

INTRODUCTION

Neurovascular dysfunction and blood-brain barrier (BBB) disruption may occur early in Alzheimer's disease (AD). The MTHFR C677T polymorphism can reduce enzyme activity and influence one-carbon metabolism, homocysteine-related endothelial stress, and vascular injury, but its relationship with BBB imaging markers in amyloid-positive individuals remains uncertain. We therefore examined whether C677T genotype was independently associated with DCE-MRI measures of BBB permeability (Ktrans) and vascular plasma volume (Vp) across the preclinical and prodromal AD continuum.

STUDY DESIGN

32 amyloid-positive participants with complete MTHFR genotype and DCE-MRI

- 1** 9 SMI
clinically unimpaired
- 2** 23 MCI
prodromal stage
- 3** 100% PET+
amyloid confirmed
- 4** Age 68.7 y
mean +/- SD 8.4

Genotype distribution Hardy-Weinberg equilibrium p=.419

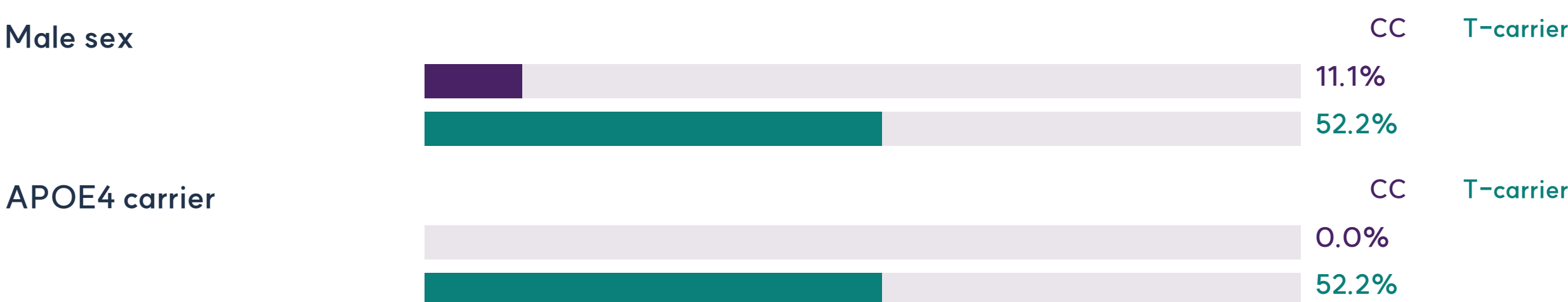
CC n=9 CT n=18 TT n=5

- 1** 3T DCE-MRI
Low-leakage dynamic contrast imaging
- 4** Patlak model
Regional Ktrans and Vp extraction
- 2** Ktrans
Permeability-related transfer constant
- 5** Vp
Vascular plasma volume; perfusion-related
- 3** ROI composites
Bilateral hippocampal, temporal, frontal and orbitofrontal regions
- 6** Primary endpoint
Prespecified bilateral hippocampal Ktrans

ANALYSIS PLAN

- 1** Dominant genetic model
CT/TT vs CC: additive coding as sensitivity analysis
- 2** Fully adjusted regression
Age, sex, education, stage, APOE4, vascular risk burden: HC3 SE
- 3** Multiplicity + robustness
Family-wise FDR: bootstrap and Freedman-Lane permutation (5,000 each)

WHY COVARIATE ADJUSTMENT MATTERED

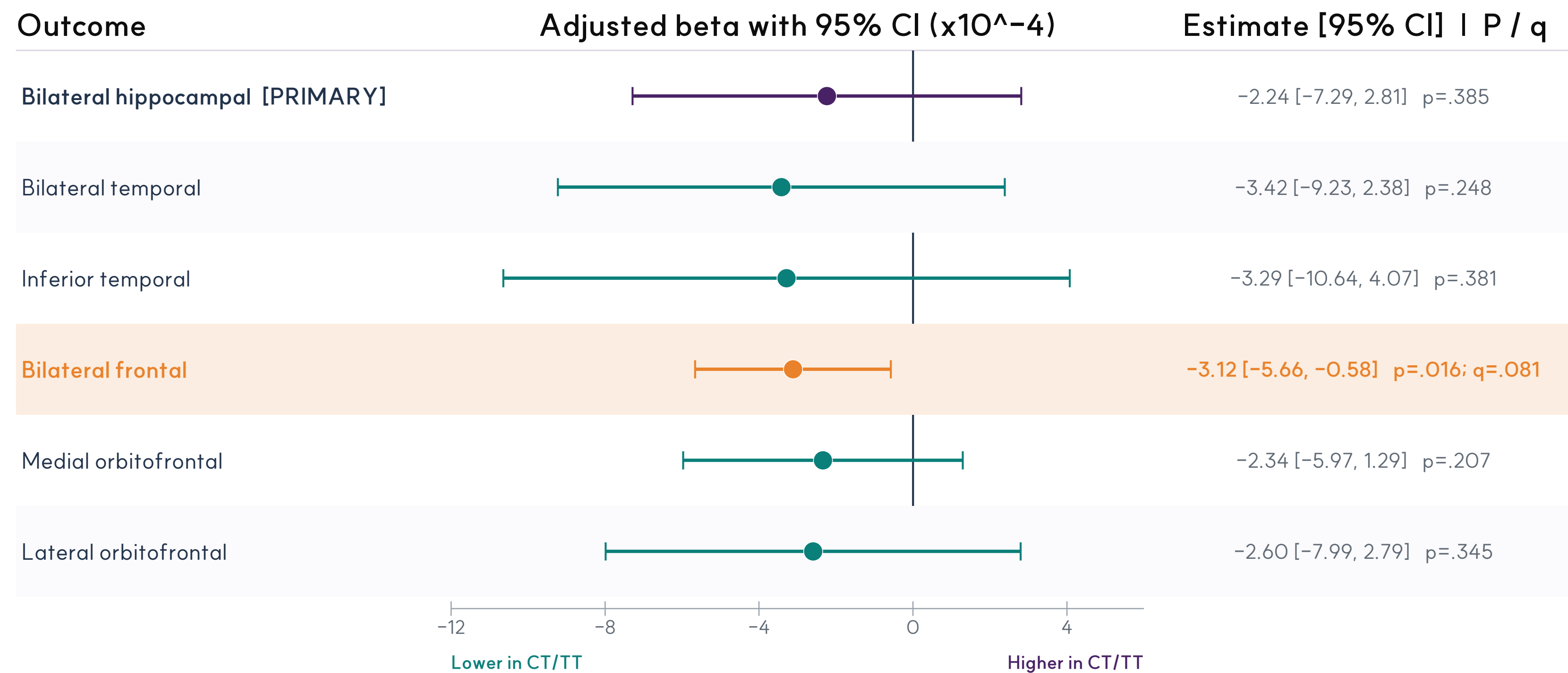


PRIMARY ENDPOINT
Null
Hippocampal Ktrans
p=.385; permutation p=.362

SECONDARY SIGNAL
Nominal
Frontal Ktrans
p=.016; FDR q=.081

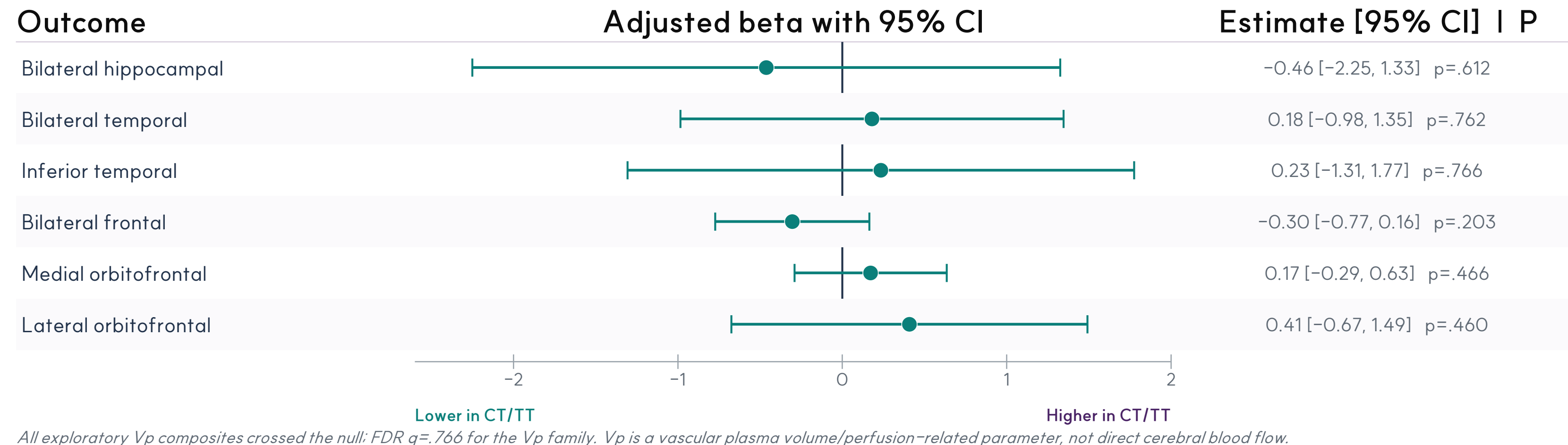
PERFUSION-RELATED Vp
No signal
No stable composite or ROI association

ADJUSTED Ktrans COMPOSITES



Dominant model (CT/TT vs CC), adjusted for age, sex, education, cognitive stage, APOE4 and vascular risk burden. Frontal association was nominal and did not survive FDR.

EXPLORATORY Vp COMPOSITES



All exploratory Vp composites crossed the null: FDR q=.766 for the Vp family. Vp is a vascular plasma volume/perfusion-related parameter, not direct cerebral blood flow.

ROBUSTNESS CHECKS

PRIMARY: HIPPOCAMPAL Ktrans

Bootstrap 95% CI: -6.79 to 3.10 x10⁻⁴
Permutation p=.362 -> consistently null

EXPLORATORY: FRONTAL Ktrans

Bootstrap 95% CI: -5.28 to -0.58 x10⁻⁴
Permutation p=.015; ROI-family p=.028; FDR q=.081

WHAT THE DATA SHOW

- 01** Primary hypothesis not supported
T-carrier status was not associated with the prespecified bilateral hippocampal Ktrans endpoint.
- 02** Frontal signal is hypothesis-generating
Lower frontal Ktrans in CT/TT was nominally significant, but FDR q=.081.
- 03** No robust perfusion-related effect
No Vp composite, medial temporal/frontal Vp family, or single Vp ROI was significant after multiplicity control.
- 04** Broad ROI scans were negative
None of 45 Ktrans or 45 Vp single-ROI tests survived FDR correction.

INTERPRETATION

- Overall, MTHFR C677T did not show a robust independent effect on BBB-related DCE-MRI measures in amyloid-positive early AD.
- The direction of the exploratory frontal signal was opposite to the expected T-allele risk direction.
- In low-leakage tissue, lower Ktrans is not equivalent to a healthier BBB; delivery, SNR, vascular input function and model assumptions can influence estimates.

At most, the genotype effect appears subtle and region-specific; replication is required before biological interpretation.

STRENGTHS & LIMITATIONS

STRENGTHS

- Amyloid-confirmed cohort
- Prespecified primary endpoint
- Clinically relevant covariate adjustment
- Cross-sectional imaging
- FDR + resampling robustness

LIMITATIONS

- Small, single-center sample (n=32)
- Sex/APOE4 imbalance
- Cross-sectional imaging
- No homocysteine, folate or B12 measures

CONCLUSION

In this amyloid-positive preclinical/prodromal AD cohort, MTHFR C677T was not independently associated with the prespecified bilateral hippocampal Ktrans measure. Although T-allele carriers showed a nominally lower frontal Ktrans signal, the association did not survive false discovery rate correction, and no robust Vp effect was observed. These findings suggest that any genotype-related BBB imaging effect is subtle and region-specific and should be validated in larger, biomarker-rich longitudinal cohorts.

