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Cognition Before and After COVID-19 Disease in Older Adults: An Exploratory Study

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Abstract.
Background: Older age is a major risk factor for severe COVID-19 disease which has been associated with a variety of neurologic complications, both acutely and chronically.
Objective: We sought to determine whether milder COVID-19 disease in older vulnerable individuals is also associated with cognitive and behavioral sequelae.
Methods: Neuropsychological, behavioral, and clinical outcomes before and after contracting COVID-19 disease, were compared in members of two ongoing longitudinal studies, the Arizona APOE Cohort and the national Alzheimer's Disease Research Center (ADRC).
Results: 152 APOE and 852 ADRC cohort members, mean age overall roughly 70 years, responded to a survey that indicated 21 APOE and 57 ADRC members had contracted COVID-19 before their ensuing (post-COVID) study visit. The mean interval between test sessions that preceded and followed COVID was 2.2 years and 1.2 years respectively for the APOE and ADRC cohorts. The magnitude of change between the pre and post COVID test sessions did not differ on any neuropsychological measure in either cohort. There was, however, a greater increase in informant (but not self) reported cognitive change in the APOE cohort ($p = 0.018$), but this became nonsignificant after correcting for multiple comparisons.
Conclusion: Overall members of both cohorts recovered well despite their greater age-related vulnerability to more severe disease.

Keywords: Alzheimer's disease, *APOE*, cognitive aging, COVID-19, mild cognitive impairment

INTRODUCTION

Numerous reports have associated COVID-19 disease with a variety of neurologic complications. The most serious complications of acute COVID-19 disease are generally limited to hospitalized patients and include delirium in 7.5–13.9% [1, 2] and acute stroke in 1.4% [3]. Older age, especially over 70 years, is a major risk factor for severe illness and death [1, 4, 5], and this remains true even following COVID vaccination [6]. Those with dementia are at even higher risk of mortality [4, 7].

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Symptoms that persist beyond 4 weeks are considered "long COVID" which has been further subdivided into subacute (4–12 weeks; and this has been further subdivided into LC28 or those lasting more than 4 weeks and LC56 or those lasting more than 8 weeks after acute COVID) and chronic or post-COVID-19 syndrome (LC84 or beyond 12 weeks) [8, 9]. Fatigue is the most common and consistently reported symptom [8–10], but other commonly reported symptoms include headache [8, 10], dyspnea [12], muscle pain and weakness [9, 10], sleep difficulties [8, 11, 13, 14], psychiatric disturbances (primarily depression and anxiety) [9, 13], cognitive symptoms typically described as "brain fog" (encompassing poor concentration, attention, and memory loss [8, 9, 15]) and even dementia [9]. Over a 6-month period, a mobile application based COVID Symptom Study captured responses from 4,182 incident COVID cases mainly from the United Kingdom, in which 558 (13.3%) reported symptoms lasting at least 4 weeks (LC28), 189 (4.5%) for at least 8 weeks (LC56), and 95 (2.3%) for at least 12 weeks (LC84) [9]. In addition to the severity of acute COVID19 disease, older age was again a major risk factor for long COVID with LC28 rising from 9.9% in those age 18–49 to 21.9% in those age 70 and older [8, 9]. Finally, long COVID has also affected patients not requiring hospitalization. Among such cases memory loss as well as difficulty concentrating and focusing are frequent [15–18]. Further, a large recently reported UK Biobank based study found, in non-hospitalized COVID survivors with MRI brain scans performed before and after COVID, small but statistically significant reductions in brain volume and diffusivity in limbic and olfactory related cortices [19].

Cognitive decline generally and memory loss in particular are highly prevalent among older individuals, and given their greater vulnerability to the effects of COVID-19 disease and its longer term sequelae, we sought to answer whether older individuals who have experienced COVID-19 show objective evidence of decline on neuropsychological tests. To do so, we leveraged an ongoing longitudinal study, the Arizona APOE Cohort Study, whose primary aim is to characterize the changes in cognitive trajectories that distinguish resilient aging from preclinical Alzheimer's disease. Among members of this cohort, we have had the opportunity to observe, on an extensive neuropsychological battery, the impact of COVID-19 disease on older individuals whose test scores following COVID-19 can be contrasted to their scores before contracting COVID-19. We also sought to replicate our findings in a national data repository from a similar multicenter effort, the Alzheimer's Disease Research Centers (ADRC), a federally funded longitudinal study that is focused on aging and dementia.

MATERIALS AND METHODS

Participants and survey

Arizona APOE Cohort [20]

Participants are cognitively unimpaired and undergo apolipoprotein E (*APOE*) genotyping at entry, and thereafter receive extensive neuropsychological testing every two years. They remain enrolled until they reach the stage of mild cognitive impairment (MCI) at which time they are transferred out of the APOE cohort and into the clinical core of the Arizona ADRC. In 2020, soon after the ADRC survey was implemented, we added a brief COVID questionnaire to the APOE cohort. Through June 2022, we identified 21 participants age 65 years and older who had been diagnosed with COVID-19 (as well as one other who died from her illness) allowing us to compare neuropsychological test scores before and after COVID-19. All survey respondents were tested in person but visit sessions were delayed in some cases due to the pandemic. A complete list of the tests administered are listed in Supplementary Table 1.

Alzheimer's disease research center cohort [20]

The ADRCs are federally funded centers that perform comprehensive and longitudinal clinical, cognitive, and behavioral examinations on individuals across the entire spectrum of Alzheimer's disease and related disorders including patients with MCI and dementia as well as unimpaired volunteers. In 2020 an optional COVID-19 Impact Survey questionnaire was offered to the ADRCs to administer in addition to the standard test battery for research participants and (if appropriate) their caregivers, and responses through December 2021 were included. ADRC participants receive the Uniform Data Set (UDS) annually, a standardized battery of neuropsychological and behavioral measures until they are too impaired to be formally tested. During the pandemic test administration changed at some centers to video or telephonic, but only those test results administered to survey respondents in the same fashion during test sessions before and after the reported COVID-19 illness were included in this report. At the time of our

query, we found 57 individuals enrolled in an NIA funded ADRC who reported having had COVID-19 with neuropsychological test results available both before and after COVID-19 through the end of December 2021. Of these, 10 received hospitalized care and the remaining 47 were treated as outpatients. A complete list of the tests administered are listed in Supplementary Table 1, although several tests performed in the outpatient subset were not administered to the hospitalized patients (Trail Making Test, MoCA, MINT, Benton Figure).

Standard protocol approvals, registrations, and patient consents

Both the ADRC and APOE Cohort studies, and the COVID surveys administered to participants in these studies have been approved by the Mayo Clinic and Banner Health Institutional Review Boards. Signed informed consent was obtained from the participants themselves in all cases, as well as from their legally authorized representative (typically a spouse) for those individuals with clinically significant cognitive impairment.

Statistics

Supplementary Table 1 lists the tests administered, corresponding score range, and major cognitive domain tested. For continuous data, the pre-post test change differences between the COVID and no-COVID groups were compared using ANCOVA with repeated measures including pre-/post visits as within-subject repeated measures and COVID grouping as the between-subject factor, and correcting for multiple comparisons by the false discovery rate (FDR) [21] at a false positive rate (q) of 0.05. Practice effects were addressed using the pre-post test interval duration between the two visits as well as the total number of epochs each participant has had and were included as covariates in the ANCOVA model with repeated measures. Due to the large number of tests, none of which were pre-specified, and relatively low number of participants, this study should be considered exploratory. p values without correction for multiple comparisons were provided in the tables, but correction using the FDR is included in the text. Effect sizes were calculated using Hedges g which accounts for the discrepant numbers of individuals in the COVID and No-COVID groups.

RESULTS

Demographic and entry characteristics of the two cohorts are summarized in Table 1. As a snapshot, the cohorts were very similar: patients were roughly age 70 years, well educated, over 70% women, predominantly white, predominantly cognitively unimpaired, and 30–40% or so *APOE* ε4 carriers. Most were tested less than a year after COVID diagnosis, and addi-

Table 1
Demographics

APOE Cohort	No COVID	COVID	*p*
n	131	21	
sex (% Female)	78.60%	71.40%	0.46
education (y)	16.5 (2.1)	16.3 (2.6)	0.73
Age at COVID survey epoch	74.8 (6.3)	72.9 (5.3)	0.17
Months from COVID to Test		6.6 (5.6)	
APOE ε4 % Carriers	24.3 (9.5)	26.0 (7.1)	0.41
White Non-Hispanic %	39.20%	42.90%	0.73
% with CV risk factors	84.70%	76.20%	0.34
Pre-Post Test Interval (y)	75.60%	81.00%	0.78
ADRC Cohort	No COVID	COVID	*p*
n	795	57	
sex (% Female)	60.60%	66.70%	0.367
education (y)	16.8 (4.8)	15.8 (2.2)	0.11
Age at COVID survey epoch	70.9 (9.2)	68.3 (13.6)	0.047
Months from COVID to Test	NA	<12	NA
APOE ε4 % Carriers	34%	31%	0.7
White Non-Hispanic %	97%	98%	0.67
% with CV risk factors	48%	44%	0.56
Pre-Post Test Interval (y)	1.31 (0.52)	1.22 (0.47)	0.25
-COVID outpatient ($n = 46$)	–	1.26 (0.47)	
-COVID hospitalized ($n = 11$)	–	1.08 (0.48)	0.27 (outpatient versus hospitalized)
% with MCI or Dementia	15.20%	8.70%	0.41

tional information on the time interval between acute COVID-19 and post-COVID testing (labelled relative to long COVID categories though none were reporting symptoms of long COVID) was available for the APOE Cohort: LC28 $n = 7$, LC56 $n = 6$, LC84 $n = 6$, missing $n = 2$. The ADRC cohort was less racially diverse and had a smaller percentage of *APOE* ε4 carriers. In the ADRC cohort 15.2% of the no-COVID group and 8.7% of the COVID group carried a diagnosis of MCI or dementia at baseline (pre-COVID epoch), but there was no significant difference in the rate of diagnostic change post-COVID between the two groups ($p = 0.28$, chi square). In the APOE cohort, none of those who contracted COVID had MCI (or other neurodegenerative diagnosis) either before or after COVID while in the no-COVID group there were 6 MCI and 1 Parkinson's disease patients at baseline and an additional 2 MCI and 1 Parkinson's disease diagnoses at follow-up. The pre-post survey test interval, as expected, was higher in the APOE cohort. Of the 57 ADRC COVID patients, 11 were hospitalized while only 1 of the (surviving) 21 APOE cohort members was hospitalized. Time between COVID-19 disease and the post-COVID testing was under a year on average in both cohorts although exact dates were missing in most of the ADRC COVID-19 cases.

Pre and post COVID-19 test results for the APOE and ADRC cohorts are summarized in Tables 2 and 3, and the hospitalized ADRC subset (10 patients) results are summarized in Supplementary Table 2. Test batteries differed between the two cohorts but cognitive and behavioral domains assessed were similar so contrasting cohort results are grouped in the tables by domain. Overall, there were no differences noted in the magnitude of change after COVID versus before COVID-19 disease on any of the memory, executive, language, visuospatial, or behavioral measures in either cohort with or even without FDR correction. (FDR $p = 0.84$ and higher for all APOE cohort measures and $p = 0.85$ and higher for all ADRC cohort measures). Consistent with the lack of the statistical significance, the effect sizes were otherwise generally small in both cohorts. The sole exception was informant-based (but not self-based) subjective decline in the APOE cohort COVID group ($p = 0.018$ with an effect size [0.65] of moderate impact). However, in a similar survey in the ADRC cohort Informants were asked to assess the degree of change resulting from the COVID pandemic as none, some, or a great deal of change. For the non-COVID group, results were 50.6%, 40.5%, and 8.9% respectively. For the COVID group results were 41.5%, 45.3%, and 13.2% respectively (no-COVID versus COVID, $p = 0.35$). The small and unbalanced sample sizes together with the small between-group effect sizes contributed to these non-significant results. We also attempted to estimate the increased and balanced sample sizes required to achieve statistical significance with FDR from the most significant tests and estimated 418 subjects in each group (COVID-19 and the No COVID control group) to achieve an FDR corrected statistical significance of 0.05 with 80% power.

DISCUSSION

In this exploratory study involving two separate cohorts of older individuals who underwent extensive neuropsychological testing both before and after acute COVID-19 disease, most of who were treated as outpatients and not reporting symptoms of "long COVID", we found little evidence of cognitive decline over the following months post-COVID-19 disease. In the APOE cohort, the COVID-19 group showed more informant based (but not self-assessed) subjective decline although similar declines were not seen in the ADRC cohort. In a small subset of patients hospitalized with COVID-19 disease from the ADRC cohort we also found no evidence of decline on any of the available few measures encompassing memory, executive, and language domains. While symptoms of psychological distress and disturbed sleep [11, 15, 16] have been frequently reported we did not find any changes related to depression, anxiety, or sleep on several relevant questionnaires.

Our findings might initially appear to be somewhat at odds with previous reports, but this likely reflects the fact that our participants were generally not severely ill acutely and were not reporting symptoms of "long COVID". Also, cognitive changes quantitatively assessed neuropsychologically, when reported in previous studies have been relatively modest. A large UK Biobank based study found, in non-hospitalized COVID survivors with MRI brain scans performed before and after COVID, that there were small but statistically significant reductions in brain volume and diffusivity in limbic and olfactory related cortices including the parahippocampal and orbitofrontal gyri. However, neuropsychological test changes were not seen on memory measures (as might have been expected from parahippocampal involvement) but instead on an attentionally demanding

Table 2
APOE cohort results

	No Covid ($n = 131$)			COVID ($n = 21$)			COVID versus No COVID Pre-Post change p ANCOVA	COVID versus No COVID Pre-Post change Effect size
	Pre	Post	Annualized change	Pre	Post	Annualized change		
Sleep								
Sleep Total (h)	7.34 (1.11)	7.39 (1.14)	0.03 (0.57)	7.65 (1.33)	7.43 (1.41)	–0.08 (0.42)	0.30	0.20
Sleep Onset (min)	17.70 (18.20)	20.13 (18.14)	0.88 (7.98)	16.95 (25.24)	13.83 (13.19)	3.28 (12.89)	0.90	0.27
Mid Night Wakings (#)	1.80 (1.53)	1.64 (1.70)	–0.17 (0.88)	1.20 (1.24)	1.06 (1.11)	–0.11 (0.46)	0.92	0.07
Mid Night Wake (min)	36.72 (52.65)	38.23 (46.75)	0.26 (28.79)	25.20 (38.07)	21.11 (27.94)	–0.05 (16.39)	0.26	0.01
Epworth Scale	5.89 (4.14)	5.71 (3.83)	–0.30 (1.73)	5.70 (4.61)	6.28 (3.65_	0.13 (1.52)	0.36	0.25
General/Subjective								
MANS Informant	10.45 (20.74)	13.55 (25.87)	0.81 (10.96)	3.82 (7.63)	19.50 (30.40)	9.06 (21.17)	0.018	0.64
MANS Self	14.69 (24.58)	16.04 (22.69)	1.41 (16.35)	12.45 (21.62)	22.05 (31.16)	4.76 (8.42)	0.36	0.22
CDR Sum of Boxes	0.034 (0.17)	0.54 (0.26)	0.017 (0.19)	0.14 (0.36)	0.024 (0.11)	–0.53 (0.20)	0.13	2.86
CDR Global Score	0.038 (0.21)	0.035 (0.20)	0.005 (0.16)	0.071 (0.18)	0 (0)	–0.32 (0.082)	0.36	2.14
Folstein MMSE	29.48 (0.91)	29.41 (1.01)	–0.04 (0.81)	29.24 (1.22)	29.38 (0.92)	0.07 (0.58)	0.78	0.14
Mattis DRS	140.68 (3.06)	140.76 (3.03)	0.10 (1.72)	140.43 (2.99)	139.24 (3.65)	–0.56 (1.98)	0.11	0.38
Depression/Anxiety								
Hamilton Depression	1.11 (2.07)	0.86 (1.30)	–0.17 (1.17)	0.32 (0.58)	0.95 (1.54)	0.17 (0.40)	0.76	0.31
Beck Depression	4.54 (3.82)	5.54 (4.16)	0.55 (2.39)	3.44 (2.99)	5.78 (6.57)	0.69 (2.36)	0.78	0.06
PAI-Somatization	47.47 (7.43)	48.86 (8.25)	0.44 (2.53)	49.10 (11.27)	49.31 (13.65)	–0.71 (0.96)	0.80	0.48
PAI-Anxiety	44.28 (5.86)	44.42 (5.73)	0.15 (2.08)	44.80 (7.22)	42.46 (4.98)	–0.54 (1.14)	0.43	0.35
PAI-Depression	46.00 (6.03)	48.17 (6.67)	1.13 (2.24)	46.50 (7.32)	47.23 (10.28)	0.75 (1.98)	0.55	0.17
PAI-Stress	42.23 (6.01)	42.63 (5.39)	0.73 (3.59)	43.50 (5.68)	44.00 (6.83)	0.83 (2.54)	0.85	0.03
GDS	2.98 (3.58)	2.86 (3.05)	–0.18 (1.83)	2.57 (3.21)	3.52 (3.88)	0.50 (0.91)	0.13	0.39
NPIQ	0.30 (1.03)	0.47 (1.37)	0.80 (1.10)	0.67 (1.32)	1.00 (1.26)	0.13 (1.11)	0.81	0.61
Memory								
AVLT Total Learning	46.83 (11.22)	45.47 (10.97)	0.81 (4.62)	43.62 (9.53)	42.05 (8.55)	–0.42 (4.15)	0.11	0.27
AVLT Short Recall	9.46 (3.54)	9.08 (3.73)	–0.21 (1.43)	8.43 (3.87)	9.14 (2.73)	0.34 (1.40)	0.97	0.39
AVLT Long Recall	9.04 (3.93)	8.72 (3.90)	–0.20 (1.55)	8.05 (3.97)	8.24 (2.98)	0.10 (1.65)	0.45	0.19
SRT Total Free Recall	92.5 (15.63)	91.11 (15.85)	–0.48 (5.68)	92.65 (12.78)	89.56 (16.67)	0.77 (3.64)	0.94	0.23
Logical Memory I	14.31 (3.59)	14.47 (3.78)	0.07 (1.90)	13.71 (3.41)	12.10 (3.92)	0.70 (1.37)	0.44	0.34
Logical memory II	13.67 (3.98)	13.57 (4.17)	–0.04 (1.70)	12.33 (3.51)	11.33 (4.16)	0.44 (1.48)	0.14	0.29
Logical Memory %	95.10 (12.88)	91.77 (22.29)	2.03 (18.35)	90.84 (14.45)	91.59 (19.05)	0.53 (8.71)	0.18	0.09
Rey-O CFT Recall	20.28 (6.69)	20.07 (7.00)	0.075 (3.09)	18.58 (6.72)	18.59 (5.98)	–0.50 (1.71)	0.46	0.20
Rey-O Recall/Copy	0.59 (0.18)	0.58 (0.18)	0.003 (0.089)	0.55 (0.18)	0.54 (0.16)	–0.018 (0.059)	0.38	0.25
Visual retention Test	6.79 (2.12)	7.07 (5.14)	0.18 (2.82)	6.00 (1.97)	6.39 (2.20)	0.19 (0.94)	0.42	0.004

(*Continued*)

Table 2
(*Continued*)

	No Covid ($n = 131$)			COVID ($n = 21$)			COVID versus No COVID Pre-Post change p ANCOVA	COVID versus No COVID Pre-Post change Effect size
	Pre	Post	Annualized change	Pre	Post	Annualized change		
Executive								
Digit Span Forward	6.80 (1.01)	6.64 (1.18)	0.07 (0.57)	6.91 (1.04)	6.57 (0.81)	0.15 (0.35)	0.82	0.15
Digit Span Backward	5.04 (1.27)	5.02 (1.39)	–0.014 (0.645)	4.81 (1.25)	4.57 (0.98)	–0.072 (0.405)	0.56	0.14
WAIS Arithmetic	11.93 (2.56)	11.36 (2.60)	–0.27 (1.06)	10.61 (2.28)	11.06 (2.69)	0.01 (1.01)	0.29	0.27
PASAT 3 s	42.28 (9.11)	47.98 (11.27)	–0.47 (6.29)	44.43 (10.99)	49.57 (9.22)	1.11 (4.08)	0.42	0.26
PASAT 2 s	35.87 (9.68)	35.14 (10.54)	–0.72 (4.54)	32.29 (9.06)	35.42 (10.57)	–0.19 (3.68)	0.72	0.12
WAIS DSS	14.17 (2.40)	13.94 (2.61)	–0.07 (1.02)	14.10 (2.84)	14.40 (3.07)	0.16 (0.60)	0.52	0.24
DSS Total Items	52.05 (10.19)	49.79 (10.49)	–1.27 (3.36)	52.24 (11.22)	51.95 (12.64)	0.05 (2.12)	0.93	0.41
Animal Fluency	20.88 (5.09)	20.47 (5.07)	–0.13 (2.63)	20.76 (4.04)	21.14 (5.53)	0.14 (2.28)	0.86	0.10
Vegetable Fluency	14.99 (4.25)	14.08 (3.94)	–0.37 (1.95)	14.52 (3.42)	14.81 (3.53)	0.12 (1.67)	0.50	0.26
TMT-A (s)	27.18 (10.13)	28.26 (8.52)	0.54 (5.54)	25.71 (7.19)	25.62 (7.05)	–0.08 (1.19)	0.64	0.12
TMT-B (s)	70.28 (35.52)	76.31 (36.05)	3.15 (14.57)	79.95 (42.75)	83.62 (40.74)	1.91 (9.29)	0.23	0.09
WCST-Categories	4.95 (1.77)	4.62 (1.98)	–0.84 (0.77)	4.53 (1.74)	3.94 (2.41)	–0.27 (1.19)	0.42	0.68
WCST-Errors	31.07 (18.19)	33.01 (21.21)	0.75 (8.90)	37.29 (20.08)	37.59 (22.66)	0.36 (11.48)	0.85	0.04
WCST-Persev Err	15.56 (10.80)	16.83 (12.15)	0.70 (4.71)	18.41 (11.89)	18.29 (12.15)	–0.14 (5.82)	0.92	0.17
Language								
WAIS Vocabulary	12.82 (1.85)	12.52 (1.71)	–0.13 (0.85)	12.33 (1.46)	12.38 (2.13)	0.078 (0.75)	0.34	0.25
WAIS Similarities	13.55 (1.75)	13.54 (1.67)	–0.014 (0.84)	13.14 (2.08)	13.24 (1.61)	–0.79 (0.89)	0.77	0.92
Boston Naming Test	55.83 (4.63)	55.76 (5.02)	0.04 (1.51)	56.05 (4.32)	55.71 (4.44)	–0.16 (1.03)	0.94	0.14
Token Test	43.06 (1.96)	43.21 (1.53)	0 (0.88)	42.86 (2.06)	43.38 (0.92)	0.31 (0.95)	0.60	0.35
COWAT	47.67 (10.75)	47.26 (11.22)	–0.20 (5.36)	47.71 (9.58)	43.91 (11.47)	1.83 (3.00)	0.23	0.40
Visuospatial								
WAIS Block Design	12.84 (2.77)	12.73 (2.68)	–0.045 (1.07)	12.81 (2.80)	12.33 (2.11)	–0.26 (0.77)	0.25	0.21
Rey-O CFTCopy	34.14 (2.97)	33.85 (3.42)	–0.17 (1.74)	33.61 (3.74)	34.29 (2.14)	0.11 (1.28)	0.69	0.17
Facial Recognition	46.05 (4.12)	45.87 (4.28)	–0.083 (2.48)	45.14 (3.85)	44.71 (5.57)	–0.24 (2.14)	0.71	0.06
Judge Line Orient	25.09 (4.33)	25.37 (4.83)	0.43 (3.65)	25.14 (3.62)	24.14 (3.29)	–0.49 (1.86)	0.28	0.27

Table 3
ADRC cohort results

	No COVID				COVID				COVID versus No COVID Post-Pre change (ANCOVA p)	COVID versus No COVID Post-Pre change Effect size (Hedges g)
		Pre	Post	Annualized difference		Pre	Post	Annualized difference		
General	*n*				*n*					
MOCA	271	25.29 (5.64)	26.05 (9.67)	0.51 (5.77)	17	25.82 (3.17)	25.41 (4.09)	–0.46 (2.01)	0.81	0.17
CDR Sum of Boxes	795	0.52 (1.73)	0.68 (2.10)	0.14 (0.77)	57	0.53 (1.85)	0.64 (2.46)	0.08 (0.62)	0.86	0.08
CDR Global Score	795	0.15 (0.34)	0.19 (0.39)	0.03 (0.17)	57	0.14 (0.34)	0.18 (0.50)	0.02 (0.26)	0.76	0.06
Depression/Anxiety										
GDS	743	1.44 (1.99)	1.71 (2.06)	0.17 (1.65)	53	1.74 (2.42)	1.72 (2.71)	–0.03 (1.75)	0.95	0.12
NPIQ Score	687	0.88 (1.57)	1.09 (1.75)	0.18 (1.51)	50	0.65 (1.09)	0.94 (1.60)	0.23 (1.33)	0.66	0.03
NPIQ Severity	687	1.23 (2.48)	1.54 (2.87)	0.0009 (0.007)	50	0.84 (1.60)	1.18 (2.04)	0.001 (0.006)	0.47	0.01
Memory										
Craft Immediate	736	21.82 (9.61)	22.23 (10.68)	0.49 (10.09)	52	20.81 (6.36)	22.73 (6.96)	1.55 (4.88)	0.80	0.11
Craft Delayed Recall	736	19.62 (11.09)	20.24 (12.61)	0.90 (11.92)	52	18.02 (6.87)	19.48 (6.60)	0.76 (5.41)	0.64	0.01
Benson Delayed	271	11.21 (8.22)	12.65 (13.21)	1.51 (13.00)	17	11.24 (2.97)	11.12 (3.87)	–0.20 (2.01)	0.65	0.14
Executive										
Digit Span Forward	736	6.99 (5.84)	7.14 (7.51)	0.08 (6.76)	52	6.75 (1.36)	6.58 (1.27)	–0.21 (1.06)	0.54	0.04
Digit Span Backward	736	5.28 (4.90)	5.66 (7.62)	0.33 (5.24)	52	5.13 (1.52)	5.19 (1.40)	0.04 (1.10)	0.61	0.06
Animal Fluency	736	21.15 (7.49)	20.70 (9.12)	–0.30 (6.86)	52	19.96 (5.71)	19.77 (5.11)	–0.16 (4.83)	0.47	0.02
Vegetable Fluency	736	14.77 (7.56)	14.32 (8.84)	–0.24 (7.88)	52	13.25 (4.19)	12.52 (3.47)	–0.57 (3.18)	0.13	0.04
TMT-A (s)	271	46.25 (102.36)	59.11(143.03)	7.87 (93.78)	17	37.00 (16.53)	40.35 (24.61)	1.70 (11.63)	0.59	0.07
TMT-B (s)	271	133.17 (162.72)	159.00 (206.62)	18.67 (140.12)	17	130.35 (94.46)	134.65 (82.95)	3.84 (63.30)	0.60	0.11
Language										
MINT	270	30.91 (7.44)	30.82 (9.00)	–0.42 (12.66)	17	28.47 (2.18)	29.06 (2.41)	0.43 (1.20)	0.43	0.07
Letter Fluency F	736	15.61 (6.26)	15.85 (9.77)	0.26 (7.50)	52	14.54 (4.14)	15.00 (3.74)	0.44 (2.48)	0.49	0.03
Letter Fluency L	736	14.93 (6.97)	15.31 (9.79)	0.42 (7.92)	52	13.65 (4.61)	13.92 (4.30)	0.29 (3.16)	0.28	0.02
Visuospatial										
Benson Figure Copy	271	15.78 (5.11)	16.90 (11.07)	0.87 (8.16)	17	15.59 (1.12)	14.88 (2.15)	–0.02 (1.40)	0.46	0.11

timed "connect the dots" type of task (the Trail making test). (Participants in neither of our two cohorts, however, declined on this test post COVID). In addition, the mean age of the test participants was under 60 years [19]. In an internet based study, Hampshire et al. surveyed more than 84,000 participants of the Great Britain Intelligence Test, an online test battery and identified over 13,000 who had been previously diagnosed with COVID-19 disease. Overall, 0.76% reported having residual symptoms driven mainly by those who required ventilator support during their acute illness, and the COVID groups overall showed modest but statistically significant reductions on a variety of non-standard cognitive tests [15]. Patients from a Neuro-COVID clinic who underwent neuropsychological testing with the NIH Toolbox did less well on a Flanker task (where the subject has to quickly indicate whether an arrow is pointing in the same of different direction as others on the screen) and a sequencing task (in which subjects have to size order items of food or animals on a list of increasing size) implying difficulties with attention and working memory [18]. While our measures of attention and working memory did not show any differences, this could reflect differences between these tests with those we administered.

Psychiatric symptoms also have been reported to be prevalent in both hospitalized and non-hospitalized COVID survivors though rates differ between studies. Depression, for example, ranges from 4.3% in a series of 538 hospitalized patients from Wuhan [12] to 45% in a pooled prevalence estimate of U.S. cases [11]. Regarding sleep, in a meta-analysis encompassing 54,231 patients from 13 countries during the first 8 months of the COVID-19 pandemic, the global pooled prevalence rate of sleep disorders was 35.7%, and the most affected patients were those with active COVID-19 disease [13]. Symptoms have included new onset insomnia and delayed wake-up times, as well as more frequent nightmares [14]. We did not find an increase in reported symptoms of insomnia or greater daytime fatigue, and while we did not specifically ask about dream quality, we did not observe any incident cases of dream enactment behavior. Given previous reports of attentional difficulties on neuropsychological tests, it is possible that COVID-related acquired sleep disorders may be contributory.

Patients with more severe acute illness represented a minority of our subjects but have been more likely to experience ongoing symptoms. Severe illness and its treatment can impact multiple organ systems which in turn can secondarily impact cognition, a factor that certainly applies to many hospitalized COVID patients [22]. Those who do contract severe disease have been found to have a high incidence of neurological sequelae that include but are not limited to cognitive decline, but the proportion of such outcomes is similar to other causes of critical illness [2]. Encephalopathy in a critical care setting portends a worse functional outcome and higher mortality [23] and in COVID-19 cases can result from multiple forms of organ failure [22] which in turn are associated with elevated serum levels of a neuroaxonal injury marker, neurofilament light [24], markers of blood-brain barrier disruption including S100B, and markers of glial cell activation including GFAP [25]. Posited mechanisms of SARS-CoV-2 CNS invasion have included hematogenous spread from infected leukocytes, infected vascular endothelial cells, and penetrance via retrograde transport from the olfactory epithelium [25]. Neuropathological pathways associated with tau hyperphosphorylation typically associated with AD have also been found to be activated in COVID-19 patients raising concern about future cognitive decline [26]. Persistent cognitive impairment has been sought in such severe cases, but even in fatal cases, while rare instances of SARS-CoV-2 encephalitis have been observed, most patients generally lack evidence of direct viral invasion of the brain, including those who suffered cerebral infarctions [27, 28].

There are several limitations to our study. Most notably, the number of individuals included remains small, and so we cannot exclude the possibility of a small impact of COVID on cognition that this study was under-powered to detect. Still, these individuals were already enrolled in longitudinal studies assessing cognition providing the unusual opportunity of detailed neuropsychological and behavioral testing before and after COVID-19 disease. Second, as previously noted, this is not a study focused on that subset of COVID survivors with a "long COVID" syndrome. These participants felt they had generally recovered. Third, we did not perform serological testing to assess the immunological status of our participants. Possibly asymptomatic carriers were included in the "no-COVID" group, but even if so, our conclusions would not be affected. Despite these limitations, our results are encouraging showing that older adults who contract COVID-19 that is not otherwise severe have an excellent chance for full recovery.

In summary, in this study of older and presumably more vulnerable adults, COVID-19 disease

that was not severe enough to necessitate ICU admission or prolonged hospitalization resolved with little evidence of any lingering neuropsychological or behavioral impairments. Whether more subtle changes may be present, or whether any acceleration of neurodegenerative diseases may eventually be found will require a much larger study and much longer period of observation to determine.

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SUPPLEMENTARY MATERIAL

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