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Supplementary webappendix

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Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

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Supplemental Table 1. Baseline demographics of the independent CDR 0·5 symptomatic AD sample (N=74)

Age	74·5 (5·4)
Female, n	36 (49%)
Education, y	14·5 (3·1)
Ethnic origin, n	
White	71 (96%)
African-American	2 (3%)
Native Hawaiian and Pacific Islander	1 (1%)
APOE-ε4+, n	51 (69%)
MMSE	25·9 (3·0)
CDR-SB	2·5 (1·0)
Episodic memory, z-score	-1·6 (1·0)
Aβ1-42, pg/mL	424 (219)
T-tau, pg/mL	607 (293)
P-tau181, pg/mL	97 (48)

Results are mean (SD) or number (%). Episodic memory is a composite score of the Associate Learning Test, Logical Memory Test, and Selective Reminding Test. AD=Alzheimer's disease, *APOE*=Apolipoprotein E, MMSE=Mini-Mental State Examination (range 0-30, with 30 as the best score), CDR-SB=Clinical Dementia Rating scale Sum of Boxes (range 0-16, with 0 as the best score), Aβ=beta amyloid, p-tau=phosphorylated tau, t-tau=total tau.

Supplementary Table 2. Overview of concepts for mild cognitive impairments

Construct	Definition			
	Psychometric test impairment	Functional impairment	Clinical dementia diagnosis according to DSM IV or ICD-10	Biomarker status
CDR 0·5 symptomatic AD[1]	Defined cut-offs not utilized	Very mild to mild change in daily functioning in memory and at least 1 non-memory domain	Some	Not needed
Amnestic MCI[2]	Yes, in memory domain	Subjective report of cognitive decline	No	Not needed
MCI due to AD[3]	Yes, in any cognitive domain	Cognitive concern reflecting a change in cognition	No	Abnormal
Prodromal AD[4]	Yes, in memory domain	Complaints of memory decline	No	Abnormal

References

1. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993; **43:** 2412–14.
2. Petersen RC. Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine* 2004; **256:** 183–94.
3. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup. *Alzheimers Dement* 2011; **7:** 270–9.
4. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007; **6:** 734–46.

Supplemental Table 3. Exact p-values for the pairwise comparisons of Table 1.

	Normal vs. stage 1	Normal vs. stage 2	Normal vs. stage 3	Normal vs. SNAP	Normal vs. unclassified	Stage 1 vs. stage 2	Stage 1 vs. stage 3	Stage 1 vs. SNAP	Stage 1 vs. unclassified	Stage 2 vs. stage 3	Stage 2 vs. SNAP	Stage 2 vs. unclassified	Stage 3 vs. SNAP	Stage 3 vs. unclassified	SNAP vs. unclassified
Age	0·0007	0·0003	<0·0001	0·0003	<0·0001	0·6531	0·0146	0·8184	0·0084	0·0393	0·4849	0·0254	0·0074	0·9222	0·0039
Female	0·3678	0·4333	0·0859	0·6665	0·1451	0·1763	0·2501	0·2482	0·3864	0·0465	0·6756	0·0778	0·0627	0·7855	0·1060
Education	0·0004	0·7729	0·2942	0·7115	0·3502	0·0127	0·0037	0·0033	0·0044	0·2665	1·000	0·3138	0·2329	0·9123	0·2775
APOE-ε4	0·0059	0·0045	0·0025	0·3787	0·7804	0·7731	0·1601	0·0744	0·1008	0·2380	0·0507	0·0758	0·0125	0·0173	0·4943
MMSE	0·0101	0·2195	<0·0001	0·5203	0·0101	0·3397	0·0024	0·0646	0·3532	0·0003	0·5019	0·1159	<0·0001	0·0791	0·0308
CDR-SB	0·3347	0·8380	0·1167	0·8884	0·7059	0·5697	0·3502	0·3239	0·8482	0·1961	0·7719	0·8300	0·1134	0·3621	0·6642
Episodic memory	0·8437	0·2302	<0·0001	0·6128	<0·0001	0·2409	<0·0001	0·5646	<0·0001	<0·0001	0·4567	<0·0001	<0·0001	0·0671	<0·0001
Aβ1-42	<0·0001	<0·0001	<0·0001	0·0396	0·1847	0·8954	0·5672	<0·0001	<0·0001	0·6425	<0·0001	<0·0001	<0·0001	<0·0001	0·0209
T-tau	0·5470	<0·0001	<0·0001	<0·0001	0·5634	<0·0001	<0·0001	<0·0001	0·8438	0·3126	0·0004	<0·0001	0·0005	<0·0001	<0·0001
P-tau181	0·9111	<0·0001	<0·0001	<0·0001	0·1929	<0·0001	<0·0001	<0·0001	0·2537	0·7014	0·0638	<0·0001	0·0955	<0·0001	<0·0001
Follow-up	0·6396	0·7969	0·1251	0·9818	0·8928	0·5625	0·0934	0·6575	0·8906	0·2185	0·8249	0·7838	0·1415	0·2084	0·8876
Progression to CDR≥0·5	0·0077	0·0002	<0·0001	0·1338	0·0005	0·1575	0·0033	0·1770	0·1716	0·0641	0·0069	0·7962	0·0001	0·1875	0·0145
Mortality	0·0180	0·0604	0·0003	0·0673	0·2077	0·7250	0·0850	0·4808	0·7018	0·0623	0·7953	0·8893	0·0187	0·1436	0·9787

Results are p-values of pairwise comparisons of Table 1. Aβ= amyloid-beta, *APOE*=Apolipoprotein E, CDR-SB=Clinical Dementia Rating scale Sum of Boxes, MMSE=Mini-Mental State Examination, p-tau=phosphorylated tau, SNAP=Suspected Non-Alzheimer Pathophysiology, t-tau= total tau.

Supplemental Table 4. Distribution of preclinical AD stages

Stage	CSF Aβ1-42 <459 pg/mL	CSF t-tau >339 pg/mL	CSF p-tau181 >67 pg/mL	Cognition <-1·25 SD	N (%)	Overall N (%)
Normal group	-	-	-	-	129 (41·5)	129 (41·5)
Stage 1	+	-	-	-	47 (15)	47 (15)
Stage 2	+	+	-	-	8 (3)	36 (12)
	+	-	+	-	5 (2)	
	+	+	+	-	23 (7)	
Stage 3	+	+	-	+	1 (0·5)	13 (4)
	+	+	+	+	12 (3·5)	
SNAP group	-	+	-	-	14 (4·5)	72 (23)
	-	+	-	+	2 (0·5)	
	-	-	+	-	9 (3)	
	-	+	+	-	45 (14·5)	
	-	+	+	+	2 (0·5)	
Unclassified	-	-	-	+	11 (3·5)	14 (4·5)
	+	-	-	+	3 (1)	

Results are number (%) of participants identified in the different stages based on CSF markers with optimal Youden cut-offs: Abnormal CSF Aβ1-42 <459 pg/mL, t-tau >339 pg/mL, p-tau181 >67 pg/mL. Cognition was an episodic memory composite score of the Associate Learning Test, Logical Memory Test, and Selective Reminding Test, with a cut-off at the lowest 10^{th} percentile: -1·25 SD. Aβ=beta amyloid, AD=Alzheimer's disease, p-tau=phosphorylated tau, SNAP=Suspected Non-Alzheimer Pathophysiology, t-tau=total tau.

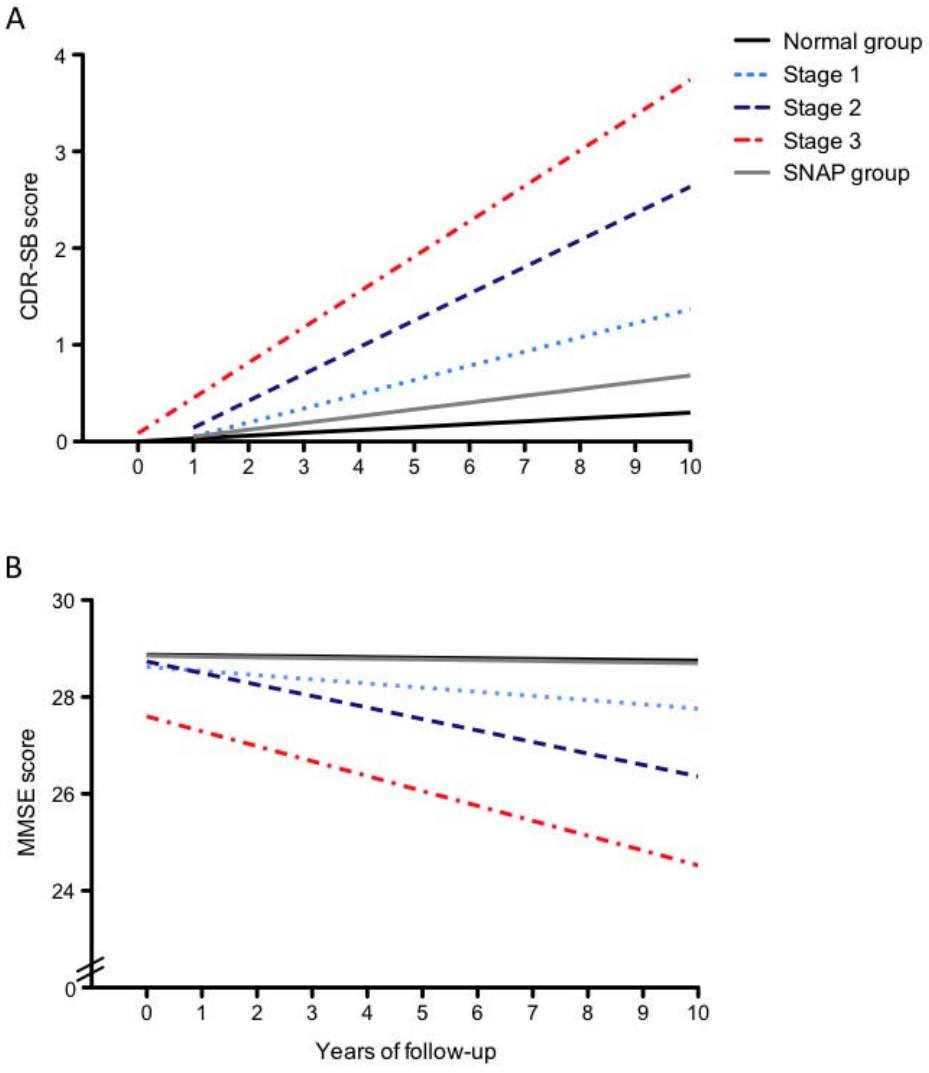
Supplemental Table 5. Preclinical AD and its outcome according to age and *APOE* genotype

A	**Baseline prevalence**		**Progression to CDR≥0·5 symptomatic AD**	
	Age ≤72 (n=169)	**Age >72 (n=142)**	**Age ≤72 (n=6)**	**Age >72 (n=25)**
No preclinical AD	125 (74%)	90 (64·5%)*	1 (1%)	9 (10%)
Normal group	90 (53·5%)	39 (27·5%)	0 (0%)	2 (5%)
SNAP group	31 (18·5%)	41 (29%)	1 (3%)	3 (7%)
Unclassified	4 (2%)	10 (7%)	0 (0%)	4 (40%)
Preclinical AD	44 (26%)	52 (36·5%)	5 (11%)	17 (33%)
Stage 1	25 (15%)	22 (15·5%)	1 (4%)	5 (23%)
Stage 2	17 (10%)	19 (13%)	2 (12%)	7 (37%)
Stage 3	2 (1%)	11 (8%)	2 (100%)	5 (45·5%)
B	**Baseline prevalence**		**Progression to CDR≥0·5 symptomatic AD**	
	***APOE*-ε4- (n=205)**	***APOE*-ε4+ (n=106)**	***APOE*-ε4- (n=18)**	***APOE*-ε4+ (n=13)**
No preclinical AD	158 (77%)	57 (53%)***	7 (4%)	3 (5%)
Normal group	97 (47%)	32 (30%)	2 (2%)	0 (0%)
SNAP group	50 (24·5%)	22 (21%)	2 (4%)	2 (9%)
Unclassified	11 (5·5%)	3 (2%)	3 (27%)	1 (33%)
Preclinical AD	47 (23%)	49 (47%)	11 (23%)	11 (22%)
Stage 1	25 (12%)	22 (21%)	2 (8%)	4 (18%)
Stage 2	18 (9%)	18 (17%)	6 (33%)	3 (17%)
Stage 3	4 (2%)	9 (9%)	3 (75%)	4 (44%)

Data are baseline number (%) of participants with and without preclinical AD, and number (%) of these participants that progressed to CDR≥0·5 symptomatic AD by dichotomous age (A) and *APOE* genotype (B) grouping. AD=Alzheimer's disease, *APOE*=Apolipoprotein E, CDR=Clinical Dementia Rating scale, SNAP=Suspected Non-Alzheimer Pathophysiology. *P<0·05 compared to age ≤72, ***p<0·001 compared to *APOE*-ε4-, based on Chi-squared tests for 2 by 2 tables.

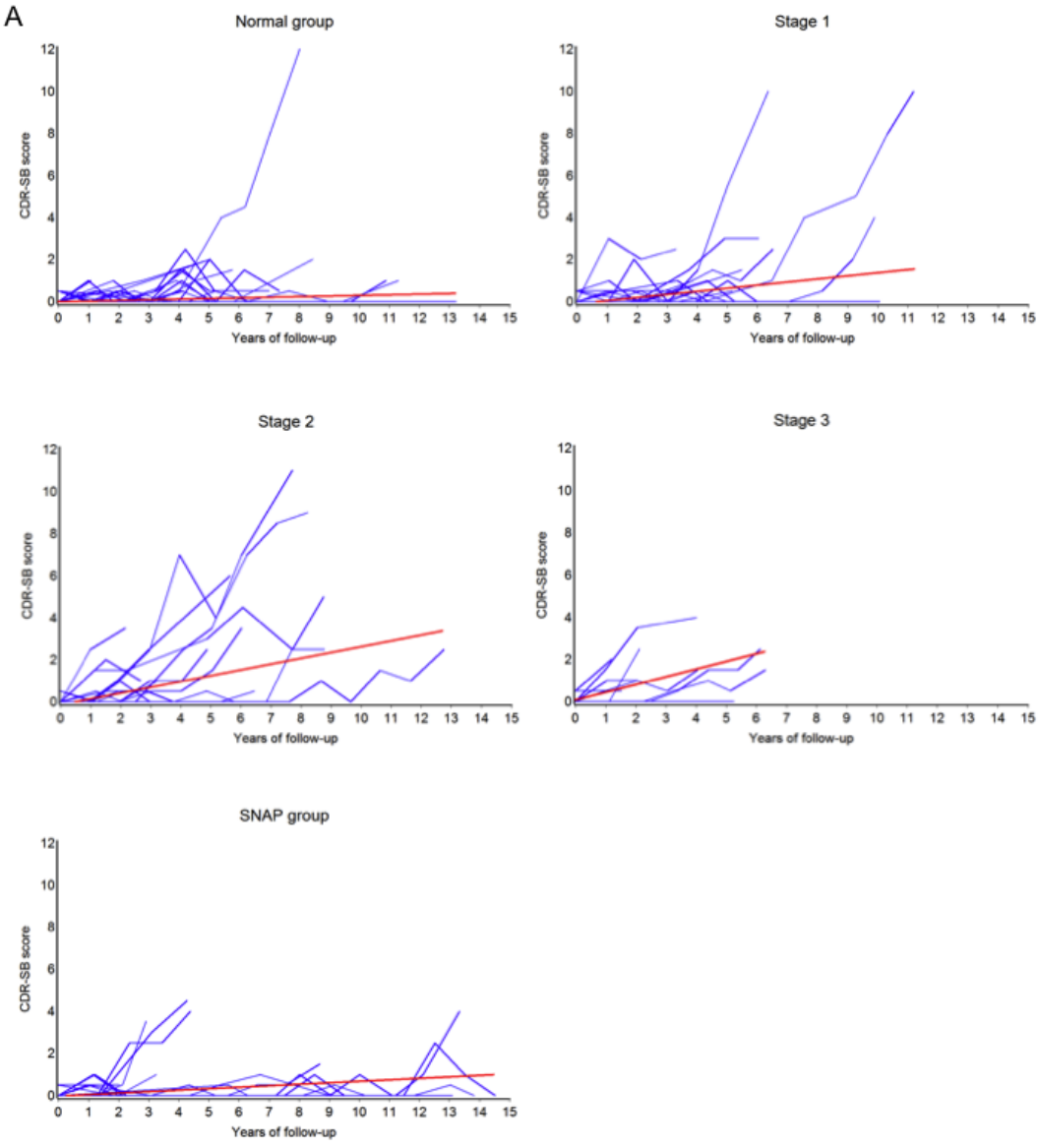
Supplemental Figure 1. Annual rate of change in CDR-SB and MMSE by preclinical AD stage

Figure legend:
Graphs show the estimated annual rate of change in CDR-SB (A) and MMSE (B), based on slopes according to each preclinical AD stage, corrected for age, gender, education, and *APOE* genotype. The black line represents participants in the normal group; light blue, stage 1; dark blue, stage 2; red, stage 3; and grey, SNAP. CDR-SB=Clinical Dementia Rating scale Sum of Boxes (range 0-18, with 0 as the best score), MMSE=Mini-Mental State Examination (range 0-30, with 30 as the best score).

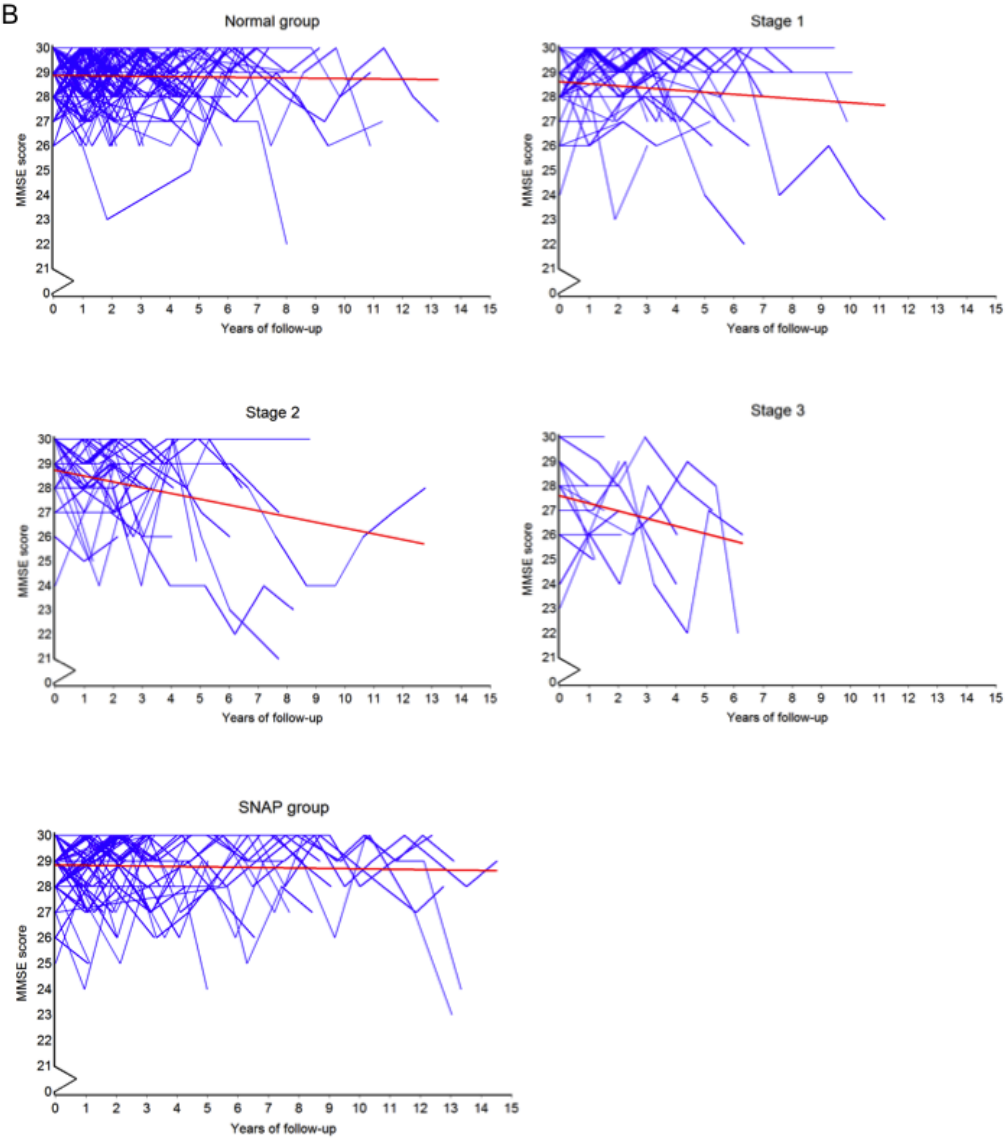


Supplemental Figure 2. Individual cognitive trajectories for CDR-SB and MMSE by preclinical AD stage

Figure legend:
Graphs show individual cognitive trajectories (blue) and the overall estimated annual rate of change (red) for CDR-SB (A) and MMSE (B) by preclinical AD stage. CDR-SB=Clinical Dementia Rating scale Sum of Boxes (range 0-18, with 0 as the best score), MMSE=Mini-Mental State Examination (range 0-30, with 30 as the best score), SNAP= Suspected Non-Alzheimer Pathophysiology.



B


Normal group
Stage 1
Stage 2
Stage 3
SNAP group
MMSE score
Years of follow-up

Supplemental Text 1. Cohort information

The overall rate of progression from CDR 0 to CDR 0.5 or greater in our sample was 10% (32/311) over an average of 4 years of follow-up. This percent is comparable to the Mayo Clinic Study of Aging (MCSA), a population based longitudinal program in which many participants have multiple imaging procedures and some have lumbar puncture. The overall rate of progression from cognitive normality to MCI in the MCSA sample was 20% (296/1450) with a median follow-up of 3·4 years, but the MCI construct in the MCSA program was unstable as 34% of MCI individuals reverted to cognitive normality at subsequent follow-up.[1] Removing the MCSA individuals who later reverted to normal leaves 196 of the 1450 (13·5%) cognitively normal persons who developed MCI/symptomatic AD, very similar to our 10%.

References

1. Roberts RO, Geda YE, Knopman DS, et al. The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. *Neurology* 2012; **78**: 342–51.

Supplemental Table 6. Preclinical AD and its outcome using different classification approaches

A) Use of different CSF cutoffs; Aβ1-42 <500, t-tau <440, p-tau181 <78 pg/ml

	Normal group	Stage 1	Stage 2	Stage 3	SNAP group	Unclassified group
Proportion stages, n	131 (42%)	85 (27%)	28 (9%)	13 (4%)	37 (12%)	17 (6%)
Progression to CDR≥0·5 symptomatic AD, n	2 (1.5%)	9 (11%)	7 (25%)	7 (54%)	2 (5%)	5 (29%)
Mortality, n	1 (1%)	7 (8%)	3 (11%)	4 (31%)	4 (11%)	1 (6%)

B) Stage 3 defined as a score in the lowest 10th percentile of any cognitive domain

	Normal group	Stage 1	Stage 2	Stage 3	SNAP group	Unclassified group
Proportion stages, n	104 (33%)	37 (12%)	28 (9%)	21 (7%)	71 (23%)	50 (16%)
Progression to CDR≥0·5 symptomatic AD, n	2 (2%)	6 (16%)	8 (29%)	8 (38%)	4 (6%)	4 (8%)
Mortality, n	0 (0%)	5 (14%)	1 (4%)	6 (29%)	4 (6%)	4 (8%)

C) Participants with a baseline CDR-SB of 0·5 excluded (n=293)

	Normal group	Stage 1	Stage 2	Stage 3	SNAP group	Unclassified group
Proportion stages, n	123 (42%)	43 (15%)	34 (12%)	11 (4%)	69 (24%)	13 (4%)
Progression to CDR≥0·5 symptomatic AD, n	2 (2%)	6 (14%)	9 (27%)	6 (55%)	4 (6%)	3 (23%)
Mortality, n	2 (2%)	5 (12%)	2 (6%)	4 (36%)	4 (6%)	0 (0%)

Results are number (%) for (A) previously applied CSF cut-offs of our center, (B) a different definition of stage 3 based on the episodic memory, semantic memory, working memory, and visuospatial composite score (described in Johnson et al 2009), and (C) only participants with CDR-SB=0 at baseline. AD=Alzheimer's disease, CDR-SB=Clinical Dementia Rating scale Sum of Boxes (range 0-18, with 0 as the best score), CSF=cerebrospinal fluid, SNAP= Suspected Non-Alzheimer Pathophysiology.

Supplemental Table 7. Prediction of the unclassified group for CDR≥0·5 symptomatic AD, mortality, and annual cognitive decline

A) Prediction of the unclassified group for CDR≥0·5 symptomatic AD and mortality

	Progression to CDR≥0·5 symptomatic AD					Mortality risk			
	5-year progression rate	Uncorrected SHR (95% CI)	Difference compared to normal group	Corrected SHR (95% CI)	Difference compared to normal group	Uncorrected HR (95% CI)	Difference compared to normal group	Corrected HR (95% CI)	Difference compared to normal group
Normal group	2%	Reference		Reference		Reference		Reference	
Unclassified group	34%	24·2 (4·7-125·5)	P=0·0002	16·4 (2·8-95·8)	P=0·0019	5·3 (0·5-59·9)	P=0·1749	2·8 (0·2-36·9)	P=0·4305

Results are 5-year progression rate (cumulative incidence rate) to CDR≥0·5 symptomatic AD and associated subhazard ratio (SHR, 95% CI) for progression to CDR≥0·5 symptomatic AD calculated using a Fine & Gray subdistribution hazards model, and hazard ratio (HR, 95% CI) for mortality calculated using Cox regression analyses. Analyses are shown as both uncorrected and corrected for baseline age, gender, education, and *APOE* genotype. AD=Alzheimer's disease, CDR=Clinical Dementia Rating scale, HR=Hazard Ratio, SHR=Subhazard Ratio, SNAP=Suspected Non-Alzheimer Pathophysiology.

B) Annual rate of change in CDR-SB and MMSE for the unclassified group

Stages	Slope CDR-SB	P-value slope	Difference compared to normal group	Slope MMSE	P-value slope	Difference compared to normal group
Normal group	0·03 (0·03)	P=0·2661	Reference	-0·01 (0·03)	P=0·6673	Reference
Unclassified group	0·33 (0·08)	P=0·0001	P=0·0007	-0·24 (0·10)	P=0·0127	P=0·0258

Data are slopes (SE) corrected for age, gender, education, and APOE genotype and comparison to other groups. AD=Alzheimer's disease, CDR-SB=Clinical Dementia Rating scale Sum of Boxes (range 0-18, with 0 as the best score), MMSE=Mini-Mental State Examination (range 0-30, with 30 as the best score), SNAP=Suspected Non-Alzheimer Pathophysiology.