Supplementary Methods

Section S1: Summary of Estimation Procedure for EBM

A. Fit a mixture model to the data for all subjects to estimate the parameters of the event distributions, $P(x|E_i)$ and $P(x|\neg E_i)$

For each population subgroup:

B. Find the characteristic event sequence $\bar{S}$ which maximizes the data likelihood $P(X|S)$ by performing a greedy ascent algorithm

C. Take MCMC samples of the data likelihood $P(X|S)$, initialized from the maximum likelihood event sequence $\bar{S}$, to estimate the uncertainty in the characteristic event sequence.

Additional Experiments

To demonstrate the clinical application of our staging system, where patients need to be staged at one point in time, we repeated all experiments using purely cross-sectional measures, i.e. excluding rates of atrophy. The results are shown in Tables S1-S3 and Figures S1-S4.

	Demographics	Cognitively normal	Mild cognitive impairment	Alzheimer's disease
All subjects	N	100	150	75
	Sex M/F	51/49 (51%)	98/52 (65%)	41/34 (55%)
	Age (years, mean ± SD)	75±5	73±7	75±8
	Education (years, mean ± SD)	15.7±2.9	15.7±3	15.1±3
	APOE +/-	22/78 (22%)	83/65 (57%)	52/23 (69%)
Amyloid+	N	36	111	69
	Sex M/F	20/16 (56%)	69/42 (62%)	38/31 (55%)
	Age (years, mean ± SD)	76±5	74±7	74±8
	Education (years, mean ± SD)	15.9±3.3	15.6±3.1	15±3
	APOE +/-	15/21 (42%)	74/37 (67%)	52/17 (75%)
APOE+	N	22	85	52
	Sex M/F	15/7 (68%)	49/36 (58%)	30/22 (58%)
	Age (years, mean ± SD)	75±6	73±6	74±8
	Education (years, mean ± SD)	15.6±3.4	15.6±3	14.8±3
	APOE +/-	22/0 (100%)	85/0 (100%)	52/0 (100%)
Amyloid+ APOE+	N	15	74	52
	Sex M/F	10/5 (67%)	43/31 (58%)	30/22 (58%)
	Age (years, mean ± SD)	77±6	74±7	74±8
	Education (years, mean ± SD)	15.5±3.8	15.7±2.9	14.8±3
	APOE +/-	15/0 (100%)	74/0 (100%)	52/0 (100%)

Table S1

Baseline demographics for whole population and population subgroups when atrophy rates are removed.

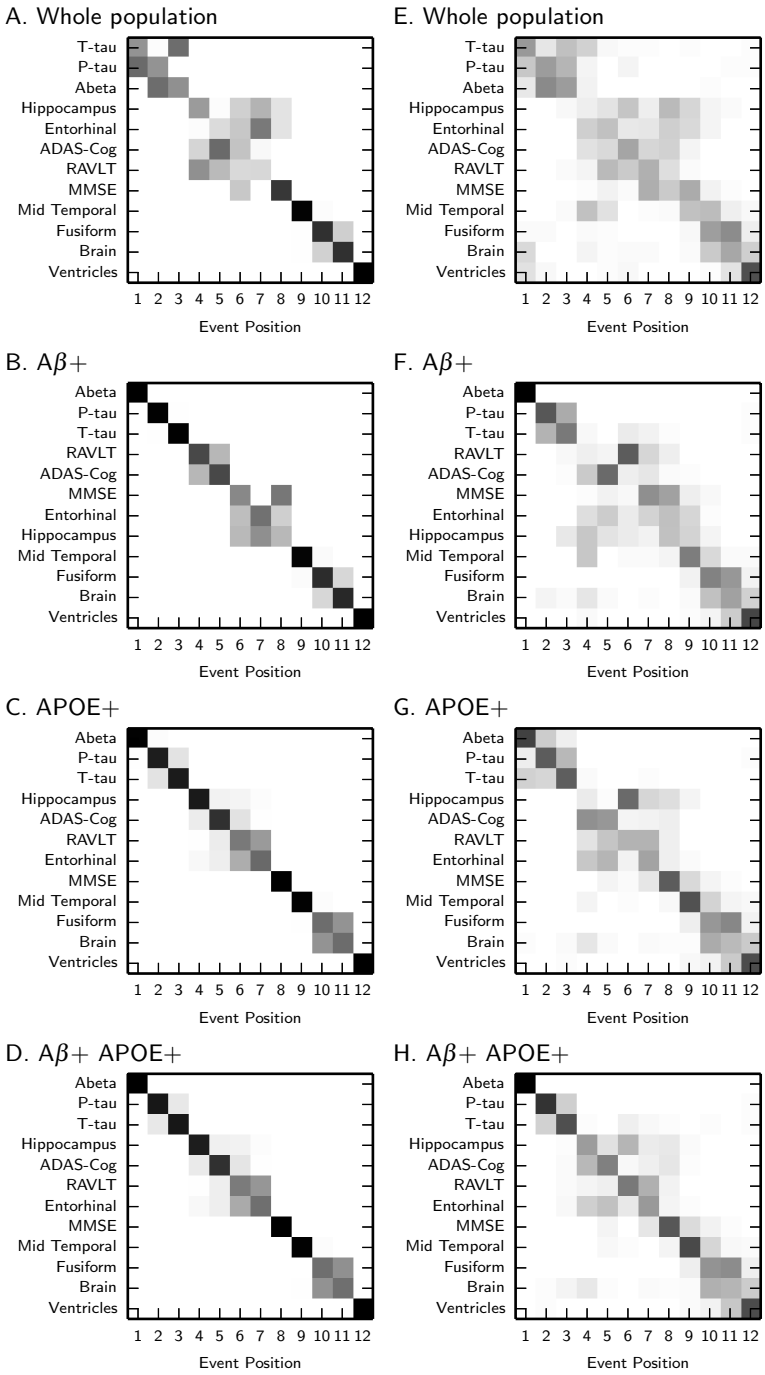


Figure S1

As Figure 1, but without using atrophy rates, i.e. using the subjects in Table S1.

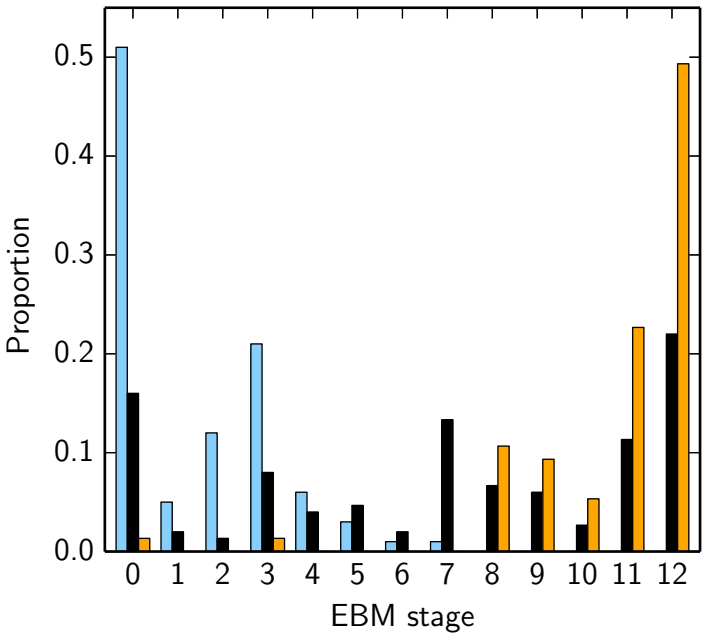


Figure S2

As Figure 2, but without using atrophy rates. Events are ordered by the maximum likelihood event sequence for the whole population as shown in Figure S1A.

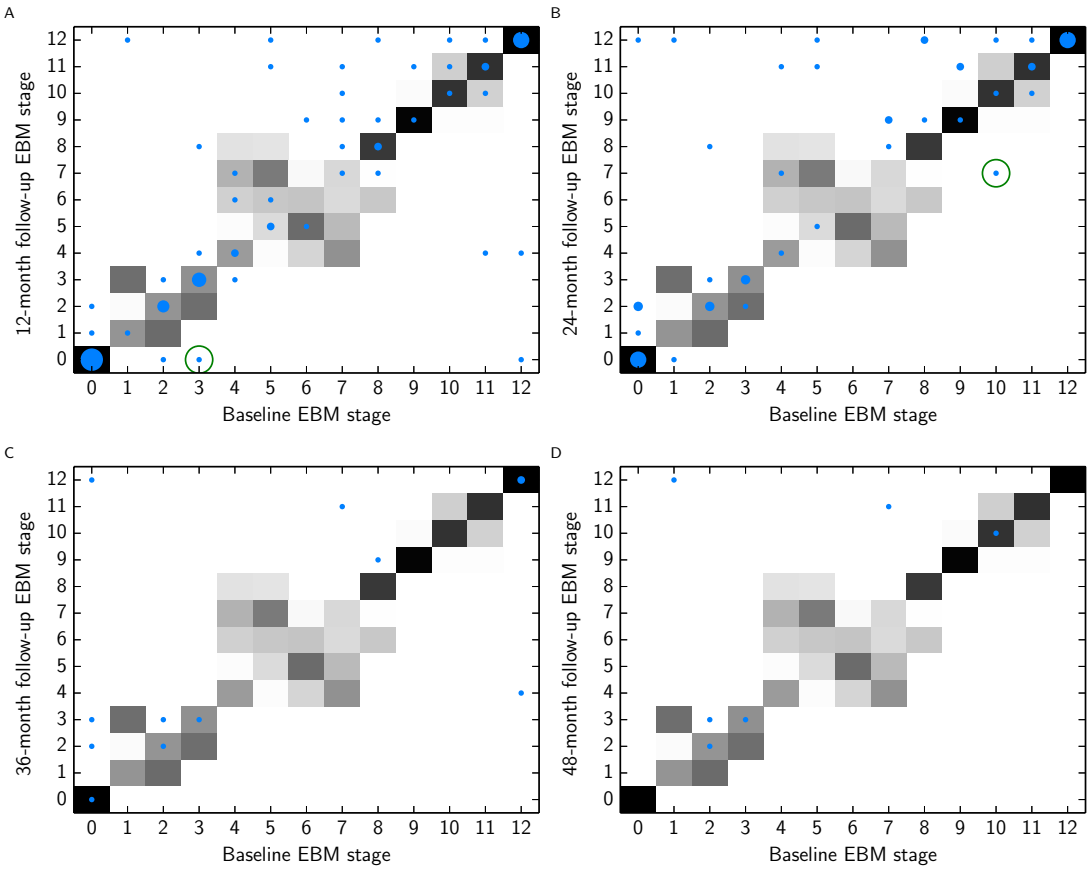


Figure S3

As Figure 3, but without using atrophy rates. Two additional follow up time points, at 36 and 48 months, met our inclusion criteria. Here, the largest dot, at (0,0) represents 17 subjects in (A) and 9 subjects in (B). The largest dot in (C) is at (12,12) and represents 2 subjects. In (D) all dots represent 1 subject.

A. MCI-converters vs. MCI-stable

	Balanced accuracy (%)	Sensitivity (%)	Specificity (%)	AUC	Threshold stage	N-c/N-s
12 months	67	72	62	0.71	8	32/103
24 months	68	68	68	0.71	8	57/68
36 months	71	83	59	0.74	6	69/51
48 months	74	84	65	0.71	5	74/20
60 months	73	84	63	0.74	5	77/16

B. CN-converters vs. CN-stable

	Balanced accuracy (%)	Sensitivity (%)	Specificity (%)	AUC	Threshold stage	N-c/N-s
12 months	95	100	91	0.95	4	2/95
24 months	79	67	91	0.78	4	6/86
36 months	70	45	95	0.69	4	9/76
48 months	66	38	94	0.68	4	13/50
60 months	70	76	64	0.75	1	17/39

Table S2

As Table 2, but without using atrophy rates.

A. MCI to Alzheimer's disease progression

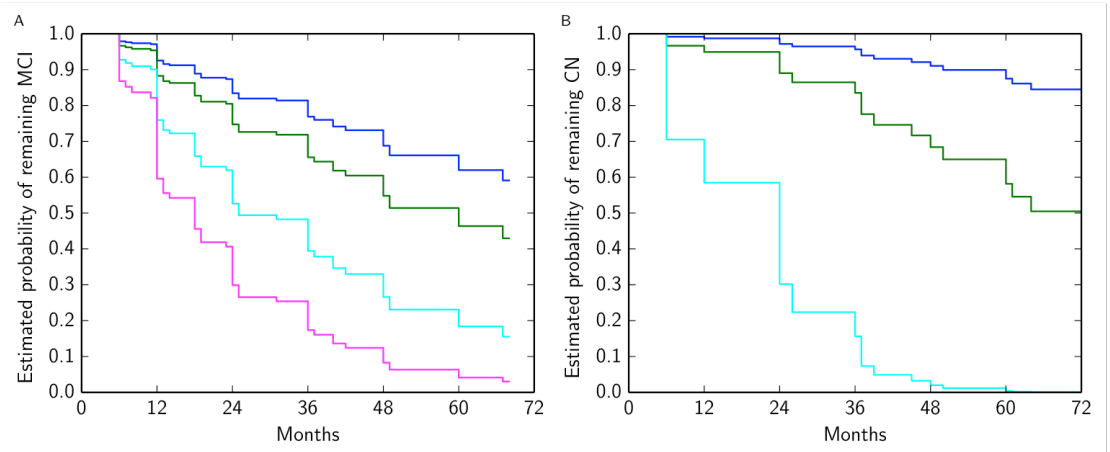
	Hazard ratio (CI)	*P*-value	Corrected hazard ratio (CI)	Corrected *P*-value
EBM Stage	1.16 (1.10-1.23)	3.34×10^{-7}*	1.17 (1.10-1.24)	3.55×10^{-7}*
Age	1.00 (0.97-1.03)	0.98	0.99 (0.96-1.02)	0.51
Education	0.98 (0.91-1.06)	0.65	0.98 (0.91-1.06)	0.6
APOE4 Carrier	1.56 (0.98-2.46)	0.059	1.32 (0.82-2.13)	0.25
Male	0.78 (0.49-1.22)	0.27	0.84 (0.50-1.43)	0.52

B. Cognitively normal to MCI progression

	Hazard ratio (CI)	*P*-value	Corrected hazard ratio (CI)	Corrected *P*-value
EBM Stage	1.66 (1.29-2.14)	1.01×10^{-4}*	1.59 (1.22-2.09)	6.72×10^{-4}*
Age	1.00 (0.91-1.10)	0.99	0.99 (0.90-1.09)	0.83
Education	1.02 (0.88-1.21)	0.76	0.99 (0.84-1.15)	0.85
APOE4 Carrier	3.00 (1.16-7.78)	0.024*	2.02 (0.68-6.00)	0.21
Male	2.00 (0.75-5.33)	0.17	1.38 (0.46-4.14)	0.57

Table S3

As Table 3, but without using atrophy rates.



Number of MCI subjects at risk at each follow up:

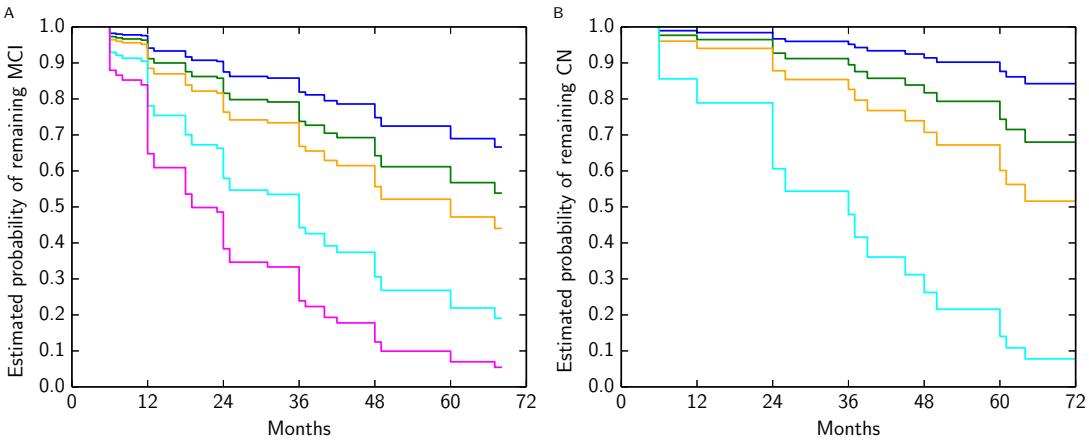
	0	12	24	36	48	60	72
All	150	128	93	68	35	23	13
Stage 0	24	23	19	17	12	8	4
Stage 1-3	17	17	15	12	6	4	3
Stage 4-8	46	40	32	22	9	7	5
Stage 9-12	63	48	27	17	8	4	1

Number of CN subjects at risk at each follow up:

	0	12	24	36	48	60	72
All	100	96	93	81	59	49	35
Stage 0	51	48	47	44	31	27	20
Stage 1-3	38	38	37	32	23	18	12
Stage 4-8	11	10	9	5	5	4	3
Stage 9-12	0	0	0	0	0	0	0

Figure S4

As Figure 4, but without using atrophy rates. These estimated probabilities are shown for the average population demographics (74.2 years of age, 15.6 years of education, APOE negative, male sex). Stages are grouped analogously to Figure 4, so that here Normal (blue) = stage 0, CSF (green) = stages 1-3, Cognition (cyan) = stages 4-8, which includes hippocampal and entorhinal cortex volume as well as cognitive test scores, Volume (magenta) = stages 9-12.



Number of MCI subjects at risk at each follow up:

	0	12	24	36	48	60	72
All	129	119	88	64	33	23	13
Stage 0	22	22	18	15	11	8	4
Stage 1-3	12	12	11	10	4	4	2
Stage 4-5	9	9	7	7	3	2	2
Stage 6-10	37	33	28	18	9	6	4
Stage 11-14	49	43	24	14	6	3	1

Number of CN subjects at risk at each follow up:

	0	12	24	36	48	60	72
All	92	91	89	77	58	48	34
Stage 0	47	47	46	42	31	27	20
Stage 1-3	30	29	28	23	17	14	11
Stage 4-5	13	13	13	11	9	7	3
Stage 6-10	2	2	2	1	1	0	0
Stage 11-14	0	0	0	0	0	0	0

Figure S5

As Figure 4, but with an additional table detailing the number of subjects at risk at each follow up time point.