

Amyloid Burden Modifies Vascular Brain-Aging Pathways to Cognition in Cognitively Normal Adults: A Harmonized Multi-Cohort Analysis

P3-07

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KEY TAKEAWAY: Amyloid burden modifies vascular risk effects on cognition through global BAG and regional Aβ– reference centile brain-aging pathways.

INTRODUCTION

In cognitively normal adults, regional brain structure is shaped by both amyloid-β (Aβ) pathology and modifiable vascular risk factors. Prior studies have linked Aβ and vascular burden separately to brain atrophy and worse cognitive performance, but it remains unclear whether these effects converge on shared brain-aging pathways. In particular, vascular risk may influence cognition through multiple structural levels: raw regional brain volumes, deviation from age- and sex-referenced normative structure, and global accelerated brain aging. Large, harmonized multi-cohort imaging analyses are therefore needed to determine whether vascular risk affects cognition through brain-aging markers that overlap with Aβ-related structural vulnerability.

METHODS

Cohorts. Cross-sectional baseline data were used from cognitively normal adults in HABS, ADNI, MCSA, and EPINETTE (N ≈ 3,000; age 43–85). Only the first visit was retained for each participant. All participants had T1-weighted MRI, Aβ status, and MMSE.

Imaging. T1 MRI processed with the ANTs cortical thickness and volumetric pipeline. Regional ROI volumes harmonized across cohorts using CovBat¹, preserving age and sex effects.

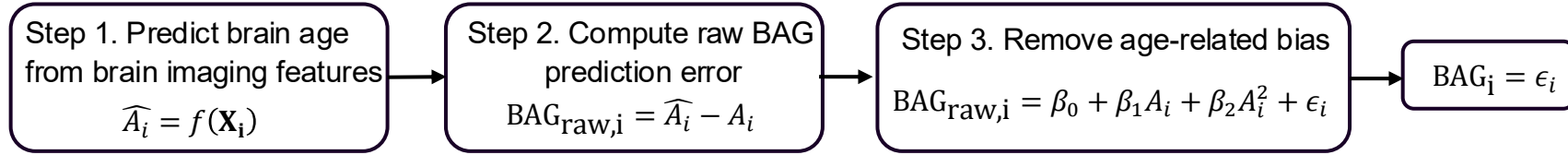
Aβ status. Determined per cohort using cohort-specific cut-points from PET, CSF, or plasma; encoded as binary Aβ–/Aβ+.

Vascular exposures. Binary indicators from clinical records/self-report: hypertension, diabetes, stroke, ever smoking, and obesity.

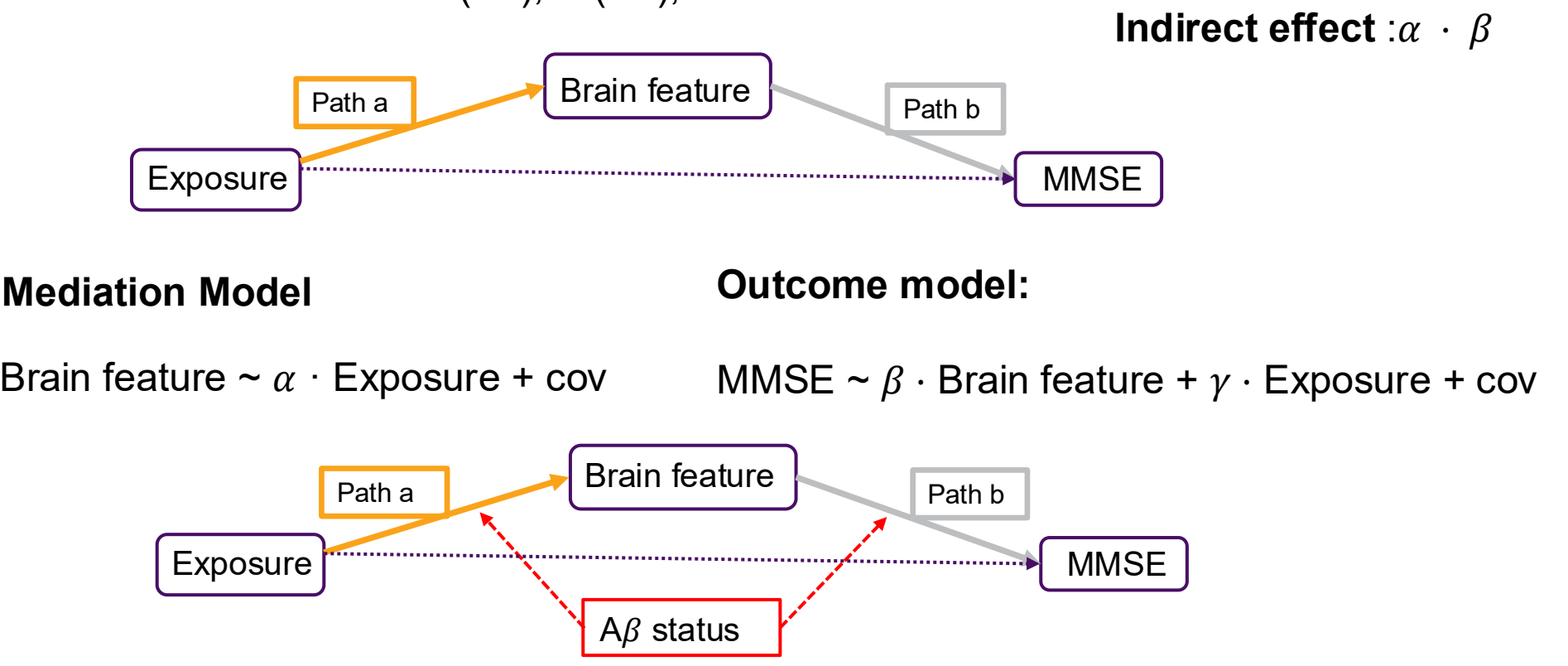
Raw regional MRI features. Sex-stratified GAMs modeled nonlinear age effects and tested ROI-specific Aβ × age interactions, with FDR correction across ROIs.

Reference centiles². Internal centiles were derived from Aβ– participants by ranking GAM-adjusted residual ROI volumes after accounting for age, sex, education, and whole brain volume. Lower centiles indicate smaller-than-reference regional volumes.

Brain Age Gap (BAG)³. BAG captured accelerated global brain aging at the subject level, with higher BAG indicating older-appearing brain structure relative to chronological age.



Mediation framework. Two-equation OLS with bootstrap inference (B = 2,000). Models were run separately using (a) BAG and (b) each regional ROI reference-centile score as the mediator. The Aβ-moderated extension fits exposure × Aβ and mediator × Aβ interactions to estimate IE(A–), IE(A+), and ΔIE.



Mediator model: Brain feature ~ α₁ · Exposure + α₂ · Aβ + α₃ · Exposure · Aβ + cov

Outcome model: MMSE ~ β₁ · Brain feature + β₂ · Exposure + β₃ · Aβ + β₄ · Exposure · Aβ + β₅ · Brain feature · Aβ + cov

Indirect effects: IE(Aβ–) = α₁ β₁; IE(Aβ+) = (α₁ + α₃)(β₁ + β₅); ΔIE = (α₁ + α₃)(β₁ + β₅) – α₁ β₁

Harmonization Removes Site Effects, Preserves Signal

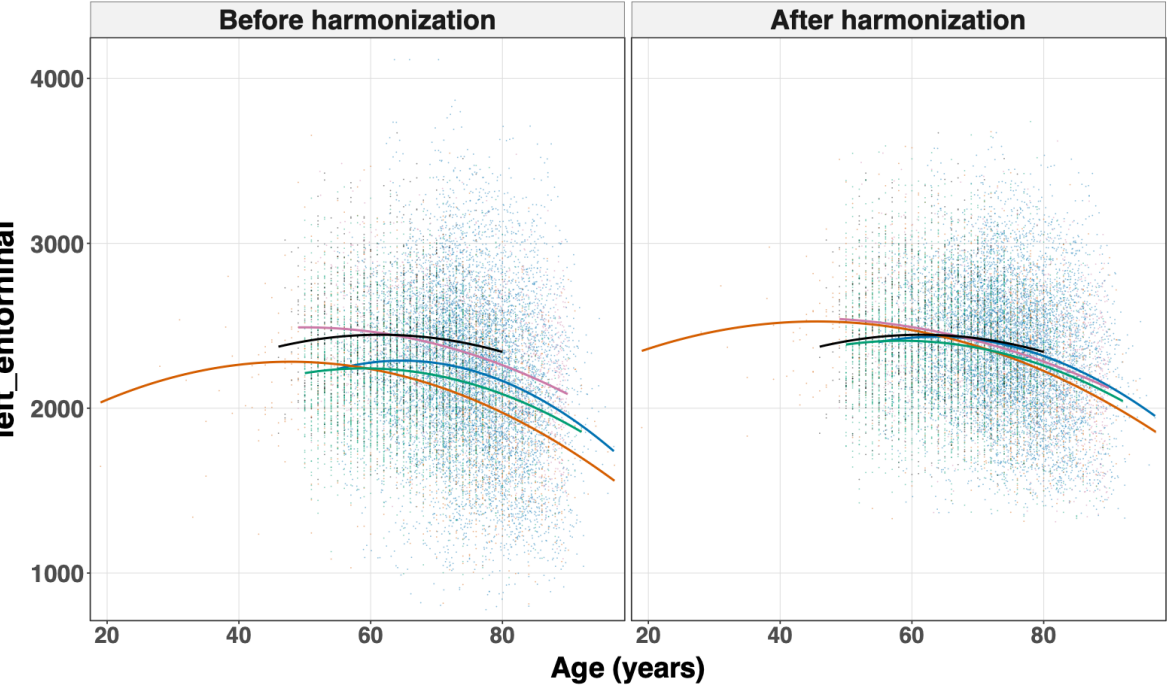


Fig. 1. CovBat substantially reduced site effects in ROI volumes while preserving GAM-modeled age and sex effects. After harmonization, ROI volume distributions showed greater overlap across HABS, ADNI, MCSA, and EPINETTE, supporting pooled cross-cohort analysis.

BAG and Reference centiles by Aβ status and sex

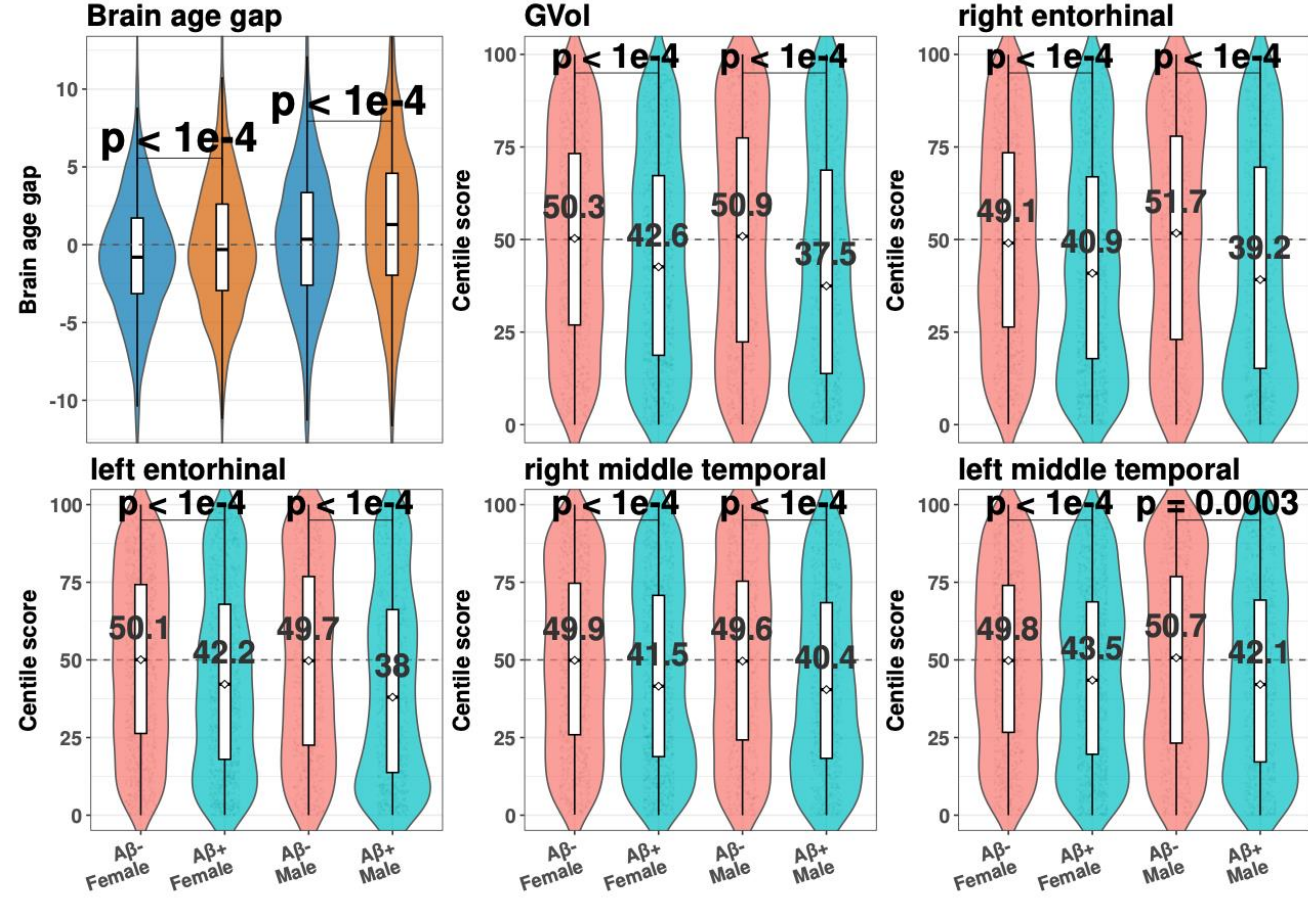


Fig. 2. Brain-aging markers differ by Aβ status within sex. BAG and reference-centile ROI score distributions are shown by Aβ status and sex. Aβ+ participants had significantly higher BAG than Aβ– participants in both females and males, indicating greater global brain aging burden. Reference-centile scores for selected cortical and volumetric ROIs also differed by Aβ status, suggesting region-specific patterns of Aβ-related brain aging beyond the global BAG measure.

Raw MRI Features: Aβ-Related Regional Structural Patterns

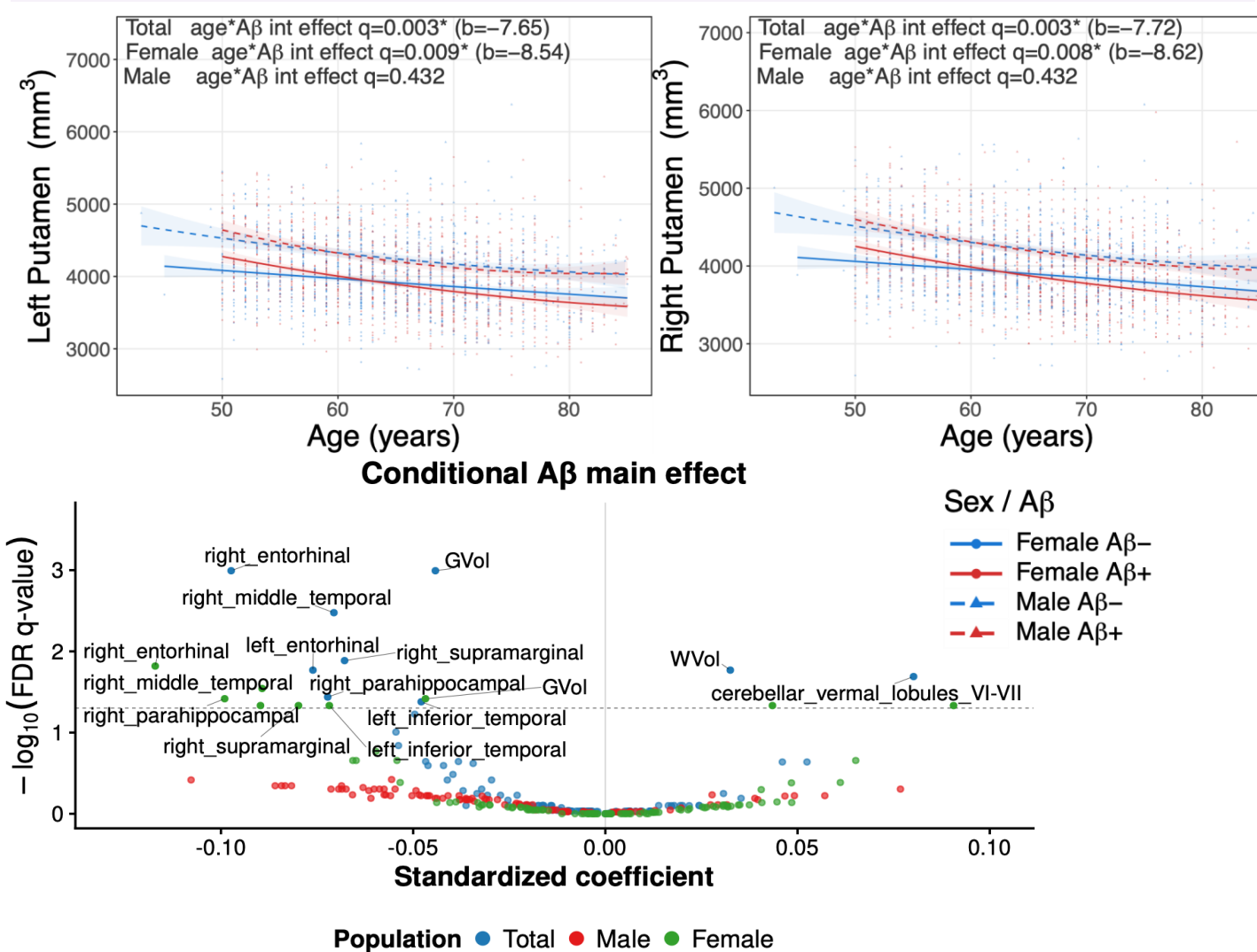


Fig. 3. Aβ-related structural patterns in raw MRI features. (Top) Sex-stratified GAMs tested ROI-specific Aβ × age effects while adjusting for nonlinear age effects, education, and whole-brain volume. Significant age-dependent Aβ effects were observed in bilateral putamen, most prominently in females. (Bottom) Volcano plots show standardized conditional Aβ main effects; labeled ROIs survived FDR q < 0.05. Aβ main effects were most evident in medial/lateral temporal regions. Summary: Using raw MRI features, Aβ pathology was associated with lower regional volumes, particularly in medial/lateral temporal regions, while Aβ-related age effects were strongest in females and most evident in bilateral putamen.

RESULTS

Brain Age Gap: Global Brain-Aging Mediation Pathways

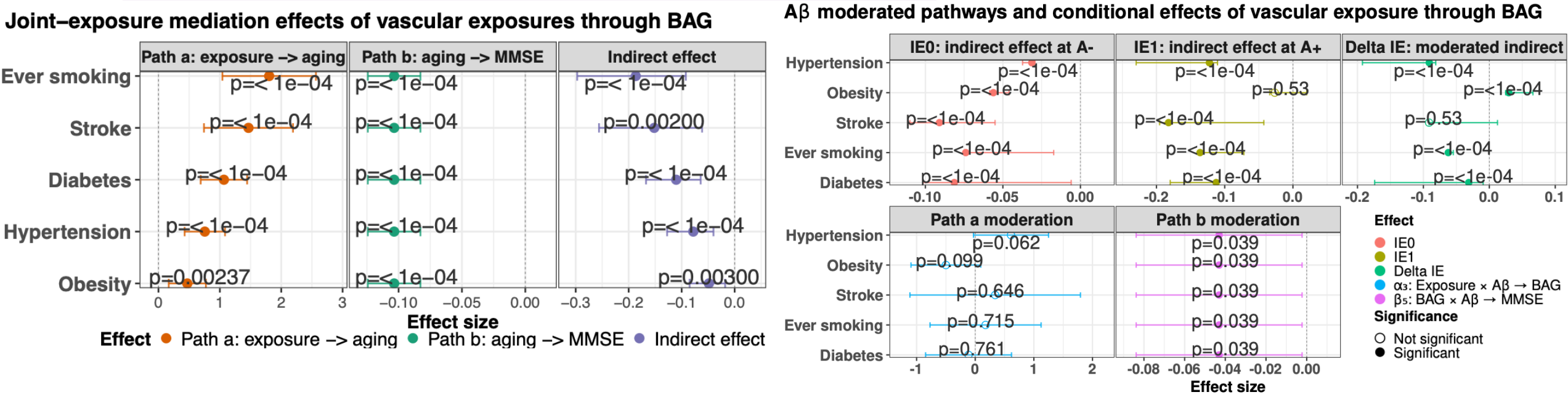


Fig. 4. BAG mediates vascular effects on cognition, amplified by Aβ status. (Left) Joint-exposure mediation models included all five vascular exposures simultaneously, so each indirect effect reflects its unique contribution after accounting for the other exposures. All five vascular exposures were associated with higher BAG, and higher BAG was associated with lower MMSE, yielding significant BAG-mediated indirect effects for all exposures. Stroke and ever smoking showed the largest BAG-mediated effects. (Right) Aβ-moderated mediation models estimated conditional indirect effects by Aβ status, with ΔIE = IE(Aβ+) – IE(Aβ–). Aβ moderation operated mainly through the BAG → MMSE path, suggesting that amyloid pathology increases the cognitive cost of accelerated brain aging rather than primarily amplifying vascular effects on BAG. Obesity showed a distinct pattern, with a significant indirect effect only in Aβ– individuals. Summary: These findings support BAG as a global brain-aging pathway linking vascular burden to cognition, with Aβ pathology amplifying selected vascular risk–brain aging–cognition associations.

Reference Centiles: Regional Brain-Aging Mediation Pathways

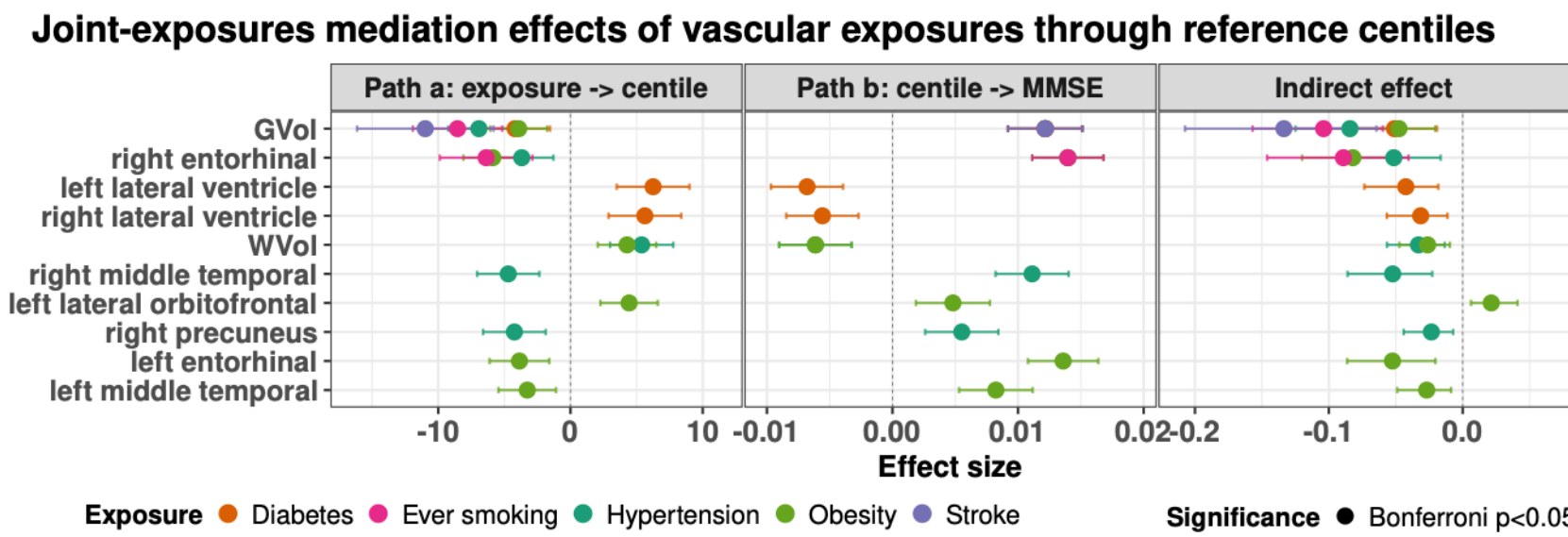
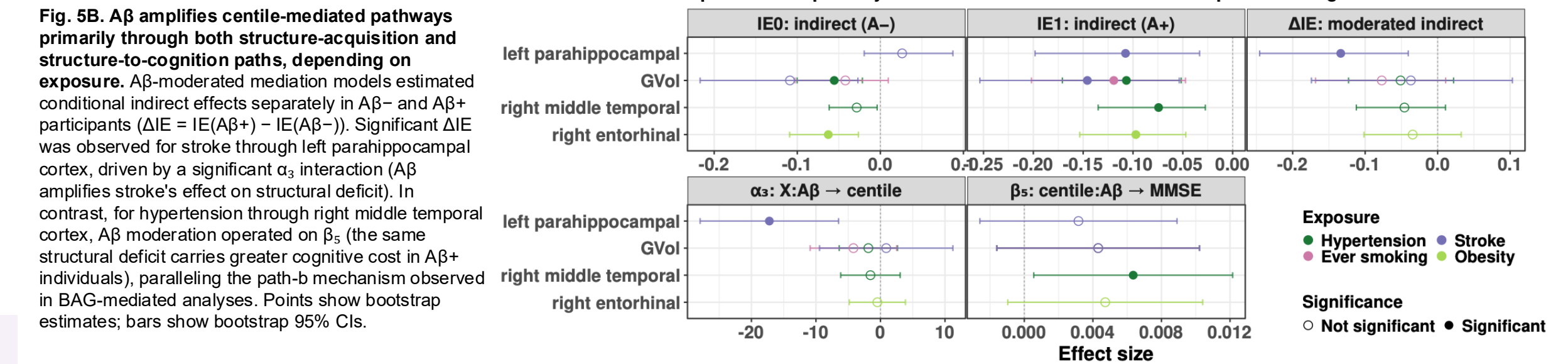


Fig. 5A. Regional reference-centile mediation links vascular exposures to cognition, converging on temporal cortex. Joint-exposure mediation models tested whether ROI reference centiles mediated associations between vascular exposures and MMSE. All five exposures showed significant indirect effects through at least one ROI. Mediating ROIs were concentrated in entorhinal and middle temporal cortex for hypertension and obesity, and in global and white matter volumes for diabetes and stroke, with lateral ventricle volumes showing positive path a effects (larger ventricles) consistent with atrophy-related expansion. Points show standardized estimates; bars show bootstrap 95% CIs.



Joint-exposure mediation network linking vascular exposures to MMSE through brain-aging markers

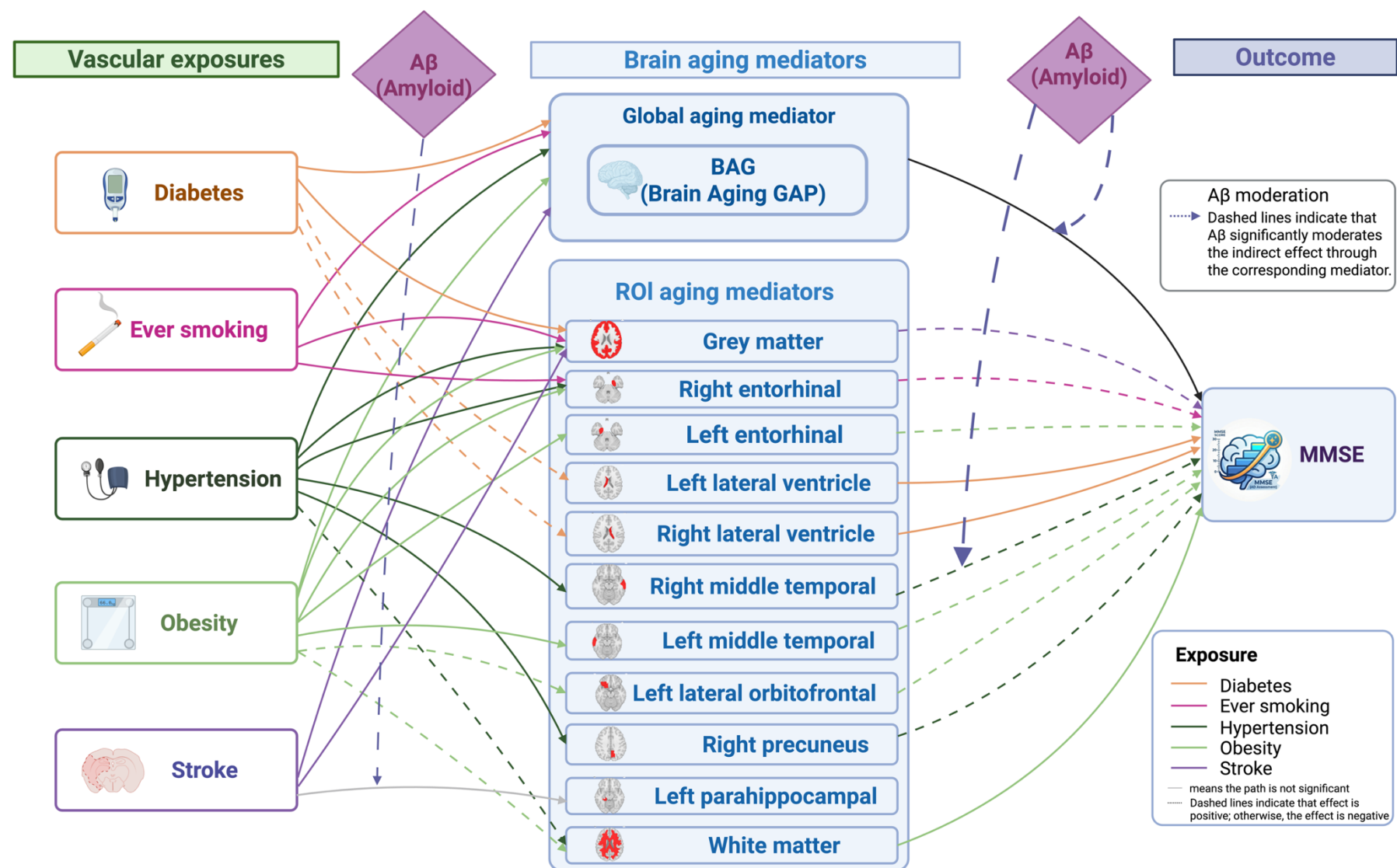


Fig. 6. Joint-exposure mediation network linking vascular exposures to MMSE through brain-aging markers. The diagram summarizes significant mediation pathways linking vascular exposures to MMSE through global and regional brain aging mediators. Vascular exposures are shown on the left, brain aging mediators in the center, and MMSE on the right. Edge color indicates the corresponding vascular exposure. Dashed colored edges indicate positive indirect effects, whereas solid colored edges indicate negative indirect effects. Thin grey edges indicate non-significant paths. Aβ is shown as a moderator, with purple dashed arrows indicating pathways in which Aβ significantly moderates the indirect effect through the corresponding mediator.

CONCLUSIONS

In cognitively normal adults, vascular risk factors influence cognition through brain-aging structural pathways that include both accelerated global brain aging and region-specific deviation from normative Aβ– structural aging. Aβ pathology is associated with lower temporal regional volumes and amplifies selected vascular risk–brain aging–cognition pathways. The convergence of amyloid- and vascular-related effects in medial and lateral temporal cortex suggests a shared structural vulnerability zone. These findings support the value of combining raw MRI features, reference centile scores, and BAG to identify early brain-aging pathways through which modifiable vascular risks may affect cognition before clinical impairment emerges.

LIMITATIONS

- Cross-sectional design limits causal interpretation. Associations are consistent with mediation but do not establish temporal ordering; longitudinal analyses are needed to evaluate within-person change over time.
- Measurement constraints in exposure, Aβ, and cognition. Heterogeneous Aβ definitions, potential exposure misclassification, and coarse MMSE scores may attenuate effects; future work will use continuous Aβ measures and domain-specific cognitive outcomes.

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