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A Pathway-Specific Polygenic Risk Score Is Associated with Tau Pathology and Cognitive Decline

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Abstract.
Background: Tauopathy is a primary neuropathological hallmark of Alzheimer's disease with a strong relationship to cognitive impairment. In the brain, tau aggregation is associated with the regulation of tau kinases and the binding ability of tau to microtubules.
Objective: To explore the potential for using specific polygenic risk scores (PRSs), combining the genetic influences involved in tau-protein kinases and the tau-protein binding pathway, as predictors of tau pathology and cognitive decline in non-demented individuals.
Methods: We computed a pathway-specific PRS using summary statistics from previous large-scale genome-wide association studies of dementia. We examined whether PRS is related to tau uptake in positron emission tomography (PET), tau levels, and the rate of tau level changes in cerebrospinal fluid (CSF). We further assessed whether PRS is associated with memory impairment mediated by CSF tau levels.
Results: A higher PRS was related to elevated CSF tau levels and tau-PET uptake at baseline, as well as greater rates of change in CSF tau levels. Moreover, PRS was associated with memory impairment, mediated by increased CSF tau levels. The association between PRS and tau pathology was significant when *APOE* was excluded, even among females. However, the effect of PRS on cognitive decline appeared to be driven by the inclusion of *APOE*.
Conclusion: The influence of genetic risk in a specific tau-related biological pathway may make an individual more susceptible to tau pathology, resulting in cognitive dysfunction in an early preclinical phase of the disease.

Keywords: Alzheimer's disease, cognitive function genetic risk scores, pathway, tau

INTRODUCTION

Alzheimer's disease (AD) is pathologically characterized by the presence of intracellular aggregations of hyperphosphorylated tau as neurofibrillary tangles [1]. Clinicopathological studies have shown

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an elevated tau burden at autopsy in AD. Recently, methods by which tau can be studied in the living brain, specifically, tau in the cerebrospinal fluid (CSF), including total tau (t-tau) and phosphorylated tau (p-tau), and tau positron emission tomography (PET), have been developed [2]. In particular, PET has provided a method that reflects not only the levels of tau deposition but also the spatial distribution of tauopathy throughout the human brain. Multiple lines of evidence suggest that CSF tau levels and tau-PET uptake are highly associated with neurodegeneration in AD, both temporally and spatially [3–6]. Recently, tau, rather than amyloid-β (Aβ), has become a critical target for developing disease-modifying AD therapeutic trials [7–9]. Therefore, elucidating the underlying principles that make people vulnerable to tau accumulation would be valuable in anti-tau clinical trials and interventions.

Tau protein is a soluble protein that is encoded by the MAPT gene, which can be modified post-translationally by phosphorylation. Abnormally hyperphosphorylated tau is the major constituent of the paired helical filaments that form neurofibrillary tangles in the neurons of AD brains. Previous neuropathologic studies suggested that aberrant hyperphosphorylation of tau is the result of the upregulation of tau kinases, leading to microtubule disassembly [10, 11]. Decreasing binding affinity of tau for microtubules is thought to promote tau aggregation and fibrillization [12, 13]. As such, variations in genes associated with tau-protein kinase activity and the tau-protein binding seem to be predictors of tau pathology. Several previous studies have supported the contribution of genetic factors involved in the two pathways related to increased CSF tau levels and tau PET uptake [14–17], but each of the genetic variants, known as single nucleotide polymorphisms (SNPs), had a fairly small effect size. Polygenic risk scores (PRSs) sum the weighted allelic dosages across the genome and have served as powerful predictors of AD pathology [18–23]. Using biological knowledge to combine variants located in genes that are involved in particular pathways allows for the calculation of pathway-specific PRSs [24, 25]. A PRS of tau-related biological pathway could directly elucidate heritable mechanisms that contribute to tau abnormality. However, there was no evidence linking such pathway-specific PRS to tau accumulation.

Tau pathology correlates well with the progression of cognitive impairment [26–28]. Moreover, CSF p-tau can accurately predict the risk of developing AD and cognitive decline in the preclinical and prodromal disease stages [29–31]. Thus, there has been increasing interest in studying the genetic underpinnings of tau pathology in AD, and researchers are undertaking studies dedicated to understanding the genetic risk factors that underlie tau-related cognitive impairment [16, 32]. However, until recently, the molecular genetic basis has been incompletely understood. To update our understanding of AD pathogenesis, a more powerful genetic predictor is required to elucidate the underlying mechanisms.

The primary goal of the current study was, therefore, to investigate the associations between the pathway-specific PRS, tau pathology, and cognitive decline by discovering whether the PRS that incorporated variations in genes involved in tau-protein kinase activity and tau-protein binding are associated with tau pathology and contribute to cognitive decline. We employed CSF biomarkers and AV1451 PET imaging in non-demented individuals to explore the impact of pathway-specific genetic risk on tau pathology. We also examined whether the PRS that we obtained is associated with longitudinal changes in CSF tau values. A previous study showed that tau propagates throughout the brain in a stereotyped pattern across postmortem-established Braak staging [33]. Here we investigated whether the PRS is associated with the Braak stages to determine the genetic influence on the development of tau pathology. Because tau levels are associated with cognitive decline, we finally tested whether CSF tau levels mediate the association between the pathway-specific PRS and worse memory performance. Given previous evidence of genetic differences with respect to gender [34–36], we also ran stratified analyses to assess the impact of PRS in females and males, separately.

MATERIALS AND METHODS

Participants

The data used in this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The ADNI was launched in 2003, and its full description is accessible on the website (http://www.adni-info.org). The ADNI study was approved by all the Institutional Ethical Review Boards of all participating centers and all participants provided written informed consent to participate in the study. Our analyses included cognitively normal older (CN) individuals, patients with mild cognitive impairment (MCI), and patients with AD dementia of European ancestry who had genotyping data

Table 1
Clinical characteristics of the study cohort

	Samples with CSF		Samples with longitudinal CSF		Samples with PET	
	F ($n=259$)	M ($n=308$)	F ($n=133$)	M ($n=173$)	F ($n=57$)	M ($n=88$)
Age (y)	72.2 (7.4)	73.6 (6.6)	72.7 (7.2)	73.3 (6.4)	77.6 (7.4)	79.4 (7.1)
Diagnosis (CN/MCI)	104/155	99/209	60/73	66/107	33/24	44/44
Education (y)	15.6 (2.7)	16.7 (2.7)	15.7 (2.6)	16.8 (2.8)	15.5 (2.6)	17.1 (2.8)
APOE ε4 (0/1/2)	162/82/15	196/89/23	87/37/9	104/56/13	39/15/3	62/22/4
CSF Aβ	1138.1 (451.0)	1047.8 (456.7)	–	–	–	–
CSF p-tau	25.5 (13.1)	24.8 (11.4)	–	–	–	–
CSF t-tau	271.6 (119.7)	260.7 (102.7)	–	–	–	–
AV45 global SUVRs	–	–	–	–	1.1 (0.2)	1.1 (0.2)
AV1451 global SUVRs	–	–	–	–	1.6 (0.2)	1.5 (0.2)

CSF, cerebrospinal fluid; PET, positron emission tomography; F, female; M, male; CN, clinically normal; MCI, mild cognitive impairment; t-tau, total tau; p-tau, phosphorylated tau; Aβ, amyloid-β.

in the ADNI1 and ADNI2/GO datasets. A subset of 567 non-demented participants also had a neuropsychological assessment and CSF biomarkers (Aβ, t-tau, and p-tau). The neuropsychological assessment was a composite score of memory based on previous sophisticated factor analyses [37]. Of the 567 participants, 306 also had longitudinal CSF measures and neuropsychological assessments (mean follow-up 3.35 ± 1.97 years). In addition, a subset of 145 non-demented participants had MRIs, AV45 PET images, and AV1451 PET images. The non-demented participants' characteristics are summarized in Table 1. The demented participants were only used to determine the PRS threshold (Supplementary Table 1).

PET imaging

The AV45 Aβ-PET and AV1451 tau-PET data that we downloaded were partially preprocessed to try to increase the data uniformity across the multicenter acquisitions. More detailed information about the imaging protocols and standardized image preprocessing steps can be found on the ADNI website (http://adni.loni.usc.edu). We used SPM12 to obtain all the preprocessed PET images, each of which was co-registered to the anatomical T1 image that was obtained at the closest time to the PET image, and subsequently normalized into MNI standard space using the parameters obtained by normalizing the T1 image. A partial volume correction was applied to the AV1451 tau-PET data using a geometric transfer matrix.

We obtained the global AV45 Aβ-PET data by averaging the size-weighted Freesurfer-defined standardized uptake value ratio (SUVR) scores across the frontal, anterior, and posterior cingulate, lateral parietal, and lateral temporal regions following a previously described protocol [38]. These mean values were intensity normalized to Freesurfer-derived whole-cerebellar uptake to obtain the SUVRs.

Next, we obtained the global AV1451 tau-PET data by averaging the size-weighted SUVR across all the Braak regions [39]. To provide the image-based stages of tau-PET, we obtained the size-weighted Braak stage ROIs, from Braak stage I (i.e., entorhinal cortex) to Braak stage VI (i.e., primary sensorimotor and primary visual cortex). All the tau-PET values were intensity normalized to the Freesurfer-derived inferior cerebellar grey matter to obtain the SUVRs.

Processing of genetic data

A total of 812 samples from ADNI1 and ADNI2/GO datasets were genotyped using the Illumina Omni 2.5M (2,369,200 variants). Standard quality control procedures were applied to the genotyping data using PLINK version v1.9 (https://www.cog-genomics.org/plink2). First, individuals with missing genotype rates greater than 0.05 were removed. In addition, we estimated the pairwise identity-by-descent (IBD > 0.125) to remove the individuals who were possibly related. Specifically, we removed 12 samples with the greater missing rate from such pairs. The SNPs were removed if they had a minor allele frequency less than 0.01, missing rates greater than 0.05, or a Hardy-Weinberg Equilibrium deviation ($p < 0.001$). To control for population heterogeneity, we carried out a principal component analysis using GCTA version 1.91.4beta [40] on a linkage disequilibrium-pruned set of autosomal SNPs obtained by performing LD pruning with PLINK and

removing 5 long-range LD regions with the HapMap phase 3 reference datasets [41]. The number of SNPs after the LD pruning was 1,540,308. We then obtained 10 principal components (PCs) and excluded 8 samples more than 6 S.D. away from any of PCs as in previous studies [42, 43]. Finally, SHAPEIT v2 (r790) [44] and IMPUTE2 [45] were used to impute ungenotyped SNPS with the 1000 Genomes Phase 1 reference dataset. Further analyses focused on autosomal SNPs with imputation quality scores greater than 0.8. After applying the standard quality control procedures, 792 individuals with more than 7 million SNPs remained.

Computation of the polygenic risk score

Gene Ontology was primarily used to map genes to the pathway-specific PRS for tau-protein kinase activity and tau-protein binding [46]. An overall PRS formed by a combination of SNPs from 60 genes (including *APOE*, as listed in Supplementary Table 2) was created for analysis. Since *APOE* is known to have a large effect size, PRS was also calculated without *APOE* (non-*APOE* PRS) to determine the effect of the PRS beyond that of *APOE* alone. We computed the two PRSs using PLINK's profile function, which computes the sum of the reference allele counts at each SNP weighted by the log odds ratio from the stage 1 analysis of the International Genomics of Alzheimer's Project [47], the most recent case-control genome-wide association study (21,982 patients with AD and 41,944 CN controls). Critically, the summation was constrained to loci with a p value below 0.5, since this was found to be an optimal choice in an earlier study [48]. For this study, we also contrasted the PRS between the AD dementia and stable CN over the follow-up to determine the appropriate p value threshold using a range of p value thresholds from $p < 1$ to $p < 1e{-}10$ (see the participant demographics in Supplementary Table 1). Interestingly, the discrimination was most significant when the threshold was 0.5 (Supplementary Figure 1). Based on these results, we used the $p = 0.5$ threshold in the subsequent analyses.

Statistical analyses

To examine the influence of PRS on baseline CSF values and tau-PET SUVRs, we used linear regression and controlled for CSF Aβ or global Aβ-PET, baseline diagnosis status, baseline age, gender, and 5 PCs to take population heterogeneity into account. When assessing the effect of PRS on cognition, we used the memory measures and included education in the model. In the Braak staging analysis, we controlled for multiple comparisons at an FDR of 0.05.

The influences of PRS on longitudinal changes in CSF p-tau and t-tau were examined with a longitudinal linear mixed-effects model (LMM). All models included the interactions between covariates and time as fixed-effect covariates. Random intercepts and slopes were included in each LMM. In all the analyses, continuous variables were centered and scaled before analysis to generate standardized effect estimates. To better understand the association between PRS and tau pathology, we conducted stratified analyses for female and male participants, separately.

To assess whether PRS was associated with cognitive performance and whether this association was mediated by tau pathology, we conducted a mediation analysis [49]. The average indirect effect and average direct effect of PRS on memory were estimated using a non-parametric bootstrapping (5000 simulations, $p < 0.05$). All statistical analyses were conducted with R statistical software.

RESULTS

PRS is associated with CSF t-tau and p-tau

In a first step, we tested whether higher PRS shows higher tau pathology in CSF. We found that PRS was highly correlated with cross-sectional CSF t-tau and p-tau concentrations after adjusting for age, gender, CSF Aβ, and diagnosis as well as the 5 PCs (Table 2). The association suggests that a higher pathway-specific PRS is associated with higher levels of t-tau ($p < 0.001$) and p-tau ($p < 0.001$). Importantly, these associations remained statistically significant even when *APOE* was removed from the PRS (t-tau: $p = 0.013$, p-tau: $p = 0.017$). When stratifying non-demented individuals by gender, there were positive

Table 2
PRS effect on CSF t-tau/p-tau in predementia

	PRS		Non-*APOE* PRS	
	β (SE)	*p*	β (SE)	*p*
Baseline t-tau	0.281 (0.048)	<0.001	0.121 (0.049)	0.013
Baseline p-tau	0.265 (0.047)	<0.001	0.114 (0.048)	0.017
Longitudinal t-tau	0.319 (0.059)	<0.001	0.159 (0.065)	0.015
Longitudinal p-tau	0.346 (0.059)	<0.001	0.164 (0.066)	0.013

PRS, polygenic risk scores; β, unstandardized β values; SE, standard errors; t-tau, total tau; p-tau, phosphorylated tau.

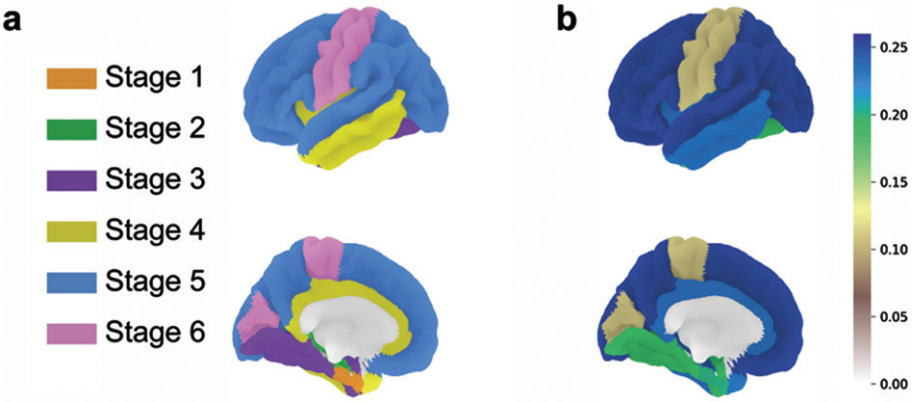

Fig. 1. PRS is associated with regional tau-PET. a) Staging systems for tau-PET to determine regional uptake. b) Beta estimates of the PRS impact on regional tau-PET SUVRs.

associations between PRS and CSF measures in females and males (Supplementary Table 3). However, the non-*APOE* PRS only exhibited a significant effect on t-tau ($p = 0.008$) and p-tau ($p = 0.007$) in the females.

PRS is associated with tau PET

Next, we tested whether a higher PRS would show a higher tau pathology in PET (i.e., global tau PET or for regions corresponding to Braak stages I–VI). Within the combined MCI and CN cohort, we found that a higher PRS showed elevated global tau levels ($p = 0.004$), when controlling for age, diagnosis, gender, global Aβ-PET, and the 5 PCs. In addition, the effect was significant with the exclusion of *APOE* ($p = 0.021$). To evaluate whether the effect of PRS on tau PET showed regional differences, we examined the association between the PRSs and SUVRs within the brain regions corresponding to Braak stages I–VI that recapitulated the spatial tau-spreading pattern from the early to the late stage of tau pathology across the cortex. We consistently detected significant associations across the regions corresponding to Braak stages I–V (Fig. 1, Table 3). However, non-*APOE* PRS was only associated with Braak stages IV–V ($p < 0.05$).

Among the females, significant effects of PRS and non-*APOE* PRS on global tau PET were observed (PRS: $p = 0.009$, non-*APOE*: $p = 0.019$). In contrast, we could not detect any association between PRS and global tau-PET ($p = 0.105$) or the non-*APOE* PRS ($p = 0.315$) in the males. The association between PRS and regional levels of tau-PET for either the females or males was somewhat different from the result for the full sample (Supplementary Table 4). In the females, the PRS was correlated with the entorhinal region, hippocampus, prefrontal cortex, and sensory association neocortex. After excluding *APOE* from the PRS, the impact of genetic risk factors on the sensory association neocortex remained. In contrast, an association was only observed between PRS and basal neocortical areas of the temporal cortex in the males.

Table 3
Effects of PRS on tau-PET uptake

	PRS		Non-*APOE* PRS	
	β (SE)	*p*	β (SE)	*p*
Global tau-PET	0.247 (0.083)	0.004	0.208 (0.089)	0.021
Braak I	0.201 (0.087)	**0.022**	0.085 (0.093)	0.361
Braak II	0.243 (0.090)	**0.007**	0.170 (0.096)	0.077
Braak III	0.185 (0.085)	**0.031**	0.142 (0.091)	0.119
Braak IV	0.231 (0.087)	**0.009**	0.234 (0.092)	**0.012**
Braak V	0.251 (0.087)	**0.005**	0.232 (0.093)	**0.014**
Braak VI	0.109 (0.095)	0.252	0.096 (0.100)	0.337

PRS, polygenic risk scores; β, unstandardized β values; SE, standard errors; t-tau, total tau; p-tau, phosphorylated tau. Bolded values were statistically significant after FDR correction.

PRS is associated with longitudinal CSF t-tau and p-tau changes

Next, we examined the associations between PRS and longitudinal changes in tau in the CSF. In the linear-mixed effects analyses, the PRS was associated with rates of aggregation in p-tau ($p < 0.001$) and t-tau ($p < 0.001$), even when excluding *APOE* from the PRS (Table 2). The association suggests that people with a higher PRS may accumulate tau more rapidly. However, the interaction between PRS and time did not reach statistical significance for

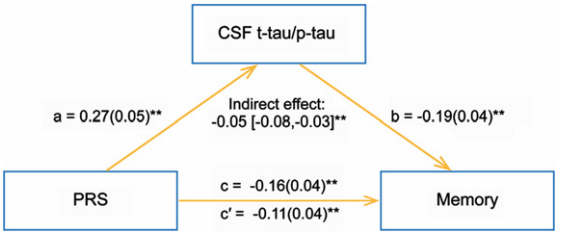

Fig. 2. Diagram of mediation model pathways relating PRS, CSF tau levels, and memory. The mediation model shows that the PRS influence on worse memory was mediated via CSF t-tau or p-tau concentration. Path-weights are displayed as beta values with standard errors in brackets, $^{**}p < 0.001$, controlling for age, gender, education, diagnosis, global Aβ-PET, and 5 PCs. C indicates the total effect of PRS on MMSE. C' indicates the direct effect of PRS on MMSE after controlling for CSF t-tau or p-tau. The indirect and direct effects of PRS on memory were determined using a non-parametric bootstrapping with 5,000 iterations.

either p-tau ($\beta = 0.022$, SE = 0.013, $p = 0.085$) or t-tau ($\beta = 0.027$, SE = 0.014, $p = 0.067$). In the stratified analyses, we found that the non-*APOE* PRS was associated with rates of aggregation over time in the females, with high PRS females experiencing greater rates of t-tau ($\beta = 0.050$, SE = 0.022, $p = 0.023$) and p-tau ($\beta = 0.040$, SE = 0.019, $p = 0.040$) aggregation. No significant association was observed for the males (Supplementary Table 3).

CSF t-tau and p-tau mediate the PRS effect on memory impairment

To assess whether PRS has a detrimental relationship with cognitive impairment via increasing tau pathology, we tested whether PRS was associated with worse memory and whether this effect was mediated via increased CSF tau. To this end, we applied causal mediation analysis with 5000 bootstrapping iterations after controlling for age, gender, education, diagnosis, CSF Aβ, and the 5 PCs. The memory performance was assessed based on the ADNI-MEM, an established composite score that summarizes the performance on multiple memory tests. We found that the PRS was significantly associated with the ADNI-MEM score ($\beta = -0.16$, $p < 0.001$) and such association was mediated via the CSF tau levels (t-tau and p-tau had the same effect, Fig. 2). The effect was considered as a partial mediation since the direct effect of the PRS on the ADNI-MEM was significant ($\beta = -0.11$, $p < 0.001$) in the presence of the mediator (i.e., CSF t-tau or p-tau). The significant mediation effect was found in the stratified analysis as well. However, the PRS effect on memory via CSF tau levels among the males was considered to be a full mediation (Supplementary Figure 2). In contrast, the pattern in the females was consistent with the results in the full samples. The non-*APOE* PRS was not associated with memory, as measured by the ADNI-MEM, although there was a possible linear effect at $p < 0.1$ for memory in the females.

DISCUSSION

In this study, we evaluated the potential for identifying a pathway-specific PRS that combines the effects of variants in the tau-protein kinase activity and tau-protein binding to predict the tau burden and cognitive function. Within the non-demented older participants, the PRS was associated with cross-sectional tau aggregation and longitudinal changes. Furthermore, CSF t-tau and p-tau significantly mediated the PRS effect on memory impairment. Females and males showed different patterns of associations between the PRS, tau deposition, and cognitive decline. Overall, our findings represent the contribution of pathway-specific PRS for understanding the mechanisms in AD pathology.

Among all the participants, the PRS was not only associated with CSF t-tau and p-tau but also with the uptake of global tau-PET independent of Aβ levels and other demographic factors. A previous study demonstrated that CSF t-tau and p-tau start to increase before tau-PET [50]. Our results suggest the value of pathway-specific PRS as predictors of tau pathology along the AD continuum. The association between tau pathology (i.e., CSF t-tau, p-tau, and tau PET) and SNPs located in genes that are part of tau-protein kinase activity or tau-protein binding pathways has been found [14–17]. However, these univariate results are often underpowered due to the small effect sizes of individual SNPs. The joint analysis of the incorporated effect of all SNPs within a pathway may have a larger combined effect size and greater statistical power for detecting an association, which could account for our observations. In particular, the influence of PRS on tau pathology, as measured by CSF or PET was above and beyond the effect of *APOE*, the strongest genetic susceptibility marker for increased risk of AD. Several recent studies indicated that *APOE* ε4 carriers have increased cerebral tau pathology [16, 51, 52]. Our current results suggest that the association between the pathway-specific PRS and tau aggregates is not driven by the inclusion of *APOE*.

We found that the PRS was correlated with general brain-wide increases in tau pathology, except in the last Braak stage, after controlling for Aβ and other demographic factors. However, the non-*APOE* PRS was not associated with the earliest regions of tau pathology, suggesting the *APOE* affects medial temporal tau pathology. This finding is consistent with recent PET studies that indicated that *APOE* ε4 carriers have increased tau PET uptake in the entorhinal cortex and hippocampus [17, 32]. Furthermore, the non-*APOE* PRS was associated with later Braak IV-V ROIs, suggesting that additional variants add much predictive power for understanding tau accumulation. Furthermore, both the PRS and non-*APOE* PRS were associated with longitudinal changes in CSF tau biomarkers, providing further support for the advantages of using pathway-specific genetic risk factors. Although their interactions with time were not significant, these results highlight that elevated genetic risk influences longitudinal tau pathology even among individuals without dementia. Overall, the significant effect of the PRS and the non-*APOE* PRS on cross-sectional and longitudinal tau accumulation suggests that the pathway-specific PRS could serve as an earlier marker of tau pathology.

The pathway-specific PRS was associated with worse memory, and the association was mediated via elevated tau levels. This finding suggests that the genes in the PRS contribute to the development of tau pathology, resulting in cognitive decline. Importantly, the effect of PRS on memory appears to be related to *APOE*-driven pathology, since the non-*APOE* PRS was not associated with memory performance. This association between tau pathology and cognitive impairment among *APOE* ε4 carriers has been found in another study [32]. Our results are also in agreement with previous observations of the effect of tau-PET on the cognitive decline [4, 53]. Hence, the present study suggested that tau pathology is a key link between pathway-specific PRS and cognitive function before the clinical symptoms of dementia.

Notably, the effect of pathway-specific PRS on CSF tau, tau-PET, and longitudinal changes in the females was consistent with observations in the full sample. However, the association between the pathway-specific PRS and tau pathology in the males showed a different pattern. Among the males, the non-*APOE* PRS was not significantly correlated with either CSF or PET levels, suggesting that the effect of the PRS on CSF tau levels and longitudinal changes appear to be driven by the inclusion of *APOE*. Notably, a recent study showed that only *APOE* ε4 homozygotes (not the heterozygotes) had increased tau deposition in males [36]. Similarly, we did not find an association between the PRS and tau PET in males with only 4 *APOE* ε4 homozygotes carriers. The stratified analysis on cognition indicated that PRS-associated memory decline is mediated by increased tau pathology in different ways in females and males, although the association seems to be driven by *APOE* in both groups. Apart from increased tau levels, the genes in the PRS may contribute to memory deficits via other biomarkers in females. These findings may explain why some older individuals have cognitive declines despite normal tau levels and may be important for understanding the mechanisms of disease development.

There are several limitations of this study. First, this study only used European populations due to the greater availability of samples. The PRS obtained and used in this study have ancestry-specific characteristics and thus the present results may not be generalizable to other racial populations. Second, the downstream mechanisms of how genetic factors become abnormal were not identified. Third, although we found that tau levels mediated pathway-specific genetic risk factors concerning cognitive decline, a lot of the variability remains unexplained. Thus, considering additional factors, such as the blood-brain barrier, metabolism, and other biomarkers will be necessary to optimize our ability to explain AD progression. Lastly, our findings need to be replicated in other larger cohorts with biomarker data and prospective neuropsychological follow-ups.

In conclusion, our results indicated that the pathway-specific PRS is predictive for identifying older individuals at risk of accumulating tau and cognitive decline. Moreover, the association is independent of Aβ. The effect of PRS in males was driven by the inclusion of *APOE*. However, the impact of the PRS in females had additional prediction power for tau deposition. The overall PRS was also associated with worse cognitive performance, mediated by the tau deposition and driven by *APOE*. These relationships have important implications for clinical treatment and biomarker studies during the preclinical period of AD.

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SUPPLEMENTARY MATERIAL

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