Vascular Risk Factors and Biomarkers

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Disclosures

- Current funding
  - NIH/Eisai (Site PI: ACTC AHEAD 3-45 Study)
  - NIH/Cognition Therapeutics (Site PI: ACTC START Study)
  - Ionis (Site PI: HERO Study)
  - NIA/NIA (VA Site PI: PREVENTABLE Study)
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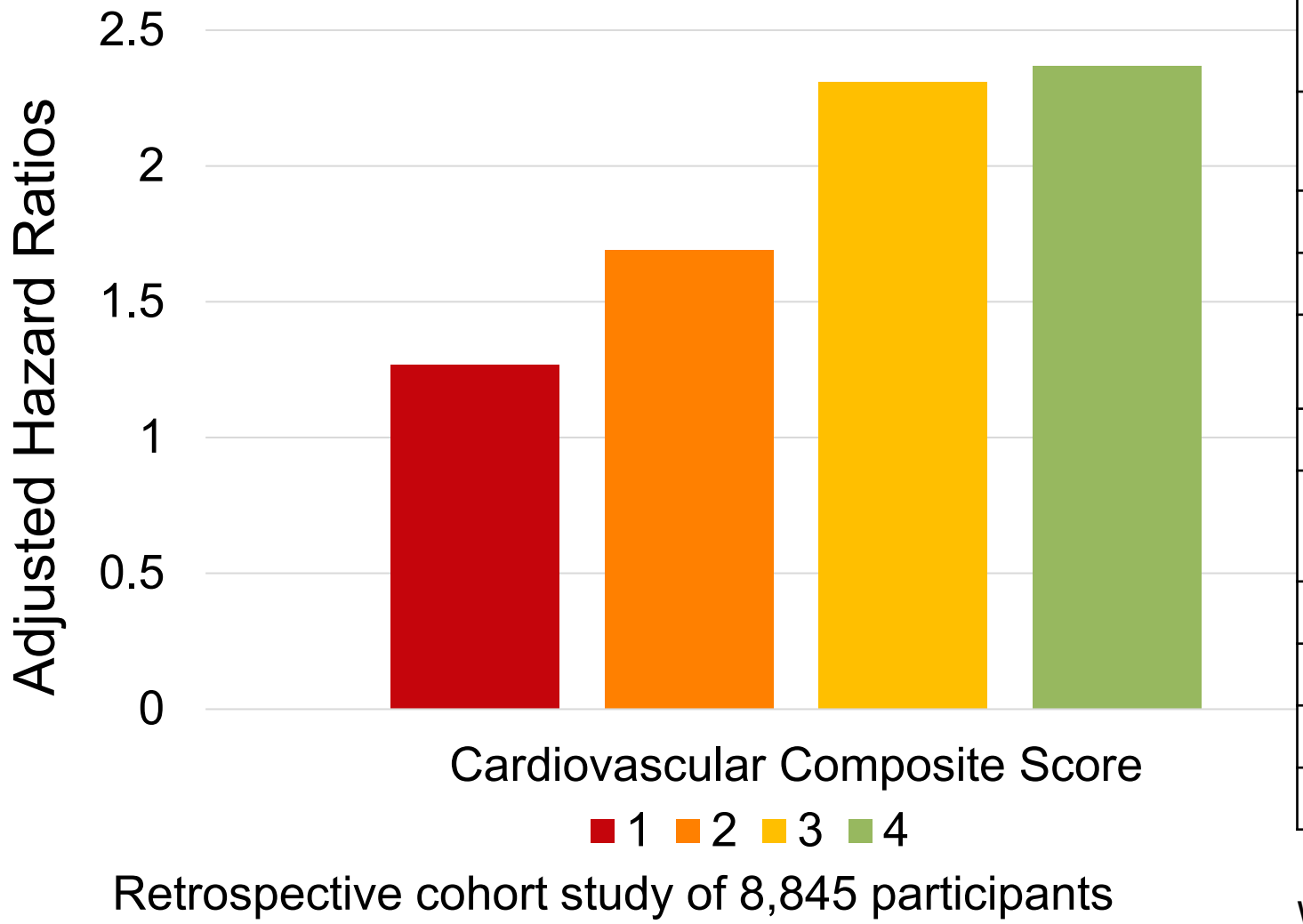
  - University of Wisconsin Dept of Medicine
  - Louis A. Holland, Sr. Family
- Other financial relationships: None
- Conflicts of Interest: None

Midlife Cardiovascular Risk Factors and Risk of Dementia in Late Life



Retrospective cohort study of 8,845 participants

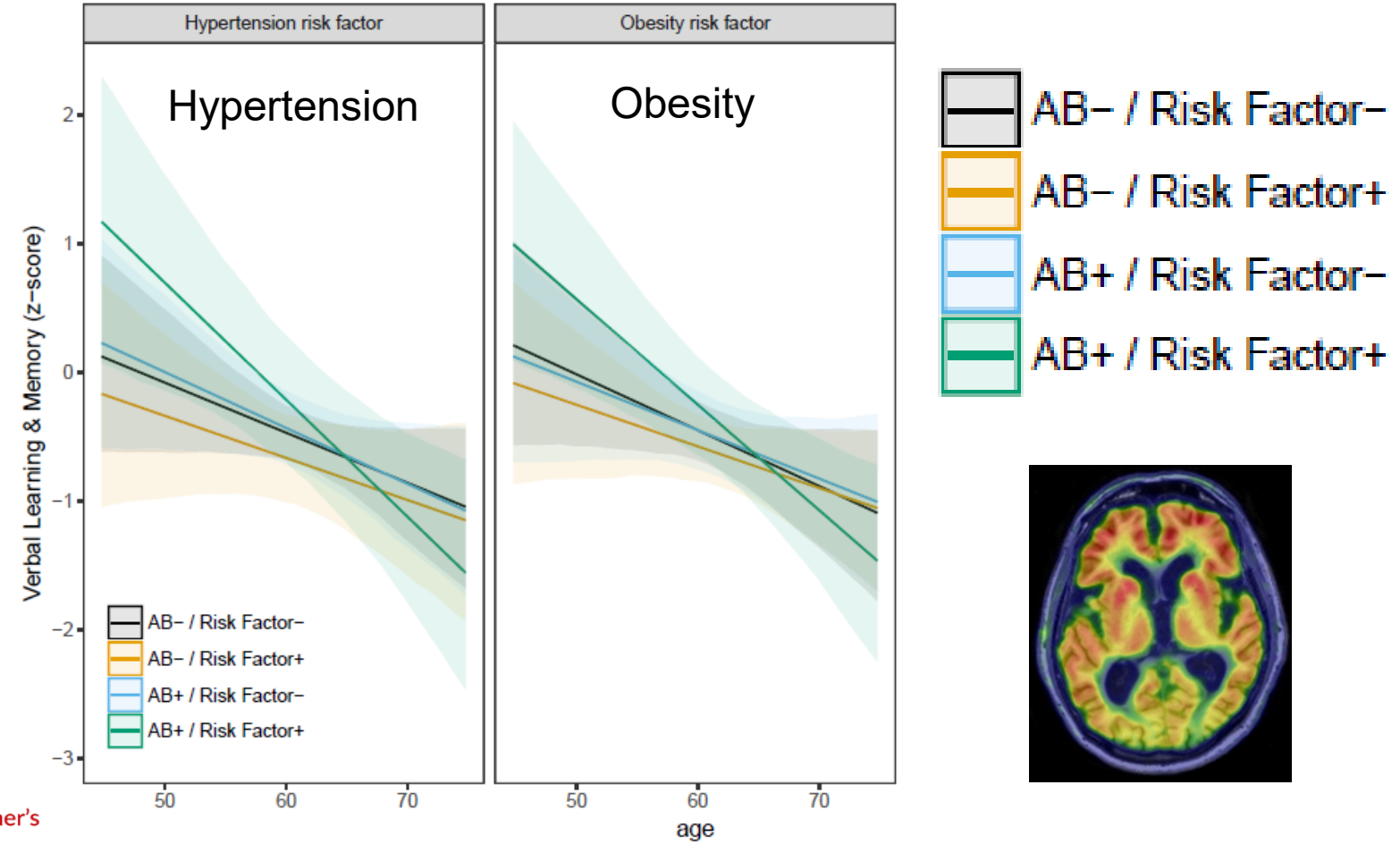
	Hazard Ratios (95% CI)
Midlife Risk Factors	
Hypertension	1.24 (1.04-1.48)
Diabetes	1.46 (1.19-1.79)
High cholesterol	1.42 (1.22-1.66)
Smoking	1.26 (1.08-1.47)
Cardiovascular composite score	
1	1.27 (1.02-1.58)
2	1.69 (1.34-2.12)
3	2.31 (1.71-3.11)
4	2.37 (1.10-5.10)

Whitmer RA et al. *Neurology* 2005;64:277.

Hypertension and Obesity Interact with Alzheimer's Pathology to Accelerate Cognitive Decline

Wisconsin Registry for Alzheimer's Prevention (WRAP)

- n = 207 cognitively unimpaired adults
- ages 40-70 years
- 3+ cognitive evaluations
- PET or CSF measures of β-amyloid



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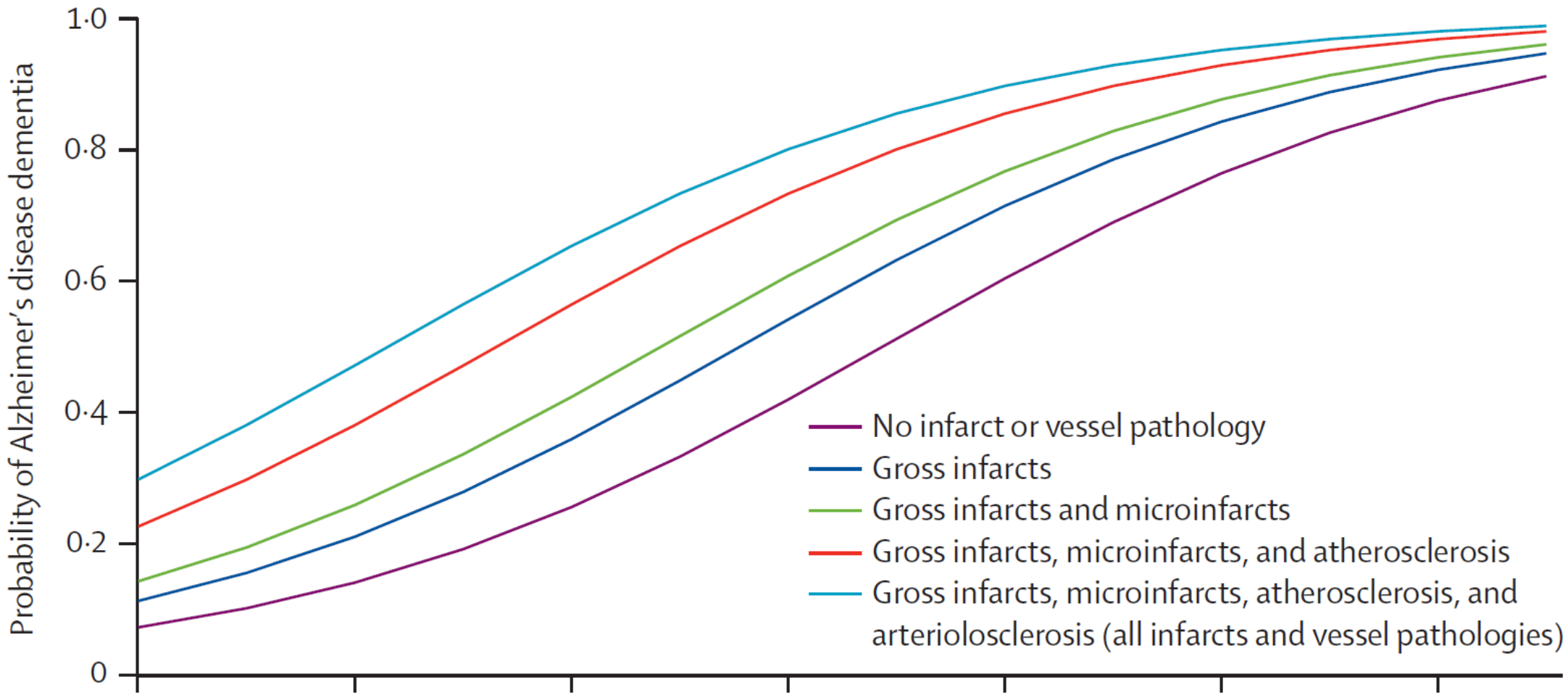
Wisconsin Alzheimer's Disease Research Center

L.R. Clark et al. *Alzheimer's & Dementia* 15 (2019) 418-428

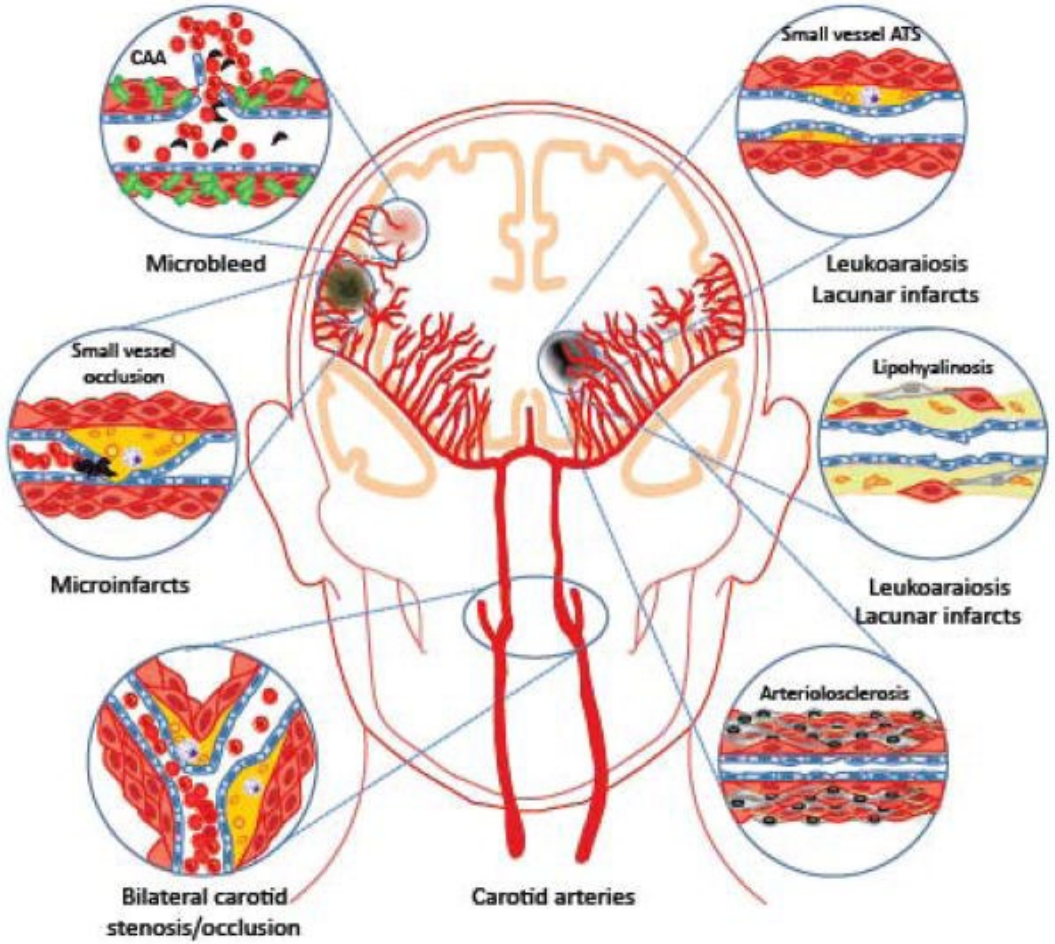
Relation of Cerebral Vessel Disease to AD Dementia and Cognitive Function



Arvanitakis Z, Capuano AW, Leurgans SE, Bennett DA, Schneider JA. *Lancet Neurol* 2016; 15: 934–43

Vascular Contributions to Alzheimer's Dementia

- Intracranial atherosclerosis
- Increased arterial stiffness
- Cerebral amyloid angiopathy
- Neurovascular unit dysfunction
- Cerebral hypoperfusion
- Hypertensive vascular remodeling
- Microinfarcts
- Impaired clearance of β-amyloid



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Vascular Contributions to Alzheimer's Dementia

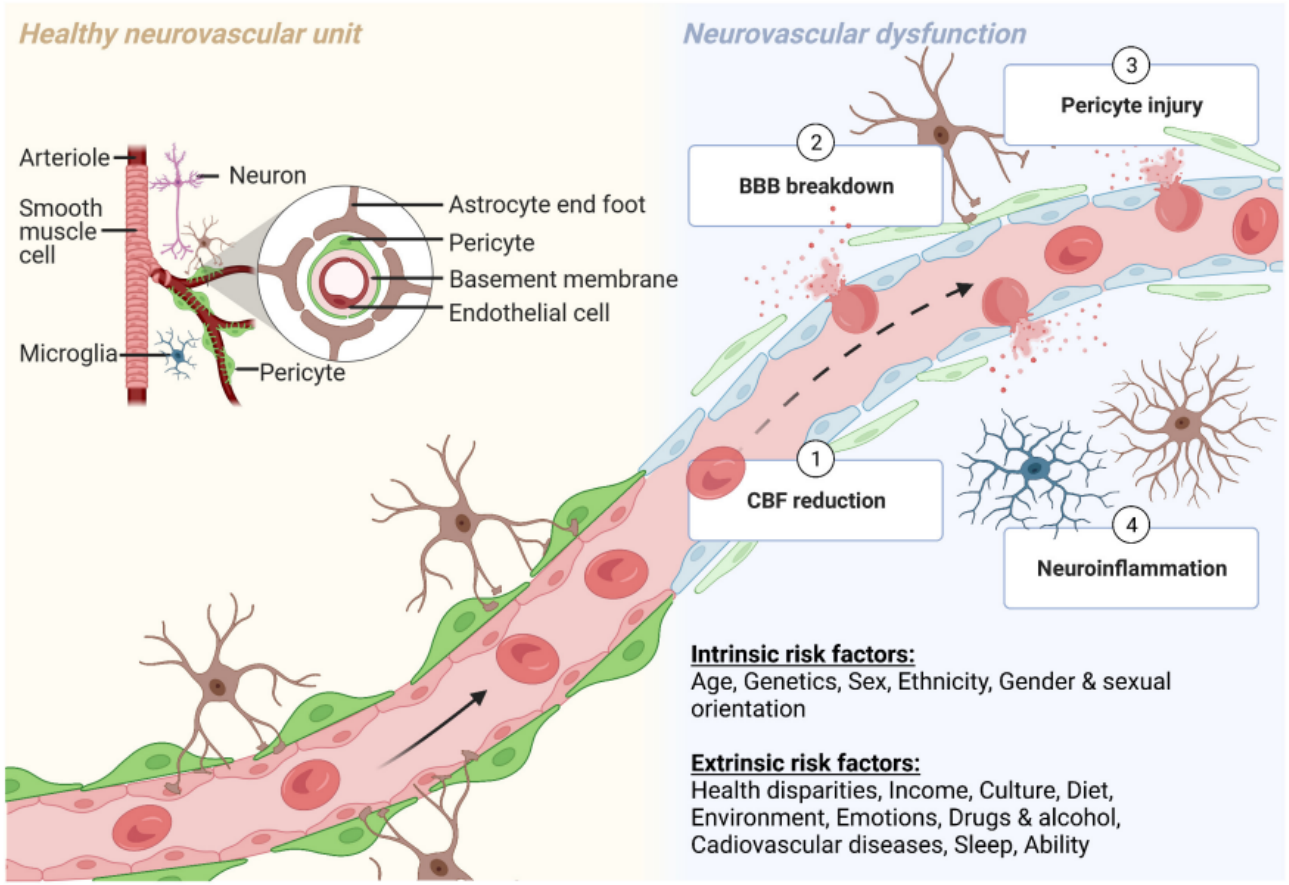
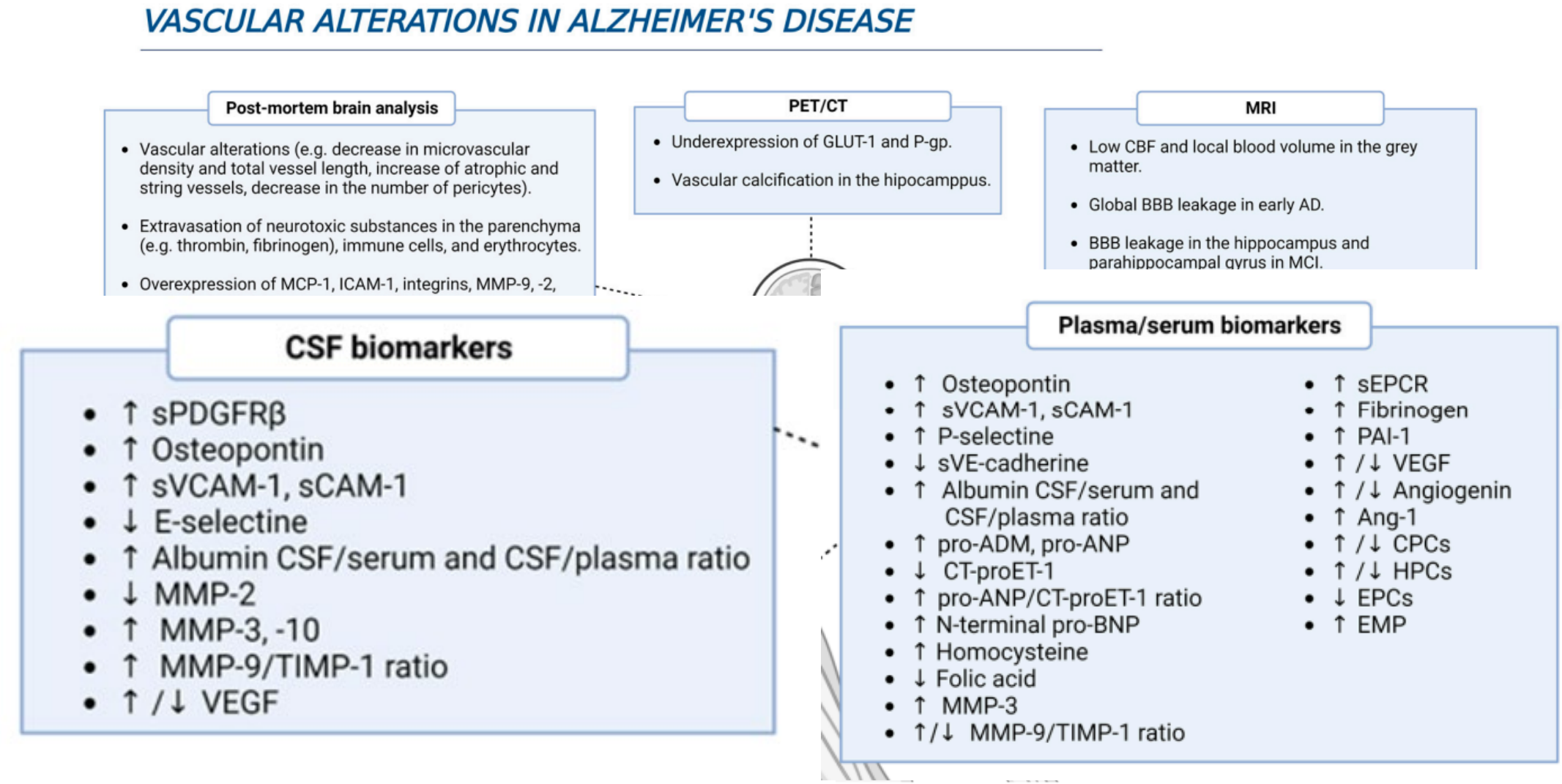


FIGURE 1 | The neurovascular unit (NVU) during normal physiological and pathological conditions. The NVU is comprised of many cell types. The blood-brain barrier (BBB) is formed by endothelial cells, which at the capillary level, are supported by pericytes. Astrocytic endfeet provide additional support to the BBB. Other cellular components of the NVU include microglia and neurons (*yellow, left side*). (1) Cerebral blood flow (CBF) reductions, (2) BBB breakdown, (3) pericyte injury, and (4) neuroinflammation all contribute to neurovascular dysfunction in many neurodegenerative diseases and disorders, including Alzheimer's disease (*blue, right side*). Both intrinsic and extrinsic factors can contribute to neurovascular dysfunction. Created with BioRender.com.

Saiyasit N, et al. Front Neurosci.2022;16:915405. doi: 10.3389/fnins.2022.915405

Vascular Biomarkers in AD Dementia



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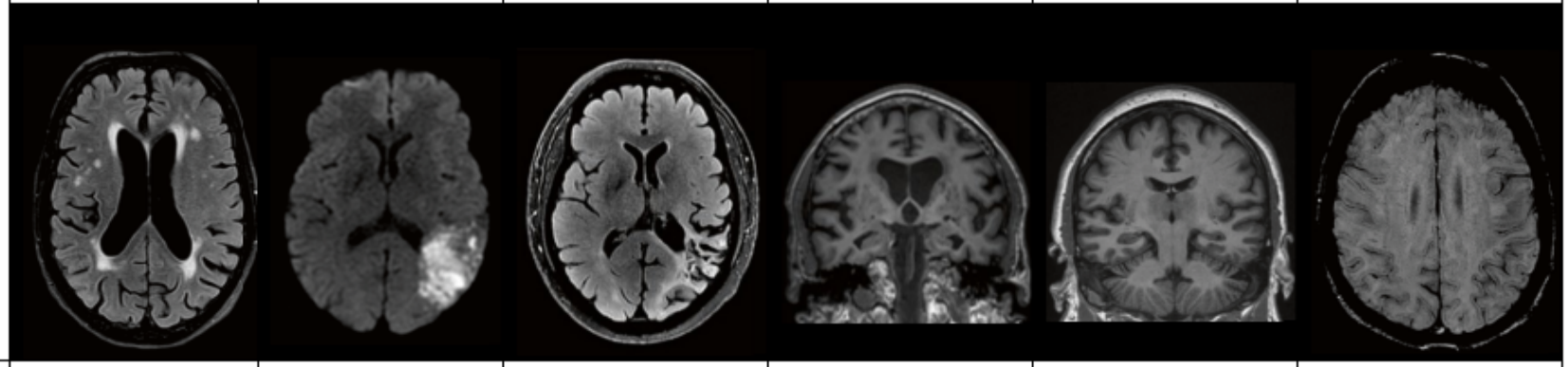
Vascular MR Imaging Phenotypes Associated with VCID

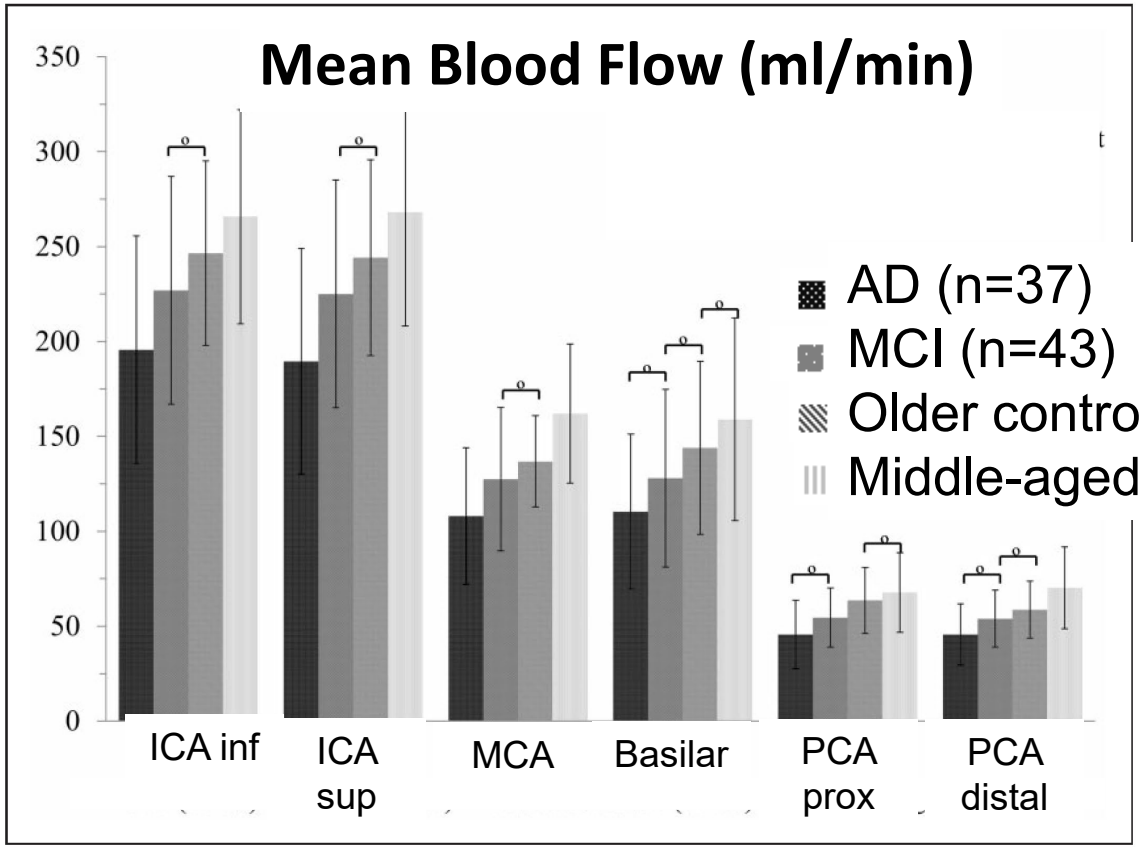
MRI Finding	White matter hyperintensities	Infarct		Atrophy	PVS*	Hemorrhagic/ Microbleeds
		Acute	Chronic			
MRI Sequence	T2 or FLAIR**	DWI***	T2 or FLAIR	T1	T1	SWI/GRE****
						
Implication on Cognition	Increased risk of cognitive deficit	Strategic-infarct dementia, increased stroke burden	Infarct number and volume correlate with poorer outcomes; frontal-sub cortical processes affected	Predicts global cognitive impairment	Presence and number associated with decline in global cognition, increased risk of stroke/dementia	Presence associated with global cognitive impairment and dementia

* PVS = Perivascular Spaces
** FLAIR = Fluid-Attenuated Inversion Recovery
*** DWI = Diffusion-Weighted Imaging
****SWI/GRE = Susceptibility Weighted Imaging/GRadient Echo

Rundek T et al. Neurotherapeutics 2022; 19:68-88.

Cerebrovascular Disease and AD Pathology Co-Occur

Wisconsin ADRC participants (n=314)



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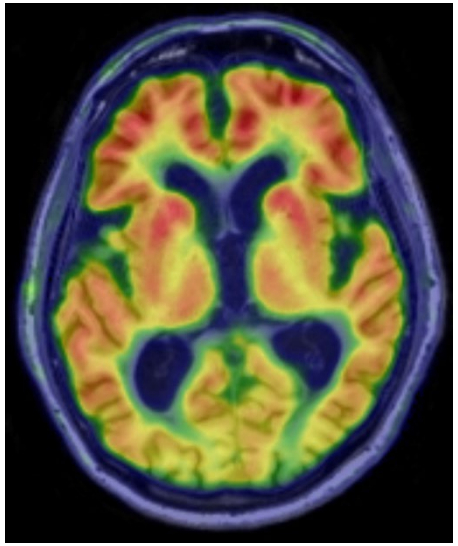
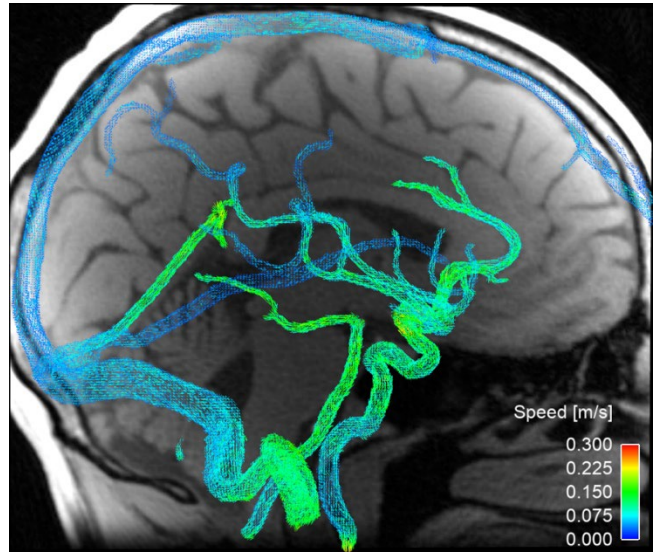
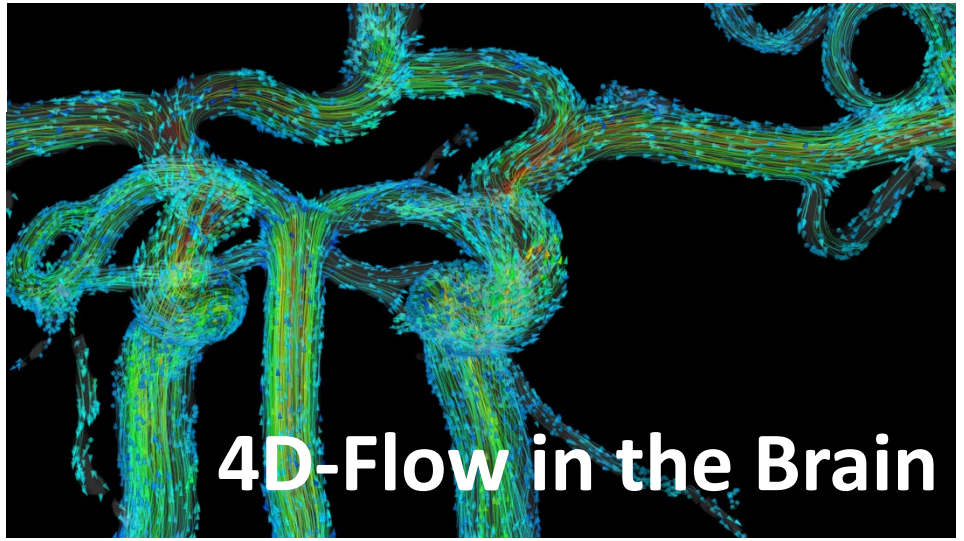






Courtesy of Leonardo Rivera-Rivera PhD, Kevin Johnson, PhD, Oliver Weiben, PhD, Laura Eisenmenger, MD

Mark VCID

Biomarkers for Vascular Contributions to Cognitive Impairment & Dementia

First phase of consortium (MarkVCID1):

- NIH-funded multisite consortium dedicated to validating promising predictive, diagnostic, target engagement and progression biomarkers of brain small-vessel diseases involved in VCID
- Performed validation studies on selected group of neuroimaging- and fluid-based candidate biomarkers for cerebral small vessel disease
- Selected 11 of 36 proposed biomarker kits for multi-site validation
- Identified subset of biomarkers with potential application in clinical trials
- Biomarkers undergoing further clinical validation in the consortium's MarkVCID2 phase

markvcid.partners.org

Biomarker Candidates	Primary Biomarker Category
MRI-based candidates	
White matter hyperintensities (WMH)	Enrich study populations for vascular disease
Peak Skeletonized Mean Diffusivity (PSMD)	Susceptibility/Risk
Free Water (FW)	Susceptibility/Risk
Arteriosclerosis (ARTS)	Susceptibility/Risk
Cerebrovascular reactivity (CVR)	Susceptibility/Risk
WMH growth/regression (WMH-G/R)	Disease Progression
Optical Coherence Tomography Angiography (OCTA)	
OCTA Retinal Vessel skeleton Density (OCTA-VSD)	Susceptibility/Risk
Fluid-based candidates	
Plasma neurofilament light (NfL)	Susceptibility/Risk
Plasma endothelial signaling kit	Risk stratification
Plasma exosome endothelial inflammation	Diagnostic classification
CSF placental growth factor (CSF-PlGF)	Disease stratification

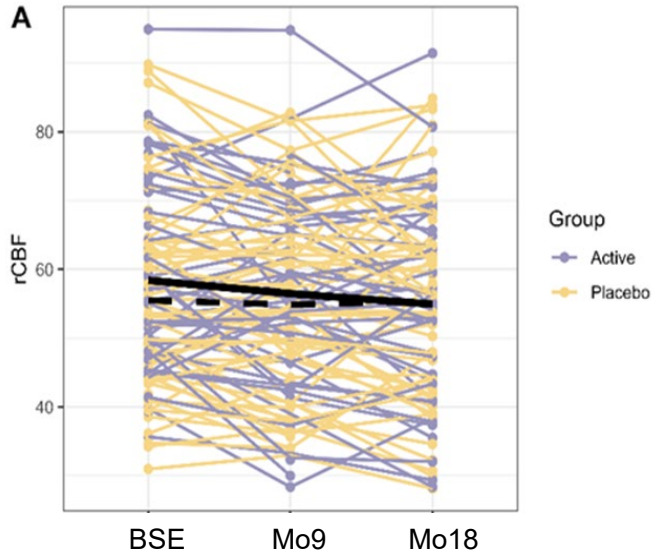
Can Vascular Biomarkers Be Used as Surrogate Outcomes in AD Prevention Clinical Trials?

Example 1:

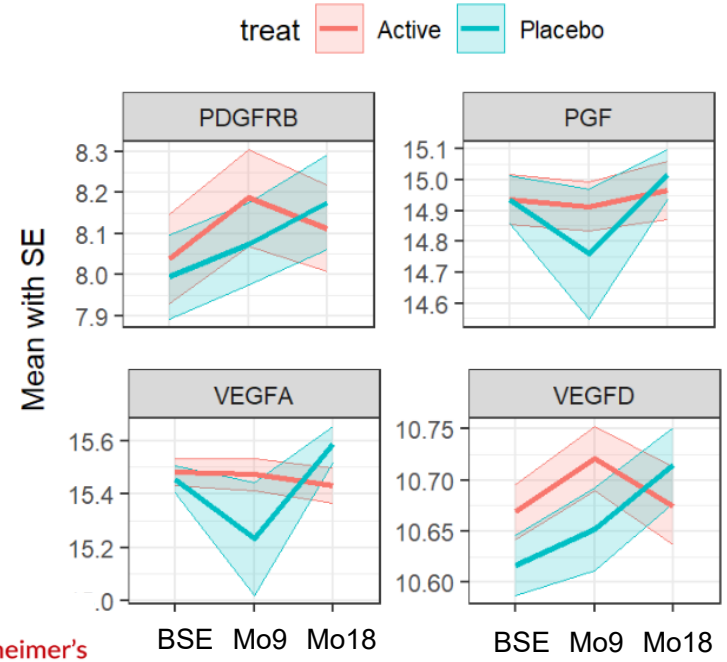
n=131 cognitively unimpaired Veterans randomized to icosapent ethyl (IPE, Vascepa®) 4 g vs placebo daily for 18 months

- Regional cerebral blood flow (rCBF) via arterial spin labeling (ASL) MRI
- Mean flow, pulsatility index, and cerebral blood flow measures on MRI 4D flow

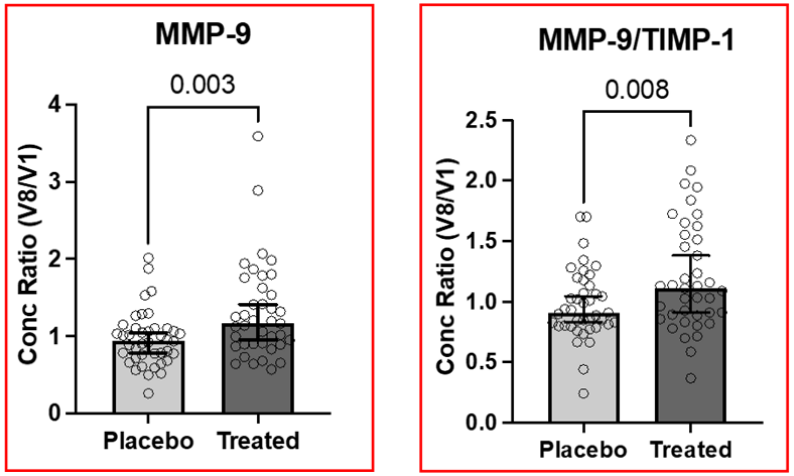
ASL-MRI



NULISA CSF BIOMARKERS



CSF METALLOPROTEINASE BIOMARKERS



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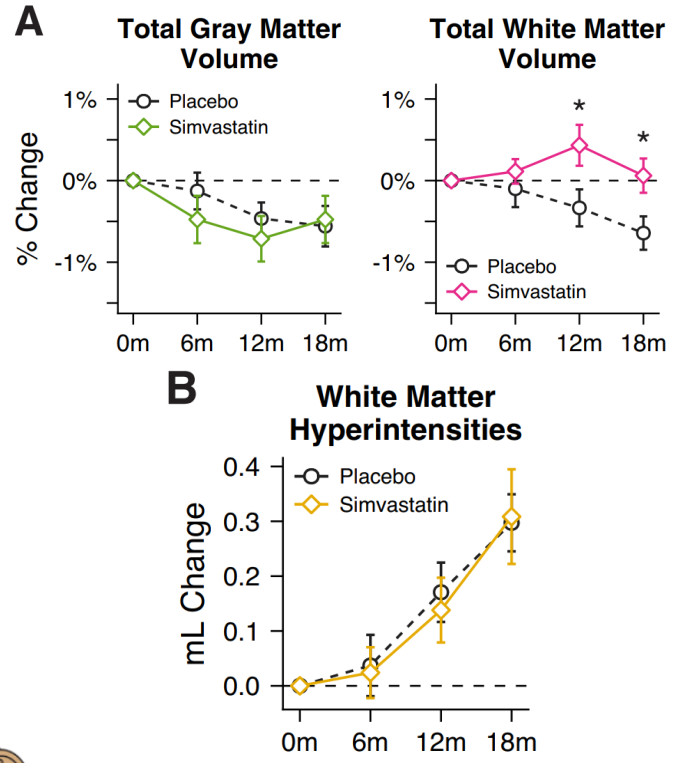
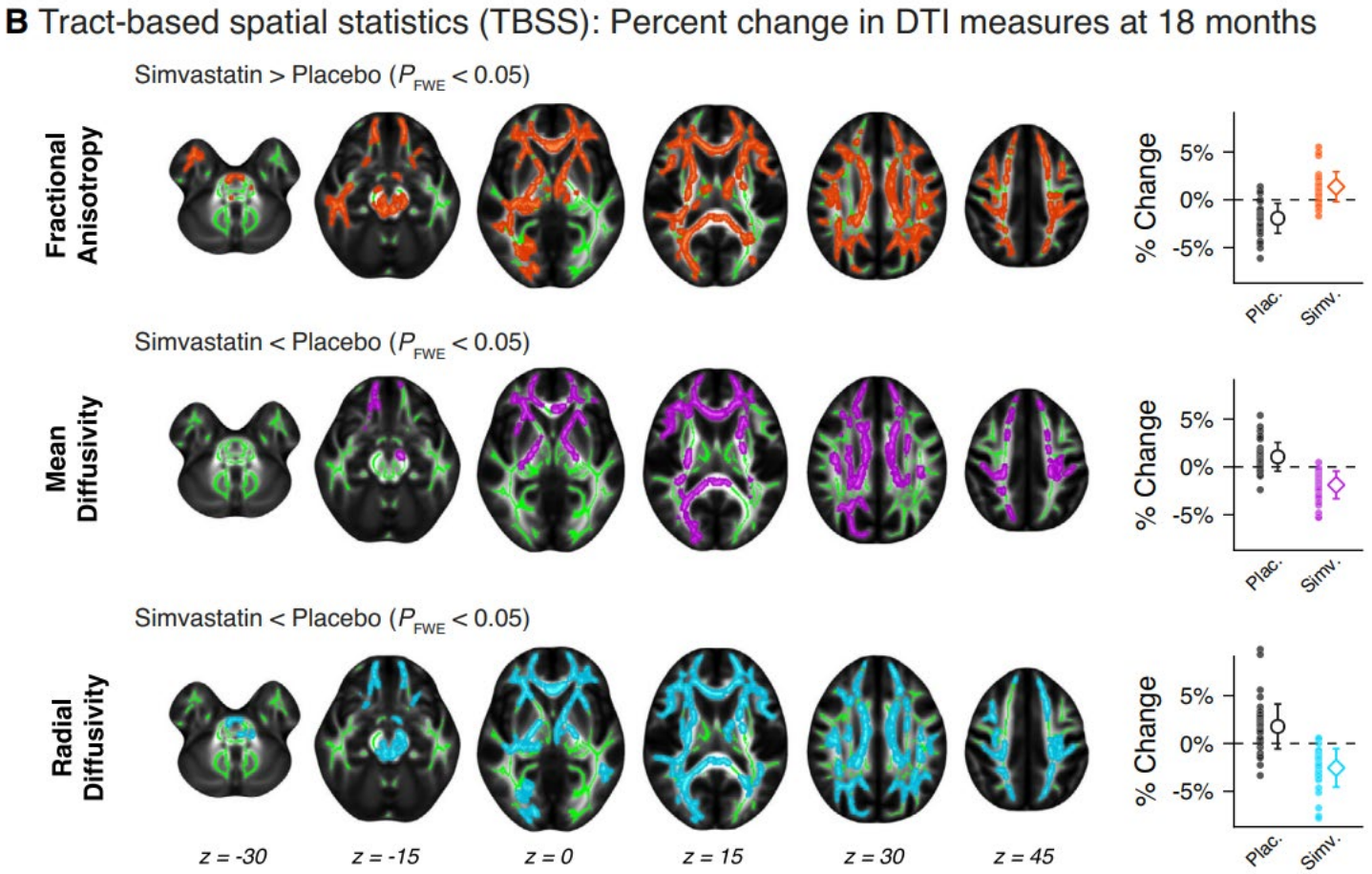
Carlsson CM, Van Hulle C, et al, (unpublished data)

Can Vascular Biomarkers Be Used as Surrogate Outcomes in AD Prevention Clinical Trials?

Example 2:
N=88 cognitively unimpaired adults randomized to simvastatin 40 mg vs placebo daily for 18 months





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N, Hunt J, …Carlsson CM. *Annals Clin Transl Neurology* 2021; 8(8): 1656–1667.

Discussion

- Further research is needed to clarify:
  - Temporal relationship between various vascular pathologies and onset of cognitive impairment
  - The relative contributions of specific vascular pathologies to cognitive decline
  - The best biomarker targets for early vascular intervention to delay AD onset and progression