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Characterization of Change in Cognition Before and After COVID-19 Infection in Essential Workers at Midlife ☆,☆☆

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ABSTRACT

Background: Research into COVID-19-related cognitive decline has focused on individuals who are cognitively impaired following hospitalization for COVID-19. Our objective was to determine whether cognitive decline emerged after the onset of COVID-19 and was more pronounced in patients with postacute sequelae of SARS-CoV-2 infection (PASC).

Methods: We analyzed longitudinal cognitive data collected during a cohort study of essential workers at midlife that continued through the COVID-19 pandemic. We used longitudinal discontinuity models, a form of causal modeling, to examine the change in cognitive performance among 276 participants with COVID-19 in comparison to contemporaneously-collected information from 217 participants who did not have COVID-19. Cognitive performance across four domains was measured before and after the pandemic. Eligible study participants were those with validated COVID-19 diagnoses who were observed before having a verified COVID-19 infection who survived their initial infection, and for whom post-COVID-19 information was also available.

Results: The mean age of the COVID-19 group was 56.0 ± 6.6 years old, while the control group was 58.1 ± 7.3 years old. Longitudinal models indicated a significant decline in cognitive throughput (β = -0.168, P = .001) following COVID-19, after adjustment for pre-COVID-19 functioning, demographics, and medical factors. Associations were larger in those with more severe COVID-19 and those who reported PASC. Observed changes in throughput were equivalent to 10.6 years of normal aging.

Conclusion: Findings from this longitudinal causal modeling study revealed that COVID-19 and PASC appeared to cause clincially relevant cognitive deterioration.

Introduction

Post-coronavirus disease 2019 (COVID-19), many survivors seek more frequent medical care for respiratory, diabetes, and neuropsychiatric disorders more than 3 to 6 months after the onset of SARS-CoV-2 infection.[1] This continuation or development of new COVID-19 symptoms and conditions three months after the initial infection and lasting for at least two months with no other explanation was termed post-acute sequelae of SARS-CoV-2 (PASC) by the World Health Organization.[2] PASC is considered present when symptoms emerge soon after infection and persist for ≥4-8 weeks after SARS-CoV-2 infection.[3] The most frequent PASC symptoms are cardiopulmonary symptoms (e.g., dyspnea and chest pain) or neuropsychiatric symptoms (e.g., brain fog, fatigue, headache, and depression).[4]

Neuropsychiatric symptoms of PASC can occur three months after initial SARS-CoV-2 infection and persist for at least eight weeks.[5] Acute and subacute infarctions are the most common neuroimaging findings in neurological PASC [6], and COVID-19-related cognitive decline (CRCD) manifests as executive dysfunction.[7,8] CRCD manifests with subjective impairments including difficulties in inattention, forgetfulness, and

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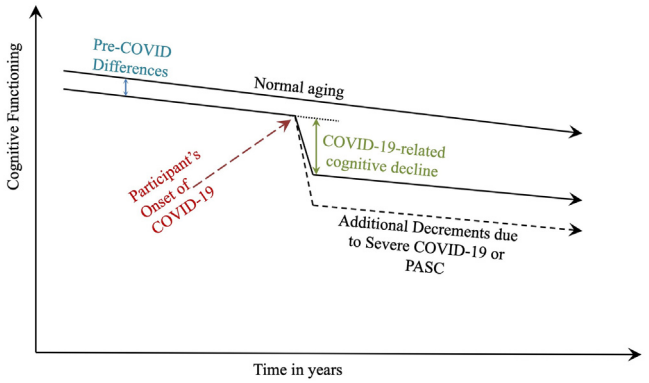


Figure 1. Expected trajectories of change in cognition before and after the onset of COVID-19.

brain fog[9] alongside headaches, fatigue, dizziness, sleep-related symptoms, and ageusia/anosmia.[10] Brain fog has been reported as an incapacitating condition among PASC patients that appears to include cognitive features,[7,9] even in cases of mild COVID-19 infections.[11] Brain fog has been reported to follow mild/moderate COVID-19 irrespective of age at infection[12] and may continue up to two years after COVID-19.[1,13]

There is growing evidence to suggest that COVID-19 causes CRCD. CRCD include common risk factors for Alzheimer's disease and related dementias (e.g., older age, lower education, depression, diabetes, and cardiovascular disease). Additionally, while subjective cognitive symptoms including Brain Fog, are important to functional limitations, they only mildly concur with changes to cognitive performance.[14] Despite growing concerns that PASC may cause CRCD, existing research lacks control groups or pre-COVID-19 cognitive assessments necessary to support such determinations.[15] Thus, this study aimed to determine whether the development of COVID-19 in a sample of aging essential workers was contemporaneous with decrements in cognitive functioning as defined in Figure 1. Specifically, we hypothesized that when using models that adjust for individual differences in cognitive ability prior to the onset of COVID-19, that the presence of COVID-19 would be associated with worse cognitive functioning (see green double-arrow line in Figure 1), and that decrements would be largest in those reporting severe COVID-19 and the presence of PASC (see dashed line in Figure 1). Also, we examined whether declines were steeper in participants with more severe disease conditions and those reporting PASC. The availability of longitudinal data dating back to 2015 allowed us to investigate whether cognitive decline emerges with SARS-CoV-2 infection or whether the observations reflected lower pre-COVID-19 functioning that rendered patients more susceptible to severe disease. We hypothesized that cognitive decline would correspond to SARS-CoV-2 infection and would be more grievous in patients with severe and acute COVID-19 or PASC.

Methods

Study Participants

Participants were drawn from essential workers (mainly first responders) enrolled in an occupation-based study of cognitive aging.[16] Eligibility was based on those who underwent computer-assisted testing on a neuropsychological assessment battery between 11/2015-12/2019 and had at least one follow-up collected between 3/2020-2/2023. Cohort participants who reported having COVID-19 symptoms and a positive COVID-19 polymerase chain reaction (PCR), antibody, or antigen test result between 3/2020 and 11/2021 were included in the COVID-19 group. The "verified" COVID-19 group included patients who provided proof of SARS-CoV-2 infection with a positive COVID-19 antigen, antibody, or PCR test. The "unverified" COVID-19 group included participants who reported positive laboratory test findings but for whom we were unable to gather the recorded evidence. The uninfected (control) group reported that, to the best of their knowledge, they had not had COVID-19 and never experienced COVID-19 symptoms or received a positive PCR, antigen, or antibody test result during the specified timeframe. In this group, we estimated a counterfactual symptom onset date using the mean onset date for those infected. Participants included in this analysis had ≥2 neuropsychological assessments during the study period, with ≥1 before and ≥1 after the onset of COVID-19 symptoms. Eligible individuals with multiple sclerosis, Parkinson's disease, dementia, or stroke before COVID-19 and participants with asymptomatic SARS-CoV-2 infections were excluded. Cognitive exams were completed during study visits before and following COVID-19 infections, so the timing of the test administration differed for each participant.

COVID-19 Severity

Acute COVID-19 was classified into three categories (symptoms described in Supplemental Table 1): mild, moderate, and severe, according to COVID-19 clinical spectrum guidelines.[17] The uninfected (control) group reported that, to the best of their knowledge, they had not had COVID-19 and never experienced COVID-19 symptoms or received a positive PCR, antigen, or antibody test result during the specified timeframe.

COVID-19 participants with PASC had at least one COVID-19-related symptom lasting ≥4 weeks. Those who did not experience any such symptoms were placed in the non-PASC group. PASC symptoms were classified into the following categories: (1) respiratory (dyspnea, sore throat, congestion, runny nose, wheezing, and cough; cardiac; chest pain or palpitations), (2) central nervous system (CNS; dizziness, vertigo, brain fog, lethargy, tinnitus, headache), (3) peripheral nervous system (PNS; loss of smell and taste, pins and needles), (4) psychiatric (anxiety, depression, and post-traumatic stress disorder), (5) musculoskeletal (body aches and pains, and joint pain), (6) gastrointestinal (nausea, vomiting, diarrhea, and weight loss), (7) fatigue ("very tired"; "low energy") or other (fever or rash).

Cognitive Functional Assessment

Cognition was assessed using the CogState Brief Battery (CBB), a computerized neuropsychological examination that detects modest cognitive abnormalities over repeated evaluations and is sensitive to dementia.[18] The CBB assessment has been described in detail previously,[16] and more information is available on the tool's website (www.cogstate.com). Briefly, cognitive performance is assessed during three game-like tasks (detection, identification, and one-card learning), including repeated trials using a green-background virtual deck of playing cards. Each task reports an average of measures within up to 88 trials in which participants respond to prompts using two keyboard keys (marked "Y" for yes and "N" for no). From these tests, we reported four metrics of executive function that we hypothesized would be sensitive to neuroinflammation or vascular disease: response speed, processing speed, cognitive throughput, and visual working memory. Reaction speed measures the detection task completion rate (answers per second). Processing speed (answers/second) measures the average number of correct answers in identification tasks.[19] Throughput measures one-card learning accuracy divided by testing speed (accurate answers/second). Visual memory was measured as accuracy on a one-card learning task (accurate answers/second).

Clinical information was used to determine whether our COVID-19 group was significantly different at the outset in these conditions of aging as compared to those who did not develop COVID-19. Data were gathered to determine the presence of a pre-COVID history of heart disease, diabetes, hypertension, depression, and hyperlipidemia. Since some of these conditions might cause cognitive complications for SARS-CoV-2 infection, we adjusted our models for cardiovascular disease, hy-

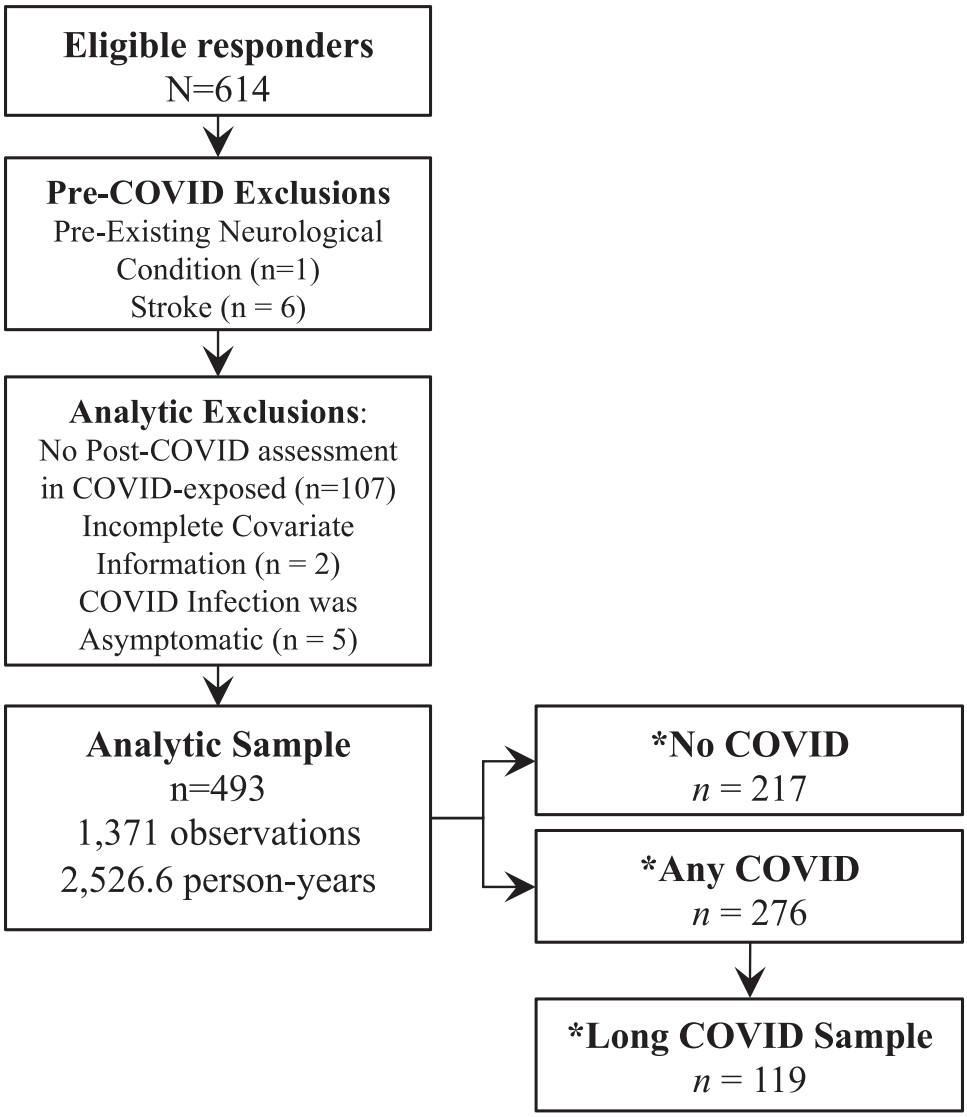


Figure 2. Sample inclusion and exclusion criteria flow chart.

perlipidemia, hypertension, and diabetes. Depressive symptoms were measured using the patient health questionnaire,[20] and post-traumatic stress disorder (PTSD) were collected using the PTSD checklist for DSM-IV (PCL-17)[21] at baseline prior to COVID-19 infection.

Initial COVID-19 symptoms, vaccination information (vaccine completion and series), hospitalization (defined as a hospital stay of ≥24 h), and diagnostic data were gathered through a self-reported survey, text messages, phone interviews, follow-up visits, and data from medical records outside the study.[17,22] Demographic data were retrieved during registration or COVID-19 visits. BMI (kg/m^2) was calculated using objective measures of height and weight.

Statistical Analysis

Linear longitudinal mixed models were used to examine the rate of cognitive decline and detect evidence of change after an acute SARS-CoV-2 infection. We used the date of COVID-19 symptom onset to detect changes across six measures of cognition by comparing trajectories of functioning pre- and post-COVID-19 using a longitudinal discontinuity design following Equation 1 below.[23] We projected the expected rate of decline before and after the infection and compared the postinfection decline with the rate among the uninfected cohort. We adjusted for learning effects using an indicator based on a participant's initial assessment of this cognitive battery. We incorporated a covariate identifying the size of the difference between those who were infected with SARS-CoV-2 and those who were not to determine the extent of preinfection differences. We did not model postinfection accelerations in cognitive decline because the annual monitoring schedule did not provide sufficient time points following infection to permit reliable estimates.

$$Y_{it} = \beta_0 + \beta_1 A_{it} + \beta_2 C_{19t} + \beta_3 EC_{19} + \beta_4 EC_{19} * t + XB + \gamma_{0i} + \gamma_{1i} t + \varepsilon_{it} \quad (1)$$

Where Y_{it} is the time-varying value for the outcome measures and varies between individuals (i) over time (t). Additionally, ***XB*** contains an array of covariates, A_{it} denotes age of subject i at time t, C_{19t} is a time-varying indicator for the onset of COVID-19 symptoms. We used EC_{19} to estimate any pre-COVID difference in the outcome among those who developed COVID-19 as compared to those who were not to model selection into COVID-19 infection as related to the dependent variable. For the unexposed group, the counterfactual symptom onset time (t = 0 in the graph above) was calculated as the average date that those in the COVID-19 group were infected. We controlled for individual differences at baseline using random intercepts (γ_{0i}) and accounted for potential variation in the rate of aging using random slopes ($\gamma_{1i}t$) such that γ_{0i} and $\gamma_{1i}t$ are distributed normally (~N[0,1]). Finally, we estimated the mean

Table 1
Participant Characteristics Stratified by COVID-19 Status (n = 493)*.

Characteristics	Control Group (n = 217)	Incident COVID-19 Group (n = 276)	P Value
Age, mean (SD), years	58.1 (7.3)	56.0 (6.6)	< .01
Body mass, kg/m^2, mean (SD)	30.9 (5.6)	30.9 (4.8)	.97
	(*N*) %	**(*N*) %**	
Gender			
Female	(17) 7.8	(13) 4.7	
Male	(200) 92.2	(263) 95.3	.15
Ethnicity/race			
White	(171) 78.8	(226) 81.9	
Black	(6) 2.8	(4) 1.5	
Hispanic	(16) 7.4	(19) 7.0	.34
Other/unknown	(24) 11.1	(27) 9.8	
Educational attainment*			
Less than high school	(9) 4.2	(8) 2.9	
High school	(40) 18.4	(51) 18.6	
Some college	(99) 45.6	(143) 52.0	
University degree	(63) 29.0	(67) 24.4	.60
Unknown	(6) 2.8	(6) 2.2	
Underlying conditions			
Depression	(18) 8.3	(33) 12.0	.19
Diabetes	(24) 11.1	(34) 12.3	.67
Hypertension	(89) 41.0	(101) 36.6	.32
Hyperlipidemia	(82) 37.8	(92) 33.3	.30
Cardiovascular disease	(51) 23.5	(46) 16.7	.06
COVID-19 verification status			
Verified	N/A	(158) 57.3	
Unverified	N/A	(118) 42.8	N/A
COVID-19 severity categorization			
Mild	N/A	(131) 47.5	
Moderate	N/A	(110) 39.9	N/A
Severe	N/A	(35) 12.7	
Variants			
Alpha, Beta	N/A	(230) 83.3	
Delta	N/A	(23) 8.3	
Epsilon	N/A	(12) 4.4	
Omicron	N/A	(11) 3.9	
Vaccination status at the onset of COVID-19			
Vaccinated, complete	N/A	(17) 6.2	
Vaccinated, partial	N/A	(2) 0.7	N/A
Unvaccinated	N/A	(247) 89.5	
Unknown	N/A	(10) 3.4	
Vaccination status as of 12/2022			
Vaccinated, complete	(170) 78.4	(162) 58.7	
Vaccinated, partial	(12) 5.5	(32) 11.6	< .01
Unvaccinated	(15) 6.9	(66) 23.9	
Unknown	(20) 9.2	(66) 23.9	
COVID-19 hospitalization†			
Hospitalized	N/A	(23) 10.2	N/A
Nonhospitalized	N/A	(248) 89.9	
ICU admission status			
ICU admission	N/A	(3) 1.1	
No ICU admission	N/A	(248) 89.9	N/A

SD, standard deviation; CNS, central nervous system; PNS, peripheral nervous system; COVID-19, coronavirus disease 2019. *P*-values comparing participants without PASC to those with long-COVID were derived from tests of proportions (Chi-squared) and from Student's t-tests as appropriate; ICU, intensive care unit; C, complete; I, incomplete. $P < .05$, 2-sided, was adopted as indicating significance.
Missing ICU data on five individuals.
* One person has unknown educational status.
† Missing hospitalization information on five individuals.

rate of cognitive decline expected after SARS-CoV-2 infection using the $EC_{19} * t$ interaction term.

Secondarily, we examined variations in COVID-19 severity and the presence of any PASC as potential moderators of the cognitive trajectories. We computed three effect-size estimates: First, we translated regression coefficients, which differ by the scales of the outcome variables, into standardized regression coefficients (labeled "b"). Second, we estimated "age-equivalent years (AEY)" as the number of years of normal cognitive aging necessary to cause similar levels of cognitive decline reflected in changes attributed to COVID-19. AEY was calculated by dividing the coefficient for the COVID-19 indicator by the coefficient of the slope attributed to age in the same model. Third, we used descriptive information alongside model-derived information to estimate the expected proportion of participants who would qualify as having a new-onset mild cognitive impairment (NOMCI)[24] at their initial post-COVID-19 visit. We did not require complete cases to evaluate change over time and incorporated data from any individual who fit the eligibility criteria. Missing data in longitudinal models is accounted for using the expectation-maximization (EM) algorithm within the longitudinal multilevel modeling.[25] Although longitudinal models are not biased by time-invariant variables such as gender, race or educational attainment, we adjusted our models for the possible confounding variables, includ-

Table 2
Participant Characteristics Without Versus with Postacute Sequelae of SARS-CoV-2 (n = 256)[*].

Characteristics	Non-PASC (n = 137)	PASC (n = 119)	P Value
Age, mean (SD), years	55.71 (6.48)	56.34 (7.11)	.46
Body mass index, mean (SD)	30.68 (4.88)	31.22 (4.55)	.36
	(*N*) %	**(*N*) %**	
Gender			
Female	(7) 5.11	(5) 4.20	.73
Male	(130) 94.89	(114) 95.80	
Ethnicity/race[†]			
White	(111) 81.02	(98) 82.35	.34
Black	(4) 2.92	(0) 0.00	
Hispanic	(9) 6.57	(9) 7.56	
Other/unknown	(13) 9.49	(12) 10.08	
Educational attainment[#]			
>High school	(3) 2.19	(5) 4.24	.50
High school	(26) 18.98	(20) 16.95	
Some college	(68) 49.64	(62) 52.54	
University degree	(36) 26.28	(29) 24.58	
Unknown	(4) 2.92	(2) 1.69	
Underlying conditions			
Depression	(12) 8.76	(19) 15.97	.08
Diabetes	(13) 9.49	(17) 14.29	.23
Hypertension	(43) 31.39	(50) 42.02	.08
Hyperlipidemia	(39) 28.47	(46) 38.66	.08
Cardiovascular disease	(17) 12.41	(27) 22.69	.03
Lingering symptoms type[$]			
Central nervous system	-	(48) 40.34	
Peripheral nervous system	-	(19) 15.97	
Muscular	-	(27) 22.69	
Psychiatric	-	(8) 6.72	
Fatigue	-	(50) 42.02	
Gastrointestinal	-	(6) 5.04	
Respiratory	-	(44) 36.97	
Other	-	(4) 3.36	
COVID-19 verification status			
Verified	(79) 57.66	(78) 65.55	.20
Unverified	(58) 42.34	(41) 34.45	
COVID-19 severity categorization			
Mild	(75) 54.74	(42) 35.29	< .01
Moderate	(57) 41.61	(48) 40.34	
Severe	(5) 3.65	(29) 24.37	
Vaccination status at the onset of COVID-19			
Completed vaccinated	(5)5.15	(7) 5.88	.35
Incomplete vaccination	(1)0.0	(1) 0.84	
Unvaccinated	(125)90.44	(108) 90.75	
Unknown	(6)4.41	(3) 2.52	
Vaccination status as of 12/2022			
Completed vaccinated	(85) 63.04	(69) 57.98	.69
Incomplete vaccination	(12) 8.76	(12) 10.98	
Unvaccinated	(30) 21.90	(32) 26.89	
Unknown	(10) 7.30	(6) 5.04	
Hospitalization status[&]			
Hospitalized	(2) 1.46	(21) 21.85	< .01
Nonhospitalized	(132) 96.35	(97) 78.15	
ICU admission status			
ICU admission	(0) 0.0	(3) 1.92	.10
No ICU admission	(137) 100	(116) 98.08	

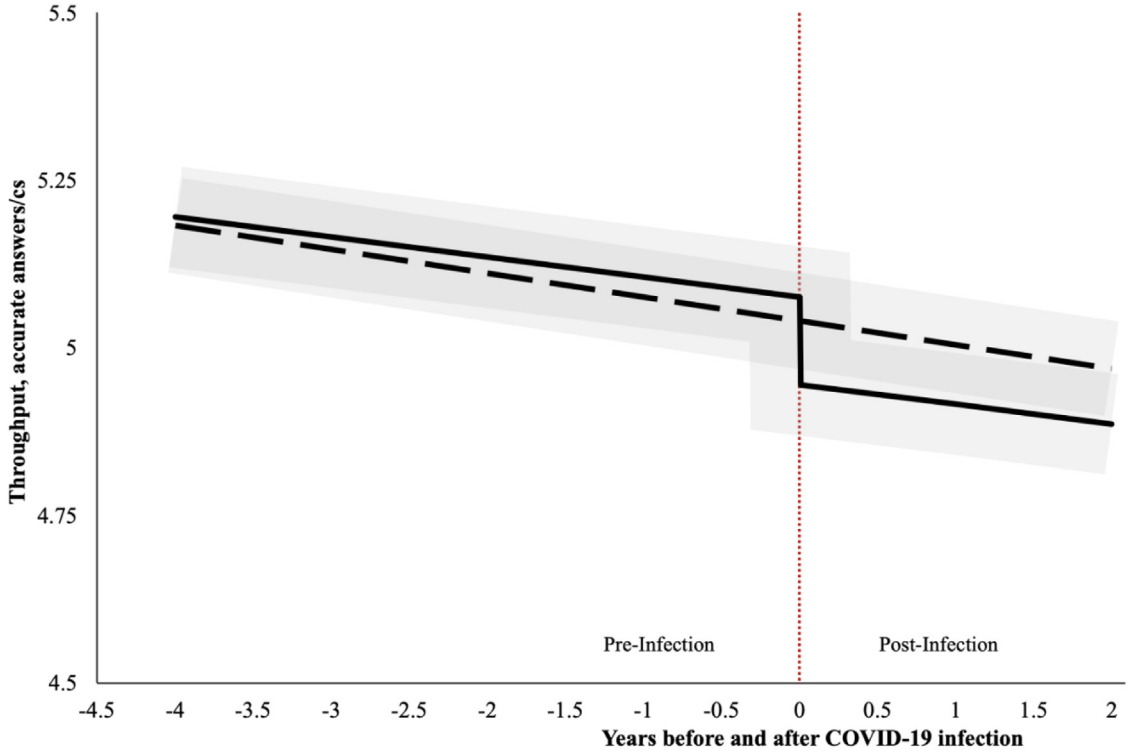
SD, standard deviation; COVID-19, coronavirus disease 2019. P-values comparing participants without PASC to those with long-COVID were derived from tests of proportions (Chi-squared) and from Student's t-tests as appropriate; ICU, intensive care unit. Two-sided alpha = 0.05 was used to indicate statistical significance.

[*] Among 276 COVID-19 group, 20 participants had unknown PASC status.
[†] Other; included participant who declined to specify race or ethnicity.
[#] One person has unknown educational status.
[$] Some participants reported more than 1 symptoms.
[&] Missing hospitalization information on PASC (1) and non-PASC (3) groups.

ing age, gender, race, BMI, education, diabetes, hypertension, cardiovascular disease, and hyperlipidemia, as well as depressive and PTSD symptoms. We included vaccination status and vaccination timing relative to the timing of infection in the descriptive analysis but not in the regression analysis due to the small number of participants who were fully vaccinated before the onset of infection. Analyses were performed in STATA-17/MP (StataCorp).

Posthoc Power Analysis

This study represents secondary data analysis of data examining cognitive functioning matched to the onset of an unexpected event during the study completion, so sample sizes were not under the researcher's control. *Posthoc* power analyses using simulations accounting for moderate intraindividual correlation in the outcome suggested that this study



	Years Before COVID-19 Diagnosis								Years After COVID-19 Diagnosis			
Risk Table	**≤-3.5**	**-3.49, -3.0**	**-2.99, -2.5**	**-2.49, -2.0**	**-1.99, -1.5**	**-1.49, 1.0**	**-0.99, -0.5**	**-0.49, -0.02**	**0.0, 0.49**	**0.5, 0.99**	**1.0, 1.49**	**1.5, 1.99**
No COVID-19	13	25	24	84	35	74	41	82	**98**	**39**	**66**	**28**
COVID-19	61	64	59	84	73	71	60	72	**117**	**51**	**30**	**20**
Total Observations	74	89	83	168	108	145	101	154	**215**	**90**	**96**	**48**

Figure 3. Trajectory plot showing expected throughput before and after the onset of COVID-19 symptoms (time 0). Expectations are stratified as SARS-CoV-2 infected (solid black line) and uninfected (black dashed line). 95% Confidence intervals are shown in translucent gray. The estimated model is $Y_{it} = 5.85 - 0.014 * A_{it} - 0.146 * C_{19t} - [0.045 * EC_{19} - 0.004 * EC_{19} * t] + XB$. Results captured by square brackets were not statistically significant. Results for all domains are shown in Table 3. Abbreviations: cs, centi-seconds.

would have power = 0.93 to detect a longitudinal change in throughput with a moderate (D > 0.2) effect size.[26]

Results

After the application of inclusion/exclusion criteria, a total of 493 eligible participants were eligible for this study (Figure 2). As shown in Table 1, the infected and uninfected groups had similar demographics and health conditions at baseline. However, those who reported SARS-CoV-2 infections were younger (mean age=56.0 years) compared to 58.1 years in the control group (P = .001). Both groups were made up of Caucasian men, and a majority had at least some college education. Those who were included in the analysis did not differ from those who were excluded in any demographics but were less likely to be vaccinated and had more severe cases of COVID-19 (Supplemental Table 2). Only 19 subjects with COVID-19 history had complete and partial vaccination at the onset of infection.

A subgroup of 46.6% (N = 119) of COVID-19 survivors reported PASC. The PASC group had more cardiac disease before COVID-19 onset than those without PASC (Table 2). Chronic fatigue (42.0%), central nervous system (CNS) (40.3%), and respiratory symptoms (36.9%) were the most common PASC symptoms. Brain fog was included as a CNS symptom 95% of the time, some with other coexisting neurological symptoms. Symptoms persisted ≥1 year for 34.46% of participants (Supplemental Table 3).

Longitudinal modeling identified slow cognitive aging over time (standardized regression coefficient β_1 = -0.253, P < .001; Figure 3 shows results for cognitive throughput in the context of the rate of cognitive aging and the size of the impact of COVID-19 on cognition). When modeling cognitive throughput, we found no difference in throughput before COVID-19 onset (β_3 = -0.016, P = .751), but identified a large statistically significant decrement in throughput among those who were infected (β_2 = -0.168, P = .001). Results are equivalent to an AEY of 10.6 years of normal aging and 18 new cases of MCI (NOMCI = 59.8%) in this sample. Similar results were also evident when examining changes in visual memory (β = -0.150, P = .004; AEY = 16.51) but we did not find large and consistent differences when examining processing speed or response speed (Table 3A).

Next, we examined whether individuals reporting more severe COVID-19 or the presence of PASC had evidence of a more rapid rate of cognitive decline than those who only reported acute symptoms (Table 3B-E). Longitudinal results comparing functioning after the onset of COVID-19 to pre-COVID-19 levels (Table 3B/C) suggested that cognitive deficits concentrated in PASC cases. While only reaction speed was associated with the onset of acute COVID-19 but not with long-term COVID-19, in participants with PASC, we found significant decrements across all four domains of cognitive performance after the onset of COVID-19, with the largest decrements involving cognitive throughput and response speed.

Analyses comparing mild with moderate/severe COVID-19 found reduced cognitive throughput and reaction speed compared with pre-COVID-19 functioning in milder COVID-19 cases. However, more severe COVID-19 cases showed larger decrements in cognition across all domains with foci in cognitive throughput and processing speed (Table 3).

Table 3
Longitudinal Degree of Association Between COVID-19 Onset Versus Cognitive Performance for the Whole Sample and Stratified by COVID-19 Severity and the Presence of Postacute Sequelae of COVID-19.

A. Incidence of Any COVID-19					
Cognitive Domain	Std. Coef.	Age Eq. Yrs.	Coef.	Std. Err.	*P*
Throughput	**-0.168**	**10.59**	**-0.146**	**0.000**	**.001**
Visual memory	**-0.150**	**16.51**	**-0.023**	**0.008**	**.004**
Reaction speed	-0.072	6.26	-0.084	0.001	.161
Processing speed	-0.074	6.73	-0.001	0.000	.154
Subgroup Analyses					
	Std. Coef.		**Coef.**	**Std. Err.**	***P***
B. Mild COVID-19					
Throughput	**-0.131**		**-0.130**	**0.051**	**.011**
Visual memory	-0.078		-1.390	0.921	.132
Reaction speed	**-0.206**		**-0.269**	**0.067**	**< .001**
Processing speed	-0.081		-0.063	0.040	.116
C. Moderate/Severe COVID-19					
Throughput	**-0.155**		**-0.190**	**0.063**	**.003**
Visual memory	**-0.108**		**-2.145**	**1.028**	**.037**
Reaction speed	**-0.129**		**-0.195**	**0.078**	**.013**
Processing speed	**-0.163**		**-0.172**	**0.055**	**.002**
D. Acute COVID-19 Alone					
Throughput	-0.070		-0.687	0.506	.175
Visual memory	-0.043		-6.771	8.066	.401
Reaction speed	**-0.133**		**-1.709**	**0.664**	**.010**
Processing speed	-0.096		-0.845	0.454	.063
E. Postacute Sequelae of COVID-19					
Throughput	**-0.203**		**-2.504**	**0.638**	**< .001**
Visual memory	**-0.142**		**-32.388**	**11.777**	**.006**
Reaction speed	**-0.188**		**-3.043**	**0.836**	**< .001**
Processing speed	**-0.121**		**-1.262**	**0.537**	**.019**

Note: All models adjusted for age, sex, race/ethnicity, educational attainment, hypertension, body mass, diabetes, post-traumatic stress symptoms, and depressive symptoms. $P < .05$, two-sided, was adopted as indicating significance. Abbreviations: COVID-19, Novel Coronavirus 2019; Std. Coef., standardized regression coefficient; Age Eq. Yrs., number of years of aging necessary to equal a similar level of cognitive decline as evident in COVID-19; Coef., regression coefficient; Std. Err., standard error; *P, P*-value. Trend-level *P*-values were determined using nonparametric trend tests. For emphasis, we showed statistically significant values in **Bold Typeface**.

Discussion

This study revealed a significant decrement in cognition among participants infected by SARS-CoV-2 consistent with previously reported cognitive decline following many other infections, including but not limited to West Nile, human immunodeficiency, hepatitis C, and chikungunya viruses.[27] Observing cognitive decline and incident mild cognitive impairment (MCI) following SARS-CoV-2 infection helps to confirm causal associations between COVID-19 and reduced cognitive performance, especially among those who have developed PASC. For example, among people who experienced symptomatic COVID-19, we found evidence of lasting decline in cognitive functioning equivalent to 10.6 years of normal aging and increased participants with MCI. These results imply an increase in cognitive dysfunction and poorer brain health after COVID-19, notably in those who experienced severe COVID-19 and PASC.

Throughput was significantly reduced with the onset of COVID-19 and over the subsequent two years, yet we observed no additional decline in throughput in the control group during the same period. Our results indicate that cognitive decline was substantial but was only sufficient to cause MCI in a small number of people in midlife. Infection severity and cognitive function are well studied,[28] though their impact on CRCD remains inconclusive. Thus, a lack of conclusive results among in-hospital studies may emerge due to the lack of pre-COVID-19 information necessary to differentiate CRCD from normal cognitive aging. Usefully, our results are comparable to those in hospitalized patients with PASC and agree with findings of cognitive impairment in mild COVID-19.[15] Results also concur with a Mendelian randomization analysis that found that host genetic predisposition to SARS-CoV-2 infection was connected to decreased cognitive function,[29] confirming that COVID-19 infection is a probable trigger of cognitive decline.[30] Studies relying on causal methodologies support the conclusion that SARS-CoV-2 infection causes cognitive decline and present the first evidence that cognitive decline emerges concurrent with SARS-CoV-2 infection.

Slower response and processing speeds alongside poorer cognitive throughput and visual memory are domain-specific results and likely indicate executive dysfunction. Executive function domains include the ability to store information in working memory while other cognitive processes are occurring, switch attention quickly from one stimulus or set of rules to another, inhibit impulsive responses, and track novel stimuli and replace old information.[31] Response speed is crucial for preventing accidents and falls in older adults and processing speed can help support time-sensitive decision-making processes and working memory [31] and are therefore critical to financial decision-making in older adults.[32] These domains represent changes in cerebral functioning including in the frontal and temporal lobes and the hippocampus.[33,34] Coincidentally, patients with severe COVID-19 have been found to have transcriptomic changes in their prefrontal cortex like those of older individuals.[35] Yet, response and processing speed are usually influenced by white-matter dysfunction although in neuroinflammatory disorders, processing dysfunction may additionally indicate difficulties in coordinating activities in the brain stem and cerebellum.[36] Executive function abnormalities can also be caused by lesions in the frontal lobes and other areas of the brain and research suggests that diffuse white matter hyperintensity volume may be more strongly associated with executive function impairments than localized lesions.[37] Future neuroimaging studies are needed to isolate the nature and extent of these diseases.

COVID-19 may induce serious behavioral issues and call for close neurological and psychiatric monitoring due to the presence of neu-

roinflammation in many neurodegenerative disorders.[38] Viral infections can indirectly impact episodic memory and can also indirectly influence memory via reduced attention or processing speed.[39] Several viruses are thought to cause central nervous system damage in humans. Survivors of herpes simplex virus encephalitis had long-term neuropsychiatric symptoms, with their development attributed to cytolysis and inflammation. The human immunodeficiency virus is linked to neurocognitive disorders.[40] Thus, further research is necessary to identify neurological manifestations of PASC attributed to various mechanisms including endothelial disruption or neuroglial dysfunction.[41]

Limitations

Generalizability may be limited because the study population of essential workers was mostly Caucasian men at midlife. Prior studies revealed no correlation between the COVID-19 research findings and conditions related to prior occupational exposures.[17] Even though the majority of our patients contracted COVID-19 when alpha/beta variants were active and therefore contracted the virus before the COVID-19 vaccination campaigns, other studies have suggested that even patients with the Omicron variant reported possible CRCD.[42] Our control group reported no influenza-like symptoms or positive COVID-19 test results during the study period but may have been asymptomatic or had a false negative result that might bias the estimated effect sizes towards the null. CRCD has no effective therapies, though COVID-19 vaccination might mitigate some PASC symptoms both before and after contracting COVID-19.[9,43] Only a small number of participants developed COVID-19 after vaccination in this study thereby preventing us from studying the potential protective effects of vaccination on CRCD.

Conclusion

We found that COVID-19-related cognitive decline (CRCD) was objectively observed and was concentrated in those who were reporting severe COVID-19 symptoms or the presence of PASC. These symptoms might qualify people for accommodations and disability payments under the *Americans with Disabilities Act* making the question of the causal nature of CRCD critical to policy makers.[44] In our study, we used a longitudinal discontinuity approach, a type of causal modeling,[45] to show that COVID-19 was causally associated with cognitive decline equivalent to 10.6 years of normal aging and with a 59.8% increase in the incidence of MCI. PASC and severe disease appeared to accelerate cognitive deterioration, especially in executive function. Cognitive decline affects daily, occupational, and social functioning, and finding the underpinnings of CRCD is crucial to mitigating its potential to reduce quality of life.[5,38,46] This study suggests that even individuals with mild COVID-19, especially those who developed PASC, might need to be evaluated for cognitive decrements. Patients, notably those with PASC, should therefore undergo routine screening with tools capable of detecting slight cognitive abnormalities.

Statement of Ethics

Informed written consent was obtained from all participants or their surrogates, and no financial compensation was provided. This study was approved by the Stony Brook University Institutional Review Board (CORIHS-A, IRB#604113).

Data Sharing Statement

Only processed deidentified data will be provided upon written request to the appropriate author due to concerns of medical confidentiality.

Clinical Significance

- In this study of essential workers, we identified large, statistically significant, changes in cognitive performance after mild to moderate COVID-19.
- Decrements in cognition were concentrated in those who also reported the presence of postacute sequelae of COVID-19.
- Cognitive decline was evident in domains of response speed, processing speed, and memory.
- Cognitive decline attributable to COVID-19 infection in people with PASC was similar in size to the effect of being 10.6 years older.

Declaration of competing interest

We have no financial conflicts of interest to disclose.

CRediT authorship contribution statement

Zennur Sekendiz: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Olga Morozova:** Writing – review & editing, Resources, Investigation, Funding acquisition, Conceptualization. **Melissa A. Carr:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation. **Ashley Fontana:** Writing – review & editing, Validation, Supervision, Project administration, Data curation. **Nikhil Mehta:** Writing – review & editing, Validation, Investigation, Data curation. **Alina Ali:** Writing – review & editing, Validation, Investigation, Data curation. **Eugene Jiang:** Writing – review & editing, Validation, Investigation, Data curation. **Tesleem Babalola:** Validation, Writing – review & editing. **Sean A.P. Clouston:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Benjamin J. Luft:** Writing – review & editing, Supervision, Resources, Project administration, Formal analysis, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmo.2024.100076.

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