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COVID-19 and Alzheimer's disease in the ADNI cohort

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Short Report

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Abstract

INTRODUCTION:

There is growing evidence that COVID-19 infection in older adults increases the risk of diagnosis of Alzheimer's disease and accelerates cognitive decline. We hypothesized that participants reporting COVID-19 infection would have greater cognitive and functional decline and greater occurrence of neuropsychiatric symptoms after COVID-19 infection in comparison to uninfected matched controls.

METHODS

This secondary data analysis from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort examined participants with and without self-reported history of COVID-19 infection comparing visits before and after infection.

RESULTS

The 16 participants included in the COVID-19 cohort and the 32 controls, had similar changes in cognitive, functionality and behavioral measures between study visits.

CONCLUSIONS

While there is evidence that COVID-19 infection increases the risk for depression, cognitive changes and conversion to dementia, this examination of a well characterized cohort of at risk and cognitive impaired individuals did not find evidence for the impact of COVID-19 after infection.

INTRODUCTION

There is growing evidence that COVID-19 infection, increases the risk of new onset dementia and accelerates cognitive decline in patients with dementia. Cognitive deficits after COVID-19 have been documented particularly in patients suffering from severe illness who experience slower recovery after infection.[1–3] Population-level data suggests that a COVID-19 diagnosis in older adults significantly increases the risk for a diagnosis of Alzheimer's disease (AD) within one year, suggesting that COVID-19 infection may accelerate the neurodegenerative process.[4] Several mechanisms have been proposed to explain the relationship between COVID-19 and dementia including increased neurotoxicity by higher beta-amyloid accumulation, oxidative stress, and viral infection increasing inflammation.[5,6] Prior experiences with other coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012, similarly suggest that coronaviruses increase the risk of cognitive impairment after recovery from acute infection.[7]

We investigated the association of COVID-19 with dementia risk leveraging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study that collects data from over 60 sites in the USA and Canada to study the progression of Alzheimer's Disease.[8] Participants are comprehensively evaluated with clinical history, cognitive status, and AD imaging and fluid biomarkers, allowing exploration of the clinical and cognitive trajectory of participants with and without a history of COVID-19 infection exposure. We compared global cognition and cognitive domain testing, functionality and behavioral data at study visits prior to and following COVID-19 infection to assess change over time. We hypothesized that participants reporting COVID-19 infection would have accelerated cognitive decline, decline in function and greater occurrence of neuropsychiatric symptoms between the visit prior to reporting COVID-19 and the following visit, in comparison to matched controls who did not report an infection.

METHODS

Study Population

This is a secondary data analysis of the Alzheimer's Disease Neuroimaging Initiative (ADNI) a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease. For 20 years, ADNI has enrolled adults with MCI, dementia and normal cognition aged 55 or older. Details of the ADNI cohort have been published previously. Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). ADNI was approved by the Institutional Review Board (IRB) of each participating site and was conducted in accordance with Federal Regulations. The participants provided their written informed consent to participate in the study that was conducted in accordance with the Declaration of Helsinki.

These analyses used data from the ADNI-3 cohort collected between 2016 and 2022. We excluded from analysis participants with incomplete data, such as not having a study visit after COVID-19 infection. Our control population included individuals who did not report a history of COVID-19 infection and were matched by age (2+/- years), diagnosis (MCI, dementia, and NC) and sex.

Outcomes and Covariates

Data was collected over two visits at least 12 months apart. COVID-19 infection was reported in the ADNI adverse events log, recorded as "Related to COVID-19 illness," categorized as definitely (confirmed COVID-19 test), probably, and possibly. We defined visit-1 as the visit occurring prior to their report of COVID-19 infection, and visit-2 occurring after their report of COVID-19 infection. We compared them to an age, diagnosis and sex-matched group of participants who completed the same assessments but did not report a history of COVID-19 infection.

Participants had a comprehensive neuropsychological assessment. To assess for global cognition the Mini Mental Status Exam (MMSE), Montreal Cognitive Assessment (MoCA), the Alzheimer's Disease

Assessment Scale - Cognitive (ADAS-COG) total scores and the Clinical Dementia Rating (CDR) global score and sum of boxes were used. Permission was obtained from PAR for the use of the MMSE and from MoCA in ADNI. To assess different cognitive domains the Rey Auditory Verbal Learning Test (RAVLT) learning and immediate scores, Auditory Verbal Learning Test (AVLT) 30 minute delayed total score, Trail Making Test Part A and B, Clock Drawing, Category Fluency, the Multilingual Naming Test (MINT) and the Logical Memory Test were used. The Functional Activities Questionnaire (FAQ) total score was used to assess activities of daily living. To assess for behavioral symptoms, the Neuropsychiatric Inventory (NPI) and the Geriatric Depression Scale (GDS) were examined.

Statistical Analysis

Descriptive analyses were performed to summarize the study participants' characteristics. Continuous variables were reported as means with standard deviations, while categorical variables were presented as frequencies and percentages. Group comparisons were conducted using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables. Changes in each outcome were evaluated between the COVID and control groups, with p-values derived from the Wilcoxon rank-sum test. All statistical analyses were performed using R version 4.4.1(R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $P < 0.05$.

RESULTS

By August 2022, 36 participants in the ADNI 3 cohort reported COVID-19 that was recorded as an adverse event. Of these participants, 20 participants were excluded for having missing data, including 13 participants who did not have a visit after reporting COVID-19 infection and with the remaining 7 participants missing a complete neuropsychology battery. The remaining 16 participants were included as the COVID-19 cohort in which one participant was hospitalized due to having COVID-19 infection, 7 participants identified as male, 12 identified as white and 2 as Latino or Hispanic ethnicity (Table 1). The control population (N = 32) was selected to match by age, diagnosis at the time of enrollment (MCI, dementia and NC) and gender from the broader ADNI 3 population who did not report a history of COVID-19 infection. None of the participants in the COVID-19 cohort had a change of cognitive diagnosis between the time points. One control participant was classified as normal at enrollment, but diagnosed with MCI at the second visit.

Table 1
Characteristics of the Sample by Condition Status

Variable		Condition status			
	N	**Overall N = 48[1]**	**Control N = 32[1]**	**Covid N = 16[1]**	**p-value[2]**
GENDER	48				> 0.999
Male		21 (44%)	14 (44%)	7 (44%)	
Female		27 (56%)	18 (56%)	9 (56%)	
RACE	48				0.565
American Indian or Alaskan Native		1 (2.1%)	1 (3.1%)	0 (0%)	
Asian		1 (2.1%)	1 (3.1%)	0 (0%)	
Native Hawaiian or Other Pacific Islander		0	0	0	
Black or African American		4 (8.3%)	2 (6.3%)	2 (13%)	
White		39 (81%)	27 (84%)	12 (75%)	
More than one race		2 (4.2%)	1 (3.1%)	1 (6.3%)	
Unknown		1 (2.1%)	0 (0%)	1 (6.3%)	
ETHNICITY	48				> 0.999
Hispanic or Latino		5 (10%)	3 (9.4%)	2 (13%)	
Not Hispanic or Latino		43 (90%)	29 (91%)	14 (88%)	
EDUCATION	48				0.392
12 years		3 (6.3%)	1 (3.1%)	2 (13%)	
17–18 years		25 (52%)	18 (56%)	7 (44%)	
13–16 years		20 (42%)	13 (41%)	7 (44%)	
AGE COVID-19 infection	48	70.85 (4.04)	70.72 (3.59)	71.13 (4.94)	0.775
DIAGNOSIS	48				0.632
Cognitive normal		29 (60%)	18 (56%)	11 (69%)	
MCI		10 (21%)	8 (25%)	2 (13%)	

[2]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

Variable		Condition status		
	N	Overall N = 48[1]	Control N = 32[1]	Covid N = 16[1]	p-value[2]
Dementia		9 (19%)	6 (19%)	3 (19%)	
[1]n (%); Mean (SD)					
[2]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test					

Cognitive and functional score results are displayed in Table 2. Neither group exhibited significant cognitive decline between both time points. Regarding global cognition we observe no significant group differences in the time 1 to time 2 change in MMSE (p = 0.644), MoCA (p = 0.757), ADAS-COG (p = 0.793) total scores, the CDR global score (p = 0.346), and sum of boxes (p = 0.574) between the COVID-19 and control groups. There were no significant group differences in change in RAVLT learning (p = 0.529 or immediate scores (p = 0.776), AVLT delayed score (p = 0.841), Trail Making Test part A (p = 0.793) or B (p = 0.555), Clock Drawing (p = 0.729), Category Fluency (p = 0.878), MINT (p = 0.872) and the Logical Memory Test (p = 0.716).

Table 2
Change of Outcomes

Variable	Condition status			
	Overall N = 48[1]	Control N = 32[1]	Covid N = 16[1]	p-value[2]
Cognition				
MMSE	-0.96 (2.67)	-0.88 (2.76)	-1.13 (2.58)	0.644
MOCA	-0.27 (2.79)	-0.41 (3.18)	0.00 (1.83)	0.757
ADAS-COG	2.80 (6.41)	2.91 (6.22)	2.58 (6.99)	0.793
CDR global score	0.07 (0.23)	0.03 (0.18)	0.16 (0.30)	0.113
CDR sum of boxes	0.39 (1.53)	0.25 (1.23)	0.66 (2.01)	0.785
RAVLT learning score	0.31 (2.58)	0.16 (2.22)	0.63 (3.24)	0.529
RAVLT immediate	-0.52 (6.44)	-0.41 (6.19)	-0.75 (7.13)	0.776
AVLT	0.92 (3.61)	0.84 (3.93)	1.06 (3.00)	0.841
Trails A	3.65 (16.30)	2.79 (13.88)	5.38 (20.72)	0.793
Trails B	3.37 (39.37)	4.59 (44.17)	0.94 (28.56)	0.555
Clock Drawing	-0.25 (0.76)	-0.28 (0.81)	-0.19 (0.66)	0.729
Category Fluency	-2.52 (5.72)	-2.88 (6.27)	-1.81 (4.52)	0.878
MINT	1.40 (10.82)	2.13 (13.22)	-0.06 (1.44)	0.872
Logical Memory	-0.42 (2.90)	-0.47 (2.69)	-0.31 (3.38)	0.716
Function				
FAQ	1.06 (4.71)	0.38 (3.51)	2.44 (6.41)	0.860
Behavioral Symptoms				
NPI	1.35 (5.92)	1.31 (6.49)	1.44 (4.76)	0.839
GDS	-0.06 (1.45)	0.06 (1.52)	-0.31 (1.30)	0.478

[2]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment; ADAS-COG, Alzheimer's Disease Assessment Scale-Cog13 (w/ delayed recall and number cancellation); CDR, Clinical Dementia Rating scale; RAVLT, Rey Auditory Verbal Learning Test; AVLT, Auditory Verbal Learning Test; Trails A & B; Clock Drawing; Category Fluency, Category Fluency (Animals); MINT, Multi-lingual Naming Test; Logical Memory, Logical Memory I and II; FAQ, Activities of Daily Living; NPI, Neuropsychiatric Inventory; GDS, Geriatric Depression Scale.

Variable	Condition status			
	Overall N = 48[1]	Control N = 32[1]	Covid N = 16[1]	p-value[2]
[1]n (%); Mean (SD)				
[2]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test				
MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment; ADAS-COG, Alzheimer's Disease Assessment Scale-Cog13 (w/ delayed recall and number cancellation); CDR, Clinical Dementia Rating scale; RAVLT, Rey Auditory Verbal Learning Test; AVLT, Auditory Verbal Learning Test; Trails A & B; Clock Drawing; Category Fluency, Category Fluency (Animals); MINT, Multi-lingual Naming Test; Logical Memory, Logical Memory I and II; FAQ, Activities of Daily Living; NPI, Neuropsychiatric Inventory; GDS, Geriatric Depression Scale.				

For level of functioning, there was no significant change in the FAQ scores (p = 0.341) between the COVID-19 and control groups between both time points (Table 2).

Regarding behavioral symptoms, there were no changes in NPI (p = 0.839) or GDS (p = 0.478) scores between the COVID-19 and control groups between both time points (Table 2). In the COVID-19 cohort, 2 participants had a clinically significant increase in NPI score at the second time point, increasing from 2 to 19 and 1 to 9, respectively. Overall, GDS scores were low in both cohorts at both visits (range 0–7) (Table 2).

DISCUSSION

In this well characterized cohort, there was no evidence of cognitive or functional changes between participants reporting overall mild COVID-19 infection and those who did not at the scheduled ADNI assessment following the illness. Similarly, participants who reported COVID-19 infection did not exhibit behavioral decline between the visit prior and post infection visit. There has been growing evidence that COVID-19 infection increases the risk for depression, cognitive changes and conversion to dementia.[4,9–11] However, given the small sample size and limited follow up time (one annual follow up visit following infection), our ability to see potential deleterious effects was limited. It is also likely that the majority of these COVID-19 infections were mild as only one participant was hospitalized following infection.

This study does not mean that COVID-19 infection cannot worsen cognitive decline. During severe COVID-19 systemic inflammation, hypoxia and brain-blood barrier dysfunction could accelerate neurodegeneration.[12] The Demmer et al cohort study found that, out of 307 participants infected with COVID-19, 33.6% were hospitalized and the rate of decline in cognitive function was faster in hospitalized participants but not different in infected participants who were not hospitalized in comparison to not infected participants.[13] This work, combined with our own, suggests that measurable acceleration in cognitive or behavioral decline is limited to those with severe infection who require hospitalization. The results inform the design of future investigations to better characterize the

relationship between COVID-19 infection and Alzheimer's disease. Following up patients for longer than a year after infection, as well as comparing mild and severe infection cases is necessary. Finally, biomarker influences on the relationship between infection and cognitive outcomes remain to be further examined.

STRENGTHS AND LIMITATIONS

Strengths of our study include a well-characterized cohort, with detailed clinical and demographic data, allowing for nuanced interpretation of findings. Limitations of our study include the limited information on COVID-19 infection such as not having vaccine status information and relying on self-report of infection status. It is possible some controls had infection and did not report it. Another limitation is that a significant number of individuals in the ADNI cohort who reported COVID-19 infection had to be excluded for missing data.

Declarations

Ethical Considerations

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. ADNI was approved by the Institutional Review Board (IRB) of each participating site and was conducted in accordance with Federal Regulations.

This secondary data analysis was approved by Vanderbilt University Medical Center Institutional Review Board IRB No. 231735. Data was de-identified and analyzed as a secondary use of existing data; therefore, informed consent was not required as per IRB determination.

Access to data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) was approved through the ADNI Data Sharing and Publications Committee (DPC). Data were accessed through the LONI Image and Data Archive (IDA) in accordance with the ADNI Data Use Agreement and applicable data-sharing policies.

Consent to Participate

The participants provided their written informed consent to participate in the study that was conducted in accordance with the Declaration of Helsinki. This secondary data analysis was approved by Vanderbilt University Medical Center Institutional Review Board IRB No. 231735. Data was de-identified and analyzed as a secondary use of existing data; therefore, informed consent was not required as per IRB determination.

Consent to Publish

Not applicable.

Data Availability

Data used in preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). All ADNI data are shared through the LONI Image and Data Archive (IDA), a secure research data repository. Authors of this paper obtained approved access to this database.

Competing Interest and Declarations

Patricia Andrews, Ke Xu and Kathleen Mather all received effort support from the subaward of the Alzheimer's Disease Neuroimaging Initiative (ADNI) which is funded by the National Institutes of Health Grant number: U19AG024904.

Patricia Andrews is Site Principal Investigator of ADNI and Paul Newhouse is Co-Investigator of ADNI and previous Site Principal Investigator.

Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Patricia Andrews, Kathleen Mather, Kiara Baker and Brian Boyd. Data analysis was performed by Ke Xu and Hakmook Kang. The first draft of the manuscript was written by Patricia Andrews and all authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

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