7-7-2023

Long COVID Clinical Phenotypes up to 6 Months After Infection Identified by Latent Class Analysis of Self-Reported Symptoms

Michael Gottlieb

Erica S. Spatz

Huihui Yu

Lauren E Wisk

Joann G. Elmore

Open Forum Infectious Diseases

MAJOR ARTICLE

Long COVID Clinical Phenotypes up to 6 Months After Infection Identified by Latent Class Analysis of Self-Reported Symptoms

Michael Gottlieb,[1,a] Erica S. Spatz,[2,3,4,a] Huihui Yu,[2,4] Lauren E. Wisk,[5] Joann G. Elmore,[5] Nicole L. Gentile,[6] Mandy Hill,[7] Ryan M. Huebinger,[7] Ahamed H. Idris,[8] Efrat R. Kean,[9] Katherine Koo,[10] Shu-Xia Li,[4] Samuel McDonald,[8,11] Juan Carlos C. Montoy,[12] Graham Nichol,[13] Kelli N. O'Laughlin,[14] Ian D. Plumb,[15] Kristin L. Rising,[9,16] Michelle Santangelo,[10] Sharon Saydah,[15] Ralph C. Wang,[12] Arjun Venkatesh,[4,17,b] Kari A. Stephens,[18,b] and Robert A. Weinstein,[19,20,21,b] INSPIRE Group[c]

[1]Department of Emergency Medicine, Rush University Medical Center, Chicago, Illinois, USA, [2]Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut, USA, [3]Department of Epidemiology, Yale School of Public Health, New Haven, Connecticut, USA, [4]Yale Center for Outcomes Research and Evaluation, Yale School of Medicine, New Haven, Connecticut, USA, [5]Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA, [6]Post-COVID Rehabilitation and Recovery Clinic, Department of Family Medicine, Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA, [7]Department of Emergency Medicine, UTHealth, Houston, Texas, USA, [8]Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [9]Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [10]Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois, USA, [11]Clinical Informatics Center, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [12]Department of Emergency Medicine, University of California, San Francisco, San Francisco, California, USA, [13]Departments of Medicine and Emergency Medicine, University of Washington, Seattle, Washington, USA, [14]Departments of Emergency Medicine and Global Health, University of Washington, Seattle, Washington, USA, [15]National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [16]Center for Connected Care, Sidney Kimmel Medical School, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [17]Department of Emergency Medicine, Yale School of Medicine, New Haven, Connecticut, USA, [18]Departments of Family Medicine, Biomedical Informatics and Medical Education, University of Washington, Seattle, Washington, USA, [19]Division of Infectious Diseases, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois, USA, [20]Department of Internal Medicine, Cook County Hospital, Chicago, Illinois, USA, and [21]The CORE Center, Chicago, Illinois, USA

Background. The prevalence, incidence, and interrelationships of persistent symptoms after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection vary. There are limited data on specific phenotypes of persistent symptoms. Using latent class analysis (LCA) modeling, we sought to identify whether specific phenotypes of COVID-19 were present 3 months and 6 months post-infection.

Methods. This was a multicenter study of symptomatic adults tested for SARS-CoV-2 with prospectively collected data on general symptoms and fatigue-related symptoms up to 6 months postdiagnosis. Using LCA, we identified symptomatically homogenous groups among COVID-positive and COVID-negative participants at each time period for both general and fatigue-related symptoms.

Results. Among 5963 baseline participants (4504 COVID-positive and 1459 COVID-negative), 4056 had 3-month and 2856 had 6-month data at the time of analysis. We identified 4 distinct phenotypes of post-COVID conditions (PCCs) at 3 and 6 months for both general and fatigue-related symptoms; minimal-symptom groups represented 70% of participants at 3 and 6 months. When compared with the COVID-negative cohort, COVID-positive participants had higher occurrence of loss of taste/smell and cognition problems. There was substantial class-switching over time; those in 1 symptom class at 3 months were equally likely to remain or enter a new phenotype at 6 months.

Conclusions. We identified distinct classes of PCC phenotypes for general and fatigue-related symptoms. Most participants had minimal or no symptoms at 3 and 6 months of follow-up. Significant proportions of participants changed symptom groups over time, suggesting that symptoms present during the acute illness may differ from prolonged symptoms and that PCCs may have a more dynamic nature than previously recognized.

Clinical Trials Registration. NCT04610515.

Keywords. cluster; COVID-19; Long COVID; phenotype; SARS-CoV-2.

Prolonged symptoms after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, often referred to as "Long COVID" or post-COVID conditions (PCCs), can be present in 10%–60% of those infected [1–4]. While a definitive case

Received 20 April 2023; editorial decision 07 May 2023; accepted 15 May 2023; published online 31 May 2023

[a]M. G. and E. S. S. contributed equally to this work.

[b]A. V., K. A. S., and R. A. W. contributed equally to this work.

[c]Study Group Team Members are listed in the Supplementary Appendix.

Correspondence: Michael Gottlieb, MD, Rush University Medical Center, 1750 West Harrison St, Suite 108 Kellogg, Chicago, IL 60612 (michaelgottliebmd@gmail.com); Robert Weinstein, MD, Rush University Medical Center, 613 W Fullerton Parkway, Chicago, IL 60614-2613 (robert_weinstein@rush.edu).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad277

definition does not exist, PCC is typically defined as new or ongoing symptoms not attributable to another cause that are present at least 4–12 weeks after SARS-CoV-2 infection [5–7].

Persistent COVID-19 symptoms—including type, frequency, and severity—vary [8]. Most studies have focused primarily on individual symptoms without consideration of clustering, with wide variations in reporting and time-points for assessment [2]. This variability and individual symptom emphasis (as opposed to symptom clusters) misses the opportunity to identify broader PCC phenotypes, to refine case definitions, and to guide monitoring and treatment strategies.

Two studies recently evaluated potential phenotypes of persistent symptoms 3 months postinfection [9, 10]. While informative, these studies were limited by reliance on electronic health records (EHRs), variations in reporting time periods, and absence of a COVID-negative comparison cohort [9, 10]. Two prospective studies evaluated participants for phenotypic clusters but had small sample sizes, limiting their ability to distinguish phenotypic clusters [11, 12]. Moreover, there is a dearth of data on phenotypes present at 6 months. Therefore, there is a critical need to better understand the potential phenotypes of PCCs and how they evolve over time.

The Innovative Support for Patients With SARS-CoV-2 Infections Registry (INSPIRE) is a prospective study designed to assess long-term symptoms and outcomes of symptomatic participants tested for COVID-19, including both SARS-CoV-2–positive and –negative participants. Latent class analysis (LCA) applies a probabilistic modeling algorithm to group individuals into mutually exclusive and exhaustive types based on their pattern of answers on a set of categorical indicator variables. Our study utilized LCA to identify phenotypes of COVID-19 presenting acutely and at 3 and 6 months postinfection.

METHODS

Study Design

INSPIRE is a national study conducted across 8 major healthcare systems that were selected for geographic and population diversity (NCT04610515). All sites recruited participants broadly without geographic or health system limitations. The study prospectively enrolled symptomatic participants who tested positive (COVID-positive) or negative (COVID-negative) for SARS-CoV-2. We followed participants longitudinally, collecting self-reported symptoms using a standardized questionnaire every 3 months starting at enrollment. Full study details were published previously [13]. Data were locked for this analysis on 13 September 2022.

Adults (age ≥18 years) were enrolled if they were fluent in English or Spanish, had self-reported symptoms suggestive of acute SARS-CoV-2 infection at time of testing (eg, fever, cough, dyspnea), and were tested within the preceding 42 days with a US Food and Drug Administration–approved/authorized molecular or antigen-based assay. Exclusion criteria included previous SARS-CoV-2 infection >42 days before enrollment and those without access to an internet-connected device (eg, smartphone, computer) needed for survey completion.

Participants received surveys via email or text and received monetary reimbursement for time to complete surveys. Surveys included questions on sociodemographics; social determinants of health; baseline health status; testing site; symptoms of SARS-CoV-2 infection; symptoms of postinfectious syndromes; subsequent reinfection with SARS-CoV-2; vaccination status; patient-reported outcomes on physical, mental, and social well-being; cognitive status; and return to work/daily activities [13]. Participants were asked to share access to their EHR data, which were used to verify COVID-19 status and supplement vaccination data from surveys. If COVID-19 information was unavailable in the EHR, participants were required to provide photographic proof of test results.

Patient Consent Statement

The parent study was funded by the Centers for Disease Control and Prevention (CDC) and approved by the institutional review boards at all 8 institutions. Participants were enrolled virtually or in-person and signed informed consent.

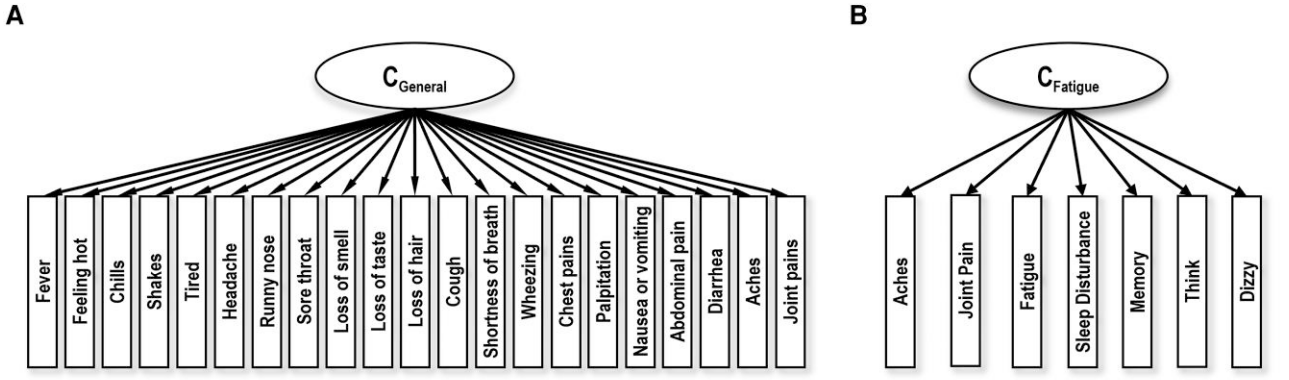
Survey Instruments

We collected data on new postinfectious symptoms informed by the CDC Person Under Investigation symptom list, which included symptoms commonly reported at the time of the survey (eg, fever, headache, anosmia) [13]. We assessed systemic symptoms using the CDC Short Symptoms Screener, which is a validated tool surveying 8 domains (fatigue, muscle aches, joint pain, unrefreshing sleep, problems going to/waking from sleep, forgetfulness, difficulty concentrating, and dizziness/fainting) [14]. To reduce participant burden, we modified the CDC Short Symptoms Screener to focus specifically on fatigue-related components [13].

Statistical Analysis

We used LCA to classify participants into symptomatically homogeneous groups, such that individual differences in the observed symptomatic patterns could be explained by differences in latent class membership [15, 16]. All LCA models were implemented in SAS using the LCA procedure (version 1.3.2, SAS Institute) [17]. Symptom numbers are reported as median and interquartile range (IQR).

We conducted the LCA separately for COVID-positive and COVID-negative participants and for acute, 3-month, and 6-month symptoms. We also explored systematic patterns of both general and fatigue-related symptoms using survey responses. We combined "unrefreshing sleep" and "problems going to/waking from sleep" under the category "sleep



C

Symptom Types	Time Point	COVID-positive			COVID-negative		
		# of Classes	Symptomatic Characteristics	Class Acronym	# of Classes	Symptomatic Characteristics	Class Acronym
General Symptoms	Acute Illness	4	Minimal number of general symptoms	Acute-COV-pos-min-symptoms	3	Minimal number of general symptoms	Acute-COV-neg-min-symptoms
			Aches, cough, tiredness, and several HEENT symptoms without loss of smell and taste	Acute-COV-pos-ACT-HEENT-without-LoST		Aches, cough, tiredness, and several HEENT symptoms without loss of smell and taste	Acute-COV-neg-ACT-HEENT-without-LoST
			Aches, cough, tiredness, and several HEENT symptoms with loss of smell and taste	Acute-COV-pos-ACT-HEENT-with-LoST		Many symptoms across multiple systems	Acute-COV-neg-MSMS
			Many symptoms across multiple systems	Acute-COV-pos-MSMS			
	3-month follow-up	4	Minimal number of general symptoms	3m-COV-pos-min-symptoms	3	Minimal number of general symptoms	3m-COV-neg-min-symptoms
			Tiredness, headache, and musculoskeletal issues	3m-COV-pos-THM		Tiredness, headache, and musculoskeletal issues	3m-COV-neg-THM
			Loss of smell and taste	3m-COV-pos-LoST		Many symptoms across multiple systems	3m-COV-neg-MSMS
			Many symptoms across multiple systems	3m-COV-pos-MSMS			
	6-month follow-up	4	Minimal number of general symptoms	6m-COV-pos-min-symptoms	3	Minimal number of general symptoms	6m-COV-neg-min-symptoms
			Tiredness, headache, and musculoskeletal issues	6m-COV-pos-THM		Tiredness, headache, and musculoskeletal issues	6m-COV-neg-THM
			Loss of smell and taste	6m-COV-pos-LoST		Many symptoms across multiple systems	6m-COV-neg-MSMS
			Many symptoms across multiple systems	6m-COV-pos-MSMS			
Fatigue Symptoms	Acute Illness	4	Minimal number of fatigue symptoms	Acute-COV-pos-min-fatigue	4	Minimal number of fatigue symptoms	Acute-COV-neg-min-fatigue
			Fatigue, sleep disturbances, and cognition symptoms	Acute-COV-pos-FS-C		Fatigue and sleep disturbances	Acute-COV-neg-FS
			Fatigue, sleep disturbances, and aches	Acute-COV-pos-FS-A		Fatigue, sleep disturbances, and aches	Acute-COV-neg-FS-A
			Maximal number of fatigue symptoms	Acute-COV-pos-max-fatigue		Maximal number of fatigue symptoms	Acute-COV-neg-max-fatigue
	3-month follow-up	4	Minimal number of fatigue symptoms	3m-COV-pos-min-fatigue	4	Minimal number of fatigue symptoms	3m-COV-neg-min-fatigue
			Fatigue and sleep disturbances	3m-COV-pos-FS		Fatigue and sleep disturbances	3m-COV-neg-FS
			Fatigue, sleep disturbances, and aches	3m-COV-pos-FS-A		Fatigue, sleep disturbances, and aches	3m-COV-neg-FS-A
			Maximal number of fatigue symptoms	3m-COV-pos-max-fatigue		Maximal number of fatigue symptoms	3m-COV-neg-max-fatigue
	6-month follow-up	4	Minimal number of fatigue symptoms	6m-COV-pos-min-fatigue	4	Minimal number of fatigue symptoms	6m-COV-neg-min-fatigue
			Fatigue and sleep disturbances	6m-COV-pos-FS		Fatigue and sleep disturbances	6m-COV-neg-FS
			Fatigue, sleep disturbances, and aches	6m-COV-pos-FS-A		Fatigue, sleep disturbances, and aches	6m-COV-neg-FS-A
			Maximal number of fatigue symptoms	6m-COV-pos-max-fatigue		Maximal number of fatigue symptoms	6m-COV-neg-max-fatigue

Figure 1. Diagrams illustrating latent class analysis models using COVID-19 general (*A*) and fatigue (*B*) symptoms. *C*, Summary of the best-fit latent class analysis models.

disturbance" due to clinical similarity and similar responses at all time-points.

We examined 12 LCA models (Figure 1). For each model, we tested solutions of 2–6 classes to identify the best solution based on indices of model fit (eg, Akaike information criterion [AIC], Consistent AIC, Bayesian information criterion [BIC], Akaike BIC), entropy, and parsimony. Model formulation and fit indices of all solutions are included in the Supplementary Appendix.

We examined model-estimated, class-specific probability of symptoms by COVID-19 status at each time period and identified systematic characteristics of each class based on homogeneity within class and separation between classes [18]. We expected to identify a class with the most symptoms and one with the least symptoms at each time period, though we anticipated to observe overall reduction in symptoms from acute stage to follow-up periods. We examined shifts in class membership across time, focusing on people who persistently had many symptoms and those who developed new symptoms (moving from classes with less to those with more symptoms) at 3- and 6-month follow-up. Finally, we examined the association between patterns of general and fatigue-related symptoms at each time period.

RESULTS

There were 5963 participants (4504 COVID-positive and 1459 COVID-negative) included in the LCA of acute symptoms; 4056 and 2856 completed the 3-month and 6-month surveys, respectively (Figure 2). Surveys were completed a median of 15 days (IQR, 7–24 days) from the index test. Participant

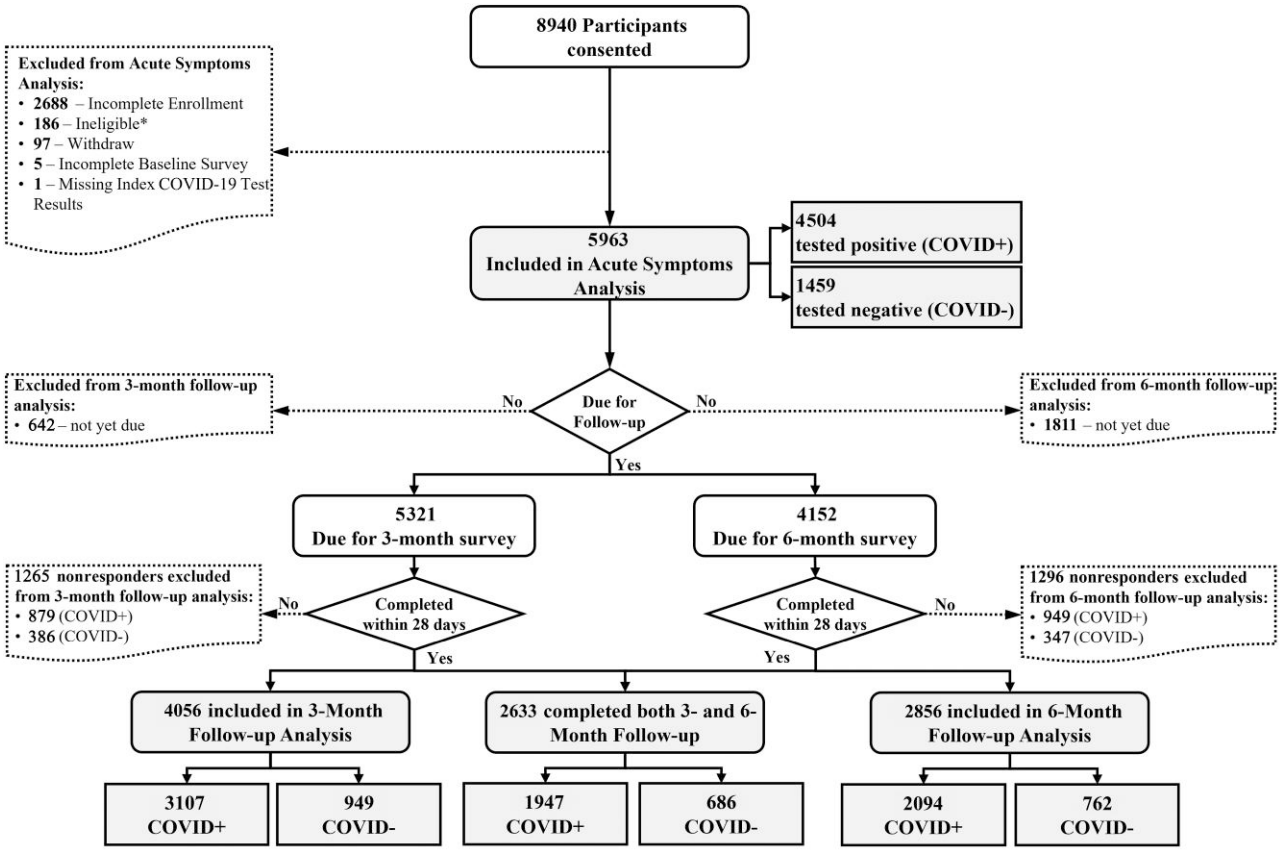


Figure 2. Participant flow diagram. *Participants who had received their index coronavirus disease 2019 (COVID-19) test >42 days before enrollment or did not have any clinical or pharmacy portals available were ineligible for enrollment.

characteristics are reported in Table 1 and the Supplementary Appendix.

Acute General Symptoms

Within the COVID-positive group, 25.7% of participants belonged to a class with significantly lower probability of all symptoms ("minimal-symptoms") (Figure 3*A*). Two other classes had high probability of aches, cough, and tiredness (ACT) and head/eyes/ears/nose/throat (HEENT) symptoms but differed by high versus low probability of loss of smell and taste (LoST) (ACT-HEENT with LoST [23.1%] vs ACT-HEENT without LoST [34.6%]). The fourth class included many miscellaneous symptoms across multiple systems (MSMS; 16.6%).

Among the COVID-negative group, 37.6% of participants belonged to a minimal-symptoms group. There was a second COVID-negative class with ACT-HEENT without LoST (42.6%). Finally, 19.9% of COVID-negative participants were in an MSMS class; however, the median number of symptoms was lower in the COVID-negative MSMS than COVID-positive MSMS class (median, 10 [IQR, 9–12] vs 14 [IQR, 12–15]).

General Symptoms at 3 and 6 Months

In the COVID-positive group, the largest 3-month class had almost no symptoms (minimal-symptoms; 72.2%). We also observed a class with predominance of tiredness, headache, and musculoskeletal symptoms (THM; 17.0%) and another class with isolated LoST (4.9%). Finally, there remained a class with MSMS (5.9%). The class categories and overall percentages at 6 months were similar.

In the COVID-negative group, the largest 3-month class also had minimal symptoms (75.7%). Another class with THM (20.0%) and a smaller class with MSMS (4.2%) were also identified. The class categories and overall percentages at 6 months were similar.

To explore changes in latent classes from baseline to 6 months, we tracked a group of participants who completed the symptom questions at all 3 time-points and visualized the shift among classes over time. Overall, 32.2% of COVID-positive participants switched between different general symptom classes from 3 to 6 months. The majority of participants in the acute minimal-symptoms class had almost no symptoms at 3 and 6 months (Figure 4*A*). Among the remainder, approximately half of

Table 1. Participant Characteristics

Variables	3 mo				6 mo			
	Overall (n = 4056)	COVID$^+$ (n = 3107)	COVID$^-$ (n = 949)	*P* Value	Overall (n = 2856)	COVID$^+$ (n = 2094)	COVID$^-$ (n = 762)	*P* Value
Age at enrollment, y				.01				.06
18–34	1708 (42.1)	1273 (41.0)	435 (45.8)		1240 (43.4)	883 (42.2)	357 (46.9)	
35–49	1256 (31.0)	1000 (32.2)	256 (27.0)		862 (30.2)	659 (31.5)	203 (26.6)	
50–64	738 (18.2)	570 (18.3)	168 (17.7)		516 (18.1)	380 (18.1)	136 (17.8)	
≥65	316 (7.8)	237 (7.6)	79 (8.3)		217 (7.6)	156 (7.4)	61 (8.0)	
Missing	38	27	11		21	16	5	
Gender				<.01				<.01
Female	2678 (66.0)	2024 (65.1)	654 (68.9)		1897 (66.4)	1356 (64.8)	541 (71.0)	
Male	1193 (29.4)	955 (30.7)	238 (25.1)		832 (29.1)	652 (31.1)	180 (23.6)	
Trans/NB/other	61 (1.5)	38 (1.2)	23 (2.4)		46 (1.6)	27 (1.3)	19 (2.5)	
Missing	124	90	34		81	59	22	
Ethnicity				.02				.06
Not of Hispanic, Latin, or Spanish origin	3409 (84.0)	2637 (84.9)	772 (81.3)		2385 (83.5)	1766 (84.3)	619 (81.2)	
Hispanic, Latin, or Spanish origin	561 (13.8)	408 (13.1)	153 (16.1)		411 (14.4)	286 (13.7)	125 (16.4)	
Missing	86	62	24		60	42	18	
Race				<.01				<.01
White	2719 (67.0)	2152 (69.3)	567 (59.7)		1914 (67.0)	1439 (68.7)	475 (62.3)	
Black or African American	325 (8.0)	208 (6.7)	117 (12.3)		239 (8.4)	149 (7.1)	90 (11.8)	
Asian	532 (13.1)	385 (12.4)	147 (15.5)		347 (12.1)	237 (11.3)	110 (14.4)	
Other/multiple	363 (8.9)	282 (9.1)	81 (8.5)		273 (9.6)	213 (10.2)	60 (7.9)	
Missing	117	80	37		83	56	27	
Educational attainment				<.01				<.01
Less than high school diploma	38 (0.9)	29 (0.9)	9 (0.9)		28 (1.0)	22 (1.1)	6 (0.8)	
High school graduate or GED	274 (6.8)	176 (5.7)	98 (10.3)		203 (7.1)	125 (6.0)	78 (10.2)	
Some college but did not complete degree	576 (14.2)	399 (12.8)	177 (18.7)		430 (15.1)	299 (14.3)	131 (17.2)	
2-y college degree	278 (6.9)	202 (6.5)	76 (8.0)		221 (7.7)	158 (7.5)	63 (8.3)	
4-y college degree	1262 (31.1)	1047 (33.7)	215 (22.7)		899 (31.5)	710 (33.9)	189 (24.8)	
More than 4-y college degree	1486 (36.6)	1155 (37.2)	331 (34.9)		981 (34.3)	714 (34.1)	267 (35.0)	
Missing	142	99	43		94	66	28	
Marital status				<.01				<.01
Never married	1440 (35.5)	1037 (33.4)	403 (42.5)		953 (33.4)	641 (30.6)	312 (40.9)	
Married/living with a partner	2175 (53.6)	1759 (56.6)	416 (43.8)		1589 (55.6)	1237 (59.1)	352 (46.2)	
Divorced/widowed/separated	401 (9.9)	283 (9.1)	118 (12.4)		281 (9.8)	194 (9.3)	87 (11.4)	
Missing	40	28	12		33	22	11	
Family income (prepandemic)				<.01				<.01
<$10 000	237 (5.8)	150 (4.8)	87 (9.2)		186 (6.5)	116 (5.5)	70 (9.2)	
$10 000–$35 000	426 (10.5)	305 (9.8)	121 (12.8)		322 (11.3)	222 (10.6)	100 (13.1)	
$35 000–$49 999	400 (9.9)	274 (8.8)	126 (13.3)		284 (9.9)	194 (9.3)	90 (11.8)	
$50 000–$74 999	531 (13.1)	405 (13.0)	126 (13.3)		379 (13.3)	281 (13.4)	98 (12.9)	
≥$75 000	2151 (53.0)	1759 (56.6)	392 (41.3)		1448 (50.7)	1128 (53.9)	320 (42.0)	
Prefer not to answer/missing	311	214	97		237	153	84	
Employment (prepandemic)				<.01				<.01
Not employed	758 (18.7)	518 (16.7)	240 (25.3)		543 (19.0)	355 (17.0)	188 (24.7)	
Employed, not essential or healthcare worker	1620 (39.9)	1282 (41.3)	338 (35.6)		1133 (39.7)	863 (41.2)	270 (35.4)	
Employed, essential or healthcare worker	1637 (40.4)	1278 (41.1)	359 (37.8)		1146 (40.1)	853 (40.7)	293 (38.5)	
Missing	41	29	12		34	23	11	
Where received COVID-19 test				<.01				<.01
At-home testing kit	517 (12.7)	411 (13.2)	106 (11.2)		230 (8.1)	164 (7.8)	66 (8.7)	
Tent/drive-up testing site	2099 (51.8)	1732 (55.7)	367 (38.7)		1525 (53.4)	1218 (58.2)	307 (40.3)	
Clinic including an urgent care clinic	590 (14.5)	408 (13.1)	182 (19.2)		453 (15.9)	309 (14.8)	144 (18.9)	
Hospital	335 (8.3)	240 (7.7)	95 (10.0)		234 (8.2)	165 (7.9)	69 (9.1)	
Emergency department	160 (3.9)	99 (3.2)	61 (6.4)		144 (5.0)	83 (4.0)	61 (8.0)	
Other	347 (8.6)	209 (6.7)	138 (14.5)		263 (9.2)	148 (7.1)	115 (15.1)	
Missing	…	8	…		…	7	…	

Table 1. Continued

Variables	3 mo				6 mo			
	Overall (n = 4056)	COVID$^+$ (n = 3107)	COVID$^-$ (n = 949)	*P* Value	Overall (n = 2856)	COVID$^+$ (n = 2094)	COVID$^-$ (n = 762)	*P* Value
Tobacco use, past 12 mo				.13				.67
Daily or near daily	223 (5.5)	157 (5.1)	66 (7.0)		168 (5.9)	116 (5.5)	52 (6.8)	
Weekly	72 (1.8)	52 (1.7)	20 (2.1)		55 (1.9)	43 (2.1)	12 (1.6)	
Less than monthly	199 (4.9)	159 (5.1)	40 (4.2)		125 (4.4)	93 (4.4)	32 (4.2)	
Monthly	57 (1.4)	45 (1.4)	12 (1.3)		39 (1.4)	29 (1.4)	10 (1.3)	
Not at all	3464 (85.4)	2666 (85.8)	798 (84.1)		2435 (85.3)	1791 (85.5)	644 (84.5)	
Missing	41	28	13		34	22	12	
Binge drinking, past 12 mo				<.01				<.01
Daily or near daily	52 (1.3)	41 (1.3)	11 (1.2)		34 (1.2)	24 (1.1)	10 (1.3)	
Weekly	364 (9.0)	303 (9.8)	61 (6.4)		261 (9.1)	215 (10.3)	46 (6.0)	
Less than monthly	930 (22.9)	712 (22.9)	218 (23.0)		640 (22.4)	473 (22.6)	167 (21.9)	
Monthly	506 (12.5)	402 (12.9)	104 (11.0)		347 (12.1)	267 (12.8)	80 (10.5)	
Not at all	2164 (53.4)	1622 (52.2)	542 (57.1)		1539 (53.9)	1092 (52.1)	447 (58.7)	
Missing	40	27	13		35	23	12	
Marijuana use, past 12 mo				.1				.2
Daily or near daily	208 (5.1)	154 (5.0)	54 (5.7)		146 (5.1)	104 (5.0)	42 (5.5)	
Weekly	189 (4.7)	156 (5.0)	33 (3.5)		125 (4.4)	100 (4.8)	25 (3.3)	
Less than monthly	456 (11.2)	363 (11.7)	93 (9.8)		328 (11.5)	250 (11.9)	78 (10.2)	
Monthly	173 (4.3)	128 (4.1)	45 (4.7)		118 (4.1)	81 (3.9)	37 (4.9)	
Not at all	2987 (73.6)	2277 (73.3)	710 (74.8)		2104 (73.7)	1536 (73.4)	568 (74.5)	
Missing	43	29	14		35	23	12	
Other drug use, past 12 mo				.15				.01
Weekly or more	32 (0.8)	20 (0.6)	12 (1.3)		20 (0.7)	9 (0.4)	11 (1.4)	
Monthly or less	319 (7.9)	243 (7.8)	76 (8.0)		239 (8.4)	179 (8.5)	60 (7.9)	
Not at all	3662 (90.3)	2816 (90.6)	846 (89.1)		2560 (89.6)	1882 (89.9)	678 (89.0)	
Missing	43	28	15		37	24	13	
Health insurance				<.01				<.01
Private and public	136 (3.4)	104 (3.3)	32 (3.4)		101 (3.5)	74 (3.5)	27 (3.5)	
Private only	2990 (73.7)	2346 (75.5)	644 (67.9)		2038 (71.4)	1528 (73.0)	510 (66.9)	
Public only	771 (19.0)	532 (17.1)	239 (25.2)		586 (20.5)	398 (19.0)	188 (24.7)	
None	159 (3.9)	125 (4.0)	34 (3.6)		131 (4.6)	94 (4.5)	37 (4.9)	
Hospitalization				<.01				<.01
No	3820 (94.2)	2888 (93.0)	932 (98.2)		2475 (86.7)	1801 (86.0)	674 (88.5)	
Yes	147 (3.6)	140 (4.5)	7 (0.7)		102 (3.6)	99 (4.7)	3 (0.4)	
Missing	89	79	10		279	194	85	
Has the COVID-19 pandemic caused you/your immediate family financial difficulties?				<.01				<.01
Not at all	2006 (49.5)	1644 (52.9)	362 (38.1)		1349 (47.2)	1050 (50.1)	299 (39.2)	
A little	1286 (31.7)	927 (29.8)	359 (37.8)		921 (32.2)	648 (30.9)	273 (35.8)	
Quite a bit	410 (10.1)	294 (9.5)	116 (12.2)		328 (11.5)	226 (10.8)	102 (13.4)	
Very much	314 (7.7)	213 (6.9)	101 (10.6)		225 (7.9)	147 (7.0)	78 (10.2)	
Missing	40	29	11		33	23	10	
In the past month, how often were you worried that your food would run out before you got money to buy more?				<.01				<.01
Never	3322 (81.9)	2613 (84.1)	709 (74.7)		2293 (80.3)	1719 (82.1)	574 (75.3)	
Sometimes	499 (12.3)	337 (10.8)	162 (17.1)		382 (13.4)	252 (12.0)	130 (17.1)	
Often	195 (4.8)	129 (4.2)	66 (7.0)		149 (5.2)	101 (4.8)	48 (6.3)	
Missing	40	28	12		32	22	10	
In the past month, has the electric, gas/oil, or water company shut off service or threatened to shut off service in your home?				<.01				<.01
No	3808 (93.9)	2940 (94.6)	868 (91.5)		2685 (94.0)	1984 (94.7)	701 (92.0)	
Threatened to shut off services	192 (4.7)	130 (4.2)	62 (6.5)		130 (4.6)	84 (4.0)	46 (6.0)	
Already shut off services	17 (0.4)	9 (0.3)	8 (0.8)		8 (0.3)	3 (0.1)	5 (0.7)	
Missing	39	28	11		33	23	10	

Table 1. Continued

Variables	3 mo				6 mo			
	Overall (n = 4056)	COVID$^+$ (n = 3107)	COVID$^-$ (n = 949)	*P* Value	Overall (n = 2856)	COVID$^+$ (n = 2094)	COVID$^-$ (n = 762)	*P* Value
Employed before the coronavirus outbreak				<.01				<.01
No	758 (18.7)	518 (16.7)	240 (25.3)		543 (19.0)	355 (17.0)	188 (24.7)	
Yes	3259 (80.4)	2561 (82.4)	698 (73.6)		2281 (79.9)	1717 (82.0)	564 (74.0)	
Missing	39	28	11		32	22	10	
Working at healthcare setting				0.34				.19
No	2398 (59.1)	1895 (61.0)	503 (53.0)		1692 (59.2)	1286 (61.4)	406 (53.3)	
Yes	861 (21.2)	667 (21.5)	194 (20.4)		588 (20.6)	431 (20.6)	157 (20.6)	
Missing	797	545	252		576	377	199	
Non-healthcare essential worker				.34				.85
No	2407 (59.3)	1902 (61.2)	505 (53.2)		1668 (58.4)	1258 (60.1)	410 (53.8)	
Yes	847 (20.9)	656 (21.1)	191 (20.1)		609 (21.3)	457 (21.8)	152 (19.9)	
Missing	802	549	253		579	379	200	
Experienced challenges with reliable general transportation in the past months				<.01				<.01
No	3862 (95.2)	2987 (96.1)	875 (92.2)		2718 (95.2)	2013 (96.1)	705 (92.5)	
Yes	194 (4.8)	120 (3.9)	74 (7.8)		138 (4.8)	81 (3.9)	57 (7.5)	
Experienced challenges with reliable medical transportation in the past months				<.01				<.01
No	3911 (96.4)	3029 (97.5)	882 (92.9)		2761 (96.7)	2047 (97.8)	714 (93.7)	
Yes	145 (3.6)	78 (2.5)	67 (7.1)		95 (3.3)	47 (2.2)	48 (6.3)	
Variant period (based on index test date; 50% cutoff)				<.01				<.01
Pre-Delta	650 (16.0)	457 (14.7)	193 (20.3)		551 (19.3)	377 (18.0)	174 (22.8)	
Delta	1507 (37.2)	1193 (38.4)	314 (33.1)		1393 (48.8)	1083 (51.7)	310 (40.7)	
Omicron	1899 (46.8)	1457 (46.9)	442 (46.6)		912 (31.9)	634 (30.3)	278 (36.5)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: COVID$^+$, tested positive for severe acute respiratory syndrome coronavirus 2; COVID$^-$, tested negative for severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; GED, General Educational Development; NB, nonbinary.

participants stayed in the same classes from 3 to 6 months, while the rest switched into different symptom classes. Among COVID-negative participants, 30.2% switched between different general symptom classes from 3 to 6 months. Many shifted to the minimal-symptom class, while a smaller portion remained within the THM and MSMS classes (Figure 4*B*).

Acute Fatigue-Related Symptoms

In the COVID-positive group, we identified a class with a low probability of fatigue-related symptoms (minimal-fatigue; 42.3%) and a class with almost all fatigue-related symptoms (maximal-fatigue; 11.8%; Figure 3*B*). We also identified 2 classes with fatigue and sleep disturbance, one characterized by additional cognitive issues (9.7%) and the other with aches (36.2%).

In the COVID-negative group, we observed a class with minimal symptoms (minimal-fatigue; 45.6%) and a class with high probabilities of all fatigue symptoms (maximal-fatigue; 11.6%). Aside from the maximal-fatigue class, notably, we did not observe a class with obvious cognitive issues in the COVID-negative cohort. The other 2 classes both had fatigue and sleep issues, though one also had aches (21.3%) while the other did not (21.4%).

Fatigue-Related Symptoms at 3 and 6 Months

In the COVID-positive group, we identified a class with almost no fatigue-related symptoms (minimal-fatigue) at 3 (64.7%) and 6 months (50.9%), compared to 42.3% acutely. We also identified a class with almost all fatigue-related symptoms (maximal-fatigue) at 3 (8.1%) and 6 months (9.5%), compared to 11.8% acutely. We identified 2 other classes with fatigue and sleep disturbance at 3 and 6 months, one with aches (12.2% and 11.8%, respectively) and the other without aches (15.1% and 27.9%, respectively). The proportion of people with no fatigue-related symptoms decreased by 13.8% from 3 to 6 months. Overall, 40.1% of COVID-positive participants switched between different fatigue classes from 3 to 6 months.

In the COVID-negative group at both 3 and 6 months, we observed similar classes, including almost no fatigue, almost all fatigue-related symptoms, and fatigue and sleep disturbances with or without aches. From 3 to 6 months, we observed an increase in the proportion of classes with almost no symptoms from 51.5% to 56.2% and a decrease in the proportion of class with almost all symptoms from 11.4% to 8.1%. Overall, 47.7% of COVID-negative participants switched between different fatigue classes from 3 to 6 months.

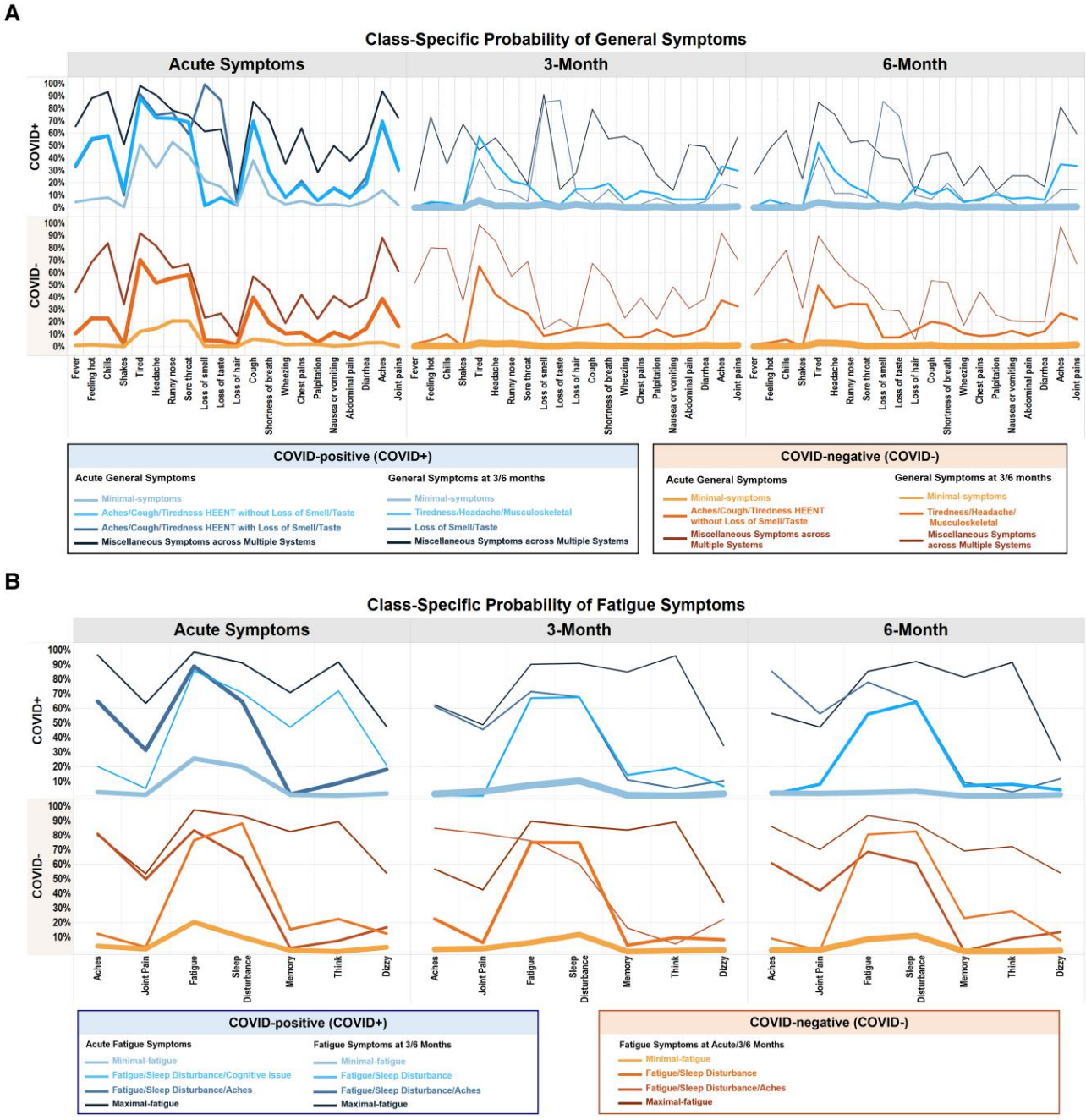


Figure 3. *A*, Model-estimated class-specific probabilities of general (*A*) and fatigue (*B*) symptoms at the acute, 3-month, and 6-month stages for both COVID-positive and COVID-negative participants. Line thickness reflects number of patients in a given class. Abbreviations: Acute, acute stage; 3/6 months: 3 or 6 months; HEENT, head/ears/eyes/nose/throat; minimal-symptoms: minimal number of symptoms in the acute stage; minimal-fatigue, minimal number of fatigue symptoms; maximal-fatigue, maximal number of fatigue symptoms.

To explore changes from 3 to 6 months, we tracked a group of participants who completed the fatigue questions at all 3 time-points and visualized the shift among symptom classes over time. In the COVID-positive group, 62% of the acute minimal-fatigue class had almost no fatigue symptoms across all 3 time-points (Figure 4*C*). Among maximal-fatigue, 21.9% of the acute group remained in this group across all 3 time-points. In the COVID-negative group, 54.4% of the acute minimal-fatigue class had almost no fatigue symptoms across all 3 time-points, while 24.6% of the acute maximal-fatigue group had almost all fatigue symptoms across all 3 time-points (Figure 4*D*).

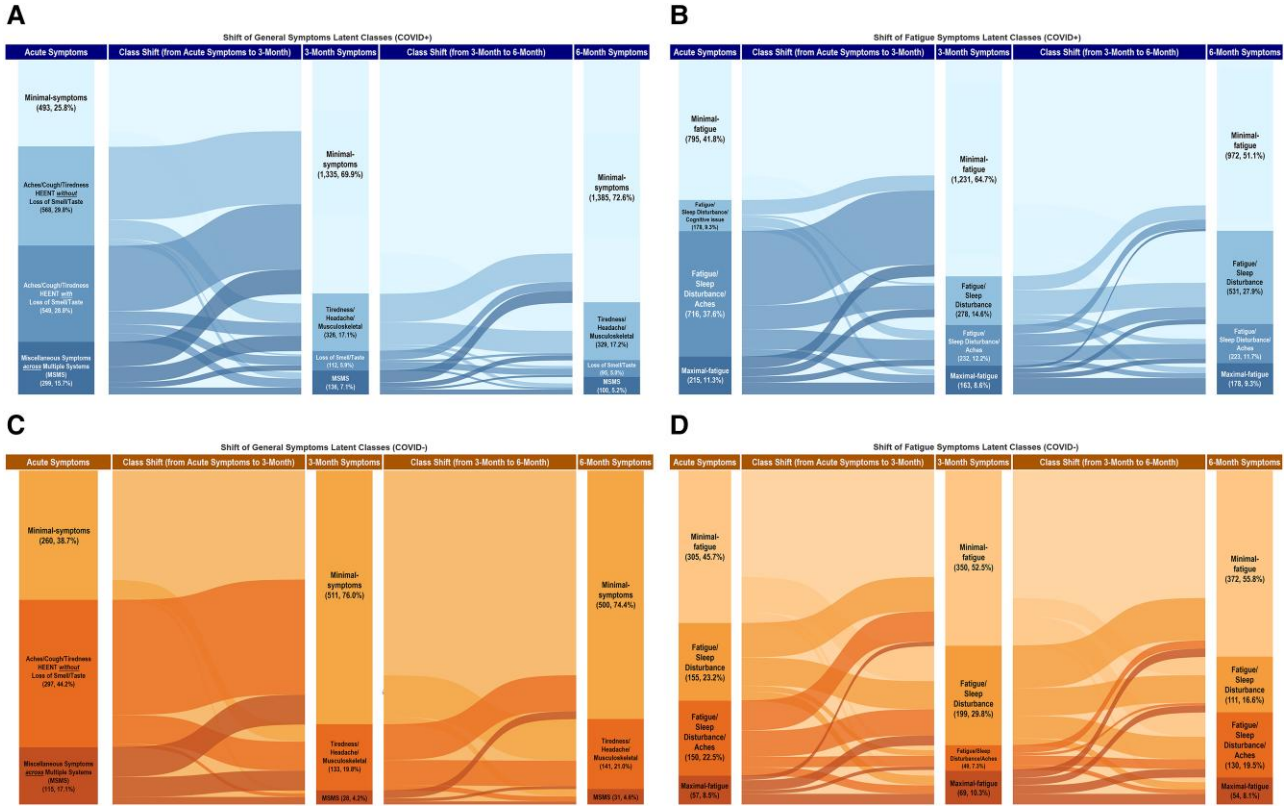


Figure 4. *A–D*, Class shifts across time periods for general symptoms among the COVID-positive (*A*) and COVID-negative (*C*) groups and for fatigue symptoms among the COVID-positive (*B*) and COVID-negative (*D*) groups. Abbreviations: HEENT, head/ears/eyes/nose/throat without loss of smell and taste; maximal-fatigue, maximal number of fatigue symptoms; minimal-fatigue, minimal number of fatigue symptoms; minimal-symptoms, minimal number of symptoms; MSMS, many symptoms across multiple systems.

Cross-tabulation Between General and Fatigue-Related Symptom LCA Classes

When assessing cross-membership between classes, we observed that those belonging to the classes with minimal general symptoms often also belonged to the classes with minimal fatigue-related symptoms at all 3 stages (Supplementary Appendix). Similarly, those with more general symptoms acutely (MSMS) were more likely to belong to the group with more fatigue-related symptoms (maximal-fatigue). However, this was no longer true at 3 and 6 months.

DISCUSSION

In this large, multicenter, longitudinal study of participants with acute symptoms who tested COVID-positive or COVID-negative, we identified distinct phenotypes of persistent symptoms for both general and fatigue-related symptom groups at 3- and 6-month follow-up. These included 4 general symptom phenotypes (minimal symptoms, tired/headache/musculoskeletal, loss of smell/taste, and many symptoms across multiple systems) and 4 phenotypes based upon fatigue-related symptoms (minimal fatigue symptoms, fatigue/sleep disturbances, fatigue/sleep disturbances/aches, broad fatigue symptoms).

While the initial general symptom groups were relatively evenly distributed, the minimal-symptom group became dominant, representing approximately 70% of participants at 3 and 6 months, suggesting that the majority experienced symptom resolution. However, approximately 30% of participants—COVID-positive and COVID-negative—had persistent symptoms, with the total number of participants in each group remaining relatively constant over time. While this is within the range of reported rates seen in prior studies, the similarities of the positive and negative cohorts suggest that some of the symptoms may not be unique to SARS-CoV-2 infection and result from disruptive effects of the pandemic or postinfectious symptoms from other illnesses. The wide range of frequencies may reflect bias in those seeking medical care or variations in the criteria used [3]. This further highlights the critical need for a clearer definition of PCCs/Long COVID and the different phenotypes and larger-scale population-based studies, as well as the value of patient-reported outcomes and inclusion of a COVID-negative comparison cohort as in our study.

There was substantial class-switching over time, suggesting that symptoms present during the acute illness may be poorly predictive of persistent symptoms. While overall numbers in each group remained stable from 3 to 6 months, one-third of participants switched between classes during that time period. We identified similar findings with fatigue, wherein the number with minimal symptoms at onset increased over time but switched to different classes. Interestingly, these findings were observed across both COVID-positive and COVID-negative cohorts, highlighting the importance of longitudinal cohorts and suggesting that symptoms may not be persistent among all people. Our data suggest that symptoms may emerge or remit over time, with participants having different symptom complexes at different time-points [8, 12, 19–21]. This adds to growing evidence that PCCs, as currently conceived, may not be a singular condition but rather a range of phenotypes that may evolve over time. Consequently, patients and clinicians should recognize that symptoms of PCCs experienced at 3 months may differ at 6 months [22].

A prior study of 233 people with persistent COVID-19 symptoms reported 3 main symptom groupings using cluster analysis (as opposed to LCA), which included musculoskeletal, cardiorespiratory, and minimal symptoms [11]. An EHR-based study reported 4 main clusters by organ system: cardiac/renal, respiratory/sleep/anxiety, musculoskeletal/nervous system, and digestive/respiratory [9]. Another EHR data–based analysis reported different phenotypes, which included persistent fatigue with bodily pain or mood swings, cognitive symptoms, and respiratory symptoms [10]. We identified some overlap with those classes in our analysis. However, we found that it was rare for a phenotype to involve only a single organ system and often involved combinations of symptoms, such as fatigue, HEENT, and musculoskeletal symptoms. This is consistent with a separate smaller study of 179 participants with persistent COVID-19 symptoms, which identified 2 main clusters (minimal symptoms and maximal symptoms) that involved multiple organ systems [12]. Together, these findings suggest a much more complex mechanism and may reflect the ability of COVID-19 to attack multiple organs through a more diffuse process [23]. Alternatively, different phenotypes may reflect different mechanisms and future work should involve mechanistic investigations of specific phenotypes to better understand the underlying cause [24]. We also identified the commonality of fatigue across multiple phenotypes, highlighting the role of fatigue-related symptoms in PCC phenotypes. The multiple phenotypes identified also highlight the challenges in developing one overarching definition of PCCs. Definitions of PCCs will likely need to consider a range of phenotypes.

Essential to our data is the comparison between COVID-positive and COVID-negative cohorts. During the acute phase, COVID-positive phenotypes overlapped with COVID-negative phenotypes, demonstrating the challenges of differentiating COVID-19 infection from other illnesses without testing. Among the longer-term symptom clusters, there also was striking similarity between the COVID-positive and COVID-negative cohorts, which may reflect the commonalties between postacute illnesses and occurrence of symptoms in the postacute phase that are not uniquely attributable to an infection in the first place. The exceptions are cognition problems and LoST in only the COVID-positive cohort. Cognition problems have been reported in multiple studies and can impact quality of life [25–27]. Our data suggest that this may be a more distinct feature of PCCs. LoST has been well-described in the COVID-positive population [28, 29], and our data further support this and demonstrate persistence at 6 months.

This study has several strengths. First, we collected data prospectively and utilized participant symptom self-report, rather than relying only on EHR data collected as part of routine care. The latter may be subject to missing information and underreport discrete symptoms, particularly for participants who choose not to seek medical care or have difficulty accessing care. By relying on prospective data from participant self-report, we were also able to elucidate new symptoms from preexisting symptoms. Second, we evaluated participants at set intervals of 3 and 6 months, to better understand persistent symptoms and trajectory over time. Third, we included a symptomatic COVID-negative cohort to identify if there were unique phenotypes that differed at 3 and 6 months among the COVID-positive group versus those with other illnesses.

Limitations

We did not explicitly ask about severity for each individual symptom. Future research is needed to better understand the linkage among specific symptoms, severity, and impact on quality of life experienced for people with PCCs to understand both the presence and degree of symptoms. While there were notable similarities between the COVID-positive and COVID-negative groups, there may be additional unidentified confounders between them. We relied upon access to internet-capable devices and a verifiable COVID-19 test, which may have biased our sample toward those with greater resources and access to care, and thus may not fully reflect the broader population [30]. There is also risk of response bias between responders versus nonresponders, which was slightly higher at 6 months. It is possible that those with more symptoms were more likely to remain active in the study. Due to the 42-day enrollment period, participants with continued symptoms may have been more likely to enroll than those who were asymptomatic. There is also a risk of recall bias regarding reporting of preceding symptoms. Additionally, COVID-19 testing may have false positives or false negatives leading to misclassification bias. Although some COVID-negative participants may have contracted COVID-19 postenrollment, and some

COVID-positive participants may have experienced reinfection postenrollment, we did ask about new infection at each survey. We are unaware of the specific illness prompting COVID-negative participants to seek testing, limiting the ability to exclude or specify different postinfectious sequelae causing these findings. We did not conduct subanalyses to assess the impact of variant, vaccination, or comorbidities upon the specific phenotypes. LoST is suggested to be less common with Omicron, and further research is needed to determine whether PCC phenotypes differ across variant strains [31–34]. Additional research should also identify differences based upon race, ethnicity, socioeconomic status, and comorbidities. While the alluvial figures suggest that symptoms present during the acute illness may be poorly predictive of prolonged symptoms, we did not perform statistical assessments of the predictors; future work is needed to identify these factors. Finally, our study is limited to only 6 months postinfection and future work is needed to understand the course beyond this time period.

CONCLUSIONS

Our study identified 4 distinct post-COVID phenotypes of general and fatigue-related symptoms. This provides further evidence that there is not a singular "Long COVID" and that people's experiences can vary. Tracked over time, the number of participants with minimal symptoms increased from acute infection to 3 months and then remained stable from 3 to 6 months postinfection. We also noted significant class-switching across time periods, suggesting that symptom complexes that individuals experience vary over time. Our findings may inform future definitions for PCCs and provide an understanding of the different phenotypes to identify health system needs to care for patients experiencing these different groups of symptoms.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Financial support. This work was supported by the CDC National Center of Immunization and Respiratory Diseases (contract number 75D30120C08008; principal investigator, R. A. W.). Partners from the CDC (I. D. B. and S. S.) assisted with study design and the preparation of this manuscript.

Potential conflicts of interest. M. G. reports funding from the Rush Center for Emerging Infectious Diseases Research Grant, Emergency Medicine Foundation/Council of Residency Directors in Emergency Medicine Education Research Grant, Emergency Medicine: Reviews and Perspectives Medical Education Research Grant, University of Ottawa Department of Medicine Education Grant, and Society of Directors of Research in Medical Education Grant. E. S. S. receives grant funding from the National Institute on Minority Health and Health Disparities (U54MD010711-01), the US Food and Drug Administration to support projects within the Yale-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI, U01FD005938), the National Institute of Biomedical Imaging and Bioengineering (R01EB028106-01), and the National Heart, Lung, and Blood Institute (R01HL151240). J. G. E. reports serving as Editor-in-Chief of Adult Primary Care topics for UpToDate. N. L. G. receives grant funding from the CDC (BAA75D301-20-75D30121C10207). A. V. reports funding for COVID-19–related studies from the Society of Academic Emergency Medicine Foundation Emerging Infectious Disease and Preparedness Grant, the Agency for Healthcare Research and Quality (R01 HS 28340-01), the Food and Drug Administration (ID: 75F40120C00174), and the Centers for Medicare and Medicaid Services. G. N. reports the following: funding for COVID-19–related studies from the National Institute of Allergy and Infectious Diseases (NIAID) (1R01AI66967), research funding from Abiomed, Vapotherm, and ZOLL Medical; consultant to CPR Therapeutics, Heartbeam Inc, Invero Health LLC, Kestra Medical Technologies, Orixha, and ZOLL Circulation; and reports a patent (Method for non-imaging ultrasound to measure blood flow during CPR) and nonprovisional patent (Method for modifying cell injury associated with reduced blood flow). K. N. O. reports funding for COVID-19–related studies from NIAID (1R01AI66967). K. L. R. reports funding for COVID-19–related studies from NIAID (1R01AI66967) and the Philadelphia Department of Public Health. All other authors report no potential conflicts.

References

1. Hirschtick JL, Titus AR, Slocum E, et al. Population-based estimates of post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC) prevalence and characteristics. Clin Infect Dis **2021**; 73:2055–64.
2. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open **2021**; 4:e2111417.
3. Groff D, Sun A, Ssentongo AE, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. JAMA Netw Open **2021**; 4:e2128568.
4. Sandler CX, Wyller VBB, Moss-Morris R, et al. Long COVID and post-infective fatigue syndrome: a review. Open Forum Infect Dis **2021**; 8:ofab440.
5. Centers for Disease Control and Prevention. Long COVID or Post-COVID conditions. **2022**. Available at: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Accessed 18 December 2022.
6. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October **2021**. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1. Accessed 18 December 2022.
7. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE guideline [NG188]. **2020**. Available at: https://www.nice.org.uk/guidance/NG188. Accessed 18 December 2022.
8. Spatz ES, Gottlieb M, Wisk LE, et al. Three-month symptom profiles among symptomatic adults with positive and negative SARS-CoV-2 tests: a prospective cohort study from the INSPIRE group. Clin Infect Dis **2023**; 76:1559–66.
9. Zhang H, Zang C, Xu Z, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. Nat Med **2023**; 29:226–35.
10. Global Burden of Disease Long COVID Collaborators; Wulf Hanson S, Abbafati C, Aerts JG, et al. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. JAMA **2022**; 328:1604–15.
11. Kenny G, McCann K, O'Brien C, et al. Identification of distinct long COVID clinical phenotypes through cluster analysis of self-reported symptoms. Open Forum Infect Dis **2022**; 9:ofac060.
12. Peluso MJ, Kelly JD, Lu S, et al. Persistence, magnitude, and patterns of postacute symptoms and quality of life following onset of SARS-CoV-2 infection: cohort description and approaches for measurement. Open Forum Infect Dis **2021**; 9: ofab640.
13. O'Laughlin KN, Thompson M, Hota B, et al. Study protocol for the innovative support for patients with SARS-COV-2 infections registry (INSPIRE): a longitudinal study of the medium and long-term sequelae of SARS-CoV-2 infection. PLoS One **2022**; 17:e0264260.

14. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC. Psychometric properties of the CDC symptom inventory for assessment of chronic fatigue syndrome. Popul Health Metr **2005**; 3:8.
15. Geiser C. Data analysis with Mplus. New York: Guilford Press, **2013**.
16. Oberski D. Mixture models: latent profile and latent class analysis. In: Robertson J, Kaptein M, eds. Modern statistical methods for HCI. Cham: Springer International Publishing, **2016**:275–87.
17. Lanza ST, Collins LM, Lemmon DR, Schafer JL. PROC LCA: a SAS procedure for latent class analysis. Struct Equ Modeling **2007**; 14:671–94.
18. Collins LM, Lanza ST. Latent class and latent transition analysis: with applications in the social behavioral, and health sciences. Hoboken, NJ: Wiley, **2010**.
19. Wisk LE, Gottlieb M, Spatz ES, et al. Association of initial SARS-CoV-2 test positivity with patient-reported well-being 3 months after a symptomatic illness. JAMA Netw Open **2022**; 5:e2244486.
20. O'Brien KK, Brown DA, McDuff K, et al. Conceptualising the episodic nature of disability among adults living with long COVID: a qualitative study. BMJ Glob Health **2023**; 8:e011276.
21. Ziauddeen N, Gurdasani D, O'Hara ME, et al. Characteristics and impact of long Covid: findings from an online survey. PLoS One **2022**; 17:e0264331.
22. Tran V-T, Porcher R, Pane I, Ravaud P. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun **2022**; 13:1812.
23. Acharya Y, Alameer A, Calpin G, Alkhattab M, Sultan S. A comprehensive review of vascular complications in COVID-19. J Thromb Thrombolysis **2022**; 53: 586–93.
24. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med **2022**; 28:911–23.
25. Frontera JA, Yang D, Medicherla C, et al. Trajectories of neurologic recovery 12 months after hospitalization for COVID-19: a prospective longitudinal study. Neurology **2022**; 99:e33–45.
26. Hellmuth J, Barnett TA, Asken BM, et al. Persistent COVID-19–associated neurocognitive symptoms in non-hospitalized patients. J Neurovirol **2021**; 27:191–5.
27. Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. Lancet Psychiatry **2022**; 9:815–27.
28. Fernández-de-Las-Peñas C, Martín-Guerrero JD, Navarro-Pardo E, Cancela-Cilleruelo I, Moro-López-Menchero P, Pellicer-Valero OJ. Exploring trajectory curves from loss of smell and taste in previously hospitalized COVID-19 survivors: the LONG-COVID-EXP-CM multicenter study. J Gen Intern Med **2022**; 37:1821–3.
29. Horberg MA, Watson E, Bhatia M, et al. Post-acute sequelae of SARS-CoV-2 with clinical condition definitions and comparison in a matched cohort. Nat Commun **2022**; 13:5822.
30. Perrin A, Turner E. Smartphones help blacks, Hispanics bridge some—but not all—digital gaps with whites. **2019**. Available at: https://policycommons.net/artifacts/616650/smartphones-help-blacks-hispanics-bridge-some/1597318/. Accessed 18 December 2022.
31. Vihta KD, Pouwels KB, Peto TE, et al. Omicron-associated changes in SARS-CoV-2 symptoms in the United Kingdom. Clin Infect Dis **2022**; 76: e133–41.
32. Menni C, Valdes AM, Polidori L, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of Omicron and Delta variant dominance: a prospective observational study from the ZOE COVID study. Lancet **2022**; 399:1618–24.
33. Wang RC, Gottlieb M, Montoy JC, et al. Association between SARS-CoV-2 variants and frequency of acute symptoms: analysis of a multi-institutional prospective cohort study - December 20, 2020 – June 20, 2022. Open Forum Infect Dis **2023**. doi: 10.1093/ofid/ofad275
34. Gottlieb M, Wang RC, Yu H, et al. Severe fatigue and persistent symptoms at 3 months following Severe Acute Respiratory Syndrome Coronavirus 2 infections during the pre-Delta, Delta, and Omicron time periods: a multicenter prospective cohort study. Clin Infect Dis **2023**; 76:1930–41. doi: 10.1093/cid/ciad045