Vascular risk factors impact cognition independent of PIB PET and MRI measures of AD and vascular brain injury

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IDeA Lab

Imaging of Dementia and Aging

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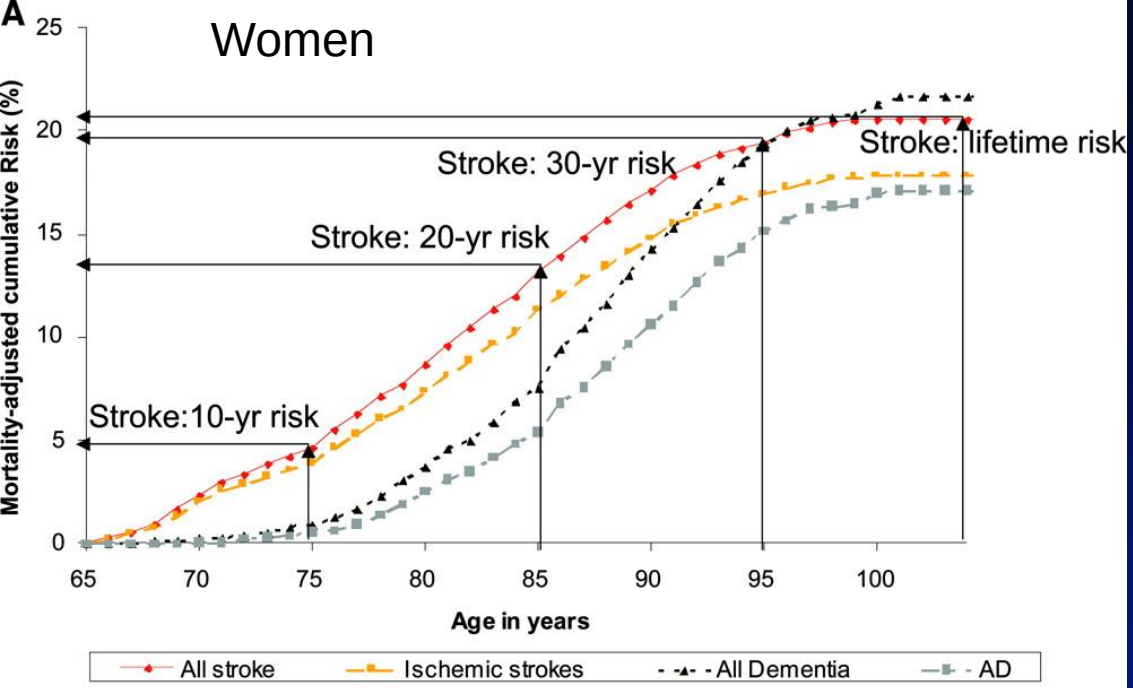
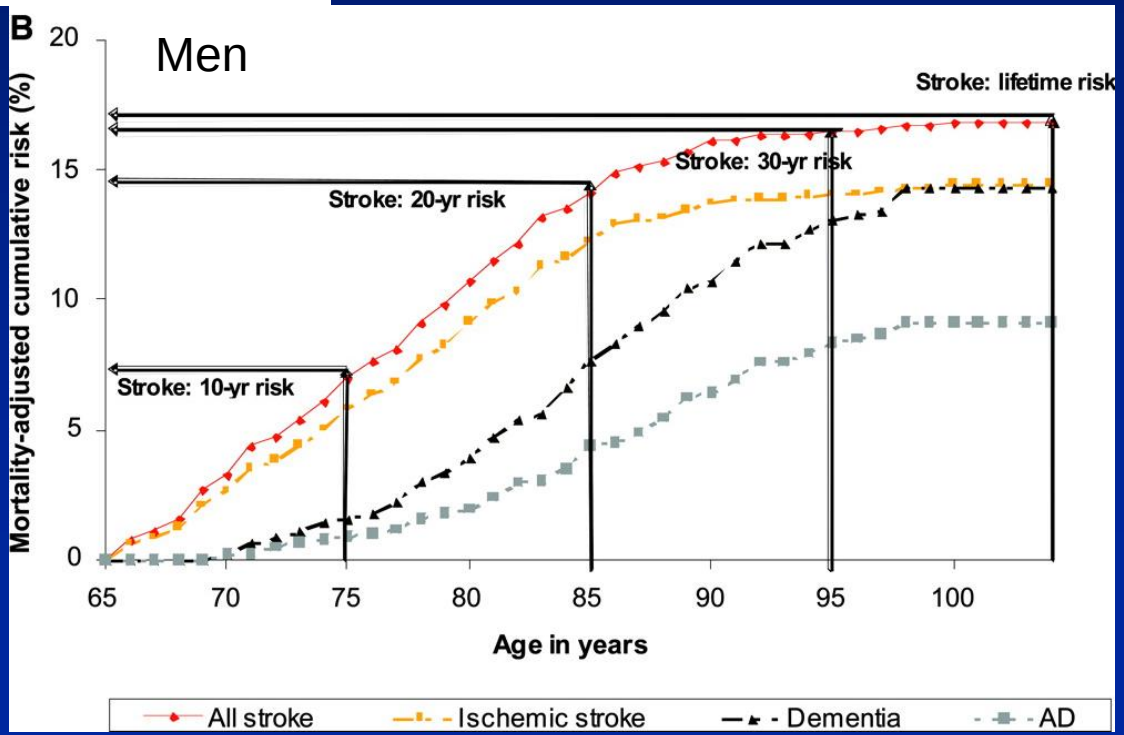
Disclosures

- P30 AG10129, P01 AG12435, R01 AG010220, R01 AG 031563 and R01 AG021028
- Consultant to Novartis

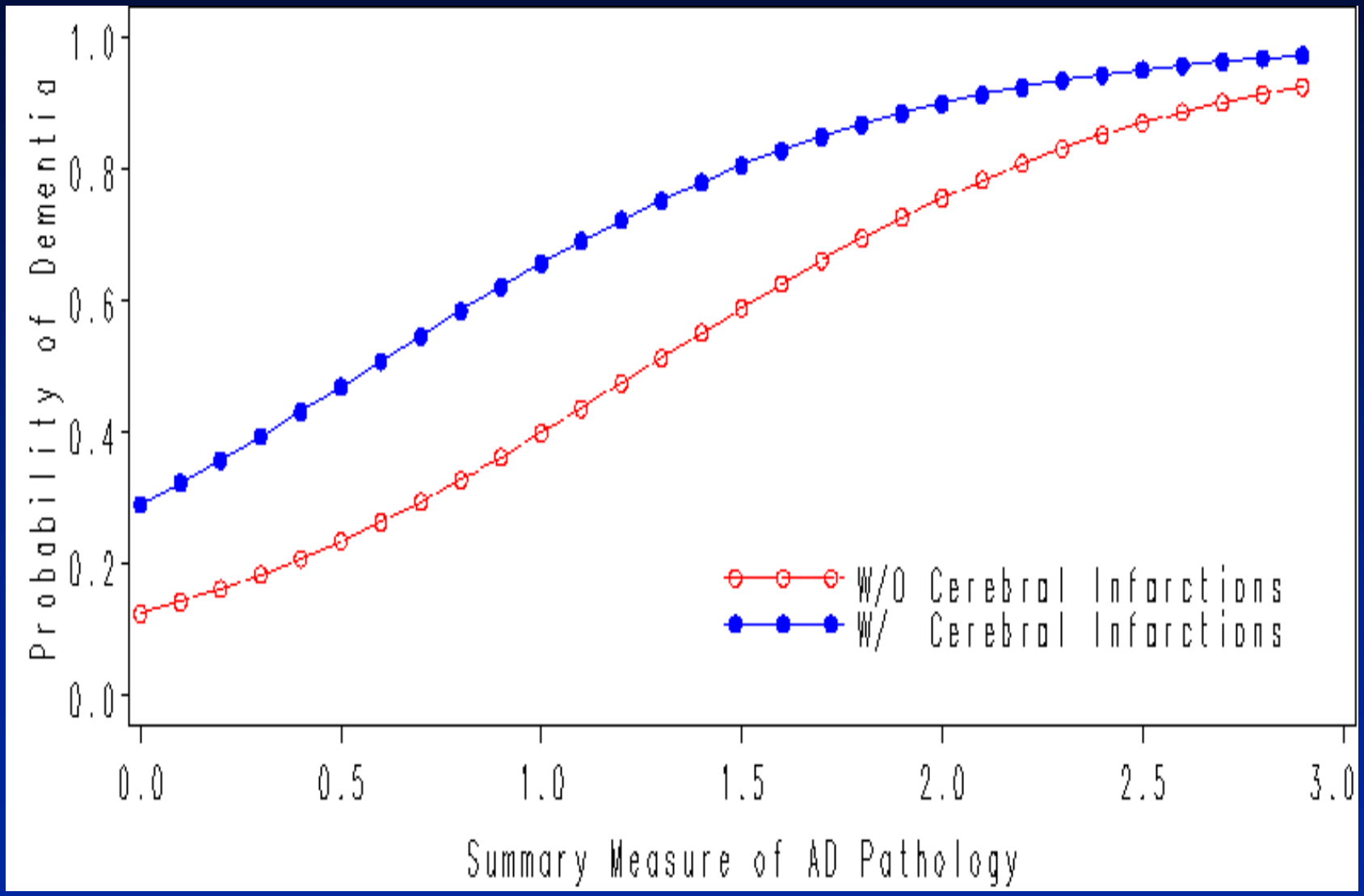
Future Risk of Stroke or Dementia at Age 65





Seshadri, S. et al.
Stroke 2006;37:345-350

Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology



Schneider JA, et al. *Neurology* 2004;62:1148-1155

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Neurobiology of Aging 33 (2012) 1006.e25–1006.e36

NEUROBIOLOGY OF AGING

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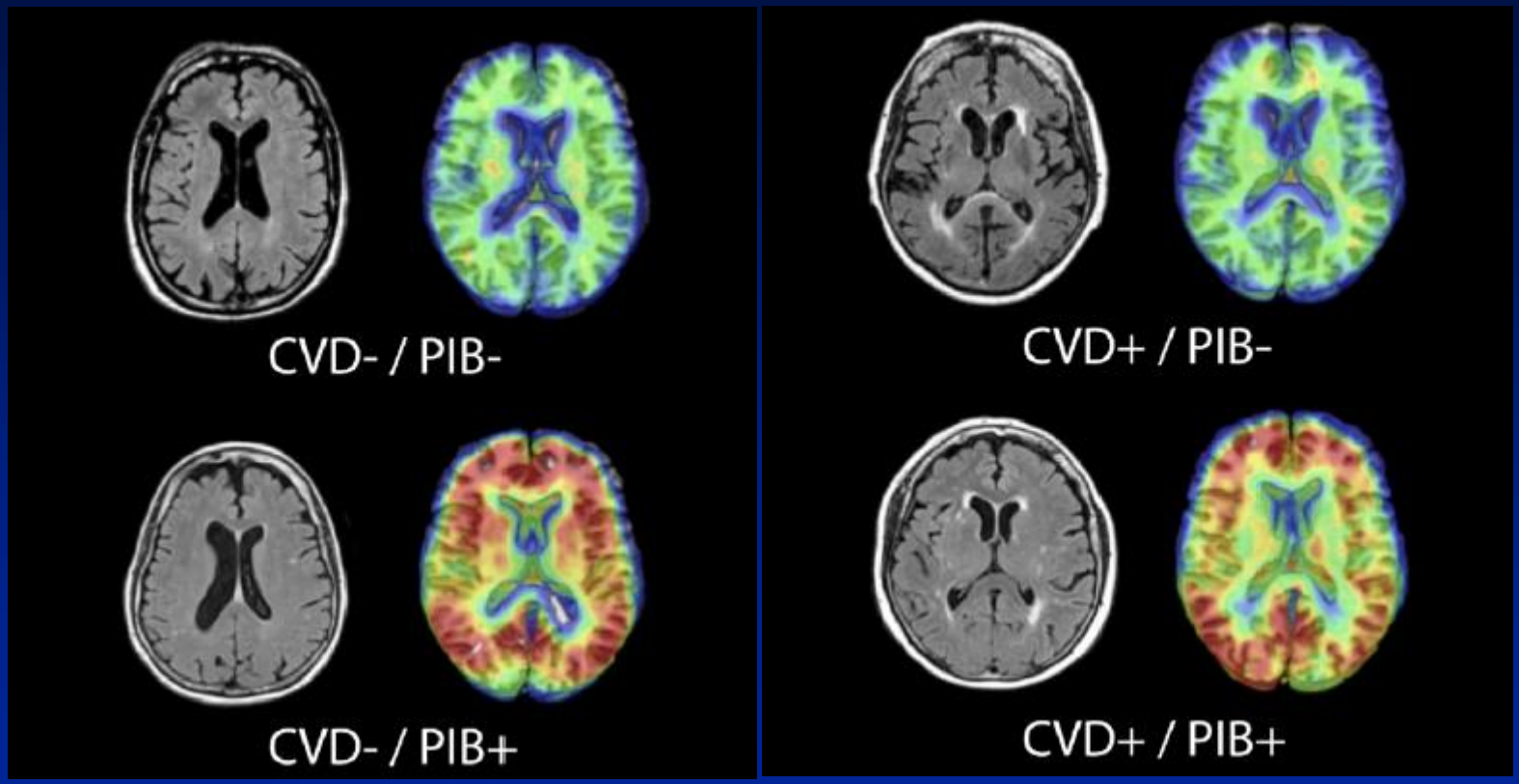
Cerebrovascular disease, beta-amyloid, and cognition in aging

Natalie L. Marchant[a,b,*], Bruce R. Reed[c], Charles S. DeCarli[c], Cindee M. Madison[a], Michael W. Weiner[d], Helena C. Chui[e], William J. Jagust[a,b]

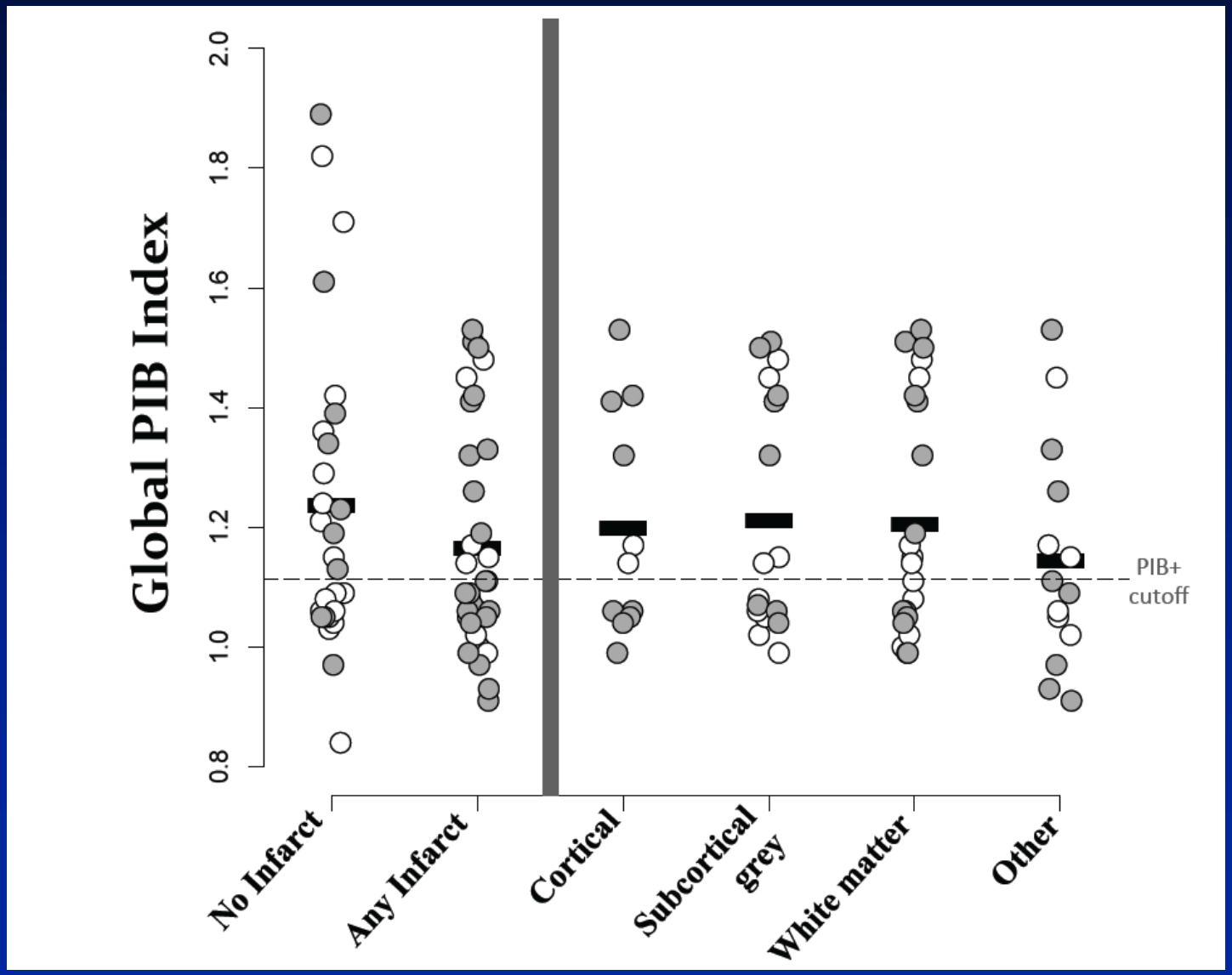
	CVD− (n = 27)	CVD+ (n = 27)	Total (n = 54)
Age	76.2 ± 6.4	77.8 ± 7	77 ± 6.7
Sex (M/F)	14/13	18/9	32/22
Education	16.2 ± 2.6	14.8 ± 2.9	15.5 ± 2.8
APOE ε4 %[a]	23.1	28	25.5
GDS	4 ± 3.7	2.4 ± 2.2	3.2 ± 3.2
MMSE	29.1 ± 1.2	28.3 ± 1.2*	28.7 ± 1.3
Composite vascular risk	0.27 ± 0.27	0.44 ± 0.27*	0.36 ± 0.27
WMH percentage of TCV	0.19 ± 0.11	0.92 ± 0.75**	0.56 ± 0.65
Infarct type (cortical/subcortical/ both)	0	1/14/2	1/14/2
PIB −/+	18/9	15/12	33/21

Group Classification



CVD+ defined as extensive WMH or infarction or both on MRI

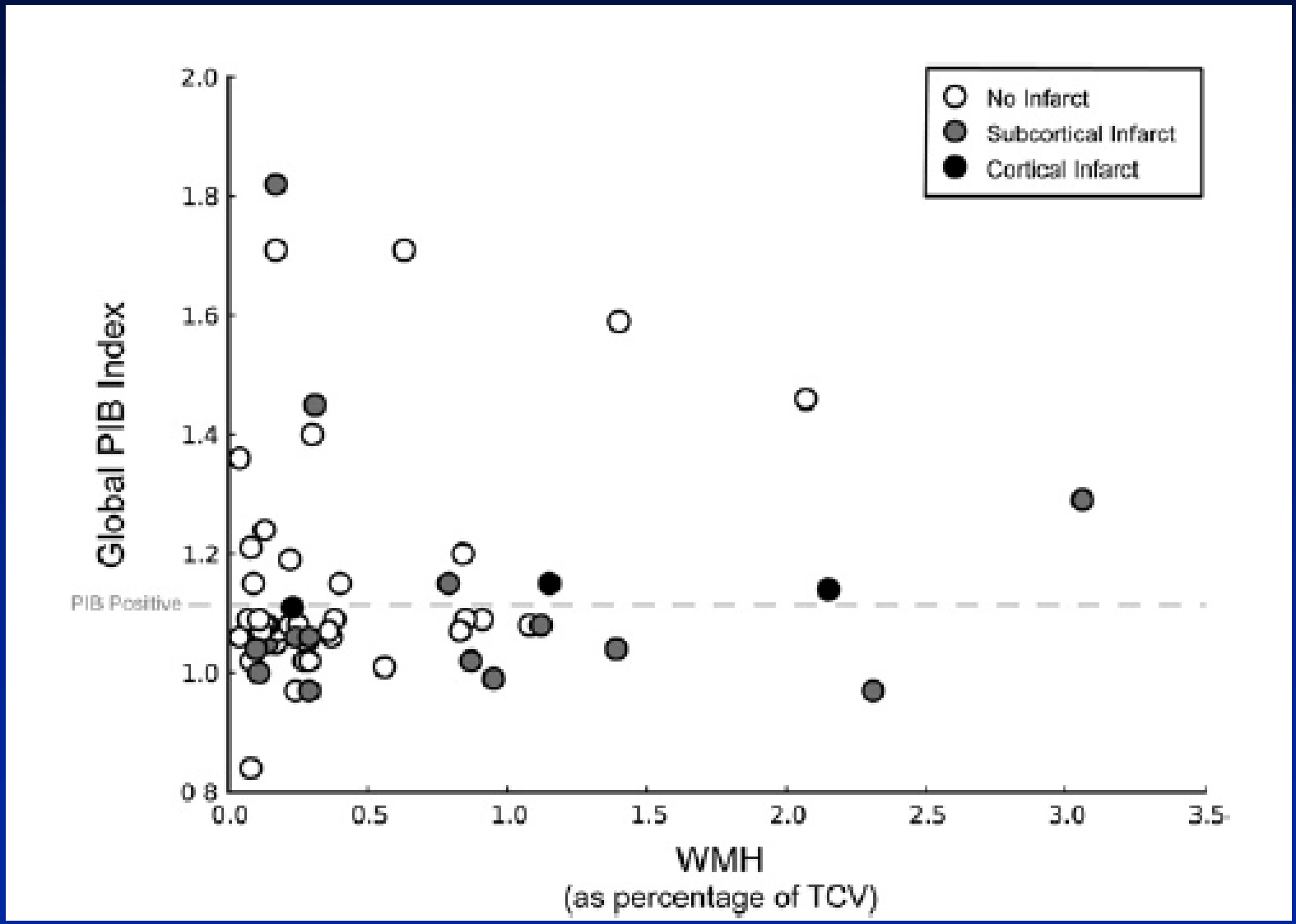
PiB Retention in Relation to Infarction



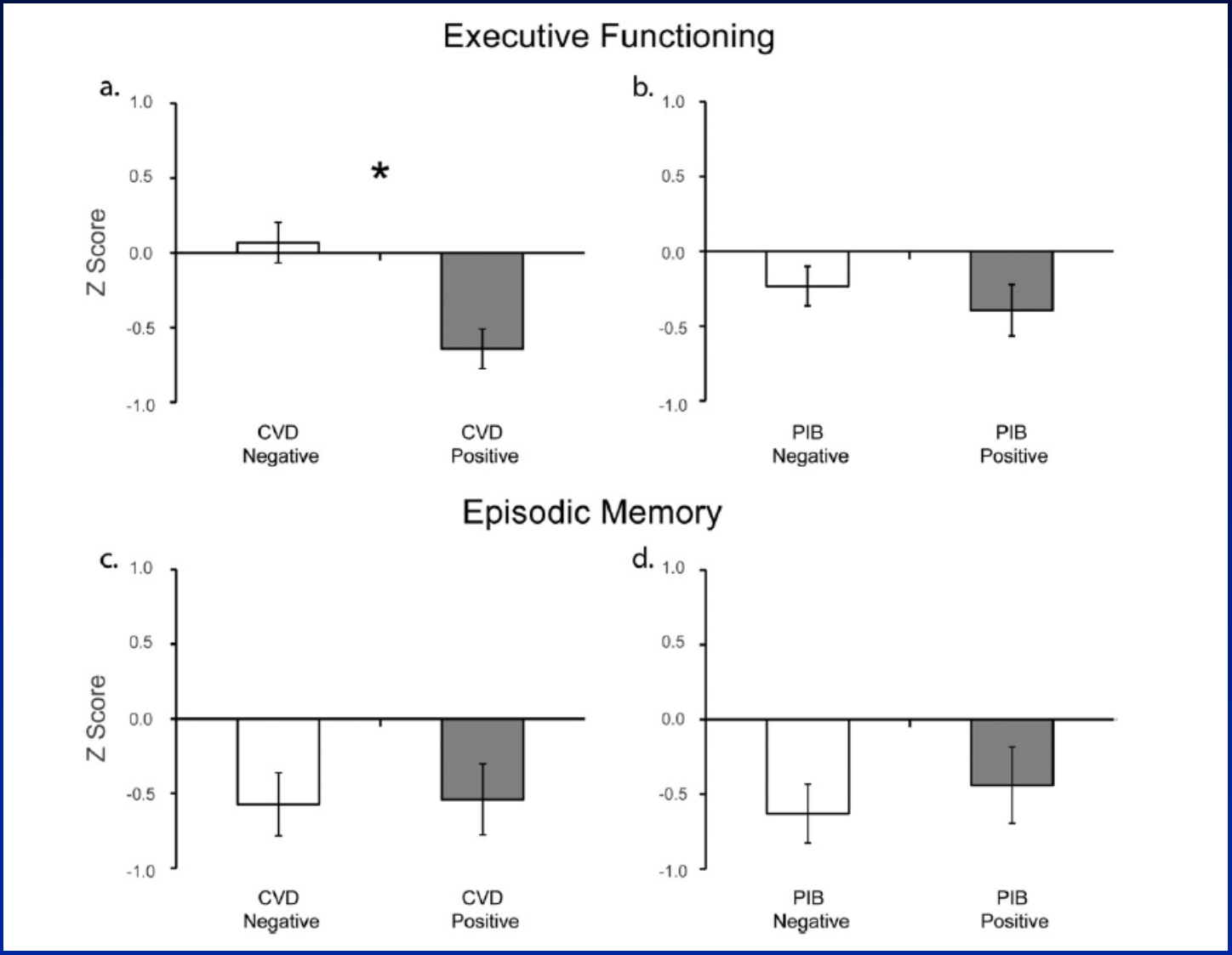
Normal Cognition

CDR ≥ 0.5

Association Between WMH volume and PiB Index



Association with Cognition



The Aging Brain and Cognition

Contribution of Vascular Injury and Aβ to Mild Cognitive Dysfunction

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JAMA Neurol. Published online February 11, 2013. doi:10.1001/2013.jamaneurol.405

	PiB− (n = 32)	PiB+ (n = 29)	*t*	χ^2	*P* Value
Age, mean (SD), y	76.6 (7.5)	79 (6.3)	$t_{59} = 1.4$		.17
Male sex	19 (59)	24 (83)		$\chi^2_1 = 4.00$	.046
Educational level, mean (SD), y	13.8 (2.9)	14.1 (2.5)	$t_{59} = 0.5$		.64
APOE ε4 allele[b]	3 (12)	10 (40)		$\chi^2_1 = 5.09$	.02
MMSE score, mean (SD)	28 (2.2)	27.4 (2.3)	$t_{59} = 1.0$		.32
GDS score, mean (SD)	1.5 (1.7)	2.4 (2.6)	$t_{57} = 1.5$		.14
Infarct+	20 (62)	14 (48)		$\chi^2_1 = 1.25$	.26
CDR ≥ 0.5	15 (47)	16 (55)		$\chi^2_1 = 0.42$	.52

Impact of Vascular disease on Cognition

Episodic Memory

	Demographics			Infarct					WMH	Aβ
	Age	Sex (Male)	Education	Cortical	Subcortical grey	White matter	Other	Number (0, 1, >1)	WMH volume	Global PIB Index
Stage 1	-.107	.064	.245							
Stage 2				-.06	-.29*	-.06	-.02	-.19	.02	-.18
Stage 3	-.24	-.02	.16		-.34*				.19	-.08

Executive Function

	Demographics			Infarct					WMH	Aβ
	Age	Sex (Male)	Education	Cortical	Subcortical grey	White matter	Other	Number (0, 1, >1)	WMH volume	Global PIB Index
Stage 1	-.01	.08	.51***							
Stage 2				-.47***	-.33*	-.17	-.2	-.14	-.21	-.15
Stage 3	-.08	-.19	.38**	-.54**					.05	-.04

Coronary Artery Disease Is Associated with Cognitive Decline Independent of Changes on Magnetic Resonance Imaging in Cognitively Normal Elderly Adults

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JAGS 60:499–504, 2012

Model	Independent Variable	Global Cognition*	Verbal Memory*	Executive Function*
1	CAD	−2.56 (0.88) .004	−2.55 (1.12) .02	−1.49 (0.67) .03
	Baseline WMH	−0.17 (0.39) .67	0.06 (0.49) .9	0.2 (0.29) .49
	Change in WMH	−1.91 (0.86) .03	−2.18 (1.1) .049	−2.56 (0.65) <.001
2	CAD	−2.55 (0.85) .003	−2.38 (1.13) .04	−1.35 (0.67) .046
	Baseline SBI	−0.14 (0.23) .56	−0.24 (0.3) .42	−0.33 (0.18) .07
	Change in SBI	−0.39 (0.17) .02	−0.23 (0.22) .28	−0.31 (0.13) .02
3	CAD	−2.53 (0.86) .004	−2.47 (1.06) .02	−1.41 (0.66) .03
	Baseline HV	0.09 (0.19) .63	0.66 (0.23) .004	0.17 (0.15) .24
	Change in HV	0.74 (0.27) .007	0.57 (0.33) .08	0.72 (0.21) .001
4	CAD	−2.43 (0.9) .007	−2.23 (1.12) .048	−1.27 (0.71) .08
	Baseline CGM	0.06 (0.15) .68	0.14 (0.18) .42	0.03 (0.11) .82
	Change in CGM	0.09 (0.1) .34	0.17 (0.12) .14	0.08 (0.07) .27
5	CAD	−2.69 (0.85) .002	−2.52 (1.06) .02	−1.51 (0.65) .02
	Change in WMH	−1.27 (0.87) .15	−1.63 (1.09) .14	−2.03 (0.66) .002
	Change in SBI	−0.24 (0.16) .14	—	−0.07 (0.12) .56
	Baseline HV	—	0.68 (0.23) .004	—
	Change in HV	0.53 (0.28) .06	0.45 (0.34) .19	0.49 (0.21) .02

Summary

- Vascular risk factors are common among older individuals
- In a high vascular risk group
  - Vascular brain injury is associated with impaired cognition
    - Impact due to extent of cerebral amyloid less prominent
  - Vascular risk factors exert effect on cognition when adjusting for vascular and degenerative brain injury

Aims

- Evaluate effect of vascular burden on change in cognition in a diverse, community based study
  - Adjusting for:
    - Amyloid Retention
    - Structural MRI

Methods

- Cognition measured with Spanish English Neuropsychological Assessment Scale (SENAS)
  - Memory
  - Executive
- MRI quantification
  - Total brain volume
  - Hippocampal volume
  - WMH
- Amyloid Imaging
  - PiB DVR

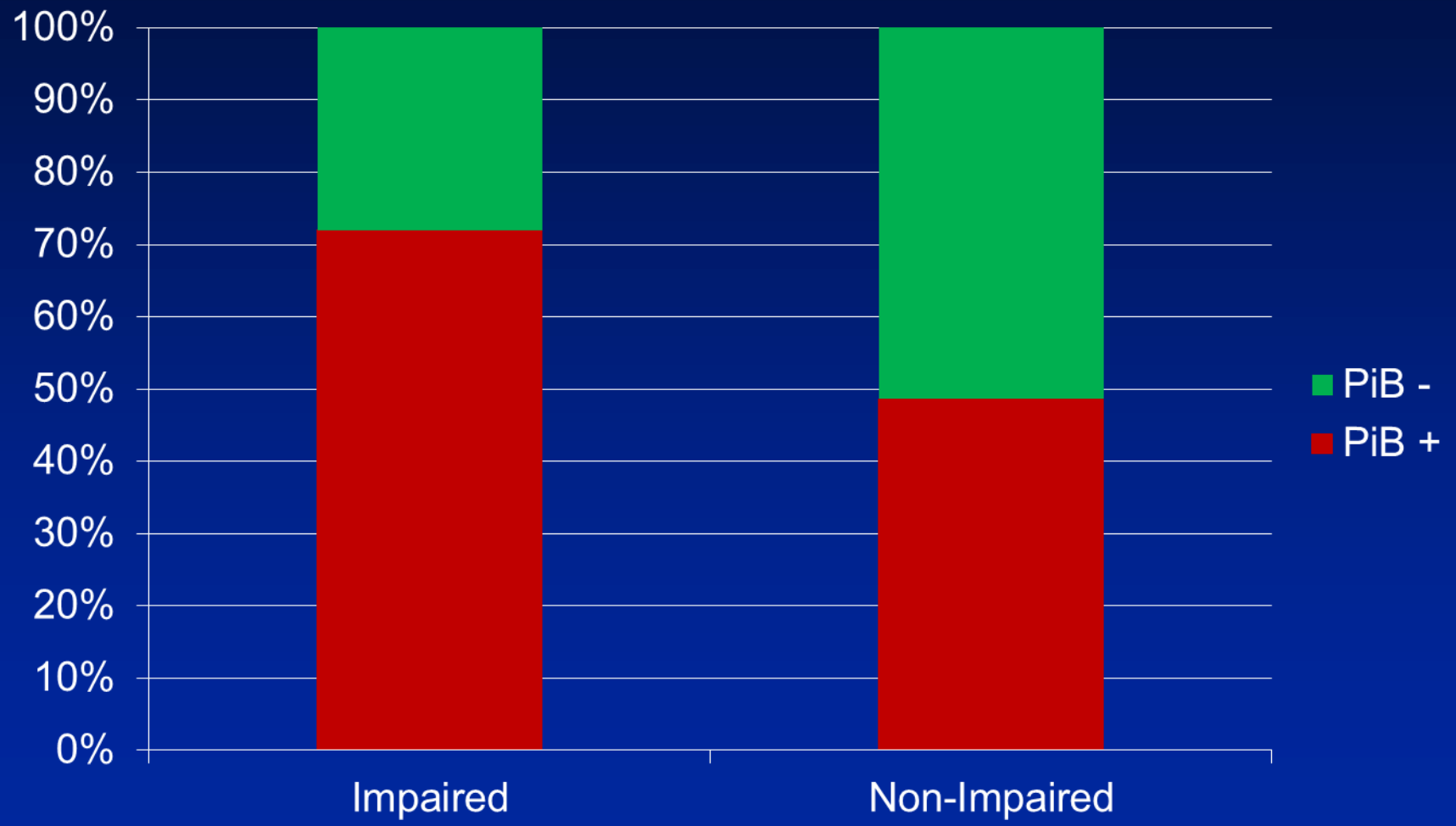
Vascular Burden

- Risk Factors
  - Hypertension
  - Diabetes
  - High Cholesterol
- Vascular Injury
  - Coronary Artery Disease
  - Stroke /TIA

Study Cohort

	Normal (N=37)	MCI (N=25)	Demented (N=3)
Years of Observation	5.7 ± 3.0	3.0 ± 2.7	4.4 ± 2.8
Age	72 ± 7	75 ± 7	80 ± 5
Gender (%F)	51%	44%	33%
Ethnicity (% Caucasian)	51%	80%	100%
Education (years)	15 ± 4	16 ± 2	17 ± 4
Vascular Burden (number)	1.7 ± 1.2	1.7 ± 1.2	1.3 ± 1.2
Episodic Memory (SD units)	0.30 ± 0.81	-0.96 ± 0.54	-1.24 ± 0.24
Executive Function (SD units)	0.13 ± 0.57	-0.07 ± 0.43	-0.51 ± 0.45
Brain Volume (%TCV)	77.8 ± 3.5	76.1 ± 5.0	72.4 ± 1.8
Hippocampus (% TCV)	0.30 ± 0.05	0.23 ± 0.06	0.19 ± 0.04
WMH (log %TCV)	-5.6 ± 1.2	-5.4 ± 1.0	-5.6 ± 0.73
Global PiB Index	1.19 ± 0.22	1.41 ± 0.36	1.75 ± 0.17

Amyloid Positivity by Impairment Category



Results

	Episodic Memory			Executive Function		
	Estimate	Std Error	P-Value	Estimate	Std Error	P-Value
MODEL 1						
Time	-0.09	0.20	NS	-0.067	0.022	0.007*
Baseline Age	-0.01	0.014	NS	-0.01	0.01	NS
Education	0.06	0.03	0.04*	0.08	0.02	<.0001*
Impaired	-0.46	0.35	0.0005*	-0.10	0.09	NS
Impaired x Time	0.01	0.081	NS	-0.024	0.018	NS
MODEL 2						
Global PiB DVR	-0.41	0.35	NS	0.18	0.24	NS
Global PiB DVR x Time	-0.21	0.07	<0.008*	-0.12	0.05	0.03*
MODEL 3						
Hippocampal Volume	315	138	0.03*	179	95	NS
Hippocampal Volume x Time	8.6	23.4	NS	35.5	17	0.05*
MODEL 4						
Vascular Burden	-0.12	0.08	NS	-0.17	0.05	0.002*
Vascular Burden x Time	-0.006	0.013	NS	0.01	0.01	NS

Conclusion I

- Vascular burden was associated with overall poorer performance on tests of executive function after adjusting for amyloid retention and structural brain differences, even in a cohort with substantial amyloid burden
  - Cause is uncertain and may reflect direct toxicity (e.g. diabetes) or increased inflammation or other unidentified process

Associations of Circulating Growth Differentiation Factor-15 and ST2 Concentrations With Subclinical Vascular Brain Injury and Incident Stroke

Charlotte Andersson, MD, PhD; Sarah R. Preis, ScD; Alexa Beiser, PhD; Charles DeCarli, MD; Kai C. Wollert, MD; Thomas J. Wang, MD; James L. Januzzi Jr, MD; Ramachandran S. Vasan, MD; Sudha Seshadri, MD

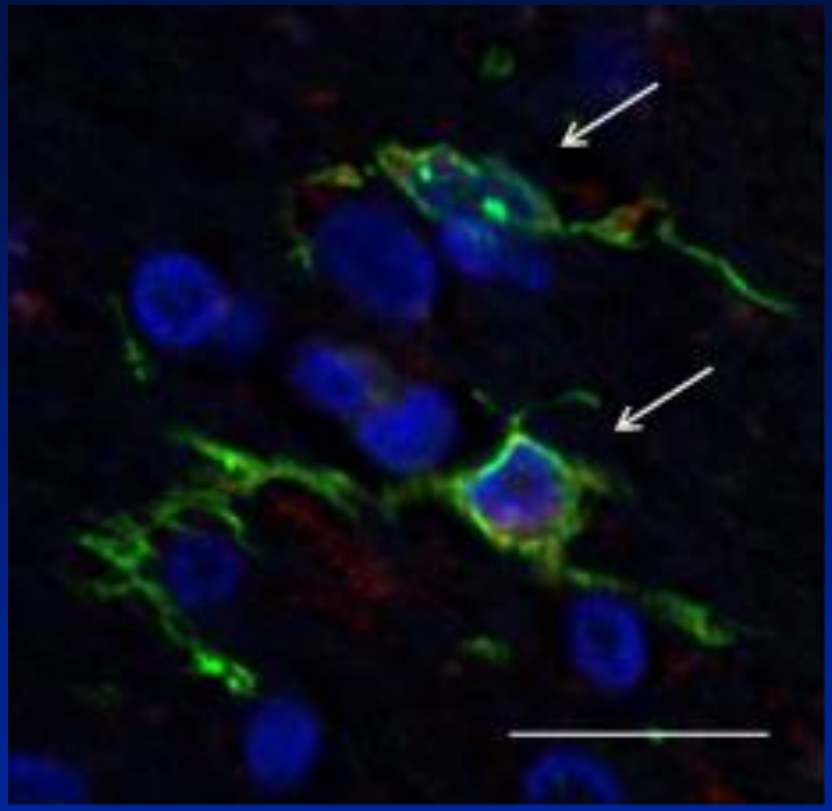
Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.009026

			Model 1, n=2127*		Model 2, n=2083†		Model 3, n=1745‡	
Outcome	Biomarker	Effect	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
Total cerebral brain volume	GDF-15§	Continuous	−1.25 (0.18)	<0.0001	−1.01 (0.19)	<0.0001	−0.86 (0.21)	<0.0001
		Quartiles						
		Q1	0.00 (ref)	…	0.00 (ref)	…	0.00 (ref)	…
		Q2	−0.24 (0.17)	0.15	−0.24 (0.17)	0.16	−0.064 (0.18)	0.73
		Q3	−0.40 (0.18)	0.03	−0.31 (0.19)	0.10	−0.15 (0.21)	0.48
		Q4	−1.18 (0.20)	<0.0001	−0.97 (0.21)	<0.0001	−0.71 (0.23)	0.002
		Test for linear trend	…	<0.0001	…	<0.0001	…	0.004
	sST2§	Continuous	−0.77 (0.19)	<0.0001	−0.58 (0.19)	0.002	−0.40 (0.20)	0.05
		Quartiles						
		Q1	0.00 (ref)	…	0.00 (ref)	…	0.00 (ref)	…
		Q2	−0.21 (0.17)	0.21	−0.10 (0.17)	0.54	−0.010 (0.18)	0.96
		Q3	−0.32 (0.17)	0.07	−0.20 (0.17)	0.24	−0.073 (0.19)	0.70
		Q4	−0.82 (0.18)	<0.0001	−0.65 (0.18)	0.0004	−0.47 (0.20)	0.02
		Test for linear trend	…	<0.0001	…	0.0005	…	0.02

Inflammation and Cognition

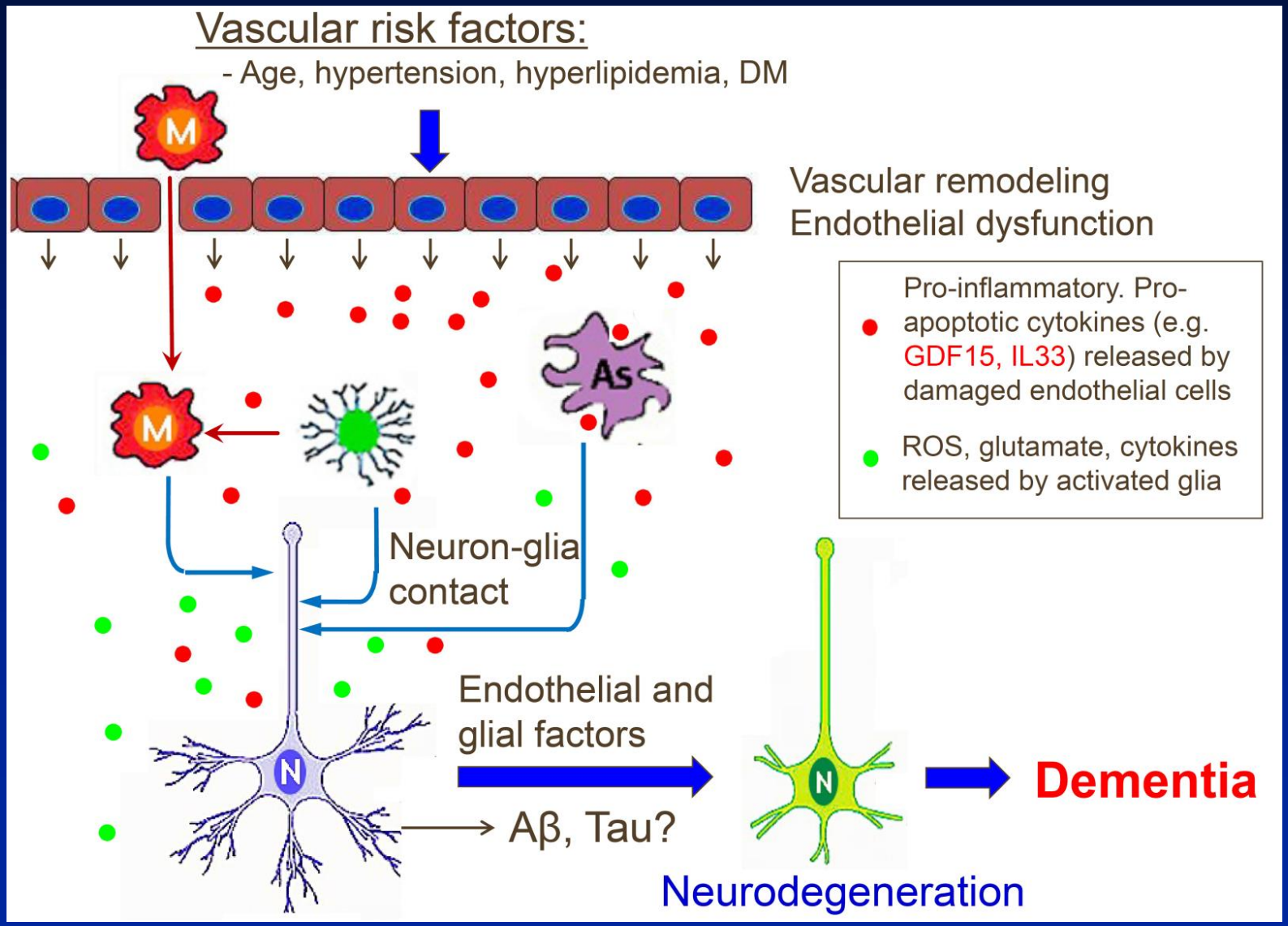
Outcome	Biomarker	Effect	Model 1, n=2463*		Model 2, n=2397†		Model 3, n=2008‡	
			β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
Visual reproductions delayed	GDF-15§	Continuous	−0.78 (0.19)	<0.0001	−0.57 (0.20)	0.004	−0.49 (0.21)	0.02
		Quartiles						
		Q1	0.00 (ref)	…	0.00 (ref)	…	0.00 (ref)	…
		Q2	−0.33 (0.17)	0.05	−0.33 (0.17)	0.06	−0.40 (0.19)	0.03
		Q3	−0.41 (0.18)	0.03	−0.30 (0.19)	0.12	−0.40 (0.21)	0.06
		Q4	−0.93 (0.21)	<0.0001	−0.78 (0.22)	0.0003	−0.62 (0.24)	0.009
		Test for linear trend	…	<0.0001	…	0.001	…	0.01
	sST2§	Continuous	−0.59 (0.19)	0.002	−0.47 (0.19)	0.02	−0.41 (0.20)	0.04
		Quartiles						
		Q1	0.00 (ref)	…	0.00 (ref)	…	0.00 (ref)	…
		Q2	−0.14 (0.17)	0.39	−0.12 (0.17)	0.49	−0.19 (0.18)	0.30
		Q3	−0.16 (0.18)	0.37	−0.11 (0.18)	0.52	−0.08 (0.19)	0.67
		Q4	−0.49 (0.18)	0.008	−0.38 (0.19)	0.04	−0.40 (0.20)	0.048
		Test for linear trend	…	0.01	…	0.06	…	0.10

GDF-15 in Brain



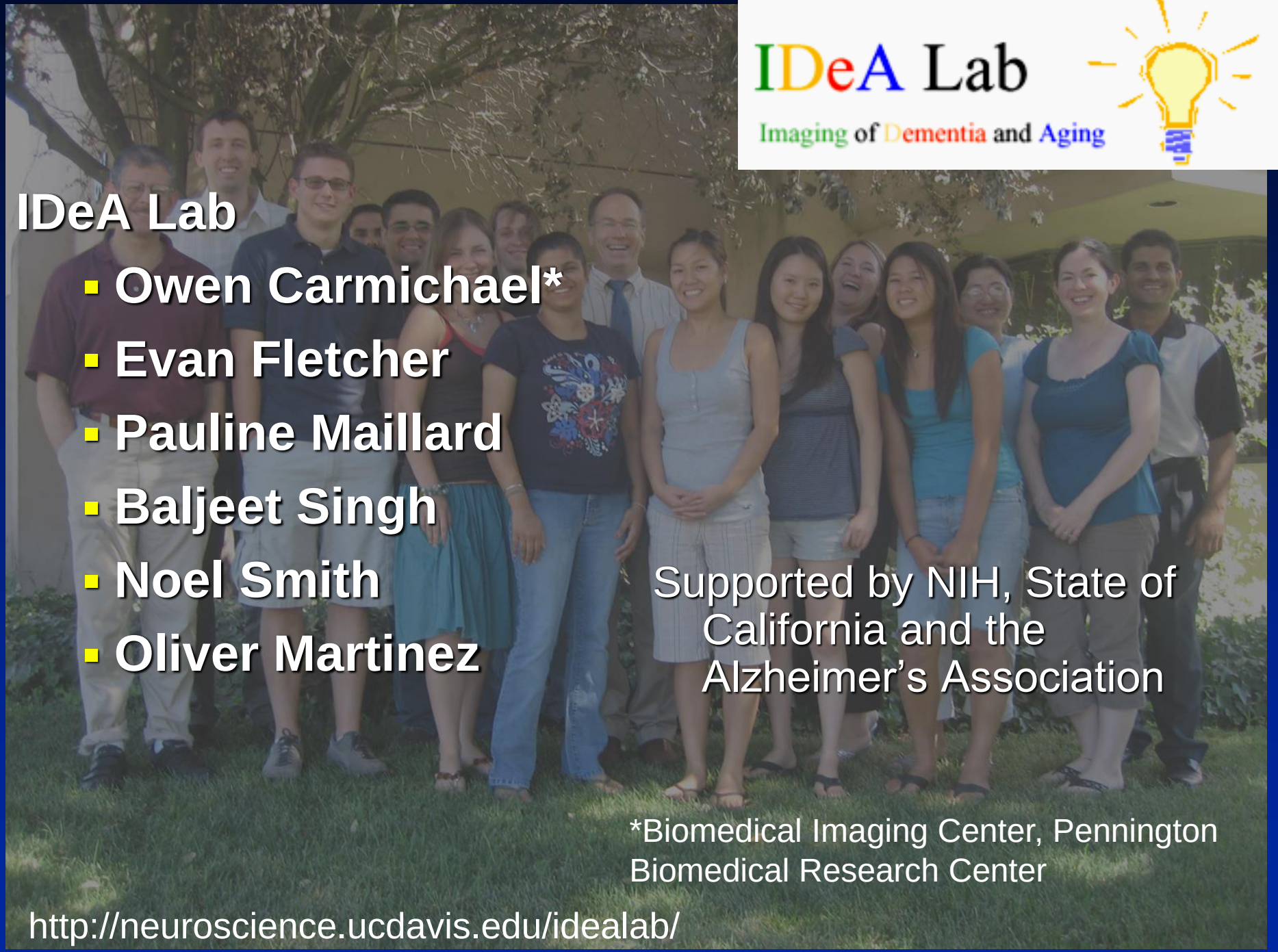
Immunostaining of human cortex from individual who had mixed dementia (AD+vascular dementia). Blue=cell nuclei stained with DAPI. Green=microglia stained with IBA-1. Red =immunostaining for GDF15. Colocalization of GDF15 is noted in microglia (arrows). Bar = 20um.

Model of Inflammation and Brain Pathology in Aging



Conclusions II

- Aging and atherosclerosis lead to increasing inflammation
- Inflammation can lead to brain injury and cognitive decline independent of vascular risk factors
- Inflammation may lead to microglial activation with release of harmful cytokines



IDeA Lab

Imaging of Dementia and Aging

IDeA Lab

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- Evan Fletcher
- Pauline Maillard
- Baljeet Singh
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- Oliver Martinez

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http://neuroscience.ucdavis.edu/idealab/