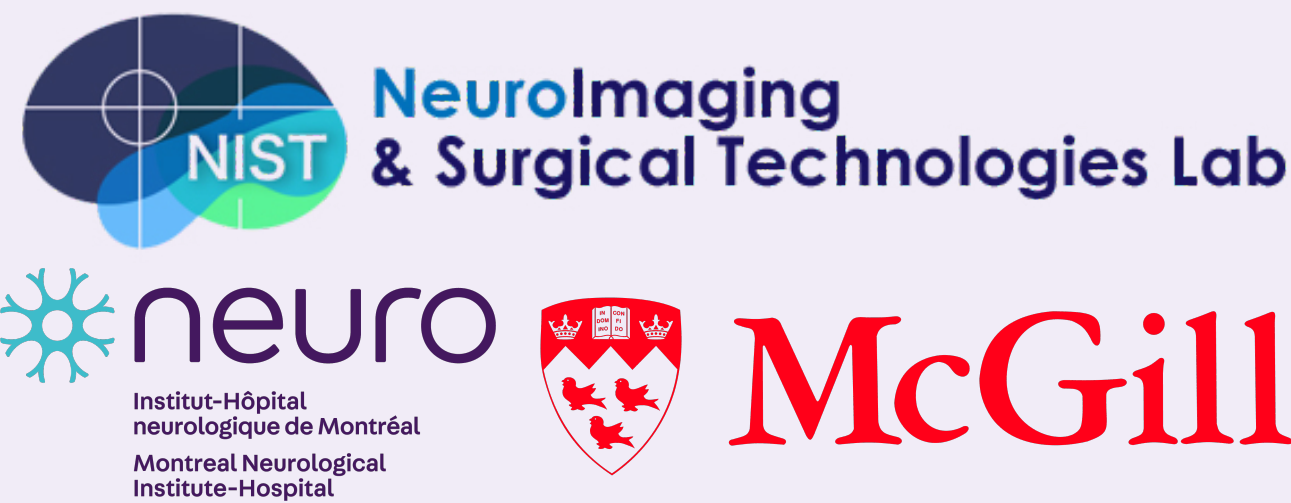


Cardiovascular Risk Decouples Hippocampal Structure from Cognitive Function in Amyloid-Positive Adults

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BACKGROUND

- Hippocampal integrity normally tracks cognition in Alzheimer's disease.
- Cardiovascular risk is a modifiable dementia risk factor, but it is unclear whether it changes the coupling between hippocampal structure and cognition or simply affects each on its own.
- Does cardiovascular risk moderate the **hippocampus-cognition relationship** in amyloid-positive adults? And does this depend on sex and disease stage?

METHODS

- Brain structure:** Hippocampus-to-ventricle ratio, HVR (HC / HC + VC);² converted to age- and sex-specific z-scores using UK biobank GAMLSS normative models.³
- Cardiovascular risk:** Framingham Risk Score (FRS); 10-year ASCVD risk.⁴
- Cognition:** ADSP-PHC harmonized composites for memory, language, and executive function.⁵
- Disease stage:** Estimated Disease Time (EDT), estimated years to dementia onset from progression modeling of ADAS-Cog and MMSE.⁶
- Sex-stratified linear mixed-effects models:**
 - Primary: FRS x HVR x time, with quadratic time (years²) and random slopes;
 - Secondary: FRS x HVR x EDT, with random intercepts, EDT tertiles for visualization.
- Covariates:** baseline age, education, APOE ε4 —FDR-corrected across 6 tests.

DATA

- 923 Aβ+ ADNI participants, 4,872 observations.**
- Amyloid positivity:** PET > 25 Centiloids or CSF Aβ+.¹
- Sample and normative reference shown in **Table 1**.

Table 1. Sample characteristics.

	Normative	ADNI Aβ+	EDT Tertiles		
	UK Biobank	Full Sample	Early	Middle	Late
N (observations)	27,434	923 (4872)	308 (2016)	307 (1672)	308 (1184)
Sex (M / F)	12,022 / 15,412	513 / 410	166 / 142	165 / 142	182 / 126
Age, years	63.4 (7.5)	73.9 (7.1)	73.5 (6.9)	74.2 (6.8)	74.0 (7.6)
Education, years	13.8 (2.6)	16.1 (2.7)	16.5 (2.6)	16.1 (2.6)	15.8 (2.9)
APOE ε4 carriers	—	557 (60%)	133 (43%)	202 (66%)	222 (72%)
FRS	—	24.2 (7.2)	25.0 (6.8)	24.9 (7.1)	22.8 (7.5)
HVR z-score	—	-2.10 (1.60)	-1.10 (1.17)	-1.92 (1.48)	-3.28 (1.31)
EDT, years	—	7.2 (5.2)	1.0 (2.4)	7.6 (1.7)	12.9 (1.4)

Values: mean (SD) or N (%); — = not applicable. FRS ceiling: 76% of females at 30%. Lower FRS in Late tertile may reflect survivorship.

RESULTS

- FRS x HVR was significant in all 6 tests (β -0.008 to -0.002): as cardiovascular risk increased, hippocampal structure predicted cognition less well (Fig 1).
- The three-way FRS x HVR x EDT interaction was significant in 5 of 6 tests (female memory not significant); in males the effect grew from early to late disease stage (Fig 2).
- Female effects were larger, but less precise, as 76% of females reached the FRS ceiling.

CONCLUSIONS

In Amyloid-positive adults, cardiovascular risk weakens the link between hippocampal structure and cognition, with patterns that differ by sex and disease stage.

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Figure 1.

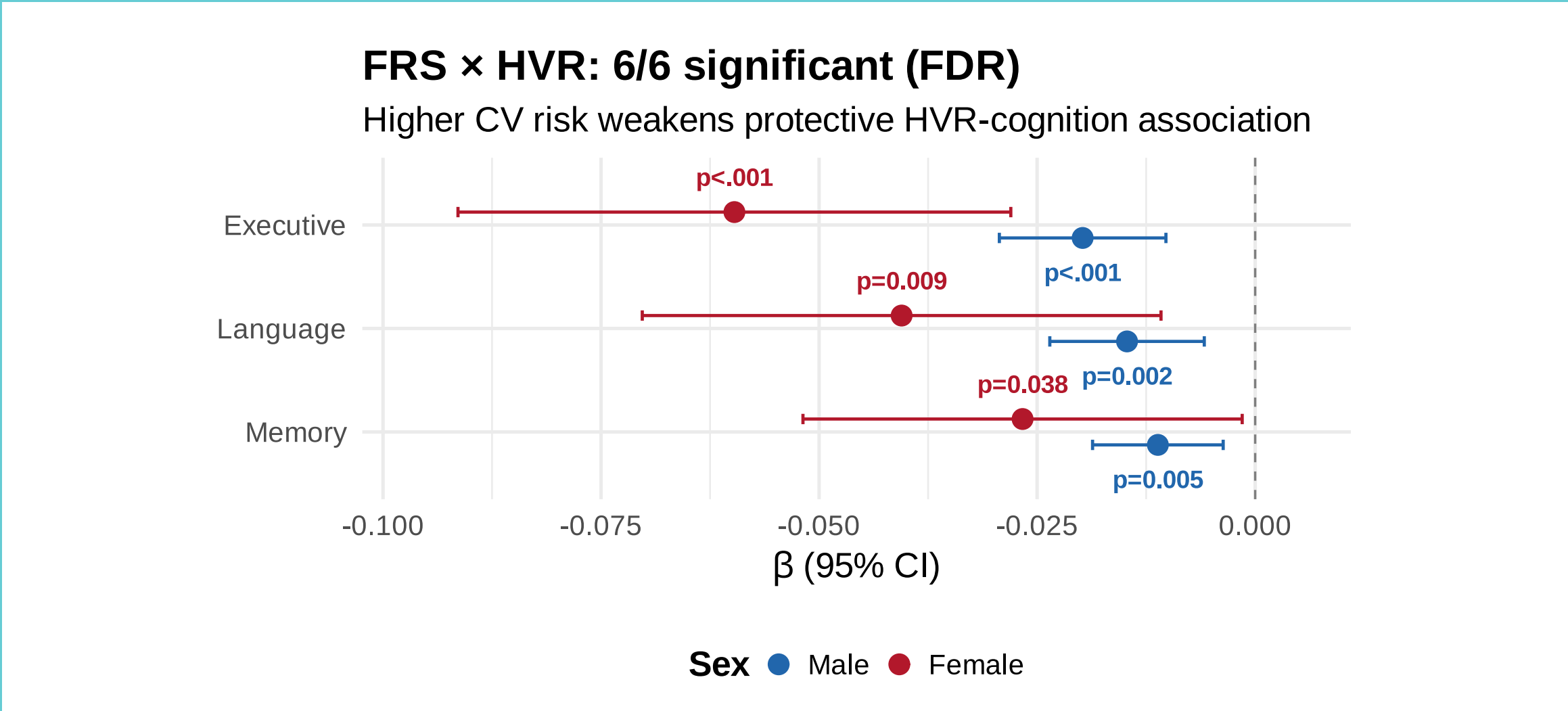
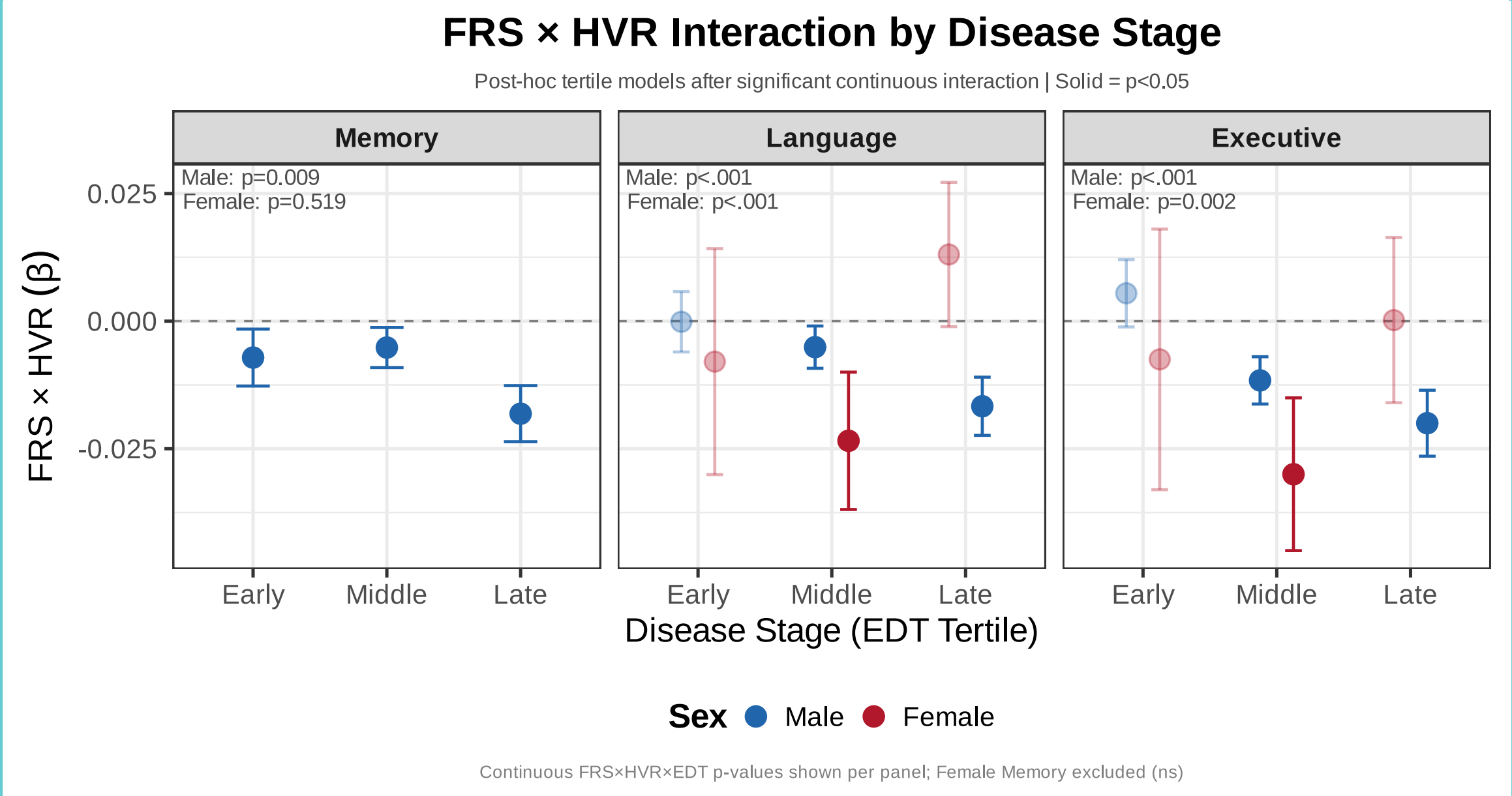


Figure 2.



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- FRS is heavily age-weighted and validated for ages 30–74; this cohort (mean ≈ 74) sits outside that range, entangling cardiovascular risk with non-modifiable aging.
- With an age-orthogonal cardiovascular measure, these associations attenuate.



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