

Supplementary Material

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

Description of TriNetX database

The data was collected and analyses were performed on June 26, 2022 from the TriNetX COVID-19 Research Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 95 million patients from 68 healthcare organizations. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. MetroHealth System, Cleveland, Ohio, IRB has determined any research using TriNetX, is not Human Subject Research and therefore exempt from IRB review.

TriNetX is a platform that de-identifies and aggregates electronic health record (EHR) data from 68 contributing healthcare systems, most of which are large academic medical institutions with both inpatient and outpatient facilities at multiple locations, across 50 states in the US. TriNetX Analytics provides web-based and secure access to patient EHR data from hospitals, primary care, and specialty treatment providers, covering diverse geographic locations, age groups, racial and ethnic groups, income levels and insurance types including various commercial insurances, governmental insurance (Medicare and Medicaid), self-pay/uninsured, worker compensation insurance, military/VA insurance among others.

Self-reported race and ethnicity data in TriNetX comes from the underlying clinical EHR systems of the contributing healthcare systems. TriNetX maps race and ethnicity data from the contributing healthcare systems to the following categories: 1) Race: Asian, American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race; and 2) Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown Ethnicity.

Covariates, propensity-score matching, statistical analysis

Supplementary Table 1. Covariates and clinical outcomes, their standardized names, codes, data types and time window that are used in the TriNetX database.

Covariates, Clinical outcomes	Name, code	Data type	Time Window
Exposure			
COVID-19 infection	<ul style="list-style-type: none"> • coronavirus 2 and related RNA [Presence] (Logical Observation Identifiers Names and Codes (LOINC) code: 9088) • COVID-19 (The International Classification of Diseases, Tenth Revision (ICD-10) code: U07.1) 	present/absent	
Outcome			
Alzheimer's disease	<ul style="list-style-type: none"> • Alzheimer's disease (ICD-10 code: G30) 		Within 360-time frame after COVID-19 diagnosis
Covariates			
Age at Index	Age at Index	continuous	
Female	F	present/absent	
Male	M	present/absent	
Asian	Asian (Demographics: 2028-9)	present/absent	
Black or African American	Black or African American (Demographics: 2054-5)	present/absent	
White	White (Demographics: 2106-3)	present/absent	
Hispanic/Latino	Hispanic or Latino (Demographics: 2135-2)	present/absent	
Not Hispanic or Latino	Not Hispanic or Latino (Demographics: 2186-5)	present/absent	
Hypertension	Essential (primary) hypertension (International Classification of Diseases, Tenth Revision or ICD-10 code: I10)	present/absent	Anytime up to 1 day before COVID-19 infection
Depression	Depressive episode (ICD-10 code: F32)	present/absent	Anytime up to 1 day before COVID-19 infection
Overweight and Obesity	Overweight and obesity (ICD-10 code: E66)	present/absent	Anytime up to 1 day before COVID-19 infection
Type 2 diabetes	Type 2 diabetes mellitus (ICD-10 code: E11)	present/absent	Anytime up to 1 day before COVID-19 infection
Hearing loss	<ul style="list-style-type: none"> • Conductive and sensorineural hearing loss (ICD-10 code: H90) • Other and unspecified hearing loss (ICD-10 code: H91) 	present/absent	Anytime up to 1 day before COVID-19 infection
Traumatic brain injury	Intracranial injury (ICD-10 code: S06)	present/absent	Anytime up to 1 day before COVID-19 infection
Heavy tobacco smoking	Nicotine dependence (ICD-10 code: F17)	present/absent	Anytime up to 1 day before COVID-19 infection

Heavy alcohol use	Alcohol related disorders (ICD-10 code: F10)	present/absent	Anytime up to 1 day before COVID-19 infection
Adverse socioeconomic and psychosocial circumstances (%)	Persons with potential health hazards related to socioeconomic and psychosocial circumstances (ICD-10 code: Z55-Z65), including: <ul style="list-style-type: none"> • Problems related to education and literacy (Z55) • Problems related to employment and unemployment (Z56) • Occupational exposure to risk factors (Z57) • Problems related to physical environment (Z58) • Problems related to housing and economic circumstances (Z59) • Problems related to social environment (Z60) • Problems related to upbringing (Z62) • Other problems related to primary support group, including family circumstances (Z63) • Problems related to certain psychosocial circumstances (Z64) • Problems related to other psychosocial circumstances (Z65) 	present/absent	Anytime up to 1 day before COVID-19 infection

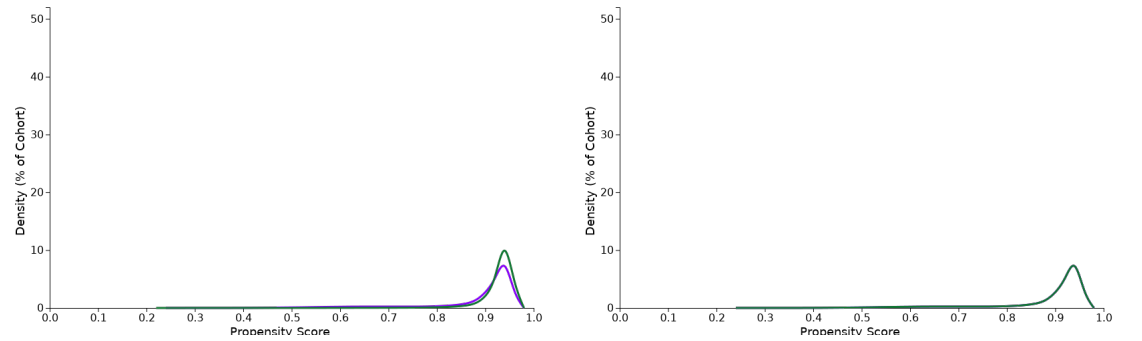
Propensity Score Matching

Propensity score matching was performed on all listed characteristics.

Cohort 1 and cohort 2 patient count before and after propensity score matching

Cohort	Patient count before matching	Patient count after matching
1 – COVID-19 cohort	410,748	410,748
2 – non-COVID-19 cohort	5,834,534	410,748

Propensity score density function - Before and after matching (cohort 1 - purple, cohort 2 - green)



Statistical methods

The proportional hazard assumption was tested using the generalized Schoenfeld approach. The TriNetX Platform calculates the hazard ratios and associated confidence intervals using R's Survival package v3.2-3. For generating hazard ratios, TriNetX sets robust=FALSE using the R survival package, which is a limitation of the TriNetX platform since it does not consider potential clustering of COVID-19 cases within the healthcare organizations or specific geolocations. All Statistical tests were conducted on 6/26/2022 within the TriNetX Analytics Platform using R's Survival package, version 3.2-3.