Older patients with Alzheimer's-related cortical atrophy who develop post-operative delirium are at increased risk of long-term cognitive decline after surgery

APPENDIX

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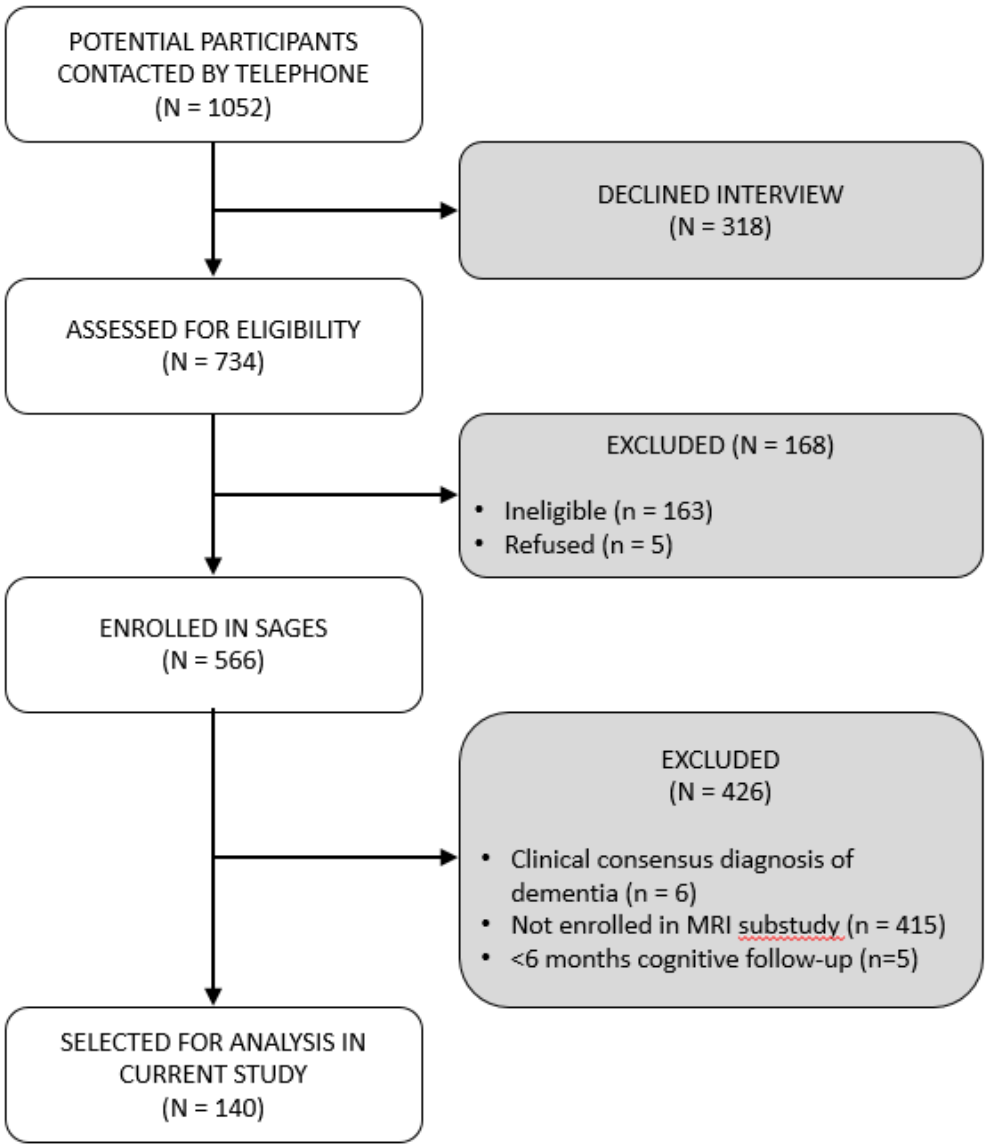
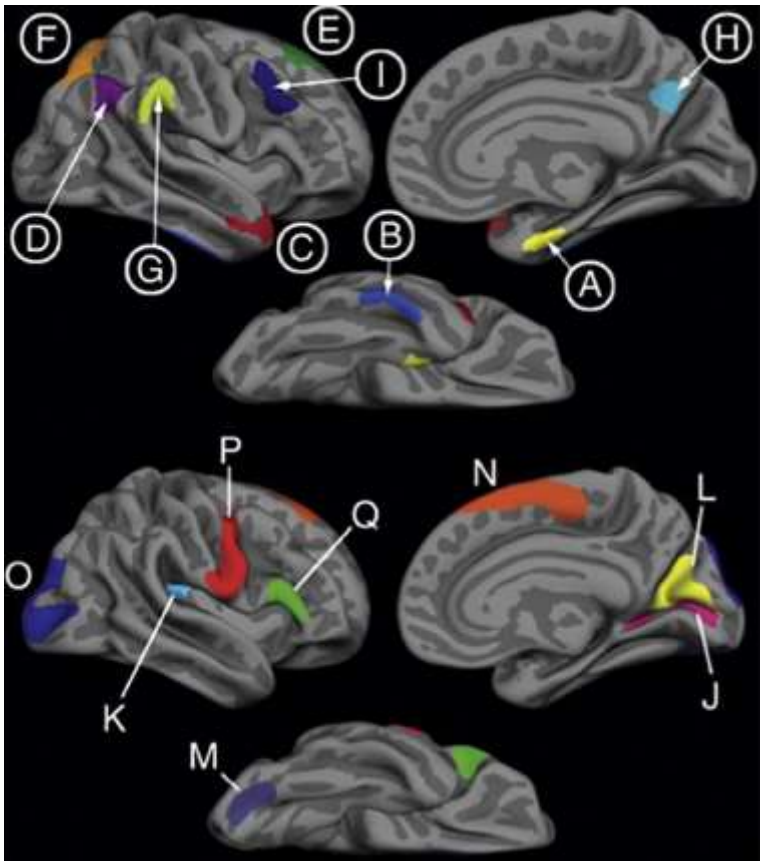
The information below is provided to give further details about our study methods including sample selection (Supplementary Figure 1), ROIs comprising the AD and Aging-Only signatures (Figure 2), sample sizes (Supplementary Table 1), and slopes used to predict effect size

(Supplementary Table 2). This appendix also provides more details on our study results including baseline characteristics by the six AD signature/delirium groups (Supplementary Table 3), baseline neuropsychological test scores (Supplementary Table 4), and unstandardized linear mixed effects (LME) model results (Supplementary Table 5). Finally, this appendix provides the results from supplementary analyses using cognitive scores without retest correction (Supplementary Table 7 and Figure 3) or with additional health measure covariates (Supplementary Table 8).

Supplementary Tables 2 and 8 are based on LME models using maximum likelihood parameter estimation and an unstructured covariance. The models included a random intercept, random time-slope from 2-36 months, fixed time indicator variables for months 1 and 2, a fixed time-slope from 2-36 months, and fixed effects for covariates. Individual slopes were derived by predicting random slope from the LME model. Average predicted slopes by group are reported.



Supplementary Figure 1. Summary of study sample selection. Eligible participants were age 70 years and older, English speaking, scheduled to undergo elective surgery with an anticipated length of stay of at least 3 days. Exclusion criteria included evidence of dementia, delirium, hospitalization within 3 months, terminal condition, legal blindness, severe deafness, history of schizophrenia or psychosis, and history of alcohol abuse. Patients who would be out of the catchment area at time of follow-up were also excluded from enrollment. For this study, participants were further excluded if they were not enrolled in the MRI sub-study (i.e. did not undergo baseline MRI) or had less than 6 months of cognitive follow-up.



<u>Supplementary Figure 2</u>. AD signature and Aging-only Signature regions of interest (ROIs)[10]. Top) "AD signature" ROIs. Bottom) "Aging-Only" ROIs, where atrophy is seen primarily in normal aging with minimal additional effects of AD. Key (circled letters denote AD signature ROIs): A: medial temporal, B: inferior temporal, C: temporal pole, D: Angular, E: superior frontal, F: superior parietal, G: supramarginal, H: precuneus, I: middle frontal, J: calcarine, K: caudal insula, L: cuneus, M: caudal fusiform, N: dorsomedial frontal, O: lateral occipital, P: precentral, Q: inferior frontal.

Supplementary Table 1. Cognitive test sample sizes by study timepoint

Timepoint	HVLT total (N)	HVLT delay (N)	Trails B (N)	GCP (N)
Baseline	140	140	139	140
Month 1	140	139	140	140
Month 2	139	139	139	139
Month 6	140	140	138	140
Month 12	135	135	134	135
Month 18	134	134	133	134
Month 24	129	128	129	129
Month 30	84	84	83	84
Month 36	121	120	121	121

Note: No baseline covariates were missing (age, sex, education)

GCP = General Cognitive Performance
HVLT = Hopkins Verbal Learning Test–Revised
Trails B = Trail Making Test B

Supplementary Table 2. Predicted slopes from months 2-36 for GCP and selected individual neuropsychological tests

Group:	HVLT total	HVLT delay	Trails B	GCP
AD Signature Tertiles				
AD signature Tertile 1	0.060 (0.589)	0.040 (0.378)	2.189 (4.932)	0.142 (0.682)
AD signature Tertile 2	-0.043 (0.459)	0.026 (0.243)	0.015 (8.441)	-0.032 (0.634)
AD signature Tertile 3	-0.019 (0.631)	-0.070 (0.307)	-2.404 (8.732)	-0.119 (0.617)
AD Signature Tertiles and Delirium				
AD signature Tertile 1, no delirium	0.047 (0.598)	0.041 (0.343)	2.405 (4.619)	0.149 (0.692)
AD signature Tertile 2, no delirium	-0.006 (0.479)	0.048 (0.237)	-0.446 (8.812)	-0.057 (0.656)
AD signature Tertile 3, no delirium	0.112 (0.564)	-0.034 (0.309)	-1.654 (7.280)	-0.007 (0.519)
AD signature Tertile 1, delirium	0.096 (0.586)	0.037 (0.476)	1.606 (5.858)	0.126 (0.680)
AD signature Tertile 2, delirium	-0.199 (0.347)	-0.070 (0.258)	1.961 (6.728)	0.075 (0.554)
AD signature Tertile 3, delirium	-0.627 (0.590)	-0.232 (0.255)	-5.777 (13.693)	-0.636 (0.800)

AD signature = Alzheimer's disease signature (average cortical thickness in 9 bilateral cortical regions of interest)
GCP = General Cognitive Performance
HVLT = Hopkins Verbal Learning Test–Revised
Trails B = Trail Making Test B

Supplementary Table 3. Sample characteristics of SAGES neuroimaging sub-cohort by AD signature tertile and delirium groups

	No Delirium			Delirium		
AD Signature Tertile	**Tertile 1**	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
N	35	38	37	13	9	8
Female Sex, n (%)	25 (71%)	19 (50%)	20 (54%)	10 (77%)	6 (67%)	5 (62%)
Non-White or Hispanic, n (%)	2 (6%)	5 (13%)	3 (8%)	1 (8%)	1 (11%)	0 (0%)
Age at Baseline Assessment, mean (SD)	75.9 (4.3)	75.6 (4.2)	76.4 (5.3)	75.3 (4.5)	76.5 (4.5)	78.8 (3.6)
Education, Years, median (IQR)	15 (13, 18)	14 (12, 18)	14 (13, 18)	14 (12, 18)	14 (12, 16)	14 (13, 16)
Charlson Comorbidity Index, mean (SD)	0.66 (0.80)	0.92 (1.02)	0.86 (1.13)	0.62 (0.96)	1.44 (1.42)	1.00 (0.93)
Baseline GCP, mean (SD)	61.0 (6.5)	58.2 (6.5)	59.2 (6.8)	57.5 (6.1)	56.4 (6.2)	54.1 (5.7)
Geriatric Depression Scale, median (IQR)	1 (1, 4)	2 (0, 4)	1 (1, 3)	1 (0, 3)	2 (2, 4)	1.5 (.5, 3)
3MS Score, median (IQR)	96 (93, 99)	94 (91, 97)	96 (91, 99)	94 (92, 96)	94 (87, 99)	89 (85, 93)
Proxy IQCODE, mean (SD)	3.13 (0.24)	3.07 (0.13)	3.17 (0.18)	3.16 (0.16)	3.13 (0.47)	3.32 (0.46)
Any ADL Impairment, n (%)	1 (3%)	3 (8%)	3 (8%)	2 (15%)	0 (0%)	1 (12%)

3MS = Modified Mini Mental State Exam
ADL = Activities of Daily Living
GCP = General Cognitive Performance
IQCODE = Informant Questionnaire on Cognitive. Decline in the Elderly
SAGES = Successful Aging after Elective Surgery

Supplementary Table 4. Baseline scores for selected individual neuropsychological tests

Group:	HVLT total	HVLT delay	Trails B	GCP
AD Signature Tertiles				
AD signature Tertile 1	22.958 (5.223)	7.688 (2.776)	232.812 (42.139)	60.025 (6.528)
AD signature Tertile 2	22.426 (5.166)	7.511 (2.166)	209.723 (56.667)	57.813 (6.422)
AD signature Tertile 3	23.067 (5.742)	7.711 (2.944)	222.477 (50.585)	58.322 (6.874)
AD Signature Tertiles and Delirium				
AD signature Tertile 1, no delirium	24.000 (4.863)	8.200 (2.386)	235.914 (43.439)	60.969 (6.524)
AD signature Tertile 2, no delirium	22.737 (5.569)	7.526 (2.357)	214.974 (52.673)	58.157 (6.498)
AD signature Tertile 3, no delirium	24.162 (5.490)	8.162 (2.833)	226.417 (51.064)	59.236 (6.826)
AD signature Tertile 1, delirium	20.154 (5.305)	6.308 (3.351)	224.462 (38.791)	57.484 (6.062)
AD signature Tertile 2, delirium	21.111 (2.759)	7.444 (1.130)	187.556 (70.348)	56.363 (6.237)
AD signature Tertile 3, delirium	18.000 (4.071)	5.625 (2.669)	204.750 (47.352)	54.094 (5.704)

AD signature = Alzheimer's disease signature (average cortical thickness in 9 bilateral cortical regions of interest)
GCP = General Cognitive Performance
HVLT = Hopkins Verbal Learning Test–Revised
Trails B = Trail Making Test B

Supplementary Table 5. Unstandardized coefficients from linear mixed effects models for associations between AD (or Aging) Signature cortical atrophy and/or Delirium on post-operative short-term and long-term change in General Cognitive Performance (GCP) score

	Model Coefficients (95% Confidence Interval)			
	Baseline	**Month 1**	**Month 2**	**Months 2-36 slope**
Model 1 – AD Signature				
AD Signature	-0.20 (-1.05, 0.64)	-0.28 (-0.69, 0.14)	0.24 (-0.11, 0.59)	-0.18 (-0.35, -0.01)
Model 2 – AD Signature				
AD Signature	-0.25 (-1.18, 0.67)	-0.24 (-0.70, 0.23)	0.14 (-0.26, 0.54)	-0.12 (-0.31, 0.08)
Delirium	-1.75 (-13.26, 9.76)	1.15 (-4.74, 7.05)	-2.60 (-7.60, 2.39)	1.53 (-0.78, 3.84)
AD Signature × delirium	-0.19 (-2.22, 1.83)	-0.25 (-1.29, 0.78)	0.51 (-0.36, 1.39)	-0.31 (-0.72, 0.09)
Model 1 – Aging Only Signature				
Aging-Only Signature	-0.94 (-2.02, 0.14)	-0.42 (-0.96, 0.12)	0.32 (-0.14, 0.78)	-0.17 (-0.40, 0.05)
Model 2 – Aging Only Signature				
Aging-Only Signature	-0.91 (-2.07, 0.24)	-0.40 (-1.00, 0.20)	0.39 (-0.12, 0.90)	-0.22 (-0.47, 0.03)
Delirium	5.67 (-17.49, 28.83)	1.33 (-10.79, 13.44)	3.24 (-7.03, 13.52)	-1.91 (-6.76, 2.94)
Aging-Only Signature × delirium	-1.05 (-3.84, 1.73)	-0.19 (-1.65, 1.26)	-0.36 (-1.60, 0.88)	0.21 (-0.38, 0.79)

All models included mean-centered covariates for age (years), female sex, and years of education.
Coefficients can be interpreted as the change in GCP score associated with a 0.10 mm (slightly less than 1.5 SD) decrease in cortical thickness in the AD or Aging-Only signature.

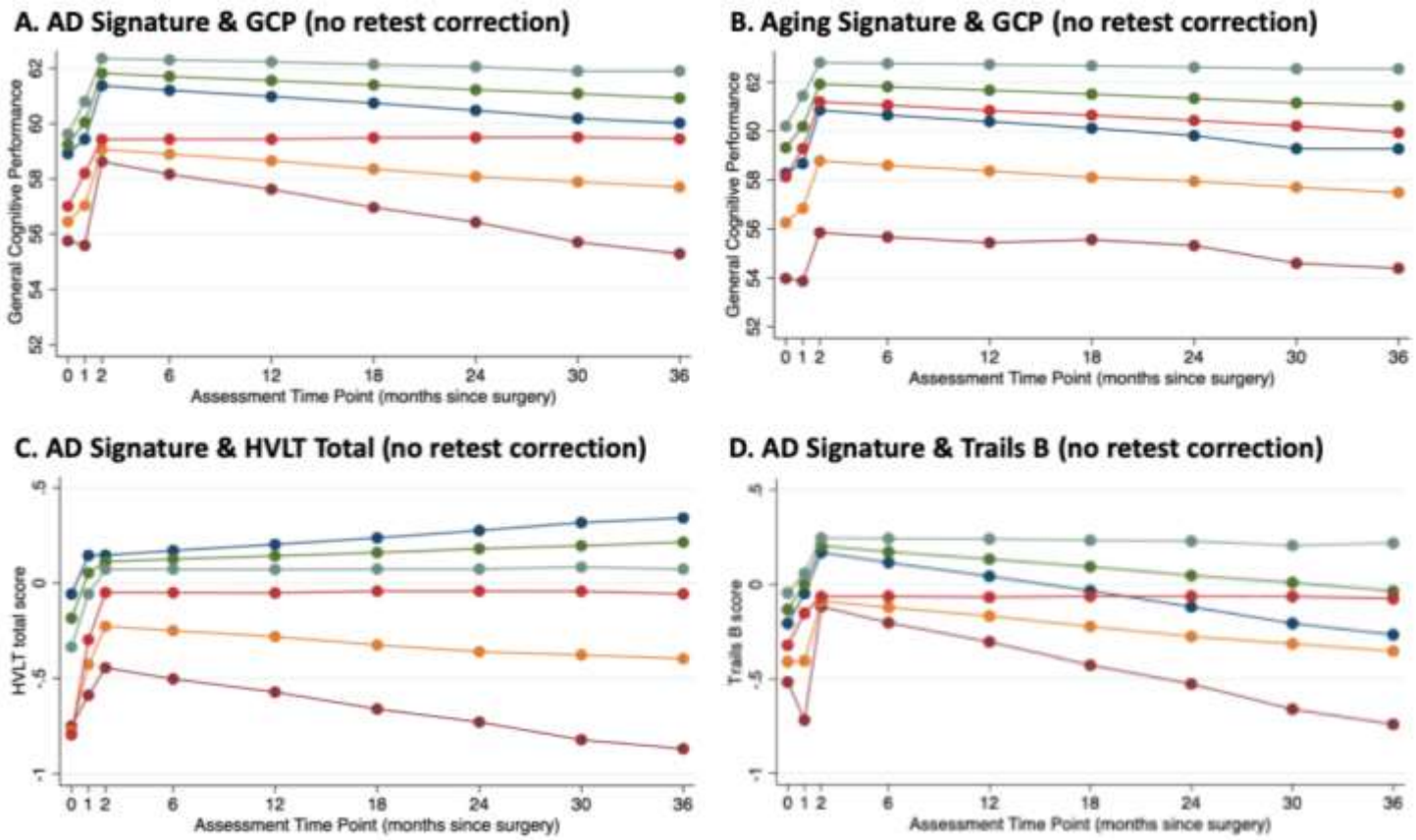
Supplementary Table 6. Covariate model coefficients for standardized cognitive outcomes (z-scores)

	Covariate Model Coefficients (95% Confidence Interval)		
	Baseline Age (years)	**Female Sex**	**Education (years)**
AD signature			
GCP Model 1	-0.053 (-0.082, -0.023)	0.325 (0.043, 0.607)	0.118 (0.067, 0.168)
GCP Model 2	-0.050 (-0.079, -0.021)	0.348 (0.071, 0.626)	0.112 (0.062, 0.162)
HVLT Total Learning	-0.038 (-0.065, -0.011)	0.588 (0.328, 0.848)	0.116 (0.070, 0.163)
HVLT Delayed Recall	-0.042 (-0.071, -0.014)	0.472 (0.203, 0.741)	0.103 (0.054, 0.151)
Trails B	-0.045 (-0.072, -0.018)	-0.028 (-0.284, 0.228)	0.078 (0.031, 0.124)
Aging-Only signature			
GCP Model 1	-0.049 (-0.079, -0.020)	0.321 (0.045, 0.596)	0.119 (0.069, 0.169)
GCP Model 2	-0.046 (-0.074, -0.017)	0.348 (0.080, 0.617)	0.115 (0.066, 0.164)

Cognitive outcome variables were standardized (i.e. z-scores). Covariates were mean-centered but not standardized; coefficients can be interpreted as the standard deviation difference in the average cognitive outcome z-score given a 1 year increase in baseline age, in females compared to males, or given a 1 year increase in education.

Supplementary Table 7. Standardized coefficients from linear mixed effects models for associations between AD (or Aging) signature cortical atrophy and/or delirium on post-operative short-term and long-term change using raw cognitive scores without retest correction

	Model Coefficients (95% Confidence Interval)			
	Baseline	**Month 1**	**Month 2**	**Months 2-36 slope**
GCP (Model 1)				
AD Signature	-0.035 (-0.179, 0.109)	-0.048 (-0.119, 0.023)	0.041 (-0.020, 0.101)	-0.030 (-0.059, -0.001)
GCP (Model 2)				
AD Signature	-0.044 (-0.201, 0.114)	-0.040 (-0.120, 0.040)	0.024 (-0.044, 0.092)	-0.020 (-0.053, 0.013)
Delirium	-0.385 (-0.726, -0.045)	-0.041 (-0.215, 0.132)	0.047 (-0.100, 0.194)	-0.035 (-0.104, 0.035)
AD Signature x delirium	-0.033 (-0.380, 0.313)	-0.043 (-0.221, 0.134)	0.088 (-0.062, 0.238)	-0.053 (-0.123, 0.016)
HVLT Total				
AD Signature	0.126 (-0.033, 0.285)	-0.034 (-0.155, 0.088)	-0.059 (-0.162, 0.044)	0.032 (-0.012, 0.076)
Delirium	-0.579 (-0.922, -0.235)	0.094 (-0.169, 0.357)	0.132 (-0.091, 0.355)	-0.109 (-0.202, -0.016)
AD Signature x delirium	-0.105 (-0.455, 0.244)	-0.120 (-0.389, 0.149)	0.012 (-0.216, 0.240)	-0.099 (-0.192, -0.007)
HVLT Delay				
AD Signature	0.118 (-0.050, 0.285)	-0.060 (-0.188, 0.067)	0.052 (-0.056, 0.160)	-0.027 (-0.077, 0.022)
Delirium	-0.473 (-0.835, -0.112)	0.150 (-0.126, 0.427)	0.144 (-0.090, 0.378)	-0.116 (-0.220, -0.011)
AD Signature x delirium	-0.054 (-0.422, 0.315)	-0.113 (-0.395, 0.169)	-0.164 (-0.403, 0.075)	0.013 (-0.091, 0.118)
Trails B				
AD Signature	0.073 (-0.092, 0.237)	-0.025 (-0.162, 0.113)	-0.013 (-0.130, 0.103)	0.067 (0.010, 0.123)
Delirium	0.290 (-0.064, 0.645)	0.143 (-0.154, 0.440)	-0.136 (-0.388, 0.116)	0.029 (-0.090, 0.148)
AD Signature x delirium	0.016 (-0.345, 0.377)	0.194 (-0.110, 0.497)	-0.221 (-0.478, 0.036)	0.032 (-0.087, 0.152)
GCP (Model 1) - Aging Only				
Aging Signature	-0.124 (-0.266, 0.018)	-0.056 (-0.127, 0.016)	0.042 (-0.019, 0.103)	-0.023 (-0.052, 0.006)
GCP (Model 2) - Aging Only				
Aging Signature	-0.120 (-0.273, 0.032)	-0.053 (-0.132, 0.026)	0.052 (-0.015, 0.119)	-0.029 (-0.061, 0.003)
Delirium	-0.430 (-0.765, -0.094)	-0.043 (-0.217, 0.131)	0.027 (-0.121, 0.175)	-0.020 (-0.091, 0.051)
Aging Signature x delirium	-0.139 (-0.506, 0.228)	-0.026 (-0.218, 0.166)	-0.048 (-0.210, 0.115)	0.028 (-0.050, 0.105)



<u>Supplementary Figure 3.</u> Group effects of cortical atrophy due to AD or aging and post-operative delirium on short- and long-term change in cognitive scores without retest correction. <u>The cortical signatures were analyzed as continuous variables,</u> but for illustration purposes, results are displayed by groups based on cortical signature tertiles (tertile 1 has the thickest cortex, tertile 3 has the thinnest cortex, interpreted as the greatest atrophy) and delirium (present [+] or absent [–]). Tertiles are generated separately for AD signature and for Aging-Only signature measures, leading to slight differences in group size. Estimated slopes are reported based on model coefficients and average cortical thickness in the respective tertile. (A) AD Signature and GCP [General Cognitive Performance]; (B) Aging Signature and GCP; (C) AD Signature and HVLT [Hopkins Verbal Learning Test – Revised total score]; (D) AD Signature and Trails B [Trail Making Test B (reverse-scored so that lower numbers indicate worse performance)]. HVLT and Trails B were transformed into z-scores.

Supplementary Table 8. Comparison of baseline (intercept) coefficients with and without additional health measures as covariates

	Baseline Coefficients [Intercept] (95% Confidence Interval)	
	Original covariates	**+Additional health covariates***
GCP (Model 1)		
AD signature	-0.035 (-0.179, 0.109)	-0.024 (-0.166, 0.118)
GCP (Model 2)		
AD signature	-0.044 (-0.202, 0.115)	-0.036 (-0.192, 0.120)
Delirium	-0.387 (-0.728, -0.045)	-0.374 (-0.711, -0.038)
AD signature x delirium	-0.033 (-0.381, 0.314)	-0.013 (-0.357, 0.330)
HVLT Total Learning		
AD signature	0.127 (-0.033, 0.286)	0.125 (-0.036, 0.285)
Delirium	-0.582 (-0.927, -0.237)	-0.584 (-0.930, -0.238)
AD signature x delirium	-0.106 (-0.457, 0.245)	-0.101 (-0.454, 0.253)
HVLT Delayed Recall		
AD signature	0.118 (-0.050, 0.286)	0.113 (-0.055, 0.281)
Delirium	-0.475 (-0.838, -0.112)	-0.478 (-0.841, -0.115)
AD signature x delirium	-0.054 (-0.423, 0.316)	-0.053 (-0.424, 0.317)
Trails B		
AD signature	-0.079 (-0.244, 0.086)	-0.067 (-0.230, 0.095)
Delirium	-0.281 (-0.637, 0.074)	-0.260 (-0.610, 0.090)
AD signature x delirium	-0.008 (-0.370, 0.354)	-0.002 (-0.359, 0.356)

*Additional baseline health measures covariates: (1) presence/absence of vascular comorbidity [confirmed or history of myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes (with or without end organ damage), cerebrovascular disease (carotid stenosis, history of stroke or transient ischaemic attack), or hemiplegia], (2) Charlson Comorbidity Index (CCI), and (3) the 15-item Geriatric Depression Scale (GDS).