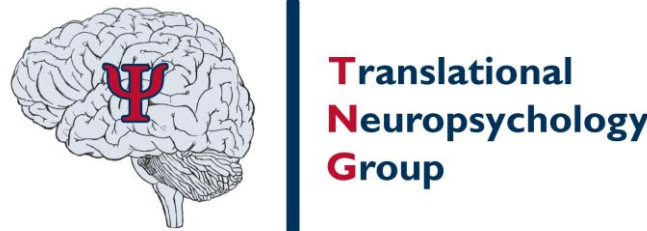




Effect of Polygenic Risk Scores for Alzheimer’s Disease on Longitudinal Cerebrospinal Fluid Biomarkers



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INTRODUCTION

Investigating polygenic risk scores (PRSs) may increase understanding of the concurrent effect of multiple genes on sporadic Alzheimer's disease (AD) and prediction of change in disease mechanisms over time. Research regarding associations between PRSs and AD-specific longitudinal cerebrospinal fluid (CSF) biomarkers is limited. Although some research exists, findings are inconsistent, and the effect of different PRSs have not been examined within the same cohort nor has their effect been assessed longitudinally following patient stratification by clinical diagnosis and Apolipoprotein E (APOE) status.

OBJECTIVE

To investigate the effect of PRSs for AD on CSF biomarkers, longitudinally, in those along the clinical continuum of sporadic AD.

METHODOLOGY

- Data from 171 individuals participating in the Alzheimer’s Disease Neuroimaging Initiative were examined, (mean age in years: 73.30 ± 7.58).
- CSF measures of amyloid beta (Aβ42) and phosphorylated tau (p-tau181) were examined over 24 months.
- Three sets of PRSs* were constructed using three thresholds:

❑ APOEonlyPRS

- Threshold 1: 51 single nucleotide polymorphisms (SNPs).
- Threshold 2: 96 SNPs.
- Threshold 3: 390 SNPs.

❑ PRSwithAPOE

- Threshold 1: 172 SNPs.
- Threshold 2: 1561 SNPs.
- Threshold 3: 455028 SNPs.

❑ PRSwithoutAPOE

- Threshold 1: 121 SNPs.
- Threshold 2: 1465 SNPs.
- Threshold 3: 454638 SNPs.

*SNPs within the entire APOE region were considered, rather than ε2 and ε4 only.

- Binomial hierarchical logistic regression and multiple hierarchical linear regression models were used to account for the effect of demographic and clinical confounding variables, as follows:

❑ Model 1: Age, sex, education, first degree family history of AD, MMSE, and x10 genetic principal components**

❑ Model 2: All variables used in Model 1, plus PRS

**the alternate CSF biomarker was also added.

Before constructing PRSs:

- Select discovery/training sample that has AD genome-wide association study (GWAS) summary statistics.
- Select independent/target sample on which GWAS has also been conducted.
- Note common variants between both samples.
- Limit SNPs to those that are closely associated by using the optimal p threshold.

Constructing PRSs:

- Take the sum of all risk alleles in the independent GWAS.
- These alleles are weighted by each risk allele’s effect size, that has been estimated from the discovery GWAS.
- Calculate for each individual [1].

CONCLUSION

- Results highlight the importance of non-APOE SNPs and SNPs across the entire APOE region, rather than the ε4 SNP alone.
- Findings support existing literature that indicates CSF Aβ levels decrease early in the disease course, but then reach a plateau, whereas p-tau continues to change throughout the progression of AD.
- Associations between PRSs and p-tau appear stronger than with Aβ.
- Differential associations observed in certain subgroups indicate that genetic factors may have a limited impact on p-tau accumulation in some individuals, with other influences playing a more significant role, (e.g., comorbidities, diet, lifestyle, or environmental factors).

RESULTS

Logistic models

PRSwithAPOE and APOEonlyPRS thresholds were associated positively with longitudinal CSF Aβ42 in ε4 carriers and in cognitively unimpaired (CU) participants.

Table 1: High PRS associated with worsening of Aβ42 in ε4 carriers.

Not controlled for p-tau181 status									
PRS & Threshold	Chi-square	df	p	Nagelkerke R ²	Wald	df	p	OR	Nagelkerke R ² Model 1
PRSwithAPOE									
2	24.988	16	0.070	0.388	5.488	1	0.019	3.092	0.303
3	26.114	16	0.052	0.403	6.281	1	0.012	3.615	0.303
APOEonlyPRS									
1	23.867	16	0.092	0.374	4.649	1	0.031	2.612	0.303
2	23.885	16	0.092	0.374	4.682	1	0.030	2.622	0.303
Controlled for p-tau181 status									
PRSwithAPOE									
2	25.891	17	0.076	0.400	4.985	1	0.026	2.948	0.325
3	27.085	17	0.057	0.415	5.643	1	0.016	3.457	0.325
APOEonlyPRS									
1	25.196	17	0.090	0.391	4.492	1	0.034	2.610	0.305
2	25.154	17	0.091	0.391	4.480	1	0.034	2.602	0.305

Table 2: High PRS associated worsening of Aβ42 in CU participants.

Not controlled for p-tau181 status									
PRS & Threshold	Chi-square	df	p	Nagelkerke R ²	Wald	df	p	OR	Nagelkerke R ² Model 1
APOEonlyPRS									
3	26.684	16	0.045	0.673	3.943	1	0.047	73.733	0.429
Controlled for p-tau181 status									
PRSwithAPOE									
2	24.307	17	0.111	0.630	4.067	1	0.044	19.577	0.444
APOEonlyPRS									
2	25.013	17	0.094	0.643	3.911	1	0.048	23.596	0.444
3	27.134	17	0.056	0.681	3.995	1	0.046	55.052	0.444

PRSwithAPOE and APOEonlyPRS thresholds were associated negatively with longitudinal CSF p-tau181 in ε4 non-carriers and in MCI ε4 non-carriers.

Table 3: High PRS associated with lack of worsening of p-tau181 in ε4 non-carriers.

Not controlled for Aβ42 status									
PRS & Threshold	Chi-square	df	p	Nagelkerke R ²	Wald	df	p	OR	Nagelkerke R ² Model 1
PRSwithAPOE									
1	26.141	16	0.052	0.321	7.598	1	0.006	0.242	0.224
2	26.391	16	0.049	0.324	7.803	1	0.005	0.249	0.224
3	22.090	16	0.140	0.277	4.333	1	0.037	0.394	0.224
APOEonlyPRS									
1	28.939	16	0.024	0.351	9.573	1	0.002	0.185	0.224
2	29.113	16	0.023	0.353	9.728	1	0.002	0.180	0.224
3	25.746	16	0.058	0.317	7.300	1	0.007	0.235	0.224
Controlled for Aβ42 status									
PRSwithAPOE									
1	26.348	17	0.068	0.323	7.723	1	0.005	0.234	0.224
2	26.463	17	0.066	0.325	7.838	1	0.005	0.246	0.224
3	22.090	17	0.171	0.277	4.332	1	0.037	0.394	0.224
APOEonlyPRS									
1	29.030	17	0.034	0.352	9.598	1	0.002	0.183	0.224
2	29.170	17	0.033	0.353	9.755	1	0.002	0.178	0.224
3	25.749	17	0.079	0.317	7.300	1	0.007	0.235	0.224

Table 4: High PRS associated with lack of worsening of p-tau181 in MCI ε4 non-carriers.

Not controlled for Aβ42 status									
PRS & Threshold	Chi-square	df	p	Nagelkerke R ²	Wald	df	p	OR	Nagelkerke R ² Model 1
PRSwithAPOE									
1	23.382	16	0.104	0.431	4.468	1	0.035	0.165	0.347
2	23.120	16	0.111	0.427	4.325	1	0.038	0.174	0.347
APOEonlyPRS									
1	25.039	16	0.069	0.456	5.417	1	0.020	0.122	0.347
2	25.384	16	0.063	0.461	5.515	1	0.019	0.103	0.347
3	23.248	16	0.107	0.429	4.276	1	0.039	0.166	0.347
Controlled for Aβ42 status									
PRSwithAPOE									
1	23.605	17	0.131	0.435	3.871	1	0.049	0.180	0.363
2	23.656	17	0.129	0.435	3.964	1	0.046	0.187	0.363
APOEonlyPRS									
1	25.357	17	0.087	0.461	4.961	1	0.026	0.132	0.363
2	25.760	17	0.079	0.467	5.084	1	0.024	0.110	0.363
3	24.153	17	0.115	0.443	4.146	1	0.041	0.168	0.363

Linear models

PRSwithoutAPOE Threshold 1 was associated positively with differential scores of longitudinal CSF p-tau181 measurements (between baseline and month 24), in MCI participants.

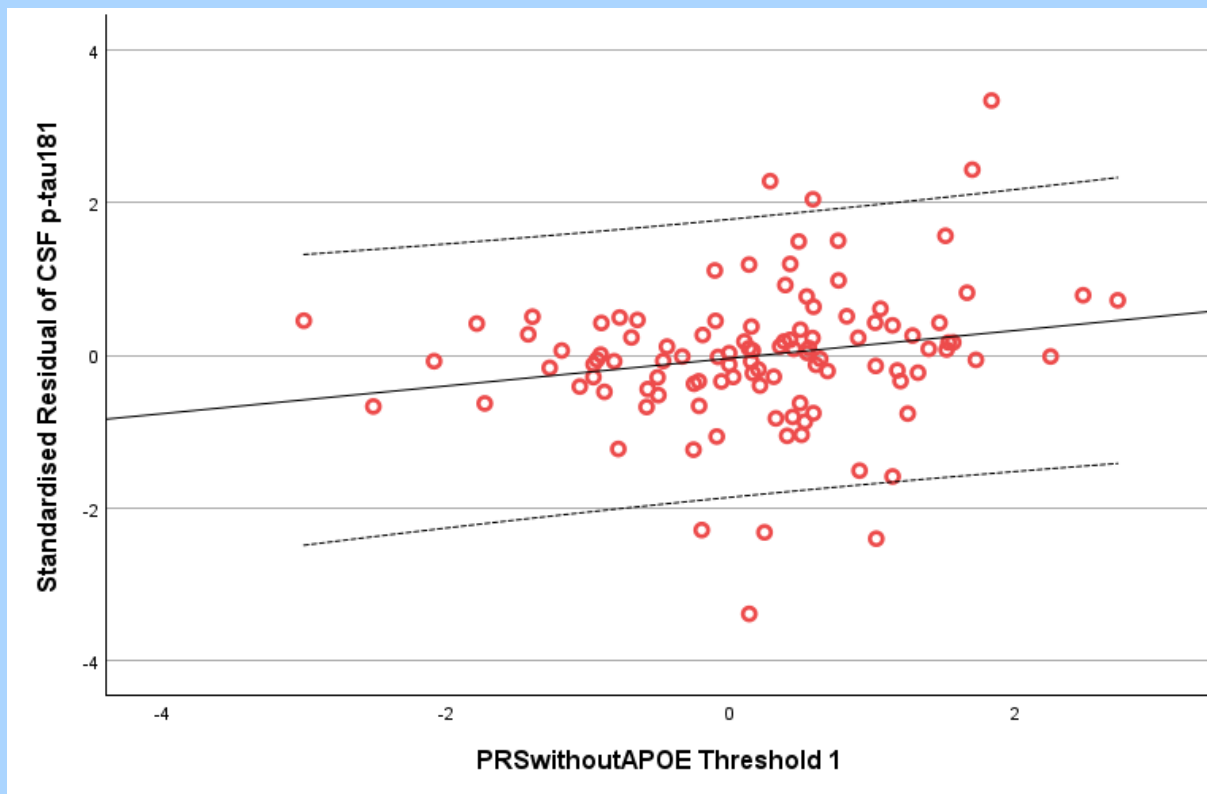


Figure 1: High PRSwithoutAPOE Threshold 1 associated with high differential scores of p-tau181 in MCI participants | **Not controlled** for Aβ42 status | R² = 0.039.

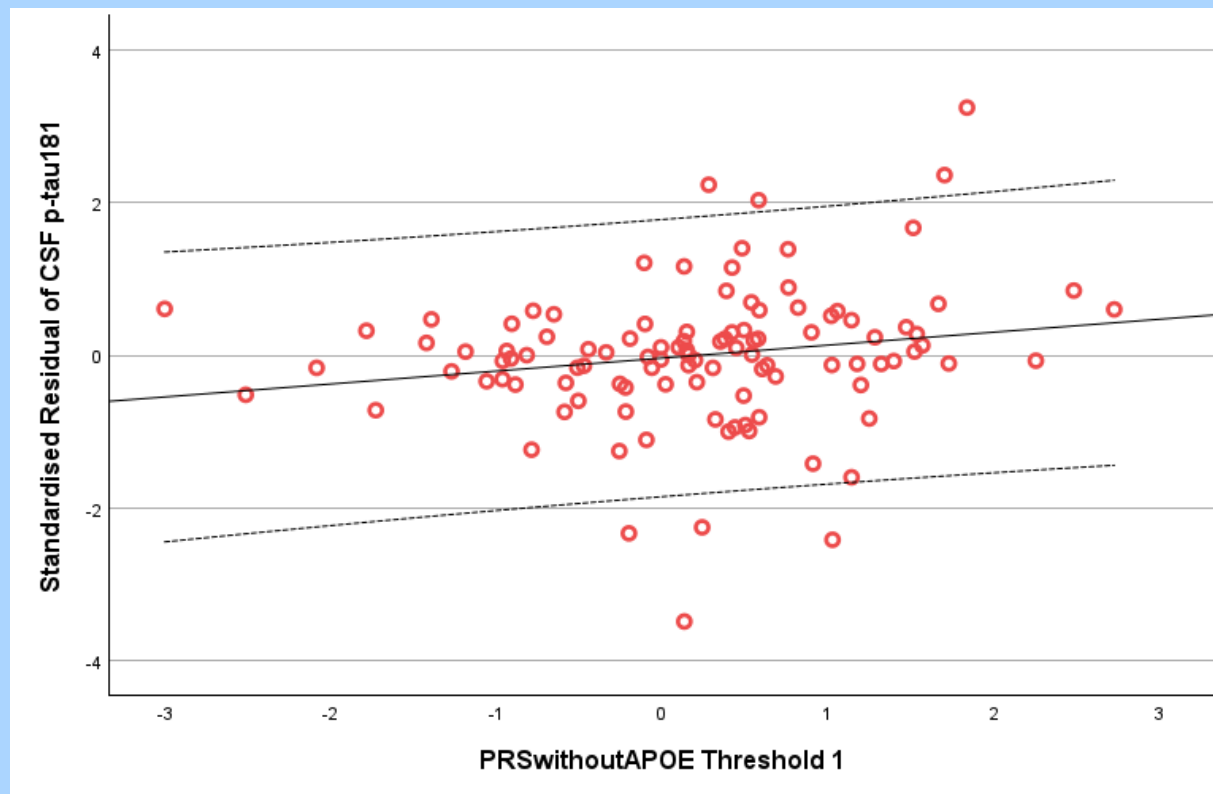


Figure 2: High PRSwithoutAPOE Threshold 1 associated with high differential scores of p-tau181 in MCI participants | **Controlled** for Aβ42 status | R² = 0.034.

PRSwithAPOE and APOEonlyPRS thresholds were associated negatively with differential scores of longitudinal CSF p-tau181 measurements (between baseline and month 24), in CU and CU ε4 non-carriers.

Table 5: High PRS associated with low differential scores of p-tau181 in CU participants.

Not controlled for Aβ42 status					
PRS & Thresholds	R Square (Model 1)	R Square (Model 2)	R Square Change	Sig. F Change (Model 2)	Standardised beta of PRS
PRSwithAPOE					
1	0.303	0.455	0.152	0.021	-0.495
2	0.303	0.442	0.140	0.028	-0.476
3	0.303	0.479	0.176	0.012	-0.520
APOEonlyPRS					
1	0.303	0.469	0.166	0.016	-0.550
2	0.303	0.465	0.162	0.017	-0.549
3	0.303	0.468	0.165	0.016	-0.554
Controlled for Aβ42 status					
PRSwithAPOE					
1	0.381	0.621	0.240	0.002	-0.648
2	0.381	0.594	0.213	0.003	-0.608
3	0.381	0.619	0.238	0.002	-0.617
APOEonlyPRS					
1	0.381	0.595	0.214	0.003	-0.634
2	0.381	0.589	0.208	0.004	-0.631
3	0.381	0.582	0.201	0.005	-0.617

Table 6: High PRS associated with low differential scores of p-tau181 in CU ε4 non-carriers.

Not controlled for Aβ42 status					
PRS & Thresholds	R Square (Model 1)	R Square (Model 2)	R Square Change	Sig. F Change (Model 2)	Standardised beta of PRS
PRSwithAPOE					
3	0.461	0.629	0.168	0.030	-0.549
Controlled for Aβ42 status					
PRSwithAPOE					
1	0.549	0.711	0.162	0.024	-0.510
2	0.549	0.725	0.176	0.017	-0.551
3	0.549	0.738	0.189	0.012	-0.585

REFERENCE

[1] Wray, N. R., Lee, S. H., Mehta, D., Vinkhuyzen, A. A. E., Dudbridge, F. and Middeldorp, C. M. (2014). Research review: Polygenic methods and their application to psychiatric traits. *Journal of Child Psychology and Psychiatry*, 55(10), 1068-1087. DOI: 0.1111/jcpp.12295.