ARTICLE

# Genetic risk for attention-deficit/hyperactivity disorder predicts cognitive decline and development of Alzheimer's disease pathophysiology in cognitively unimpaired older adults

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Attention-deficit/hyperactivity disorder (ADHD) persists in older age and is postulated as a risk factor for cognitive impairment and Alzheimer's Disease (AD). However, these findings rely primarily on electronic health records and can present biased estimates of disease prevalence. An obstacle to investigating age-related cognitive decline in ADHD is the absence of large-scale studies following patients with ADHD into older age. Alternatively, this study aimed to determine whether genetic liability for ADHD, as measured by a well-validated ADHD polygenic risk score (ADHD-PRS), is associated with cognitive decline and the development of AD pathophysiology in cognitively unimpaired (CU) older adults. We calculated a weighted ADHD-PRS in 212 CU individuals without a clinical diagnosis of ADHD (55–90 years). These individuals had baseline amyloid-β (Aβ) positron emission tomography, longitudinal cerebrospinal fluid (CSF) phosphorylated tau at threonine 181 (p-tau$_{181}$), magnetic resonance imaging, and cognitive assessments for up to 6 years. Linear mixed-effects models were used to test the association of ADHD-PRS with cognition and AD biomarkers. Higher ADHD-PRS was associated with greater cognitive decline over 6 years. The combined effect between high ADHD-PRS and brain Aβ deposition on cognitive deterioration was more significant than each individually. Additionally, higher ADHD-PRS was associated with increased CSF p-tau$_{181}$ levels and frontoparietal atrophy in CU Aβ-positive individuals. Our results suggest that genetic liability for ADHD is associated with cognitive deterioration and the development of AD pathophysiology. Findings were mostly observed in Aβ-positive individuals, suggesting that the genetic liability for ADHD increases susceptibility to the harmful effects of Aβ pathology.

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## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by impairing and pervasive symptoms of inattention, hyperactivity-impulsivity, or both [1]. ADHD is conceptualized as a neurodevelopmental disorder of childhood, with persistence rates in adulthood ranging from 11 to 80% [2]. Significant impairment can be observed throughout the lifespan, including in older adulthood [3]. According to a recent meta-analysis, the prevalence of ADHD in older adults (>50 years) is approximately 2.18% [4]. Furthermore, as the geriatric population grows, the absolute number of patients aged 50 years and older fulfilling the criteria for diagnosis of ADHD will likely increase [3]. Therefore, understanding the disorder's association with prevalent age-related diseases is a pressing concern.

The association between ADHD and age-related cognitive impairment is of particular interest. Throughout the lifespan, cognitive deficits across various neurocognitive domains have been extensively described in ADHD [1]. Additionally, cognitive function in older adults with ADHD may closely resemble early manifestations of neurodegenerative conditions [5]. Recent population-based

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large epidemiological studies suggested that ADHD is associated with a higher risk for mild cognitive impairment (MCI) and Alzheimer's disease (AD) [6–8]. These findings rely primarily on electronic health records, which improves the generalizability of results but can present biased estimates of ADHD and dementia prevalence due to unclear diagnostic accuracy, modifications in diagnostic criteria and coding systems over time, and data entry errors [9]. Since the differential diagnosis between undiagnosed ADHD and early dementia can be challenging [5], it is crucial to clarify whether ADHD is a risk factor for MCI and AD dementia or misdiagnosis due to symptom overlap [5]. Additionally, it is unclear whether ADHD is associated with progressive cognitive decline in older age, above and beyond the cognitive deficits originating in childhood [1].

An obstacle to investigating age-related cognitive decline in ADHD is the absence of large-scale studies following patients with childhood-diagnosed ADHD into older age. An alternative approach is to consider the association of well-established dimensional biomarkers of ADHD and AD in samples not selected for ADHD. The ADHD polygenic risk score (ADHD-PRS) represents the combined genetic liability for the disorder and is highly associated with ADHD diagnosis and related traits in independent clinical and population samples [10, 11]. In this study, we explored the association of ADHD-PRS with cognitive impairment in older age. More specifically, we tested the following hypotheses: (1) ADHD-PRS is associated with progressive cognitive decline in cognitively unimpaired (CU) older people; (2) the association between ADHD-PRS and cognitive decline varies according to baseline Aβ burden; (3) ADHD-PRS is associated with brain tau pathology and degeneration.

## MATERIALS AND METHODS

### Participants

We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD (http://adni.loni.usc.edu; for more information, see previous reports [12]). ADNI's inclusion criteria relevant for this study are age between 55 and 90, absence of major depression or bipolar disorder (DSM-IV criteria) within the past one year, no history of schizophrenia (DSM-IV criteria), and a Geriatric Depression Scale (GDS) score less than 6 [12]. According to the ADNI criteria, participants were classified as CU if they had no memory complaints, a Clinical Dementia Rating (CDR) score of 0 and a Mini-Mental State Exam (MMSE) score of 24 to 30 [12]. After the baseline assessment, subjects returned at six months, one year, and annually after that. All data were downloaded from the ADNI data repository in December 2021. Institutional Review Boards of all involved sites approved the ADNI study, and all research participants or their authorized representatives provided written informed consent.

For this study, we included CU participants from ADNI with baseline medical data, baseline Aβ [$^{18}$F]florbetapir positron emission tomography (PET), whole-genome information, and a minimum of two clinical assessments with neuropsychological testing. Genotype data were available from 1674 individuals. Three hundred and twenty-three were excluded after genotype data quality control, as previously described [13]. From the 1324 remaining individuals, 939 were cognitively impaired, and 385 were CU. From the 385 CU individuals, we excluded 170 since they had no baseline Aβ [$^{18}$F]florbetapir PET and 3 since they had no follow-up assessments. Finally, 212 participants were included in our analyses (Supplementary Fig. 1). Similar baseline demographic and clinical characteristics were observed between included and excluded CU individuals (Supplementary Table 1). The mean number of observations with complete data was 3.6, with a minimum of 2 and a maximum of 7 observations per individual.

### Polygenic risk score

Data were available across three genotyping platforms: (1) the Human610-Quad platform, (2) the HumanOmniExpress, and (3) Omni 2.5 M platform. Imputation and merging of the different platforms were performed as previously described [13]. ADHD-PRS was calculated using the additive model, which is the weighted sum of risk alleles for ADHD according to the most recent genome-wide association study (GWAS) [14]. The calculation was performed using the PRSice software v2.2 [15]. Independent single nucleotide polymorphisms (SNPs) were classified based on a 250-kb window and 0.1 r2 linkage disequilibrium criteria. After applying the quality control filters, 212,846 variants were retained for PRS analysis. Only genes located outside the MHC region (chr6: 26–33 Mb) were included. Nine ADHD-PRSs were calculated using subsets of SNPs selected according to the following GWAS *p*-value thresholds: 1, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0.005, and 0.0005. Main analyses were performed with the threshold of 1, assuming all genetic markers contributed to ADHD diagnosis. ADHD-PRSs were transformed into z-scores for better visualization. To investigate populational structure, principal components analysis was conducted using PLINK 1.9 [16]. We retained seven principal components to account for any ancestry differences in genetic structure that could bias the results, as previously done for ADNI datasets [13].

### Cognitive function

Each participant from ADNI was submitted to a broad clinical and neuropsychological assessment in selected visits. Our primary outcome was cognitive function as measured by the Preclinical Alzheimer's Cognitive Composite (PACC) adapted in the ADNI study [17]. The PACC was developed to detect the first signs of cognitive decline in CU subjects with biomarker evidence of AD pathology. The PACC adapted for ADNI was obtained by summing the following four standardized z-scores: Alzheimer Disease Assessment Scale - Cognitive Subscale Delayed Word Recall, Logical Memory Delayed Recall, MMSE, and Trail-Making Test B Time to Completion [17]. Higher scores in PACC indicate better cognitive performance. To explore specific aspects of cognitive function, we used the ADNI composite score for executive function (ADNI-EF) [18] and the ADNI composite score for memory function (ADNI-Mem) [19]. The ADNI-EF includes the performance on WAIS-R Digit Symbol Substitution, Digit Span Backwards (Trails A and B), Category Fluency, and Clock Drawing [18]. The ADNI-Mem includes the Rey Auditory Verbal Learning Test, AD Assessment Schedule – Cognition, MMSE, and Logical Memory [19]. For both, higher scores indicate better performance.

### MRI and PET

Magnetic resonance imaging (MRI) and [$^{18}$F]florbetapir Aβ-PET were acquired following ADNI protocols and pre-processed as previously described [20]. Briefly, MRIs were segmented into probabilistic gray matter (GM) maps using the SPM12 segmentation tool. Each GM probability map was then non-linearly registered (with modulation) to a stereotaxic space using DARTEL and smoothed with a Gaussian kernel of full-width half maximum of 8 mm to generate GM density voxel-based morphometry (VBM) images. We visually inspected all images to ensure proper alignment to the ADNI template. [$^{18}$F]Florbetapir standardized uptake value ratio (SUVR) images used the whole cerebellum as the reference region and were generated from a weighted average of the mean uptake from the cortical GM of frontal, anterior and posterior cingulate, lateral parietal, and temporal regions [21]. Individuals with [$^{18}$F]florbetapir SUVR higher than 1.11 were classified as Aβ-positive, a widely validated cutoff for this population [21].

### CSF p-tau$_{181}$

Cerebrospinal fluid (CSF) tau phosphorylated at threonine 181 (p-tau$_{181}$) was measured using fully automated Elecsys immunoassays (Roche Diagnostics). Measurements outside the analytical range (<8 pg/mL or >120 pg/mL) were handled by setting them to the lower or upper detection limit, as recommended [22]. One individual presenting CSF p-tau$_{181}$ concentrations three standard deviations above the mean was considered an outlier and excluded from the analyses.

### Statistical analysis

Statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, Texas USA) and voxel-wise statistics using MATLAB software version 9.2 (http://www.mathworks.com) with VoxelStats package [23]. We used random field theory (RFT) to correct brain imaging results for multiple comparisons. The association between ADHD-PRS and baseline demographic characteristics was explored using linear or logistic

**Table 1.** Baseline demographic and clinical characteristics of the population.

| | Overall ($N = 212$) | Aβ-negative ($N = 137$) | Aβ-positive ($N = 75$) |
|---|---|---|---|
| Age, y, mean (SD) | 73.1 (5.9) | 72.2 (5.7) | 74.8 (5.9) |
| Sex, No. (%) | | | |
| Female | 116 (54.7) | 64 (46.7) | 52 (69.3) |
| Male | 96 (45.3) | 73 (53.3) | 23 (30.7) |
| Race, No. (%) | | | |
| White | 212 (100) | 137 (100) | 75 (100) |
| Ethnicity, No. (%) | | | |
| Not Hispanic/Latino | 210 (99.1) | 136 (99.3) | 74 (98.7) |
| Unknown | 2 (0.9) | 1 (0.7) | 1 (1.3) |
| Years of education, mean (SD) | 16.6 (2.5) | 16.8 (2.4) | 16.2 (2.6) |
| *APOE* ε4, No. carriers (%) | 63 (29.7) | 28 (20.4) | 35 (46.6) |
| Follow-up, y, mean (SD) | 3.9 (1.5) | 4 (1.4) | 3.7 (1.5) |
| [$^{18}$F]Florbetapir SUVR, mean (SD) | 0.77 (0.11) | 0.70 (0.04) | 0.89 (0.10) |
| CSF p-tau$_{181}$, pg/mL [a], mean (SD) | 22.58 (9.37) | 20.34 (6.99) | 26.45 (11.52) |
| PACC, mean (SD) | −0.14 (2.6) | 0.03 (2.6) | −0.48 (2.6) |
| ADNI-EF, mean (SD) | 0.85 (0.82) | 0.96 (0.84) | 0.63 (0.74) |
| ADNI-Mem, mean (SD) | 1.06 (0.56) | 1.11 (0.56) | 0.98 (0.53) |
| VRFs [b], mean (SD) | 1.55 (1.15) | 1.47 (1.12) | 1.70 (1.20) |
| GDS, mean (SD) | 0.88 (1.11) | 0.95 (1.18) | 0.74 (0.97) |
| BMI [c], mean (SD) | 27.68 (5.17) | 27.87 (5.27) | 27.33 (5.01) |

*SD* standard deviation, *y* years, *APOE* ε4 apolipoprotein E ε4, *SUVR* standardized uptake value ratio, *CSF* cerebrospinal fluid, *p-tau$_{181}$* hyperphosphorylated tau, *Aβ* amyloid-β, *PACC* Preclinical Alzheimer's Cognitive Composite, ADNI-EF Alzheimer's Disease Neuroimaging Initiative composite score for executive function, *ADNI-Mem* Alzheimer's Disease Neuroimaging Initiative composite score for memory function, *VRFs* vascular risk factors, *GDS* Geriatric Depression Scale, *BMI* body mass index.

[a]Total of 193 subjects (122 Aβ-negative and 71 Aβ-positive).

[b]Represents the sum of VRFs.

[c]Total of 212 subjects (136 Aβ-negative and 75 Aβ-positive).

regressions. A two-sided *p*-value lower than 0.05 was considered statistically significant.

We analyzed the data using linear mixed-effects models, which can adequately account for correlations induced by repeated measurements within subjects and automatically handle missing values. Linear mixed-effects models were used to assess the main effects of ADHD-PRS on cognitive function (Model 1, Supplementary Material). To test the hypothesis that ADHD-PRS is associated with progressive cognitive decline, we examined the interaction between ADHD-PRS and time (Model 2, Supplementary Material). To test whether the association between ADHD-PRS and cognitive decline varies according to baseline Aβ burden, we added an interaction between ADHD-PRS, time, and Aβ-PET (Model 3, Supplementary Material). Cohen's $f^2$ allows the estimation of the effect size within the context of mixed-effects linear models and was obtained as previously described [24]. Cohen's $f^2 \geq 0.02$, $f^2 \geq 0.15$, and $f^2 \geq 0.35$ represent small, medium, and large effect sizes, respectively [24].

In exploratory analyses, we tested the association between ADHD-PRS and longitudinal changes in CSF p-tau$_{181}$ or VBM. For that, we evaluated the interaction between ADHD-PRS and time, also with linear mixed-effects models (Models 4 and 5, respectively, Supplementary Material). Following a significant triple interaction between ADHD-PRS, time, and Aβ-PET, analyses with CSF p-tau$_{181}$ and brain atrophy were conducted stratifying individuals according to their Aβ status. All models were adjusted for sex, age at baseline, apolipoprotein E ε4 (*APOE* ε4) carriership status (carriers vs. non-carriers), years of education, and ancestry (using the first seven principal components, as previously performed for ADNI datasets [13]). Furthermore, as recommended for proper adjustment in genetic studies, we adjusted for the interaction between the independent variables and each covariate [25]. Time was defined as years from baseline for each participant. Mixed models were fit including subject-specific random slopes and intercepts to cluster the multiple assessments per individual.

We conducted the primary analyses including all SNPs (ADHD-PRSs with a threshold of 1). Sensitivity analyses with additional thresholds were performed and can be found in the Supplementary Material. Additionally, we performed sensitivity analyses to explore the role of potential confounders previously associated with ADHD and AD dementia, such as vascular risk factors (VRFs) [1, 26], depression symptoms [1, 26], and body mass index (BMI) [1, 26]. VRF burden was assessed using a composite score, and a score equal to or higher than two was defined as elevated [27] (Supplementary Material). Depression symptoms were assessed using baseline GDS scores.

## RESULTS

A total of 212 participants had genetic data and Aβ-PET measures at baseline (Supplementary Fig. 1). From those, 196 and 193 participants had CSF p-tau$_{181}$ and MRI data, respectively (Supplementary Fig. 1). The mean (SD) age of the sample at baseline was 73.1 (5.96) years, 116 (54.7%) were women, and all self-reported being White (210 as Not Hispanic/Latino). The mean and median observation time was 3.96 and 4.05 years, respectively (SD = 1.5, interquartile range = 3.01–5.31, maximum follow-up of 6 years). Table 1 shows participants' characteristics at baseline. ADHD-PRSs were normally distributed (Supplementary Fig. 2) and were not associated with age, sex, or *APOE* ε4 carrier status (Supplementary Table 2). Higher ADHD-PRS was associated with decreased years of education and with higher BMI (Supplementary Table 2). ADHD-PRS was not associated with the length of follow-up (Supplementary Table 2). Additionally, there was no difference in ADHD-PRS between participants based on the number of assessments (ranging from 2 to 7, Supplementary Fig. 3A). Finally, there was no difference in ADHD-PRS between participants assessed in different time points (baseline, 6, 12, 24, 26, 48, 60, and 72 months, Supplementary Fig. 3B).

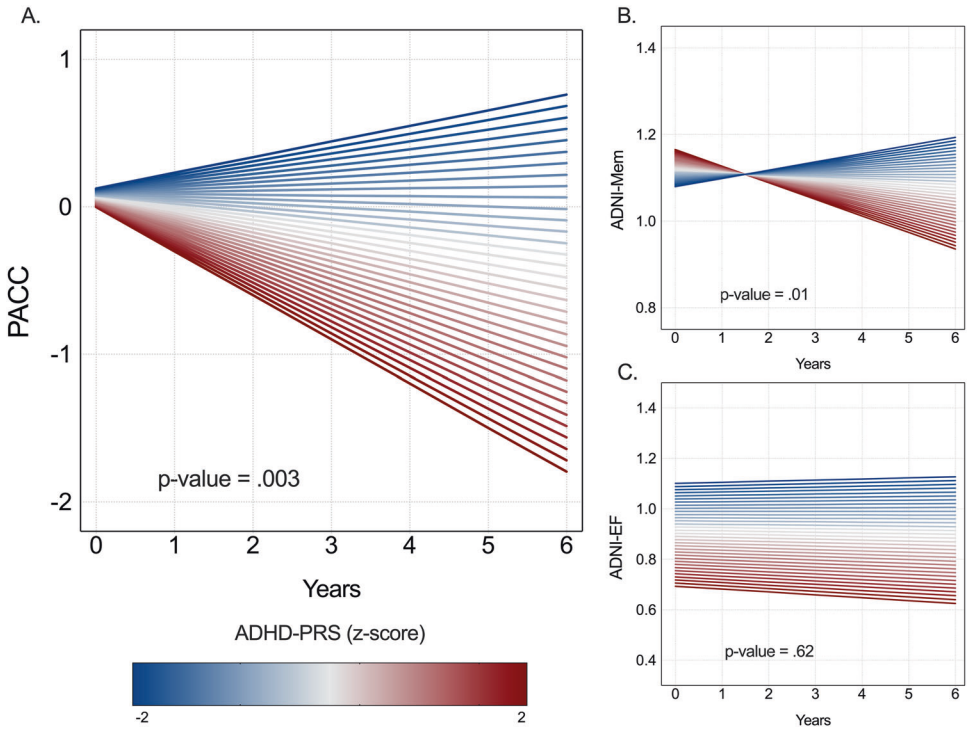


**Fig. 1 Higher ADHD-PRS is associated with longitudinal cognitive decline over 6 years in CU older adults.** Figure 1 shows that higher ADHD-PRS was associated with decreased performance on general cognitive performance (**A**, PACC) and memory (**B**, ADNI-Mem), but not executive function (**C**, ADNI-EF), over time. The *p*-values represent the effect of ADHD-PRS on cognition over time. Lines reflect the estimated marginal means from mixed effect models analyses. The model is described in the Supplementary Material (model 2). Abbreviations: ADHD-PRS attention-deficit/hyperactivity disorder polygenic risk score, CU cognitively unimpaired, PACC Preclinical Alzheimer's Cognitive Composite, ADNI-Mem Alzheimer's Disease Neuroimaging Initiative composite score for memory function, ADNI-EF Alzheimer's Disease Neuroimaging Initiative composite score for executive function, PCs principal components.

These findings support the absence of attrition bias in our analyses.

### ADHD-PRS is associated with a persistent executive function deficit from baseline

We observed a significant main effect of ADHD-PRS on ADNI-EF ($\beta = -0.09$, 95% CI $= -0.18$ to $-0.008$, $p$-value $= 0.03$), suggesting that higher ADHD-PRS was related to a persistent executive function deficit in all time points including baseline (Supplementary Fig. 4A). No significant effect was observed for ADHD-PRS in the model with PACC global cognitive composite as the outcome variable ($\beta = -0.12$, 95% CI $= -0.44$ to 19, $p$-value $= 0.45$; Supplementary Fig. 4B) or in the model containing ADNI-Mem as the outcome variable ($\beta = 0.01$, 95% CI $= -0.05$ to .08, $p$-value $= 0.63$; Supplementary Fig. 4C).

### ADHD-PRS associates with longitudinal cognitive decline

We observed a significant interaction between ADHD-PRS and time on PACC, demonstrating that higher ADHD-PRS was associated with a higher decline in general cognitive performance over 6 years (ADHD-PRS x time; $\beta = -0.10$, 95% CI $= -0.16$ to $-0.03$ $p$-value $= 0.003$; Fig. 1A) with a Cohen's $f^2$ of .21, indicating a medium effect size. As a comparison, the Cohen's $f^2$ for baseline [$^{18}$F]florbetapir Aβ-PET, a well-established predictor of cognitive decline in AD, was 0.48, indicating a large effect size. Similar findings were observed for ADNI-Mem (ADHD-PRS x time; $\beta = -0.01$, 95% CI $= -0.02$ to $-0.002$, $p$-value $= 0.01$; Fig. 1B), indicating that higher ADHD-PRS was related to a progressive decline in memory function. No longitudinal effects were observed for ADNI-EF (ADHD-PRS x time; $\beta = -0.003$, 95% CI $= -0.01$ to .01, $p$-value $= 0.62$; Fig. 1C).

### ADHD-PRS and Aβ show an interaction in longitudinal cognitive decline

We observed a significant interaction between ADHD-PRS and baseline Aβ-PET on worsening cognitive performance, indicating that the association between higher ADHD-PRS and decreased PACC scores over time was present in Aβ-positive but not in Aβ-negative individuals (ADHD-PRS x time x baseline Aβ-PET; $\beta = -0.17$, 95% CI $= -0.31$ to $-0.02$, $p$-value $= 0.01$; Fig. 2A). Similar findings were obtained for ADNI-Mem (ADHD-PRS x time x baseline Aβ-PET; $\beta = -0.02$, 95% CI $= -0.05$ to $-0.0001$, $p$-value $= 0.04$; Fig. 2B), but not ADNI-EF (ADHD-PRS x time x baseline Aβ-PET; $\beta = 0.001$, 95% CI $= -0.03$ to .03, $p$-value $= 0.92$; Fig. 2C).

### ADHD-PRS associates with forthcoming tau pathology and brain atrophy in Aβ-positive individuals

Higher ADHD-PRS was highly associated with increased CSF p-tau$_{181}$ over time in Aβ-positive individuals (ADHD-PRS x time; $\beta = 0.05$, 95% CI $= .01$ to .08, $p$-value $= 0.003$, Fig. 3B). On the other hand, no significant association was observed for Aβ-negative individuals (ADHD-PRS x time; $\beta = -0.003$, 95% CI $= -0.02$ to 0.01, $p$-value $= 0.70$, Fig. 3A). Similarly, ADHD-PRS was associated with longitudinal neurodegeneration as measured by reduction of GM density in the superior frontal gyrus and supramarginal gyrus (Fig. 4B) in Aβ-positive individuals.

### Sensitivity analyses

The aforementioned findings were replicated using most ADHD-PRS thresholds, supporting the robustness of our results (Supplementary Table 3). In addition, similar findings were obtained by adjusting for possible confounders such as VRFs,

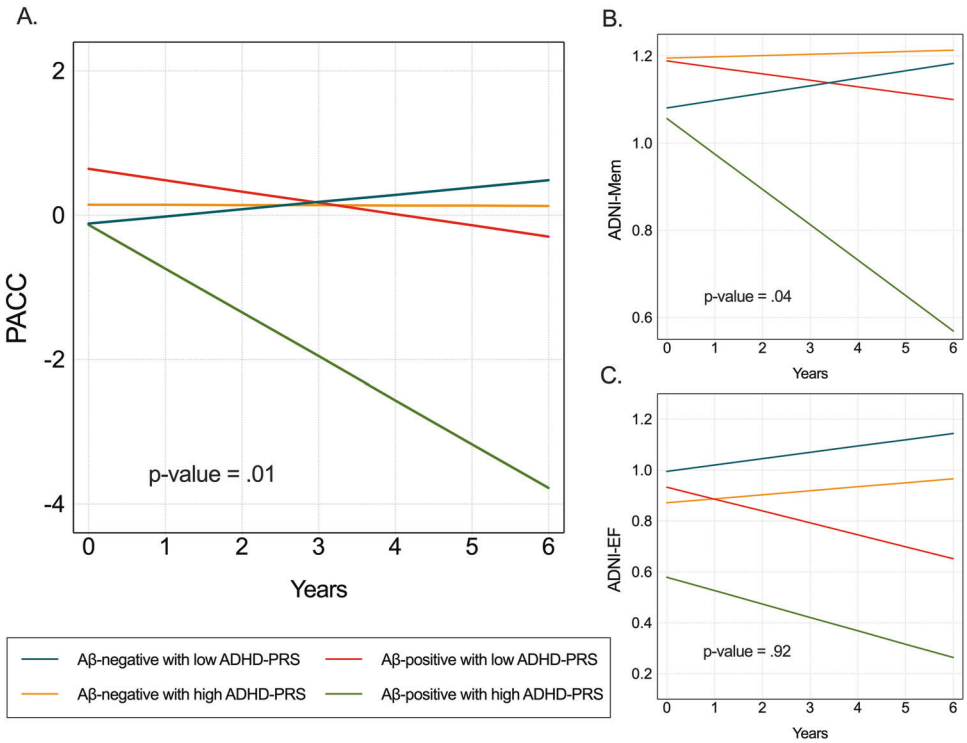


**Fig. 2 Aβ-positivity and high ADHD-PRS potentiated longitudinal cognitive impairment in CU older adults.** Figure 2 shows that higher ADHD-PRS was associated with decreased performance on general cognitive performance (**A**, PACC) and memory (**B**, ADNI-Mem) over time only in Aβ-positive individuals. No significant interaction was observed for executive function (**C**, ADNI-EF). The *p*-values represent the significance of the interaction term between ADHD-PRS and baseline Aβ burden on cognition over time. Lines reflect the estimated marginal means from mixed effect models analyses. Low ADHD-PRS includes z-score of −1, and high ADHD-PRS includes z-score of 1. The model is described in the Supplementary Material (model 3). Abbreviations: ADHD-PRS attention-deficit/hyperactivity disorder polygenic risk score, CU cognitively unimpaired, PACC Preclinical Alzheimer's Cognitive Composite, ADNI-Mem Alzheimer's Disease Neuroimaging Initiative composite score for memory function, ADNI-EF Alzheimer's Disease Neuroimaging Initiative composite score for executive function, Aβ amyloid-β, PCs principal components.

depression symptoms, and BMI (Supplementary Table 4, Supplementary Table 5, and Supplementary Table 6).

## DISCUSSION

This study aimed to determine whether ADHD-PRS was associated with longitudinal cognitive impairment in CU older adults and whether this association was related to the core markers of AD pathology. For the first time, we described that higher ADHD-PRS was associated with progressive longitudinal cognitive decline, particularly in memory function. Furthermore, cognitive decline was mostly observed in Aβ-positive individuals, suggesting that individuals carrying a genetic liability for ADHD are characterized by cognitive susceptibility to the presence of Aβ pathology. Finally, in Aβ-positive individuals, higher ADHD-PRS was associated with longitudinal increases in CSF p-tau$_{181}$ and brain atrophy in frontal and parietal brain regions. These findings suggest that the genetic liability to ADHD increases the susceptibility to cognitive decline, tau pathology, and neurodegeneration in the presence of Aβ pathology in the brain of older individuals.

Our results corroborate previous studies showing deficits in executive function among older adults with ADHD [3, 28]. We observed that higher genetic liability for ADHD was associated with executive function deficits, which remained relatively constant over time. These results are unsurprising and consistent with previous literature showing an association between higher ADHD-PRS and decreased executive function during childhood [10]. Importantly, our study provides unique evidence that higher ADHD-PRS was associated with progressive cognitive decline, predominantly in the memory domain. Since the prototypical clinical phenotype of AD is progressive amnestic symptoms [26], our results support previous epidemiological findings demonstrating that ADHD might be a risk factor for cognitive decline, potentially leading to MCI and dementia syndromes due to AD [6–8]. A large body of evidence supports that Aβ pathology is a major contributor to cognitive decline in older age [29–33]. Furthermore, longitudinal studies observed that CU Aβ-positive individuals have an increased risk for progression to MCI, with hazard ratios ranging from 14.6 (Aβ-positive/tau-positive vs. Aβ-negative/tau-negative) to 2.4 (Aβ-positive/tau-negative vs. Aβ-negative/tau-negative) [29]. Our analyses revealed that the effect of ADHD-PRS on cognition was roughly half the effect size of Aβ (Cohen's $f^2$ of .21 and .48, respectively), suggesting the genetic risk of ADHD as a relevant risk factor for cognitive decline.

We found that future cognitive decline in older adults is associated with the presence of both high ADHD-PRS and brain Aβ pathology. Specifically, ADHD-PRS potentiated the effects of Aβ on longitudinal clinical and pathophysiological progressions in our older population. It is postulated that abnormal Aβ deposition triggers a cascade of events leading to AD progression [26]. Although brain Aβ load is associated with AD-related cognitive decline [34], Aβ pathology alone seems not to be not sufficient to cause it [34]. For example, it is well established that around 30% of CU individuals older than 55 years of age present brain Aβ pathology and that a large portion of these individuals remains cognitively intact during their lives [35]. This supports that the association between Aβ accumulation and cognitive deterioration depends on patients' intrinsic resilience and susceptibility mechanisms. Together, the results above indicate that the genetic

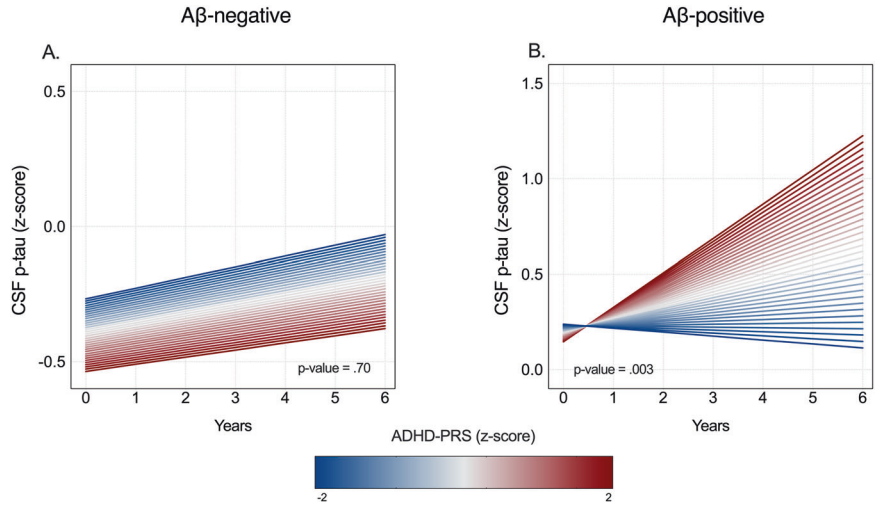


**Fig. 3 ADHD-PRS is associated with the development of tau pathology over 6 years only in Aβ-positive individuals.** Figure 3 shows that ADHD-PRS was associated with increased CSF p-tau$_{181}$ in Aβ-positive (**B**) but not in Aβ-negative (**A**) individuals over a 6-year time frame. The *p*-values represent the significance of the interaction term between ADHD-PRS and baseline Aβ burden on CSF p-tau over time. Lines reflect the estimated marginal means from the mixed effect models analyses. The model is described in the Supplementary Material (model 4). Abbreviations: CSF cerebrospinal fluid, p-tau tau phosphorylated at threonine 181, Aβ amyloid-β, ADHD-PRS attention-deficit/hyperactivity disorder polygenic risk score.

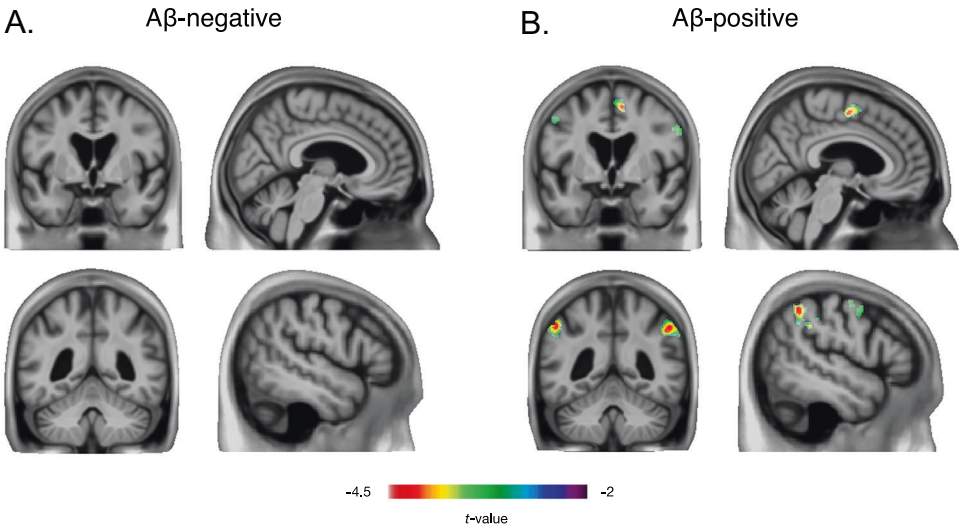


**Fig. 4 ADHD-PRS is associated with longitudinal brain atrophy over 6 years in the frontal and parietal cortices of CU Aβ-positive older individuals.** Figure 4 shows that ADHD-PRS was associated with a longitudinal decrease in GM density in the superior frontal gyrus and supramarginal gyrus of CU Aβ-positive (**B**), but not Aβ-negative (**A**), older individuals. The t-statistical parametric images show the result of the voxel-wise linear mixed-effects model testing the interaction between ADHD-PRS and time on GM. We used RFT to correct the results for multiple comparisons at a threshold of $P < 0.001$. The model is described in the Supplementary Material (model 5). Abbreviations: ADHD-PRS attention-deficit/hyperactivity disorder polygenic risk score, CU cognitively unimpaired, GM gray matter, Aβ amyloid-β, RFT random field theory.

liability to ADHD plays a role in increasing the susceptibility to the harmful effects oft in the human brain.

A widely held view in the AD field posits that Aβ triggers the spread of tau pathology, leading to neurodegeneration and cognitive impairment [34]. In line with this hypothesis, our study showed that the association between ADHD-PRS and cognitive decline was accompanied by a longitudinal increase in CSF levels of p-tau$_{181}$, a well-validated marker of brain tau pathology [36]. Our findings suggest that ADHD-PRS is related to both tau deposition and cognitive decline in Aβ-positive individuals, highlighting the genetic liability for ADHD as a relevant factor influencing AD progression in the presence of Aβ pathology.

We showed that higher ADHD-PRS was associated with brain atrophy in frontal and parietal brain regions in Aβ-positive individuals. Specifically, decreased GM density over time was observed in the superior frontal gyrus and supramarginal gyrus. Previous AD studies have shown that brain atrophy closely correlates with tau deposition and cognitive deficits, being a well-established marker of disease progression [37]. In CU populations, AD-related brain atrophy has been reported predominantly in the medial temporal cortex. In contrast, reduced cortical thickness in regions such as the superior frontal gyrus and supramarginal gyrus is present in later stages of AD [37]. Interestingly, atrophy in parietal and frontal cortices has been demonstrated in middle-aged [38] and older adults [39] with ADHD. These results suggest that while in our study ADHD-PRS-related atrophy in the superior and supramarginal gyrus was Aβ pathology-dependent, it recapitulated regions showing atrophy in ADHD rather than early

AD. This supports the notion that the combination of underlying ADHD-related vulnerability with Aβ pathology is a factor associated with cognitive dysfunction in older adults.

This study should be viewed in light of some limitations. First, our sample did not have a detailed clinical assessment for ADHD diagnosis. Since ADHD is a relatively recent diagnostic category, older adults are unlikely to have received the diagnosis as children [1]. Thus, ADHD-PRS in our results may identify either asymptomatic older adults with genetic susceptibility to ADHD and/or patients with undiagnosed ADHD. Based on ADNI's eligibility criteria, individuals included in this study had a GDS of less than 6 and had no memory complaints. Thus, since ADHD in adults is associated with increased depressive symptoms [1] and subjective memory deficits [40], our sample may consist of individuals with a lower genetic risk for ADHD when compared to the general population. In addition, the fact that neuropsychiatric conditions such as depression, bipolar disorder, or schizophrenia were not included in the ADNI cohort further limits the external validity of our results. The sample included in this study likely represents a less affected population when compared to the general ADHD population treated in clinical centers, where psychiatric comorbidities are the rule rather than the exception [1]. Our findings were replicated after adjustment for potential confounders such as VRFs, depression symptoms, and BMI. However, future prospective studies should explore the role of other shared risk factors between ADHD and AD, including traumatic brain injury, alcohol abuse, and physical inactivity [1, 26]. The population used to generate ADHD-PRS [12] and our study population were composed almost exclusively of white participants. Therefore, future studies in ADHD and AD should focus on enrolling more diverse populations. An additional limitation is that our findings were not corrected for a PRS of AD, and we cannot exclude the possibility that the genetic risk for ADHD is carrying part of the genetic risk for AD. However, previous findings showed no genetic correlation between ADHD and AD [14]. Moreover, all our models were adjusted for *APOE* ε4 carrier status, which is the strongest genetic risk factor for late-onset AD [34]. Finally, no adjustments were made to control type I error, and consequently, the analyses should be considered exploratory.

To conclude, our results suggest that ADHD-PRS can be used to inform the risk of cognitive decline in Aβ-positive CU older adults. Since ADHD-PRS was associated with cognitive decline in our entire population, ADHD-PRS may also be used to predict cognitive deterioration in the absence of AD biomarkers. Importantly, ADHD-PRS was associated with longitudinal CSF p-tau hyperphosphorylation and brain atrophy in frontoparietal but not temporal regions in Aβ-positive individuals, suggesting that an ADHD-related brain susceptibility to the harmful effects of Aβ plays a role in the early development of AD in genetically vulnerable patients. Prospective studies following patients with ADHD up to older age will be needed to (1) confirm the association with cognitive decline; (2) corroborate the interaction between ADHD and Aβ pathology leading to cognitive decline; (3) explore whether changes in biomarkers of AD pathology are observed earlier in ADHD compared to the general population; and (4) investigate whether cognitive impairment in ADHD is associated with neurodegeneration in frontal and parietal regions, rather than temporal regions, as we observed in this study. In addition, replicating our findings may lead to protocols to systemically assess AD in older patients with ADHD and assess ADHD in individuals with cognitive decline. Finally, future studies could also explore the efficacy of stimulant treatment in patients with ADHD and cognitive decline.

## DATA AVAILABILITY

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.Loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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## AUTHOR CONTRIBUTIONS

DTL and TAP conceived the study. DTL, JPF-S, BB, CT, PCLF, and TAP prepared the figures and tables. DTL drafted the manuscript with input from JPF-S, BB, CT, PCLF, WSB, AC, JL, PP, TM-S, LT-R, DLT, VLV, ADC, OLL, WEK, TKK, PR-N, EZ, BSGM, LAR, and TAP. DTL, JPF-S, BB, CT, PCLF, LAR, and TAP performed the acquisitions, processing, quality control, and/or interpretation of the data. TAP, LAG, and BSGM supervised this work. JL, PP, TM-S, and LT-R assisted in calculating the polygenic risk scores. DLT assisted in the statistical analyses. All authors revised and approved the final manuscript.

## COMPETING INTERESTS

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## ADDITIONAL INFORMATION

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