Genetic Correlation between Alzheimer's disease and COVID-19

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Jingchun Chen, M.D., Ph.D.

Associate Research Professor

Nevada Institute of Personalized Medicine

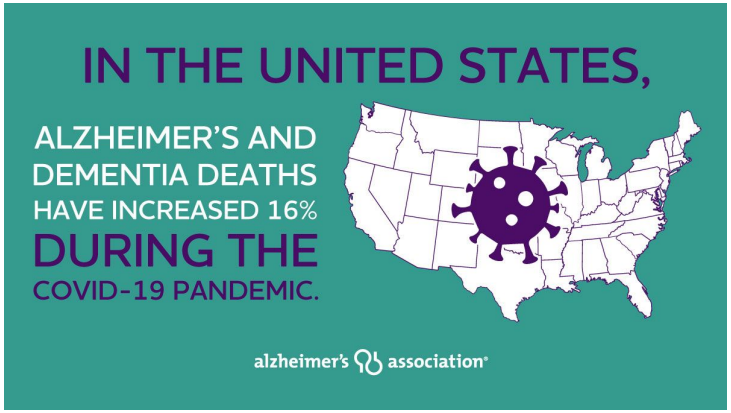
University of Nevada, Las Vegas

One of Research Leaders of COBRE grant

Outlines

1. Background
2. Datasets and Methods
3. Results
4. Conclusion
5. Acknowledge

Background



COVID-19: spread worldwide and was declared as a pandemic by WHO in March 2020

WHO (11/07/2022)): 96,206,427 confirmed cases
1,060,430 deaths in U.S. (https://covid19.who.int/).

Clinical manifestations:

- pneumonia, dry cough, fever, headache, sore throat, loss of taste or smell. Most cases have mild symptoms with a low fatality rate, recover on their own.
- 20% of the patients develop severe symptoms including ARDS, septic shock, and multiple organ dysfunction syndrome, rapid death.
- Extra-pulmonary manifestations: neurological disorders, such as Alzheimer's disease (AD).
- Long-term or post-infection effect of COVID-19: neurological disorders, diabetes, etc.

COVDID-19 PATIENTS HAVE HIGHER RISK FOR AD

> J Alzheimers Dis. 2022;89(2):411-414. doi: 10.3233/JAD-220717.

Association of COVID−19 with New−Onset Alzheimer's Disease

Lindsey Wang [1], Pamela B Davis [2], Nora D Volkow [3], Nathan A Berger [1], David C Kaelber [4], Rong Xu [5]

Affiliations + expand

PMID: 35912749 DOI: 10.3233/JAD-220717

In a retrospective cohort study of 6,245,282 older adults (age ≥65 years) who had medical encounters between 2/2020-5/2021

people with COVID-19 were at significantly increased risk for new diagnosis of AD within 360 days after the initial COVID-19 diagnosis

(hazard ratio or HR:1.69, 95% CI: 1.53-1.72), especially in people age ≥85 years and in women.

- **Why COVID-19 patients have high risk for AD?**

- **Any genetic correlation between the COVID-19 and AD?**

Datasets and Methods

AD Genotyping Datasets (dbGaP):

NIA/LOAD Family Study: (phs000168): 90% European ancestry
C12: case = 1278, control = 1293
C34: case = 1042, control = 952
GenADA(GSK) (phs000219): European ancestry
case = 799, control = 778

total =6142

Imputation: Michigan Imputation Server

COVID-19 GWAS summary statistics(https://www.covid19hg.org/):

Largest data released on April 8,2022 (HGI7)(previous cohorts HGI5, 6 are also downloaded)
3 phenotypes with **European**, all population, or African American

- Critical COVID-19
- Hospitalized COVID-19
- COVID-19 infection

AD GENOTYPING SAMPLE SIZE

Dataset	Cases	Controls	total
ADc12	1278	1293	2571
ADc34	1042	952	1994
ADAGen	799	778	1577
total	3119	3023	6142

COVID-19 GWAS SAMPLE SIZE

	HGI5			HGI6			HGI7		
Phenotype	Cases	Controls	total	Cases	Controls	total	Cases	Controls	total
Critical Cond.(A2_eur)	5101	1383241	1388342	7805	890667	898472	13769	1072442	1086211
Hospitalization(B2_eur)	9986	1877672	1887658	21288	1807961	1829249	32519	2062805	2095324
Infection(C2_eur)	38984	1644784	1683768	98761	2169767	2268528	122616	2475240	2597856
Critical Cond.(A2_all)	5870	1155203	1161073	8779	1001875	1010654	18152	1145546	1163698
Hospitalization(B2_all)	12888	1295966	1308854	24274	2061529	2085803	44986	2356386	2401372
Infection(C2_all)	36590	1668938	1705528	112612	2474079	2586691	159840	2782977	2942817

Methods –cont'd

- **Polygenic analysis**: PRSICE-2 to calculate PRSs

  PRS = # of effect allele in SNP1 * effect size1 + # of effect allele in SNP2 * effect size2 +…

  multiple thresholds (x 6/traits): 5e-8, 1e-5, 1e-3, 1e-1, 1, "best-fit" threshold

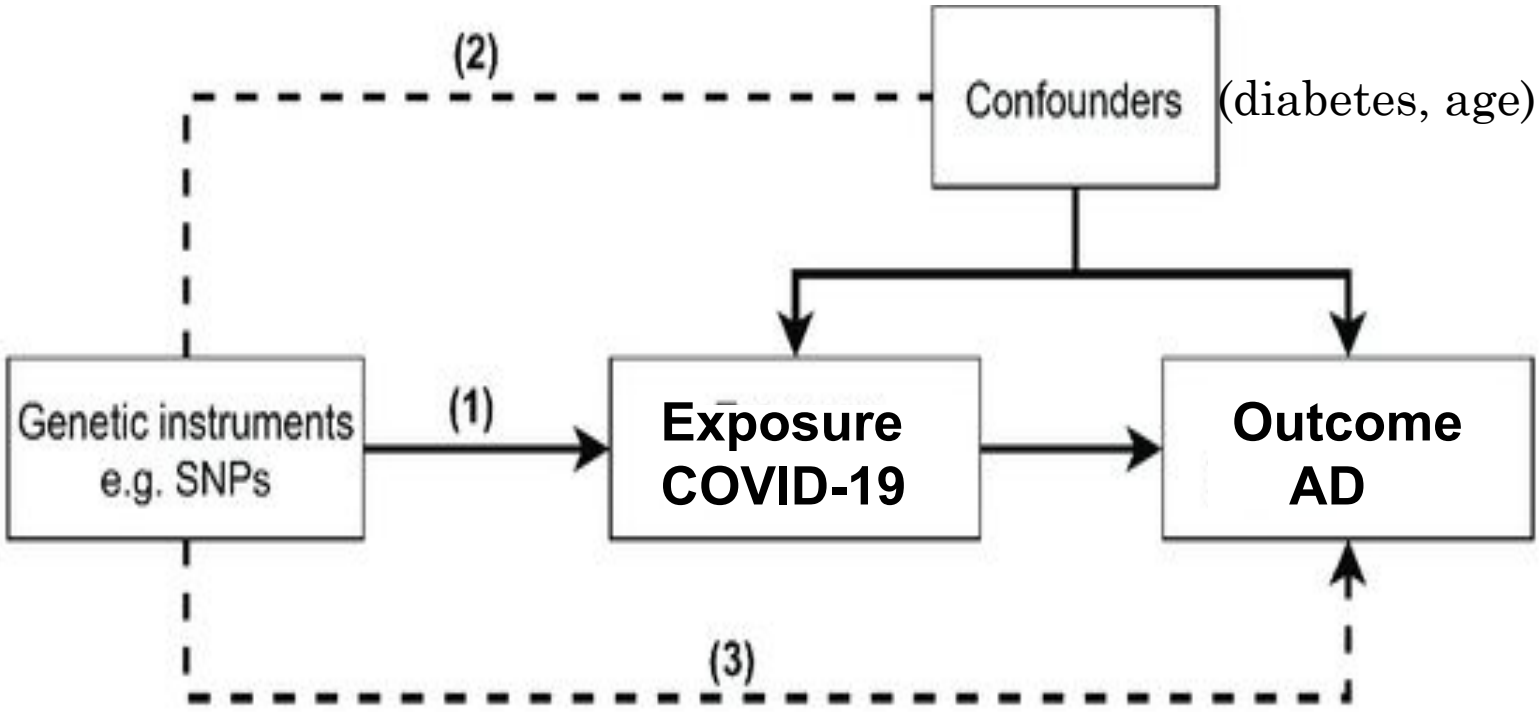
- **LD Score Regression (LDSC)**

  LDSC is a command line tool for estimating heritability and genetic correlation from GWAS summary statistics.

- **Mendelian randomization (MR)**

  Causal effects of the COVID-19 outcomes on AD

The diagram and three key assumptions of Mendelian randomization



(1) SNPs are robustly associated with the exposure
(2) SNPs are not associated with the confounding variables
(3) SNPs are only associated with the outcome via the exposure

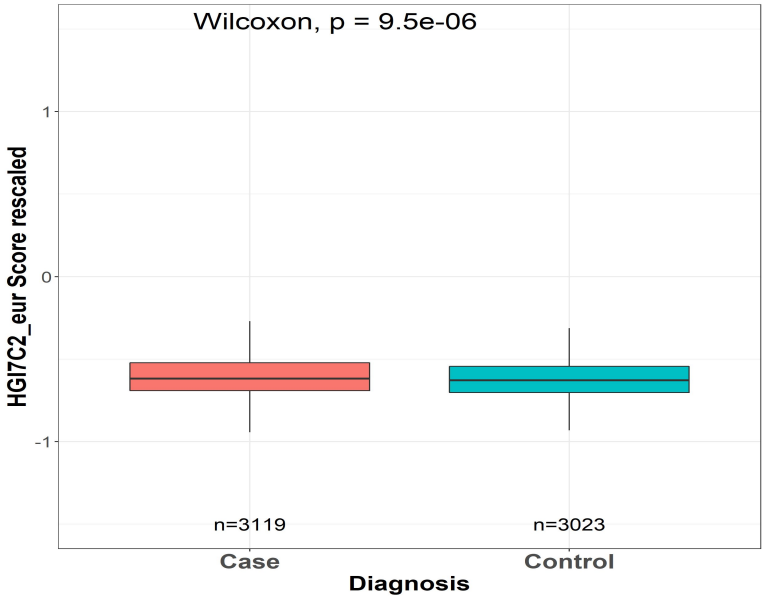
Results

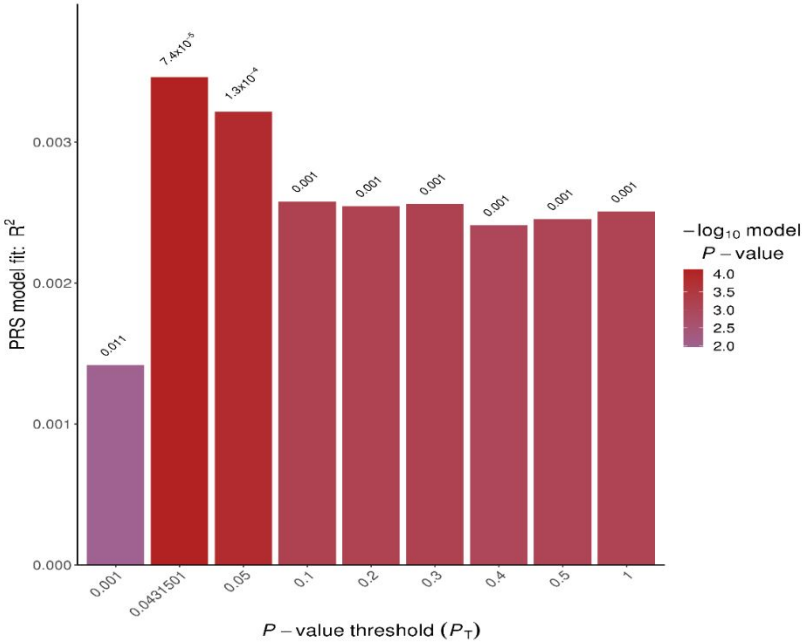
COVID-19 Infection and severity are highly associated with AD diagnosis from "best-fit" PRSice-2 model

COVID-19 phenotypes	P_T	R^2	Coeff.	SE	SNP#	No adjust. for age, sex, and APOE			adjust. for age, sex, and APOE		
						OR (CI 95%)	*P*-val	q-val	OR(CI95%)-adj.	*P*-adj.	q-val-adj.
Critical Cond.(A2)	0.0039	0.002	274.6	87.1	8553	1.08(1.03-1.14)	**1.62E-03**	**2.43E-03**	1.10(1.04-1.17)	**5.60E-04**	**8.40E-04**
Hospitalization (B2)	0.0003	0.001	112.5	46.3	1275	1.06(1.01-1.12)	**0.015**	**0.015**	1.06(1.00-1.12)	**0.042**	**0.042**
infection (C2)	0.0432	0.003	1929.0	486.8	59061	1.11(1.05-1.17)	**7.43E-05**	**2.23E-04**	1.15(1.09-1.22)	**1.29E-06**	**3.87E-06**

COVID-19 infection and critical condition are significantly correlated with AD, even after adjusted for sex, age, and *APOE* genotypes

COVID-19 INFECTION (HGI7C2) AND AD





Results from different COVID-19 cohorts

Cohort	Phenotype	No adjust. for age, sex, and APOE				adjust. for age, sex, and APOE				COVID-19
		SE	z-value	*P*	OR(95%CI)	SE	z-value	*P*	OR(95%CI)	Case/Ctr
HGI5A2_eur	Critical Cond.	0.03	-1.98	0.0477	0.95(0.90-1.00)	0.03	-2.29	0.0222	0.94(0.89-0.99)	5101/1383241
HGI5B2_eur	Hospitalization	0.03	4.39	**1.15E-05**	1.12(1.06-1.18)	0.03	3.66	**0.0003**	1.11(1.05-1.17)	9986/1877672
HGI5C2_eur	Infection	0.03	3.76	0.0002	1.10(1.05-1.16)	0.03	4.22	**2.40E-05**	1.13(1.07-1.19)	38984/1644784
HGI6A2_ALL	Critical Cond.	0.03	4.32	**1.59E-05**	1.12(1.06-1.18)	0.03	4.55	**5.36E-06**	1.14(1.08-1.20)	8779/1001875
HGI6B2_ALL	Hospitalization	0.03	2.27	0.0234	1.06(1.01-1.11)	0.03	1.69	0.0902	1.05(0.99-1.11)	24274/2061529
HGI6C2_ALL	Infection	0.03	4.01	**6.04E-05**	1.11(1.05-1.17)	0.03	3.77	**1.61E-04**	1.11(1.05-1.18)	112612/2474079
HGI6B2_eur	Hospitalization	0.03	2.14	0.0324	1.06(1.00-1.11)	0.03	1.90	0.0573	1.06(1.00-1.12)	21288/1807961
HGI6C2_eur	Infection	0.03	3.47	**0.0005**	1.09(1.04-1.15)	0.03	3.62	**0.0003**	1.11(1.05-1.17)	98761/2169767
HGI7A2_ALL	Critical Cond.	0.03	3.32	**0.0009**	1.09(1.04-1.15)	0.03	3.61	**0.0003**	1.11(1.05-1.17)	18152/1145546
HGI7B2_ALL	Hospitalization	0.03	2.58	**0.0100**	1.07(1.02-1.12)	0.03	2.38	0.0172	1.07(1.01-1.13)	44986/2356386
HGI7C2_ALL	Infection	0.03	3.98	**6.93E-05**	1.11(1.05-1.17)	0.03	4.18	**2.94E-05**	1.13(1.07-1.19)	159840/2782977
HGI7A2_eur	Critical Cond.	0.03	3.15	**0.0016**	1.08(1.03-1.14)	0.03	3.45	**0.0006**	1.10(1.04-1.17)	13769/1072442
HGI7B2_eur	Hospitalization	0.03	2.43	**0.0152**	1.06(1.01-1.12)	0.03	2.04	0.0417	1.06(1.00-1.12)	32519/2062805
HGI7C2_eur	Infection	0.03	3.96	**7.43E-05**	1.11(1.05-1.17)	0.03	4.84	**1.29E-06**	1.15(1.09-1.22)	122616/2475240

Genetic correlation from LDSC

Trait 1	Trait 2	rg	se	Z	P
AD2019Jansen	HGI7A2-eur	0.224	0.091	2.452	**0.0142**
AD2019Jansen	HGI7B2-eur	0.241	0.089	2.708	**0.0068**
AD2019Jansen	HGI7C2-eur	0.153	0.101	1.503	0.1329

Causal effects of COVID-19 on AD (Mendelian randomization)

	exposure	method	nsnp	b	se	pval
Critical cases	HGI7A2-eur	MR Egger	28	0.012	0.008	0.140
	HGI7A2-eur	Weighted median	28	0.009	0.005	0.051
	HGI7A2-eur	Inverse variance weighted	28	0.008	0.004	0.072
	HGI7A2-eur	Simple mode	28	0.010	0.008	0.201
	HGI7A2-eur	Weighted mode	28	0.009	0.004	**0.040**
Hospitalization	HGI7B2-eur	MR Egger	33	0.027	0.015	0.074
	HGI7B2-eur	Weighted median	33	0.018	0.007	**0.015**
	HGI7B2-eur	Inverse variance weighted	33	0.013	0.008	0.082
	HGI7B2-eur	Simple mode	33	0.032	0.012	**0.013**
	HGI7B2-eur	Weighted mode	33	0.023	0.007	**0.003**
infection	HGI7C2-eur	MR Egger	14	0.051	0.024	0.054
	HGI7C2-eur	Weighted median	14	0.050	0.016	**0.002**
	HGI7C2-eur	Inverse variance weighted	14	0.032	0.013	**0.019**
	HGI7C2-eur	Simple mode	14	0.052	0.026	0.068
	HGI7C2-eur	Weighted mode	14	0.050	0.016	**0.007**

Conclusions

- Polygenic analysis indicates a strong positive genetic correlation between AD diagnosis and different phenotypes of COVID-19, including COVID-19 infection, critical condition, and hospitalization;
- Adjusted for age, sex, and *APOE* genotyping, the genetic correlation still holds true;
- LDSC shows the positive correlation between COVID-19 critical condition, hospitalization and AD, but not the COVID-19 infection;
- MR analysis shows genetic risk for COVID-19 may have some causal effects on AD.

Future Direction

- Identify shared genes/pathways (multi-omics data) at the cell-type specific levels, such as immune cells

- Identify targets for therapeutic intervention.

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