
Cortical thickness changes precede high levels of amyloid by at least 7 years

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SUPPLEMENTARY INFORMATION

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Obs.	ADNI NC (Obs=2252)	BACS (Obs=807)	LCBC (Obs=1511)	Overall (Obs=4570)
Age				
Mean (SD)	75.7 (6.45)	78.0 (5.95)	63.5 (14.2)	72.1 (11.4)
Median [Min, Max]	75.6 [55.8, 95.0]	77.9 [57.4, 96.3]	69.7 [30.1, 89.5]	74.0 [30.1, 96.3]
Sex				
Female	1177 (52.3%)	465 (57.6%)	901 (59.6%)	2543 (55.6%)
Male	1075 (47.7%)	342 (42.4%)	610 (40.4%)	2027 (44.4%)
N	(N=461)	(N=165)	(N=425)	(N=1051)
Sex				
Female	257 (55.7%)	96 (58.2%)	254 (59.8%)	607 (57.8%)
Male	204 (44.3%)	69 (41.8%)	171 (40.2%)	444 (42.2%)
N Timepoints				
Mean (SD)	4.89 (2.30)	4.87 (2.62)	3.56 (1.42)	4.35 (2.15)
Median [Min, Max]	5.00 [2.00, 11.0]	4.00 [2.00, 14.0]	3.00 [2.00, 7.00]	4.00 [2.00, 14.0]
Follow-up interval (years)				
Mean (SD)	4.46 (2.85)	5.41 (3.54)	5.97 (3.99)	5.22 (3.53)
Median [Min, Max]	4.00 [0.507, 13.1]	4.48 [0.504, 15.4]	4.52 [0.522, 16.0]	4.03 [0.504, 16.0]
APOE ε4 carrier				
No	316 (68.5%)	121 (73.3%)	165 (38.8%)	602 (57.3%)
Yes	139 (30.2%)	44 (26.7%)	88 (20.7%)	271 (25.8%)
Missing	6 (1.3%)	0 (0%)	172 (40.5%)	178 (16.9%)
Education (years)				
Mean (SD)	16.5 (2.63)	17.0 (1.96)	16.8 (2.50)	16.7 (2.49)
Median [Min, Max]	16.0 [6.00, 20.0]	17.0 [12.0, 22.0]	16.0 [9.00, 19.0]	16.0 [6.00, 22.0]
Missing	0 (0%)	0 (0%)	71 (16.7%)	71 (6.8%)

Supplementary Table 1

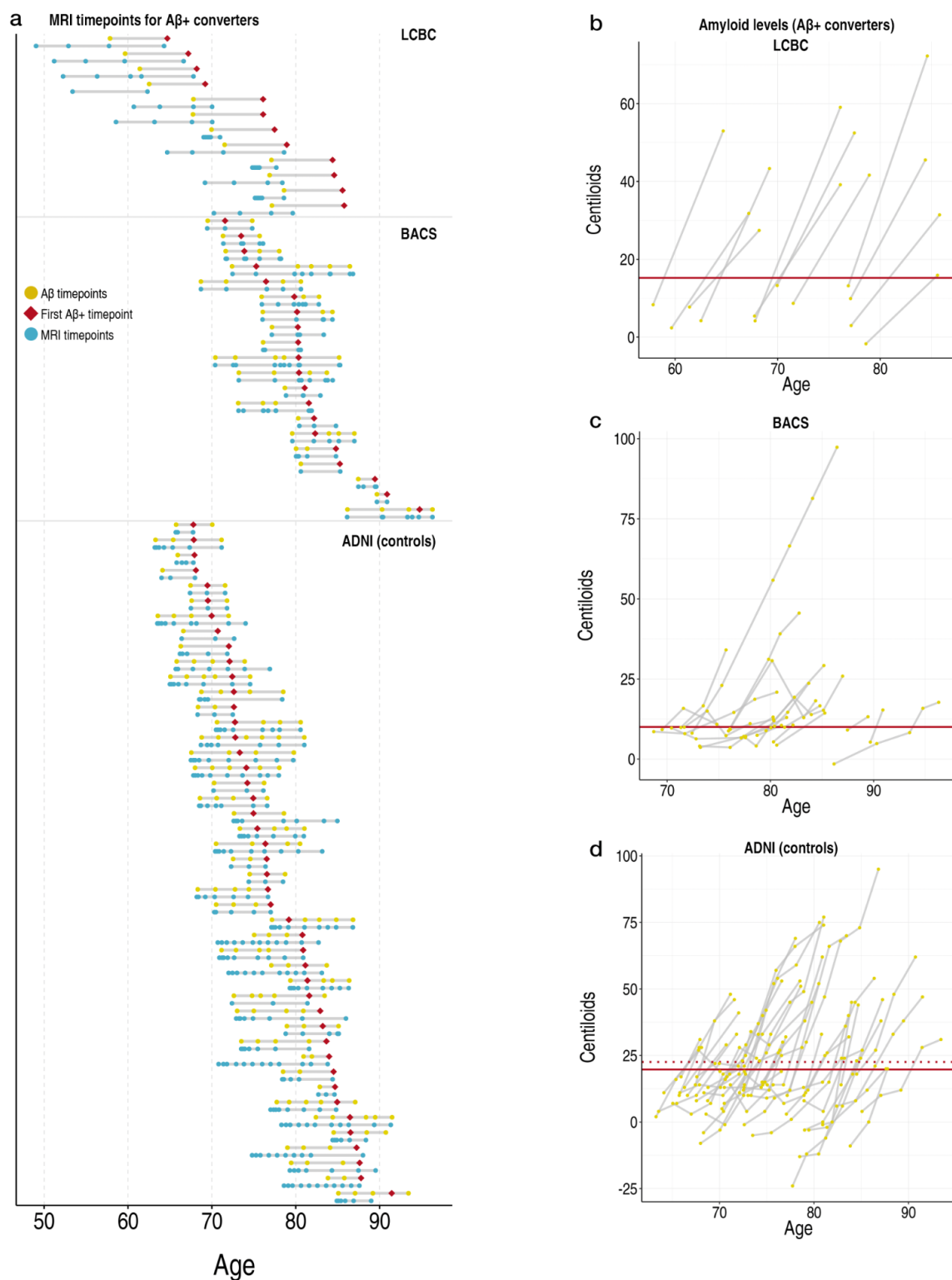
Description of the total combined MRI cohort.

	A β -	A β + converters	p-value	A β - (matched)	p-value	Cohort N (LCBC, BACS, ADNI NC)
Obs	1844	290		589		
N	411	62		124		
Age (baseline)	68.9 (9.9)	70.9 (8.0)	0.0691	70.8 (7.5)	0.879	
Age (mean)	71.4 (9.2)	72.9 (7.5)	0.155	72.7 (7.3)	0.835	
Sex, male	178 (43%)	28 (45%)	0.784	58 (47%)	0.835	
N Timepoints	4.5 (2.2)	4.7 (2.1)	0.51	4.8 (2.1)	0.826	
Follow-up Interval	5.6 (3.6)	4.4 (3.1)	0.00669	4.4 (3.0)	0.876	
Positive for APOE ϵ 4	71 (19%)	25 (42%)	0.000123	23 (20%)	0.0029	(94, 84, 249)
Education	17.0 (2.3)	16.8 (2.4)	0.647	17.1 (2.1)	0.404	(128, 84, 252)
MMSE	29.2 (1.0)	29.0 (1.4)	0.211	29.1 (1.0)	0.437	(137, 84, 252)
			0.136			-
CVLT Learning	51.3 (9.8)	51.1 (9.4)	0.924	51.4 (10.7)	0.907	(137, 84, 0)
	^a		0.668			-
CVLT Immediate	11.1 (3.2)	10.8 (2.9)	0.711	10.9 (3.1)	0.896	(137, 84, 0)
	^a		0.86			-
CVLT Delayed	11.5 (3.2)	11.2 (2.8)	0.644	11.4 (3.1)	0.77	(137, 84, 0)
	^a		0.941			-
Composite Memory (ADNI MEM)	1.2 (0.6)	1.2 (0.5)	0.656	1.1 (0.6)	0.383	(0, 0, 165)
	^a		0.892			-
BMI	26.9 (4.8)	28.1 (5.6)	0.131	26.9 (5.3)	0.164	(133, 69, 250)
	^a		0.0958			-
Systolic Blood Pressure	134.1 (16.0)	131.3 (16.9)	0.277	135.1 (15.3)	0.184	(25, 66, 250)
	^a		0.222			-
Diastolic blood pressure	77.5 (10.8)	74.6 (8.8)	0.0361	77.9 (11.2)	0.0549	(25, 66, 250)
	^a		0.0704		0.0668	-

Supplementary Table 2 (Extended Data Table 1)

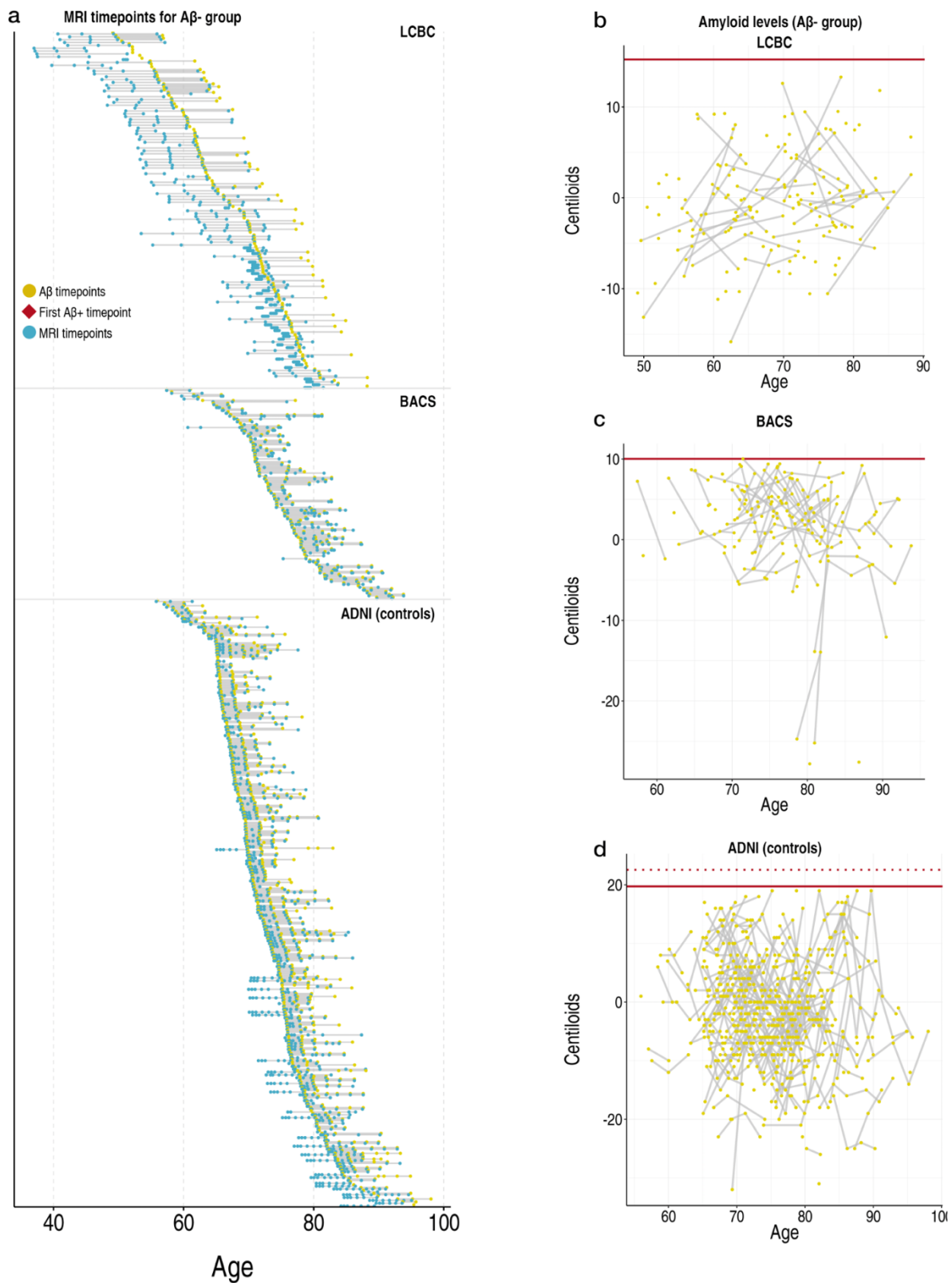
Description of A β - and A β + converter groups in the main sample and the matched A β - group (1-year cutoff).

Data are mean (SD) or number (%). Cognitive, BMI and blood pressure variables are reported for baseline measures. MMSE=mini-mental state, CVLT=California Verbal Learning Test. APOE=apolipoprotein. The p-value columns reflect group-difference tests between 1) the A β + converter and A β - group, and 2) between the A β + converter and matched A β - group after matching on age and follow-up data (Methods). P-values reflect chi-square tests for categorical variables and independent samples t-tests for continuous variables.^a denotes p-values from group-difference t-tests additionally corrected for baseline age. To facilitate interpretation of possible confounding variables, raw p-values are shown with no correction for multiple comparisons applied.



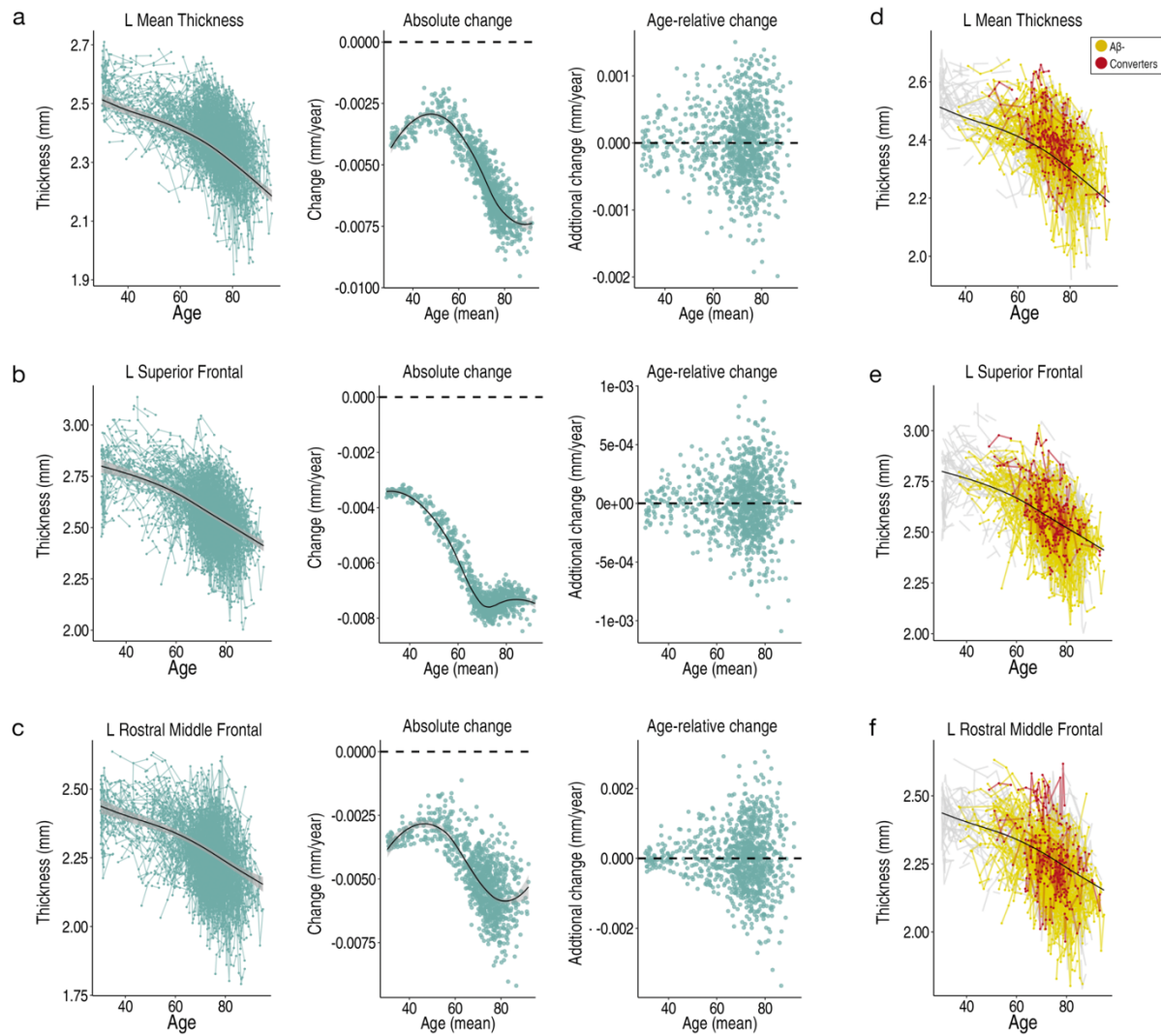
Supplementary Figure 1

Amyloid PET data: Aβ+ converter group. **a** Time trajectories of Aβ PET/MRI scans for the initial 77 converters (as in Fig. 1). The Aβ PET scans for each participant are in yellow and the first Aβ+ scan is depicted with a red diamond (later scans are also Aβ+). Below each is the MRI scans on that participant in blue. **b-d** Amyloid levels in centiloids for the initial 77 converters in each sample. The sample-specific threshold for Aβ-positivity is shown as a solid red line (note we used the Florbetapir threshold in ADNI, as depicted by the solid red line [Florbetaben threshold shown as dotted red line]). Thresholds and centiloid calculations followed published values for BACS^{1,2} and ADNI (Methods), whereas we calculated the conversion threshold in LCBC with gaussian mixture modelling and converted the values to centiloids via the GAAIN pipeline³ (SI Fig. 37).



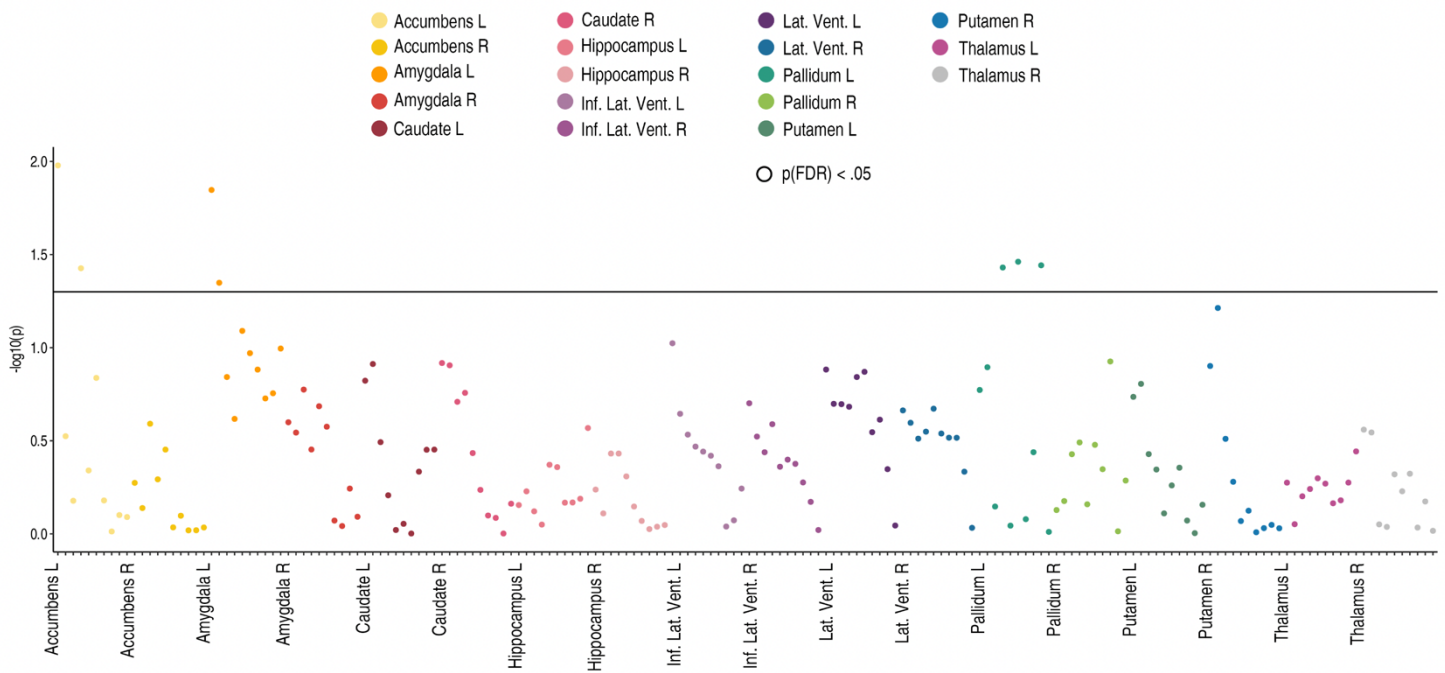
Supplementary Figure 2

Amyloid PET data: A β - group. **a** Time trajectories of A β PET/MRI scans for A β - group. The A β PET scans for each participant are in yellow and the first A β + scan would be depicted with a red diamond (all were A β -). Below each is the MRI scans on that participant in blue. **b-d** Amyloid levels in centiloids for the A β - group in each sample. The sample-specific threshold for A β -positivity is shown as a solid red line (note we used the Flortetapir threshold in ADNI, as depicted by the solid red line [Flortetaben threshold shown as dotted red line]).



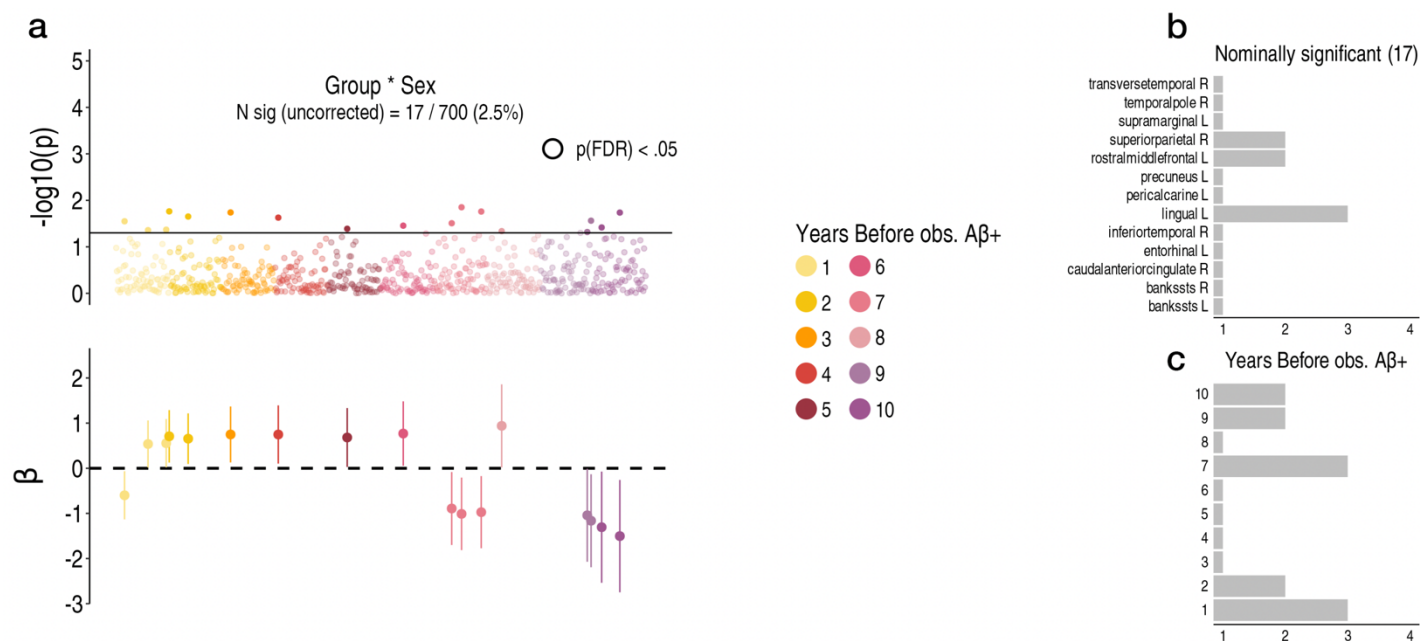
Supplementary Figure 3

Cortical thickness trajectories a-c Longitudinal data was used to estimate change in cortical thickness relative to a person's age, modelling the adult lifespan trajectories using GAMMs with random individual-specific slopes across the cortex (shown for three example thickness measures). Leftmost plots: cortical thickness age trajectories (data corrected for sex, cohort, and scanner field strength). Middle plots: estimated absolute change per individual (datapoints) as a function of their mean age across timepoints. Rightmost plots: estimated age-relative change per individual (i.e. random slopes) as a function of their mean age across timepoints. **d-f** Cortical thickness age trajectories with the data from Aβ+ converters and the Aβ- group overlain.



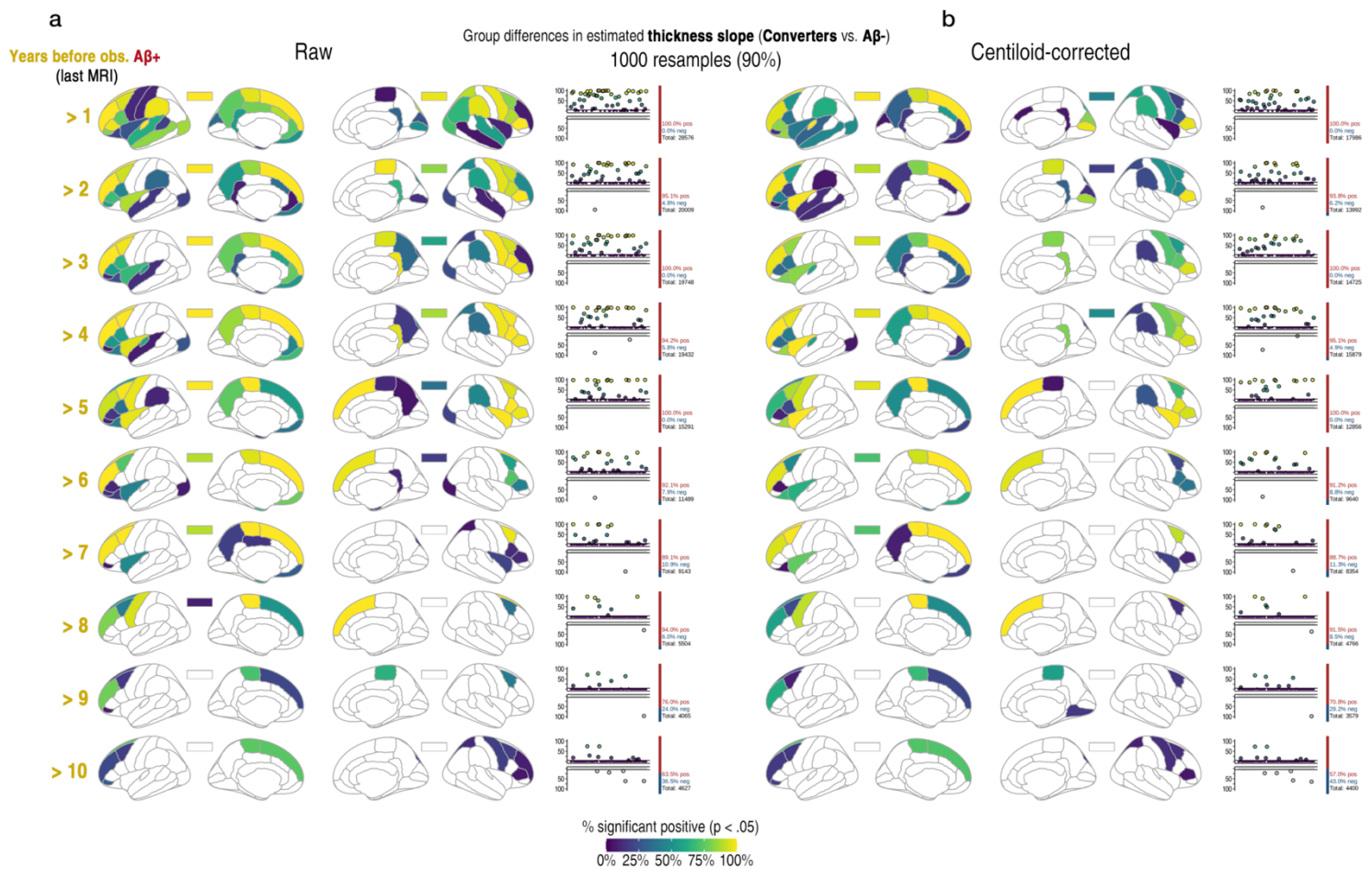
Supplementary Figure 4

Differences in estimated subcortical volumetric change between converter and A β - groups. Log-transformed p-values for the group effect on 18 bilateral subcortical structures from the aseg atlas. The horizontal line depicts $p = 0.05$ (uncorrected). Effects were tested across 18 structures and 10 year cutoffs. Seven effects reached nominal significance at an uncorrected level, but none survived FDR correction for multiple comparisons.



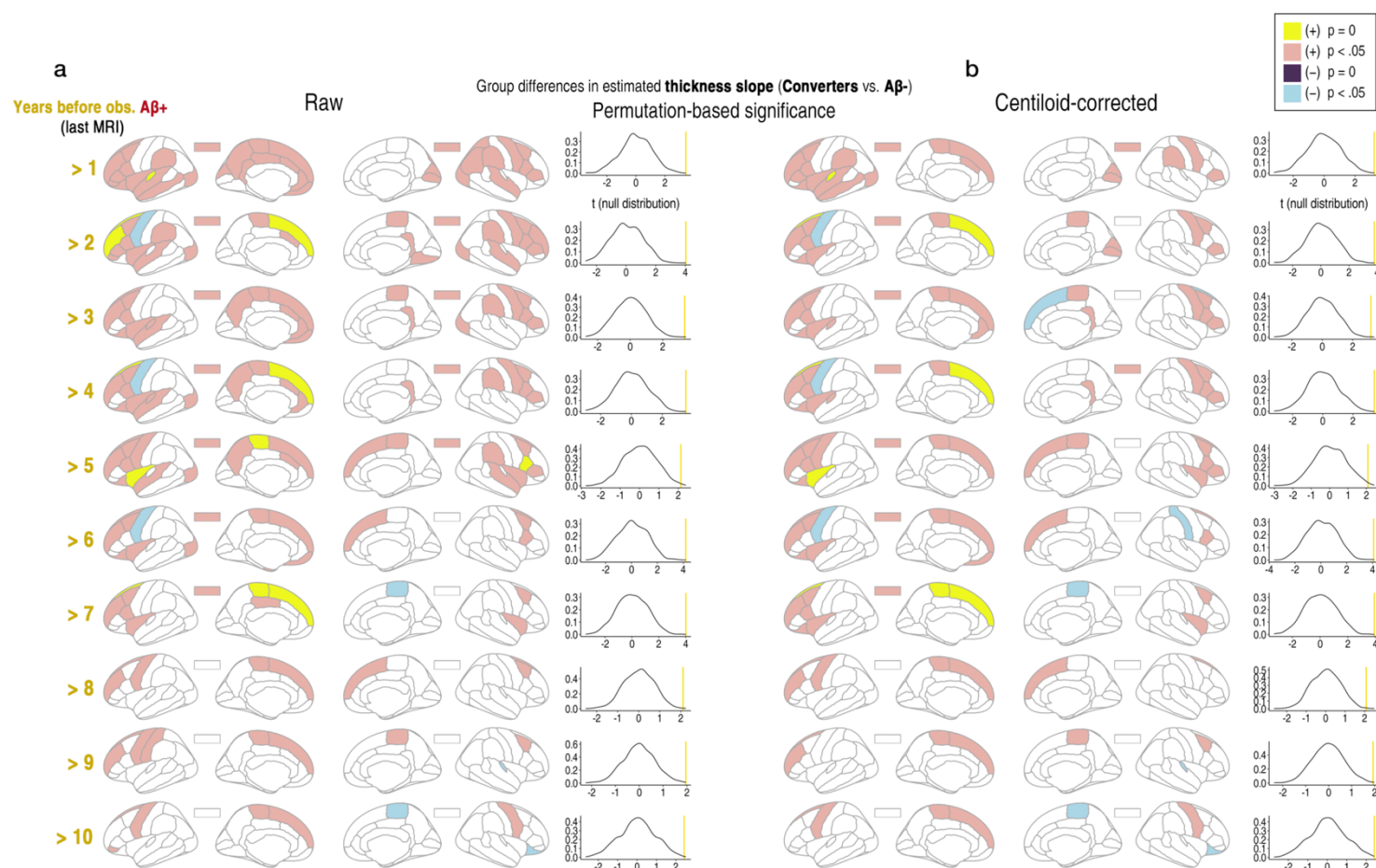
Supplementary Figure 5

Exploratory analysis of sex × group (converter vs. Aβ⁺ group) interactions on estimated cortical thickness change. **a** p-values (above) and standardized β (below). The line depicts p = 0.05 (uncorrected). β's are shown only for effects reaching nominal significance (p < .05). Effects were tested across 70 parcels and 10 follow-up cutoffs; no effects survived FDR-correction. **b** Summary of regions showing nominally significant results and at the cutoffs at which they were observed. These uncorrected effects were spatially and directionally inconsistent across cutoffs. Though we found no evidence for sex × group interactions, the analysis should be interpreted as exploratory, as it is likely to be underpowered.



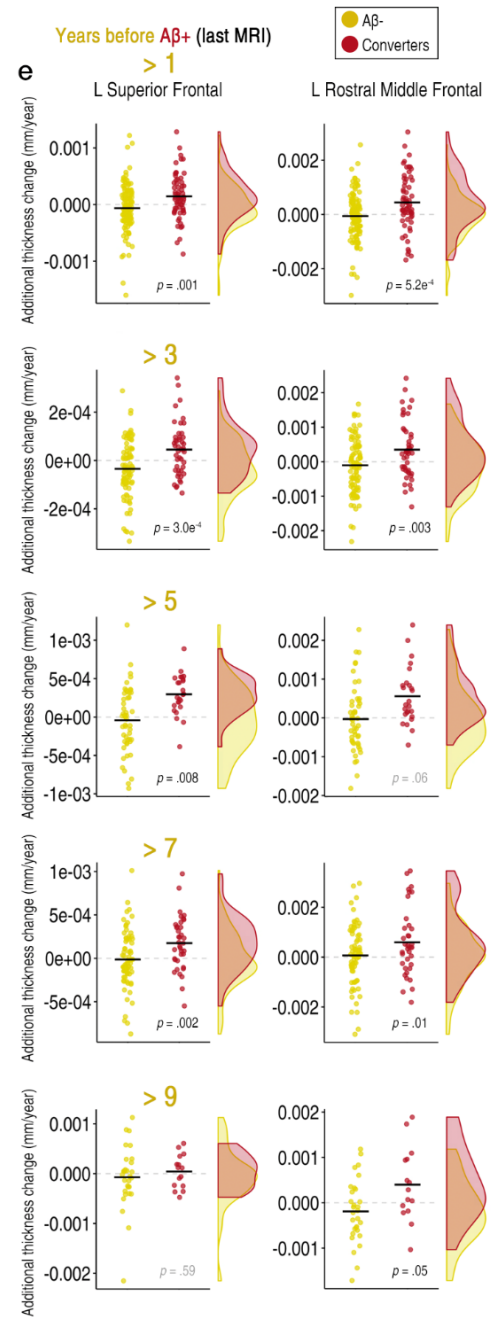
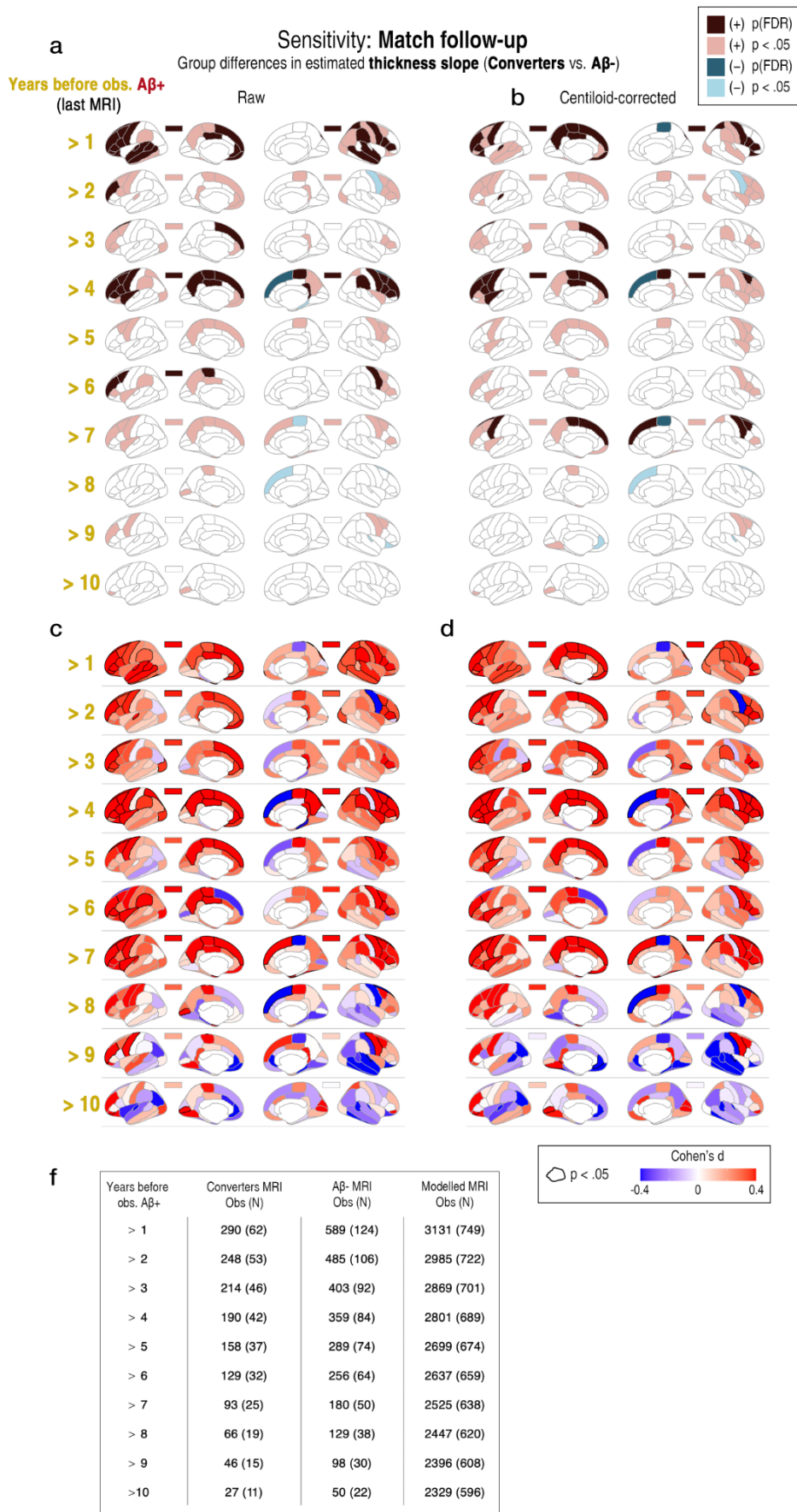
Supplementary Figure 6

Resampling-based robustness check. **a** Maps and plots show the number of times there was a positive significant difference at $p < .05$ when resampling the data drawing 90% of the estimates from each group 1,000 times (70,000 parcel-wise tests). Coloured regions exceeded the nominal 5% chance false positive rate. Each plot shows the percentage count of the number of times we observed a positive and negative effect when the difference was significant at $p < .05$. This illustrates the significance results were robust to sample variations and not driven by only a few observations, though caution is warranted around inferential interpretation.



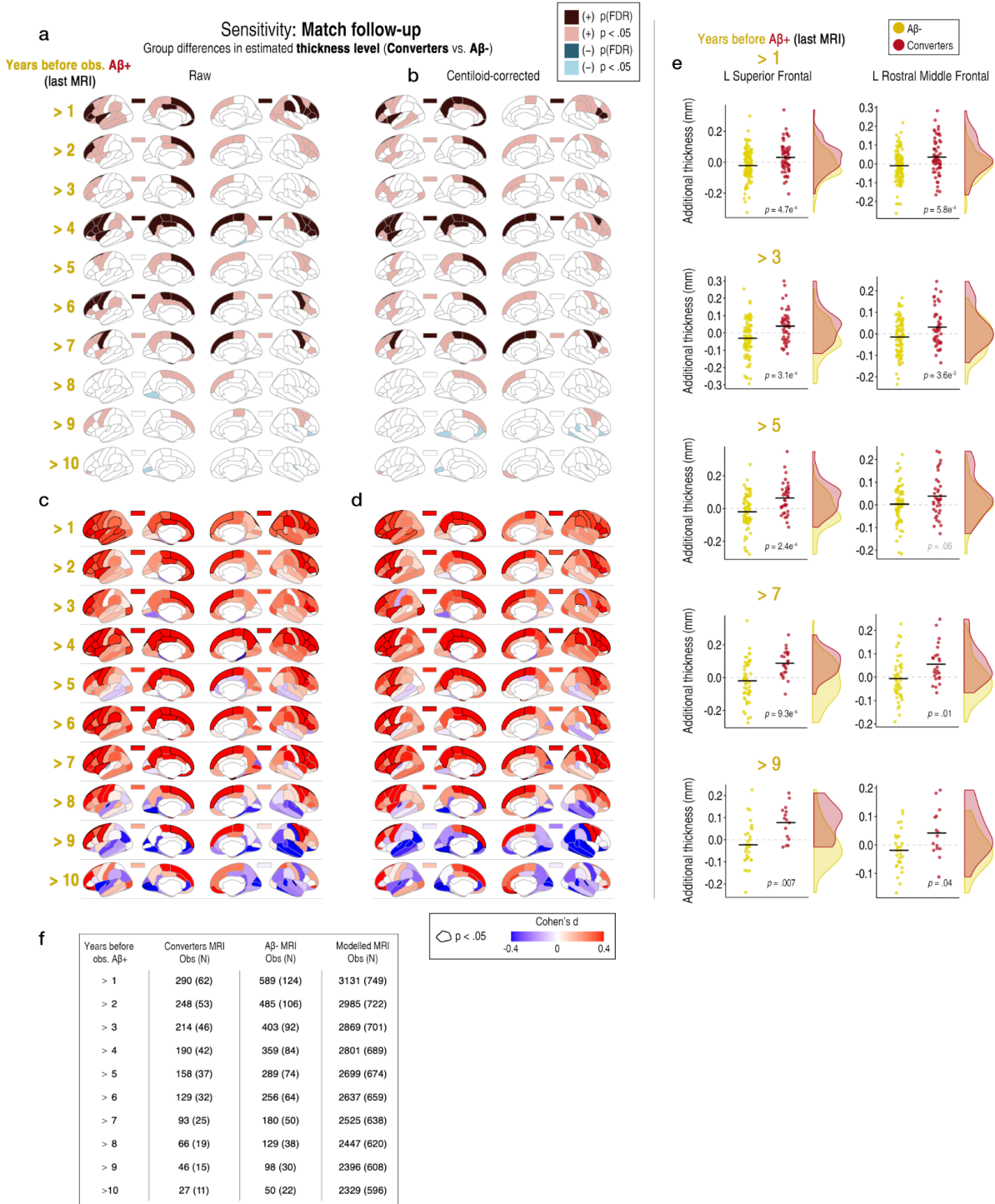
Supplementary Figure 7

Permutation-based significance testing. Significance results across 1000 permutations to evaluate whether observed group differences in estimated cortical thickness change (slopes) could be explained by group differences in variance. Null distributions were generated by randomly flipping the sign of the residuals from a null model excluding group (wild bootstrap resampling), followed by recomputing group comparisons on the resampled slopes. Any group differences arising in these null models would reflect variance imbalance alone. Red/blue parcels reflect empirical p-values < .05 for positive/negative effects, whereas yellow parcels indicate empirical p-values of zero (i.e., the observed test statistic was more extreme than any value in the null distribution). Density plots show the observed test statistic for an example ROI (left superior frontal cortex) overlaid on the null distribution. This illustrates the observed effects were not due to group differences in the variance of the slope estimates⁴.



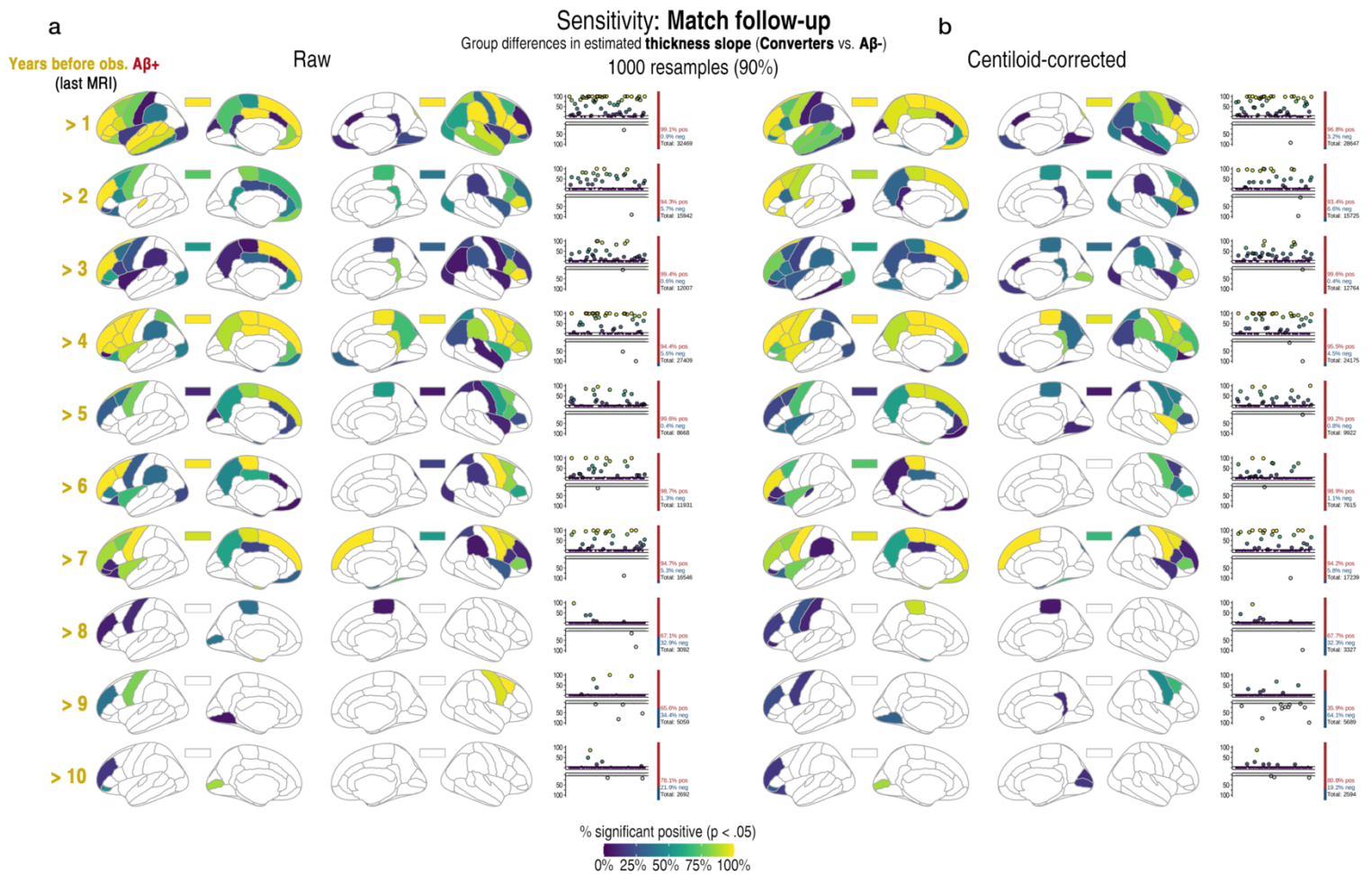
Supplementary Figure 8 (Extended Data Figure 1)

Sensitivity analysis matching groups on follow-up data (Y = estimated thickness change). **a-b** Significance results for the group difference in cortical thickness slopes between A β ⁺ converters and A β ⁻ groups at each cutoff after repeating the analysis drawing two one-to-one matched samples from the A β ⁻ group based on age, the number of MRI scans and time interval covered. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. Note that negative effects that survived correction were not consistently found across similar analyses (see [Extended Data Figs. 2, 3, 5](#)). **a** “Raw” group differences unadjusted for amyloid levels. **b** Differences after adjusting for the mean centroid values across PET scans prior to the first A β ⁺ scan. **c-d** Effect size maps. **e** Differences plotted for two example FDR-significant ROIs at five time cutoffs (datapoints corrected for sex, cohort, mean age, N timepoints, and interval between first and last MRI timepoint). **f** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both A β groups and the total sample submitted to the GAMMs. Source Data files are provided.



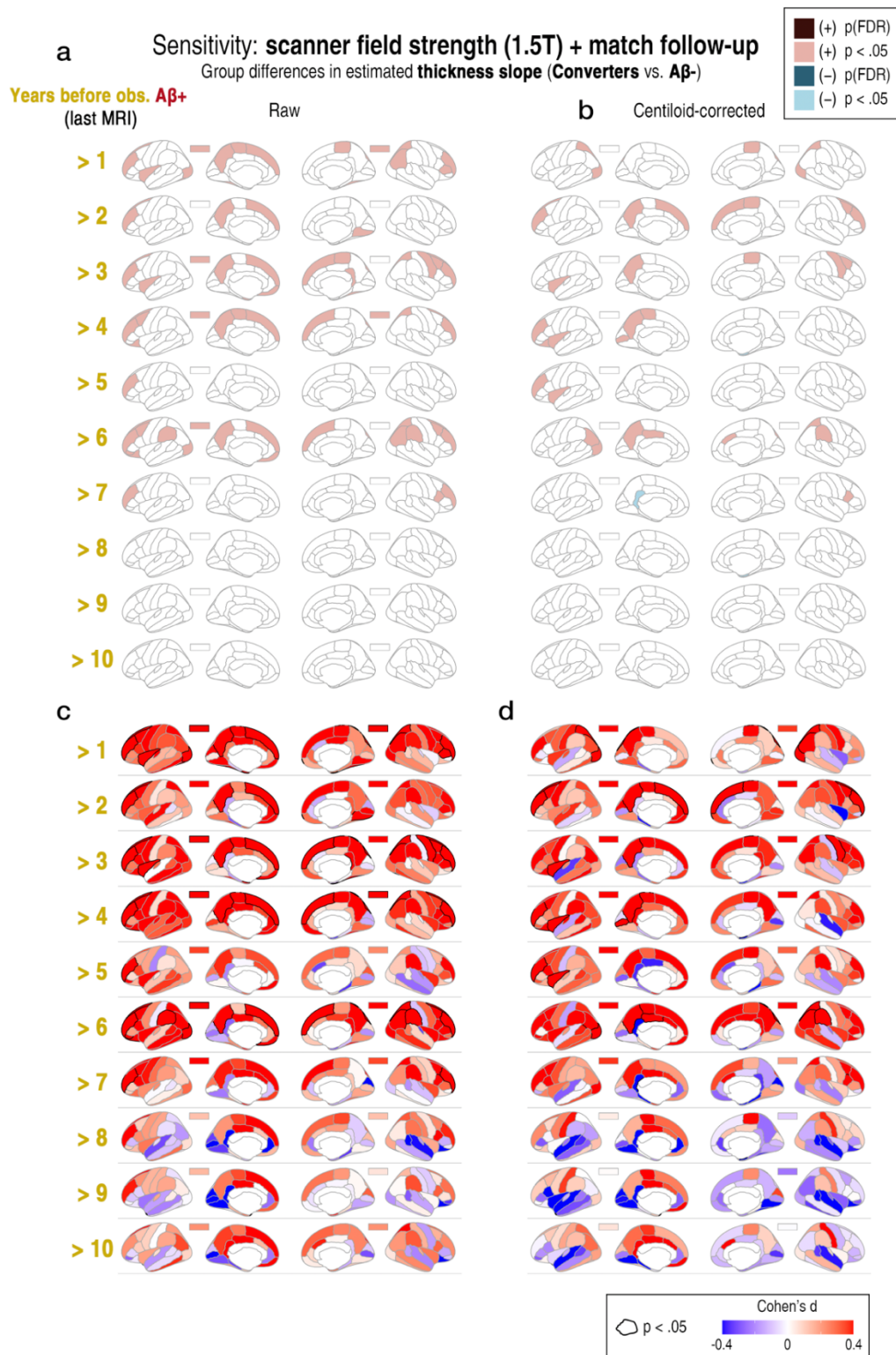
Supplementary Figure 9 (Extended Data Figure 2)

Sensitivity analysis matching groups on follow-up data (Y = estimated thickness level). **a-b** Significance results for the group difference in cortical thickness intercept between $A\beta^+$ converters and $A\beta^-$ groups at each cutoff after repeating the analysis drawing two one-to-one matched samples from the $A\beta^-$ group based on age, the number of MRI scans and time interval covered. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[FDR] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. Compare with [Extended Data Figs. 1, 3](#). **a** “Raw” group differences unadjusted for amyloid levels. **b** Differences after adjusting for the mean centiloid values across PET scans prior to the first $A\beta^+$ scan. **c-d** Effect size maps. **e** Differences plotted for two example FDR-significant ROIs at five time cutoffs (datapoints corrected for sex, cohort, mean age, N timepoints, and interval between first and last MRI timepoint). **f** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both $A\beta$ groups and the total sample submitted to the GAMMs. Source Data files are provided.



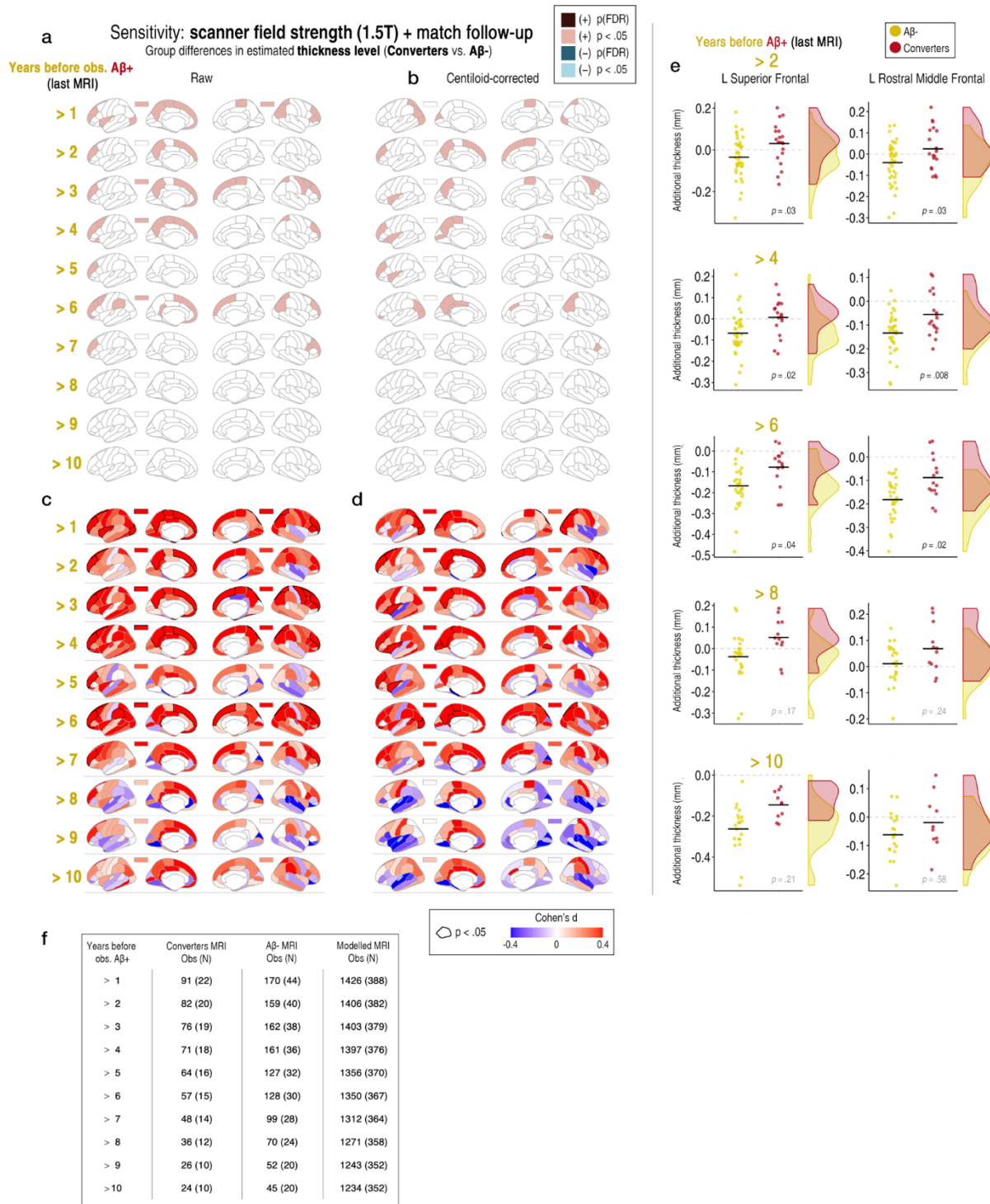
Supplementary Figure 10

Resampling-based robustness check after matching groups on follow-up data. **a** Maps and plots show the number of times there was a positive significant difference at $p < .05$ when resampling the data drawing 90% of the estimates from each group 1,000 times (70,000 parcel-wise tests). Coloured regions exceeded the nominal 5% chance false positive rate. Each plot shows the percentage count of the number of times we observed a positive and negative effect when the difference was significant at $p < .05$. This illustrates the reported significance results were robust to sample variations and not driven by only a few observations, though caution is warranted around inferential interpretation.



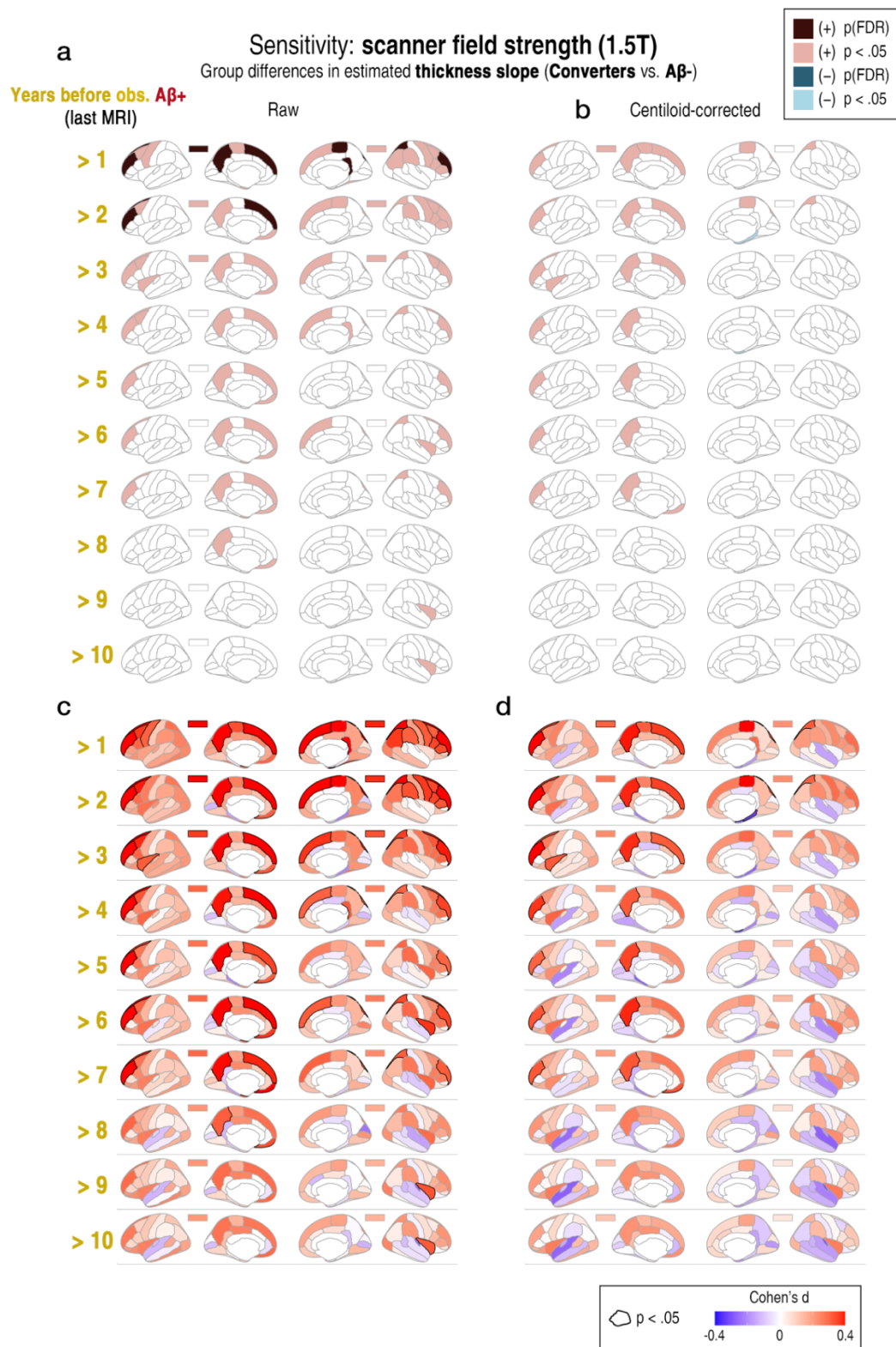
Supplementary Figure 11

Sensitivity analysis matching groups on a single scanner field strength (1.5T) and follow-up data. Y = estimated thickness slope. **a-b** Significance results for the group difference in estimated cortical thickness change between A β ⁺ converters and A β ⁻ groups at each cutoff after repeating the analysis drawing two one-to-one matched samples from the A β ⁻ group based on age, the number of MRI scans and time interval covered. Light red/blue parcels reflect significance at p < .05 for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at p[FDR] < .05 (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** "Raw" group differences unadjusted for amyloid levels. **b** Differences after adjusting for the mean centiloid values across PET scans prior to the first A β ⁺ scan. **c-d** Effect size maps. See [SI Fig. 12f](#) for a description of the exact sample sizes used.



Supplementary Figure 12

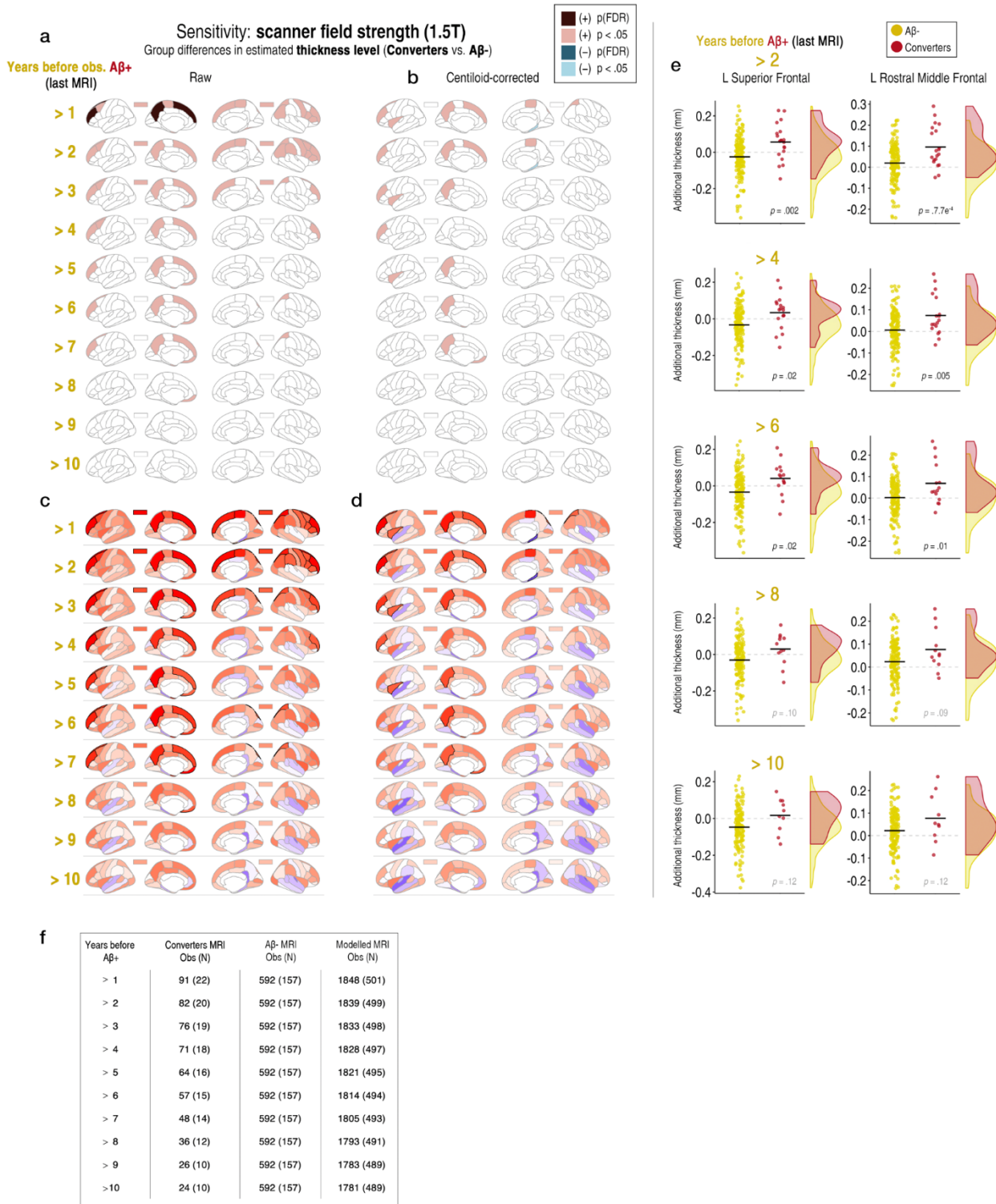
Sensitivity analysis matching groups on a single scanner field strength (1.5T) and follow-up data. Y = estimated thickness intercept (intercept-only models; Methods). **a-b** Significance results for the group difference in cortical thickness level between Aβ⁺ converters and Aβ⁻ groups at each cutoff, after repeating the analysis drawing two one-to-one matched samples from the Aβ⁻ group based on the number of MRI scans and time interval covered. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** "Raw" group differences unadjusted for amyloid levels. **b** Differences after adjusting for the mean centiloid values across PET scans prior to the first Aβ⁺ scan. **c-d** Effect size maps. **e** Differences plotted for two example ROIs at five time cutoffs. Datapoints corrected for sex, cohort, mean age, N timepoints, and interval between first and last MRI timepoint. **f** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both Aβ groups and the total sample submitted to the GAMMs.



Supplementary Figure 13

Sensitivity analysis matching groups on a single scanner field strength only (1.5T). Y = estimated thickness slope. **a-b** Significance results for the group difference in estimated cortical thickness change between A β ⁺ converters and A β ⁻ groups at each cutoff after repeating the analysis using only 1.5T scans. Light red/blue parcels reflect significance at p < .05 for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at p[FDR] < .05 (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** "Raw" group differences unadjusted for amyloid levels. **b**

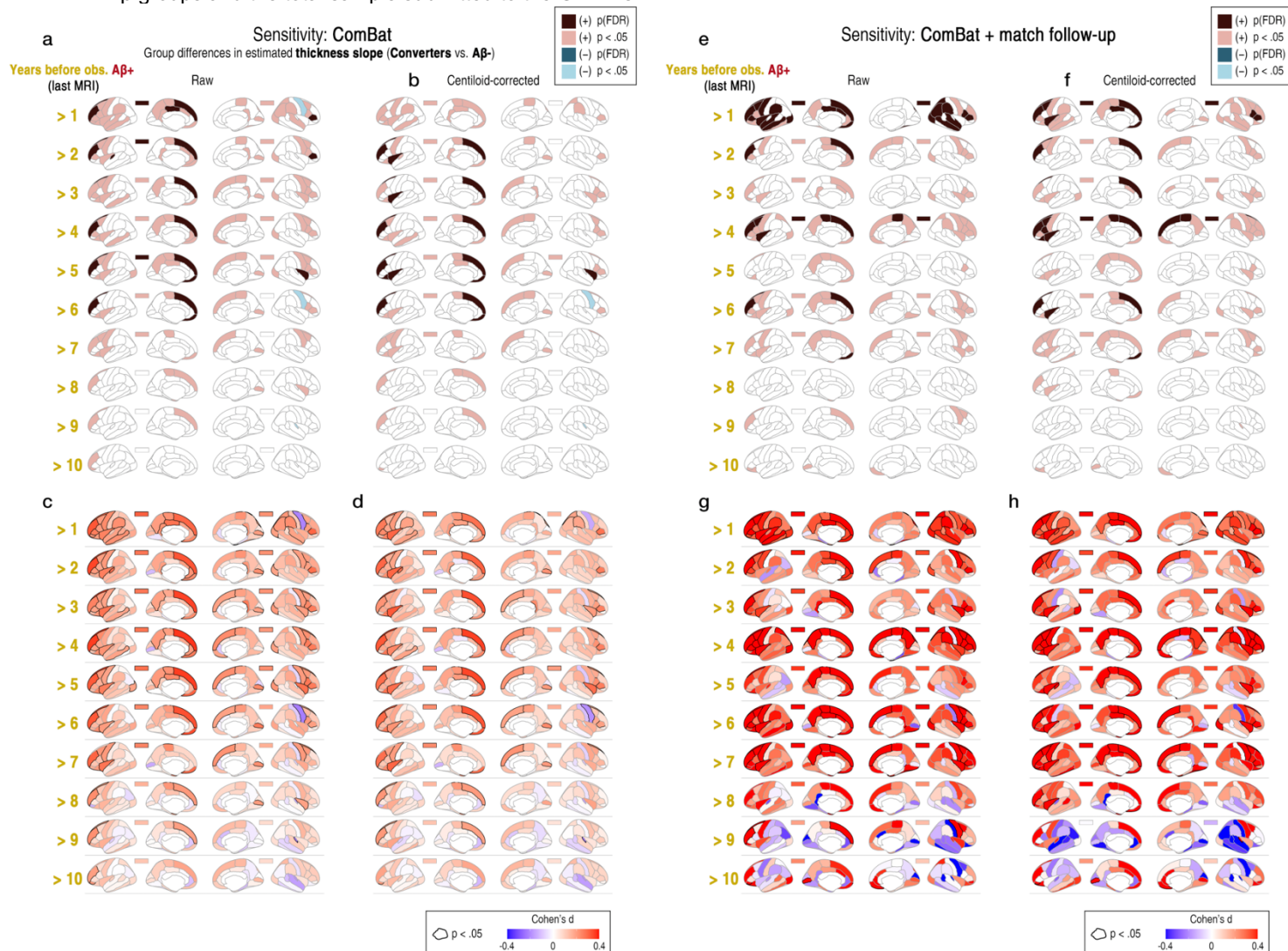
Differences after adjusting for the mean centroid values across PET scans prior to the first A β ⁺ scan. **c-d** Effect size maps. See [SI Fig. 14f](#) for a description of the exact sample sizes used.



Supplementary Figure 14

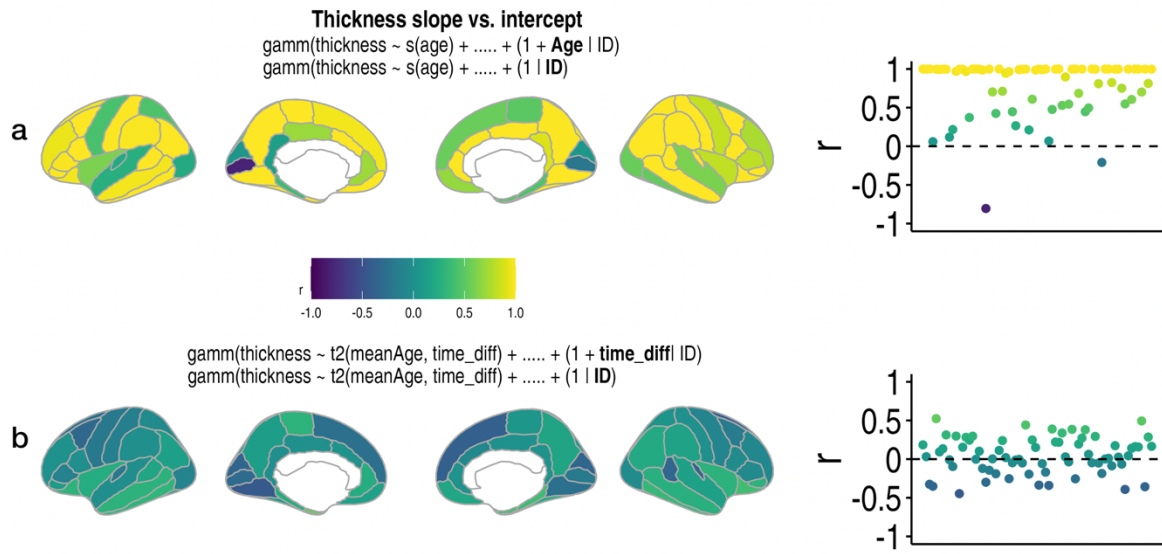
Sensitivity analysis matching groups on a single scanner field strength only (1.5T). Y = estimated thickness intercept (intercept-only models; Methods). **a-b** Significance results for the group difference in cortical thickness level between A β ⁺ converters and A β ⁻ groups at each cutoff after repeating the analysis using only 1.5T scans. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[FDR] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** "Raw" group differences unadjusted for amyloid levels. **b** Differences after adjusting for the mean centroid values across PET scans prior to

the first $A\beta^+$ scan. **c-d** Effect size maps. **e** Differences plotted for two example FDR-significant ROIs at five time cutoffs. Datapoints corrected for sex, cohort, mean age, N timepoints, and interval between first and last MRI timepoint. **f** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both $A\beta$ groups and the total sample submitted to the GAMMs.



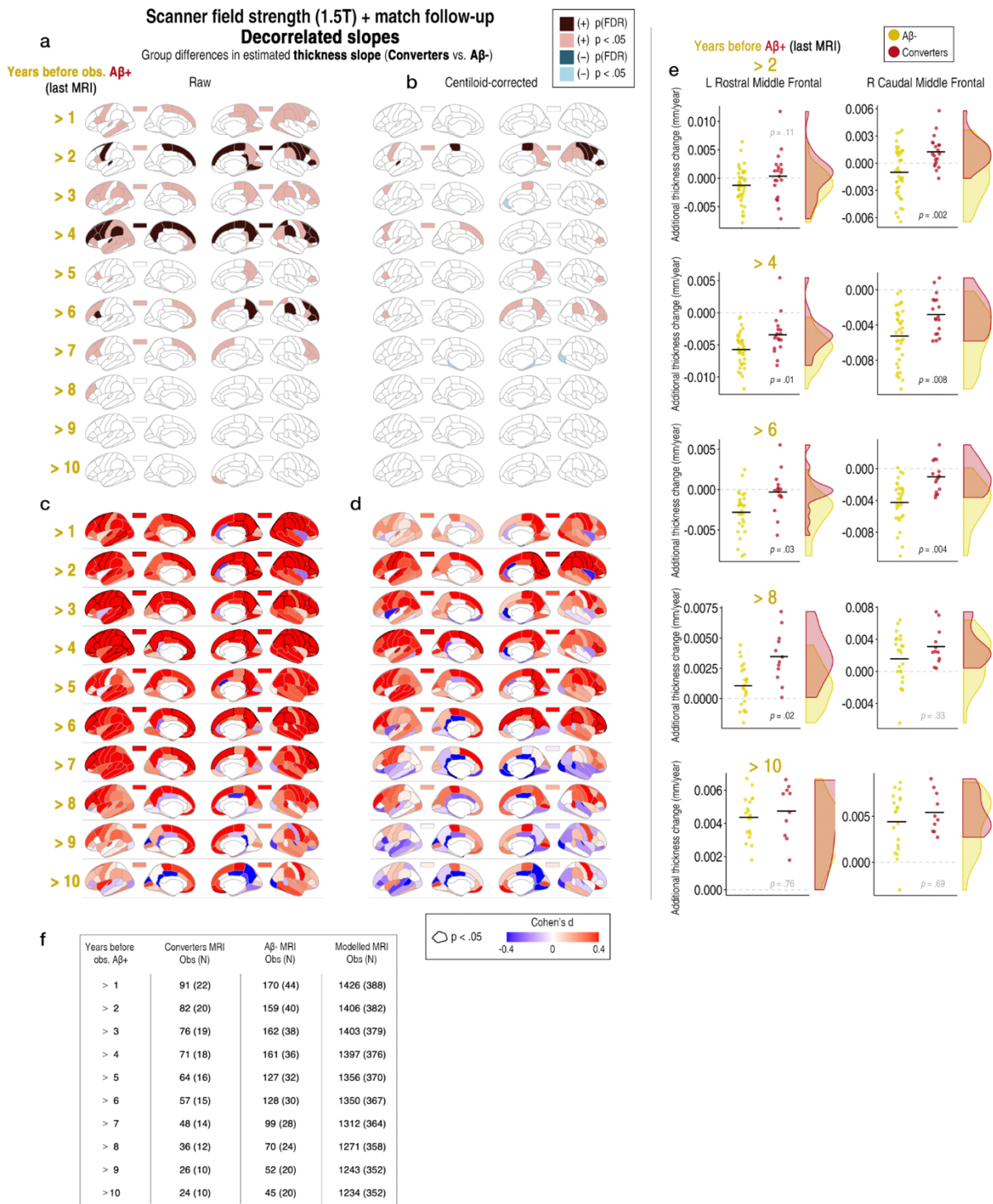
Supplementary Figure 15 (Extended Data Figure 3)

Sensitivity analyses using Longitudinal ComBat⁷. **a-b** Significance results for the group difference in estimated cortical thickness change between $A\beta^+$ converters and $A\beta^-$ groups at each cutoff after using Longitudinal ComBat for site harmonization. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). We modelled scanner (for LCBC and BACS) and scanner strength in ADNI with different identifiers. The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** "Raw" differences unadjusted for amyloid levels. **b** Differences after correcting for quantitative $A\beta$ (mean centiloids across PET scans prior to the first $A\beta^+$ scan). **c-d** Effect size maps. **e-g** Sensitivity analyses using Longitudinal ComBat in matched $A\beta^+$ converter and $A\beta^-$ groups (as in a-d). For a description of the exact sample sizes used, see Fig. 1d (a-d) and Extended Data Fig. 1 (e-h). Source Data files are provided.



Supplementary Figure 16

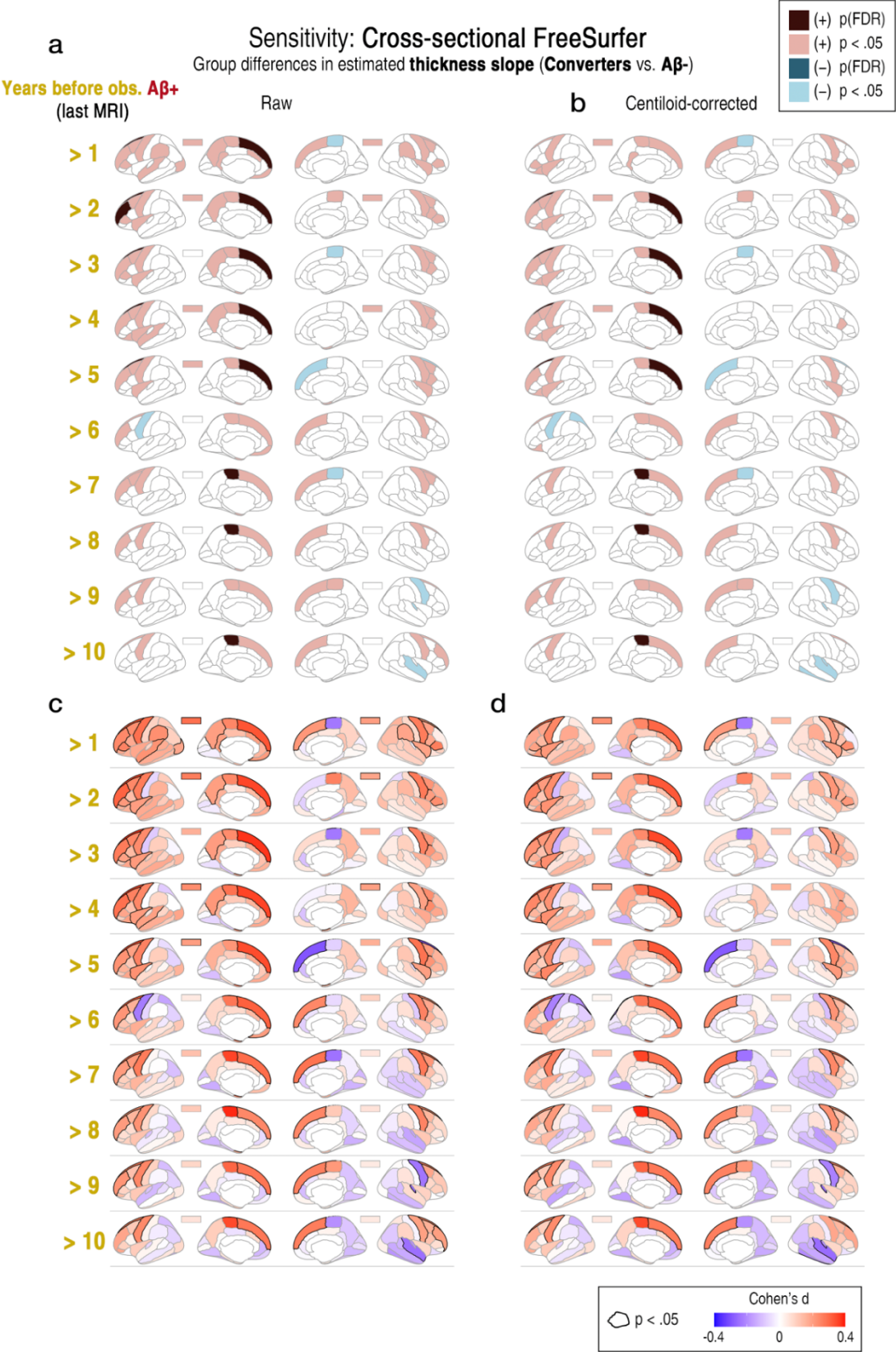
Correlations between the model-estimated random slope and intercept (intercept-only random effects model) in our initial models. To statistically help separate the effects, we ran alternative models using a tensor smooth interaction between mean age and time from mean age, and used the slopes from these models to test group differences in cortical thickness change, with (SI Fig. 18) and without (SI Fig. 17) correcting for the intercept from the intercept-only model.



Supplementary Figure 17

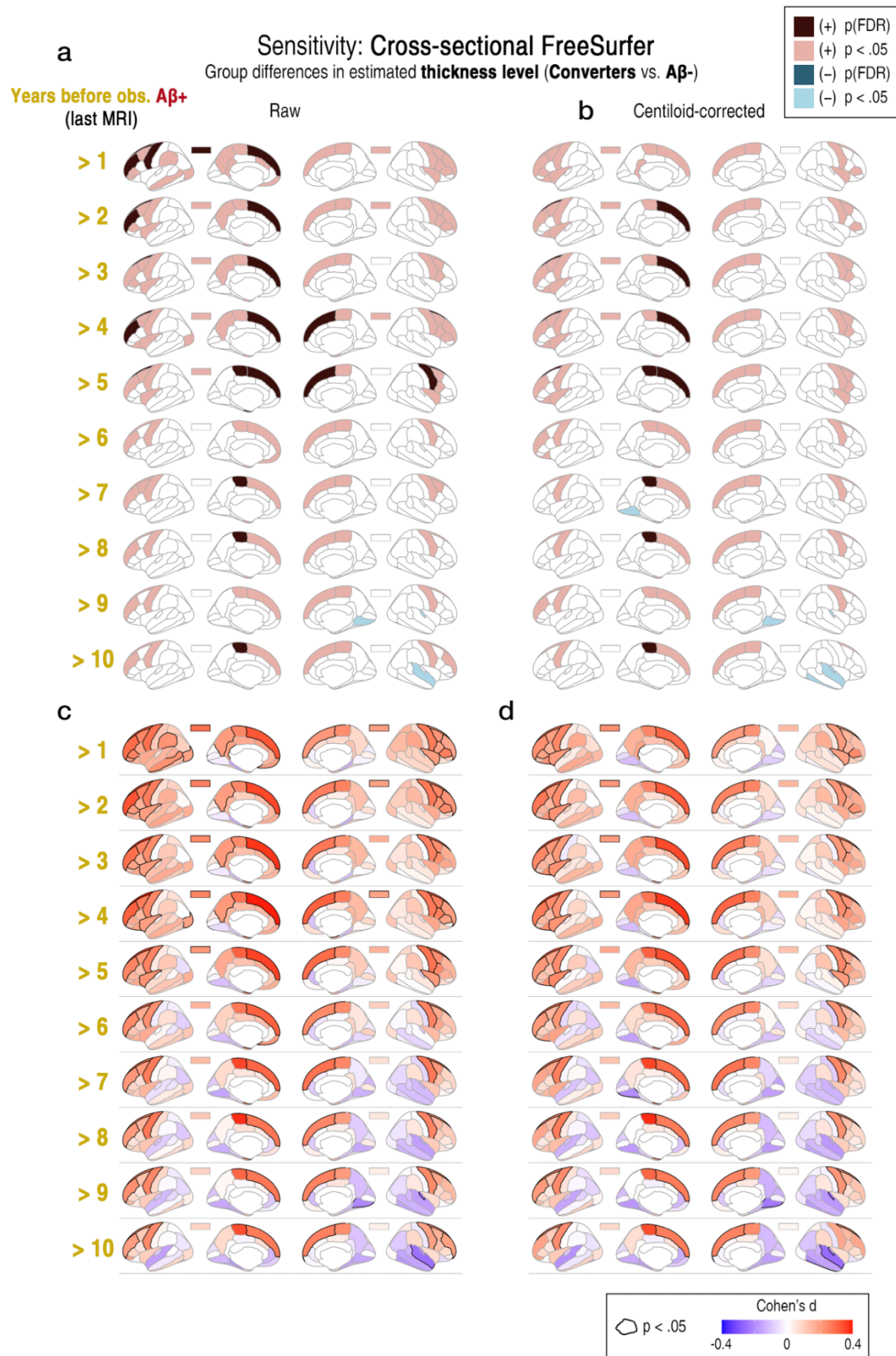
Differences in cortical thickness change between matched Aβ⁺ converter and Aβ⁻ groups (models isolating slope from intercept effects). **a-b** Differences in estimated cortical thickness change between Aβ⁺ converters and Aβ⁻ groups matched on scanner field strength (1.5T scans only), age and follow-up data, using alternative GAMMs to statistically separate slope from intercept effects (tensor smooth interaction models; Methods). Models shown are unadjusted for the intercept (compare with SI Fig. 18 for adjusted results). Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** "Raw" differences unadjusted for amyloid levels. **b** Differences after correcting for the mean centiloid values across PET scans prior to the first Aβ⁺ scan. **c-d** Effect size maps. **e** Differences plotted for two example FDR-significant ROIs at five timepoint cutoffs. Datapoints corrected for sex, cohort, mean age, N timepoints, and interval between first and last MRI timepoint. **f** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both Aβ groups and the total sample submitted to the GAMMs.

for sex, cohort, mean age, N timepoints, and interval between first and last MRI timepoint. See [SI Fig. 17f](#) for a description of the exact sample sizes used.



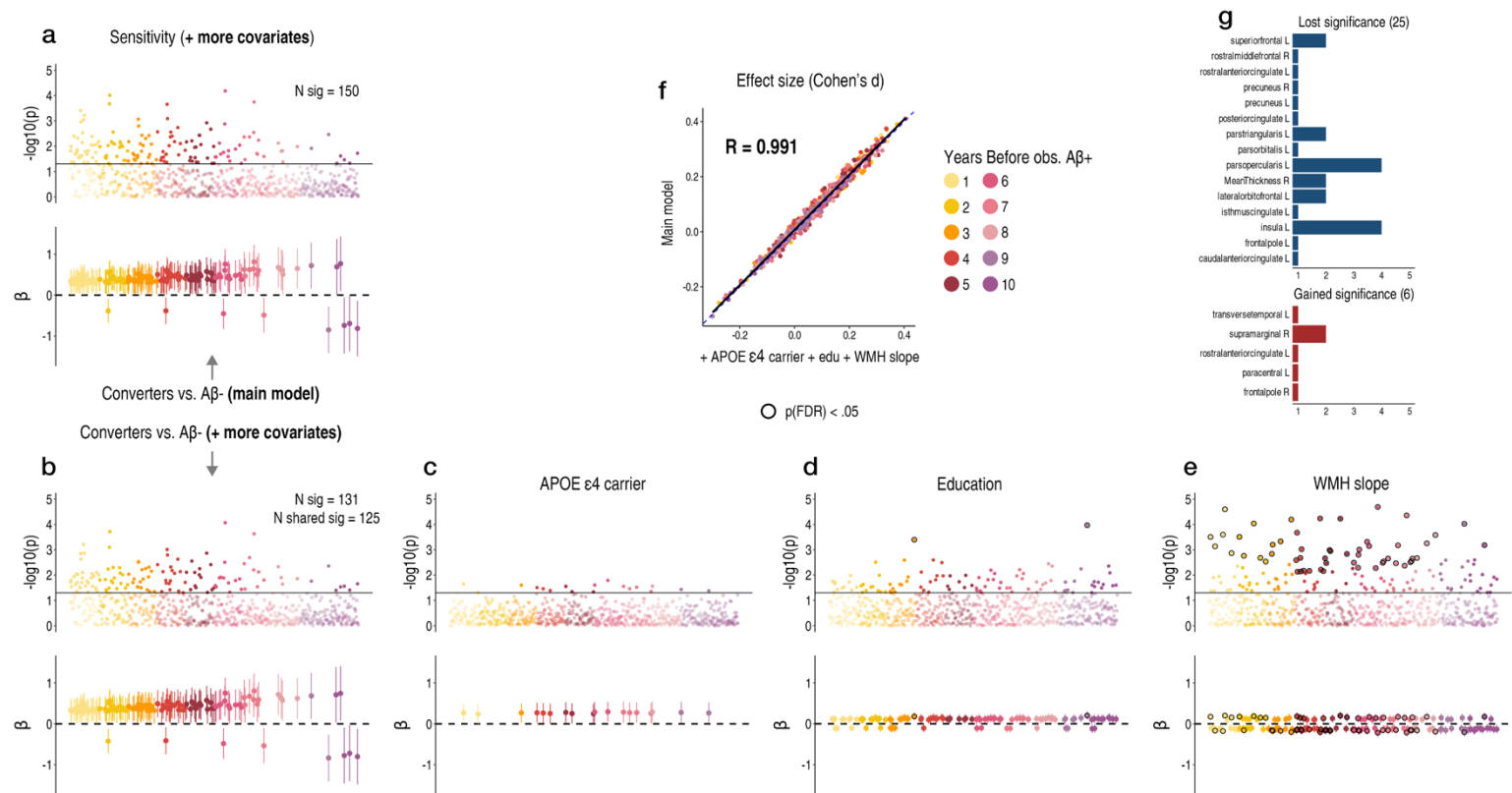
Supplementary Figure 20

Sensitivity analyses using cross-sectional FreeSurfer pipeline. Results from the main analysis (as in [Fig. 1e-h](#), Y = estimated cortical thickness change) using cross-sectionally processed MRI scans with FreeSurfer. See [Fig. 1d](#) for a description of the exact sample sizes used.



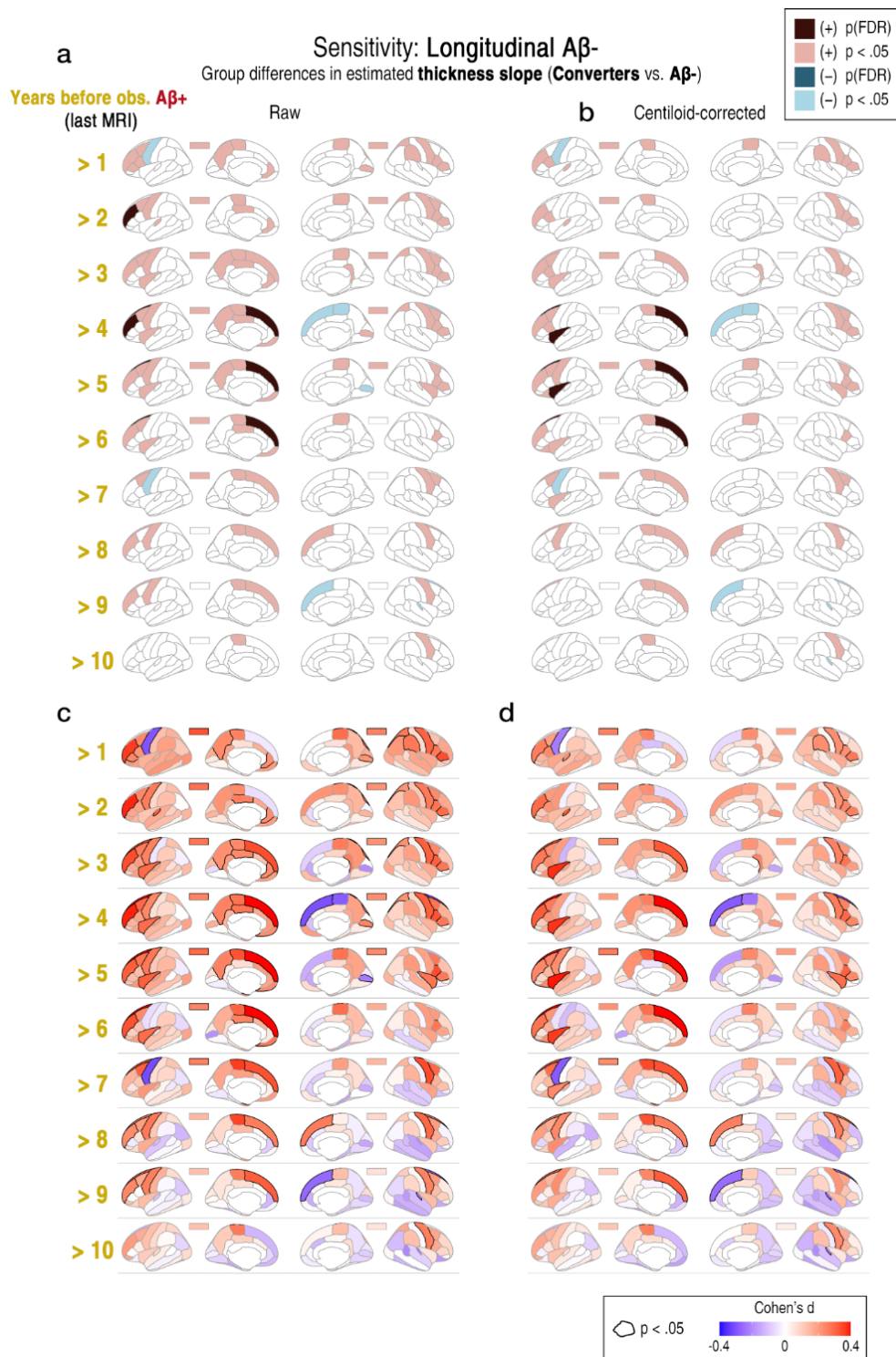
Supplementary Figure 21

Sensitivity analyses using cross-sectional FreeSurfer pipeline. Results from the main analysis (as in Fig. 2b-e, Y = estimated cortical thickness level) using cross-sectionally processed MRI scans with FreeSurfer. See Fig. 1d for a description of the exact sample sizes used.



Supplementary Figure 22 (Extended Data Figure 4)

Sensitivity analyses correcting for additional covariates. **a** p -values (above) and standardized β (below) for the group effect in our main model using a subset with available genetic, education, and WMH information (max N converters = 64, max N $A\beta^-$ = 364 [1-year cutoff], linear models). The line depicts $p = 0.05$ (uncorrected). β 's are shown only for effects that were significant at $p < .05$. Effects are tested across 70 parcels * 10 year cutoffs. Note we did not re-apply correction to the group effect in this reduced sample (see Fig. 1) since the aim of this analysis is to test the stability of the results when adding additional covariates. **b** Group effects in the control models, using APOE $\epsilon 4$ status, education, and WMH accumulation as additional covariates. 125 out of the 131 regions shared significance status. The partial effect of each covariate is shown in **c-e**. Black outlines depict FDR-corrected significant hits applied per map, suggesting only WMH was significantly associated with cortical thinning. Note the sample is comparable to that described in **a**. **f** The full set of 700 effect sizes for the group-difference in our main model correlated at $r = 0.991$ with the control model including additional covariates around the identity line (in blue). **g** Summary of effects that lost and gained significance ($p < .05$). WMH accumulation was modeled as random slopes using GAMMs, similarly as described for cortical thickness trajectories. Education was operationalized as education years. Overall, this sensitivity analysis indicates group differences in cortical thinning are not driven by differences in APOE $\epsilon 4$ status, education, nor WMH accumulation. Error bars depict 95% CI. Source Data files are provided.

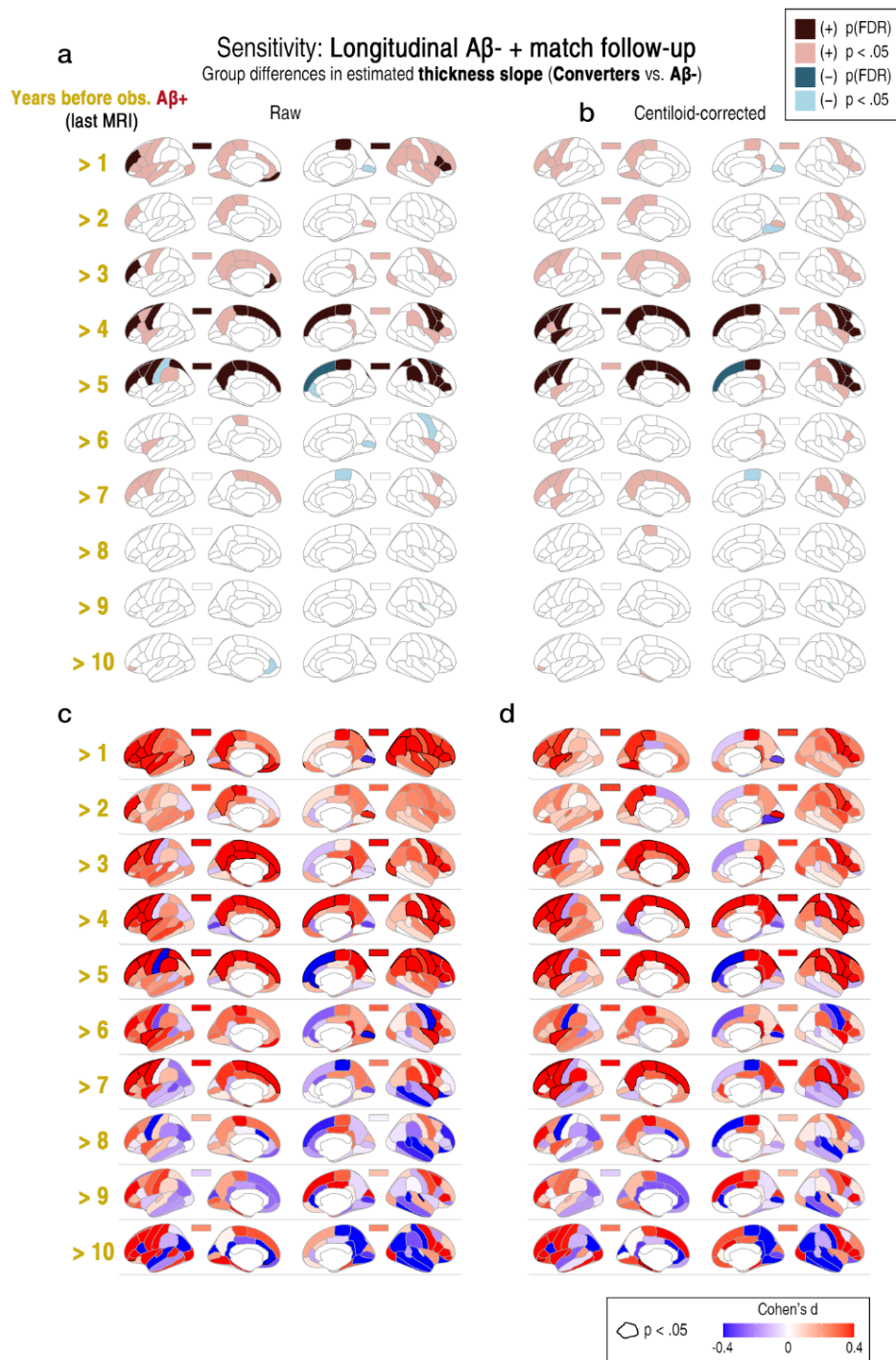


e

Years before obs. A β +	Converters MRI Obs (N)	Included A β - MRI Obs (N)	Modelled A β - MRI Obs (N)	Modelled MRI Obs (N)
> 1	290 (62)	1249 (274)	1604 (375)	4146 (1000)
> 2	248 (53)	1249 (274)	1604 (375)	4104 (991)
> 3	214 (46)	1249 (274)	1604 (375)	4070 (984)
> 4	190 (42)	1249 (274)	1604 (375)	4046 (980)
> 5	158 (37)	1249 (274)	1604 (375)	4014 (975)
> 6	129 (32)	1249 (274)	1604 (375)	3985 (970)
> 7	93 (25)	1249 (274)	1604 (375)	3949 (963)
> 8	66 (19)	1249 (274)	1604 (375)	3922 (957)
> 9	46 (15)	1249 (274)	1604 (375)	3902 (953)
>10	27 (11)	1249 (274)	1604 (375)	3883 (949)

Supplementary Figure 23

Sensitivity analyses ensuring longitudinally confirmed A β ⁻. Differences in estimated cortical thickness change between converter and A β ⁻ groups using a restricted A β ⁻ group comprised of individuals with A β ⁻ values at follow-up (N = 274, obs = 1249). On average A β ⁻ was confirmed 4.9 (SD = 3.9) years after the last MRI. We ensured the last MRI in the A β ⁻ group was acquired before the last confirmed A β ⁻ PET then reran the GAMMs. We included the MRI trajectories of A β ⁻ individuals with a single PET timepoint in the GAMM modelling to boost power. At the next step, we discarded these estimates in the group-difference tests. **a-b** Significance results for the group difference in estimated cortical thickness change between A β ⁺ converters and A β ⁻ nonconverter groups at each cutoff. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** “Raw” differences unadjusted for quantitative amyloid. **b** Differences after correcting for the mean centiloid values across PET scans prior to the first A β ⁺ scan. **c-d** Effect size maps. **e** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both A β groups, the total sample submitted to the GAMMs, and the A β ⁻ group included in the linear tests (i.e., those with longitudinal A β ⁻ confirmation).

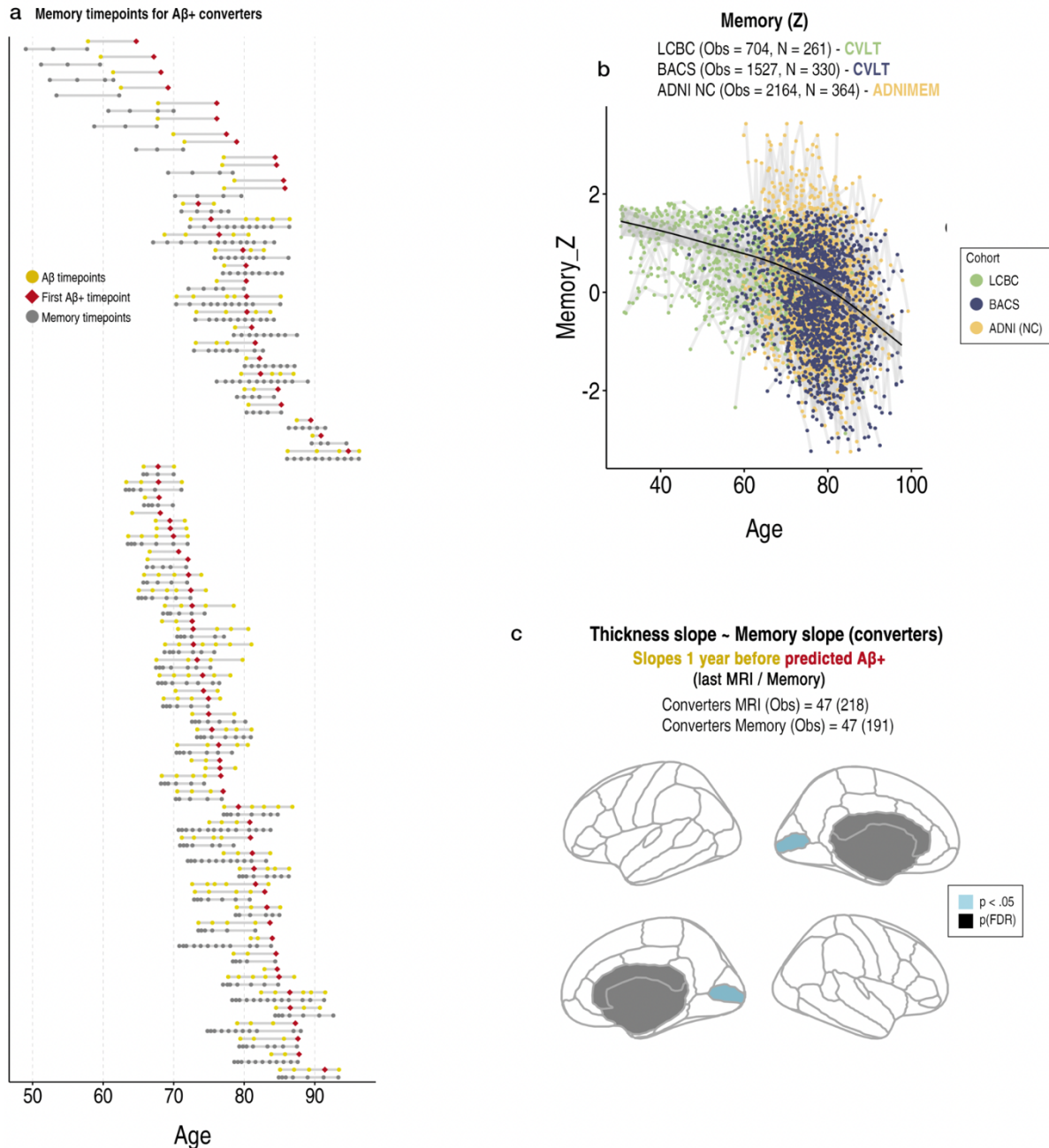


e

Years before obs. A β +	Converters MRI Obs (N)	Included A β - MRI Obs (N)	Modelled A β - MRI Obs (N)	Modelled MRI Obs (N)
> 1	290 (62)	451 (92)	587 (124)	3129 (749)
> 2	248 (53)	452 (84)	528 (106)	3028 (722)
> 3	214 (46)	373 (70)	467 (92)	2933 (701)
> 4	190 (42)	338 (63)	430 (84)	2872 (689)
> 5	158 (37)	241 (53)	319 (74)	2729 (674)
> 6	129 (32)	187 (44)	254 (64)	2635 (659)
> 7	93 (25)	123 (34)	181 (50)	2526 (638)
> 8	66 (19)	89 (24)	128 (38)	2446 (620)
> 9	46 (15)	77 (24)	94 (30)	2392 (608)
> 10	27 (11)	29 (12)	57 (22)	2336 (596)

Supplementary Figure 24

Sensitivity analyses ensuring longitudinally confirmed A β - in matched groups. Differences in estimated cortical thickness change between matched converter and A β - groups using a restricted A β - group comprised of individuals with A β - values at follow-up (N = 274, obs = 1249). We ensured the last MRI in the A β - group was acquired before the last confirmed A β - PET then reran the GAMMs. We excluded the MRI trajectories of A β - individuals with a single PET timepoint from the group matching procedure and their estimates were thus not included in the group-difference tests. **a-b** Significance results for the group difference in estimated cortical thickness change between A β + converters and A β - groups at each cutoff. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **a** “Raw” differences unadjusted for quantitative amyloid. **b** Differences after correcting for the mean centiloid values across PET scans prior to the first A β + scan. **c-d** Effect size maps. **e** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both A β groups, the total sample submitted to the GAMMs, and the A β - group included in the linear tests (i.e., those with longitudinal A β - confirmation).



Supplementary Figure 25

Exploratory analysis examining the relationship between individual cortical thickness trajectories and longitudinal memory performance in converters using MRI and memory data acquired at least one year before predicted A β +

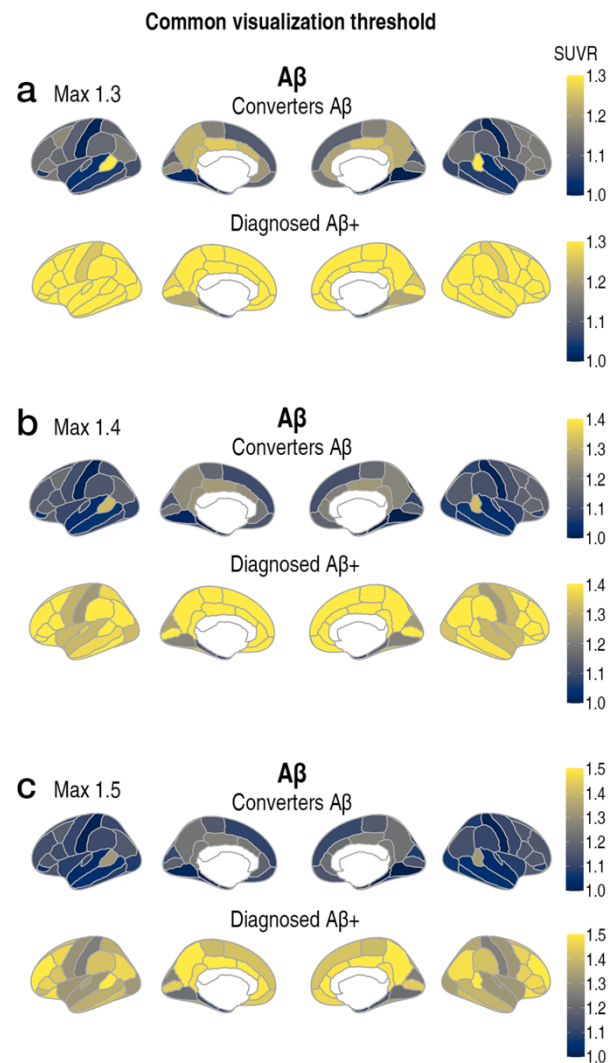
a Time trajectories of A β PET/Memory observations for an initial 74 converters (with longitudinal memory scores). The A β PET scans for each participant are in yellow and the first A β scan is depicted with a red diamond (later scans are also A β +).

Below each are the Memory observations on that participant in grey. For LCBC and BACS, memory was operationalized as the first principal component across immediate, delayed and free recall scores on the California Verbal Learning Memory test (explaining 90%), which was then Z-scored across both samples. For ADNI (normal controls), we used all available observations on the ADNI_MEM variable, which was then Z-scored within sample. We combined the Z-scored Memory observations and used the sample-specific A β -positivity threshold to ensure the last Memory observation included in the analysis was acquired at least one year before the participant was predicted to become A β +.

b In the resulting longitudinal data (total 4395 observations on 955 subjects), we estimated subject-specific memory intercepts and slopes using GAMMs of age on Memory, adjusting for sex, cohort, and a dummy variable to model practice effects. With the brain and memory slope estimates in the converter group, we tested the relationship between thickness change and memory change, with linear models adjusting for sex, cohort, a person's mean age, number of MRI timepoints, and the time interval between the first and last MRI.

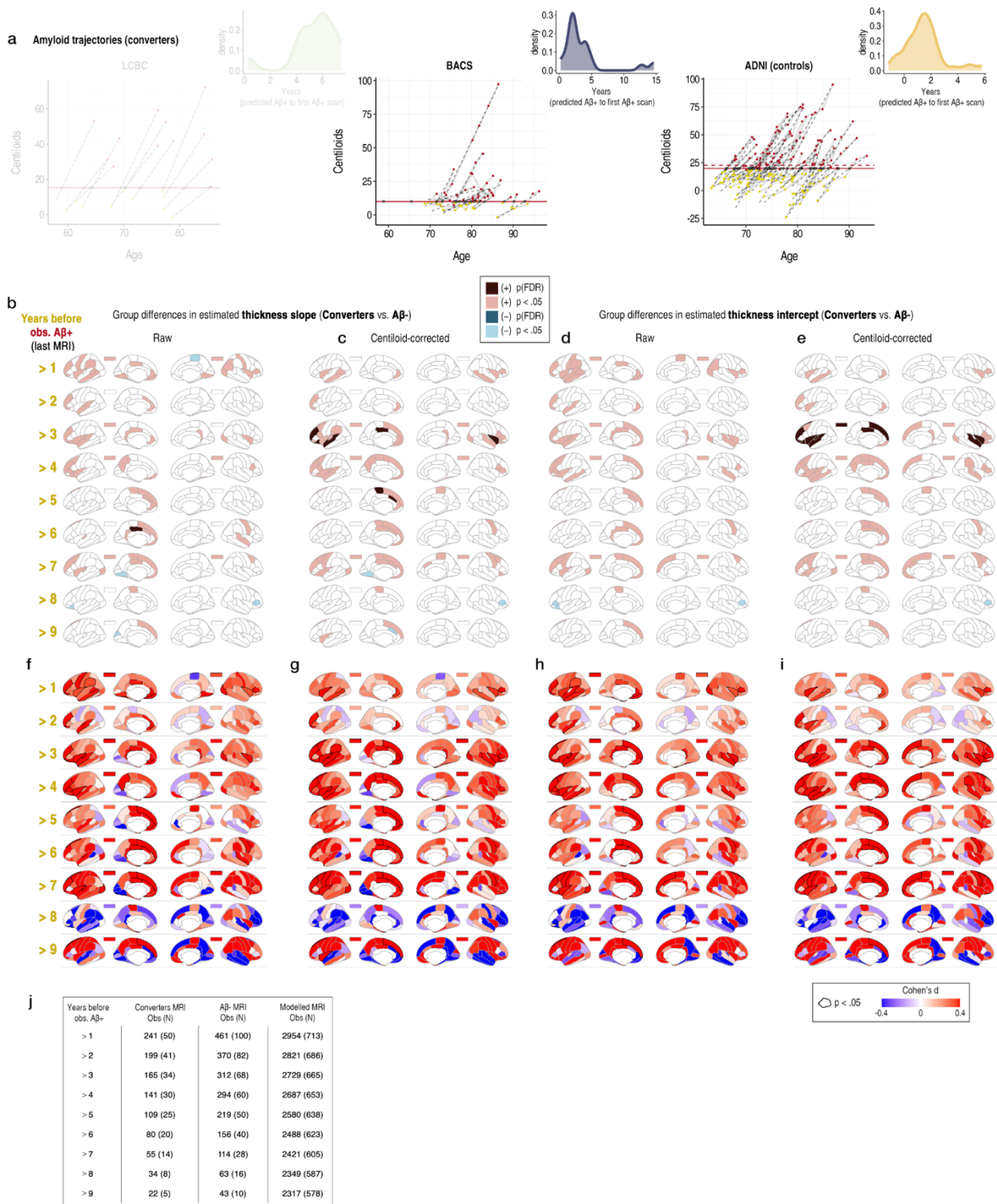
c Effects were tested across 68 cortical parcels. None survived FDR correction for multiple comparisons. Note that

memory slopes computed via this method otherwise yield robust brain-memory change relationships within and across cognitively healthy samples (SI Fig. 38).



Supplementary Figure 26

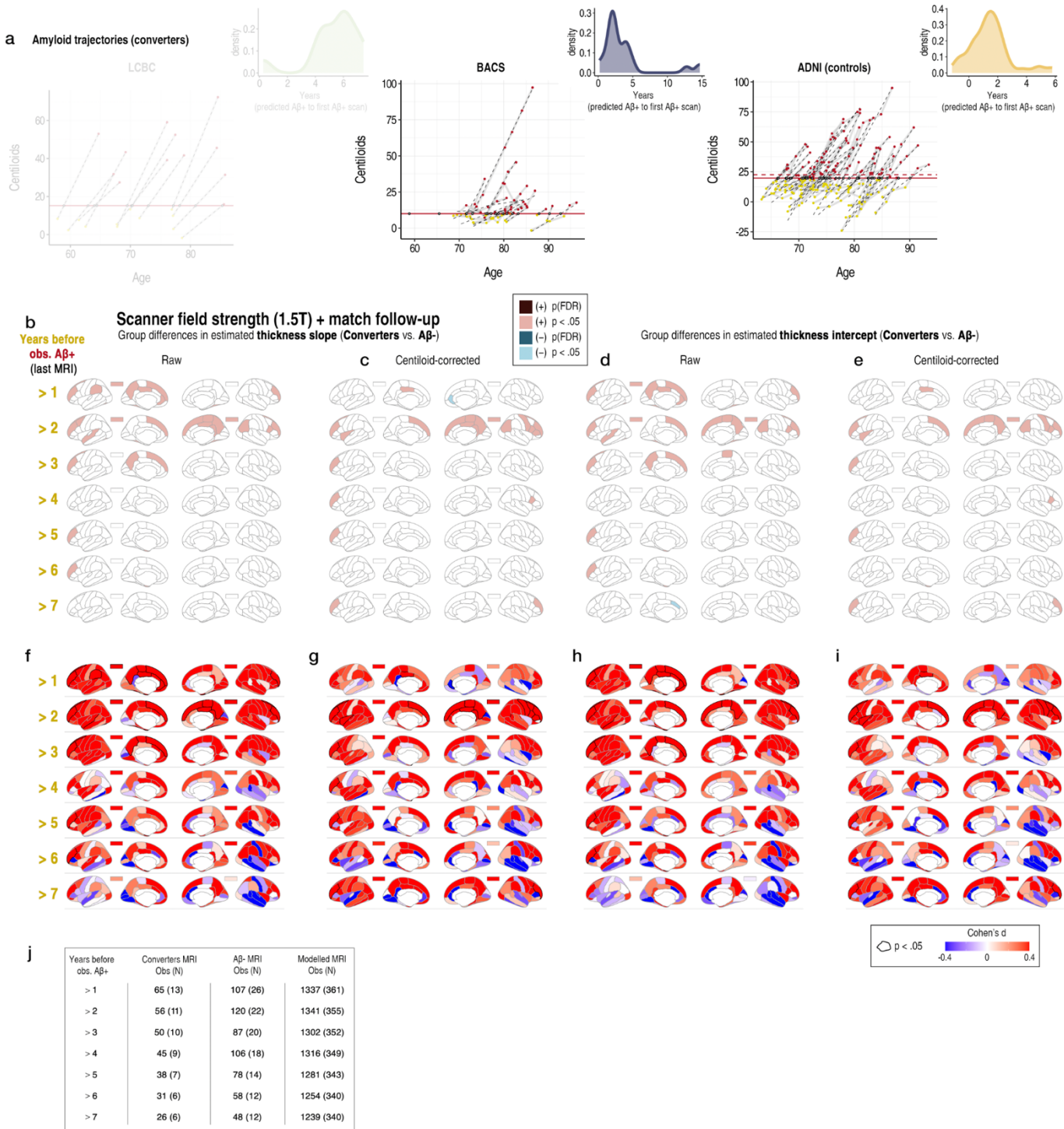
a Average tracer-corrected SUVR map in the converter group and independent sample of A β ⁺ individuals with an MCI or AD diagnosis shown for three common visualization thresholds.



Supplementary Figure 27

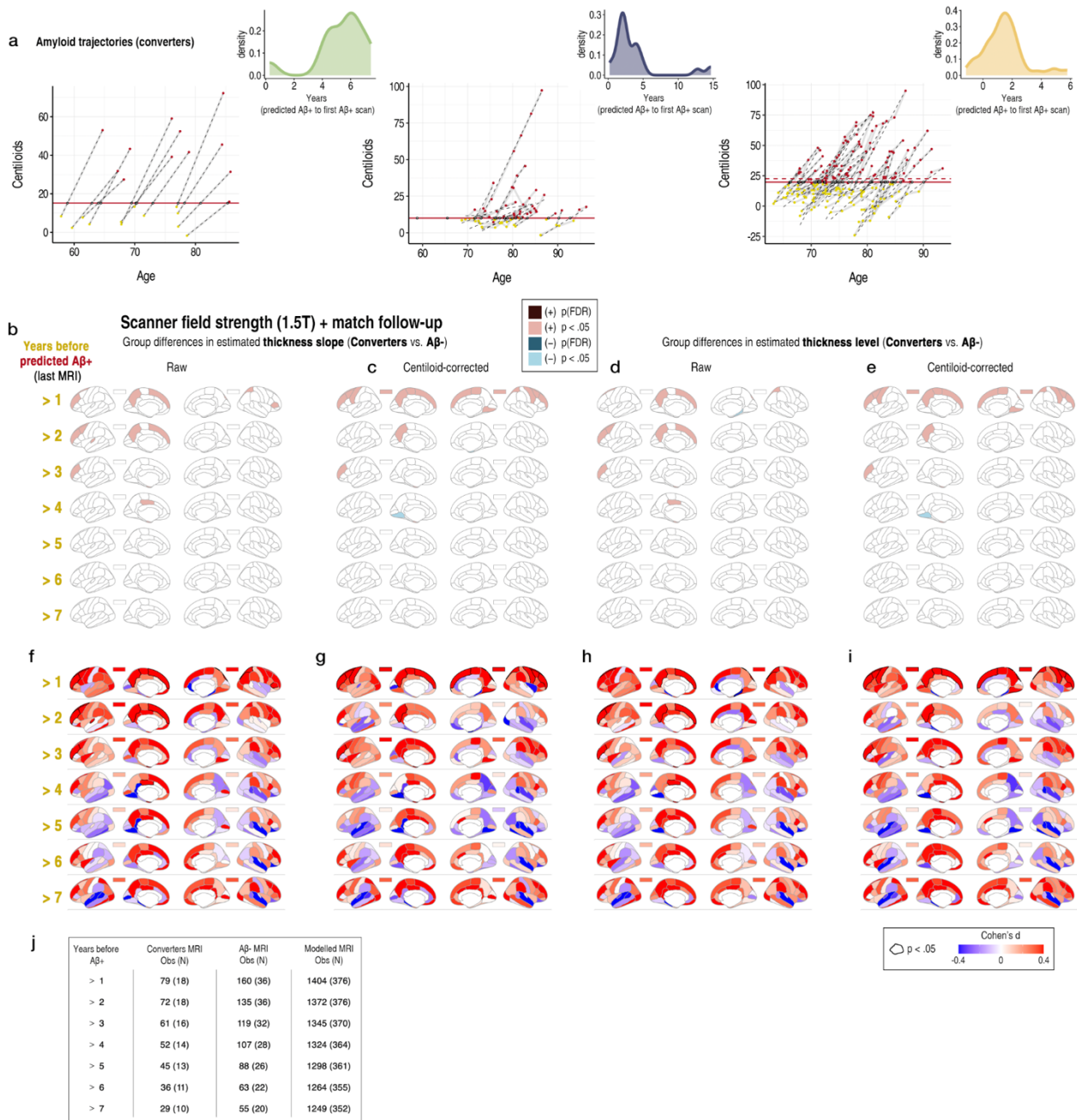
Differences in estimated slope and intercept of cortical thickness between matched converter and Aβ- groups after discarding the data from LCBC converters (GAMMs). **a-c** Amyloid trajectories in centiloids for the Aβ+ converters in each sample (linear model across PET timepoints; raw data in [SI Figs. 1-2](#)). The sample-specific threshold for Aβ positivity is shown as a solid red line (Methods), and predicted age on crossing the threshold is shown by a white dot (note we used the Florbetapir threshold in ADNI). Inset plots show the time from predicted to observed Aβ positivity (i.e. first Aβ+ scan) for each sample. Note that as LCBC only had two PET timepoints, more individuals were predicted to cross the Aβ+ threshold several years before they were observed Aβ+, illustrating how time cutoffs based on years to the first Aβ+ scan should be interpreted with caution. We therefore reran the analysis discarding the data from LCBC converters in the GAMMs. **b-c** Significance results for the group-difference in estimated cortical thickness between Aβ+ converters and Aβ- groups at each cutoff, with and without adjusting for quantitative amyloid (mean centiloids across PET scans prior to the first Aβ+ scan). **d-e** Significant differences in cortical thickness level

(intercept), with and without adjusting for amyloid. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **f-i** Effect size maps. **j** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both A β groups and the total sample submitted to the GAMMs. Groups were matched on age and follow-up data.



Supplementary Figure 28
 Differences in estimated slope and intercept of cortical thickness between matched converter and A β - groups using only 1.5T scans and after discarding the data from LCBC converters (GAMMs). **a-c** Amyloid trajectories

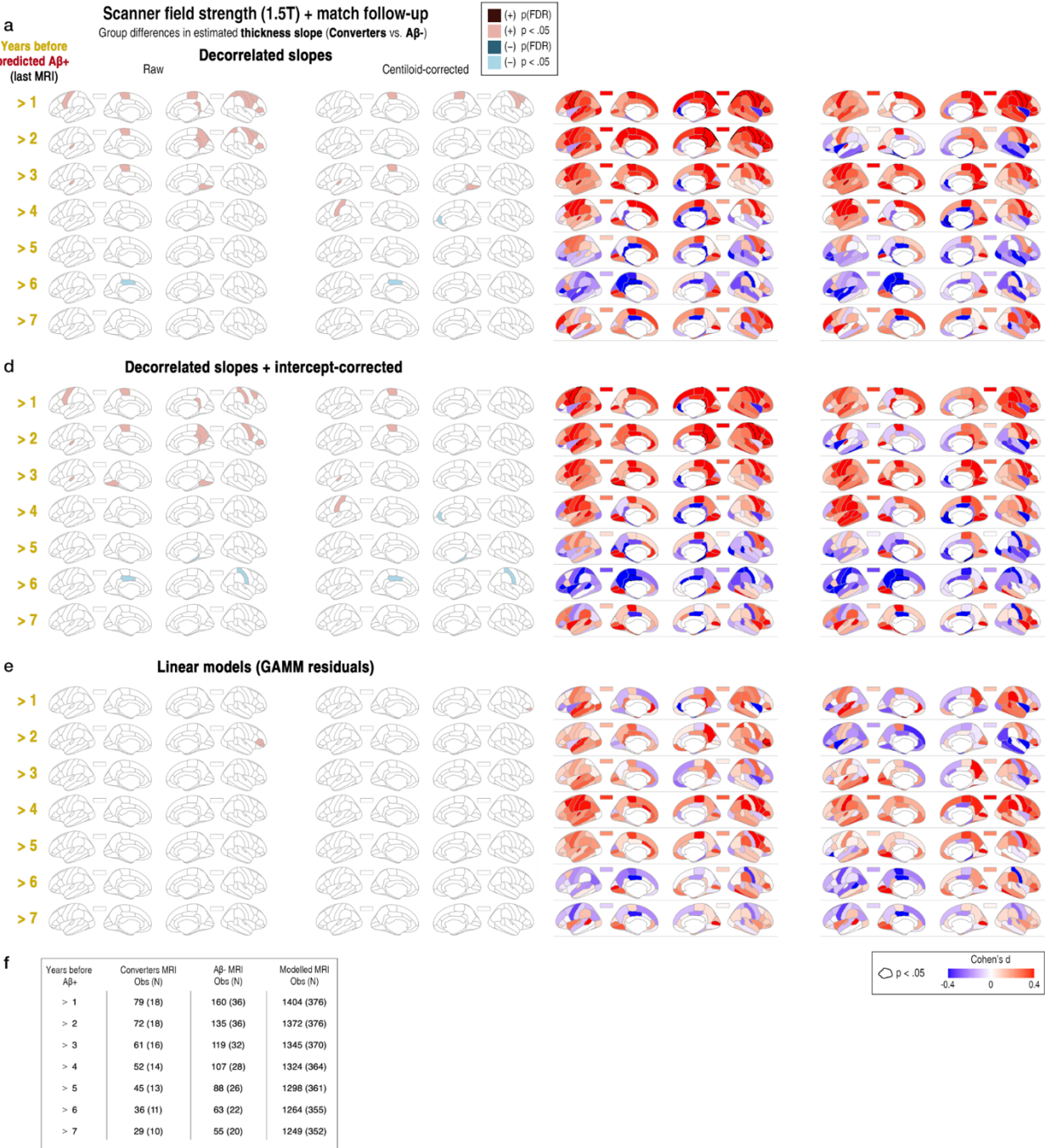
in centiloids for the A β ⁺ converters in each sample (linear model across PET timepoints; raw data in [SI Figs. 1-2](#)). See [Fig. 4](#). Note that as LCBC only had two PET timepoints, more individuals were predicted to cross the A β ⁺ threshold several years before they were observed A β ⁺, illustrating how time cutoffs based on years to the first A β ⁺ scan should be interpreted with caution. We reran the analysis discarding the data from LCBC converters in the GAMMs. **b-c** Significant differences in estimated cortical thickness change, with and without adjusting for amyloid levels. **d-e** Significant differences in cortical thickness level (intercept), with and without adjusting for amyloid. Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **f-i** Effect size maps. **j** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both A β groups and the total sample submitted to the GAMMs. Groups were matched on age, and follow-up data.



Supplementary Figure 29

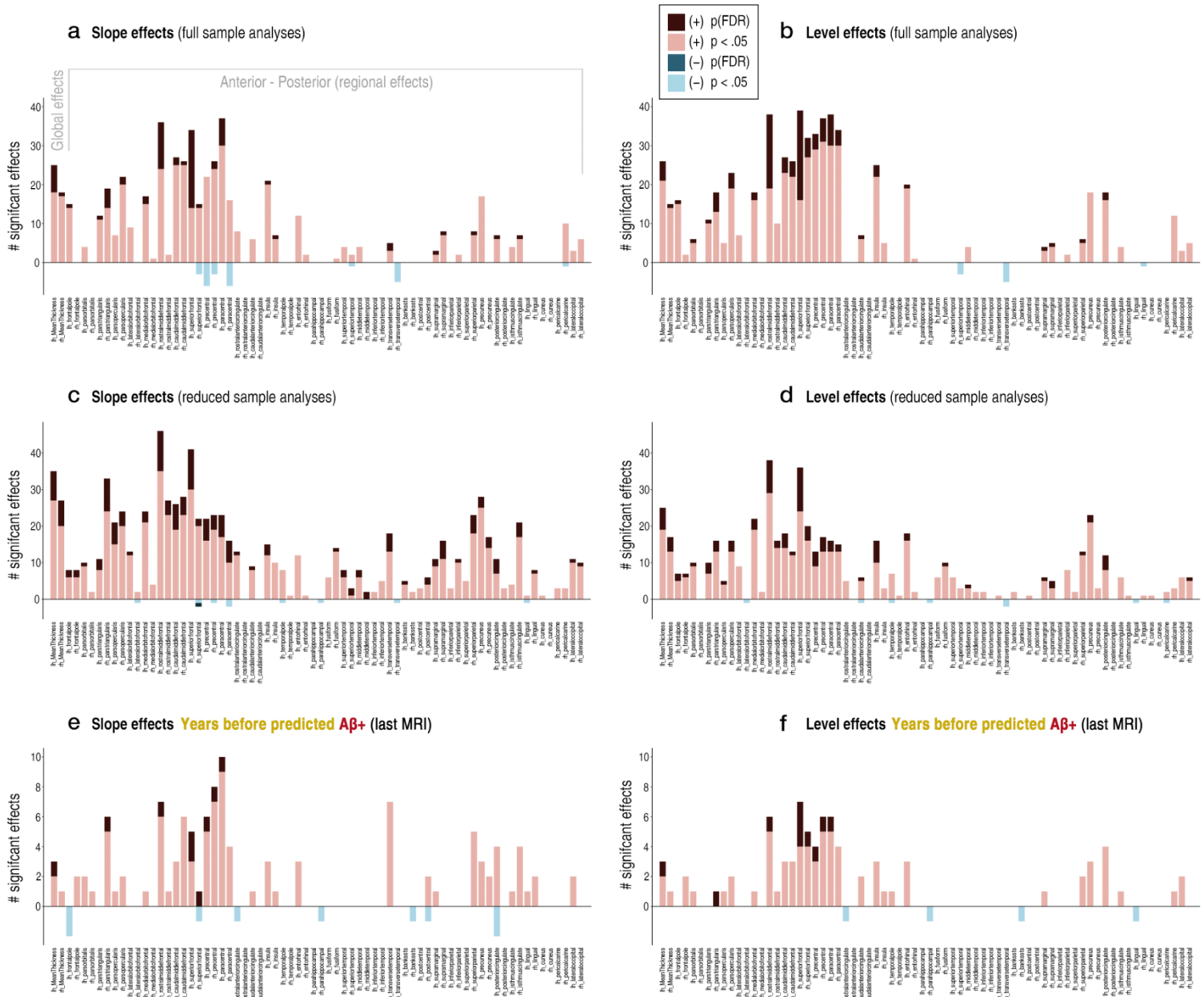
Differences in estimated slope and intercept of cortical thickness between matched converter and A β - groups using predicted age at amyloid positivity (1.5T scans only). **a-c** Amyloid trajectories in centiloids for the A β ⁺ converters in each sample. **b-c** Significant differences in estimated cortical thickness change, with and without adjusting for amyloid levels (mean centiloids across PET scans prior to the first A β ⁺ scan). **d-e** Significant differences in estimated cortical thickness level, with and without adjusting for amyloid. Light red/blue parcels reflect significance

at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). The rectangles above each brain hemisphere depict the results for mean cortical thickness. **f-i** Effect size maps. **i f** The number of MRI observations and N in the mixed-model estimation at each time cutoff, shown for both A β groups and the total sample submitted to the GAMMs. Groups were matched on age, and follow-up data.



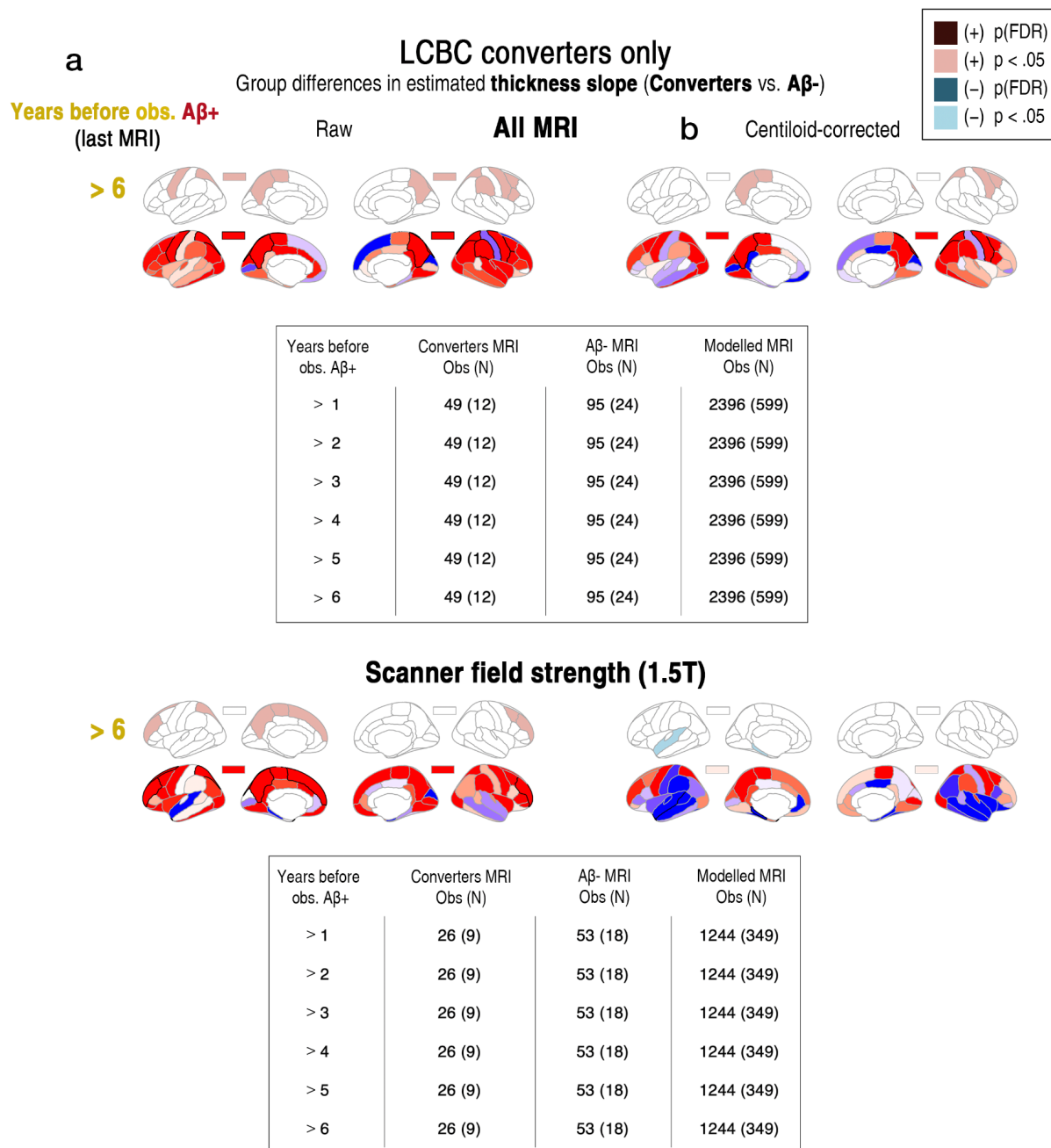
Supplementary Figure 30
Differences in cortical thickness change between matched A β + converter and A β - groups - models isolating slope from intercept effects using predicted age at amyloid positivity (1.5T scans only). **a-b** Significant differences in cortical thickness change between A β + converters and A β - groups matched on scanner field strength (1.5T scans only), age and follow-up data. Models shown **a** before and **b** after adjusting for cortical thickness level (intercept), and **c** using simple linear models (linear slope across timepoints after regressing out nonlinear age). Light red/blue parcels reflect significance at $p < .05$ for positive/negative effects (uncorrected). Dark red/blue parcels reflect positive/negative effects that survived correction at $p[\text{FDR}] < .05$ (70 two-sided tests per map, linear models). **f** The number of MRI

observations and N in the mixed-model estimation at each time cutoff, shown for both A β groups and the total sample submitted to the GAMMs.



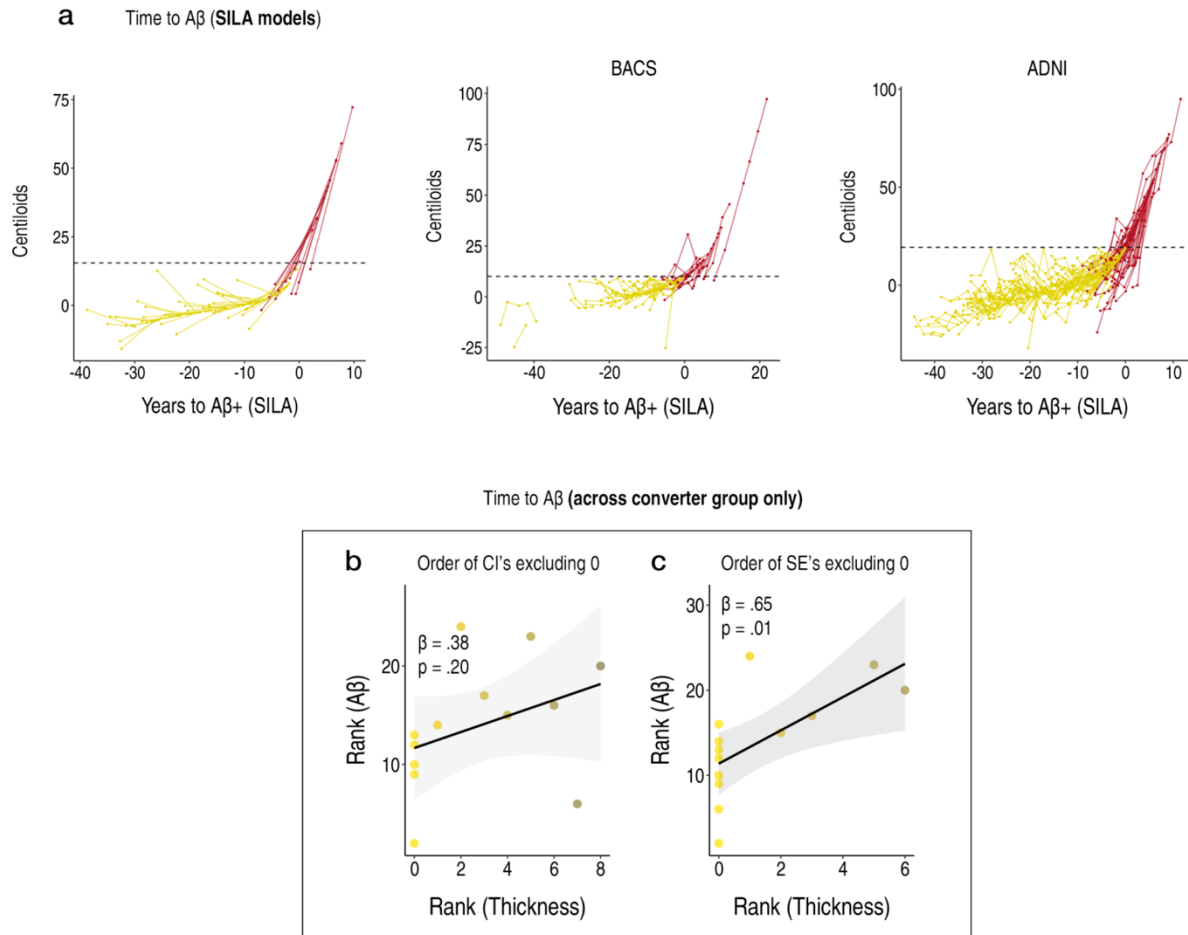
Supplementary Figure 31 (Extended Data Figure 5)

Summary of the number of reported significant effects and their directions across main and supplementary analyses (raw differences uncorrected for A β levels). The plots are organized to show global and regional effects in the anterior-posterior direction. Light red/blue bars reflect the count of significant hits at an uncorrected level ($p < .05$) for positive/negative effects. Dark red/blue parcels reflect the count of positive/negative significant hits that survived correction at $p[\text{FDR}] < .05$ (stacked bars) **a-b** Effects across all main and sensitivity analysis variations that incorporated the full sample (e.g. main, Combat, cross-sectional FreeSurfer etc.). Significant regional differences in estimated cortical thickness change (slope) and **b** cortical thickness level between A β ⁺ converters and A β ⁻ groups at all cut-offs (years to observed A β ⁺) **c-d** Significant change and level effects across all analysis variations that incorporated a reduced sample size (e.g., matched samples, single scanner field strength etc.) at all cut-offs (years to observed A β ⁺) **e-f** Significant change and level effects across analyses in the complementary sample defined by time-to-predicted A β ⁺ at all cut-offs (years before predicted A β ⁺). We observed high agreement in positive effects across all analyses, whereas negative effects were sparse, regionally inconsistent, and only one survived correction for multiple comparisons. Source Data files are provided.



Supplementary Figure 32

Differences in estimated cortical thickness change between matched converter and A β - groups after discarding the data from BACS and ADNI converters (i.e., retaining only the converters from LCBC).

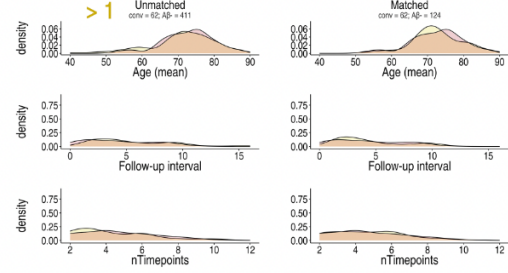


Supplementary Figure 33

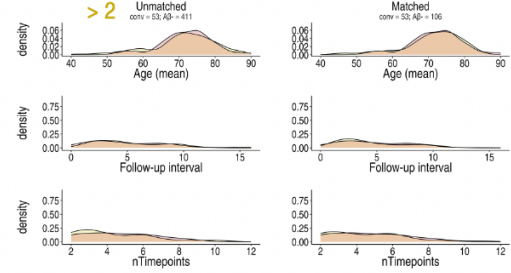
Sensitivity analyses using time-to-A β positivity estimates from Sampled Iterative Local Approximation (SILA⁸) models in the converter group. **a** SILA models of time-to-A β positivity in each cohort. We re-estimated the temporal order of thickness changes within regions showing significant differences in thickness between converter and A β ⁻ groups with SILA-derived time-to-A β estimates across all MRIs in the converter group (477 MRI scans; N = 76; shown in red). The point at which the derivative CI excluded zero was used to estimate the rank order of thickness changes (Methods). **b** The correlation between the temporal order of A β change and thickness change (derived using CIs). **c** The correlation between the temporal order of A β change and thickness change (derived using standard errors). Compare with Fig. 5.

Sensitivity 1: match follow-up

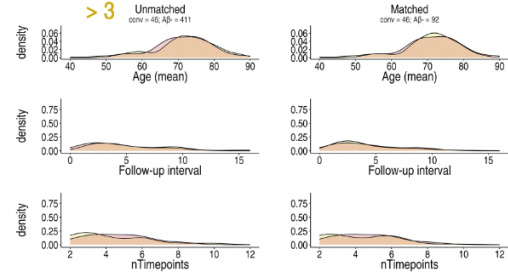
Years before A β + (last MRI)



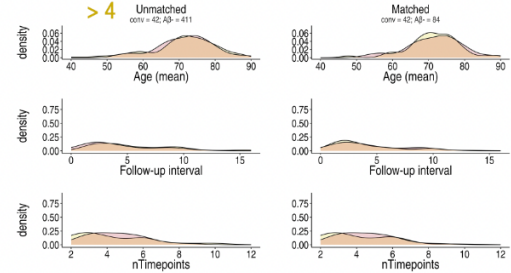
Years before A β + (last MRI)



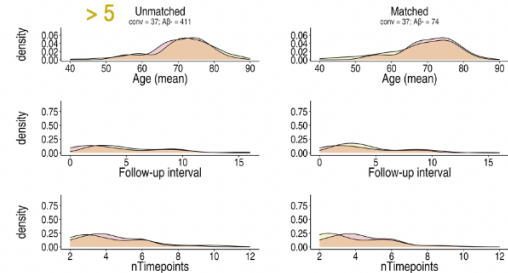
Years before A β + (last MRI)



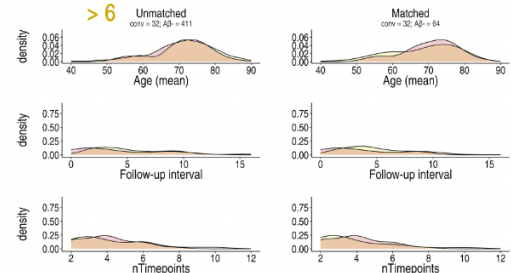
Years before A β + (last MRI)



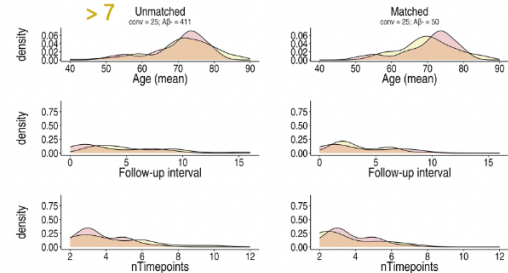
Years before A β + (last MRI)



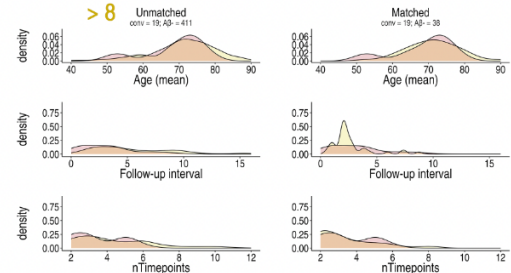
Years before A β + (last MRI)



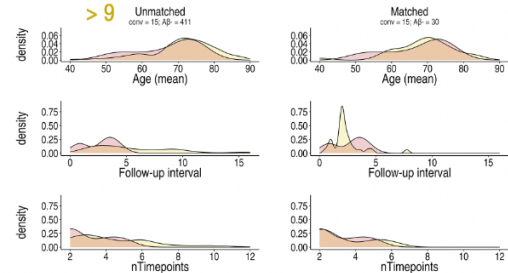
Years before A β + (last MRI)



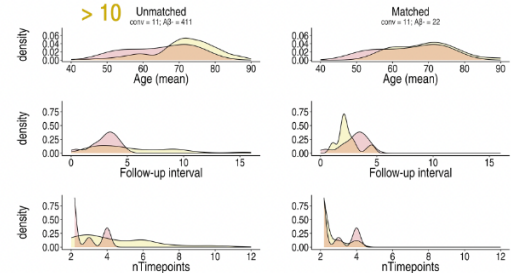
Years before A β + (last MRI)



Years before A β + (last MRI)



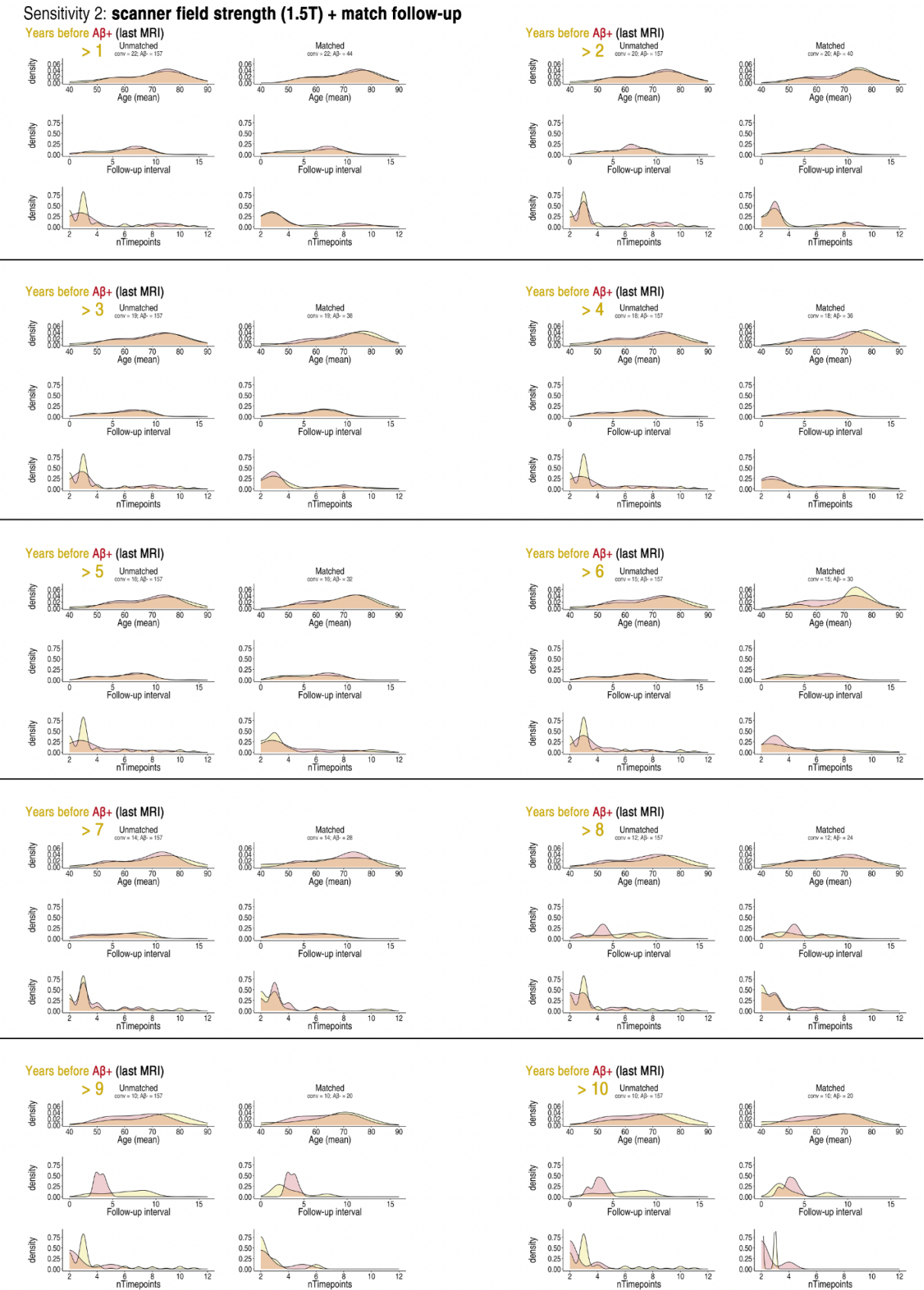
Years before A β + (last MRI)



Supplementary Figure 34

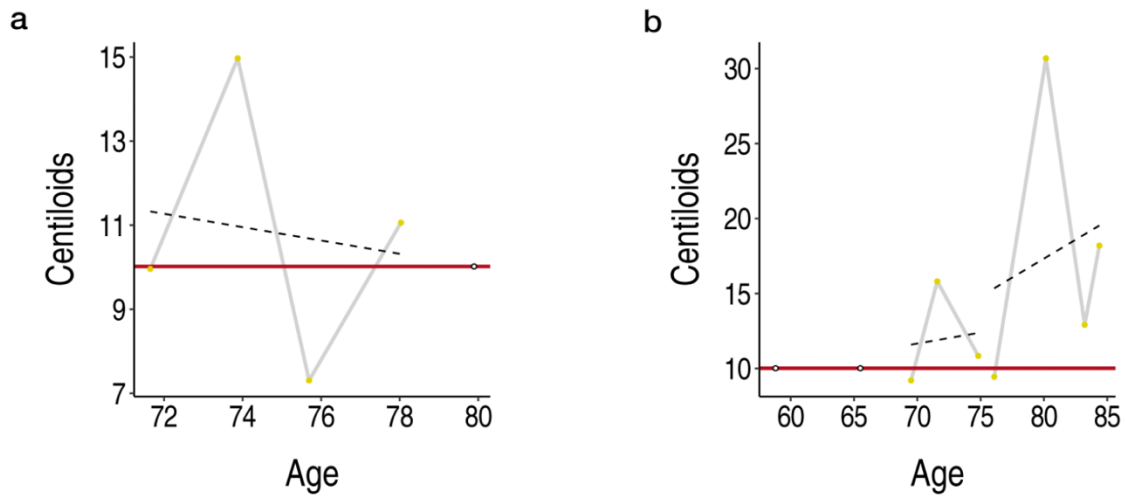
Matching groups on follow-up data. At each time cut-off we drew a matched sample from the A β - group, based on mean age, the number of MRI timepoints, and the time interval covered in the converter group. Because the N of the

converter group was smaller (max N = 62 [1 year cutoff]), we repeated the matching twice, drawing two one-to-one matched samples from the A β - group.



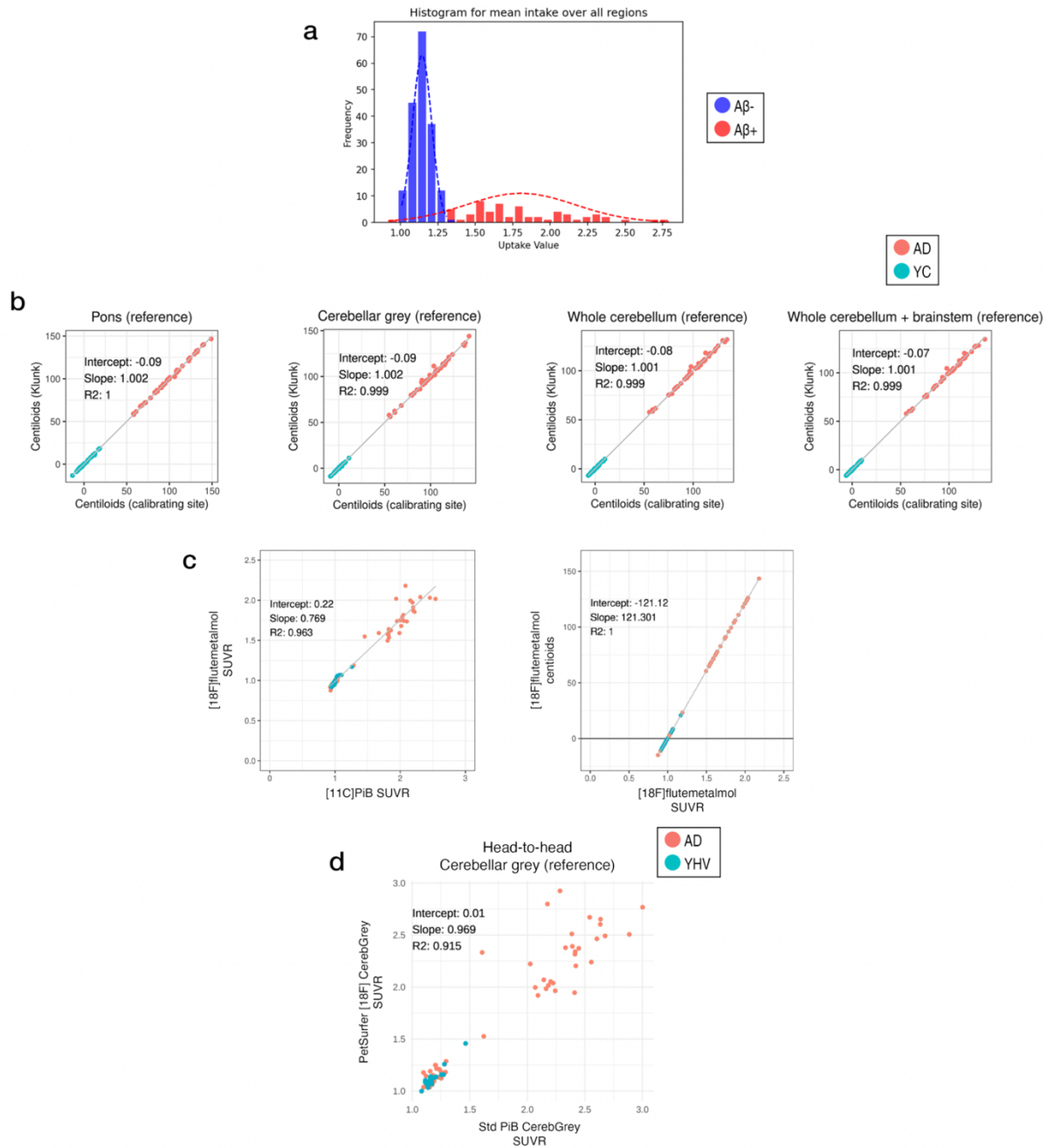
Supplementary Figure 35

Matching groups on scanner field strength (1.5T) and follow-up data. At each time cut-off we drew a matched sample from the A β - group, based on mean age, the number of MRI timepoints, and the time interval covered in the converter group. Because the N of the converter group was smaller (max N = 22 [1 year cutoff + 1.5T scans only]), we repeated the matching twice, drawing two one-to-one matched samples from the A β - group.



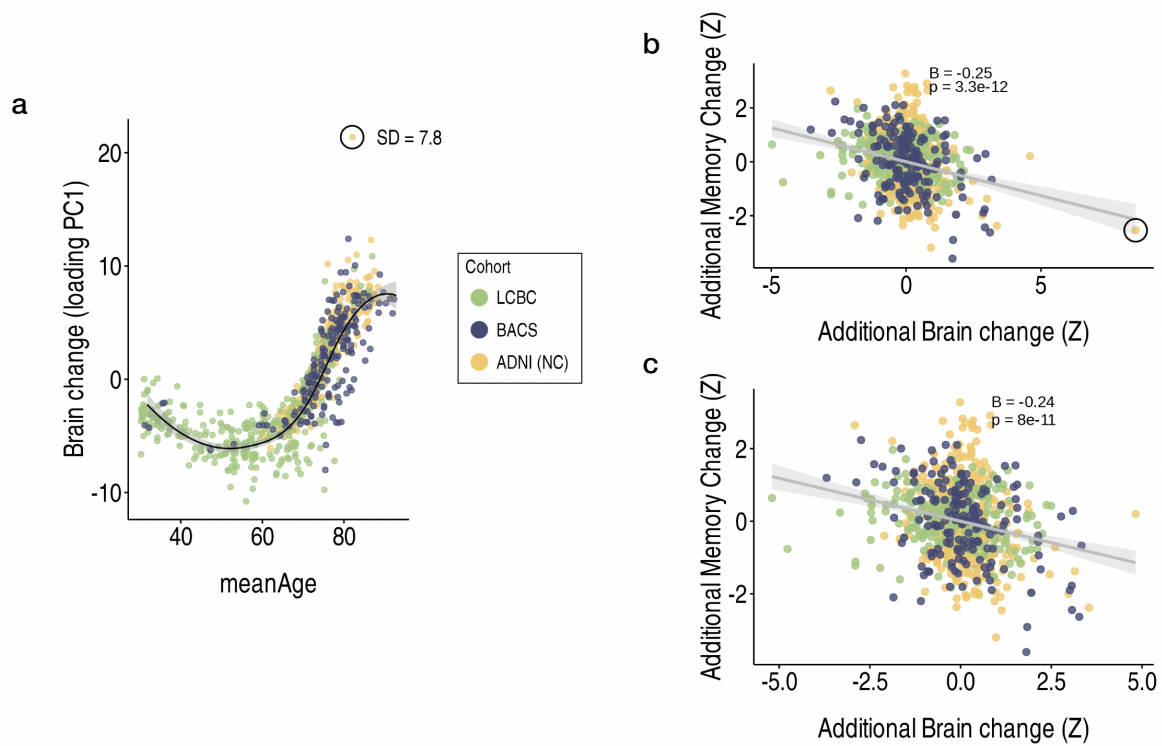
Supplementary Figure 36

a For analyses using predicted age at A β positivity, one converter was excluded as their centiloid slope over time was negative (despite their unambiguous A β + status), such that their predicted age on crossing the sample-specific A β + threshold in centiloids was too high (white dot). **b** Two converters were predicted to cross the threshold at very low ages, likely attributable to measurement error in their A β PET trajectories.



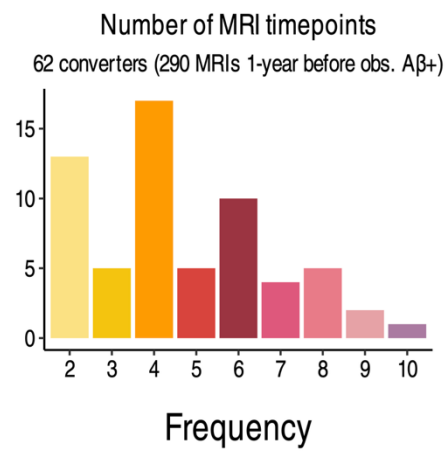
Supplementary Figure 37

Aβ modelling and centiloid calibration with GAAIN pipeline (LCBC [18F]flutemetamol-PET). **a** Results of gaussian mixed modelling to define Aβ status in LCBC data. Note the one individual with SUVr<1.0 estimated on the Aβ+ distribution was set to Aβ-. **b** Replication of published centiloid values using standard pipeline. The calculated anchorpoint group means were 1.014 (YC₀ WholeCerebellum) and 2.086 (AD₁₀₀ WholeCerebellum) (whole cerebellum reference). Results were within the expected individual (±5%) and group (±2%) tolerances and expected agreement with published results ($r^2 > .99$) in Klunk et al.³ **c** Replication of correlation between 18F SUVr units (standard pipeline) and [11C]PiB SUVr units (standard pipeline) in head-to-head AD-control GAAIN data ('GE_flutemetamol.xlsx'; <https://www.gaain.org/centiloid-project>). **d** Correlation between PiB SUVr units (standard pipeline) and 18F SUVr units using site-specific pipeline (PetSurfer) in head-to-head AD-control GAAIN data. The calculated group mean anchorpoints for the cerebellar gray reference were 1.176 (YC₀ CerebellarGray) and 2.439 (AD₁₀₀ CerebellarGray). Estimation of PiB SUVr units from 18F SUVr units derived from PetSurfer pipeline: $PiB = (SUVr_{18F} - 0.006) / 0.969$. Centiloid equation: $CL = 100 * (PiB - 1.176) / (2.439 - 1.176)$.



Supplementary Figure 38

ADNI outlier. **a** One strong outlier ($SD = 7.8$) in the brain change data of ADNI controls was identified and removed from all MRI analyses. **a** The outlier was detected via the principal component (PC1) of absolute change across the top 50 brain features with accelerated change in AD (see ⁹). We removed this outlier from all MRI analyses due to unrealistic change values. **b-c** Note that their inclusion strengthened (rather than attenuated) the association between brain and memory decline in cognitively healthy adults (see ¹⁰; unpublished results). The outlier was an A β - subject, but we did not test how their inclusion affected the results of the present paper.



Supplementary Figure 39

The number of MRI timepoints in 62 converters at the minimal time window (290 observations 1-year before obs. A β +; [Fig. 1](#)).

Supplementary Note 1

For LCBC, all subjects underwent a [^{18}F]Flutemetamol amyloid-PET scan to assess cortical A β burden¹¹. Images were acquired on a GE HealthCare Discovery PET/CT 690 scanner at Aleris Hospital and Radiology, Oslo, Norway. PET images were processed using PetSurfer, the MRI-PET analysis tool within the FreeSurfer (v7.1.0) package. The intensities were processed with Region-Based Voxel-wise Partial Volume Correction (RBV-PVC) and scaled by the cerebellar cortex (left and right). The resulting uptake values were then further analyzed with the sklearn (v1.5.1) toolbox. Principal component analysis was used to extract the first principal component (PC1) from the standardized uptake value ratios (SUVR) in the region of interest described by Mormino et al.¹². Next, assuming data normality, PC1 was used to estimate the parameters of the Gaussian Mixture Model (GMM) with two mixture components; thus, two distributions were estimated. This allowed the probability of each observation belonging to each distribution to be calculated. Those falling under the distribution with the higher mean were classified as A+ participants.

Supplementary Note 2

Dataset access

Requests for access to the raw data can be directed to the Principal Investigators of the contributing studies: LCBC (Anders M. Fjell; anders.m.fjell@psykologi.uio.no). BACS, data are available on request to William J. Jagust (jagust@berkeley.edu). ADNI (<https://adni.loni.usc.edu/data-samples/access-data/>).

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doi:<https://doi.org/10.1007/b98882>.
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