Study on protein biomarker panel for Alzheimer' disease: Australian Imaging Biomarkers and Lifestyle Study of Aging

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CRC for Mental Health

AUSTRALIA ECU EDITH COWAN UNIVERSITY

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

The McCusker Foundation
for Alzheimer's Disease Research Inc
Research to understand, diagnose, prevent & treat Alzheimer's disease

The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

Study is conducted between Perth (40%) and Melbourne (60%)

CSIRO P-Health*
University of Melbourne*
Neurosciences Australia Ltd (NSA)*
Edith Cowan University (ECU)*
Mental Health Research Institute (MHRI)*
National Ageing Research Institute (NARI)
Austin Health
University of WA (UWA)
CogState Ltd.
Charles Gairdner Hospital radiology and nuclear medicine

**denotes signatories to the AIBL study contract*

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The AIBL Study

- Launched in November 2006; prospective longitudinal study
- Aims to improve understanding of the causes and diagnosis of AD, and help develop preventative strategies

Baseline **Follow-up: 18 month** **36 month** **54 month** **72 month**

Current Status

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OVERVIEW: AIBL is the most comprehensive, longitudinal study of its kind in Australia, and aims to discover a way to develop biomarkers, diagnose patients earlier and prevent disease onset.

COHORT

N = 1,112 (Baseline) (aged 60+ yrs)

- Healthy Controls
- Subjective Memory Complainers
- Mild cognitive Impairment
- Alzheimer's Disease

METHODOLOGY

- Cognitive and clinical assessment
- Biomarkers
- Vascular
- Diet & Lifestyle
- Neuroimaging

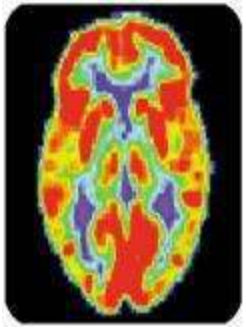
AIBL Longitudinal cohort summary

	Total NMC	Total SMC	Total MCI	NMC/SMC-(MCI/AD)#	MCI-(AD)#	AD
0M	372	396	133	21	33 (24.8% MCI progressed)*	211
ApoE4	106 (28.5%)	101 (25.5%)	66 (49.6%)	10 (47.6%)	25 (75.8%)	131 (62.1%)
Age (sd)	69.8 (7.0)	70.3 (7.0)	75.8 (7.5)	73.9 (8.3)	76.3 (7.2)	78.2 (8.6)
18M	317	375	82	21	17 (20.7%)*	197
ApoE4	88 (27.8%)	98 (26.1%)	32 (39.0%)	11 (52.4%)	9 (52.9%)	136 (69.0%)
Age (sd)	71.1 (6.9)	71.4 (6.6)	76.6 (7.7)	72.1 (7.3)	78.0 (6.7)	78.6 (8.1)
36M	301	309	55	24	6 (10.9%)*	154
ApoE4	84 (27.9%)	81 (26.2%)	23 (41.8%)	9 (37.5%)	5 (83.3%)	106 (68.8%)
Age (sd)	71.5 (6.1)	73.1 (6.8)	77.2 (7.4)	73.5 (6.8)	78.3 (64)	79.3 (7.8)
54M	261	299	51	9	2 (9.1% of the 22 tested)	102
ApoE4	69 (26.4%)	79 (26.4%)	17 (33.3%)	4 (44.4%)	1 (50.0%)	72 (70.6%)
Age (sd)	72.9 (6.3)	74.0 (6.5)	77.5 (6.6)	77 (7.8)	86.5	80.2 (7.7)
72M	137	163	23			13
ApoE4	31 (22.6%)	44 (27.0%)	10 (43.5%)			7 (53.8%)
Age (sd)	74.1 (5.9)	75.7 (6.3)	77.7 (7.2)			81.8 (7.3)

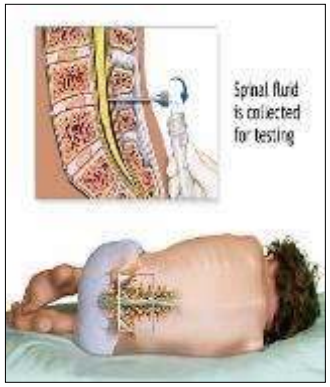
#Subset of NMC/SMC and MCI who change diagnosis at the next time point. These people are included in current time point's total NMC, SMC and MCI tallies. *(%) of the MCI group at each time point. (NMC) Non Memory Complainer, (SMC) Subjective Memory Complainer, (MCI) Mild Cognitive Impairment, (AD) Alzheimer's disease.

Types of biomarkers

Brain Imaging

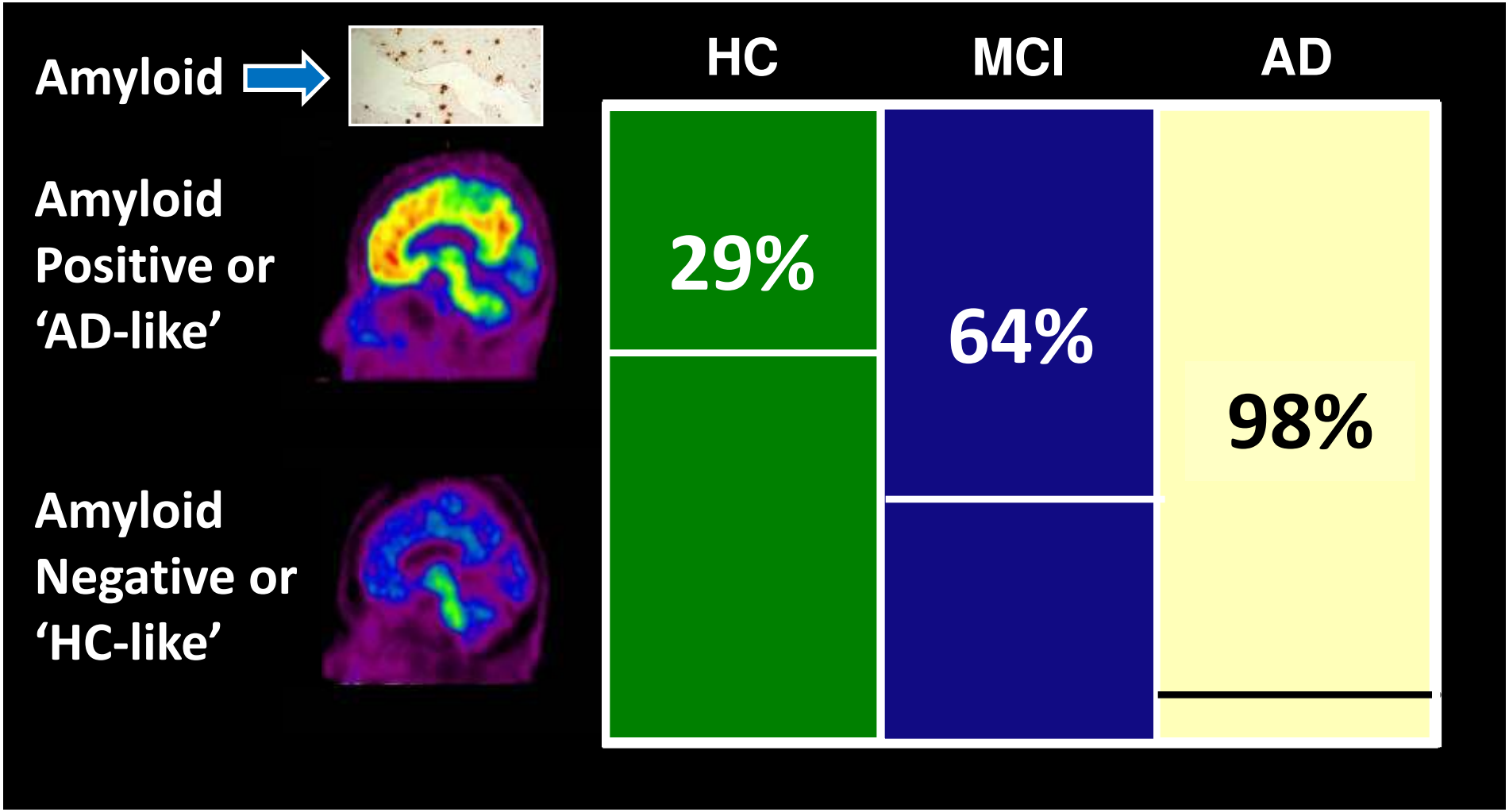


CSF Biomarkers



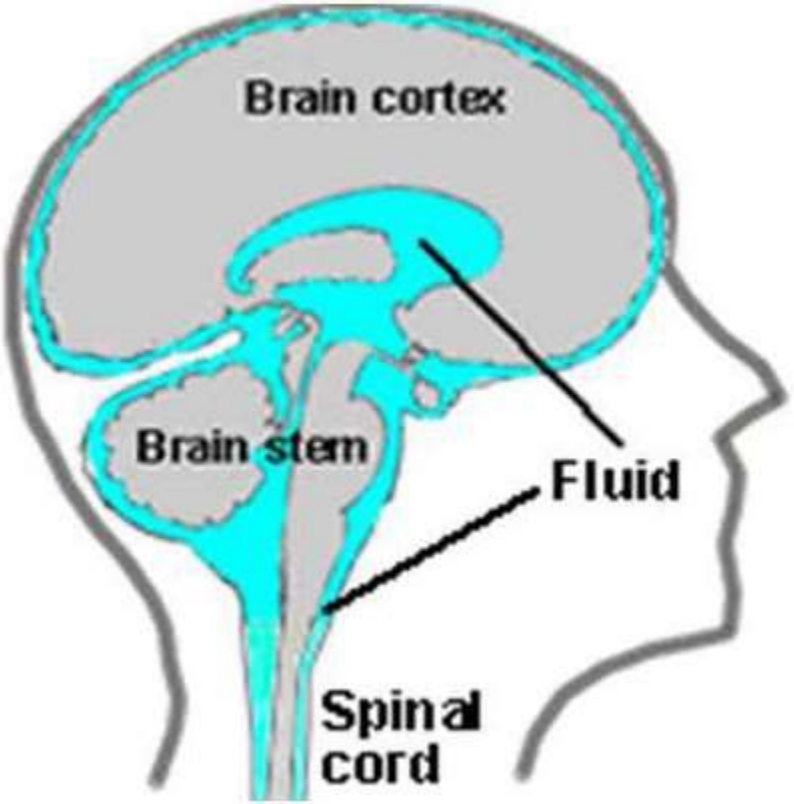
Blood Biomarkers

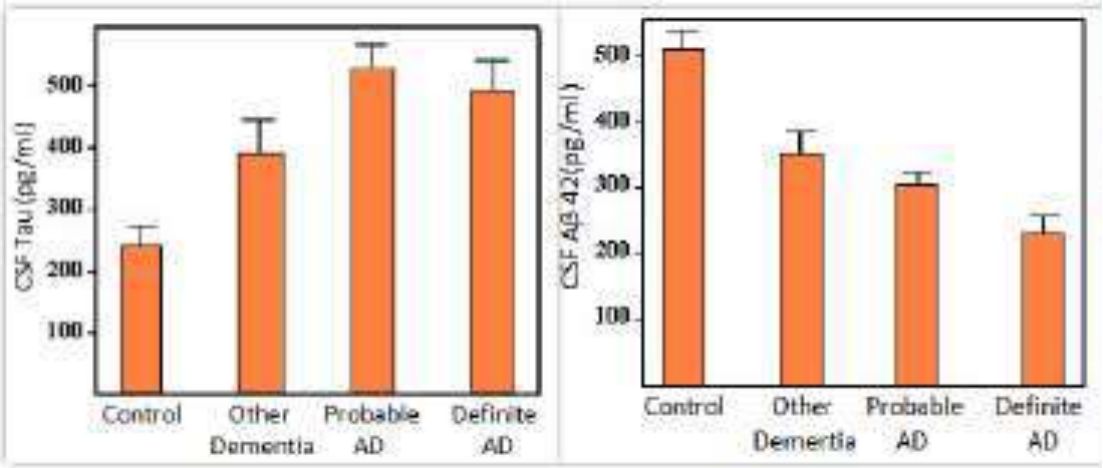
Amyloid Load in the Brain of AIBL Participants: PiB +ve volunteers (%)



Significant differences between the three groups ($p<0.001$)

Why use CSF as a source of biomarker?





Sensitivity:86%
Specificity: 85%

CSF is in direct contact with the extracellular space of the brain and can therefore reflect biochemical changes

Rationale behind Blood

- Imaging biomarkers are gold standard but not widely accessible and there is fear associated with Lumbar puncture.
- Blood biomarkers have the advantage but until recently were not sufficiently accurate.
- Blood biomarkers therefore offer the perfect method for enhancing utility of neuroimaging and CSF biomarkers.

Blood Biomarkers

A BLOOD TEST for AD

- Most recent
- Could form a least expensive form of test for AD
- Could be easily accessible
- least invasive

By Quantification of abundance of various proteins in blood

Multivariate Protein Signatures of Pre-Clinical Alzheimer's Disease in the Alzheimer's Disease Neuroimaging Initiative (ADNI) Plasma Proteome Dataset

Daniel Johnstone[1,2], Elizabeth A. Milward[1,3], Regina Berretta[1,2], Pablo Moscato[1,2]*, for the Alzheimer's Disease Neuroimaging Initiative

A Blood-Based Algorithm for the Detection of Alzheimer's Disease

Sid E. O'Bryant[a] Guanghua Xiao[b] Robert Barber[a] Joan Reisch[b]
James Hall[f] C. Munro Cullum[c,d] Rachelle Doody[h] Thomas Fairchild[g]
Perrie Adams[c] Kirk Wilhelmsen[i] Ramon Diaz-Arrastia[d]
Texas Alzheimer's Research and Care Consortium

Plasma multianalyte profiling in mild cognitive impairment and Alzheimer disease

William T. Hu, David M. Holtzman, Anne M. Fagan, et al.
Neurology; Published online before print August 1, 2012;
DOI 10.1212/WNL.0b013e318266fa70

ORIGINAL ARTICLE

A blood-based predictor for neocortical Aβ burden in Alzheimer's disease: results from the AIBL study

SC Burnham[1,15], NG Faux[2,15], W Wilson[3], SM Laws[4,5], D Ames[6,7], J Bedo[8], AI Bush[2], JD Doecke[9], KA Ellis[6], R Head[10], G Jones[11,12], H Kiiveri[1], RN Martins[4,5], A Rembach[2], CC Rowe[11,12], O Salvado[13], SL Macaulay[14], CL Masters[2], VL Villemagne[11] Alzheimer's Disease Neuroimaging Initiative[16,17] Australian Imaging, Biomarkers and Lifestyle Study Research Group[18]

Blood-Based Protein Biomarkers for Diagnosis of Alzheimer Disease

James D. Doecke, PhD; Simon M. Laws, PhD; Noel G. Faux, PhD; William Wilson, PhD; Samantha C. Burnham, PhD; Chiou-Peng Lam, PhD; Alinda Mondal, MSc; Justin Bedo, PhD; Ashley I. Bush, MD; Belinda Brown, BSc; Karl De Ruyck, BSc; Kathryn A. Ellis, PhD; Christopher Fowler, BSc; Veer B. Gupta, PhD; Richard Head, PhD; S. Lance Macaulay, PhD; Kelly Pertile, BSc; Christopher C. Rowe, MD; Alan Rembach, PhD; Mark Rodrigues, MSc; Rebecca Rumble, BSc; Cassandra Szoeke, MD; Kevin Taddei, BSc; Tania Taddei, BSc; Brett Trounson, BSc; David Ames, MD; Colin L. Masters, MD; Ralph N. Martins, PhD; for the Alzheimer's Disease Neuroimaging Initiative and Australian Imaging Biomarker and Lifestyle Research Group

Research Article

Plasma proteins predict conversion to dementia from prodromal disease ☆

Abdul Hye[a,1], Joanna Riddoch-Contreras[a,1], Alison L. Baird[a], Nicholas J. Ashton[a], Chantal Bazenet[a], Rufina Leung[a], Eric Westman[a,b], Andrew Simmons[a], Richard Dobson[a], Martina Sattlecker[a], Michelle Lupton[a,c], Katie Lunnon[d], Aoife Keohane[a], Malcolm Ward[e], Ian Pike[e], Hans Dieter Zucht[e], Danielle Pepin[f], Wei Zheng[f], Alan Tunnicliffe[f], Jill Richardson[g], Serge Gauthier[h,i], Hilkka Soininen[j], Iwona Kłoszewska[k], Patrizia Mecocci[l], Magda Tsolaki[m], Bruno Vellas[n], Simon Lovestone[a,o,p,*]

Predicting conversion to MCI

apoE	MIP-1α
apoA-II	Resistin
Eotaxin-3	SGOT
Transthyretin	CD5
BNP	CRP
Peptide YY	Fas Ligand

Diagnostic accuracy of AD

CRP	Tenascin C
PPY	Factor VII
FABP	VCAM-1
Adiponectin	CD5
IL-18	CRP
B-2M	Fas Ligand

Diagnosis of MCI/AD

ApoE	IL-10
FAS	IL-12p40
Cortisol	IL-13
CRP	IL-15
BNP	PPY
IL-3	Resistin
SCF	SAP

Predicting neocortical amyloid burden

Abeta42	VCAM-1
CXCL-13	IGFBP2
IgM-1	ANGPF2
IL-17	CD40
PPY	CRP

Diagnosis of AD

IGFBP2	EGFR
PPY	IL17
CEA	Homocysteine
Cortisol	CD40
B2M	SOD
VCAM1	MMP2
EGFR	MIP1α
IL17	APOE

Ten proteins predicting conversion to AD

Transthyretin	CC4
Clusterin	PEDF
Cystatin C	A1 AT
A1 Acid G	RANTES
ICAM1	ApoC3

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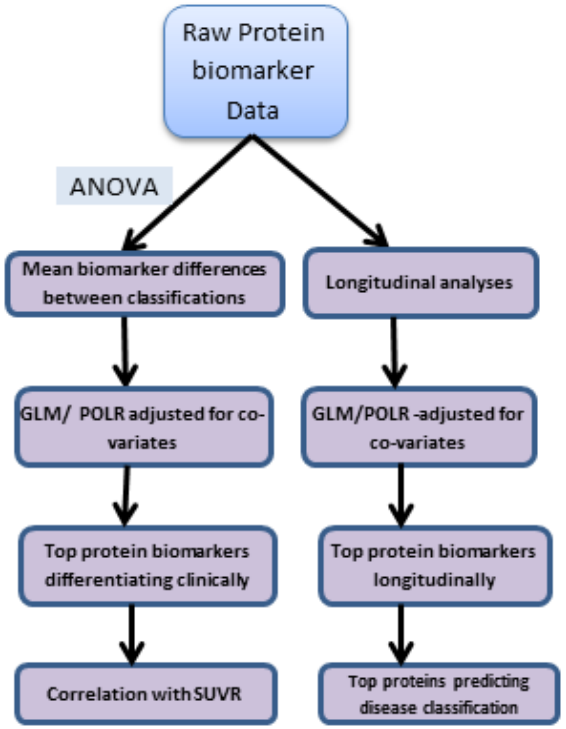
Biomarker Panels
MSD Platform

Human Chemokine 9-plex	Human Neuro D 5-Plex Custom Assay	Custom 6-plex	Human Vascular Injury Panel II	Custom 7-plex	Custom 4-plex
Eotaxin, *MIP-1ß,* *Eotaxin-3,* *TARC,* *IL-10,* *IL-8,* *MCP-1,* *MDC,* *MCP-4*	*TPO* *IL-18,* *FABP-3,* *PPY,* *chemo I-309*	A2M, Adiponectin, B2M, Clusterin, FVII, TNC	SAA, CRP, ICAM-1, VCAM-1	IL-1a IL-13 IL-15 IL-16 IL-17 MIP-1a TNF-a	Ang-2 sFAS Resistin EGF

Demographics

	Baseline			18 months			36 months			
	HC	MCI	AD	HC	MCI	AD	HC	MCI	AD	p-value
Count	554	65	92	543	51	116	463	42	87	
Age (Mean SD)	69.79 (6.51)	74.84 (7.54)	77.01 (7.43)	71.12 (6.34)	76.05 (7.28)	78.68 (7.63)	72.71 (6.38)	76.44 (6.66)	79.71 (7.12)	<0.0001
Gender (F/M)	330/224	36/29	52/40	328/215	23/28	67/49	279/184	23/19	46/41	
ApoE4 (-ve/+ve)	401/153	32/33	28/64	395/148	32/19	34/82	341/122	22/20	26/61	<0.0001
MMSE (Median IQR)	29 (2)	27 (3)	21 (4.25)	29 (2)	27 (3)	19 (8)	29 (2)	26.5 (3)	16 (11)	<0.0001
SUVR (N)	127	32	21	116	19	23	85	17	18	
SUVR (Mean SD)	1.36 (0.38)	2.02 (0.57)	2.29 (0.5)	1.35 (0.37)	2.03 (0.63)	2.32 (1.35)	1.4 (0.39)	1.84 (0.64)	2.43 (0.59)	<0.0001
Hip Vol (N)	116	26	15	110	17	20	74	15	12	
Hip Vol (Mean SD)	0.0041 (0.00031)	0.0038 (0.00047)	0.0036 (0.00034)	0.0041 (0.00032)	0.0038 (0.0005507)	0.0034 (0.00376)	0.0041 (0.00032)	0.0039 (0.00048)	0.0033 (0.00053)	<0.0001



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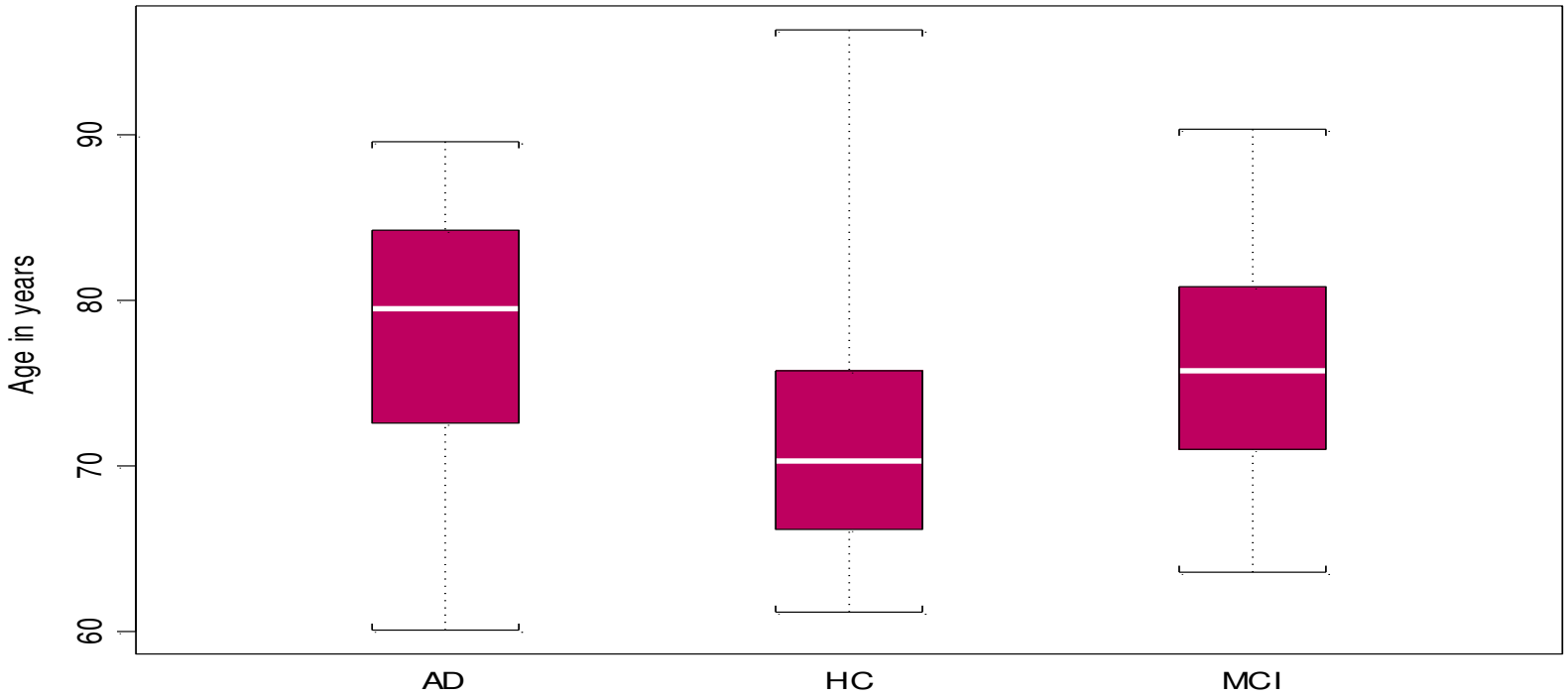
Age differences across different clinical groups



The HC group are on average approximately 5.7 years younger than MCI while AD are on average 1.2 years older. The latter difference is not significant while the HC ages are significantly lower than the other two ($p<0.0001$).

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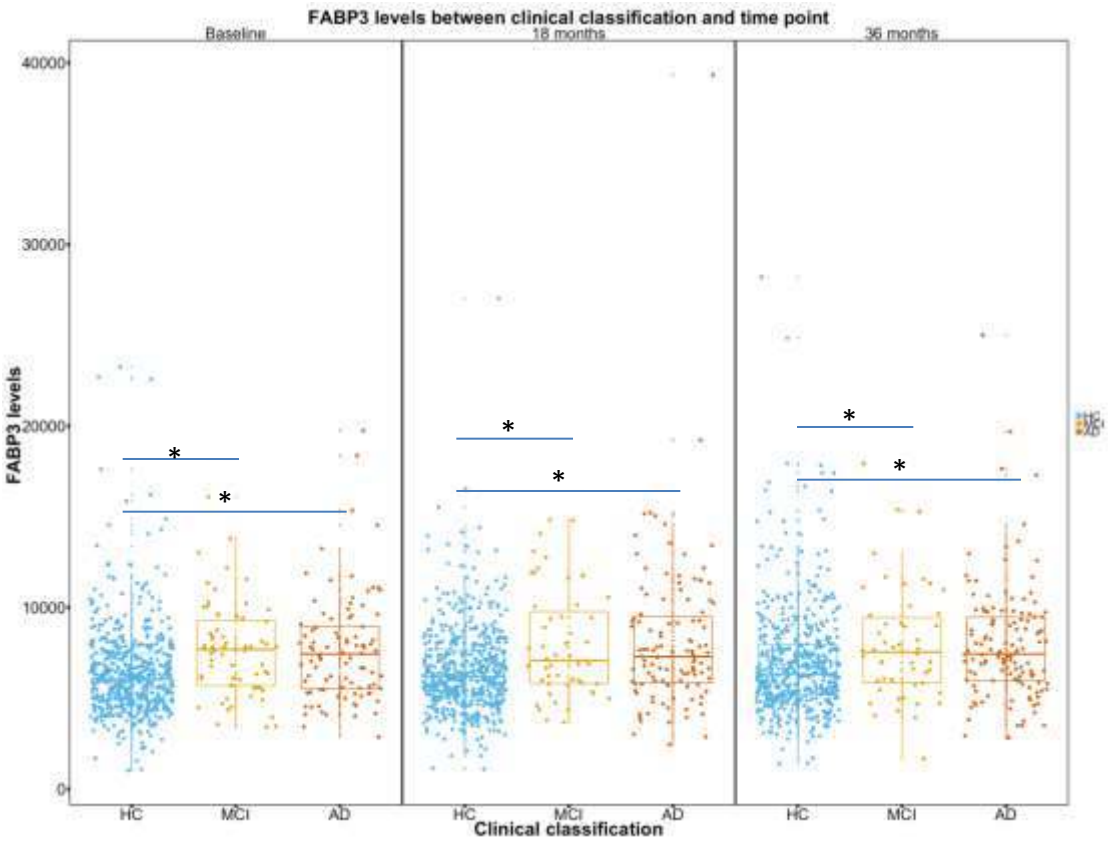
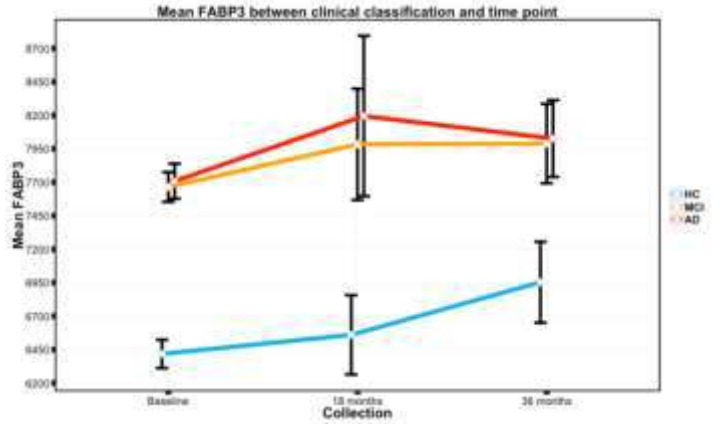
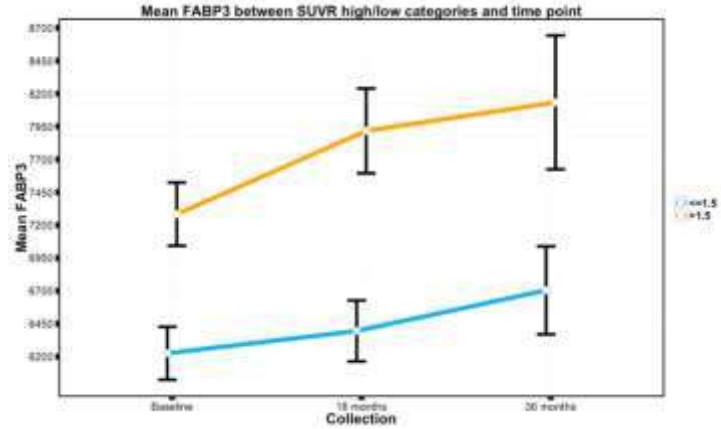
Fatty Acid Binding Protein 3

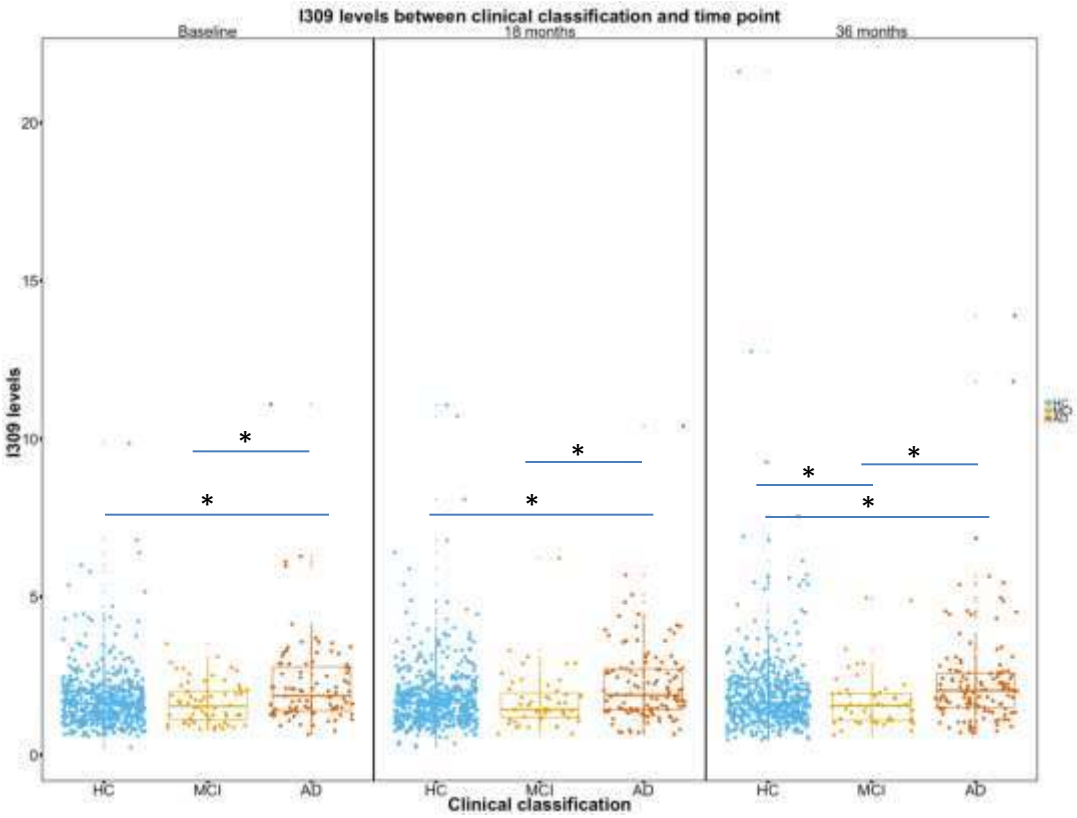


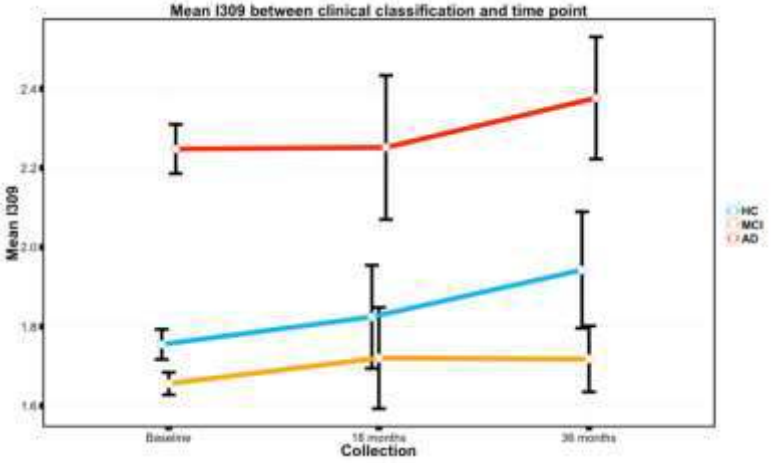


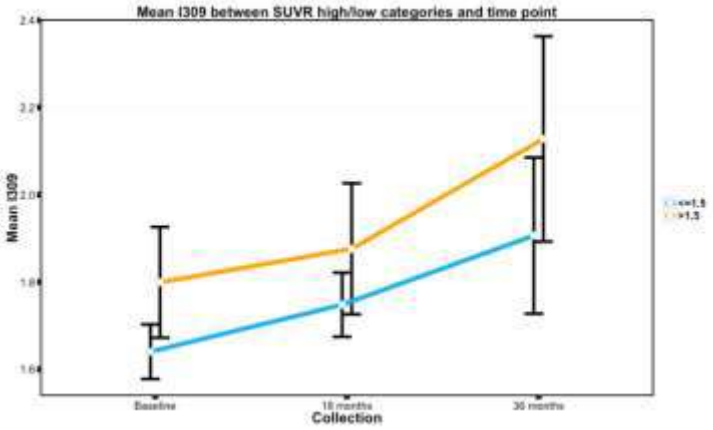


	All three groups		HC vs MCI		HC vs AD		MCI vs AD	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Baseline	2.02E-08	0.3356	2.18E-05	0.1285	3.41E-06	0.8375	0.9936	0.4419
18 Months	3.03E-09	0.2022	0.0001	0.1219	5.15E-08	0.4821	0.8588	0.8237
36 months	1.14E-05	0.6319	0.0096	0.7746	0.0001	0.4757	0.8671	0.5791

Chemokine I309

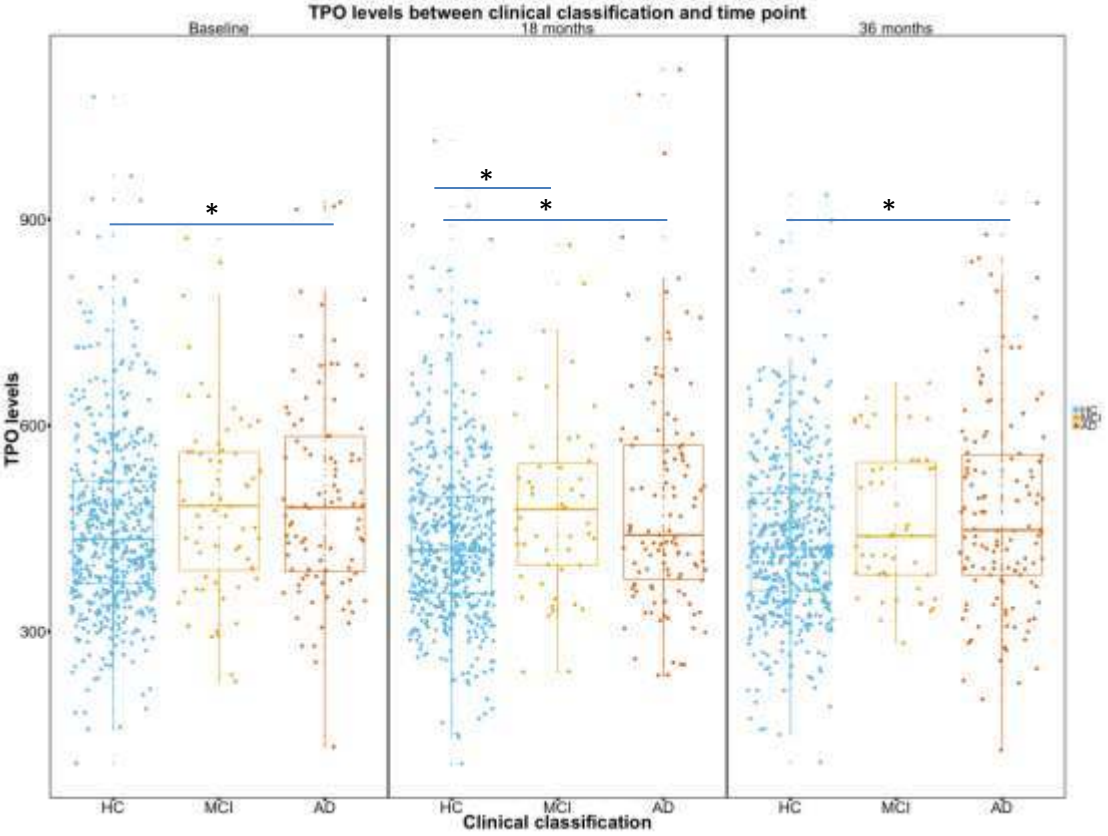


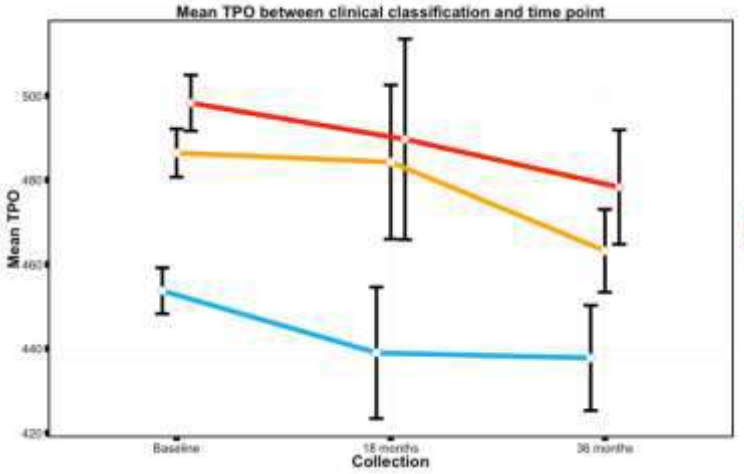


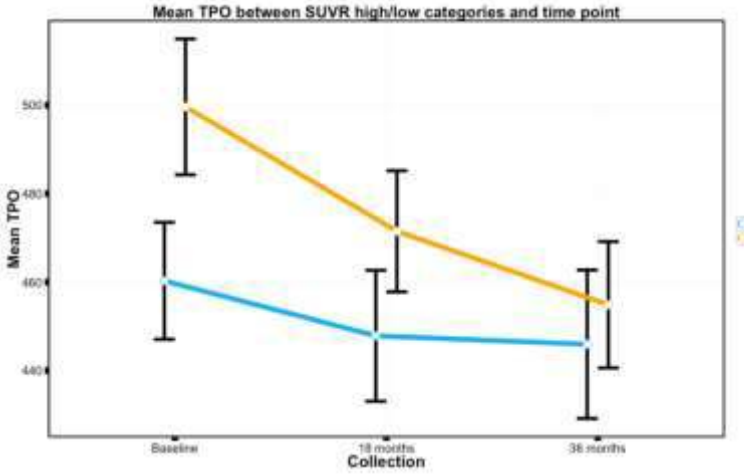


	All three groups		HC vs MCI		HC vs AD		MCI vs AD	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Baseline	0.0015	0.2862	0.5181	0.1170	1.13E-05	0.0167	0.0010	0.0066
18 Months	0.0021	0.9447	0.3690	0.0669	0.0001	0.1752	0.0028	0.0202
36 Months	0.0054	0.5469	0.1233	0.0118	0.0001	0.5706	0.0007	0.0266

Thrombopoietin

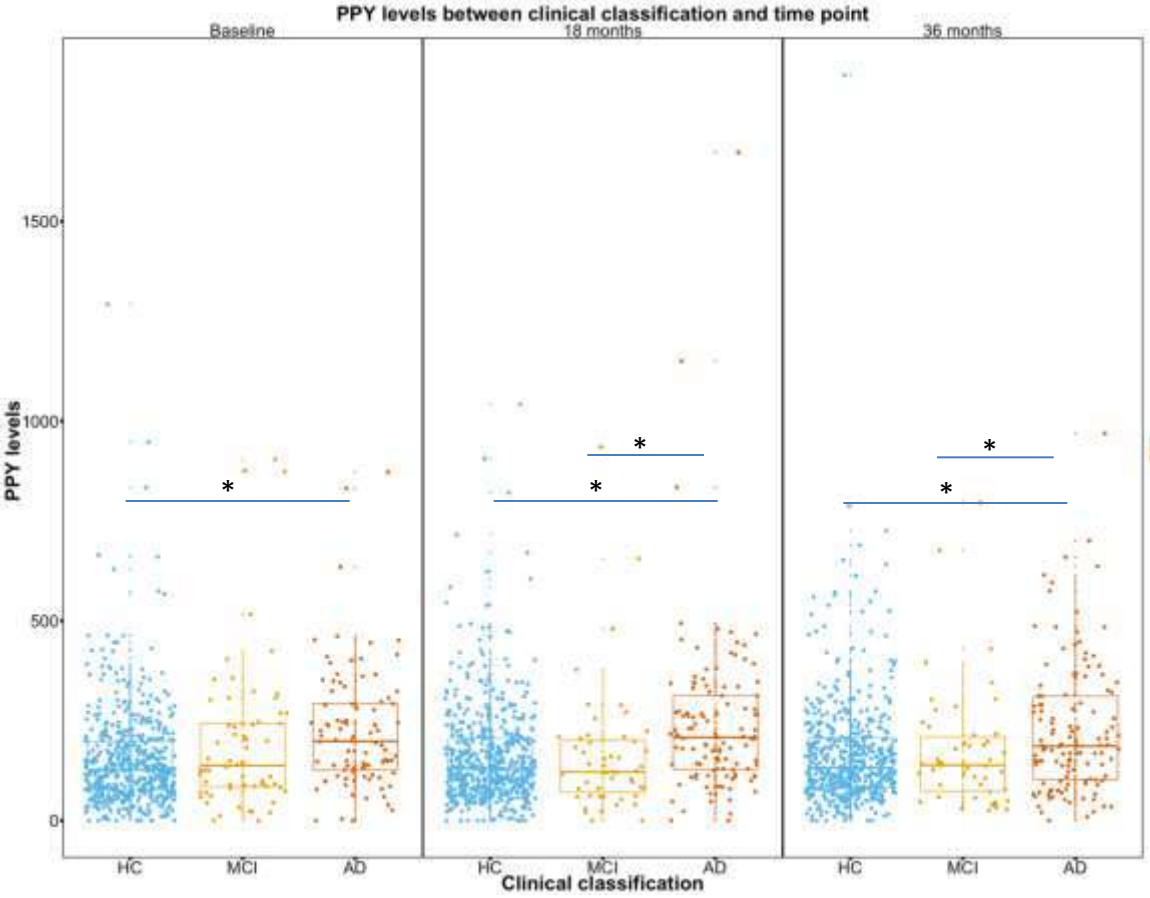


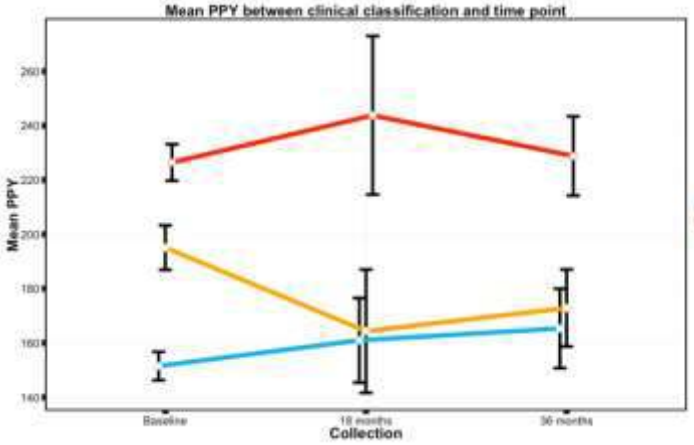


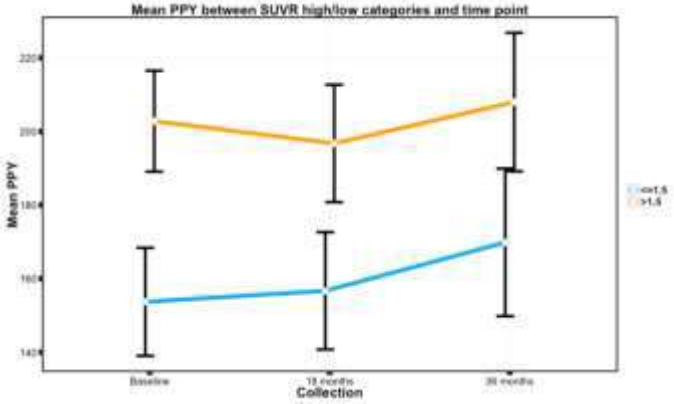


	All three groups		HC vs MCI		HC vs AD		MCI vs AD	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Baseline	0.0012	0.0356	0.0563	0.2509	0.0039	0.0502	0.5974	0.5387
18 Months	0.0005	0.0172	0.0176	0.0276	0.0034	0.0836	0.8974	0.4575
36 Months	0.0012	0.1789	0.1478	0.6842	0.0023	0.4755	0.5599	0.3682

Pancreatic Polypeptide Y

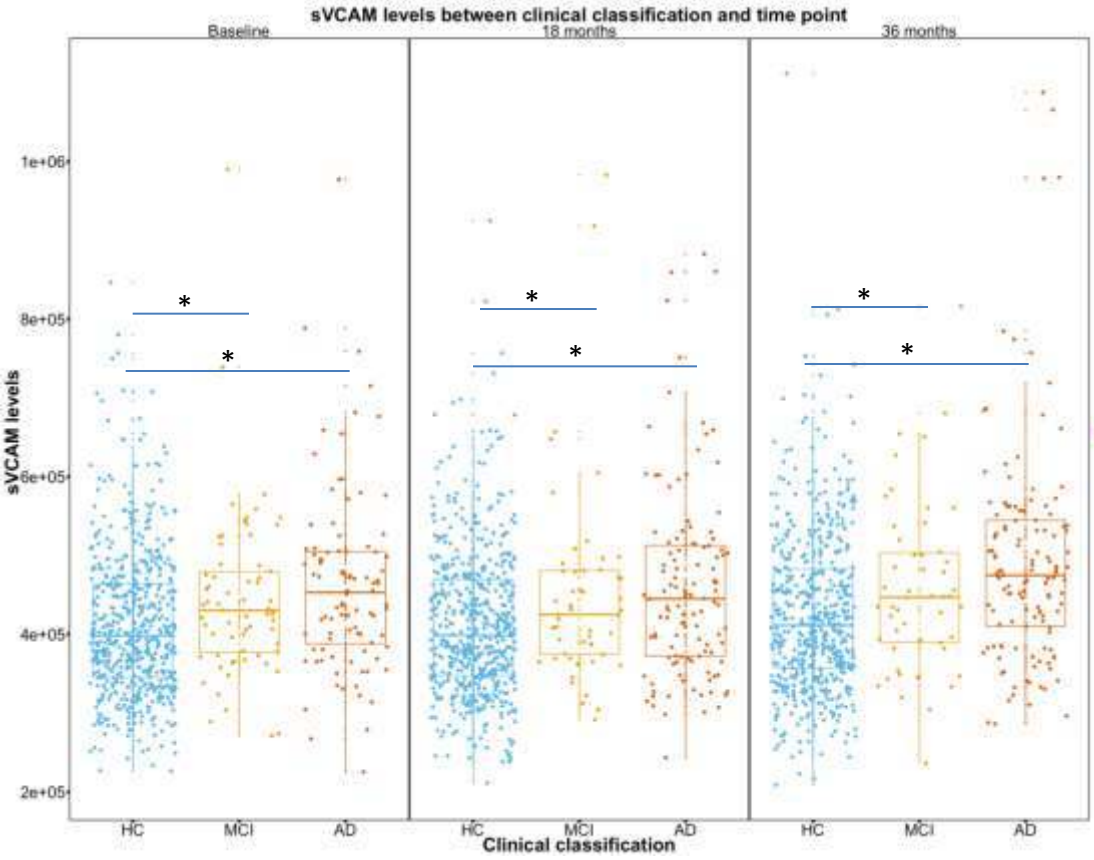


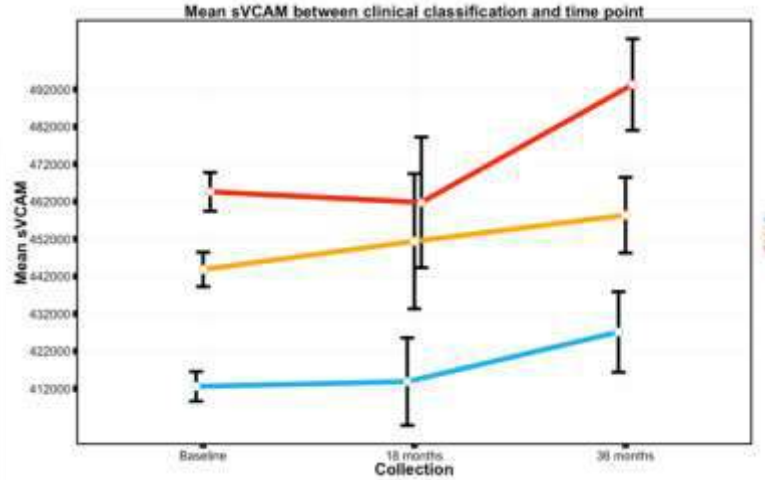


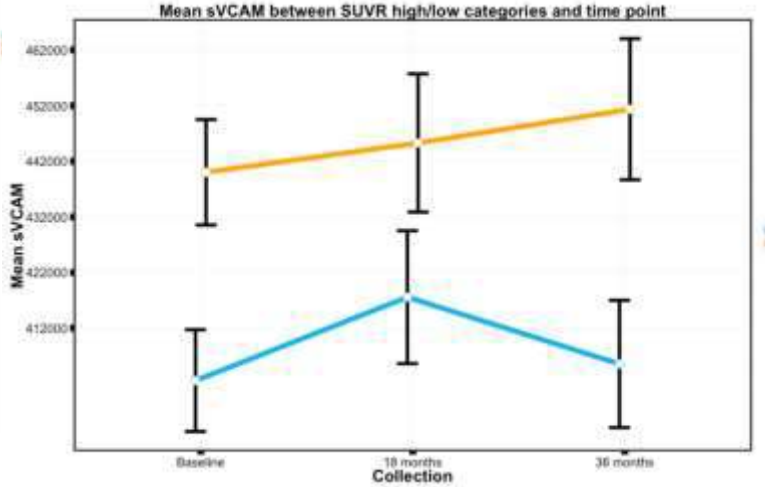


	All three groups		HC vs MCI		HC vs AD		MCI vs AD	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Baseline	3.16E-05	0.1075	0.1249	0.9325	7.56E-06	0.0370	0.0775	0.1454
18 Months	3.65E-05	0.0443	0.4921	0.0557	1.44E-07	0.0100	0.0002	0.0001
36 Months	0.0004	0.2124	0.7835	0.1079	2.56E-05	0.0651	0.0111	0.0119

Soluble Vascular Cell Adhesion Molecule 1



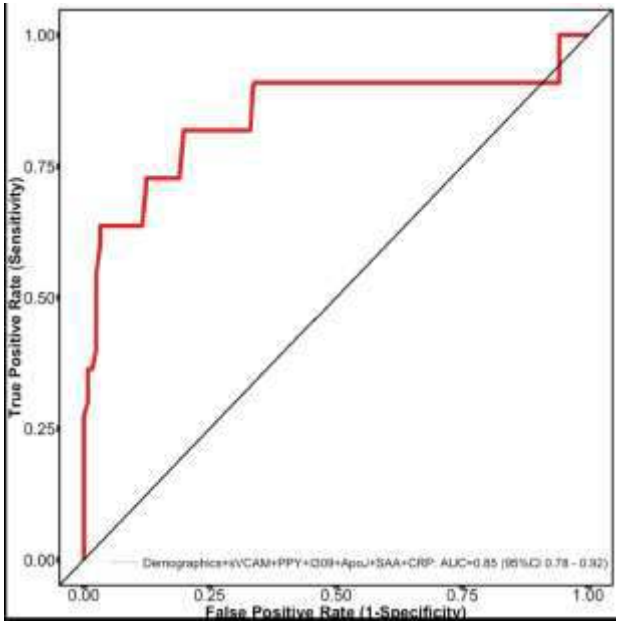




	All three groups		HC vs MCI		HC vs AD		MCI vs AD	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Baseline	7.59E-06	0.1634	0.0120	0.3654	4.09E-05	0.0855	0.3422	0.7705
18 Months	3.82E-05	0.5612	0.0336	0.6051	0.0001	0.5823	0.5645	0.8394
36 Months	1.67E-07	0.0134	0.0351	0.2046	1.60E-07	0.0136	0.1919	0.6776

Significant markers

- List of Important markers from this study: FABP3, CI309, TPO, PPY, sVCAM1, SAA, sICAM1, CRP, A2M, B2M, Adipo, apoJ.



ROC: ROC plot using apoe4, Age, sVCAM, PPY, I309, ApoJ, SAA and CRP. A similar sensitivity and specificity was seen at all three time points at approx 78-79%, with AUC ~85%.

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Correlation with PiB-load

Biomarkers	Correlation with MCI	Correlation with AD
TPO	0.315 (BL), 0.563 (18M)	
FABP3	0.522 (BL), 0.434 (18M)	0.399 (36M)
PPY	0.345 (BL), 0.328 (18M)	
I309	0.354 (BL)	
B2M	0.237(BL)	
Adipo	0.258 (18M), 0.382 (36M)	
A2M	0.235 (36M)	
ApoJ	-0.265 (36M)	-0.294(18M)

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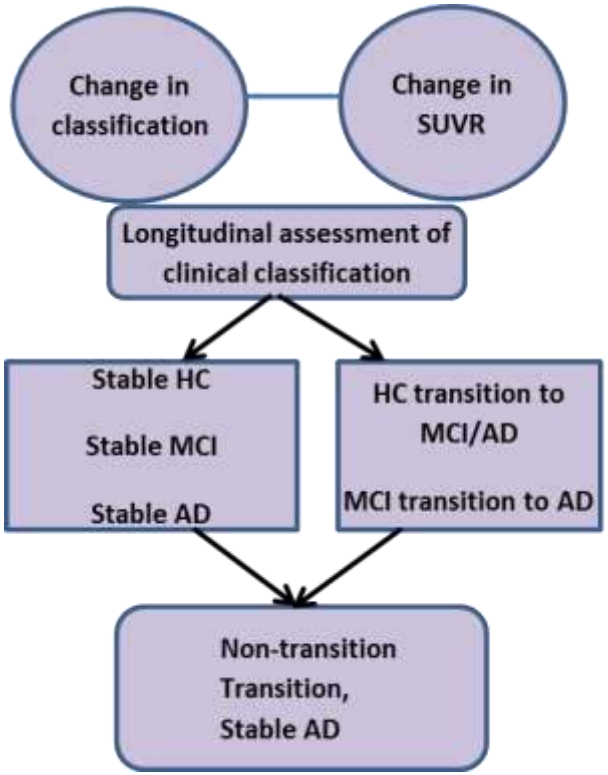
Transitional vs. non-transitional biomarkers

	Baseline			18 months			36 months			
	non-transition	Stable AD	Transition	non-transition	Stable AD	Transition	non-transition	Stable AD	Transition	p-value
Count	554	92	65	538	92	80	459	57	76	
Age (Mean SD)	69.79 (6.51)	77.01 (7.43)	74.84 (7.54)	71.12 (6.37)	78.53 (7.49)	76.71 (7.63)	72.74 (6.41)	79.79 (6.81)	77.37 (7.26)	<0.0001
Gender (F/M)	330/224	52/40	36/29	325/213	52/40	41/39	277/182	31/26	40/36	
ApoE4 (-ve/+ve)	401/153	28/64	32/33	392/146	28/64	41/39	337/122	16/41	36/40	<0.0001
MMSE (Median IQR)	29 (2)	21 (4.25)	27 (3)	29 (2)	18 (7)	26 (3)	29 (2)	13 (9)	25.5 (4.25)	<0.0001
SUVR (N)	127	21	32	114	15	29	84	6	30	
SUVR (Mean SD)	1.36 (0.38)	2.29 (0.5)	2.02 (0.57)	1.34 (0.36)	2.3 (0.52)	2.1 (1.34)	1.41 (0.39)	2.29 (0.7)	2.09 (0.69)	<0.0001
Hip Vol (N)	116	15	26	108	13	26	73	4	24	
Hip Vol (Mean SD)	0.0041 (0.00031)	0.0036 (0.00034)	0.0038 (0.00047)	0.0041 (0.00032)	0.0035 (0.0003596)	0.0037 (0.00353)	0.0041 (0.00033)	0.0034 (0.00051)	0.0037 (0.00059)	<0.0001



Rembach et al., 2013; J Alz Dis; 40: 95-104.

Biomarkers	Non-transition vs. Stable AD	Non-Transition vs. Transition
	Adjusted	Adjusted
PPY	0.007 (BL), 0.001 (18M),0.04 (36M)	0.032 (BL)
I309	0.018 (BL)	
TPO	0.019 (18M)	0.006 (18M)
SAA	0.049 (BL), 0.001 (18M)	0.010 (18M)
sVCAM	0.037 (BL), 0.001 (36M)	0.006 (36M)
Adipo	0.0016 (18M)	

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