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β -Amyloid–Dependent and –Independent Genetic Pathways Regulating CSF Tau Biomarkers in
Alzheimer Disease

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Author(s):

Atul Kumar, PhD¹; Shorena Janelidze, PhD¹; Erik Stomrud, MD, PhD^{1,2}; Sebastian Palmqvist, MD, PhD^{1,2}; Oskar Hansson, MD, PhD^{1,2}; Niklas Mattsson-Carlsson, MD, PhD^{1,3,4} on behalf of for the Alzheimer's Disease Neuroimaging Initiative

Corresponding Author:

Atul Kumar, atul.0298@gmail.com

Affiliation Information for All Authors: 1. Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; 2. Memory Clinic, Skåne University Hospital, Malmö, Sweden; 3. Department of Neurology, Skåne University Hospital, Lund, Sweden; 4. Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden

Equal Author Contribution:

Oskar Hansson, MD, PhD and Niklas Mattsson-Carlsson are co-senior authors

Contributions:

Atul Kumar: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Shorena Janelidze: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Erik Stomrud: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Sebastian Palmqvist: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Oskar Hansson: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Niklas Mattsson-Carlgren: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

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Abstract

Background: Abnormal metabolism of amyloid- β ($A\beta$) and soluble P-tau, as well as neurodegeneration, are key components of Alzheimer's disease (AD), but it is unclear how these different processes are related to genetic risk factors for AD.

METHOD: In the Swedish BioFINDER study, we tested associations between a priori defined polygenic risk scores (PRSs) for AD (excluding Single Nucleotide Polymorphism [SNPs] within the apolipoprotein E [*APOE*] region in the main analysis) and biomarkers in cerebrospinal fluid (CSF) (Total tau [T-tau] and Phosphorylated tau181 [P-tau181], $A\beta$ 1-38, $A\beta$ 1-40, $A\beta$ 1-42 and $A\beta$ 1-42/1-40, neurofilament light [NfL]) in Cognitively Unimpaired (CU) individuals (n=751), and in Mild Cognitive Impairment (MCI) (n=212), and AD dementia (n=150) patients. Results were validated in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset with 777 individuals (AD=119, MCI=442, and CU=216).

Result: A PRS with SNPs significant at $P < 5e-03$ (~1742 variants) were associated with higher CSF P-tau181 (beta=0.13, $P=5.6e-05$) and T-tau (beta=0.12, $P=4.3e-04$). The associations between PRS and tau measures were partly attenuated but remained significant after adjusting for A β status. A β pathology mediated 37% of the effect of this PRS on tau levels. A β -dependent and independent subsets of the PRS were identified and characterized. There were also associations between PRSs and CSF A β biomarkers with nominal significance, but not when corrected for multiple comparisons. There were no associations between PRSs and CSF NfL.

Conclusion: Genetic pathways implicated in causing AD are related to altered levels of soluble tau through both A β -dependent and A β -independent mechanisms, which may have relevance for anti-tau drug development.

Keywords: Alzheimer's Disease, Polygenic Risk Score, Cerebrospinal Fluid, tau, Amyloid- β .

Introduction

Alzheimer's disease (AD), the most common neurodegenerative disease, is characterized by the accumulation of β -amyloid (A β) plaques, tau tangles [1], neurodegeneration, and cognitive loss [2, 3, 4]. Different pathophysiological processes can be monitored in AD using biomarkers in cerebrospinal fluid (CSF) and plasma [5, 6].

Several hereditary, behavioral, and environmental influences affect the risk for AD. A few cases have Mendelian inheritance trends, which often result in the early onset of symptoms through altered metabolism of A β [7], but for most patients, the genetic

predisposition is more complex [8]. The most common genetic risk factor is variants of the apolipoprotein E (*APOE*) gene [9], which is believed to mainly increase the risk for AD through modulating the accumulation of A β [10]. In addition, genome-wide association studies (GWAS) have identified additional SNPs with risk effects for AD dementia. Still, it remains unclear which of the different key pathophysiological processes in AD are mainly affected by the many SNPs with low or medium effect sizes for AD risk.

Multiple genetic risk variants, with a minor individual contribution to disease risk, can be combined in polygenic risk scores (PRSs). This has been used to forecast the probability of neurological diseases with complex traits such as schizophrenia and bipolar disorder [11]. Such scores combine genome-wide knowledge to compensate for the phenotypic heterogeneity found in specific traits by suggesting that several variants of small impact sizes have a cumulative, non-multiplicative effect.

This study aimed to test associations between genetic risk factors for AD (beyond *APOE*) and biomarkers reflecting abnormal metabolism of A β , soluble phosphorylated tau (P-tau), and neurodegeneration to understand different aspects of AD pathophysiology using CSF biomarkers as proxies for relevant brain changes. We used a priori defined PRSs based on the results of a recent major AD meta-analysis (consisting of 21,982 late-onset AD cases and 41,944 cognitively normal controls) [12] and tested them in a cohort of cognitively unimpaired (CU) individuals as well as patients with mild cognitive impairment (MCI) and AD dementia in the BioFINDER study. In addition, we validated our findings in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.

Method

Standard protocol approvals, registrations, and patient consents

The Regional Ethics Committee in Lund, Sweden, approved the BioFINDER study. All subjects gave written informed consent. The local ethical committees of all involved sites gave ethical approval in ADNI.

Study participants

The study included 751 CU older adults, 212 patients with MCI, and 149 AD dementia patients from the Swedish BioFINDER sample (clinical trial no. NCT01208675; www.biofinder.se), for whom age, education, gender, and biomarker data were available. Details on recruiting have previously been provided [13, 14], and the supplement contains additional information. Following research guidelines [15], the CU group consisted both of normal controls (N=569) and patients with subjective cognitive decline (SCD) (N=182).

Validation Sample

We validated parts of the findings in participants (CU, MCI, and AD) from the ADNI (using the phases ADNI-1, ADNI-GO, and ADNI-2; <http://adni.loni.usc.edu>). CSF T-tau, P-tau181, and A β 1-42 biomarker data was available for 986 ADNI participants (AD=186, MCI=510, and CU=290) of European ancestry (Supplement contains additional information). To prevent overfitting due to the non-independence of the GWAS discovery sample and the target sample, 209 ADNI participants who were part of the Kunkle et al. study [12] (used to generate the PRS) were omitted before the PRS estimation, resulting in a final sample of 777 individuals (AD=119, MCI=442, and CU=216).

Genotyping and preparation of genetic data

For genotyping, the Illumina platform GSA-MDA v2 was utilized. Quality control (QC) was performed at the subject and single nucleotide polymorphism (SNP) levels according to

established protocols [16]. Person-based quality control included consistency between chip-inferred and self-reported gender, call rates (1% cut-off), and intense heterozygosity. In addition, high-quality variants (autosomal, bi-allelic variants with Hardy–Weinberg Equilibrium (HWE) $P > 5e-08$, Minor Allele Frequency [MAF] $\geq 5\%$ and with a call rate of $> 99\%$) were used. Similar QC was applied for the ADNI subjects. The supplement provides more information on the imputation and QC for both genetic data.

Fluid Biomarkers

CSF handling followed a structured pre-analytical protocol [17]. CSF A β peptides (including A β 1-42, A β 1-40, and A β 1-38), total tau (T-tau), and tau phosphorylated at threonine 181 (P-tau181) were analyzed using Euroimmun immunoassays (EI) (EUROIMMUN AG, Lübeck, Germany), as previously described [18]. A pathological A β -status was defined as CSF A β 1-42/A β 1-40 > 0.091 [19]. CSF NfL concentration was determined using a sensitive sandwich ELISA method (NF-light ELISA kit; UmanDiagnostics AB, Ume, Sweden) as previously described [20, 21].

CSF samples' collection and handling in ADNI are described elsewhere [22]. In brief, CSF T-tau, P-tau181, and A β 1-42 in ADNI were measured using the Elecsys immunoassay at the Biomarker Research Laboratory, University of Pennsylvania, USA, according to the preliminary kit manufacturer's instructions and as described in previous studies [23].

Polygenic Score Calculation

Using the weighted effect for each SNP, the PRS was determined using PLINK2 [24]. SNPs were pruned using PLINK's clump function with an $r^2 < 0.1$ over 1000 kilobase pairs before PRS estimation. *APOE* is the most well-known risk factor for AD, with high levels of linkage disequilibrium in the area surrounding the locus. Therefore, when generating the PRS for

AD, SNPs falling within the *APOE* region (chr19:44400000-46500000; GRCh37/hg19 assembly) were omitted from the dataset. In addition, to test how *APOE* status might affect the significance of the identified PRSs, we also generated PRS models that included the *APOE* region variants. To define PRS for AD, we used publicly available summary statistics from published GWAS studies (not overlapping with the BioFINDER dataset) [12]. To determine acceptable p-value thresholds, we iterated over a range of values ($P < 0.05$ to $P < 5 \times 10^{-8}$) to generate PRS1-7 models (e.g., PRS1 includes all variants significant at $P < 0.05$; details given in eMethod).

Identification of the Tau specific PRS variants that are independent versus dependent of $A\beta$

We used a heuristic approach to generate PRS-components associated with tau biomarkers, independent and dependent on $A\beta$. For this, we first created “n” different PRSs (n=number of variants in full PRS) by removing one particular variant [“i”], leaving “n-1” variants. We next tested if the effect of these pruned PRSs on tau biomarkers was mediated via $A\beta$ status. The pruned PRSs were arranged in the ascending order of p-value of association between the independent variable (PRS) and $A\beta$ (the top PRS was the most strongly associated with $A\beta$ in the absence of i^{th} variant). Using this ranked list of variants, we recreated “n” different PRSs, with an ascending number of variants (e.g., the first PRS only included the top variant, the second PRS had the top two variants, the third PRS the top three variants, and so on), and again used mediation analysis to measure how much of the effect of each of the new increasingly complex PRSs on tau biomarkers that were mediated via $A\beta$ status. This approach identified novel PRSs having strong associations with tau biomarkers that were $A\beta$ -

independent. We followed a similar approach to identify novel PRSs that had effects on tau biomarkers dependently on $A\beta$, by repeating the procedure but arranging the variants in descending order of p-value of association between PRS and $A\beta$.

Statistical Analyses

We used linear regression models to investigate the relationship of PRSs with biomarker levels. The biomarkers were rank-based inverse normal transformed and used as dependent variables in linear regression models, adjusted for the covariates age, gender, education, *APOE* $\epsilon 4$ and $\epsilon 2$ counts (0, 1, 2) [not for PRS including the *APOE* region variants], MMSE and the top 10 principal components from the principal component analysis on the entire set of genotype data. In addition, logistic regression models were used for the PRS on dichotomized biomarkers (including the same covariates).

We used bootstrapping techniques to assess the indirect effect in mediation analysis (n=1000 bootstrap samples).

Each set of association analyses was corrected for a family-wise error rate using Bonferroni correction. Associations below a Bonferroni corrected p-value of 0.05 were considered significant. All the statistical analysis was conducted in R programming (version 4.0.2).

Data availability

Anonymized BioFINDER data will be shared by request from a qualified academic investigator for the sole purpose of replicating procedures and results presented in the article if data transfer agrees with EU legislation on the general data protection regulation and decisions by the Swedish Ethical Review Authority and Region Skåne, which should be regulated in a material transfer agreement.

Genome-wide summary statistics used to generate Alzheimer's PRS can be downloaded from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)—an NIA/NIH-sanctioned qualified-access data repository, under accession NG00075. For ADNI data: Data is stored (publicly available) at the Ioni database (<https://ida.ioni.usc.edu/>).

Results

The demographic information of the study population is shown in Table 1. In addition, the available sample size (based on the diagnostic group) for different biomarkers is given in eTable 1.

Association between PRS and tau measures

We first tested associations between PRS (excluding *APOE* region variants [non-*APOE*-PRS]) and CSF T-tau and P-tau181 in the BioFINDER study population. PRS2 (including 1742 SNPs significant at $P < 5e-03$ in the original GWAS for AD dementia versus controls [12]) showed the strongest association with both CSF T-tau ($P = 4.3e-04$) and CSF P-tau181 ($P = 5.6e-05$). It was followed by PRS4 (including 63 SNPs significant at $P < 5e-05$), showing significant associations with CSF T-tau ($P = 7.8e-03$) and CSF P-tau181 ($P = 1.3e-02$). In addition, PRS3 (including 279 SNPs significant at $P < 5e-04$) and PRS7 (including 12 SNPs significant at $P < 5e-08$) were significantly associated with T-tau ($P = 9.9e-03$ and $1.4e-02$ respectively) whereas PRS5 (including 31 SNPs significant at $P < 5e-06$), PRS6 (including 19

SNPs significant at $P < 5e-07$) and PRS7 were significantly associated with CSF P-tau181 ($P = 3.1e-02$, $5e-02$ and $5.1e-03$ respectively) (Figure 1; eTables 2-3).

We also tested the association between CSF T-tau and P-tau181 and PRS, including the APOE region variants (*APOE*-PRS). All the PRSs showed significant association with T-tau and P-tau181 with a p -value $< 1.2e-05$ (eTables 2-3).

Association between PRS and A β measures

Next, we tested associations between PRS and A β biomarker measurements (A β 1-38, A β 1-40, A β 1-42, A β 42/A β 40 ratio) in BioFINDER. Due to its bimodal distribution, the A β 42/A β 40 ratio was used as a dichotomous rather than a continuous variable [18]. Non-*APOE* PRS2 and PRS4 had nominally significant associations with A β 42/A β 40, but no associations were significant after Bonferroni correction (Figure 2; eTables 4-7).

All the *APOE*-PRSs showed significant association with A β 1-42 and A β 42/A β 40 ratio ($P < 6.2e-09$ and $P < 1.2e-05$ respectively). However, there was no significant association between the *APOE*-PRSs and A β 1-38 and A β 1-40 (eTables 4-7).

Associations between PRS and NfL

There were no significant associations between the tested non-*APOE*-PRSs and CSF NfL levels. However, we found all the *APOE*-PRSs showing significant association with CSF NfL ($P < 2.8e-02$) (eTable 8).

Association between PRS and tau measures adjusted for A β status

To test if the PRS associations with tau measures were dependent on A β or not we reperformed the analysis for associations with tau measures for the significant non-*APOE*-PRSs while adjusting for the CSF A β 42/A β 40 ratios in BioFINDER. PRS2 was still

significantly associated with CSF T-tau ($P=1.4e-02$) and P-tau181 ($P=7.3e-03$) (Figure 3; eTables 9-10), but the strength and significance level of the association was attenuated after adjusting for A β status. We, therefore, conducted a mediation analysis to determine the degree to which A β mediated the impact of PRS2 (being the most significant non-*APOE*-PRS predicting CSF P-tau181) on CSF P-tau181 levels, a well-studied biomarker for altered metabolism of soluble tau in AD [25]. As a result, the association between PRS2 and levels of CSF P-tau181 was mediated in part (37%) by A β positivity (Figure 4; eTable 11). We also found that the association between PRS4 and CSF P-tau181 was 40% mediated by A β positivity (eTable 11).

Stratified analysis based on clinical status

We performed subgroup analyses to test the association between PRS and CSF biomarker levels in the CU, MCI, and AD groups. In CU, the non-*APOE*-PRS2 had significant associations with CSF T-tau ($P=2e-02$; eTable 12) and P-tau181 ($P=6.5e-03$; eTable 13). None of the non-*APOE*-PRSs in any group had a significant association with CSF A β biomarkers or NfL (eTables 14-18).

The *APOE*-PRS2 to PRS7 in the CU and MCI groups had significant associations with CSF T-tau ($P<1.8e-06$ and $P<2e-02$ respectively; eTable12), P-tau181 ($P<4.2e-06$ and $P<4.1e-02$ respectively; eTable13), A β 1-42 ($P<8.4e-05$ and $P<1.2e-02$ respectively; eTable14) and A β 42/A β 40 ratio ($P<2e-06$ and $P<7.6e-04$ respectively; eTable15). *APOE*-PRS1 was associated with CSF A β 1-42 in CU ($P=3e-02$). We did not find any significant association between the *APOE*-PRSs and CSF A β 1-38, A β 1-40 and NfL (eTables 16-18).

Stratified analysis based on *APOE*- ϵ 4 status

We performed another stratified analysis based on *APOE*- ϵ 4 status (negative=0 ϵ 4 alleles; positive=1-2 ϵ 4 alleles). In the *APOE*- ϵ 4 positive group, PRSs2-7 had significant associations with CSF T-tau ($P < 1.2 \times 10^{-3}$ [non-*APOE*-PRS] and $P < 1.4 \times 10^{-3}$ [*APOE*-PRS]; eTable 19) and P-tau181 ($P < 1 \times 10^{-2}$ [non-*APOE*-PRS] and $P < 3.6 \times 10^{-5}$ [*APOE*-PRS]; eTable 20). *APOE*-PRS1 was significantly associated with CSF P-tau181 ($P = 4.7 \times 10^{-3}$) in the *APOE*- ϵ 4 positive group. In the *APOE*- ϵ 4 negative group, only PRS2 had significant associations with CSF T-tau ($P = 3.1 \times 10^{-3}$ [non-*APOE*-PRS] and $P = 4.2 \times 10^{-3}$ [*APOE*-PRS]; eTable 19) and P-tau181 ($P = 4 \times 10^{-4}$ [non-*APOE*-PRS] and $P < 1.4 \times 10^{-3}$ [*APOE*-PRS]; eTable 20).

In the *APOE*- ϵ 4 positive group, *APOE*-PRS2 to PRS7 were significantly associated with CSF A β 1-42 ($p < 1.5 \times 10^{-3}$; eTable 21) and A β 42/A β 40 ratio ($p < 2.9 \times 10^{-3}$; eTable 22). PRS1 showed significant association with CSF A β 1-42 ($P = 1.2 \times 10^{-2}$ [non-*APOE*-PRS] and $P = 9.9 \times 10^{-5}$ [*APOE*-PRS]; eTable 21). Non-*APOE*-PRS4 to PRS6 were found to be significantly associated with A β 42/A β 40 ratio ($p < 3.8 \times 10^{-2}$; eTable 22).

In the *APOE*- ϵ 4 negative group, non-*APOE*-PRS2 was found to be significantly associated with A β 42/A β 40 ratio ($p = 3.1 \times 10^{-2}$; eTable 22). However, there was no significant association between any PRSs and CSF A β 1-38, A β 1-40 and NfL in this stratified analysis (eTables 23-25).

PRS-variants specific to tau and independent of A β

The above findings indicated that A β pathology partially regulated the impact of PRS2 on CSF P-tau181. We hypothesized that this non-*APOE*-PRS might be heterogeneous, with certain genetic components exerting their influence by the aggregation of A β pathology and others acting independently of A β pathology on tau metabolism. We investigated non-*APOE*-PRS2 (consisting of 1742 variants) using a heuristic technique (see method section). We found 853 variants whose absence from the PRS strengthened the association between the

PRS and A β compared to the full PRS2 (step 1). We also discovered 890 variants that, when removed from the PRSs, weakened the association between the PRS and A β compared to the full PRS2 (eTable 26). Arranging these PRSs in the ascending order of p-value of association between PRS and A β we recreated different PRSs, each with an ascending number of variants (step 2). We identified 79 other PRS models (with an increasing number of components) for which there was no significant mediation by A β (on CSF P-tau181). However, these PRSs still predicted CSF P-tau181 significantly (both when adjusting and when not adjusting for A β). Among these 79 PRS models, a model containing 1683 variants (PRS2-Incl-1683) was identified as an optimal A β -independent subset as it did not show any difference in the effect size on CSF P-tau181 when adjusted for A β ($\beta=0.08$, $P=2.3e-03$) and when not adjusted ($\beta=0.08$, $P=7.5e-03$) (eTable 27).

Finally, to identify the subset of the PRS that was likely acting on CSF P-tau181 through A β , we constructed a PRS that contained variants that did not overlap with the A β -independent PRSs. This PRS model (PRS2-R-Incl-19) included the 19 variants that were not part of any A β -independent-PRS (eTable 28). We call this PRS model the “Exclusive A β dependent PRS model.” This model had a very similar effect on A β (the mediator) ($\beta=0.14$, $P=6.6e-21$) and on CSF P-tau181 (when not adjusted for A β) ($\beta=0.15$, $P=7.3e-07$). When corrected for A β , the model’s effect on CSF P-tau181 was markedly reduced and non-significant ($\beta=0.02$, $P=5.7e-01$), supporting that the components included affected CSF P-tau181 through the accumulation of A β .

Further, we tested a model with both “PRS2-Incl-1683” and “PRS2-R Incl-19” as predictors of CSF P-tau181, along with the previously used covariates. Both these PRSs were found to be significantly and independently associated with CSF P-tau181 when not adjusting for A β status (PRS2-Incl-1683: $\beta=0.08$, $P=4.9e-03$; PRS2-R-Incl-19: $\beta=0.15$, $P=5e-07$).

After adjusting the analysis for A β status, PRS2-R-Incl-19 (as expected) lost the association with CSF P-tau181 ($\beta=0.02$, $P=5.2e-01$), whereas the association between PRS2-Incl-1683 and CSF P-tau181 was unchanged ($\beta=0.08$, $P=2.2e-03$) (eTable 29).

Validation in ADNI

We replicated our findings in an independent data set from ADNI, using 777 CU, MCI, and AD samples of European ancestry. PRS5 (including 29 SNPs significant at $P<5e-06$) showed the strongest association with both CSF T-tau ($P=4.7e-03$) and CSF P-tau181 ($P=1.9e-03$) after applying the Bonferroni correction for multiple comparisons. It was followed by PRS4 (including 80 SNPs significant at $P<5e-05$), showing significant associations with CSF T-tau ($P=3.7e-02$) and CSF P-tau181 ($P=3.8e-02$) (Figure 5; eTable 30-31). PRS7 (including ten SNPs significant at $P<5e-08$) was found to be significantly associated with CSF A β 1-42 ($P=3.6e-02$) (eFigure 1; eTable 32). PRS2 (including 2185 SNPs significant at $P<5e-03$), which was associated with the BioFINDER tau measures, did not show significant associations with ADNI tau measures (CSF T-tau [$P=9e-01$], CSF P-tau181 [$P=9.2e-01$]) (eTable 30-31).

We also tested for PRS associations with tau measures while adjusting for CSF A β 1-42 to see if the association for significant PRSs (PRS4 and PRS5) were independent of A β . We observed a nominal increase in the association p-value for PRS4 and PRS5 with CSF T-tau ($P=4.5e-02$ and $6.7e-03$ respectively) and P-tau181 ($P=4.6e-02$ and $2.8e-03$ respectively). Still, the effect size remained unchanged in both the A β adjusted and unadjusted analysis (eFigure 2; eTable 33-34), indicating that PRS4 and PRS5 for ADNI participants were tau-specific and independent of A β .

In addition, we also conducted a mediation analysis to determine the extent of A β mediation on PRS4 predicting CSF P-tau181 levels in ADNI. Our result indicated that the

association between PRS4 and levels of CSF P-tau181 in ADNI was not mediated by A β positivity (eFigure 3; eTable 35). This analysis further confirmed that the PRS4 for ADNI participants was tau specific and independent of A β .

Discussion

We investigated whether a priori defined PRSs for AD (characterized by contrasting AD dementia versus controls) were associated with different levels of AD-related fluid biomarkers in a cohort with participants ranging from CU to MCI and AD patients. Our main findings were that PRSs (beyond *APOE* region variant) for AD were associated with higher levels of CSF tau biomarkers (with most substantial effects for comparatively inclusive PRSs) rather than biomarkers of A β and neurodegeneration. The same was true within CU and MCI groups when stratified by clinical status. Taken together, these findings suggest that AD-associated PRS models are related to pathophysiological changes of AD, including altered tau metabolism such as increased neuronal production and secretion of tau.

The PRS analyses revealed a significant relationship between an overall greater load of AD-associated genetic risk factors beyond *APOE*, measured by the PRS-metric, and increased CSF T-tau and P-tau181. These results indicate that the genetic profile contained within the PRSs modulate AD pathogenesis in terms of tau metabolism. A recent finding [26, 27] showed that soluble P-tau (plasma or CSF) is very closely related to A β pathology and that soluble P-tau mediates the effects of A β on tau tangles. Therefore, increased production, phosphorylation, or secretion of tau (caused by A β) might be essential for the development of tau tangles and, later on neurodegeneration. Our results show a strong association of AD-related PRS with increased P-tau. This genetic evidence suggests that the increased extracellular levels of tau may be an important drug target in AD.

We also observed that the association between PRS and tau markers (CSF T-tau and P-tau181) remained when adjusting for A β 42/A β 40. This suggests that the genetic risk factors in the PRS affect tau metabolism through mechanisms that are partly independent of A β pathology. We even isolated a subset of the PRS, which appeared to be utterly independent of A β (PRS2-Incl-1683). These findings may suggest differential underlying biological mechanisms that could be targeted to affect and prevent pathological metabolism of A β and tau, respectively. Furthermore, since pathological changes in AD start 15-20 years before clinical presentation [28] and clinical trials are increasingly focused on early, even preclinical, disease stages [29], such mechanisms may be relevant to target also very early, in individuals who only have mild or no cognitive impairment.

Our results on PRS and AD biomarkers extend the knowledge in a field where previous studies have presented somewhat mixed results. Some studies have, like us, found associations between PRSs (or polygenic hazard scores, PHS) and AD biomarkers. In recent analyses in the ADNI cohort, PHSs for AD were associated with CSF T-tau and P-tau181 [30] and plasma P-tau181 [31], and these associations were independent of *APOE*. One of these studies [30] also reported a nominal association level between PHS and CSF A β . Another study with CU and MCI individuals found that PHS was associated with CSF A β and CSF T-tau [32]. These results are comparable with and support our results for associations between PRS and CSF biomarkers. A PRS study on MCI patients from four European cohorts also reported a similar finding to ours, using CSF A β , T-tau and P-Tau181 [33]. Associations between PRS and CSF T-tau and P-tau181 were reported in a study with only AD patients, but the same study could not establish an association with A β (for a PRS without *APOE*) [34]. A study using the European Medical Information Framework Alzheimer's Disease Multimodal Biomarker Discovery (EMIF-AD MBD) data reported a significant PRS association with CSF A β 1-42 but not with CSF T-Tau and P-Tau levels [35].

A study based on a pre-dementia (MCI) sample of participants showed a significant association with CSF A β 1-42 and minimal associations with CSF T-tau and P-tau, which is in line with the existing evidence that T-tau and P-tau are later markers of AD compared to A β measures [36]. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging showed no correlation between PRS and either of CSF T-Tau, P-Tau, and A β levels in a smaller (570 CU and 73 AD dementia patients) sample [37], possibly due to fewer individuals with AD pathology in the sample. Some of the differences between studies may reflect different statistical power to detect effects.

In some cases, this could be driven by overly homogenous populations with a restricted range of biomarker levels. Differences in the disease stage, and sometimes even differences in SNPs included in the PRSs, are other potential explanations for the different results in different cohorts. But in summary, well-powered studies that take in the full range of AD from preclinical to MCI and dementia stages appear to demonstrate that AD-related PRSs are associated with biomarker changes reflecting both abnormal tau and A β metabolism. Some biomarkers, however, do not appear to be strongly regulated by SNPs (beyond the *APOE* region), which is evident from the comparative result of association of the PRS models generated by including and excluding *APOE* region variants. But the same biomarkers showed a stronger association with the PRS models (in full as well as stratified analysis by clinical status) generated using *APOE* region variants.

The exact relationship between A β and tau pathologies in AD is still unclear. Our analyses identified partly A β independent genetic pathways to tau pathology. However, other studies have suggested that tau mediates A β toxicity, e.g., by interacting with Fyn kinase via its amino-terminal projection domain [38]. This may open for the hypothetical possibility that pathological tau could mediate a relationship between risk genes and A β pathology. However, since we did not find any significant associations between non-*APOE*-PRSs and

CSF A β (when correcting for multiple comparisons), we could not test if tau mediated effects of genes on A β . Larger studies or studies focusing on specific relevant genes may be needed for this.

We found the most robust results for non-*APOE*-PRS2 in BioFINDER and conducted detailed analyses of gene enrichment in PRS2 and the two restricted PRSs (A β -independent-PRS and A β -dependent-PRS) (detailed results and discussion in the supplement; eTables 36-44; eFigures 4-7. The gene ontology (biological process) term “Amyloid-Beta Clearance” was enriched in the overall PRS2, but not in the restricted A β -independent-PRS, further confirming that this restricted PRS might be tau specific and A β -independent.

For the A β -dependent-PRS set, two terms (“Amyloid Plaque” and “Amyloidosis”) were explicitly enriched. Enrichment of these two terms specifically for this PRS supports our finding that the genes involved contribute towards abnormal A β formation. These results confirm and strengthen the use of this PRS to study A β -dependent genetic effects (beyond the *APOE*) on tau metabolism.

Though we could not establish any association between non-*APOE*-PRS and NfL, a recent study found an association between non-*APOE*-PRS and NfL in individuals without A β 1-42 pathology [39]. Our analysis was not stratified by measures of A β pathology. Future studies may continue to elucidate associations between PRS and NfL.

Using the independent ADNI cohort, we could replicate the associations for PRS4 with CSF T-tau and P-tau181, and for PRS5 with CSF P-tau181. Importantly, these associations in ADNI were independent of A β status, supporting the findings in BioFINDER that the genetic pathways regulating CSF tau metabolism are largely independent of A β . However, we could not validate the PRS2 association with tau measures. There are several possible reasons why PRS2 was not validated in ADNI. First, variants with identical effect sizes may have different allele frequencies across populations, which would result in

heterogeneous allele substitution effects. Second, PRS2 has a large genetic diversity (constructed using 1742 variants in BioFINDER and 2185 variants in ADNI), introducing variability. Third, using different gene-centring genotyping platforms for the datasets might cause this discrepancy. Another possibility is the varying and relatively small sample size of unique individuals in both the cohorts could have influenced the total number of variants with the good quality available after the imputation.

Our study is not without limitations. Although the BioFINDER cohort has robust phenotyping for CSF tau and A β biomarkers, the sample size was comparatively small. This could be one of the reasons that we were unable to detect associations between non-APOE-PRS2 and CSF T-tau and P-tau181 in the AD and MCI groups (smaller sample sizes than the CU group). Due to the small sample size, we just included gene variants with MAF > 0.05. A larger sample size may account for rarer SNPs and make findings stratified for APOE or clinical status more interpretable. The study also has strengths. The BioFINDER cohort reflects a population of consecutively recruited patients and healthy controls that are less selected than trial-like populations (e.g. ADNI), which supports the generalizability of the findings. In addition, the use of a priori defined PRSs partly overcome the issue of multiple testing by integrating many SNPs into a small number of metrics of different complexity.

In conclusion, our results extend the knowledge about the relationship between genetic risk for AD beyond *APOE* and AD-related biomarkers. Our stratified analysis based on the *APOE* genotype showed stronger associations in the *APOE*- ϵ 4 positive group for all the PRS with the CSF biomarkers (CSF T-tau, P-tau181, A β 1-42 and A β 42/A β 40 ratio). This suggests that our genetic findings are independent of APOE- ϵ 4. Our findings suggest that integrating PRS models with biomarker data holds promise for understanding genetic pathways linked to disease development. Future directions also include testing interactions between SNPs, biomarker levels, and disease stage to understand how SNPs may affect

disease processes at different time points during the disease development. Genetic studies may also be done using longitudinal biomarker data. Finally, although our results mainly point to genetic effects at the group level, future studies may test if specific SNPs can be combined with biomarker data to improve subject-level management of patients in clinical practice and clinical trial design.

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WNL-2022-200655_coinvestigator_appendix -- <http://links.lww.com/WNL/C24>

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Authors' contributions

AK, NMC, and OH developed the hypothesis and study design. SJ, SP, and ES collected the biomarker data, patient information, and blood samples for genotyping. SJ analyzed the biomarker data. AK and NMC performed the statistical analysis and wrote the first draft of the manuscript. NMC and OH obtained funding. AK, NMC, and OH had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to reviewing the manuscript and approved the final version of the manuscript to be published.

Table 1: Baseline demographics of the participants in BioFinder study

	CU(Aβ-)	CU (Aβ+) 	MCI (Aβ-)	MCI (Aβ+) 	AD (Aβ-)	AD (Aβ+) 	Total	P-Value
N	545	206	64	148	17	132	1112	
Female (%)	330 (60.5)	122 (59.2)	21(32.8)	70 (47.3)	9 (53)	83 (62.8)	635 (57.1)	0.03
Age (years)	71.1 (6.1)	73.1 (4.8)	68.4 (6)	73 (5.2)	78 (5.9)	72.9 (8.53)	71.9 (6.3)	1.19e-05
Education (years)	12.3 (3.4)	12.2 (3.7)	10.5 (3.3)	11.4 (3.5)	9.4 (3.8)	10.4 (3.3)	11.8 (3.6)	0.02
APOE ϵ4 (0/1/2)	409/131/5	81/98/27	45/16/3	44/78/26	8/7/2	40/69/23	627/399/86	1.33e-09
APOE ϵ2 (0/1/2)	456/85/4	189/16/1	54/9/1	135/13/0	16/1/0	127/5/0	977/129/6	0.002
MMSE (Median) (IQR)	29 (30-28)	29 (30-28)	28 (29-26)	26 (28-25)	21 (24-19)	21 (24-19)	29 (30-27)	<2e-16
CSF T-tau	286.2 (86.4)	472.9 (190)	280.4 (86.1)	558 (212.4)	379.2 (123.2)	653.8 (208)	401.7 (202.9)	4.1e-04
CSF p-tau181	36.8	71.3	37.3	86.3	58.2	122.2	65	6.8e-04

	(12.5)	(36.4)	(15.1)	(35.4)	(30.2)	(45.4)	(45.8)	
CSF Aβ1-38	1893.5 (468.7)	2047 (490)	1748.1 (463.4)	1926.7 (460.3)	1300.6 (434.4)	1849.3 (491.4)	1903.7 (484.3)	8.6e-03
CSF Aβ1-40	5768.3 (1962.3)	6469.6 (2218.4)	5460 (2110.1)	5932.1 (2079.3)	3721.2 (1560.8)	5678.1 (2076.1)	5860.3 (2078)	4.6e-02
CSF Aβ1-42	740.3 (242.1)	401.8 (159.8)	690.3 (256.8)	331.3 (120.3)	409.9 (167.8)	304.1 (119.4)	563.5 (278.9)	6.6e-05
CSF NFL	895 (484)	1109 (696.8)	1203.7 (835.3)	1652.7 (1840.5)	1682.1 (796.2)	1801.8 (1693.2)	1180.7 (934.8)	4.9e-01

Age, education, and CSF Biomarker data are mean (standard deviation). CU=Cognitively unimpaired; MCI=mild cognitive impairment; IQR=Inter Quartile Range. The group mean difference was calculated based on ANOVA.

Figure 1. Associations between Polygenic Risk Scores (PRS) and tau measures. The x-axis represents the 7 different PRS models at different p-value thresholds based on the GWAS summary statistics (PRS1 ≤ 0.05 , PRS2 $\leq 5e-3$, PRS3 $\leq 5e-4$, PRS4 $\leq 5e-5$, PRS5 $\leq 5e-6$, PRS6 $\leq 5e-7$, PRS7 $\leq 5e-8$). The models were adjusted for age, gender, education, baseline MMSE, *APOE* $\epsilon 2$ and $\epsilon 4$ count, and the top 10 principal components (PC) from the principal component analysis (PCA) on the entire set of genotype data. The y-axis shows the negative log of the p-value for the significance of associations between PRS models with different tau measures. The values on the top of each bar show the association's effect size (beta-coefficient). The horizontal dotted line shows the p-value threshold of 0.05. *These PRSs were significant after Bonferroni-correction at p-value < 0.05 .

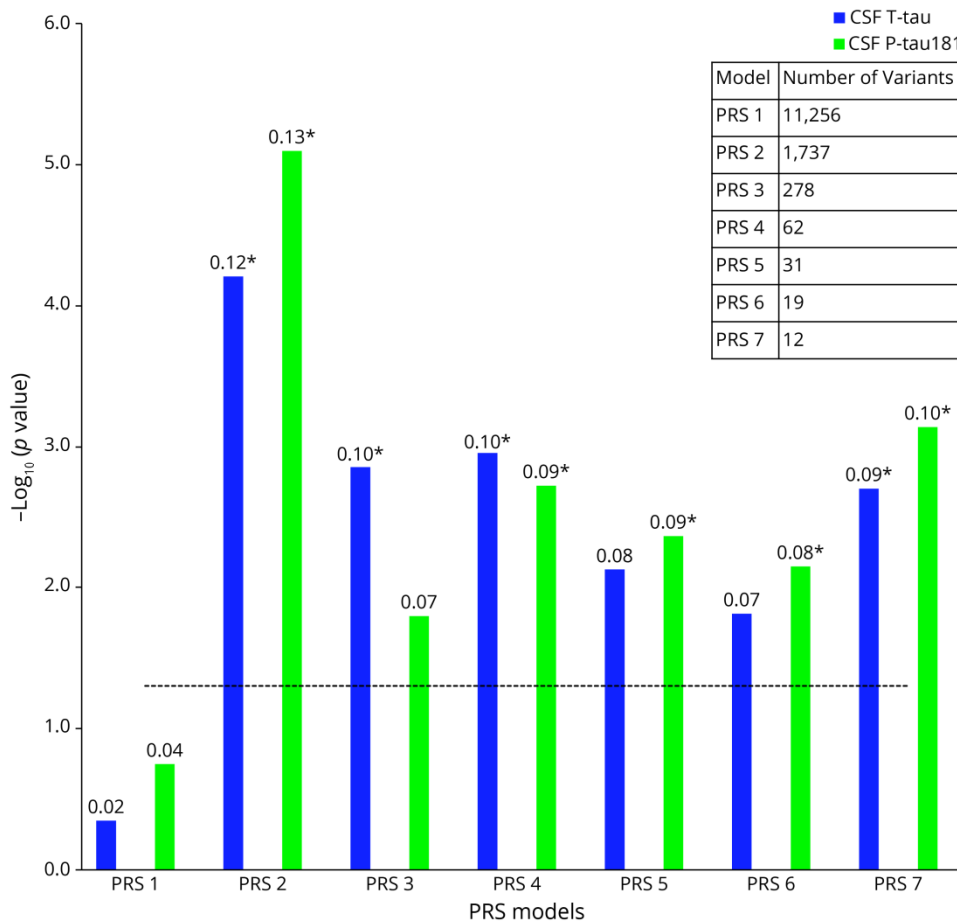


Figure 2: Associations between Polygenic Risk Scores (PRS) and β -amyloid measures.

The x-axis represents the 7 different PRS models at different p-value thresholds based on the GWAS summary statistics (PRS1 \leq 0.05, PRS2 \leq 5e-3, PRS3 \leq 5e-4, PRS4 \leq 5e-5, PRS5 \leq 5e-6, PRS6 \leq 5e-7, PRS7 \leq 5e-8). The models were adjusted for age, gender, education, baseline MMSE (not for the intercept), *APOE* ϵ 2 and ϵ 4 count, and the top 10 principal components (PC) from the principal component analysis (PCA) on the entire set of genotype data. The y-axis shows the negative log of the p-value showing the significance of association for PRS models with different β -amyloid measures. The values on the top of each bar show the association's effect size (beta-coefficient). For negative effect size, the bar is inverted. CSF A β 42/A β 40 is used as a dichotomous variable here (with 1= A β positive). The horizontal dotted line shows the p-value threshold of 0.05.

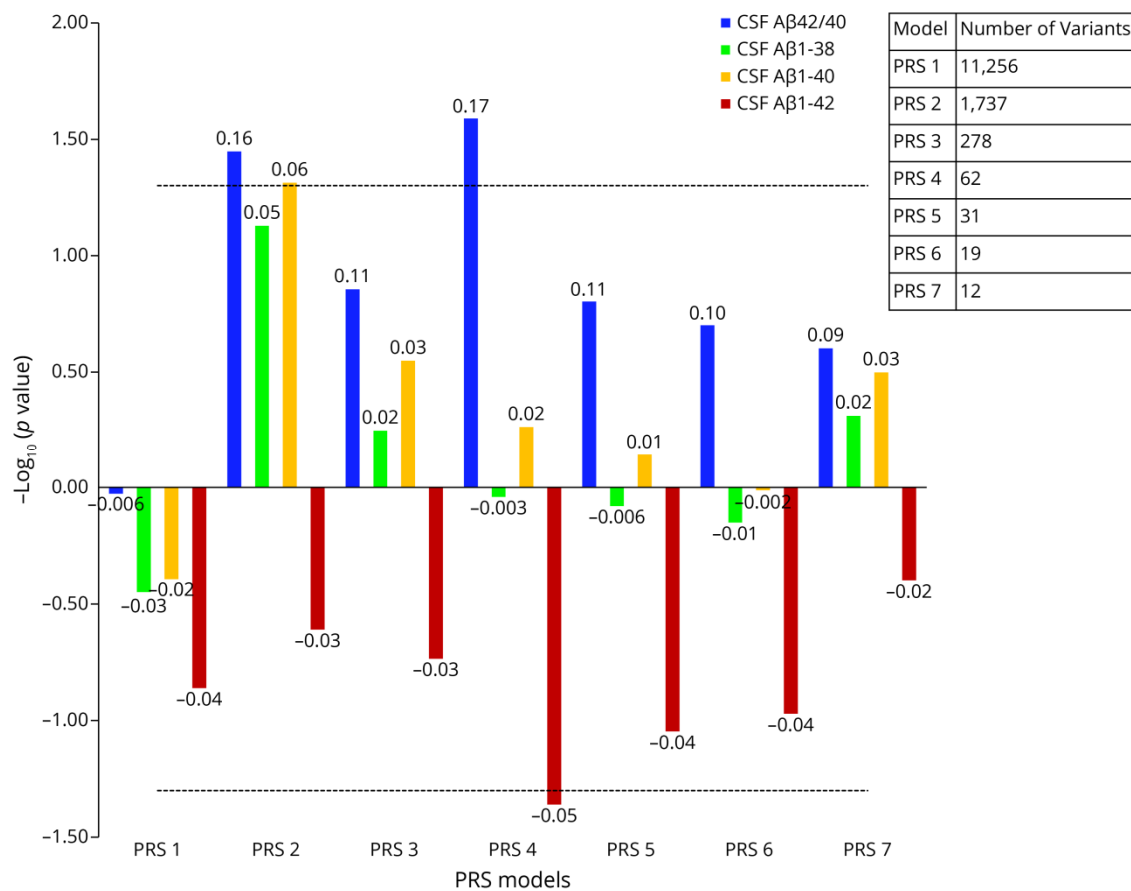


Figure 3. Associations between significant Polygenic Risk Scores (PRS) and tau measures adjusted for CSF A β 42/A β 40 ratios. The x-axis shows the different PRS models (this analysis only included models that were significantly associated with tau measures when not adjusted for CSF A β 42/A β 40 ratios, see Figure 1). The models were adjusted for age, gender, education, baseline MMSE (not for the intercept), *APOE* ϵ 2 and ϵ 4 count, and the top 10 principal components (PC) from the principal component analysis (PCA) on the entire set of genotype data, as well as CSF A β 42/A β 40 ratios). The y-axis shows the negative log of the p-value for the significance of associations between PRS models with different tau measures. The values on the top of each bar show the association's effect size (beta-coefficient). The horizontal dotted line shows the p-value threshold of 0.05. *These PRSs were significant after adjusted for CSF A β 42/A β 40 ratios and Bonferroni-correction at p-value < 0.05.

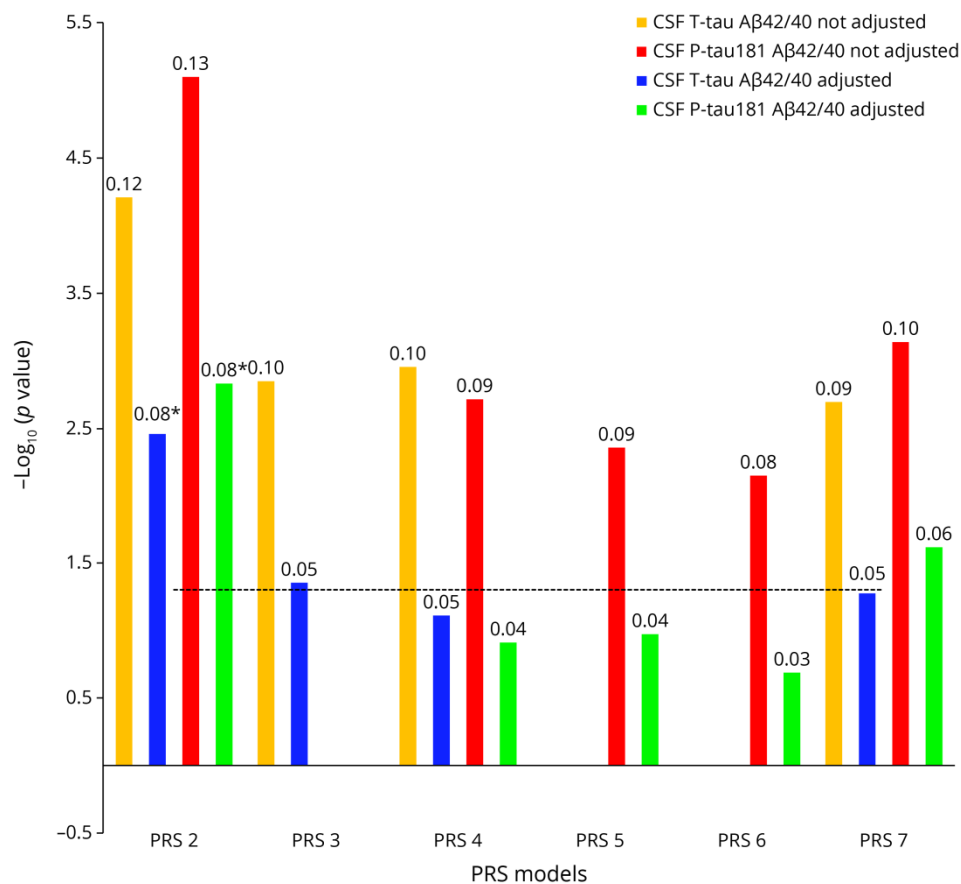


Figure 4: Mediation analysis between PRS, A β status and CSF P-tau181. Mediation analysis with PRS2 as a predictor of CSF P-tau181, mediated by A β status. The figure includes the following standardized regression coefficients: a, the effect of PRS on A β ; b, the effect of A β on CSF P-tau181 level; c, the direct association between PRS and CSF P-tau181 level; c', the association between PRS and CSF P-tau181 level when adjusting for A β ; and c-c', the mediated effect on CSF P-tau181 level (with % mediation).

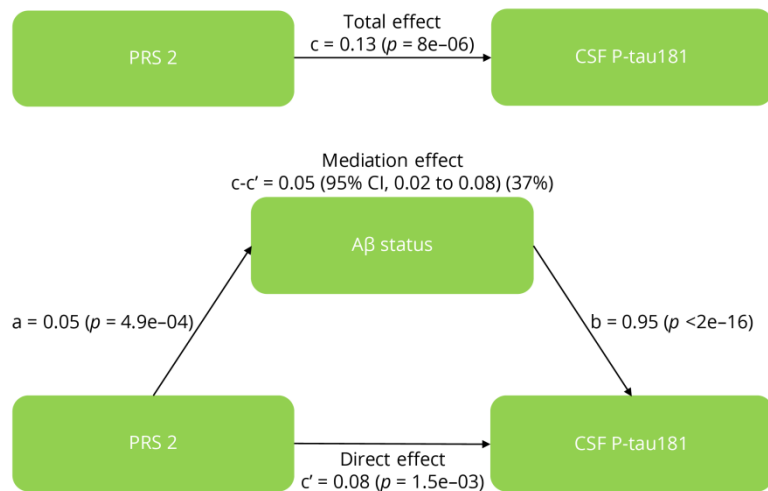
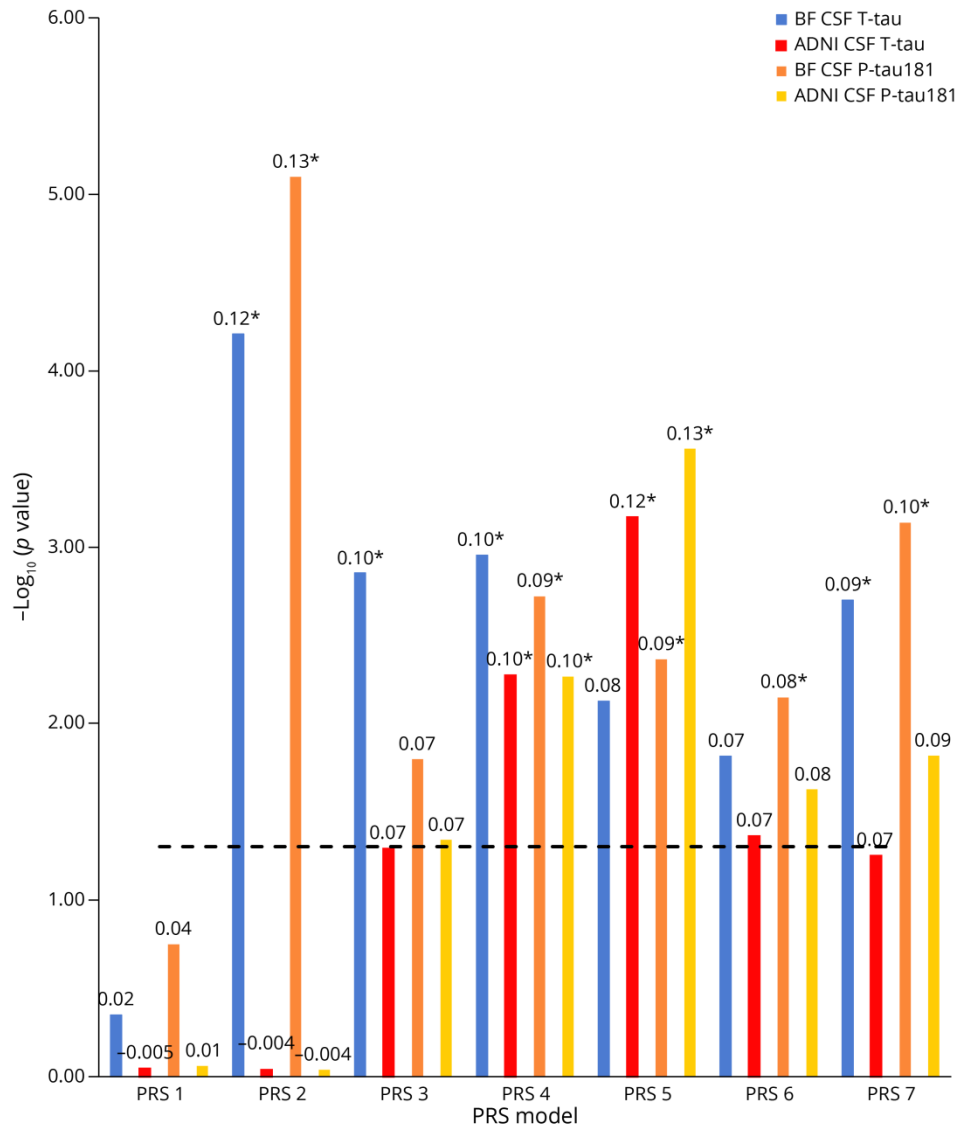


Figure 5. Comparative results for associations between Polygenic Risk Scores (PRS) and tau measures in BioFinder (BF) and ADNI. The x-axis represents the 7 different PRS models at different p-value thresholds based on the GWAS summary statistics (PRS1 \leq 0.05, PRS2 \leq 5e-3, PRS3 \leq 5e-4, PRS4 \leq 5e-5, PRS5 \leq 5e-6, PRS6 \leq 5e-7, PRS7 \leq 5e-8). The models were adjusted for age, gender, education, baseline MMSE, *APOE* ϵ 2 and ϵ 4 count, and the top 10 principal components (PC) from the principal component analysis (PCA) on the entire set genotype data. The y-axis shows the negative log of the p-value for the significance of associations between PRS models with different tau measures. The values on the top of each bar show the association's effect size (beta-coefficient). The horizontal dotted line shows the p-value threshold of 0.05. *These PRSs were significant after Bonferroni-correction at p-value < 0.05.



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