

Blood Volume Influences Blood Biomarker Associations With MRI Atrophy, FDG Hypometabolism, and Cognitive Decline in Alzheimer's Disease

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INTRODUCTION

Blood-based biomarkers (BBMs) have emerged as promising indicators of Alzheimer's disease (AD) risk¹.

We previously demonstrated that blood volume (BV) influences AD BBM concentrations and modifies BBM-based amyloid PET classification in cognitively unimpaired (CU) individuals, consistent with physiologic dilution².

Here, we tested whether BV modifies BBM associations with MRI atrophy, FDG-PET hypometabolism, and cognitive decline.

METHODS

Sample: A retrospective analysis of participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Sample sizes ranged by outcome:

- N=206 participants in MRI analyses
- N=311 participants in PET analyses
- N=483 participants in cognitive decline analyses

Outcomes:

- MRI Knudsen-Boundary Shift Integral (KN-BSI) as a measure of whole-brain atrophy
- FDG-PET meta-ROI SUVR as a measure of AD-vulnerable hypometabolism
- Incident conversion from 1) CU to MCI/AD, or 2) MCI to AD

Exposures:

- BBMs including $A\beta_{42}$, $A\beta_{42/40}$, p-tau₂₁₇, p-tau_{217/A\beta_{42}}, GFAP, and NfL
- Estimated BV (Nadler formula)
- BBM $\times$ BV interaction terms

Statistical analysis:

- Imaging outcomes were assessed using linear regression models adjusted for age, sex, APOE4 carrier status, and diagnosis
- β coefficients were standardized for visualization; unstandardized for inference
- Diagnostic conversion was assessed using Cox proportional hazards models

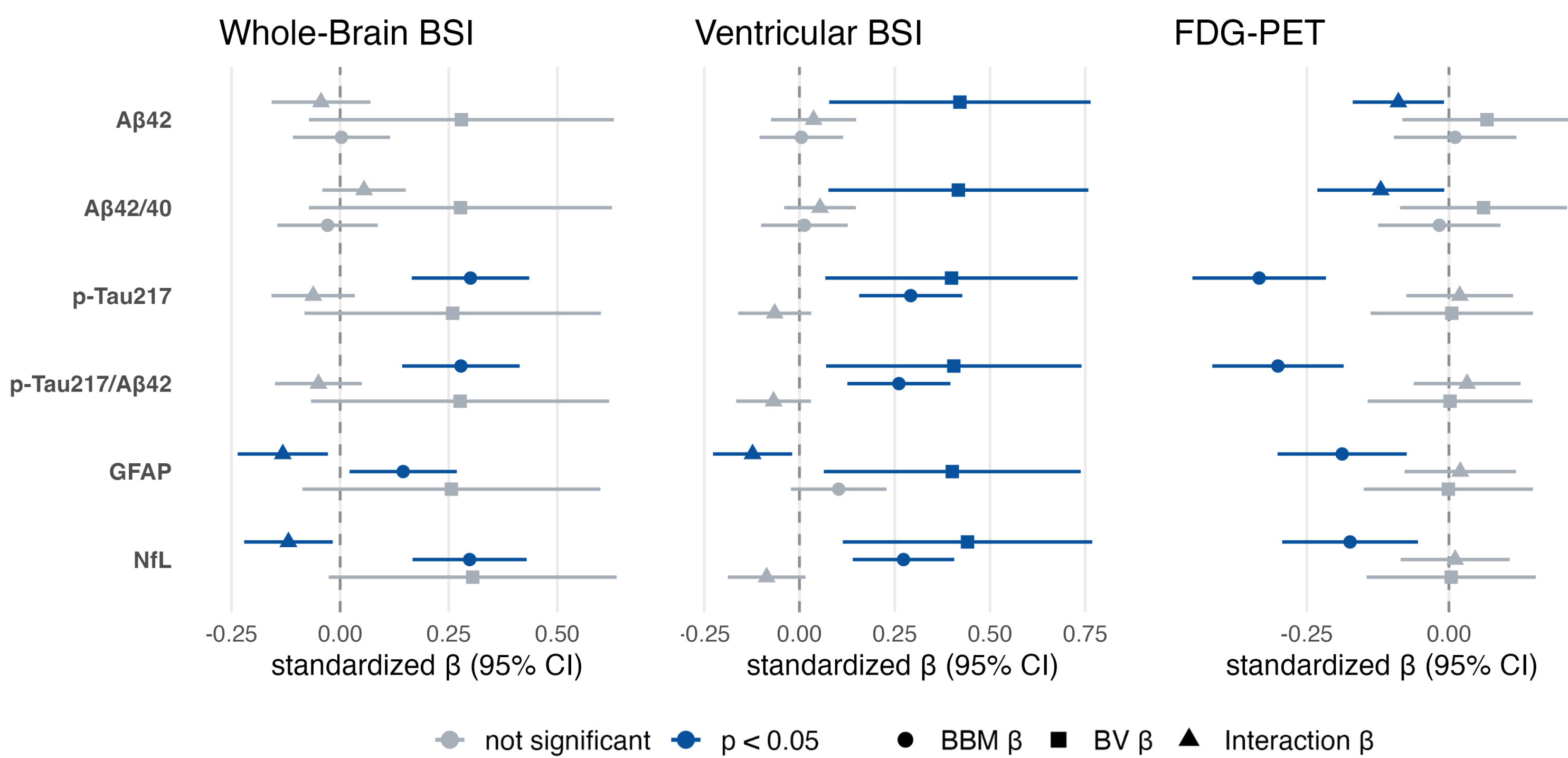


Figure 1. Standardized BBM and BBM $\times$ BV associations with neuroimaging outcomes. Forest plots show β coefficients and 95% CIs for BBM main effects, BV main effects, and BBM $\times$ BV interactions. Standardized β coefficients were used for visualization; statistical inference was based on unstandardized models.

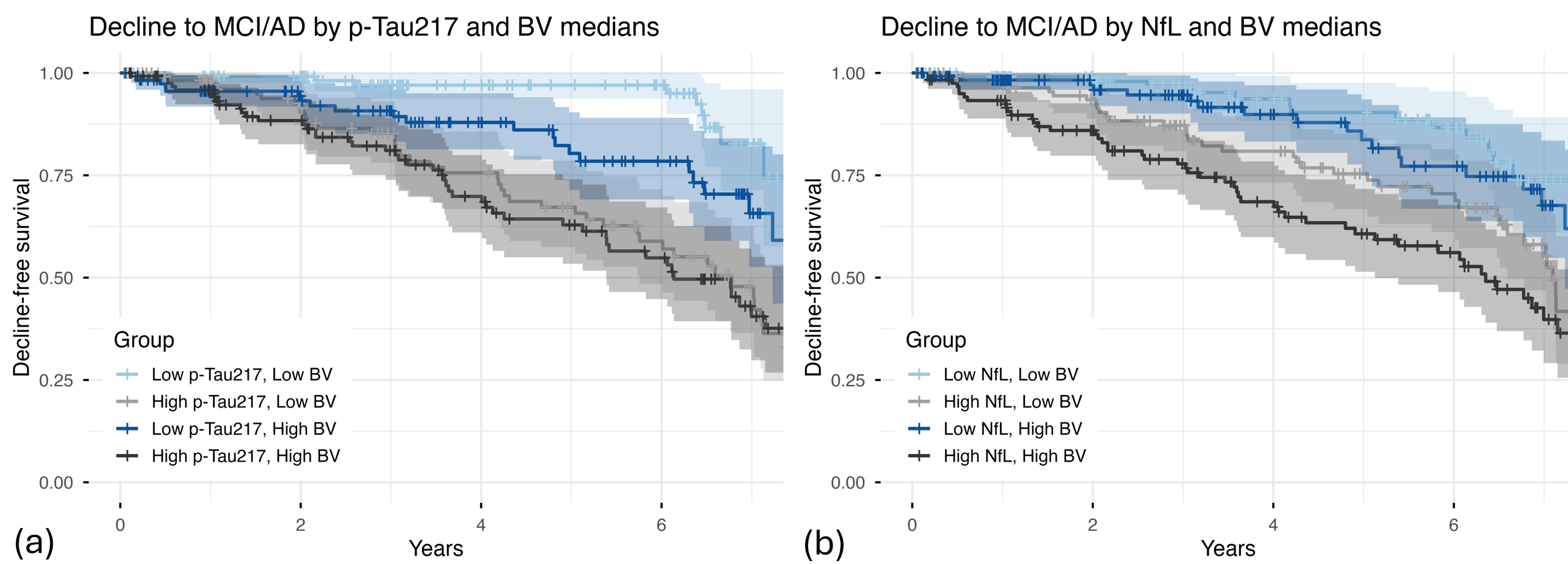


Figure 2. Kaplan-Meier curves for decline-free survival by baseline BBM and BV strata. Curves show time from CU status to incident MCI/AD stratified by median (a) p-tau₂₁₇, (b) NfL, and BV. Kaplan-Meier curves are shown for visualization; Cox models using continuous, standardized predictors were used for inference.

Table 1. Baseline characteristics by analytic cohort.

Variable	KN-BSI analysis	FDG-PET analysis	Cognitive decline analysis
N	206	311	483
Age, median [IQR]	76.16 [71.32, 81.79]	75.06 [70.59, 80.19]	72.04 [67.21, 77.23]
Sex = Male (%)	120 (58.3)	188 (60.5)	215 (44.5)
Diagnosis (%)			
CU	83 (40.3)	85 (27.3)	483 (100.0)
MCI	37 (18.0)	149 (47.9)	
AD	86 (41.7)	77 (24.8)	
APOE4 Carrier = 1 (%)	111 (53.9)	152 (48.9)	178 (36.9)
$A\beta_{42}$ (pg/mL), median [IQR]	25.02 [22.65, 28.66]	24.17 [20.91, 28.30]	25.89 [22.20, 29.44]
$A\beta_{42/40}$, median [IQR]	0.08 [0.08, 0.09]	0.08 [0.08, 0.09]	0.09 [0.08, 0.10]
p-Tau ₂₁₇ /A β_{42} , median [IQR]	-1.91 [-2.25, -1.55]	-1.96 [-2.31, -1.63]	-2.32 [-2.52, -2.09]
p-Tau ₂₁₇ (log ₁₀ pg/mL), median [IQR]	-0.50 [-0.83, -0.16]	-0.57 [-0.89, -0.26]	-0.90 [-1.09, -0.69]
GFAP (log ₁₀ pg/mL), median [IQR]	2.30 [2.10, 2.46]	2.25 [2.07, 2.41]	2.12 [1.98, 2.27]
NfL (log ₁₀ pg/mL), median [IQR]	1.39 [1.24, 1.52]	1.36 [1.23, 1.49]	1.21 [1.08, 1.34]
BV (L), mean (SD)	4.64 (0.89)	4.65 (0.87)	4.50 (0.95)

RESULTS

MRI Atrophy:

- Higher p-tau₂₁₇, p-tau_{217/A\beta_{42}}, GFAP, and NfL were each associated with greater whole-brain atrophy
- BV significantly attenuated associations of GFAP and NfL with atrophy

FDG-PET:

- Lower $A\beta_{42}$ and $A\beta_{42/40}$ were associated with FDG-PET hypometabolism in AD-vulnerable regions, with significant attenuation at higher BV
- p-tau₂₁₇ and p-tau_{217/A\beta_{42}} showed weaker associations without significant BV modification

Cognitive decline:

- In CU participants, higher p-tau₂₁₇, p-tau_{217/A\beta_{42}}, and GFAP predicted conversion to MCI/AD. NfL demonstrated a significant BV-dependent interaction, while p-tau₂₁₇ showed a trend toward BV attenuation
- In MCI participants, conversion to AD was strongly associated with all BBMs, without significant BV modification

CONCLUSIONS & FUTURE WORK

BV modified select BBM associations with neuroimaging and diagnostic conversion in a biomarker-, outcome-, and stage-specific manner. These findings suggest that physiologic dilution may be important for interpreting plasma AD biomarkers across imaging and clinical outcomes.

REFERENCES

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