Predicting Alzheimer's Disease Using Common Cerebrovascular Imaging Biomarkers

Revealing a Novel Cerebrovascular Signature of Alzheimer's Risk: A Comparative Cross-Sectional Study of Structural MRI and Amyloid PET Biomarkers

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Background.

- **How Alzheimer's disease (AD) is currently defined:**
  - presence of cognitive impairment
  - accumulation of amyloid-β (Aβ) plaques[1,2]
- **Cerebrovascular Disease (CVD) Risk Factors associated with AD**
  - Age and apolipoprotein-E ε4 (APOE-ε4) genotype[3]
  - Comorbid Conditions[2,3,4,5]: Hypertension, Diabetes and Hyperlipidemia
- **Problem:** Lack of evidence supporting use of CVD markers when screening for AD [2,3]
- **Challenge:** How to integrate CVD biomarkers when assessing risk of AD?
  Approach: Using MRI-based CVD markers[6] to predict Aβ-PET[2] status in ADNI
  - MRI biomarkers used[3,7]
    - cerebral microbleeds (CMBs)
    - ischemic infarction
    - white matter hyperintensities (WMH)
- **Hypothesis**: CVD burden would be positively associated with amyloid accumulation in all groups even when stratified by cognitive status.

Methods

- **Data Source:** Alzheimer's Disease Neuroimaging Initiative database[8] *(N=1,352)*
- **Stratification of Participants**
  - Cognitive Status:
    - Cognitively Unimpaired (CU)
    - Mild Cognitive Impairment (MCI)
    - Dementia (DEM)
  - Presence of CVD Measures
    - Occurrence of CMBs (superficial or deep)
    - Occurrence of Ischemic Infarcts
- **Processing Volumetric Data:**
  - WMH volume (WMHv) and medial temporal lobe volume (MTLv)
    - normalized to whole-brain volume
    - log-transformed
- **Determining Odds Ratio:**
  - Adjusted Odds Ratio (OR) found using logistic regression for dichotomized Aβ-PET status in different CVD measures of interest
- **Factors Adjusted For:**
  - Age, Sex, APOE-ε4 genotype, cognition (MoCA)

Results

- **Associations Between CVD Imaging Biomarkers and Amyloid Positivity Across All Groups**
  - Significant Association
    - WMHv *(OR=1.25, p<.001)*
    - superficial CMBs *(OR=1.45 p<.001)*
  - No Significant Association
    - Deep CMBs *(OR = 0.88, p<.12)*
    - Ischemic Infarction *(OR=1.01, p<.9)*
- **Analysis of Significance By Cognitive Status**
  - WMHv– positively associated with Aβ-PET in all cohorts
    - Cognitively Unimpaired (CU): OR=1.25, p<0.001
    - Mild Cognitive Impairment (MCI): OR=1.15, p<0.001
    - Dementia (DEM): OR=2.17, p<0.001
  - Superficial CMBs— positively associated with Aβ-PET in all cohorts
    - Cognitively Unimpaired (CU): OR=1.38, p<0.001
    - Mild Cognitive Impairment (MCI): OR=1.37, p<0.001
    - Dementia (DEM): OR=2.17, p<0.001
  - Deep CMBs- Biphasic Relationship
    - CU- significant negative association *(OR=0.51, p<.001)*
    - MCI- positive association *(OR=1.32, p=0.037)*
    - DEM- positive association *(OR=2.99, p=0.011)*
  - **Ischemic Infarcts-** Mixed Relationship
    - CU- positive association *(OR=1.31, p=0.005)*
    - MCI & DEM- no correlation

Conclusions

- Emphasizes the importance of cerebrovascular factors in AD pathogenesis
- Several CVD biomarkers are predictive of AD at various stages of the disease
- Possible novel relationships may be important for early detection of preclinical AD
- More longitudinal studies are necessary to examine impact on later cognitive decline
- WMHv appears to be a better predictor for amyloidosis than the established measure of MTLv in the overall cohort
- Study generalizability is limited by ascertainment bias and lack of diversity, which may underestimate the prevalence and effects of mixed AD-CVD pathology in our analysis
- Future directions include developing a way to predict amyloidosis by combining certain CVD factors and currently accepted predictive measures like MTLv, age, APOE4 status, sex, cognition, and comorbidities

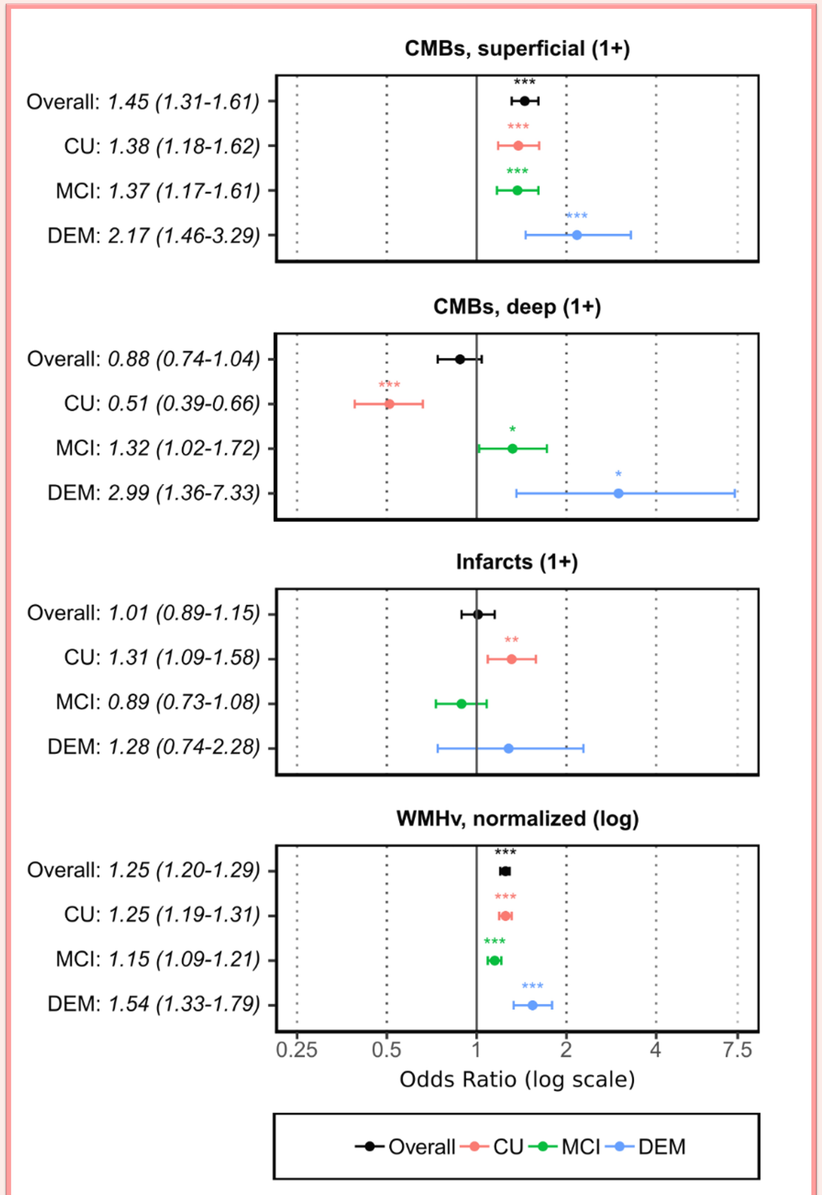
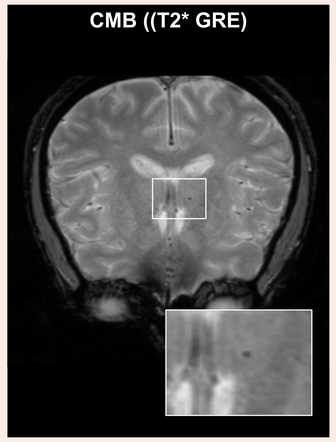
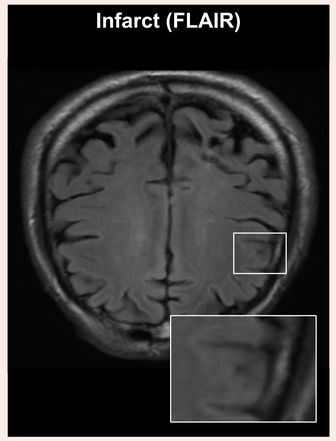


Figure 1: **Differential prediction of Aβ-PET positivity by CVD-related MRI findings.**
Forest plots show the adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for each cohort: Each cohort, CU (red), MCI (green), and DEM (blue) are compared to the overall effect (black). ORs were derived from logistic regression models adjusted for relevant covariates. CMBs and WMHv are shown to be significant predictors in varying degrees across cohorts. Ischemic infarcts were only significant predictors in the CU cohort, only. Statistical significance is denoted as follows: *p < .05, **p < .01, ***p < .001.





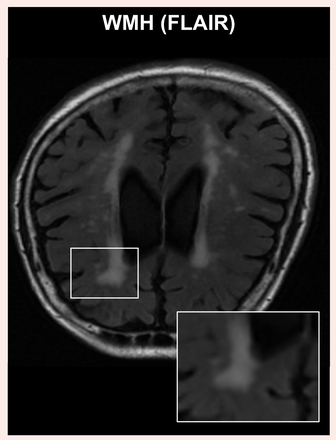


Table 1: Baseline demographic and clinical characteristics

Characteristic[1]	Cognitively Unimpaired		Mild Cognitive Impairment		Dementia	
	Aβ- N=413	Aβ+ N=198	Aβ- N=237	Aβ+ N=294	Aβ- N=29	Aβ+ N=181
Age, years	70 (6)	73 (7)	70 (8)	73 (7)	76 (8)	74 (8)
Sex, male	184 (45%)	72 (36%)	134 (57%)	160 (54%)	24 (83%)	100 (55%)
Education, years	16.78 (2.34)	16.53 (2.48)	16.35 (2.46)	16.29 (2.61)	16.62 (2.24)	15.51 (2.61)
APOE4, alleles						
0	313 (77%)	97 (49%)	180 (78%)	91 (31%)	23 (79%)	47 (26%)
1	87 (21%)	89 (45%)	46 (20%)	151 (52%)	6 (21%)	88 (49%)
2	6 (1.5%)	11 (5.6%)	5 (2.2%)	51 (17%)	0 (0%)	43 (24%)
MoCA, score	26.05 (2.58)	25.65 (2.51)	23.7 (3.0)	22.5 (3.3)	18.2 (4.0)	16.9 (4.6)
MTLv, normalized (log)	-4.21 (0.10)	-4.22 (0.10)	-4.23 (0.10)	-4.28 (0.11)	-4.31 (0.13)	-4.38 (0.12)
WMHv, normalized (log)	-6.84 (1.33)	-6.24 (1.42)	-6.47 (1.40)	-6.03 (1.36)	-6.02 (1.01)	-5.69 (1.13)
CMBs, present						
Any location (1+)	84 (21%)	47 (24%)	58 (25%)	95 (32%)	6 (21%)	73 (41%)
Superficial (1+)	61 (15%)	42 (21%)	45 (19%)	82 (28%)	5 (18%)	66 (37%)
Deep (1+)	27 (6.6%)	10 (5.1%)	12 (5.1%)	27 (9.2%)	1 (3.6%)	18 (10%)
Infarct (1+)	24 (6.8%)	22 (12%)	17 (8.7%)	23 (9.1%)	1 (4.3%)	7 (4.5%)
Aβ-PET burden, cl[2]	4 (-2, 10)	45 (29, 74)	2 (-4, 8)	70 (47, 96)	-2 (-12, 8)	88 (67, 109)

[1] Mean (SD); n (%); Median (IQR); [2]cl = centiloids
for missing values.

See Supplemental Table 1

Table 2: Prediction of Aβ-PET status in the overall cohort

Characteristic	OR[1]	95% CI[2]	p-value
Age, years	1.05	1.04, 1.06	<0.001
Sex, male	0.66	0.60, 0.71	<0.001
APOE4, alleles	5.66	5.24, 6.11	<0.001
MoCA, score	0.89	0.88, 0.90	<0.001
MTLv, normalized (log)	0.12	0.08, 0.17	<0.001
WMHv, normalized (log)	1.25	1.20, 1.29	<0.001
CMBs, superficial (1+)	1.45	1.31, 1.61	<0.001
CMBs, deep (1+)	0.88	0.74, 1.04	0.12
Infarction (1+)	1.01	0.89, 1.15	0.9

[1]OR = Odds Ratio, [2]CI = Confidence Interval.

Table 3: Adjusted Odds Ratios for Aβ+ PET by AD Risk Factors and CVD Imaging Biomarkers in Multiple Cognitive Cohorts

	Established AD Risk Factors							
	Cognitively Unimpaired (CU)		Mild Cognitive Impairment (MCI)		Dementia (DEM)		Overall Cohort	
Characteristic	OR[1]	p-value	OR[1]	p-value	OR[1]	p-value	OR[1]	p-value
Age, years	1.09	<0.001	1.05	<0.001	0.99	0.200	1.05	<0.001
Sex, male	0.57	<0.001	0.79	<0.001	0.20	<0.001	0.66	<0.001
APOE4, alleles	3.98	<0.001	6.62	<0.001	10.50	<0.001	5.66	<0.001
MoCA, score	0.98	0.074	0.95	<0.001	0.93	<0.001	0.89	<0.001
MTLv, normalized (log)	1.07	0.800	0.09	<0.001	0.01	<0.001	0.12	<0.001
CVD Imaging Biomarkers								
WMHv, normalized (log)	1.25	<0.001	1.15	<0.001	1.54	<0.001	1.25	<0.001
CMBs, superficial (1+)	1.38	<0.001	1.37	<0.001	2.17	<0.001	1.45	<0.001
CMBs, deep (1+)	0.51	<0.001	1.32	0.037	2.99	0.011	0.88	0.120
Infarction (1+)	1.31	0.005	0.89	0.200	1.28	0.400	1.01	0.900

[1]OR=Odds Ratio

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