Alzheimer's disease biomarker characteristics in cognitively normal longitudinally followed subjects with memory, executive and multi-domain subtle cognitive impairment

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e-methods

ADNI cohort

The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California –San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.
Inclusion criteria were as follows: 1) Hachinski Ischemic Score ≤4; 2) Permitted medications stable for 4 weeks prior to screening; 3) Geriatric Depression Scale score < 6; 4) visual and auditory acuity adequate for neuropsychological testing; good general health with no diseases precluding enrollment; 5) 6 grades of education or work history equivalent; 6) Ability to speak English or Spanish fluently; 7) A study partner with 10 hours

per week of contact either in person or on the telephone and who could accompany the participant to the clinical visits. HC had to score 24-30 in mini-mental state examination, 0 in the clinical dementia rating and be above years of education (YoEd) adjusted delayed memory recall cut-offs (16 YoEd: ≥9, 8–15 YoEd: ≥5 and 0-7 YoEd: ≥3).

CSF collection and AB_{1-42} measurement

CSF was collected into polypropylene collection tubes or syringes provided to each site, transferred into polypropylene transfer tubes without any centrifugation step followed by freezing on dry ice within 1 hr after collection, and overnight shipment to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center on dry ice. The samples were thawed for 1 hour at room temperature, gently mixed and divided into aliquots (0.5 ml). The aliquots were stored in bar code–labeled polypropylene vials at -80°C. The analyte-specific detection antibodies were HT7, for tau, and 3D6, for the N-terminus of Aβ [1].

Table e-1. Criteria for classifying ADNI subjects into the different CN, preclinical AD stages described in this study.

	Abnormal Aβ	Abnormal Neuronal Injury	Abnormal Cognitive Changes
Stage 0	-	-	-
Stage 1	+	-	-
Stage 2	+	+	-
Stage 3	+	+	+
SNAP	-	+	±
SCINIB	±	-	+

SCINIB: Subjective cognitive impairment with normal neuronal injury biomarkers; SNAP: Suspected non-amyloid pathology.

+: Abnormal; -: Normal; ±: Normal or abnormal.

Table e-2. Characteristics of the subjects included in the study, including the language SCI category.

	CN	SMC	Executive SCI	Memory SCI	Multi-domain SCI	Language SCI	p-value
5th Percentile	(n=294)	(n=71)	(n=40)	(n=64)	(n=40)	(n=13)	
Age (years)*	73.9 (5.5)	71.6 (5.2)	77.0 (5.2)	74.9 (6.4)	78.0 (5.8)	73.7 (5.7)	<0.0001[a,b,d]
Gender (% male)	45.9%	35.2%	47.5%	73.4%	60.0%	23.1%	0.0001[c,d]
APOE ε4 (%)	26.6%	33.8%	27.5%	30.0%	27.5%	38.5%	0.79
SMC	-	-	28.3%	21.1%	22.2%		1.0
ADAS-Cog†	8.0 (5.1-10.0)	7.0 (5.0-9.0)	10.3 (8.0-13.0)	13.0 (11.0-15.0)	14.7 (10.9-16.5)	7.3 (6.3-11.0)	<0.0001[b,c,d]
MMSE†	29.0 (29.0-30.0)	29.0 (29.0-30.0)	29.0 (29.0-30.0)	29.0 (28.0-30.0)	28.0 (27.0-29.3)	29.0 (28.0-30.0)	0.0001[c,d,e]
Memory†	1.06 (0.78-1.39)	1.07 (0.84-1.37)	0.84 (0.63-1.04)	0.30 (0.15-0.44)	0.32 (0.07-0.51)	0.74 (0.64-0.93)	<0.0001 [b,c,d,e]
Executive†	0.92 (0.54-1.44)	0.92 (0.48-1.33)	-0.20 [(-0.36)-(-0.09)]	0.63 (0.28-0.94)	-0.29 [(-0.59)-(-0.14)]	0.92 (0.48-1.33)	<0.0001 [b,c,d]
10th Percentile	(n=260)	(n=63)	(n=50)	(n=59)	(n=75)	(n=15)	
Age (years)*	73.6 (5.4)	71.5 (5.2)	76.5 (5.0)	74.3 (5.8)	77.5 (6.1)	72.7 (6.8)	<0.0001[a,b,d]
Gender (% male)	44.2%	34.9%	44.0%	76.3%	60.0%	26.7%	<0.0001[c,d]
APOE ε4 (%)	27.8%	31.7%	30.0%	25.5%	29.3%	26.7%	0.98
SMC	-	-	26.0%	27.1%	16.0%	13.3%	0.32
ADAS-Cog†	7.2 (5.0-10.0)	6.0 (5.0-9.0)	9.3 (7.0-11.6)	12.3 (11.0-14.2)	14.0 (10.7-16.0)	7.3 (6.7-9.3)	<0.0001[b,c,d]
MMSE†	29.0 (29.0-30.0)	29.0 (29.0-30.0)	29.0 (29.0-30.0)	29.0 (29.0-30.0)	29.0 (27.5-29.0)	29.0 (28.0-30.0)	<0.0001[d,e]
Memory†	1.10 (0.82-1.42)	1.14 (0.86-1.43)	0.92 (0.76-1.13)	0.37 (0.21-0.48)	0.44 (0.20-0.55)	0.80 (0.68-0.94)	<0.0001 [b,c,d,e]
Executive†	1.00 (0.58-1.51)	0.95 (0.58-1.41)	-0.09 [(-0.23)-(0.08)]	0.74 (0.58-1.17)	-0.08 [(-0.48)-(0.08)]	0.37 (0.30-0.65)	<0.0001 [b,c,d,e]

ADAS-Cog : Alzheimer's Disease Assessment Scale - Cognitive Subscale; CN: Cognitively normal; MMSE: Mini Mental State Examination; SCI: Subtle cognitive impairment; SMC: Subjective memory complaints;

*Mean (standard deviation); †Median (1st quartile-3rd quartile). [a]CN and SMC comparison $p<0.05$; [b]CN and executive SCI comparison $p<0.05$; [c]CN and memory SCI comparison $p<0.05$; [d]CN and multi-domain SCI comparison $p<0.05$; [e]CN and language SCI comparison $p<0.05$. p-values in the last columns were based on ANOVA except gender and *APOE* which were based on fisher exact test.

Table e-3. Amyloid burden and neurodegeneration biomarkers in CN, SMC and the different SCI categories, including language SCI.

	CN	SMC	Ex. SCI	Mem. SCI	MD SCI	Lang. SCI	p-value CN vs. SMC	p-value CN vs. Ex. SCI	p-value CN vs. Mem.SCI	p-value CN vs. MD SCI	p-value CN vs. Lang. SCI
5th Percentile											
CSF $A\beta_{1-42}$	211.8 (169.4-241.6)	213.0 (160.0-242.7)	207.9 (159.0-243.5)	196.4 (148.0-233.5)	171.2 (137.5-213.1)	231.5 (172.4-257.9)	0.77	0.92	0.059	0.009	0.38
CSF T-Tau	56.4 (45.0-81.3)	59.7 (45.0-80.2)	68.5 (48.7-92.4)	67.0 (49.9-89.3)	58.4 (40.8-81.3)	55.1 (48.0-72.9)	0.85	0.67	0.42	0.076	0.72
CSF P-Tau_{181}	24.4 (18.8-39.4)	30.9 (23.6-46.7)	29.3 (23.5-43.1)	30.6 (20.4-38.7)	27.4 (17.3-34.6)	16.8 (15.1-29.3)	0.0008	0.15	0.28	0.57	0.079
MRI-aHV	743.2 (159.5-1271.1)	783.5 (439.6-1374.5)	645.1 (124.4-1157.0)	755.1 (30.5-1374.4)	567.7 [(-116.5)-(1003.2)]	1057.3 [(-601.3)-(1373.4)]	0.42	0.89	0.82	0.91	0.78
MRI-SPARE-AD	-1.4 [(-1.8)-(-1.1)]	-1.1 [(-1.6)-(-0.7)]	-1.2 [(-1.5)-(-0.7)]	-1.2 [(-1.6)-(-0.9)]	-0.9 [(-1.4)-(-0.5)]	-1.6 [(-1.8)-(-0.8)]	0.002	0.23	0.013	0.003	0.49
WMH	0.20 (0.08-0.58)	-	0.36 (0.12-0.70)	0.22 (0.09-0.37)	0.34 (0.25-0.73)	0.20 (0.07-0.27)	-	0.50	0.96	0.14	0.50
Posterior cingulate PET	2.1 (2.0-2.2)	-	2.0 (1.9-2.1)	2.1 (1.9-2.2)	2.0 (1.9-2.0)	2.0 (2.0-2.1)	-	0.026	0.40	0.049	0.42
PET-HCI	8.5 (6.8-10.6)	5.6 (5.2-6.9)	8.9 (7.2-11.4)	8.1 (7.0-11.2)	10.2 (7.8-16.3)	8.8 (5.7-12.2)	0.084	0.69	0.69	0.075	0.70
10th Percentile											
CSF $A\beta_{1-42}$	211.8 (166.6-243.5)	213.0 (160.0-243.5)	203.0 (156.2-245.7)	196.4 (147.5-235.5)	171.2 (137.5-194.5)	171.2 (137.5-194.5)	0.75	0.10	0.11	0.005	

CSF T-Tau	56.4 (44.6-78.0)	57.0 (43.5-80.4)	63.6 (49.8-86.4)	63.6 (45.9-79.2)	63.5 (42.8-98.8)	63.5 (42.8-98.8)	0.95	0.72	0.63	0.40
CSF P-Tau$_{181}$	24.1 (18.3-37.9)	30.3 (23.6-47.5)	28.5 (22.0-43.4)	31.4 (19.7-42.7)	28.3 (19.6-36.3)	28.3 (19.6-36.3)	0.0008	0.054	0.08	0.76
MRI-aHV	778.5 (179.5-1297.1)	763.4 (408.3-1359.3)	675.2 (151.2-1196.7)	908.0 (306.7-1379.7)	148.7 [(-222.0)-(860.8)]	148.7 [(-222.0)-(860.8)]	0.60	0.59	0.84	0.11
MRI-SPARE-AD	-1.4 [(-1.8)-(-1.1)]	-1.1 [(-1.6)-(-0.7)]	-1.1 [(-1.5)-(-0.6)]	-1.3 [(-1.6)-(-1.0)]	-1.1 [(-1.7)-(-0.5)]	-1.1 [(-1.7)-(-0.5)]	0.001	0.038	0.059	0.039
WMH	0.22 (0.08-0.58)	-	0.27 (0.11-0.57)	0.23 (0.08-0.39)	0.28 (0.18-0.62)	0.28 (0.18-0.62)	-	0.98	0.84	0.55
Posterior cingulate PET	2.1 (2.0-2.2)	-	2.1 (2.0-2.1)	2.1 (1.9-2.2)	2.0 (1.9-2.0)	2.0 (1.9-2.0)	-	0.24	0.70	0.019
PET-HCI	8.6 (6.7-10.7)	5.5 (5.2-6.3)	8.6 (7.3-10.2)	8.2 (6.9-12.1)	10.3 (7.0-14.6)	10.3 (7.0-14.6)	0.03	0.99	0.80	0.06

aHV: Adjusted hippocampal volume; CN: Cognitively normal; CSF: Cerebrospinal fluid; Ex.: Executive; Lang.: Language; MD: Multi-domain; Mem.: Memory; PET-HCI: PET hypometabolic convergence index; SCI: Subtle cognitive impairment; SMC: Subjective memory complaints; MRI-SPARE-AD: MRI Spatial Pattern of Abnormalities for Recognition of Early Alzheimer's disease; WMH: White matter hyperintensities.

Linear regression models are adjusted for age and gender.

Table e-4. Amyloid burden and neuronal injury biomarkers in CN, SMC and the different SCI categories using only subjects who had the different biomarker measurements available.

	CN	Ex. SCI	Mem. SCI	MD SCI	p-value CN vs.		
					Ex. SCI	Mem.SCI	MD SCI
5th Percentile	(n=145)	(n=16)	(n=29)	(n=16)			
CSF $A\beta_{1-42}$	213.0 (168.0-240.9)	210.0 (162.6-245.7)	198.0 (147.0-229.1)	165.7 (137.5-195.0)	0.94	0.13	0.01
CSF T-Tau	54.8 (44.6-77.8)	61.9 (49.4-88.5)	70.3 (50.0-90.1)	60.2 (41.4-90.8)	0.93	0.28	0.29
CSF P-Tau_{181}	25.8 (19.5-41.8)	26.6 (19.8-34.8)	32.3 (21.5-37.1)	28.3 (20.1-33.4)	0.98	0.75	0.31
MRI-aHV	607.5 (132.2-1210.3)	728.8 (438.3-1056.0)	909.1 (60.5-1419.3)	139.5 [(-178.0)-(928.7)]	0.20	0.37	0.56
MRI-SPARE-AD	-1.4 [(-1.7)-(-1.2)]	-1.2 [(-1.5)-(-0.6)]	-1.1 [(-1.6)-(-0.7)]	-0.9 [(-1.4)-(-0.6)]	0.082	0.0081	0.011
PET-HCI	8.4 (6.7-10.5)	7.9 (6.6-9.3)	7.8 (6.5-10.6)	10.6 (7.8-14.7)	0.88	0.81	0.064
10th Percentile	(n=127)	(n=25)	(n=29)	(n=27)			
CSF $A\beta_{1-42}$	211.8 (166.6-243.5)	203.0 (156.2-245.7)	196.4 (147.5-235.5)	171.2 (137.5-194.5)	0.10	0.11	0.005
CSF T-Tau	56.4 (44.6-78.0)	63.6 (49.8-86.4)	63.6 (45.9-79.2)	63.5 (42.8-98.8)	0.72	0.63	0.40
CSF P-Tau_{181}	24.1 (18.3-37.9)	28.5 (22.0-43.4)	31.4 (19.7-42.7)	28.3 (19.6-36.3)	0.054	0.08	0.76
MRI-aHV	778.5 (179.5-1297.1)	675.2 (151.2-1196.7)	908.0 (306.7-1379.7)	148.7 [(-222.0)-(860.8)]	0.59	0.84	0.11
MRI-SPARE-AD	-1.4 [(-1.8)-(-1.1)]	-1.1 [(-1.5)-(-0.6)]	-1.3 [(-1.6)-(-1.0)]	-1.1 [(-1.7)-(-0.5)]	0.038	0.059	0.039
PET-HCI	8.4 (6.7-10.6)	8.5 (7.2-9.6)	7.8 (6.1-10.9)	9.5 (7.0-13.5)	0.96	0.84	0.24

aHV: Adjusted hippocampal volume; CN: Cognitively normal; CSF: Cerebrospinal fluid; Ex.: Executive; Lang.: Language; MD: Multi-domain; Mem.: Memory; PET-HCI: PET hypometabolic convergence index; SCI: Subtle cognitive impairment; SMC: Subjective memory complaints; MRI-SPARE-AD: MRI Spatial Pattern of Abnormalities for Recognition of Early Alzheimer's disease; WMH: White matter hyperintensities.

Linear regression models are adjusted for age and gender.

Table e-5. Classification into preclinical dementia stages including language SCI.

Preclinical AD Stage	CN	SMC	Executive SCI	Memory SCI	Language SCI	Multi-domain SCI
5th Percentile						
Stage 0	69 (37.5%)	12 (35.3%)	-	-	-	-
Stage 1	27 (14.7%)	7 (20.6%)	-	-	-	-
Stage 2	40 (21.7%)	9 (26.5%)	-	-	-	-
Stage 3	-	-	9 (42.9%)	12 (37.5%)	1 (14.3%)	10 (55.6%)
SNAP	48 (26.1%)	6 (17.6%)	6 (28.6%)	7 (21.9%)	2 (28.6%)	3 (16.7%)
SCINIB	-	-	6 (28.6%)	13 (40.6%)	4 (57.1%)	5 (27.8%)
Total	184 (100%)	34 (100%)	21 (100%)	32 (100%)	7 (100%)	18 (100%)
10th Percentile						
Stage 0	63 (39.1%)	11 (36.7%)	-	-	-	-
Stage 1	24 (14.9%)	4 (13.3%)	-	-	-	-
Stage 2	33 (20.5%)	9 (30.0%)	-	-	-	-
Stage 3	-	-	11 (44.0%)	11 (37.9%)	1 (14.3%)	16 (42.1%)
SNAP	41 (25.5%)	6 (20.0%)	8 (32.0%)	4 (13.8%)	2 (28.6%)	11 (28.9%)
SCINIB	-	-	6 (24.0%)	14 (48.3%)	4 (57.1%)	1 (28.9%)
Total	161 (100%)	30 (100%)	25 (100%)	29 (100%)	7 (100%)	38 (100%)

AD: Alzheimer's disease; CN: Cognitively normal; SCI: Subtle cognitive impairment; SCINIB: Subjective cognitive impairment with normal neuronal injury biomarkers; SMC: Subjective memory complaints; SNAP: Suspected non-amyloid pathology.

Figure e-1. Subjects with a CN diagnosis in each visits and number of conversion from CN to MCI or CN to AD in each follow-up visit.

	Remain CN	MCI conversion	AD conversion
Bl	ADNI 1: 229 ADNI GO/2: 293		
6m	ADNI 1: 222 ADNI GO/2: 275	2	
12m	ADNI 1: 215 ADNI GO/2: 200	4	
24m	ADNI 1: 209 ADNI GO/2: 146	9	
36m	ADNI 1: 186 ADNI GO/2: 5	7	1
48m	ADNI 1: 137 ADNI GO/2: 2	5	
60m	ADNI 1: 122	3	
72m	ADNI 1: 112	6	
84m	ADNI 1: 89	12	1
96m	ADNI 1: 45	9	1

References

1. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI. Acta neuropathologica 2011;121:597-609.