**Excess Mortality with Alzheimer’s Disease or Related Dementias as an Underlying or Contributing Cause: Comparing the First and Second Year of the COVID-19 Pandemic in the United States**

Ruijia Chen ScD1, Marie-Laure Charpignon MS2, Rafeya Villanueva Raquib MS3, Jingxuan Wang MS1, Erika Meza MPH1, Hélène E. Aschmann PhD1, Michelle A. DeVost MPH1, Alyssa Mooney PhD4, Kirsten Bibbins-Domingo PhD MD1,5,Alicia R. Riley PhD6, Mathew V. Kiang ScD7, Yea-Hung Chen PhD1, Andrew C. Stokes PhD8, M. Maria Glymour ScD1

1 Department of Epidemiology and Biostatistics, University of California, San Francisco

2 Institute for Data, Systems, and Society, Massachusetts Institute of Technology

3 Department of Global Health, Boston University School of Public Health

4 Institute for Health Policy Studies, University of California, San Francisco

5 Department of Medicine, University of California, San Francisco

6 Department of Sociology, University of California, Santa Cruz

7 Department of Epidemiology and Population Health, Stanford University School of Medicine

8 Department of Global Health, Boston University School of Public Health

***Corresponding Author:***

M. Maria Glymour, ScD

Department of Epidemiology and Biostatistics, University of California, San Francisco

550 16th Street, 2nd Floor, Box #0560, San Francisco, CA 94158

(415) 476-2300

maria.glymour@ucsf.edu

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**Key Points**

**Question:** How did mortality with Alzheimer’s Disease or Related Dementias (ADRD) as a contributing or underlying cause change during the COVID-19 pandemic?

**Findings:** This nationwide study indicated a large increase in deaths with ADRD as an underlying or contributing cause during year 1 of the pandemic (March 2020 to February 2021) compared to pre-pandemic mortality rates, but substantial declines from year 1 to year 2 (March 2021 to February 2022). The largest declines were among nursing home residents.

**Meaning:** Vaccine access or policy changes during pandemic year 2 may have reduced mortality among people with ADRD living in nursing homes.

**Abstract**

**IMPORTANCE:** Adults withAlzheimer’s Disease or Related Dementias (ADRD) are particularly vulnerable to the direct and indirect effects of the COVID-19 pandemic. Deaths associated with ADRD increased substantially in the first year of the pandemic. It is unclear whether mortality associated with ADRD declined when better prevention strategies, testing, and vaccines became widely available in year 2 of the pandemic. These protections may have varied by group and setting.

**OBJECTIVE**:To compare pandemic-era excess in deaths associated with ADRD between year 1 and year 2 of the pandemic overall and by age, sex, race and ethnicity, and place of death.

**DESIGN:** Retrospective, time series analysis of observational data (2014-2022).

**SETTING:** Nationwide study of US deaths.

**PARTICIPANTS: All** US decedents aged 65 years and older with ADRD as an underlying or contributing cause of death from 2014 through February 2022 (*N* = 2,334,101 deaths).

**Exposure(s):** Covid-19 pandemic

**MAIN OUTCOMES AND MEASURES:**Pandemic-era excess deaths with ADRD were defined as the difference between deaths with ADRD as an underlying or contributing cause observed from March 2020 to February 2021 (year 1) and March 2021 to February 2022 (year 2) compared to expected deaths during this period. Expected deaths were estimated using data from January 2014 to February 2020 fitted with autoregressive integrated moving average models.

**RESULTS:** We estimated 94,688 (95% PI, 84,192-104,891) pandemic-era excess deaths with ADRD in year 1 and 21,586 (95% PI, 10,631-32,450) in year 2. Declines in ADRD-related deaths in year 2 were substantial for every age group, sex, and racial and ethnic group evaluated. Pandemic-era ADRD-related excess deaths declined among nursing home/long-term care residents (from 34,259 (95% PI, 25,819 - 42,677) in year 1 to -22,050 (95% PI, -30,765 − -13,273) in year 2), but excess deaths at home remained high (from 34,487 (95% PI, 32,815 - 36,142) in year 1 to 28,804 (95% PI, 27,067- 30,571) in year 2).

**CONCLUSIONS AND RELEVANCE:**Large increases inmortality with ADRD as an underlying or contributing cause of death occurred in pandemic year 1 but were largely mitigated in pandemic year 2. The largest declines were observed for deaths with ADRD in nursing homes.

**Key words:** Excess mortality, COVID-19, Alzheimer’s disease, dementia, vaccine coverage

**Introduction**

Older adults with Alzheimer’s Disease or Related Dementias (ADRD) are particularly vulnerable to the direct and indirect impacts of the COVID-19 pandemic.1 Individuals with ADRD may have difficulty adopting behavioral changes to reduce infection risk or regulating contact in high-risk settings. Common comorbidities among older adults with ADRD increase risk of death if infected with SARS-CoV-2.2,3 Social isolation resulting from COVID-19 lockdowns may exacerbate depression and loneliness among individuals with ADRD, increasing their risk of hospitalization and mortality.4,5 Disruptions in care and services may have disproportionately affected individuals with ADRD.6 In the early pandemic period, excess mortality disproportionately affected older adults with ADRD in long-term care facilities, likely due to factors such as high prevalence of comorbidities among nursing home residents, staff shortages, isolation from family and friends, and challenges in implementing and enforcing infection prevention and control measures .1 Sex and racial/ethnic disparities in excess mortality from ADRD were also noted, with more excess deaths in women (vs. men) and non-Hispanic Black and Hispanic (vs. non-Hispanic White) older adults in the early pandemic.1,7

While research has documented substantial excess mortality among individuals with ADRD in the early pandemic, it is unclear how its magnitude changed as the pandemic evolved.1 Pharmaceutical and non-pharmaceutical preventive measures became widely available in the second year of the pandemic, but vaccine distribution and uptake of other measures were inconsistent.8,9 Tracking excess mortality associated with ADRD over the pandemic is critical to inform policy and research priorities, as changes in mortality provide insights into whether current preventive measures are effective at protecting older adults with ADRD. In this study, we assessed pandemic-era changes in mortality with ADRD as an underlying or contributing cause comparing pandemic year 1 (March 2020 to February 2021) to pandemic year 2 (March 2021 to February 2022), in the overall population and by age, sex, race and ethnicity, and place of death.

**Methods**

**Data**

Final death certificate data from January 2014 to December 2021 and provisional death certificate data from January 2022 to February 2022 for individuals age 65 years or older were extracted from the National Center for Health Statistics (NCHS) mortality surveillance system.10,11 We considered deaths with any mention of ADRD on the death certificate, including as the underlying cause or any of up to 19 listed contributing conditions as deaths with ADRD. ADRD was classified by International Classification of Diseases, Tenth Revision codes (ICD-10) and included: unspecified dementia, Alzheimer's disease, vascular dementia, and other degenerative diseases of the nervous system (see **eTable 1**for a listing of ICD-10 codes). Throughout the manuscript, we labeled these as “ADRD-related deaths”for parsimony. We considered deaths among adults aged 65 years and older because this population accounts for most ADRD-related mortality.10,12 We obtained age-, sex-, race/ethnicity-, and state- specific population estimates from the U.S. Census Bureau Population Estimates Program. We calculated excess mortality rates in 2020 and 2021 using the corresponding year's July population estimates as the denominator. Since the 2022 population estimate is not yet available, we used the July 2021 population estimates as the denominators to calculate death rates in January 2022 and February 2022.

The NCHS provided bridged-race death data from 2014 to 2020 and single-race death data from 2018 to 2022. Therefore, we combined 2014-2017 bridged-race data and 2018-2022 single-race data to estimate race-specific excess mortality. To evaluate the potential bias associated with combining single and bridged-race data, we compared both numerators (death counts) and denominators (population size) using single- vs bridged-race categories for the period during which both data sources were available, i.e., 2018-2020 (**eFigure 1**). Differences between the two data sources in both total death counts and population counts were very small for all groups except non-Hispanic American Indian and Alaska Native (AIAN) individuals. Given the discrepancies between single-race and bridged-race data among AIAN, we did not include AIAN decedents.

**Exposures and Stratification Variables**

Pandemic year 1 was defined as March 2020 through February 2021; year 2 was defined as March 2021 through February 2022. We also considered four waves of the pandemic based on the dominant viral variant: Early pandemic (March 1, 2020 - September 31, 2020), Alpha wave (October 1, 2020 - June 30, 2021), Delta wave (July 1, 2021 - November 31, 2021), and Omicron wave (December 1, 2021 - February 28, 2022).

Additional stratification variables included age (65-74 years; 75-84 years; 85 and older), sex (male; female), race and ethnicity (non-Hispanic White; non-Hispanic Black; Hispanic; non-Hispanic Asian or Pacific Islander), and place of death (medical facilities, including inpatient, outpatient, emergency room, dead on arrival; decedent’s home; nursing home/long-term care; hospice facility; or other).

**Statistical Analysis**

We defined pandemic-era excess ADRD-related deaths as the difference between observed and expected deaths over the same period in the absence of the pandemic. To estimate expected deaths, we fitted auto-regressive integrated moving-average models (ARIMA) to monthly ADRD-related death count data from January 2014 to February 2020. We used this pre-pandemic prediction model to forecast the number of ADRD-related deaths that would have been expected in the absence of the pandemic, accounting for historical mortality trends and seasonality.13 We selected the model with the lowest Akaike information criterion and calculated monthly excess deaths as observed minus expected deaths. We calculated total excess deaths by summing all monthly excess deaths and calculated corresponding 95% prediction intervals (PI) by simulating the expected death model 10,000 times, selecting the 2.5 and 97.5 percentiles, and subtracting them from the number of observed deaths. We calculated risk ratios as the observed number of deaths divided by the expected number of deaths. To facilitate comparison across groups, we calculated excess mortality rates per 100,000 individuals, as the number of excess deaths divided by the corresponding population size.

We performed stratified analyses by age, sex, race and ethnicity, and place of death. To facilitate comparison across groups, excess deaths were age-standardized in 10-year categories to the 2000 population when applicable.

**Sensitivity and Exploratory Analyses**

To validate the performance of the ARIMA model, we performed sensitivity analyses using data from 2014 to 2018 to forecast monthly death rates from January to December 2019. All observed deaths fell within the 95% PI of the expected deaths, suggesting accurate predictions (**eTable 2**). In an additional sensitivity analysis, we “imputed” single-race monthly death data for 2014-2017 bridged-race monthly death data (**eTable 3**). To understand whether excess ADRD-related deaths were primarily due to SAS-CoV-2 infections, we cross-classified ADRD deaths and COVID-19 deaths into four groups and analyzed the corresponding trends: 1) ADRD as an underlying cause, COVID-19 as a contributing cause; 2) ADRD as an underlying cause, COVID-19 not listed as a contributing cause; 3) COVID-19 as an underlying cause, ADRD listed as a contributing cause; and 4) neither COVID-19 nor ADRD as an underlying cause (e.g., cancer deaths), but ADRD as a contributing cause.

We conducted exploratory analyses to investigate potential reasons for notable declines in excess deaths between years 1 and 2. First, to understand how changes in population size in nursing home during the pandemic might have influenced the estimate of excess deaths in nursing home, we obtained the monthly number of nursing home residents from the Centers for Medicare & Medicaid Services (CMS) for the years 2019 to 2022 and calculated the adjusted observed number of deaths by comparing the number of total residents from March 2020 to February 2022 to the corresponding monthly number in 2019 (see online supplemental text for details). Second, we evaluated trends in other causes of death at home or in nursing-homes to investigate the possibility of frailty selection, i.e., the frailest individuals with ADRD would have died in pandemic year 1, leaving an unusually small number of individuals with ADRD at risk of death in year 2. We compared the temporal patterns of ADRD-related deaths with four other leading causes of death: cancer, heart disease, respiratory disease, and cerebrovascular disease. To facilitate comparisons, we defined a baseline monthly mortality level for each cause, estimated as the average death count over the 12 months preceding the pandemic (March 2019-February 2020 inclusive).Third, we used weekly COVID-19 vaccination data from the CDC COVID Data Tracker to understand how vaccination may have affected excess mortality. Specifically, we assessed how changes in annualized excess ADRD-related deaths differed by vaccine coverage across US states (see supplemental document for details).14

All analyses were performed using R, version 4.2.1. This study used publicly available data, was not subject to Human Subjects Review, and followed the STROBE guidelines.

**Results**

In pandemic year 1, there were 509,179 ADRD-related deaths among individuals aged 65 years and older (i.e., ADRD as an underlying or contributing cause), of which 12.3% had COVID-19 as an underlying cause. Based on pre-pandemic death rates, 414,491 (95% PI, 404,289- 424,987) ADRD-related deaths were expected in pandemic year 1, implying a year 1 excess of 94,688 (95% PI, 84,192-104,891) ADRD-related deaths. In pandemic year 2, ADRD-related deaths declined to 435,156, implying a year 2 excess of 21,586 (95% PI, 10,631-32,450) ADRD-related deaths (**Figure 1**). Among the ADRD-related deaths in year 2, COVID-19 was listed as an underlying cause for only 4.6%. The pandemic-era excess in ADRD-related deaths thus declined by 77% from year 1 to year 2. In pandemic year 2, there was a decline in the number of ADRD-related deaths both with COVID-19 (*N*decline=45,761) and without COVID-19 (*N*decline =22,427) listed as an underlying or contributing cause (see ***eFigure 2***).

Pandemic-era excess ADRD-related death rates declined substantially between the 1st and 2nd year of the pandemic for every age group, sex, and racial and ethnic groups evaluated (**Table 1, eTable 3**).

Year 2 of the pandemic saw major declines in ADRD-related deaths occurring in long-term care facilities (**eTable 4**): from 34,259 (95% PI, 25,819-42,677) crude excess deaths in year 1 to -22,050 (95% PI, -30,765− -13,273) excess deaths in year 2. In contrast, in year 2, there were only modest declines in ADRD-related deaths occurring at home (from 34,487 (95% PI, 32,815-36,142) to 28,804 (95% PI, 27,067-30,571).

The patterns of changes in monthly ADRD-related mortality were similar for men and women (**Figure 2**), with substantial declines following vaccination rollouts in mid-December 2020. The number of observed deaths continued to decline during the Alpha wave, increased during the Delta wave, and increased substantially during the Omicron wave.

The early pandemic was characterized by large racial/ethnic disparities in excess deaths. In April 2020, excess ADRD-related deaths per 100,000 persons were 64 for Black adults (95% PI, 58-70); White: 30 (95% PI, 24-35); Latino: 33 (95% PI, 28-37); Asian: 25 (95% PI, 21-30) (**Figure 3**). After the mortality peak late in pandemic year 1 and the beginning of vaccine rollout, ADRD-related deaths decreased for all racial/ethnic groups. Between March and June 2021, non-Hispanic White individuals experienced fewer ADRD-related deaths than expected.

Long-term care facilities were hard hit in the early pandemic (**Figure 4**). After vaccine rollout began, ADRD-related deaths in long-term care facilities declined significantly, with lower-than-expected deaths throughout the Delta wave and most of the Omicron wave. In contrast, ADRD-related deaths occurring at home remained elevated throughout year 2 of the pandemic, even after vaccine rollout began. ADRD-related deaths in medical facilities fell after vaccine rollout but increased during the Delta wave.

We investigated potential reasons for declines in excess deaths. First, after adjusting the observed number of deaths based on the percentage changes in the population size of nursing home residents from CMS, a significant decline in excess deaths in year 2 was still observed (year 1: 34,149, 95% CI (25,709 - 42,567; year 2: -2,914, 95% CI (-22,050- -330,765), although the decline became smaller than using the unadjusted observed death. The overall monthly trend in deaths using the adjusted observed deaths was similar to the trend observed using unadjusted observed deaths (**eFigure 3**). These findings suggest that decline in excess deaths in nursing homes cannot be fully explained by declines in population size. Second, comparing across causes of death in nursing homes, we found ADRD-related mortality increased from the pre-pandemic average by 60% in year 1 of the pandemic but only 18% in year 2; patterns were similar for other causes of death that move in tandem with COVID-19, including heart disease (51% elevation in year 1, 12% elevation in year 2), respiratory (31% in year 1 and 10% in year 2), and cerebrovascular diseases (35% in year 1 and 18% in year 2) compared to their respective 12-month pre-pandemic baselines. In contrast, the magnitude of cancer-related deaths occurring in nursing homes remained consistently below historical levels (77 % of pre-pandemic levels in year 1 of the pandemic and 82% of pre-pandemic levels in year 2), from April 2020 onwards (**eFigure 4**). Third, in states in the highest tertiles of pandemic year 1 excess deaths, reductions in pandemic-era excess ADRD-related mortality in year 2 were correlated with both vaccination coverage (*r* = -.54, *p* = .03) and velocity (*r* = -.67, *p* =.003) (**eFigure 45**). These patterns of correlation were not observed in states in the lowest tertile of excess deaths in year 1.

**Discussion**

Using a comprehensive national data set, we found a large excess in ADRD-related deaths in pandemic year 1 which declined significantly in pandemic year 2. We observed declines in ADRD-related deaths both with and without COVID-19 listed as an underlying or contributing cause. Declines in mortality occurred for every age, sex, and racial/ethnic group examined. ADRD-related deaths in long-term care facilities accounted for most of the decline, whereas ADRD-related deaths that occurred at home and in medical facilities remained elevated throughout the pandemic compared to pre-pandemic death rates.

People living with ADRD were uniquely vulnerable to the pandemic. Our findings are consistent with prior research showing large adverse effects of the first year of the pandemic on older adults with ADRD.1,15 For example, a Medicare-based study showed that in 2020, all-cause mortality was 26% higher than expected in people with ADRD compared to prior years.1 Evaluating whether ADRD-related deaths declined in the 2nd year of the pandemic gives insight into whether people with ADRD are benefiting from the evidence and technologies for prevention and treatment developed over the 1st year of the pandemic – including vaccination. We observed a decline in excess deaths during the alpha wave across all groups and settings, whereas an increase in excess deaths was observed during the delta wave. These divergent patterns across waves may not only be attributed to changes in public health policies and interventions but may also reflect differences in infectivity associated with different variants.

ADRD-related deaths fell in pandemic year 2, primarily due to reductions in deaths in long-term care facilities. This finding cannot be explained by relocations from nursing homes to community residences since no similar decline was observed for cancer deaths in nursing homes, which are unlikely to be accelerated or triggered by COVID-19. The frailty selection hypothesis alone is not sufficient to explain the results. If the frailty selection hypothesis is supported, we would expect to see reductions in all leading causes of death. However, cancer deaths in nursing homes remained similar between years 1 and 2. Our findings that faster vaccine rollout and greater coverage were associated with larger reductions in ADRD-related deaths in year 2 suggests that access to vaccines, both for persons living with ADRD and their care providers, may play a key role in reducing excess deaths. Vaccination among staff and residents may lower excess deaths in nursing homes directly through preventing viral transmission and infection and indirectly through reducing social isolation.16 Other factors, including improved surveillance testing of staff members, might have also explained the declines in excess deaths in long-term care facilities.17

Relatedly, the persistently high levels of ADRD-related deaths occurring at home suggest that community-dwelling older adults with ADRD may not have benefited similarly from COVID preventive measures. Community-dwelling older adults with dementia were more likely to put off care during the pandemic than those who live in nursing homes, potentially contributing to high excess home deaths.18 Efforts to reduce excess deaths among community-dwelling older adults living with ADRD are imperative.

Research conducted prior to the pandemic has yielded inconsistent results on racial/ethnic disparities in ADRD mortality.19–23 While we could not directly assess racial/ethnic disparities in ADRD-related mortality without population data on the number of individuals living with ADRD by race and ethnicity, our analysis of mortality differences by race/ethnicity highlights concerning patterns in excess ADRD-related death during the pandemic. Our findings for year 1 suggest that Black older adults with ADRD experienced substantially higher *excess* deaths in the early pandemic. Due to the segregation of nursing home facilities, Black individuals with ADRD may be more likely to cluster in nursing homes that have worse infection rates.24–26 Discrimination in medical settings and differential prevalence of comorbidities may also have contributed to this excess mortality. Racial/ethnic disparities in pandemic-era excess ADRD-related deaths persisted despite declines in ADRD-related deaths across all racial/ethnic groups in year 2 of the pandemic. These findings highlight the need to monitor inequalities and attend to how structural racism can exacerbate vulnerability to ADRD-related and COVID-19 mortality.

**Strengths and Limitations**

Our data may not fully capture deaths among *all* individuals with ADRD, if ADRD was undiagnosed or if the diagnosis was not considered to contribute to cause of death.27 However, the patterns of temporal changes in ADRD-related excess deaths that our study revealed are corroborated unpublished Medicare data, which showed a decline in excess deaths *among individuals with ADRD* in 2021.28 Our findings may underestimate the number of ADRD-related deaths from racial/ethnic minority groups in whom ADRD underdiagnosis is common.29 Finally, the 2022 death certificate data are provisional. Although analyzing finalized death certificates would be ideal, using currently available data is critical to inform timely policy responses.

This study has several strengths. The inclusion of 2020, 2021, and early 2022 data allowed us to capture the dynamics of the pandemic’s impact on individuals who lived with ADRD. Most prior research relied on underlying-cause-of-death classification.7,15 Our inclusion of both the underlying and contributing causes of death likely lessens the impact of misclassification of both ADRD and COVID-19.30,31 Our time series models starting in 2014 accounted for pre-pandemic temporal trends in deaths, for example due to population aging or increased ADRD diagnoses.32

**Conclusions**

Pandemic-era mortality with ADRD as an underlying or contributing cause has been extremely high. These deaths are often preventable, and ADRD-related mortality fell markedly in long-term care settings later in the pandemic. Vaccinations were likely critical to these improvements. Our findings underscore the urgent need to mitigate the pandemic’s impacts on community-dwelling older adults with ADRD.

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**Author Contributions:**

Concept and design: Chen R, Stokes, Glymour

Acquisition, analysis, or interpretation of data: All coauthors

Drafting of the manuscript: Chen R, Glymour

Critical revision of the manuscript for important intellectual content: All coauthors

Statistical analysis: Chen R, Charpignon, Raquib, Wang, Chen, Y-H

Obtained funding: Bibbins-Domingo

Administrative, technical, or material support: Chen R, Devost, Chen, Y-H

Supervision: Glymour

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