The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

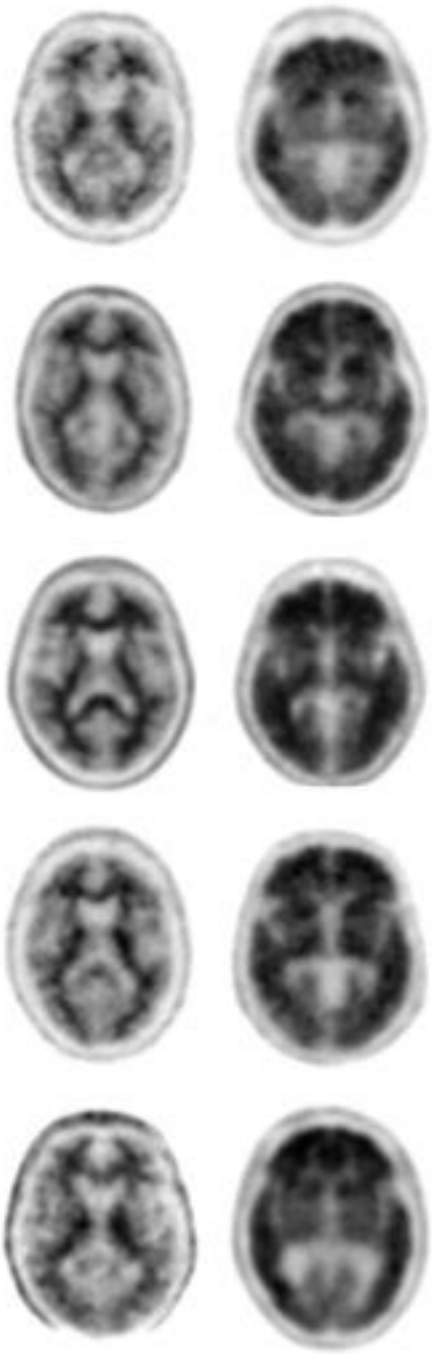
aibl

(AUSTRALIAN ADNI)

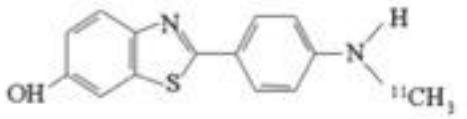
July 2014 UPDATE

Christopher Rowe MD – *Neuroimaging stream leader*

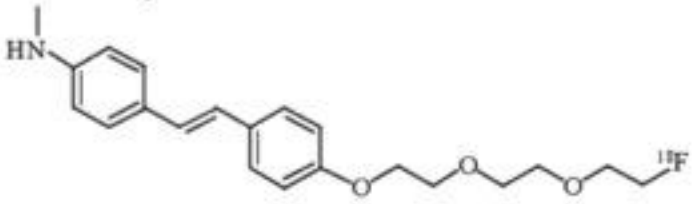
Aβ ligands



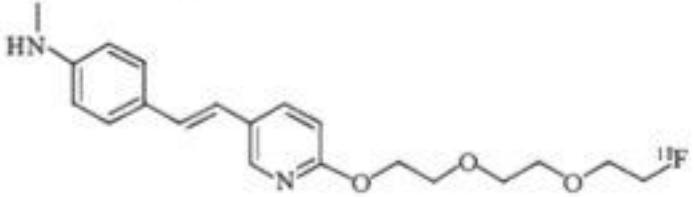
^{11}C-PiB



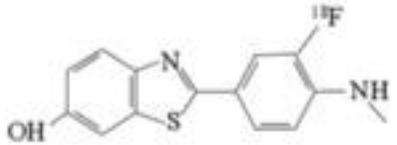
^{18}F-florbetaben



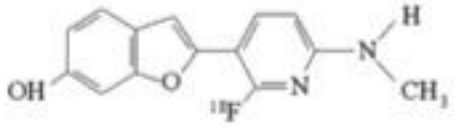
^{18}F-florbetapir



^{18}F-flutemetamol



^{18}F-NAV4694



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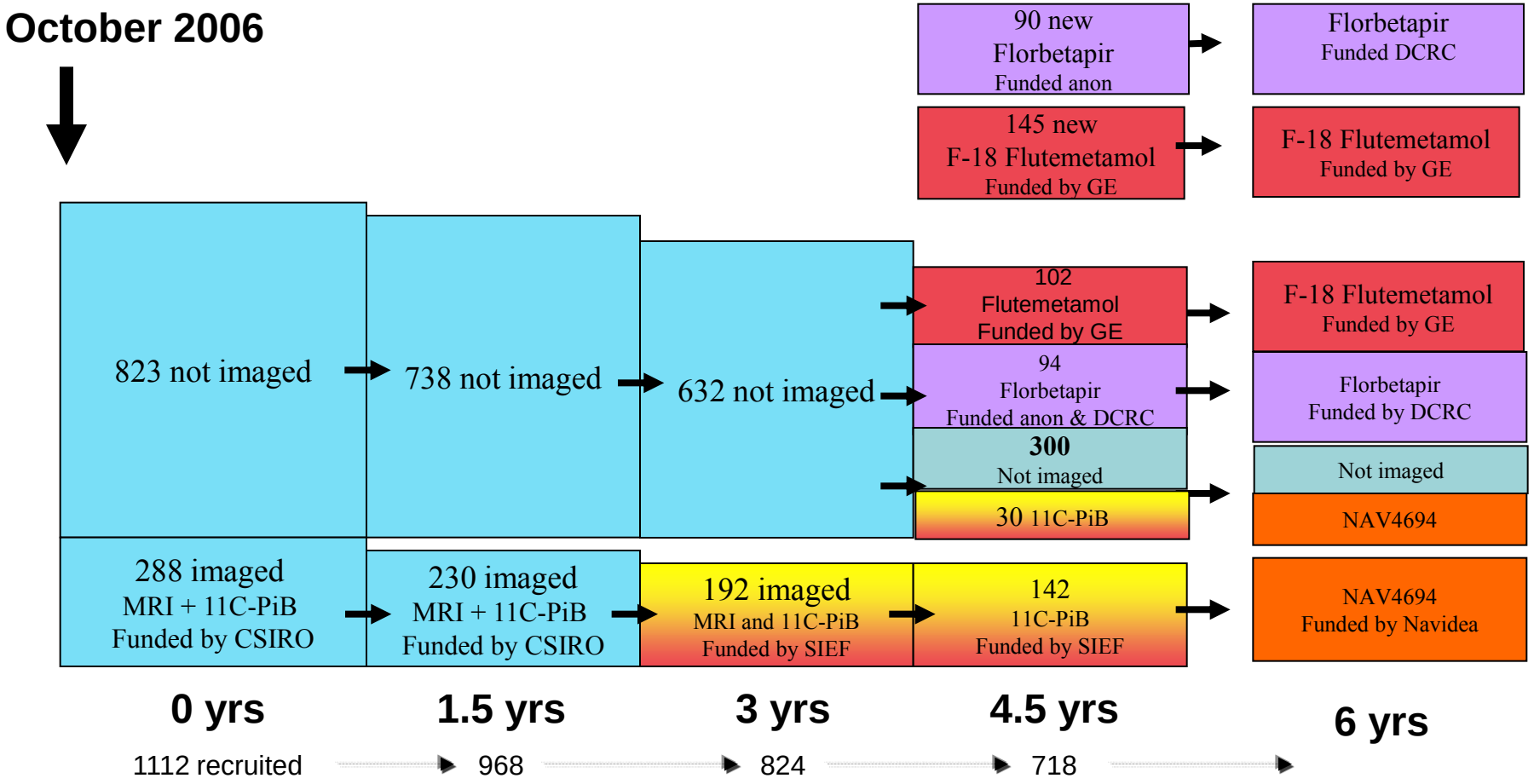
The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing.

2014-15
240 for **TAU** imaging
(Avid and GE)

150 Vietnam
AIBL-VETS
Funded by Piramal
US DOD



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The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing.

4.5 year data release coming soon

PiB Baseline (288), 3 years (173), 4.5 yrs (141)

Plus 230 added from original cohort (flutemetamol, florbetapir or PiB at 4.5 yrs)

i.e. amyloid scan status known in 371 subjects with 4.5 yrs of follow-up.

Plus 250 new recruits (160 flute, 90 FBP)

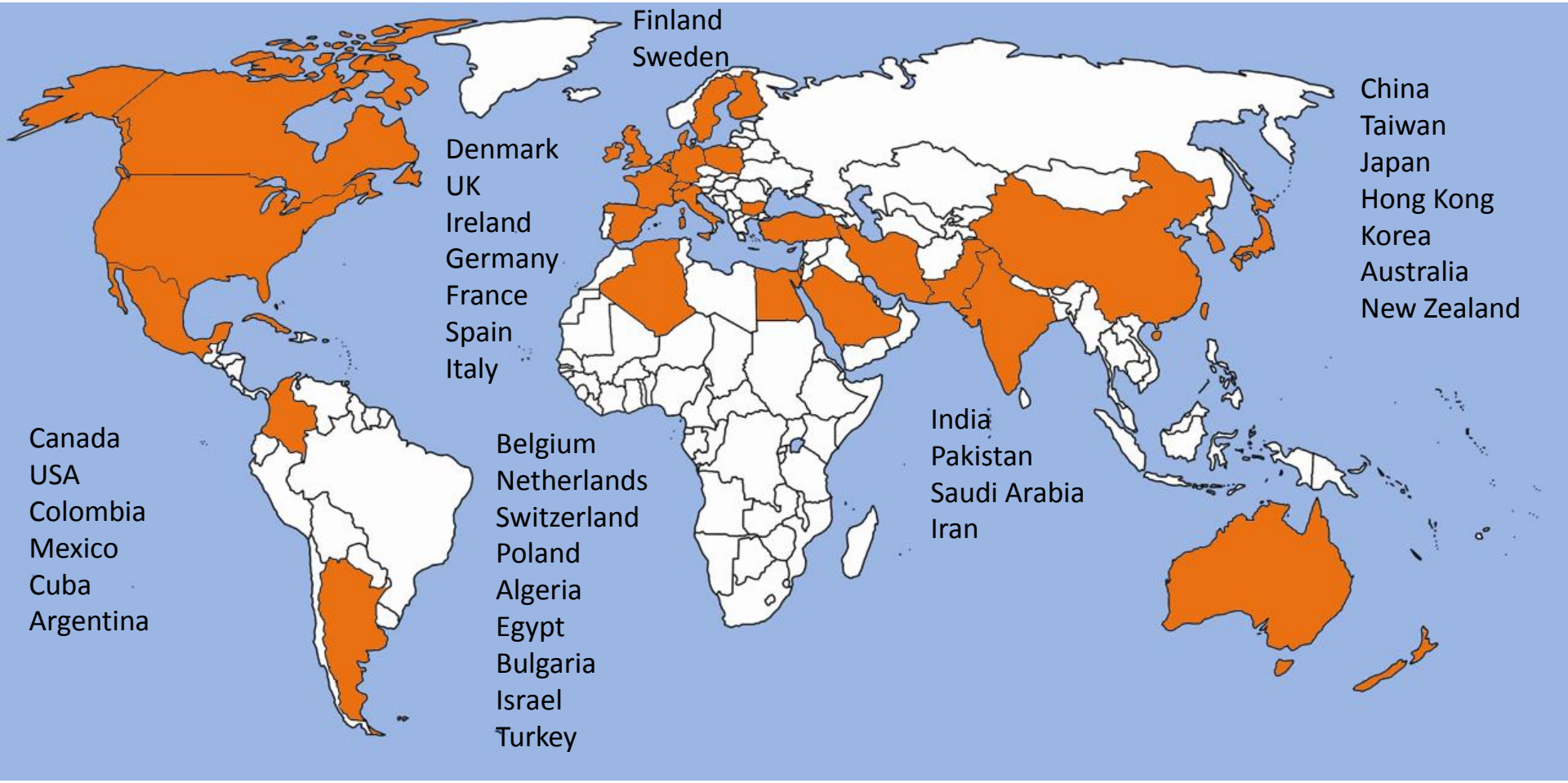
www.adni.loni.usc.edu

- Data and Samples

- Access Data

CSIRO Austin Health Mental Health Research Institute NARI The University of Melbourne ECU Edith Cowan University Alzheimer's Australia Living with dementia

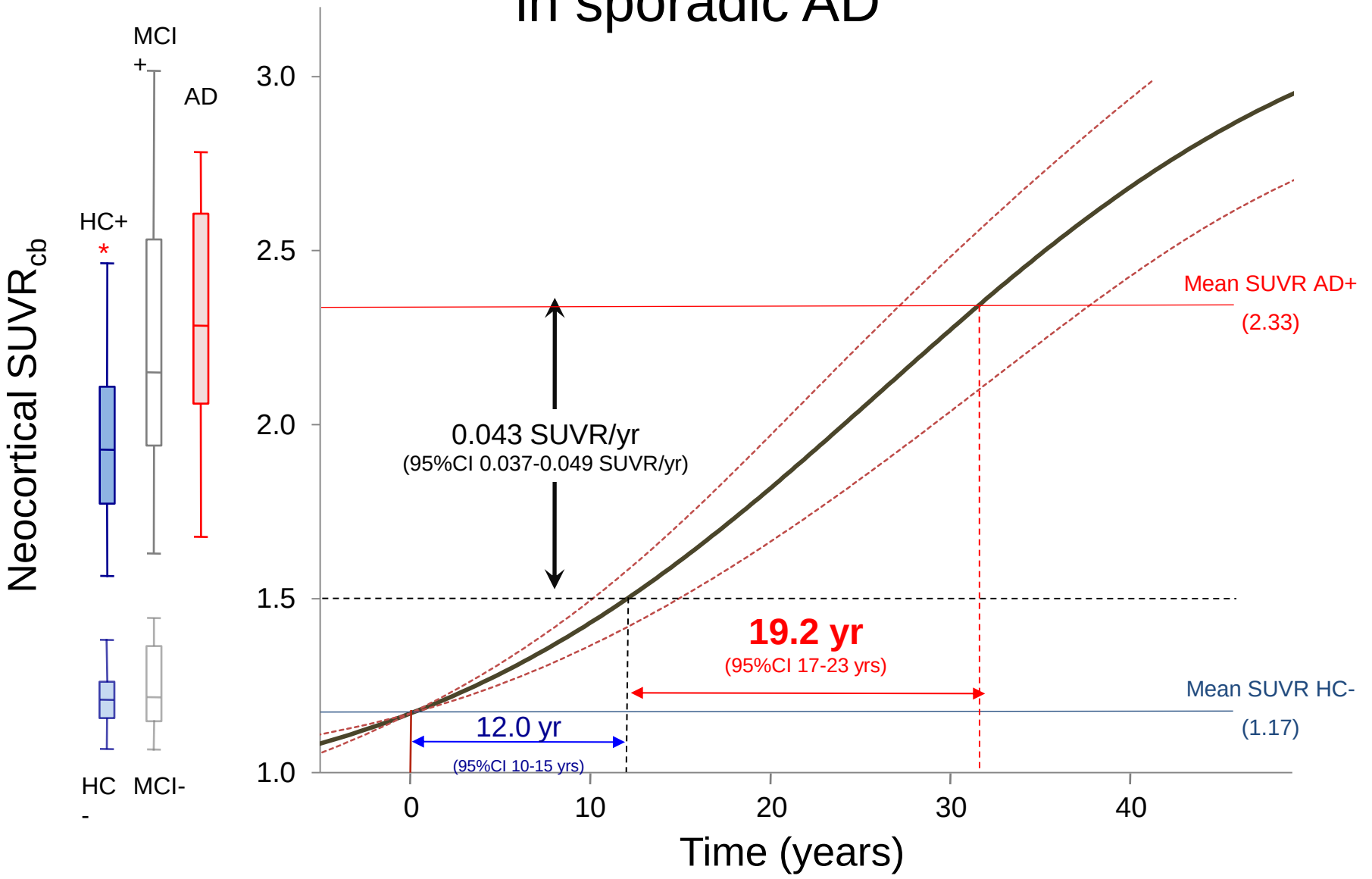
610 research groups granted access to AIBL@LONI through ADNI website



Includes access granted to the following companies:

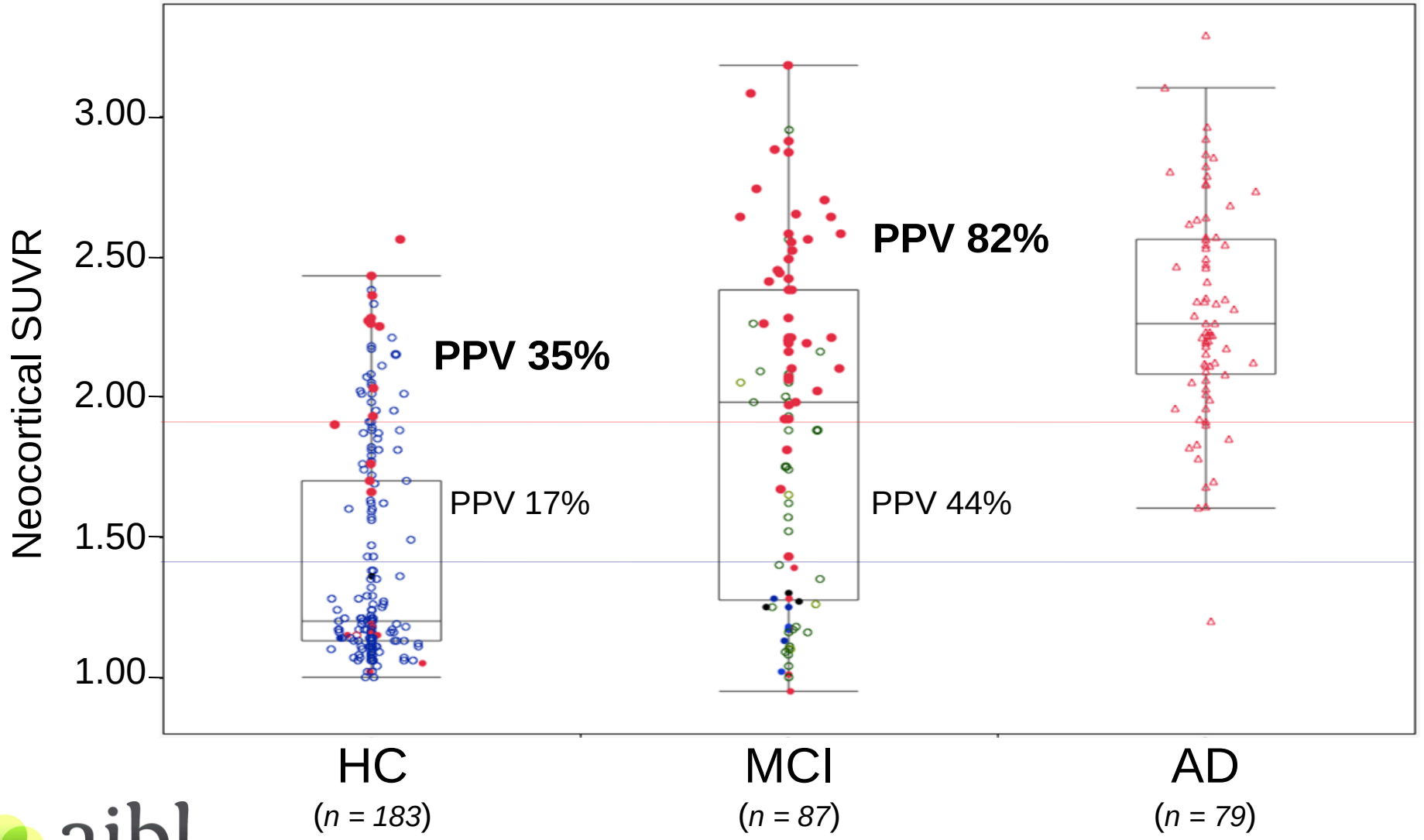
Abbott Labs, Abiant, ADM diagnostics, Astra Zeneca, Avid, BioClinica, Biogen Idec, Bristol-Myers Squibb, Cogstate Cytokinetics, Eisai, Elan, Eli Lilly, GE Health Care, General Resonance, Genetech, Imorphics, Iris Biotechnologies, Janssen, Johnson Johnson, M and M Scientific, Merck & Co, Mimvista, Pentara Corp, Pfizer, Philips, Predixion software, Rancho Biosciences, Servier, Siemens, Soft team solutions, UCB, United Biosource Corp.

The natural history of Aβ deposition in sporadic AD



Villemagne VL, et al. 2013 Lancet Neurology

3 year clinical progression rate vs PiB SUVR



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Rowe CC, et al. Ann Neurology 2013

HC to MCI or AD over 3 years (n=183; 13% progressed)

	HC positive for marker	OR	PPV	NPV
HV	46	2.2	0.20	0.90
e4	74	2.1	0.18	0.91
EM<-0.5	22	4.2	0.32	0.90
PiB	53	4.8	0.26	0.93
PiB+e4	34	5.7	0.29	0.93
PiB+HV	17	10	0.47	0.92
PiB+EM	10	16	0.50	0.94

AIBL composite EM Z-score <-1 (n=49), OR 11, PPV 35%, NPV 96% without correction for age or education.

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MCI to AD over 3 years (n=87; 59% progressed)

	MCI positive for marker	Odds Ratio	PPV	NPV
HV	48	4	0.67	0.65
ApoE-ε4	50	5	0.74	0.66
CVLT<-1.5	61	11	0.80	0.74
PiB	60	15	0.77	0.82
PiB+ε4	47	16	0.79	0.81
PiB+HV	35	44	0.83	0.90
PiB+CVLT	43	na	0.86	1.00

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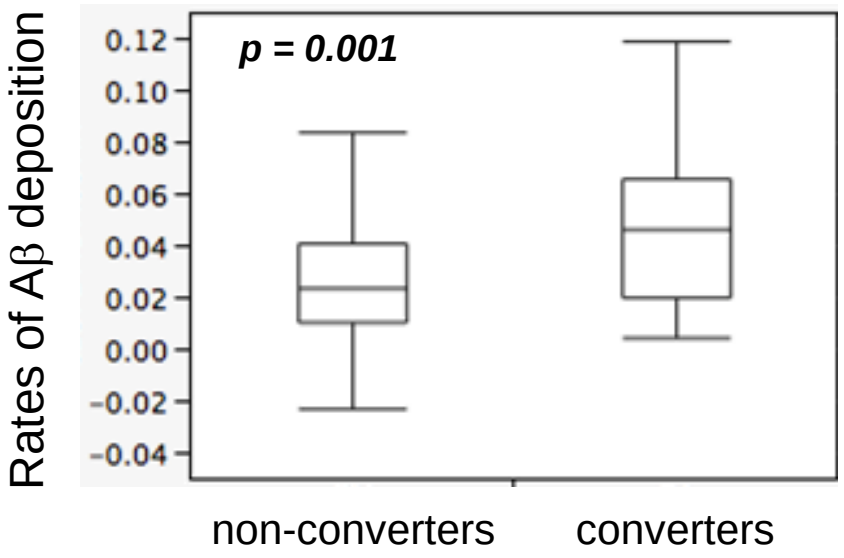
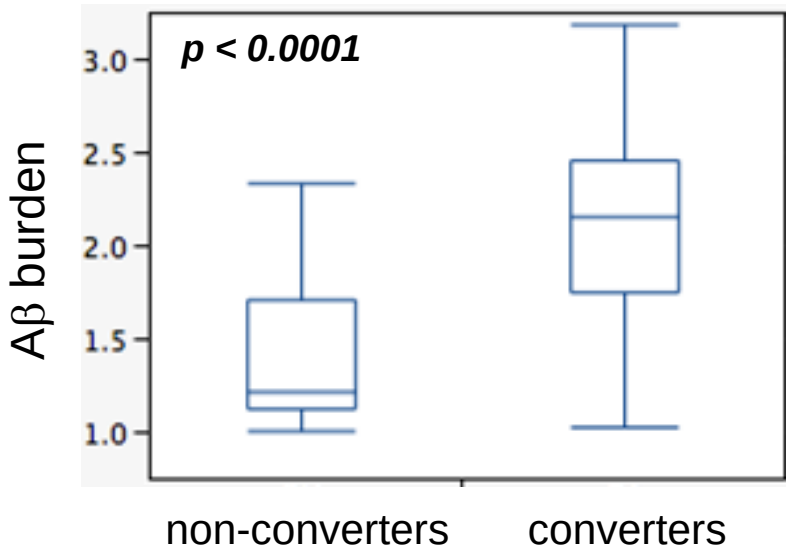
Rowe CC, et al. Ann Neurology 2013

Initial Aβ burden is a better predictor of progression from MCI to AD than the rate of Aβ accumulation





OR = 5.4

OR = 15

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Relation between rate of Aβ deposition and rate of episodic memory decline in HC

Accumulators

(*n=120*)

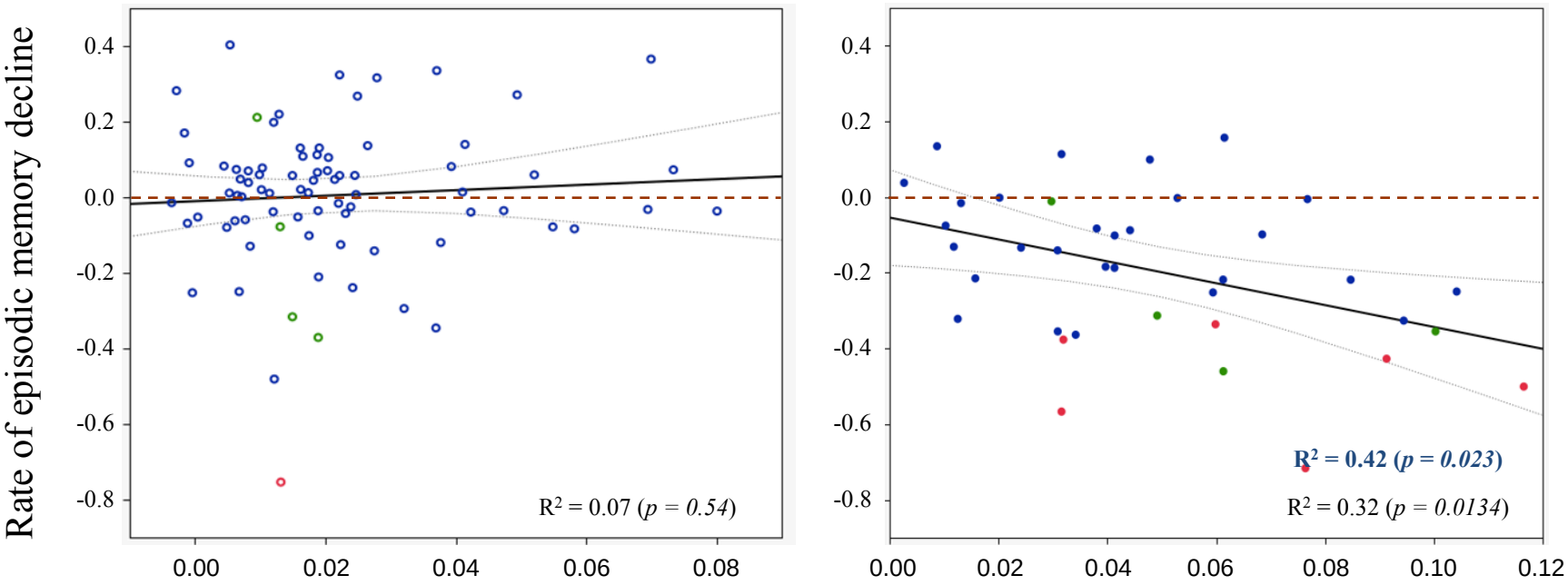
4.5-year follow-up

PiB-

(*n=80*)

PiB+

(*n=40*)



Rate of Aβ deposition (*SUVR/yr*)

adjusted for age, gender, education, ApoE

Relation between rate of Aβ deposition and rate of episodic memory decline

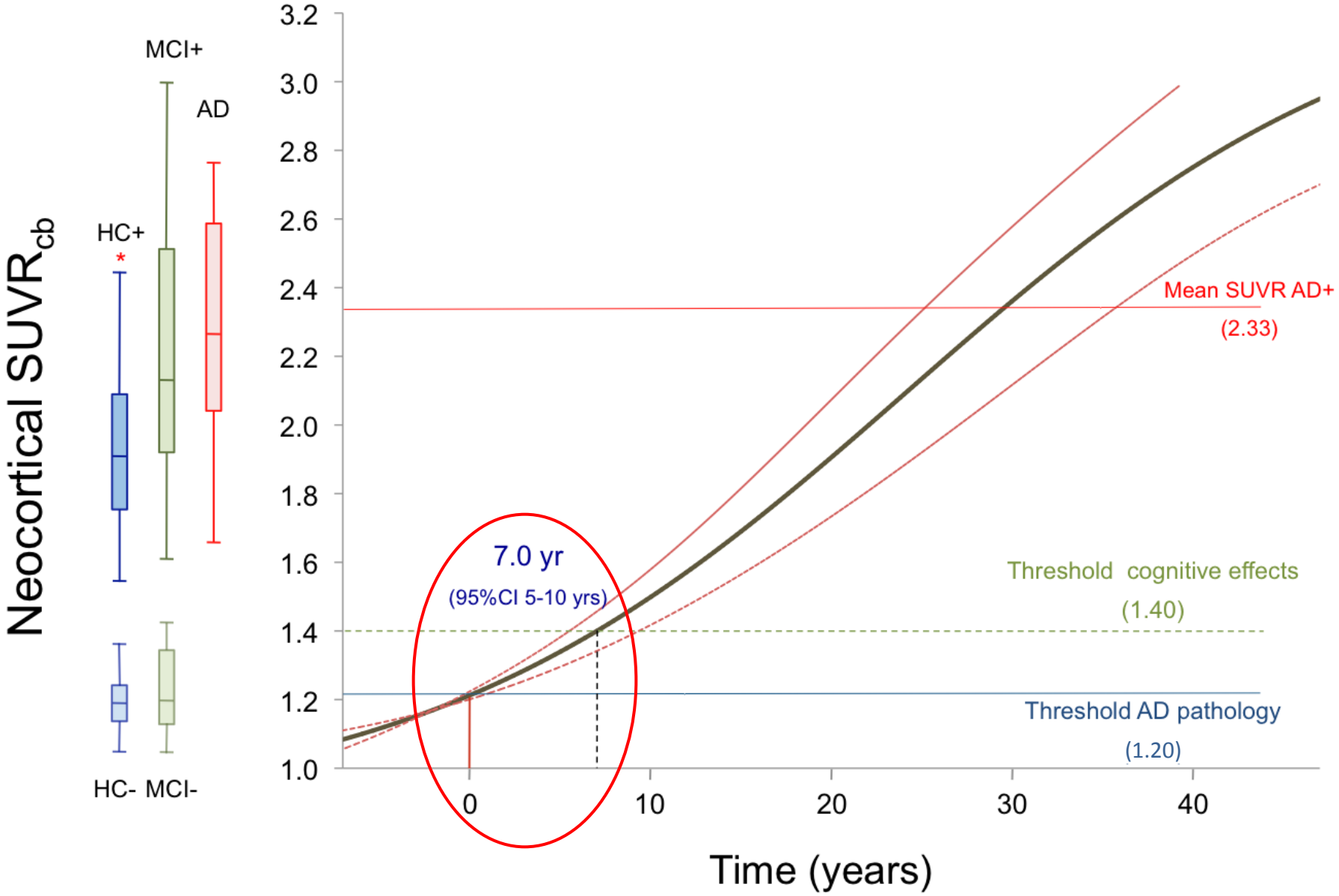
4.5-year follow-up

Accumulators

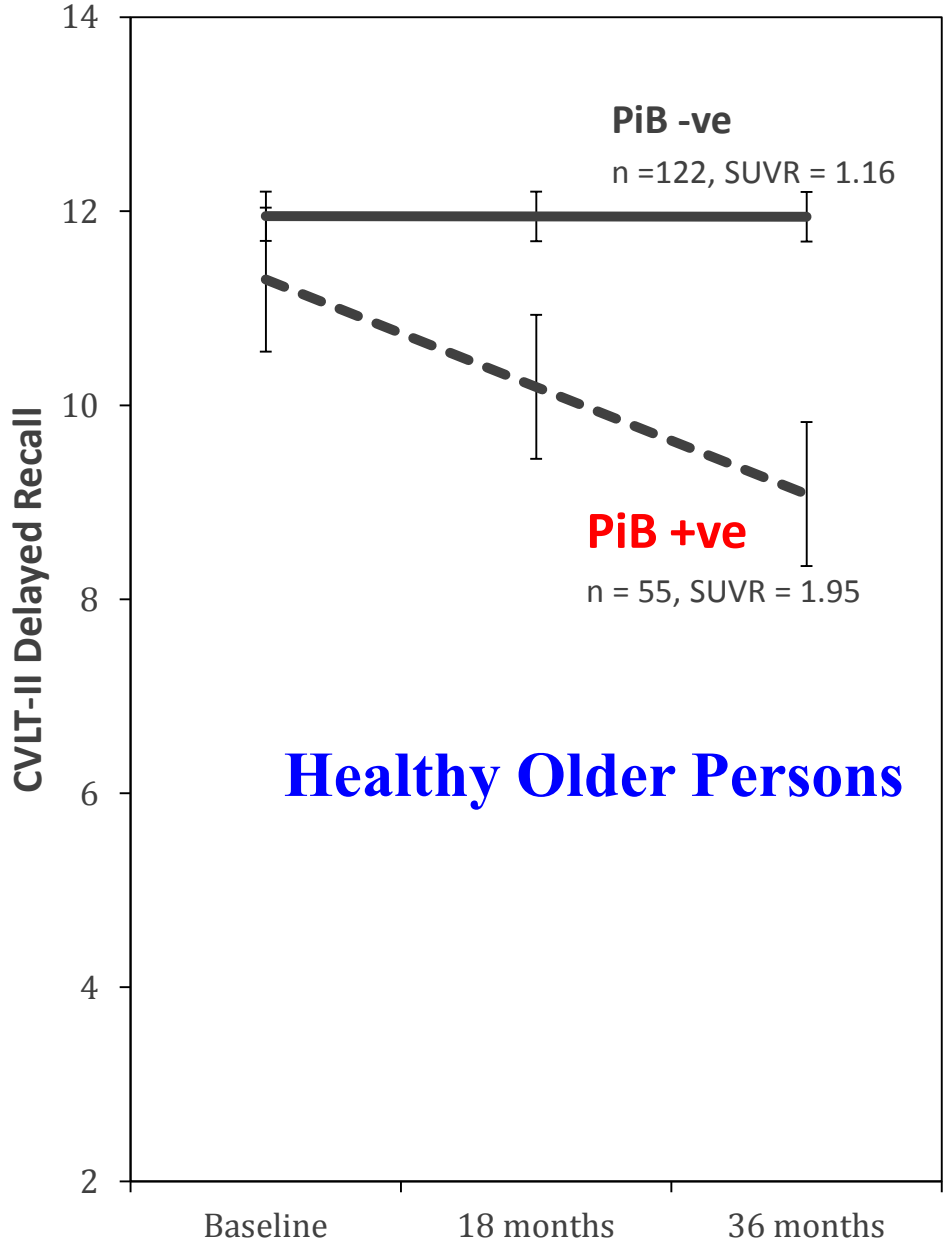
(*n=120*)

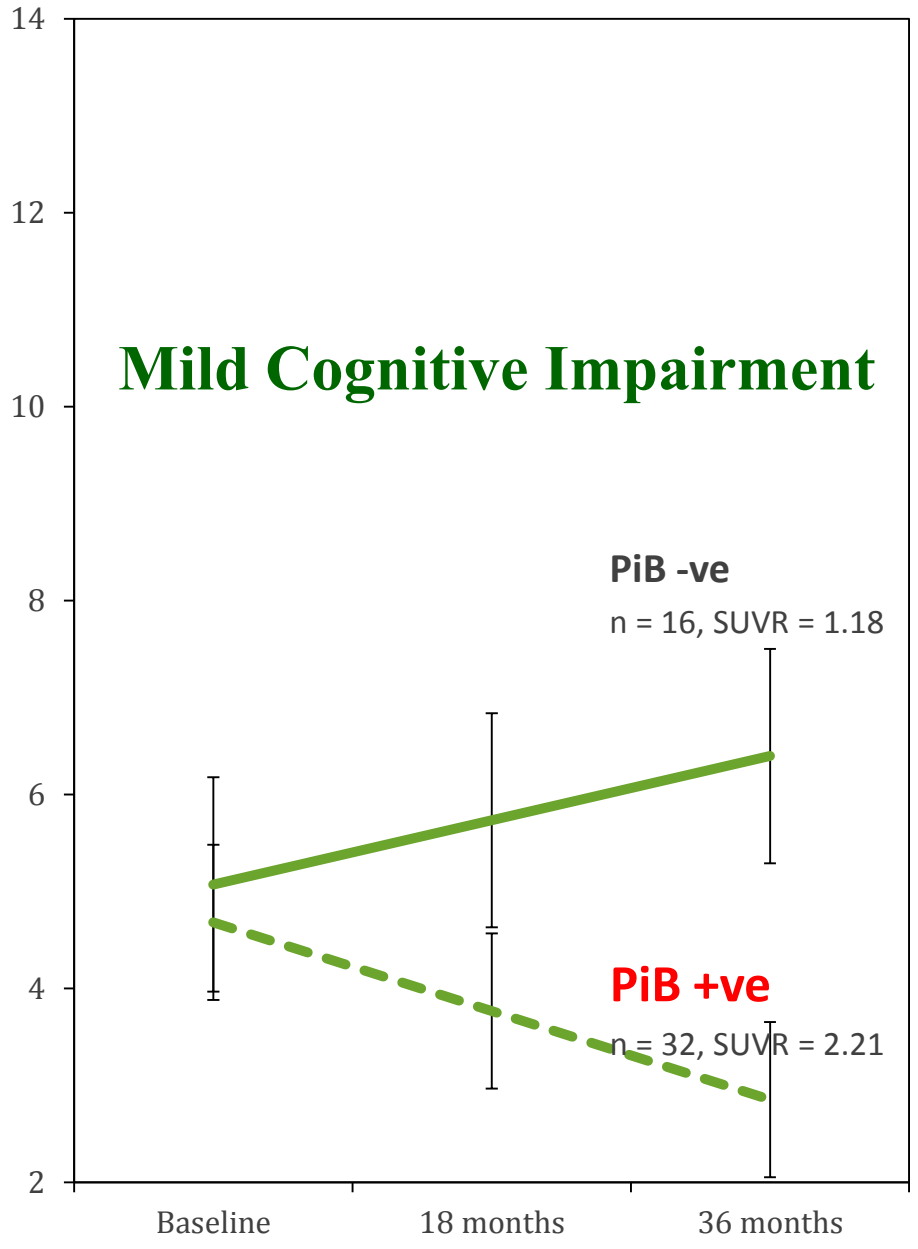
THRESHOLD	adjusted for age, gender, yoe, ApoE	+adjusting baseline SUVR
PiB SUVR 1.2 (n=68)	$R^2 = 0.19$ (*p = 0.0353*)	$R^2 = 0.35$ (*p = 0.313*)
PiB SUVR 1.3 (n=48)	$R^2 = 0.28$ (*p = 0.0162*)	$R^2 = 0.38$ (*p = 0.060*)
PiB SUVR 1.4 (n=42)	$R^2 = 0.30$ (*p = 0.0150*)	$R^2 = 0.39$ (*p = 0.028*)
PiB SUVR 1.5 (n=40)	$R^2 = 0.31$ (*p = 0.0134*)	$R^2 = 0.42$ (*p = 0.023*)
PiB SUVR 1.6 (n=37)	$R^2 = 0.31$ (*p = 0.0383*)	$R^2 = 0.41$ (*p = 0.031*)
PiB SUVR 1.9 (n=21)	$R^2 = 0.40$ (*p = 0.080*)	$R^2 = 0.48$ (*p = 0.067*)

Optimal window for anti-Aβ intervention



Memory Test Performance over 3 years

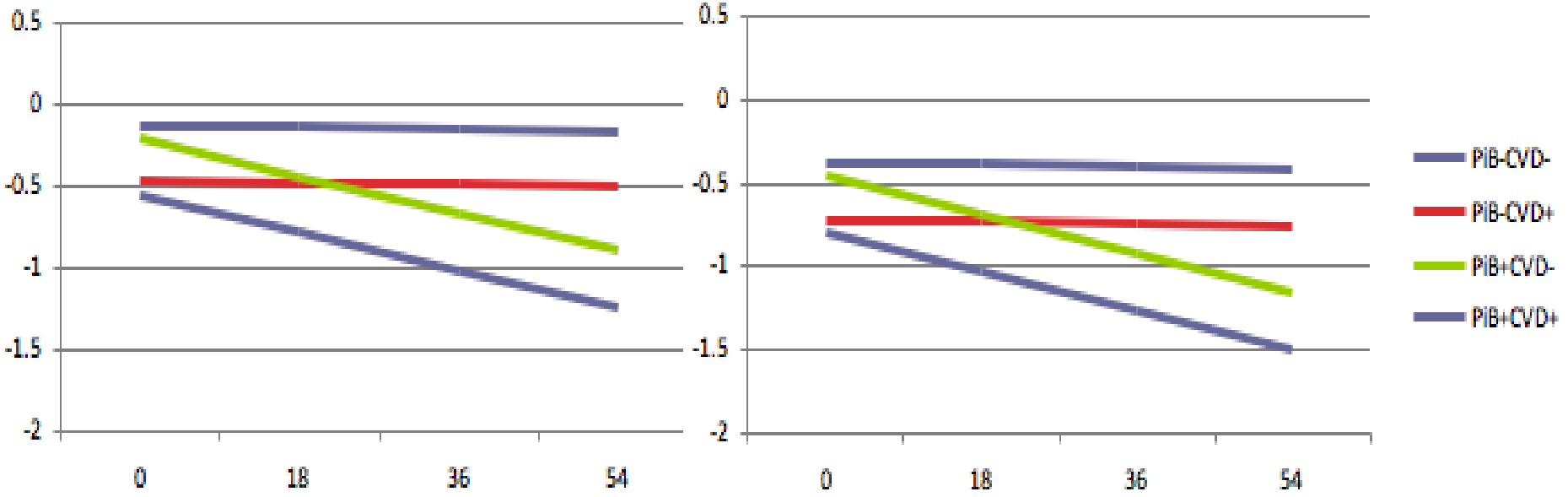




PiB, Cerebrovascular Disease and Episodic Memory

Females

Males

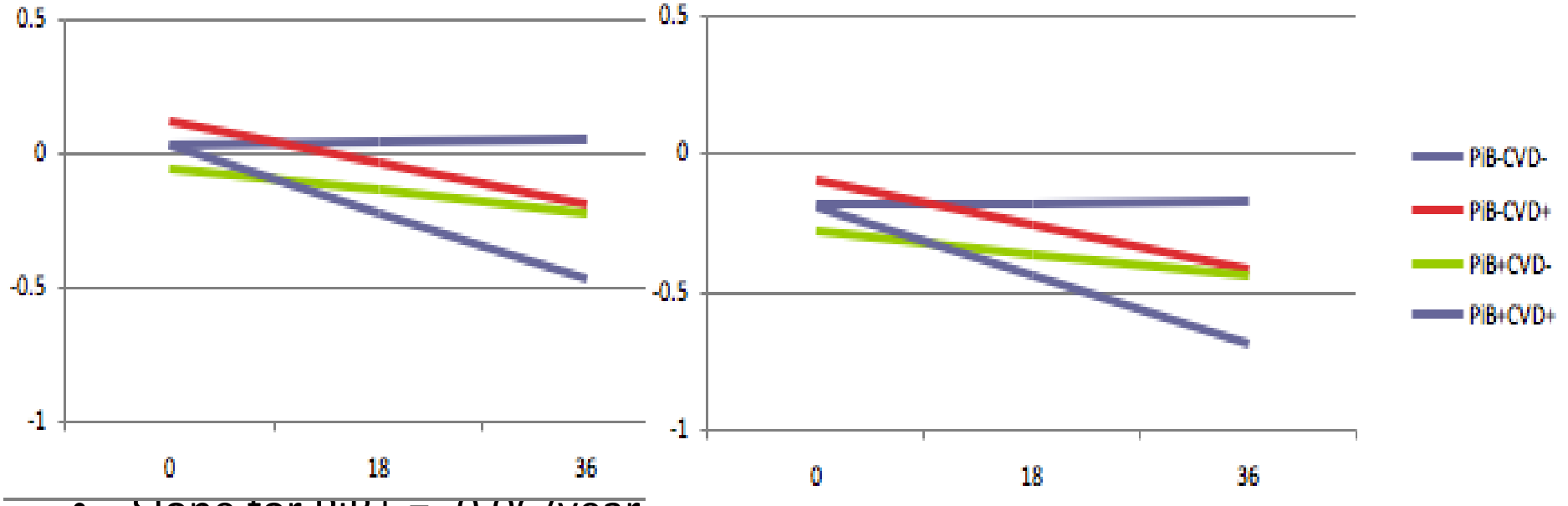


- Slope for PiB+ = -0.14 per year (p<0.001)
- Significant time x age interaction (p=0.008).
- Significant main effect but not time interaction for CVD (p=0.01), gender (p=0.01) and YOE (p<0.001)

Executive Function

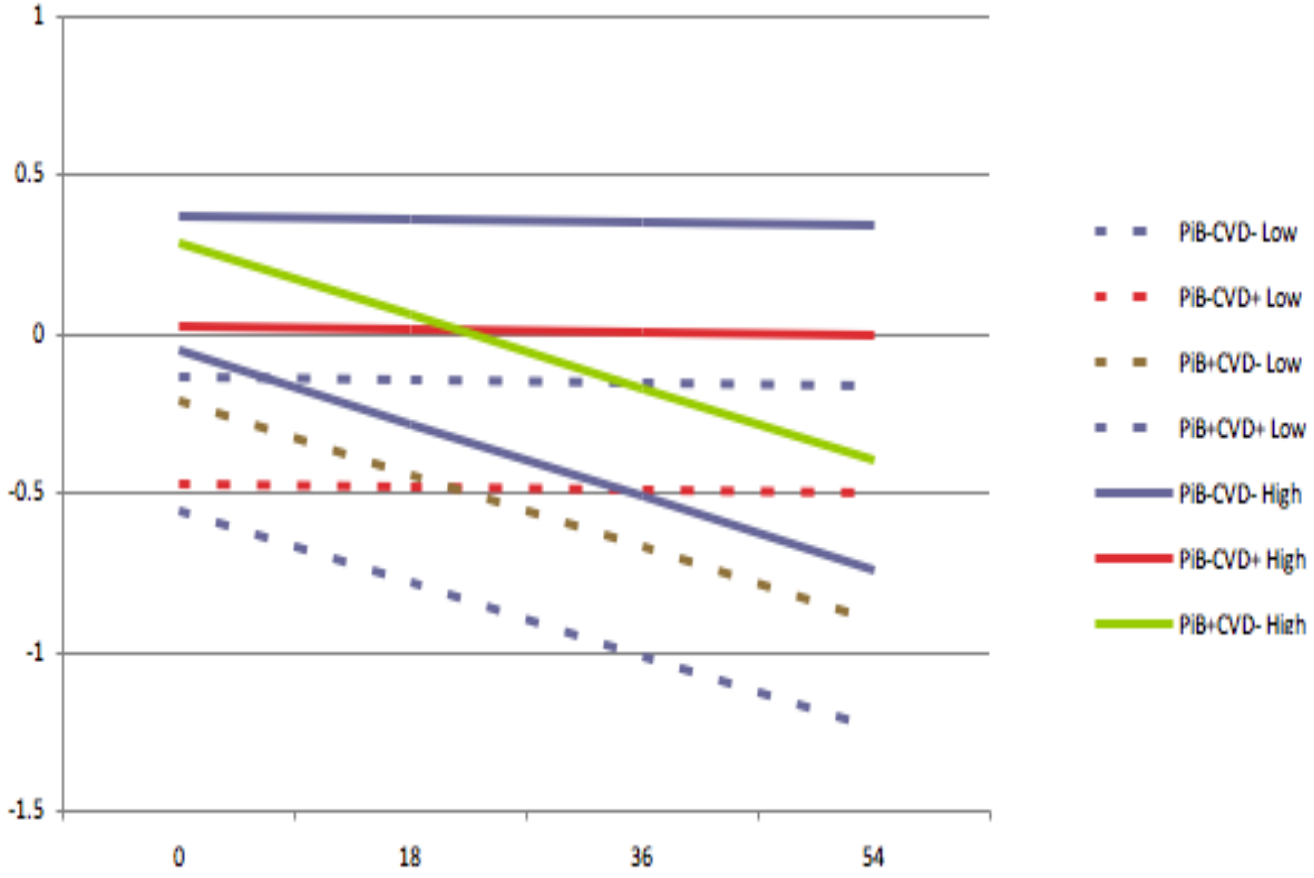
Females

Males



- Slope for PiB+ = -0.06/year (p=0.09)
- Slope for CVD = 0.1/year (p=0.01)
- Significant main effects of gender, education, age
- Significant x time effect of CVD, trend for PiB+

Episodic Memory and Educational Attainment



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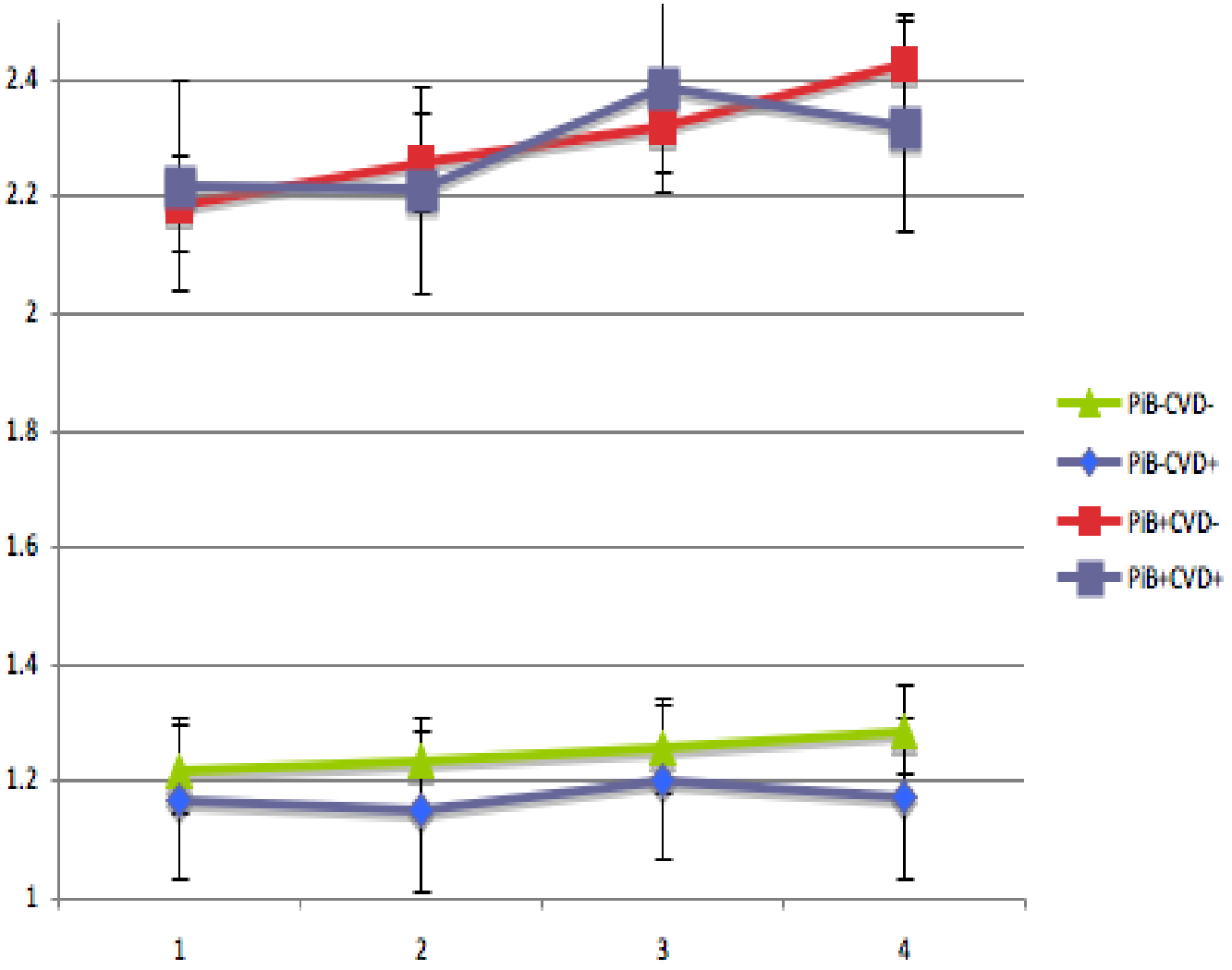
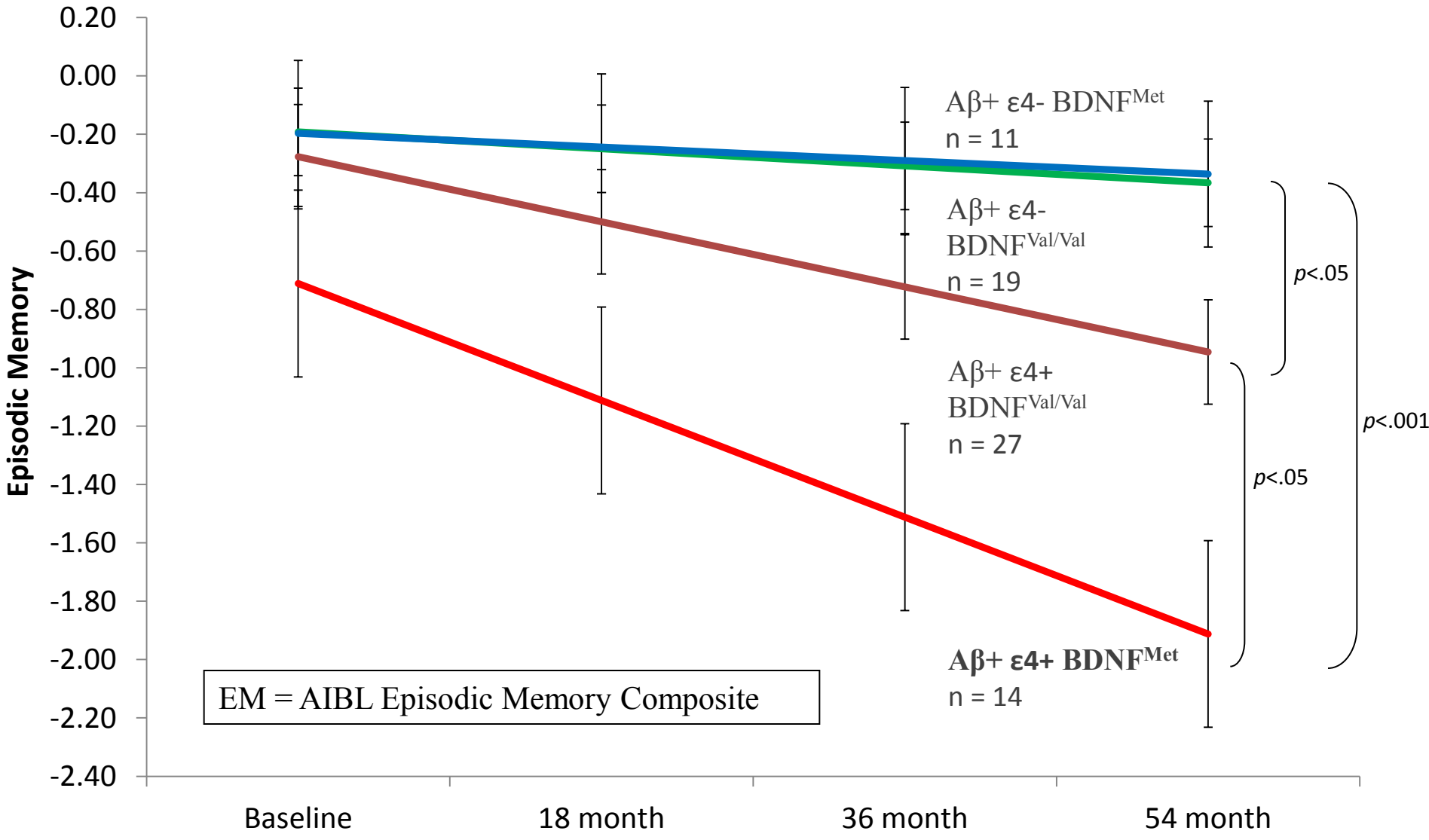
- Significant main effect but not time interaction for CVD ($p=0.01$), gender ($p=0.01$) and YOE ($p<0.001$)

PiB, CVD and Change in PiB SUVR



HA Aβ+ 54 months: Effect of *APOE & BDNF*



Conclusions and general summary

- **High Aβ :** Healthy older adults: faster cognitive decline; ↑ progression to MCI
- **Low Aβ :** Healthy older adults: no decline

- ***APOE* ε4**
  - High Aβ + ε4 carriage → faster cognitive decline over 54 months (Mormino et al., in press)

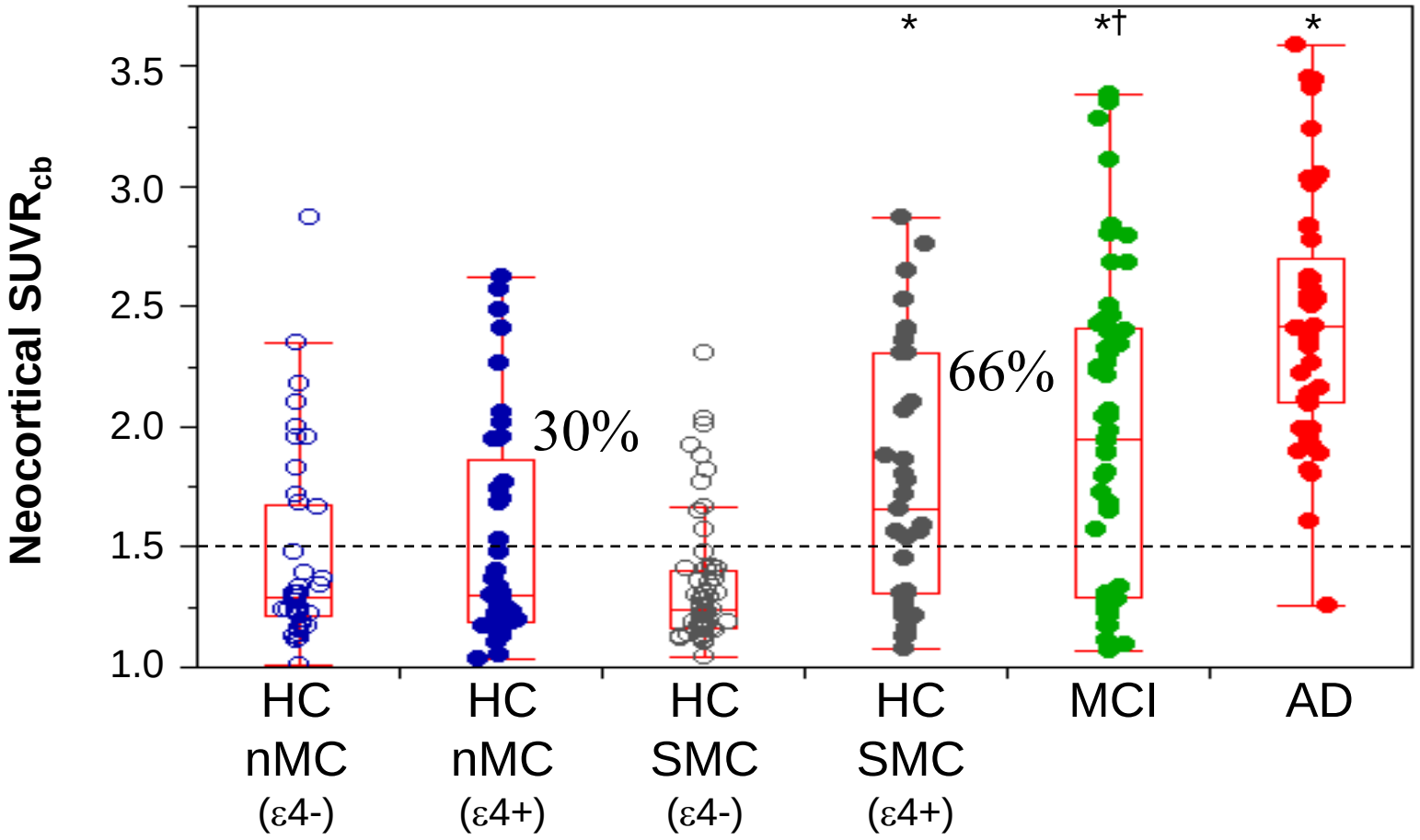
- ***BDNF* Val66Met**
  - No effect on individuals with low Aβ
  - Healthy older adults with high Aβ
    - Met carriers → ↑ memory decline/hippocampal atrophy

High Aβ + ε4 carriage + *BDNF*^{Met} → ↑↑ memory decline

Subjective Memory Complaint

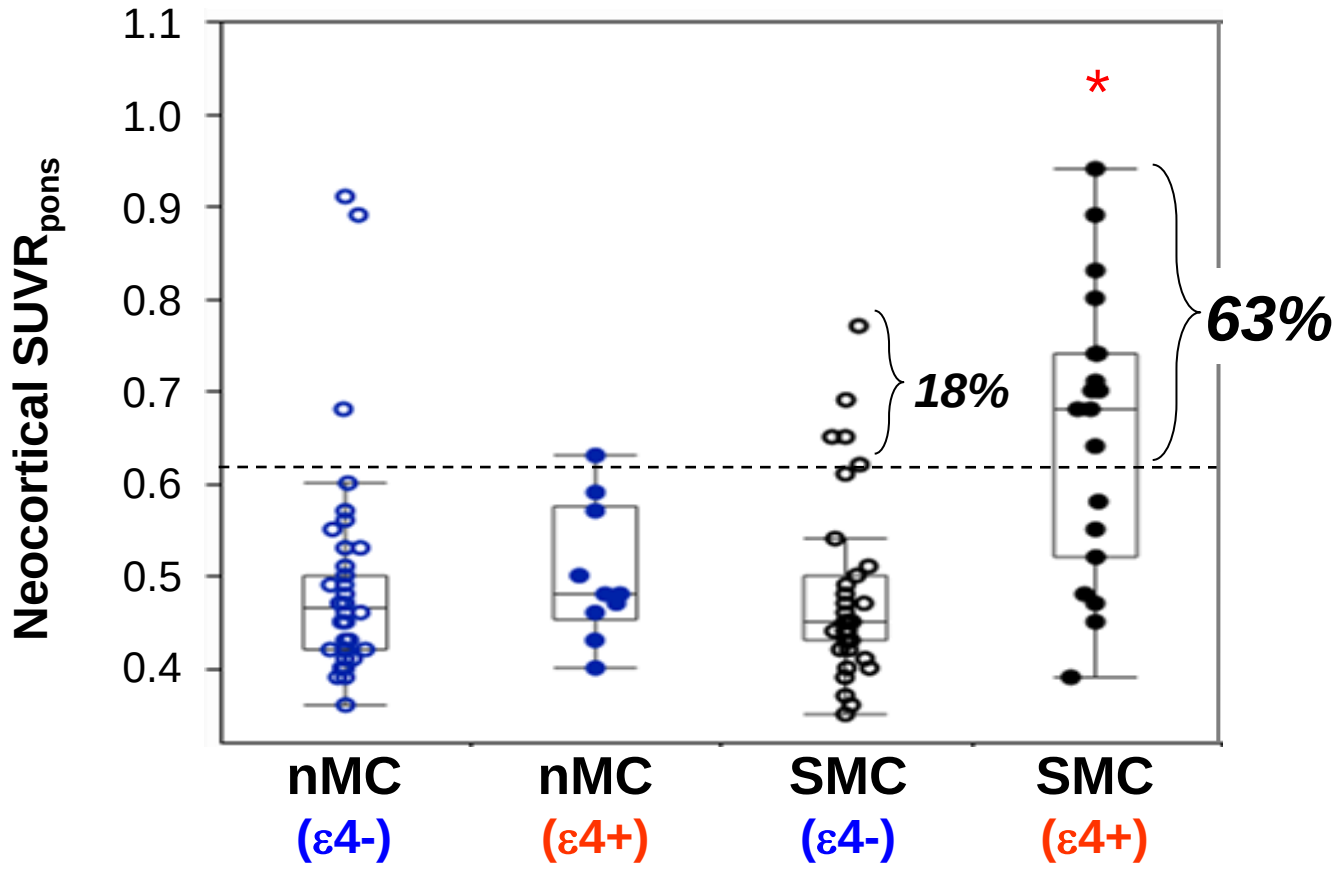
- SMC is associated with higher scores on anxiety scales but correlations with poorer cognitive performance and amyloid burden have been inconsistent - though tending towards an association.
- In the original AIBL imaging cohort of 177 HC 54% were SMC i.e. answered yes to “Do you have difficulty with your memory?” with normal psychometric test results.
- We only found higher anxiety scores and no overall increase in PiB+ve prevalence.

But there was a difference when SMC was associated with ApoE-ε4



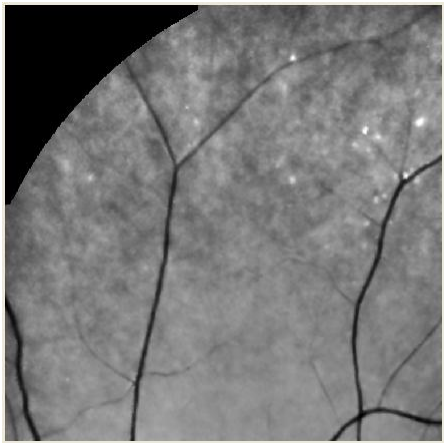
Rowe CC, et al. Neurobiology of Aging. 2010; 31:1275-1283.

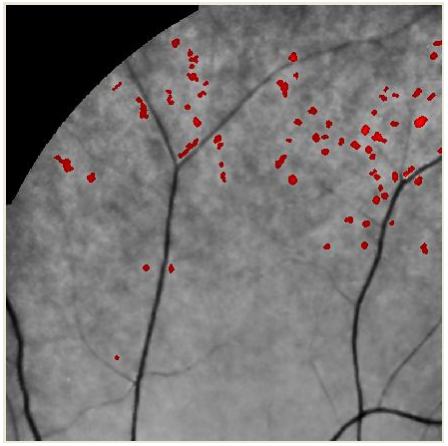
^{18}F-flutemetamol SUVR



**Significantly different from nMC, p <0.05*

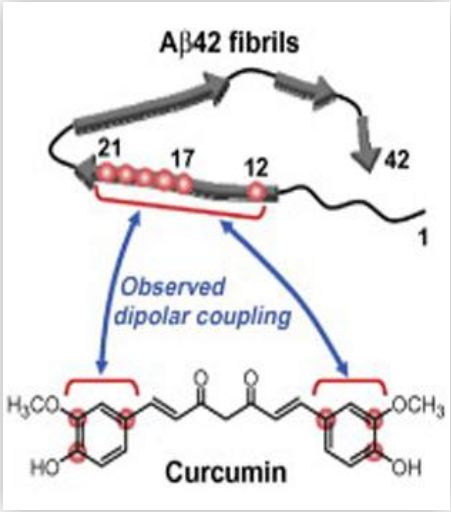
Retinal amyloid fluorescence imaging





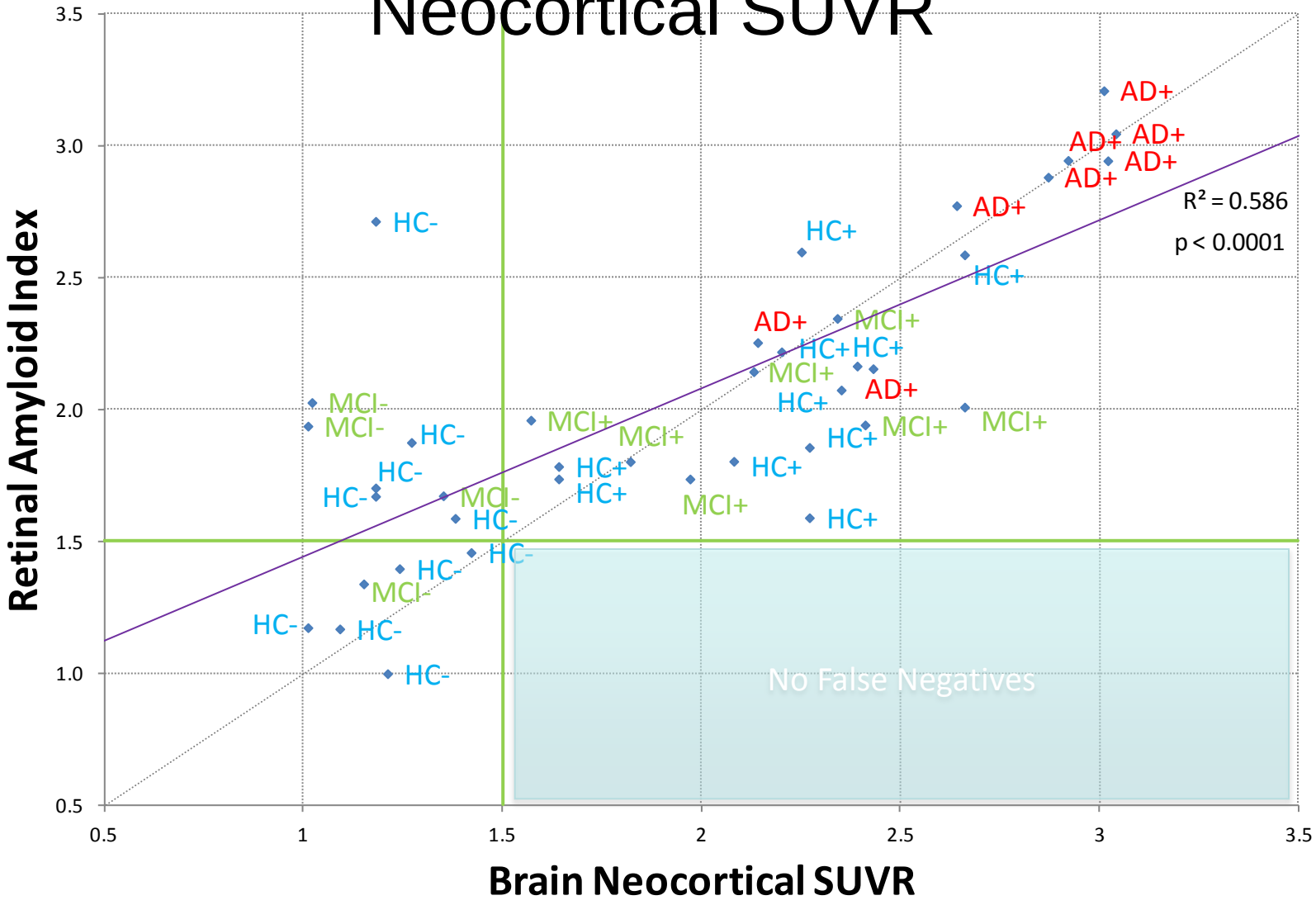
NeuroVision Imaging
Los Angeles, CA

Proprietary curcumin formulation with scientifically tested and defined chemical content and high-bioavailability.



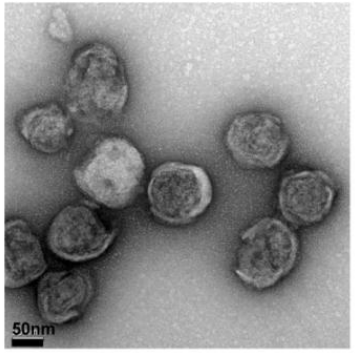
Koronyo-Hamaoui et al. NeuroImage 2011;
Masuda et al. Bioorg Med Chem. 2011

Retinal amyloid index correlates with Neocortical SUVR



Exosomes as biomarkers for AD

- Exosomes = Extracellular membrane vesicles, 50-130nm in diameter
- Secreted by a variety of mammalian cells
- Isolated from a variety of biological fluids
  - serum, plasma, CSF, milk, urine, saliva, etc...
- Contain protein and RNA (including miRNA)



- **Source of circulating biomarkers**
- **Contain many proteins involved in neurodegenerative diseases**

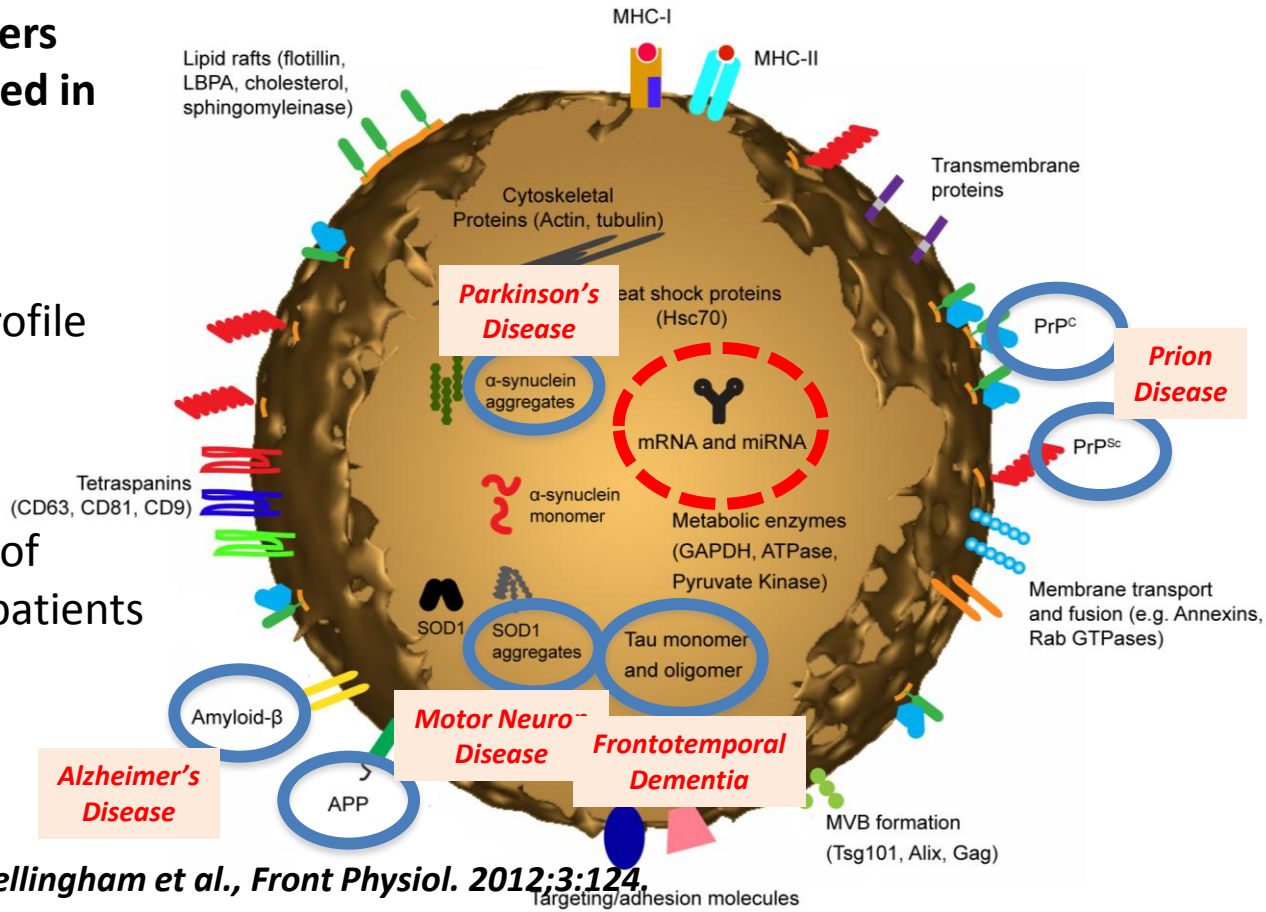
Current Study:

- AIM: to identify AD miRNA profile in blood derived exosomes

- APPROACH:

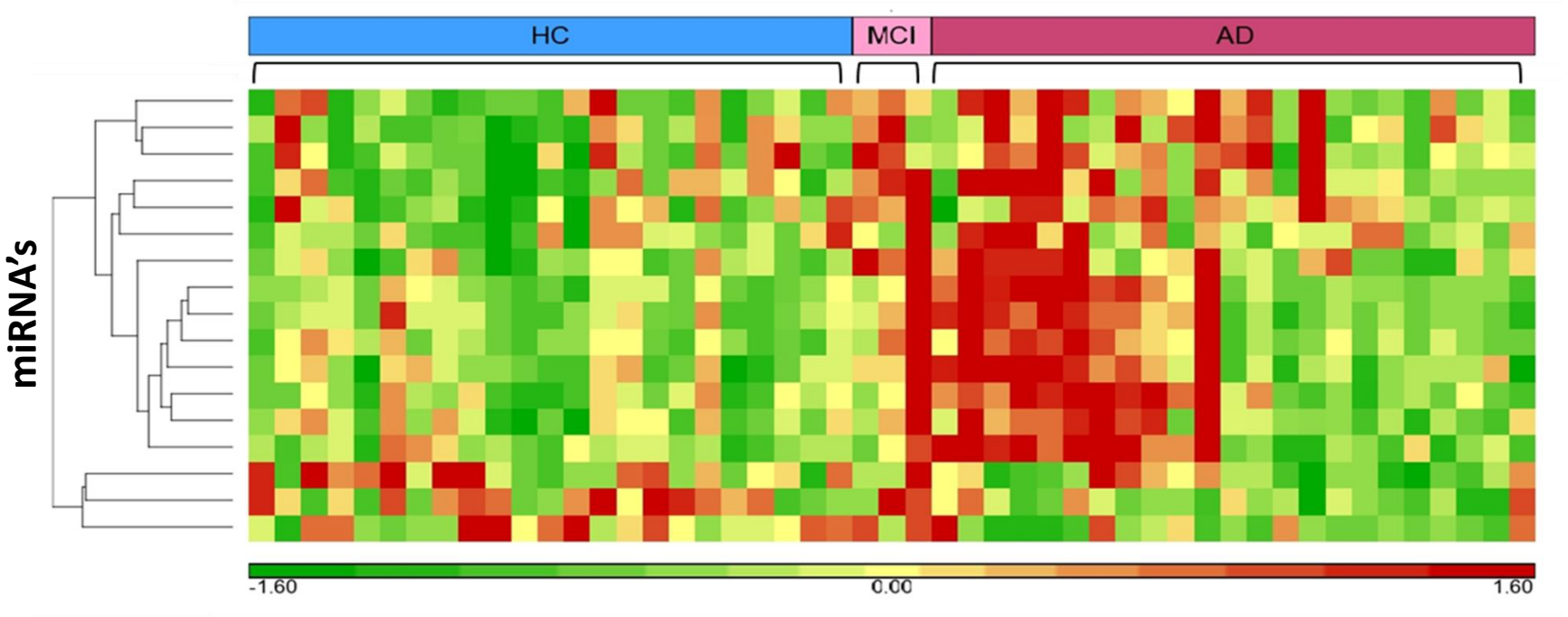
isolated exosomes from blood of healthy aged controls and AD patients

- Profile the exosomal miRNA using next gen sequencing
- validate the miRNA profile using qPCR



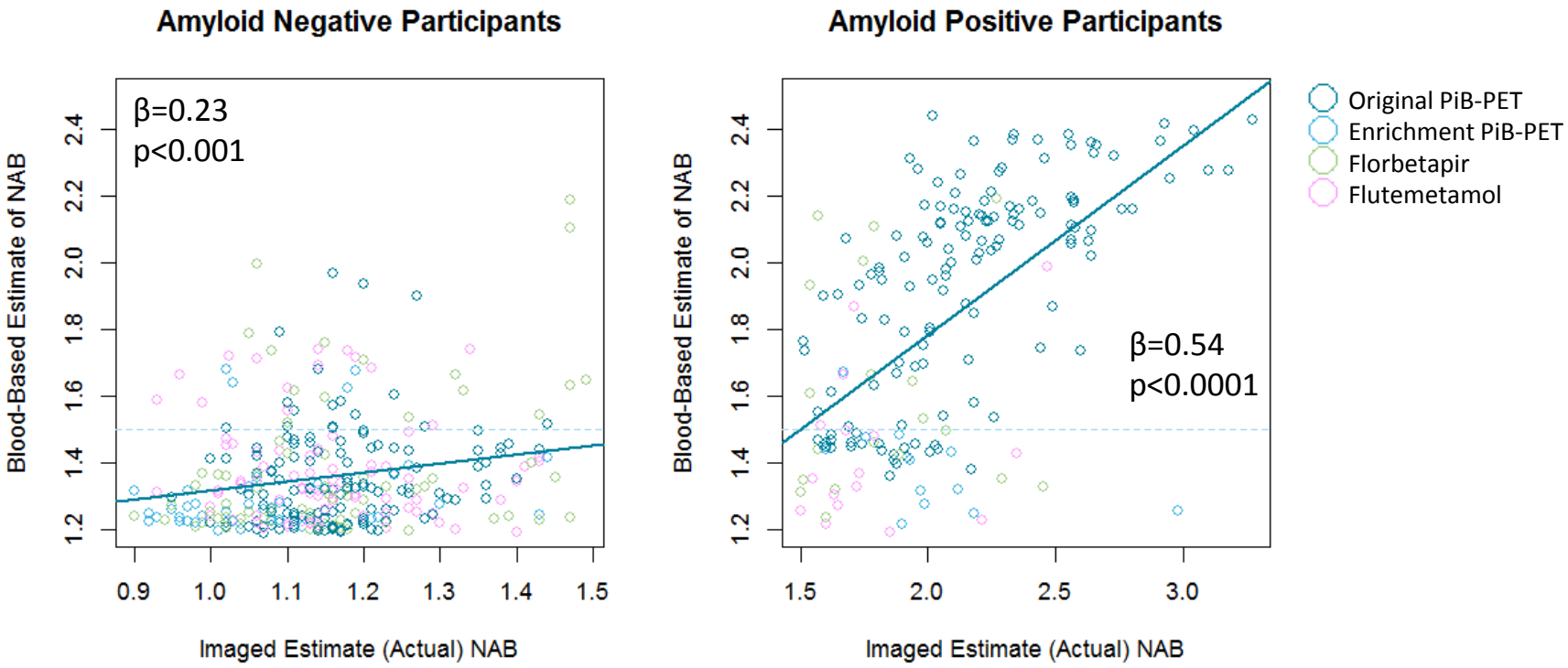
Bellingham et al., Front Physiol. 2012;3:124.

Differentially expressed exosomal miRNA in AD patients



- 17 miRNA were found to be significantly deregulated (p (AD Vs HC) ≤ 0·05)
- There are two major clusters:
  - Cluster 1 contains 15 miRNA which were found to be up-regulated.
  - Cluster 2 contains 3 miRNA which were found to be down-regulated.
- Validation in 15 AD and 35 Healthy Controls blind to diagnosis using qPCR:
  - 13/15 AD correctly identified (Sensitivity of 87%) (2 patients high Aβ / APOε4 negative)
  - 27/35 HC correctly identified (Specificity of 77%) (5 subjects high Aβ / 3 APOε4 positive)

Correlation of Imaged and Blood-Based Estimates of Neocortical Amyloid Burden (NAB)



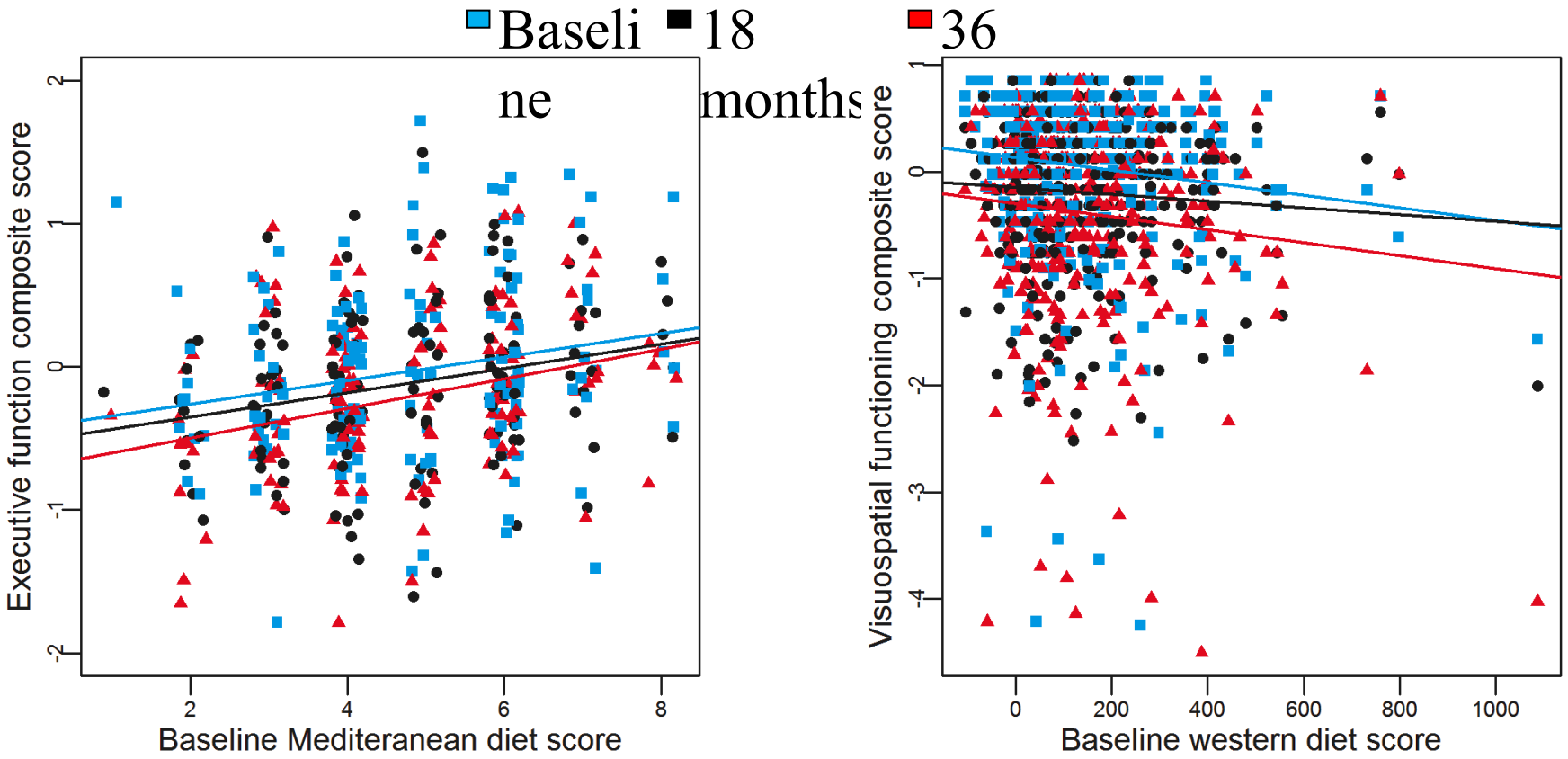
Burnham et al Predicting AD from a blood based biomarker profile
Jul 14 4-5:30pm O2-13-06 Hall A1

Bivariate correlates of progression to Alzheimer's disease over 54 Months

	No	Yes	Odds	χ^2	*p*	Odds ratio (95%CI)	PPV (95%CI)	NPV (95%CI)
HC Progressed to MCI/AD								
Predicted PiB Negative	304 (95.30%)	15 (4.70%)	0.05					
Predicted PiB Positive	240 (90.37%)	26 (9.63%)	0.11	4.75	0.003	2.16 (1.12-4.17)	9.90% (8.18%-11.95%)	95.16% (93.30%-96.52%)
MCI Progressed to AD								
Predicted PiB Negative	10 (71.43%)	4 (28.57%)	0.40					
Predicted PiB Positive	7 (20.00%)	28 (80.00%)	4.00	9.51	0.002	10.00 (2.41-41.58)	71.62% (60.74%-80.45%)	79.85% (63.14%-90.16%)

APOE genotype-dependent effects of diet and physical activity on cognition and Alzheimer's-related pathology: Data from the AIBL Study of Ageing

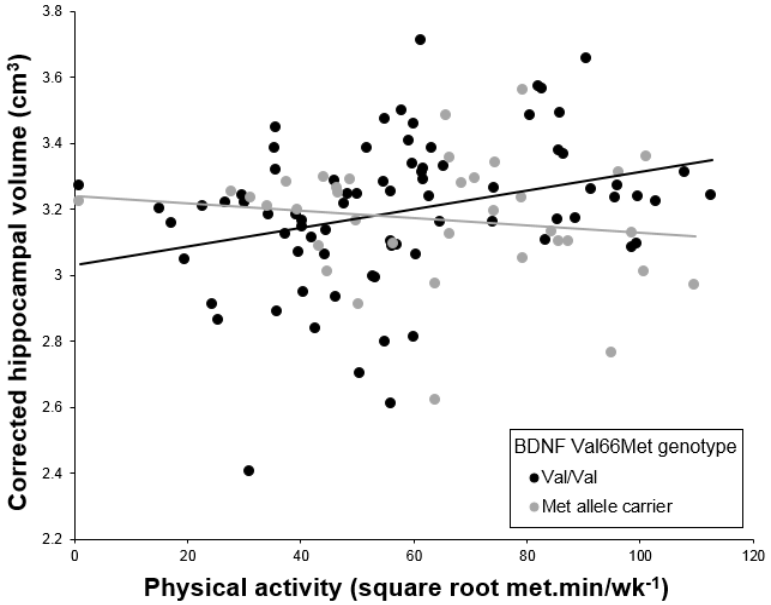
Rainey-Smith *et al*., Jul 14 2014, 2:15PM - 3:45PM, Hall A3, O2-02-05

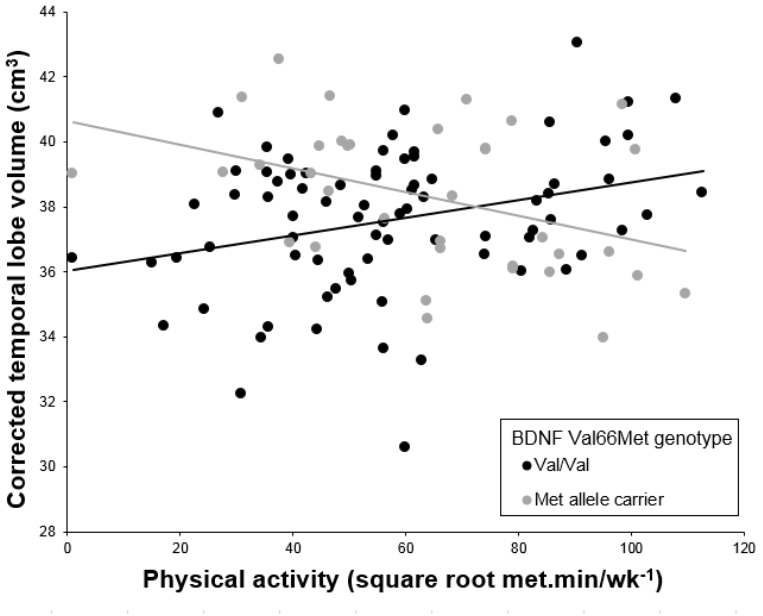


Linear mixed models (LMM) analyses: $p < 0.01$. Controlling for age, gender, years of education, country of birth, body mass index, energy intake.

Gardener, Rainey-Smith et al, 2014, Molecular Psychiatry (In press).

Higher levels of PA associated with larger temporal lobe and hippocampal volume in BDNF Val/Val homozygotes





Significant interaction of the BDNF Val66Met variant with physical activity was observed for hippocampal and temporal lobe volumes (volumes corrected for intracranial volume).

This association did not exist in BDNF Met carriers.

Future Directions for AIBL Imaging

- Further refine prognostic value and comparative effectiveness of imaging and blood biomarkers
- Examine genetic and environmental influences on rate of decline in Aβ+ve HC
- Add Tau imaging
- Create a new pool of amyloid scan positive HC and MCI for early intervention trials
- Use AIBL infrastructure to support the A4 and DIAN therapy trials

Acknowledgements and thanks

aibl
The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

AIBL is a large collaborative study and a complete list of contributors and the management committee can be found at **www.aibl.csiro.au**

This research was funded in part by the Science and Industry Endowment Fund and CSIRO.

We thank all who took part in the study.

SCIENCE AND INDUSTRY ENDOWMENT FUND