Title: Impact of COVID-19 pandemic and long-COVID on cognitive decline, new-onset Alzheimer's disease and related dementia (ADRD), and racial/ethnic disparities in ADRD burden.

Investigators: Sumedha Gupta (PI), Kosali Simon (NBER affiliate mentor), and Brea L. Perry.

Statement of Need. This application addresses the intersection of two major population health crises – the COVID-19 pandemic and the rising global burden of Alzheimer's disease and related dementias (ADRD). Over 5 million people (1.6% of U.S. population) were affected by ADRD in 2014,[1] making it the fifth most common cause of death for Americans aged 65+ and costing up to $215 billion in health care expenses per year.[2] 2018 estimates project ADRD burden to double, affecting 13.9 million people by 2060. However, whether the COVID-19 pandemic has (1) changed the trajectory of population-level cognitive decline, (2) increased ADRD prevalence, or (3) accelerated the progression of cognitive decline among those with pre-existing ADRD (1-3 referred together hereon as $ADRD\ prevalence$) in the aging US population is unknown.

By January 2023, over 96 million individuals in the U.S. had contracted SARS-CoV2, with nearly 1.1 million COVID-19 deaths,[3] 80% of which were in persons aged 65+.[4] Moreover, COVID-19 mortality rates have been twice as high in older adults with ADRD than those without.[5] The pandemic may have impacted the population prevalence of ADRD in 2 ways. First, higher COVID-19 mortality in patients with/at-risk-of ADRD may imply a lower risk of future ADRD in the surviving population, leading to a lower population ADRD prevalence relative to projections. Second, since nearly a third of COVID-19 patients exhibit neurological symptoms, including cognitive impairment, and COVID-19 survivors are 1.69 times more likely to receive a new ADRD diagnosis within a year of COVID-19 diagnosis (possible manifestation of long-COVID), the pandemic may have increased population $ADRD\ prevalence$.[6,7,8] These explanations have never been tested using large, national samples and rigorous causal inference methods. Moreover, no prior study has examined which clinical, setting-of-care, and contextual factors are most predictive of post-COVID $ADRD\ prevalence$ – an exercise that could reveal underlying mechanisms affecting the two conditions absent any causal relationship between them.

Also critical is understanding whether and how the pandemic may contribute to differences in $ADRD\ prevalence$ across racial/ethnic and socioeconomic groups. ADRD risk is twice as high in racial/ethnic minorities than whites and also significantly higher in socioeconomically disadvantaged (low income/ less educated individuals), regardless of the pandemic,[9,10,11,12] and racial/ethnic minoritized and socioeconomically disadvantaged individuals suffered significantly higher COVID-19-related mortality rates than their white or more advantaged counterparts.[13,14,15] If COVID-19 infection is associated with elevated $ADRD\ prevalence$, the pandemic may have exacerbated existing cognitive health and ADRD disparities.

Project Aims. This study responds to urgent calls for additional research on underlying mechanisms and continuous surveillance of impacts of COVID-19 on $ADRD\ prevalence$ by addressing two aims:

Specific Aim 1: **Characterize changes in population prevalence of $\boldsymbol{ADRD\ prevalence}$ since onset of COVID-19 pandemic and examine sub-population differences in changes in $\boldsymbol{ADRD\ prevalence}$ by race/ethnicity and socioeconomic status.** We hypothesize that population $ADRD\ prevalence$ has increased during the pandemic, particularly in communities with higher pre-pandemic ADRD rates or higher COVID-19 incidence. $ADRD\ prevalence$ of interest in ADRD-naïve older adults will be examined 1- and then 3-5 years post initial COVID-19 diagnosis (short- and medium-term follow-up). Secondary outcomes of interest include incidence of post-COVID-19 health outcomes (e.g., incident cardiovascular outcomes) and healthcare utilization predictive of subsequent new ADRD diagnosis.[16]

Specific Aim 2: Identify clinical, setting-of-care, and contextual factors associated with post-COVID-19 $\boldsymbol{ADRD\ prevalence}$ at the community and individual level. We will examine what features of the COVID-19 experience at the community- and individual- level (e.g., COVID-19 related hospitalization, long covid/brain fog symptoms, COVID-19 vaccinations, hospital bed shortages) affect subsequent $ADRD\ prevalence$, adjusting for potential individual- and community-level confounders. We hypothesize that pre-existing multilevel (individual-, neighborhood-, county-, state- levels) vulnerabilities may further interact with individual/community COVID-19 experiences to affect $ADRD\ prevalence$.

This research will advance the NBER Center for Aging and Health Research goals by expanding our understanding of challenges associated with the compounding impact of the pandemic on short- and medium-term population $ADRD\ prevalence$, in preparation for an R01 to study longer-term outcomes. Understanding factors associated with post-COVID-19 $ADRD\ prevalence$, especially long-COVID, is important for providers and policy makers for health and long-term care planning, and resource distribution to most at-risk sub-populations.

Data. Patient health data include ***Medicare claims data*** with deidentified beneficiary information including demographics (age, sex, race/ethnicity), zip5 of residence, living arrangements, and diagnoses (MCI, ADRD, COVID-19, long-COVID, comorbidities) captured using ICD-10 codes and prescription claims. Comorbidities confounded with patient ADRD trajectories will be controlled for using covariate indicators for patient ever received a diagnosis for diabetes, obesity, or cardiovascular disease. Community COVID-19 data will include

COVID-19 cases and mortality data from multiple trackers (e.g., ***CDC***,[17] ***Johns Hopkins***,[18] ***NY Times***,[19] ***COVID Tracking Project***[20]), and community pandemic-economic loss (e.g., county (un)employment and wages from ***BLS LAUS***[21] and ***QCEW***[22]). Community contextual factors are ZIP5 median household income, poverty rate and health-uninsured rates from ***U.S. Census ACS***[23], county number of nursing home residents per capita, incarcerated rate, and healthcare resources (ICU and hospital beds, and active medical doctors per 1000) from ***U.S. HRSA Area Health Resources File***; from public-use ***CMS Provider of Service* files** hospital characteristics (number of beds, profit status, county, hospital category, and medical school affiliation). ***AHRQ Social Determinants of Health Data***[24] (zip5 and county, annually for 2011-2020, with expected updates during study period) and composite community vulnerability measures (e.g., ***Area Deprivation Index***[25] and ***CDC Social Vulnerability Index*** at zip code, census tract, county levels[26].

Research Design. Using claims data, we will construct 2 parallel cohorts of ADRD-naive beneficiaries aged 65+: pre-pandemic *control* (e.g., Jan. 2015 – Mar. 2020) and pandemic *treated* (e.g., Jan. 2017 – Mar. 2022) groups, each with 13 quarters of pre- and 8 quarters of post- periods. Using the number of enrollees (overall or by relevant sub-group (e.g., by race category), we will construct and compare rates of, for instance, new-onset ADRD in pandemic relative to the pre-pandemic group**.** Specifically, **for Specific Aim 1**, proxying beneficiary's community with zip5 of their residence, we will use event study regressions to examine how cumulative rates of new-onset ADRD evolved in the zip5 leading up to and following COVID-19 pandemic onset in March 2020, by comparing the accumulation of new ADRD diagnoses in the 8-quarters of the post-period of the pandemic group with those in the control pre-pandemic group. Our estimates will reveal whether the pandemic has been associated with higher rates of new-onset ADRD. Specifically, the cumulative rate of new ADRD diagnosis in group $g \in$ {*control, treated*}, zip5 z, and quarter-year $t \in [-13, 8]$ will be modeled as:

$$y_{gzt} = \sum_{a=-13}^{-5} \alpha_a \cdot 1\left(TSE_{gzt} = -a\right) + \sum_{b=0}^{8} \beta_b \cdot 1\left(TSE_{gzt} = b\right) + X'_{gzt} + \mu_g + \gamma_t + \theta_z + \epsilon_{gzt} \quad (Model\ 1)$$

where, TSE_{gzt} is the number of quarters since start of the *post* period for treated group, avoiding concerns about bias in estimates in case of staggered timing of treatment.[27] $TSE_{gzt} = 0$ for the pre-pandemic control. X'_{azt} are time variant community variables, including cumulative county COVID-19 mortality rate. μ_g and θ_z are group g and zip5 fixed effects, respectively, to capture fixed level differences in new-onset ADRD rates between groups, and across zip5 during the study period; quarter-year fixed effects, γ_t, capture secular trends. The reference period will be the year *prior* to *post period* ($TSE_{gzt} \in$ [-4,-1]), estimated with heteroscedasticity robust standard errors clustered at county level. The resulting event study coefficients α_a and β_b will trace out pandemic deviations from common trends in quarters leading up to and following pandemic onset, respectively. We will also estimate model (1) in samples stratified by race/ethnicity, socioeconomic status (e.g., above/below 100FPL, by college education) and pre-pandemic rates of new-ADRD diagnosis (i.e., above/below median, or continuous zip5 pre-pandemic new-ADRD rate). Comparing quarterly new-onset ADRD rates in the pandemic vs prepandemic cohorts (just shifted back in time), will provide seasonally adjusted changes in new-onset ADRD rates associated with the pandemic. **For Specific Aim 2**, first, proxying community by zip5 we will examine how new-onset ADRD rate changes in pandemic may vary by baseline community vulnerability and COVID-19 experiences by estimating augmented versions of model (1) with interactions of the set of event-time indicators with measures of baseline community vulnerability (e.g., pre-pandemic zip5 ADRD prevalence and poverty rate, and cumulative county COVID-19 death rates). **For all Aims,** we will also estimate patient-level logistic regressions for $ADRD\ prevalence$ within 1 year and 3 years post initial COVID-19 diagnosis, controlling for baseline comorbidities, incidence of (long) COVID, COVID-19 related hospitalization/ICU care, and individual and community socioeconomic and demographic factors. In future we also plan to extend these analyses using the ***Health and Retirement Study (HRS)-Medicare linked data (currently 1992-2018)***, when they become available for the pandemic period. In addition to Medicare variables, HRS-Medicare data include, from the biennial HRS survey, beneficiary physical and mental health histories spanning middle to old age (e.g., ADRD diagnosis and MMSE cognitive health screenings capturing cognition changes prior to, often delayed ADRD diagnosis[28,29]), functional limitations, disability, education, employment, assets and income, lifestyle and activities, social networks, and proxy measures of available informal care for over 30,000 people aged 50+. Again, constructing prepandemic control and pandemic treatment cohorts of respondents aged 65+, we will estimate pandemic associated changes in cognition scores among ADRD naïve and prepandemic ADRD diagnosed respondents, after controlling for baseline comorbidities and cognitive health, COVID-19 incidence, family structure, and individual and community socioeconomic and demographic factors. Team has prior experience using both Medicare claims and HRS data. These complimentary analyses will shed light on whether the pandemic may have more broadly accelerated age-related cognitive decline in ADRD naïve patients, with impending cognitive impairment/ADRD diagnosis, and existing ADRD patients, both predicting even greater cognitive impairment and ADRD related healthcare needs in the future.

Budget: $2,000 for Medicare Data Re-use for one year. $4,374 conference travel funds to present early-stage work for feedback at, for instance, Gerontology Society of America Annual Scientific Meetings. $15,626 for 1 month of summer salary support for Gupta and $28,000 for RA costs (through NBER payroll) for Medicare (and potentially HRS-Medicare) data analysis.

[1] U.S. burden of Alzheimer's disease, related dementias to double by 2060 | CDC Online Newsroom |CDC

[2] Monetary Costs of Dementia in the United States | NEJM. Accessed February 14, 2023. https://www.nejm.org/doi/full/10.1056/NEJMsa1204629

[3] Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, September 22. https://covid.cdc.gov/covid-data-tracker

[4] Centers for Disease Control and Prevention. COVID-19 Risks and Vaccine Information for Older Adults. US Department of Health and Human Services, CDC; 2021, August 4. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html

[5] Gilstrap L, Zhou W, Alsan M, Nanda A, Skinner JS. Trends in Mortality Rates Among Medicare Enrollees With Alzheimer Disease and Related Dementias Before and During the Early Phase of the COVID-19 Pandemic. JAMA Neurol. 2022 Apr 1;79(4):342-348. doi: 10.1001/jamaneurol.2022.0010. PMID: 35226041; PMCID: PMC8886452.

[6] Tavares-Júnior JWL, de Souza ACC, Borges JWP, et al. COVID-19 associated cognitive impairment: A systematic review. *Cortex*. 2022;152:77-97. doi:10.1016/j.cortex.2022.04.006

[7] Alzheimer's-like signaling in brains of COVID-19 patients - Reiken - 2022 - Alzheimer's & Dementia - Wiley Online Library. Accessed February 6, 2023. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12558

[8] Wang L, Davis PB, Volkow ND, Berger NA, Kaelber DC, Xu R. Association of COVID-19 with New-Onset Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2022;89(2):411-414. doi:10.3233/JAD-220717

[9] Data shows racial disparities in Alzheimer's disease diagnosis between Black and white research study participants | National Institute on Aging (nih.gov)

[10] Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer Disease Incidence: A Prospective Cohort Study. *Archives of Neurology*. 2002;59(11):1737-1746. doi:10.1001/archneur.59.11.1737

[11] 2020 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2020;16(3):391-460. doi:10.1002/alz.12068

[12] Evans DA, Hebert LE, Beckett LA, et al. Education and Other Measures of Socioeconomic Status and Risk of Incident Alzheimer Disease in a Defined Population of Older Persons. *Archives of Neurology*. 1997;54(11):1399-1405. doi:10.1001/archneur.1997.00550230066019

[13] Poulson M, Geary A, Annesi C, et al. National Disparities in COVID-19 Outcomes between Black and White Americans. *J Natl Med Assoc*. 2021;113(2):125-132. doi:10.1016/j.jnma.2020.07.009

[14] Glance LG, Thirukumaran CP, Dick AW. The Unequal Burden of COVID-19 Deaths in Counties With High Proportions of Black and Hispanic Residents. Med Care. 2021 Jun;59(6):470–6

[15] Upshaw TL, Brown C, Smith R, Perri M, Ziegler C, Pinto AD. Social determinants of COVID-19 incidence and outcomes: A rapid review. *PLOS ONE*. 2021;16(3):e0248336. doi:10.1371/journal.pone.0248336

[16] Xie, Yan, et al. "Long-term cardiovascular outcomes of COVID-19." *Nature medicine* 28.3 (2022): 583-590.

[17] CDC. COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/ (2020).

[18] COVID-19 United States Cases by County - Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/us-map.

[19] *covid-19-data: An ongoing repository of data on coronavirus cases and deaths in the U.S*. (Github).

[20] The COVID Tracking Project. https://covidtracking.com/.

[21] Local area unemployment statistics home page. https://www.bls.gov/lau/ (2008).

[22] Quarterly Census of Employment and wages. https://www.bls.gov/cew/ (2020).

[23] American Community Survey (ACS) (census.gov)

[24] Social determinants of health database (beta version). https://www.ahrq.gov/sdoh/data-analytics/sdohdata.html.

[25] Neighborhood Atlas - Home. https://www.neighborhoodatlas.medicine.wisc.edu/.

[26] CDC/ATSDR's Social Vulnerability Index (SVI). https://www.atsdr.cdc.gov/placeandhealth/svi/index.html (2021).

[27] Callaway B, Sant'Anna PHC. Difference-in-Differences with multiple time periods. *Journal of Econometrics*. 2021;225(2):200-230. doi:10.1016/j.jeconom.2020.12.001

[28] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98. doi: 10.1016/0022-3956(75)90026-6. PMID: 1202204.

[29] Dubois B, Padovani A, Scheltens P, Rossi A, Dell'Agnello G. Timely Diagnosis for Alzheimer's Disease: A Literature Review on Benefits and Challenges. J Alzheimers Dis. 2016;49(3):617-31. doi: 10.3233/JAD-150692.