Long COVID and recovery from Long COVID: Quality of life impairments and subjective cognitive decline at a median of 2 years after initial infection

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Abstract

Background: Quality of life (QoL) and cognition for those with Long COVID is not well-characterized, but existing research suggests impairments in both persist beyond 12 months after initial illness.

Methods: In this cross-sectional study, 435 participants with SARS-CoV-2 infection, confirmed with laboratory test or physician diagnosis, between March 2020 and December 2021 completed self-report surveys between March 2022 and September 2022 (n=7305 sent surveys; response rate=6.0%). Multi-domain QoL and cognitive concerns were evaluated using PROMIS-29 and the Cognitive Change Index-12. Those not recovered from COVID-19 at time of survey ("Current Long COVID"; n=181) and those who recovered from COVID-19 in >3 months ("Recovered Long COVID"; n=34), were combined to form a Long COVID group (n=215) and were compared with those who recovered from COVID in ≤3 months ("Without Long COVID"; n=220).

Results: Nearly half the participants (47.7%) were surveyed more than 2 years from initial infection (median=23.3 months; IQR=18.6, 26.7). The Long COVID group showed significantly greater proportion of moderate-to-severe impairment in all health domains assessed compared to those Without Long COVID (all $p<0.05$). The Recovered Long COVID group showed significantly lower prevalence of fatigue, pain, depression, and physical and social function impairment compared to those with Current Long COVID (all $p<0.05$). However, compared to patients Without Long COVID, the Recovered Long COVID group had greater prevalences of fatigue, pain ($P\leq0.06$) and subjective cognitive decline (61.8% vs 29.1%; $p<0.01$).

Multivariate relative risk (RR) regression indicated Long COVID risk was greater for older age groups (RR range 1.46-1.52; all $p\leq0.05$), those without a bachelor's degree (RR=1.33; 95% CI=1.03-1.71; $p=0.03$), and those with 3 or more comorbidities prior to SARS-CoV-2 infection (RR=1.45; 95% CI=1.11-1.90; $p<0.01$). Each additional symptom experienced during acute COVID-19 was associated with a 14% greater Long COVID risk (RR=1.14, 95% CI=1.10-1.18; $p<0.01$).

Conclusions: Long COVID is associated with long-term cognitive complaints and diminished quality of life. Older age, not having a bachelor's degree, and pre-existing comorbidities are risk factors for prolonged or non-recovery from COVID-19. Recovery from Long COVID was reported by a subset of those with Long COVID, though clinically significant cognitive complaints, fatigue, and pain persisted.

Introduction & Objective

Evidence throughout the novel coronavirus-19 (COVID-19) pandemic has demonstrated that a significant proportion of those infected with SARS-CoV-2 (the virus that causes COVID-19) experience a "continuation or development of new symptoms" more than 3 months after initial infection, termed a "post COVID-19 condition" (PCC or "Long COVID") by the World Health Organization (WHO).(1–6) Fatigue, post-exertional malaise, unrefreshing sleep, pain, and neurocognitive symptoms have been consistently associated with Long COVID even after mild acute infections,(3, 4, 6–13) drawing comparisons to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).(3)

The association of Long COVID with impairments in both quality of life (QoL) and cognition are persistent and significant.(4, 7–10, 12, 14–17) The data on symptoms more than 2 years after infection are limited and confined largely to research involving hospitalized patients and medical record studies.(12, 14, 16, 18) As such, the long term relationship between mild-to-moderate COVID-19 illness and QoL, which is not routinely captured in the medical record, is unclear. Impacts on memory and attention have also been associated with Long COVID at follow-up intervals of > 6 months.(4, 8, 19, 20) Changes in cognition can be difficult to assess given the need for repeated neuropsychological measurement. However, a body of literature has shown that subjective cognitive decline is a meaningful measure of cognitive changes.(21–24) Since objective testing is often indicated after subjective complaints arise, subjective cognitive decline has clinical relevance, and it has been associated with future cognitive impairment in older adults.(23, 25, 26)

While the 6 to 12 months following COVID-19 illness are currently the best characterized, recent studies that include follow-up of 24 months continue to identify significant health impairments.(7, 14, 27, 28) Further work is necessary to elucidate the experience of Long COVID beyond 12 months after initial infection and investigate the potential for recovery from Long COVID.

In this study, we used validated measures to characterize QoL and subjective cognitive decline 4–30 months after initial infection among patients with medical record confirmed COVID-19, a majority not hospitalized during the acute illness. We compared the Long COVID group (> 3 month recovery to baseline health) to those Without Long COVID (≤ 3 month recovery) and investigated social and health factors associated with self-reported Long COVID.

Methods

Participant Selection

We collected all inpatient and outpatient medical records within an urban, university-affiliated medical system of adults with 1) either a positive SARS-CoV-2 polymerase chain reaction (PCR) test result or a clinical diagnosis of COVID-19 (n = 120 diagnosed by PCR, 27.5%; see Supplemental Information) between March 2020 and December 2021 and 2) a patient ZIP code within the state as part of the Centers for Disease Control and Prevention's (CDC) COVID-RELIEF (Research on COVID-19 Long Term Effects) project. All those identified were selected for follow-up. Patients with an available email address were emailed an invitation to join a COVID-19 research project. All participants who provided data on their COVID-19 recovery and at least partially completed the outcome measures and demographics were included in the analysis (N = 435; response rate = 6.0%; Fig. 1). Surveys were completed between March 2022 and September 2022, at least 4 months after initial infection for all participants.

Flow diagram outlining the creation of the analytic sample for this study (N = 435) and the grouping of Long COVID (n = 215) vs Without Long COVID (n = 220) within the sample. Percentages were computed by dividing each *n* by the number of individuals in the preceding box.

Study Measures

Participants completed surveys remotely via a secure instance of Research Electronic Data Capture (REDCap). The surveys collected basic sociodemographics (all categorical variables self-classified) and information about acute COVID-19 illness, including hospitalization, pre-COVID comorbidities, the number of symptoms experienced out of 11 core symptoms (see Supplemental Information),(29) recovery status (asked as “Have you returned to your pre-COVID baseline health?”), and time to recovery, if applicable (See Supplemental Information).

The Long COVID group was defined as all participants who were not recovered at time of survey (Current Long COVID) or who recovered more than 3 months after initial infection (Recovered Long COVID). The comparison group (Without Long COVID) were those who reported recovery to pre-COVID baseline health in ≤ 3 months. Participants completed the 29-item Patient Reported Outcomes Measures Information System v2.0 (PROMIS) survey, which has 7 subscales composed of four questions each (Likert ratings from 1–5 where 1 indicates no impairment and higher values indicate more frequent or more severe impairment; individual subscale score range, 4–20) assessing the current status of the following health domains that impact quality of life: physical function, anxiety, depression, fatigue, sleep disturbance, social function (i.e., ability to participate in social roles and activities), and pain interference.(30, 31) For all scales but the social and physical function scales, higher scores indicate greater impairment. To measure subjective cognitive decline, participants completed the 12-item Cognitive Change Index (CCI-12),(32) modified to ask for comparisons of current memory to pre-COVID-19 baseline. The CCI-12 items are captured on a 1–5 Likert scale and summed (range: 12–60), with greater scores indicating more severe perceived changes.(24, 32) An additional item, not included in the sum total, assessed participants’ concern about cognitive changes on a 1–5 Likert scale.

Statistical Analysis

Descriptive statistics were calculated for each group and compared with *t*-tests for continuous variables and Chi-square tests for categorical variables. Raw PROMIS totals were converted to normalized T-scores for each domain and participants were classified as having moderate or severe domain-specific impairment based on clinically validated thresholds.(31, 33, 34) The CCI-12 scores were summed, with scores ≥ 20 indicating subjective cognitive decline.(21, 24, 35) A threshold of one standard deviation (sample-derived) above the validated clinical threshold (i.e., > 32) was chosen to explore severity differences by group. Participants were classified as having cognitive concerns if they reported being at least “Slightly Concerned” about memory changes since COVID-19. For each domain, we compared the proportion of moderate-to-severe impairment across groups using Chi-squared tests or Fisher’s exact test and a significance level of $\alpha = 0.05$. Bonferroni correction was applied to comparisons of moderate or above impairment but not severe due to small sample size.

To model the relative risk (RR) of social and health factors associated with Long COVID, we fit a quasi-Poisson regression with a robust error variance using Long COVID (comprised of Current Long COVID and Recovered Long COVID) as a binary outcome.(36, 37) All independent variables were selected *a priori*, and

unadjusted bivariate RRs were estimated for each variable. Variables with an unadjusted association ($p < 0.10$) were included in the multivariable model.

Missing Data & Sensitivity Analyses

The proportions of observations with missing data were generally low (< 1% for 40.4% of variables with at least 1 missing observation, see Supplemental Table S1). Missing PROMIS and CCI-12 values were mean-imputed. Sensitivity analyses were conducted by inputting extreme values (i.e., all lowest values for Long COVID group and highest values for Without Long COVID comparison, see Supplemental Information). For each categorical variable in the regression model, missing values were coded as a separate category. Groups with n < 5 were dropped from the regression model, as preliminary modeling indicated high leverage from these groups. Hospitalization was not included in the model due to a high proportion of missingness (13.1%; See Supplemental Information).

Data were analyzed with R v4.3.1. The study was approved by the University of Washington Institutional Review Board (IRB) and by the CDC in accordance with CDC policy and applicable regulations. Written informed consent was obtained from all survey respondents; a waiver of informed consent was granted by the University of Washington IRB for de-identified data collection from the health record and survey recruitment messages.

Results

Descriptive Statistics

Slightly more than half of the participants recovered ≤ 3 months after the acute illness (Without Long COVID, 220/435, 50.6%). Of the Long COVID group (215/435, 49.4%), most were Current Long COVID (181/215, 84.2%) and a minority were Recovered Long COVID (34/215, 15.8%). Approximately 61.1% of the overall sample was age 50 or over, and the age distributions did not differ significantly between the Long COVID and Without Long COVID groups ($P = 0.19$). When compared to the group Without Long COVID, the Long COVID group had a greater percentage of women (65.6–55.9%, $p < 0.05$) and people without a bachelor's degree (39.5–25.9%, $p < 0.01$) (Table 1). A greater proportion of the Long COVID group had been hospitalized during acute illness (7.0–1.8%, $p < 0.01$), had a respiratory comorbidity prior to COVID-19 (17.2–10.0%, $p < 0.05$), and had 3 or more comorbidities (8.8–3.2%, $p < 0.05$). The group Without Long COVID reported experiencing approximately 2 fewer symptoms during acute illness than the Long COVID group ($p < 0.01$) and 1 fewer current symptom ($p < 0.01$). The Recovered Long COVID group was not significantly different from the Current Long COVID group for these descriptive variables (See Supplemental Table 2).

Table 1
Descriptive Statistics Comparing Long COVID (> 3 Month Recovery from SARS-CoV-2 Infection) to Without Long COVID (≤ 3 Month Recovery) Assessed Cross-Sectionally at a Median of 2 Years After Initial Infection.

	Total (N = 435)	Long COVID (N = 215)	Without Long COVID (N = 220)	p-value*
Age				0.19
20–34	61 (14.0%)	24 (11.2%)	37 (16.8%)	
35–49	105 (24.1%)	53 (24.7%)	52 (23.6%)	
50–64	148 (34.0%)	81 (37.7%)	67 (30.5%)	
65+	118 (27.1%)	54 (25.1%)	64 (29.1%)	
Gender				**0.03****
Male	166 (38.2%)	71 (33.0%)	95 (43.2%)	
Female	264 (60.7%)	141 (65.6%)	123 (55.9%)	
Other	3 (0.7%)	2 (0.9%)	1 (0.5%)	
Education				**< 0.01**
Advanced degree	123 (28.3%)	48 (22.3%)	75 (34.1%)	
Bachelor's degree	166 (38.2%)	79 (36.7%)	87 (39.5%)	
No bachelor's degree	142 (32.6%)	85 (39.5%)	57 (25.9%)	
Race				0.60
White	340 (78.2%)	163 (75.8%)	177 (80.5%)	
Asian	27 (6.2%)	14 (6.5%)	13 (5.9%)	
Black	27 (6.2%)	13 (6.0%)	14 (6.4%)	
American Indian-Alaska Native	8 (1.8%)	6 (2.8%)	2 (0.9%)	
Other	20 (4.6%)	12 (5.6%)	8 (3.6%)	
Hispanic Ethnicity				0.40

	Total (N = 435)	Long COVID (N = 215)	Without Long COVID (N = 220)	p-value*
Not Hispanic	385 (88.5%)	187 (87.0%)	198 (90.0%)	
Hispanic	39 (9.0%)	22 (10.2%)	17 (7.7%)	
COVID Hospitalization	19 (4.4%)	15 (7.0%)	4 (1.8%)	**< 0.01**
Missing	57 (13.1%)	39 (18.1%)	18 (8.2%)	
Pre-Infection Comorbidities				
Cardiovascular (Non-Hypertension)	39 (9.0%)	25 (11.6%)	14 (6.4%)	**0.05**
Hypertension	86 (19.8%)	47 (21.9%)	39 (17.7%)	0.30
Diabetes	30 (6.9%)	19 (8.8%)	11 (5.0%)	0.10
Respiratory	59 (13.6%)	37 (17.2%)	22 (10.0%)	**0.03**
Clotting	18 (4.1%)	11 (5.1%)	7 (3.2%)	0.30
Auto-immune	41 (9.4%)	22 (10.2%)	19 (8.6%)	0.60
Pre-Infection Comorbidity Count				**0.04**
0	253 (58.2%)	117 (54.4%)	136 (61.8%)	
1	106 (24.4%)	50 (23.3%)	56 (25.5%)	
2	50 (11.5%)	29 (13.5%)	21 (9.5%)	
3 or more	26 (6.0%)	19 (8.8%)	7 (3.2%)	
Acute Symptom Total; Mean (SD)[†]	5.34 (2.83)	6.40 (2.66)	4.32 (2.60)	**< 0.01**
Current Symptom Total; Mean (SD)	1.04 (1.73)	1.76 (2.07)	0.34 (0.85)	**< 0.01**
Recovery Time (mos); Median (IQR)	0.46 (0.20, 1.973)	7.89[‡] (5.92, 13.6)	0.39 (0.16, 0.73)	**< 0.01**
Time Since Infection (mos); Median (IQR)	23.3 (18.6, 26.7)	24.1 (19.3, 26.8)	22.5 (17.6, 26.7)	**< 0.01**

	Total (N = 435)	Long COVID (N = 215)	Without Long COVID (N = 220)	p-value*

* Significance testing conducted with *t*-tests for continuous variables and Chi-squared tests for categorical.. ** Results shown for pairwise comparison of Males and Females. † Symptom totals (both during the acute phase of COVID-19 and current) are counted out of 11 core symptoms defined by the Centers for Disease Control and Prevention: fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea. ‡ Includes n = 34 in the Long COVID group who were recovered at time of survey.

[INSERT Table 1]

Current Impairments

The Long COVID group showed significantly increased prevalence of current health impairment in every domain assessed, compared with the group Without Long COVID (all $p < 0.01$; Table 2). Subjective cognitive decline was prevalent in both the Long COVID and comparison groups (72.1% and 29.1%, respectively). After cognitive decline, fatigue (40.9%), pain (35.8%), physical function impairment (35.8%), and anxiety (27.4%) were most prevalent in the Long COVID group, whereas in the group Without Long COVID, the next most prevalent impairments after cognitive decline were anxiety (10.0%), physical function (8.7%), fatigue (8.2%), and depression (7.3%). Social function impairment was > 8 times as prevalent in the Long COVID group (22.8%) than in those Without Long COVID (2.7%).

Among those with at least moderate severity impairment in each domain, a greater proportion had severe fatigue (27.3%), anxiety (37.3%), and cognitive decline (55.5%) in the Long COVID group compared with those Without Long COVID (0%, 9.1%, and 23.4%, respectively; Table 2). While pain interference and physical function impairment were more prevalent overall in the Long COVID group (both $p < 0.01$), severity in these domains was not different between the two groups.

Table 2
Prevalence of Self-Reported Impairment Across 8 Health Domains by Group

	Total (N = 435)	Long COVID (N = 215)	Without Long COVID (N = 220)	Prevalence Ratio (95% CI)	p-value
Physical Function	96 (22.1%)	77 (35.8%)	19 (8.6%)	4.17 (2.62, 6.64)	**< 0.01**
Severe	17 (17.7%)	14 (18.2%)	3 (15.8%)	1.15 (0.37, 3.61)	1.0
Anxiety	81 (18.6%)	59 (27.4%)	22 (10.0%)	2.76 (1.75, 4.33)	**< 0.01**
Severe	24 (29.6%)	22 (37.3%)	2 (9.1%)	4.10 (1.05, 16.0)	**0.01**
Depression	54 (12.4%)	38 (17.7%)	16 (7.3%)	2.44 (1.40, 4.24)	**< 0.01**
Severe	7 (13.0%)	7 (18.4%)	0	–	0.09
Fatigue	106 (24.4%)	88 (40.9%)	18 (8.2%)	4.98 (3.11, 7.97)	**< 0.01**
Severe	24 (22.6%)	24 (27.3%)	0	–	**0.01**
Sleep Disturbance	54 (12.4%)	42 (19.5%)	12 (5.5%)	3.58 (1.94, 6.61)	**< 0.01**
Severe	8 (14.8%)	8 (19.0%)	0	–	0.18
Social Function	55 (12.6%)	49 (22.8%)	6 (2.7%)	8.36 (3.66, 19.1)	**< 0.01**
Severe	16 (29.1%)	16 (32.7%)	0	–	0.17
Pain	92 (21.1%)	77 (35.8%)	15 (6.8%)	5.30 (3.15, 8.92)	**< 0.01**
Severe	14 (15.2%)	11 (14.3%)	3 (20.0%)	0.71 (0.23, 2.26)	0.7
Cognitive Decline	219 (50.3%)	155 (72.1%)	64 (29.1%)	2.49 (1.99, 3.11)	**< 0.01**
Severe	101 (46.1%)	86 (55.5%)	15 (23.4%)	2.37 (1.49, 3.77)	**< 0.01**
Cognitive Concern	246 (56.6%)	165 (76.7%)	81 (36.8%)	2.10 (1.75, 2.54)	**< 0.01**

	Total (N = 435)	Long COVID (N = 215)	Without Long COVID (N = 220)	Prevalence Ratio (95% CI)	p-value

Percentages in the “Severe” rows represent the proportion of severe cases among those exceeding thresholds for moderate-to-severe impairment in each domain. All domains except Cognitive Decline and Cognitive Concern assessed with the Patient Reported Outcomes Measurement Information System (PROMIS)-29 v2.0 subscales with raw totals converted to T-scores. T-scores ≥ 60 indicated moderate impairment, ≥ 70 indicated severe for all domains except Physical Function and Social Function, for which T-scores ≤ 40 indicated moderate impairment, ≤ 30 indicated severe. Cognitive domains assessed with the Cognitive Change Index-12. Sum totals ≥ 20 indicated moderate Cognitive Decline, ≥ 33 indicated severe. Cognitive Concern assessed with 1-item and defined as “Slight Concern” or above. Significance testing conducted with Chi-squared tests or Fisher’s Exact test for expected cell counts ≤ 5. Bonferroni correction applied to moderate-to-severe impairment comparisons but not severe comparisons due to small sample size. Prevalence ratios not calculable for domains where no severe cases were observed in the Without Long COVID group.

The Recovered Long COVID group (n = 34) showed an elevated prevalence of current moderate-to-severe impairment in multiple domains compared to those Without Long COVID (Fig. 2). A majority of the Recovered Long COVID group reported cognitive decline since COVID-19 (61.8%). The next most prevalent impairments were fatigue and pain (20.6% each), anxiety (17.6%), and physical function (14.7%). Cognitive decline and pain were significantly more prevalent in the Recovered Long COVID group compared with those Without Long COVID (both $p < 0.05$). We also observed an elevated prevalence of fatigue that was not statistically significant ($P = 0.06$). A greater proportion of the Recovered Long COVID group (67.6%) reported concern about memory changes since COVID-19 compared to those Without Long COVID (36.8%; $p < 0.01$; results not shown). Compared with the Current Long COVID group, the Recovered Long COVID group showed decreased prevalence of fatigue, depression, pain, and both social and physical function impairment (all $p < 0.05$).

Long COVID Risk Factors

Results from the multivariable regression indicated that age, education, pre-COVID-19 comorbidities, and the number of acute phase symptoms were all associated with Long COVID (Table 3). Compared with those with an advanced degree, patients without a bachelor’s degree had approximately 33% greater adjusted risk of Long COVID (adjusted RR [aRR] = 1.33; 95% CI = 1.03, 1.71; $P = 0.03$). Compared with those 20–34 years old, older patients had increased risk, ranging from a 47% greater adjusted risk for ages 35–49 (aRR = 1.47; 95% CI = 1.01, 2.13; $p < 0.05$) to a 52% greater risk for ages 50–64 (aRR = 1.52; 95% CI = 1.06, 2.18; $p < 0.05$). Women had a 23% greater risk of Long COVID than men (aRR = 1.23; 95% CI = 1.00, 1.51; $P = 0.06$). Patients with 3 or more comorbidities before COVID-19 had a 45% elevated risk of Long COVID compared to those with no comorbidities (aRR = 1.45, 95% CI = 1.11, 1.90; $p < 0.01$) and each additional symptom during the acute infection was associated with 14% greater risk in the full multivariable model (aRR = 1.14; 95% CI = 1.10, 1.18; $p < 0.01$).

Discussion

In this study, patients who self-reported Long COVID were compared with those who reported recovering from symptoms within 3 months of the acute phase of COVID-19. The results suggest a range of

impairments across different QoL domains are associated with a lack of recovery from COVID-19 within 3 months, and these impairments can be detected at a median of 2 years after initial infection. Among the Long COVID group, a minority (15.8%) reported being fully recovered from COVID-19 at time of survey, with a median reported recovery time of 7.9 months (Recovered Long COVID). While acute infection severity (approximated with total symptom count) was found to be associated with Long COVID risk, > 80% of this sample were not hospitalized during the acute phase of infection, indicating that mild-to-moderately severe infection still confers measurable risk for concerning long-term sequelae. Beyond physical complaints, including fatigue and pain, the Long COVID group showed significantly decreased social function and increased anxiety, depression, and subjective cognitive decline.

Our findings indicate that recovery from Long COVID occurs in some domains. The prevalence of moderate-to-severe fatigue, pain, depression, and both physical and social functional impairment were all significantly lower in the Recovered Long COVID group than in the Current Long COVID group. Of concern, however, the prevalence of cognitive decline, fatigue, and pain remained elevated in the Recovered Long COVID group compared with the Without Long COVID group. This may indicate that some domains of Long COVID-related impairment are more amenable to recovery than others. Alternatively, those reporting recovery from Long COVID may not subjectively attribute current functional impairment to COVID-19, or their functional impairments could have preceded COVID-19. Investigating the interactions between patient-reported outcome domains and their longitudinal trajectories could help advance the understanding of Long COVID and support recovery.

Quality of Life and Subjective Cognitive Decline

The QoL impairments detected in this study are similar to pooled prevalences calculated from 12 published studies of Long COVID in which all participants were hospitalized.(16) The impact on social function associated with Long COVID was prominent – 33% had severe impairment – and is consistent with qualitative work that identified Long COVID symptomatology as a barrier to social well-being.(38) Similarly, the prevalence of severe anxiety was 37% among Long COVID patients with anxiety, and among the overall Long COVID group, more than 10% reported severe anxiety. While moderate-to-severe pain and physical function impairment were more prevalent in the Long COVID group than among those Without Long COVID, the prevalences of severe impairment among those with at least moderate impairment in these domains were not significantly different. These findings underscore the importance of cognitive, mental health and social function impairments in Long COVID, which may increase in prevalence over time relative to other sequelae.(7, 12, 39)

The high proportion of cognitive decline, even among patients Without Long COVID, could indicate underrecognized long-term cognitive impacts of COVID-19. Early report of perceived cognitive deficit has been associated with later post-COVID condition.(20) The CCI-12 cut-offs used to operationalize cognitive decline in the present study have not undergone extensive validation. However, 93% of this sample with a CCI-12 score ≥ 20 reported concern about memory changes, whereas only 17% of those with a score of < 20 reported concern, suggesting the threshold measures differences relevant for patients. The proportion

of subjective cognitive decline in this sample is notably higher than population-based and meta-analytic prevalence estimates from data collected before the COVID-19 pandemic, but different methodologies among studies prevents a clear comparison.(40, 41) Neurocognitive symptoms of Long COVID have been associated with decreased likelihood of working full-time and have been qualitatively connected to social isolation and work discrimination.(38, 42) A large medical record study of post-acute sequelae at 2 years post-infection found a greater 2-year cumulative disability burden from both neurological and mental health symptoms than from fatigue, pulmonary symptoms, or musculoskeletal symptoms.(18) Since subjective cognitive decline has been associated with more severe future cognitive impairment in patients without Long COVID-19,(25) the currently reported memory concerns suggest the clinical importance of carefully monitoring the cognitive trajectory of those who do not recover from COVID-19 within 3 months. Future studies examining the longitudinal correlates of subjective cognitive decline in the context of Long COVID would be valuable.

Long COVID Risk Factors

The regression model results suggest that a higher level of education attainment is associated with recovery from COVID-19, adding to existing published evidence indicating education and other social determinants of health (SDOH) are associated with Long COVID risk.(43) Participants without a bachelor's degree had approximately 53% greater unadjusted Long COVID risk than those with an advanced degree and 33% greater with control for comorbidities and infection severity among other variables. This disparity could be connected to a differential capacity to utilize socially-determined resources (for example, paid time off from work) to aid recovery.(44, 45) Post-COVID conditions have been associated with greater odds of unemployment and lower odds of full-time employment, effects that were in turn strongly associated with both education and gender but not other SDOH variables.(42) Losing or lacking full-time employment could affect health insurance coverage and limit access to care. Discrimination and stigma experienced by those with Long COVID may create barriers in healthcare, occupational, and institutional settings that are more difficult to circumvent for those with less education or other marginalized identities.(38) Though female gender was not statistically significant in our multivariate results, the lower bound of the 95% confidence interval for its effect estimate was 0.996, indicating it may be associated with Long COVID risk. Rigorous, intersectional investigation of how education, employment, gender, and other SDOH variables affect COVID-19 recovery within multilayered, interlocking social structures is crucial to identify how to mitigate inequitable long-term effects.(46–48)

Table 3
Bivariate and Multivariable Relative Risk Regression Model Results Predicting Self-Reported Long COVID.

	Unadjusted models		**Multivariable model***	
	RR (95% CI)	p-value	Adj. RR (95% CI)	p-value
Age				
20–34	Reference	–	Reference	–
35–49	1.28 (0.89, 1.85)	0.18	1.47 (1.01, 2.13)	**0.05**
50–64	1.39 (0.99, 1.96)	**0.06**	1.52 (1.06, 2.18)	**0.03**
65+	1.16 (0.81, 1.68)	0.42	1.48 (1.01, 2.18)	**0.05**
Gender				
Male	Reference	–	Reference	–
Female	1.25 (1.01, 1.53)	**0.03**	1.23 (1.00, 1.51)	0.06
Education				
Advanced Degree	Reference	–	Reference	–
Bachelor's Degree	1.22 (0.93, 1.60)	0.17	1.12 (0.87, 1.46)	0.38
No bachelor's Degree	1.53 (1.18, 1.99)	**< 0.01**	1.33 (1.03, 1.71)	**0.03**
Race				
White	Reference	–	Reference	–
Asian	1.08 (0.74, 1.59)	0.66	1.12 (0.75, 1.67)	0.59
Black	1.00 (0.67, 1.51)	0.96	0.90 (0.62, 1.29)	0.57
American Indian/Alaska Native	1.56 (1.03, 2.37)	**0.03**	1.09 (0.67, 1.78)	0.73
Other	1.25 (0.67, 1.88)	0.23	1.06 (0.66, 1.71)	0.81
Hispanic Ethnicity				
Not Hispanic	Reference	–	–	–
Hispanic	1.16 (0.86, 1.56)	0.32	–	–
Pre-Infection Comorbidities				
No Comorbidities	Reference	–	Reference	–
1	1.02 (0.80, 1.30)	0.87	0.93 (0.74, 1.18)	0.56
2	1.25 (0.96, 1.64)	0.12	1.15 (0.89, 1.50)	0.29

	Unadjusted models		Multivariable model*	
3 or more	1.58 (1.21, 2.07)	**< 0.01**	1.45 (1.11, 1.90)	**< 0.01**
Total Number of Acute Symptoms	1.15 (1.11, 1.19)	**< 0.01**	1.14 (1.10, 1.18)	**< 0.01**

* A total of 424 participants were included in the final model. “Missing” categories for age (n = 3), gender (n = 2), and education (n = 4), and the Other category for gender (n = 3) were dropped from the analysis due to group size of < 5. Not displayed: “Missing” categories for race (n = 12) and ethnicity (n = 10). *RR* Relative Risk, *CI* Confidence Interval

Strengths and Limitations

The strengths of this analysis include the long follow-up time after confirmed diagnosis, the Without Long COVID comparison group, and the sub-grouping of Long COVID into those with Current Long COVID and Recovered Long COVID. Patient-reported recovery and symptom measures of Long COVID provide data that are not easily captured in electronic health records, as ICD codes for symptoms are not consistently used. However, since these data are cross-sectional and were reported retrospectively, reverse causation and recall bias cannot be ruled out. The QoL impairments detected with PROMIS measures may have preceded COVID, and worse current health and current cognitive decline could affect recall of past comorbidities, infection severity, and COVID-19 recovery. Furthermore, we were unable to account for the effect of repeat infections. Given the low response rate (6.0%), this sample may not be representative of the larger pool of eligible patients. Survey data could not be linked to EHR data to compare the survey responders to non-responders in terms of demographics and clinical characteristics. The proportion of Long COVID was substantially higher in this sample than prevalence of Long COVID estimated in in population-based studies,(49) which may be due to response bias. Patients who attribute current health impairments to COVID-19 could have been more likely to provide consent and respond to survey, increasing their proportion in the sample relative to those who do not attribute current health to COVID-19 or who do not have current impairments. Those who died in the interim time between SARS-CoV-2 infection and the study could not be included, so their experience of Long COVID was not captured. The analysis of social factors was limited to gender, education, race, and ethnicity, all of which were self-classified based on United States Census categories.

Of note, 77% of participants were first diagnosed with COVID-19 in 2020, when either wild-type or the alpha variant were prominent and before the wide dissemination of COVID-19 vaccines. While this feature precludes analyzing the effect of vaccination and limits generalizability of findings to more recent variants, it furthers our understanding of Long COVID among people infected early in the pandemic – roughly 94 million globally and 20 million in the United States by the end of 2020, according to WHO estimates.(50)

Conclusion

Using validated measures of health, this cross-sectional study found a high prevalence of current subjective cognitive decline and diminished QoL at a median of 24 months after SARS-CoV-2 infection

for people who reported they did not recover from COVID-19 within 3 months. Older age, education, and co-morbidities were associated with Long COVID. Compared to the Current Long COVID group, the Recovered Long COVID subgroup showed evidence of recovery in most health domains, however, compared to the Without Long COVID group, significant deficits were identified in fatigue, pain, and most notably in cognition. Future work could investigate SDOH-related disparities in recovery and the differential effects of SARS-CoV-2 variants and vaccination. Furthermore, prospective longitudinal studies combining subjective and objective health measures would be valuable for mapping the trajectories of physical, neurological, and mental health associated with Long COVID.

Abbreviations

aRR
Adjusted Relative Risk
CCI
12–Cognitive Change Index 12
CDC
Centers for Disease Control and Prevention
COVID
19–Coronavirus Disease 2019
CI
Confidence Interval
ICD
10–CM–International Classification of Diseases, 10th Revision, Clinical Modification
ME/CFS
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
PCC
Post COVID–19 Condition
PCR
Polymerase Chain Reaction
PROMIS
Patient Reported Outcome Measurement Information System
QoL
Quality of Life
REDCap
Research Electronic Data Capture
RR
Relative Risk
SARS
CoV–2–Severe Acute Respiratory Syndrome Coronavirus 2
SDOH

Social Determinants of Health
WHO
World Health Organization

Declarations

Ethics approval and consent to participate

This study was approved by the University of Washington Institutional Review Board (IRB) and by the Centers for Disease Control and Prevention (CDC) in accordance with CDC policy and applicable regulations. Written informed consent was obtained from all survey respondents; a waiver of informed consent was granted by the University of Washington IRB for de-identified data collection from the health record and survey recruitment messages.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

W.S. conceived of the research question, analyzed and interpreted the data, prepared figures and tables, and drafted and edited the manuscript. A.F. and Q.V. contributed to the research question, study design, data collection, data analysis, and manuscript review and editing. H.F. provided manuscript review and editing. N.G., N.S., S.V., T.E.W., J.B., J.C., J.L., and E.U. contributed to study design, data collection, and manuscript review and editing.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

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Figures

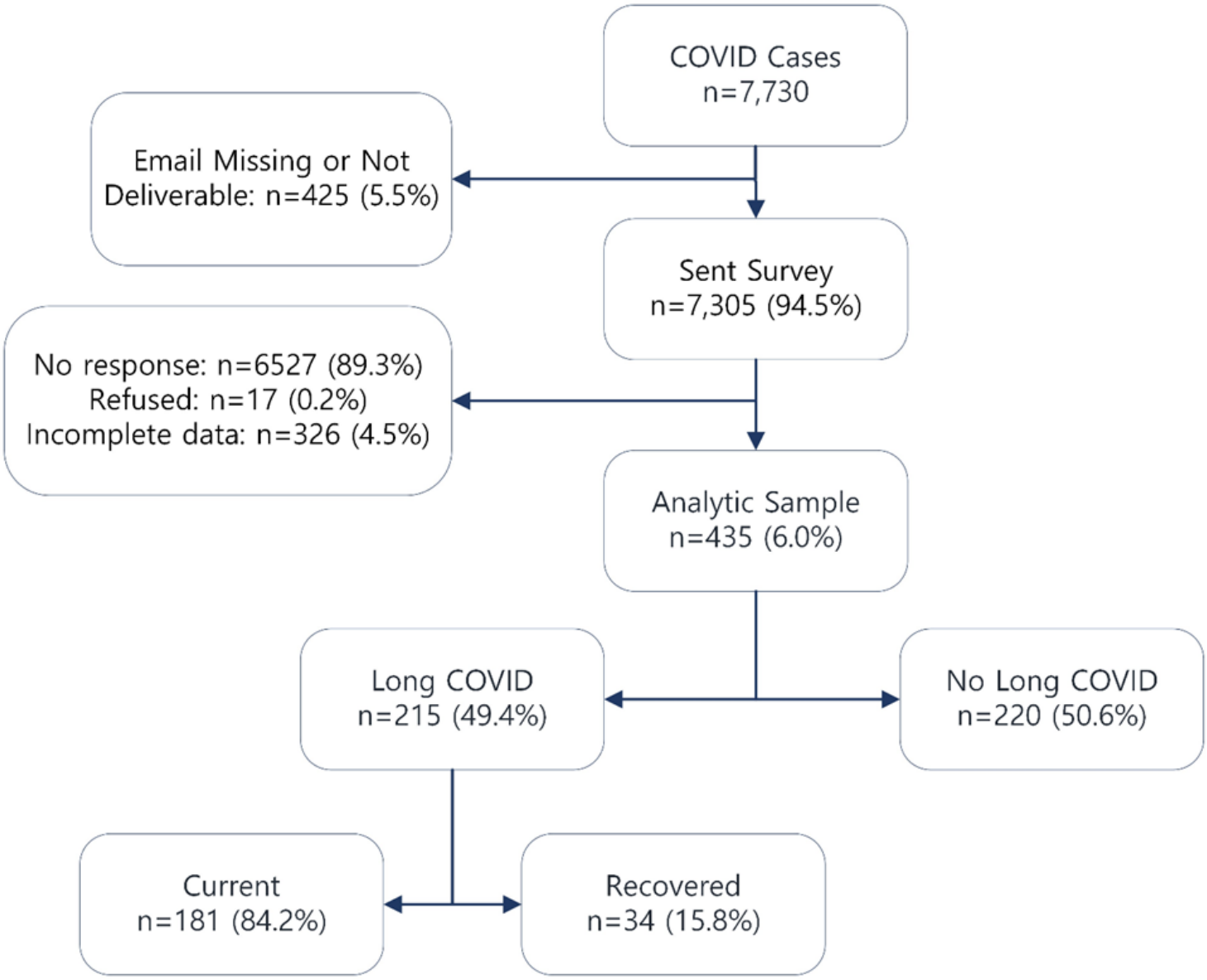

Figure 1

Participant Flow Diagram

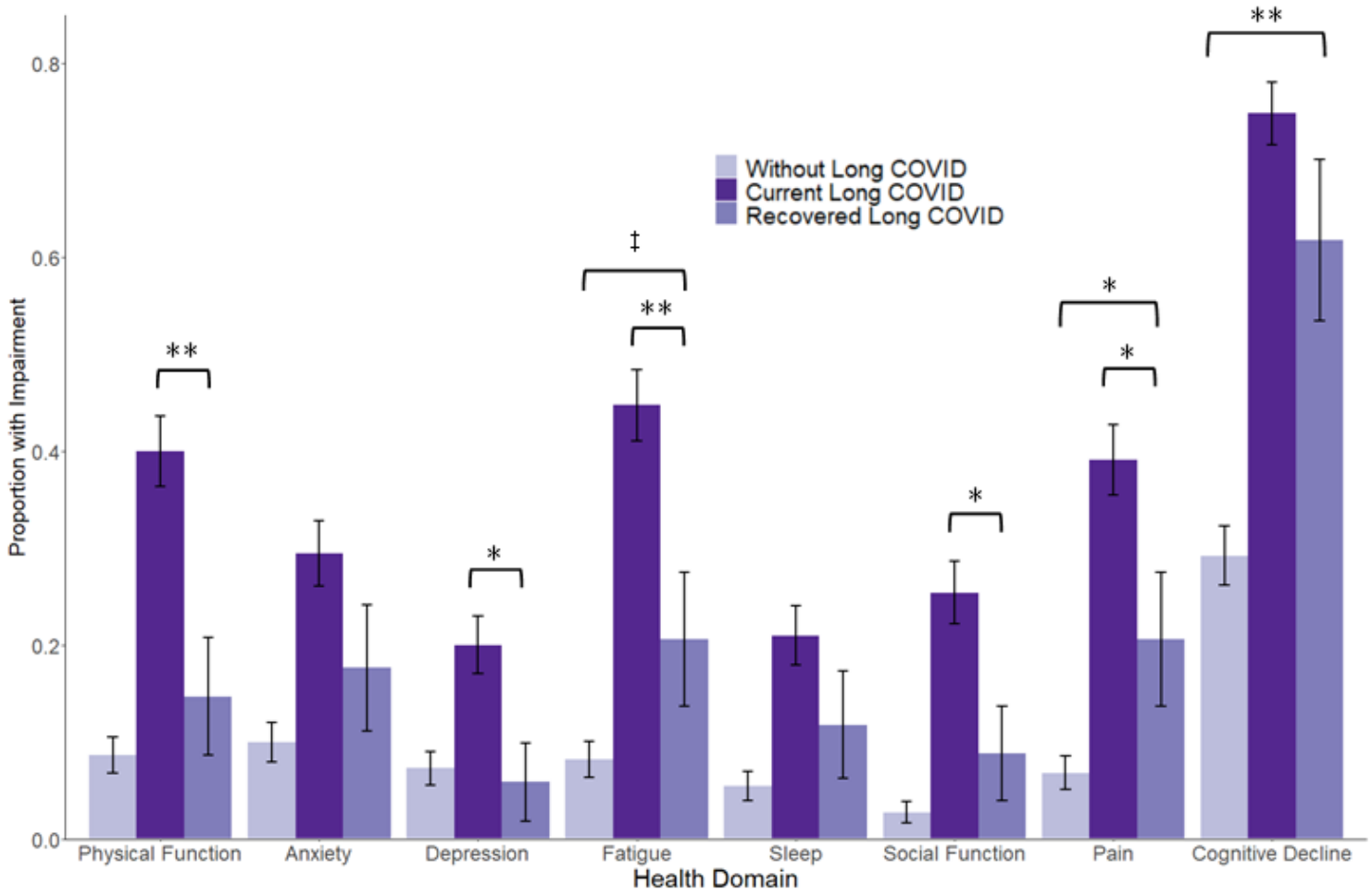

Figure 2

Prevalence of Impairment Across 8 Health Domainsfor Without Long COVID-19 (n=220), Current Long COVID (n=181), and Recovered Long COVID (n=34) Groups

Pairwise comparisons of proportions were performed with Chi-squared or Fisher's exact tests. The Current Long COVID group was significantly different from the Without Long COVID group in every domain (significance testing not shown). *p<.05 **p<.01 $^{‡}p$<.10

Supplementary Files

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