COVID-19 breakthrough infections and hospitalizations among vaccinated patients with dementia in the United States between December 2020 and August 2021

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Abstract

Introduction: There is lack of data on COVID-19 breakthrough infections in vaccinated patients with dementia in the United States.

Methods: This is a retrospective cohort study of 262,847 vaccinated older adults (age 73.8 ± 6.81 years old) between December 2020 and August 2021.

Results: Among the fully vaccinated patients with dementia, the overall risk of COVID-19 breakthrough infections ranged from 8.6% to 12.4%. Patients with dementia were at increased risk for breakthrough infections compared with patients without dementia, with the highest odds for patients with Lewy body dementia (LBD) (adjusted odds ratio or AOR: 3.06, 95% confidence interval or CI [1.45 to 6.66]), followed by vascular dementia (VD) (AOR: 1.99, 95% CI [1.42 to 2.80]), Alzheimer’s disease (AD) (1.53, 95% CI [1.22 to 1.92]), and mild cognitive impairment (MCI) (AOR: 1.78, 95% CI [1.51 to 2.11]). The incidence rate of breakthrough infections among fully vaccinated patients with dementia increased since December 2020 and accelerated after May 2021. The overall risk for hospitalization after breakthrough infections in patients with dementia was 39.5% for AD, 46.2% for VD, and 30.4% for MCI.

Discussion: These results highlight the need to continuously monitor breakthrough severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and outcomes in vaccinated patients with dementia.

Keywords
Alzheimer’s Disease, breakthrough infections, COVID-19, frontotemporal dementia, Lewy body dementia, mild cognitive impairment, patient electronic health records, vaccine, dementia, vascular dementia

1 INTRODUCTION

An estimated 5.8 million Americans 65 years of age or older and 50 million people worldwide are living with Alzheimer’s and other dementias.1 Strong risk factors for cognitive decline and dementia include cardiovascular diseases, diabetes, obesity, hypertension, kidney diseases, and psychiatric disorders,2–5 many of which are also demonstrated risk factors for coronavirus disease 2019 (COVID-19) infection and adverse outcomes.6–12 Our previous study based on the early pandemic data showed that patients with dementia, including
Alzheimer’s disease (AD) and vascular dementia (VD) were at increased risk for COVID-19 infection and severe outcomes, especially among African Americans, even after controlling for demographic factors and comorbidities.

In the United States, vaccines have been approved to prevent COVID-19 infection including two messenger RNA (mRNA) vaccines developed by Pfizer-BioNTech and Moderna and an adenovirus vaccine by Johnson & Johnson (J&J). Clinical trial data showed an efficacy of 95% for the Pfizer-BioNTech vaccine, 94.1% for the Moderna vaccine, and 66.3% for the J&J vaccine in preventing COVID-19 infection. However, both older adults and patients with dementia were under-represented in clinical trials for COVID-19 vaccines. For example, in the clinical trial for Pfizer-BioNTech vaccine, the median age for the 37,706 participants was 52 years and included only 18 individuals with dementia (0.05%). Vaccines are very effective, but breakthrough infections have been recorded, highlighting the need to understand the populations that might be most vulnerable, including patients with AD and other types of dementia, as we have entered a worrisome new phase of the pandemic with emerging virus variants.

2 | METHODS

2.1 Database description and study population

We used the cloud-based TriNetX Analytics network platform, which allows access to de-identified data of > 84 million unique patients from 61 health care organizations in the United States. Multiple studies have used TriNetX Analytics network platform to study risk, disparity, sequelae, temporal trends, clinical characteristics, and outcomes of COVID-19. Our study population comprised 262,847 older adults (age ≥65 years) who were vaccinated between December 2020 and August 2021 and who had no COVID-19 infection prior to vaccination. 2764 of whom had a diagnosis of AD, 1244 had a diagnosis of VD, 259 had a diagnosis of Lewy body dementia (LBD), 229 had a diagnosis of frontotemporal dementia (FTD), and 4385 had a diagnosis of mild cognitive impairment (MCI).

TriNetX Analytics is a federated cloud-based network providing web-based real-time secure access to patient electronic health records (EHRs) from hospitals, primary care and specialty treatment providers of diverse geographic locations, age groups, race/ethnic groups, and income levels. Although the data are de-identified, end-users can use TriNetX Analytics built-in statistical and informatics functions to work on patient-level data for cohort selection, propensity-score matching, analyzing incidence and prevalence of events in a cohort, and comparing characteristics and outcomes between matched cohorts. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from institutional review board approval.

The status of COVID-19 was based on the Current Procedural Terminology (CPT) code “Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) disease” and the related ICD-10 diagnosis code of “Sars coronavirus 2 and related rna” (TNX:LAB:9088). The status of COVID-19 vaccination was based on the Current Procedural Terminology (CPT) code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage” (TNX:LAB:9088). The status of COVID-19 vaccination was based on the Current Procedural Terminology (CPT) code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted, for intramuscular use” (TNX:LAB:9088). The status of COVID-19 vaccination was based on the Current Procedural Terminology (CPT) code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage, for intramuscular use” (TNX:LAB:9088). The status of COVID-19 vaccination was based on the Current Procedural Terminology (CPT) code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, for intramuscular use” (TNX:LAB:9088). The status of COVID-19 vaccination was based on the Current Procedural Terminology (CPT) code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage, for intramuscular use” (TNX:LAB:9088). The status of COVID-19 vaccination was based on the Current Procedural Terminology (CPT) code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted, for intramuscular use” (TNX:LAB:9088). The status of COVID-19 vaccination was based on the Current Procedural Terminology (CPT) code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage, for intramuscular use” (TNX:LAB:9088).

The status of full vaccination was based on the code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted” (TNX:LAB:9088). The status of full vaccination was based on the code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted; second dose” (TNX:LAB:9088). The status of full vaccination was based on the code “Immunization administration by intramuscular injection of SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage; second dose” (TNX:LAB:9088).

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed sources. Vaccines are effective against coronavirus disease 2019 (COVID-19) infection, but breakthrough infections have been recorded. However, there is lack of data on the risks, disparity, time trends, and outcomes of breakthrough infections in vaccinated patients with dementia in the United States. The relevant citations are appropriately cited.

2. Interpretation: Our findings show that the risks of breakthrough infections among fully vaccinated patients with dementia ranged from 8.6% to 12.4%, significantly higher than propensity-score matched patients without dementia. The incidence rates of breakthrough infections among fully vaccinated patients with dementia accelerated after May 2021. Breakthrough infections in fully vaccinated patients with dementia were associated with significant hospitalization.

3. Future directions include continuing to evaluate breakthrough infections in vaccinated patients with dementia infections, especially with the emergence of different virus variants and continuing to monitor outcomes including hospitalization and mortality associated with breakthrough infections patients with dementia.
TABLE 1 Covariates and their standardized names, codes, and data types that are used in the TriNeX database

| Covariate                                      | Name, code                                             | Data type         |
|------------------------------------------------|--------------------------------------------------------|-------------------|
| Age at index                                   | Age at index                                           | Continuous        |
| Female                                         | F                                                      | Present/absent    |
| Male                                           | M                                                      | Present/absent    |
| White (Demographics)                           | White (Demographics: 2106-3)                          | Present/absent    |
| Black or African American                      | Black or African American (Demographics: 2054-5)      | Present/absent    |
| Hispanic/Latino (Demographics: 2135-2)        | Present/absent                                         |                   |
| Asian (Demographics: 2028–9)                  | Present/absent                                         |                   |
| Hypertension (ICD-10 code: I10-I16)            | Present/absent                                         |                   |
| Heart diseases (ICD-10 code: I20-I25)          | Present/absent                                         |                   |
| Cerebrovascular diseases (ICD-10 code: I60-I69)| Present/absent                                         |                   |
| Obesity/overweight (ICD-10 code: E66)          | Present/absent                                         |                   |
| Type 2 diabetes mellitus (ICD-10 code: E11)   | Present/absent                                         |                   |
| Cancer (ICD-10 code: C00-D49)                  | Present/absent                                         |                   |
| Chronic lower respiratory diseases (ICD-10 code: J40-J47) | Present/absent                                      |                   |
| Chronic kidney disease (ICD-10 code: N18)      | Present/absent                                         |                   |
| Diseases of liver (ICD-10 code: K70-K77)       | Present/absent                                         |                   |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10 code: D50-D89) | Present/absent                                      |                   |
| Tobacco use (ICD-10 code: Z72.0)               | Present/absent                                         |                   |
| Alcohol-related disorders (ICD-10 code: F10)   | Present/absent                                         |                   |
| Anxiety (ICD-10 code: F40-F48)                 | Present/absent                                         |                   |
| Depressive episode (F32)                       | Present/absent                                         |                   |
| Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (ICD-10 code: F20-F29) | Present/absent                                      |                   |
| Sleep disorders (ICD-10 code: G47)             | Present/absent                                         |                   |
| Persons with potential health hazards related to socioeconomic and psychosocial circumstances (ICD-10 code: Z55-Z65) | Present/absent                                      |                   |

The status of AD was based on ICD-10 diagnosis code of “AD” (G30), VD on (F01), LBD on “Dementia with Lewy bodies” (G31.83), FTD on (G31.0), and MCI on "MCI, so stated" (G31.84). Other subtypes of dementia were not examined due to their small sample sizes.

2.2 Statistical analysis

The following analyses were performed. For each analysis, the outcome of breakthrough COVID-19 infection was examined 14 days after vaccination. All statistical analyses were performed on the TriNetX Analytics Platform at significance set at P-value < .05 (two-sided).

The list of covariates, and their standardized names, codes and data types that are used in the TriNetX database are described in Table 1. These covariates included demographics (age, gender, race/ethnicity); socioeconomic determinants of health (SDOHs) that were based on ICD-10 code “persons with potential health hazards related to socioeconomic and psychosocial circumstances” (Z55-Z65), which includes “problems related to education and literacy” (Z55), “problems related to employment and unemployment” (Z56), “occupational exposure to risk factors” (Z57), “problems related to housing and economic circumstances” (Z59), “problems related to upbringing” (Z62), among others; nursing home stay; comorbidities that are demonstrated risk factors for COVID-19.6-12

The following statistical analyses were performed:

- We examined the overall risks of breakthrough infections in the vaccinated patients with dementia and patients without dementia during the 8-month period between December 2020 and August 2021. The odds of breakthrough infections in the vaccinated patients with dementia were calculated by comparing to those without dementia, after propensity score matching (1:1 using a nearest neighbor greedy matching) for covariates listed in Table 1. Separate analysis was performed for AD, VD, LBD, FTD, and MCI.
• We examined how the risk of breakthrough infections in the fully vaccinated patients with dementia population evolved during the period of December 1, 2020 and August 1, 2021. The rates of new cases of COVID-19 infection, measured by cases/person-day, in the vaccinated population stratified by age, gender, and race were examined. Separate analyses were done for dementia subtypes and non-dementia.

• We investigated how age, gender, and race differentially affected the risk of vaccine breakthrough infection among fully vaccinated population. The stratified cohort comprised fully vaccinated patients with dementia patients who had one of the following demographic factors: female, older (age ≥80 years), African American. The comparison cohorts comprised patients with dementia who had one of the following corresponding demographic factors: male, younger (age 65 to 79 years), Caucasian. Cohorts were propensity-score matched on other demographics and covariates listed in Table 1. Separate analyses were done for specific dementia subtypes and non-dementia.

• The overall risks for hospitalizations in patients who had breakthrough infections (breakthrough cohort) were examined and compared with those in patients who had no breakthrough infections (non-breakthrough cohort). Two cohorts were propensity-score matched for the covariates listed in Table 1. Hospitalizations were followed starting on the day of breakthrough infections for the breakthrough cohort or 14 days after full vaccination for the non-breakthrough cohort up to August 1, 2021. Kaplan-Meier analysis was performed to estimate the probability of hospitalizations. Comparison of outcomes between patients with versus without breakthroughs were made using Cox proportional hazards model. The proportional hazard assumption was tested using the generalized Schoenfeld approach. When the assumption was violated, the Cox model was stratified by the variate violating the proportional hazards assumption. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Separate analyses were done for AD, VD, and MCI and non-dementia. LBD and FTD were not examined due to limited sample sizes. Mortality was not examined due to small sample sizes. For The Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant statistical de-identification, the TriNetX platform does not report actual cohort counts <10. The numbers of deaths in the cohorts during the study period were all <10, preventing an accurate estimate of the death rates.

3 RESULTS

3.1 Patients’ characteristics (as of August 1, 2021)

The study population comprised 262,847 vaccinated older adults (age ≥65 years). Demographic characteristics of the patients and sample sizes are shown in Table 2. Patients with dementia including AD and VD were older than those without dementia. There were more women

in the vaccinated population except for patients with LBD. Compared to other cohorts, the cohort with VD had more African Americans (25.9%). The prevalence of adverse socio-economic status and nursing home stay was also higher in the dementia population than in patients without dementia.

Patients with dementia, regardless of subtype, had a higher prevalence of comorbidities that are demonstrated risk factors for COVID-19 including hypertension, obesity, type 2 diabetes, heart diseases, cerebrovascular diseases, cancers, chronic respiratory diseases, liver diseases, chronic kidney diseases, substance use disorders (including tobacco and alcohol use), and neuropsychiatric disorders. For example, the prevalence of hypertension in vaccinated patients with AD and VD was 69.9% and 79.7%, as compared to 37.9% in vaccinated patients without dementia.

3.2 Overall accumulated risks for breakthrough infections in the vaccinated patients between December 2020 and August 2021

Between December 2020 and August 2021, the overall risk of breakthrough infections beginning 14 days following vaccination in older adults without dementia was 5.6%. The risks of breakthrough infections were significantly higher in patients with various types of dementia: 10.3% for AD, 12.5% for VD, 14.3 for LBD, 11.8% for FTD, and 11.6% for MCI (Table 3).

Among 262,847 vaccinated older adults in the database, 225,763 (85.9%) were fully vaccinated and received both doses of Pfizer-BioNTech or Moderna mRNA vaccines. The overall risks of breakthrough infections in fully vaccinated patients were lower than those in the general vaccinated populations. Among the fully vaccinated older adults, patients with dementia had significantly higher risks of breakthrough infections compared to patients without dementia, which was consistent across all five dementia types (Table 3). Subsequent analyses focused on breakthrough infections in the fully vaccinated population.

3.3 Dementia is associated with increased risk of breakthrough infections in vaccinated population between December 2020 and August 2021

As seen in Table 2, the demographics (age, gender, and race/ethnicity) prevalence of adverse SDOHs and status of nursing home stay were different in the vaccinated older adult population with dementia from those without dementia. For example, patients with dementia were older than those without dementia. After propensity-score matching for demographics, SDOHs, and nursing home stay status, fully vaccinated patients with dementia had significantly increased odds of breakthrough infections compared to the matched cohort of patients without dementia, with the highest risk for patients with LBD (adjusted odds ratio [AOR]: 3.06, 95% confidence interval [CI]: 1.45 to
Table 2 Patient characteristics of vaccinated older adult population (as of August 1, 2021) for the various dementia subtypes and for non-dementia in the TriNetX database

| Vaccinated patient characteristics (age ≥65 years) | All | AD | VD | LBD | FTD | MCI | Non-dementia |
|----------------------------------------------------|-----|----|----|-----|-----|-----|--------------|
| Total no. of patients                              | 262,847 | 2764 | 1244 | 259 | 229 | 4385 | 252,926 |
| Age (mean ± SD)                                    | 73.8 ± 6.81 | 80.7 ± 6.78 | 80.2 ± 6.87 | 77.9 ± 6.8 | 75.1 ± 6.77 | 77.6 ± 6.89 | 73.6 ± 6.72 |
| Gender                                             |                |                |                |                |                |                |               |
| Female                                             | 149,470 (56.9%) | 1803 (65.2%) | 734 (59.0%) | 99 (38.2%) | 121 (52.8%) | 2468 (56.3%) | 143,560 (56.8%) |
| Male                                               | 113,355 (43.1%) | 961 (34.8%) | 510 (41.0%) | 160 (61.8%) | 108 (47.2%) | 1917 (43.7%) | 109,344 (43.2%) |
| Race/ethnicity                                     |                |                |                |                |                |                |               |
| White                                              | 190,630 (72.5%) | 1918 (69.9%) | 782 (62.9%) | 191 (73.7%) | 183 (79.9%) | 3373 (76.9%) | 183,562 (72.6%) |
| Black or African American                          | 35,534 (13.5%) | 517 (18.7%) | 322 (25.9%) | 40 (15.4%) | 28 (12.2%) | 623 (14.2%) | 33,728 (13.3%) |
| Hispanic/Latino                                    | 21,609 (8.2%) | 218 (7.9%) | 95 (7.6%) | 10 (3.9%) | 17 (7.4%) | 266 (6.1%) | 21,021 (8.3%) |
| Asian                                              | 14,289 (5.4%) | 111 (4.0%) | 44 (3.5%) | 10 (3.9%) | 10 (4.4%) | 127 (2.9%) | 13,947 (5.5%) |
| Unknown                                            | 20,751 (7.9%) | 204 (7.4%) | 87 (7.0%) | 21 (8.1%) | 13 (5.7%) | 247 (5.6%) | 20,087 (7.9%) |
| Comorbidities                                      |                |                |                |                |                |                |               |
| Hypertension                                       | 103,061 (39.2%) | 1904 (69.9%) | 992 (79.7%) | 153 (59.1%) | 128 (55.9%) | 2915 (66.5%) | 95,957 (37.9%) |
| Heart diseases                                     | 30,317 (11.5%) | 628 (22.7%) | 391 (31.4%) | 64 (24.7%) | 52 (23.1%) | 1071 (24.4%) | 27,701 (11.0%) |
| Cerebrovascular diseases                           | 20,070 (7.6%) | 763 (27.6%) | 653 (52.5%) | 77 (29.7%) | 53 (23.1%) | 1323 (30.2%) | 16,875 (6.7%) |
| Obesity/overweight                                 | 28,651 (10.9%) | 341 (12.3%) | 225 (18.5%) | 30 (11.6%) | 19 (8.3%) | 801 (18.3%) | 26,879 (10.6%) |
| Type 2 diabetes                                    | 36,750 (14.0%) | 723 (26.2%) | 450 (36.2%) | 59 (22.8%) | 51 (22.7%) | 1128 (25.7%) | 33,940 (13.4%) |
| Cancer                                             | 41,965 (16.0%) | 1016 (36.8%) | 607 (48.8%) | 47 (18.1%) | 41 (17.9%) | 966 (22.0%) | 37,980 (15.0%) |
| Chronic respiratory diseases                       | 30,283 (11.5%) | 527 (19.1%) | 322 (25.9%) | 47 (18.1%) | 41 (17.9%) | 966 (22.0%) | 27,899 (11.0%) |
| Chronic kidney diseases                            | 19,457 (7.4%) | 554 (20.0%) | 348 (28.0%) | 45 (17.4%) | 26 (11.4%) | 776 (17.7%) | 17,410 (6.9%) |
| Liver diseases                                     | 12,574 (4.8%) | 169 (6.1%) | 120 (9.6%) | 21 (8.1%) | 15 (6.6%) | 419 (9.6%) | 11,547 (4.6%) |
| Blood disorders (involving immune mechanisms)      | 41,965 (16.0%) | 1016 (36.8%) | 607 (48.8%) | 88 (34.0%) | 68 (29.7%) | 1638 (37.4%) | 37,980 (15.0%) |
| Tobacco use                                        | 10,360 (3.9%) | 147 (5.3%) | 113 (9.1%) | 11 (4.2%) | 15 (6.6%) | 277 (6.3%) | 9635 (3.8%) |
| Alcohol use                                        | 3589 (1.4%) | 93 (3.4%) | 70 (5.6%) | 10 (3.9%) | 10 (4.4%) | 198 (4.5%) | 3094 (1.2%) |
| Anxiety                                            | 29,050 (11.1%) | 894 (32.3%) | 512 (41.2%) | 105 (40.5%) | 80 (34.9%) | 1672 (38.1%) | 25,592 (10.1%) |
| Major depression                                   | 20,346 (7.7%) | 862 (31.2%) | 491 (39.5%) | 94 (36.3%) | 73 (31.9%) | 1447 (33.0%) | 17,250 (6.8%) |
| Psychotic disorders                                | 1269 (0.5%) | 144 (5.2%) | 113 (9.1%) | 38 (16.7%) | 17 (7.4%) | 155 (3.5%) | 821 (0.3%) |
| Sleep disorders                                    | 32,753 (12.5%) | 837 (30.3%) | 470 (37.8%) | 137 (52.9%) | 84 (36.7%) | 1802 (41.1%) | 29,234 (11.6%) |
| Nursing home                                       | 1639 (0.6%) | 90 (3.3%) | 77 (6.2%) | 14 (5.4%) | 10 (4.4%) | 104 (2.4%) | 1251 (0.5%) |
| Adverse socio-economic factors (SDOHs)             | 4037 (1.5%) | 156 (5.6%) | 104 (8.4%) | 20 (7.7%) | 10 (4.4%) | 260 (5.9%) | 3451 (1.4%) |

Abbreviations: All, all older adults population; AD, Alzheimer’s disease; FTD, frontotemporal dementia; MCI, mild cognitive impairment; LBD, Lewy body dementia; VD, vascular dementia.

Number of cases and percentage (%) are shown.

6.66), followed by VD (AOR: 1.99, 95% CI: 1.42 to 2.80), AD (1.53, 95% CI: 1.22 to 1.92), and MCI (AOR: 1.79, 95% CI: 1.51 to 2.11).

Patients with dementia had a higher prevalence of comorbidities that are known risk factors for COVID-19 (Table 2). After further matching for these comorbidities, patients with dementia were no longer at a significantly increased risk for breakthrough infections compared with matched patients without dementia (Figure 1). These results document that the significantly higher risk for breakthrough infection in patients with dementia was largely accounted for by comorbidities that were prevalent in patients with dementia.
### Table 3

The overall risk of breakthrough infections in vaccinated and fully vaccinated older adult populations 14 days after vaccination between December 2020 and August 2021

| Vaccination status | Cohort | Patients in cohort | Patients with outcomes | Risk  | P value |
|--------------------|--------|-------------------|-----------------------|-------|---------|
| Vaccinated         | AD     | 2,764             | 284                   | 10.3% | <.001   |
|                    | VD     | 1,244             | 155                   | 12.5% | <.001   |
|                    | LBD    | 259               | 37                    | 14.3% | <.001   |
|                    | FTD    | 229               | 27                    | 11.8% | <.001   |
|                    | MCI    | 4385              | 510                   | 11.6% | <.001   |
|                    | Non-dementia | 252,926         | 14,067               | 5.6%  | Ref     |
| Fully vaccinated   | AD     | 2341              | 202                   | 8.6%  | <.001   |
|                    | VD     | 1016              | 104                   | 10.2% | <.001   |
|                    | LBD    | 225               | 28                    | 12.4% | <.001   |
|                    | FTD    | 198               | 19                    | 9.6%  | .007    |
|                    | MCI    | 3885              | 402                   | 10.4% | <.001   |
|                    | Non-dementia | 217,064         | 11,048                | 5.1%  | Ref     |

Abbreviations: AD, Alzheimer’s disease; FTD, frontotemporal dementia; MCI, mild cognitive impairment; LBD, Lewy body dementia; VD, vascular dementia. Fully vaccinated: received second dose of Pfizer-BioNTech or Moderna mRNA vaccine.

### 3.4 Time trends of breakthrough infections in fully vaccinated patients with dementia stratified by age, race, and gender between December 2020 and August 2021

We examined how breakthrough infections among the fully vaccinated older adults with and without dementia evolved between December 2020 and August 2021. The rate of new cases of breakthrough infections, measured by cases/person-day, in the fully vaccinated patients with AD, VD, and MCI, and older adults without dementia steadily increased from December 2020 to August 2021, in all age, race, and gender groups (Figure 2). Compared to MCI and non-dementia patients, patients with AD and VD had higher incidence rates with steeper increases after May 2021. LBD and FTD patients were not examined due their limited sample sizes.

### 3.5 Racial, gender, and age disparities of breakthrough infection among fully vaccinated patients with dementia

We then investigated how age, gender, and race affected the risk of breakthrough among fully vaccinated patients for AD, VD, LBD, FTD, MCI, and non-dementia (Figure 3). In the dementia population, we observed that older individuals with AD (age ≥80 years) had higher risks for breakthrough infections than younger patients with AD (age 65 to 79 years) (AOR: 1.56, 95% CI: 1.09 to 2.22) after matching for gender, race, SDOHs, nursing home stay, and comorbidities. No significant age disparities were observed for other dementia types. Among the fully vaccinated population without dementia, older individuals had higher odds of breakthrough infection than matched cohorts of younger ones (AOR: 1.24, 95% CI: 1.17 to 1.31).

Gender disparities were observed for AD and VD. Fully vaccinated women with AD had a lower risk for breakthrough infections than men after propensity-score matching for age, race, SDOHs, nursing home stay, and comorbidities (AOR: 0.68, 95% CI: 0.47 to 0.98). Fully vaccinated women with VD had a lower risk for breakthrough infections than men with VD after propensity score matching for age, race, SDOHs, nursing home stay, and comorbidities (AOR: 0.52, 95% CI: 0.31 to 0.87). No significant gender disparities were observed for other dementia types.

No significant racial disparities were observed among the fully vaccinated patients for AD, VD, LBD, FTD, and MCI. Among the fully vaccinated population without dementia, African Americans had lower odds of breakthrough infection than Caucasians, after propensity score matching for age, gender, SDOHs, nursing home stay, and comorbidities (AOR: 0.90, 95% CI: 0.85 to 0.96).

### 3.6 Overall risks for hospitalizations among patients with dementia who had breakthrough infections

We compared the overall risks of hospitalizations in the fully vaccinated patients who had breakthrough infections for AD, VD, MCI, and non-dementia (Figure 4). Among 202 patients with AD who had breakthrough infections, 80 were hospitalized after infection (39.5%), significantly higher than the 1.5% in the 2139 patients with AD who had no breakthrough infections (hazard ratio [HR]: 54.1, 95% CI: 34.0 to 86.0). Among 104 patients with VD who had breakthrough infections, 48 were hospitalized after infection (46.2%), significantly higher than the 2.3% in the 912 patients with AD who had no breakthrough infections (HR: 36.4, 95% CI: 21.2 to 62.6). Among 402 patients with MCI who had breakthrough infections, 122 were hospitalized after infection (30.4%), significantly higher than the 1.1% in the 3483 patients
(A) Odds of breakthrough infections in fully vaccinated patients with dementia  
(12/1/2020 – 8/1/2021)  
(matched for demographics and SDOHs)

| Patients | Comparison | Outcome | AOR (95% CI) | p    |
|----------|------------|---------|--------------|------|
| AD       | Non-dementia | COVID−19 | 1.53 (1.22−1.92) | <.001|
| VD       | Non-dementia | COVID−19 | 1.99 (1.42−2.80) | <.001|
| LBD      | Non-dementia | COVID−19 | 3.06 (1.45–6.46) | 0.002|
| FTD      | Non-dementia | COVID−19 | 2.00 (0.90–4.41) | 0.083|
| MCI      | Non-dementia | COVID−19 | 1.78 (1.51–2.11) | <.001|

(B) Odds of breakthrough infections in fully vaccinated patients with dementia  
(12/1/2020 – 8/1/2021)  
(matched for demographics, SDOHs and comorbidities)

| Patients | Comparison | Outcome | AOR (95% CI) | p    |
|----------|------------|---------|--------------|------|
| AD       | Non-dementia | COVID−19 | 1.07 (0.87–1.32) | 0.523|
| VD       | Non-dementia | COVID−19 | 1.05 (0.78–1.41) | 0.764|
| LBD      | Non-dementia | COVID−19 | 1.86 (0.98–3.54) | 0.057|
| FTD      | Non-dementia | COVID−19 | 2.00 (0.90–4.41) | 0.082|
| MCI      | Non-dementia | COVID−19 | 1.16 (1.00–1.35) | 0.05 |

FIGURE 1 The odds of breakthrough infection 14 days after full vaccination during the period of December 2020 to August 2021 in fully vaccinated patients with various types of dementia as compared with fully vaccinated patients without dementia. (A) Cohorts were propensity-score matched for demographics (age, gender, and race/ethnicity), adverse socioeconomic determinants of health (SDOHs), and nursing home stay status; (B) cohorts were propensity score matched for demographics (age, gender, race/ethnicity), adverse SDOHs, nursing home stay status, and comorbidities listed in Table 1.

with MCI who had no breakthrough infections (HR: 41.9, 95% CI: 28.6 to 61.6). Among 11,048 patients without dementia who had breakthrough infections, 2301 were hospitalized after infection (20.8%), significantly higher than the 0.4% in the 206,016 patients without dementia who had no breakthrough infection (HR: 68.0, 95% CI: 62.5 to 74.1).

4 | DISCUSSION

Vaccinated patients with dementia had an overall risk for breakthrough infections ranging from 10.3% for AD to 14.3% for LBD, significantly higher than the 5.6% in the vaccinated older adults without dementia. After propensity-score matching for demographics, SDOHs, and nursing home stay status, fully vaccinated patients with dementia had a significantly increased odds of breakthrough infections compared with the matched cohort of patients without dementia, with the highest risk for patients with LBD (AOR: 3.06), followed by VD (AOR: 1.99), MCI (AOR:1.78), and AD (AOR:1.53). After further matching for comorbidities, patients with dementia no longer displayed a significantly increased risk for breakthrough infections compared with matched patients without dementia. These results indicate that the higher risk for breakthrough infections in patients with dementia compared to those without dementia was largely accounted for by their high prevalence of comorbidities that are also demonstrated risk factors for COVID-19 infection, such as hypertension, type 2 diabetes, heart diseases, and cancers. Overall, our findings highlight the importance for vaccinated older adults, particularly those with dementia, to continue to take protective preventive measures such as wearing masks. In addition, vaccinated patients with dementia who had certain comorbidities, many of which are also demonstrated risk factors for
FIGURE 2  Time trend of incidence rates of breakthrough infections in fully vaccinated patients with dementia and in patients without dementia between December 2020 and August 2021, stratified by gender, race, and age
Demographic disparities of breakthrough infections in fully vaccinated population
(12/1/2020 – 8/1/2021)

| Subgroup (matched) | Subgroup (matched) | AOR (95% CI) |
|--------------------|--------------------|-------------|
| AD                 |                    |             |
| >= 80 year         | 65–79 years        | 1.56 (1.09–2.22) |
| Female             | Male               | 0.68 (0.47–0.98) |
| African American   | Caucasian           | 0.84 (0.53–1.35) |
| VD                 |                    |             |
| >= 80 year         | 65–79 years        | 1.35 (0.83–2.19) |
| Female             | Male               | 0.52 (0.31–0.87) |
| African American   | Caucasian           | 1.67 (0.91–3.05) |
| LBD                |                    |             |
| >= 80 year         | 65–79 years        | 1.00 (0.38–2.63) |
| Female             | Male               | 1.00 (0.38–2.62) |
| African American   | Caucasian           | 1.00 (0.30–3.36) |
| FTD                |                    |             |
| >= 80 year         | 65–79 years        | 1.00 (0.37–2.74) |
| Female             | Male               | 1.00 (0.39–2.58) |
| African American   | Caucasian           | 1.00 (0.30–3.36) |
| MCI                |                    |             |
| >= 80 year         | 65–79 years        | 1.18 (0.93–1.50) |
| Female             | Male               | 0.92 (0.72–1.18) |
| African American   | Caucasian           | 1.30 (0.91–1.85) |
| Non-dementia       |                    |             |
| >= 80 year         | 65–79 years        | 1.24 (1.17–1.31) |
| Female             | Male               | 0.91 (0.87–0.95) |
| African American   | Caucasian           | 0.90 (0.85–0.96) |

In contrast, this study shows significant age differences for breakthrough infections among fully vaccinated dementia patients as well as non-dementia patients, with older individuals (age ≥80 years) being more susceptible to breakthrough infections than those aged 65 to 79 years. This might reflect the age-related decline in immunity that not only would increase susceptibility to infection but also reduce the prophylactic efficacy of vaccinations.30–31 We also observed significant gender disparity for breakthrough infections among fully vaccinated dementia patients as well as non-dementia patients. Women were less susceptible to breakthrough infections than men, after matching for age, race/ethnicity, SDOHs, nursing home stay, and comorbidities. The mechanism(s) underlying this difference warrant further investigation. However, we observed no racial disparities of vaccine breakthrough infection in fully vaccinated dementia and non-dementia patients after matching for other demographics, socioeconomic status, and comorbidities, suggesting that vaccines are effective in preventing infection regardless of race.

The trend analyses showed that the incidence rate of breakthrough infections in fully vaccinated patients with dementia increased steadily.
from December 2020 to May 2021 and then accelerated between May and August 2021. The rapid increase may be due to the emergence and dominance of the Delta variant, the relaxation of prevention measures, or the fading of immunity in those who were vaccinated as soon as the vaccines became available. The highly transmissible Delta variant was the dominant strain of the COVID-19 virus circulating in the United States in August 2021. A recent study in the UK showed that the effectiveness of two doses of BNT162b2 vaccine against the Delta variant is 88%, lower than the 93.7% against the alpha variant. The accelerated increase between May and August 2021 in incidence rate is worrisome, highlighting the importance of follow-up studies to monitor risk and incidence rates of breakthrough infections in the vaccinated patients with dementia against different virus variants.

The outcomes analysis showed that the risk for hospitalization in dementia patients with breakthrough infections ranged from 30.4% for MCI to 46.2% for VD, significantly higher than in those without breakthrough infections (AD: 1.5%, VD: 2.3%, MCI: 1.1%). Although we are unable to determine whether the breakthrough infections were asymptomatic, symptomatic, or severe based on patient EHR, these outcomes suggested that the breakthrough infections indeed resulted in significant adverse outcomes among the vaccinated patients with dementia. Due to the small sample sizes at the time of our study, the numbers of deaths were too small to estimate mortality rates.

Our study has several limitations. First, the observational, retrospective nature of this study of patient EHR data could introduce selection, information, testing, and follow-up biases. Second, the population in the TriNetX EHR database represents people who had medical encounters with health care systems and does not necessarily represent the entire US population. The generalizability of the results from the TriNetX platform remains unknown and needs to be validated in other populations. Third, TriNetX database includes 4.5 million older adults (age ≥65 years) who had a recent medical encounter with health care organizations between December 2020 and August 2021, among whom only 7.6% were identified as vaccinated based on

FIGURE 4 Kaplan-Meier curves for hospitalization 14 days after vaccinations in fully vaccinated patients with breakthrough infections compared with propensity-score matched patients without breakthrough infection between December 2020 and August 2021. Shaded areas represent 95% confidence intervals (CIs)
their medical records. It is likely that most vaccinations were done outside of health care organizations and were not necessarily captured in patient EHRs. This limitation may not have impacted our findings, as we focused on vaccinated patients who had documented vaccination data in their EHRs, and we made no comparisons to unvaccinated persons. However, findings from this study need to be validated in other vaccinated populations. Fourth, we are unable to determine whether the vaccine breakthrough COVID-19 cases were caused by the Delta variant. Future studies utilizing other data resources are needed to examine these questions.

Future studies are warranted, including (1) continuing to evaluate breakthrough infections in vaccinated patients with dementia, especially with the emergence of different virus variants; (2) continuing to monitor outcomes including hospitalization and mortality associated with breakthrough infections in patients with dementia.

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CONFLICTS OF INTEREST
Pamela B. Davis has served on External Advisory Board of University of Chicago, Board of trustees of Judson foundation, Board of directors of clinical research forum, Board of directors BioEnterprise. Lindsey Want, David C. Kaelber, and Rong Xu have no outside interests to declare. Lindsey Wang, David C. Kaelber, Pamela B. Davis, and Rong Xu have no financial interests to disclose.

AUTHOR CONTRIBUTIONS
Rong Xu conceived and designed the study. Lindsey Wang conducted experiments, performed data analysis, and prepared tables and figures in the study. Rong Xu wrote the manuscript. Pamela B. Davis and David C. Kaelber critically contributed to both data interpretation and manuscript preparation. All authors approved the final manuscript. Rong Xu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We confirm the originality of content.

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