} carriers.
- Plasma biomarkers were within the range.

RELN-COLBOS carriers vs non-carriers (adult lifespan)



- Cognitive function has a non-linear trajectory in *RELN-COLBOS* carriers.

- Brain metabolism and brain volume may be preserved** in cognitively unimpaired cases.

- Plasma A β 42/40 and NfL are within the expected age-related increase** compared to non-carriers and to age-matched external cohorts, whereas **plasma GFAP may trend toward lower levels** in *RELN-COLBOS*-only carriers