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SCHOOL OF MEDICINE

Neuropsychology of Vascular Aging and Alzheimer's Lab

Vascular Biomarkers and Cognitive Decline in Alzheimer's Disease Risk

Katherine Bangen, Ph.D., ABPP-CN

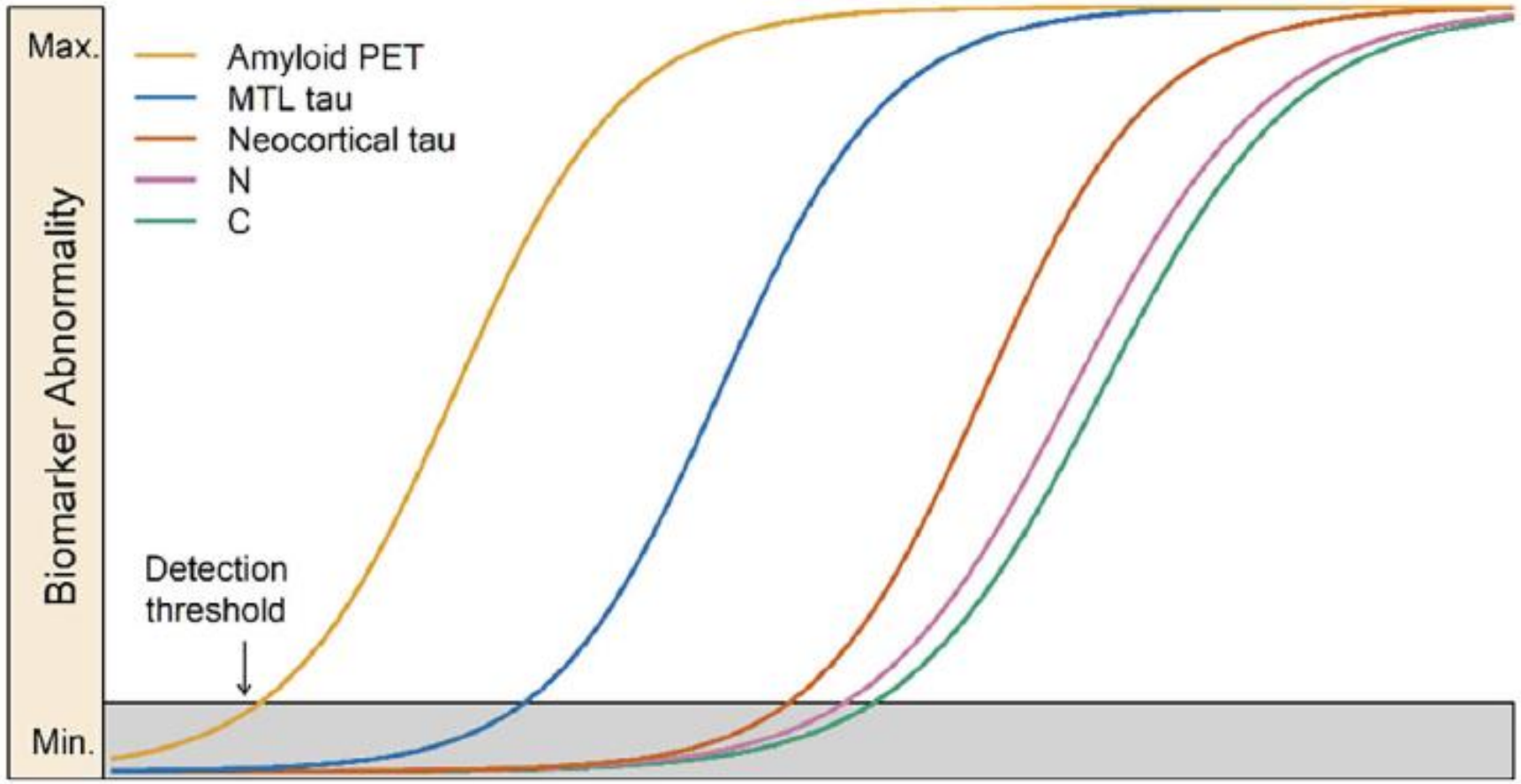
Associate Professor, Department of Psychiatry

University of California, San Diego

Disclosures

- None

Proposed Trajectories of Biomarkers in Alzheimer's Disease



Note: N = neurodegeneration; C = clinical symptoms

Jack et al. (2024). *Alzheimers Dement.*

Vascular and AD Mixed Pathology is Common

- Vascular pathology mixed with AD pathology is very common in aging, mild cognitive impairment, and Alzheimer's disease

- primary pathology was vascular-only

- vascular-only, AD+vascular, & AD+vascular+other most common
- 7.8% had pure AD

- AD+vascular+other was most common
- 3% pure AD

Kapasi et al., (2017). *Acta Neuropath.*

ELSEVIER

CrossMark

Alzheimer's & Dementia 11 (2015) 394-403

Alzheimer's & Dementia

Aggregate effects of vascular risk factors on cerebrovascular changes in autopsy-confirmed Alzheimer's disease

Katherine J. Bangen[a], Daniel A. Nation[b], Lisa Delano-Wood[a,b], Gali H. Weissberger[c], Lawrence A. Hansen[d,e], Douglas R. Galasko[b,d], David P. Salmon[d], Mark W. Bondi[b,a,*]

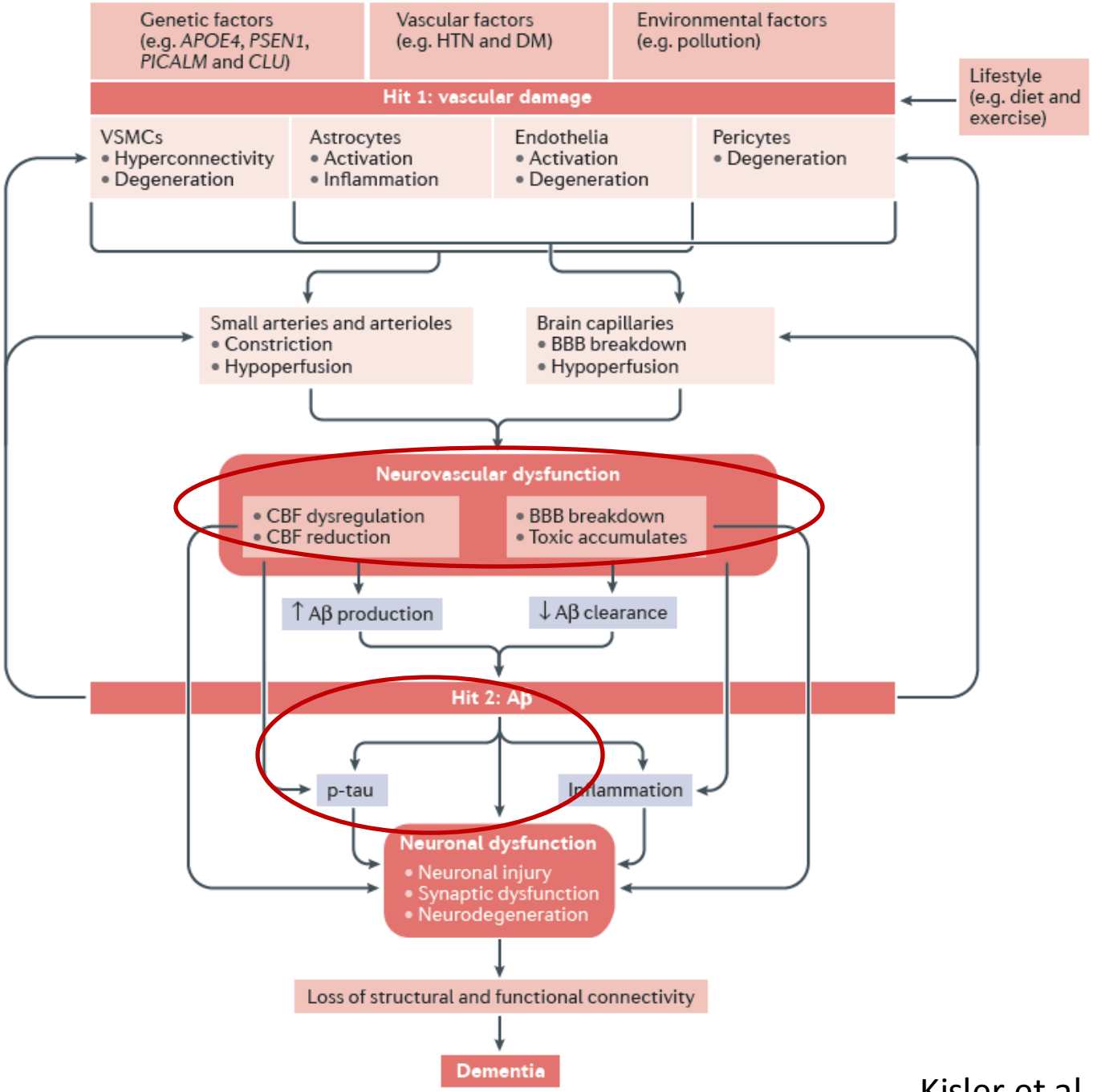
[a]*Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA*
[b]*Veterans Affairs San Diego Healthcare System, San Diego, CA, USA*
[c]*San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA*
[d]*Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA*
[e]*Department of Pathology, University of California, San Diego, La Jolla, CA, USA*

- AD+CVC and AD-CVC (“pure AD”) groups had similar level of cognitive impairment
- AD+CVC was associated with less severe AD pathology (lower Braak stage)
- Findings suggest vascular pathology influences clinical expression of AD, even in patients with autopsy-confirmed AD and relatively mild CVD

Bangen et al. (2015). *Alzheimers Dement.*

Vascular Biomarker Methods

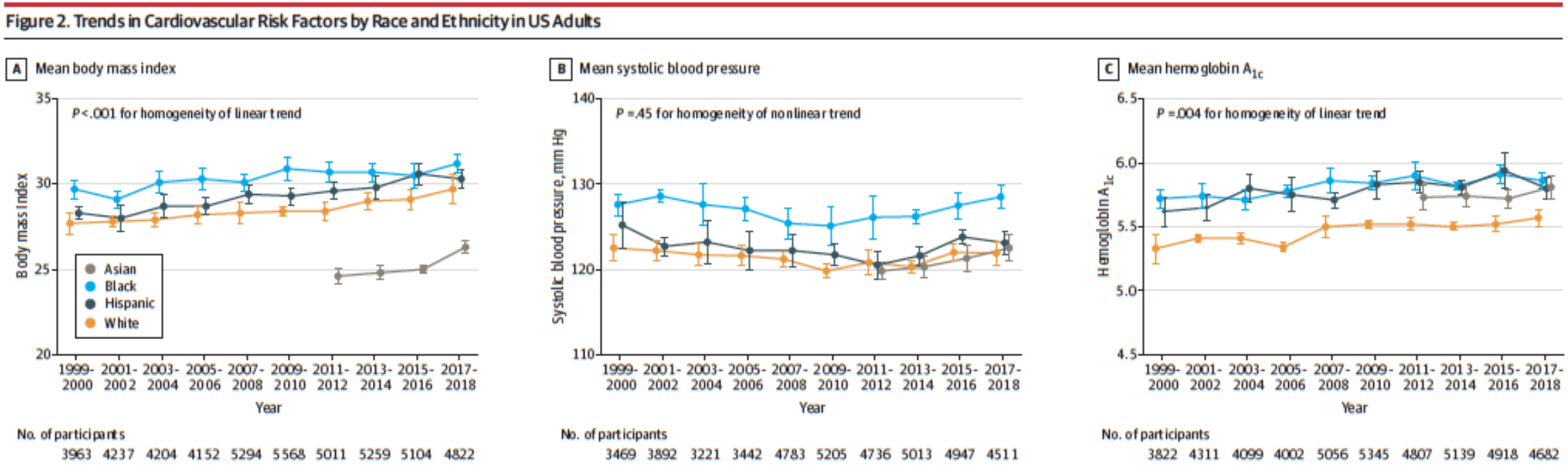
Current AD Biomarker Methods



Kisler et al., (2017). *Nat Rev Neurosci.*

Vascular Risk Factors are Common

- Even more common among older adults and underrepresented groups



CDC (2023); CDC (2021); He et al., (2021). *JAMA*.; Livingston et al. (2024). *Lancet.*.

Vascular Risk Factors are Often Undiagnosed

Table 1a. Estimated crude prevalence of diagnosed diabetes, undiagnosed diabetes, and total diabetes among adults aged 18 years or older, United States, 2017–2020

Characteristic	Diagnosed diabetes Percentage (95% CI)	Undiagnosed diabetes Percentage (95% CI)	Total diabetes Percentage (95% CI)
Total	**11.3 (10.3–12.5)**	**3.4 (2.7–4.2)**	**14.7 (13.2–16.4)**
Age in years			
18–44	3.0 (2.4–3.7)	1.9 (1.3–2.7)	4.8 (4.0–5.9)
45–64	14.5 (12.2–17.0)	4.5 (3.3–6.0)	18.9 (16.1–22.1)
≥65	24.4 (22.1–27.0)	4.7 (3.0–7.4)	29.2 (26.4–32.1)

- CDC estimates ~23% of adults with diabetes are undiagnosed
- Relying on self-report under-identifies these important conditions

https://www.cdc.gov/diabetes/php/data-research/index.html

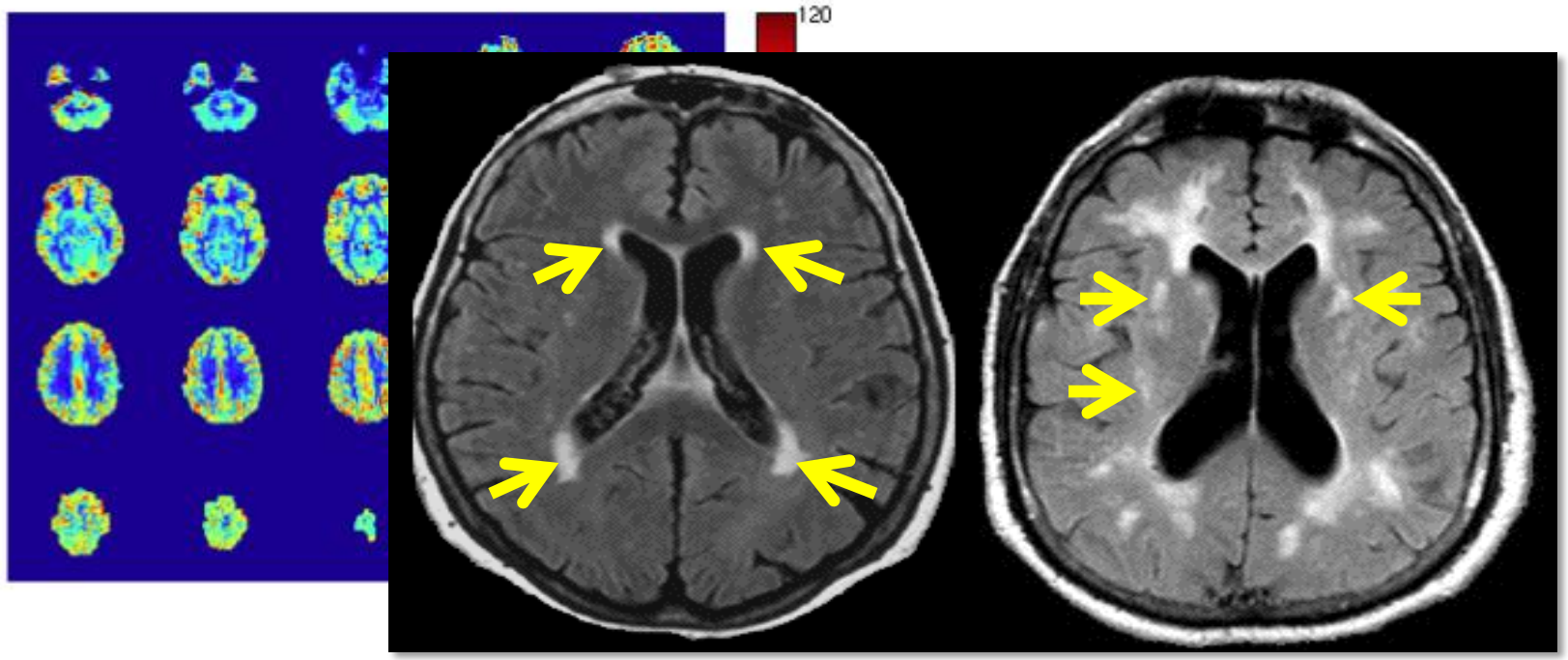
Methods

Vascular Risk Assessment

- Diabetes
- Blood pressure
- Aggregate vascular risk (e.g., Framingham Stroke Risk Profile)
- Arterial stiffness
  - pulse pressure (systolic BP – diastolic BP)
  - pulse wave velocity (SphygmoCor XCEL device)

Magnetic Resonance Imaging

- Cerebral blood flow
- White matter lesions
- Myelin water fraction
- Arterial compliance



Arterial Stiffness and Brain Aging

- **Arterial stiffening** increases in aging and may be an independent risk factor for pathological brain aging

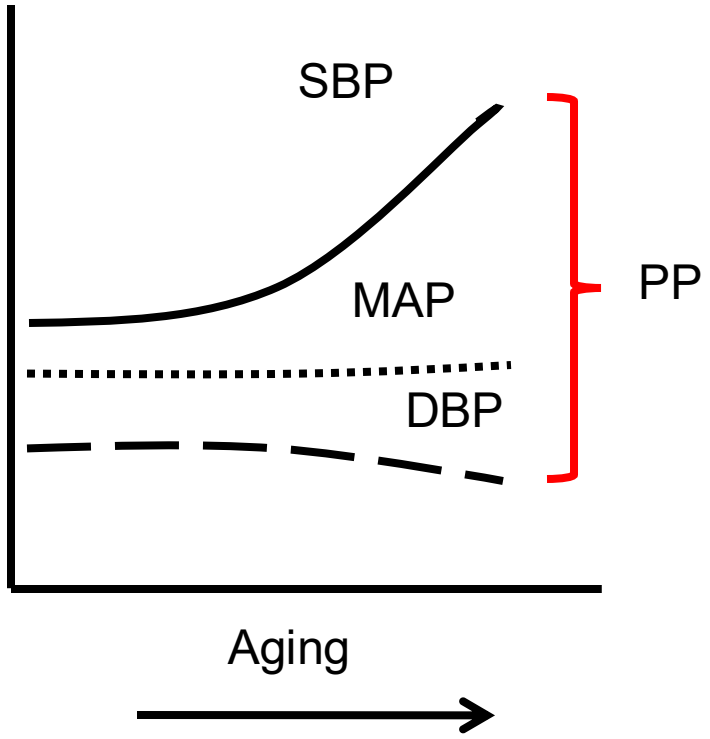
↑ Arterial Stiffness →

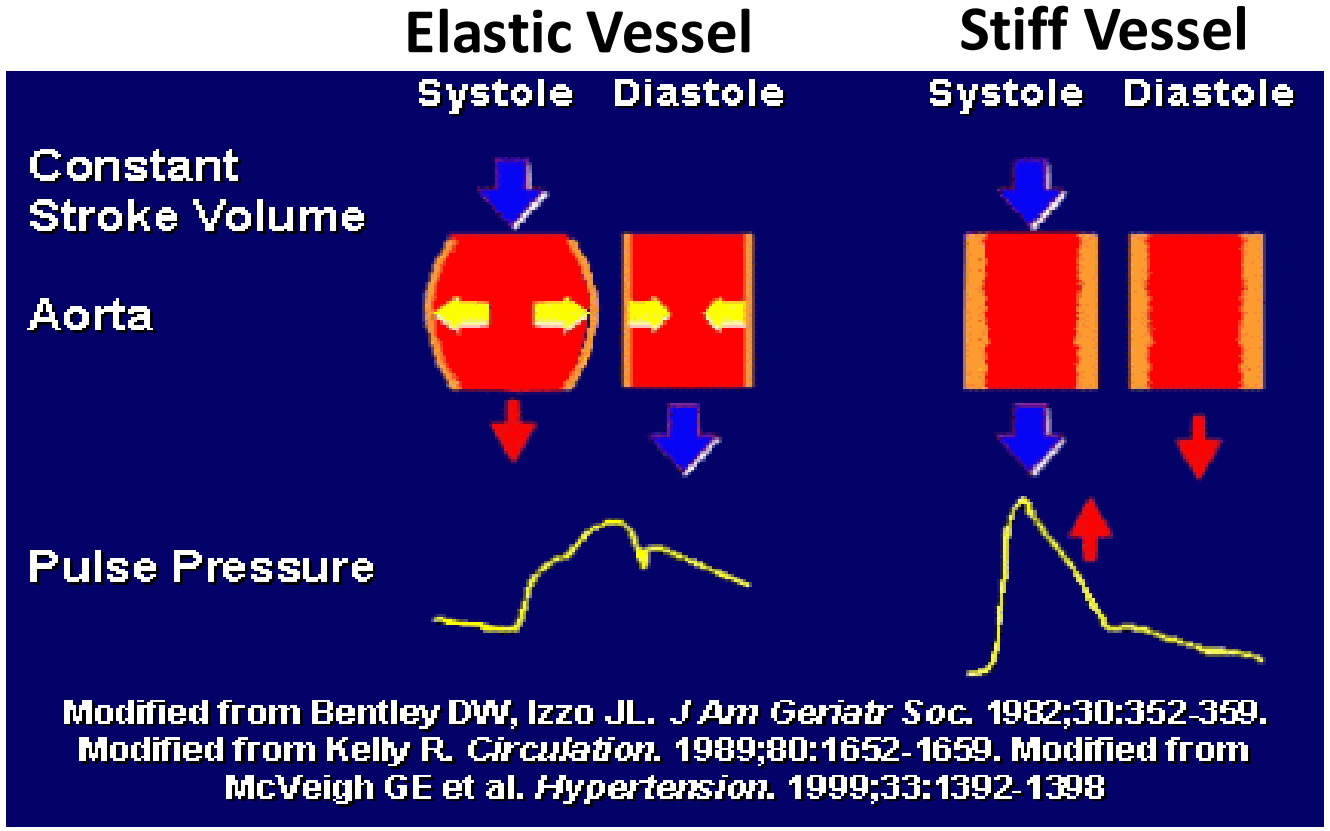
Damage to vulnerable microvasculature & associated tissue

Chronic hypoperfusion & ischemia of brain tissue

1. Pulse Pressure

Elevated pulse pressure (systolic bp – diastolic bp) = surrogate marker of arterial stiffening



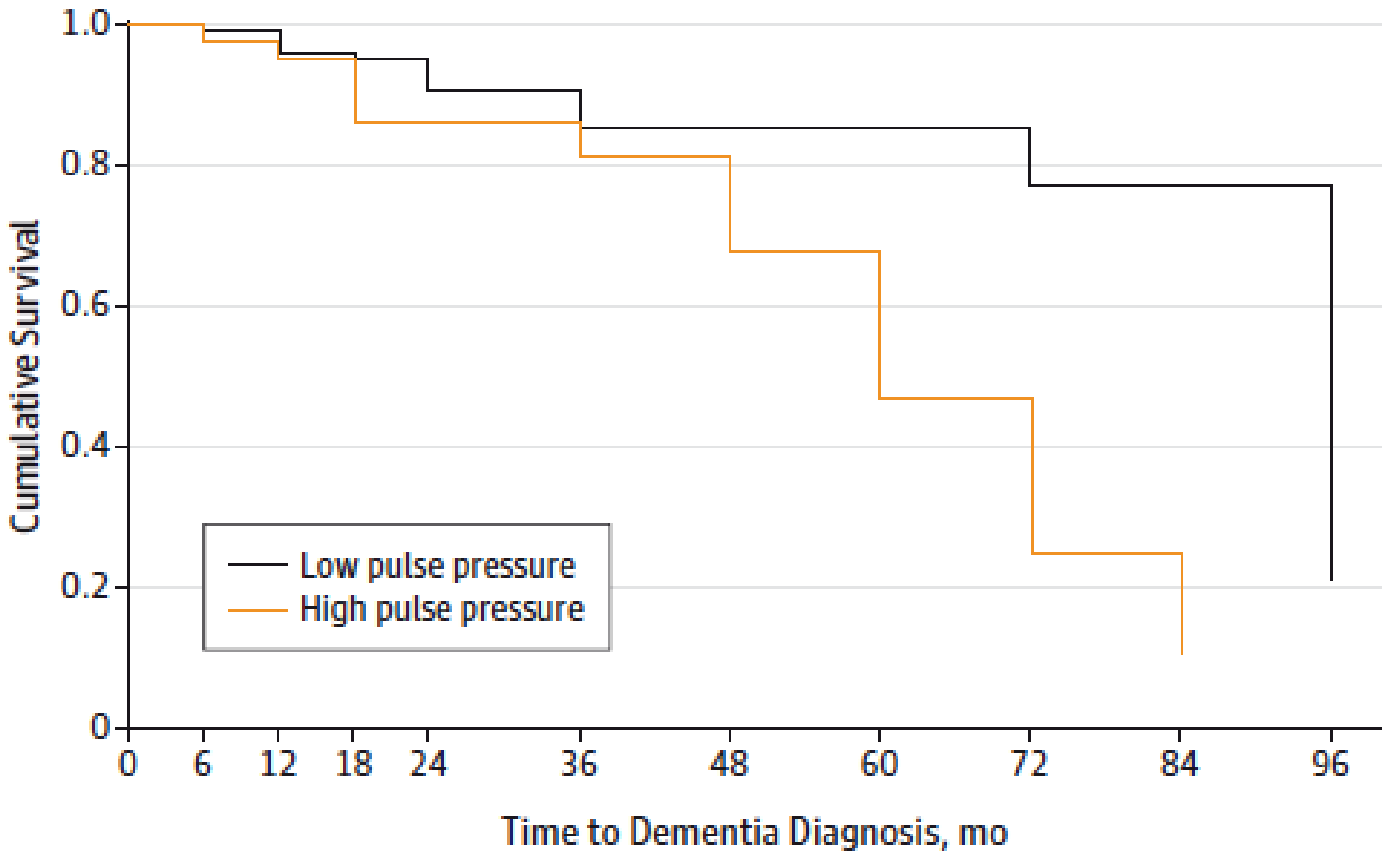


Mitchell et al., (2009) *Journal of Applied Physiology*

1. Pulse Pressure, Cognition, and Biomarkers

- Elevated PP has been linked to **cognitive decline and AD biomarkers**
  - **Cognitive decline** (Nation et al., 2016)
  - **Functional decline** (Werhane et al., 2016)
  - **Progression to dementia** (Nation et al., 2015)
  - **AD biomarkers** (Nation et al., 2015; Weigand et al., 2020)

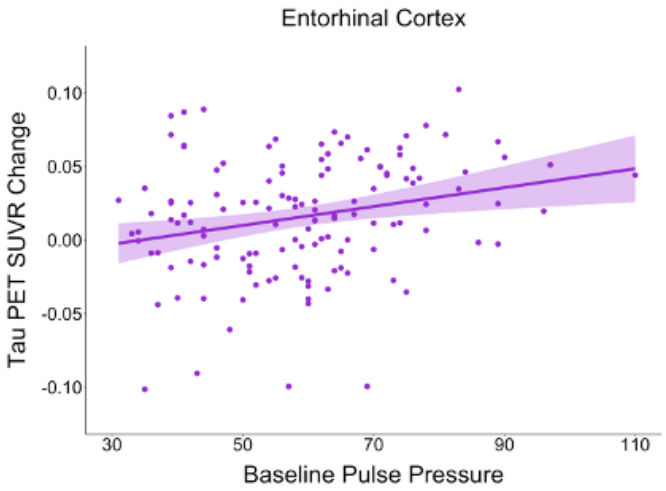
Higher Pulse Pressure Relates to More Rapid Progression to Dementia

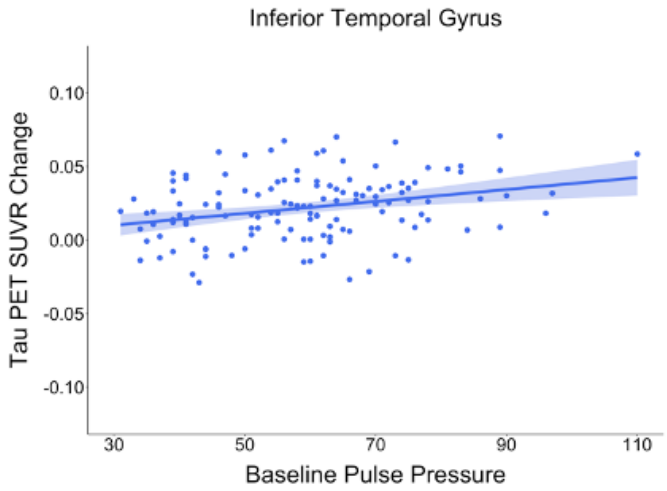


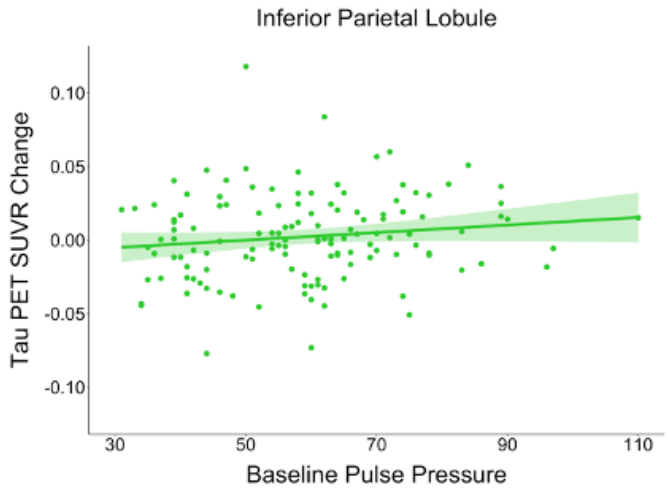
Nation, Edmonds, Bangen, et al. (2015). *JAMA Neurol.*

Higher Pulse Pressure Predicts Longitudinal Accumulation of Tau PET

Alex Weigand
Clin Psych JDP Student



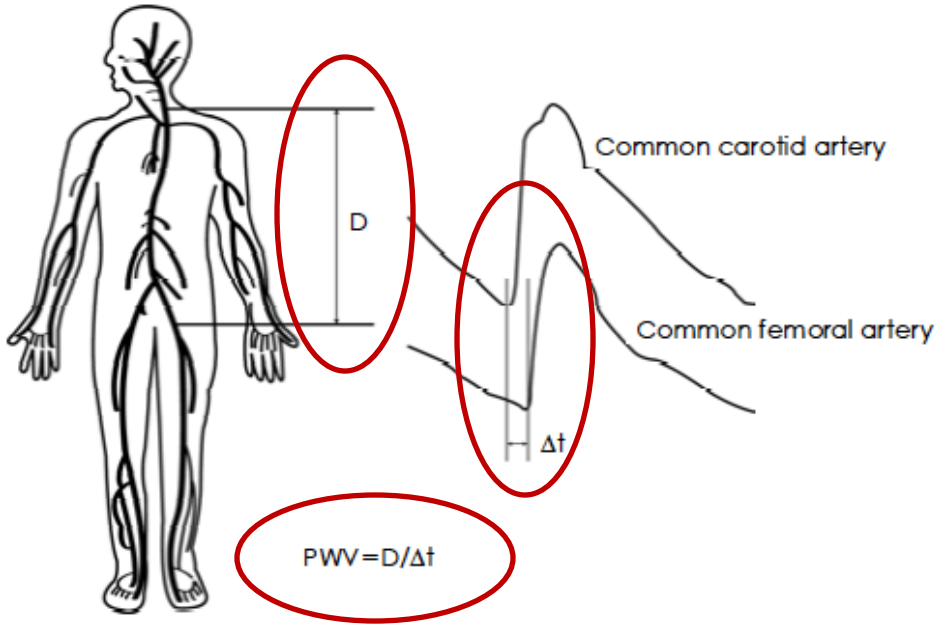




- Higher pulse pressure predicted increased tau PET accumulation over 12 months for all three ROIs adjusting for age, sex, cognitive diagnosis, APOE status, and baseline tau PET signal

Weigand, Nation, Delano-Wood, Bangen, et al. (2020). *AAIC.*

2. Carotid-Femoral PWV Measurement



- A direct measure of arterial stiffening (vs pulse pressure)
- Carotid pulse measured using tonometer and femoral pulse measured through pulsations in cuff around thigh
- Pulse transit time (Δt) is time interval between onset of carotid and femoral pulse wave upstroke
- Pulse wave travel distance (D), between carotid and femoral pulse wave recording point, is measured over body surface with a tape measure
- Carotid-femoral PWV calculated as distance divided by pulse transit time (meters/second)
- Higher PWV indicates stiffer aorta

Rhee et al., (2008)

ADRC PWV Project

- Our previous work has focused on pulse pressure (surrogate marker) rather than pulse wave velocity (direct measure)
- It remains unclear how arterial stiffening may ***interact*** with AD risk factors to affect **cognition**

Goal: To investigate the ***synergistic effects*** of AD risk factors (**APOE ε4 and AD biomarker positivity) & elevated pulse wave velocity** on **cognitive functioning**

Bangen *et al. Alzheimer's Research & Therapy* (2021) 13:121
https://doi.org/10.1186/s13195-021-00851-2

Alzheimer's
Research & Therapy

RESEARCH Open Access

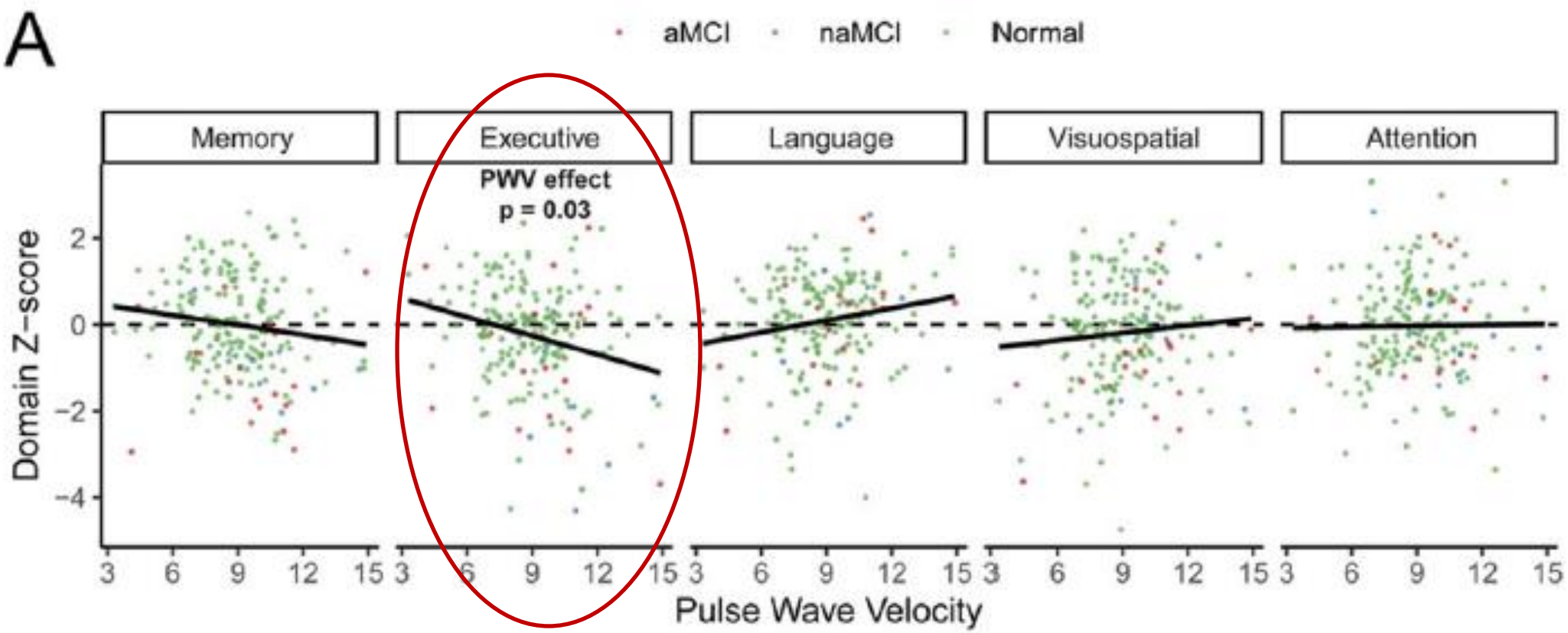
Arterial stiffening acts synergistically with APOE genotype and AD biomarker status to influence memory in older adults without dementia

Katherine J. Bangen[1,2*], Denis S. Smirnov[3,4], Lisa Delano-Wood[2,5], Christina E. Wierenga[1,2], Mark W. Bondi[2,5], David P. Salmon[4] and Douglas Galasko[4]

ADRC Participants with PWV

	Normal	MCI
N	168	26
Age	74.5 ± 5.8	76.9 ± 6.4
Female	93 (55%)	9 (35%)
Education	16.8 ± 2.4	16.2 ± 2.1
APOE e4+	65 (39%)	14 (54%)
Hispanic	16 (10%)	2 (8%)
MMSE	29.2 ± 1.2	28.1 ± 1.5
DRS	139.9 ± 3.3	133.1 ± 5.3
GDS	1.1 ± 1.7	1.7 ± 1.5
Framingham SRP (%)	9.9 ± 7.8	13.1 ± 7.8
PWV	8.8 ± 2	9.9 ± 2.5
Pulse Pressure	50.6 ± 14	54.8 ± 13.1
Memory Component	0.2 ± 1	-1.1 ± 1.1
Language Component	0.1 ± 1	0 ± 1.3
Visuospatial Component	-0.1 ± 1.2	-0.7 ± 1.3
Executive Component	-0.1 ± 1.1	-1.1 ± 1.7
Attention Component	0 ± 1.1	-0.2 ± 1.1

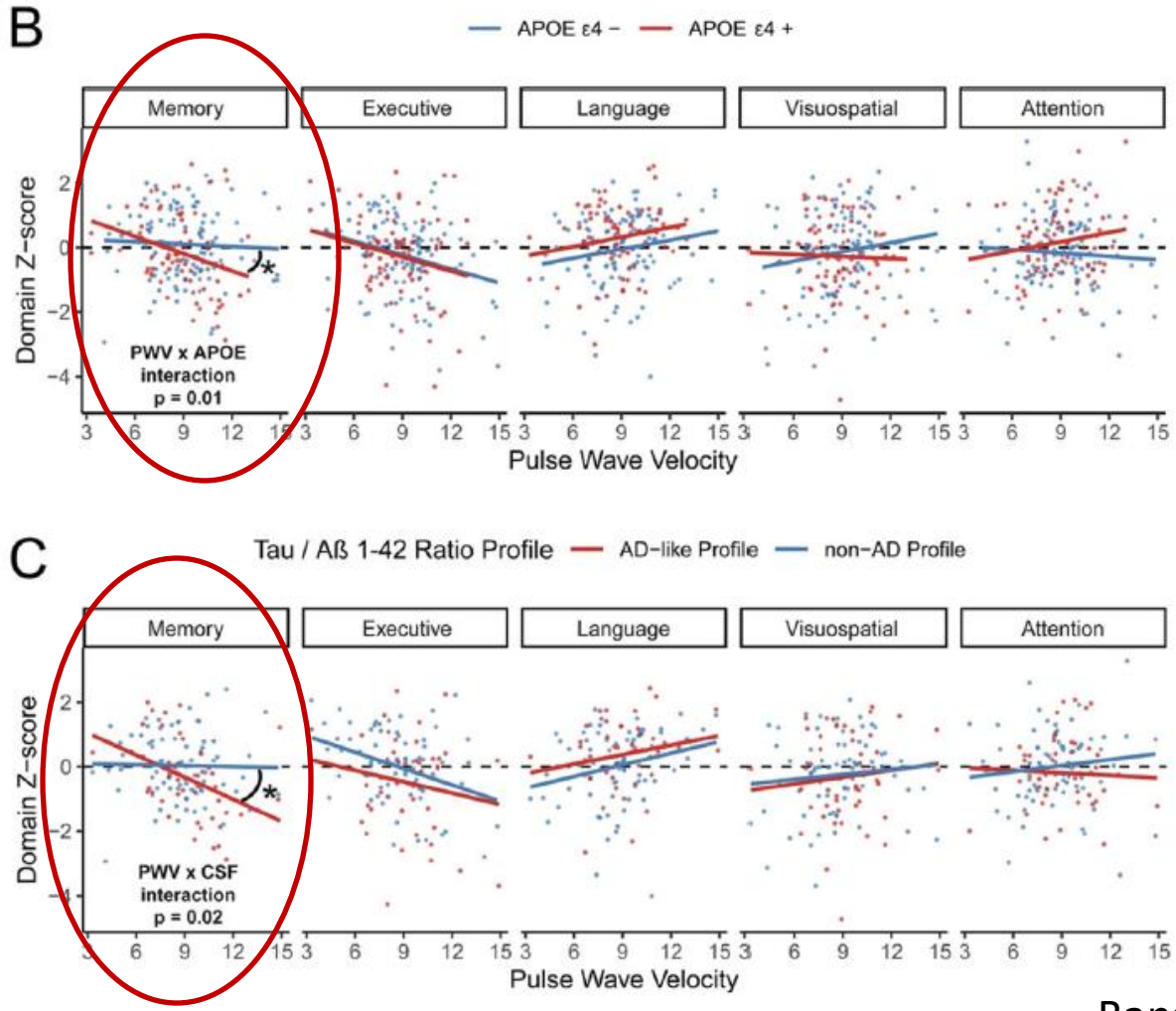
PWV Correlates with Executive Function



*Adjusted for age, sex, educ

Bangen, et al. (2021). *Alzheimers Res Ther.*

PWV Interacts with APOE and AD Biomarkers to Predict Memory

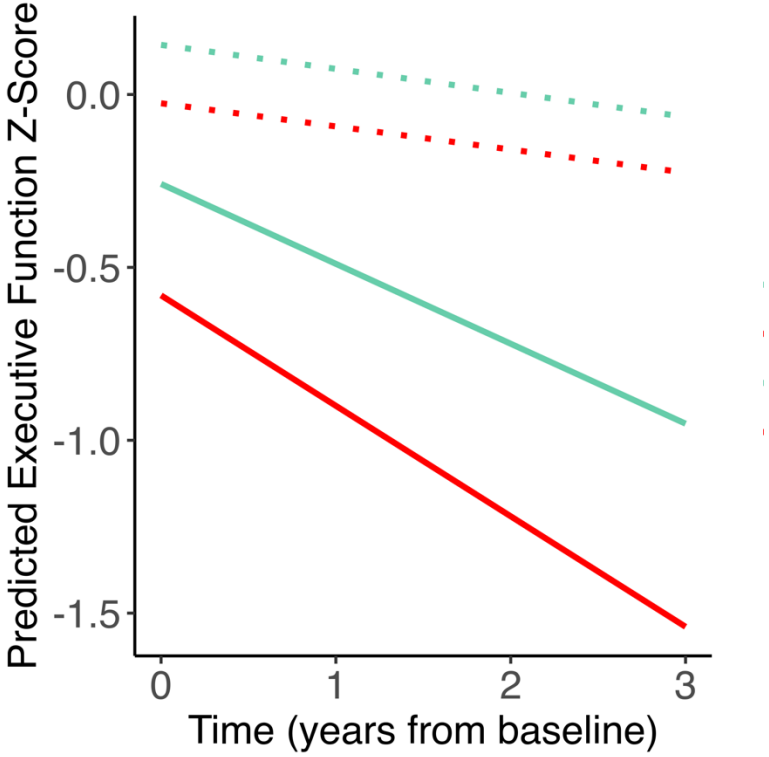


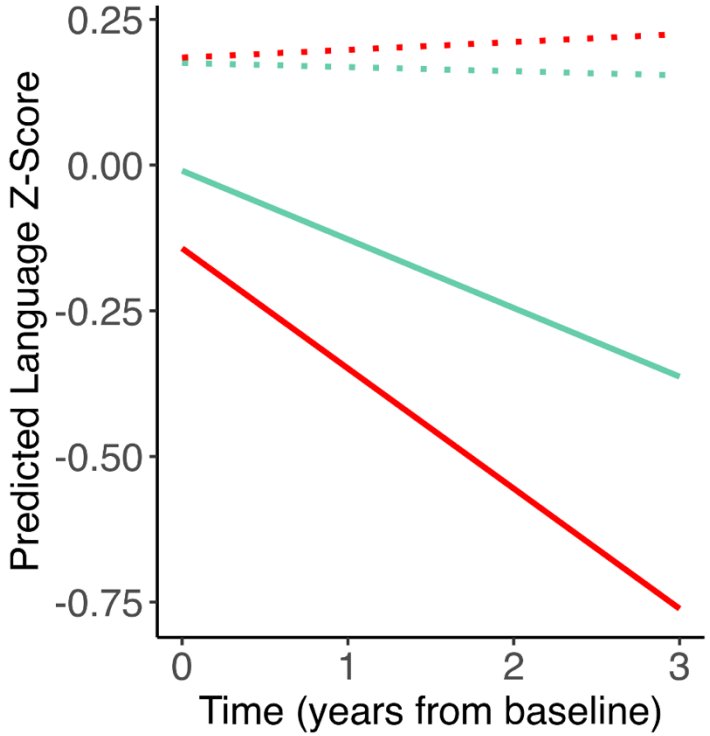
*Adjusted for age, sex, educ

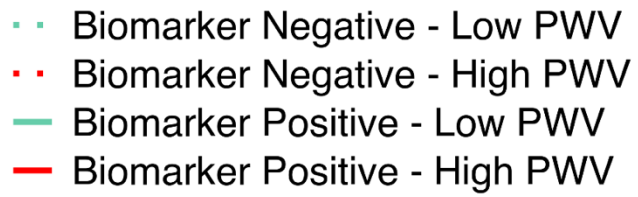
Bangen, et al. (2021). *Alzheimers Res Ther.*

PWV and AD Biomarkers Predict Decline

Lauren Edwards
Clin Psych JDP Student







*Adjusted for age, sex, educ, vascular risk burden (FSRP), and cognitive status (MCI versus CU).
High PWV is defined as the highest tertile for visualization.

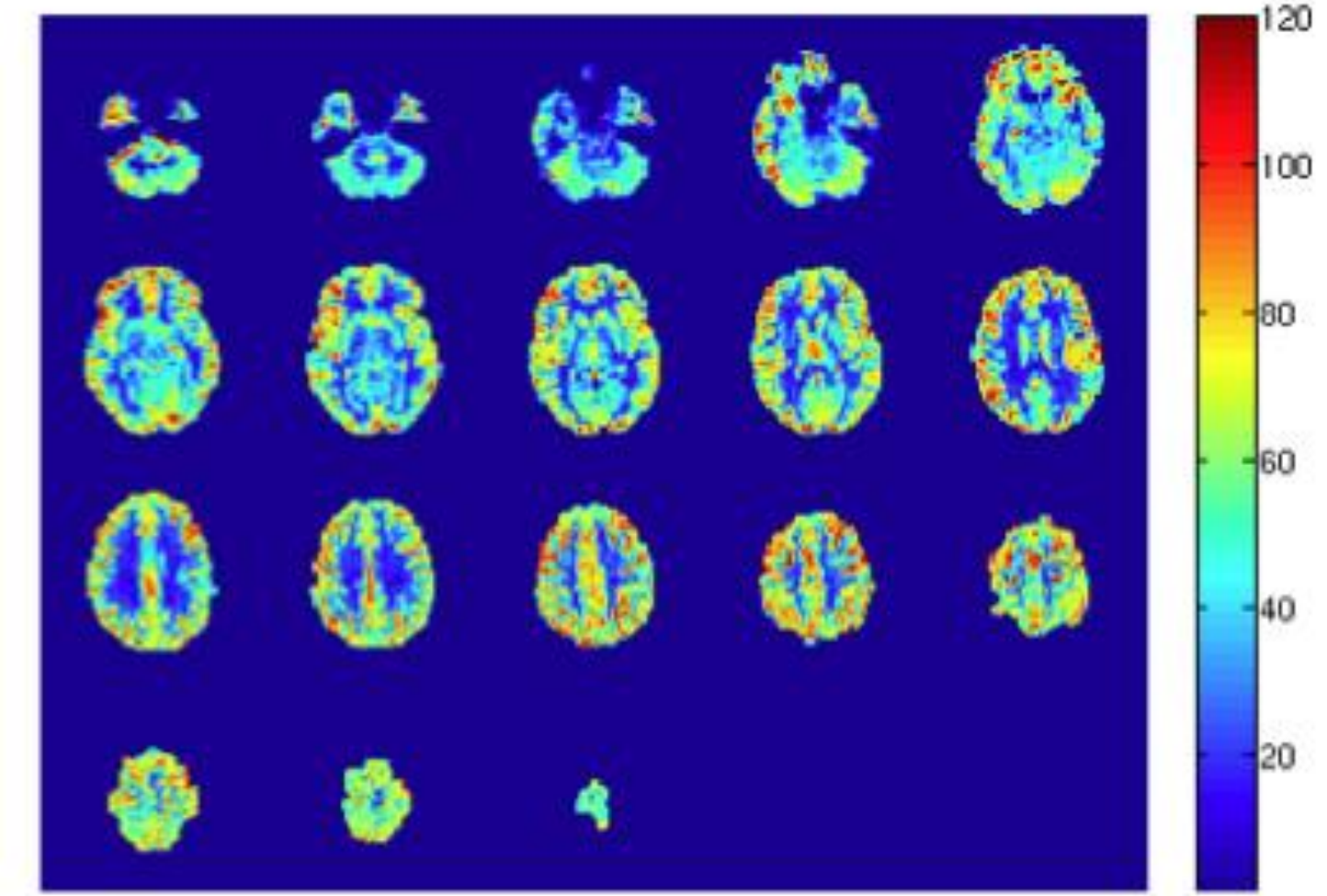
Edwards, et al. (under review)

PWV and AD Biomarkers Predict Decline

- First study (to our knowledge) examining interactive effects of PWV and CSF AD biomarkers on cognitive decline measured by comprehensive neuropsychological assessment
- Findings support synergistic relationship between AD and vascular pathologies in influencing cognitive decline
- Arterial stiffness can be reduced through behavioral strategies and pharmacological interventions
- PWV is a promising marker to assess risk of decline, and possibly a target of interventions to delay/prevent cognitive decline

Mitchell, Hypertension, 2014; Edwards, et al. (under review)

3. Resting Cerebral Blood Flow as a Biomarker



CBF maps collected
at UCSD CFMRI

Cerebral Circulation - Cognition and Behavior 6 (2024) 100206

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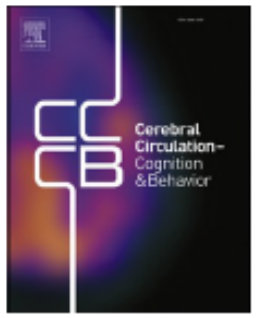
Cerebral Circulation - Cognition and Behavior

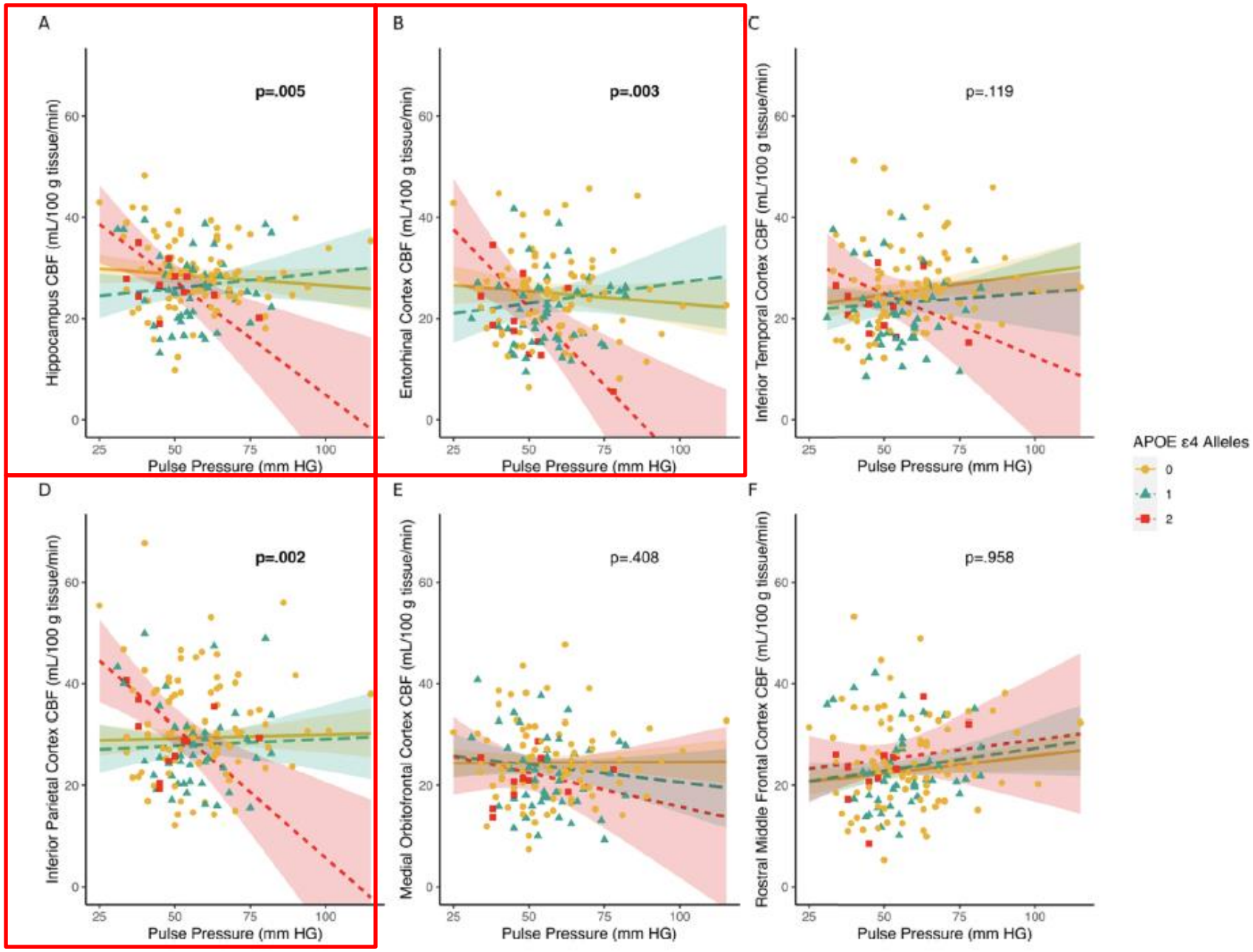
journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior



Pulse pressure and APOE ε4 dose interact to affect cerebral blood flow in older adults without dementia

Lauren Edwards [a], Kelsey R. Thomas [b,c], Alexandra J. Weigand [a], Emily C. Edmonds [d,e], Alexandra L. Clark [f], Einat K. Brenner [c], Sarah J. Banks [g], Paul E. Gilbert [a,h], Daniel A. Nation [i], Lisa Delano-Wood [c,j], Mark W. Bondi [c,j], Katherine J. Bangen [b,c,*], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a] San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[b] Research Service, VA San Diego Healthcare System, San Diego, CA, USA
[c] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA
[d] Banner Alzheimer's Institute, Tucson, AZ, USA
[e] Departments of Neurology and Psychology, University of Arizona, Tucson, AZ, USA
[f] Department of Psychology, University of Texas at Austin, Austin, TX, USA
[g] Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA
[h] Department of Psychology, San Diego State University, San Diego, CA, USA
[i] Department of Psychology, University of California Irvine, Irvine, CA, USA
[j] Psychology Service, VA San Diego Healthcare System, San Diego, CA, USA



Lauren Edwards
Clin Psych JDP Student

Fig. 1. Interaction between pulse pressure and APOE ε4 allele dose on CBF in A) hippocampus, B) entorhinal cortex, C) inferior temporal cortex, D) inferior parietal cortex, E) medial orbitofrontal cortex, and F) rostral middle frontal cortex. Predicted slopes and raw data points are shown. Omnibus interaction p values are included and bolded where significant ($p < 0.05$).

Original Article

JCBFM

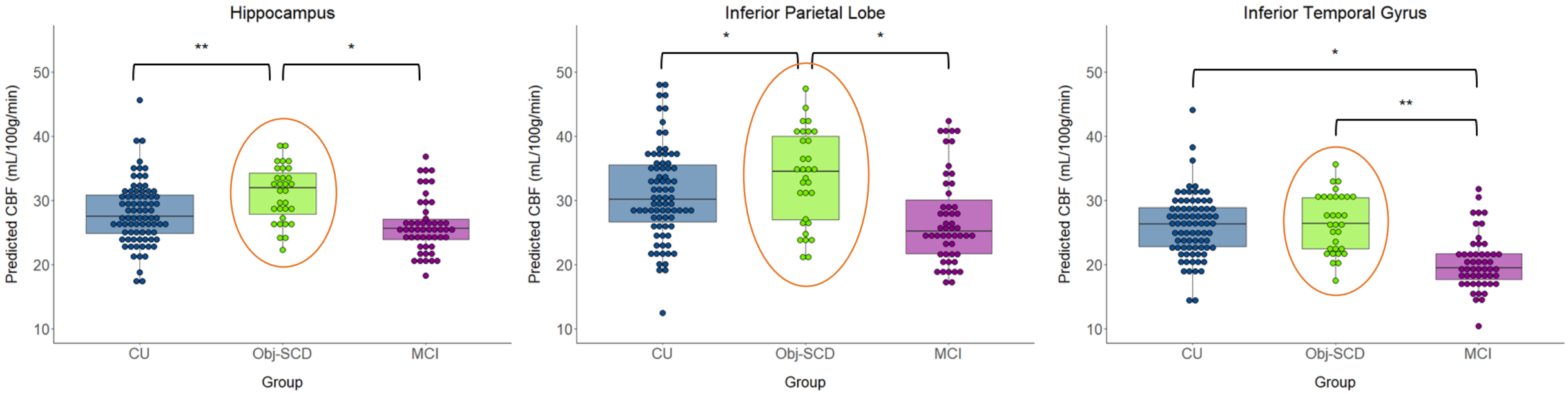
Journal of Cerebral Blood Flow & Metabolism
2021, Vol. 41(5) 1001–1012

DOI: 10.1177/0271678X20935171
journals.sagepub.com/home/jcbfm
SAGE

Regional hyperperfusion in older adults with objectively-defined subtle cognitive decline

Kelsey R Thomas[1,2], Jessica R Osuna[1,2], Alexandra J Weigand[1,2,3], Emily C Edmonds[1,2], Alexandra L Clark[1,2], Sophia Holmqvist[1], Isabel H Cota[1], Christina E Wierenga[1,2], Mark W Bondi[2,4] and Katherine J Bangen[1,2]; for the Alzheimer's Disease Neuroimaging Initiative*

Pre-MCI: Objective Subtle Cognitive Decline



- We found an inverted-U pattern of CBF signal across prodromal AD stages in regions susceptible to early AD pathology
- May reflect neurovascular dysregulation whereby higher CBF is needed to maintain cognitive functioning relative to MCI participants, yet is also reflective of early cognitive inefficiencies that distinguish Obj-SCD from those with unimpaired cognition

Alexandra L Clark[1], Sophia Holmqvist[1], Isabel H Costa[1], Christina E Wierenga[1,2], Mark W Bondi[1,2], and Katherine J Bangen[1,2]; for the Alzheimer's Disease Neuroimaging Initiative*

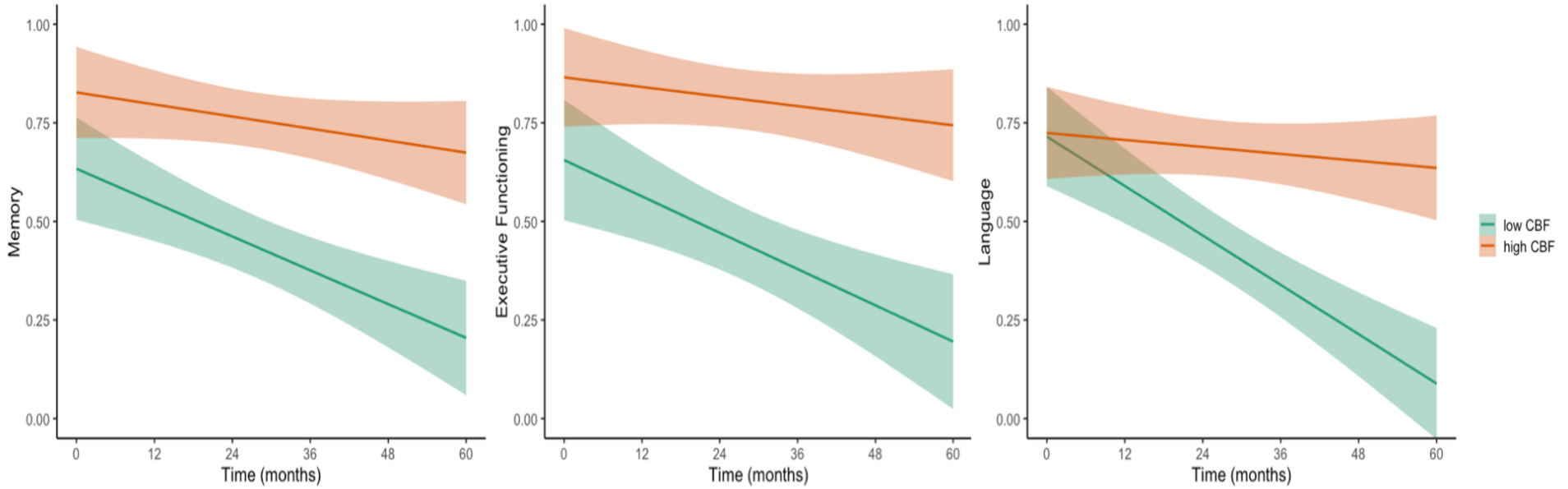
Thomas et al., 2020

Journal of Alzheimer's Disease 81 (2021) 1711–1725
DOI 10.3233/JAD-201474
IOS Press

Entorhinal Perfusion Predicts Future Memory Decline, Neurodegeneration, and White Matter Hyperintensity Progression in Older Adults

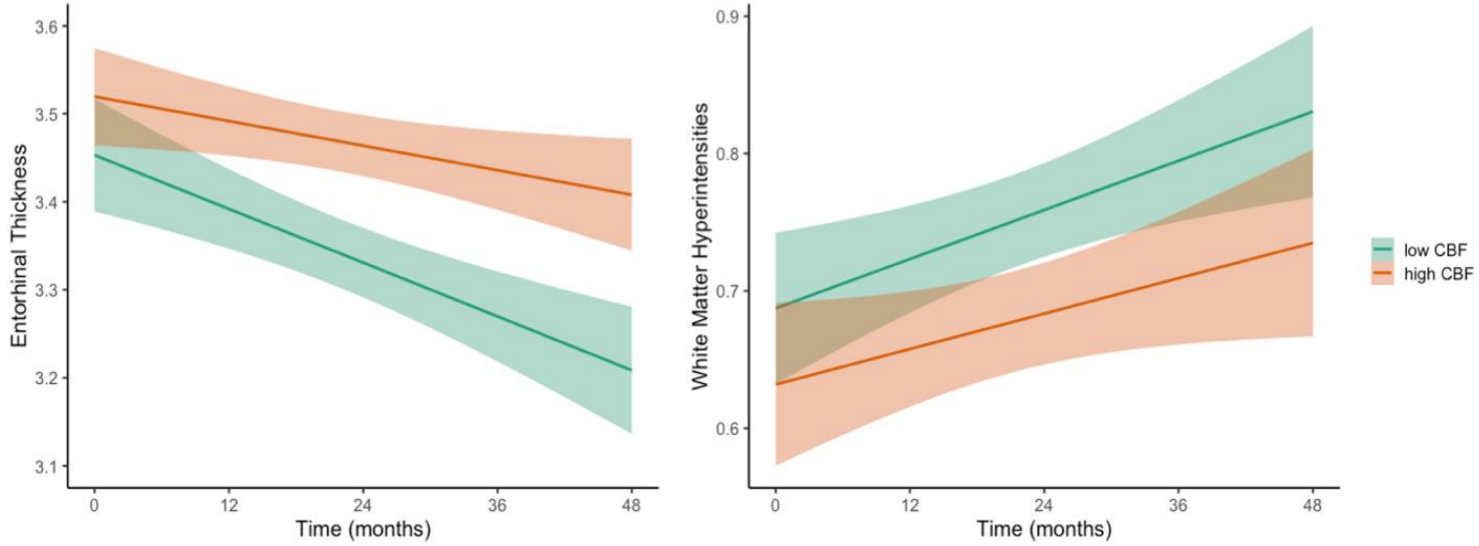
Katherine J. Bangen[a,b,*], Kelsey R. Thomas[a,b], Danielle L. Sanchez[c], Emily C. Edmonds[a,b], Alexandra J. Weigand[d], Lisa Delano-Wood[b,e], Mark W. Bondi[b,e] and for the Alzheimer's Disease Neuroimaging Initiative[1]

Reduced CBF Predicts Future Cognitive Decline



- Adjusting for demographics, APOE ε4 positivity, CSF p-tau/Aβ, and neuronal metabolism (i.e., FDG SUVR), lower baseline entorhinal CBF predicted faster rates of decline in memory, executive functioning, and language

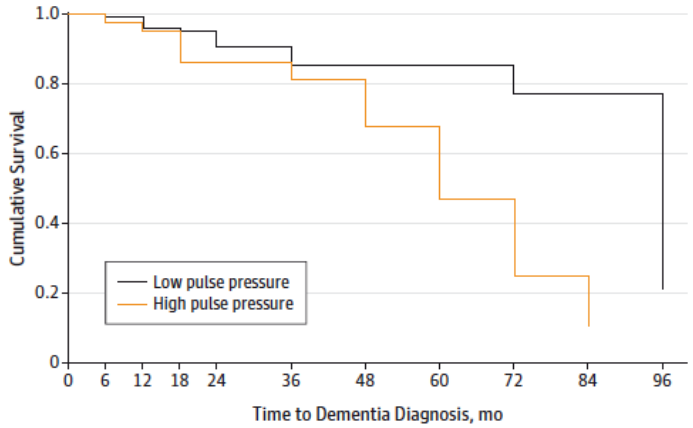
Reduced CBF Predicts Future Neurodegeneration and WMH Progression

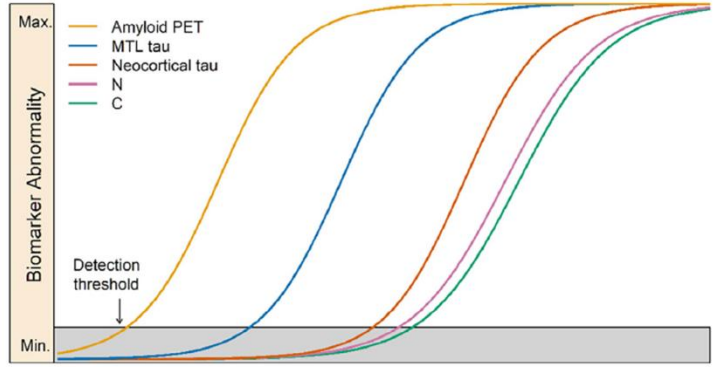


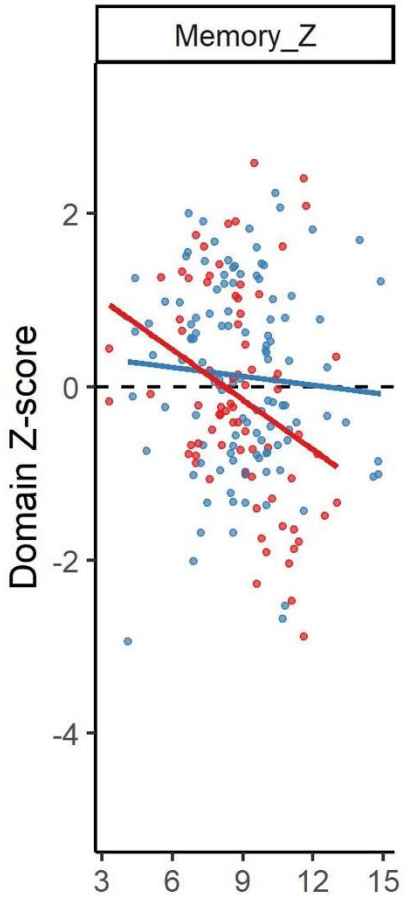
- Adjusting for demographics, APOE ε4 positivity, CSF p-tau/Aβ, and neuronal metabolism (i.e., FDG SUVR), lower baseline entorhinal CBF predicted faster rates of entorhinal thinning and WMH progression

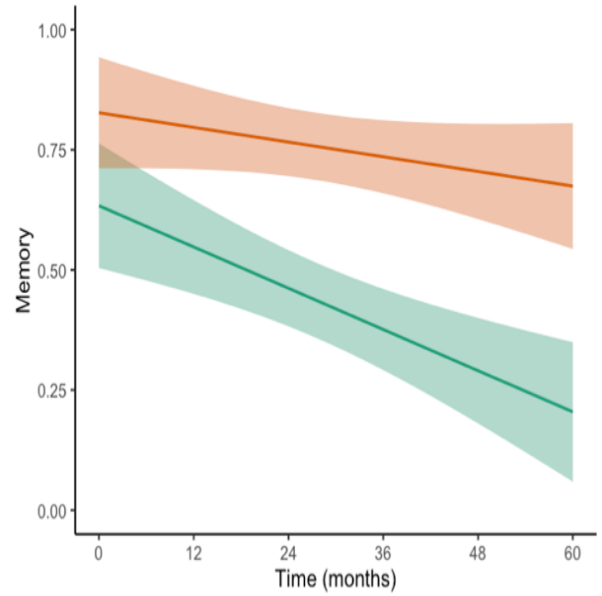
Expanding the Model

- ✓Vascular contributions









Midlife Timeline

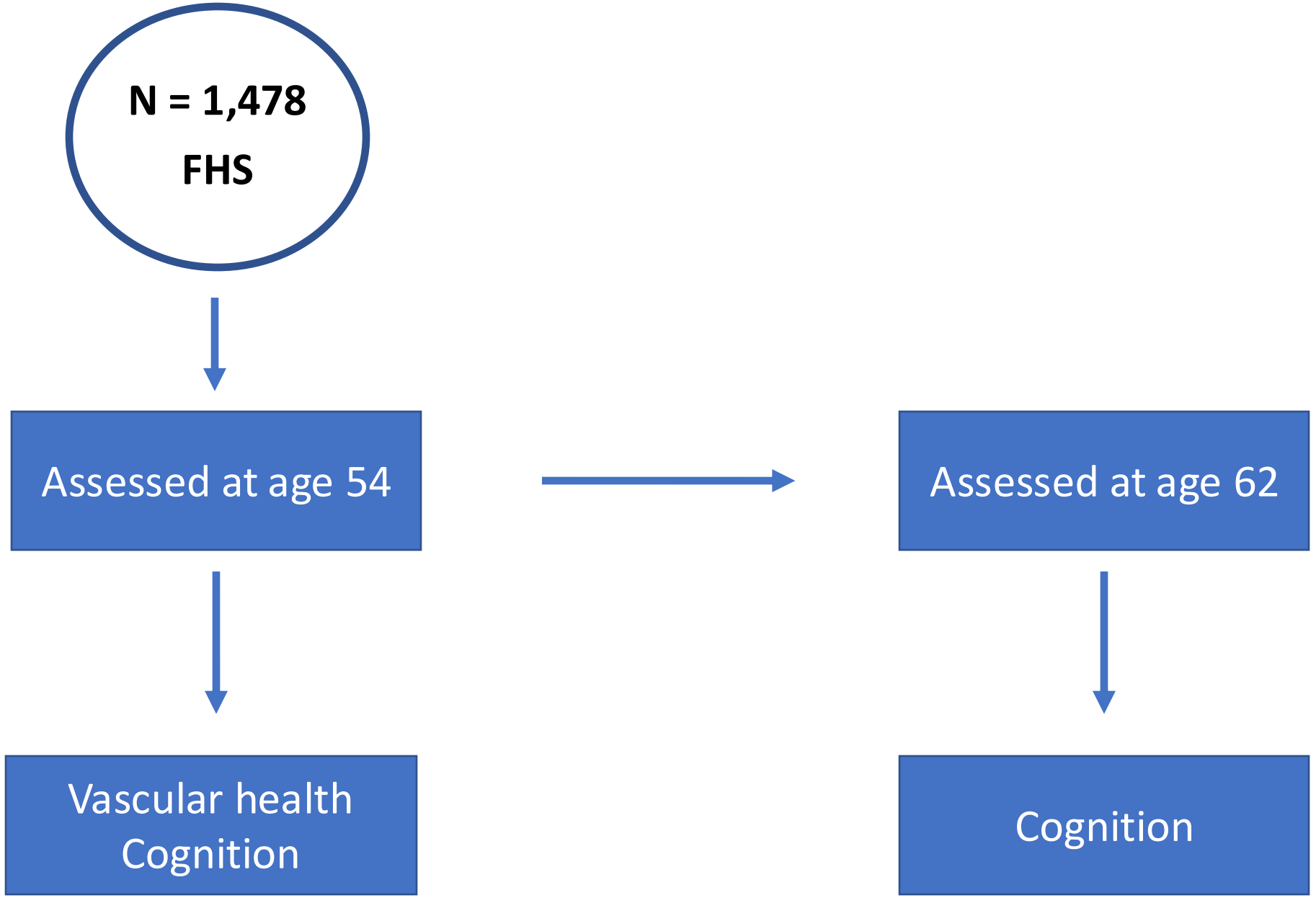
- Vascular factors – especially in mid-life – are some of the most important risk factors for dementia
  - Midlife smoking, diabetes, prehypertension, and hypertension associated with increased risk for dementia in late life
  - Hazard ratio for dementia for diabetes was almost as high as that for APOE ε4 genotype
    - (1.77 versus 1.98)
  - Chronicity
- Vascular factors are potentially modifiable
- Yet most studies of dementia begin around age 60 or 65

Gottesman et al. (2017). *JAMA Neurol.*

APOE Genotype Modifies the Relationship between Midlife Vascular Risk Factors and Later Cognitive Decline

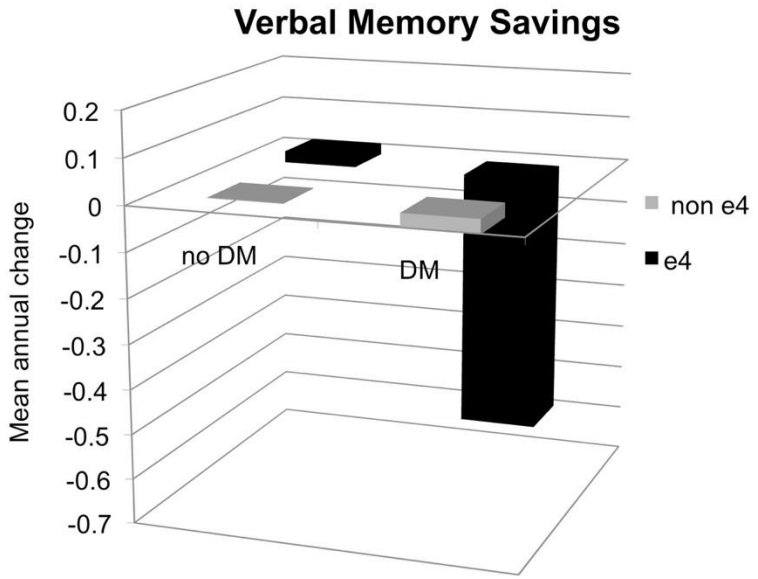
Katherine J. Bangen, PhD,* Alexa Beiser, PhD,†‡§ Lisa Delano-Wood, PhD,*‖ Daniel A. Nation, PhD,¶ Melissa Lamar, PhD,# David J. Libon, PhD,** Mark W. Bondi, PhD,*¶ Sudha Seshadri, MD,†‡ Philip A. Wolf, MD,†‡ and Rhoda Au, PhD†‡

Background: Vascular risk factors have been associated with cognitive decline; however, it remains unclear whether apolipoprotein E (APOE) genotype modifies this relationship. We aimed to further elucidate these relationships and extend previous findings by examining data from a more comprehensive cognitive assessment than used in prior studies. *Methods:* In all, 1436 participants from the prospective Framingham Offspring Cohort Study underwent health examination from 1991 to 1995, followed by a baseline neuropsychological assessment (1999-2003) and a repeat neuropsychological assessment approximately 8 years later (2004-2009). Multivariate linear regression analyses were performed to examine the relationship among midlife vascular risk factors, presence of the APOE ε4 allele, and cognitive change. *Results:* APOE genotype significantly modified the associations between both midlife hypertension and cardiovascular disease and decline in language abilities and midlife diabetes and decline in verbal memory, attention, and visuospatial abilities. Associations between increased midlife vascular risk burden and greater cognitive decline were observed among APOE ε4 carriers but not noncarriers. *Conclusions:* The present findings revealed a subgroup at increased risk for cognitive decline (APOE ε4 carriers with midlife exposure to vascular risk factors) and suggest that treatment of vascular risk factors during midlife may reduce the risk of cognitive impairment later in life, particularly among APOE ε4 carriers. **Key Words:** Apolipoprotein E—cognition—vascular risk—aging—diabetes—hypertension—cardiovascular disease.



Bangen et al. (2013). *J Stroke Cerebrovas. Dis.*

Vascular Risk, APOE, & Cognition



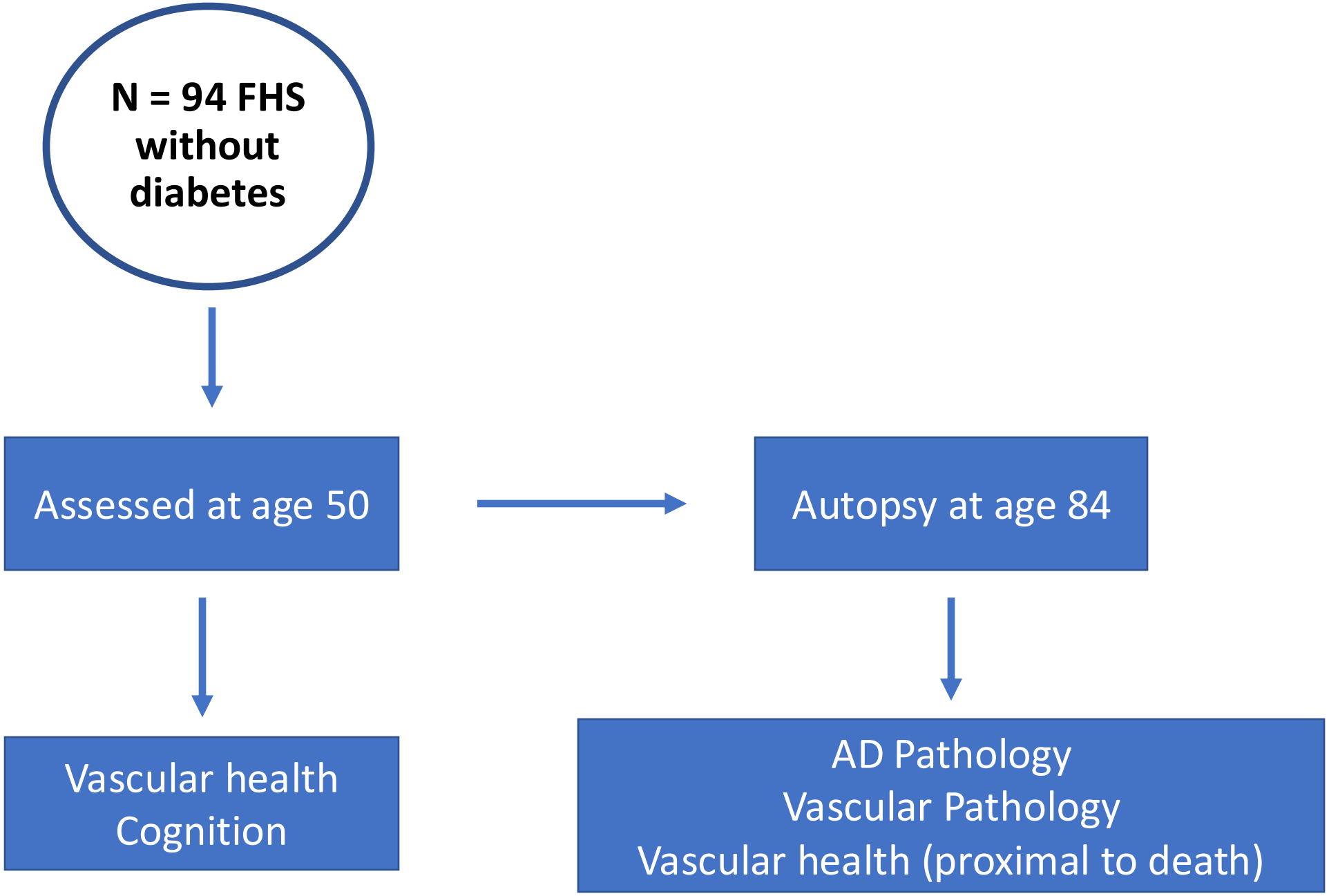
- Midlife vascular risk & APOE interact to predict cognitive decline

Journal of Alzheimer's Disease 53 (2016) 1553–1562
DOI 10.3233/JAD-160163
IOS Press

Interaction Between Midlife Blood Glucose and APOE Genotype Predicts Later Alzheimer's Disease Pathology

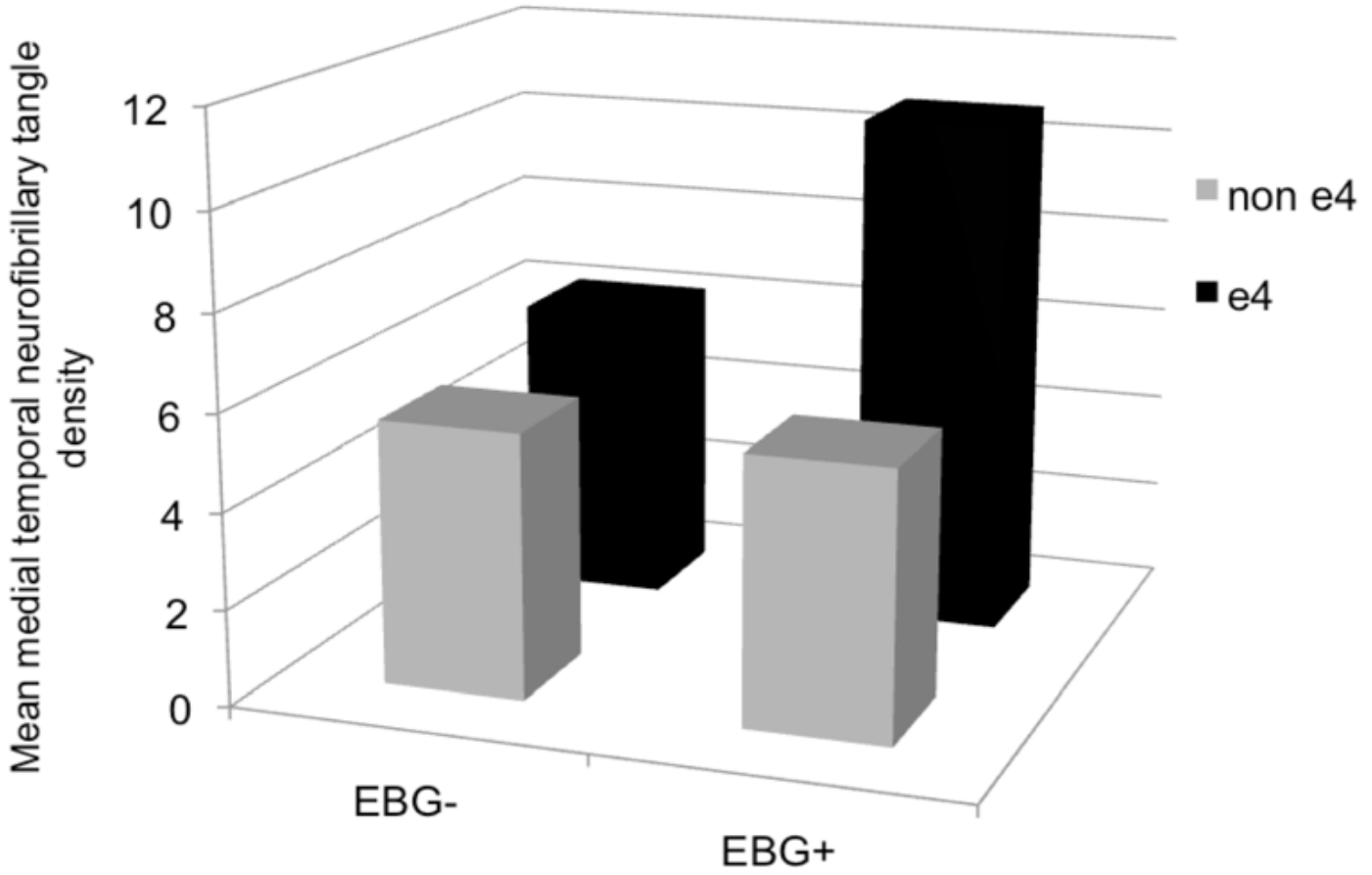
Katherine J. Bangen[a,b,*], Jayandra J. Himali[c,d], Alexa S. Beiser[c,d,e], Daniel A. Nation[f], David J. Libon[g], Caroline S. Fox[d,h], Sudha Seshadri[c,d], Philip A. Wolf[c,d], Ann C. McKee[c,d], Rhoda Au[c,d] and Lisa Delano-Wood[a,b]

[a]*Research Service, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA*
[b]*Department of Psychiatry, University of California, San Diego School of Medicine, La Jolla, CA, USA*
[c]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[d]*The Framingham Heart Study, Framingham, MA, USA*
[e]*Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA*
[f]*Department of Psychology, University of Southern California, Los Angeles, CA, USA*
[g]*Department of Geriatrics and Gerontology, Rowan University School of Osteopathic Medicine, Stratford, NJ, USA*
[h]*Division of Endocrinology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA*



Bangen et al. (2013). *J Stroke Cerebrovas. Dis.*

Vascular Risk, APOE, & Neuropath

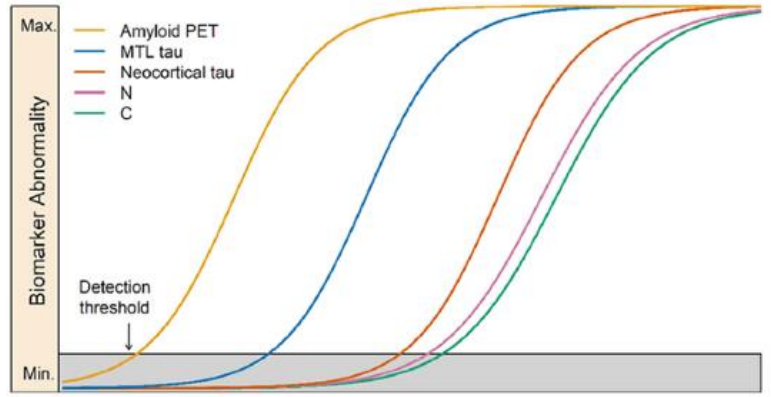


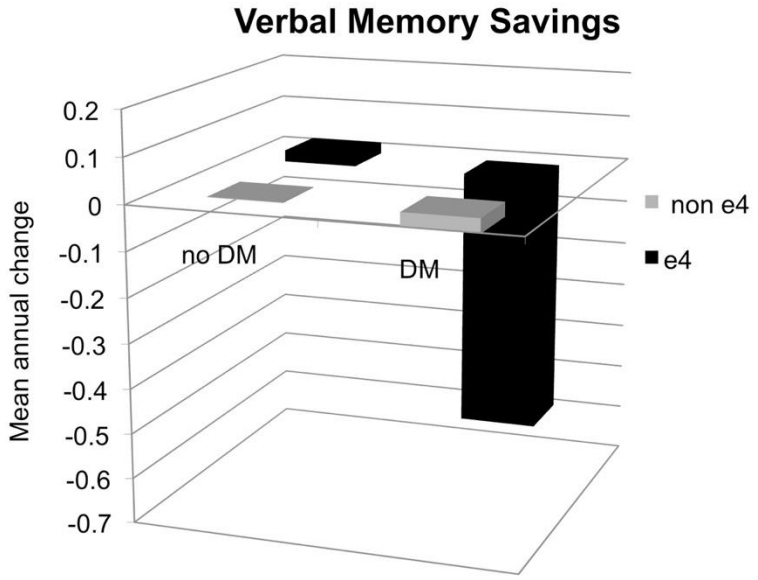
- Midlife blood glucose and APOE interact to influence AD pathology
- Altered glucose metabolism may be linked to processes promoting tau accumulation (Freude et al., 2005; Schubert et al., 2004)

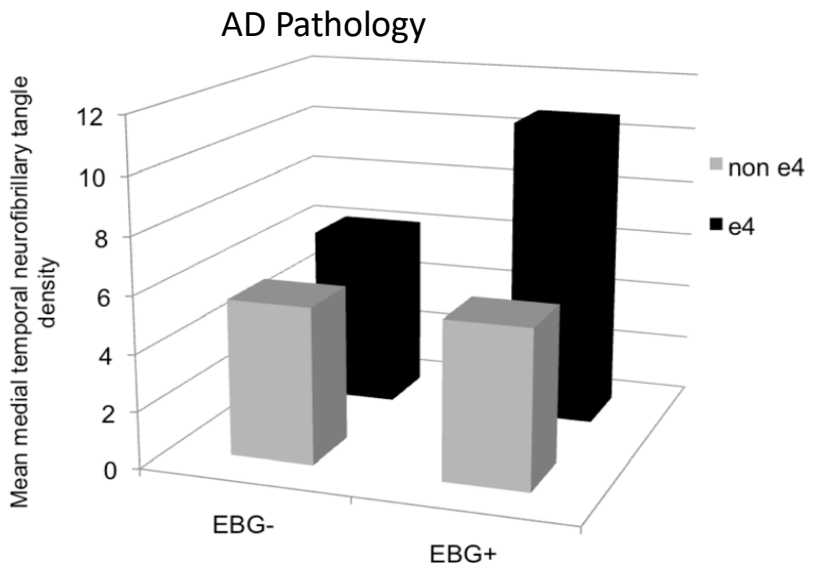
Bangen et al. (2016). *J Alzheimers Dis.*

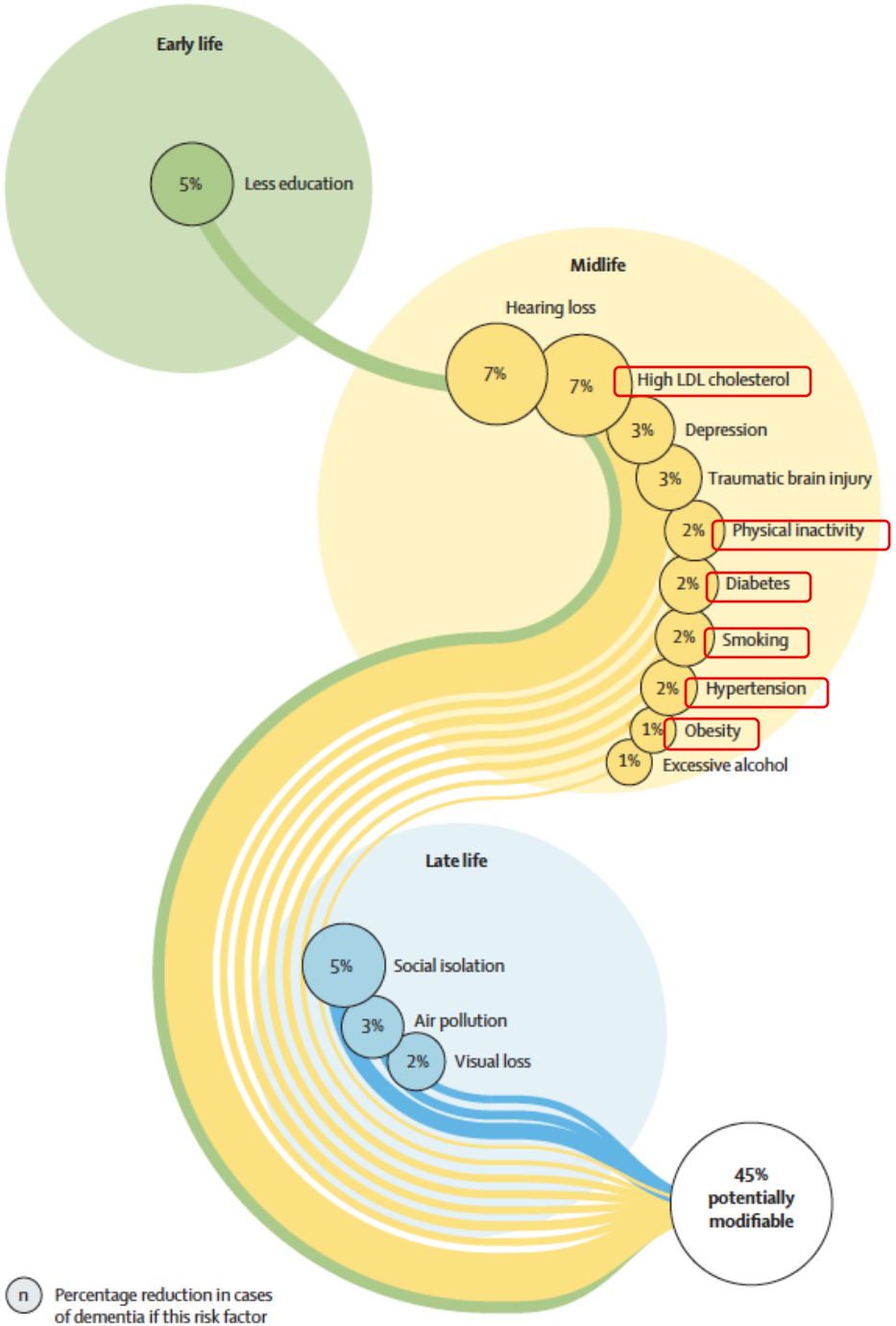
Expanding the Model

- ✓Vascular contributions
- ✓Midlife









Dementia prevention, intervention, & care: 2024 report of the *Lancet* Commission

- "Modifying 14 risk factors might prevent or delay nearly half of dementia cases"
- Nearly half of these risk factors are vascular risk factors

Livingston et al. (2024). *Lancet.*

Treatment of Hypertension for Dementia Prevention

SPRINT MIND Randomized Control Trial

- Intensive tx group: systolic bp < 120 mm Hg
- Standard tx group: systolic bp <140 mm Hg

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group: Intensive — No. With Outcome/Person-Years	Intensive — Cases per 1000 Person-Years	Standard — No. With Outcome/Person-Years	Standard — Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	*P* Value
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

Williamson et al., (2019) *JAMA.*

Summary

- Cerebrovascular risk factors are common & (esp when present in midlife) increase ADRD risk
- Mixed vascular pathology and AD pathology is very common
- Cerebrovascular disease increases odds of dementia among individuals with co-existing AD pathology
- Proposed mechanisms of effect of vascular risk on AD include damaging microcirculation and interfering with amyloid clearance
- Differences in risk factors across racial and ethnic groups may be moderated by social determinants of health
- Subtle/subclinical cerebrovascular changes on MRI predict future decline
  - Vascular markers have potential as useful biomarkers and potential tx targets
- Lifestyle changes and tx of vascular risk factors may have a large impact on prevention of clinical dementia
  - SPRINT MIND: Intensive BP control reduced risk of MCI and combined MCI/dementia

Sweeney et al., Nature Neuroscience, 2018; Arvanitakas et al., Stroke, 2011; Kapasi et al., Acta Neuropathol, 2017; Mitchell et al., Brain, 2011; Weller et al., Acta Neuropathol., 2009; Williamson et al., JAMA, 2019

Future Directions

- ✓Vascular contributions
  - ✓Lifestyle changes and tx of vascular risk factors may have a large impact on primary prevention of clinical dementia
  - ✓New biomarkers: blood brain barrier permeability, cerebral arterial compliance
- ✓Midlife
  - ✓Opportunities for earlier intervention to preventing cognitive decline
  - ✓Current grants focus on midlife
- ✓Sensitive neuropsychological measures
  - ✓Earlier detection of individuals at risk
  - ✓Expanded study of subtle cognitive decline
- ✓Clinical research cohorts including individuals from varied backgrounds

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Collaborators:

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