

Cortical gray-white matter contrast alterations precede amyloid- β positivity and macrostructural changes in older adults without dementia

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Background

Early Alzheimer's disease (AD) involves subtle cortical changes that may precede atrophy. Magnetic resonance imaging (MRI) microstructural markers may detect earlier pathology than classical morphometry.

Aims

- identify associations between demographic, genetic, clinical participant characteristics, and cortical micro- and macro-structural integrity, as measured by GWC and MD, and volume and thickness, respectively (Fig. 1)
- quantify the extent of shared/divergent variance between MRI features reflecting cortical micro- and macro-structural integrity, on a global and regional scale (Fig. 2)
- examine the cross-sectional relation between cortical A β burden and MRI features reflecting cortical micro- and macro-structural integrity (Fig. 3)
- approximate the time at which MRI features reflecting cortical micro- and macro-structural integrity become affected relative to clinically meaningful amounts of cortical A β aggregates (Fig. 4)

Table 1 Demographics and Clinical Characteristics at Baseline

Variable	Overall N = 1,323*	A β - N = 994*	A β + N = 329*	p
Age, years	68.00 (8.66)	66.47 (8.07)	72.60 (8.76)	<0.001 [†]
Sex, female	746 (56%)	574 (58%)	172 (52%)	0.083 [‡]
Education, years	14.61 (3.96)	14.73 (3.93)	14.26 (4.00)	0.10 [†]
CDR				<0.001 [§]
0 - Normal	1,083 (82%)	874 (88%)	209 (64%)	
0.5 - Very mild	239 (18%)	120 (12%)	119 (36%)	
MMSE	28.87 (1.45)	29.07 (1.20)	28.20 (1.91)	<0.001 [†]
(Missing)	125	77	48	
APOE- ϵ 4 carriership (%)	528 (40%)	320 (32%)	208 (63%)	<0.001 [‡]
carriers)				
A β -PET, Centiloids	18.64 (31.00)	3.56 (9.01)	64.18 (29.31)	<0.001 [†]
est. Total Intracranial	1491.8 (175.4)	1490.9 (176.1)	1494.4 (173.6)	0.5 [†]
Volume, cm ³				

A β positivity was defined on a cutoff of CL > 24.1.

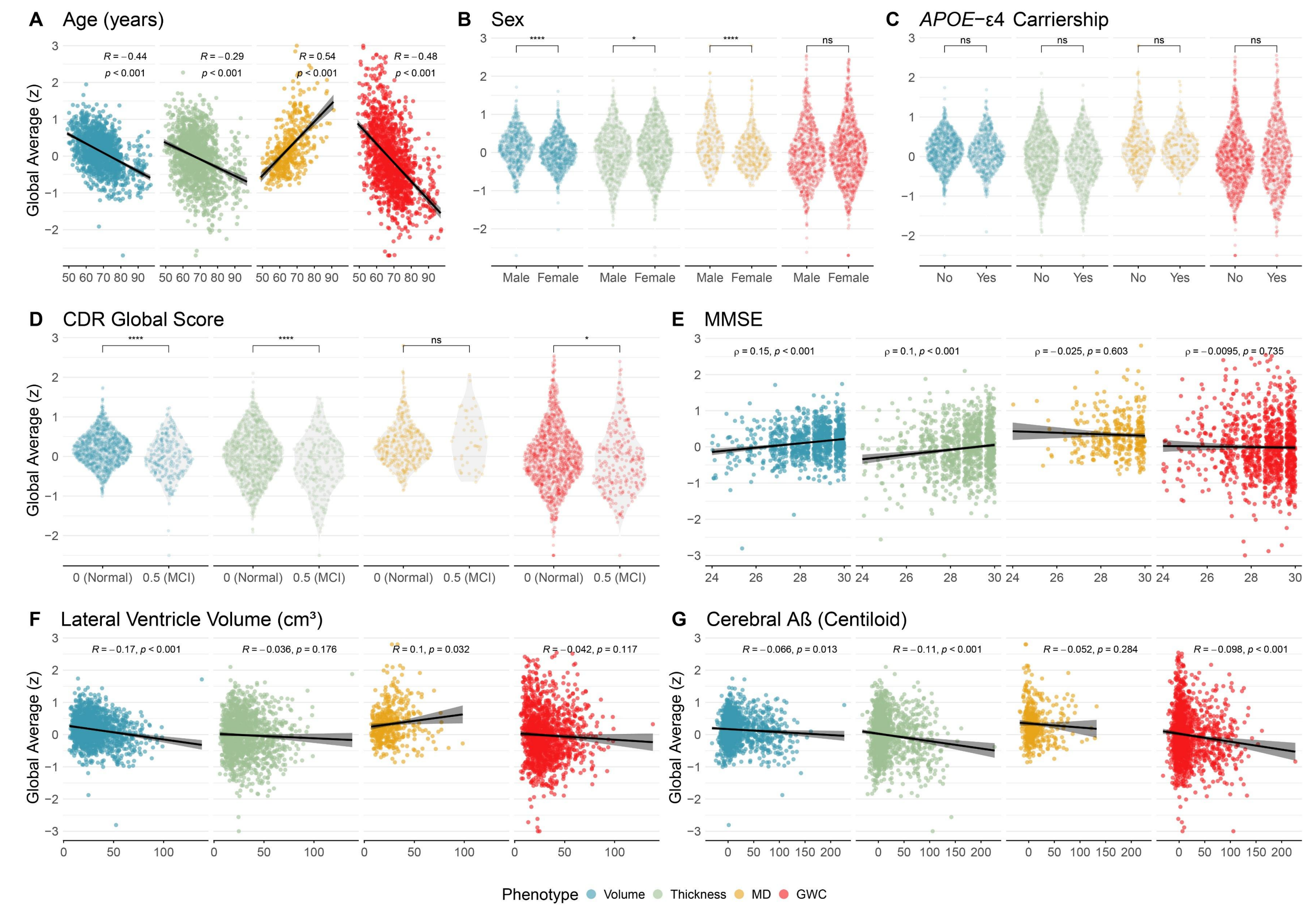
Abbreviations: A β , amyloid- β ; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; PET, Positron Emission Tomography; GWC, Gray-White Matter Contrast; MD, Mean Diffusivity

*Mean (SD); n (%) [†]Wilcoxon rank sum test [‡]Pearson's Chi-squared test [§]Fisher's exact test

Methods

We analyzed cross-sectional harmonized* MRI and amyloid- β (A β) positron emission tomography (PET) data from 1323 non-demented AMYPAD participants. Cortical volume, thickness, gray-white matter contrast (GWC), and mean diffusivity (MD) were related to global A β burden and estimated time to A β -positivity** using regression, correlation, and change-point analyses.

Fig. 1: Global averages of micro- and macrostructural cortex properties are differentially affected by demographic and clinical characteristics



*MRI harmonization (ComBat)

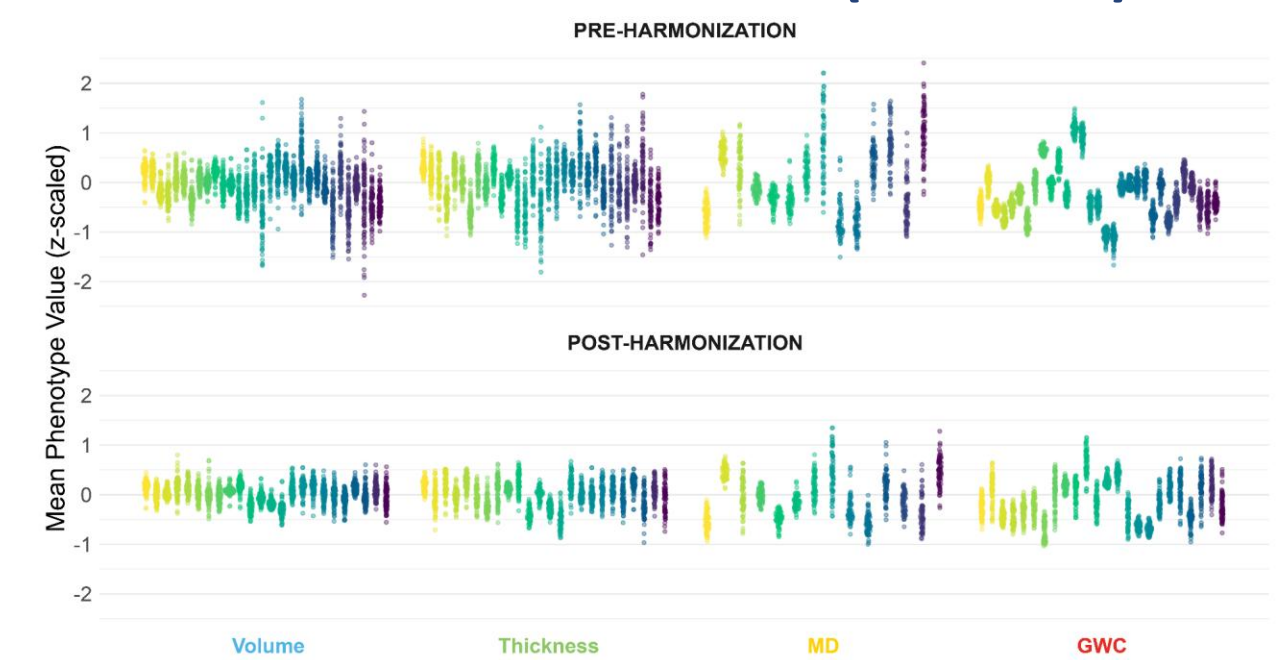


Fig. 2: Global and regional inter-phenotypic correlations

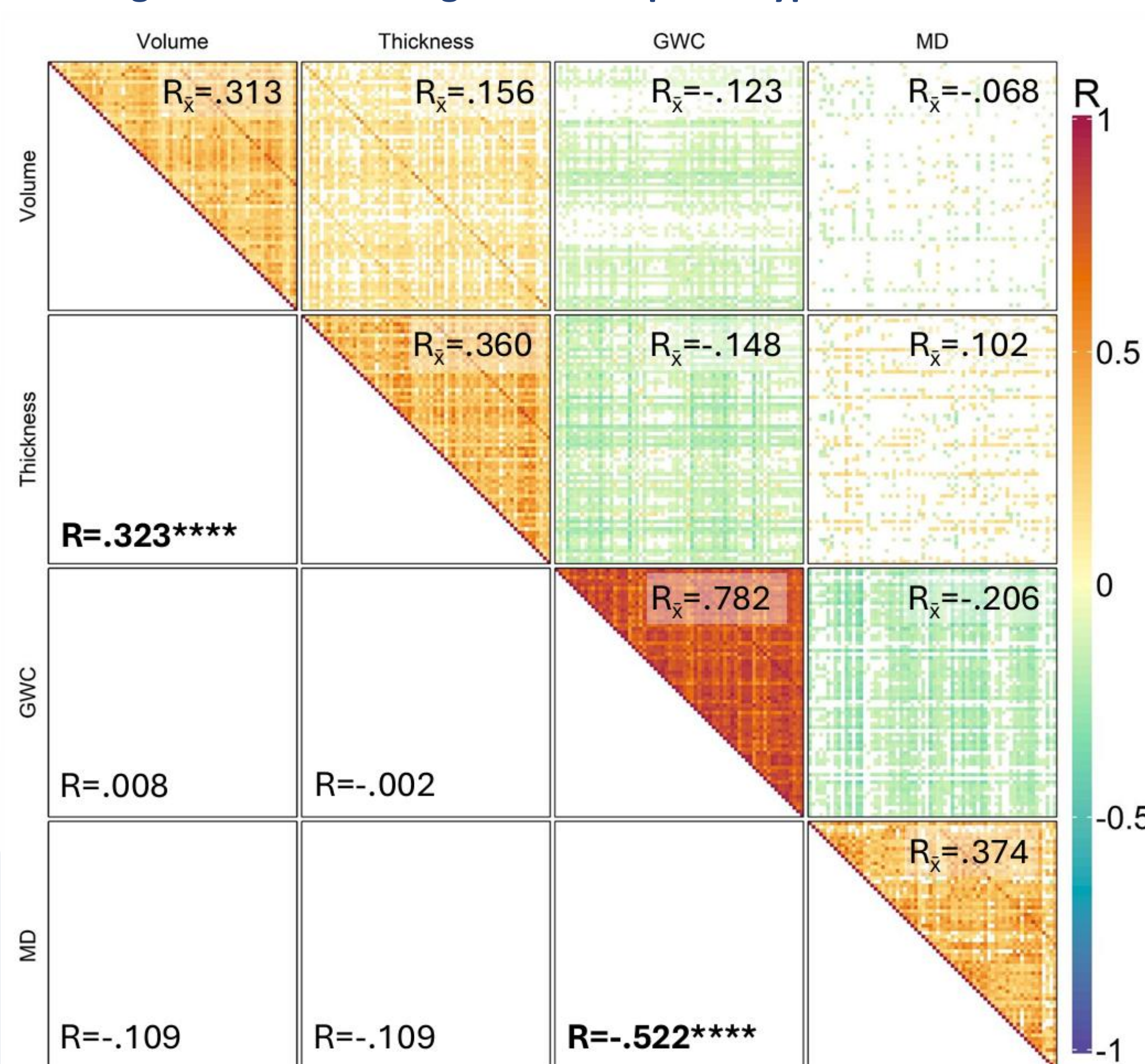


Fig. 3: Global A β burden is mostly related to boundary-based measures, less to volume and MD

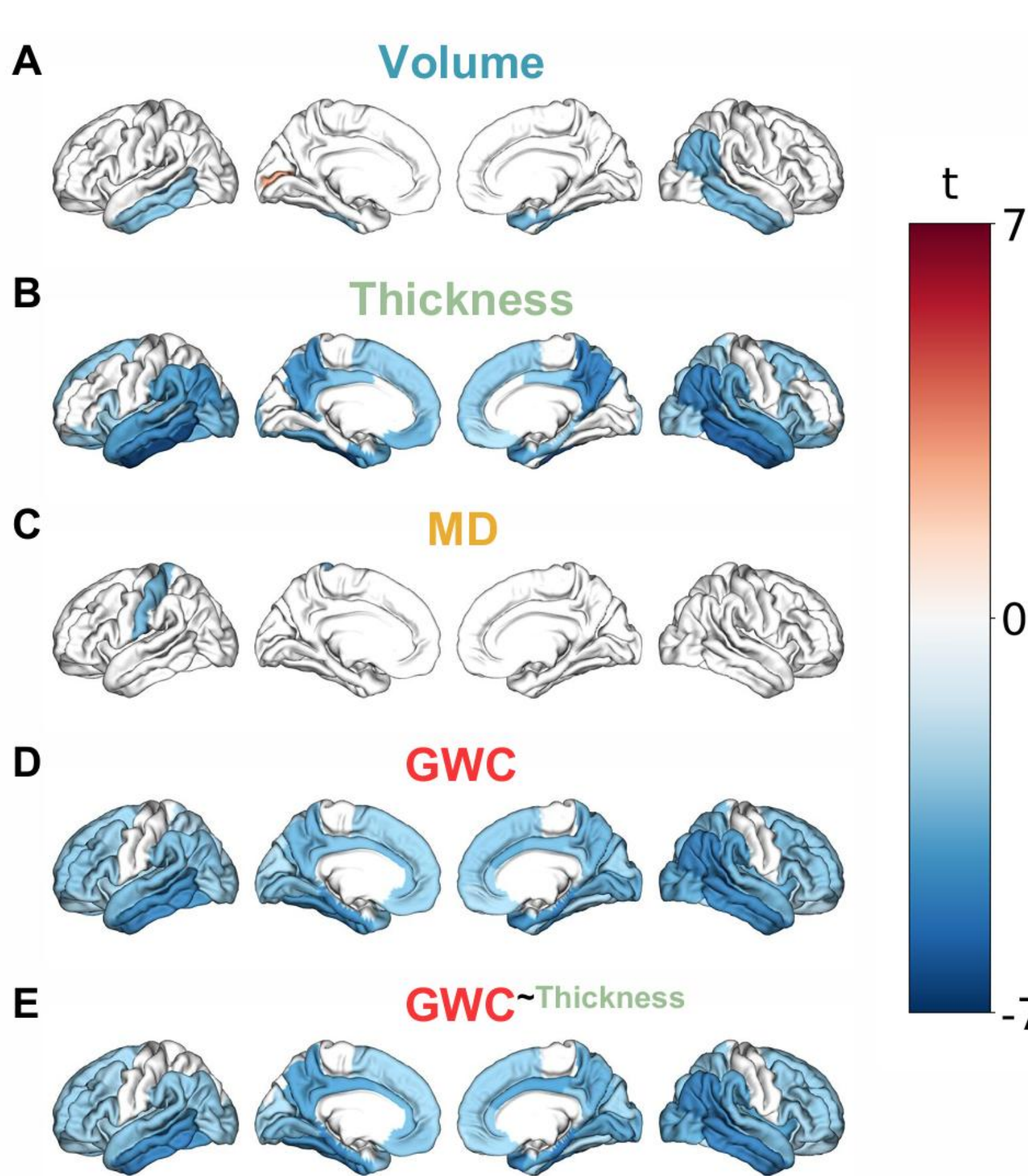
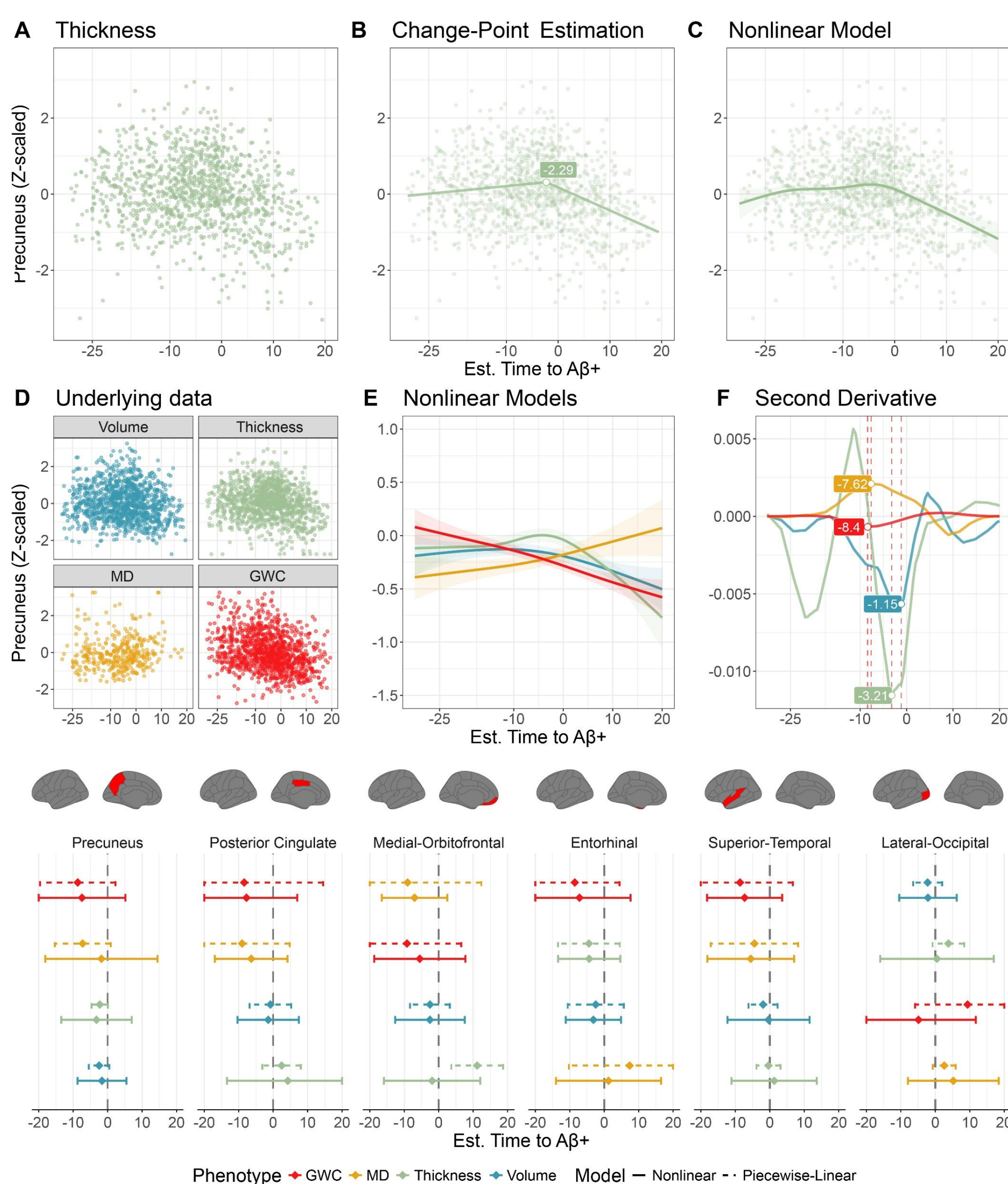


Fig. 4: AD-related phenotype changes occur earlier for GWC than for macrostructural cortex measures



Conclusions

Our findings indicate that cortical microstructural MRI measures, particularly GWC, show patterns that are partially independent from classical morphometric measures such as cortical volume and thickness. Alterations in GWC were detectable years before amyloid- β positivity and cortical atrophy. This positions GWC as a sensitive marker of early brain changes in preclinical Alzheimer's disease.

FDR-corrected significance-thresholded correlation matrices for regional and global metrics; Top right diagonal: Regional correlations across 68 cortical regions of the gyrus-based Desikan–Killiany atlas show similar patterns, with evident left-right coupling. Left bottom diagonal: Correlations of global averages (mean of all z-scaled regional phenotypes) of each phenotype and their binned p-values

Multivariate linear model t-values of significant effects (after FDR-correction) of global A β burden, measured with Centiloid, on local macrostructural (A-B) and microstructural (C-D) properties, corrected for age, sex, clinical dementia rating.