PRESENTING AUTHOR'S NAME & RESEARCH TITLE

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Genetic impact of COVID-19 infection and severity on Alzheimer's disease

PURPOSE/BACKGROUND

The COVID-19 pandemic, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted many facets of our life, including neurodegenerative disorders such as Alzheimer's disease (AD). Notably, AD has emerged as a key comorbidity of COVID-19 infection, and the aging population is highly susceptible to COVID-19 infection with higher death rate. Leveraging large publicly available large genome-wide association study (GWAS) data, this study examined the overlapping genetic liability between AD and COVID-19 disease. Our goal is to better understand the genetic impact of COVID-19 on AD and discover new strategies for better prevention and treatments.

MATERIALS & METHODS

The COVID-19 GWASs from the European population (HGI7_Eur released on 04/08/2022) were downloaded from the COVID-19 Host Genetics Initiative website. Three categories of COVID-19 phenotypes vs. regular population were included in this study: 1) critically ill cases of COVID-19 (A2, case/ctrl = 13,769/1,072,442); 2) hospitalization due to moderate or severe COVID-19 (B2, case/ctrl = 32,519/2,062,805); 3) COVID-19 susceptibility with all cases (C2, case/ctrl = 2,475,240/12,597,856). AD genotyping datasets included the NIA/LOAD cohort and the Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease (GenADA) Study (total case/ctrl = 3,119/3,023). In this study, we conducted polygenic risk score (PRS) analyses (PRSice v2.3.5) at multiple GWAS *P*-value thresholds (P_T: $5x10^{-8}$, $1x10^{-5}$, $1x10^{-3}$, $1x10^{-1}$, 1.0) and "best-fit" GWAS P_T ranging from $5x10^{-8}$ to 1 with an incremental interval of 0.00005. Significant correlation was determined when the associated *P*-val < 0.017(0.05/3) with multiple test correction. We also rescaled PRSs [-1,1] and conducted logistic regression analyses to compare the odds ratios and re-evaluate the association with adjustment for other covariates, such as age, sex, and *APOE* genotyping (rs429358 and rs7412).

RESULTS

We found significant positive correlations between AD diagnosis and genetic risk for different phenotypes of COVID-19. As seen in **Table 1**, AD was significantly associated with COVID-19 infection (***P* = 7.43E-05**, coeff. = 1928.98), critical COVID-19 (***P* = 0.00162,** coeff. = 274.59), and hospitalization (***P* = 0.01523**, coeff. = 112.47). Adjusted for age, sex, and *APOE* genotyping, AD was still significantly associated with COVID-19 infection **[*P-adj.* = 1.29E-06,** OR(CI95%)-adj. = 1.878(1.457-2.428)], critical COVID-19 [***P-adj.* = 0.00056,** OR(CI95%)-adj. = 1.496(1.191-1.882)], and marginal association with hospitalization [***P-adj.* = 0.04172**, OR(CI95%)-adj. = 1.265(1.009-1.586)]. Multiple positive associations were also found as significant between AD diagnosis and genetic risk for COVID-19 infection at different GWAS P_T **(Fig. 1**.)

Table 1. COVID-19 Infection and severity are highly associated with AD diagnosis from "best-fit" PRSice-2 model

phenotypes	Case	Ctrl	total	P_T	R^2	Coeff.	SE	SNP#	OR (CI 95%)	*P*-val	OR(CI95%)-adj.	*P*-adj.
Critical Cond.(A2)	13769	1072442	1086211	0.0039	0.002	274.6	87.1	8553	1.395(1.134-1.716)	**0.00162**	1.496(1.191-1.882)	**0.00056**
Hospitalization (B2)	32519	2062805	2095324	0.0003	0.001	112.5	46.3	1275	1.288(1.050-1.581)	**0.01523**	1.265(1.009-1.586)	0.04172
infection (C2)	122616	2475240	2597856	0.0432	0.003	1929.0	486.8	59061	1.595(1.268-2.013)	**7.43E-05**	1.878(1.457-2.428)	**1.29E-06**

Note: Case, control (Ctrl), and total are the sample size included in the most recent COVID-19 GWASs from HGI7 for European population; P_T: *P*-value threshold from GWAS *P*-value; R^2: how much variance explained by the model; Coeff.: coefficient; SE: standard error; SNP#: how many number of SNPs are included in the "best-fit" model; OR: odds ratio from logistic regression analyses with rescaled PRSs [-1 1] without any adjustment; CI: confident interval without any adjustment; *P*-val: association *P*-value between PRSs and AD diagnosis without any adjustment; *P*-adj.: association *P*-value between PRSs and AD diagnosis with adjustment for age, sex, and APOE genotyping (rs429358 and rs7412); OR(CI95%)-adj.: odds ratio and 95% confident interval with adjustment for age, sex, and *APOE* genotyping (rs429358 and rs7412). *P*-val in bold represents statistically significant.

RESULTS (Continued)

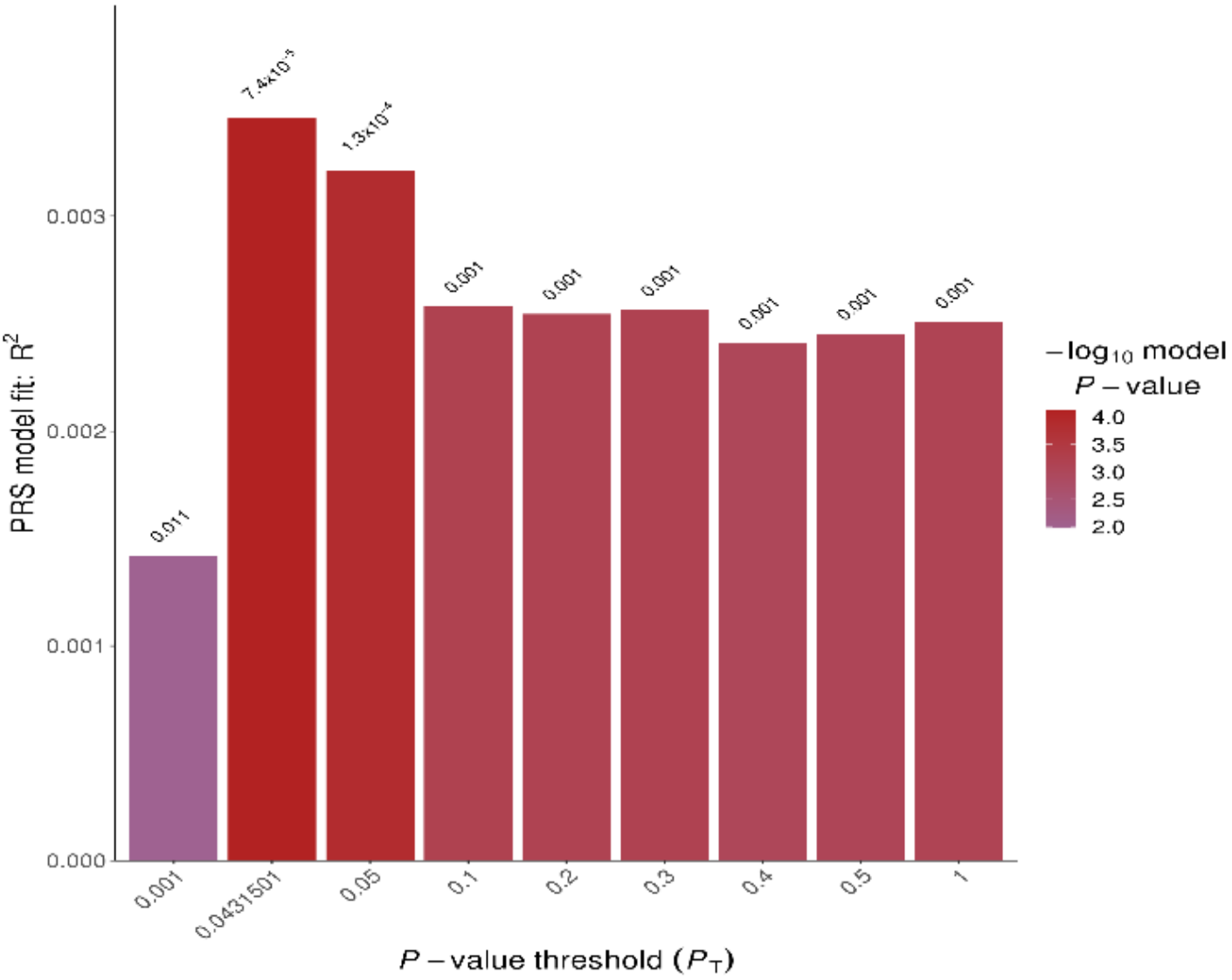

Fig. 1. Bar plot showing significant associations between AD and PRSs for COVID-19 infection (C2) at multiple P_T ranging from 0.001 to 1 with the best P_T at 0.0432. The highest bar indicates the "best-fit" PRS associated with AD.

X-axis: *P* value threshold. Y-axis: PRS model fit R^2 indicates how much variance explained by the model. Color indication gradient is based on a -log model *P*-value.

DISCUSSION/CONCLUSION

Using the polygenic risk score approach, we identify a strong genetic correlation between AD diagnosis and genetic risks for COVID-19 (infection, critical illness, and hospitalization), suggesting that COVID-19 patients from different clinical manifests all have higher genetic risk to develop AD. With the ongoing outbreak of COVID-19 and the high vulnerability of AD from COVID-19 infection, our findings highlight the importance offering preventative measures to patients with COVID-19 and provide a genetic base for understanding the neurological impact of COVID-19.