

# Causal effect of COVID-19 on Alzheimer's disease: A Mendelian randomization study

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## Abstract

It was reported that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may cause brain size reduction and cognitive decline. Whether COVID-19 may contribute to the development of Alzheimer's disease (AD) is not known. We conducted genetic correlation and Mendelian randomization (MR) analyses to assess genetic relationships and potential causal associations between AD and three COVID-19 outcomes (SARS-CoV-2 infection, COVID-19 hospitalization, and critical COVID-19) by utilizing genome-wide association study datasets on these traits. A map of COVID-19-driven molecular pathways was constructed to investigate potential mechanisms underlying the COVID-19 and AD connection. Genetic correlation analyses indicated that AD had a significant positive genetic correlation with hospitalized COVID-19 ( $r_g = 0.271$ ). The MR analysis from the inverse-variance-weighted model showed that genetic liabilities to hospitalized COVID-19 (odds ratio: 1.02, 95% confidence interval: 1.01–1.03) and critical COVID-19 (1.01, 1.00–1.02) were associated with an increased risk for AD. However, no causal effect of genetic liability to SARS-CoV-2 infection on AD was detected (1.03, 0.97–1.09). A total of 60 functionally interconnected genes were reported to mediate the COVID-19-AD connection, which showed functional enrichment in immunity-related pathways and tissue enrichment in the lung and brain. Our study suggests that severe COVID-19 may contribute to the development of AD, while suffering a mild case of COVID-19 may not increase the risk for AD. The influence of COVID-19 on AD may be mediated by immunity-related pathways acting predominantly in the lung and brain.

## KEYWORDS

Alzheimer's disease, COVID-19, GWAS, Mendelian randomization

## 1 | INTRODUCTION

Since the inception of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection pandemic, a large number of studies have sought to investigate the risk factors for COVID-19 and the organismal consequences of this disease.<sup>1–3</sup> Although the core clinical presentations of COVID-19 occur in the respiratory system,

neurological manifestations are common among individuals with the infection or patients who recovered after acute COVID-19 infection. Mounting evidence points to the neurotropic and neuroinvasive properties of the virus.<sup>4–6</sup> It is well documented that the coronavirus SARS-CoV-2 invades the central nervous system, impacting the structure, metabolism, function, and activity of the brain.<sup>4–6</sup> Therefore, COVID-19 poses a remarkable threat to the brain health

of affected individuals, with distinctly differential prognoses in various subpopulations.

While the vast majority of studies have focused on risk factors in the immune, respiratory, or cardiovascular systems, studies investigating brain changes following COVID-19 remain scarce. In a recent study, Douaud et al.<sup>7</sup> reported brain structure changes after COVID-19 infection. They performed paired brain scans on 401 COVID-19 patients from the UK Biobank before and after COVID-19 infection and compared them to those collected from non-COVID-19 controls. Larger-than-expected reductions in gray matter thickness and global brain size were observed along with changes in markers of olfactory tissue damage and a larger cognitive decline between the two time points.<sup>7</sup>

Both brain size reduction and cognitive decline are core features of Alzheimer's disease (AD). Therefore, there is a vital concern about the possible association of COVID-19 with an increased risk for the development of AD. Longitudinal observations may help us to answer this question. However, since AD results from a gradual accumulation of pathological changes in brain tissue, following up a cohort may take a long time.

The Mendelian randomization (MR) framework tests for potential causative associations between exposure and outcome by utilizing genetic variants as instrumental variables.<sup>8,9</sup> In this study, we evaluated potential causal associations between three COVID-19 outcomes and AD by MR analysis of the summary genome-wide association study (GWAS) datasets. Shared genes were extracted by comparing genome-wide genes reported for each trait, then a map of COVID-19-driven molecular pathways was constructed.

## 2 | METHODS

### 2.1 | GWAS summary datasets

We sought to evaluate the potential contribution of COVID-19 to AD using MR analysis of GWAS summary results. The study is based on publicly available GWAS summary results, including SARS-CoV-2 infection (112 612 cases, and 2 474 079 controls, with 88.9% of participants being of European origins), hospitalized COVID-19 (24 274 cases and 2 061 529 controls, with 87.7% participants being of European origin), critical COVID-19 (8779 cases and 1 001 875 controls, with 94.9% participants being of European origin), and AD (71 880 cases and 383 378 controls).<sup>10</sup> The COVID-19 datasets were obtained from the COVID-19 Host Genetics Initiative (HGI) GWAS.<sup>11</sup> The "SARS-CoV-2 infection" label reflects the overall susceptibility to the virus, whereas the "hospitalized" and "critical COVID-19" labels represent the severity of the disease. Therefore, we collectively called the latter two outcomes "severe COVID-19." The effects (values and directions) of single nucleotide polymorphisms (SNPs) were harmonized between each pair of datasets after the exclusion of those with conflicting alleles.

### 2.2 | Genetic correlation analysis

The genetic correlations between AD and COVID-19 outcomes were calculated using linkage disequilibrium (LD) score regression.<sup>12,13</sup> The 1000 Genome Project Phase 3 was used to estimate the LD structure for European populations.<sup>12-14</sup> SNPs were filtered by 1.1 million variants, a subset of 1000 Genomes and HapMap3, with minor allele frequency above 0.05.

### 2.3 | MR analysis

The main analyses were performed using the inverse-variance-weighted (IVW) model, which assumes an intercept of zero and estimates the causality by a fixed-effect meta-analysis.<sup>15</sup> Multiple complementary MR methods were used for evaluating the sensitivity of the causal associations, including weighted median (WM), MR-Egger, penalized WM, penalized IVW, robust IVW, leave-one-out analysis, generalized summary-data-based Mendelian randomization (GSMR), and MR-pleiotropy residual sum and outlier (MR-PRESSO).<sup>15-19</sup> We further evaluated the potential correlated horizontal pleiotropy of the MR estimates using causal analysis using summary effect estimates (CAUSE).<sup>20</sup> The MendelianRandomisation,<sup>9</sup> GSMR,<sup>18</sup> MR-PRESSO,<sup>19</sup> and CAUSE<sup>20</sup> packages were used for the statistical analyses.

We harmonized each pair of the exposure and outcome datasets by aligning the effect allele for exposure and outcome and obtained variant effects and standard errors of each dataset. For each exposure trait, SNPs with genome-wide significance ( $p < 5 \times 10^{-8}$ ) were selected as instrumental variants (IVs) and further pruned using a clumping  $r^2$  cutoff of 0.05 on a 1 Mb window. The European subset of the 1000 Genome Project Phase 3 was used to estimate the LD structure.<sup>21</sup> In an MR analysis, pleiotropy is a potential source of bias and may inflate the estimation of the causal effect.<sup>22</sup> The heat exposure integrated deprivation index (HEIDI) statistical approach is used to detect and eliminate genetic instruments with ostensible pleiotropic effects on both the exposure and the outcome.<sup>18,23</sup> We used a  $p$ -value threshold of 0.01 for the outlier detection analysis in HEIDI, which removes 1% of SNPs by chance if there is no pleiotropic effect.<sup>4</sup> The intercept from the MR-Egger regression was utilized to evaluate the average horizontal pleiotropy.<sup>17</sup> The IVs are not all valid when MR Egger intercepts significantly differs from zero. The significant associations between mental disorders and COVID-19 were determined by IVW-based false discovery rate (FDR)  $< 0.05$ .

### 2.4 | Tissue-specific expression analysis and knowledge-based analysis

To identify the tissue specificity of a phenotype, SNP-based tissue enrichment analysis was conducted by functional mapping and annotation (FUMA),<sup>24</sup> which utilizes gene-property analyses to test associations between tissue-specific gene expression profiles in general GTEx V8

tissues and GWAS hits. Tissue-specific expression analysis for AD was further validated using phenotype-cell-gene association (PCGA).<sup>25,26</sup>

For each set of genes, their tissue specificity was measured against each of the differentially expressed gene sets using the hypergeometric test.<sup>24</sup> Pathway enrichment analyses of a set of genes were conducted using FUMA,<sup>24</sup> involving the Kyoto Encyclopedia of Genes and Genomes (KEGG). Protein-protein interaction (PPI) analysis was conducted using STRING v11.<sup>27</sup>

GWAS results for COVID-19 and AD were obtained from the GWAS Catalog database<sup>28</sup> and utilized for inferring genome-wide risk genes. The genes were further filtered to retain protein-coding genes only. Gene overlaps among COVID-19 and AD gene sets were assessed by the R package SuperExactTest,<sup>29</sup> with the total gene number in the genome set as 30 000.

A detailed description of the methods is provided in the Supporting Information File.

## 2.5 | Construction of COVID-19-driven pathways regulating AD

To explore the potential connection between COVID-19 and AD at the molecular level, we performed large-scale literature data mining and built a map of molecular pathways connecting COVID-19 and AD. The data mining was performed within the Pathway Studio ([www.pathwaystudio.com](http://www.pathwaystudio.com)) environment,<sup>30</sup> containing structured descriptions of approximately 14 million unique associations extracted from >40 million scientific references. The downstream targets of COVID-19 and upstream regulators of AD were identified. Respective references were inspected manually for quality control. The relationships with no polarity or those indirectly related to the activity of COVID-19 or AD were removed. The remaining relationships were utilized to construct the network describing the molecular pathways driven by COVID-19 to facilitate AD. Pathway enrichment analyses of the disease-gene associations were conducted by FUMA.<sup>24</sup>

## 3 | RESULTS

### 3.1 | Genetic correlation analysis

Genetic correlation analyses indicated that AD had a significant positive genetic correlation with hospitalized COVID-19 ( $r_g = 0.271$ ,  $p = 0.013$ , FDR = 0.039, Table 1). However, AD did not have genetic correlations with SARS-CoV-2 infection ( $r_g = 0.167$ ,  $p = 0.119$ ) or critical COVID-19 requiring mechanical ventilation or extracorporeal membrane oxygenation ( $r_g = 0.118$ ,  $p = 0.290$ ).

### 3.2 | MR analysis

We extracted 14, 22, and 17 IVs for SARS-CoV-2 infection, hospitalized COVID-19, and critical COVID-19, respectively. Our

**TABLE 1** Genetic correlations between Alzheimer's disease (AD) and the COVID-19 outcomes

Trait 1	Trait 2	$r_g$ (SE)	Z	p	FDR
AD	SARS-CoV-2 infection	0.118 (0.112)	1.06	0.290	0.290
AD	Hospitalized COVID-19	0.271 (0.110)	2.47	0.013	0.039
AD	Critical COVID-19	0.167 (0.107)	1.56	0.119	0.178

Abbreviations: FDR, false discovery rate;  $r_g$ , genetic correlation coefficient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error.

MR analysis indicated that genetically determined liability to COVID-19 hospitalization (odds ratio [OR]: 1.02, confidence interval: 1.01–1.03,  $p = 7.53 \times 10^{-3}$ , FDR = 0.023) and critical COVID-19 (1.01, 1.00–1.02,  $p = 0.022$ , FDR = 0.033) were associated with an increased risk for AD. However, no causal effects of genetic liability to SARS-CoV-2 infection on AD were detected (1.03, 0.97–1.09,  $p = 0.365$ ) (Table 2 and Supporting Information: Table 1).

The sensitivity analyses revealed that the directions of causal effect estimates across the methods were largely the same (Supporting Information: Table 1). Tests of MR-Egger regression did not support the directional pleiotropy of the IVs for the MR analysis (MR-Egger intercept < 0.01,  $p > 0.05$ ). The MR-PRESSO, HEIDI, and leave-one-out analyses did not support the existence of outliers in the MR analyses (Supporting Information: Figures 1 and 2). CAUSE-based MR analysis showed that the causal model tended to be a better fit in the MR analyses between two severe COVID-19 outcomes and AD (Supporting Information: Figures 3 and 4).

### 3.3 | Tissue-specific expression analysis and knowledge-based analysis

Tissue-specific expression analysis showed that disease-gene associations for hospitalized COVID-19 were significantly enriched in lung and spleen tissue compartments (Figure 1A), while associations for AD were significantly enriched in lungs, blood, and spleen (Figure 1B). PCGA-based tissue-specific expression analysis for AD identified 20 significantly enriched tissues, with the top three tissues being the spleen, whole blood, and lung (Supporting Information: Table 2).

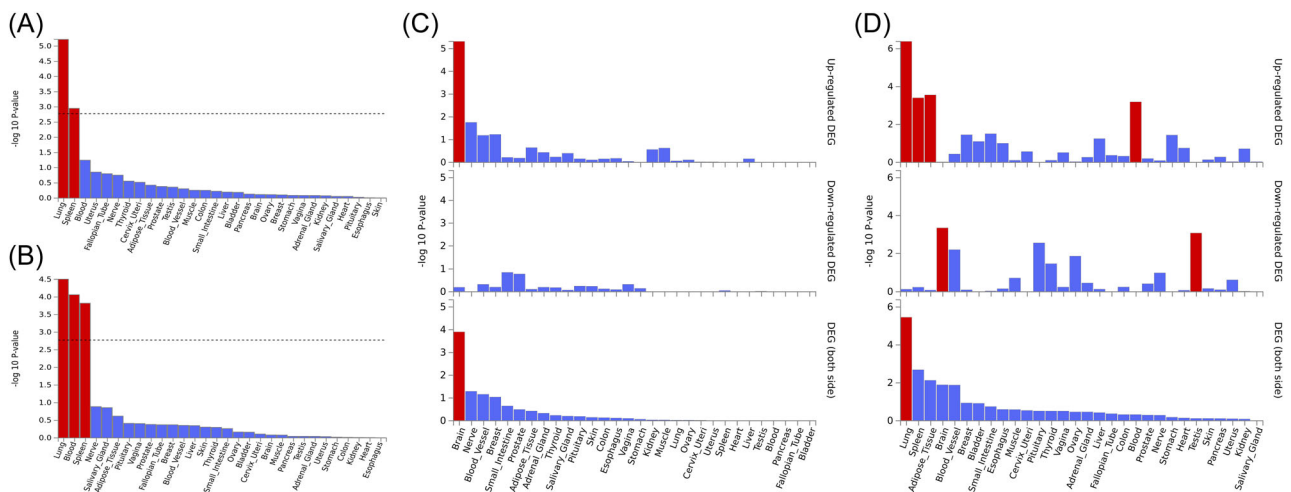
There were 258 and 769 genome-wide protein-coding risk genes for COVID-19 and AD, respectively. A set of 19 genes were shared between COVID-19 and AD, including ANO3, CCDC171, CSMD1, DAB1, ECHDC3, EDAR, FAT1, GLIS3, GRIN2B, LUZP2, NAALADL2, NKAIN2, NTM, RBFOX1, RBMS3, SHANK2, ST18, TCF7L2, and UNC5D. This set of shared genome-wide risk genes was larger than expected ( $p = 4.26 \times 10^{-5}$ ). Gene-based tissue enrichment analysis showed that these 19 genes were upregulated in the brain (Figure 1C).

Literature-based pathway analysis allowed us to map 60 genes connecting COVID-19 and AD (Figure 2, Supporting Information: Tables 3 and 4). Gene-based tissue enrichment analysis showed that

**TABLE 2** Causal effects of the COVID-19 outcomes on Alzheimer's disease

Exposure	Method	Effect (SE)	OR (95% CI)	N_IV	p	FDR
SARS-CoV-2 infection	IVW	0.028 (0.031)	1.03 (0.97–1.09)	14	0.365	0.365
SARS-CoV-2 infection	Weighted median	0.031 (0.033)	1.03 (0.97–1.10)	14	0.343	
SARS-CoV-2 infection	MR-Egger	0.052 (0.074)	1.05 (0.91–1.22)	14	0.486	
SARS-CoV-2 infection	GSMR	0.126 (0.101)	1.13 (0.93–1.38)	14	0.214	
SARS-CoV-2 infection	MR-PRESSO	0.028 (0.031)	1.03 (0.97–1.09)	14	0.381	
Hospitalized COVID-19	IVW	0.019 (0.007)	1.02 (1.01–1.03)	22	7.53E-03	0.023
Hospitalized COVID-19	Weighted median	0.018 (0.010)	1.02 (1.00–1.04)	22	0.063	
Hospitalized COVID-19	MR-Egger	-0.007 (0.023)	0.99 (0.95–1.04)	22	0.766	
Hospitalized COVID-19	GSMR	0.218 (0.080)	1.24 (1.06–1.45)	22	6.30E-03	
Hospitalized COVID-19	MR-PRESSO	0.019 (0.007)	1.02 (1.01–1.03)	22	0.013	
Critical COVID-19	IVW	0.013 (0.006)	1.01 (1.00–1.02)	17	0.022	0.033
Critical COVID-19	Weighted median	0.013 (0.007)	1.01 (1.00–1.03)	17	0.069	
Critical COVID-19	MR-Egger	0.008 (0.017)	1.01 (0.98–1.04)	17	0.626	
Critical COVID-19	GSMR	0.130 (0.065)	1.14 (1.00–1.29)	17	0.046	
Critical COVID-19	MR-PRESSO	0.013 (0.006)	1.01 (1.00–1.02)	17	0.036	

Abbreviations: CI, confidence interval; FDR, false discovery rate; GSMR, generalized summary-data-based Mendelian randomization; IVW, inverse-variance weighted; MR-Egger, Mendelian randomization-Egger; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; N\_IV: number of instrumental variables; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error.

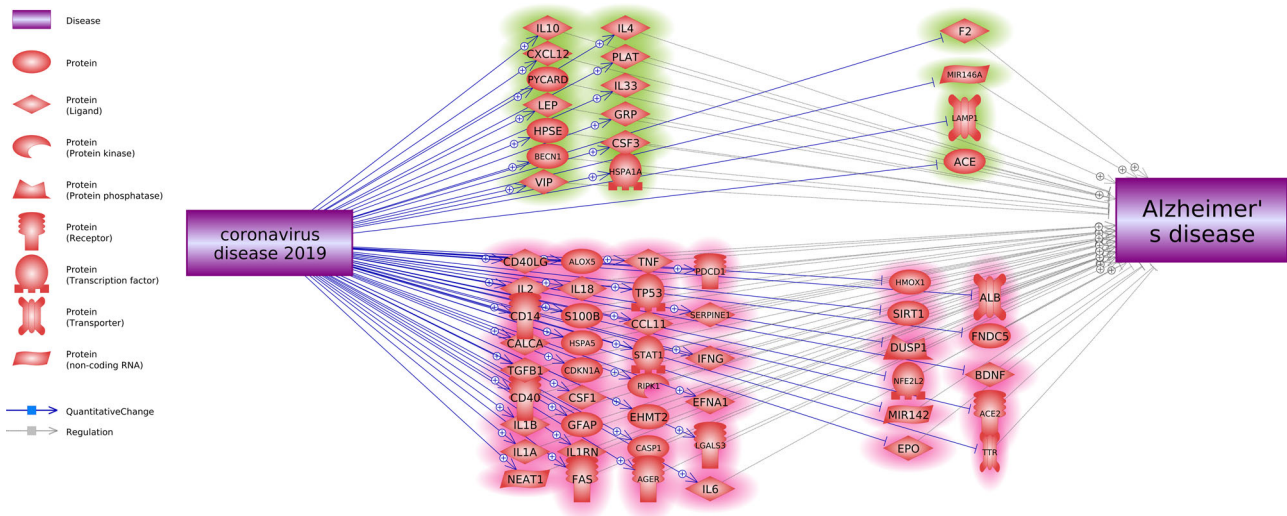


**FIGURE 1** Tissue expression enrichment analyses. (A) Tissue-specific expression analysis for hospitalized COVID-19. (B) Tissue-specific expression analysis for AD. (C) Gene-based tissue enrichment analysis of the shared genome-wide risk genes between COVID and AD. (D) Gene-based tissue enrichment analysis of the 60 genes connecting COVID-19 and AD. Significantly enriched differentially expressed gene (DEG) sets ( $p_{\text{Bonferroni}} < 0.05$ ) are highlighted in red. AD, Alzheimer's disease.

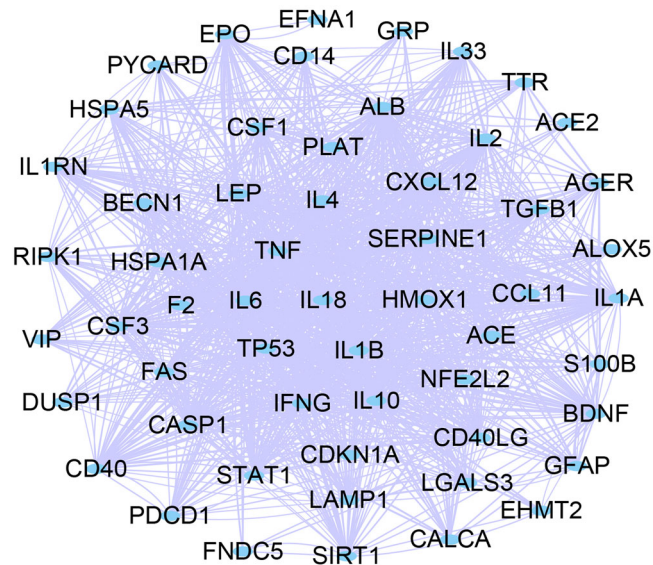
these 60 genes were upregulated in the lung, spleen, adipose tissue, and blood, but downregulated in the brain and testis (Figure 1D). In the KEGG-based pathway analysis of the shared gene set, enrichment of “cytokine interaction with their receptors” and other immunity-related pathways was detected (Supporting Information: Figure 5). PPI analysis

using the STRING database showed that the set of 60 shared proteins forms a tightly interconnected network (Figure 3). Functional analysis of these genes showed that the effects of COVID-19 on AD are synergistic with both intrinsic and extrinsic AD-promoting pathways (Figure 2). Specifically, COVID-19 quantitatively activated 32 out of 36 known AD





**FIGURE 2** A map of molecular pathways connecting COVID-19 and Alzheimer's disease (AD). Quantitative genetic changes driven by COVID-19 exert more negative (highlighted in red) than positive (highlighted in green) effects on AD.



**FIGURE 3** Protein-protein interactions among the risk genes shared between COVID-19 and AD. Line sizes are proportional to the combined scores of the interactions. AD, Alzheimer's disease.

promoters, while its influence on the set of known AD inhibitors was balanced, with 11 inhibitors being deactivated and 13 activated. These results suggest that the impact of COVID-19 on AD may be exerted mainly through the activation of AD promoters, which may partially explain the increased risk of AD for COVID-19 patients.

#### 4 | DISCUSSION

Although detailed quantification of the impact of COVID-19 on the risk of developing AD would require at least a decade of observations, some studies have already reported that hospitalized

COVID-19 patients have a higher frequency of memory issues after discharge (OR: 1.9) than those who recovered at home.<sup>31</sup> This type of study design, however, may not distinguish causal relationships from nondirectional associations stemming from confounding factors and is prone to an error of reverse causation.

Our findings indicate that severe forms of COVID-19 are indeed associated with an increased risk for AD. Thus, our work provides further evidence supporting the contribution of severe COVID-19 to cognitive impairment, in line with recent studies suggesting that SARS-CoV-2 infection may result in tau hyperphosphorylation and the damaging "leakage" of RyR2 channels associated with AD.<sup>32</sup> In particular, in hospitalized patients with COVID-19 encephalopathy, the levels of AD-associated biomarkers were increased to levels higher than those observed in non-COVID controls with clinically diagnosed mild cognitive impairment or AD.<sup>33</sup>

To our surprise, the GWAS hits of AD were enriched in genes highly expressed in the lung, blood, and spleen, rather than in the brain itself, which suggests a close relationship between lung function and AD. This observation supports previous studies indicating that mid-life worsening of lung health may be linked to mild cognitive decline and dementia, both in smokers and nonsmokers.<sup>34</sup>

Functional analyses showed that the 60 COVID-19-AD shared genes are expressed at a high level in the lung, spleen, adipose tissue, and blood, supporting the involvement of the local immune responses in both pathologies. In the brain, these genes were mostly downregulated, possibly reflecting pathophysiological changes occurring in AD. Pathway analysis showed that the severity-related set of 60 genes is enriched in cytokine- and immunity-related signaling functions, consistent with the cytokine storm being the major driver of COVID-19 morbidity.<sup>35</sup> The STRING-derived map of PPIs (Figure 3) demonstrates high interconnectivity between mapped molecules, with an emphasis on a large, central core of well-known key cytokine signaling players, including IL-6, TNF- $\alpha$ , IL-1B, and interferon- $\gamma$ .

Our data showed that the mild type of COVID-19, a form of nonhospitalized virus infection, did not confer additional risk for AD. In Douaud et al.'s<sup>7</sup> study, brain size reductions and cognitive decline remained significant even after excluding the 15 hospitalized COVID-19 patients from the initial dataset. While the findings described above are certainly concerning, dissection of the genetic component underlying severe COVID-19 and AD gives hope that the deleterious changes occurring in nonhospitalized cases may be reversible and followed by attenuation or partial recovery over time.

The main strength of the study is that MR analysis is generally less affected by confounding and reverse causation than traditional observational studies. The MR framework leverages genetic variants to evaluate the causative association between exposure and outcome. We must acknowledge the potential influence of pleiotropy as a source of potential bias. Therefore, validation of the study findings in additional follow-up cohorts is warranted.

In summary, our study suggests that the potential effect of COVID-19 on AD may be severity-dependent: genetic liability to severe COVID-19 may contribute to the development of AD, while nonhospitalized cases of COVID-19 may not significantly increase the risk for a cognitive decline of Alzheimer's type. The influence of COVID-19 on AD may be mediated by immunity-related pathways acting predominantly in the lung and brain.

#### AUTHOR CONTRIBUTIONS

Fuquan Zhang conceived the project and supervised the study. Fuquan Zhang analyzed the data. Fuquan Zhang, Hongbao Cao, and Ancha Baranova wrote the manuscript. All authors read and approved the final manuscript.

#### ACKNOWLEDGMENTS

The authors would like to thank all investigators and participants from the COVID-19 Host Genetics Initiative and other groups for sharing these data.

#### CONFLICT OF INTERESTS

The authors declare no conflict of interest.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Covid19 Host Genetics Initiative, <https://www.covid19hg.org/> and Psychiatric Genomics Consortium, <https://www.med.unc.edu/pgc/download-results/>

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Baranova A, Cao H, Zhang F. Causal effect of COVID-19 on Alzheimer's disease: a Mendelian randomization study. *J Med Virol.* 2022;1-7.

[doi:10.1002/jmv.28107](https://doi.org/10.1002/jmv.28107)