

## Supplementary Online Content

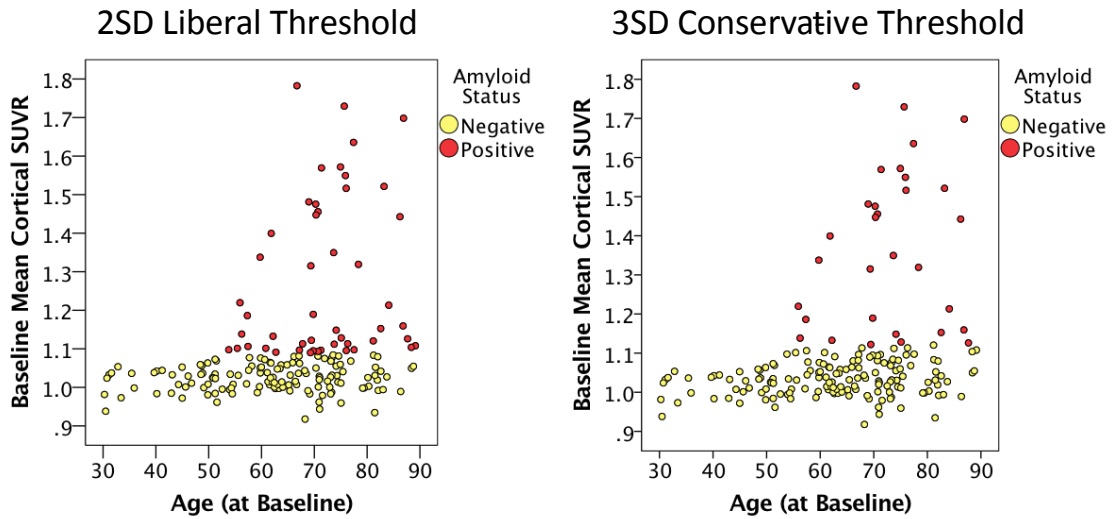
Farrell ME, Kennedy KM, Rodrigue KM, et al. Association of longitudinal cognitive decline with amyloid burden in middle-aged and older adults: evidence for a dose-response relationship. *JAMA Neurol*. Published online May 30, 2017. doi:10.1001/jamaneurol.2017.0892

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This supplementary material has been provided by the authors to give readers additional information about their work.

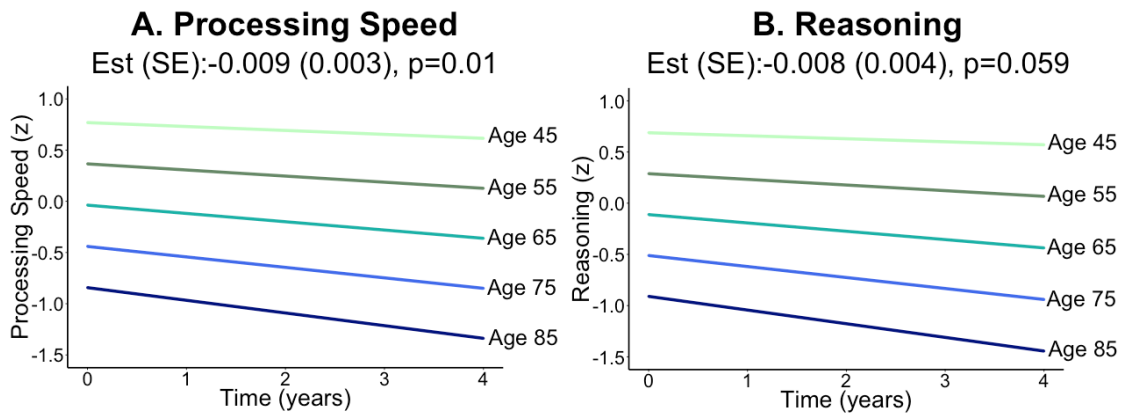
**eMethods. Description of Simple Slope Method for SUVR x Time Figures**

In order to evaluate the cause of the significant SUVR x time interactions, estimated means were computed for four values of SUVR that ranged from low to high (1.0, 1.2, 1.4, 1.6) across four years for each cognitive measure that was significant. Estimated means were computed by first building the full linear model for each cognitive variable with all fixed effects and their associated parameter estimates as generated by the linear mixed model. Next, the x value of each term was entered into the linear model. Covariate terms in the model were set to defaults for categorical variables (Sex=male; APOE: non-carrier) and means for continuous variables (Age=66.4, Education years =15.6). Time was set to 0 to generate baseline predicted values and 1 to generate follow-up values. Finally, each of the 5 values of SUVR was entered separately to generate model projections of cognitive performance at baseline and at the follow-up interval four years later. The baseline and follow-up model projections for each of the five SUVR values were then used to estimate trajectories of change in cognition over time at increasing values of SUVR.

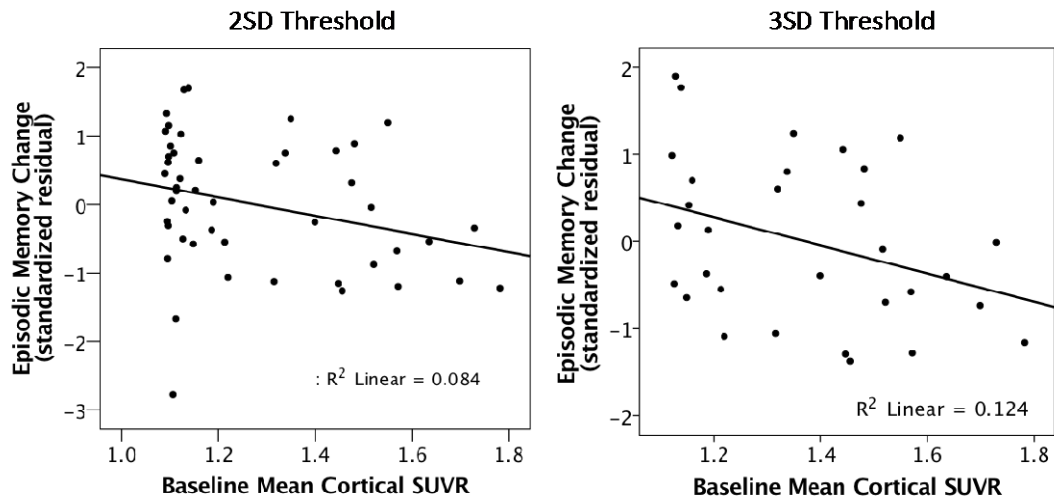


**eFigure 1. Amyloid Burden throughout the Lifespan with Different Positivity Thresholds.**

Amyloid burden at baseline (Baseline Mean Cortical SUVR) is plotted as a function of age at baseline. Additionally, the dichotomization of SUVR into Amyloid Positive (red) and Amyloid Negative (yellow) groups is shown, with a threshold at 1.09 (left) and 1.12 (right) based on 2 or 3 standard deviations, respectively, above the mean uptake in the youngest subjects (age 30-39).

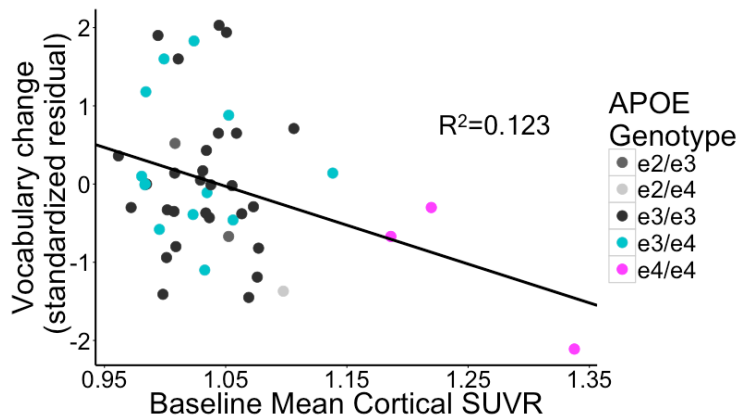


**eFigure 2. Increasing Age at Baseline associated with Increasing Decline in Processing Speed and Reasoning in Amyloid Negative Adults.** Using simple slope analysis, the projected trajectory of (A) processing speed and (B) reasoning change over time was plotted for different ages in the amyloid-negative subsample. Increasing age was predictive of greater decline in processing speed, and marginally predictive of greater decline in reasoning



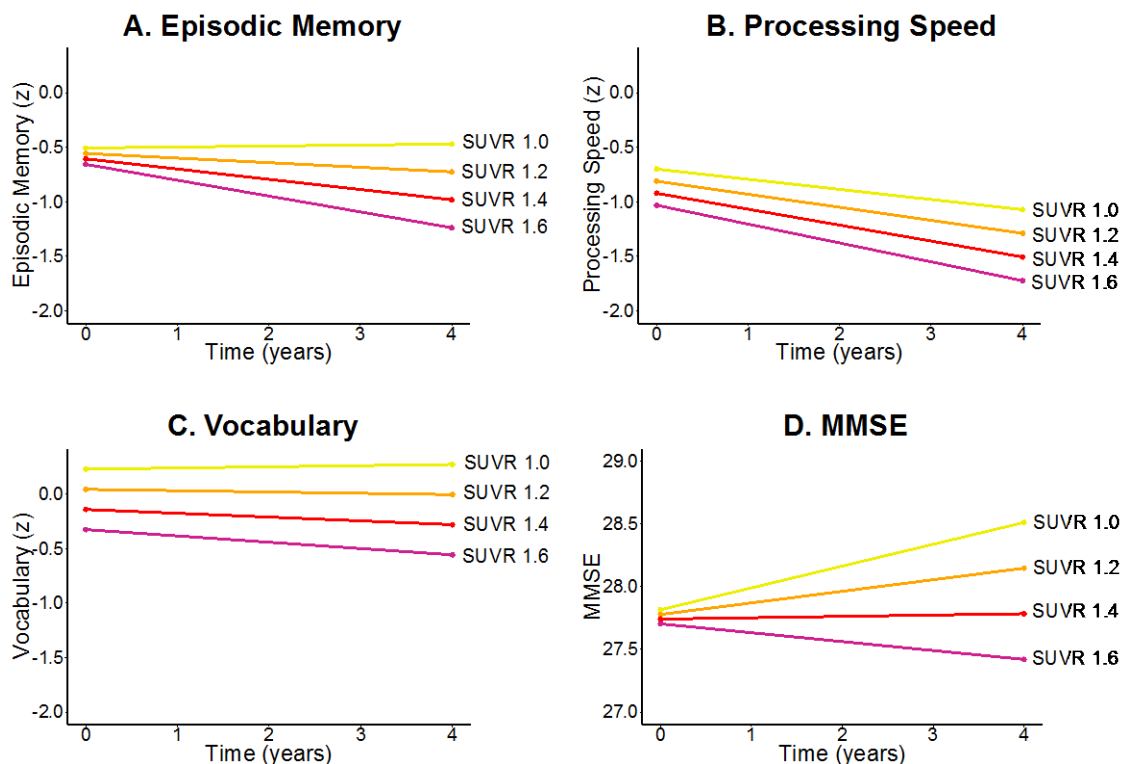
**eFigure 3. Dose-Response Relationship between Baseline Amyloid Burden and Episodic Memory Decline in Amyloid-Positive Individuals.**

Scatterplots of the individual episodic memory change scores are shown (adjusted for age, sex, education and APOE) as a function of baseline SUVR for the amyloid positive subjects, based on the 2SD (left) and 3SD (right) thresholds. Within this smaller sample, increasing SUVR predicted increasingly negative trajectories of change in episodic memory.



**eFigure 4. Dose-Response Relationship Between Baseline Amyloid Burden and Vocabulary in Middle-Aged Adults Driven by Three APOE- $\epsilon$ 4 Homozygotes.**

Restricting the analysis to middle-aged adults (age 40-59 at baseline), yielded a significant SUVR x Time interaction for vocabulary with increasing SUVR predicting declining vocabulary. However, a post-hoc examination of the three participants with the highest SUVRs (shown in magenta) revealed that these three were APOE  $\epsilon$ 4/ $\epsilon$ 4 homozygotes—the only three in this middle-aged sample. When these three participants were removed from the analysis, the effect became non-significant.



**eFigure 5. Projections of the Impact of Increasing Magnitude of Baseline SUVR over a 4-Year Time Interval on 4 Measures of Cognition in Older Adults.** Linear Mixed Models were used to assess the impact of increasing baseline amyloid burden (SUVR) on the trajectory of cognitive performance from Year 0 to Year 4 in older adults alone (age 60-89 at baseline). Similar to the results in the whole sample (age 40-89), the SUVR x Time interaction was significant for (a) episodic memory, (b) processing speed, (c) vocabulary and (d) MMSE, indicating a dose-response relationship between baseline amyloid burden and cognitive change. In order to evaluate the significant SUVR x time interactions, estimated means were computed for each time point based on increasing values of SUVR (1.0, 1.2, 1.4, 1.6). Across episodic memory, processing speed, vocabulary and MMSE, the model projected that high levels of SUVR (1.6) consistently predicted cognitive decline, while negative or low levels of SUVR (1.0, 1.2) predicted modest or no cognitive decline (or in the case of MMSE, a practice effect).

## Supplemental Materials



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		Baseline Amyloid Status		t (or $\chi^2$ )	p	
Whole Sample (age 40-89) (n=174)		Amyloid Positive (n=31)	Amyloid Negative (n=143)			
Age (years)		66.44 ± 11.74	72.86 ± 9.18	65.06 ± 11.80	-3.46	0.001 <sup>a</sup>
Baseline SUVR		1.09 ± 0.16	1.37 ± 0.20	1.04 ± 0.04	-18.44	<.001
Education (years)		15.55 ± 2.29	16.65 ± 2.15	15.32 ± 2.27	-2.98	0.003
Time between visits (years)		3.82 ± 0.32	3.84 ± 0.23	3.81 ± 0.34	-0.43	0.667
Gender (No. male (%))		65 (37%)	9 (29%)	56 (39%)	1.06	0.303
APOE (No. ε4 carrier (%))		38 (23%)	11 (36%)	27 (20%)	3.68	0.055
MMSE	Year 0	28.3 ± 1.24	28.2 ± 1.21	28.3 ± 1.24	0.71	0.478
	Year 4	28.9 ± 1.31	28.5 ± 1.21	28.9 ± 1.32	1.76	0.080
	Change	0.55 ± 1.55	0.32 ± 1.74	0.60 ± 1.51	0.91	0.366
Episodic Memory (z)	Year 0	-0.01 ± 0.81	-0.14 ± 0.67	0.02 ± 0.84	0.98	0.331
	Year 4	-0.06 ± 0.85	-0.49 ± 0.99	0.03 ± 0.81	3.17	0.002
	Change	-0.05 ± 0.78	-0.35 ± 0.77	0.01 ± 0.78	2.36	0.019
Processing Speed (z)	Year 0	0.01 ± 0.95	-0.34 ± 0.92	0.09 ± 0.94	2.32	0.021
	Year 4	-0.36 ± 1.00	-0.90 ± 0.99	-0.25 ± 0.97	3.41	0.001
	Change	-0.37 ± 0.47	-0.56 ± 0.53	-0.33 ± 0.44	2.52	0.013
Reasoning (z)	Year 0	-0.00 ± 0.90	-0.29 ± 0.88	0.06 ± 0.90	1.92	0.056
	Year 4	-0.09 ± 0.97	-0.55 ± 1.01	0.01 ± 0.94	2.93	0.004
	Change	-0.09 ± 0.61	-0.26 ± 0.75	-0.05 ± 0.58	1.74	0.084
Vocabulary (z)	Year 0	0.00 ± 1.00	0.11 ± 1.15	-0.04 ± 0.96	-0.76	0.448
	Year 4	-0.01 ± 0.97	-0.05 ± 1.21	0.00 ± 0.92	0.27	0.787
	Change	0.01 ± 0.39	-0.16 ± 0.48	0.04 ± 0.36	2.65	0.009

**eTable 1. Sample demographics.**

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Means and standard deviations (or percentages for categorical variables) are presented for all predictors, covariates and cognitive outcome variables for the full sample. Independent t-tests and chi-square tests were used to test for differences between amyloid positive and negative groups, using the more stringent 3SD threshold. Individuals who were amyloid positive at baseline were older, more educated, and marginally more likely to be APOE e4 carriers than amyloid negative individuals. Amyloid positive individuals also exhibited greater decline (based on change scores) in episodic memory, processing speed, vocabulary and a trend for reasoning than amyloid negative individuals. However, these change scores are unadjusted for covariates, and the primary analyses with linear mixed models are more appropriate tests to properly measure the relationship between amyloid burden and cognitive decline while accounting for possible confounds with covariates such as age. <sup>a</sup>*p*<.05 in italics

		Cognitive Outcome	Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		MMSE	
Effect	Statistic		3SD A $\beta$ Status Threshold	2SD A $\beta$ Status Threshold	3SD A $\beta$ Status Threshold	2SD A $\beta$ Status Threshold	3SD A $\beta$ Status Threshold	2SD A $\beta$ Status Threshold	3SD A $\beta$ Status Threshold	2SD A $\beta$ Status Threshold
Effects of Time	Time	<i>Est (SE)</i>	1.26 (0.87)	<b>1.46 (0.70)</b>	0.74 (0.53)	0.82 (0.43)	0.45 (0.45)	0.60 (0.34)	2.25 (1.93)	1.65 (1.53)
		<i>p</i>	0.151	<b>0.042</b>	0.165	0.061	0.317	0.079	0.246	0.282
	SUVR x Time	<i>Est (SE)</i>	-1.18 (0.63)	<b>-1.20 (0.52)</b>	-0.41 (0.37)	-0.45 (0.30)	-0.44 (0.32)	<b>-0.54 (0.26)</b>	<b>-2.54 (1.27)</b>	<b>-2.17 (1.05)</b>
		<i>p</i>	0.064	<b>0.021</b>	0.271	0.133	0.170	<b>0.040</b>	<b>0.048</b>	<b>0.039</b>
	A $\beta$ Status x Time	<i>Est (SE)</i>	0.00 (0.26)	-0.01 (0.18)	0.03 (0.15)	0.00 (0.11)	0.05 (0.13)	-0.00 (0.09)	-0.45 (0.53)	-0.26 (0.37)
		<i>p</i>	0.987	0.96	0.862	0.987	0.701	0.993	0.398	0.487
	Age x Time	<i>Est (SE)</i>	-	-	<b>-0.01 (0.00)</b>	<b>-0.01 (0.00)</b>	-	-	-	-
		<i>p</i>			<b>0.001</b>	<b>0.001</b>				
Other Main Effects	SUVR	<i>Est (SE)</i>	0.46 (0.59)	0.33 (0.52)	-0.56 (0.64)	-0.57 (0.53)	-0.49 (0.73)	-1.12 (0.60)	0.35 (1.01)	0.05 (0.83)
		<i>p</i>	0.429	0.53	0.384	0.28	0.501	0.063	0.729	0.948
	A $\beta$ Status	<i>Est (SE)</i>	0.34 (0.24)	0.18 (0.17)	-0.03 (0.27)	-0.04 (0.19)	0.14 (0.30)	-0.21 (0.21)	0.18 (0.42)	0.03 (0.30)
		<i>p</i>	0.158	0.29	0.911	0.839	0.651	0.334	0.66	0.932
	Age	<i>Est (SE)</i>	<b>-0.02 (0.00)</b>	<b>-0.02 (0.00)</b>	<b>-0.04 (0.01)</b>	<b>-0.04 (0.01)</b>	<b>0.02 (0.01)</b>	<b>0.02 (0.01)</b>	<b>-0.02 (0.01)</b>	<b>-0.02 (0.01)</b>
		<i>p</i>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.003</b>	<b>0.007</b>	<b>0.001</b>	<b>0.001</b>
	Ed.	<i>Est (SE)</i>	<b>0.08 (0.02)</b>	0.08 (0.05)	0.04 (0.03)	0.04 (0.03)	<b>0.21 (0.03)</b>	<b>0.21 (0.03)</b>	0.04 (0.04)	0.03 (0.04)
		<i>p</i>	<b>&lt;0.001</b>	0.108	0.102	0.104	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.387	0.413
	Sex	<i>Est (SE)</i>	<b>0.78 (0.10)</b>	<b>0.86 (0.21)</b>	<b>0.38 (0.12)</b>	<b>0.38 (0.12)</b>	0.24 (0.14)	0.22 (0.14)	<b>0.50 (0.15)</b>	<b>0.50 (0.15)</b>
		<i>p</i>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.002</b>	<b>0.002</b>	0.087	0.12	<b>0.001</b>	<b>0.002</b>
	APOE	<i>Est (SE)</i>	-0.01 (0.11)	0.01 (0.11)	0.21 (0.14)	-0.22 (0.14)	0.02 (0.16)	-0.03 (0.16)	0.30 (0.18)	-0.30 (0.18)
		<i>p</i>	0.893	0.955	0.123	0.122	0.88	0.829	0.095	0.093

**eTable 2. Summary of Parameter Estimates from Linear Mixed Models with both Amyloid Status and SUVR.**

Parameter estimates and standard errors are reported above for each cognitive outcome in the whole sample. Both SUVR and Amyloid Status (2SD or 3SD threshold) was included in these models, to assess whether continuous SUVR was a significant predictor of cognitive decline even

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after accounting for amyloid status. Even while accounting for Amyloid Status (2SD threshold), the Amyloid Status x Time interaction was significant for episodic memory, vocabulary, and MMSE. Accounting for Amyloid Status (3SD threshold), MMSE remained significant and episodic memory was marginally significant.  $p < .05$  in bold.

Cognitive Outcome		Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		Reasoning (z)		MMSE		
Effect	Statistic	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status	
Effects of Time	Time	<i>Est (SE)</i>	0.35 (0.18)	<b>-0.35</b> (0.14)	<b>0.49</b> (0.20)	0.22 (0.24)	0.18 (0.09)	<b>-0.16</b> (0.07)	<b>0.68</b> (0.28)	0.47 (0.33)	<b>0.80</b> (0.36)	0.32 (0.28)
		<i>p</i>	0.053	<b>0.011</b>	<b>0.017</b>	0.363	0.053	<b>0.023</b>	<b>0.016</b>	0.151	<b>0.029</b>	0.250
	A $\beta$ Status x Time	<i>Est (SE)</i>	<b>-0.29</b> (0.13)	<b>-0.40</b> (0.15)	-0.11 (0.08)	-0.16 (0.09)	<b>-0.14</b> (0.07)	<b>-0.20</b> (0.08)	-0.09 (0.11)	-0.12 (0.13)	-0.19 (0.27)	-0.28 (0.31)
		<i>p</i>	<b>0.028</b>	<b>0.009</b>	0.161	0.081	<b>0.044</b>	<b>0.011</b>	0.412	0.327	0.472	0.361
	Age x Time	<i>Est (SE)</i>		-	<b>-0.01</b> (0.00)	-0.01 (0.00)		-	<b>-0.01</b> (0.00)	<b>-0.01</b> (0.00)		
		<i>p</i>			<b>0.001</b>	0.001			<b>.022</b>	<b>0.019</b>		
Other Main Effects	A $\beta$ Status	<i>Est (SE)</i>	0.14 (0.13)	-0.19 (0.15)	-0.09 (0.14)	-0.16 (0.17)	-0.05 (0.16)	-0.29 (0.19)	-0.18 (0.14)	-0.28 (0.17)	-0.04 (0.22)	-0.01 (0.26)
		<i>p</i>	0.292	0.210	0.524	0.369	0.772	0.123	0.222	0.099	0.856	0.651
	Age	<i>Est (SE)</i>	<b>-0.02</b> (0.00)	-0.02 (0.00)	<b>-0.04</b> (0.01)	-0.04 (0.01)	<b>0.02</b> (0.01)	0.02 (0.01)	<b>-0.03</b> (0.01)	-0.03 (0.01)	<b>-0.02</b> (0.01)	-0.02 (0.01)
		<i>p</i>	<b>&lt;0.001</b>	<0.001	<b>&lt;0.001</b>	<0.001	<b>0.016</b>	0.004	<b>&lt;0.001</b>	<0.001	<b>0.001</b>	0.001
	Ed.	<i>Est (SE)</i>	<b>0.07</b> (0.02)	0.08 (0.02)	0.04 (0.03)	0.04 (0.03)	<b>0.20</b> (0.03)	0.21 (0.03)	<b>0.09</b> (0.03)	0.10 (0.03)	<b>0.08</b> (0.03)	0.08 (0.03)
		<i>p</i>	<b>0.001</b>	<0.001	0.147	0.116	<b>&lt;0.001</b>	<0.001	<b>&lt;0.001</b>	<0.001	<b>0.023</b>	0.016
	Sex	<i>Est (SE)</i>	<b>0.77</b> (0.10)	0.78 (0.10)	<b>0.38</b> (0.12)	0.39 (0.12)	0.22 (0.14)	0.25 (0.14)	0.07 (0.12)	0.06 (0.12)	<b>0.50</b> (0.15)	0.51 (0.15)
		<i>p</i>	<b>&lt;0.001</b>	<0.001	<b>.002</b>	0.002	0.119	0.077	0.575	0.596	<b>0.002</b>	0.001
	APOE	<i>Est (SE)</i>	-0.01 (0.11)	0.01 (0.11)	-0.24 (0.14)	-0.23 (0.14)	-0.08 (0.16)	-0.04 (0.16)	0.14 (0.13)	0.16 (0.13)	-0.33 (0.18)	-0.31 (0.18)
		<i>p</i>	.934	0.906	0.080	0.104	0.609	0.827	0.310	0.236	0.060	0.080

**eTable 3. Summary of Parameter Estimates from Linear Mixed Models with Amyloid Status instead of SUVR.** Parameter estimates and standard errors are reported above for each cognitive outcome in the whole sample. The primary predictor of interest for

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these analyses was the Amyloid Status x Time interaction, assessing whether the presence of tracer uptake above the amyloid positivity threshold (either 2SD or 3SD) was predictive of greater cognitive decline than uptake below the threshold. The Amyloid Status x Time interaction was significant for episodic memory and vocabulary, regardless of positivity threshold. Unlike the analyses with continuous SUVR, there was not a significant Amyloid Status x Time for MMSE or processing speed. Similar to the continuous SUVR analyses, we detected a significant Age x Time interaction for processing speed and reasoning, such that old age was also associated greater cognitive decline, independent of amyloid burden. Education x Time, APOE x Time, Sex x Time, and Age x SUVR x Time estimates for all cognitive variables failed to reach marginal significance and were removed from the models. Notably, the Education x Time interaction was marginally significant in the primary continuous SUVR model for MMSE, and thus the terms in the linear mixed models differ between the continuous SUVR and dichotomized amyloid status analyses. However, including or removing the Education x Time interaction did not change whether the Amyloid Status x Time interaction was significant. <sup>a</sup> $p < .05$  in bold.

		Cognitive Outcome	Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		MMSE	
Effect	Statistic	2SD A $\beta$ Status Threshold	3SD A $\beta$ Status Threshold	2SD A $\beta$ Status Threshold	3SD A $\beta$ Status Threshold	2SD A $\beta$ Status Threshold	3SD A $\beta$ Status Threshold	2SD A $\beta$ Status Threshold	3SD A $\beta$ Status Threshold	
Effects of Time	Time	<i>Est (SE)</i>	<b>1.46 (0.70)</b>	1.52 (0.91)	<b>1.88 (0.58)</b>	<b>2.14 (0.83)</b>	0.52 (0.38)	0.31 (0.60)	<b>2.85 (1.35)</b>	3.78 (2.00)
		<i>p</i>	<b>0.042</b>	0.109	<b>0.002</b>	<b>0.015</b>	0.183	0.612	<b>0.040</b>	0.064
	SUVR x Time	<i>Est (SE)</i>	<b>-1.33 (0.54)</b>	<b>-1.36 (0.66)</b>	-0.48 (0.30)	-0.49 (0.42)	-0.48 (0.30)	-0.34 (0.44)	-1.91 (1.05)	-2.52 (1.44)
		<i>p</i>	<b>0.018</b>	<b>0.048</b>	0.115	0.259	0.112	0.438	0.075	0.086
	Age x Time	<i>Est (SE)</i>	-	-	<b>-0.02 (0.01)</b>	<b>-0.03 (0.01)</b>	-	-	-	-
		<i>p</i>	-	-	<b>.001</b>	<b>0.006</b>	-	-	-	-
Other Main Effects	SUVR	<i>Est (SE)</i>	0.33 (0.52)	0.79 (0.63)	-0.52 (0.54)	-0.64(0.72)	<b>-1.72 (0.73)</b>	-1.37 (1.03)	-0.59 (0.78)	-0.43 (1.04)
		<i>p</i>	0.527	0.216	.340	0.379	<b>0.022</b>	0.277	.454	0.685
	Age	<i>Est (SE)</i>	<b>-0.03 (0.01)</b>	-0.02 (0.01)	<b>-0.04 (0.01)</b>	-0.03 (0.02)	0.01 (0.02)	0.01 (0.24)	-0.02 (0.01)	-0.02 (0.02)
		<i>p</i>	<b>.004</b>	0.109	<b>0.001</b>	0.055	0.361	0.682	0.109	0.318
	Ed.	<i>Est (SE)</i>	0.08 (0.05)	0.07 (0.07)	-0.03 (0.05)	-0.04 (0.09)	<b>0.27 (0.08)</b>	<b>0.30 (0.13)</b>	<b>0.15 (0.06)</b>	0.10 (0.09)
		<i>p</i>	0.108	0.294	.581	0.68	<b>0.001</b>	<b>0.025</b>	<b>.020</b>	0.294
	Sex	<i>Est (SE)</i>	<b>0.86 (0.21)</b>	<b>0.93 (0.29)</b>	0.48 (0.25)	0.62 (0.37)	0.16 (0.34)	0.10 (0.54)	<b>0.75 (0.28)</b>	0.47 (0.40)
		<i>p</i>	<b>&lt;0.001</b>	<b>0.003</b>	0.61	0.103	0.652	0.862	<b>0.011</b>	0.253
	APOE	<i>Est (SE)</i>	-0.03 (0.21)	0.02 (0.27)	-0.11 (0.58)	-0.05 (0.34)	0.37 (0.35)	0.56 (0.51)	0.02 (0.28)	0.16 (0.38)
		<i>p</i>	0.902	0.944	0.671	0.895	0.288	0.277	0.952	0.684

**eTable 4. Summary of Parameter Estimates from Linear Mixed Models for Amyloid Positive Adults Only.**

Parameter estimates and standard errors are reported above for each cognitive outcome in amyloid positive adults, with positivity determined for both 2SD and 3SD thresholds. The primary predictor of interest, the SUVR x Time interaction, was significant for episodic memory and marginally significant for MMSE, regardless of positivity threshold. This indicates that there is a dose-response relationship between amyloid burden and episodic memory decline within the smaller amyloid positive only sample. Unlike in the whole sample, the SUVR x Time interaction failed to reach

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significance for processing speed or vocabulary. . Education x Time, APOE x Time, Sex x Time, and Age x SUVR x Time estimates for all cognitive variables failed to reach marginal significance and were removed from the models. <sup>a</sup>p<.05 in bold.



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Cognitive Outcome		Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		Reasoning (z)		MMSE			
Effect	Statistic	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status	2SD A $\beta$ Status	3SD A $\beta$ Status		
Effects of Time	Time	<i>Est (SE)</i>	-0.60 (2.06)	0.26 (1.66)	-1.17 (1.20)	-0.40 (0.93)	1.54 (1.02)	1.04 (0.78)	0.15 (1.26)	0.82 (1.24)	2.95 (4.23)	1.69 (3.26)	
		<i>p</i>	0.773	0.875	0.331	0.671	0.132	0.184	0.906	0.512	0.487	0.605	
	SUVR x Time	<i>Est (SE)</i>	0.64 (2.00)	-0.21 (1.60)	1.27 (1.16)	0.61 (0.91)	-1.46 (0.99)	-0.97 (0.76)	-0.19 (1.23)	-0.32 (1.22)	-4.31 (4.15)	-2.80 (3.14)	
		<i>p</i>	0.751	0.898	0.274	0.508	0.142	0.201	0.876	0.791	0.302	0.375	
	Age x Time	<i>Est (SE)</i>	-	-	-0.01 (0.00)	<b>-0.01 (0.00)</b>	-	-	-	-0.01 (0.00)	-	-	
		<i>p</i>	-	-	0.044	<b>0.01</b>	-	-	-	0.059	-	-	
	Ed. x Time	<i>Est (SE)</i>	-	-	-	-	-	-	-	-	<b>0.14 (0.06)</b>	<b>0.12 (0.06)</b>	
		<i>p</i>	-	-	-	-	-	-	-	-	<b>0.039</b>	<b>0.040</b>	
	Other Main Effects	SUVR	<i>Est (SE)</i>	-0.82 (1.90)	-0.82 (1.52)	0.09 (2.07)	0.10 (1.64)	<b>4.32 (2.18)</b>	<b>3.89 (1.80)</b>	<b>5.23 (1.99)</b>	<b>3.41 (1.59)</b>	6.37 (3.36)	4.24 (2.60)
			<i>p</i>	0.668	0.589	0.967	0.95	<b>0.049</b>	<b>0.024</b>	<b>0.009</b>	<b>0.034</b>	0.059	0.105
Age		<i>Est (SE)</i>	<b>-0.01 (0.00)</b>	<b>-0.02 (0.01)</b>	<b>-0.04 (0.01)</b>	<b>-0.04 (0.01)</b>	<b>0.02 (0.01)</b>	<b>0.02 (0.01)</b>	<b>-0.04 (0.01)</b>	<b>-0.04 (0.01)</b>	<b>-0.02 (0.01)</b>	<b>-0.02 (0.01)</b>	
		<i>p</i>	<b>0.006</b>	<b>0.001<sup>a</sup></b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	.011	<b>0.005</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.004</b>	<b>0.002</b>	
Ed.		<i>Est (SE)</i>	<b>0.07 (0.03)</b>	<b>0.08 (0.02)</b>	<b>0.08 (0.03)</b>	<b>0.06 (0.03)</b>	<b>0.18 (0.03)</b>	<b>0.19 (0.03)</b>	<b>0.10 (0.03)</b>	<b>0.10 (0.03)</b>	-0.00 (0.05)	0.02 (0.05)	
		<i>p</i>	<b>0.005</b>	<b>0.001</b>	<b>0.012</b>	<b>0.029</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.001</b>	<b>0.001</b>	0.932	0.687	

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	<b>Sex</b>	<i>Est (SE)</i>	<b>0.74 (0.11)</b>	<b>0.75 (0.11)</b>	<b>0.29 (0.14)</b>	<b>0.30 (0.13)</b>	0.26 (0.15)	0.26 (0.14)	0.03 (0.13)	-0.02 (0.12)	<b>0.43 (0.18)</b>	<b>0.49 (0.17)</b>
		<i>p</i>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.039</b>	<b>0.022</b>	0.080	0.066	0.800	0.866	<b>0.021</b>	<b>0.006</b>
	<b>APOE</b>	<i>Est (SE)</i>	0.02 (0.14)	0.003 (0.13)	<b>-0.39 (0.17)</b>	<b>-0.34 (0.16)</b>	-0.18 (0.18)	-0.19 (0.17)	0.11 (0.16)	0.12 (0.15)	-0.41 (0.23)	<b>-0.45 (0.21)</b>
		<i>p</i>	0.903	0.979	<b>0.024</b>	<b>0.033</b>	0.330	0.251	0.483	0.415	0.073	<b>0.034</b>

**eTable 5. Summary of Parameter Estimates from Linear Mixed Models for Amyloid Negative Adults Only.**

Parameter estimates and standard errors are reported above for each cognitive outcome in amyloid negative adults, with negativity determined for both 2SD and 3SD thresholds. . There were no significant SUVR x Time interactions for any cognitive variable regardless of threshold, suggesting relatively high SUVR within the amyloid negative range is not associated with cognitive decline. However, there was a significant Age x Time interaction for processing speed (and a marginal significant Age x Time for reasoning), such that old age was predictive of greater processing speed decline, independent of amyloid burden (see eFigure 3). There was also a significant Education x Time interaction for MMSE, such that increasing education was associated with more positive change in MMSE. APOE x Time, Sex x Time, and Age x SUVR x Time estimates for all cognitive variables failed to reach marginal significance and were removed from the models. <sup>a</sup>p<.05 in bold.

Cognitive Outcome		Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		Reasoning (z)		MMSE	
		<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>
Effects of Time	Time	2.87 (1.73)	0.103	-1.34 (1.00)	0.188	<b>2.18</b> <b>(0.89)</b>	<b>0.019</b>	-0.40 (1.04)	0.704	-3.83 (3.35)	0.26
	SUVR x Time	-2.63 (1.65)	0.118	1.08 (0.96)	0.263	<b>-2.05</b> <b>(0.86)</b>	<b>0.021</b>	0.38 (1.00)	0.705	4.32 (3.20)	0.184
Other Main Effects	SUVR	-0.54 (1.72)	0.754	1.28 (2.05)	0.537	1.74 (2.24)	0.441	0.06 (1.93)	0.974	-0.04 (2.96)	0.988
	Age	0.02 (0.02)	0.315	-0.03 (0.02)	0.263	0.03 (0.03)	0.239	-0.04 (0.02)	0.117	-0.04 (0.03)	0.224
	Ed.	<b>0.10</b> <b>(0.04)</b>	<b>0.038<sup>a</sup></b>	0.06 (0.06)	0.281	<b>0.17</b> <b>(0.06)</b>	<b>0.009</b>	0.07 (0.05)	0.181	0.10 (0.07)	0.148
	Sex	<b>0.83</b> <b>(0.19)</b>	<b>&lt;0.001</b>	0.03 (0.25)	0.903	0.43 (0.27)	0.122	0.23 (0.23)	0.324	0.29 (0.31)	0.352
	APOE	-0.10 (0.19)	0.579	0.14 (0.24)	0.575	-0.22 (0.27)	0.413	0.01 (0.29)	0.95	-0.61 (0.30)	0.051

**eTable 6. Summary of Parameter Estimates from Linear Mixed Models for Middle-Aged Adults Only.**

Parameter estimates and standard errors are reported above for each cognitive outcome in the middle-aged subsample (n=51). There was a significant SUVR x Time interaction for vocabulary, such that increasing SUVR predicted increasingly negative change. The SUVR x Time interaction failed to reach statistical significance for any other cognitive variable. There was also a significant main effect of time for vocabulary, with individuals showing improvement over time. Age x Time, Education x Time, APOE x Time, Sex x Time, and Age x SUVR x Time estimates for all cognitive variables failed to reach marginal significance and were removed from the models. <sup>a</sup>p<.05 in bold.

Cognitive Outcome		Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		Reasoning (z)		MMSE	
		<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>	<i>Est</i> (SE)	<i>p</i>
Effects of Time	Time	1.06 (0.43)	0.016 <sup>a</sup>	1.26 (0.42)	0.003	0.50 (0.22)	0.024	1.72 (0.63)	0.007	2.33 (0.89)	0.01
	SUVR x Time	-1.03 (0.38)	0.008	-0.53 (0.22)	0.019	-0.46 (0.19)	0.019	-0.29 (0.33)	0.389	-1.63 (0.79)	0.041
	Age x Time	-	-	-0.02 (0.01)	0.005	-	-	-0.02 (0.01)	0.009	-	-
Other Main Effects	SUVR	-0.25 (0.38)	0.509	-0.56 (0.40)	0.173	-0.92 (0.47)	0.049	-0.82 (0.42)	0.053	-0.19 (0.64)	0.77
	Age	-0.02 (0.01)	0.017	-0.04 (0.01)	<0.001	0.001 (0.01)	0.912	-0.02 (0.01)	0.017	-0.03 (0.01)	0.012
	Ed.	0.07 (0.03)	0.005	0.05 (0.03)	0.137	0.22 (0.04)	<0.001	0.10 (0.03)	0.001	0.08 (0.03)	0.04
	Sex	0.73 (0.12)	<0.001	0.46 (0.14)	0.002	0.17 (0.17)	0.312	0.01 (0.14)	0.969	0.58 (0.19)	0.002
	APOE	-0.05 (0.15)	0.729	0.29 (0.17)	0.104	-0.11 (0.20)	0.58	-0.23 (0.17)	0.193	0.09 (0.23)	0.682

**eTable 7. Summary of Parameter Estimates from Linear Mixed Models for Older Adults Only.**

Parameter estimates and standard errors are reported above for each cognitive outcome in the older adult subsample (n=123). Results were very similar to those for the larger sample aged 40-89, suggesting the whole sample effects were primarily driven by the older adults. The SUVR x Time interaction was significant for episodic memory, processing speed, vocabulary and MMSE, indicating a significant dose-response relationship between baseline amyloid burden and cognitive change (see eFigure5). There was also a significant positive main effect of Time for episodic memory, processing speed, vocabulary, reasoning and MMSE, indicating that there was an increase over time in these variables independent of amyloid burden. Next, we detected a significant Age x Time interaction for processing speed and reasoning, such that old age was associated with greater cognitive decline, independent of amyloid burden. The Age x Time interaction failed to reach marginal significance for the remaining cognitive variables and was removed from the models. Education x Time, APOE x Time, Sex x Time, and Age x SUVR x Time estimates for all cognitive variables failed to reach marginal significance and were removed from the models. <sup>a</sup>p<.05 in italics.