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Higher cortical thickness/volume in Alzheimer's-related regions: Protective factor or risk factor?

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Abstract

Some evidence suggests a biphasic pattern of changes in cortical thickness wherein higher, rather than lower, thickness is associated with very early Alzheimer's disease (AD) pathology. We examined whether integrating information from AD brain signatures based on mean diffusivity (MD) can aid in the interpretation of cortical thickness/volume as a risk factor for future AD-related changes. Participants were 572 men in the Vietnam Era Twin Study of Aging who were cognitively unimpaired at baseline (mean age=56 years; range=51–60). Individuals with both high thickness/volume signatures and high MD signatures at baseline had lower cortical thickness/volume in AD signature regions and lower episodic memory performance 12 years later compared to those with high thickness/volume and low MD signatures at baseline. Groups did not differ in level of young adult cognitive reserve. Our findings are in line with a biphasic model in which increased cortical thickness may precede future decline and establish the value of examining cortical MD alongside cortical thickness to identify subgroups with differential risk for poorer brain and cognitive outcomes.

Keywords

Alzheimer's disease; neuroimaging; signatures; cortical thickness; mean diffusivity

INTRODUCTION

Structural brain measures derived from magnetic resonance imaging (MRI) are commonly used to study disease progression across the Alzheimer's disease (AD) continuum. A large literature has detailed robust findings in which lower cortical thickness is associated with mild cognitive impairment (MCI) or AD within a single timepoint (Singh et al., 2006, Tabatabaei-Jafari et al., 2015) or predicts future cognitive decline associated with AD (Li et al., 2012, Kulason et al., 2019). According to the National Institute on Aging-Alzheimer's Association AT(N) research framework for AD, biomarkers are grouped into measures of abnormal levels of amyloid (A), tau (T), and neurodegeneration (N). Biomarkers in the (N) group include structural MRI and, while neurodegeneration is not specific for AD, it can be used to monitor disease progression and provides added prediction of future cognitive decline (Jack et al., 2018).

In order to improve the specificity of the relationship between structural MRI measures and AD-related changes, some groups have developed composite scores of structural MRI metrics (e.g., thickness or volume) in AD-vulnerable brain regions (Bakkour et al., 2013, Bakkour et al., 2009, Dickerson et al., 2009, Dickerson et al., 2011, Dickerson and Wolk, 2012, McEvoy et al., 2009, McEvoy et al., 2011, Sabuncu et al., 2011). These composite scores, commonly termed "AD signatures," have been shown to be useful tools in predicting symptom severity, AD-related biomarkers, and progression to AD dementia (Bakkour et al., 2009, Dickerson et al., 2009, McEvoy et al., 2009, Dickerson et al., 2011, McEvoy et al., 2011, Putcha et al., 2011, Sabuncu et al., 2011, Dickerson and Wolk, 2012, Bakkour et al., 2013). The majority of studies on AD signatures have involved adults over 70 years of age and with some degree of cognitive impairment. Findings have demonstrated that lower cortical thickness AD signature scores (representing comparatively thinner cortex) were associated with increased risk of future cognitive decline (Bakkour et al., 2009, Dickerson et al., 2009, McEvoy et al., 2009, Dickerson et al., 2011, McEvoy et al., 2011, Putcha et al., 2011, Sabuncu et al., 2011, Dickerson and Wolk, 2012, Bakkour et al., 2013).

In stark contrast, some studies among cognitively unimpaired (CU) adults in middle age and early old age have found that greater, rather than lower, cortical thickness may be associated with very early AD pathology. Previous cross-sectional studies have found greater cortical thickness among amyloid-positive, tau-negative CU individuals compared to CU individuals without amyloid or tau pathology, but thinner cortex among individuals who had already developed clinical symptoms and progressed to MCI or AD dementia (Fortea et al., 2014, Montal et al., 2018, Batzu et al., 2020, Salvado et al., 2022). In previous work by our group, we examined two AD signatures among CU, middle-aged adults (average baseline age = 56 years) to predict incident MCI 12 years later (Williams et al., 2021). One signature, based on cortical thickness and hippocampal volume (hereafter referred to as the "cortical thickness/volume signature"), was previously validated using data from the Alzheimer's Disease Neuroimaging Initiative (McEvoy et al., 2009, McEvoy et al., 2011). In these studies, MCI participants with lower thickness/volume AD signature scores, indicating lower cortical thickness and hippocampal volume, were more likely to progress to AD than those with higher scores. The other signature was a novel signature based on gray matter mean diffusivity (MD) in these same regions, where higher signature scores were associated

with increased AD risk (Williams et al., 2021). We hypothesized that the MD signature would be more sensitive to AD-related changes because microstructural changes are likely to predate macrostructural changes (Weston et al., 2015). Although the difference was not statistically significant, we found that cortical thickness/volume signature scores at baseline tended to be higher among CU individuals who progressed to MCI 12 years later compared to a group that remained CU over the same time period. However, when group differences in cortical thickness/volume signatures were examined cross-sectionally at each of the three assessment timepoints, individuals who currently had MCI tended to have lower thickness/volume signature scores compared to individuals who were currently CU. In contrast, higher MD signature scores consistently predicted both subsequent MCI and concurrent MCI.

Evidence suggests a possible inverted-U pattern in which cortical thickness initially increases in very early disease stages and subsequently decreases with disease progression and onset of symptoms (Montal et al., 2018). Higher cortical thickness that occurs early on the AD continuum may represent a response to disease pathology, neuroinflammation, compensatory neural hypertrophy, or a combination of these and other processes that are not well understood (Iacono et al., 2008, Torso et al., 2022). A cross-sectional study among CU adults enriched for family history of AD found that greater pathological levels of CSF β-amyloid (Aβ), phosphorylated tau, and several glial markers were associated with higher cortical gray matter volume and increased glucose metabolism in AD-related brain regions, supporting the idea that early AD pathological processes may be associated with higher cortical volume in some individuals (Salvado et al., 2022). A longitudinal study by Pegueroles and colleagues (2017) reported a slower rate of cortical atrophy over a 2-year period among CU Aβ-positive individuals compared to CU Aβ-negative individuals, whereas those with both Aβ and tau pathology showed accelerated rates of cortical atrophy. They suggested that their longitudinal results are in line with such an inverted-U pattern of cortical thickness; however, they noted that possible differences in cognitive reserve may complicate this interpretation. It is possible that individuals with higher cortical thickness in the context of AD-related pathology may have higher pre-existing levels of cognitive reserve, which may be associated with longstanding higher cortical thickness. Higher pre-existing cognitive reserve and cortical thickness may allow for greater cognitive resilience, i.e., the maintenance of cognitive abilities in the face of AD-related changes and could explain associations between higher cortical thickness and AD pathology (Kremen et al., 2022). To our knowledge, this hypothesis has not been explicitly tested.

Thus, a group of CU individuals with high cortical thickness may actually be composed of two subgroups with markedly different future trajectories. Understanding the difference between high cortical thickness indicating a risk versus a protective factor carries important implications for early identification of AD and the use of cortical thickness as a marker of disease progression. We hypothesized that using measures sensitive to early AD-related changes in combination with cortical thickness at a single timepoint can better characterize an individual's trajectory of disease risk and elucidate these subgroups. Gray matter MD is a diffusion-based MRI measure that has been shown to be a particularly useful and sensitive neuroimaging biomarker of brain structural integrity, and increased values have been found among individuals with MCI or AD (Weston et al., 2015, Fellgiebel et al., 2004, Ray et al., 2006, Scola et al., 2010). Prior work from our group has demonstrated that gray matter MD

is both heritable and, at a given timepoint, influenced by genetic factors that are distinct from those influencing cortical thickness (Elman et al., 2017, Gillespie et al., 2017). We have also shown that a novel AD signature based on gray matter MD aided prediction of incident MCI among CU adults in their 50s (Williams et al., 2021), captured unique phenotypic and genetic variance not otherwise explained by thickness/volume signatures or general brain aging, and robustly predicted thickness/volume signatures over a decade later (Williams et al., 2022). These findings are in line with changes in this MD signature preceding changes in a thickness/volume signature.

Given this demonstrated utility of MD signatures, we examined whether level of cortical thickness could be contextualized as either a risk or protective factor when examined alongside MD signatures among 572 men from three waves of the Vietnam Era Twin Study of Aging (VETSA, baseline age = 56 years). We first examined linear relationships among both AD signatures, *global* MRI measures, and memory performance. We focused on the memory domain given its integral involvement in AD. Next, to examine whether MD signatures may help indicate whether cortical thickness is a risk versus a protective factor, we created two subgroups that each had high thickness/volume at baseline: those with high values for both AD signatures (HighCT-HighMD) and those with high cortical thickness/volume signatures and low MD signatures (HighCT-LowMD). In our sample, we found that higher MD signatures consistently predicted both concurrent MCI and later MCI (Williams et al., 2021). Thus, the HighCT-HighMD group was hypothesized to be at greater risk for future decline. We tested subgroup differences in level (main effect of subgroup differences) and maintenance (group differences in slope across time, tested as an interaction between subgroup and timepoint) of AD signatures and memory performance. We also examined subgroup differences in level and maintenance of *global* cortical thickness across the three study waves in order to compare these *global* changes with changes in more AD-specific regions captured by the thickness/volume signature. Given that the thickness/volume signature is a composite of several different brain regions, in follow-up analyses, we examined whether the correlations between thickness/volume and MD in each subgroup were driven by any particular brain regions. Finally, in order to examine whether group differences might be explained by pre-existing differences in cognitive reserve, we tested differences in young adult cognitive reserve measured at average age 20.

METHODS

Participants

The Vietnam Era Twin Study of Aging (VETSA) is a longitudinal study of cognitive and brain aging and risk for Alzheimer's disease beginning in middle age (Kremen et al., 2013). Participants were 572 men from VETSA. This community-dwelling sample of male twins is similar to nationally representative samples of American men in their age range with respect to health, education, and lifestyle characteristics (Schoeneborn and Heyman, 2009). All served in the United States military at some point between 1965 and 1975, but approximately 80% reported no combat exposure. Participants were 56.26 (SD = 2.59) years old at wave 1 with an average education of 13.89 (SD = 2.13, range = 8–20) years. The sample consisted of men who self-identified as American Indian (<1%), Black or African

American (6.3%), multiracial (1.2%), and White (91.8%). Most (96.3%) were non-Hispanic. Table 1 displays sample characteristics both for the full sample and for HighCT-HighMD and HighCT-LowMD subgroups.

For the first set of analyses examining linear relationships among variables of interest, all CU participants with AD signature data at any wave were included in analyses (n = 572); 62% (355) participants had data at all three waves. Subgroup analyses included all participants who were CU at wave 1, had high thickness/volume signatures at wave 1, and had data on MD signatures at wave 1, regardless of cognitive status at subsequent waves (n = 147); 69% (102) had data at all three waves. The average between-wave interval was 5.8 years. Subgroup analyses excluded participants with low thickness/volume signatures. To maximize sample size of these groups, high and low values of AD signatures were determined using a median split based on signature values at wave 1. For analyses related to MCI, exclusionary criteria included conditions that could contribute to cognitive impairment unrelated to MCI: seizure disorder, multiple sclerosis, stroke, HIV/AIDS, schizophrenia, or severe substance dependence (Kremen et al., 2014). The study was approved by the Institutional Review Boards at the University of California, San Diego (UCSD), Boston University, and the Massachusetts General Hospital (MGH). Written informed consent was obtained from all participants.

MRI acquisition and processing

Images at wave 1 (baseline) were acquired on Siemens 1.5T scanners at UCSD and MGH. Images at wave 2 were acquired with a GE 3T Discovery 750x scanner (GE Healthcare, Waukesha, WI, USA) with an 8-channel phased array head coil at UCSD and with a Siemens Tim Trio (Siemens USA, Washington, D.C.) with a 32-channel head coil at MGH. Images at wave 3 were acquired at UCSD with two GE 3T Discovery 750x scanners with eight-channel phased array head coils. Volumetric segmentation (Fischl et al., 2002, Fischl et al., 2004) and cortical surface reconstruction (Dale and Sereno, 1993, Dale et al., 1999, Fischl et al., 2002, Fischl et al., 2004) methods were performed with FreeSurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu). Structural (Dale and Sereno, 1993, Dale et al., 1999, Fischl et al., 2002, Fischl et al., 2004, Kremen et al., 2010, McEvoy et al., 2015) and diffusion (Elman et al., 2017, Gillespie et al., 2017) MR images were processed as described previously, and more detail is available in supplementary materials.

Alzheimer's disease brain signatures

AD signature scores were calculated as described previously (Williams et al., 2021, Williams et al., 2022). Briefly, we used an AD brain signature that was previously developed by our group using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (McEvoy et al., 2009, McEvoy et al., 2011). The regions and weights used in this signature were derived using a data-driven approach to identify a pattern of regional atrophy specific to mild AD. This signature is a weighted average of thickness in seven cortical regions (entorhinal cortex, middle temporal gyrus, bank of superior temporal sulcus, superior temporal gyrus, isthmus cingulate, lateral orbitofrontal cortex, medial orbitofrontal cortex), plus hippocampal volume, with separate weights for left and right hemisphere regions (referred to as "thickness/volume signature").

For the structural and diffusion data, we regressed out effects of age and scanner model for each ROI, as well as estimated intracranial volume for the hippocampus to control for differences in head size, which affect volume but not thickness measures. Standardized residuals of ROIs were then weighted according to their ability to discriminate between ADNI AD cases and controls and summed together to form the thickness/volume signature scores. Given that there is, as yet, no independently created AD gray matter MD signature, we applied these same weightings to the MD values for each ROI (including the hippocampus) and carried out the same steps to generate our novel MD signature scores (Williams et al., 2021, Williams et al., 2022)

Definition of mild cognitive impairment

We used the Jak-Bondi approach to diagnose MCI (Bondi et al., 2008, Jak et al., 2009). In a direct comparison of ADNI participants with diagnoses based on Petersen criteria, Jak-Bondi diagnoses were associated with a higher proportion of participants progressing to AD, a lower proportion reverting to normal, a higher proportion being AD biomarker-positive, and a higher proportion being *APOE*-ε4 positive (Bondi et al., 2014).

Participants completed a neuropsychological battery comprising 18 tests that encompassed six cognitive domains: memory, executive functioning, attention, language, visuospatial ability, and processing speed (Kremen et al., 2014). Criteria for impairment within a domain required performance on 2+ tests that were each >1.5 SDs below age- and education-adjusted normative means. Although the Jak-Bondi approach allows for different impairment cutoffs(Jak et al., 2009), requiring performance > 1 SD below normative means on 2+ tests is most common. However, in prior work with Drs. Jak and Bondi, we used the more conservative threshold of 1.5 SDs because of the younger age of the VETSA sample (Granholm et al., 2017). The more commonly used threshold identified an unrealistic 32% of this relatively young sample as having MCI. In line with psychometric principles, we determined that the threshold needed to be more conservative given the expected lower base rate of MCI in a sample as young as the VETSA cohort.

To account for longstanding differences in cognitive performance, all scores were adjusted for a measure of general cognitive ability that was previously administered to participants at an average age of 20 years (Lyons et al., 2017b). Scores for returning participants from waves 2 and 3 were additionally adjusted for practice and attrition effects using a replacement-subjects method as described previously (Ronnlund et al., 2005, Elman et al., 2018).

Cognitive reserve

We define cognitive reserve as an individual's total cognitive resources at a given point in time (Kremen et al., 2022). Young adult cognitive reserve was measured using a test of global cognitive ability that participants took at average age 20 years (Armed Forces Qualification Test; AFQT). The AFQT has a high correlation with other tests of general cognitive ability and IQ (Lyons et al., 2017a, Lyons et al., 2009). The AFQT was administered to participants again at each VETSA wave; correlations between scores at

average age 20 and scores in midlife ranged from 0.73 to 0.85, reflecting substantial stability over time (Lyons et al., 2009).

Statistical analysis

All analyses were conducted using R v4.0.5 (Team, 2020). Packages used included 'lme4' and 'lmerTest' (linear mixed effects models) as well as 'jtools' (creation of plots). In all longitudinal models, random nested intercepts were included to control for repeated measures within subjects across waves and nesting of individuals within pairs to adjust for correlations within-person and across twin dyads, respectively. In cross-sectional models, a random intercept for twin pairs was included. We used a false discovery rate of 0.05 to correct for multiple comparisons for each set of analyses(Benjamini and Hochberg, 1995); original *p*-values are reported. Prior to analyses, all continuous measures were standardized within each timepoint by subtracting the mean of all subjects' value at that timepoint from each individual's value and dividing by the standard deviation of all subjects' values at that timepoint. Outliers were identified by visual inspection in the AD signature data, and winsorization was applied to signature values that were greater than 3 standard deviations above or below the mean ($n = 18$). Partial residuals and 95% confidence intervals are displayed in all figures. Effect sizes were calculated using a standardized mean difference (SMD) measure analogous to Cohen's *d* (Cohen, 1992, Moore et al., 2014).

Linear relationships among AD signatures, global mean cortical thickness, and memory performance—First, we examined basic linear relationships among AD signatures, *global* mean cortical thickness, and memory performance among CU individuals using linear mixed effects models. Data from participants at any wave at which they were CU were included; models accounted for repeated observations of participants if they contributed data at multiple waves. Covariates included age and MRI scanner strength (coded as '1' for wave 1 and 0 for waves 2 and 3). Separate models were used to test each relationship. Beta estimates from models as well as correlation coefficients are reported.

Subgroup differences in level and maintenance of AD signatures, global mean cortical thickness, and memory performance—Next, we examined group differences in level and maintenance of AD signatures and memory performance between the two subgroups: those with high values for both AD signatures at baseline (HighCT-HighMD), and those with high cortical thickness/volume and low MD signatures at baseline (HighCT-LowMD). Only individuals who were CU at wave 1 were included in these analyses. In these analyses, group differences in the level of a measure was tested using a main effect of group (HighCT-HighMD vs. HighCT-LowMD). Group differences in longitudinal maintenance of measures, or the degree to which decline over time is minimized (Kremen et al., 2022), were tested using an interaction term between study wave and group in each model. Subgroup differences in maintenance of *global* mean cortical thickness were also examined in order to compare with subgroup differences in the more AD-specific thickness/volume signature. Nonsignificant interaction effects were removed from models before estimating main effects, representing subgroup differences in level of each measure across all study waves. Only a main effect of group was tested for differences in level of young adult cognitive reserve. All models controlled for baseline thickness/

volume signatures and age. Models predicting episodic memory included baseline memory performance as an additional covariate.

Subgroup differences in regional associations between cortical thickness/volume and mean diffusivity—To understand whether the correlations between thickness/volume and MD in each subgroup were driven by particular brain regions, we explored regional correlations between cortical thickness or hippocampal volume and the MD signature. Following the same steps used to create the AD signatures described above, each ROI in the thickness/volume signature was residualized for age and scanner, as well as estimated intracranial volume for the hippocampus. Correlations between each residualized ROI and the overall MD signature were examined.

RESULTS

The two subgroups (HighCT-HighMD and HighCT-LowMD) did not differ in age, years of education, proportion of individuals with an *APOE*- ε4 allele, young adult cognitive reserve, baseline memory performance, or proportion of individuals on each scanner model within timepoints. Individuals in both groups were above the median for thickness/volume (by definition), but the HighCT-LowMD subgroup had significantly higher thickness/volume signature scores at baseline compared to the HighCT-HighMD subgroup. As such, we adjusted for baseline thickness/volume differences between groups. By design, the HighCT-LowMD subgroup also had significantly lower baseline MD signature scores compared to the HighCT-HighMD subgroup. Differences in MRI measures at subsequent waves were examined in longitudinal mixed models reported below.

Linear relationships among AD signatures, global mean cortical thickness, memory performance, and cognitive reserve in CU individuals

Among CU individuals, higher cortical thickness/volume signatures were overall associated with lower MD signatures ($\beta = -0.42$, $r = -0.50$, $p < .001$, Figure 1a). *Global* mean cortical thickness was positively associated with thickness/volume signatures ($\beta = 0.72$, $r = 0.78$, $p < .001$, Figure 1b) and inversely with MD signatures ($\beta = -0.44$, $r = -0.56$, $p < .001$, Figure 1c). Memory performance was not associated with either AD signature (ps > 0.05) in linear mixed effects models.

Subgroup differences in level and maintenance of AD signatures, global mean cortical thickness, memory performance, and cognitive reserve

After equating the two subgroups on baseline cortical thickness/volume signatures (i.e., controlling for baseline thickness/volume signatures in models), the HighCT-HighMD group showed greater decline in thickness/volume signatures across waves and had significantly lower thickness/volume signatures compared to the HighCT-LowMD group by wave 3 (wave 3 SMD = 0.40, $p = 0.016$, Figure 2a). The significance of the group-by-wave interaction effect in this model ($p = 0.048$) did not survive correction for multiple comparisons; however, all other group differences reported remained significant. In contrast to decline in thickness/volume in AD-related regions captured by the signature among the High CT-HighMD group, *global* mean cortical thickness was significantly lower in the

HighCT-HighMD group across all waves compared to the HighCT-LowMD group (SMD = 0.23, $p = 0.021$; Figure 2b), with the magnitude of group differences across waves remaining similar as evidenced by a nonsignificant interaction term. The two subgroups also showed stable differences in MD signatures over time as evidenced by a nonsignificant interaction between group and wave and a significant main effect of group (SMD = 0.90, $p < .001$; Figure 2c).

Controlling for baseline thickness/volume signatures and baseline memory performance, the HighCT-HighMD group additionally showed significantly greater decline in episodic memory performance across waves (group-by-wave interaction term $p = 0.024$) such that the HighCT-HighMD group demonstrated lower memory performance by wave 3 compared to the HighCT-LowMD group (wave 3 SMD = 0.41, $p = 0.007$; Figure 2d).

Subgroup differences in regional associations between cortical thickness/volume and mean diffusivity

In the HighCT-LowMD subgroup, correlations between cortical thickness or hippocampal volume and MD within individual regions belonging to each signature were negative or near-zero (rs = 0.05 to −0.33; Figure 3a). In contrast, among the HighCT-HighMD subgroup, a mix of positive and negative correlations were observed (rs = −0.20 to 0.28; Figure 3b). As can be seen in Figure 3, the strongest correlations were in the lateral temporal lobes (left middle and superior temporal regions). These were positive for the HighCT-HighMD subgroup and negative for the HighCT-LowMD subgroup. More specifically, for the HighCT-HighMD subgroup, cortical thickness in the left hemisphere superior temporal region showed one of the strongest positive associations with the MD signature ($r = 0.22$). For the HighCT-LowMD subgroup, this region showed one of the strongest negative associations with the MD signature ($r = −0.30$). Correlations between hippocampal volume and the MD signature were similar and weak across both subgroups (rs = −0.05 to 0.06).

It is possible that these stronger correlations in the left middle and superior temporal regions were driving results with the overall AD signatures. To test whether this was the case, we repeated the same analysis examining subgroup differences in level and maintenance of memory scores using subgroups defined by values from a “temporal region signature” rather than the overall AD composite signature. Two temporal region signatures, one using cortical thickness and one using cortical MD, were created using weighted averages of left middle temporal and left superior temporal regions, as these were the two ROIs that showed the strongest associations with the MD signature (Figure 3). We used the same weights for these ROIs as are used in the overall AD signature. High and low values (determined using a median split) of these temporal region thickness/volume and MD signatures were used to define two subgroups: 1) High Temporal Thickness and High Temporal MD, and 2) High Temporal Thickness and Low Temporal MD. We found that subgroups defined by values on these temporal region signatures showed no differences in level or maintenance of memory scores over time (ps = 0.428, 0.750, respectively), in contrast to the significant differences in maintenance of memory scores using subgroups defined with the overall AD signatures (Figure 2D).

DISCUSSION

Our results demonstrate that higher cortical thickness/volume in AD-related regions among CU individuals may not be a uniformly protective factor, and that using measures of cortical MD alongside cortical thickness can elucidate meaningful subgroups with differing trajectories of brain and cognitive outcomes. Among individuals with high thickness/volume signature scores at baseline, individuals that additionally had high values on MD signature scores showed significantly lower thickness/volume signatures and episodic memory performance by wave 3. In contrast, group differences in *global* mean cortical thickness remained stable across waves, suggesting that brain changes predominantly occurred in AD-relevant regions. These findings overall establish the value of considering cortical MD alongside measures of cortical thickness/volume to determine whether higher cortical thickness/volume may represent a protective or risk factor for a CU individual.

Prior work has proposed a biphasic model of changes in cortical thickness along the AD continuum, wherein cortical thickness may initially increase in very early disease states, possibly reflecting an inflammatory or neuronal hypertrophy response to Aβ pathology, and subsequently decrease with progression of disease pathology and onset of clinical symptoms (Montal et al., 2018). According to this model, higher cortical thickness early on the AD continuum may be accompanied by mirrored low MD, before reaching an inflection point at which cortical thickness decreases, MD increases, and clinical symptoms emerge (Montal et al., 2018). Figure 4a, adapted from work by Montal and colleagues (Montal et al., 2018), displays this proposed biphasic model. Studies examining early AD-related changes in MD are mixed, with some reporting higher gray matter MD in CU individuals associated with tau-PET and subsequent cognitive decline (Rodriguez-Vieitez et al., 2021) or among presymptomatic individuals with autosomal dominant AD (Weston et al., 2020). Other studies have shown initial lower gray matter MD in CU individuals with evidence of AD-related pathology (Montal et al., 2018) or in presymptomatic individuals with autosomal-dominant AD (Fortea et al., 2010).

Results from our sample are in line with changes in MD occurring before changes in thickness/volume, given that we previously showed that baseline MD signatures robustly predicted thickness/volume signatures 12 years later, but not the reverse (Williams et al., 2022). We have also found that cross-sectionally, higher MD signatures were associated with having MCI at each timepoint. In addition, higher baseline (age 56) MD signatures among CU individuals were associated with progression to MCI at later timepoints (Williams et al., 2021). Results from the current study demonstrate stable, higher MD signatures among the HighCT-HighMD group across the three study waves. Post-hoc results from the present study also suggest that the HighCT-HighMD group was more likely to progress to MCI by wave 3; however, there were only 11 individuals with MCI at wave 3 in these subgroups (compared to 91 CU individuals), and these results are tentative given limited power.

Building on the work by Montal and colleagues, Figure 4b provides our conceptualization of hypothetical changes in cortical thickness/volume and cortical mean diffusivity across the AD continuum that is in line with our results from VETSA. In our model, cortical thickness/volume follows the same biphasic pattern proposed by Montal et al. However, unlike the

Montal et al. model, our model proposes that changes in MD precede changes in cortical thickness/volume. In Figure 4b, an at-risk group of individuals with both high cortical thickness/volume and high MD can be observed, which represents the HighCT-HighMD subgroup described in the present study. The model that proposes simultaneous changes in MD and cortical thickness/volume, as shown in Figure 4a, does not allow for the possibility of an at-risk subgroup with both high thickness/volume and high MD as observed in the present study. While we did not observe an inverted biphasic pattern in MD in our previous work, it may be that the inflection point of changes in MD occurs earlier than the inflection point of changes in cortical thickness and, therefore, before the baseline age of our study. The current study was not designed to assess possible biphasic changes in MD; however, in line with previous findings, this possibility is depicted in a dashed line in Figure 4b. Additional work is thus needed to further examine how the utility and optimal combination of AD brain signatures may change at different ages and disease states. Figure 4c displays proposed age-related changes for individuals who are at less risk of developing AD (represented by the HighCT-LowMD group in the present study). AD-related changes may still emerge for this group, but would occur later according to this model.

We are aware of one other longitudinal study that examined possible biphasic changes in cortical thickness among individuals with preclinical AD (Pegueroles et al., 2017). Pegueroles and colleagues found that CU Aβ-positive individuals showed reduced cortical atrophy in medial frontal regions and the precuneus over a 2-year period compared to atrophy rates among CU Aβ-negative individuals. Those with both Aβ and tau pathology showed accelerated rates of cortical atrophy in medial temporal areas. Their results are consistent with a biphasic pattern of cortical thickening during preclinical AD in the context of Aβ positivity, compared to cortical thinning in the context of synergistic Aβ and tau pathology. Our current results are also in line with a biphasic model of changes in cortical thickness, and our findings suggest that higher cortical thickness in lateral temporal regions that is accompanied by high MD signatures is indicative of increased AD risk (Figure 3). Within each subgroup, thickness/volume and MD signatures were not highly correlated, though the HighCT-HighMD group showed a different pattern of correlations (a mix of positive and negative correlations, rs = −0.20 to 0.28, average r = 0.05) compared to the HighCT-LowMD group (generally negative, rs = −0.33 to 0.05, average r = −0.12). Biphasic changes in cortical thickness occurring alongside increased cortical MD may explain the positive correlations observed in the HighCT-HighMD group. Moreover, these low to moderate associations in both groups are in line with previous evidence demonstrating changes in MD occurring before changes in thickness/volume (Williams et al., 2022). If AD-related changes in the measures occurred simultaneously, one would predict a strong relationship within a single timepoint. These measurements may also be capturing individuals along different stages of a biphasic trajectory in the HighCT-HighMD group, contributing to weaker cross-sectional correlations. Collectively, the study of Pegueroles et al. and the current study emphasize that similar values of cortical thickness/volume may capture heterogeneous subgroups, as well as the need to account for possible AD-related biphasic changes in cortical thickness/volume if these measures are to be used as markers of disease progression in research or in clinical trials.

Pegueroles et al. also discussed how the relationship between cognitive reserve and increased tolerance of neurodegenerative processes may complicate interpretation of higher cortical thickness among CU individuals with AD-related changes. It is possible that individuals with higher pre-existing levels of cognitive reserve also have higher pre-existing levels of cortical thickness, and that higher cortical thickness in the context of AD-related pathology does not represent a transient increase but rather reflects longstanding differences in cortical thickness. While we are unable to evaluate possible transient changes or static differences in cortical thickness between subgroups prior to the baseline wave of our study, our results show that young adult cognitive reserve did not differ between subgroups. Additionally, previous work by our group has shown that both the phenotypic and genetic associations between neocortical volume (the product of cortical thickness and surface area) and general cognitive ability are driven primarily by surface area rather than thickness (Vuoksimaa et al., 2015). These findings thus support the idea that higher cortical thickness/volume associated with AD-related changes is not otherwise explained by differences in earlier cognitive reserve.

Limitations of the present study include differences in scanner strength from wave 1 (1.5 T) to waves 2 and 3 (3 T), which may affect inferences about within-subject change in MRI measures across waves. However, all MRI measures were adjusted for scanner type, z-scored at each wave, and scanner strength was included as a covariate in all longitudinal analyses with MRI measures to reduce the influence of scanner differences. Regardless, the amount of relative change should be comparable for all individuals. Partial volume effects may bias measures of MD, such that increased contributions of signal from CSF due to subtle cortical thinning may result in increased MD. However, we utilized a method to weight MD values based on the fraction of gray matter tissue in multiple samples across the cortical ribbon to reduce these effects. Moreover, prior work from our group demonstrating that the MD and thickness/volume signatures each capture some unique genetic and phenotypic information that is not otherwise explained by general brain aging (Williams et al., 2022), as well as previous studies showing that variation in cortical and subcortical grey matter MD is partly influenced by genetic factors that are distinct from genetic factors influencing cortical thickness or subcortical volumes (Elman et al., 2017, Gillespie et al., 2017), suggests that this MD signature is not redundant with thickness/volume signatures and instead captures meaningful additional information. The MD signature used in the present study is based on regions and weights created for a cortical thickness/volume signature, not MD. It is possible that a signature optimized for MD may yield different regions and weights specific to AD-related changes in cortical MD (Williams et al., 2021). While the changes observed in the HighCT-HighMD group are interpreted as AD-related based on the differential regional changes in cortical thickness and memory, we were unable to confirm these changes as AD-specific based on AD biomarkers such as amyloid or tau. Importantly, generalizability may be limited given that the VETSA sample comprises only men and is largely White and non-Hispanic. Additional work examining AD signatures among more representative samples is required. Despite this generalizability limitation, participants in the VETSA sample are very similar to American men in their age range with respect to health, lifestyle, and education characteristics (Schoeneborn and Heyman, 2009), thereby improving

generalizability compared to studies with samples that may be enriched for family history of AD or genetic risk for AD, or samples with high educational attainment.

CONCLUSIONS

An AD signature based on cortical MD can be used to determine whether higher cortical thickness/volume may represent an early indicator of risk or a protective factor for future cognitive and brain decline in CU individuals. We found that individuals with high values in both MD and thickness/volume signatures at baseline had lower thickness/volume specifically in AD-related brain regions and lower memory performance 12 years later compared to those with high thickness/volume and low MD signatures. The results also support the idea that higher cortical thickness/volume associated with AD-related changes is not otherwise explained by differences in earlier cognitive reserve. Disentangling the heterogeneity in cortical thickness using measures of MD may identify important subgroups and improve precision in very early identification of AD risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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L.K.M. holds stock in CorTechs Laboratories, Inc. A.M.D. was a Founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc., and the Mohn Medical Imaging and Visualization Centre. He receives funding through research grants with General Electric Healthcare. The terms of these arrangements have been reviewed by and approved by the University of California, San Diego in accordance with its conflict of interest policies.

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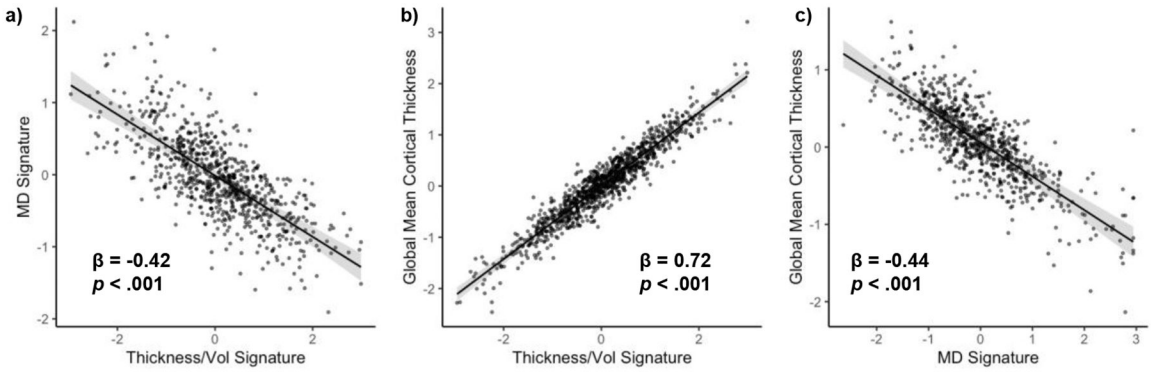

Figure 1. Linear relationships among AD signatures and *global* mean cortical thickness in cognitively normal individuals.

Overall, higher MD signatures are associated with lower thickness/volume signatures (a). The signatures display strong relationships with *global* mean cortical thickness (b and c). These models include only CN individuals; partial residuals after controlling for age and scanner strength differences are displayed.

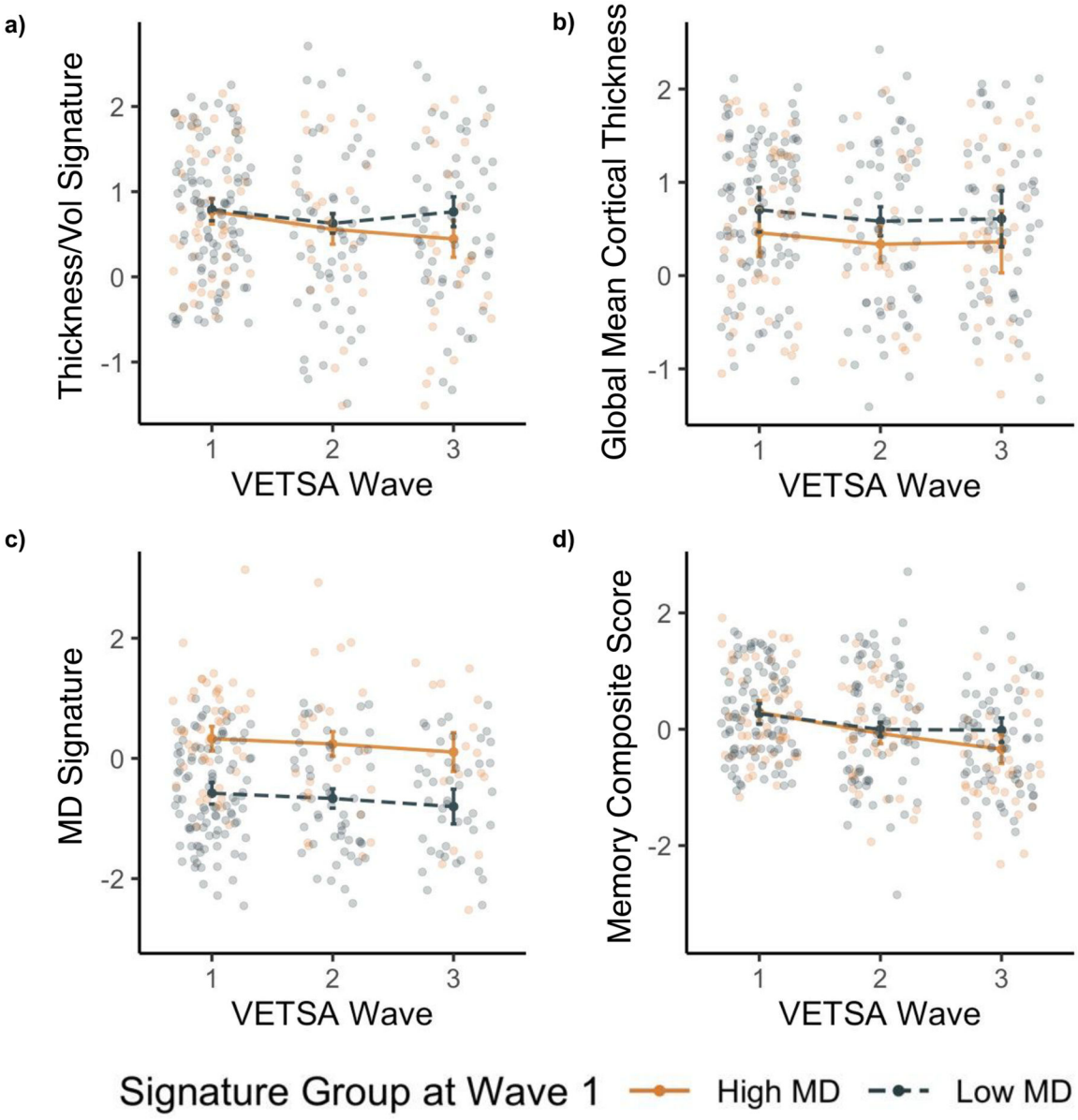

Figure 2. Subgroup differences in a) maintenance of thickness/volume signatures, b) level of global mean cortical thickness, c) level of MD signatures, and d) maintenance of memory performance.

Both groups had higher cortical thickness/volume signatures at wave 1 and differed in MD signatures (high vs. low). However, the HighCT-HighMD group had lower cortical thickness/volume scores compared to the HighCT-LowMD group at baseline, so all models controlled for baseline values of this measure. All were CU at wave 1. Model D additionally controls for baseline memory performance.

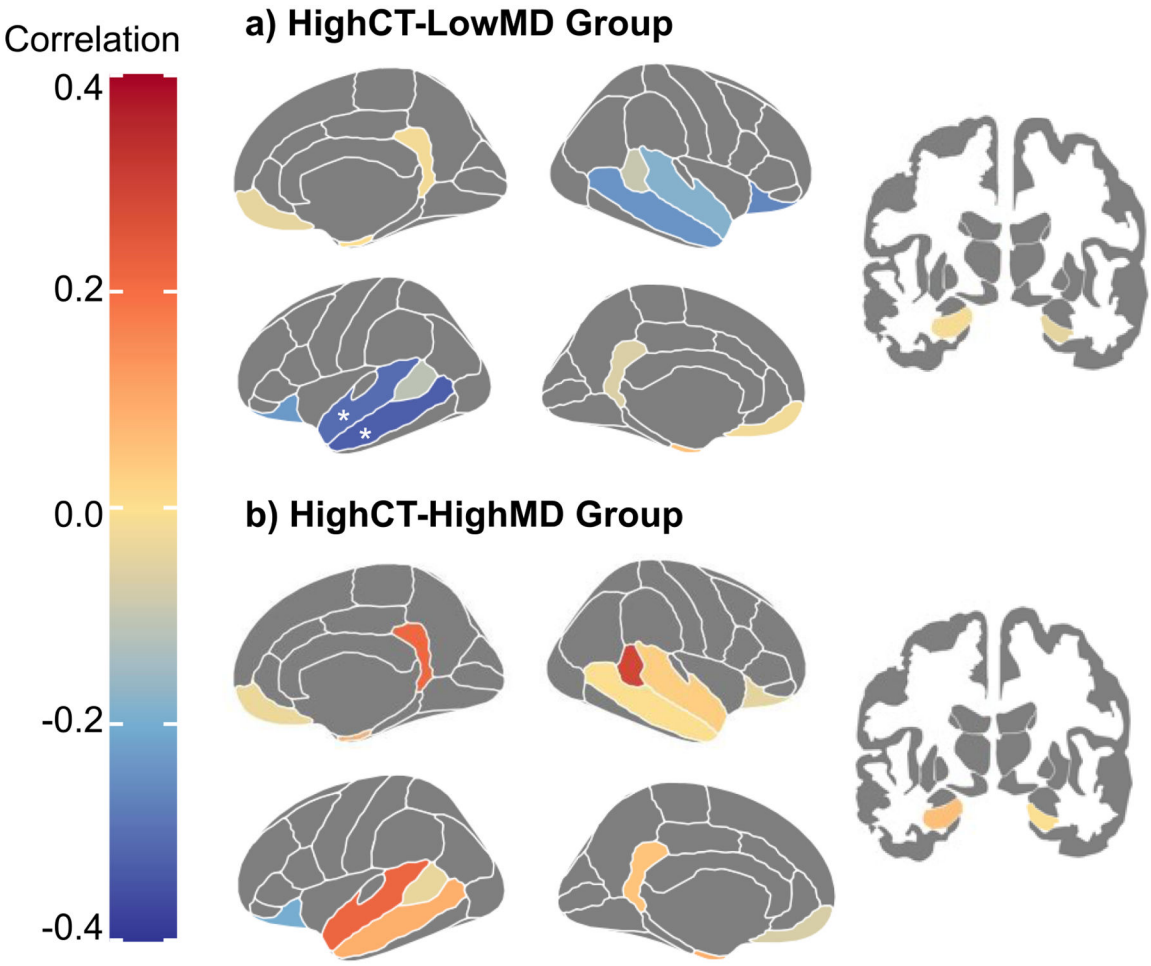

Figure 3.

Correlations between cortical thickness or hippocampal volume and MD within individual regions belonging to each signature for a) HighCT-LowMD subgroup and b) HighCT-HighMD subgroup. Warmer colors (orange, red) represent positive correlations, and cooler colors (green, blue) represent negative correlations. White asterisks indicate significant regional correlations after FDR correction for multiple comparisons.

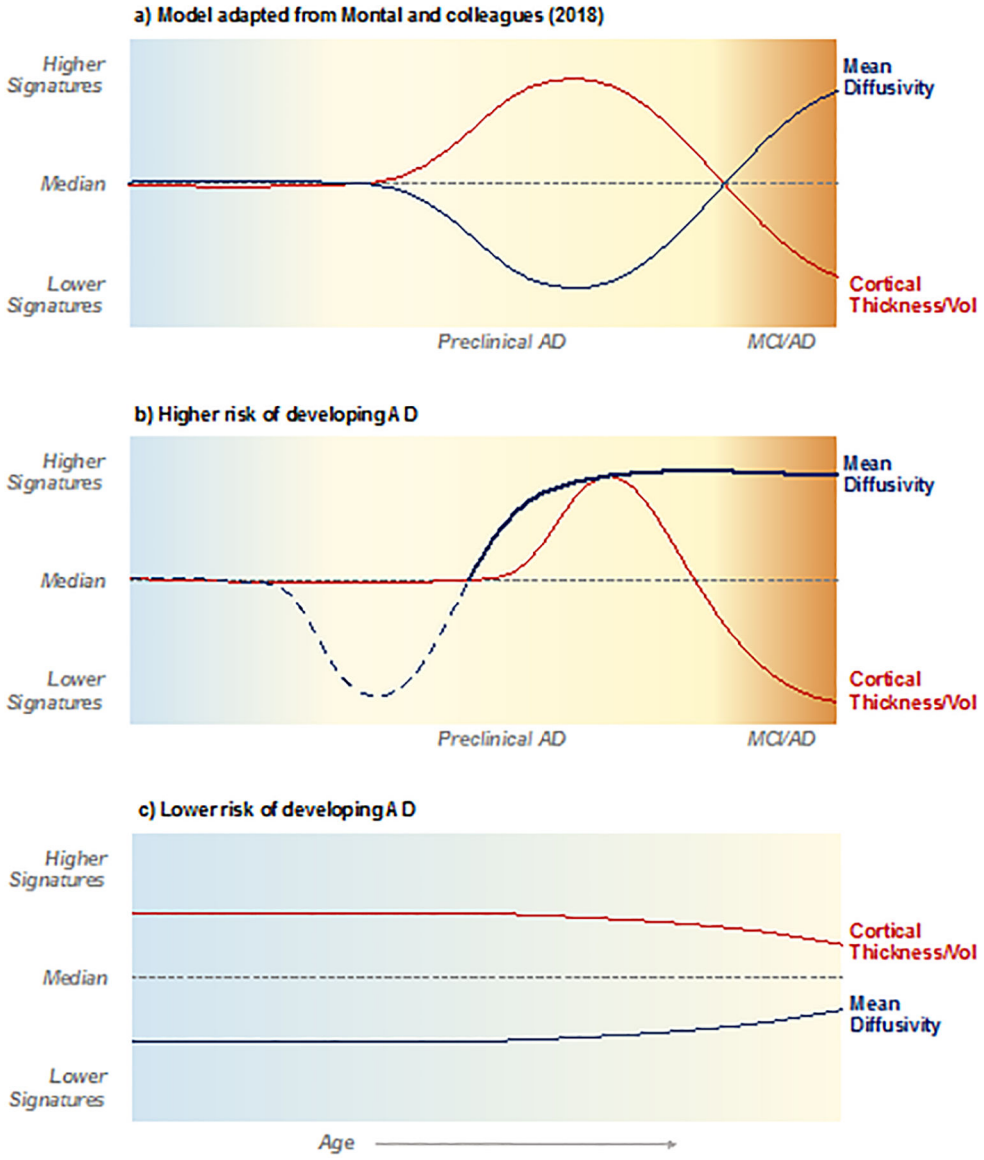

Figure 4. Proposed models of changes in cortical thickness/volume and cortical MD along the AD continuum.

Background gradient colors represent stages (blue = age-related changes not tied to a pathological process; yellow = increased risk for AD; orange = clinical AD). **a)** Model adapted from Montal and colleagues (2018). Biphasic changes in MD mirror changes in cortical thickness. **b)** Model in line with results from VETSA. According to our model, changes in cortical MD precede changes in cortical thickness/volume, and increased cortical MD is associated with AD-related changes. Cortical thickness/volume follows a biphasic pattern of changes, whereby it initially increases among individuals at-risk for AD-related changes before decreasing with progression of disease pathology and onset of clinical symptoms. A transient decrease in MD was not observed. If MD follows a biphasic trajectory as previously suggested, it may be that the inflection point occurred prior to our baseline timepoint. Alternatively, AD-related change in MD may by monotonic. These two possibilities are indicated with dashed lines. **c)** Proposed trajectory for individuals at

lower risk of developing AD (e.g., HighCT-LowMD subgroup), depicting relatively stable thickness/volume and MD signatures. AD-related changes may still emerge for this group, but would occur later according to this model.

Table 1.

Sample characteristics for the full sample, HighCT-HighMD, and HighCT-LowMD subgroups.

Measures that were *z*-scored are reported only for subgroups, given values were standardized within each wave.

	Full sample (*n* = 572)	HighCT-HighMD (*n* = 48)	HighCT-LowMD (*n* = 99)
Age			
Wave 1	56.26 (2.57)	56.25 (2.59)	55.58 (2.67)
Wave 2	61.80 (2.58)	61.69 (2.63)	61.19 (2.68)
Wave 3	67.59 (2.62)	67.12 (2.65)	67.03 (2.85)
Education	13.92 (2.13)	13.40 (2.06)	14.32 (2.26)
Age 20 general cognitive ability	0.35 (0.70)	0.30 (0.72)	0.43 (0.75)
Memory composite score at wave 1	0.12 (0.95)	0.43 (0.89)	0.32 (0.95)
APOE-ε4 allele *n* (%)	137 (24.0%)	14 (29.2%)	23 (23.2%)
Thickness/volume signatures (*z*)			
Wave 1		0.66 (0.56)	0.94 (0.64)
Wave 2	--	0.42 (0.93)	0.65 (0.85)
Wave 3		0.23 (0.83)	0.73 (0.70)
MD signatures (*z*)			
Wave 1		0.37 (0.43)	−0.75 (0.49)
Wave 2	--	0.28 (0.89)	−0.64 (0.79)
Wave 3		0.07 (0.93)	−0.53 (0.71)
Global mean cortical thickness (*z*)			
Wave 1		0.39 (0.74)	0.86 (0.73)
Wave 2	--	0.28 (1.03)	0.59 (0.82)
Wave 3		0.22 (0.95)	0.66 (0.89)