

Amyloid- β -Positivity Predicts Cognitive Decline but Cognition Predicts Progression to Amyloid- β -Positivity

Supplemental Information

Supplemental Methods

Rationale for logistic regression model versus generalized linear mixed-effects model

Our question of interest was to identify individuals at elevated risk of entering the Alzheimer's disease continuum as determined by progression to β -amyloid ($A\beta$) positivity. We therefore wished to consider all individuals who progress to $A\beta$ -positivity equivalently, regardless of time to progression, as they are all at elevated risk and could therefore be appropriate candidates for intervention. We provide a hypothetical example to illustrate our motivation for choosing the logistic regression approach:

<i>Visit #</i>	<i>Participant 1</i>	<i>Participant 2</i>	<i>Participant 3</i>
1	0	0	0
2	1	1	0
3	1	NA	0
4	1	NA	0
5	1	NA	1

The table above presents three hypothetical participants, and we will assume they all had the same low scores on baseline cognitive composites. A 0 indicates that they were $A\beta$ -negative, and a 1 indicates $A\beta$ -positive. NA indicates no data from that timepoint.

We chose to conduct a logistic regression with the outcome variable indicating whether an individual progressed from $A\beta$ -negative at baseline to $A\beta$ -positive at any point during follow-up or remained $A\beta$ -negative throughout. Under the logistic regression model, all three of the above participants will be treated identically as they each will have the same value for their

dependent variable (i.e., they are all classified as converters). Coefficients from this model can be interpreted as reflecting risk at the unit of the individual. In other words, is an individual at elevated risk, regardless of *when* progression occurs?

This approach was chosen rather than a generalized linear mixed-effects model (GLMM) with the logit, or a logistic regression for longitudinal data that includes an outcome variable indicating A β status at each timepoint. Although the logistic regression model includes length of follow-up as a covariate, a benefit of the longitudinal GLMM is that it directly incorporates all timepoints, which may better address differences in follow-up time such as variation in conversion trajectories (timing and even reversion from A β -positive at one follow-up visit to A β -negative during a later visit to be included).

Under the longitudinal model, each row will contribute to the association between baseline cognition and A β -positivity. Coefficients of the fixed-effects from the GLMM would indicate odds of being A β -positive *at each timepoint*, which, along with the random-effects, allows for differentiation of subjects with different conversion profiles. Therefore, the participants above will differentially affect the coefficient, i.e., the effect of baseline cognition. Participant 1 will increase the effect of baseline cognition more than Participant 2 due to having multiple A β -positive timepoints. Participant 3 will decrease the effect of baseline cognition relative to the other two because they have multiple A β -negative timepoints. In contrast, because our interest was in identifying all individuals at elevated risk, the number of follow-up assessments after conversion is not relevant and should not be used to alter this level of risk. The logistic regression model addresses this specific question with easy-to-interpret results.

Rationale for survival analysis

This still leaves open the issue of differential follow-up times between individuals that convert versus those who remain stable. It may be that if individuals who remained A β -negative

were followed for longer, they would eventually become A β -positive. Therefore, we conducted survival analyses that more directly address this issue as well as timing of conversion by testing the association between baseline cognitive performance and time to event (either conversion to A β -positive or censored at last follow-up). In this case, Participants 1 and 2 from the example above will be considered equivalent. That is, they both convert at time 2, and the number of follow-ups beyond this event does not matter. Participant 3 is treated differently under this model in that they have a longer time to event and would weaken the effect of baseline cognition relative to the other two participants. From a conceptual standpoint, this model splits the difference between the other two models. It more directly addresses the issue of follow-up time and, consistent with our goals, the number of A β -positive assessments following conversion does not alter an individual's risk.

Supplemental Tables & Figures

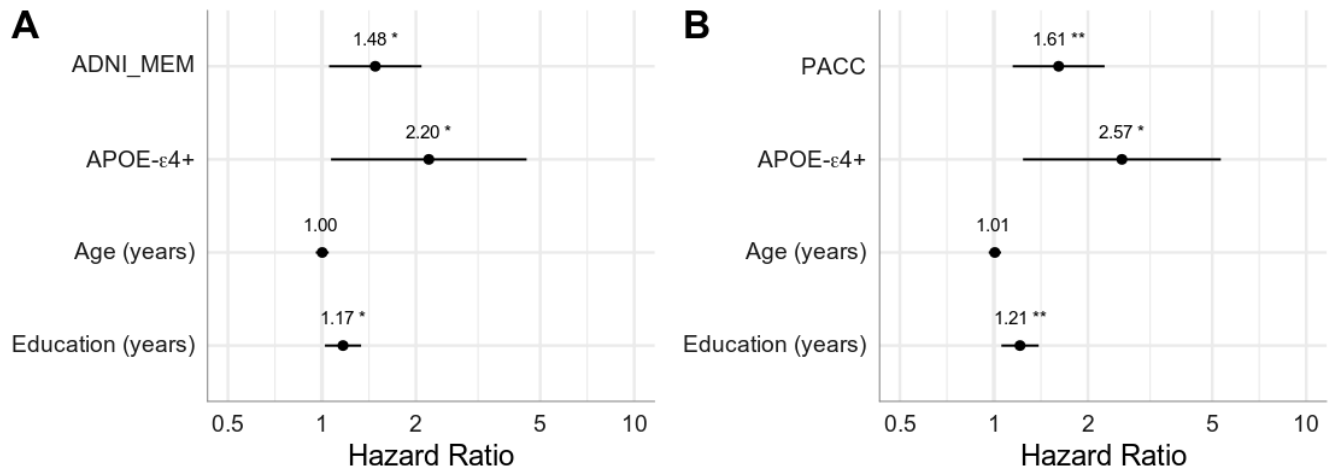
Supplemental Table S1. Baseline sample characteristics of individuals with mild cognitive impairment with converted to A β -positivity versus remained A β -negative. Mean (SD) presented for continuous variables, count (%) presented for categorical variables. An asterisk indicates a significant ($p < 0.05$) difference between the two groups.

	MCI Aβ-stable	MCI Aβ-converter
n	117	21
Age (years)	70.46 (8.08)	70.54 (8.31)
Gender (male)	63 (53.8%)	10 (47.6%)
APOE- ϵ 4 status (ϵ 4+)	20 (17.1%)	8 (38.1%)
Education* (years)	15.96 (2.56)	17.43 (2.31)
Length of follow-up (years)*	3.22 (1.33)	3.44 (1.21)
Baseline CSF A β * (pg/ml)	1474.67 (245.65)	1269.88 (278.38)
Baseline CSF P-tau* (pg/ml)	18.86 (7.71)	23.28 (7.82)
ADNI_MEM	0.59 (0.69)	0.46 (0.57)
PACC	-3.25 (3.15)	-3.40 (2.42)

Supplemental Table S2. Baseline executive function performance predicting future conversion to A β -positivity. Results of three logistic regression models using the ADNI Executive function composite (ADNI_EF) to predict later conversion to A β -positivity. Model 1 includes: ADNI_EF and covariates. Model 2 includes: ADNI_EF, dichotomous p-tau+ status, and covariates. Model 3 includes: ADNI_EF, continuous levels of baseline CSF A β and p-tau, and covariates. Measures are all taken from baseline and predict future progression to A β -positivity. Cognitive scores and continuous CSF A β were converted to z-scores and reverse coded such that higher scores indicate poorer performance and more abnormal levels of A β , respectively.

Predictors (units)	Model 1			Model 2			Model 3		
	Odds Ratios	95% CI	p	Odds Ratios	95% CI	p	Odds Ratios	95% CI	p
(Intercept)	0.01	0.00 – 2.32	0.102	0.00	0.00 – 0.10	0.004	0.00	0.00 – 0.06	0.002
ADNI_EF (sd)	1.37	0.87 – 2.21	0.180	1.56	1.03 – 2.40	0.036	1.53	1.01 – 2.33	0.045
APOE- ϵ 4 status (ϵ 4+)	1.99	0.75 – 5.13	0.156	2.94	1.20 – 7.11	0.017	3.24	1.33 – 7.79	0.008
Age (years)	0.97	0.91 – 1.04	0.406	0.99	0.94 – 1.05	0.856	1.00	0.95 – 1.06	0.902
Education (years)	1.19	1.01 – 1.42	0.040	1.25	1.07 – 1.48	0.006	1.25	1.08 – 1.48	0.005
Length of follow-up (years)	1.42	1.17 – 1.72	<0.001	1.45	1.21 – 1.75	<0.001	1.44	1.20 – 1.73	<0.001
P-Tau+				2.03	0.95 – 4.27	0.063	-	-	-
CSF A β (sd)							2.57	1.74 – 3.91	<0.001
CSF P-tau (sd)							1.58	1.11 – 2.31	0.012

Supplemental Figure S1. Baseline cognitive performance and risk of progression to A β -positivity. Results of two Cox proportional hazard models using A) the ADNI Memory composite (ADNI_MEM) and B) the Preclinical Alzheimer Cognitive Composite (PACC). Measures are all taken from baseline and predict time to event (conversion to A β -positivity or censored at last follow-up). Cognitive scores were converted to z-scores and reverse coded such that higher scores indicate poorer performance. Hazard ratios are presented with asterisks indicating significant estimates (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Lines represent 95% confidence intervals.



Supplemental Figure S2. Baseline cognitive performance and continuous measures of CSF A β and p-tau associated with risk of progression to A β -positivity. Results of two Cox proportional hazard models using A) the ADNI Memory composite (ADNI_MEM) and B) the Preclinical Alzheimer Cognitive Composite (PACC). Measures are all taken from baseline and predict time to event (conversion to A β -positivity or censored at last follow-up). Cognitive scores were converted to z-scores and reverse coded such that higher scores indicate poorer performance. CSF A β and P-tau were entered as continuous variables. Both measures were z-scored and CSF A β was reverse coded such that higher values on both indicates abnormality. Hazard ratios are presented with asterisks indicating significant estimates (* p <0.05, ** p <0.01, *** p <0.001). Lines represent 95% confidence intervals.

