Polygenic Effect on Tau Pathology Progression in Alzheimer's Disease

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Objective: Polygenic variation accounts for a substantial portion of the risk of Alzheimer's disease (AD), but its effect on the rate of fibrillar-tau accumulation as a key driver of dementia symptoms is unclear.
Methods: We combined the to-date largest number of genetic risk variants of AD (n = 85 lead single-nucleotide polymorphisms [SNPs]) from recent genome-wide association studies (GWAS) to generate a polygenic score (PGS). We assessed longitudinal tau-positron emission tomography (PET), amyloid-PET, and cognition in 231 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Using the PGS, together with global amyloid-PET, we predicted the rate of tau-PET increases in Braak-stage regions-of-interest and cognitive decline. We also assessed PGS-risk enrichment effects on the required sample size in clinical trials targeting tau pathology.
Results: We found that a higher PGS was associated with higher rates of tau-PET accumulation, in particular at elevated amyloid-PET levels. The tau-PET increases mediated the association between PGS and faster cognitive decline. Risk enrichment through high PGS afforded sample size savings by 34%.
Interpretation: Our results demonstrate that the PGS predicts faster tau progression and thus cognitive decline, showing utility to enhance statistical power in clinical trials.

ANN NEUROL 2023;00:1–11

Alzheimer's disease (AD) is the major cause of dementia with an estimated 50 million cases worldwide.[1] The development of tau is a disease-defining pathology that drives cognitive decline in AD.[2] The rates of tau-accumulation and associated symptomatic worsening vary substantially between patients[3, 4]; however, little is known about those factors that determine the rate of tau progression in AD,[5, 6] thus hampering the assessment of treatment efficacy in ongoing clinical trials and the prognosis of dementia in clinical praxis.

Here, we propose to use a polygenic score (PGS) for the prediction of tau progression in AD, which could be utilized to select individuals with faster tau progression in clinical trials. The PGS is a powerful tool to assess an individual's genetic risk for AD by integrating the effects of multiple single-nucleotide polymorphisms (SNPs) discovered in genome-wide association studies (GWAS).[7] Previous studies demonstrated that PGSs show utility for the prediction of AD risk[8, 9] and age at dementia onset.[9, 10]

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26588

Received Jun 23, 2022, and in revised form Nov 2, 2022. Accepted for publication Dec 19, 2022.

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So far, studies examining the value of a PGS for predicting tau pathology have been limited to cross-sectional assessments,[10–13] leaving the question unaddressed whether a PGS is associated with faster rates of fibrillar tau progression.[14]

Against this background, our primary aim was to investigate the value of PGS for the prediction of longitudinal changes in fibrillar tau and thus the rate of cognitive worsening. Our secondary aim was to test the generalizability of the abovementioned association between PGS and the progression of fibrillar tau. In light of previous studies showing a strong association between elevated beta-amyloid (Aβ) levels and higher cortical fibrillar tau,[15, 16] we primarily focused on Aβ as a modulating factor. As previous PGSs were associated with higher Aβ,[11, 13, 17] we further tested whether the PGS is associated with faster fibrillar tau accumulation merely as a consequence of the effect on Aβ, or by interacting with Aβ and thus modulating the effects of Aβ on fibrillar tau development. This is of interest for risk stratification strategies in clinical trials, because an interaction between PGS and Aβ for predicting tau progression would render the PGS an important factor that could inform Aβ-based risk enrichment in clinical trials on AD. Given previous reports of sex-dependent effects of genetic AD-risk variants on tau-pathology,[18, 19] we further assessed whether sex modulated the effects of the PGS on tau-PET.

For the present work, we leveraged two recently published GWAS that included up to 1.1 million participants[20, 21] and more than doubled the number of known independent AD risk variants. All analyses were controlled for APOE ε4, which is the strongest genetic risk factor of AD dementia.[22] We tested the genetic associations in deeply phenotyped individuals who were longitudinally assessed with neuropsychological testing and molecular PET tracers of fibrillar tau and Aβ in the Alzheimer's Disease Neuroimaging Initiative (ADNI),[23] one of the world's largest multicenter biomarker studies on AD.

TABLE 1. Sample Characteristics

	tau-PET (n = 231)
Age, yr	74.41 (55–92)
Sex (M/F)	118 M / 113 F
Diagnosis (CN/MCI/AD)	133CN / 73MCI / 25AD
Aβ status (% positive)[a]	52.4%
APOE ε4 (% positive)	47.6%
Ethnicity (% white)	88.7%
tau-PET follow-up time, yr	1.88 (0.75–5.37)
tau-PET follow-up visits	2.5 (2–5)
Amyloid-PET follow-up, yr[b]	5.63 (1.82–10.20)
ADNI-MEM follow-up, yr[c]	5.52 (0.95–15.07)
ADAS13 follow-up, yr[d]	5.6 (0.82–15.12)

Unless otherwise indicated, the summary statistics are presented as mean [range].
[a]Aβ status at baseline is available for 206 participants.
[b]Longitudinal amyloid-PET data are available for 186 participants.
[c]Longitudinal ADNI-MEM measures are available for 230 participants.
[d]Longitudinal ADAS13 measures are available for 224 participants.
Aβ = beta-amyloid; AD = Alzheimer's disease; ADAS = Alzheimer's Disease Assessment Scale; APOE = apolipoprotein E; CN = cognitively normal; F = female; M = male; MCI = mild cognitive impairment; MEM = episodic memory, N = sample size.

Methods

ADNI Participants

We included 231 ADNI participants based on the availability of longitudinal tau-PET (for follow-up duration see Table 1) and genotype data (accessed on January 19, 2021). For participants fitting the inclusion criteria, we further acquired all available amyloid-PET and cognitive measures. Participants were classified by ADNI as cognitively normal (CN, Mini-Mental State Exanimation [MMSE] ≥ 24, Clinical Dementia Rating [CDR] = 0, no memory concerns), mildly cognitively Impaired (MCI, MMSE ≥ 24, CDR = 0.5, objective memory loss measured by education adjusted scores on the Wechsler Memory Scale Memory II, preserved activities of daily living), or AD dementia following standard diagnostic criteria.[24] Ethnicity was determined based on self-report. Principal component analysis (PCA) was used to quantify patterns of population structure via flashPCA.[25] Ethical approval was obtained by ADNI, all participants provided written informed consent.

Genotyping Procedures and Quality Control in ADNI

The missing genotypes were first imputed based on the haplotype reference consortium (HRC) reference panel v1.1[26] using Minimac4 on the Michigan imputation server,[27] separately by cohort, as ADNI genotypes were genotyped on three different Illumina arrays, namely Human610-Quad (620,901 markers), HumanOmniExpress (730,525 markers), and HumanOmni2.5-8 (2,379,855 markers). Prior to the imputation, strand, positions, and ref/alt assignments were updated if inconsistent between ADNI genotypes and the HRC reference panel. SNPs were removed if

they had differing alleles, inconsistent allele frequencies (>0.2 difference), no equivalent in the reference panel, or if they were palindromic SNPs with a minor allele frequency (MAF) >0.4 (via www.well.ox.ac.uk/~wrayner/tools/HRC-1000G-check-bim-v4.3.0.zip). SNPs with an imputation $r^2 < 0.5$ were excluded.

Calculation of the Polygenic Score

We followed the recently developed Polygenic Risk Score Reporting Standards.[28]

Genetic Risk Variants. We considered variants associated with AD or AD related dementias (ADD) at a genome-wide significant level of $p \leq 5 \times 10^{-8}$ in the most recent and largest AD/ADD GWAS including 111,326 cases of 677,663 controls and 90,338 cases of 1,036,225 controls, respectively.[20, 21] After removal of all APOE variants, combination of the two datasets resulted in a total of 85 independent SNPs (Supplementary Table S1; linkage disequilibrium [LD] $r^2 \leq 0.2$ in the European 1000G populations CEU, GBR, IBS, and TSI).

Generation of Polygenic Score. The PGS was calculated in PLINK 2.0 (www.cog-genomics.org/plink/2.0/)[29] as the sum over the weighted number of alleles per SNP, using the respective log(OR) as weights. Stage II log(OR) were used for SNPs from Bellenguez et al 2022.[20] Wightman et al report effect sizes per cohort; hence, we conducted a meta-analysis of all cohorts that used a binary AD phenotype (rmeta; https://cran.r-project.org/web/packages/rmeta/index.html). The PGS was then divided by the number of included variants and finally standardized across all participants.

In addition, for a sensitivity analysis we calculated a PGS excluding 5 SNPs that are within 500 kb distance to known frontotemporal dementia (FTD) loci (non-FTD PGS).[30, 31]

Image Acquisition and Processing

All MRI and PET data in the ADNI cohort were obtained on 3 T scanners using standardized scanning protocols (http://adni.loni.usc.edu/methods/documents/). The tau-PET was assessed in 6 × 5 minutes blocks, 75–105 minutes post-injection of [18F]AV1451. Similarly, amyloid-PET was assessed in 4 × 5 minutes blocks, 50–70 minutes post injection of [18F]AV45 or in 4 × 5 minutes blocks, 90–110 minutes post injection of [18F]FBB.

Recorded PET images were co-registered and averaged, and further standardized with respect to the orientation, voxel size, and intensity by the ADNI PET core.[32] Next, we processed T1w images and PET data using the Advanced Normalization Tools (ANTs) toolbox (http://stnava.github.io/ANTs/). PET images were rigidly co-registered to the participant's T1w image in native space. Based on the ANTs longitudinal cortical thickness pipeline, T1w images were bias field corrected, brain extracted, and segmented into gray matter, white matter, and cerebrospinal fluid tissue maps. Based on ANTs high-dimensional warping algorithm, the preprocessed T1w images were further non-linearly normalized to MNI space. We then used the derived spatial registration parameters in order to transform the MindBoggle DKT atlas brain parcellation[33] and reference regions to the individual PET scans to obtain PET region of interest (ROI) values.

The tau-PET standardized uptake value ratio (SUVR) values were computed by normalizing the target ROIs to the mean tracer uptake of the eroded white matter, based on recent recommendations for longitudinal tau-PET assessments.[34, 35] Summary tau-PET measures were computed for three a priori established composite ROIs as defined by the Braak post-mortem staging of tau pathology (Figure 1A).[36] Global tau-PET values were calculated as the mean of cortical tau-PET SUVRs.

Global amyloid-PET values were calculated as the mean cortical grey matter SUVRs (frontal, lateral temporal, lateral parietal, and anterior/posterior cingulate) divided by whole cerebellum.[37] Aβ status was determined based on pre-established cutoffs, that is, 1.11 for AV45-PET and 1.08 for FBB-PET.[38] To obtain comparable quantification of the Aβ levels across tracers, we converted the global amyloid-PET values to the centiloid scale.[39, 40]

Cognitive Assessment

Global cognition was assessed through the extended Alzheimer's Disease Assessment Scale (ADAS13), which is an extension of the 11-item cognitive subscale of the ADAS,[41] including in addition tests of delayed word recall and number cancellation.[42] Memory performance was assessed using the pre-established composite memory score ADNI-MEM.[43] The ADNI-MEM score includes the Rey Auditory Verbal Learning Test, the ADAS, the Wechsler Logical Memory I and II, and the word recall of the MMSE.[43]

Statistical Analysis

To ensure that our findings were not affected by outliers, measurements deviating ± 3 standard deviations from the sample mean were excluded. Including outliers in a sensitivity analysis yielded consistent results. The tau-PET SUVR measures were log-transformed prior to analysis to approximate a normal distribution.

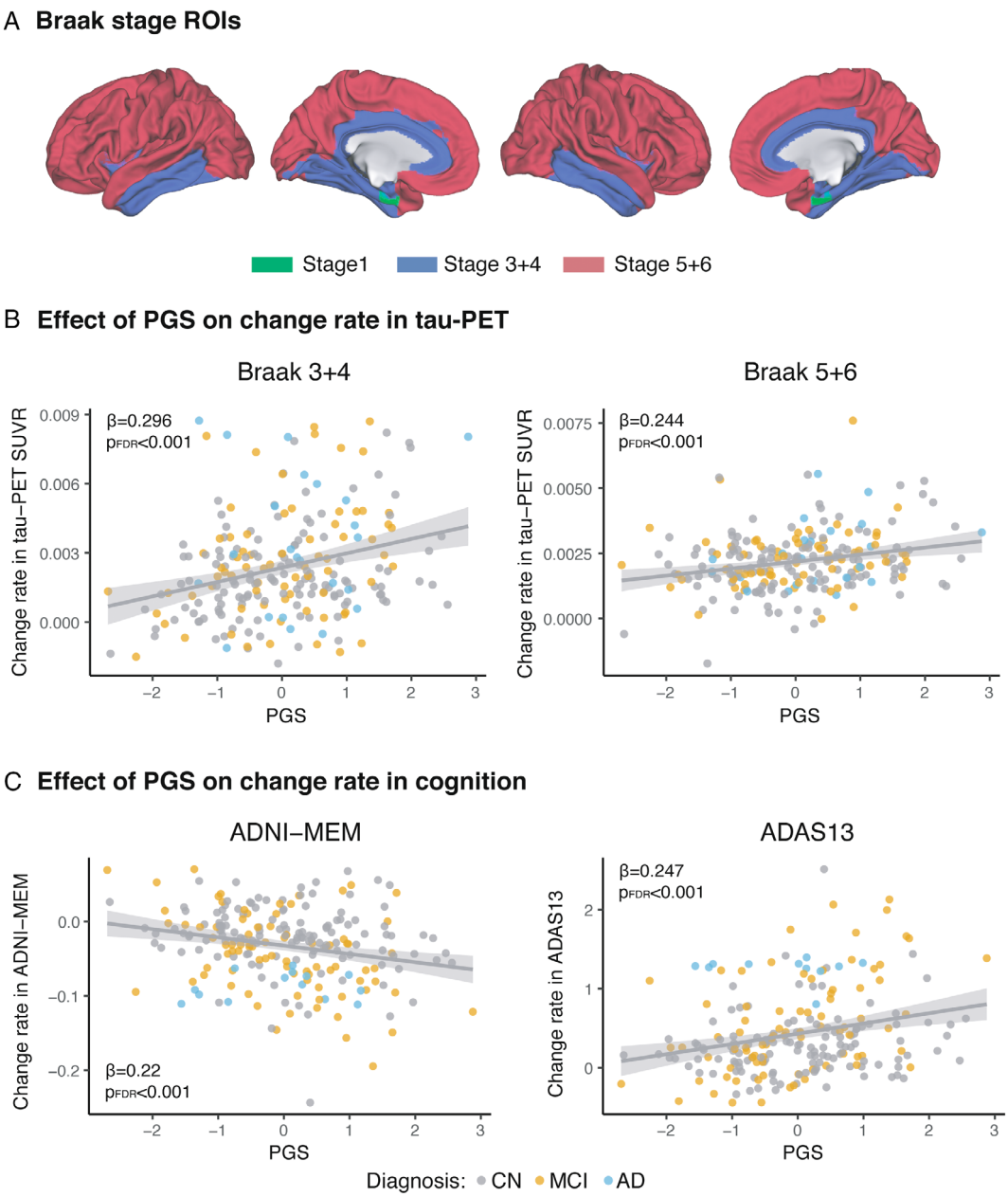

FIGURE 1: Spatial mapping of Braak stage-specific ROIs and the association between PGS and rate of change in tau-PET and cognition. Surface rendering of the composite Braak-stage ROIs[36] that were used to determine regional tau-PET uptake. Braak stage 2 (hippocampus) was not included due to the off-target binding of the AV1451 tau-PET tracer (A). Scatterplots showing the regression line (solid gray) and 95% CI (shaded area) for the associations between PGS and the rate of change in tau-PET SUVRs (B) and cognition (C). Standardized β-values and FDR corrected *p*-values are shown. Observations are color coded by diagnosis. ADAS13 = Alzheimer's Disease Assessment Scale cognitive subscale; AD = Alzheimer's disease; ADNI-MEM = Alzheimer's Disease Neuroimaging Initiative memory composite; CN = cognitively normal; MCI = mild cognitive impairment; PGS = polygenic score.

To examine the associations between the PGS and the rates of change in either tau-PET, amyloid-PET, or cognition, we first determined the subject-level rate of change for each of the biomarkers and cognitive performance, using a previously established approach.[44] To that end, we used linear mixed-effect regression analyses to model the rate of change at the subject-level, including time as the independent variable, with the random terms being slope and intercept. Using the thus estimated rates of change as the dependent variables, we tested in univariate linear regression analyses the PGS as the predictor. Similarly, for cross-sectional data, we tested in separate regression analyses whether the PGS predicted the different biomarkers. Results were corrected for multiple comparisons using the false discovery rate (FDR)[45] with a significance level of 0.05.

To test whether the associations between PGS and changes in cognition were mediated via changes in tau-PET uptake, we conducted mediation analyses. To that end, PGS was treated as predictor, changes in global tau-PET levels as a mediator and ADNI-MEM or ADAS13 scores as outcomes. The significance of the mediation was assessed using 1,000 bootstrapped iterations, as implemented in the "mediation" R package.

Next, we performed sensitivity analyses in subgroups categorized by amyloid status, where the effect of PGS on tau-PET change was tested in each of the subgroups. Significance and 95% confidence intervals (CIs) of effects were determined using 1,000 bootstrapped iterations. In order to test whether the distribution of the bootstrapped regression coefficients significantly differ between the groups, we performed a two-sample *t*-test comparing the standardized β-values between both groups.

We further tested the interaction between the PGS and global amyloid-PET at baseline on tau-PET change and confirmed the robustness of the association using robust Wald test.

All above-mentioned models were controlled for age, sex, education, diagnosis, ethnicity, APOE genotype, the first 10 principal components to correct for population stratification and maximum follow-up time.

In order to test whether sex modulates the association between PGS and tau-PET increases, we tested in linear regression analyses the interaction PGS by sex on the rate of tau-PET changes in the whole sample as well in subgroups stratified by Aβ status.

Finally, we estimated sample size required for detection of hypothetical treatment effects on the rate of tau-PET change at power = 0.8 and treatment effect size of 20% or 40%. In a first step, the individual PGSs were residualized by regressing out age, sex, education, diagnosis, ethnicity, APOE genotype, and the first 10 principal components in order to render the stratified analyses of the PGS—to be conducted in the next step—independent of these potential confounders. Subjects were stratified into quartiles of the residualized PGSs and sample size estimates were conducted using the "pwr" R package using the following parameters: two-sample *t*-test, two-tailed, type I error rate = 0.05, power = 0.8. Sample size estimates were repeated for alternative stratifications including Aβ status (Aβ+ vs Aβ-), APOE ε4 status (ε4 carrier vs non-carrier), and combinations of these stratification factors.

All statistical analyses were performed using R (http://www.R-project.org). Standardized β-coefficients are reported throughout to facilitate comparison of associations across biomarkers.

Results

The PGS Is Associated with Tau Accumulation and Cognitive Decline

We computed a PGS based on 85 independent lead SNPs from two recent GWAS,[20, 21] excluding the APOE locus on chr19 (for lead SNPs see Supplementary Table S1). Using linear mixed effects models, we estimated the individual rates of change in tau-PET obtained from three a priori established composite ROIs as defined by Braak staging (Fig 1A). We tested the PGS as a predictor of the estimated rates of change in tau-PET in each ROI, controlling for age, sex, education, diagnosis, ethnicity, APOE genotype, the first 10 principal components of the population structure and maximum follow-up.

A higher PGS was associated with higher accumulation rates of tau-PET in cortical regions (Braak 3 + 4 ROI: $\beta = 0.296$, $p_{FDR} < 0.001$; Braak 5 + 6 ROI: $\beta = 0.244$, $p_{FDR} < 0.001$; Figure 1B), but not in entorhinal Braak 1 ROI ($p_{FDR} = 0.646$). A higher PGS was further associated with a faster decline in episodic memory (ADNI-MEM: $\beta = -0.22$, $p_{FDR} < 0.001$; Figure 1C) and global cognitive performance (ADAS13: $\beta = 0.247$, $p_{FDR} < 0.001$; Fig 1C) over a period of 5.6 years on average (range = 0.8–15 years).

Bootstrapped mediation analyses showed that higher rates of global tau-PET accumulation mediated the effect of the PGS on the rate of change in ADNI-MEM (mediation effect: $\beta = -0.003$ [95% CI: −0.005, −0.001], $p < 0.001$, proportion mediated = 28.9%; Figure 2A) and ADAS13 (mediation effect: $\beta = 0.026$ [95% CI: 0.009, 0.050], $p < 0.001$, proportion mediated = 19.6%; Figure 2B), suggesting that the effect of the PGS on the rate of tau-PET explains the association between a higher PGS and faster cognitive decline.

As several of the variants included in the PGS are in gene loci for FTD, in a sensitivity analysis we computed a PGS excluding the FTD loci and tested the association with tau-PET rates of change. We found that after excluding the FTD loci, a higher PGS was still associated with higher accumulation rates of tau-PET in cortical regions (Braak 3 + 4 ROI: $\beta = 0.288$, $p_{FDR} < 0.001$; Braak 5 + 6 ROI: $\beta = 0.225$, $p_{FDR} = 0.001$).

We also tested the association between the PGS and cross-sectional levels of tau-PET and cognition in an analogous way and found a higher PGS to be associated with higher tau-PET levels in Braak stages 1–4 (Braak 1 ROI: $\beta = 0.296$, $p_{FDR} < 0.001$; Braak 3 + 4 ROI: $\beta = 0.245$, $p_{FDR} < 0.001$) and lower memory scores (ADNI-MEM: $\beta = -0.161$, $p_{FDR} = 0.003$).

Aβ Levels Do Not Mediate but Modulate the PGS Effect on Tau Accumulation

First, we replicated previous findings of associations with increased Aβ,[17] observing that a higher PGS was

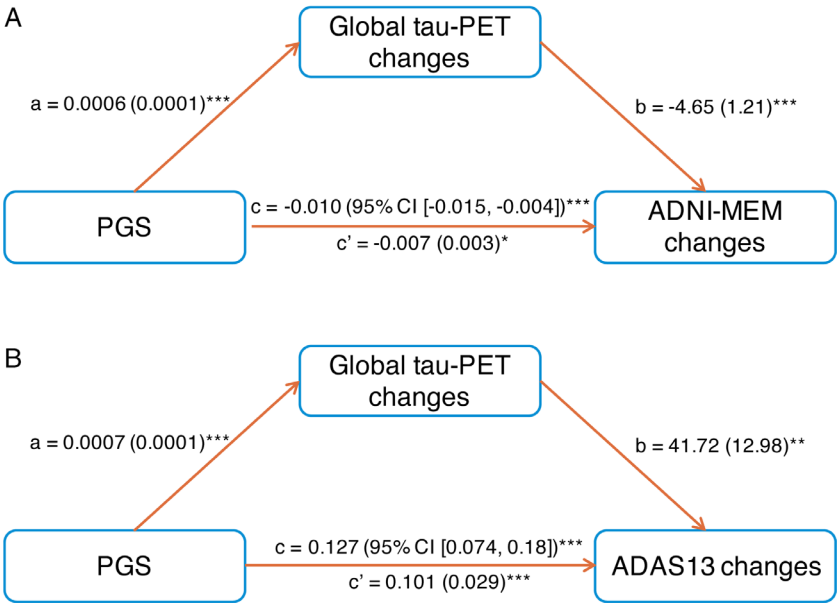

FIGURE 2: The rate of change in global tau-PET mediates the effect of PGS on change rate in cognition. Path model illustrating the mediation analyses. The effect of PGS on the rate of change in global tau-PET mediated the effect of PGS on rate of change in ADNI-MEM (A) and ADAS13 (B). Path weights are displayed as β-values with standard errors displayed in brackets. The path weight *c* indicates the effect of PGS on changes in cognitive measures (ie, either ADNI-MEM or ADAS13) without taking global tau-PET changes into account, the path coefficient *c'* indicates the corresponding effects of PGS after accounting for the mediator global tau-PET changes. The total effect was determined using bootstrapping with 1,000 iterations. Models were controlled for age, sex, education, APOE genotype, diagnosis, PC1-10, and ethnicity. ADAS13 = Alzheimer's Disease Assessment Scale cognitive subscale; ADNI-MEM = Alzheimer's Disease Neuroimaging Initiative memory composite; PGS = polygenic score.

associated with faster rates of global amyloid-PET accumulation ($\beta = 0.16$, $p_{FDR} = 0.036$). Next, we tested whether the effect of the PGS on changes in tau-PET is independent of changes in amyloid-PET. When controlling for changes in amyloid-PET in addition to the other covariates, the effects of the PGS on the rate of change in tau-PET remained significant in Braak stage 3 + 4 ($\beta = 0.291$, $p < 0.001$) and Braak stage 5 + 6 ($\beta = 0.260$, $p = 0.002$), suggesting that the association between the PGS and increases in amyloid-PET does not account for the association between the PGS and tau-PET changes.

However, we found evidence for more pronounced effects of the PGS in presence of elevated levels of Aβ (Figure 3A). When participants were stratified by amyloid status, in cortical brain regions beyond the entorhinal cortex (ie, Braak-stages 3–6), the effect of the PGS on tau changes is significantly stronger (Braak 3 + 4: $t(1949) = -6.269$, $p < 0.001$; Braak 5 + 6: $t(1995.5) = -13.102$, $p < 0.001$) in the Aβ + participants compared with the Aβ- participants. In contrast, for Braak stage 1 ROI (including the entorhinal cortex), we found that the effect of PGS on tau changes is stronger ($t[1990.9] = 59.789$, $p < 0.001$) in the Aβ- participants compared with the Aβ+ participants. These results suggest that the PGS is associated with enhanced tau-PET accumulation in the presence of abnormally elevated Aβ levels tracking Braak-staging of tau accumulation across the course of AD, but with age-related tau-PET increase restricted to the entorhinal cortex in participants without elevated levels of Aβ.

Given that higher abnormal levels of Aβ are a strong driver of fibrillar tau accumulation in the cortex,[3] we tested whether the PGS modulates Aβ-related increases in the rate of tau accumulation. In regression analysis, we found a significant interaction of the PGS by baseline amyloid-PET on subsequent increase in tau-PET (Braak 5 + 6; interaction term $\beta = 0.177$, $p = 0.04$; Figure 3B). To ensure that the interaction was not driven by any outliers, we conducted robust regression analysis, confirming our results (Wald test, $F = 4.22$, $p = 0.041$). Together, these results suggest that the PGS shows a synergistic effect with elevated levels of Aβ on the rate of tau-PET increases such that the PGS is associated with enhanced tau-PET accumulation particularly in individuals with higher abnormal levels of Aβ.

No Sex-Dependent Effects of the PGS on Tau Accumulation

We next investigated whether sex modifies the association between the PGS and the rate of tau-PET changes. Neither in the whole sample nor in an analysis stratified by Aβ status, the interaction effect of the PGS by sex on the rate of tau accumulation was significant ($p > 0.05$).

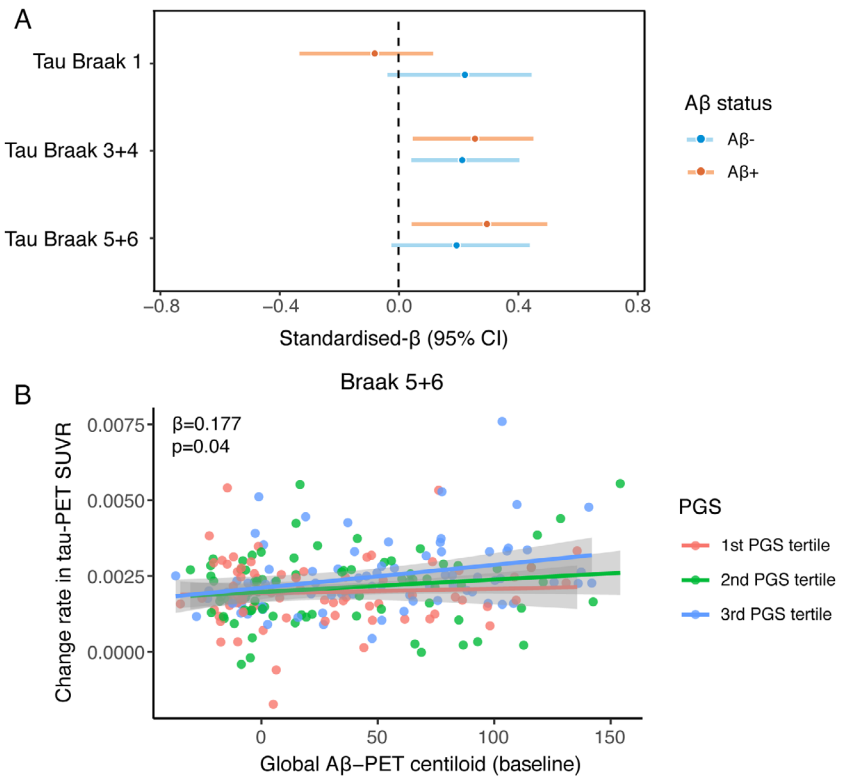

FIGURE 3: PGS modulates the effect of baseline amyloid-PET on change rate in tau-PET. Regression weights of the association between the PGS and change rate in tau-PET SUVRs stratified by amyloid-PET status (Aβ+ [red color] vs Aβ- [*blue color*]) are shown (A). Weights are indicated as standardized β-values with 95% confidence intervals (CI) derived from 1,000 bootstrapped iterations. Scatterplot showing the rate of change in tau-PET SUVRs as a function of baseline amyloid-PET centiloid (B). Regression lines are shown for the group including participants with 1st PGS tertile (*red*), 2nd PGS tertile (*green*), and 3rd PGS tertile (*blue*); the shaded area represents the 95% CI. Note that PGS levels were stratified by tertiles only for illustrational purposes, whereas the regression analyses to estimate the regression weights was computed based on the predictor PGS as a continuous variable. Aβ = beta-amyloid; PGS = polygenic score.

TABLE 2. Estimated Sample Size Required for Detecting Intervention Effects on Tau-PET Changes in the Full Sample And in a Subgroup of Aβ+ Individuals at Power = 0.8

		Required number of participants per arm to detect intervention effect of	
Group subgroup		20%	40%
All	All participants	225	49
	APOE ε4+	201 (−11%)	44 (−10%)
	4th PGS quartile	183 (−19%)	40 (−18%)
Aβ+	All Aβ+ participants	188	41
	APOE ε4+	185 (−2%)	40 (−2%)
	4th PGS quartile	126 (−33%)	27 (−34%)

Note: Percentage in brackets indicates the percentage of sample size reduction relative to the reference group of no stratification within either whole group (all participants) or the Aβ+ group (all Aβ+ participants).
APOE ε4+ = APOE ε3/ε4 and APOE ε4/ε4 carrier, 4th PGS quartile = group in upper quartile of residualized PGS scores, Aβ+ = abnormally high amyloid-PET.

PGS Increases Sensitivity to Detect Tau-Targeting Intervention Effects

Finally, we tested the utility of a higher PGS for risk enrichment in clinical trials targeting fibrillar tau. To this end, we estimated the sample size needed to detect hypothetical treatment effects that reduced the rate of increase in tau-PET by 20% and 40% when stratified by PGS scores (lowest vs highest quartile of PGS). We estimated the PGS effects on the sample size needed for the whole group and in the group restricted to Aβ+ individuals. For a clinical trial on tau-PET changes regardless of Aβ status, results showed that the PGS stratification yielded a saving in sample size by 18 to 19% compared with the no-stratification scenario, depending on the size of the assumed treatment effect (Table 2). For a clinical trial restricted to Aβ+ participants, stratification by PGS yielded a reduction in sample size needed by 33–34% compared with no stratification (Table 2). Previous studies found the APOE ε4 genotype to be associated with faster tau accumulation in AD.[5] When compared with the stratification based on APOE ε4 status (presence of absence of APOE ε4 allele), there was a substantial advantage of PGS stratification (Table 2). No synergistic effects were observed for stratification based on PGS and APOE ε4 status.

Discussion

Here, we combined longitudinal molecular PET with a comprehensive set of lead SNPs from the to-date largest GWAS on AD for the polygenic prediction of the rate of fibrillar tau progression and cognitive changes. Our primary finding shows that a higher PGS was associated with faster tau accumulation over an average of 1.9 years follow-up, which in turn mediated the PGS effect on faster cognitive decline. These results demonstrate that the accelerated increase in pathologic tau underlies the association between the PGS and symptomatic worsening in AD. Our findings support the utility of the PGS for risk enrichment in clinical trials, which may yield substantial savings in sample size needed to test treatment effects on the progression of tau pathology in AD.

Our study makes important contributions toward a clinically relevant PGS-based prediction of increases in tau pathology and thus cognitive decline in AD. We demonstrated for the first time that a PGS predicts longitudinal changes in fibrillar tau as assessed by tau-PET, that is, the best-established biomarker of fibrillar tau pathology recently adopted as outcome measure in several clinical trials on AD.[46] Our results suggest that the value of the PGS for the prediction of tau-PET changes translates into a reduction of the required sample size by up to 34% in clinical trials targeting tau pathology. Importantly, risk stratification by the PGS more than doubles the sample-size reduction compared to that by the APOE-ε4 based stratification, supporting the added value of the PGS for the prediction of tau progression in clinical trials. The development of powerful predictors for risk stratification is a pressing need, as the rate of change per year in tau-PET ranges between 0.5 and 3% in cognitively normal Aβ+ individuals and 3 to 8% in symptomatic individuals.[47] Thus, in a clinical trial targeting tau, the control group would show a substantial variability of tau-PET changes over 2 years of follow-up, rendering feasible intervention effects on tau difficult to detect. Therefore, the PGS could be of great value to identify individuals of imminent worsening of tau accumulation in clinical trials and may support individualized disease management within a precision medicine guided strategy.[7]

Although a PGS can be constructed based on a larger number of SNPs selected at a more liberal *p*-value threshold,[48] we focused our analysis on genome-wide significant lead SNPs. Compared with a PGS that relies on a broader genetic background, this approach has key advantages regarding clinical applications. First, it facilitates establishing cutoff values for risk stratification. Second, it enhances comparability between studies and the interpretability of the PGS that could be compromised when including a larger number of SNPs with potentially spurious associations.[48, 49] A strength of our study is the inclusion of over 42 novel lead SNPs,[20, 21] which increased the statistical power to predict changes in tau-PET and cognition. We note that although the effect of a PGS derived from AD-risk variants on prediction of longitudinal cognitive worsening has been previously supported,[17, 20] it has not been exempted of conflicting evidence.[50, 51] Smaller sample sizes and risk variant numbers in previous PGSs might explain this discrepancy.[50, 51] Also, it is unclear to what extent previous PGSs were associated with faster changes in fibrillar tau progression. Here, we demonstrate that the predictive power of the present PGS on cognitive changes is dependent on the effect of tau-PET changes. Overall, the current study substantially adds to previous studies that used a lower number of SNPs for constructing a PGS and were confined to cross-sectional analyses of pathologic tau.[11, 12, 14]

Our secondary aim was to examine possible factors that moderate the association between the PGS and tau progression, primarily focusing on Aβ deposition. As the presence of elevated levels of Aβ in the cortex is a major driver of cortical increases in fibrillar tau in AD,[3, 15] it is possible that the effect of the PGS on tau-PET changes is indirectly caused through a PGS-related increase in Aβ accumulation. However, we demonstrated that the PGS effect on tau-PET changes cannot be reduced to an

indirect effect of PGS on levels of amyloid-PET as controlling for amyloid-PET changes did not diminish the PGS effects on tau-PET. We did however observe a differential effect of Aβ, where Aβ- individuals show an association between higher PGS and age-related tau-pathology restricted to the entorhinal cortex, while Aβ+ individuals show stronger PGS effects in typical AD brain areas. Our results are in line with previous longitudinal studies showing that AD-like tau-PET pathology occurs in cortical brain areas beyond the entorhinal cortex in the presence of elevated Aβ levels,[3, 15] whereas age-related increases in tau-PET occur typically in the entorhinal cortex also in the absence of elevated levels of Aβ.[52] Furthermore, we observed a cross-talk between PGS and baseline levels of amyloid-PET on the rate of subsequent change in tau-PET, suggesting that the PGS affects the formation of tau pathology in cortical brain regions downstream of the abnormally elevated Aβ. In contrast, previous studies on APOE ε4 status reported that the effect of APOE ε4 on higher cortical tau-PET accumulation were due to the effect on increased levels of Aβ.[53, 54] Taken together, these results suggest different roles of the APOE ε4 allele and PGS for the prediction of tau-PET changes, where presence of the APOE ε4 allele contributes to cortical tau-progression indirectly via increasing levels of Aβ, but it is the PGS that is associated with faster rates of tau-accumulation once abnormal levels of Aβ are present.

We did not find sex to modulate the effect of the PGS on the rate of tau-PET changes, despite sex-dependent genetic effects on tau-pathology exists for APOE ε4 genotype, where the association between APOE ε4 and tau-accumulation is stronger in females compared with males.[18, 19] The current study controlled for APOE ε4 genotype and is therefore not in conflict with these previous findings.

For the interpretation of our findings, several limitations should be considered. First, the included AD GWAS were primarily conducted in European-ancestry individuals,[20, 21] and the included ADNI participants were primarily self-reporting as white. We caution that the results may not generalize to individuals of other ethnic backgrounds and recognize the need to include underrepresented ethnic and racial backgrounds.[55] Second, our PGS was limited to common variants (MAF ≥ 0.01), and potential epistatic effects and gene-environment interactions were not considered. Third, it should be mentioned that 268 AD cases and 173 healthy controls from ADNI were included in the Stage II analysis of the large-scale GWAS.[20] However, the outcome in that GWAS was clinical diagnosis and not tau-PET, and the ADNI participants were a minor subset of a total of over 788,000 participants (including >111,000 AD cases), rendering any risk of circularity negligible. Last, we did not investigate potential variant-specific contributions to the prediction of tau accumulation. Both the predictive value and pathomechanistic pathways vary between different variants.[56] Previous studies focusing on particular lead SNPs showed associations for genetic variants in genes including BIN1,[57, 58] among others[59, 60] to be associated with alterations in tau-pathology in AD. However, the small effect size attributed to each risk variant reduces its potential predictive value on a specific phenotype like contribution to tau pathology. Therefore, the current study focused on the cumulative effects across a larger set of SNPs for the prediction of the rate of tau pathology in order to maximize the predictive power.

In conclusion, the present PGS is a promising tool for the prediction of the rate of tau-progression that will enhance risk enrichment in clinical trials and potentially inform therapeutic decisions for treating tau pathology in AD. Future studies will be needed in order to test potential interactions between the PGS and other known risk factors of AD such as lifestyle factors and cerebrovascular changes. Furthermore, the presence of variants that are protective against tau-progression, in genes such as Klotho,[61] may somewhat compensate the effects of a PGS. Thus, the current study encourages future studies to explore additional predictors toward establishing a comprehensive and cost-effective prediction model for the progression of tau pathology.

Acknowledgments

The study was supported by the German Center for Neurodegenerative Diseases (DZNE), Legerlotz Foundation (to M.E.), LMUexcellent (to M.E.), FöFoLe (to An.R.) and by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) grant for major research instrumentation (DFG, INST 409/193-1 FUGG).

Parts of the data used in preparation of this manuscript were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI study contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this article. ADNI data collection and sharing for this project was funded by the ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging, and Bioengineering, and through contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company;

CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). Open Access funding enabled and organized by Projekt DEAL.

Author Contributions

An.R. and M.E. contributed to the conception and design of the study; An.R., S.F., and R.M. contributed to the acquisition and analysis of data; An.R., M.E., S.F., N.F., R.M., A.R., and M.D. contributed to drafting the text or preparing the figures.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability

Data used in this study are available from the ADNI database (adni.loni.usc.edu) upon registration and compliance with the data usage agreement.

References

1. World Health Organisation (WHO). *Global status report on the public health response to dementia*, Geneva: World Health Organisation (WHO). 2021.
2. La Joie R, Visani AV, Baker SL, et al. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. Sci Transl Med 2020;12:eaau5732.
3. Jack CR Jr, Wiste HJ, Schwarz CG, et al. Longitudinal tau PET in ageing and Alzheimer's disease. Brain 2018;141:1517–1528.
4. McDade E, Wang G, Gordon BA, et al. Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease. Neurology 2018;91:e1295–e1306.
5. Jack CR, Wiste HJ, Weigand SD, et al. Predicting future rates of tau accumulation on PET. Brain 2020;143:3136–3150.
6. Smith R, Strandberg O, Mattsson-Carlgren N, et al. The accumulation rate of tau aggregates is higher in females and younger amyloid-positive subjects. Brain 2020;143:3805–3815.
7. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet 2018;19:581–590.
8. Escott-Price V, Myers AJ, Huentelman M, Hardy J. Polygenic risk score analysis of pathologically confirmed Alzheimer disease. Ann Neurol 2017;82:311–314.
9. Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: development and validation of a polygenic hazard score. PLoS Med 2017;14:e1002258.
10. Cruchaga C, Del-Aguila JL, Saef B, et al. Polygenic risk score of sporadic late-onset Alzheimer's disease reveals a shared architecture with the familial and early-onset forms. Alzheimers Dement 2018;14:205–214.
11. Tan CH, Fan CC, Mormino EC, et al. Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition. Acta Neuropathol 2018;135:85–93.
12. Zettergren A, Lord J, Ashton NJ, et al. Association between polygenic risk score of Alzheimer's disease and plasma phosphorylated tau in individuals from the Alzheimer's disease neuroimaging initiative. Alzheimers Res Ther 2021;13:17.
13. Darst BF, Koscik RL, Racine AM, et al. Pathway-specific polygenic risk scores as predictors of amyloid-beta deposition and cognitive function in a sample at increased risk for Alzheimer's disease. J Alzheimers Dis 2017;55:473–484.
14. Zhou X, Li YYT, Fu AKY, Ip NY. Polygenic score models for Alzheimer's disease: from research to clinical applications. Front Neurosci 2021;15.
15. Sanchez JS, Becker JA, Jacobs HIL, et al. The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. Sci Transl Med 2021;13:eabc0655.
16. Schöll M, Lockhart SN, Schonhaut DR, et al. PET imaging of tau deposition in the aging human brain. Neuron 2016;89:971–982.
17. Mormino EC, Sperling RA, Holmes AJ, et al. Polygenic risk of Alzheimer disease is associated with early- and late-life processes. Neurology 2016;87:481–488.
18. Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. JAMA Neurol 2018;75:989–998.
19. Buckley RF, Mormino EC, Rabin JS, et al. Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. JAMA Neurol 2019;76:542–551.
20. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet 2022;54:412–436.
21. Wightman DP, Jansen IE, Savage JE, et al. A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. Nat Genet 2021;53:1276–1282.
22. Escott-Price V, Shoai M, Pither R, et al. Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease. Neurobiol Aging 2017;49:214.e7–214.e11.
23. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's disease neuroimaging initiative 3: continued innovation for clinical trial improvement. Alzheimers Dement 2017;13:561–571.
24. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's disease neuroimaging initiative (ADNI): clinical characterization. Neurology 2010;74:201–209.
25. Abraham G, Qiu Y, Inouye M. FlashPCA2: principal component analysis of biobank-scale genotype datasets. Bioinformatics 2017;33:2776–2778.
26. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet 2016;48:1279–1283.
27. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. Nat Genet 2016;48:1284–1287.
28. Wand H, Lambert SA, Tamburro C, et al. Improving reporting standards for polygenic scores in risk prediction studies. Nature 2021;591:211–219.

29. Chang CC, Chow CC, Tellier LC, et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 2015; 4:7.

30. Ciani M, Benussi L, Bonvicini C, Ghidoni R. Genome wide association study and next generation sequencing: a glimmer of light toward new possible horizons in frontotemporal dementia research. Front Neurosci 2019;13:506.

31. Pittman AM, Myers AJ, Duckworth J, et al. The structure of the tau haplotype in controls and in progressive supranuclear palsy. Hum Mol Genet 2004;13:1267–1274.

32. Jagust WJ, Landau SM, Koeppe RA, et al. The ADNI PET core: 2015. Alzheimers Dement 2015;11:757–771.

33. Klein A, Tourville J. 101 labeled brain images and a consistent human cortical labeling protocol. Front Neurosci 2012;6:171.

34. Young CB, Landau SM, Harrison TM, et al. Influence of common reference regions on regional tau patterns in cross-sectional and longitudinal [18F]-AV-1451 PET data. Neuroimage 2021;243:118553.

35. Schwarz CG, Therneau TM, Weigand SD, et al. Selecting software pipelines for change in flortaucipir SUVR: balancing repeatability and group separation. Neuroimage 2021;238:118259.

36. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259.

37. Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann Neurol 2012;72:578–586.

38. Landau SM, Thomas BA, Thurfjell L, et al. Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. Eur J Nucl Med Mol Imaging 2014;41:1398–1407.

39. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement 2015;11:1-15.e1-4.

40. Royse SK, Minhas DS, Lopresti BJ, et al. Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. Alzheimers Res Ther 2021;13:99.

41. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.

42. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's disease assessment scale that broaden its scope. The Alzheimer's disease cooperative study. Alzheimer Dis Assoc Disord 1997;11:S13-21.

43. Crane PK, Carle A, Gibbons LE, et al. Development and assessment of a composite score for memory in the Alzheimer's disease neuroimaging initiative (ADNI). Brain Imaging Behav 2012;6:502–516.

44. Preische O, Schultz SA, Apel A, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat Med 2019;25:277–283.

45. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B Methodol 1995;57:289–300.

46. Cummings J, Lee G, Ritter A, et al. Alzheimer's disease drug development pipeline: 2020. Alzheimers Dement 2020;6:e12050.

47. van der Kant R, Goldstein LSB, Ossenkoppele R. Amyloid-beta-independent regulators of tau pathology in Alzheimer disease. Nat Rev Neurosci 2020;21:21–35.

48. Chatterjee N, Shi J, Garcia-Closas M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. Nat Rev Genet 2016;17:392–406.

49. Warren M. The approach to predictive medicine that is taking genomics research by storm. Nature 2018;562:181–183.

50. Porter T, Burnham SC, Milicic L, et al. Utility of an Alzheimer's disease risk-weighted polygenic risk score for predicting rates of cognitive decline in preclinical Alzheimer's disease: a prospective longitudinal study. J Alzheimers Dis 2018;66:1193–1211.

51. Carrasquillo MM, Crook JE, Pedraza O, et al. Late-onset Alzheimer's risk variants in memory decline, incident mild cognitive impairment, and Alzheimer's disease. Neurobiol Aging 2015;36:60–67.

52. Harrison TM, La Joie R, Maass A, et al. Longitudinal tau accumulation and atrophy in aging and alzheimer disease. Ann Neurol 2019; 85:229–240.

53. Salvado G, Grothe MJ, Groot C, et al. Differential associations of APOE-epsilon2 and APOE-epsilon4 alleles with PET-measured amyloid-beta and tau deposition in older individuals without dementia. Eur J Nucl Med Mol Imaging 2021;48:2212–2224.

54. Ghisays V, Goradia DD, Protas H, et al. Brain imaging measurements of fibrillar amyloid-beta burden, paired helical filament tau burden, and atrophy in cognitively unimpaired persons with two, one, and no copies of the APOE epsilon4 allele. Alzheimers Dement 2020;16: 598–609.

55. Martin AR, Kanai M, Kamatani Y, et al. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet 2019; 51:584–591.

56. Andrews SJ, Fulton-Howard B, Goate A. Interpretation of risk loci from genome-wide association studies of Alzheimer's disease. Lancet Neurol 2020;19:326–335.

57. Franzmeier N, Ossenkoppele R, Brendel M, et al. The BIN1 rs744373 Alzheimer's disease risk SNP is associated with faster Abeta-associated tau accumulation and cognitive decline. Alzheimers Dement 2021;17:103–115.

58. Franzmeier N, Rubinski A, Neitzel J, et al. The BIN1 rs744373 SNP is associated with increased tau-PET levels and impaired memory. Nat Commun 2019;10:1766.

59. Deming Y, Dumitrescu L, Barnes LL, et al. Sex-specific genetic predictors of Alzheimer's disease biomarkers. Acta Neuropathol 2018; 136:857–872.

60. Cruchaga C, Kauwe JS, Harari O, et al. GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. Neuron 2013;78:256–268.

61. Neitzel J, Franzmeier N, Rubinski A, et al. KL-VS heterozygosity is associated with lower amyloid-dependent tau accumulation and memory impairment in Alzheimer's disease. Nat Commun 2021;12: 3825.