

Functional status as a diagnostic marker and health outcome in long COVID.

By

Kristen Kehl-Floberg, MSOT, OTR/L, BCG

A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

(Clinical Investigation)

At the

University of Wisconsin – Madison

2025

Date of final oral examination: March 31, 2025

This dissertation is approved by the following members of the Final Oral Committee:

Dorothy Farrar Edwards, Professor, School of Medicine and Public Health and School of Education (committee chair)

Richard Chappell, Professor, School of Medicine and Public Health

Beth Fields, Associate Professor, School of Education

Ronald Gangnon, Professor, School of Medicine and Public Health

Aurora Pop-Vicas, Associate Professor, School of Medicine and Public Health

Christine Sorkness, Professor, School of Medicine and Public Health

ABSTRACT

Approximately one-third of adults who have had COVID-19 experience a novel and disabling multi-system syndrome termed “long COVID”. Long COVID can impair performance of complex daily routines that are vital to independence (e.g. caregiving, work and school, and community life). The disability caused by long COVID is expected to cost billions of dollars of lost wages in the U.S. alone.

Although daily functioning is proposed diagnostic criterion for long COVID, there is insufficient scientific evidence describing and operationalizing the functional impairments experienced by people with this disorder (NASEM, 2024). Measures of functional impairment have not been included in large EMR-based phenotyping studies attempting to develop a consensus clinical definition of the disorder. Post-infection changes in functional status are not well-understood, and clinical screening instruments have been found to be non-sensitive to functionally impactful symptoms such as long COVID brain fog. Because of these gaps, individuals with long COVID might not be accurately identified or referred for recommended interventions (Chuang et al., 2023; Venkatesan, 2021).

This research aimed to: (1) describe demographics, pre-infection symptoms and functional status indicators, and long COVID symptoms (2) identify patterns and predictors of functional impairment in long COVID, and (3) explore the impact of age on functional status, in a retrospective cohort study of people with COVID-19 enrolled in the *All of Us* Research Program through July 2022. We found that long COVID increased the likelihood of functional impairment independent of age or pre-infection symptoms, and that this relationship was complex and multidirectional. We also demonstrated the feasibility of using harmonized medical records and survey data in the *All of Us* Research Program to explore daily functioning as both a

diagnostic marker and health outcome.

Assessing both pre-illness functional status and post-illness functional status changes can improve diagnostic accuracy and sensitivity and guide intervention research so that people with long COVID can return to thriving and meaningful lives.

ACKNOWLEDGEMENTS

I thank first the patients and participants who entrusted to research their personal experiences and information, both from the Madison community and through the *All of Us* Research Program. The All of Us Research Program would not be possible without the partnership of its participants. To those who I learned from during testing sessions, to the hundred-thousand I did not meet face-to-face, and to my many former patients - thank you for your trust and generosity.

This work would not have been possible without generous funding awards from the UW-Madison Institute for Clinical and Translational Research TL1 Pre-doctoral Trainee award from 2021 (5TL1TR002375-05) to 2023 (2TL1TR002375-06); the Gertrude Gatson Fund 233 PRJ22AW 176000, and the Marsh Center Fund 233 PRJ56ZI 176000 from the University of Wisconsin–Madison Occupational Therapy Program and Kinesiology Department.

Thanks to my primary mentor Dr. Dorothy Edwards for her inspiration and counseling throughout my career, her unflagging support for a balance of family and academic life, and honest talks that catalyzed growth. I am also grateful to my advisory committee mentors for their generosity through many hours of instruction, consultation, guidance, and ability to challenge my limitations (both perceived and actual); Dr.'s Richard Chappell, Beth Fields, Ron Gangnon, Aurora Pop-Vicas, and Christine Sorkness.

Thanks to all at the Functional Cognition Lab and the OT department, whose work made the long COVID brain fog study successful; Rebecca Gray, Emily Danzl, Emma Freisburg, Laura Yipp, Jamie Bednarz, Alea Sullivan, Miranda Dahmen, Cassandra Summers, Emily Unmacht, and Kari Becker. Thanks to Dr.'s Tim Marks and Gordon Giles for collaboration and philosophical conversation; you have been my discipline home. Thanks to the many informal

mentors, supervisors, and instructors who have encouraged me to believe in my path; these include Art Walaszek, Cynthia Carlsson, Daniel Bolt, Stephanie Stegman, Monica Perlmutter, Trudy Mallinson, and Sharon Gartland.

Finally, thanks to my parents, Michael Kehl and Ann Haase Kehl, for supporting me in everything I have ever attempted within a life rich with opportunities and purpose; my sister and fellow rehabilitation therapist Dr. Nora Rose Beck for her unfailing understanding; and to my late grandparents, Emil and Fayne Haase and Edwin and Carol Kehl, who inspired fascination and reverence for the experiences of aging and dementia. Thanks to my parents in-law John Warren Floberg and Martha Hickner for their love and support. Thanks, forever, to my loving and gentle husband John Martin Floberg for insisting that I should do this (and then insisting often that I should continue doing it). Thanks most of all to my beautiful and delightful children, James Ennis and Marta Rose, for their patience, loving hearts, joyful spirits, and curious minds.

TABLE OF CONTENTS

Section	Page number
Abstract	ii
Acknowledgements	iv
List of Abbreviations	viii
Chapter 1. Introduction and literature review	1
Disease History	1
Long COVID definitions, epidemiology, and mechanisms	2
Definition and terminology	2
Epidemiology, impact, and risk factors	4
Demographic factors associated with long COVID	5
Mechanisms	6
Current approaches to generating diagnostic evidence	8
Impact on daily functioning: State of the science and measurement considerations	9
Measurement considerations	14
Guiding Theories, Frameworks, and Approaches	16
Daily functioning	16
The International Classification of Functioning (ICF)	16
The Person-Environment-Occupation-Performance Model	18
Aging and lifespan development	19
Biological theories of aging	19
Lifespan Development and Lifespan Psychology	20
Population health: Frameworks for health and statistical inference	21
Social Determinants of Health	22
Causal and associative inference methods in population health	23
Phenotyping using health records data	23
Objectives	25
Chapter 2. Specific Aims	26
Chapter 3. Methods	28
Design and data source	28
Sample	28
<i>Table 1. Identification of cohort: COVID-19 illness indicators</i>	29
Symptom-based classification of long COVID symptomatic versus recovered participants	35
<i>Table 2. Long COVID symptoms/conditions used in cohort discovery and classification</i>	35
<i>Box 1. Standard concept names of descendent conditions removed from cognition and functional findings ancestor condition categories</i>	40
Variables	42

Infection variants active at time of first infection	42
Demographics	42
Number of long COVID symptoms/conditions present before and after infection	42
Functional status indicators	43
Self-reported daily functioning and health (aim 1 only):	43
Occupational therapy billing and procedure codes	43
“Finding of functional performance and activity” codes	44
Quantitative bias analysis of cohort discovery	45
Analysis	45
Chapter 4. Manuscript 1: Associations of Demographics, Pre-infection Functional Status, and Pre-infection Symptom Burden With Developing Long COVID: A Retrospective Cohort Study From the All of Us Research Program.	47
Chapter 5. Manuscript 2: Functional impairment in people with Long COVID symptoms: A retrospective cohort study of EHR data from the All of Us Research Program.	73
Chapter 6. Manuscript 3: Older age and long COVID symptoms independently increase functional impairment after COVID-19: An analysis of All of Us Research Program data.	99
Chapter 7. Conclusion	139
Appendix A. Extended cohort discovery and long COVID symptom description <i>All of Us</i> Research Program data structure	145
Appendix B. Functional Status Indicators	158
Appendix C. Quantitative bias analysis (Aim 1 only)	164
Appendix D. Model fitting notes	168
Aim 1	168
Aim 2	179
Aim 3	205
Appendix E: Expanded results	219
References	231

List of Abbreviations

COVID-19	Coronavirus Disease 2019
EHR	Electronic health record(s)
ICD	International Classification of Disease
ICF	International Classification of Functioning
NASEM	National Academies of Sciences, Engineering, and Medicine
N3C	National COVID Cohort Collaborative
PACS	Post-acute COVID-19 syndrome
PASC	Post-acute sequelae of COVID-19
PCC	Post-COVID condition
SARS-CoV-2	Severe acute respiratory syndrome of coronavirus, second type
SCC	Subjective cognitive complaint
WHO	World Health Organization

Chapter 1. Introduction and Literature Review

Disease history

In late 2019, a novel strain of the severe acute respiratory syndrome – coronavirus type 2 (SARS-CoV-2) was detected in humans in Wuhan, China. The SARS-CoV-2 pathogen proved highly infectious, spreading rapidly and causing a respiratory illness termed coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared it a global pandemic on March 11, 2020 (World Health Organization). As of the end of January 2025, the WHO estimated that over seven million people have died from COVID-19 since it emerged (WHO, 2025b).

By July of 2020, reports were surfacing of people who had survived an initial infection but were experiencing new or ongoing, persistent, and sometimes debilitating symptoms, some with post-illness rehabilitation needed to prevent disability (Brugliera et al., 2020; Ceravolo et al., 2020; de Sire et al., 2022). In addition to reports of major neurologic disease during the acute phase of illness (Ahmed et al., 2020; Julie Helms et al., 2020; J. Helms et al., 2020), clinical research teams were reporting unresolved multi-system issues emerging after the initial illness in both hospitalized (Almeria et al., 2020; Higgins et al., 2020) and non-hospitalized (Tenforde et al., 2020) patients. Recommendations followed to monitor patients for persistent health changes after illness (Crook et al., 2021; The Lancet, 2020).

However, post-acute monitoring was a low priority for population health and clinical services that were absorbed with containing spread and treating people with acute illness. Prior to the development of vaccines and medications, acute COVID-19 illness management and infection prevention required significant health care resources. Staff were reassigned or furloughed, facilities converted, and supplies diverted to cover acute COVID-19 care. Emphasis

in this early time was focused on improving survival, and over-taxed health care systems neither anticipated nor had resources available to address long-term post-illness effects. As a result, patients were often unable to either access services or convince providers that there was something wrong with their health (Ladds et al., 2020). To obtain support and advice, people around the world began connecting with one another on social media (Goërtz et al., 2020; McCorkell et al., 2021). This spontaneous collective began referring to their experience as “long haul COVID” (later, simply “long COVID”) (Callard & Perego, 2021), and gave rise to the Patient-Led Research Collaborative for Long COVID (McCorkell et al., 2021). The Collaborative insisted on recognition of long COVID as a distinct and real phenomenon through rigorous patient-driven research (e.g. Davis et al., 2021) and has authored impactful and innovative science to understand long COVID mechanisms and impacts (Al-Aly et al., 2024; Davis et al., 2021; Thaweethai et al., 2023). Long COVID is now recognized by policy makers, researchers, health care providers, and the public at large. As vaccines and antiviral treatments have improved survival and the virus has become endemic, a growing amount of scientific and clinical attention has shifted to long COVID.

Long COVID definitions, epidemiology, and mechanisms

Definition and terminology

“Long COVID” is a patient-generated term for a chronic systemic health condition featuring new-onset or exacerbated, and persistent, symptoms and health conditions after COVID-19 infection (Al-Aly et al., 2024; McCorkell et al., 2021; Mendelson et al., 2020; NASEM, 2024; Thaweethai et al., 2023). Multiple organ systems may be involved, including neurologic, gastrointestinal, endocrine, and others (Brannock et al., 2022; Reese et al., 2023; Zhang et al., 2023). Common presentations include fatigue, post-exertional malaise (profound

and prolonged fatigue lasting days to weeks following exertion (Haunhorst et al., 2024)), cognitive impairment, headache, breathing difficulty, musculoskeletal pain or weakness, sleep disturbance, and mood disorder (Crook et al., 2021) among many others (Davis et al., 2021; Davis et al., 2023; Zhang et al., 2023). Multiple terms for the disorder have been used by researchers across disciplines. “Chronic Covid-19” was proposed from a virology perspective (Baig, 2021), retaining an etiological link to the initial infection. “Post-acute Sequelae of COVID-19 (PASC)” first appeared in 2021 in a preprint of an implementation study (Peluso et al., 2021). It has since become widely used across disciplines, giving an open-ended allowance to include any follow-on observations, but stopping short of implying a diagnosis. “Post-acute COVID-19 syndrome” (PACS; Nalbandian et al., 2021), “post-COVID syndrome” (PCS; Iqbal et al., 2021), and the WHO’s “post-COVID-19 condition” (2025a) explicitly assert that the sequelae comprise an distinct health condition. Because the original patient-driven term of “long COVID” continues to be preferred by patients and patient-led advocacy and research groups, the present work will henceforth use the terms “long COVID symptoms/conditions” to refer to collections or single conditions and “long COVID” to refer to the syndrome overall.

The clinical diagnostic criteria for long COVID are still evolving (see “Current Approaches and Gaps in Evidence”). Most definitions include a combination of disease exposure, temporality, symptom presentation, symptom duration, and disability or decreased functional status. Common parameters include lab-confirmed SARS-CoV-2 infection (Soriano et al., 2022), a minimum of three months’ delay from infection onset (NASEM, 2024; Soriano et al., 2022), a minimum number and duration of symptoms (Soriano et al, 2022), the presence of some combination of symptoms (Soriano et al, 2022), considerations for special populations

(Soriano et al, 2022), an impact on daily functioning (NASEM, 2024; Soriano et al, 2022) and no alternative diagnostic explanation (NASEM, 2024; Soriano et al., 2022).

Epidemiology, economic impact, and risk factors

Estimating the prevalence of long COVID is a challenge compounded by the heterogeneity of outcome and classification, range of quality and availability of public health data, and rapid evolution of both the virus and its treatment over time. A recent meta-analysis found pooled global estimates of 36% (95% CI = 33%-40%) and a pooled U.S. estimated prevalence of about 30% (95% CI 24%-38%), with an I^2 measure of 100 (indicating the maximum possible proportion of true variance and minimum possible proportion of sampling error ($p < 0.001$)) (Hou et al., 2025). The U.S. Household Pulse Survey posted November 1 2023 estimated that between 7.7 and 23 million U.S. adults experience persistent long COVID (National Center for Health Statistics, 2024). This was at least 6% of the U.S. adult population, a percentage that had remained stable on this survey since January 2023 (Ford et al., 2023). Long COVID affects people of all demographic identities and disease severity (Banic et al., 2022), resulting in disability during some of the most productive years of life. The ensuing economic impact of this novel cause of disability in the U.S. is unsustainable; according to a 2022 report, up to 4 million people were out of work due to long COVID symptoms, which was projected to result in over \$170 billion in lost wages annually (Bach, 2022). Assuming respiratory symptoms would become the predominant sequelum, Cutler (2022) estimated that the long-term costs of long COVID would be similar to those of chronic obstructive pulmonary disease, totalling 2.6 trillion dollars per year due to loss of health. The prevalence and impact of long COVID make research supporting evidence-based diagnosis and interventions critical.

Demographic factors associated with long COVID

Several demographic factors are consistently associated with the development of long COVID. Most observational studies find approximately 60-70% of their sample to be female, and female sex has been identified as both an independent risk factor (Jacobs et al., 2023) and interacting with age to increase risk (Vasilevskaya et al., 2023). Black and Hispanic respondents have been shown to have higher burdens of SARS-CoV-2 infection and illness severity (Mackey et al., 2021), long COVID symptoms and conditions (Jacobs et al., 2023; Khullar et al., 2023), and access to health services post-hospitalization (Cañas et al., 2024). This is reiterated in the need for higher inclusion of people of color in COVID-19 clinical research (Gilmore-Bykovskiy et al., 2021). Older age is an independent risk factor for both SARS-CoV-2 infection and severe illness, the latter conferring additional risk for long COVID (Tana et al., 2023). However, the evidence concerning functional status is relatively mixed for this age group. Studies on long COVID's effect on functioning in middle-aged adults is plentiful, but many use assessment of employment status (Jaywant et al., 2024), absenteeism, or sick leave (Nielsen et al., 2022), precluding inclusion of older adults. An analysis of the Household Pulse survey data counterintuitively found that prevalence of self-reported significant activity limitations was lower in older compared to middle-aged adults (Ford et al., 2023), which the authors postulate may be due to selection bias. In hospitalized older adults, lower baseline functional status increased the odds of post-discharge functional limitations (Izaguirre et al., 2023) and functional limitations were associated with lower health-related quality of life (Shanbehzadeh et al., 2023). Another analysis of the Household Pulse survey data through 2022 found that long COVID was twice as prevalent in respondents with pre-existing disabilities (40.6%) compared to those

without (18.9%) (Hall et al., 2024). The evidence suggests that these demographic factors may moderate long COVID risk.

Mechanisms

The pathophysiology of long COVID is another area of ongoing investigation and many remaining questions. Early evidence found that SARS-CoV-2 binds to and enters cells via ACE-2 receptors, which are extensively expressed in organ systems associated with long COVID symptoms, including cardiopulmonary, gastrointestinal, and central nervous systems (Crook et al., 2021; Hoffmann et al., 2020). Viral persistence, immune dysregulation, microbiome dysbiosis, and prothrombotic inflammation have been explored as putative mechanisms (Al-Aly et al., 2024).

A high-quality systematic review of the evidence on the mechanisms of long COVID (Diar Bakerly et al., 2024) summarized the available evidence of physical changes associated with long COVID overall, and with particular symptoms and symptom clusters. In the acute infection phase, SARS-CoV-2 is associated with immune dysregulation which may contribute to developing long COVID symptoms, particularly fatigue, positional orthostatic tachycardia syndrome (POTS), and cognitive dysfunction. Multiple studies have also found viral persistence outside of the respiratory system; this may lead to sustained T-cell activation and increased monocyte levels. There is well-established evidence that cytokine-mediated inflammation is observable and associated with micro and macro vascular insults, endothelial dysfunction, and clotting issues, which have implications for pain, fatigue, neurocognitive function, and cardiopulmonary symptoms. Neurocognitive symptoms have been associated with structural neuronal damage to axons and astrocytes caused by direct entry and binding of the SARS-CoV-2 pathogen in the brain, as well as microbleeds, cerebral hypometabolism and hypoperfusion, and

changes in cerebral blood flow associated with endothelial dysfunction. Links with autoimmune disorders are of interest but not yet fully established. There is relatively low quality or amount of evidence on the mechanisms of persistent lung dysfunctions (such as reduced forced expiratory volume, total lung capacity, and diffusing capacity) associated with respiratory symptoms, gene expression related to immune function, gut microbiome, and cardiac pathology in non-hospitalized patients. The authors also noted overall poor to moderate quality of studies, high risk of bias, and poor reporting of racial and ethnic diversity.

A related interest is the connections between symptom phenotypes (or groupings of observable patterns) (Newton et al., 2013) and pathophysiologic pathways. A study by Liew and colleagues (2024) profiled over 300 plasma proteins in $n=657$ previously hospitalized patients. They found elevated myeloid inflammation and complement activation markers in participants with long COVID and specific inflammatory marker profiles in people with (a) cardiorespiratory, fatigue, and mood symptoms, (b) gastrointestinal symptoms, and (c) cognitive impairment. Bergamaschi et al (2024) also focused on previously hospitalized patients in whom immune response markers suggested dysfunction for up to one year in symptomatic participants. Subjective cognitive changes and “brain fog”, which are particularly concerning for functional impairment (Vanichkachorn et al., 2021), were associated with hypoperfusion across frontal, parietal, and temporal cortices (particularly in the right cerebral hemisphere) (Ajčević et al., 2023), areas that are crucial in complex executive functions such as task switching, planning, prospective memory, and focus. Brain fog was also found to be associated with in-vitro tauopathic signatures at the time of infection in neuronal cells, which may increase the propensity for later neuropathology (Di Primio et al., 2023). Several non-systematic reviews

have proposed plausible links with additional cerebrovascular (Fekete et al., 2025), vascular (Shabani et al., 2023) and mitochondrial (Molnar et al., 2024) mechanisms.

Current Approaches to Generating Diagnostic Evidence

Because many long COVID symptoms and conditions overlap and co-occur in other disorders, a unique challenge and goal of long COVID research has been to determine what constitutes long COVID, and to classify which patients have long COVID and which do not. A diagnostic code - IDC-10-U09.9 for “Post COVID Condition, Unspecified” (CDC, 2021) - was not authorized until more than a year after the first published reports of patients with ongoing issues (Ladds et al., 2020; Mendelson et al., 2020; The Lancet, 2020). Prior to the uptake of this diagnostic code, people with long COVID were not labeled with an ICD code that could be discovered in the electronic health record (EHR) for either clinical care or research purposes. Without the substance of a measurable differential diagnostic criterion, this diagnostic code is a diagnosis of exclusion based on symptom presentation only.

Electronic health records have been a major source of data in large studies attempting to differentiate phenotypes of symptoms and clinical signs that present uniquely in long COVID. Several U.S. research initiatives have been launched to study recovery from COVID-19 in large samples, and most make some use of EHR data. The National Institutes of Health’s Researching COVID to Enhance Recovery (RECOVER) program and its analyses through the National COVID Cohort Collaborative (N3C) have used both retrospective analysis of EHR data and prospective data collection to characterize the disorder. Another group within the U.S. Veteran’s Administration used high through-put modeling to compare the outcomes, drug utilization, and other characteristics of patients with COVID-19 to those of patients with influenza (Al-Aly et al., 2021; Bowe et al., 2023). Investigators have developed innovative classification and grouping

approaches to discover patterns of symptoms; these include “big data” methods such as high-throughput modeling, hierarchical or k-means clustering, survival analysis, and other machine learning approaches (Brannock et al., 2022; Davis et al., 2021; Gentilotti et al., 2023; Mina et al., 2023; Prabhakaran et al., 2022; Reese et al., 2023; Zhang et al., 2023). Many have used the symptom patterns observed using these methods to describe a system of diagnostic operationalization and coding, attempting empirical discovery of the novel disorder’s various symptomatic presentations. While these studies have contributed important descriptions of long COVID, there is varying concurrence between their diagnostic phenotypes. Additionally, there is a lack of evidence on the relationships between long COVID symptom or condition development and these same symptoms’ prevalences prior to COVID-19 infection (Thaweethai et al., 2023).

Impact on Daily Functioning: State of the science and measurement considerations.

The WHO and the National Academies of Science, Engineering, and Math (NASEM) have included an impact on daily functioning (Soriano et al., 2022) or disability (NASEM, 2024) in their definition of long COVID, and call for research to operationalize and develop measurements for long COVID-related functional change and disability (NASEM, 2024). However, the incorporation of daily functioning into definition studies has been applied heterogeneously if at all. The above-mentioned phenotyping studies using EHR data have centered predominantly on symptom occurrences. This is a reasonable first step using widely available data, since symptoms can be assessed easily by patient report, and both symptoms and laboratory values are uniformly codified and documented in health records. Most EHR-based phenotyping studies have not included data on how disability manifests (in diagnostic codes) or is treated (in referral and procedure codes for rehabilitation therapies), so their resulting diagnostic classifications exclude this important diagnostic feature. (The exception, a study of

pediatric long COVID or multisystem inflammatory syndrome in children (Lorman et al., 2023), included EHR functional status observations among all other observations in their machine learning approach, but did not retain or analyze these observations). Thus, EHR is an untapped source of data representing functional status change. While the above-mentioned large-scale and rigorous studies have marshalled an extraordinary amount of data into useful generalizable phenotypes and diagnostic hallmarks (Thaweethai et al., 2023), data on functional status should be included for a complete definition and taxonomy of long COVID. If function is not considered in data-driven definition studies despite being critical to accurate identification and effective intervention, these definition studies will not fulfill the diagnostic criteria proposed by the WHO.

Because exclusive use of EHR data presents challenges of detection bias (Deer et al., 2021; Rando et al., 2021), smaller-scale studies have attempted to address functional status, with varied effectiveness. A common outcome has been vocational participation (e.g. Brehon et al., 2022), which limits eligibility as it does not capture change in people who did not work outside the home prior to infection (e.g. full-time students or family caregivers, retirees, and people on public assistance such as Medicaid). A 2024 umbrella review by Gutzeit and colleagues (2024) netted 95 studies mentioning functional impairment, a nearly 100% increase from the previous review of the topic 18 months prior (Lemhöfer et al., 2022). Despite this growth, this review found that methodological and theoretical limitations persisted in these works. Notably, fewer than half of the studies reported the instruments used to measure functioning. In the evidence published since, there have been relatively few studies assessing daily functioning using standardized measures appropriate for the range of adults with long COVID.

Several exploratory studies have proposed assessment instruments of daily functioning based on the WHO's International Classification of Functioning (ICF) (WHO, 2001) (Badinlou et al., 2023; Costa et al., 2024; Köseoğlu et al., 2023; Monteiro et al., 2023) or the ICF Checklist (Ursescu et al., 2024) (See below, "Guiding Theories and Frameworks" for a description of the ICF). Ursescu and colleagues (2024) conducted a well-designed study of the ClinFIT tool, a short scale based on the ICF components of *body structures*, *body functions*, and *daily activities*) in a small sample of 49 post-acute rehabilitation patients. The ClinFIT follows the ICF Checklist's scoring on an ordinal scale from 0 ("no problem") to 4 ("complete problem"). The authors reported score frequencies in both the sub-acute (4-12 week) and long COVID (>12 week) periods. The sample was recruited from a rehabilitation facility and was primarily comprised of formerly hospitalized participants with a high prevalence of respiratory symptoms. Thus, their ICF body structure/function component scores showed many respiratory and related components (e.g. activity intolerance) and relatively few non-respiratory long COVID symptoms. This sample did not include individuals with milder COVID-19 illness courses and did not characterize the tool's utility within more diverse symptom presentations (such as those with fatigue, brain fog, abdominal, or mood disturbances).

Following a procedure referred to as "linking", several teams tested participants with non-ICF instruments and then re-coded ("linked") the scores to fit into an ordinal scale of impairment in each ICF component (Costa et al., 2024; Köseoğlu et al., 2023). Costa and colleagues tested $n=52$ people with moderate to severe COVID-19 infection and no cognitive impairment, using existing validated assessment tools for cardiopulmonary functioning (various clinical metrics), fatigue (Fatigue Severity Scale), mood (Hospital Anxiety and Depression Scale), and quality of life (European Quality of Life Index). These instruments were chosen

based on the assumption that they either directly or indirectly assessed aspects of health that would impact daily functional status as represented in the ICF. Scores from these non-ICF instruments were then re-coded by two raters to a five-level ordinal scale (or 4 levels for conditions associate with anxiety) of ICF qualifier (0 = “no deficiency” through 4 = “complete disability” in matching or analogous ICF codes. “Functioning” was thus primarily framed in terms of body structures and functions, not performance of daily routines within the contexts and environments valued by participants. Upon linking, only the cardiopulmonary assessments’ response levels could be matched one-to-one to a 5-level structure; all others required levels to be dropped, collapsed, or reinterpreted. Inter-rater reliability of the links (not the initial instrument scores) was reported as non-weighted Cohen’s *kappa* statistics, falling between 0.57-0.87. The design and assumptions of this study contained risks to content and construct validity, assessments of which were not reported. The sample was biased toward people with severe illness but no cognitive impairments, so does not generalize to a significant proportion of long COVID symptomatic participants. The other linking study (Köseoğlu et al., 2023) administered the Modified Barthel Index and the Mini-Mental Status Examination. This study dichotomized the ICF’s ordinal scale from a 0-4 point to a binomial 0 (“no problem”) to 1 (“at least some problem”) without a description of their rating process. Additionally, the measures they chose may not have been able to capture more subtle functioning changes. The Barthel Index items have a four-level ordinal structure which has lower precision than the original ICF checklist, and the Mini-Mental Status Exam has been shown to have low sensitivity to subtle impairment in older adults (Arevalo-Rodriguez et al., 2021). These characteristics of the chosen assessment instruments may have resulted in low discrimination of subtle or relapsing-remitting deficits

common in long COVID. The authors reported only central tendency and spread of omnibus tests only, and did not test reliability or validity of this tool.

Badinlou (2023) provided more detailed connections between common long COVID outcomes and ICF body functions (mental, sensory, organ, and musculoskeletal functions) and daily activities. However this study was also limited by several design and methodological issues. Stepwise variable selection was used to choose the relevant items in their scale, an approach which is susceptible to inflating their model's discrimination indices and coefficient betas, inappropriately estimated p -values, and increased residual confounding, among other issues. These characteristics of stepwise variable selection raise the risk of type 1 error, resulting in a final scale that may be biased (see Harrell, 2001, pp. 67-69). They did not report assessments of this bias nor the psychometric properties of their final scoring tool.

Only one study explored the ICF Checklist (Monteiro et al., 2023) and associated the scores with long COVID symptoms. In a sample of 53 participants, many long COVID symptoms lacked a one-to-one match, or showed varying matches over time, in the ICF. For instance the symptom of "dysgeusia" associated with the ICF components of fatigue, pain, and irritability at 3 months and energy/drive, attention, memory, and emotional function at 6-12 months. This study's findings reveal the limitations of the ICF checklist's utility in long COVID.

Across these studies we note a tendency for investigators to focus on *body functions and structures* and a lower emphasis on *activity limitations* within the ICF taxonomy (e.g., Köseoğlu et al., 2023; Ursescu et al., 2024). This further entrenches the disease characterization in biophysical dimensions without the impact on functional performance as a metric or outcome. We also noted that the ICF and long COVID symptoms often did not match in these studies, however their low statistical power and dichotomization of ordinal responses results in some

difficulty comparing conclusions. Dichotomizing ordinal response scales into binary “can” or “cannot” levels (Köseoğlu et al., 2023; Monteiro et al., 2023) eliminated information about degrees of change that was available in the item’s original multi-level structure. Because daily functioning contains broad ranges of both performance and satisfaction, dichotomization may have resulted in lost definition in variance. Both losses are critical for test-retest reliability, accurate disease description, and therapeutic intervention planning. Additionally, these changes make it impossible to include results in future meta-analyses with larger aggregate samples, which would be necessary for robust conclusions as these samples were relatively small.

Given the exploratory nature and varied quality of many of these studies, we found support for the National Academies of Sciences, Engineering and Medicine’s assertion (2024) that rigorous examination of an operational definition of the functional impacts of long COVID, and subsequent development of a measurement instrument that offers research and clinical utility, is necessary to advance this evidence.

Measurement Considerations

Among the diagnostic criteria proposed for long COVID, the measurement of “impact on daily functioning” (National Academies of Sciences Engineering and Medicine, 2024; Soriano et al., 2022) is distinctive for several reasons. First, long COVID’s impact on daily functioning is not universally assessed with a uniform instrument among adults who have not had major disabling health events. Although sensitive, valid, and reliable screening tools exist, they are typically intended for rehabilitation settings and not included in typical primary care assessment batteries. Second, valid and reliable tools that are built to capture the range of functioning over time are critical, because long COVID symptoms frequently follow a relapsing/remitting pattern (Al-Aly et al., 2024; Davis et al., 2023). Third, daily functioning is distinctive among the

proposed diagnostic criteria in its non-biological nature. Many of the most common symptoms of long COVID could result in functional status declines if sufficiently severe. Although some long COVID symptoms appear to be more strongly associated with disability (e.g. cognition and fatigue (Vanichkachorn et al., 2021)), from a strictly biological lens it may be argued functional impairment is a “second-order” effect that would disappear if effective treatments were developed for the underlying causes of symptoms. However, this presumes that its relationship to the other diagnostic criteria is unidirectional and causal, which has not been established. Additionally, its inclusion is consistent with the WHO’s definition of health as not merely the absence of disease but rather as a physical, mental, and contextual *state* that allows one to participate in society (2001). In this framework, change in participation - in the ability to live their chosen and previously well-managed lives – may be the experience that drives people to seek care. This makes it one of the most important health outcomes from a patient’s perspective.

Decreased ability to complete daily routines and activities was reported early in the pandemic by patients and is emphasized in the proposed diagnostic criteria and research priorities of the WHO and NASEM. Emphasizing the diagnostic importance of daily functioning in long COVID is in line with the contemporary trend of measuring the *impacts* of symptoms, not just their presence, on health and disability. Failing to produce evidence to guide the assessment of daily functioning leaves current sufferers to wait for the necessarily slow and gradual pace of biological research to produce a biomedical cure, with no measurement or importance given to their current state in the meantime. Deficits in daily functional performance are treatable with Occupational Therapy interventions (AOTA, 2020) which has been recommended as part of multidisciplinary care for people with long COVID (Crook et al., 2021; Groff et al., 2021; Rolin et al., 2022; Venkatesan, 2021) especially those with cognitive deficits

(Watters et al., 2021). Therefore the inclusion of functioning in the definition of long COVID necessitates an approach to describing the disorder that is aligned with the WHO framework, and which has not been part of biomedical research for other diseases and disorders.

Guiding Theories, Frameworks, and Approaches

This work focuses on the operationalization of functional status using variables found within harmonized EHR data. It is informed by theoretical approaches from the study of daily functioning, lifespan development, population health, epidemiology, and medical informatics.

Daily Functioning

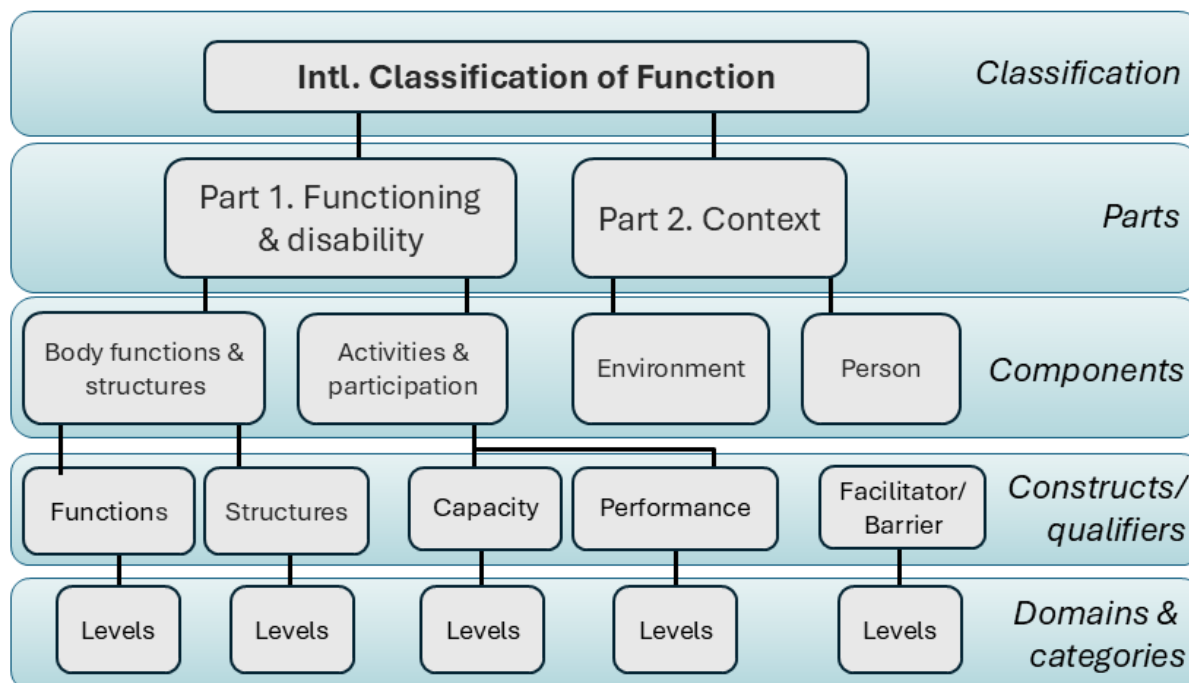
“Daily functioning” refers to the performance of routines and activities in daily life. Functioning is complex, multi-faceted, and multi-factorial. This work uses the term “functional status” to denote the degree of functioning on a spectrum from highly effective performance (high) to reliance on others for care (low). Evidence of functional status within the EHR can be found in several related EHR observations. The first is the billing codes entered by rehabilitation service providers for services rendered to improve or restore functional status in individuals who are experiencing health-related functional status decline. The second type is observation or diagnostic concepts that correspond to hierarchical vocabularies such as the WHO classifications. The latter may be triggered and recorded given the services provided by rehabilitation or other health care service providers. These are based on several related frameworks of functioning: the WHO International Classification of Functioning (ICF; WHO, 2001) and the Person-Environment-Occupation-Performance model (PEOP;).

The International Classification of Functioning (ICF)

The International Classification of Functioning, Disability, and Health (ICF) is the WHO's vocabulary for codifying health (Figure 1). It was developed alongside the International Classification of Disease (ICD) version 9 in recognition of a conceptual shift in defining health away from strictly symptoms and diseases. The WHO built the ICF around their 1948 definition of health as “*a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.*” (WHO, 2001, p. 6). In this framework, ability (or disability) results from an interaction between environmental affordances/barriers, participation in activities, body structures and functions, and person factors such as values and context. These elements are stratified into *Parts* (Functioning & Disability, and Context), *Components* (Body Functions & Structures, Activities & Participation, Environment, and Person), *Constructs/Qualifiers* (Body Functions, Body Structures, Activity Capacity, Activity Performance, and Contextual Facilitators/Barriers), and *Domains & Categories* which are the discrete domains and categories, each scored into *Levels* on an ordinal scale of function (Figure 1). The ICF “provides a scientific, operational basis for describing, understanding and studying health and health-related states, outcomes and determinants” by framing a structured relationship between functioning-related health observations, and symptoms and conditions found in electronic health records and codified by the International Classification of Diseases, version 10 (ICD-10). Participation in daily routines was thereby codified in the WHO's definition of health. Functioning and disability observations in the EHR may be coded within this framework as companions to the biomedically-derived classification of disease (ICD).

Figure 1

The International Classification of Functioning (ICF)



Adapted from: WHO, 2001, Box 7

The Person-Environment-Occupation-Performance Model: a Systems theory framework

In its development, the ICF incorporated a prior framework developed by Occupational Therapists called the Person-Environment-Occupation-Performance model (PEOP; Law et al., 1996). The PEOP broke down daily functioning into transacting components following a systems theory-based structure. In this model, functional performance is the output from a complex and dynamic process between the person (including values and perspectives, abilities, skills, and physical or mental condition), the task at hand (including characteristics, materials and demands), and the environment or climate of the work (temporal urgency or allowance, physical built or natural environment, social supports and cues). Occupational Therapy (OT) addresses disability through a systems perspective by using peoples' existing routines for both performance-based assessment and embedded intervention ("Occupational Therapy practice

framework: Domain and process (4th ed.).", 2020). This provides a unique plan of care for each person to optimize the fit between the person (abilities, needs, values), their environment (e.g. tools, built environment, social relationships and other resources) and the interconnected tasks and routines (or “occupations”) they need to do in order to thrive. The PEOP is distinct from the ICF in its simpler structure and its emphasis on performance of an occupation (rather than participation in society) as the outcome. It is used as an organizing structure for OT assessment, care planning, intervention, and outcome documentation.

The present work uses the ICF’s vocabulary to identify and organize the functional concepts available in harmonized EHR data. It uses the PEOP as a clinical lens through which to frame questions and select variables exploring the relationship between person-specific factors (e.g. symptoms and conditions, disease characteristics, and demographics), their contexts and tasks (e.g. functional status finding observation codes), and the assistance or independence with which they carry out their daily routines (in therapeutic procedure billing codes).

Aging and lifespan development

Because age impacts the risks for COVID-19 infection, long COVID symptom development, and functional impairment, this work explores the relationships of these outcomes cross-sectionally at different ages. We define “age” as the quantitative measure of accumulated years alive (measured as years of age), and “aging” as the changes occurring during this accumulation and the processes underlying these changes. Because years of age is commonly assessed and available in health research, this work uses the continuous value of years of age as a proxy for aging, then uses biological and lifespan development theories to guide interpretation of the findings’ implications for aging.

Biological theories of aging

Biological theories of aging aim to understand how and why living organisms age. Generally, these approaches assume that living organisms maintain a balance between cell regeneration and senescence (death) and that aging represents a loss of this balance, thereby contributing to decay and eventual expiration of the organism's viability. Mechanistic hypotheses have predominantly endorsed either *damage-* or *program-*driven processes underlying this imbalance. Damage theories hold that reactive oxidative species cause irreversible damage to proteins, which then disrupts protein homeostasis. Damage may contribute to decreased immune function, which has implications for susceptibility to infectious diseases such as COVID-19, the body's ability to recover from illness and cope with inflammation, and the development of protein-related neurologic tauopathies (da Costa et al., 2016). Program theories suggest that organisms age through a predictable sequence of decline as cells expend finite regenerative resources (da Costa et al., 2016; Nakamura et al., 2017) and has been the basis of studies showing that epigenetic factors (such as environment, social resources, diet, and physical activity) moderate genetic expression of traits that contribute to longevity and health (e.g., Akbarian et al., 2013). These epigenetic moderating relationships inform selection of variables measuring social determinants of health (see below) to include in the present work's models.

Lifespan Development and Lifespan Psychology

Whereas biological theories of aging focus on losses occurring within the body, the theory of lifespan psychology frames aging as an active engagement in regulation of loss, facilitated by the accumulation of experiences and skills gained over the lifespan (Baltes & Smith, 2004). An individual achieves adaptive development (and thus aging) through *selective optimization with compensation*, making aging an active experience in which the individual's

agency and skills interact with their circumstances. For instance, an older adult may select functional activities or routines to optimize the balance of routines, using resources afforded by their “culture” (societal context, e.g. health care services, social connectedness) to compensate for decreases or shifts in other activities. In EHR data or surveys, selective optimization with compensation may take the form of differences between older and younger individuals in health care utilization, patterns of diagnosed conditions or observations, or self-rated health and functional status. Lifespan psychology also outlines the influences of *normative* (typical or expected) and *non-normative* age or historical contexts upon lifespan development, providing a structure for considering the impact of the COVID-19 pandemic upon the health of different age groups and the aging process. In this theoretical structure, the COVID-19 pandemic may be described as both a *history-graded* influence (experienced by all people living within a given timespan) and a *non-normative* influence (events that “disrupt the sequence and rhythm of the expected life cycle and so generate conditions of uncertainty” (Baltes & Smith, 2004, pp. 126-129). This framework is used in this work to guide interpretation of age-related and period-related differences in observations of functional status and health before versus after COVID-19 infection.

Population health: Frameworks for health and statistical inference

The study of the novel and evolving phenomenon of long COVID can benefit from the statistical power and approximation of population variance offered by large datasets with diverse demographic, geographic, and health status representation. This work includes variables contained within the Social Determinants of Health framework, and utilizes regression modeling as a powerful tool for exploring multiple complex variables’ relationship with an outcome (Harrell, 2001) with data from the National Institutes of Health *All of Us* Research Program.

Social Determinants of Health

As suggested by the evidence above supporting both the biological and lifespan development theories of aging, the social and environmental contexts in which a person lives can have enormous impacts on their health. To illustrate the relationships between aging and these contexts, the U.S. Department of Health and Human Services (DHHS) have formalized a model called the “Social Determinants of Health”, or SDH (DHHS, 2025), which includes *economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context*. This framework is based on population health evidence that exposure to distinct and overlapping conditions moderates health across the lifespan. Longitudinal studies of aging such as the Midlife in the United States Study (MIDUS) provide data that has revealed the role of psychological, social, and biological factors on variations in health within and across age cohorts. These studies also demonstrate that many of the effects of SDOH on health are nested. For instance, neighborhood of residence (the built environment SDOH), has been found to partially predict chronic health outcomes (Durfey et al., 2019; Kind & Buckingham, 2018). The built environment is in turn shaped by public policy (the social and community context SDOH), which impacts health outcomes through such influences as the remaining effects of “redlining” city planning policies (Mujahid et al., 2021), accessibility of the built environment (Gell et al., 2015), and exposure to pollution (Paul et al., 2019). SDOH also account for protective and supporting forces, for instance education and sustained social engagement which have been found to moderate brain health in later life (Perry et al., 2021; Wilson & Bennett, 2017). Based on the evidence that SDOH have significant impacts on long COVID risk and outcomes, the present work uses this framework to organize and select

meaningful and available variables to build into multivariable risk models, which will allow more accurate effect estimation.

Causal and associative inference methods in population health

Many of the phenotyping studies of long COVID have adopted a causal inference framework. Observational designs, while not randomized, offer approaches that can facilitate causal inferences; these include establishing temporality between exposure and response, and identifying sufficient and necessary exposures through estimation of attributable risk and use of methods that help characterize bias and unmeasured confounding, matching or balancing samples, and prioritizing accuracy over parsimony when building predictive models (Austin, 2011; Harrell, 2001; Ho et al., 2007; WHO, 2007; Pattanayak et al., 2011; Stuart, 2010). This work uses some of these approaches to maximize rigor, but is framed from an exploratory, hypothesis-generating perspective as the evidence on characterizing functional status from EHR-derived data is not as well-established as that of symptom-driven phenotyping. We therefore begin this work with minimal prior evidence to incorporate or inform our approaches and hypotheses. The present work explores temporality and effect estimation between functional status observations, COVID-19 infection, and long COVID symptoms. We use multivariable associative and main effects modeling strategies to estimate confounding, effect modification and interactions, and effect sizes with a restricted set of variables known to influence long COVID functional outcomes (Harrell, 2001).

Phenotyping using health records data

“Phenotyping”, in general, is the analysis of patterns of observable traits in a living organism (Robinson, 2012). Often applied in genetics and genome-wide association studies

(GWAS) (Newton et al., 2013), phenotyping can be applied to explore patterns of any observable variable. Generally, the EHR-based phenotyping studies of long COVID have aimed to identify grouping of symptoms or biomarkers (laboratory test values) among people with post-COVID-19 health changes to differentiate long COVID as (a) a true clinical syndrome from non-presentation or other viruses such as influenza (Al-Aly et al., 2021) and (b) consisting of various and potentially distinct presentations (phenotypes). Data of interest include symptoms and conditions (Gentilotti et al., 2023; Gonzalez Aleman et al., 2024; Kitsios et al., 2024; Mina et al., 2023; Prabhakaran et al., 2022; Reese et al., 2023; Thaweethai et al., 2023; Zhang et al., 2023), laboratory measures of putatively important biomarkers (Deer et al., 2021; Erlandson et al., 2024), and health or medical outcomes and drug utilization (Al-Aly et al., 2021). Long COVID investigators often report the results of data-reduction techniques that group occurrences of symptoms or laboratory values using similarity metrics or distance. These include high-dimensional analysis, high-throughput linear modeling such as least absolute shrinkage (LASSO) (e.g., Thaweethai et al., 2023), cluster analyses (Davis et al., 2021), survival analysis (Davis et al., 2021), principal components analysis (e.g., Gentilotti et al., 2023), and latent class analyses (e.g., Kitsios et al., 2024). The phenotyping literature also provides guidance for navigating potential sources of bias and limitations inherent in electronic health records research (Newton et al., 2013). The present work reviews the long COVID phenotyping literature as a starting point for variable selection and methodological and interpretive guidance in seeking patterns of symptom and functional impairments, and employs correlation matrix-based unsupervised hierarchical clustering with clinical expertise validation as the primary phenotyping approach.

Objective

This work explores EHR-derived indicators of functional status as an outcome and risk factor for long COVID in people with a history of COVID-19 infection enrolled in the *All of Us* Research Program. This includes building a cohort using *All of Us* researcher tools, characterizing the sample's demographic and disease distributions, extracting and testing EHR- and survey-based indicators of functional status, and modeling main effects of demographic and disease factors on functional status. This work will describe long COVID in the *All of Us* study, and is an initial step in characterizing functional status from EHR data in a population-based sample by exploring and reporting reproducible quantitative approaches to functional status phenotyping in persons with a history of SARS-CoV-2 infection. Ultimately, this research will aid in diagnostic accuracy and treatment so that people with long COVID may return to meaningful activities and optimal health.

Chapter 2. Specific Aims

Aim 1

Compare the baseline demographics, daily function, and disease characteristics between participants with and without long COVID symptoms in a diverse population-based sample of people with COVID-19 enrolled in the All of Us Research Program.

This analysis describes the demographics and long COVID symptoms in the All of Us Research Program through July 2022 (curated data release version 7). This informs hypothesis-generation by identifying variables to be included in associative and predictive models to identify risk factors for long COVID symptoms and functional change.

Aim 2

Characterize risk factors and predictors of decreased functional status in people with versus without at least one symptom of long COVID in the All of Us Research Program.

Hypothesis 1: After adjusting for sociodemographic factors, disease factors, and symptoms, female sex and older age will predict different functional status. This is based on the evidence that age increases the likelihood of comorbidities that affect overall health status which may contribute to functional decline, and given the higher prevalence of long COVID symptoms in women and middle to older adults that has been reported consistently in other population-based samples.

Aim 3

Compare the risk factors and predictors of post-infection functional status changes in older adults versus younger adults with and without at least one symptom of long COVID in the All of Us Research Program.

Hypothesis 1: Older age will be associated with poorer functional outcomes, adjusted for demographics, infection variant, and pre-infection functional indicators and symptom prevalence.

Hypothesis 2: In people with at least one long COVID symptom/condition, functional status will be most strongly associated with symptom clusters entailing cognition and fatigue compared to other symptom clusters.

Chapter 3. Methods

Design and data source

This was a retrospective cohort study of participants enrolled in the U.S. National Institutes of Health *All of Us* Research Program through July 2022 (curated data release version 7.0)(National institutes of Health, 2022-2025; Ramirez et al., 2022). *All of Us* is a national biobank including functional status data and is one of the world's most comprehensive population health datasets (Zeng et al., 2024). *All of Us* recruits participants from all 50 U.S. States and three territories. The program utilizes community-relevant recruitment methods to over-recruit from geographic and demographic groups that are under-represented in medical and health research. Participants share their baseline function and health data through surveys, biospecimens, and the release of EHR data (the latter subsequently scraped every three months). These data are then harmonized under the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) (Observational Health Data Sciences and Informatics, 2024) using the hierarchical Athena standard medical vocabulary and coding of all conditions (Odysseus Data Services, 2023). This ensures consistency across data collection sites and regions, and comparability with billing and treatment codes. The program, data snapshots, and data methods can be viewed at <https://www.researchallofus.org/data-tools/>.

Sample

This work included *All of Us* participants 18 years of age and older with at least one incidence of any indicator of COVID-19 illness. Disease indicators were (a) laboratory values for positive PCR, antigen, or positive antibody test, (b) self-reported illness consistent with COVID-19 reported on the 2021-2022 *All of Us* COVID-19 Participant Experiences (COPE) survey, or

(c) the ICD-10 code for COVID-19 (U07.7) (See Table 1 or Appendix A). Informed consent for sharing electronic health records and survey data was obtained from all participants by their respective *All of Us* Health Provider Organizations, which are responsible for participant recruitment and enrollment. All Health Provider Organization partners delegated IRB oversight to the *All of Us* Central IRB.

Table 1

Identification of cohort: COVID-19 illness indicators

Name	Concept Id	Vocab	Code	Roll-up Count	Item Count
2019-ncov coronavirus, sars-cov-2/2019-ncov (covid-19), any technique, multiple types or subtypes (includes all targets), non-cdc	40218804	HCPCS	U0002	0	1,020
2019-nCoV Coronavirus, SARS-CoV-2/2019-nCoV (COVID-19), any technique, multiple types or subtypes (includes all targets), non-CDC, making use of high throughput technologies as described by CMS-2020-01-R	704058	HCPCS	U0004	0	1
Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique, making use of high throughput technologies as described by CMS-2020-01-R	704059	HCPCS	U0003	0	1,143
Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel	36660845	LOINC	LP418968-6	985	0
Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel - Respiratory specimen by NAA with probe detection	36661384	LOINC	95380-2	0	985
Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel Respiratory specimen Microbiology Panels	36661218	LOINC	LP419290-4	985	0

Influenza virus A and B and SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	36661376	LOINC	95422-2	0	330
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	756055	OMOP Extension	OMOP4 873969	0	384
Measurement of Severe acute respiratory syndrome coronavirus 2 antibody	37310258	SNOMED	1.24046 E+15	0	263
SARS-CoV-2 (COVID-19)	36662140	LOINC	LP4175 40-4	92,959	0
SARS-CoV-2 (COVID-19) Ab	36661733	LOINC	LP4179 14-1	9,362	0
SARS-CoV-2 (COVID-19) Ab [Interpretation] in Serum or Plasma	723480	LOINC	94661-6	0	3,037
SARS-CoV-2 (COVID-19) Ab [Presence] in Serum or Plasma by Immunoassay	586515	LOINC	94762-2	0	1,146
SARS-CoV-2 (COVID-19) Ab [Units/volume] in Serum or Plasma by Immunoassay	586522	LOINC	94769-7	0	309
SARS-CoV-2 (COVID-19) Ab Serum or Plasma Microbiology	36661221	LOINC	LP4186 84-9	4,130	0
SARS-CoV-2 (COVID-19) Ab panel	36661883	LOINC	LP4181 22-0	2	0
SARS-CoV-2 (COVID-19) Ab panel - Serum or Plasma by Immunoassay	706179	LOINC	94504-8	0	2
SARS-CoV-2 (COVID-19) Ab panel Serum or Plasma Microbiology Panels	36661105	LOINC	LP4192 86-2	2	0
SARS-CoV-2 (COVID-19) Ag	36661764	LOINC	LP4180 19-8	1,262	0
SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	723477	LOINC	94558-4	0	1,222
SARS-CoV-2 (COVID-19) Ag [Presence] in Upper respiratory specimen by Immunoassay	36032419	LOINC	96119-3	0	40
SARS-CoV-2 (COVID-19) Ag Respiratory specimen Microbiology	36660801	LOINC	LP4186 93-0	1,222	0
SARS-CoV-2 (COVID-19) Ag Upper respiratory specimen Microbiology	36033457	LOINC	LP4209 31-0	40	0
SARS-CoV-2 (COVID-19) clade	1620066	LOINC	LP4227 36-1	47	0
SARS-CoV-2 (COVID-19) clade [Type] in Specimen by Molecular genetics method	36033653	LOINC	96896-6	0	47

SARS-CoV-2 (COVID-19) clade XXX Microbiology	1618285	LOINC	LP4274 06-6	47	0
SARS-CoV-2 (COVID-19) IgA	36662109	LOINC	LP4184 30-7	167	0
SARS-CoV-2 (COVID-19) IgA Serum or Plasma Microbiology	36660931	LOINC	LP4186 85-6	167	0
SARS-CoV-2 (COVID-19) IgA Ab [Presence] in Serum or Plasma by Immunoassay	723473	LOINC	94562-6	0	167
SARS-CoV-2 (COVID-19) IgG	36661886	LOINC	LP4179 15-8	5,025	0
SARS-CoV-2 (COVID-19) IgG Serum or Plasma Microbiology	36661046	LOINC	LP4186 88-0	3,500	0
SARS-CoV-2 (COVID-19) IgG Serum, Plasma or Blood Microbiology	36660768	LOINC	LP4186 89-8	2,090	0
SARS-CoV-2 (COVID-19) IgG Ab [Presence] in Serum or Plasma by Immunoassay	723474	LOINC	94563-4	0	2,920
SARS-CoV-2 (COVID-19) IgG Ab [Presence] in Serum, Plasma or Blood by Rapid immunoassay	706181	LOINC	94507-1	0	2,090
SARS-CoV-2 (COVID-19) IgG Ab [Units/volume] in Serum or Plasma by Immunoassay	706177	LOINC	94505-5	0	749
SARS-CoV-2 (COVID-19) IgG+IgM	36661646	LOINC	LP4179 56-2	991	0
SARS-CoV-2 (COVID-19) IgG+IgM Serum or Plasma Microbiology	36660914	LOINC	LP4186 90-6	991	0
SARS-CoV-2 (COVID-19) IgG+IgM Ab [Presence] in Serum or Plasma by Immunoassay	723479	LOINC	94547-7	0	991
SARS-CoV-2 (COVID-19) IgM	36661975	LOINC	LP4179 16-6	396	0
SARS-CoV-2 (COVID-19) IgM Serum or Plasma Microbiology	36661274	LOINC	LP4186 91-4	299	0
SARS-CoV-2 (COVID-19) IgM Serum, Plasma or Blood Microbiology	36660777	LOINC	LP4186 92-2	97	0
SARS-CoV-2 (COVID-19) IgM Ab [Presence] in Serum or Plasma by Immunoassay	723475	LOINC	94564-2	0	275
SARS-CoV-2 (COVID-19) IgM Ab [Presence] in Serum, Plasma or Blood by Rapid immunoassay	706180	LOINC	94508-9	0	97

SARS-CoV-2 (COVID-19) IgM Ab [Units/volume] in Serum or Plasma by Immunoassay	706178	LOINC	94506-3	0	37
SARS-CoV-2 (COVID-19) lineage	1619966	LOINC	LP4227 39-5	17	0
SARS-CoV-2 (COVID-19) lineage [Identifier] in Specimen by Molecular genetics method	36033652	LOINC	96895-8	0	17
SARS-CoV-2 (COVID-19) lineage XXX Microbiology	1618914	LOINC	LP4274 05-8	17	0
SARS-CoV-2 (COVID-19) N gene	36661396	LOINC	LP4175 99-0	1,151	0
SARS-CoV-2 (COVID-19) N gene [Presence] in Nasopharynx by NAA with probe detection	715272	LOINC	94760-6	0	36
SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with probe detection	757678	LOINC	95409-9	0	9
SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection	706161	LOINC	94533-7	0	671
SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1	586524	LOINC	94756-4	0	468
SARS-CoV-2 (COVID-19) N gene Nasopharynx Microbiology	36660752	LOINC	LP4187 02-9	36	0
SARS-CoV-2 (COVID-19) N gene Nose Microbiology	36660970	LOINC	LP4191 79-9	9	0
SARS-CoV-2 (COVID-19) N gene Respiratory specimen Microbiology	36661286	LOINC	LP4187 03-7	1,107	0
SARS-CoV-2 (COVID-19) ORF1ab region	36661401	LOINC	LP4179 06-7	1,267	0
SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	723478	LOINC	94559-2	0	1,265
SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Specimen by NAA with probe detection	723464	LOINC	94639-2	0	2
SARS-CoV-2 (COVID-19) ORF1ab region Respiratory specimen Microbiology	36661250	LOINC	LP4187 06-0	1,265	0
SARS-CoV-2 (COVID-19) ORF1ab region XXX Microbiology	36661194	LOINC	LP4187 07-8	2	0
SARS-CoV-2 (COVID-19) RdRp gene	36661801	LOINC	LP4175 98-2	3,774	0

SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	706160	LOINC	94534-5	0	3,764
SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Specimen by NAA with probe detection	706173	LOINC	94314-2	0	18
SARS-CoV-2 (COVID-19) RdRp gene Respiratory specimen Microbiology	36660902	LOINC	LP4187 08-6	3,764	0
SARS-CoV-2 (COVID-19) RdRp gene XXX Microbiology	36660887	LOINC	LP4187 09-4	18	0
SARS-CoV-2 (COVID-19) RNA	36661507	LOINC	LP4175 41-2	89,445	0
SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	586528	LOINC	94745-7	0	1
SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	723476	LOINC	94565-9	0	2,005
SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection	586526	LOINC	94759-8	0	273
SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection	706163	LOINC	94500-6	0	63,160
SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by Sequencing	715261	LOINC	94822-4	0	107
SARS-CoV-2 (COVID-19) RNA [Presence] in Specimen by NAA with probe detection	706170	LOINC	94309-2	0	27,394
SARS-CoV-2 (COVID-19) RNA Nasopharynx Microbiology	36661317	LOINC	LP4186 94-8	2,274	0
SARS-CoV-2 (COVID-19) RNA Respiratory specimen Microbiology	36661115	LOINC	LP4186 95-5	63,160	0
SARS-CoV-2 (COVID-19) RNA Saliva Microbiology	36660966	LOINC	LP4186 96-3	107	0
SARS-CoV-2 (COVID-19) RNA XXX Microbiology	36661244	LOINC	LP4186 98-9	27,394	0
SARS-CoV-2 (COVID-19) RNA panel	36661522	LOINC	LP4175 39-6	5,080	0
SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	706158	LOINC	94531-1	0	1,342
SARS-CoV-2 (COVID-19) RNA panel - Specimen by NAA with probe detection	706169	LOINC	94306-8	0	3,740

SARS-CoV-2 (COVID-19) RNA panel Respiratory specimen Microbiology Panels	36661036	LOINC	LP4192 88-8	1,342	0
SARS-CoV-2 (COVID-19) RNA panel XXX Microbiology Panels	36660924	LOINC	LP4192 89-6	3,740	0
SARS-CoV-2 (COVID-19) S protein RBD neutralizing antibody [Presence] in Serum or Plasma by sVNT	36031734	LOINC	96603-6	0	476
SARS-CoV-2 (COVID-19) sequencing and identification panel	1620099	LOINC	LP4227 40-3	40	0
SARS-CoV-2 (COVID-19) sequencing and identification panel - Specimen by Molecular genetics method	36033651	LOINC	96894-1	0	40
SARS-CoV-2 (COVID-19) sequencing and identification panel XXX Microbiology Panels	1618441	LOINC	LP4275 24-6	40	0
SARS-CoV-2 (COVID-19) spike protein receptor binding domain (RBD)	36033856	LOINC	LP4212 35-5	476	0
SARS-CoV-2 (COVID-19) spike protein receptor binding domain (RBD) neutralizing antibody	36033858	LOINC	LP4212 34-8	476	0
SARS-CoV-2 (COVID-19) spike protein receptor binding domain (RBD) neutralizing antibody Serum or Plasma Microbiology	36033625	LOINC	LP4218 40-2	476	0
SARS-CoV+SARS-CoV-2 (COVID-19)	36661687	LOINC	LP4187 74-8	1,075	0
SARS-CoV+SARS-CoV-2 (COVID-19) Ag	36661520	LOINC	LP4187 62-3	1,075	0
SARS-CoV+SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	757685	LOINC	95209-3	0	1,075
SARS-CoV+SARS-CoV-2 (COVID-19) Ag Respiratory specimen Microbiology	1618075	LOINC	LP4276 54-1	1,075	0
COPE Survey (Any version): In the past month, have you been sick for more than one day with a new illness related to COVID-19 or flu-like symptoms?: Yes	1332898			9,138	
COVID-19	37311061	SNOMED	8405390 06	17,384	17,384
Lower respiratory infection caused by SARS-CoV-2	3663281	SNOMED	8.8053E +17	1,663	0

Symptom-based classification of long COVID symptomatic vs. recovered participants

Participants with COVID-19 history were grouped by whether their EHR showed at least one diagnosis or observation code contained in a list of long COVID symptoms and conditions (Table 2). Participants were classified as “symptomatic” if they had at least one entry in the EHR of any of these, entered at least 28 days after their first incidence of any COVID-19 infection indicator; the rest were classified as “recovered”, having no EHR entry of these sequelae codes following their first COVID-19 infection. Several empirical definitions of long COVID include exacerbations or relapses of pre-infection conditions (Al-Aly et al., 2024; Davis et al., 2021; Thaweethai et al., 2023). Therefore we queried *any* mention of the symptoms/conditions in our list, rather than *first* mention. This broad inclusion reflects the absence of a single symptom-driven indicator of long COVID’s differential diagnosis, and the reports that many patients’ long COVID experience includes exacerbated or increased symptoms of previously-diagnosed disorders. Appendix A reports the long COVID sequelae codes and selection process.

Table 2. Long COVID symptoms/conditions used in cohort discovery and classification

Standard Concepts	OMOP Concept ID	Source	Vocab	Code	String collapsed
Abdominal pain	200219	Standard	SNOMED	21522001	"abdominal"
Anxiety	441542	Standard	SNOMED	48694002	"anxiety", "anxi*"
Chest pain	77670	Standard	SNOMED	29857009	"chest", "cardiac"
Chronic fatigue syndrome	432738	Standard	SNOMED	52702003	"chronic fatigue", "myalgic encephalomyelitis"
Cognitive disorder (collapsed into "impaired cognition")	40480615	Standard	SNOMED	443265004	"cognitive", "neurocognitive"
Cognitive function finding (collapsed into "impaired cognition")	4162723	Standard	SNOMED	373930000	[not collapsed, heterogeneous]
Cough	254761	Standard	SNOMED	49727002	"cough", "clearing throat"

Depression screening positive	762504	Standard	SNOMED	4.28181E+14	"depression", "screening"
Depressive disorder	440383	Standard	SNOMED	35489007	"depressive", "depression"
Depressive episode	3656234	Standard	SNOMED	871840004	
Diarrhea	196523	Standard	SNOMED	62315008	"diarrhea", "diarrheal"
Disorder of menstruation	443431	Standard	SNOMED	386804004	"*men*
Disturbance in sleep behavior (collapsed into "Sleep")	4204989	Standard	SNOMED	53888004	"sleep"
Dizziness	4223938	Standard	SNOMED	404640003	"dizziness", "dizzy", "vertigo"
Dyspnea	312437	Standard	SNOMED	267036007	"dyspnea", "*pnea", "gasping"
Eruption	140214	Standard	SNOMED	271807003	"eruption", "acne*", "rash", "eruption", "erythroderma", "exanthematous", "Fox-Fordyce", "rocacea", "Keratin*", "pityriasis", "psoriasis", "psoriatic", "dermatitis"
Fatigue	4223659	Standard	SNOMED	84229001	"asthenia"
Fever	437663	Standard	SNOMED	386661006	"fever", "*pyrexia"
Finding of pattern of menstrual cycle (collapsed into "menstrual disorder")	4095940	Standard	SNOMED	248968007	"menstru*", "amenorrhea"
Finding of sexual function	4041277	Standard	SNOMED	118202007	
Headache	378253	Standard	SNOMED	25064002	"headache", "head"
Impaired cognition	443432	Standard	SNOMED	386806002	"cognitive", "impairment", "behavioral"
Irregular periods(collapsed into "menstrual disorder")	196168	Standard	SNOMED	80182007	
Joint pain	77074	Standard	SNOMED	57676002	"arthralgia", "joint"
Lightheadedness	4297376	Standard	SNOMED	386705008	[do not collapse] "malaise and fatigue", "fatigue"
Loss of sense of smell	4185711	Standard	SNOMED	44169009	
Loss of taste	4289517	Standard	SNOMED	36955009	

Malaise (under "Lightheadedness" heirarchy)	4272240	Standard	SNOMED	367391008	
Muscle fatigue	4214612	Standard	SNOMED	80449002	"muscle"
Muscle pain	442752	Standard	SNOMED	68962001	"myalgia*", "pain", "muscle", "pleurodynia", "fibrositis", "fibromyalgia", "polymyalgia", "claudication", "migraine"
Musculoskeletal chest pain	4092930	Standard	SNOMED	281245003	"pleurodynia", "myalgia", "pain", "Scapulargia", "Xiphodynia", "syndrome"
Palpitations	315078	Standard	SNOMED	80313002	"heart", "palpitations"
Paraesthesia	4236484	Standard	SNOMED	91019004	""*esthesia", "sensation", "pins",
Post-acute COVID-19	705076	Standard	OMOP Extension	OMOP5160861	U09.9
Postural orthostatic tachycardia syndrome (POTS)	4159659		SNOMED	371073003	(No hierarchy)
Postviral fatigue syndrome	4202045	Standard	SNOMED	51771007	
Sleep disorder (collapsed into "Sleep")	435524	Standard	SNOMED	39898005	"sleep*", "dream", "*somnia", "somnolence"
Tachycardia	444070	Standard	SNOMED	3424008	"tachycardia**"

An initial symptom list was compiled of post-COVID sequelae that were found across multiple phenotyping studies (e.g., Al-Aly et al., 2021; Zhang et al., 2023). These were collapsed into diagnostically-related groups according to the Observational Medical Outcomes Partnership – Common Data Model (OMOP-CDM) harmonized data vocabulary (Observational Health Data Sciences and Informatics, 2024; Odysseus Data Services, 2023). This list was then cross-checked with sequelae listed by the CDC (Centers for Disease Control and Prevention, 2023), reports from the patient-led research collaborative (Davis et al., 2021), and author and co-author

knowledge of patient experience encountered in a long COVID follow-up clinic and a community-based study of long COVID. The final list consisted of 44 symptom/sequelae ancestor categories. Using the *All of Us* Data Browser and Researcher Workbench, all EHR entries of each symptom concept code for our sample were queried singly to create a concept set incorporating all descendent codes contained within that symptom or condition code. This was performed iteratively for each of the 44 sequelae. These were then arranged and reduced to contain one incidence of the code per person; long COVID symptomatic group incidences were indexed to the earliest mention of the code recorded 28 days or longer after their COVID infection. Additionally, the pre-COVID incidence of all symptoms was obtained for all participants, being the first mention of the code documented from five years to 28 days prior to infection. These datasets were then joined one by one in alphabetical order to the main dataset. Appendix A details these processes.

The queried diagnostic categories in Table 2 contained 1,013 discrete descendent diagnostic concepts. Descendent concepts containing attributions to specific (non-COVID-19) diseases (e.g., “*cancer-related fatigue*”, “*memory impairment due to multiple sclerosis*”) were retained for several reasons. First and most broadly, there is probable variation in how post-COVID pathophysiology interacts with other diseases processes; therefore, the potential for these health outcomes to develop or worsen in the setting of other premorbid diagnoses could not be assumed to be independent of the physical toll of COVID recovery, and some outcomes may have been potentiated by this toll. Second, the increased precision of having all types of a given diagnostic category provided opportunities for future analysis that would not be possible had their diagnostic variations been removed or collapsed. Third and finally, incident counts of many outcomes attributed to diseases other than COVID-19 were often found to be small, necessitating

collapse into other categories for statistical analysis and *All of Us* reporting rules and exerting little or negligible pull on the presentation in a large dataset.

The post-infection interval of 28-days before first symptom occurrence was chosen to capture health and daily functioning beginning after the presumptive acute infection phase but still within 90 days post-infection. A 28-day window is sooner post-infection than the 90-day window used in other studies (e.g. Thaweethai et al., 2023) and the WHO proposed diagnostic criteria (Soriano et al., 2022). However, a shorter interval is of clinical interest for targeted rehabilitation services because it reveals the prevalence of functional status indicators and symptom burden within the 90-day timeframe that is allowable under the U.S. Family Medical Leave Act (1993). Because functional impairment is proposed as part of this diagnostic classification, we wished to characterize long COVID in a timeframe that would be clinically useful in the U.S. for utilizing skilled rehabilitation following acute infection as the indexing event. After importing every incidence of the condition codes, we removed concepts that were not applicable to long COVID (e.g. developmental disorders) or were redundant (covered under other concept hierarchies).

After importing every incidence of the condition codes we removed concepts that were redundant (covered under other concept hierarchies). For instance, under the “Cognition” and “Impaired Cognition” concept, “Normal Cognition” was removed to match the presumptive absence of impairment in other participants with no data value (N/A). Also removed were psychological concepts from the Diagnostic and Statistical Manual (American Psychiatric Association, 2013). DSM concepts for psychological functioning also appeared in the “Finding of functional performance and activity” concept. These were removed, retaining this variable’s

concepts that aligned with the ICF's components of function. Box 1 shows the concepts removed.

Box 1

Standard concept names of descendent conditions removed from cognition and functional findings ancestor condition categories

“Cognitive concepts removed”

Normal cognition
 Suicidal behavior
 Delusion of persecution
 Homicidal thoughts
 Worried
 Anxiety about body function or health
 Suicidal intent
 Delusions
 Thoughts of violence
 Deficient knowledge of preconception health practices
 Cognitive developmental delay
 Below average intellect
 Paranoid delusion
 Anxiety about treatment
 Thoughts of self harm
 Has access to planned means of suicide
 Repetitive routines
 Obsessional thoughts
 Planning suicide
 Dangerous and harmful thoughts
 Low intelligence
 Grinding teeth
 Human immunodeficiency virus infection with cognitive impairment
 Suicidal
 Suicidal thoughts
 Mood-congruent delusion
 Paranoid ideation
 Attention deficit hyperactivity disorder
 Attention deficit hyperactivity disorder, predominantly inattentive type
 Child attention deficit disorder
 Undifferentiated attention deficit disorder
 Attention deficit hyperactivity disorder, predominantly hyperactive impulsive type
 Attention deficit hyperactivity disorder, combined type
 Hyperkinetic conduct disorder
 Developmental coordination disorder

“Finding of functional performance and activity” concepts removed

Attention deficit hyperactivity disorder
 Attention deficit hyperactivity disorder, predominantly inattentive type
 Child attention deficit disorder
 Undifferentiated attention deficit disorder
 Attention deficit hyperactivity disorder, predominantly hyperactive impulsive type
 Attention deficit hyperactivity disorder, combined type
 Hyperkinetic conduct disorder
 Developmental coordination disorder
 Developmental disorder of motor function
 Developmental delay in fine motor function
 Hyperkinesis with developmental delay
 Ineffective breathing pattern
 Adjustment to life threatening illness
 Difficulty coping
 Lack of exercise
 Gets no exercise

Variables

Infection variants active at time of first infection

A time-bound variable was created to infer variant exposure at date of first SARS-CoV-2 infection. Periods began and ended around the emergence of major variants as reported by Markov et al.(2023) Our variant periods were “pre-VOC/wild type” from January-November 2020, “pre-VOC/alpha/beta from November 2020 – April 2021, “alpha/beta/delta” from April-August 2021, “delta” from August-December 2021, “omicron_BA1-BA2” from December 2021 – April 2022, and “omicron_BA2-BA5” from April 2022 – July 2022 (data release cut-off date).

Demographics

Age, sex assigned at birth, race, and ethnicity were included. Education level was included as a proxy for the impact of social determinants of health due to its impact on access to health-supporting societal resources (U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion, 2025), as financial concerns (Case et al., 2022) and greater unmet social needs (Eligulashvili et al., 2024) have been found to be associated with more numerous and persistent long COVID symptoms.

Number of long COVID symptoms/conditions present before and after infection

For each participant, a gross measure of pre-infection symptom burden was computed by tallying all long COVID symptom categories with at least one incidence in the EHR between 28 days and five years *prior to* first COVID infection. This included all symptoms (e.g. headache, joint pain, cough) and conditions (ME/CFS, POTS, and post-viral fatigue syndromes) used in cohort discovery. For long COVID symptomatic participants only, an additional tally was computed for the post-infection period.

Functional status indicators

This included self-reported daily functioning at enrollment (Aim1), and EHR-derived procedure and diagnostic codes between January 1, 2015 to four weeks prior to first infection (all aims) as follows:

Self-reported daily functioning and health (aim 1 only):

Long COVID has been shown to affect complex and “chosen” activity patterns, such as productivity and leisure, more dramatically than basic self-care (Carter et al., 2022; Nielsen et al., 2022). We explored these in Aim 1 through participant responses on the “Overall Health” survey taken at enrollment to assess self-reported performance of physically demanding daily activities, social roles, and mental/cognitive impact on performance.

Occupational therapy billing and procedure codes:

For each participant, a tally was computed of the number incidences of medical billing codes for therapeutic procedures provided by occupational therapists and occupational therapy evaluation codes reflecting level of complexity of the evaluation. Occupational therapy is the therapeutic discipline designated by the Centers for Medicare and Medicaid Services (CMS) to address deficits in daily performance, making it the most specific discipline for addressing functional performance impairments (CMS, 2020). CMS maintains codes and definitions for clinicians to record the medical necessity of services and procedures in the medical record. The codes that record evaluation by an occupational therapist are cataloged under the CPT code directory. These codes only occur in the medical record of a patient with concerns for “performance deficits (i.e., relating to physical, cognitive, or psychosocial skills) *that result in activity limitations and/or participation restrictions*” (CMS, 2020, emphasis added). This

indicator of functional status is therefore highly specific – it is not documented for a person who does not report concern for and/or present with functional performance deficits. Three codes are available to document the complexity of the clinician’s evaluation to determine performance deficits and the therapeutic plan of care. These reflect the level of complexity of functional change from baseline, and are “Low” (97165), “Medium (97166), and “High” (97167). One additional code to document the need for re-evaluation (97168) frequently used when the patient has a decrease in status (due to, e.g., surgical procedure, poor prognosis, and/or complication of medical conditions). CMS language delineating these code definitions can be found in Appendix B.

“Finding of functional performance and activity” codes

The procedure codes under the vocabulary hierarchy “Finding of Functional Performance and Activity” were used (Appendix B). These codes include observations documented by rehabilitation and respiratory therapy providers. For modelling, we collapsed these into a multinomial variable with three categories roughly corresponding to ranges of functional impairment that may be inferred from these codes. The three levels of presumed severity were 0 = “No functional performance difficulty”, 1 = “Some functional performance difficulty”, and 2 = “Severe functional performance difficulty” or “Dependent on others for care”). We noted that this hierarchy includes ‘function’ concepts corresponding to current and former classification schemes from the Diagnostic and Statistical Manual of Psychological Disorders (American Psychiatric Association, 2013), which were removed based on their correspondence to a different functional framework, redundancy with the mood and cognitive functioning symptom variables, or inappropriateness as a predictor for the current question.

Code for grouping and filtering these observations is reported in Appendix B.

Quantitative bias analysis of cohort discovery

Non-parametric propensity score matching with the “Matchit” R package was used to explore between-group balance of factors which could affect the development of long COVID (Stuart, 2010). Results from these analyses were used to report bias in the sample, and for interpretation of findings and directions for future work. Matching was not done as this was superfluous to the descriptive aims of these studies. Results are reported in Appendix C.

Analysis

Cohort discovery, cleaning, data wrangling, and statistical analyses were completed in Jupyter cloud computing notebooks, using R versions 4.4.1-2. Regression model fitting followed established processes (Andersen & Skovgaard, 2010; Harrell, 2001) for binomial logistic regression (Aim 1), and ordinal probit logistic regression (Aims 2 and 3). This process began with a complex model including all candidate variables with prior evidence of effect on risk for long COVID or functional status change, continuous variables fitted with natural (restricted) cubic splines, and interaction terms for each aim’s predictors of interest. This was followed with an iterative, non-automated process comparing the starting model to subsequent models with simplified fits of predictors considered important as potential main effects or confounders. The Bayesian Information Criterion (BIC) delta was the main decision guide, with consideration also given to likelihood ratio tests for non-nested models. Model fit was checked by plotting residuals on continuous variables, checking predictor collinearity, and checking assumptions of ordinality for Aims 2 and 3 models. For poorly fitting models, adjustments were made based on the model fit checks, then this process was repeated (as noted in the individual paper supplementals). Modelling and hypothesis testing were completed using the rms package (Harrell, 2024). The covariates and their sources for each aim are tabulated in Appendix D.

R packages “stats” (R Core Team and contributors worldwide, 2025), “rms” (Harrell, 2024), “corrplot” (Wei, 2021), and the “tidyverse” suite (Hadley Wickham, 2019) were used. Data analysis was performed in the *All of Us* Researcher Workbench, Jupyter notebooks cloud computing environment, using R programming language (R Core Team, 2022).

Chapter 4. Manuscript 1

Associations of Demographics, Pre-infection Functional Status, and Pre-infection Symptom Burden With Developing Long COVID: A Retrospective Cohort Study From the *All of Us* Research Program.

ABSTRACT

Over seven million U.S. adults experienced “long COVID”, or persistent health issues after COVID-19. Multiple guidelines suggest including functional status in long COVID diagnostic criteria. Few population studies have explored associations between pre-infection functional status and long COVID.

DESIGN & METHODS. Retrospective cohort study of associations between pre-infection functional status, pre-infection occurrences of long COVID symptoms, and demographics, with ≥ 1 long COVID symptom post-infection. Health records and survey responses of participants with history of COVID-19 enrolled the *All of Us* Research Program through July 2022 were analyzed.

RESULTS. $N = 66,971$ participants were included. 25,332 had no record of post-COVID symptoms (recovered group) and 41,639 had at least one symptom (long COVID group). The long COVID group was older (median 63 vs. 60), more frequently female (65% versus 61%) or Black (22% versus 19%), and had higher pre-infection prevalence of common long COVID symptoms (median 6 vs. 1). The adjusted odds of developing long COVID symptoms increased with years of age, female sex, lower functional status and lower self-reported mental health, and having had more symptoms prior to first COVID-19 infection (within 99% confidence limits).

CONCLUSIONS AND IMPLICATIONS. Greater pre-illness symptom and functional burden, female sex, and older age increased risk of long COVID. There were different associations with health record-derived versus self-reported functional indicators. Thorough assessment of pre-infection functioning and symptoms may enhance care for people with long COVID.

Among U.S. adults with a history of SARS-CoV-2 infection, 7.7 to 23 million experience persistent post-acute symptoms¹ termed “long COVID”.² About 7.5% of U.S. adults reported long COVID symptoms in June 2024, and about 5.5% reported activity limitations as a result.³ Long COVID is a patient-generated term for new-onset or exacerbated, and persistent, symptoms and health conditions after COVID-19 infection.^{2,4-8} Common presentations include fatigue, post-exertional malaise, cognitive impairment, headache, breathing difficulty, musculoskeletal pain or weakness, sleep disturbance, and mood disorder⁹ among many others.¹⁰⁻¹² Long COVID symptoms affect complex and “chosen” activity patterns (such as productivity and leisure) more dramatically than basic self-care.^{13,14} Thus, the disability from long COVID forces some people to abandon complex routines and roles in work, family, and community life.^{6,15}

Clinical diagnostic definitions and criteria of long COVID are an urgent and ongoing focus of study.² Multiple research initiatives have been launched to study recovery from COVID-19 in large samples with the goal of identifying phenotypes (or groups) of symptoms and biomarkers,^{10,16-21} many using electronic health records (EHR). These rigorous studies have marshalled an extraordinary amount of data into various phenotypes and diagnostic hallmarks,²² providing vital direction on the disease and its impact. However, few have included quantifiable indicators of daily functioning,²³ despite early patient reports describing profound impact on daily life^{6,24} and several proposed criteria asserting that an impact on daily functioning is a critical diagnostic component.^{2,25} The World Health Organization’s (WHO) working list of core criteria to define long COVID stipulated that the impact on activity participation should be included in diagnosis.²⁵ The National Academies of Sciences, Engineering and Medicine have recently reiterated that functional impairment could be a key element in disease definition, and called for research into its operationalization and measurement.² Because most EHR-based

phenotyping studies do not include data on how disability manifests or is treated, their resulting diagnostic classifications exclude this diagnostic feature.

Additionally, although post-infection presentations have been thoroughly investigated, studies of pre-infection occurrence of these same symptoms, conditions, and functional impairments are limited.^{16,26} Most studies that explore the emergence of symptoms and conditions after COVID-19 have not compared this to their pre-infection prevalence.²² Additionally, pre-infection disability due to chronic health issues has been found to be associated with an over two-fold increase in long COVID.²⁷ Because long COVID includes worsened or exacerbated conditions that were previously well-managed, pre-infection symptoms and functional status may be relevant to both estimating risk of developing long COVID and tailoring management strategies.²²

The primary aim of this study is to compare demographic characteristics, pre-infection functional status, and pre-infection occurrences of some of the most common long COVID symptoms between participants with and without long COVID in a diverse population-based sample of people with COVID-19 enrolled in the All of Us Research Program through July 1, 2022. Our secondary aim is to estimate the adjusted odds of developing at least one long COVID condition based on (a) demographics, (b) pre-infection daily functioning, and (c) the number of long COVID symptoms/conditions occurring prior to infection.

METHODS

Design and data source

This is a retrospective cohort study of participants enrolled in the U.S. National Institutes of Health *All of Us* Research Program through July 2022 (curated data repository version 7.0), Controlled tier C2022Q4R9,²⁸ accessed through the *All of Us* Researcher Workbench.²⁹ *All of Us*

is among the most comprehensive population-level biobanks in the world.³⁰ Participants come from all 50 U.S. States and three territories, and are over-recruited from groups that are historically underrepresented in medical research. They share their baseline function and health data through surveys, biospecimens, and release of EHR data which is subsequently scraped every three months. The program and data snapshots can be viewed at <https://www.researchallofus.org/data-tools/>.

Sample

All of Us participants 18 years of age and older with at least one incidence of any indicator of COVID-19 illness were included. Diagnostic indicators were (a) laboratory values for positive PCR, antigen, or positive antibody test, (b) self-reported illness consistent with COVID-19 reported on the 2021-2022 *All of Us* COVID-19 Participant Experiences (COPE) survey, or (c) the ICD-10 code for COVID-19 (U07.7). Informed consent for sharing EHR and survey data was obtained from all participants. *All of Us* Health Provider Organizations responsible for participant recruitment and enrollment delegated IRB oversight to the *All of Us* Central IRB.

Long COVID and Recovered participant groups

Participants with COVID-19 history were grouped by whether their EHR showed at least one diagnosis or observation code from a list of 38 long COVID symptoms and conditions. Participants were classified in the “long COVID” group if they had at least one entry of any of these entered at least 28 days after their first COVID-19 infection; the rest were classified in the “recovered” group, having no EHR entry of these sequelae codes following their first COVID-19 infection. Proposed empirical definitions of long COVID include exacerbations or relapses of pre-infection conditions.^{5,11,22} Therefore “any mention” of the symptoms/conditions in this list

was included, rather than “first mention”. For the present analysis, the first entry of each code was the indexing incidence. Symptom persistence could not be determined from the *All of Us* data structure. Appendix A reports the long COVID sequelae codes and selection process.

Data sources and variables

Surveys: Demographics, self-reported health, and self-reported function at study enrollment.

All of Us participants provide self-report of their health and daily functional status data through validated self-report measures from the PROMIS battery and *All of Us*-designed surveys at enrollment. This study used responses to “The Basics” (demographics), “Overall Health” (daily functioning and mental health) and “Covid-19 Participant Experience” (COPE) (self-reported COVID-19 symptoms between May 2020 – March 2021) surveys.

Long COVID symptoms and conditions.

Indicators of possible long COVID were chosen a-priori based on the Centers for Disease Control and Prevention’s list of symptoms³¹ and emergency billing code for Post-COVID conditions,³² prior phenotyping and patient-led literature, and the authors’ clinical and community research experience. These sources yielded a broad list of 44 conditions or condition categories (“descendent” codes), which fell under 38 condition categories (“ancestor” codes) within the *All of Us* data table structure. These 38 broad ancestor diagnoses were queried for all participants. For each diagnostic category, we retained the first incidence in the five years prior to infection (pre-infection occurrence) and the first incidence 28 days or more after the infection (post-infection occurrence). (The latter designated a participant as “long COVID” or “Recovered”.) Selection process and rationale, condition categories, and exclusions are reported in Appendix A.

Total number of long COVID symptoms/conditions present prior to infection

For each participant, a gross measure of pre-infection symptom burden was computed by tallying all long COVID symptom categories with at least one incidence in the EHR between 28 days and five years *prior to* first COVID infection. This included all symptoms (e.g. headache, joint pain, cough) and conditions (ME/CFS, POTS, and post-viral fatigue syndromes) used in cohort discovery.

Infection variants active at time of first infection

We created a time-bound variable to infer variant exposure at date of first SARS-CoV-2 infection. Periods began and ended around the emergence of major variants as reported by Markov et al.³³ Our variant periods were “pre-VOC/wild type” from January-November 2020, “pre-VOC/alpha/beta from November 2020 – April 2021, “alpha/beta/delta” from April-August 2021, “delta” from August-December 2021, “omicron_BA1-BA2” from December 2021 – April 2022, and “omicron_BA2-BA5” from April 2022 – July 2022 (data release cut-off date).

Demographics

Age, sex assigned at birth, race, and ethnicity were included. In addition we included education level as a proxy for the impact of social determinants of health due to its impact on access to health-supporting societal resources³⁴, as financial concerns³⁵ and greater unmet social needs³⁶ have been found to be associated with more numerous and persistent long COVID symptoms.

Pre-COVID daily functioning

Pre-infection functional status was indicated with self-reported daily functioning in two ways: enrollment surveys and functional status findings recorded in EHR procedure and diagnostic codes between January 1, 2015 to four weeks prior to first infection. Survey responses were queried for self-reported performance of physically demanding daily activities, social roles,

and mental/cognitive impact on performance. From the EHR, the incidences of medical billing codes for therapeutic procedures provided by occupational therapists were tallied (Occupational therapy is the therapeutic discipline designated by CMS to address deficits in daily performance, making it a highly specific discipline for indicating functional impairment.)³⁷ Additionally, procedure codes under the vocabulary hierarchy “Finding of Functional Performance and Activity”, entered before the first COVID infection, were grouped into three levels of presumable severity (“No functional performance difficulty”, “Some functional performance difficulty”, and “Dependent on others for care”). (Appendix B.)

Quantitative bias analysis of cohort discovery

Potential cohort bias was examined using non-parametric propensity score matching. Bias was estimated for (a) participant enrollment before first COVID infection (retained for this analysis) versus after (excluded) (see Appendix C).

Analysis

Demographic variables were graphed to visually assess distribution, and tested for significance using Welch’s *t* test (normal), Mann-Whitney U test (non-normal), or χ^2 test (categorical). Unadjusted odds ratios were computed for pre-COVID baseline survey responses on acquired demographics, social and financial variables, and daily functioning. Binomial logistic regression with a logit link function was used to model the odds of developing at least one long COVID symptom, based on demographics, COVID variant, and pre-infection presence of long COVID symptoms/conditions and daily functioning. Linearity, interaction terms, and residual fit were assessed according to established procedures³⁸. All odds were computed in relation to the mean or median for continuous covariates, or the category with the largest representation for categorical covariates. The model specification process and final fit statistics

are described in Appendix D. Data access and analysis was performed in the *All of Us* Researcher Workbench, Jupyter notebooks cloud computing environment, using R programming language.³⁹ Cohort discovery, data cleaning and organization, and statistical analyses were completed by the first and second author in Jupyter cloud computing notebooks, using R packages “stats”,⁴⁰ “rms”,⁴¹ “corrplot”,⁴² and the “tidyverse” suite.⁴³

RESULTS

104,992 participants met inclusion criteria of at least one COVID-19 illness. 21,201 participants with missing demographic survey responses were removed, and an additional five participants who had erroneous diagnostic codes in their EHR (concept name and code was for SARS-CoV-2, but the dates of diagnosis corresponded with previous SARS-type virus outbreaks in the early 2000’s). For the present analysis, participants who enrolled after their first COVID-19 indicator were also removed; this allowed use of enrollment questionnaires as pre-infection self-reported baseline functioning and health data. The final sample was $N = 66,971$ participants, with 41,639 showing at least one symptom (long COVID group) and 25,332 showing no EHR record of post-COVID symptoms (recovered group).

Quantitative bias analysis of cohort discovery

Pre- versus post-infection enrollment exhibited 45% overlap; this relatively low match suggests that these two groups may be different across one or more important population parameters, potentially due to programmatic influences on recruitment (discussed in Appendix C).

Demographics

Demographic distributions are shown in Table 1. The majority of this sample had their first infection during the pre-variant/wild type period, during which the proportion of long COVID participants outnumbered that of recovered participants by almost 2 to 1. long COVID

participants were about 3 years older (median 63 (24) versus 60 (28)), and had slightly higher percentages of female sex, female gender, and Black or African American participants than recovered participants. Groups were effectively equivalent in Hispanic/Latino ethnicity.

[Insert Table 1 about here]

Pre-infection daily functioning

EHR-recorded billing code indicators of daily functioning are displayed in Figure 1. The long COVID group had a higher proportion of difficulty with daily functioning (10% vs. 4%) and dependence on others for care (6% vs. 2%) than the recovered group (Table 1). Figure 1 illustrates the functional observations.

[Insert Figure 1 about here]

Pre-infection prevalence of long COVID symptoms and conditions

The range of pre-infection symptoms with any occurrence was 0-23. The long COVID group had a higher median number of pre-infection symptoms of long COVID (6(6) vs. 1(4), Table 1, Figure 2). The distributions and proportions of the number of participants with any observations under these broad categories prior to infection are shown in Table 2 and Figure 3. There were no pre-infection observations of POTS, PVFS, ageusia, and anosmia.

[Insert Figure 2 about here]

[Insert Table 2 about here]

[Insert Figure 3 about here]

Correlations were computed to test the symptom categories for collinearity (Appendix E). There were no correlations above 0.53. Moderate to low correlations were found between

depression and anxiety ($r^* = 0.53$), abdominal pain with both diarrhea ($r^* = 0.32$) and chest pain ($r^* = 0.32$), dyspnea with both chest pain ($r^* = 0.4$) and cough ($r^* = .33$), ME/CFS and fatigue ($r^* = 0.34$), musculoskeletal and generic chest pain ($r^* = 0.33$), and sleep and depression (0.31). Correlations between long COVID symptoms were computed and grouped using first principal component analysis (Figure 4). The strongest groupings were (a) joint pain, sleep, functional performance difficulty, cognition, anxiety, and depression; (b) abdominal pain, diarrhea, fever, tachycardia, cough, chest pain, dyspnea, palpitations, dizziness and headache. Fatigue was observed to have a moderate correlation across both groups. Menstrual dysfunction and sexual dysfunction had the lowest correlations with the rest of the variables. ME/CFS was moderately correlated with fatigue only.

[Insert Figure 4 about here]

Adjusted odds of developing long COVID ≥ 1 symptom or condition

Adjusted odds are reported in Table 3. See Appendix D for model fitting process.

[Insert Table 3 about here]

Age, race, ethnicity, and sex assigned at birth

Odds of long COVID increased with years of age. Compared to the mean of 62 years, younger participants had about 0.72 (0.67-0.77) odds at age 25 and 0.94 (0.93-0.95) odds at age 55. By contrast, older participants' odds were 1.12 (1.09-1.15) at age 75, and 1.23 (1.18-1.28) at age 85. Slightly lower odds were seen for male sex (0.95, 0.89-0.99 $P=0.008$) and Hispanic or Latino ethnicity (0.85, 0.72-0.99, $P=0.008$). Race was not significant in this model (all confidence intervals crossed 1.0).

Pre-infection functional and health status

Odds were higher for people who rated their mental health and cognitive functioning as “Good” (1.19, 1.09-1.31) or “Poor” (1.23, 1.00-1.50) compared to “Excellent”. Odds were also higher for those who had severe functional impairments per EHR codes (1.51, 1.28-1.79), but were not significant for less severe impairment. Self-rated ability to perform physical daily activities, social role performance and satisfaction, and the total occupational therapy billing units in the 5 years prior to infection, were also non-significant.

Pre-infection occurrence of long COVID symptoms/conditions

Odds and log likelihood increased significantly and dramatically with increasing number of pre-infection symptoms. We contrasted the odds for the median (four) with the minimum, maximum, and quartiles. Lower odds were seen for people with zero symptoms (0.08, 0.07-0.08) and one symptom (0.19, 0.18-0.20). The odds increased substantially at the third quartile of seven symptoms (1.73, 1.65-1.80) and dramatically at the maximum of 23 symptoms (34.62, 24.94-48.09).

DISCUSSION

This retrospective cohort study is the first examination of long COVID among participants in the *All of Us* Research Program. To our knowledge, it is also the first population-level study to explore the prevalence of pre-infection occurrences of long COVID symptoms and functional status levels, and their associations with developing post-COVID symptoms.

We found that some pre-existing functional impairment indicators were associated with increased risk of developing long COVID symptoms. Interestingly, we noted different strength and directions of associations from the self-reported versus EHR-derived functional status indicators. Lower pre-infection self-rated mental health/cognition was associated with

developing long COVID, while ability to perform physical daily activities was not. This was somewhat surprising since most of the concepts contained in the “Finding of Functional Status and Activity” code hierarchy describe physical (e.g. motor and mobility) performance and relatively few cognitive or behavioral observations. This discrepancy could be due to different latent constructs being measured, or under-detection of slight or moderate functional decreases in EHR data.⁴⁴ Because self-reported functional impairments in long COVID are sometimes dismissed⁶ or not measured with instruments validated with this population,^{45,46} exploring change from pre- to post-infection using instruments with face validity to the patient experience may provide more accurate insights. The findings of the present study provide evidence that poor cognition/mental health and some daily functioning limitations may interact with one another to increase risk for long COVID.

This exploration of the pre-infection incidences of symptoms and conditions common in long COVID revealed several significant insights. First, the distribution of these conditions relative to one another are remarkably similar between long COVID participants and asymptomatic participants; with a few exceptions of very slight magnitude, the conditions that were more prevalent in participants who later developed long COVID symptoms were also more prevalent in participants who later recovered, and vice-versa. However, there was a striking difference in the *proportion* of each group experiencing each symptom, often twice as high or more in those who later developed at least one long COVID symptom/condition. Second, we noted several conditions with high pre-infection prevalence: joint pain was the most frequently observed (62% of long COVID participants and 30% of recovered participants), followed by chest and abdominal pain, sleep disturbance, mood disorders, cough, and dyspnea. By contrast, several of the cardinal long COVID symptoms displayed lower pre-infection prevalences in both

groups, and greater differences between the long COVID and recovered groups; these included fatigue (34% of long COVID participants and 13% of asymptomatic participants), cognition (12% and 4%), and ME/CFS (5% and 2%). This supports the proposed criterion that exacerbations of pre-infection conditions, in addition to those newly developed, must be understood in order to define and treat long COVID. Further, this may suggest that some health conditions feature mechanistic links that potentiate later development of long COVID conditions, such as autoimmune or cardiac systemic reactions to SARS-CoV-2 infection.⁵ Elucidating pre-infection condition incidence may provide direction for the growing body of mechanistic research.

These results are consistent with literature suggesting that long COVID can include exacerbations, decompensations, and increased impact of prior health conditions.^{5,12,22} In the current study, many (but not all) participants who developed long COVID experienced pre-infection health issues found in long COVID phenotypes, with symptomatic participants having a wide range of medical histories and pre-infection burden. Although risk of post-infection symptoms increased dramatically with the number of pre-infection symptoms, participants with no EHR record of prior symptoms also developed long COVID. Thus prior symptom burden, although associated with increased risk, was neither necessary nor sufficient to support a singular causal link. Nevertheless, the assessment of pre-infection health, including the presence and interactions between ongoing health needs, should be considered in research and clinical management of post-infection symptom presentations. A future analysis of long COVID participants could explore pre- versus post-infection changes in symptom and condition distribution, repeated versus new conditions, and dimensional reduction to explore and compare phenotypes.

The finding that earlier periods of first infection increased the likelihood of developing symptoms (Appendix E) calls for additional context and exploration. The opportunities to develop symptoms would presumably increase with time. This dataset's cut-off date of July 2022 left little time for people in the last variant period to develop symptoms, and we did not control for time from first infection to first symptom. Additionally, there is some evidence, if not consensus, that vaccination against COVID-19 has some protective effect against long COVID symptoms.^{16,47} Thus, both the calendar time at first infection and the availability of vaccines starting in 2021 may have influenced the number of people who developed symptoms in our sample. The significance of time since infection and vaccination may be explored in a future analysis.

Limitations

This analysis contains several limitations. First, retrospective studies using EHR data are limited by detection bias.^{44,48} In *All of Us*, several sources of clinically relevant functional and disease severity data are unavailable, and we were unsuccessful in finding proxies for severity of infection or long COVID symptoms. Admitting diagnoses and narrative notes (where functional status is often described) are suppressed in *All of Us* for privacy. This precluded connections between incidences of COVID-19 and hospitalizations, and did not allow use of language learning models or other text-to-data methods of data extraction. Medication with Remdesivir, used in acute treatment, was also explored as proxy for disease severity. The cut-off date for this *All of Us* data set predated FDA approval of Remdesivir by about six months. We found that about 800 participants had been prescribed remdesivir, presumably for experimental or off-label treatment. This relatively small number was insufficient to make inferences across the sample, and may have been confounded by access to clinical trials; thus, Remdesivir was not used as a

proxy for illness severity. Prospective studies using tools that measure disease and symptom severity, as well as the patient experience, continue to be critical.

CONCLUSION

The pre-infection baseline symptoms and functional statuses of participants in *All of Us* with COVID-19 infection are varied and associated with post-infection status. Advancing age, pre-infection self-reported mental and cognitive health, EHR observations indicating severe functional impairment, and the number of long COVID symptoms occurring prior to infection, all increased the odds of at least one symptom after infection. The relationships between age and functioning and the changes from pre-infection to post-infection for people with post-COVID symptoms are areas of future study.

ACKNOWLEDGEMENTS

We extend greatest appreciation to the participants enrolled in the *All of Us* Research Program, who have generously agreed to share their ongoing health data. The first author also thanks the *All of Us* researcher workbench support staff for their expertise and service, as well as Dr. Beth Fields for editing and mentorship. Additional dataset building support was provided by Anoop Mayampurath, and by the University of Wisconsin Data Science Hub.

FUNDING

This work was supported by a T32 training grant to the first author from 2021 (5TL1TR002375-05) to 2023 (2TL1TR002375-06) through the University of Wisconsin-Madison School of Medicine and Public Health, and through a Gertrude Gatson Fund grant PRJ22AW from the University of Wisconsin-Madison Occupational Therapy Program. The *All of Us* Research Program is supported by the National Institutes of Health, Office of the Director:

Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

DATA AVAILABILITY STATEMENT

This study used data from the *All of Us* Research Program's Controlled Tier Dataset version 7, available to authorized users on the [Researcher Workbench](#).

TABLES

Table 1. Demographic, functioning, and long COVID disease characteristics in *All of Us* participants through July 2022.

	Long COVID participants	Recovered (No long COVID symptoms)	<i>Test, P</i>
n (total 66,971)	41639	25,332	
age (mean (SD))	61.07 (16.03)	57.73 (16.81)	$t = -25.406$, $df = 51519$, $P < 2.2e-16$ [-3.68, -3.00]
age (median (IQR))	63 (24)	60 (28)	$W = 467263123$, $P < 2.2e-16$
Total number of pre-pandemic symptoms of long COVID (mean (SD))	6.11 (3.96)	2.45 (2.94)	$t = -136.83$, $df = 64375$, $P < 2.2e-16$ [-3.73, -3.59]
Total number of pre-pandemic symptoms of long COVID (median (IQR))	6 (6)	1 (4)	$W = 224992918$, P -value $< 2.2e-16$
Variant of Concern			$X^2 = 6438.3$, $df = 5$, $P < 2.2e-16$
Pre-VOC/wild type	21632 (52.0)	7575 (29.9)	
Pre-VOC, alpha, and beta	10138 (24.3)	6446 (25.4)	
alpha, beta, and delta	3317 (8.0)	1922 (7.6)	
delta	3538 (8.5)	2945 (11.6)	
omicron BA1-BA2	2629 (6.3)	3615 (14.3)	
omicron BA2-BA5	385 (0.9)	2829 (11.2)	
Gender (%)			$X^2 = 106.78$, $df = 4$, $P < 2.2e-16$
Female	27120 (65.1)	15504 (61.2)	
Gender Identity: Additional Options	37 (0.1)	21 (0.1)	
Gender Identity: Non Binary	76 (0.2)	57 (0.2)	
Gender Identity: Transgender	47 (0.1)	25 (0.1)	

Male	14359 (34.5)	9725 (38.4)	
Sex assigned at Birth (%)			$X^2 = 106.35$, $df = 2$, $P < 2.2e-16$
Female	27230 (65.4)	15571 (61.5)	
Male	14403 (34.6)	9754 (38.5)	
Race (%)			$X^2 = 222.18$, $df = 4$, $P < 2.2e-16$
Asian	989 (2.4)	999 (3.9)	
Black or African American	9311 (22.4)	4822 (19.0)	
Middle Eastern or North African	293 (0.7)	201 (0.8)	
More than one population	805 (1.9)	536 (2.1)	
White	30241 (72.6)	18774 (74.1)	
Ethnicity (%)			$X^2* = 13.997$, $df = 1$, $P = 0.0001831$
Not Hispanic or Latino	40681 (97.7)	24631 (97.2)	
Pre-infection functional performance diagnostic codes	41639	25,332	
No Functional Performance Difficulty	34718 (83)	23985 (95)	
Some Functional Performance Difficulty	4240 (10)	949 (4)	
Dependent on Others for Care	2681 (6)	398 (2)	
Pre-infection OT CPT codes billed (median(IQR))	0 (1)	0 (0)	$W = 466262838$, $P < 2.2e-16$
* = Run with Yeats' continuity correction			

Table 2. Pre-infection prevalence of common post-COVID symptoms and conditions in *All of Us* participants through July 2022.

PASC symptom/condition group	<i>Asymptomatic participants (of 25,332)</i>	%	<i>Long COVID(of 41,639)</i>	%
Abdominal	5237	21	18803	45
Anxiety	4148	16	17717	43
Chest Pain	5054	20	19400	47
Cognition	1117	4	5131	12
Cough	3977	16	15833	38
Depression	3634	14	16639	40
Diarrhea	2076	8	9273	22
Dizziness	2398	9	10388	25
Dyspnea	3308	13	14670	35
Fatigue	3339	13	14172	34
Fever	1390	5	5537	13
Functional Performance	1368	5	6946	17
Headache	2603	10	11051	27
Joint Pain	7626	30	25675	62
ME/CFS (Chronic Fatigue)	430	2	2228	5
Menstrual Disorder	1475	6	4304	10
Muscle Pain	1253	5	6528	16
Musculoskeletal Chest Pain	648	3	3220	8
Palpitations	1469	6	6308	15
Paresthesia	1169	5	5111	12
Positional Orthostatic Tachycardia Syndrome (POTS)	0	0	0	0
Post-viral Fatigue Syndrome	0	0	0	0
Rash	2965	12	11488	28

Not Hispanic or Latino	1.00	1.00	1.00			0.84	0.83	0.85
Hispanic or Latino	0.85	0.72	1.00	-2.65	0.01	0.81	0.79	0.84
Variant								
Pre VOC	1.00	1.00	1.00			0.84	0.83	0.85
Pre VOC, alpha, beta	0.61	0.57	0.65	-19.54	<0.000	0.76	0.74	0.78
Alpha, beta, delta	0.48	0.44	0.53	-19.32	<0.000	0.72	0.69	0.74
delta	0.33	0.30	0.36	-32.74	<0.000	0.63	0.61	0.66
Omicron BA1-BA2	0.17	0.16	0.19	-50.91	<0.000	0.47	0.45	0.50
Omicron BA2-BA5	0.02	0.02	0.03	-61.11	<0.000	0.10	0.09	0.12
Approximate functional level based on "Finding of Functional Performance or Activity" code								
No Functional Performance Difficulty	1.00	1.00	1.00			0.84	0.83	0.85
Some Functional Performance Difficulty	0.93	0.82	1.04	-1.66	0.10	0.83	0.81	0.85
Dependent on Others for Care	1.51	1.28	1.79	6.42	0.00	0.89	0.87	0.90
Number of long COVID symptoms/conditions present prior to infection (Quartiles)								
0	0.08	0.07	0.08	-82.83	<0.000	0.29	0.27	0.31
1	0.19	0.18	0.20	-91.66	<0.000	0.50	0.48	0.52
4	1.00	1.00	1.00			0.84	0.83	0.85
7	1.73	1.65	1.80	24.80	<0.000	0.90	0.89	0.91
23	34.62	24.93	48.09	21.14	<0.000	0.99	0.99	1.00
Self-rated ability to complete physical daily activities								
Completely	1.00	1.00	1.00			0.84	0.83	0.85
Mostly	1.04	0.97	1.12	1.51	0.13	0.84	0.83	0.86
Moderately	1.03	0.94	1.13	0.87	0.39	0.84	0.83	0.86
A little	0.95	0.84	1.06	-1.23	0.22	0.83	0.81	0.85
Not at all	0.81	0.63	1.04	-2.21	0.03	0.81	0.77	0.85
No Answer	1.02	0.73	1.44	0.17	0.86	0.84	0.79	0.88

Self-rated social role performance and satisfaction (composite)									
2	1.04	0.95	1.15	1.15	0.25	0.84	0.83	0.86	
3	1.03	0.94	1.12	0.77	0.44	0.84	0.83	0.85	
4	1.00	1.00	1.00			0.84	0.83	0.85	
5	1.06	0.97	1.15	1.68	0.09	0.85	0.83	0.86	
6	1.00	0.91	1.10	0.11	0.91	0.84	0.82	0.85	
7	0.96	0.85	1.08	-0.88	0.38	0.83	0.81	0.85	
8	1.03	0.90	1.19	0.58	0.56	0.84	0.82	0.86	
9	0.95	0.77	1.16	-0.70	0.49	0.83	0.80	0.86	
10	0.81	0.62	1.06	-1.98	0.05	0.81	0.76	0.85	
Self-rated mental health (mood and cognitive function)									
Excellent	1.00	1.00	1.00			0.83	0.82	0.84	
Very Good	1.06	0.98	1.15	2.04	0.04	0.84	0.83	0.85	
Good	1.19	1.09	1.31	4.98	<0.000	0.85	0.84	0.87	
Fair	1.11	0.99	1.25	2.29	0.02	0.84	0.83	0.86	
Poor	1.23	1.00	1.50	2.62	0.01	0.86	0.83	0.88	
Pre-infection total CPU's billed									
0	1.00	1.00	1.00			0.84	0.83	0.85	
5	1.00	0.99	1.01	0.76	0.45	0.84	0.83	0.85	
20	1.01	0.97	1.05	0.76	0.45	0.84	0.83	0.85	
80	1.05	0.89	1.24	0.76	0.45	0.85	0.82	0.87	
700	1.53	0.36	6.39	0.76	0.45	0.89	0.66	0.97	

REFERENCES

1. National Center for Health Statistics USCB. *Household Pulse Survey - Long COVID*. 2024. <https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm>
2. National Academies of Sciences Engineering and Medicine. *A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences*. The National Academies Press; 2024.
3. Cohen J, Rodgers YVM. Long COVID Prevalence, Disability, and Accommodations: Analysis Across Demographic Groups. *J Occup Rehabil*. Jun 2024;34(2):335-349. doi:10.1007/s10926-024-10173-3
4. McCorkell L, G SA, H ED, Wei H, Akrami A. Patient-Led Research Collaborative: embedding patients in the Long COVID narrative. *Pain Rep*. 2021;6(1):e913. doi:10.1097/pr9.0000000000000913
5. Al-Aly Z, Davis H, McCorkell L, et al. Long COVID science, research and policy. *Nat Med*. Aug 2024;30(8):2148-2164. doi:10.1038/s41591-024-03173-6
6. Ladds E, Rushforth A, Wieringa S, et al. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Serv Res*. Dec 20 2020;20(1):1144. doi:10.1186/s12913-020-06001-y
7. Mendelson M, Nel J, Blumberg L, et al. Long-COVID: An evolving problem with an extensive impact. *S Afr Med J*. Nov 23 2020;111(1):10-12. doi:10.7196/SAMJ.2020.v111i1.15433
8. The Lancet. Facing up to long COVID. *Lancet*. Dec 12 2020;396(10266):1861. doi:10.1016/s0140-6736(20)32662-3
9. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. *BMJ*. Jul 26 2021;374:n1648. doi:10.1136/bmj.n1648
10. Zhang H, Zang C, Xu Z, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med*. Jan 2023;29(1):226-235. doi:10.1038/s41591-022-02116-3
11. Davis EH, Assaf SG, Mccorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *eClinicalMedicine*. Aug 2021;38:101019. *EClinicalMedicine*. doi:10.1016/j.eclinm.2021.101019
12. Davis EH, Mccorkell L, Vogel MJ, Topol JE. Long COVID: major findings, mechanisms and recommendations. *Nature Reviews Microbiology*. Mar 2023;21(3):133-146. doi:10.1038/s41579-022-00846-2
13. Nielsen TB, Leth S, Pedersen M, et al. Mental Fatigue, Activities of Daily Living, Sick Leave and Functional Status among Patients with Long COVID: A Cross-Sectional Study. *International journal of environmental research and public health*. Nov 9 2022;19(22)doi:10.3390/ijerph192214739
14. Carter SJ, Baranuskas MN, Raglin JS, Pescosolido BA, Perry BL. Functional Status, Mood State, and Physical Activity Among Women With Post-Acute COVID-19 Syndrome. *Int J Public Health*. 2022;67:1604589. doi:10.3389/ijph.2022.1604589
15. Vanichkachorn G, Newcomb R, Cowl CT, et al. Post-COVID-19 syndrome (long haul syndrome): Description of a multidisciplinary clinic at Mayo Clinic and characteristics of the initial patient cohort. *Mayo Clin Proc*. Jul 2021;96(7):1782-1791. doi:10.1016/j.mayocp.2021.04.024
16. Brannock DM, Chew FR, Preiss JA, et al. Long COVID risk and pre-COVID vaccination: An EHR-based cohort study from the RECOVER program. medRxiv. 20221007 ed2022.
17. Gentilotti E, Górska A, Tami A, et al. Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. *EClinicalMedicine*. Aug 2023;62:102107. doi:10.1016/j.eclinm.2023.102107
18. Mina Y, Enose-Akahata Y, Hammoud DA, et al. Deep Phenotyping of Neurologic Postacute Sequelae of SARS-CoV-2 Infection. *Neurol Neuroimmunol Neuroinflamm*. Jul 2023;10(4)doi:10.1212/nxi.0000000000200097
19. Prabhakaran D, Day G, Munipalli B, et al. Neurophenotypes of COVID-19: risk factors and recovery trajectories. *Brain Behav Immun Health*. Dec 21 2022;doi:10.21203/rs.3.rs-2363210/v1

20. Reese JT, Blau H, Casiraghi E, et al. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes. *EBioMedicine*. Jan 2023;87:104413. doi:10.1016/j.ebiom.2022.104413
21. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594(7862):259-264. doi:10.1038/s41586-021-03553-9
22. Thaweethai T, Jolley ES, Karlson WE, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA*. Jun 13 2023;329(22):1934. doi:10.1001/jama.2023.8823
23. Hou Y, Gu T, Ni Z, Shi X, Ranney ML, Mukherjee B. Global Prevalence of Long COVID, its Subtypes and Risk factors: An Updated Systematic Review and Meta-Analysis. *medRxiv*. Jan 6 2025;doi:10.1101/2025.01.01.24319384
24. Callard F, Perego E. How and why patients made Long Covid. *Soc Sci Med*. Jan 2021;268:113426. doi:10.1016/j.socscimed.2020.113426
25. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. Apr 2022;22(4):e102-e107. doi:10.1016/s1473-3099(21)00703-9
26. Mandel HL, Colleen G, Abedian S, et al. Risk of post-acute sequelae of SARS-CoV-2 infection associated with pre-coronavirus disease obstructive sleep apnea diagnoses: an electronic health record-based analysis from the RECOVER initiative. *Sleep*. May 11 2023;Sleep. doi:10.1093/sleep/zsad126
27. Hall JP, Kurth NK, McCorkell L, Goddard KS. Long COVID Among People With Preexisting Disabilities. *Am J Public Health*. Nov 2024;114(11):1261-1264. doi:10.2105/ajph.2024.307794
28. National institutes of Health. Data from: All of Us, Curated data repository version 7, Controlled Tier C2022Q4R9. 2022-2025. Deposited April 15, 2023.
29. Ramirez AH, Sulieman L, Schlueter DJ, et al. The All of Us Research Program: Data quality, utility, and diversity. *Patterns (N Y)*. Aug 12 2022;3(8):100570. doi:10.1016/j.patter.2022.100570
30. Zeng C, Schlueter DJ, Tran TC, et al. Comparison of phenomic profiles in the All of Us Research Program against the US general population and the UK Biobank. *J Am Med Inform Assoc*. Apr 3 2024;31(4):846-854. doi:10.1093/jamia/ocad260
31. Centers for Disease Control and Prevention. Long COVID or Post-COVID Conditions. https://www.cdc.gov/covid/long-term-effects/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/
32. New ICD-10-CM code for Post-COVID Conditions, following the 2019 Novel Coronavirus (COVID-19) (2021).
33. Markov PV, Ghafari M, Beer M, et al. The evolution of SARS-CoV-2. *Nat Rev Microbiol*. Jun 2023;21(6):361-379. doi:10.1038/s41579-023-00878-2
34. U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion. Healthy People 2030: Social Determinants of Health. Accessed April 15, 2025. <https://odphp.health.gov/healthypeople/priority-areas/social-determinants-health/literature-summaries>
35. Case KR, Wang CP, Hosek MG, et al. Health-related quality of life and social determinants of health following COVID-19 infection in a predominantly Latino population. *J Patient Rep Outcomes*. Jun 23 2022;6(1):72. doi:10.1186/s41687-022-00473-8
36. Eligulashvili A, Darrell M, Gordon M, et al. Patients with unmet social needs are at higher risks of developing severe long COVID-19 symptoms and neuropsychiatric sequela. *Sci Rep*. Apr 2 2024;14(1):7743. doi:10.1038/s41598-024-58430-y
37. Centers for Medicare and Medicaid Services. Billing and Coding: Therapy Evaluation, Re-Evaluation and Formal Testing. A53309. DHHS, CMS. Accessed 10/3/2024, 2024. <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53309>
38. Harrell FE. *Regression Modeling Strategies*. 2nd ed. Springer Series in Statistics. Springer; 2001.
39. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2022.
40. *The R Stats Package*. Version 4.3.0-4.4.3. R Foundation for Statistical Computing; 2025.
41. Harrell FE. *Regression Modeling Strategies*. CRAN; 2024.

42. *Visualization of a Correlation Matrix (corrplot)*. Version 0.92. R Foundation for Statistical Computing; 2021.
43. *Welcome to the tidyverse*. Version 2.0.0. R Foundation for Statistical Computing; 2019. <https://tidyverse.tidyverse.org>, <https://github.com/tidyverse/tidyverse>
44. Deer RR, Rock AM, Vasilevsky N, et al. Characterizing Long COVID: Deep Phenotype of a Complex Condition. *eBioMedicine*. Dec 2021;74:103722. doi:10.1016/j.ebiom.2021.103722
45. Gutzeit J, Weiß M, Nürnberger C, et al. Definitions and symptoms of the post-COVID syndrome: an updated systematic umbrella review. *Eur Arch Psychiatry Clin Neurosci*. Jul 25 2024;doi:10.1007/s00406-024-01868-y
46. Lemhöfer C, Appel SK, Häuser W, Hettich N, Kohls M, Polidori CM. Post-COVID: Alles eine Frage der Definition? *DMW - Deutsche Medizinische Wochenschrift*. Oct 2022;147(21):1391-1397. Post-COVID: Alles eine Frage der Definition? doi:10.1055/a-1940-1222
47. Mukherjee S, Singer T, Venkatesh A, et al. Vaccination prior to SARS-CoV-2 infection does not affect the neurologic manifestations of long COVID. *Brain Commun*. 2025;7(1):fcae448. Brain Commun. doi:10.1093/braincomms/fcae448
48. Rando HM, Bennett TD, Byrd JB, et al. Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. *medRxiv*. Mar 26 2021;medRxiv. doi:10.1101/2021.03.20.21253896

Chapter 5. Manuscript 2

TITLE: Functional impairment in people with Long COVID symptoms: A retrospective cohort study of EHR data from the *All of Us* Research Program.

Kristen Kehl-Floberg, MSOT, OTR/L, BCG

Emma Freisberg, BS

Aurora Pop-Vicas, MD, MPH

Ron Gangnon, PhD

Dorothy Edwards, PhD

ABSTRACT

BACKGROUND: Impaired performance of daily routines and activities is experienced by some people with long COVID (symptoms and conditions persisting after recovery from COVID-19 infection). Functional impairment has been recommended as a diagnostic criterion for long COVID, but few population-level studies have explored its prevalence and risk factors using EHR data. This study aimed to estimate functional status using standard medical concepts, and to identify main effects for functional impairment after COVID-19 infection by demographic, health, and disease factors. We hypothesized that long COVID symptoms, female sex, and older age would increase risk for post-infection functional impairment after adjusting for sociodemographic and disease factors.

METHODS: This cohort study of participant data in the *All of Us* Research Program through July 2022 explored functional status in participants with versus without ≥ 1 common long COVID condition or symptom. We report descriptive statistics and standard mean differences in functional impairment indicators found in the EHR from an ordinal probit logistic regression model.

FINDINGS: $N=83,786$ participants met inclusion criteria, with 52,349 long COVID symptomatic participants and 31,437 asymptomatic (recovered). The most significant contributors to the likelihood of functional impairment were lower pre-infection functional status ($X^2=3610.4$) older age ($X^2: 655.6$), earlier SARS-CoV-2 variant ($X^2: 602.8$), and presence of pre-infection symptoms ($X^2: 441.0$). Having ≥ 1 long COVID symptom was associated with greater functional impairment ($X^2: 387.2$) even after adjusting for older age and pre-infection symptoms (25 year-old SMD: 0.49, 99% CI: 0.35-0.59, $p < 0.000$, versus 75 year-old SMD: 0.16, 99% CI: 0.11 – 0.22, $p < 0.000$). Female sex showed a small effect for slightly better functioning compared to males ($X^2: 49.7$, SMD: -0.1, 99% CI: -0.13 - -0.06, $p < 0.000$).

INTERPRETATION: Having at least one long COVID symptom after infection was associated with functional impairment even after adjusting for years of age and number of pre-infection symptoms. Sex showed a negligible effect. Pre- and post-illness presence of long COVID symptoms and levels of daily functioning should be assessed as part of long COVID evaluation and care planning.

FUNDING: This work was supported by a T32 training grant to the first author from 2021 (5TL1TR002375-05) to 2023 (2TL1TR002375-06) through the University of Wisconsin-Madison School of Medicine and Public Health, and through a data processing grant from the University of Wisconsin-Madison Occupational Therapy Program. The

All of Us Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

RESEARCH IN CONTEXT PANEL

Evidence before this study

Functional impairment – decreased ability to perform daily routines – is both an outcome and a proposed diagnostic marker of long COVID (persistent health issues after COVID-19 infection). However, its prevalence and risk factors have not been studied in large population-level datasets.

Added value of this study

In a sample of 83,786 participants in the *All of Us* Research Program, having at least one long COVID symptom increased risk for functional impairment, even when adjusting for years of age and pre-infection occurrences of long COVID symptoms. Pre-infection functional impairments and infection during earlier COVID-19 variants also had large effects. Female sex was mildly associated with better functional status.

Implications of all the available evidence

Pre- and post-infection functional status may be under-represented in electronic medical records, and should be assessed as part of evaluation and care planning. More evidence is needed to validate instruments for measuring the functional status changes experienced by people with long COVID symptoms and conditions.

BACKGROUND

Long COVID is the experience of new or worsening health conditions and symptoms that persist for months or years after recovery from coronavirus 2019 (COVID-19), the illness caused by the novel 2019 strain of severe acute respiratory virus (SARS-CoV-2).^{1,2} Prevalence estimates vary, with global cumulative incidence estimated at ~409 million adults,³ and pooled estimates at ~34% of COVID-19 survivors.⁴ In the U.S., long COVID affects 29-32% of COVID-19 survivors,⁴ or about 6-7% of the total adult population.⁵

The symptoms and health conditions of long COVID can be sufficiently severe to cause disability in work, education, community, and family life. At the last availability of population surveillance data for the U.S., about 5.5% of U.S. adults reported having long COVID that limited their activity.⁵ The prevalence of persistent disability appeared to be increasing year-over-year at that time, suggesting unaddressed functional impairment. This increases vulnerability to financial insecurity, isolation, and loss of social structures that support health^{6,7} particularly for people with pre-existing disability.⁸ Long COVID can occur regardless of COVID-19 severity⁹ and may contribute to disability during the most productive years of life. The ensuing economic impact of this novel cause of disability is unsustainable; in 2022, an estimated 4 million U.S. adults were out of work due to long COVID symptoms, projected to result in over \$170 billion in lost wages annually.¹⁰ In the same time period, people with long COVID had excess healthcare utilization and cost.¹¹ The prevalence and economic impact of long COVID create a critical need to understand the extent and degree of disability in this population.

Functional impairment is both a known health outcome and a proposed diagnostic marker of long COVID. The National Academies of Science, Engineering and Medicine have recommended that an operational definition of functioning, and a corresponding measurement instrument with research and clinical utility, is needed to advance the science and clinical treatment of long COVID.¹² This recommendation aligns with the World Health Organization's proposed diagnostic criteria for long COVID, which includes assessment of the impact of symptoms/conditions on daily activities.¹³ Although there is accumulating evidence showing the detrimental effects of long COVID on functional status, it is primarily from single-center studies with varying operational definitions.¹⁴ In diagnostic research, rigorous high-throughput studies have synthesized large amounts of symptom data into proposed generalizable phenotypes and diagnostic hallmarks,^{1,15-20} with variation in their phenotypic findings.^{4,21} However, most of these studies have not included data on how disability manifests (in diagnostic codes) or is treated (in referral and procedure codes for rehabilitation therapies). Consequently, the resulting diagnostic classifications lack

evidence characterizing the prevalence, severity, and diagnostic utility of functional status, leading to incomplete taxonomies of the disorder. To build on this research, indicators of post-infection functional status should be incorporated into data-driven definitions.

This study aimed to (a) estimate functional impairment after COVID-19 infection using standard medical concepts found in EHR billing and diagnostic codes, and (b) identify main effects for lower functional status after COVID-19 infection by demographic, health, and disease factors among participants in the *All of Us* Research Program. We hypothesized that having long COVID symptoms following infection, female sex, and older age would be associated with higher likelihood of post-infection functional impairment after adjusting for sociodemographic and disease factors. This is given that age increases likelihood of comorbidities and overall health status that may contribute to functional decline, and given the higher prevalence of long COVID symptoms in women and middle to older adults that has been reported consistently in other population-based samples.⁴

METHODS

Design and data source

This retrospective cohort study analyzed EHR data from participants enrolled in the U.S. National Institutes of Health *All of Us* Research Program through July 1, 2022 (curated data repository version 7.0, CR2022Q4R9).²² *All of Us* is a national biobank with participants from 50 U.S. states and three territories. Participants' functional and health data is shared through EHR data, released at baseline and every three months thereafter, and harmonized. *All of Us* utilizes community-relevant recruitment methods to over-recruit from geographic and demographic groups that are under-represented in medical and health research. The program, data snapshots, and data methods can be viewed at <https://www.researchallofus.org/data-tools/>. See Appendix A.

Sample

This study included *All of Us* participants who (a) were 18 years of age and older, (b) responded to demographic survey questions, and (c) had at least one incidence of any indicator of COVID-19 illness. Indicators included codes for positive PCR, antigen, or positive antibody test, self-reported illness consistent with COVID-19 reported on the 2021-2022 *All of Us* COVID-19 Participant Experiences (COPE) survey, and the ICD-10 COVID diagnostic code *U07.7*. The first infection was the indexing incidence for this study. (Appendix A, Table S.A.1.) Informed consent for sharing EHR and survey data was obtained from all participants by *All of Us* Health Provider

Organizations responsible for participant recruitment and enrollment. All sites delegated Institutional Review Board (IRB) oversight to the *All of Us* Central IRB.

Demographics

We included the demographic variables of age, sex assigned at birth, race, and ethnicity, and the social factor of education level (expressed as “highest grade completed”) based on evidence of differences in risks for long COVID or functional impairment (see Appendix A for full rationale.)

Long COVID status

Participants were grouped into one of two long COVID categories. Participants were classified as “long COVID symptomatic” if their EHR showed at least one incidence of at least one diagnosis or observation code entered at least 28 days after their first incidence of any COVID-19 infection indicator. Participants with no post-infection symptoms were classified as “recovered”. Indicators of possible long COVID were chosen a-priori based on the Centers for Disease Control and Prevention’s list of symptoms,²³ the emergency billing code for “Post-COVID Condition, Unspecified”, *U07.7*,²⁴ prior phenotyping and patient-led literature,^{1,2,15-21,25-27} and the authors’ clinical and community-level research experience (Appendix A, Table S.A.2). The first entry of each code was the indexing incidence.

Pre- and post-infection burden of long COVID symptoms and conditions

Diagnosis codes and dates of entry were included within two time periods: 5 years to 28 days prior to first infection (pre-infection symptoms) and 28 days or longer after infection (post-infection symptoms; also used as the long COVID cohort indicator). For each period, the total number of symptom/condition categories with at least one incidence were summed to indicate symptom burden. Because the definition of long COVID from the Patient-Led Research Collaborative includes exacerbations or relapses of pre-infection conditions,^{1,3,27} we queried “any mention” of the symptoms/conditions in the list. The post-infection interval of 28-days before first symptom occurrence was chosen to capture health and daily functioning beginning after the presumptive acute infection phase but still within 90 days post-infection. A 90-day timeframe is also the U.S. Family Medical Leave Act’s mandated leave period, and is thus a clinically important period for working-aged adults’ utilization of skilled rehabilitation prior to returning to work. Appendix A reports the long COVID sequelae codes and selection process.

SARS-CoV-2 Variant exposure

To approximate the variant exposure at the date of the indexing SARS-CoV-2 infection, a ‘variant period’ variable was created. Periods began and ended around the emergence of major variants as reported by Markov et al.^{25, Fig. 3a} Resultant periods were “pre-VOC/wild type” from January-November 2020, “pre-VOC/alpha/beta from November 2020 – April 2021, “alpha/beta/delta” from April-August 2021, “delta” from August-December 2021, “omicron_BA1-BA2” from December 2021 – April 2022, and “omicron_BA2-BA5” from April 2022 – July 2022 (this dataset’s cut-off date). See Appendix A for all long COVID condition concept codes queried.

Functional status

Evidence of functional status was obtained from EHR procedure and diagnostic codes in the EHR. As for symptoms (above), these were queried within pre- and post-infection time periods: Between 28 days and 5 years prior to the first infection starting as early as January 1, 2015 (pre-infection function) and ≥ 28 days after first infection (post-infection function). Observations were imported for (a) occupational therapy (OT) evaluation billing codes (low, moderate, and high complexity, and re-evaluation), and (b) the EHR observation “Finding of Functional Performance and Activity” (OMOP Code 4089214, SNOMED code 248536006). OT evaluation was chosen as an indicator because it is the therapeutic discipline designated by CMS to address deficits in daily performance, making it the most specific discipline for functional performance deficits.²⁸ OT evaluations are billed according to the level of evaluation complexity required to assess the patient’s functional status relative to their prior or baseline status. Ordinal score values were assigned to each evaluation level, giving 1 = *Low Complexity*, 2 = *Moderate Complexity*, and 3 = *High Complexity*. The *Re-Evaluation* code is typically billed in the case of concerns for a decline in functioning in a patient already receiving OT services. Thus this code often implies an increase in complexity from either low to moderate or moderate to high. Based on this usage and exploratory correlations, re-evaluation was collapsed into the “moderate” level of complexity. EHR observations under “Finding of Functional Performance and Activity” were filtered for rehabilitation or participation concepts aligned with the WHO International Classification of Functioning, Disability, and Health (ICF)²⁹ describing level of independence and/or characteristics of observable daily activity performance. Presumptive severity of functional impairment was then inferred in consultation between the first author and clinical experts, and given the hierarchy 0 = No impairment, 1 = some impairment, 2 = severe impairment. These ordinal levels of OT evaluation and functional performance finding were summed to create pre- and post-infection daily functional status scores, expressed as a 6-level ordinal variable (0 = no impairment, 6 = severe impairment). See Appendix B.

Analysis

Demographics were graphed to visually assess distribution and tested using Welch's t test (normal), Mann-Whitney U test (non-normal), or X^2 test (categorical). Missingness in symptom and functional status observations (no incidence of that observation) was presumed to indicate a lack of medical need. Distributions of long COVID symptoms/conditions and functional impairments were tallied and graphed as proportions of the sample. An ordinal probit logistic regression model was fitted for main effects on the probability of mean functional status level by demographic, variant, long COVID status, and functional status factors. The probit link function was chosen for this ordinal-structured functional status outcome to frame the underlying continuous distribution of functional performance, which is not naturally binned into categorical levels. This permitted interpretation of a latent mean difference in functional status levels given changes in covariate values or levels³⁰ and is thus appropriate to ranges of possible functional performance observations contained within and above the levels inferred from the EHR-derived indicators. Model linearity, interaction terms, and residual fit were assessed with established procedures.³⁰ Variables included in the regression model were chosen a-priori based on the available literature. Covariate details (rationale, structure, and data sources) and model fitting process are reported in Appendix D.

Data analysis was performed in the *All of Us* Researcher Workbench Jupyter notebooks cloud computing environment, using R programming language. Cohort discovery, data cleaning, organization, transformation, and statistical analyses were completed by the first and second author using R versions 4.3.0-4.3.3, packages "stats", "tidyverse", and "rms". (See Appendix A).

FINDINGS

Demographic, symptom, and functional status summary statistics

A total of $N=83,786$ participants met inclusion criteria, with $n=52,349$ long COVID symptomatic participants (having at least one long COVID symptom), and $n=31,437$ recovered participants (Figure 1). Long COVID symptomatic participants had a higher mean age (60.51 ± 24 versus 57.53 ± 28 years), and higher proportions of female (64.8% versus 61.6%) and black or African-American (20.2% versus 17.5%) participants, as well as lower educational attainment (maximum of high school/GED in 16.9% versus 14.3%; maximum of an advanced degree in 24.2% versus 29.2%). This group also had higher proportions of infections early in the

pandemic (51.8% versus 30.8%), and lower functional status scores both pre- and post-infection (“0” or “unimpaired” at 83% versus 93.2%, and 86.8% versus 96.7%, resp.).

Pre-infection occurrences of the long COVID symptoms used in cohort discovery were computed for both groups (Table 2, Figure 2). Post-infection occurrences were computed for the long COVID symptomatic group only (Table 2). Long COVID symptomatic participants had a higher median number of pre-infection symptom occurrences (5 ± 5) than recovered participants (1 ± 4) (Table 1). There were no recorded incidences under the categories of ageusia, anosmia, muscle fatigue, positional orthostatic tachycardia syndrome, or post-viral fatigue syndrome, either before or after infection. The most common symptom (both pre- and post-infection) was joint pain.

Following infection, long COVID symptomatic participants had a mean of 3.61 ± 3.0 post-COVID symptoms. The diagnostic code for “Post COVID condition” was used in only 309 (0.5%). A correlation matrix of post-infection symptoms found very low to moderate unsquared Pearson’s R correlations (Table 3). The highest-correlated symptoms were depression with anxiety (0.42), chest pain with musculoskeletal chest pain (0.31) and dyspnea (0.30), fatigue with ME/CFS (0.30), abdominal pain with diarrhea (0.24), and dyspnea with cough (0.21).

Main effects model ANOVA and adjusted standard mean differences

Figure 3 shows the ANOVA results of each variable’s contribution to omnibus main effects. Table 4 reports standard mean differences in functional impairment by covariates and interactions. At a 99% confidence level ($p < 0.0001$), significant main effects for greater mean functional impairment were found for all variables and interaction terms except ethnicity (OR: -0.32, 99% CI: -0.15- -0.09, $p < 0.5$).

Long COVID symptomatic participants showed a strong moderate effect for greater functional impairment after infection compared to recovered participants ($X^2 = 2240.6$, SMD: 0.20, 99% CI: 0.16-0.25, $p < 0.000$). Age also demonstrated a moderate main effect ($X^2 = 655.58$) when considered alone. Compared to age 65, mean impairment at 25 years of age was lower (SMD: -0.38, 99% CI: -0.43 - -0.34, $p < 0.000$) whereas at age 85 it was greater (SMD: 0.24, 99% CI: 0.21-0.27, $p < 0.000$).

Similarly, the number of pre-infection incident long COVID symptoms and conditions had a moderate to large effect on post-infection functional status ($X^2 = 440.95$). Compared to participants with the sample median of four prior symptom categories, participants with one symptom (first quartile) showed slightly better functional status (SMD: -0.08, 99% CI: -0.13 - -0.04, $p = 0.001$) whereas those with seven symptoms (third quartile) showed poorer

(SMD: 0.10, 99% CI: 0.08-0.11, $p < 0.0000$), and those with the maximum of 23 symptoms showed significantly more impairment (SMD: 0.74, 99% CI: 0.64-0.83, $p < 0.0000$).

In a three-way interaction between years of age, long COVID group, and number of pre-infection symptoms, the differences between symptomatic and recovered participants grew smaller when both years of age and number of pre-infection symptoms was greater. Among participants with no pre-infection record of any common long COVID symptoms, symptomatic participants of all ages still showed greater mean impairment than recovered participants; however, this difference was largest for younger participants and smallest for older. For long COVID symptomatic participants with no pre-infection symptoms, those at 25 years of age had a larger mean difference in functioning (SMD: 0.73, 99% CI: 0.62-0.84, $p < 0.000$) than those at 75 years of age (SMD: 0.44, 99% CI: 0.36-0.51, $p < 0.000$). This relationship was also observed among participants with up to 7 prior symptoms (the third quartile), with all numbers trending closer together (SMD values nearer to 0). This pattern showed that greater pre-infection health burden and higher age both narrowed the functional impairment differences between participants of different long COVID status.

Female/intersex participants exhibited slightly lower mean impairment (better function) than males (SMD: -0.10, 99% CI: -0.13 - -0.06, $p < 0.000$), however this effect size was small.

The largest main effect found was for pre-infection functional level ($X^2 = 3610.44$). Compared to participants with no indicators of pre-infection functional impairment, post-infection functional impairment was higher for those with ‘some’ pre-infection impairment (SMD: 0.74, 99% CI: 0.69-0.79, $p < 0.000$) and highest for those with ‘severe’ pre-infection impairment (SMD: 1.23, 99% CI: 1.17-1.29, $p < 0.000$). Interaction terms for this variable with age and long COVID group were tested and found to contribute to greater error and poorer model fit with these data; thus, these were not analyzed. A large main effect was also found for variant during first infection ($X^2 = 602.84$). Black or African American participants showed moderately higher mean functional impairment compared to White participants (SMD: 0.18, 99% CI: 0.14-0.22, $p < 0.000$). Impairment was very slightly higher for participants with high school or GED level of education (compared to college-educated) (SMD: 0.06, 99% CI: 0.01-0.10, $p < 0.001$). Hispanic or Latino ethnicity was non-significant (SMD: -0.32, 99% CI: -0.15-0.09, $p < 0.5$).

INTERPRETATION

This retrospective cohort study of harmonized U.S. population EHR data from the *All of Us* Research Program is among the first studies to examine functional impairment related to long COVID at the population-level,

as well as one of the first studies exploring long COVID in *All of Us*. This study aimed to estimate functional status using standard medical concepts of EHR observations, and to identify main effects for functional impairment after COVID-19 infection by demographic, health, and disease factors. In our model, our hypotheses that long COVID symptoms and older age would be associated with lower functional status were supported. Both showed positive main effects for greater functional impairment when contrasted singly. Additionally, both age and pre-infection prevalence of long COVID symptoms reduced the functional status difference between long COVID groups. Our hypothesis that female sex would be associated with post-infection functional status was not supported, and the difference between male and female or intersex participants' likelihood was very small.

Our findings that older age and long COVID increased the likelihood of experiencing functional impairment are consistent with the growing body of research.^{14,31,32} The finding that prior symptom burden resulted in larger differences between younger participants than older ones has several potential interpretations. First, we did not control for all-cause mortality, as this was not available in *All of Us* at the time this data was queried. Considering our high proportion of symptomatic participants with early-wave infections combined with higher mortality among older adults in early waves,³³ it is reasonable to assume that younger participants were more likely than older participants to survive severe infections, and thus have subsequent opportunities for assessment and treatment functional deficits. Second, pre-infection symptom burden may suggest greater overall health burden, which may in turn have increased the potential for functional impairment independent of long COVID status.

Although the single largest effect size was from pre-infection functional status, interaction terms with this variable resulted in inferior model fit indices with these data. Several sources of noise and imprecision in this study's functional outcome variable may have contributed to this. We built an ordinal representation of functional status by concatenating two other variables expressing different but related observations. Although both contributing variables were ordinal (making an additive combination sensible), assumptions were made about the middle levels to arrive at this structure. In the OT evaluation codes, collapsing "Re-evaluation" into the "Moderate" level introduces potential variance from differences between participants moving from low to moderate complexity and those moving from moderate to high. Similarly, the "Finding of Functional Performance and Activity" EHR observation contains only observation concepts, but no modifiers for severity. We thus inferred the two extremes ("None", "Severe") from codes that were highly likely to fall into such extremes, then grouped all that remained into a middle "Some" level. Both variables satisfied the assumptions of ordinality, and upon model fit testing we found

adequate evidence that the combined variable had relatively parallel slopes. Nonetheless, the middle values should be interpreted as very general indicators. This illustrates the challenges inherent in EHR-based inference, and emphasizes the need for standardized, scalable, sensitive, and reliable functional impairment measurement instruments that can be documented within or in addition to existing EHR vocabularies.

This study's cohort displayed different characteristics compared to some COVID-19-specific cohort studies. The long COVID symptomatic group was proportionally much larger than the recovered group, which is comparable to some phenotyping studies^{16,17} but higher than others¹⁹ and recent pooled prevalence in the U.S. of about 30%.⁴ This study's long COVID symptomatic participant assignment - based on just one or more symptom - may err on the side of sensitivity over specificity, particularly since this dataset that is not specific to COVID-19. Without the ability to directly ask participants about persistent post-COVID symptoms, severity, and functional performance, and with only 0.5% utilization of the Post-Covid Condition CMS emergency billing code (compared to 26% in the prospectively-designed RECOVER and N3C cohorts)¹⁹ validation tools for this classification scheme were limited. The demographic distributions were overall consistent with prior studies, although there were not enough observations from some underrepresented racial and ethnic groups to gain insight into their risk for post-COVID functional impairment. By contrast, compared to prospective studies that assessed functional status directly using validated measures,^{14,34} this sample showed a lower than expected prevalence of functional impairment in long COVID symptomatic participants, which may be an underestimate of the true prevalence in this sample. Long COVID has been shown to affect cognitively- and physically-complex areas such as productivity and leisure more dramatically than basic self-care³² so many patients may not appear to need treatment or be served within the typical referral pathway to rehabilitation services despite serious difficulty performing complex activities.³⁵ As a result, these individuals would not be represented in our use of occupational therapy evaluation codes as an indicator of functional status. Additionally, there was lower than expected representation of long COVID conditions that are particularly disabling, with only 14% prevalence of cognitive impairment, no incidences of positional orthostatic tachycardia syndrome (POTS), and no diagnostic code in the data structure for post-exertional malaise (PEM). All three of these are reported to be prevalent and debilitating in long COVID.^{1-3,18,27,36,37} Additionally, *All of Us* does not include narrative notes, where functional data is often recorded; this results in an inability to process text discovery of this source of data in the health record. Finally, it was not possible in the present analysis to characterize severity of infection, nor level of medical care required, as links between encounters and conditions

(e.g., admitting diagnoses) are suppressed in *All of Us* for privacy. The relative contributions of under-assessment versus overly-sensitive group assignment are questions for future analyses. Taken together, these results suggest that the lack of a clear framework for assessing complex functional limitations specific to long COVID results in little guidance for clinicians, limited structure in the EHR to record functional status observations, and increased potential for underutilization of rehabilitation therapies.^{38,39}

This study demonstrated that EHR-derived indicators of functional status are available and feasible for use in large population datasets. These findings and processes may be used to increase the accurate and timely identification of long COVID and its impact on functional status. Based on our finding that both long COVID symptoms and pre-infection functional status increased the likelihood of post-infection functional impairment, we echo the recommendations of the WHO and NASEM to operationalize functioning, validate assessment tools, and integrate the assessment of functional status into both the evolving data-driven definitions and the clinical intervention workflows for people affected by long COVID symptoms and conditions.

FUNDING

This work was supported by a T32 training grant to the first author from 2021 (5TL1TR002375-05) to 2023 (2TL1TR002375-06) through the University of Wisconsin-Madison School of Medicine and Public Health, and through a Gertrude Gatson Fund grant from the University of Wisconsin-Madison Occupational Therapy Program. The All of Us Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

ACKNOWLEDGEMENTS

We extend greatest appreciation to the participants enrolled in the *All of Us* Research Program, who have generously agreed to share their ongoing health data. Thanks as well and to the *All of Us* researcher workbench support staff for their expertise and service. The first author thanks the coauthors for their support and mentorship, and additionally thanks Richard Chappell for statistical support, and Beth Fields for editing and conceptual

mentorship. Additional dataset building support was provided by Anoop Mayampurath, and by the University of Wisconsin Data Science Hub.

TABLES

Table 1. Demographic, disease, and functional status characteristics, by group

	Recovered (n=31437)		Long COVID symptomatic (n=52349)		
			Mean / %	SD	
Age (mean, SD)	57.53	28	60.51	24	$t = -25.159$, $df = 63845$, $p\text{-value} < 2.2e-16$
Sex at birth (n, %)					$\chi^2 = 92.052$, $df = 2$, $p\text{-value} < 2.2e-16$
Female or Intersex	19360	61.6	33945	64.8	
Male	12077	38.4	18404	35.2	
Race (n, %)					$\chi^2 = 245.45$, $df = 4$, $p\text{-value} < 2.2e-16$
Asian	1241	3.9	1239	2.4	
Black or African American	5508	17.5	10574	20.2	
Middle Eastern or North African	246	0.8	367	0.7	
More than one population	692	2.2	1066	2	
White	23750	75.5	39103	74.7	
Ethnicity = Not Hispanic or Latino (n, %)	30548	97.2	51069	97.6	$\chi^2 = 11.259$, $df = 1$, $p\text{-value} = 0.0007922$
Education level (n, %)					$\chi^2 = 315.9$, $df = 8$, $p\text{-value} < 2.2e-16$
Advanced Degree	9193	29.2	665	24.2	
College Graduate	8473	24.6	12639	24.1	
Some College	7721	24.6	15151	28.9	
High School/GED	4493	14.3	8833	16.9	
Some High School	1024	3.3	1915	3.7	
Middle School	147	0.5	340	0.6	
Elementary	<50	<1.0	<50	<0.1	
No Formal Education	<50	<1.0	<50	<1.0	
No Answer	364	1.2	756	1.4	
Variant (n, %)					$\chi^2 = 7454.8$, $df = 5$, $p\text{-value} < 2.2e-16$
Pre-VOC	9694	30.8	27123	51.8	
Pre-VOC/alpha/beta	7904	25.1	13057	24.9	
Alpha/beta/delta	2580	8.2	4352	8.3	
Delta	3890	12.4	4365	8.3	
Omicron/BA1/BA2	4319	13.7	3028	5.8	

Omicron/BA2/BA5	3050	9.7	424	0.8	
Total number of long COVID symptoms (mean, SD)	NA	NA	3.61	3	NA
Total number of long COVID symptoms occurring prior to infection (median, IQR)					$W = 362791538$, p-value < 2.2e-16
	1	4	5	5	
Functional performance level (1) (n, %)					$\chi^2 = 1799.4$, df = 2, p-value < 2.2e-16
No Performance Difficulty	30615	97.4	46156	88.2	
Some Functional Performance Difficulty	580	1.8	3848	7.4	
Severe Functional Performance Difficulty	242	0.8	2345	4.5	
Post-infection OT Evaluation level (n, %)					$\chi^2 = 126.82$, df = 4, p-value < 2.2e-16
Low complexity	136	0.4	711	1.4	
Moderate complexity	89	0.3	268	1.0	
High complexity	<50	<0.1	<50	<0.1	
Re-evaluation	<50	<0.01	<50	<0.1	
None	31184	99.2	51289	98	
Pre-infection functional score (n, %)					$\chi^2 = 1804.5$, df = 5, p-value < 2.2e-16
0	29295	93.2	43443	83	
1	1383	4.4	5262	10	
2	608	2.2	3377	6.5	
3	63	0.2	219	0.4	
4	<50	<0.1	<50	0.1	
5	<50	<0.1	<50	<0.1	
Post-infection functional score (n, %)					$\chi^2 = 2240.5$, df = 4, p-value < 2.2e-16
0	30391	96.7	45432	86.8	
1	674	2.1	4093	7.8	
2	335	1.1	2617	5	
3	35	0.3	169	0.3	
4	<50	<0.1	<50	<0.1	
5	<50	<0.1	<50	<0.1	
Days from first infection to "Finding of Functional Performance and Activity" code					$\chi^2 = 0$, df = 1, p-value = 1
90 days or fewer	269		1491		
Past 90 days	571		4717		

Table 2. Comparison of symptom frequency pre- and post-infection, shown by group

	Symptoms within 5 years preceding first infection				Symptoms after infection	
	Recovered participants		Long COVID symptomatic participants		Long COVID symptomatic participants	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Abdominal	6106	7.29	22653	27.04	13439	20.07
Anxiety	4805	5.73	21635	25.82	17870	26.68
Chest Pain	5795	6.92	23228	27.72	14541	21.71
Cognition	4592	5.48	18774	22.41	9528	14.23
Cough	4133	4.93	20084	23.97	15709	23.46
Depression	2378	2.84	11108	13.26	6260	9.35
Diarrhea	2773	3.31	12426	14.83	6712	10.02
Dizziness	3841	4.58	17338	20.69	12252	18.29
Dyspnea	3881	4.63	16970	20.25	11345	16.94
Fatigue	1600	1.91	6522	7.78	3545	5.29
Fever	2980	3.56	13240	15.80	5676	8.48
Headache	1260	1.50	6057	7.23	3874	5.78
Joint Pain	9006	10.75	31093	37.11	20968	31.31
Loss of Smell	0	0.00	0	0.00	0	0.00
Loss of Taste	0	0.00	0	0.00	0	0.00
ME/CFS	496	0.59	2685	3.20	1304	1.95
Menstrual Disorder	1712	2.04	5338	6.37	2365	3.53
Muscle Fatigue	0	0.00	0	0.00	0	0.00
Muscle Pain	1450	1.73	7783	9.29	3848	5.75
Musculoskeletal Chest Pain	746	0.89	3848	4.59	1907	2.85
Palpitations	1671	1.99	7578	9.04	4365	6.52
Paraesthesia	1365	1.63	6170	7.36	3233	4.83
Post-COVID condition, NOS	NA	NA	NA	NA	309	0.46
Post-viral Fatigue Syndrome	0	0.00	0	0.00	0	0.00
POTS	0	0.00	0	0.00	0	0.00
Rash	3444	4.11	13745	16.40	7381	11.02
Sexual Dysfunction	268	0.32	1063	1.27	515	0.77
Sleep	4717	5.63	22029	26.29	18419	27.50
Tachycardia	1397	1.67	5831	6.96	3759	5.61

Table 3. Post-infection symptom correlation matrix

	abdominal	anxiety	chest pain	cough	depression	diarrhea	dizziness	dyspnea	fatigue	fever	headache	cognition	joint pain	me cfs	menstruation	muscle pain	msk chest pain	palpitations	paraesthesia	sexual function	rash	sleep	tachycardia	post COVID NOS
abdominal	1.00	0.10	0.18	0.09	0.09	0.24	0.11	0.13	0.12	0.14	0.12	0.06	0.06	0.03	0.10	0.10	0.07	0.07	0.07	0.02	0.06	0.06	0.14	0.02
anxiety	0.10	1.00	0.09	0.06	0.42	0.10	0.07	0.06	0.10	0.06	0.11	0.13	0.03	0.04	0.06	0.07	0.05	0.06	0.06	0.03	0.05	0.15	0.10	0.03
chest pain	0.18	0.09	1.00	0.14	0.09	0.11	0.16	0.30	0.14	0.11	0.14	0.08	0.09	0.04	-0.01	0.11	0.31	0.15	0.08	0.00	0.05	0.10	0.16	0.04
cough	0.09	0.06	0.14	1.00	0.07	0.08	0.07	0.21	0.12	0.15	0.14	0.03	0.06	0.03	0.02	0.09	0.05	0.05	0.05	0.00	0.04	0.07	0.09	0.06
depression	0.09	0.42	0.09	0.07	1.00	0.11	0.08	0.08	0.12	0.06	0.11	0.16	0.05	0.04	0.04	0.08	0.05	0.01	0.05	0.02	0.04	0.18	0.09	0.03
diarrhea	0.24	0.10	0.11	0.08	0.11	1.00	0.10	0.12	0.14	0.14	0.10	0.07	0.06	0.03	0.02	0.08	0.04	0.05	0.05	0.00	0.07	0.08	0.12	0.02
dizziness	0.11	0.07	0.16	0.07	0.08	0.10	1.00	0.15	0.17	0.07	0.13	0.08	0.06	0.05	0.01	0.06	0.05	0.14	0.09	0.00	0.05	0.08	0.10	0.02
dyspnea	0.13	0.06	0.30	0.21	0.08	0.12	0.15	1.00	0.19	0.14	0.10	0.07	0.05	0.06	-0.01	0.08	0.04	0.14	0.07	-0.01	0.04	0.15	0.19	0.07
fatigue	0.12	0.10	0.14	0.12	0.12	0.14	0.17	0.19	1.00	0.14	0.13	0.10	0.08	0.30	0.02	0.10	0.06	0.08	0.10	0.02	0.07	0.14	0.11	0.05
fever	0.14	0.06	0.11	0.15	0.06	0.14	0.07	0.14	0.14	1.00	0.09	0.04	0.03	0.04	0.02	0.08	0.04	0.04	0.04	0.01	0.06	0.04	0.17	0.01
headache	0.12	0.11	0.14	0.14	0.11	0.10	0.13	0.10	0.13	0.09	1.00	0.07	0.07	0.06	0.05	0.12	0.06	0.07	0.10	0.02	0.04	0.08	0.08	0.04
cognition	0.06	0.13	0.08	0.03	0.16	0.07	0.08	0.07	0.10	0.04	0.07	1.00	0.04	0.04	-0.01	0.05	0.03	0.02	0.04	0.00	0.03	0.09	0.06	0.03
joint pain	0.06	0.03	0.09	0.06	0.05	0.06	0.06	0.05	0.08	0.03	0.07	0.04	1.00	0.04	-0.02	0.12	0.08	0.03	0.09	0.01	0.05	0.09	0.03	0.01
me cfs	0.03	0.04	0.04	0.03	0.04	0.03	0.05	0.06	0.30	0.04	0.06	0.04	0.04	1.00	0.02	0.05	0.03	0.04	0.05	0.02	0.03	0.06	0.03	0.05
menstruation	0.10	0.06	-0.01	0.02	0.04	0.02	0.01	-0.01	0.02	0.02	0.05	-0.01	-0.02	0.02	1.00	0.02	0.02	0.02	0.02	0.06	0.04	-0.03	0.03	0.01
muscle pain	0.10	0.07	0.11	0.09	0.08	0.08	0.06	0.08	0.10	0.08	0.12	0.05	0.12	0.05	0.02	1.00	0.09	0.05	0.09	0.05	0.05	0.07	0.05	0.03
msk chest pain	0.07	0.05	0.31	0.05	0.05	0.04	0.05	0.04	0.06	0.04	0.06	0.03	0.08	0.03	0.02	0.09	1.00	0.03	0.05	0.01	0.03	0.04	0.04	0.01
palpitations	0.07	0.06	0.15	0.05	0.01	0.05	0.14	0.14	0.08	0.04	0.07	0.02	0.03	0.04	0.02	0.05	0.03	1.00	0.06	0.01	0.04	0.04	0.14	0.03
paraesthesia	0.07	0.06	0.08	0.05	0.05	0.05	0.09	0.07	0.10	0.04	0.10	0.04	0.09	0.05	0.02	0.09	0.05	0.06	1.00	0.01	0.05	0.06	0.04	0.03
sexual function	0.02	0.03	0.00	0.00	0.02	0.00	0.00	-0.01	0.02	0.01	0.02	0.00	0.01	0.02	0.06	0.05	0.01	0.01	0.01	1.00	0.01	0.00	0.00	0.01
rash	0.06	0.05	0.05	0.04	0.04	0.07	0.05	0.04	0.07	0.06	0.04	0.03	0.05	0.03	0.04	0.05	0.03	0.04	0.05	0.01	1.00	0.03	0.05	0.01
sleep	0.06	0.15	0.10	0.07	0.18	0.08	0.08	0.15	0.14	0.04	0.08	0.09	0.09	0.06	-0.03	0.07	0.04	0.04	0.06	0.00	0.03	1.00	0.06	0.03
tachycardia	0.14	0.10	0.16	0.09	0.09	0.12	0.10	0.19	0.11	0.17	0.08	0.06	0.03	0.03	0.03	0.05	0.04	0.14	0.04	0.00	0.05	0.06	1.00	0.03
post COVID NOS	0.02	0.03	0.04	0.06	0.03	0.02	0.02	0.07	0.05	0.01	0.04	0.03	0.01	0.05	0.01	0.03	0.01	0.03	0.03	0.01	0.01	0.03	0.03	1.00

Table 4. Adjusted standardized mean differences in functional status by model covariates

	SMD	Std. Error	Lower	Upper	Z	P (0.01)
Group: Long COVID symptomatic participants						
Long COVID symptomatic participants (compared to asymptomatic participants)	0.20	0.03	0.16	0.25	8.20	<0.0000
Age						
Long COVID symptomatic participants at age cuts compared to sample mean (62 years)						
25	0.38	0.02	0.43	0.34	22.00	<0.0000
35	0.28	0.01	0.32	0.25	20.00	<0.0000
45	0.18	0.01	0.20	0.15	20.00	<0.0000
55	0.07	0.00	0.08	0.06	20.00	<0.0000
62	0.00	0.00	0.00	0.00	NA	
75	0.14	0.01	0.12	0.15	20.00	<0.0000
85	0.24	0.01	0.21	0.27	20.00	<0.0000
Sex (compared to male)						
Female/Intersex	0.10	0.01	0.13	0.06	7.00	<0.0000

Race (compared to white)						
Black or African American	0.18	0.02	0.14	0.22	10.80	0.0000
Asian	0.17	0.05	0.30	0.03	3.20	0.0013
Middle Eastern or North African	0.11	0.09	0.34	0.13	1.20	0.2389
More than One Population	0.08	0.05	0.21	0.06	1.40	0.1558
Ethnicity						
Hispanic or Latino	0.32	0.05	0.15	0.09	0.68	0.5000
Highest grade completed (compared to Some college or college grad)						
Less than high school	0.02	0.07	0.17	0.20	0.27	0.7879
Some high school or GED	0.06	0.02	0.01	0.10	3.39	0.0007
Some college or college grad	0.00	0.00	0.00	0.00	NA	NA
Advanced degree	0.14	0.02	0.18	0.09	8.22	0.0000
Variant, compared to pre-VOC						
Pre-VOC/alpha/beta	0.15	0.02	0.19	0.11	9.10	<0.0000
Alpha/beta/delta	0.21	0.03	0.27	0.14	8.30	<0.0000
delta	0.31	0.03	0.38	0.25	12.40	<0.0000
Omicron/BA1/BA2	0.52	0.03	0.60	0.44	17.10	<0.0000
Omicron/BA2/BA5	0.99	0.07	1.16	0.82	15.20	<0.0000
Pre-infection symptom totals (by quartiles)						
0	0.08	0.02	0.13	0.04	3.40	0.0006
1	0.07	0.02	0.10	0.03	3.80	0.0001
4	0.00	0.00	0.00	0.00	NA	NA
7	0.10	0.01	0.08	0.11	15.20	0.0000
23	0.74	0.05	0.64	0.83	15.20	0.0000
Pre-infection functional performance level (from OMOP code 4089214), compared to no impairment						
Some	0.74	0.02	0.69	0.79	38.00	<0.0000
Severe	1.23	0.02	1.17	1.29	55.00	<0.0000
Three-way interaction: Long COVID group, age, and prior symptom burden						
Long COVID symptomatic participants with no prior symptoms compared to asymptomatic participants, at age cuts:						
25	0.73	0.06	0.62	0.84	13.00	<0.0000
45	0.61	0.04	0.53	0.69	15.00	<0.0000
65	0.50	0.04	0.43	0.56	14.00	<0.0000
75	0.44	0.04	0.36	0.51	12.00	<0.0000

Long COVID symptomatic participants with 7 prior symptoms compared to asymptomatic participants, at age cuts:						
25	0.45	0.05	0.35	0.56	8.60	<0.0000
45	0.34	0.04	0.27	0.41	9.50	<0.0000
65	0.22	0.03	0.17	0.27	8.20	<0.0000
75	0.16	0.03	0.11	0.22	5.60	<0.0000

FIGURES

Figure 1.

Cohort diagram

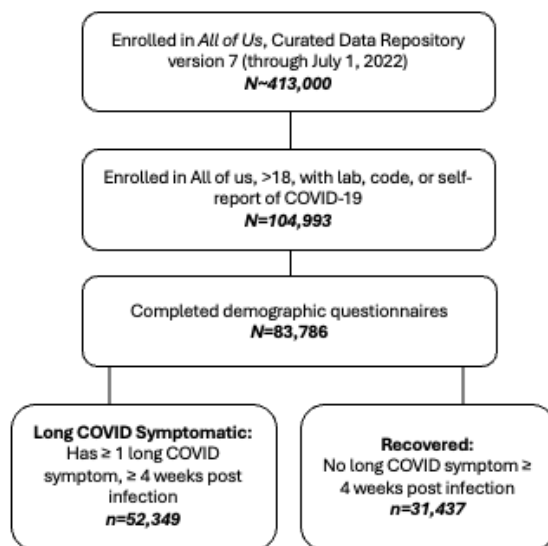


Figure 2.

Pre-infection prevalence of symptoms in each group

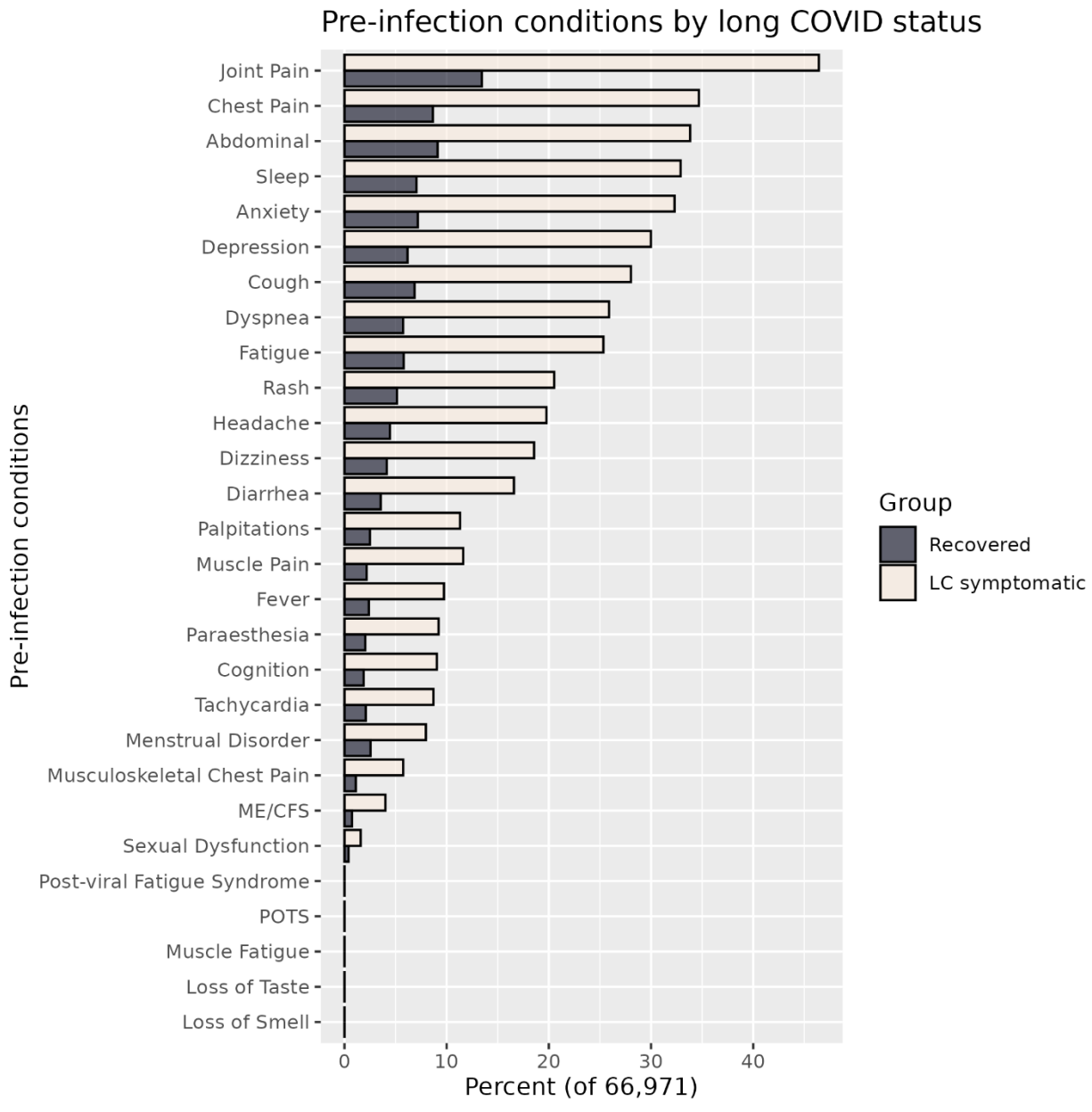
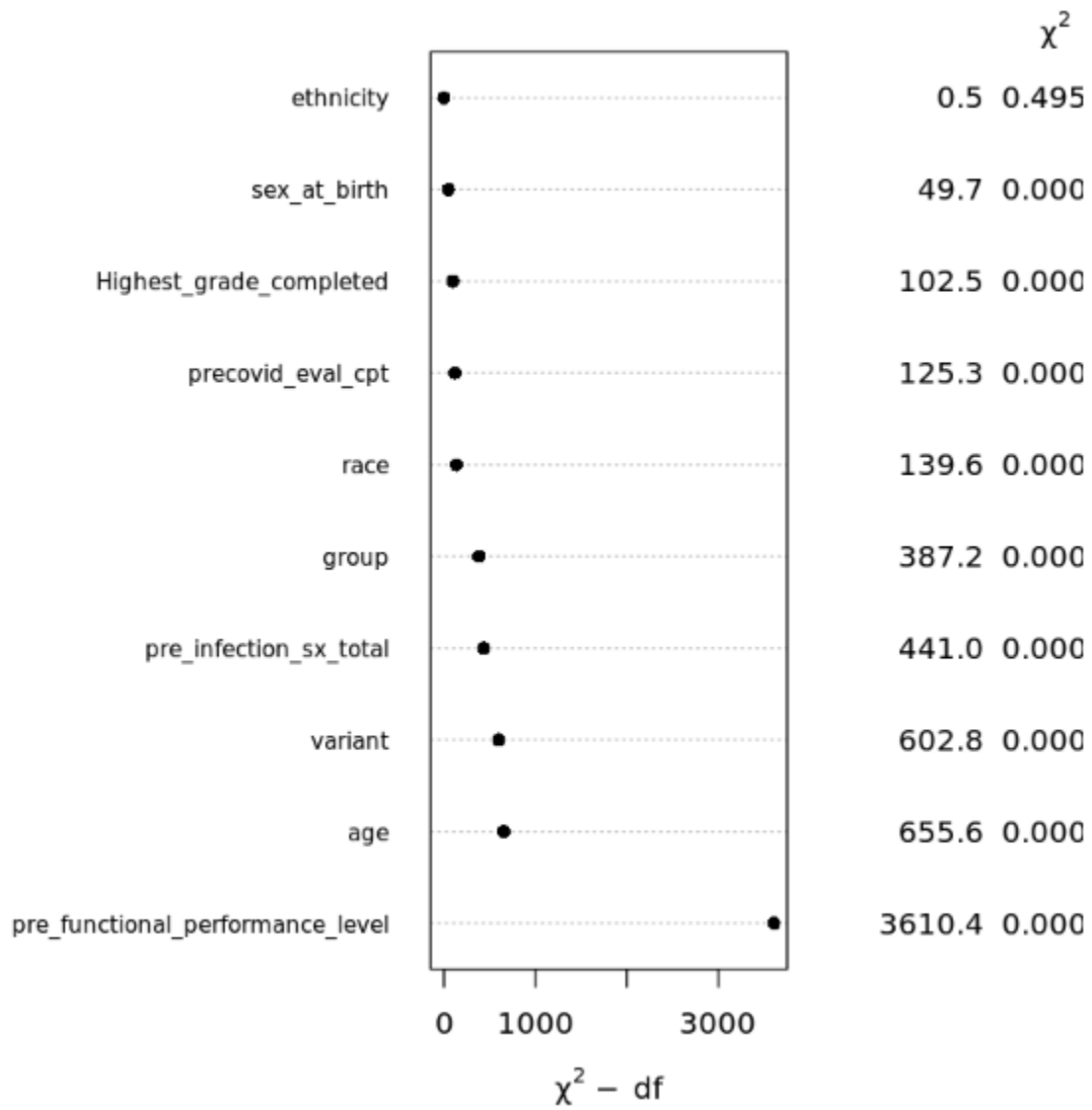


Figure 3.

Main effects χ^2 of covariates on the outcome of functional status impairment

REFERENCES

1. Thaweethai T, Jolley ES, Karlson WE, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA*. Jun 13 2023;329(22):1934. doi:10.1001/jama.2023.8823
2. Davis EH, Mccorkell L, Vogel MJ, Topol JE. Long COVID: major findings, mechanisms and recommendations. *Nature Reviews Microbiology*. Mar 2023;21(3):133-146. doi:10.1038/s41579-022-00846-2
3. Al-Aly Z, Davis H, McCorkell L, et al. Long COVID science, research and policy. *Nat Med*. Aug 2024;30(8):2148-2164. doi:10.1038/s41591-024-03173-6
4. Hou Y, Gu T, Ni Z, Shi X, Ranney ML, Mukherjee B. Global Prevalence of Long COVID, its Subtypes and Risk factors: An Updated Systematic Review and Meta-Analysis. *medRxiv*. Jan 6 2025;doi:10.1101/2025.01.01.24319384
5. National Center for Health Statistics USCB. *Household Pulse Survey - Long COVID*. 2024. <https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm>
6. Ladds E, Rushforth A, Wieringa S, et al. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Serv Res*. Dec 20 2020;20(1):1144. doi:10.1186/s12913-020-06001-y
7. Vanichkachorn G, Newcomb R, Cowl CT, et al. Post-COVID-19 syndrome (long haul syndrome): Description of a multidisciplinary clinic at Mayo Clinic and characteristics of the initial patient cohort. *Mayo Clin Proc*. Jul 2021;96(7):1782-1791. doi:10.1016/j.mayocp.2021.04.024
8. Cohen J, Rodgers YVM. Long COVID Prevalence, Disability, and Accommodations: Analysis Across Demographic Groups. *J Occup Rehabil*. Jun 2024;34(2):335-349. doi:10.1007/s10926-024-10173-3
9. Banic M, Jankovic Makek M, Samarzija M, et al. Risk factors and severity of functional impairment in long COVID: a single-center experience in Croatia. *Croat Med J*. Feb 28 2022;63(1):27-35. doi:10.3325/cmj.2022.27
10. Bach K. New data shows long Covid is keeping as many as 4 million people out of work. Published August 24, 2022. Accessed Feb. 28, 2023, <https://www.brookings.edu/research/new-data-shows-long-covid-is-keeping-as-many-as-4-million-people-out-of-work/#:~:text=The%20economic%20burden%20of%20lost,total%20U.S.%20gross%20domestic%20product>
11. Koumpias AM, Schwartzman D, Fleming O. Long-haul COVID: healthcare utilization and medical expenditures 6 months post-diagnosis. *BMC Health Serv Res*. Aug 8 2022;22(1):1010. doi:10.1186/s12913-022-08387-3
12. National Academies of Sciences Engineering and Medicine. *A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences*. The National Academies Press; 2024.
13. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. Apr 2022;22(4):e102-e107. doi:10.1016/s1473-3099(21)00703-9
14. Gutzeit J, Weiß M, Nürnberger C, et al. Definitions and symptoms of the post-COVID syndrome: an updated systematic umbrella review. *Eur Arch Psychiatry Clin Neurosci*. Jul 25 2024;doi:10.1007/s00406-024-01868-y
15. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594(7862):259-264. doi:10.1038/s41586-021-03553-9
16. Appel SK, Nürnberger C, Bahmer T, et al. Definition of the Post-COVID syndrome using a symptom-based Post-COVID score in a prospective, multi-center, cross-sectoral cohort of the German National Pandemic Cohort Network (NAPKON). *Infection*. Apr 8 2024;doi:10.1007/s15010-024-02226-9
17. Gentilotti E, Górska A, Tami A, et al. Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. *EClinicalMedicine*. Aug 2023;62:102107. doi:10.1016/j.eclinm.2023.102107
18. Prabhakaran D, Day G, Munipalli B, et al. Neurophenotypes of COVID-19: risk factors and recovery trajectories. *Brain Behav Immun Health*. Dec 21 2022;doi:10.21203/rs.3.rs-2363210/v1
19. Reese JT, Blau H, Casiraghi E, et al. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes. *EBioMedicine*. Jan 2023;87:104413. doi:10.1016/j.ebiom.2022.104413
20. Zhang H, Zang C, Xu Z, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med*. Jan 2023;29(1):226-235. doi:10.1038/s41591-022-02116-3
21. Deer RR, Rock AM, Vasilevsky N, et al. Characterizing Long COVID: Deep Phenotype of a Complex Condition. *eBioMedicine*. Dec 2021;74:103722. doi:10.1016/j.ebiom.2021.103722
22. National institutes of Health. Data from: All of Us, Curated data repository version 7, Controlled Tier C2022Q4R9. 2022-2025. Deposited April 15, 2023.

23. Centers for Disease Control and Prevention. Long COVID or Post-COVID Conditions. https://www.cdc.gov/covid/long-term-effects/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/
24. New ICD-10-CM code for Post-COVID Conditions, following the 2019 Novel Coronavirus (COVID-19) (2021).
25. Markov PV, Ghafari M, Beer M, et al. The evolution of SARS-CoV-2. *Nat Rev Microbiol*. Jun 2023;21(6):361-379. doi:10.1038/s41579-023-00878-2
26. Silva-Passadouro B, Tamasauskas A, Khoja O, et al. A systematic review of quantitative EEG findings in Fibromyalgia, Chronic Fatigue Syndrome and Long COVID. *Clin Neurophysiol*. May 6 2024;163:209-222. doi:10.1016/j.clinph.2024.04.019
27. Davis EH, Assaf SG, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *eClinicalMedicine*. Aug 2021;38:101019. EClinicalMedicine. doi:10.1016/j.eclinm.2021.101019
28. Centers for Medicare and Medicaid Services. Billing and Coding: Therapy Evaluation, Re-Evaluation and Formal Testing. A53309. DHHS, CMS. Accessed 10/3/2024, 2024. <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53309>
29. World Health Organization. *International Classification of Functioning, Disability and Health (ICF)*. 2001. <https://www.who.int/classifications/icf/en/>
30. Harrell FE. *Regression Modeling Strategies*. 2nd ed. Springer Series in Statistics. Springer; 2001.
31. Sivan M, Parkin A, Makower S, Greenwood DC. Post-COVID syndrome symptoms, functional disability, and clinical severity phenotypes in hospitalized and nonhospitalized individuals: A cross-sectional evaluation from a community COVID rehabilitation service. *J Med Virol*. Apr 2022;94(4):1419-1427. doi:10.1002/jmv.27456
32. Nielsen TB, Leth S, Pedersen M, et al. Mental Fatigue, Activities of Daily Living, Sick Leave and Functional Status among Patients with Long COVID: A Cross-Sectional Study. *International journal of environmental research and public health*. Nov 9 2022;19(22)doi:10.3390/ijerph192214739
33. Zhang JJ, Dong X, Liu GH, Gao YD. Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality. *Clin Rev Allergy Immunol*. Feb 2023;64(1):90-107. doi:10.1007/s12016-022-08921-5
34. Mazer B, Ehrmann Feldman D. Functional Limitations in Individuals With Long COVID. *Archives of physical medicine and rehabilitation*. Sep 2023;104(9):1378-1384. doi:10.1016/j.apmr.2023.03.004
35. Hellmuth J, Barnett TA, Asken BM, et al. Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients. *J Neurovirol*. Feb 2021;27(1):191-195. doi:10.1007/s13365-021-00954-4
36. McCorkell L, G SA, H ED, Wei H, Akrami A. Patient-Led Research Collaborative: embedding patients in the Long COVID narrative. *Pain Rep*. 2021;6(1):e913. doi:10.1097/pr9.0000000000000913
37. Almeria M, Cejudo JC, Deus J, Krupinski J. Long Neurocognitive and Neuropsychiatric Sequelae in Participants with Post-COVID-19 Infection: A Longitudinal Study. *Neurol Int*. Aug 16 2024;16(4):853-868. doi:10.3390/neurolint16040064
38. Kehl-Floberg K, Gangnon R, Edwards D. OT Utilization in Long COVID: Insights From the All of Us Research Program. In: *American Occupational Therapy Association (AOTA INSPIRE) Annual Conference & Expo, March 21-23, 2024, Orlando, Florida*. American Occupational Therapy Association; 2024:1-1.
39. Kehl-Floberg K, Pop-Vicas A, Giles G, Edwards D. The Functional Consequences of Long COVID Need to Be Addressed by Occupational Therapists. *Am J Occup Ther*. Sep 1 2024;78(5)doi:10.5014/ajot.2024.050707
40. Rando HM, Bennett TD, Byrd JB, et al. Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. *medRxiv*. Mar 26 2021;medRxiv. doi:10.1101/2021.03.20.21253896

Chapter 6. Manuscript 3

**Older age and long COVID symptoms independently increase functional impairment after
COVID-19: An analysis of *All of Us* Research Program data.**

Kristen Kehl-Floberg*

Emma Friesburg

Ron Gangnon

Dorothy Edwards

* Corresponding author: kekehl@wisc.edu

Abstract

BACKGROUND AND OBJECTIVES: Long COVID is a global health challenge that can cause disability and loss of health-promoting roles and routines. Older adults are at particularly high risk, however there is little evidence from health records data connecting long COVID symptoms and risk factors to functional outcomes in older adults. We hypothesized that older age would be associated with greater functional impairment after adjusting for long COVID symptoms. Our secondary exploratory hypothesis is that symptom clusters that include cognition and fatigue will be associated with greater functional impairment.

DESIGN AND METHODS: Retrospective cohort study using data from the *All of Us* Research Program. Participants with history of COVID-19 were classified as long COVID symptomatic (at least one long COVID symptom 28 days after infection) or recovered (no symptoms after infection). Descriptive statistics for demographics, exploratory hierarchical cluster analysis of symptoms, and an ordinal probit regression model for main effects on level of functional impairment after COVID-19 were computed.

RESULTS: Long COVID symptomatic participants tended to be older (mean 65.1% vs. 57.53%), and were more frequently female (64.8% vs. 61.6%) and Black (20.2% vs. 17.5%). Post-infection functional impairment was greater in older-aged ($X^2=675.62$) and long COVID symptomatic participants ($X^2=353.32$). The differences in mean functional status between cases and controls were greater at younger-aged (at 25 years of age SMD: -0.60, 99% CI: -0.70 - -0.50, $p < 0.000$) compared to older-aged participants (85 years of age SMD: 0.37, 99% CI: 0.31 – 0.43, $p < 0.000$). Large and significant main effects were also found for pre-illness functioning ($X^2=3637.87$), infection variant ($X^2=596.66$), and number of pre-COVID symptoms ($X^2=395.51$).

The symptom cluster containing fatigue and cognition was most strongly correlated with post-infection functional impairment (0.26).

DISCUSSION AND IMPLICATIONS: Both older age and long COVID symptoms both independently increased the likelihood of post-infection functional impairment, even when controlling for other risk factors. The post-COVID infection assessment and care of older adults should include measurement of functional change from pre-infection baseline using instruments that are able to detect functional status changes in older people.

KEYWORDS

Older adult, Long COVID, Functional status, Functional performance and activity, Activities of daily living.

Introduction

Long COVID – persistent exacerbations or new onset of health conditions following a COVID-19 infection (Al-Aly et al., 2024) – has become a global health challenge affecting about 30% of adults who have had COVID-19 (Hou et al., 2025). Long COVID symptoms can be severe enough to cause disability by decreasing *functional status* (the ability to perform daily activities and routines). For this reason, functional status has been proposed as a diagnostic criterion of this evolving disorder (National Academies of Sciences Engineering and Medicine, 2024; Soriano et al., 2022).

Older adults may be at particularly high risk for functional impairment in long COVID. Older age is an independent risk factor for SARS-CoV-2 infection (Hou et al., 2025), as well as severe COVID-19 which confers additional risk for long COVID (Tana et al., 2023). In addition, older age is associated with functional impairment in the general population (Chatterji et al., 2015), and older adults who were hospitalized for COVID-19 have shown high proportions of poor functional status both before and after illness (Izaguirre et al., 2023). Long COVID related disability affects complex and “chosen” activities such as leisure, social, volunteer/paid work, and family or household activities (Carter et al., 2022; Nielsen et al., 2022), and participation in complex activities is associated with lower risk for functional impairment (Kail & Carr, 2017). Thus, Long COVID-related functional impairment may potentiate risk for poorer future health outcomes in older adults.

Despite these associations, the evidence concerning the impact of long COVID on functional status is relatively mixed for older adults. Studies of long COVID’s effect on functioning in middle-aged adults are comparatively plentiful. Many studies measure functional status using assessments of employment status (Jaywant et al., 2024), absenteeism, or sick leave

(Nielsen et al., 2022). Although these are important outcomes, they may not reflect the functional impairments among adults who are retired, caregiving for family, or volunteering. Selection and reporting biases are other potential confounders. For instance, in analysis of U.S. Census Bureau Household Pulse survey data, the prevalence of self-reported activity limitation was *lower* in older compared to middle-aged adults (Ford et al., 2023), a counterintuitive finding which the authors postulate may have been due to selection bias. In hospitalized older adults, lower baseline functional status increased the odds of post-discharge functional limitations (Izaguirre et al., 2023) and functional limitations were associated with lower health-related quality of life in older adults (Shanbehzadeh et al., 2023). In a sample of veterans, frailty - a related but distinct construct to functional status - was 1.54 times more likely in older adults with long COVID than matched recovered participants (Seligman et al., 2024).

In addition to the variation in functional presentation, long COVID symptoms themselves may present differently in older adults compared to middle or younger adults. The above-mentioned veterans study found that the most common symptoms among older vets were fatigue, anemia, gait abnormality, muscle fatigue, and arthritis (Seligman et al., 2024). While symptom prevalences vary somewhat across studies (Hou et al., 2025), gait abnormality, anemia, and arthritis are not the most prevalent in studies that do not stratify by age. Conversely, symptoms and conditions that are consistently found to be highly prevalent are missing from this list, notably cognitive dysfunction and pain which more common among older people in the general population. This may be due to known assessment challenges contributing to under-detection of cognitive dysfunction (Cahan et al., 2024; Prabhakaran et al., 2022; Schild et al., 2024; Verveen et al., 2024) or patients' use of compensatory strategies (De Vito et al., 2024). This discrepancy

suggests that data-driven definitions and phenotypes should consider differences in presentation by age for optimal accuracy and clinical utility.

Age-related differences in symptom presentation have also been under-reported in many large-scale studies that have aimed to identify diagnostic frameworks of long COVID. The aims of EHR-based phenotyping studies of long COVID have been to identify subtypes that differentiate long COVID as (a) a true clinical syndrome from non-presentation or other viruses such as influenza (Al-Aly et al., 2021) and (b) various presentations of symptoms and conditions (Gentilotti et al., 2023; Gonzalez Aleman et al., 2024; Kitsios et al., 2024; Mina et al., 2023; Prabhakaran et al., 2022; Reese et al., 2023; Thaweethai et al., 2023; Zhang et al., 2023), laboratory measures of putatively important biomarkers (Deer et al., 2021; Erlandson et al., 2024), and medical outcomes and drug utilization (Al-Aly et al., 2021). These studies have reported phenotypes, but not their relationships with functional status.

The primary aim of this study is to compare the likelihood of post-infection functional status changes in older versus younger adults with and without long COVID symptoms in a population-level dataset. We hypothesize that older age will be associated with greater functional impairment after adjusting for long COVID symptoms. Our secondary exploratory hypothesis is that symptom clusters that include cognition and fatigue will be associated with greater functional impairment.

Materials and Methods

Design and data source

This was a retrospective cohort study of participants enrolled in the U.S. National Institutes of Health *All of Us* Research Program through July 2022 in the Controlled Tier of curated data release version 7.0 (National institutes of Health, 2022-2025). *All of Us* is a

longitudinal cohort study recruiting participants from all 50 U.S. States and three territories. Participants share their health information through surveys, biospecimens, and EHR data transfer. EHR data is taken at baseline and subsequently every three months. All EHR observations in *All of Us* are harmonized and structured according to the Observational Medical Outcomes Partnership – Common Data Model (Observational Health Data Sciences and Informatics, 2024; Odysseus Data Services, 2023). This ensures consistency across data collection sites and regions, and comparability with billing and treatment codes (see Appendix A). *All of Us* utilizes community-relevant recruitment methods to over-recruit from geographic areas and demographic groups that are under-represented in medical and health research. The program, data snapshots, and data methods can be viewed at <https://www.researchallofus.org/data-tools/>. (Appendix A.)

Sample

We included *All of Us* participants 18 years of age and older with at least one incidence of any indicator of COVID-19. COVID-19 indicators included lab results, self-reported illness consistent with COVID-19, and the ICD-10 COVID diagnostic code *U07.7*. Informed consent for sharing electronic health records and survey data was obtained from all participants their respective *All of Us* Health Provider Organizations responsible for participant recruitment and enrollment. All sites delegated IRB oversight to the *All of Us* Central IRB.

Participants were then grouped into two long COVID groups. Participants were classified as “long COVID symptomatic” if they had at least one incidence of at least one of 38 broad long COVID symptom/condition categories, entered at least 28 days after their first incidence of the COVID-19 infection indicators. Participants with no post-infection symptoms were classified as “recovered”. The definition of long COVID from the Patient-Led Research Collaborative

includes exacerbations or relapses of pre-infection conditions (Al-Aly et al., 2024; Davis et al., 2021; Thaweethai et al., 2023), therefore we queried “any mention” of the symptoms/conditions in our list. The post-infection interval of 28-days before first symptom occurrence was chosen to capture health and daily functioning beginning after the presumptive acute infection phase but still within 90 days post-infection. Because the present analysis explores functional impairment as part of this diagnostic classification, this shorter delay was selected to characterize functional changes in the setting of long COVID within a timeframe that would be clinically useful in the U.S. for utilizing skilled rehabilitation. Appendix A reports disease indicators, long COVID sequelae, and selection process.

Long COVID symptoms and conditions.

The list of long COVID symptoms was selected a-priori based on the Centers for Disease Control and Prevention’s list of symptoms (Centers for Disease Control and Prevention, 2023) and emergency billing code for “Post-COVID Condition, Unspecified”, *U07.7*,(2021) prior phenotyping and patient-led literature (Al-Aly et al., 2021; Appel et al., 2024; Davis et al., 2021; Davis et al., 2023; Deer et al., 2021; Gentilotti et al., 2023; Markov et al., 2023; Prabhakaran et al., 2022; Reese et al., 2023; Silva-Passadouro et al., 2024; Thaweethai et al., 2023; Zhang et al., 2023), and the authors’ clinical experience and community-based research. Diagnosis codes and dates of entry were included within two time periods: 5 years to 28 days prior to first infection (pre-infection symptoms) and 28 days or longer after infection (post-infection symptoms; also used as the long COVID cohort indicator). For each period, the total number of symptom/condition categories with at least one incidence were summed to indicate symptom burden. Because the definition of long COVID from the Patient-Led Research Collaborative

includes exacerbations or relapses of pre-infection conditions,^{1,3,27} we queried “any mention” of the symptoms/conditions in the list. The first entry of each code was the indexing incidence.

Our selection process and rationale, condition categories, and exclusions are reported in Appendix A.

Infection variants active at time of first infection

We created a time-bound variable to infer variant exposure at date of first SARS-CoV-2 infection. Periods began and ended around the emergence of major variants as reported by Markov et al.(2023, Fig. 3a) Resultant periods were “pre-VOC/wild type” from January-November 2020, “pre-VOC/alpha/beta from November 2020 – April 2021, “alpha/beta/delta” from April-August 2021, “delta” from August-December 2021, “omicron_BA1-BA2” from December 2021 – April 2022, and “omicron_BA2-BA5” from April 2022 – July 2022 (the data release cut-off date for *All of Us* curated data release 7).

Daily functioning indicators

We obtained evidence of daily functioning from EHR procedure and diagnostic codes entered between 28 days and 5 years prior to the first infection starting as early as January 1, 2015 (pre-covid function) and ≥ 28 days after first infection (post-covid function). The indicators imported were (a) occupational therapy (OT) evaluation billing codes (low, moderate, and high complexity, and re-evaluation), and (b) observations under the EHR coding hierarchy “Finding of Functional Performance and Activity”. OT evaluation was chosen as an indicator because it is the therapeutic discipline designated by the U.S. Centers for Medicare and Medicaid Services (CMS) to address deficits in daily performance, making it the most specific discipline for functional performance deficits (Centers for Medicare and Medicaid Services, 2020). The

complexity levels were given the ordinal values of 0 = no observation, 1 = low complexity, 2 = moderate complexity or re-evaluation, and 3 = high complexity. The “Finding of Functional Performance and Activity” observations were filtered for rehabilitation or participation concepts aligned with the WHO International Classification of Functioning, Disability, and Health (ICF) (2001) to describe level of independence and/or characteristics of observable daily activity performance, as documented in rehabilitation and/or acute care encounters. Presumptive severity of functional impairment was then inferred in consultation between the first author and clinical experts, and given the ordinal levels 0 = No impairment, 1 = some impairment, 2 = severe impairment. These two EHR variables were summed to pre- and post-infection daily functional status as a 0-5 level ordinal variable. Functional status indicator descriptions, definitions, and classification codes are reported in Appendix B.

Model variable selection

All variables for modelling were chosen a-priori based on the available literature. In addition to age we included sex assigned at birth, race, and ethnicity, as these are associated with long COVID risk (Jacobs et al., 2023; Khullar et al., 2023; Tana et al., 2023; Vasilevskaya et al., 2023) and its relationship with functional status (Ford et al., 2023; Izaguirre et al., 2023). We included education level, expressed as “highest grade completed” due to its impact on the lifespan, health, and access to health-supporting societal resources such as income and health insurance (U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion, 2025). These have been found to be associated with differences in number and persistence of symptoms and decreased quality of life after COVID-19 infection (Case et al., 2022; Eligulashvili et al., 2024). The covariates and their data sources are tabulated in Appendix D.

Analysis

This study used population health and phenotyping analysis approaches. Demographics were graphed to visually assess distribution, and tested using Welch's t test (normal), Mann-Whitney U test (non-normal), or X^2 test (categorical). Distributions of long COVID symptoms/conditions and functional impairments were tallied and graphed as proportions of the sample. Groupings of long COVID symptoms in long COVID symptomatic were explored using hierarchical cluster analysis with Spearman's ρ (b). An ordinal probit logistic regression model for main effects was fitted for the probability of decreased mean functional status. Model linearity, interaction terms, and residual fit were assessed with established procedures (Harrell, 2001). Data analysis was performed in the *All of Us* Researcher Workbench, Jupyter notebooks cloud computing environment, using R programming language (R Core Team, 2022). Cohort discovery, cleaning, dataset building, and statistical analyses were completed by the first and second author in Jupyter cloud computing notebooks, using R versions 4.3.0 - 4.4.3. We used R packages "stats" (R Core Team and contributors worldwide, 2025), "rms" (Harrell, 2024), and the "tidyverse" suite (Hadley Wickham, 2019).

Results

Demographics

After removing participants who did not respond to demographic questions, the analyzable sample was $N=83,786$, with $n=52,349$ participants having at least one long COVID symptom (long COVID symptomatic) and $n=31,437$ recovered participants (Figure 1). Distributions of our demographic, variant, and functional status pre- and post-infection are presented in Table 1. Compared to recovered participants, the long COVID symptomatic group

had a higher mean age (65.51 versus 57.53 years), and higher proportion of female/intersex (64.8% versus 61.6%) and black or African-American (20.2% versus 17.5%) participants. The symptomatic group had a higher proportion of infections in the pre-variant time period (51.8% versus 30.8%; Appendix E), and greater mean number of symptoms prior to infection, at 5.83 (SD 3.98) in symptomatic versus 2.30 (SD 2.86) in recovered participants. A lower proportion of long COVID symptomatic participants had advanced degrees (24.2%, versus 29.2% of recovered participants). The groups were not meaningfully different in proportions of Hispanic/Latino ethnicity. Among long COVID symptomatic participants, the mean number of long COVID symptoms after infection was 3.61 (SD 2.72).

[Insert Table 1 about here]

[Insert Figure 1 about here]

Indicators of functional status suggested a higher burden of functional impairment among long COVID symptomatic both pre- and post-infection. Pre-infection functional performance indicators showed some impairment in 9.5% of long COVID symptomatic (compared to 3.8% of recovered participants) and severe functional impairment in 5.8% (compared to 1.8%; $X^2=1799.4$). Pre-infection OT evaluations, although infrequent overall, were more frequent among long COVID symptomatic ($X^2=83786$) as was higher pre-infection functional impairment ($X^2=83786$).

Model adjusted standardized mean differences in functional impairment

The final model was fitted with variables noted above, with interaction terms between long COVID group with age and pre-infection number of symptoms. The ANOVA omnibus test showing each covariate's contribution to the overall main effect is displayed in Appendix D,

Table S.C.3, Figure S.C.1. Adjusted standard mean differences in functional impairment are tabulated in Table 2.

[Insert Table 2 about here]

Main effects and interactions of age and long COVID group

Both age and long COVID increased the likelihood of poorer functional status. Older age increased the degree of functional impairment in both symptomatic and recovered participants ($X^2 = 685.5$). Among cases, compared to the age mean of 62 years, 85 year olds had greater impairment (SMD: 0.26, 99% CI: 0.23 – 0.30, $p < 0.000$) and 25 year olds had less impairment (better functional status: SMD: -0.42, 99% CI: -0.48 - -0.39, $p < 0.000$). In recovered participants the trend was similar, however a greater spread was noted between the younger (SMD: -0.60, 99% CI: -0.70 - -0.50, $p < 0.000$) and older-aged groups (SMD: 0.37, 99% CI: 0.31 – 0.43, $p < 0.000$). Long COVID symptomatic participants also showed increased functional impairment as a whole compared to recovered participants ($X^2 = 345.1$, SMD: 0.34, 99% CI: 0.31 – 0.38, $p < 0.000$).

The interaction between long COVID status and age was explored by contrasting Long COVID symptomatic participants with recovered participants at each age cut ($X^2 = 16.02$). Compared to recovered participants, symptomatic participants at younger ages showed greater difference in average impairment than at older ages. For instance, at age 25 the standard mean difference between groups was 0.52 (99% CI: (0.39, 0.65), $p < 0.000$), whereas at age 85 the difference was smaller at 0.23 (99% CI: 0.16, 0.31, $p < 0.000$). These differences in degree notwithstanding, older participants with long COVID symptoms were still more likely to experience functional impairment than their recovered peers (Figure 2).

[Insert Figure 2 about here]

Main effects for pre-infection functional status

The largest effect size in this model was contributed by pre-infection functional status ($X^2 = 3656.3$). Among symptomatic participants, post-infection functional status was substantially worse given some prior impairment (SMD: 0.74, 99% CI: 0.69, 0.79, $p < 0.000$) and nearly twice that level given severe prior impairment (SMD: 1.23, 99% CI: 1.18, 1.29, $p < 0.000$). The predicted probability of post-infection functional impairment was greater at each age cut. In this model, 85 year-olds with *no* prior impairment were as likely as 35 year-olds with *some* impairment to experience post-infection impairments. A similar overlap was observed between *some* and *severe* impairment age groups, with 65 year-olds with some impairment being about as likely to experience post-infection functional impairment as 25 year-olds with severe impairment. This also exhibits progressively greater spread in probability between youngest to oldest ages at increasing levels of prior functional impairment (Figure 3).

[Insert Figure 3 about here]

Main effect of pre-infection symptom burden

The number of symptoms experienced prior to the first COVID-19 infection had a moderate effect on post-infection functioning ($X^2 = 373.9$). Compared to the median of 4 symptoms, post-infection functional status was better for participants with one prior symptom (first quartile; SMD: -0.14, 99% CI: -0.159 - -0.122, $p < 0.000$) and worse for participants with seven prior symptoms (third quartile; SMD: 0.11, 99% CI 0.091, 0.119, $p < 0.000$). Greater years of age increased the probability of post-infection functional impairment at all prior symptom levels through about 15 symptoms (above which the intervals overlapped). 85 year olds with no prior symptom burden were as likely to develop post-infection functional impairment as 25 year-olds with 12-15 symptoms or 45 year-olds with 9-11 symptoms (Figure 4).

[Insert Figure 4 about here]

Long COVID symptoms and symptom clusters (symptomatic group)

Among long COVID symptomatic participants, the incidence of each long COVID symptom category was computed (Table 3 and Figure 5). The most frequently observed conditions were joint pain (31.31%), sleep disturbance (27.5%), and anxiety (26.68%). Several of the most commonly-reported symptoms in other literature were less frequent in this sample, including fatigue (14.56%) and cognition (5.8%). There were no observations of POTS, PVFS, muscle fatigue, loss of smell, or loss of taste.

[Insert Table 3 about here]

[Insert Figure 5 about here]

Figure 6 shows the results of a hierarchical cluster analysis with groupings made off of first-order branches. Where necessary to divide very large clusters, clinically relevant or similar sub-clusters were divided at second-order branches. These clusters were Fatigue/Cognition/Sleep/Mood ($n= 35428$), Paraesthesias/Headache/Pain/Chest pain ($n= 31960$), Respiratory/Abdominal pain/Fever/Tachycardia ($n= 28645$), Dizziness/Palpitations/Skin rash ($n=15487$), and reproductive/menstrual dysfunction ($n=2793$) (Appendix E). Correlations between each cluster and the post-infection functional status score showed that the largest cluster (Fatigue/Cognition/Sleep/Mood) was the most strongly correlated at 0.26 (Table 4). Data reduction methods and resulting cluster compositions are expanded in Appendix E.4.

[Insert Figure 6 about here]

[Insert Table 4 about here]

Discussion

This retrospective cohort study of participants in the *All of Us* Research Program study was among the first to investigate the likelihood of post-infection functional status changes associated with long COVID in a population-level dataset. This was also the first study to use *All of Us* Research Program data to explore the incidences of long COVID symptoms, symptom-driven phenotypes of long COVID, and their correlations with functional status.

Our hypothesis that older age would be associated with greater functional impairment was supported, both before and after adjusting for long COVID symptoms. The interaction between age and long COVID status revealed an intriguing difference across age groups, as younger participants with long COVID symptoms showed larger functional impairment differences (compared to recovered participants) than older adults, and these between-group differences decreased as age increased. In other words, while the risk of functional impairment was increased independently by both years of age and long COVID status, the functional status difference between symptomatic and recovered participants was smaller – but still of moderate strength - at older ages. There are several factors not represented in these data that may have contributed to this. First, at the time this dataset was built there was no variable showing all-cause mortality. Thus, deaths were not accounted for, and it is highly likely that older aged participants had more deaths after their COVID-19 infections relative to younger ages (Hou et al., 2025; Tana et al., 2023). This would pre-empt later referrals to the rehabilitation services that billed the functional observations used in this study. Additionally, older adults may under-report functional status changes (Ford et al., 2023) or attempt to compensate for cognitive impairments (De Vito et al., 2024) rather than present for care. If this was true of the older adults in this sample, they would then appear less impacted by functional impairment which could bias the

standardized mean differences towards the null. Finally, it is possible that the differences observed at older age cuts were smaller not because these participants were less impaired but rather because older adults overall are more likely to have already experienced lower functional status (Chatterji et al., 2015), resulting in a floor effect on this difference. Baseline status notwithstanding, long COVID symptomatic participants in this study were more impaired than recovered participants at all ages, with moderate to high effect sizes. Together, these findings reveal that the relationships between functional status, age, and long COVID are complex and multi-factorial, and that older adults may experience a different impact of other function- and disease-related factors than younger or middle-aged adults.

Our secondary exploratory hypothesis was also supported: The hierarchical cluster analysis of post-infection symptoms found that the cluster containing cognition and fatigue (along with sleep, mood, and chronic fatigue syndrome) was the most strongly correlated with functional impairment. This is consistent with evidence that many complex daily activities are cognitively demanding (Marks et al., 2023; Rog et al., 2014), and that cognition and fatigue are strongly associated with disability in long COVID (Vanichkachorn et al., 2021). We note that the cluster compositions found in this study are similar to several other large data-driven phenotyping studies (for instance, fatigue with cognition (Gentilotti et al., 2023; Thaweethai et al., 2023), joint, muscle or other pain (Gentilotti et al., 2023), and respiratory (Gentilotti et al., 2023)). This suggests that these clusters, though exploratory, have concurrent validity with previously identified symptom-driven phenotypes.

There were substantial differences in the incidences of several of the most common long COVID symptoms. These include fatigue, cognitive impairment, and muscle pain, as well as conditions such as chronic fatigue syndrome and postural orthostatic tachycardia syndrome.

Compared to a recent meta-analysis of pooled data which found that the most common symptom was memory problems (11%) followed by muscle weakness, breathlessness, and dyspnea (Hou et al., 2025), these data showed only 5.8% prevalence of cognitive impairment of any kind. We also found no incidences of either positional orthostatic tachycardia syndrome or post-viral fatigue syndrome, and no diagnostic code for the particularly debilitating symptom of post-exertional malaise (Haunhorst et al., 2024) which has been named as a long COVID research priority (Al-Aly et al., 2024; Patient-led Research Collaborative for Long COVID, 2024).

There are several interpretations of these discrepancies in symptom prevalence suggestive of low assessment sensitivity and age-related differences in symptom presentation. First, the markedly lower prevalence of cognitive impairment may be a result of low sensitivity of common neuropsychological screening tools to the cognitive impairments experienced in long COVID ‘brain fog’, even in patients who report that their cognitive changes led to loss of employment and social roles (Cahan et al., 2024; Pihlaja et al., 2023; Verveen et al., 2024). Because a positive test result on an assessment instrument is required in order for a diagnostic code entered into an individual’s health record (and hence discovered in EHR data), and considering our finding of comparatively lower prevalence of cognitive impairment compared to many other studies, it is possible that our EHR-based design may underestimate the incidence of the cognitive issues experienced by people with long COVID. Thus, lower measurement sensitivity may have contributed to cognition being particularly affected by the propensity for detection bias in EHR-based phenotyping methods (Newton et al., 2013). Conversely, the comparatively high prevalence of joint pain may have stemmed from the relatively high mean age in this sample of 64 and the higher prevalence of arthritis in this age cohort, which was found to be the fifth most-common symptom in a sample of older adults (Seligman et al., 2024).

This reinforces the vital need to for clinical assessment to capture detailed and meaningful data on the functional impacts of symptoms on the patient's ability to perform daily life routines.

Several additional characteristics of electronic medical research data must be considered in interpreting these findings. Unlike RECOVER (National Institutes of Health, 2023), N3C (Reese et al., 2023) ORCHESTRA (Gentilotti et al., 2023), *All of Us* is not specific to long COVID. The health records data used in this study represents care provided, documented, and billed for “in the wild”. Although this brings with it the challenge of lower precision of disease-specific data and confounding from unmeasured but meaningful factors such as participants' subjective report of symptom severity, it offers the ecological validity of showing the care that was actually delivered in a large national sample. Our long COVID case classification of “at least one long COVID symptom or condition” after COVID-19, though used in other studies (Hou et al., 2025), yielded a somewhat unexpectedly high prevalence of 62% which is more than two times higher than recent pooled estimates of around 30% (Hou et al., 2025). Without the benefit of participants' subjective report of change after COVID infection, our data lacked a ‘gold standard’ against which to validate this classification scheme. Thus there may have been a high proportion of false positives, classifying as “symptomatic” some participants whose symptoms and conditions were not attributable to their COVID infection.

Conversely, our estimate of the incidence of functional change after COVID-19 may be an underestimate, particularly for small changes in daily functioning from baseline. This is because functioning was inferred from clinical observations that are often documented in the health record during an acute or sub-acute inpatient rehabilitation course. In ambulatory, primary, and short-stay acute encounters, daily functioning may be less likely to have been measured and documented in this coding taxonomy, as patients may present weeks or months

after infection and appear healthy enough to return home without further assessment. Quantified results would then not be recorded in the health record, precluding the detection of the true variance of long COVID-related functional change across age cohorts. This underscores the diagnostic need for valid and reliable measurement instruments of functional change in individuals with long COVID across ages (NASEM, 2024) as well as age-indexed phenotyping approaches. Between a highly sensitive case/control classifier and a highly specific outcome indicator, the true prevalence of functional impairment in *All of Us* participants with long COVID may, in reality, be much higher than these findings suggest.

Directions for future work

This study revealed several important questions for future inquiry. First, our models were built as exploratory main effects models as this study is among the first to explore an EHR-derived composite functional status variable constructed from other EHR observations. Building and validating predictive models for the outcome of functional impairment would allow the application of a causal inference framework to these data and comparison of the model's performance in other cohorts. Second, the exploratory symptom phenotypes found here could be more fully developed as validated phenotypic models, calibrated to respond to differences in age or other demographic characteristics, and incorporated into multivariable models to gain greater insight into their relationships with functional status. Third, as *All of Us* is a longitudinal dataset, future data releases will provide opportunities to update these findings, incorporating increased precision of long COVID diagnosis and risk factors as the evidence evolves. Fourth, this study's classification of participants as having long COVID versus having recovered was based on a list of symptoms and conditions chosen a-priori from other studies. Utilizing high-throughput and high-dimensional data methods to find patterns across the health record would contribute new

information on the relationships between symptoms and functional status to the growing literature on this novel disorder. Finally, these findings reinforce the need for psychometric validation of the measurement tools for functional performance used to characterize the impact of long COVID on daily life. Without a standard measure that is valid and reliable across age groups, post-COVID general functional decline in older adults may be overlooked, under-prioritized, or masked by similar observations related to aging (Chatterji et al., 2015).

Conclusion

Age and long COVID symptoms both independently increased functional impairment following COVID-19, however older adults with long COVID may present with more subtle differences. Older adults with long COVID symptoms may experience functional decline that is independent of the functional decline associated with normal aging, and should be carefully assessed for change from baseline. Choosing and validating instruments that can detect functional status changes in older individuals is critical to both the diagnostic accuracy of long COVID and for referral to rehabilitation services so that older adults with long COVID can return to healthy and engaged lives.

Acknowledgements

We extend greatest appreciation to the participants enrolled in the *All of Us* Research Program who have generously agreed to share their ongoing health data. The first author also thanks the the *All of Us* researcher workbench support staff for their expertise and service, Beth Fields for editing and mentorship, Richard Chappell for biostatistics support, and Aurora Pop-Vicas and Christine Sorkness for cohort discovery variable identification. Additional dataset building support and mentorship was provided by Anoop Mayampurath, and by the University of Wisconsin Data Science Hub.

Data availability statement

This study used data from the *All of Us* Research Program's Controlled Tier Dataset version 7, available to authorized users on the [Researcher Workbench](#).

Funding

This work was supported by a T32 training grant to the first author from 2021 (5TL1TR002375-05) to 2023 (2TL1TR002375-06) through the University of Wisconsin-Madison School of Medicine and Public Health, and through a Gertrude Gatson Fund grant from the University of Wisconsin-Madison Occupational Therapy Program. The All of Us Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

Conflict of interest

The authors declare that they have no conflict of interest from other duties, engagements, or compensation.

Tables

Table 1.

Demographic, disease, and functional distributions

	Recovered (n=31437)		Long COVID symptomatic (n=52349)				
Age (mean, SD)	57.53	28	60.51	24	$t = -25.159, df = 63845, p\text{-value} < 2.2e-16$		
Total number of long COVID symptoms (mean, SD)	NA	NA	3.61	3	NA		
Total number of long COVID symptoms occurring prior to infection (mean, SD)					$t = -301.5, df = 52818, p\text{-value} < 2.2e-16$		
	2.30	2.86	5.83	3.98			
variant (n, %)					$X^2 = 7454.8, df = 5, p\text{-value} < 2.2e-16$		
pre_VOC	9694	30.8	27123	51.8			
pre_VOC_alpha_beta	7904	25.1	13057	24.9			
alpha_beta_delta	2580	8.2	4352	8.3			
delta	3890	12.4	4365	8.3			
omicron_BA1_BA2	4319	13.7	3028	5.8			
omicron_BA2_BA5	3050	9.7	424	0.8			
sex_at_birth (n, %)					$X^2 = 92.052, df = 2, p\text{-value} < 2.2e-16$		
Female or intersex	19360	61.6	33945	64.8			
Male	12077	38.4	18404	35.2			
Race (n, %)					$X^2 = 245.45, df = 4, p\text{-value} < 2.2e-16$		
Asian	1241	3.9	1239	2.4			
Black or African American	5508	17.5	10574	20.2			
Middle Eastern or North African	246	0.8	367	0.7			
More than one population	692	2.2	1066	2			

White	23750	75.5	39103	74.7			
Ethnicity = Not Hispanic or Latino(1) (n, %)	30548	97.2	51069	97.6	X ² = 11.259, df = 1, p-value = 0.0007922		
Pre-infection functional performance level (2) (n, %)					X ² = 1799.4, df = 2, p-value < 2.2e-16		
No Performance Difficulty	29665	94.4	44328	84.7			
Some Functional Performance Difficulty	1204	3.8	4966	9.5			
Severe Functional Performance Difficulty	568	1.8	3055	5.8			
Education level (n, %)					X ² = 315.9, df = 4, p-value < 2.2e-16		
Advanced Degree	9193	29.2	665	24.2			
College (some or graduate)	16194	51.5	27790	53.1			
High School (some or GED)	5517	17.5	10748	20.5			
Less than high school	169	0.5	390	0.7			
No Answer	364	1.2	756	1.4			
Pre-COVID OT evaluation level of complexity					X ² = 83786, df = 1, p-value < 2.2e-16		
None	30996	98.6	51052	97.5			
Low complexity	261	0.8	862	1.6			
Moderate complexity	128	0.4	328	0.6			
High complexity	40	0.1	61	0.1			
Re-evaluation	<40	<0.1	46	0.1			
Post-infection functional score (n, %)					X ² = 83786, df = 1, p-value < 2.2e-16		
0	30391	96.7	45432	6.8			
1	674	2.1	4093	7.8			
2	335	1.1	2617	5			
3	<40	<0.1	169	0.3			
4	<40	<0.1	<40	0.1			
Notes: 1 = Pearson's Chi-squared test with Yates' continuity correction. 2 = Inferred from "Finding of Functional Performance and Activity" (OMOP Code 4089214, SNOMED code 248536006)							

Table 2*Adjusted standard mean differences in likelihood of post-infection functional impairment*

	SMD	Std. Error	Interval	Z-score	p
Age, compared to mean (62 years)					
Long COVID symptomatic					
25	-0.42	0.02	(-0.481, -0.368)	-19.00	< 0.000
35	-0.31	0.02	(-0.351, -0.269)	-19.00	< 0.000
45	-0.20	0.01	(-0.22, -0.169)	-19.00	< 0.000
55	-0.08	0.00	(-0.091, -0.070)	-19.00	< 0.000
65	0.03	0.00	(0.030, 0.039)	19.00	< 0.000
75	0.15	0.01	(0.129, 0.169)	19.00	< 0.000
85	0.26	0.01	(0.229, 0.299)	19.00	< 0.000
Recovered					
25	-0.60	0.04	(-0.695, -0.503)	-16.00	< 0.000
35	-0.44	0.03	(-0.507, -0.367)	-16.00	< 0.000
45	-0.28	0.02	(-0.319, -0.231)	-16.00	< 0.000
55	-0.11	0.01	(-0.132, -0.095)	-16.00	< 0.000
65	0.05	0.00	(0.041, 0.056)	16.00	< 0.000
75	0.21	0.01	(0.177, 0.244)	16.00	< 0.000
85	0.37	0.02	(0.313, 0.432)	16.00	< 0.000
Female sex (compared to male)					
Female	-0.097	0.01	(-0.13, -0.061)	-7.00	p <-0.000
Race (compared to largest group, white)					
Black	0.18	0.02	(0.14, 0.221)	10.90	p < 0.0000
Asian	-0.17	0.05	(-0.30, -0.029)	-3.10	p = 0.0017
Middle Eastern.North African	-0.10	0.09	(-0.33, 0.132)	-1.10	p = 0.2640
More than one	-0.07	0.05	(-0.21, 0.064)	-1.40	p= 0.1661
Ethnicity (compared to larges group, Non-Hispanic)					
Hispanic or Latino	-0.03	0.05	(-0.15, 0.093)	-0.59	p = 0.56
Education level (compared to largest group, Some College or Graduate)					
Less than HS	0.02	0.07	(-0.162, 0.207)	0.31	p = 0.7577
HS/GED	0.06	0.02	(0.013, 0.100)	3.37	p = 0.0008
Advanced Degree	-0.14	0.02	(-0.183, -0.095)	-8.17	p < 0.0000

Infection variant					
pre-VOC	1.61	0.11	(1.34, 1.89)	15.1	$p < 0.000$
	1.47	0.11	(1.19, 1.75)	13.6	$p < 0.000$
	1.41	0.11	(1.13, 1.69)	12.9	$p < 0.000$
	1.31	0.11	(1.02, 1.59)	11.9	$p < 0.000$
	1.10	0.11	(0.82, 1.39)	9.9	$p < 0.000$
	0.63	0.12	(0.31, 0.95)	5.1	$p < 0.000$
Long COVID symptomatic compared to Recovered participants					
Long COVID symptomatic	0.34	0.02	(0.31, 0.38)	19.0	$p < 0.0000$
Pre-infection functional status					
Some	0.02		(0.69, 0.79)	39.0	$p < 0.000$
Severe	0.02		(1.18, 1.29)	55.0	$p < 0.000$
Pre-infection symptom totals (compared to median=4)					
0	-0.14	0.01	(-0.159, -0.122)	-19.0	$p < 0.000$
1	-0.11	0.01	(-0.119, -0.091)	-19.00	$p < 0.000$
7	0.11	0.01	(0.091, 0.119)	19.0	$p < 0.000$
23	0.67	0.03	(0.578, 0.756)	19.0	$p < 0.000$
Long COVID symptomatic compared to recovered participants, at each age cut					
25	0.52	0.05	(0.39, 0.65)	10.4	< 0.000
35	0.47	0.04	(0.37, 0.57)	12	< 0.000
45	0.42	0.03	(0.35, 0.50)	14.5	< 0.000
55	0.38	0.02	(0.32, 0.43)	17.8	< 0.000
65	0.33	0.02	(0.28, 0.38)	18.2	< 0.000
75	0.28	0.02	(0.23, 0.34)	12.8	< 0.000
85	0.23	0.03	(0.16, 0.31)	7.8	< 0.000
Group by Sex					
Female Long COVID symptomatic	0.00	0.00	(0.000, 0.000)	0.0	NA
Male Long COVID symptomatic	-0.10	0.01	(-0.13, -0.061)	-0.7	$p < 0.000$
Female Recovered	-0.34	0.02	(-0.39, -0.296)	-19.0	$p < 0.000$
Male Recovered	-0.44	0.02	(-0.50, -0.381)	-19.0	$p < 0.000$

Table 3

Long COVID symptom/condition frequencies and percentages among long COVID symptomatic

Symptom	<i>n</i>	%
joint pain	20968	31.31
sleep	18419	27.50
anxiety	17870	26.68
depression	15709	23.46
chestpain	14541	21.71
abdominal	13439	20.07
dyspnea	12252	18.29
fatigue	11345	16.94
cough	9528	14.23
rash	7381	11.02
dizziness	6712	10.02
diarrhea	6260	9.35
headache	5676	8.48
palpitations	4365	6.52
cognition	3874	5.78
muscle pain	3848	5.75
tachycardia	3759	5.61
fever	3545	5.29
paraesthesia	3233	4.83
menstruation	2365	3.53
msk chest pain	1907	2.85
me cfs	1304	1.95
sexual function	515	0.77
post COVID NOS	309	0.46
loss of smell	0	0.00
loss of taste	0	0.00
muscle fatigue	0	0.00
pots	0	0.00
pvfs	0	0.00

Table 4.**Correlations of symptom clusters with post-infection functional level.**

		Dizzy, palpitations, skin	Respiratory, abdominal, fever, tachycardia	Pain, paraesthesia, headache, chest pain	Fatigue, cognition, sleep, mood
Postcovid functional score	-0.03	0.09	0.20	0.19	0.26
	Reproductive	0.03	0.04	0.01	0.03
		Dizzy/ palpitations/ skin	0.17	0.16	0.12
			Respiratory/ abdominal/fever/ tachycardia	0.24	0.20
				Paraesthesia/ headache/pain/ chest pain	0.17

Figures

Figure 1

Cohort flow diagram

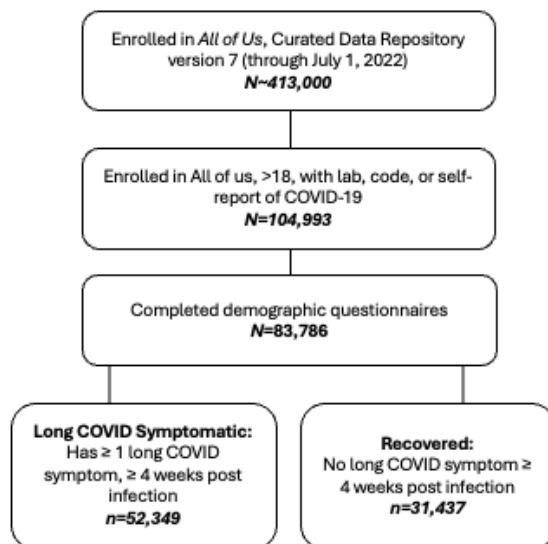


Figure 2. Predicted probability of functional impairment by long COVID status and age.

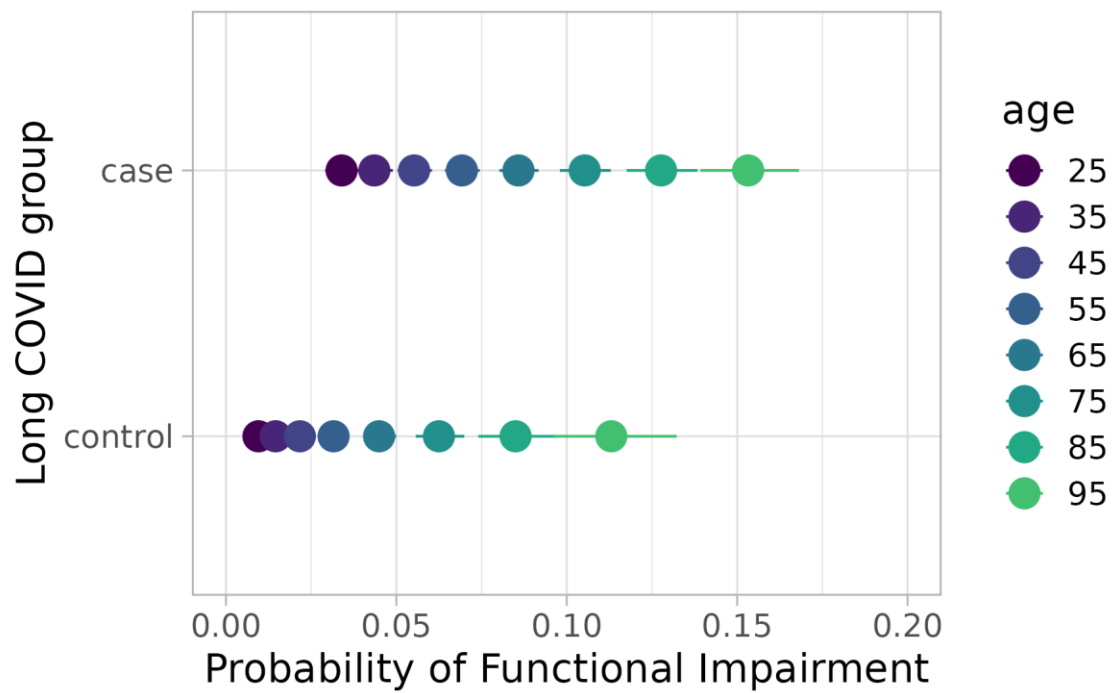


Figure 3

Predicted probability of post-infection functional impairment, by pre-infection functional status and age.

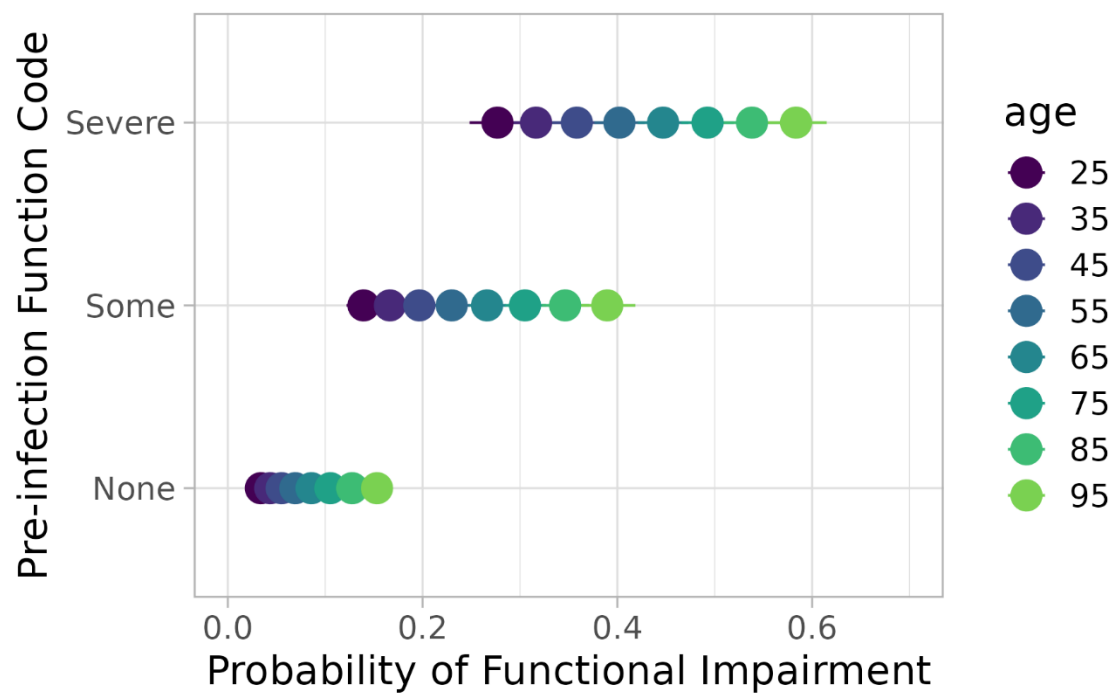
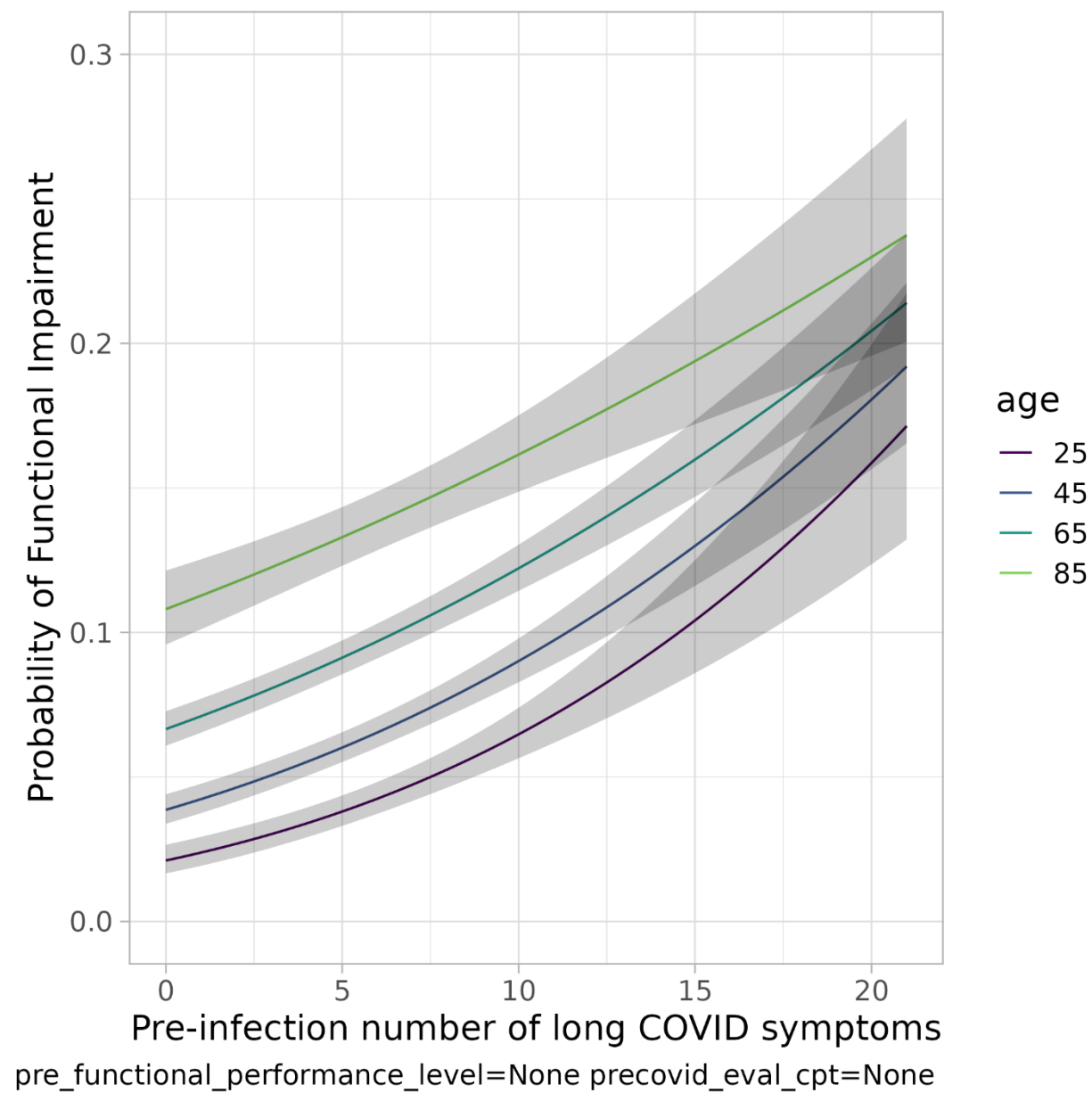


Figure 4

Predicted probability of post-infection functional impairment, by age and pre-infection number of symptoms

**Figure 5**

Frequency of long COVID symptoms and conditions among long COVID symptomatic

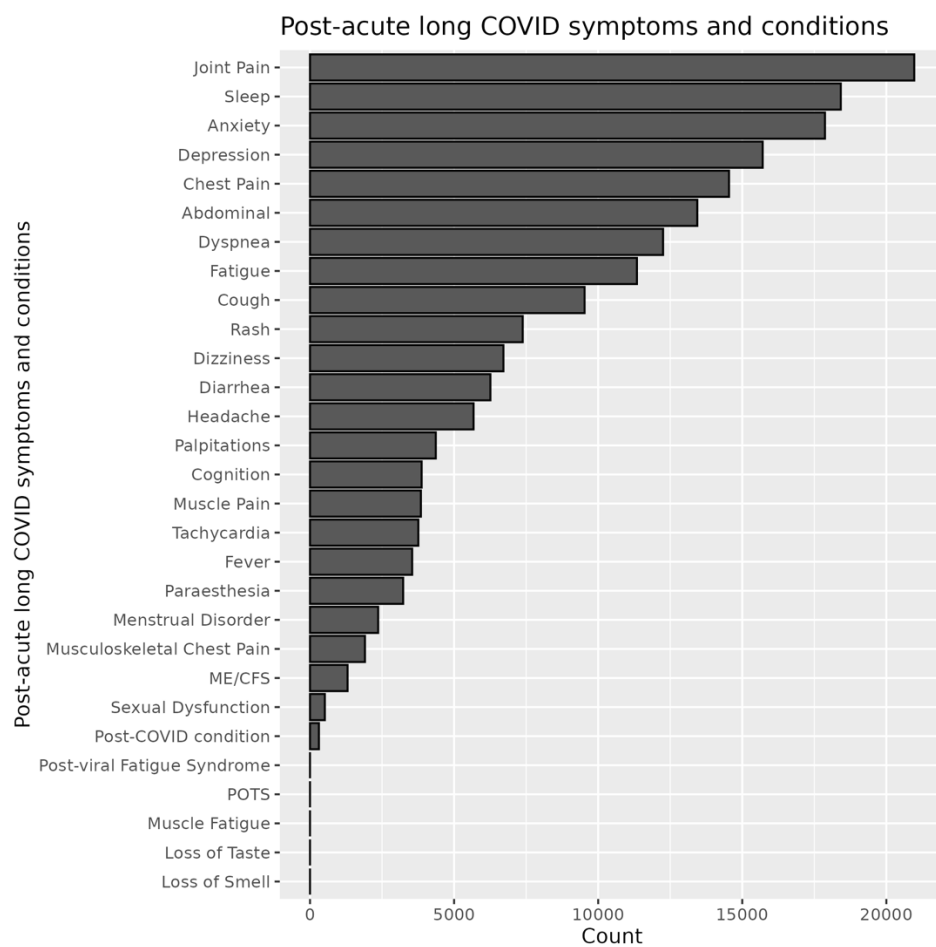
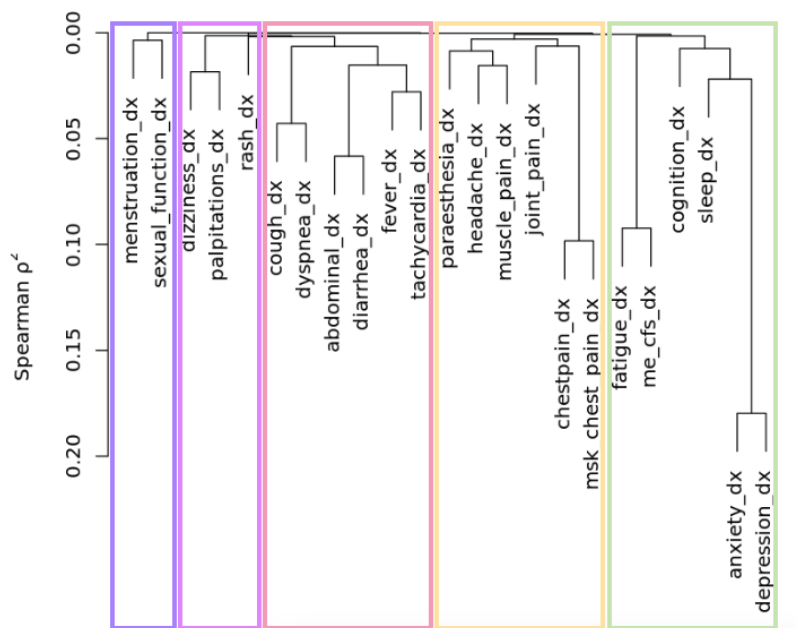


Figure 6

Long COVID symptom/condition clusters



References

- Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nat Med*, *30*(8), 2148-2164. <https://doi.org/10.1038/s41591-024-03173-6>
- Al-Aly, Z., Xie, Y., & Bowe, B. (2021). High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*, *594*(7862), 259-264. <https://doi.org/10.1038/s41586-021-03553-9>
- Appel, S. K., Nürnberger, C., Bahmer, T., Förster, C., Polidori, C. M., Kohls, M., Kraus, T., Hettich-Damm, N., Petersen, J., Blaschke, S., Bröhl, I., Butzmann, J., Dashti, H., Deckert, J., Dreher, M., Fiedler, K., Finke, C., Geisler, R., Hanses, F.,... Witzenzrath, M. (2024). Definition of the Post-COVID syndrome using a symptom-based Post-COVID score in a prospective, multi-center, cross-sectoral cohort of the German National Pandemic Cohort Network (NAPKON). *Infection*. <https://doi.org/10.1007/s15010-024-02226-9>
- Cahan, J., Finley, J. A., Cotton, E., Orban, Z. S., Jimenez, M., Weintraub, S., Sorets, T., & Koralnik, I. J. (2024). Cognitive functioning in patients with neuro-PASC: the role of fatigue, mood, and hospitalization status. *Front Neurol*, *15*, 1401796. <https://doi.org/10.3389/fneur.2024.1401796>
- Carter, S. J., Baranauskas, M. N., Raglin, J. S., Pescosolido, B. A., & Perry, B. L. (2022). Functional Status, Mood State, and Physical Activity Among Women With Post-Acute COVID-19 Syndrome. *Int J Public Health*, *67*, 1604589. <https://doi.org/10.3389/ijph.2022.1604589>
- Case, K. R., Wang, C. P., Hosek, M. G., Lill, S. F., Howell, A. B., Taylor, B. S., Bridges, J., MacCarthy, D. J., Winkler, P., & Tsevat, J. (2022). Health-related quality of life and social determinants of health following COVID-19 infection in a predominantly Latino population. *J Patient Rep Outcomes*, *6*(1), 72. <https://doi.org/10.1186/s41687-022-00473-8>
- Centers for Disease Control and Prevention. (2021). *New ICD-10-CM code for Post-COVID Conditions, following the 2019 Novel Coronavirus (COVID-19)*. Retrieved from <https://www.cdc.gov/nchs/data/icd/announcement-new-icd-code-for-post-covid-condition-april-2022-final.pdf>
- Centers for Disease Control and Prevention. (2023). *Long COVID or Post-COVID Conditions*. https://www.cdc.gov/covid/long-term-effects/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/
- Centers for Medicare and Medicaid Services. (2020). *Billing and Coding: Therapy Evaluation, Re-Evaluation and Formal Testing. A53309*. DHHS, CMS. Retrieved 10/3/2024 from <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53309>
- Chatterji, S., Byles, J., Cutler, D., Seeman, T., & Verdes, E. (2015). Health, functioning, and disability in older adults--present status and future implications. *Lancet*, *385*(9967), 563-575. [https://doi.org/10.1016/s0140-6736\(14\)61462-8](https://doi.org/10.1016/s0140-6736(14)61462-8)
- Davis, E. H., Assaf, S. G., McCorkell, L., Wei, H., Low, J. R., Re'Em, Y., Redfield, S., Austin, P. J., & Akrami, A. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*, *38*, 101019. <https://doi.org/10.1016/j.eclinm.2021.101019> (EClinicalMedicine)

- Davis, E. H., Mccorkell, L., Vogel, M. J., & Topol, J. E. (2023). Long COVID: major findings, mechanisms and recommendations. *Nature Reviews Microbiology*, *21*(3), 133-146. <https://doi.org/10.1038/s41579-022-00846-2>
- De Vito, A. N., Emrani, S., Correia, S., Coutinho, M. T., & Lee, A. (2024). Compensatory strategy use in diverse older adults with subjective cognitive complaints. *Aging Ment Health*, 1-8. <https://doi.org/10.1080/13607863.2024.2367060>
- Deer, R. R., Rock, A. M., Vasilevsky, N., Carmody, L., Rando, H., Anzalone, J. A., Basson, D. M., Bennett, D. T., Bergquist, T., Boudreau, A. E., Bramante, T. C., Byrd, B. J., Callahan, J. T., Chan, E. L., Chu, H., Chute, G. C., Coleman, D. B., Davis, E. H., Gagnier, J.,...Robinson, N. P. (2021). Characterizing Long COVID: Deep Phenotype of a Complex Condition. *EBioMedicine*, *74*, 103722. <https://doi.org/10.1016/j.ebiom.2021.103722>
- Eligulashvili, A., Darrell, M., Gordon, M., Jerome, W., Fiori, K. P., Congdon, S., & Duong, T. Q. (2024). Patients with unmet social needs are at higher risks of developing severe long COVID-19 symptoms and neuropsychiatric sequela. *Sci Rep*, *14*(1), 7743. <https://doi.org/10.1038/s41598-024-58430-y>
- Erlanson, K. M., Geng, L. N., Selvaggi, C. A., Thaweethai, T., Chen, P., Erdmann, N. B., Goldman, J. D., Henrich, T. J., Hornig, M., Karlson, E. W., Katz, S. D., Kim, C., Cribbs, S. K., Laiyemo, A. O., Letts, R., Lin, J. Y., Marathe, J., Parthasarathy, S., Patterson, T. F.,...McComsey, G. A. (2024). Differentiation of Prior SARS-CoV-2 Infection and Postacute Sequelae by Standard Clinical Laboratory Measurements in the RECOVER Cohort. *Ann Intern Med*, *177*(9), 1209-1221. <https://doi.org/10.7326/m24-0737>
- Ford, N. D., Slaughter, D., Edwards, D., Dalton, A., Perrine, C., Vahratian, A., & Saydah, S. (2023). Long COVID and Significant Activity Limitation Among Adults, by Age — United States, June 1–13, 2022, to June 7–19, 2023. *MMWR Morb Mortal Wkly Rep* *2023*, *72*, 866-970. <https://doi.org/http://dx.doi.org/10.15585/mmwr.mm7232a3>
- Gentilotti, E., Górska, A., Tami, A., Gusinow, R., Mirandola, M., Rodríguez Baño, J., Palacios Baena, Z. R., Rossi, E., Hasenauer, J., Lopes-Rafegas, I., Righi, E., Caroccia, N., Cataudella, S., Pasquini, Z., Osmo, T., Del Piccolo, L., Savoldi, A., Kumar-Singh, S., Mazzaferri, F.,...Tacconelli, E. (2023). Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. *EClinicalMedicine*, *62*, 102107. <https://doi.org/10.1016/j.eclinm.2023.102107>
- Gonzalez Aleman, G., Vavougiou, G. D., Tartaglia, C., Uvais, N. A., Guekht, A., Hosseini, A. A., Lo Re, V., Ferreccio, C., D'Avossa, G., Zamponi, H. P., Figueredo Aguiar, M., Yecora, A., Ul Haq Katshu, M. Z., Stavrou, V. T., Boutlas, S., Gourgoulisanis, K. I., Botero, C., González Insúa, F., Perez-Lloret, S.,...de Erausquin, G. A. (2024). Age-dependent phenotypes of cognitive impairment as sequelae of SARS-CoV-2 infection. *Front Aging Neurosci*, *16*, 1432357. <https://doi.org/10.3389/fnagi.2024.1432357>
- Hadley Wickham, M. A., Jennifer Bryan, Winston Chang, Lucy D'Agostino McGowan, Romain François, Garrett Golemund, Alex Hayes, Lionel Henry, Jim Hester, Max Kuhn, Thomas Lin Pedersen, Evan Miller, Stephan Milton Bache, Kirill Müller, Jeroen Ooms, David Robinson, Dana Paige Seidel, Vitalie Spinu, Kohske Takahashi, Davis Vaughan, Claus Wilke, Kara Woo, Hiroaki Yutani. (2019). *Welcome to the tidyverse*. In (Version 2.0.0) R Foundation for Statistical Computing. <https://tidyverse.tidyverse.org>, <https://github.com/tidyverse/tidyverse>

- Harrell, F. E. (2001). *Regression Modeling Strategies* (2nd ed.). Springer.
- Harrell, F. E. (2024). *Regression Modeling Strategies*. In (Vol. 6.8-2): CRAN.
- Haunhorst, S., Dudziak, D., Scheibenbogen, C., Seifert, M., Sotzny, F., Finke, C., Behrends, U., Aden, K., Schreiber, S., Brockmann, D., Burggraf, P., Bloch, W., Ellert, C., Ramoji, A., Popp, J., Reuken, P., Walter, M., Stallmach, A., & Puta, C. (2024). Towards an understanding of physical activity-induced post-exertional malaise: Insights into microvascular alterations and immunometabolic interactions in post-COVID condition and myalgic encephalomyelitis/chronic fatigue syndrome. *Infection*. <https://doi.org/10.1007/s15010-024-02386-8>
- Hou, Y., Gu, T., Ni, Z., Shi, X., Ranney, M. L., & Mukherjee, B. (2025). Global Prevalence of Long COVID, its Subtypes and Risk factors: An Updated Systematic Review and Meta-Analysis. *medRxiv*. <https://doi.org/10.1101/2025.01.01.24319384>
- Izaguirre, P., Arakaki, É., Boero, J. V., Zalazar, Á., Ghirlanda, M., & Caruso, D. (2023). Functional Status in Older Adults Following Hospitalization for Covid-19: A Cohort Study. *Ann Geriatr Med Res*. <https://doi.org/10.4235/agmr.23.0071>
- Jacobs, M. M., Evans, E., & Ellis, C. (2023). Racial, ethnic, and sex disparities in the incidence and cognitive symptomology of long COVID-19. *J Natl Med Assoc*, *115*(2), 233-243. <https://doi.org/10.1016/j.jnma.2023.01.016>
- Jaywant, A., Gunning, F. M., Oberlin, L. E., Santillana, M., Ognyanova, K., Druckman, J. N., Baum, M. A., Lazer, D., & Perlis, R. H. (2024). Cognitive Symptoms of Post-COVID-19 Condition and Daily Functioning. *JAMA Netw Open*, *7*(2), e2356098. <https://doi.org/10.1001/jamanetworkopen.2023.56098>
- Kail, B. L., & Carr, D. C. (2017). Successful Aging in the Context of the Disablement Process: Working and Volunteering as Moderators on the Association Between Chronic Conditions and Subsequent Functional Limitations. *J Gerontol B Psychol Sci Soc Sci*, *72*(2), 340-350. <https://doi.org/10.1093/geronb/gbw060>
- Khullar, D., Zhang, Y., Zang, C., Xu, Z., Wang, F., Weiner, M. G., Carton, T. W., Rothman, R. L., Block, J. P., & Kaushal, R. (2023). Racial/ethnic disparities in post-acute sequelae of SARS-CoV-2 infection in New York: an EHR-based cohort study from the RECOVER program. *J Gen Intern Med*, *38*(5), 1127-1136. <https://doi.org/10.1007/s11606-022-07997-1>
- Kitsios, G. D., Blacka, S., Jacobs, J. J., Mirza, T., Naqvi, A., Gentry, H., Murray, C., Wang, X., Golubykh, K., Qurashi, H., Dodia, A., Risbano, M., Benigno, M., Emir, B., Weinstein, E., Bramson, C., Jiang, L., Dai, F., Szigethy, E.,...Morris, A. (2024). Subphenotypes of self-reported symptoms and outcomes in long COVID: a prospective cohort study with latent class analysis. *BMJ open*, *14*(3), e077869. <https://doi.org/10.1136/bmjopen-2023-077869>
- Markov, P. V., Ghafari, M., Beer, M., Lythgoe, K., Simmonds, P., Stilianakis, N. I., & Katzourakis, A. (2023). The evolution of SARS-CoV-2. *Nat Rev Microbiol*, *21*(6), 361-379. <https://doi.org/10.1038/s41579-023-00878-2>
- Marks, T. S., Giles, G. M., Kehl-Floberg, K. E., & Edwards, D. F. (2023). Screening older adults for potential deficits in IADL using the Menu Task and Medi-Cog-R [Conference abstract]. *Alzheimer's & Dementia*, *19*(S19). <https://doi.org/doi.org/10.1002/alz.079778>
- Mina, Y., Enose-Akahata, Y., Hammoud, D. A., Videckis, A. J., Narpala, S. R., O'Connell, S. E., Carroll, R., Lin, B. C., McMahan, C. C., Nair, G., Reoma, L. B., McDermott, A. B., Walitt, B., Jacobson, S., Goldstein, D. S., Smith, B. R., & Nath, A. (2023). Deep

- Phenotyping of Neurologic Postacute Sequelae of SARS-CoV-2 Infection. *Neurol Neuroimmunol Neuroinflamm*, 10(4). <https://doi.org/10.1212/nxi.0000000000200097>
- National Academies of Sciences Engineering and Medicine. (2024). *A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences*. The National Academies Press. <https://doi.org/10.17226/27768>
- National institutes of Health. (2022-2025). *All of Us, Curated data repository version 7, Controlled Tier C2022Q4R9* (National Institutes of Health). https://docs.google.com/document/d/1tr-WqlUsJicbF9QeCkvvhvQmMiSivEg4vSLiQ0A5zR_4/edit?tab=t.0#heading=h.e7ppu6uf0bea
- National Institutes of Health. (2023). *Researching COVID to Enhance Recovery (RECOVER)*. <https://recovercovid.org/>
- Newton, K. M., Peissig, P. L., Kho, A. N., Bielinski, S. J., Berg, R. L., Choudhary, V., Basford, M., Chute, C. G., Kullo, I. J., Li, R., Pacheco, J. A., Rasmussen, L. V., Spangler, L., & Denny, J. C. (2013). Validation of electronic medical record-based phenotyping algorithms: results and lessons learned from the eMERGE network. *J Am Med Inform Assoc*, 20(e1), e147-154. <https://doi.org/10.1136/amiajnl-2012-000896>
- Nielsen, T. B., Leth, S., Pedersen, M., Harbo, H. D., Nielsen, C. V., Laursen, C. H., Schiøttz-Christensen, B., & Oestergaard, L. G. (2022). Mental Fatigue, Activities of Daily Living, Sick Leave and Functional Status among Patients with Long COVID: A Cross-Sectional Study. *Int J Environ Res Public Health*, 19(22). <https://doi.org/10.3390/ijerph192214739>
- Observational Health Data Sciences and Informatics. (2024). *Standardized Data: The OMOP Common Data Model*. <https://www.ohdsi.org/data-standardization/>
- Odysseus Data Services, I. (2023). ATHENA - OHDSI Vocabularies Repository. In (Vol. Version 1.13.0.23.230616.0657).
- Patient-led Research Collaborative for Long COVID. (2024). Towards a Patient-Driven National Research Action Plan: Recommendations for the National Research Action Plan on Long COVID. In.
- Pihlaja, R. E., Kauhanen, L. S., Ollila, H. S., Tuulio-Henriksson, A. S., Koskinen, S. K., Tiainen, M., Salmela, V. R., Hastbacka, J., & Hokkanen, L. S. (2023). Associations of subjective and objective cognitive functioning after COVID-19: A six-month follow-up of ICU, ward, and home-isolated patients. *Brain Behav Immun Health*, 27, 100587. <https://doi.org/10.1016/j.bbih.2023.100587>
- Prabhakaran, D., Day, G., Munipalli, B., Rush, B., Pudalov, L., Niazi, S., Brennan, E., Powers, H., Durvasula, R., Athreya, A., & Blackmon, K. (2022). Neurophenotypes of COVID-19: risk factors and recovery trajectories. *Brain Behav Immun Health*. <https://doi.org/10.21203/rs.3.rs-2363210/v1>
- R Core Team. (2022). R: A language and environment for statistical computing. In. Vienna, Austria: R Foundation for Statistical Computing.
- R Core Team and contributors worldwide. (2025). *The R Stats Package*. In (Version 4.3.0-4.4.3) R Foundation for Statistical Computing.
- Reese, J. T., Blau, H., Casiraghi, E., Bergquist, T., Loomba, J. J., Callahan, T. J., Laraway, B., Antonescu, C., Coleman, B., Gargano, M., Wilkins, K. J., Cappelletti, L., Fontana, T., Ammar, N., Antony, B., Murali, T. M., Caufield, J. H., Karlebach, G., McMurry, J. A.,...Robinson, P. N. (2023). Generalisable long COVID subtypes: findings from the

- NIH N3C and RECOVER programmes. *EBioMedicine*, 87, 104413.
<https://doi.org/10.1016/j.ebiom.2022.104413>
- Rog, L. A., Park, L. Q., Harvey, D. J., Huang, C. J., Mackin, S., & Farias, S. T. (2014). The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults. *Clin Neuropsychol*, 28(2), 215-236.
<https://doi.org/10.1080/13854046.2013.876101>
- Schild, A. K., Scharfenberg, D., Regorius, A., Klein, K., Kirchner, L., Yasemin, G., Lülling, J., Meiberth, D., Schweitzer, F., Fink, G. R., Jessen, F., Franke, C., Onur, O. A., Jost, S. T., Warnke, C., & Maier, F. (2024). Six-month follow-up of multidomain cognitive impairment in non-hospitalized individuals with post-COVID-19 syndrome. *Eur Arch Psychiatry Clin Neurosci*. <https://doi.org/10.1007/s00406-024-01863-3>
- Seligman, B., Wysham, K. D., Shahoumian, T., Orkaby, A. R., Goetz, M. B., Osborne, T. F., Smith, V. A., Maciejewski, M. L., Hynes, D. M., Boyko, E. J., & Ioannou, G. N. (2024). Change in frailty among older COVID-19 survivors. *J Am Geriatr Soc*.
<https://doi.org/10.1111/jgs.19255>
- Shanbehzadeh, S., Zanjari, N., Yassin, M., Yassin, Z., & Tavahomi, M. (2023). Association between long COVID, functional activity, and health-related quality of life in older adults. *BMC Geriatr*, 23(1), 40. <https://doi.org/10.1186/s12877-023-03757-w>
- Silva-Passadouro, B., Tamasauskas, A., Khoja, O., Casson, A. J., Delis, I., Brown, C., & Sivan, M. (2024). A systematic review of quantitative EEG findings in Fibromyalgia, Chronic Fatigue Syndrome and Long COVID. *Clin Neurophysiol*, 163, 209-222.
<https://doi.org/10.1016/j.clinph.2024.04.019>
- Soriano, J. B., Murthy, S., Marshall, J. C., Relan, P., & Diaz, J. V. (2022). A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*, 22(4), e102-e107. [https://doi.org/10.1016/s1473-3099\(21\)00703-9](https://doi.org/10.1016/s1473-3099(21)00703-9)
- Tana, C., Moffa, L., Falasca, K., Vecchiet, J., Tana, M., Mantini, C., Ricci, F., Ticinesi, A., Meschi, T., Cipollone, F., & Giamberardino, M. A. (2023). Approach to COVID-19 in older adults and indications for improving the outcomes. *Ann Med*, 55(2), 2265298.
<https://doi.org/10.1080/07853890.2023.2265298>
- Thaweethai, T., Jolley, E. S., Karlson, W. E., Levitan, B. E., Levy, B., Mccomsey, A. G., Mccorkell, L., Nadkarni, N. G., Parthasarathy, S., Singh, U., Walker, A. T., Selvaggi, A. C., Shinnick, J. D., Schulte, M. C. C., Atchley-Challenner, R., Horwitz, I. L., Foulkes, S. A., Aberg, A. J., Adolphi, L. N.,...Zisis, S. (2023). Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *Jama*, 329(22), 1934.
<https://doi.org/10.1001/jama.2023.8823>
- U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion. (2025). *Healthy People 2030: Social Determinants of Health*. Retrieved April 15 from <https://odphp.health.gov/healthypeople/priority-areas/social-determinants-health/literature-summaries>
- Vanichkachorn, G., Newcomb, R., Cowl, C. T., Murad, M. H., Breeher, L., Miller, S., Trenary, M., Neveau, D., & Higgins, S. (2021). Post-COVID-19 syndrome (long haul syndrome): Description of a multidisciplinary clinic at Mayo Clinic and characteristics of the initial patient cohort. *Mayo Clin Proc*, 96(7), 1782-1791.
<https://doi.org/10.1016/j.mayocp.2021.04.024>

- Vasilevskaya, A., Mushtaque, A., Tsang, M. Y., Alwazan, B., Herridge, M., Cheung, A. M., & Tartaglia, M. C. (2023). Sex and age affect acute and persisting COVID-19 illness. *Sci Rep*, 13(1), 6029. <https://doi.org/10.1038/s41598-023-33150-x>
- Verveen, A., Verfaillie, S. C. J., Visser, D., Koch, D. W., Verwijk, E., Geurtsen, G. J., Roor, J., Appelman, B., Boellaard, R., van Heugten, C. M., Horn, J., Hulst, H. E., de Jong, M. D., Kuut, T. A., van der Maaden, T., van Os, Y. M. G., Prins, M., Visser-Meily, J. M. A., van Vugt, M.,...Knoop, H. (2024). Neuropsychological functioning after COVID-19: minor differences between individuals with and without persistent complaints after SARS-CoV-2 infection. *Clin Neuropsychol*, 1-16. <https://doi.org/10.1080/13854046.2024.2379508>
- World Health Organization. (2001). *International Classification of Functioning, Disability and Health (ICF)*. WHO. <https://www.who.int/classifications/icf/en/>
- Zhang, H., Zang, C., Xu, Z., Zhang, Y., Xu, J., Bian, J., Morozuk, D., Khullar, D., Zhang, Y., Nordvig, A. S., Schenck, E. J., Shenkman, E. A., Rothman, R. L., Block, J. P., Lyman, K., Weiner, M. G., Carton, T. W., Wang, F., & Kaushal, R. (2023). Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med*, 29(1), 226-235. <https://doi.org/10.1038/s41591-022-02116-3>

Chapter 7. Conclusion

This series of retrospective cohort studies using data from the *All of Us* Research Program demonstrated the feasibility of using functional status indicators in the EHR as a health outcome in population-level datasets. This was the first attempt to define functional status from EHR data in people with long COVID, and resulted in a reproducible quantitative approach for exploring functional status in large health datasets. Together, these findings showed that long COVID and functional impairment have complex and multi-directional relationships, and suggest a clinical picture of long COVID that encompasses varying degrees of risk from pre-infection health and functioning.

This innovative use of these standard medical codes in multivariable models allowed us to show that long COVID was independently associated with lower functional status both before and after COVID-19 infection, even when adjusting for years of age and prior symptom burden. Using temporal indexing, we established a multidirectional relationship between long COVID and functional status, revealing that lower functional status is both a risk factor and an outcome of long COVID. Additionally, this approach permitted functional status to be analyzed for correlations with symptom phenotypes generated through hierarchical cluster analysis, demonstrating through a combination of machine learning and associative inference that functional status is strongly related to symptom-driven phenotypic presentation. Finally, it allowed us to disentangle the effects of age from those of long COVID, showing that older adults with long COVID can experience functional decline beyond that which may be expected in the course of normal aging.

Additionally, this work addressed gaps in the literature on the prevalence and impact of pre-infection occurrence of common long COVID symptoms and conditions (Al-Aly et al., 2024;

Thaweethai et al., 2023). This knowledge may be used to tailor long COVID interventions more specifically for people with prior history of conditions that worsen after COVID infection, such as revising management strategies of pre-infection conditions or proactively referring to rehabilitation services. This knowledge may also help guide inquiry on mechanisms of long COVID development.

We identify several indications of validity of these results. First, the finding that long COVID symptoms were associated with poorer functioning are consistent with numerous smaller or single-center studies (Banic et al., 2022; Jacobson et al., 2021; Monteiro et al., 2023; Shanbehzadeh et al., 2023; Vanichkachorn et al., 2021), suggesting that both our symptom-driven cohort classification and the EHR-derived functional indicators were reasonable initial approximations of true long COVID and functional status. Second, although the functional concepts we started with did not always express degree of functional status, the variables built from them demonstrated evidence of ordinality and good model fit, allowing confident discernment of functional status in this large dataset. Finally, our exploratory phenotyping procedure generated symptom subgroups that were similar to those reported in other large cohort studies such as RECOVER (Thaweethai et al., 2023) and ORCHESTRA (Gentilotti et al., 2023).

Interpretation of our findings requires consideration of the range and manner of assessment and coding of functioning in the health record. The EHR-derived functional status indicators did not always converge with self-reported functional status (aim 1): Some survey items were associated with EHR-derived functional levels (mental health and cognition), but others were not (satisfaction with and performance of social roles, and physical ability to perform daily tasks). There are several potential sources of these differences. First and most fundamentally, it may simply reflect that the perspective of a clinician observer (whose

documented observations populated the EHR variables) is different from a patient-participant (whose experiential self-report is represented in survey data). Participants giving different ratings in different domains is consistent with findings that self-reported functional status often does not correlate across domains of function (Grimmer et al., 2013).

It may additionally signify that the EHR-measured constructs are different from one another, as well as from patient report. For instance, functional performance in the “Finding of Functional Performance and Activity” concept was often expressed as deficits in body structures and body functions (which were not correlated with patient report of physical ability), but relatively infrequently as deficits in activity participation (WHO, 2001). Physical performance skills are fairly straight-forward to measure, thus it is not surprising that functional status in long COVID studies has often been inferred by component skills or aptitudes of body structures and functions (e.g. mobility (Owen et al., 2025), fatigue, and mood (Costa et al., 2024)). However, this approach has generated conflicting findings. For instance, a study of survivors of severe illness requiring extracorporeal membrane oxygenation found that, at 6 months, 73.7% were independent in daily life while at the same time 52.6% had cognitive impairments (Guenther et al., 2023). These findings should preclude one another, as full independence includes cognitively complex tasks and routines (Alosco et al., 2012; Baum et al., 2008; Marks et al., 2020).

A complete representation of functioning includes performance of daily routines within the contexts and environments valued by participants (Gutzeit et al., 2024; Law et al., 1996; WHO, 2001) which may underlie participants’ self-ratings. In the *All of Us* EHR data, contextual and environmental influences may have been more strongly represented by the occupational therapy evaluation codes than by the activity codes. The occupational therapy evaluation level of complexity is the result of assessment of function as a multifactorial concept inclusive of context

and meaning in addition to observable skills (AOTA, 2020; Law et al., 1996; World Health Organization, 2001). Thus, a greater range of influences on performance may have been assessed in the OT codes compared to the functional activity codes compared to the more skills-focused “Finding of functional performance and activity” codes, and these may have aligned better with patient report. The ecological validity of the approach piloted in this work would be strengthened with longitudinal self-report data, as this could reflect the range of functional independence and the fluctuating course of many long COVID symptoms. Both self-report and clinical observations may be needed to obtain full and detailed data on the changes in daily life experienced by people with long COVID.

Detection bias must be considered in large cohort studies, these included. We found evidence of under-detection of cognitive impairment among people with at least one long COVID symptom in these data (aim 3). Given prior literature showing high false positive rates and low sensitivity of neuropsychological screening tools in people with long COVID (Cahan et al., 2024; Prabhakaran et al., 2022; Schild et al., 2024; Verveen et al., 2024), this finding supports the need for cognitive screening tools that are validated for use in people with brain fog and have good concurrent validity with subjective cognitive decline (Kirchberger et al., 2023; Schaap et al., 2022). Assessments that use *functional cognition* (Marks et al., 2021a, 2021b; Marks et al., 2023) or *performance-based* (Puente et al., 2014) approaches (which aim to estimate the relative contribution of cognitive abilities to successful daily functioning) have been found to be more sensitive to cognitive impairment than neurocognitive tools. Because long COVID brain fog has shown a pronounced impact on daily routines (Alim-Marvasti et al., 2024; Schaap et al., 2022), assessments that focus on the contributions of cognition to functional performance may be optimal (Watters et al., 2021). This is an area of emerging study.

Directions for future work

The ability to quantify and model functional status using standard medical concepts used in the EHR is significant, and provides a foundation for several opportunities to advance the research on functional status as a health outcome in long COVID and beyond. Within long COVID, the ability to incorporate EHR-derived functional status indicators in future large population-level studies of long COVID could improve diagnostic accuracy and definition of the disorder. In these data, phenotyping methods could be further applied to develop aim 3's exploratory subgroup analysis into a deeper exploration of symptom subtypes inclusive of functioning, and to explore age-specific phenotypes of long COVID symptoms. In addition to yielding insights for long COVID, this data-driven method may also be used to characterize functional status impacts from other diseases or within normal aging. One example (with similarities to brain fog) is mild cognitive impairment (MCI) in older adults. Older adults with MCI often show only small or non-significant differences in many cognitive screening tests (Petersen, 2004). Thus, functional status assessment has been recommended as part of MCI diagnostic assessment (Petersen et al., 2018). Our functional outcomes were compiled from separate procedure and ICD-10 diagnostic codes, which are widely used in EHR documentation and could thus be replicated in other EHR-based studies. Functional status is a central element in the WHO definition of health, and the methods piloted herein provide a means to estimate functioning retrospectively without requiring scores on the ICF checklist. This opens opportunities to strengthen our understanding of outcomes in neurologic, cardiac, and aging research and clinical care at population scale, which in turn may inform targeted and effective interventions and health policies. Outside of *All of Us*, work is underway to test and develop assessments of long COVID symptoms and conditions such as brain fog, post-exertional malaise,

and performance of complex daily routines; these works are critical to optimal clinical care and would eventually contribute to more accurate EHR data on this disorder and subsequent population-level cohort studies.

Conclusions

In summary, this novel use of EHR-derived functional status observations demonstrated how high-quality harmonized EHR data can be used to detect differences in functional status as an outcome of long COVID and combined with symptom data to refine the data-driven definitions of this disorder. I applied this innovative variable using multivariable regression methods to reveal that functional status is both a risk factor and an outcome of long COVID. This work contributed a reproducible and scalable quantitative approach for including functional status in large-scale studies examining the definitions and outcomes of long COVID, with potential applications in the study of other disease outcomes. Valid and reliable assessment tools that identify impairments from long COVID are essential for accurate diagnosis, definition, and clinical care, so that people with long COVID can return to optimal health and chosen life routines.

Appendix A. Long COVID symptoms discovery and analysis

All of Us Research Program data structure

All EMR observations in *All of Us* are harmonized and structured according to the Observational Medical Outcomes Partnership – Common Data Model (OMOP-CDM; Observational Health Data Sciences and Informatics, 2024; Odysseus Data Services, 2023). This ensures consistency across data collection sites and regions, and comparability with billing and treatment codes. *All of Us* utilizes community-relevant recruitment methods to over-recruit from geographic and demographic groups that are under-represented in medical and health research. The program, data snapshots, and data methods can be viewed at <https://www.researchallofus.org/data-tools/>.

Identification of cohort: COVID-19 illness indicators

Name	Concept Id	Vocab	Code	Roll-up Count	Item Count
2019-ncov coronavirus, sars-cov-2/2019-ncov (covid-19), any technique, multiple types or subtypes (includes all targets), non-cdc	40218804	HCPCS	U0002	0	1,020
2019-nCoV Coronavirus, SARS-CoV-2/2019-nCoV (COVID-19), any technique, multiple types or subtypes (includes all targets), non-CDC, making use of high throughput technologies as described by CMS-2020-01-R	704058	HCPCS	U0004	0	1
Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique, making use of high throughput technologies as described by CMS-2020-01-R	704059	HCPCS	U0003	0	1,143
Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel	36660845	LOINC	LP418968-6	985	0
Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel - Respiratory specimen by NAA with probe detection	36661384	LOINC	95380-2	0	985
Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel Respiratory specimen Microbiology Panels	36661218	LOINC	LP419290-4	985	0
Influenza virus A and B and SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	36661376	LOINC	95422-2	0	330

Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	756055	OMOP Extension	OMOP4873969	0	384
Measurement of Severe acute respiratory syndrome coronavirus 2 antibody	37310258	SNOMED	1.24046E+15	0	263
SARS-CoV-2 (COVID-19)	36662140	LOINC	LP417540-4	92,959	0
SARS-CoV-2 (COVID-19) Ab	36661733	LOINC	LP417914-1	9,362	0
SARS-CoV-2 (COVID-19) Ab [Interpretation] in Serum or Plasma	723480	LOINC	94661-6	0	3,037
SARS-CoV-2 (COVID-19) Ab [Presence] in Serum or Plasma by Immunoassay	586515	LOINC	94762-2	0	1,146
SARS-CoV-2 (COVID-19) Ab [Units/volume] in Serum or Plasma by Immunoassay	586522	LOINC	94769-7	0	309
SARS-CoV-2 (COVID-19) Ab Serum or Plasma Microbiology	36661221	LOINC	LP418684-9	4,130	0
SARS-CoV-2 (COVID-19) Ab panel	36661883	LOINC	LP418122-0	2	0
SARS-CoV-2 (COVID-19) Ab panel - Serum or Plasma by Immunoassay	706179	LOINC	94504-8	0	2
SARS-CoV-2 (COVID-19) Ab panel Serum or Plasma Microbiology Panels	36661105	LOINC	LP419286-2	2	0
SARS-CoV-2 (COVID-19) Ag	36661764	LOINC	LP418019-8	1,262	0
SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	723477	LOINC	94558-4	0	1,222
SARS-CoV-2 (COVID-19) Ag [Presence] in Upper respiratory specimen by Immunoassay	36032419	LOINC	96119-3	0	40
SARS-CoV-2 (COVID-19) Ag Respiratory specimen Microbiology	36660801	LOINC	LP418693-0	1,222	0
SARS-CoV-2 (COVID-19) Ag Upper respiratory specimen Microbiology	36033457	LOINC	LP420931-0	40	0
SARS-CoV-2 (COVID-19) clade	1620066	LOINC	LP422736-1	47	0
SARS-CoV-2 (COVID-19) clade [Type] in Specimen by Molecular genetics method	36033653	LOINC	96896-6	0	47
SARS-CoV-2 (COVID-19) clade XXX Microbiology	1618285	LOINC	LP427406-6	47	0
SARS-CoV-2 (COVID-19) IgA	36662109	LOINC	LP418430-7	167	0

SARS-CoV-2 (COVID-19) IgA Serum or Plasma Microbiology	36660931	LOINC	LP41868 5-6	167	0
SARS-CoV-2 (COVID-19) IgA Ab [Presence] in Serum or Plasma by Immunoassay	723473	LOINC	94562-6	0	167
SARS-CoV-2 (COVID-19) IgG	36661886	LOINC	LP41791 5-8	5,025	0
SARS-CoV-2 (COVID-19) IgG Serum or Plasma Microbiology	36661046	LOINC	LP41868 8-0	3,500	0
SARS-CoV-2 (COVID-19) IgG Serum, Plasma or Blood Microbiology	36660768	LOINC	LP41868 9-8	2,090	0
SARS-CoV-2 (COVID-19) IgG Ab [Presence] in Serum or Plasma by Immunoassay	723474	LOINC	94563-4	0	2,920
SARS-CoV-2 (COVID-19) IgG Ab [Presence] in Serum, Plasma or Blood by Rapid immunoassay	706181	LOINC	94507-1	0	2,090
SARS-CoV-2 (COVID-19) IgG Ab [Units/volume] in Serum or Plasma by Immunoassay	706177	LOINC	94505-5	0	749
SARS-CoV-2 (COVID-19) IgG+IgM	36661646	LOINC	LP41795 6-2	991	0
SARS-CoV-2 (COVID-19) IgG+IgM Serum or Plasma Microbiology	36660914	LOINC	LP41869 0-6	991	0
SARS-CoV-2 (COVID-19) IgG+IgM Ab [Presence] in Serum or Plasma by Immunoassay	723479	LOINC	94547-7	0	991
SARS-CoV-2 (COVID-19) IgM	36661975	LOINC	LP41791 6-6	396	0
SARS-CoV-2 (COVID-19) IgM Serum or Plasma Microbiology	36661274	LOINC	LP41869 1-4	299	0
SARS-CoV-2 (COVID-19) IgM Serum, Plasma or Blood Microbiology	36660777	LOINC	LP41869 2-2	97	0
SARS-CoV-2 (COVID-19) IgM Ab [Presence] in Serum or Plasma by Immunoassay	723475	LOINC	94564-2	0	275
SARS-CoV-2 (COVID-19) IgM Ab [Presence] in Serum, Plasma or Blood by Rapid immunoassay	706180	LOINC	94508-9	0	97
SARS-CoV-2 (COVID-19) IgM Ab [Units/volume] in Serum or Plasma by Immunoassay	706178	LOINC	94506-3	0	37
SARS-CoV-2 (COVID-19) lineage	1619966	LOINC	LP42273 9-5	17	0
SARS-CoV-2 (COVID-19) lineage [Identifier] in Specimen by Molecular genetics method	36033652	LOINC	96895-8	0	17

SARS-CoV-2 (COVID-19) lineage XXX Microbiology	1618914	LOINC	LP42740 5-8	17	0
SARS-CoV-2 (COVID-19) N gene	36661396	LOINC	LP41759 9-0	1,151	0
SARS-CoV-2 (COVID-19) N gene [Presence] in Nasopharynx by NAA with probe detection	715272	LOINC	94760-6	0	36
SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with probe detection	757678	LOINC	95409-9	0	9
SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection	706161	LOINC	94533-7	0	671
SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1	586524	LOINC	94756-4	0	468
SARS-CoV-2 (COVID-19) N gene Nasopharynx Microbiology	36660752	LOINC	LP41870 2-9	36	0
SARS-CoV-2 (COVID-19) N gene Nose Microbiology	36660970	LOINC	LP41917 9-9	9	0
SARS-CoV-2 (COVID-19) N gene Respiratory specimen Microbiology	36661286	LOINC	LP41870 3-7	1,107	0
SARS-CoV-2 (COVID-19) ORF1ab region	36661401	LOINC	LP41790 6-7	1,267	0
SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	723478	LOINC	94559-2	0	1,265
SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Specimen by NAA with probe detection	723464	LOINC	94639-2	0	2
SARS-CoV-2 (COVID-19) ORF1ab region Respiratory specimen Microbiology	36661250	LOINC	LP41870 6-0	1,265	0
SARS-CoV-2 (COVID-19) ORF1ab region XXX Microbiology	36661194	LOINC	LP41870 7-8	2	0
SARS-CoV-2 (COVID-19) RdRp gene	36661801	LOINC	LP41759 8-2	3,774	0
SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	706160	LOINC	94534-5	0	3,764
SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Specimen by NAA with probe detection	706173	LOINC	94314-2	0	18
SARS-CoV-2 (COVID-19) RdRp gene Respiratory specimen Microbiology	36660902	LOINC	LP41870 8-6	3,764	0
SARS-CoV-2 (COVID-19) RdRp gene XXX Microbiology	36660887	LOINC	LP41870 9-4	18	0

SARS-CoV-2 (COVID-19) RNA	36661507	LOINC	LP41754 1-2	89,445	0
SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	586528	LOINC	94745-7	0	1
SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	723476	LOINC	94565-9	0	2,005
SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection	586526	LOINC	94759-8	0	273
SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection	706163	LOINC	94500-6	0	63,160
SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by Sequencing	715261	LOINC	94822-4	0	107
SARS-CoV-2 (COVID-19) RNA [Presence] in Specimen by NAA with probe detection	706170	LOINC	94309-2	0	27,394
SARS-CoV-2 (COVID-19) RNA Nasopharynx Microbiology	36661317	LOINC	LP41869 4-8	2,274	0
SARS-CoV-2 (COVID-19) RNA Respiratory specimen Microbiology	36661115	LOINC	LP41869 5-5	63,160	0
SARS-CoV-2 (COVID-19) RNA Saliva Microbiology	36660966	LOINC	LP41869 6-3	107	0
SARS-CoV-2 (COVID-19) RNA XXX Microbiology	36661244	LOINC	LP41869 8-9	27,394	0
SARS-CoV-2 (COVID-19) RNA panel	36661522	LOINC	LP41753 9-6	5,080	0
SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	706158	LOINC	94531-1	0	1,342
SARS-CoV-2 (COVID-19) RNA panel - Specimen by NAA with probe detection	706169	LOINC	94306-8	0	3,740
SARS-CoV-2 (COVID-19) RNA panel Respiratory specimen Microbiology Panels	36661036	LOINC	LP41928 8-8	1,342	0
SARS-CoV-2 (COVID-19) RNA panel XXX Microbiology Panels	36660924	LOINC	LP41928 9-6	3,740	0
SARS-CoV-2 (COVID-19) S protein RBD neutralizing antibody [Presence] in Serum or Plasma by sVNT	36031734	LOINC	96603-6	0	476
SARS-CoV-2 (COVID-19) sequencing and identification panel	1620099	LOINC	LP42274 0-3	40	0
SARS-CoV-2 (COVID-19) sequencing and identification panel - Specimen by Molecular genetics method	36033651	LOINC	96894-1	0	40

SARS-CoV-2 (COVID-19) sequencing and identification panel XXX Microbiology Panels	1618441	LOINC	LP42752 4-6	40	0
SARS-CoV-2 (COVID-19) spike protein receptor binding domain (RBD)	36033856	LOINC	LP42123 5-5	476	0
SARS-CoV-2 (COVID-19) spike protein receptor binding domain (RBD) neutralizing antibody	36033858	LOINC	LP42123 4-8	476	0
SARS-CoV-2 (COVID-19) spike protein receptor binding domain (RBD) neutralizing antibody Serum or Plasma Microbiology	36033625	LOINC	LP42184 0-2	476	0
SARS-CoV+SARS-CoV-2 (COVID-19)	36661687	LOINC	LP41877 4-8	1,075	0
SARS-CoV+SARS-CoV-2 (COVID-19) Ag	36661520	LOINC	LP41876 2-3	1,075	0
SARS-CoV+SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	757685	LOINC	95209-3	0	1,075
SARS-CoV+SARS-CoV-2 (COVID-19) Ag Respiratory specimen Microbiology	1618075	LOINC	LP42765 4-1	1,075	0
COPE Survey (Any version): In the past month, have you been sick for more than one day with a new illness related to COVID-19 or flu-like symptoms?: Yes	1332898			9,138	
COVID-19	37311061	SNOMED	84053900 6	17,384	17,384
Lower respiratory infection caused by SARS-CoV-2	3663281	SNOMED	8.8053E+ 17	1,663	0

Symptom-based classification of long COVID groups: Symptomatic vs. Recovered

An initial list of sequelae was compiled from phenotyping studies (e.g., Al-Aly et al., 2021; Zhang et al., 2023). This list was then cross-checked with sequelae listed by the CDC (Centers for Disease Control and Prevention, 2023), reports from the patient-led research collaborative [e.g. Davis et al], and co-author knowledge of patient experience encountered in a long COVID follow-up clinic. These were collapsed into diagnostically-related groups as organized under the Athena Health Observational Medical Outcomes Partnership – Common Data Model (OMOP-CDM) harmonized data vocabulary (Observational Health Data Sciences and Informatics, 2024; Odysseus Data Services, 2023). Athena is a hierarchical compendium of health concepts (e.g. diagnoses, observations, medications) organized into tree-like branching relationships. Distinct “descendent” concepts branch off of broad categories of “ancestor” concepts. The final list consisted of 44 symptom/sequelae ancestor categories.

Using the *All of Us* Data Browser and Researcher Workbench, each symptom concept code was queried singly to create a concept set incorporating all occurrences of all descendent codes contained within that symptom for each participant with at least one COVID-19 infection.

These were then arranged by date of recording. Two occurrences were then selected; the first occurrence between 28 days and 5 years prior to the first COVID infection (pre-infection incidence) and the first code 28 days or more after the first COVID infection (post-infection incidence, marking a participant as a long COVID symptomatic group member). This was performed iteratively for each long COVID symptom

dataset individually, creating one dataset for each symptom containing only the first pre- and post-infection (if any) incidences for each participant. These datasets were then joined one by one in alphabetical order to the main dataset, using person ID number as the foreign key.

The post-infection interval of 28-days before first symptom occurrence was chosen to capture health and daily functioning beginning after the presumptive acute infection phase but still within 90 days post-infection. A 28-day window is sooner post-infection than the 90-day window in other studies (Thaweethai et al., 2023) and the WHO proposed diagnostic criteria. (Soriano et al., 2022) However, a shorter interval is of clinical interest for targeted rehabilitation services because it reveals the prevalence of functional status indicators and symptom burden within the 90-day timeframe that is allowable under the U.S. law ("29 USC Ch. 28: Family and Medical Leave Act," 1993). Because functional impairment is proposed as part of this diagnostic classification, we wished to characterize long COVID in a timeframe that would be clinically useful in the U.S. for utilizing skilled rehabilitation.

The list of queried diagnostic categories is in Table S.A.1. Under these categories were 1,013 discrete descendent diagnostic concepts. We chose not to remove descendent concepts containing attributions to specific (non-COVID-19) diseases (e.g., "*cancer-related* fatigue", "memory impairment *due to multiple sclerosis*"), resulting in an attribution-agnostic grouping. This was for several reasons. First and most broadly, there is probable variation in how post-COVID pathophysiology interacts with other diseases processes; therefore the possibility of development or worsening of these health outcomes in the setting of other premorbid diagnoses could not be assumed to be independent of the physical toll of COVID recovery, and some outcomes may have been potentiated by this toll. Second, the increased granularity of having all types of a given diagnosis provided opportunities for future analysis that would not be possible had we removed or collapsed their diagnostic variations. Third and finally, we found the patient counts of many diagnostically-attributed outcomes were small (fewer than $n=50$), necessitating collapse into other categories for statistical analysis and *All of Us* reporting rules, and exerting little or negligible pull on the symptoms' effect given the size of this dataset.

Table S.A.1. Long COVID symptoms/conditions used in Cohort discovery and classification

Standard Concepts	OMOP Concept ID	Source	Vocab	Code	String collapsed
Abdominal pain	200219	Standard	SNOMED	21522001	"abdominal"
Anxiety	441542	Standard	SNOMED	48694002	"anxiety", "anxi*"
Chest pain	77670	Standard	SNOMED	29857009	"chest", "cardiac"
Chronic fatigue syndrome	432738	Standard	SNOMED	52702003	"chronic fatigue", "myalgic encephalomyelitis"
Cognitive disorder (collapsed into "impaired cognition")	40480615	Standard	SNOMED	443265004	"cognitive", "neurocognitive"
Cognitive function finding (collapsed into "impaired cognition")	4162723	Standard	SNOMED	373930000	[not collapsed, heterogeneous]
Cough	254761	Standard	SNOMED	49727002	"cough", "clearing throat"
Depression screening positive	762504	Standard	SNOMED	4.28181E+14	"depression", "screening"
Depressive disorder	440383	Standard	SNOMED	35489007	"depressive", "depression"
Depressive episode	3656234	Standard	SNOMED	871840004	
Diarrhea	196523	Standard	SNOMED	62315008	"diarrhea", "diarrheal"
Disorder of menstruation	443431	Standard	SNOMED	386804004	"*men*

Disturbance in sleep behavior (collapsed into "Sleep")	4204989	Standard	SNOMED	53888004	"sleep"
Dizziness	4223938	Standard	SNOMED	404640003	"dizziness", "dizzy", "vertigo"
Dyspnea	312437	Standard	SNOMED	267036007	"dyspnea", "*pnea", "gasping"
Eruption	140214	Standard	SNOMED	271807003	"eruption", "acne*", "rash", "eruption", "erythroderma", "exanthematous", "Fox-Fordyce", "roceacea", "Keratin*", "pityriasis", "psoriasis", "psoriatic", "dermatitis"
Fatigue	4223659	Standard	SNOMED	84229001	"asthenia"
Fever	437663	Standard	SNOMED	386661006	"fever", "*pyrexia"
Finding of functional performance and activity	4089214	Standard	SNOMED	248536006	
Finding of pattern of menstrual cycle (collapsed into "menstrual disorder")	4095940	Standard	SNOMED	248968007	"menstru*", "amenorrhea"
Finding of sexual function	4041277	Standard	SNOMED	118202007	
Headache	378253	Standard	SNOMED	25064002	"headache", "head"
Impaired cognition	443432	Standard	SNOMED	386806002	"cognitive", "impairment", "behavioral"
Irregular periods (collapsed into "menstrual disorder")	196168	Standard	SNOMED	80182007	
Joint pain	77074	Standard	SNOMED	57676002	"arthralgia", "joint"
Lightheadedness	4297376	Standard	SNOMED	386705008	[do not collapse] "malaise and fatigue", "fatigue"
Loss of sense of smell	4185711	Standard	SNOMED	44169009	
Loss of taste	4289517	Standard	SNOMED	36955009	
Malaise (under "Lightheadedness" heirarchy)	4272240	Standard	SNOMED	367391008	
Muscle fatigue	4214612	Standard	SNOMED	80449002	"muscle"
Muscle pain	442752	Standard	SNOMED	68962001	"myalgia*", "pain", "muscle", "pleurodynia", "fibrositis", "fibromyalgia",


```

        'Low intelligence',
        'Grinding teeth',
        'Human immunodeficiency virus infection
with cognitive impairment',
        'Suicidal',
        'Suicidal thoughts',
        'Mood-congruent delusion',
        'Paranoid ideation'
    )))

```

```

Cognition %>%
filter(standard_concept_name != "Attention deficit hyperactivity disorder" &
        standard_concept_name != "Attention deficit hyperactivity disorder,
predominantly inattentive type" &
        standard_concept_name != "Child attention deficit disorder" &
        standard_concept_name != "Undifferentiated attention deficit disorder" &
        standard_concept_name != "Attention deficit hyperactivity disorder,
predominantly hyperactive impulsive type" &
        standard_concept_name != "Attention deficit hyperactivity disorder,
combined type" &
        standard_concept_name != "Hyperkinetic conduct disorder" &
        standard_concept_name != "Developmental coordination disorder")

```

Under the “Finding of Functional Performance and Activity” concept, psychological concepts from the DSM series and developmental diagnoses were removed as follows:

```

functional_performance %>%
filter(standard_concept_name != "Attention deficit hyperactivity disorder" &
        standard_concept_name != "Attention deficit hyperactivity disorder,
predominantly inattentive type" &
        standard_concept_name != "Child attention deficit disorder" &
        standard_concept_name != "Undifferentiated attention deficit disorder" &
        standard_concept_name != "Attention deficit hyperactivity disorder,
predominantly hyperactive impulsive type" &
        standard_concept_name != "Attention deficit hyperactivity disorder,
combined type" &
        standard_concept_name != "Hyperkinetic conduct disorder" &
        standard_concept_name != "Developmental coordination disorder" &
        standard_concept_name != "Developmental disorder of motor function" &
        standard_concept_name != "Developmental delay in fine motor function" &
        standard_concept_name != "Hyperkinesia with developmental delay" &
        standard_concept_name != "Ineffective breathing pattern" &
        standard_concept_name != "Adjustment to life threatening illness" &
        standard_concept_name != "Difficulty coping" &
        standard_concept_name != "Lack of exercise" &
        standard_concept_name != "Gets no exercise")

```

Appendix B. Functional Status Indicators

S.B.1. Occupational therapy evaluation – Centers for Medicare and Medicaid codes.

The Centers for Medicare and Medicaid Services (CMS) maintains codes and definitions for clinicians to record the medical necessity of services and procedures in the medical record. The codes that record evaluation by an occupational therapist are cataloged under the CPT code directory and are 97165-97168 (see below). These codes only occur in the medical record of a patient with concerns for “performance deficits (i.e., relating to physical, cognitive, or psychosocial skills) *that result in activity limitations and/or participation restrictions*” (CMS, 2020, emphasis added). This indicator of functional status is therefore highly specific – it is not documented for a person who does not report concern for and/or present with functional performance deficits.

Three codes are available to document the complexity of the clinician’s evaluation to determine performance deficits and the therapeutic plan of care. One additional code documents the need for re-evaluation, frequently used when the patient has a decrease in status (due to, e.g., surgical procedure, poor prognosis, and/or complication of medical conditions). CMS defines these as follows:

97165: Occupational therapy evaluation, low complexity, requiring these components:

An occupational profile and medical and therapy history, which includes a brief history including review of medical and/or therapy records relating to the presenting problem; ... , requiring these components:
An occupational profile and medical and therapy history, which includes a brief history including review of medical and/or therapy records relating to the presenting problem; An assessment(s) that identifies 1-3 performance deficits (ie, relating to physical, cognitive, or psychosocial skills) that result in activity limitations and/or participation restrictions; and Clinical decision making of low complexity, which includes an analysis of the occupational profile, analysis of data from problem-focused assessment(s), and consideration of a limited number of treatment options. Patient presents with no comorbidities that affect occupational performance. Modification of tasks or assistance (eg, physical or verbal) with assessment(s) is not necessary to enable completion of evaluation component. Typically, 30 minutes are spent face-to-face with the patient and/or family.

97166 Occupational therapy evaluation, moderate complexity, typical time with patient 45 minutes, Occupational therapy evaluation, moderate complexity, typical time with patient’s family 45 minutes, Occupational therapy evaluation, moderate complexity, requiring these components:

An occupational profile and medical and therapy history, which includes an expanded review of medical and/or therapy records and additional review of physical, cognitive,... , Occupational therapy evaluation, moderate complexity, typical time with patient and family 45 minutes, OCCUPATIONAL THERAPY EVAL MOD COMPLEX 45 MINS, Occupational therapy evaluation, moderate complexity, requiring these components: An occupational profile and medical and therapy history, which includes an expanded review of medical and/or therapy records and additional review of physical, cognitive, or psychosocial history related to current functional performance; An assessment(s) that identifies 3-5 performance deficits (ie, relating to physical, cognitive, or psychosocial skills) that result in activity limitations and/or participation restrictions; and Clinical decision making of moderate analytic complexity, which includes an analysis of the occupational profile, analysis of data from detailed assessment(s), and consideration of several treatment options. Patient may present with comorbidities that affect occupational performance. Minimal to moderate modification of tasks or assistance (eg, physical or verbal) with assessment(s) is necessary to enable patient to complete evaluation component. Typically, 45 minutes are spent face-to-face with the patient and/or family.

97167 Occupational therapy evaluation, high complexity, requiring these components:

An occupational profile and medical and therapy history, which includes review of medical and/or therapy records and extensive additional review of physical, cognitive, or psychosocial history related to current functional performance; An assessment(s) that identifies 5 or more performance deficits (ie, relating to physical, cognitive, or psychosocial skills) that result in activity limitations and/or participation restrictions; and Clinical decision making of high analytic complexity, which includes an analysis of the patient profile, analysis of data from comprehensive assessment(s), and consideration of multiple treatment options. Patient

presents with comorbidities that affect occupational performance. Significant modification of tasks or assistance (eg, physical or verbal) with assessment(s) is necessary to enable patient to complete evaluation component. Typically, 60 minutes are spent face-to-face w..., Occupational therapy evaluation, high complexity, typical time with patient and family 60 minutes, Occupational therapy evaluation, high complexity, requiring these components: An occupational profile and medical and therapy history, which includes review of medical and/or therapy records and extensive additional review of physical, cognitive, or ps... | [Health Care Activity] - [Therapeutic or Preventive Procedure], Occupational therapy evaluation, high complexity, typical time with patient 60 minutes, Evaluation of occupational therapy established plan of care, typically 60 minutes, TYPICALLY, 60 MINUTES ARE SPENT FACE-TO-FACE WITH THE PATIENT AND/OR FAMILY.

97168 Re-evaluation of occupational therapy established plan of care, requiring these components: An assessment of changes in patient functional or medical status with revised plan of care; An update to the initial occupational profile to reflect changes in... | [Health Care Activity] - [Therapeutic or Preventive Procedure], Occupational therapy re-evaluation of established plan of care, typical time with patient 30 minutes, Re-evaluation of occupational therapy established plan of care, typically 30 minutes, Occupational therapy re-evaluation of established plan of care, typical time with patient and family 30 minutes, Re-evaluation of occupational therapy established plan of care, requiring these components: An assessment of changes in patient functional or medical status with revised plan of care; An update to the initial occupational profile to reflect changes in condition or environment that affect future interventions and/or goals; and A revised plan of care. A formal reevaluation is performed when there is a documented change in functional status or a significant change to the plan of care is required. Typically, 30 minutes are spent face-to-face with the patient and/or family.

S.B.2. “Finding of functional performance and activity” codes

These codes include observations documented by rehabilitation and respiratory therapy providers, or based on evaluation findings by the providers. For modelling, these were collapsed into a multinomial variable with three categories roughly corresponding to ranges of functional impairment that may be inferred from these codes. These categories were as follows:

1. “No functional performance impairment” was given for normal” or “independent” findings, as well as all participants with “NA” values indicating no need for medical care for or observations of functional impairment.
2. “Some functional performance impairment” was given for codes that may have been documented for a range of functional levels. For instance “Dependence on wheelchair” could be true of a person with acute change in mobility that affects their daily functioning profoundly, and could also be true of a person who had mastered wheelchair mobility and performed their daily routines without assistance. This suggests the important caveat for interpretation that this level has high heterogeneity and low resolution for small increments of difference in level of performance.
3. “Dependent on others for care” was given for codes which explicitly describe dependence (e.g. “Bed-ridden”) and those typically only given in critical care settings (e.g. respiratory dependence codes).

The following dplyr code was used to group these observations:

```
dplyr::mutate(pre_functional_performance_dx = forcats::fct_na_value_to_level
(pre_functional_performance_dx, "None")) |>
dplyr::mutate(pre_functional_performance_dx_factor =
fct_collapse(pre_functional_performance_dx,
  "No Functional Performance Difficulty" = c("None",
                                             "Get up and go test - normal",
                                             "Exercises regularly"),
  "Some Functional Performance Difficulty" = c(
    "Difficulty walking",
    "Reduced mobility",
    "Impaired mobility",
    "Physical activity finding",
    "Dependence on supplemental oxygen",
    "Wheelchair bound",
    "Caregiver role strain",
    "Dependence on wheelchair",
    "Finding related to ability to mobilize",
    "Finding related to ability to move",
    "Finding of functional performance and
activity",
control",
    "Disorders of attention and motor
    "Walking disability",
    "Activity exercise pattern",
    "Finding related to ability to cope with
pain",
    "Difficulty producing voiced sounds",
    "Loss of voice",
    "Activity intolerance",
    "Fine motor impairment"),
  "Dependent on Others for Care" = c(
    "Dependence on aspirator",
```

```
device",
                                "Dependence on enabling machine or
                                "Dependence on respirator",
                                "Bed-ridden",
                                "Dependence on respiratory device",
                                "Dependence on ventilator",
                                "Unable to mobilize")) |>
dplyr::mutate(pre_functional_performance_dx_factor =
fct_relevel(pre_functional_performance_dx_factor,
            "No Functional Performance Difficulty",
            "Some Functional Performance Difficulty",
            "Dependent on Others for Care"))
```

Appendix C: Sensitivity analysis for Quantitative bias analysis of cohort discovery

(Aim 1 only)

Enrollment pre- vs. post-first infection:

Balance between the two groups' distributions of factors which could affect the development of long COVID was assessed using non-parametric propensity score matching in the MatchIt R package. The binary outcome of pre-illness versus post-illness enrollment was regressed on COVID variant, primary demographics of race and sex at birth, and the socioeconomic variable of education level. To ensure a match was attempted for all cases, matching without replacement was used. A generalized linear model with logit link functions was fitted with 'nearest' matching. Model fit was assessed with standardized difference in means and plots.

Model:

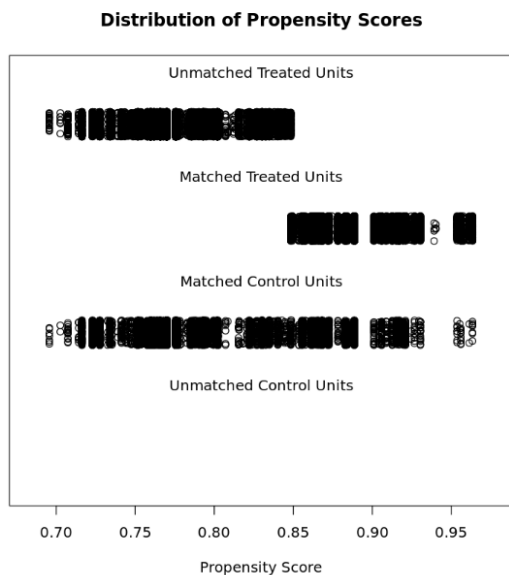
```
match <- matchit(enrollment_date ~ variant + race + sex_at_birth + Highest_grade_completed,
  data = full_data2, method = "nearest", distance = "glm",
  ratio = 1,
  replace = FALSE)
```

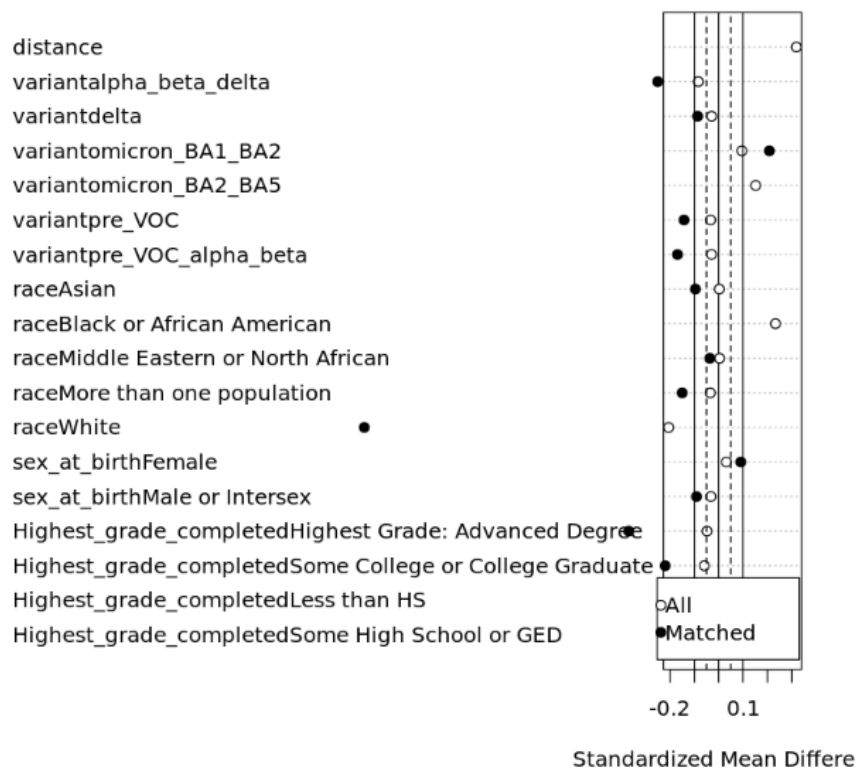
Result

Pre-infection enrollees were fitted as the control ($n=16815$) compared to post-infection fitted as cases ($n=66971$). Most of the sample enrolled prior to their earliest indication of COVID-19. For the unmatched samples, substantial standard mean differences (>0.1) were seen for overall distance (0.32), later omicron variant period (B2-B5) (0.15), Black or African American (0.2331) and White (-0.2056) race, and having completed some or all of high school (0.1174). After balancing, standard mean differences generally increased (grew further from zero), indicating that a good balance on these covariates between pre- and post-illness enrollees could not be achieved.

Overlaps between the treated pre-infection ('control') and post-infection ('treated') groups is visualized in Figure C.1. There is about 45% overlap between the matched post-infection cases and the matched pre-infection controls; this relatively low match overall indicates that propensity score matching is not appropriate for these data. This suggests that these two groups may be different across one or more important population parameters, which may have been related to programmatic influences on recruitment that affect the sample over time such as adjustments in recruitment to increase sample diversity or the addition of new study sites in previously under-represented regions or patient populations.

Fig. C. 1.





Sample Sizes:

	Control	Treated
All	16815	66971
Matched	16815	16815
Unmatched	0	50156
Discarded	0	0

Summary of Balance for All Data:

Variable	Std. Mean Diff.
distance	0.3189
variantalpha_beta_delta	-0.0836
variantdelta	-0.0290
variantomicron_BA1_BA2	0.0951
variantomicron_BA2_BA5	0.1522
variantpre_VOC	-0.0332
variantpre_VOC_alpha_beta	-0.0294
raceAsian	0.0025
raceBlack or African American	0.2331
raceMiddle Eastern or North African	0.0035
raceMore than one population	-0.0341
raceWhite	-0.2056
sex_at_birthFemale	0.0319
sex_at_birthMale or Intersex	-0.0319
Highest_grade_completedHighest Grade: Advanced Degree	-0.0481

Highest_grade_completedSome College or College Graduate	-0.0585
Highest_grade_completedLess than HS	0.0209
Highest_grade_completedSome High School or GED	0.1174

Summary of Balance for Matched Data:

	Std. Mean Diff.
distance	1.8529
variantalpha_beta_delta	-0.2505
variantdelta	-0.0863
variantomicron_BA1_BA2	0.2084
variantomicron_BA2_BA5	0.8219
variantpre_VOC	-0.1422
variantpre_VOC_alpha_beta	-0.1691
raceAsian	-0.0957
raceBlack or African American	1.6786
raceMiddle Eastern or North African	-0.0361
raceMore than one population	-0.1499
raceWhite	-1.4552
sex_at_birthFemale	0.0908
sex_at_birthMale or Intersex	-0.0908
Highest_grade_completedHighest Grade: Advanced Degree	-0.3692
Highest_grade_completedSome College or College Graduate	-0.2197
Highest_grade_completedLess than HS	0.1560
Highest_grade_completedSome High School or GED	0.6181

Appendix D. Model Fitting Notes.

Aim 1

Summary of final fit

The optimal model balance between R^2 and BIC delta (smaller value) was found for an additive model with linear fits for age and pre-infection CPT unit count and a restricted cubic spline with four knots for pre-infection prevalence of long COVID symptoms. For this paper's aim, parsimoniousness was favored over accuracy for a simple descriptive model.

Final Model Fit Indices

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	65464	LR chi2	25359.80	R2	0.437	C	0.845
FALSE	24809	d.f.	40	R2(40,65464)	0.321	Dxy	0.691
TRUE	40655	Pr(> chi2)	<0.0001	R2(40,46221.3)	0.422	gamma	0.691
max deriv	5e-09			Brier	0.153	tau-a	0.325

Aim 1 Model fitting procedure

Model fitting processes recommended by Harrell (2001) and Andersen & Skovgaard (2010) were followed for binomial logistic regression with a logit link function for continuous, ordinal, and nominal variables (Table S.D.1). First, a large model was fitted including all variables found in prior literature to be related to long COVID risk or outcomes. This was fitted with natural (restricted) cubic splines for continuous variables, and interaction terms for age with baseline survey responses for performance of physical daily activities and mental/cognitive health, as well as approximate baseline level of functional impairment per EMR entries of “Finding of Functional Activity and Performance” (see Table S.A.1). Modelling and hypothesis testing was completed using the rms package (Harrell, 2024). Using $n/15$ or $n/20$ observations per regression coefficient as a guide, we found degrees of freedom in our starting model, indexed to the smaller control group, to be $N=25,332$, yielding $25,332/20 = 1,266$ degrees of freedom.

Table D.1

Aim 1 Variables for model

Type	Covariate	Sources
Demographics	Age Sex at birth Race Ethnicity	Self-reported “Basics” survey responses at enrollment EMR
Acquired demographics/SDH	Education (highest level completed)	Self-reported “Basics” survey responses
SARS-CoV-2 Variant	The calendar period between the starts of major variants of concern in which the first infection occurred.	Self-report of symptoms on the COPE surveys EMR condition and measurement codes (SNOMED, OMOP, and ICD-10 vocabularies).

Pre-infection health and symptoms	<p>Pre-infection total number of long COVID symptom categories with at least one incidence*</p> <p>Self-Reported mental health and cognition</p> <p>Self-Reported ability to perform physically-demanding daily activities</p> <p>Self-Reported social role performance and satisfaction (composite score summing two ordinal items, values 2(~excellent)-10(~very poor))</p>	<p>Self-reported “Overall Health” survey responses at enrollment</p> <p>EMR condition codes (SNOMED, OMOP, and ICD-10 vocabularies).</p>
Pre-infection daily Functioning	<p>Pre-infection total number of occupational therapy codes*</p> <p>Incidences of at least one pre-infection functional performance finding diagnostic codes*, collapsed into three levels.</p>	EMR condition and procedure codes (SNOMED, OMOP, and ICD-10 vocabularies).
Note. * = Entered in EMR between January 1, 2020 and four weeks before first infection date.		

Initial full model

```

initial_full <- rms::lrm(sx_notebook_group == "case" ~
  variant +
  rcs(age,7) +
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  rcs(pre_infection_sx_total,4) +
  rcs(cpt_total_precovid,5) +
  pre_functional_performance_dx_factor +
  social_scale +
  Rate_your_mental_health +
  Can_you_complete_daily_activities +
  rcs(age,7):Can_you_complete_daily_activities +
  rcs(age,7):Rate_your_mental_health +
  rcs(age,7):pre_functional_performance_dx_factor,
data = temp3, y=TRUE, x=TRUE)

```

Structured model tests of complexity

We tested the initial full model against simplified models with reduced spline knots. The best fitting spline structures were seven for age, four for pre-infection number of symptoms, and six for pre-infection number of CPT billing units.

Table D.2

Aim 1 continuous variable spline reductions:

Model	LR	R2	C-index / AUC	Δ BIC	Decision
Initial_full (reference)	25467.72	0.439	0.846	--	--
Age knot reductions					
Age 6 knots	25457.67	0.438	0.846	121.50	The R2 value for the reduced fit is 0.006 lower than the initial model, and the delta BIC is significantly lower than 0(+/-10) indicating the original model's BIC is the smaller of the two and the R2 difference is significant. Retain 4 knots for pre infection sx total.
Age 5 knots	25435.11	0.438	0.846	230.48	
Age 4 knots	25413.74	0.438	0.846	340.66	
Pre-infection total number of symptoms					
Sx 3 knots	25053.11	0.433	0.844	-9.84	The R2 value for the reduced fit is 0.006 lower than the initial model, and the delta BIC is

					significantly lower than 0(+/-10) indicating the original model's BIC is the smaller of the two and the R2 difference is significant. Retain 4 knots for pre infection sx total.
Pre-infection total number of therapy billing units					
CPT 6 knots	25470.98	0.438	0.846	-6.75	
CPT 4 knots	25464.41	0.438	0.846	6.57	
CPT 3 knots	25463.85	0.438	0.846	16.18	The R2 values across these models are equivalent to the model with fewer age splines and are 0.001 point lower than the initial full model. The BIC delta provides strong evidence that the 3-knot model is a better fit. Reduce to 3 knots for cpt total.

Spline-corrected model:

```
initial_full_3 <- rms::lrm(sx_notebook_group == "case" ~
  variant +
  rcs(age,4) +
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  rcs(pre_infection_sx_total,4) +
  rcs(cpt_total_precovid,3) +
  pre_functional_performance_dx_factor +
  social_scale +
  Rate_your_mental_health +
  Can_you_complete_daily_activities +
  rcs(age,4):Can_you_complete_daily_activities +
  rcs(age,4):Rate_your_mental_health +
  rcs(age,4):pre_functional_performance_dx_factor,
  data = temp3, y=TRUE, x=TRUE)
```

Assumptions of linearity

There is very strong evidence that linear fits for both age and CPT code count are better fits for these data. However, this further reduces the R2 value. We proceeded to test additivity assumptions with both.

Table D.3

Aim 1 models without spline functions:

Model	LR test X^2	Df	R2	p	AUC	Δ BIC	Decision
-------	---------------	----	----	---	-----	--------------	----------

Initial_full_3 (reference)	--	--	0.438	--	0.846	--	--
Age linear	38.89	26	0.437	0.049	0.845	224.21	There is strong evidence that a linear function is a better fit for age.
Symptoms linear	1982.493	1979.02	0.409	2.0	0.837	-1958.79	Sx linear is a much poorer fit.
CPT codes linear	1.04	1.0	0.438	0.31	0.846	9.07	There is moderate evidence that a linear function is a better fit for CPT codes.
Age AND CPT linear	39.98	27	0.437	0.05	0.845	233.22	

Checking interaction terms: comparing to additive models

We started with two models that removed all interaction terms, one with all splines retained and one model with linear fits for age and CPT counts (as indicated in linearity tests above). The second (linear age and CPT) model with no interactions had the larger difference of the two (BIC delta 111.53 vs. 98.54) indicating a smaller BIC and better fit to the data for the model with more linear parameters. Models with linear fits for age and CPT units plus dropped single interaction terms were then compared to the model with all interactions and linear fits for age and CPT codes. All were significant for better fits without the interaction terms. The largest BIC delta was thus found for a linear fit for age and CPT count, and no interaction terms. This is the model going forward.

Table D.4

Aim 1 testing dropped interaction terms:

Model	LR	R2	C-index / AUC	Δ BIC	Decision
Initial_full_4 (reference)	25369.69	0.437	0.846	--	--
Additive only (omit all interactions)					
No interaction terms, all splines retained	25377.22	0.437	0.845	98.54	
No interactions, linear age and CPT	25359.80	0.437	0.845	111.53	This BIC delta is the largest, and favors the additive model with no interaction terms and linear fits for both age and CPT codes. This will be our model going forward.
Drop age*self-rated physical activity	25366.00	0.437	0.845	46.90	
Drop age*self-rated mental health	25364.92	0.437	0.845	45.81	
Drop age*functional performance EMR code	25368.27	0.437	0.845	18.81	

Full model check:					
-------------------	--	--	--	--	--

Revised working model:

```
Initial_full_5 <- rms::lrm(sx_notebook_group == "case" ~      # aim1_no_int_linear
  variant +
  age +
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  rcs(pre_infection_sx_total,4) +
  social_scale +
  Rate_your_mental_health +
  Can_you_complete_daily_activities +
  pre_functional_performance_dx_factor +
  cpt_total_precovid,
  data = temp3, y=TRUE, x=TRUE)
```

Test for main effects

An alternative model was fitted with main effects for all demographics, pre-infection total number of symptoms, and pre-infection functional performance factor. The model with main effects had a higher R2 (0.447), BUT a BIC delta of -1170.39 giving extremely strong evidence that the main effects model is a much poorer fit for these data. The model 'initial_full_5' is the final model for analysis.

Final fitted model:

```
final_fit <- rms::lrm(sx_notebook_group == "case" ~
  variant +
  age +
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  rcs(pre_infection_sx_total,4) +
  social_scale +
  Rate_your_mental_health +
  Can_you_complete_daily_activities +
  pre_functional_performance_dx_factor +
  cpt_total_precovid,
  data = temp3, y=TRUE, x=TRUE)
```

Model fit checks

Residual fits on continuous variables

Figure D.1
Aim 1 residual fit of age

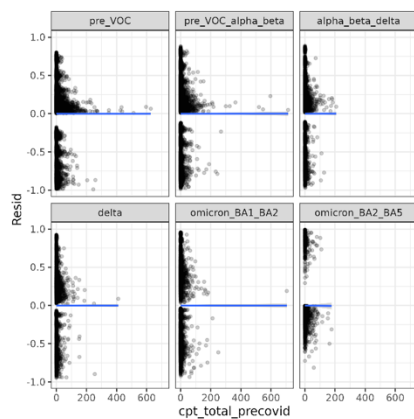


Figure D.2
Aim 1 residual fits of total number of occupational therapy CPT units billed in five years preceding infection

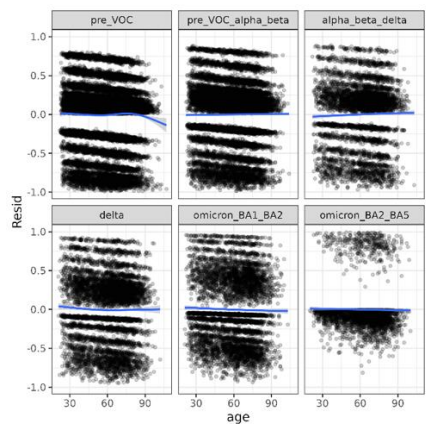


Figure D.3
Aim 1 residual fits of total number of long COVID symptom/condition types occurring prior to infection

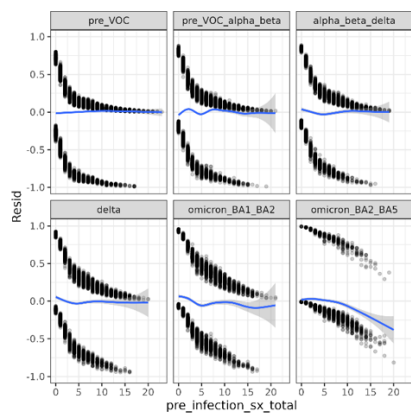


Figure D.4
Aim 1 probability of developing symptoms after infection, by age

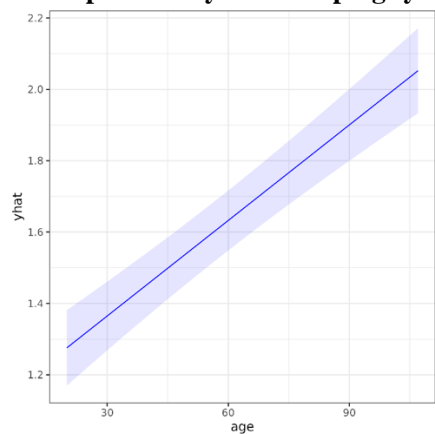


Table D.5
Final Model Fit Indices

		Model Likelihood		Discrimination		Rank Discrim.	
		Ratio Test		Indexes		Indexes	
Obs	65464	LR chi2	25359.80	R2	0.437	C	0.845
FALSE	24809	d.f.	40	R2(40,65464)	0.321	Dxy	0.691
TRUE	40655	Pr(> chi2)	<0.0001	R2(40,46221.3)	0.422	gamma	0.691
max deriv	5e-09			Brier	0.153	tau-a	0.325

Table D.6
Aim 1 ANOVA omnibus test of effects

Model fit ANOVA

	Chi-Square	d.f.	P
variant	5744.3010	5	0.0000
age	182.0550	1	0.0000
sex_at_birth	7.0171	1	0.0081
race	9.3608	4	0.0527
ethnicity	7.0007	1	0.0081
Highest_grade_completed	10.4879	4	0.0330
pre_infection_sx_total	11316.3800	3	0.0000
Nonlinear	1950.3980	2	0.0000
social_scale	11.4296	8	0.1785
Rate_your_mental_health	29.2189	5	0.0000
Can_you_complete_daily_activities	10.8828	5	0.0538
pre_functional_performance_dx_factor	46.6759	2	0.0000
cpt_total_precovid	0.5775	1	0.4473
TOTAL	15793.2100	40	0.0000

Appendix D. Model Fitting (cont.)

Aim 2.

Summary of final model

Probit Ordinal Regression Model

```
orm(formula = postcovid_functional_score ~ group + variant +
    age + sex_at_birth + race + ethnicity + Highest_grade_completed +
    pre_functional_performance_level + precovid_eval_cpt + rcs(pre_infection_sx_total,
    3) + group:rcs(pre_infection_sx_total, 3) + group:age, data = temp2,
    x = TRUE, y = TRUE, family = probit)
```

Frequencies of Responses

	0	1	2	3	4	5
	75823	4767	2952	204	35	5

		Model Likelihood Ratio Test	Discrimination Indexes	Rank Discrim. Indexes
Obs	83786	LR chi2 10983.52	R2 0.227	rho 0.323
Distinct Y	6	d.f. 28	R2(28,83786) 0.123	
Median Y	1	Pr(> chi2) <0.0001	R2(28,21671.4) 0.397	
max deriv	0.003	Score chi2 10503.29	Pr(Y>=median)-0.5 0.409	
		Pr(> chi2) <0.0001		

D.1. Aim 2 Model fitting procedure

We followed model fitting processes recommended by Harrell(2001) for a main effects model using an ordinal probit regression model for the composite outcome of post-infection functional status (OT evaluation CPT level + EMR code for functional findings inferred level). Natural (restricted) cubic splines were used for continuous variables, and interaction terms for age with long COVID group and approximate baseline level of functional impairment per EMR entries of “Finding of Functional Activity and Performance” (see Table S.A.1). Modelling and hypothesis testing was completed using the rms package.(Harrell, 2024)

1. Variables of interest

Demographics of age, sex assigned at birth, race, and ethnicity were all included, as evidence suggests that these may moderate long COVID risk(Jacobs et al., 2023; Khullar et al., 2023; Vasilevskaya et al., 2023) and its relationship with functional status.(Ford et al., 2023; Izaguirre et al., 2023) Education level, expressed as “highest grade completed”, was a proxy for the impact of social determinants of health due to its relationship with access to other health-supporting societal resources,(U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion, 2025) which have been found to associate with more numerous and persistent symptoms and quality of life after infection.(Case et al., 2022; Eligulashvili et al., 2024)

Table D.1.

Variables for model 1: Full sample post-infection functional status

Type	Covariate	Sources	Modifier, mediator, or confounder?
Demographics	Age Sex at birth Race Ethnicity	Self-reported “Basics” survey responses at enrollment EMR	
Acquired demographics/SDH	Education (highest level completed)	Self-reported “Basics” survey responses	
SARS-CoV-2 Variant	The calendar period between the starts of major variants of concern in which the first infection occurred.	Self-report of symptoms on the COPE surveys EMR condition and measurement codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Pre-infection indicators of daily functioning	Occupational therapy evaluation code, level of complexity (0 = no evaluation, 4 = high complexity). Incidences of at least one pre-infection functional performance finding diagnostic codes*, collapsed into three levels (0 = No difficulty, 1 = Some difficulty, 2 = Severe difficulty).	EMR condition and procedure codes (SNOMED, OMOP, and ICD-10 vocabularies).	

Note. * = Entered in EMR between January 1, 2020 and four weeks before first infection date.			

Table S.D.2.
Variables for model 2: Cases' post-infection functional status

Type	Covariate	Sources	Confounder, mediator, or moderator?
Demographics	Age Sex at birth Race Ethnicity	Self-reported "Basics" survey responses at enrollment EMR	
Acquired demographics/SDH	Education (highest level completed)	Self-reported "Basics" survey responses	
SARS-CoV-2 Variant	The calendar period between the starts of major variants of concern in which the first infection occurred.	Self-report of symptoms on the COPE surveys EMR condition and measurement codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Pre-infection indicators of daily functioning	Occupational therapy evaluation code, level of complexity (0 = no evaluation, 4 = high complexity). Incidences of at least one pre-infection functional performance finding diagnostic codes*, collapsed into three levels (0 = No difficulty, 1 = Some difficulty, 2 = Severe difficulty).	EMR condition and procedure codes (SNOMED, OMOP, and ICD-10 vocabularies).	

Symptoms	Pre-infection number of long COVID symptoms Post-infection number of long COVID symptoms Hierarchical cluster of symptoms	EMR condition and measurement codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Note. * = Entered in EMR between January 1, 2020 and four weeks before first infection date.			

Aim 2 Primary demographics

Age, sex assigned at birth, race, and ethnicity were included. Older age is an independent risk factor for SARS-CoV-2 infection, as well as severe illness which confers additional risk for long COVID.(Tana et al., 2023) However, the evidence concerning functional status is relatively mixed for this age group. Studies on long COVID's effect on functioning in middle-aged adults is plentiful, but many use assessment of employment status,(Jaywant et al., 2024) absenteeism, or sick leave,(Nielsen et al., 2022) precluding inclusion of older adults. An analysis of the Household Pulse survey data counterintuitively found that prevalence of self-reported significant activity limitations was lower in older compared to middle-aged adults,(Ford et al., 2023) which the authors postulate may be due in part to selection bias. In hospitalized older adults, lower baseline functional status increased the odds of post-discharge functional limitations (Izaguirre et al., 2023) and functional limitations were associated with lower health-related quality of life.(Shanbehzadeh et al., 2023) Female sex appears to increase risk. Most observational studies' samples are approximately 60-70% female, and female sex has been identified as both an independent risk factor(Jacobs et al., 2023) and interacting with age to increase risk.(Vasilevskaya et al., 2023) Black and Hispanic respondents have been shown to have higher burdens of SARS-CoV-2 infection and illness severity,(Mackey et al., 2021) long COVID symptoms and conditions,(Jacobs et al., 2023; Khullar et al., 2023) and lower access to health services post-hospitalization.(Cañas et al., 2024) This reiterates the need for higher inclusion of people of color in COVID-19 clinical research overall.(Gilmore-Bykovskyi et al., 2021) The evidence suggests that these demographics all may moderate long COVID risk, thus we have included them in our model.

Aim 2 Detailed iterative model fitting

Initial full model

The general approach was to fit a complex model and test reductions systematically. The first model fitted age with 5-knot restricted (natural) cubic splines to allow for non-linear effects, and a less-flexible fit for pre-infection symptom totals due to the small range of values in this variable (0-23). Interaction terms were included for group (case vs. control) with variables we found were related to development of long COVID symptoms in a previous analysis. These were: number of pre-infection incidences of long COVID symptoms/conditions, and age (also fitted with a 5-knot spline function, as above). An interaction term was also included for group with race as a potential modifier of group membership, based on the above literature review's findings of increased prevalence and risk for long COVID among some racial groups.

Starting model:

```
initial_full <- orm(postcovid_functional_score ~
  group +
  variant +
  rcs(age, 5)+
  sex_at_birth +
  race +
  ethnicity +
```

```

Highest_grade_completed +
pre_functional_performance_level +
pre_covid_eval_cpt +
pre_infection_sx_total +
  group:pre_infection_sx_total +
  group:racs(age,5) +
  group:race,
data = temp2, y=TRUE, x=TRUE, family=probit)

```

S.D.3. Structured model tests of complexity

The initial (full) model was then against models with reduced or increased spline knots and linear fits for age and pre-infection symptom incidences. The Bayesian Information Criterion (BIC) was chosen as the estimator of error, computed consistently following the convention “starting model – revised model” with the effective sample size given by:

$$N - 1/N^2 * (n1^3 + n2^3 + n3^3... nk^3)$$

With n ~ number of people in each category of the Y outcome variable functional impairment score. For this sample, this is

$$83786 - 1/83786^2 * (75823^3 + 4767^3 + 2707^3 + 307^3 + 145^3 + 32^3 + 5^3) = 21,672$$

Continuous variable spline reductions:

Model	R2	LR X2	df	p	Δ BIC	Decision
Initial full	0.218					
Age knot changes and linearity						
Age 4 knots	0.218				14.7537	Superior to starting model
Age 6 knots	0.218				-15.0069	Inferior to starting model. There is sufficient evidence that age has a non-linear relationship to functional impairment scores, and that a 4-knot spline function is the optimal fit for these data. Reduce the number of age spine knots to 4.
Age linear	0.217	43.1439	6.0	1.092396e-07	16.7588	There is very strong evidence that age has a linear relationship with decreasing functional status. The reduction in R2 value is relatively small. Compare 4-knot model with linear model for age.
Age 4 knots - Age linear		37.930	4.0	1.158426e-07	2.0051	There is strong evidence that the linear fit for age is better than the 4-knot fit for age. Retain a linear fit for age.
Total number of symptoms: splines versus linearity (starting model)						
Sx 3 knots	0.218	57.478	2	3.301803e-13	37.5105	Superior to initial model
Sx 4 knots	0.219	71.982	4	8.881784e-15	31.9836	Superior to initial model
Sx 5 knots	0.219	83.294	6	7.771561e-16	23.3878	Superior to initial model. There is very strong evidence that all spline fits for pre-

						infection symptoms are superior to the linear fit for symptoms. A 4-knot spline function shows the best balance between higher R2 and lower BIC. Retain 4 knot spline for pre-infection symptom total.
--	--	--	--	--	--	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Updated working model:

```
Initial_full3 <- orm(postcovid_functional_score ~
  group +
  variant +
  age+
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  pre_functional_performance_level +
  precovid_eval_cpt +
  rcs(pre_infection_sx_total,4) +
  group:rcs(pre_infection_sx_total,4) +
  group:age +
  group:race,
  data = temp2, y=TRUE, x=TRUE, family=probit)
```

Interaction terms vs. additive fits: Checking fit of interaction terms

Testing dropped interaction terms:

Model	R2	Δ BIC	Decision
Initial full, 4 knots for pre-infection sx, linear fit for age	0.219		
Removal of interaction terms singly			
A) No interactions	0.217	-26.3249	Inferior to reference model
B) Drop group:pre-infection sx	0.217	-41.3902	Inferior to reference model
C) Drop group:age	0.218	-17.8004	Inferior to reference model
D) Drop group:race	0.219	39.3950	Superior to reference model.
E) Keep group:sx only	0.218	21.0484	Superior to reference model
F) Keep group:age only	0.217	-2.0660	Inferior to reference model
G) Keep group:race only	0.217	-62.2329	Inferior to reference model. Compare the two superior models, D and E.
D - E		-18.3467	Retain model D, interaction terms for group:pre-infection symptoms and group:age. Remove interaction term for group:race.

Updated working model:

```

initial_full4 <- orm(postcovid_functional_score ~
  group +
  variant +
  age+
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  pre_functional_performance_level +
  precovid_eval_cpt +
  rcs(pre_infection_sx_total,4) +
  group:rcs(pre_infection_sx_total,4) +
  group:age,
  data = temp2, y=TRUE, x=TRUE, family=probit)

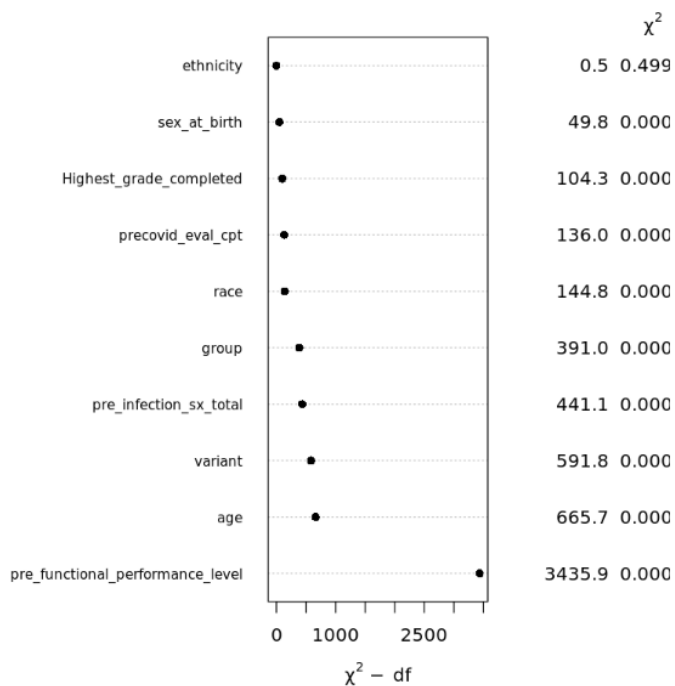
```

Test for main effects

ANOVA Ominbus test for main effects

	Chi squared	df	P
group (Factor+Higher Order Factors)	391.0134148	5	0.00000
All Interactions	103.1507891	4	0.00000
variant	591.843768	5	0.00000
age (Factor+Higher Order Factors)	665.7164734	2	0.00000
All Interactions	27.7132192	1	0.00000
sex_at_birth	49.7932121	1	0.00000
race	144.84467	4	0.00000
ethnicity	0.4560198	1	0.49949
Highest_grade_completed	104.2958233	4	0.00000
pre_functional_performance_level	3435.861828	2	0.00000
precovid_eval_cpt	135.9875407	4	0.00000
pre_infection_sx_total (Factor+Higher Order Factors)	441.0799817	6	0.00000
All Interactions	70.6259405	3	0.00000
Nonlinear (Factor+Higher Order Factors)	70.2685761	4	0.00000
group * pre_infection_sx_total (Factor+Higher Order Factors)	70.6259405	3	0.00000
Nonlinear	69.7063713	2	0.00000
Nonlinear Interaction : f(A,B) vs. AB	69.7063713	2	0.00000
group * age (Factor+Higher Order Factors)	27.7132192	1	0.00000
TOTAL NONLINEAR	70.2685761	4	0.00000
TOTAL INTERACTION	103.1507891	4	0.00000
TOTAL NONLINEAR + INTERACTION	104.4265401	6	0.00000
TOTAL	9217.414313	30	0.00000

Importance of single predictors in the full model



Caption: Computed by partial Wald X2 minus the predictor degrees of freedom Wald X2 values, including contributions from all higher-order effects.

Alternative Aim 2 models with main effects were then fitted for the five largest contributors from this omnibus test: Pre-infection functional performance level, age, variant at first infection, pre-infection symptom total, and group (case vs. control).

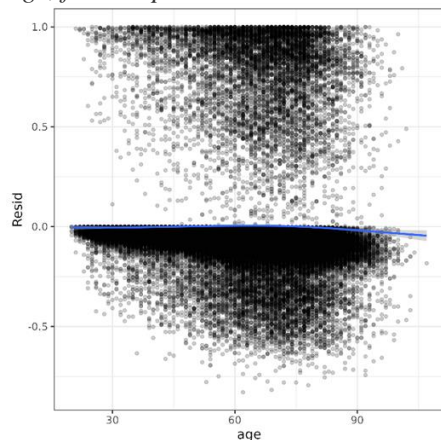
Model	R2	Δ BIC	Decision
Model D, 4 knots for pre-infection sx, linear fit for age	0.219		
Main effects models compared to working model			
ME disease, demographics, and pre-infection functioning	0.221	-320.7993	Inferior to prior model, too much noise.
Demographic main effects	0.219	-0.2589	Very slightly not as good
Disease and pre-infection sx main effects	0.221	-89.7853	Inferior to prior model

Pre-infection functional status	0.219	-64.1966	Inferior to prior model. As groups, demographic, disease/pre-infection symptom, and pre-infection functional status did not show main effects in these data. Retain the current model.
---------------------------------	-------	----------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

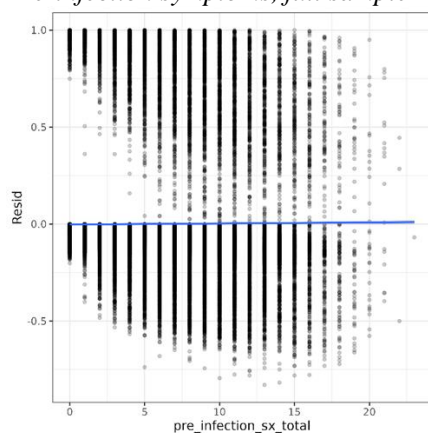
3. Check model assumptions

Residual plots vs. fitted values and individual predictors

Age, full sample



Pre-infection symptoms, full sample



Aim 2 Ordinal structure of the outcome “postcovid_functional_score”

The assumption of ordinality was compared for three different link functions: a proportional odds model (logit link function), probit ordinal model (probit link function) and a cumulative odds model (log-log link function) (Table S.D.3.a, Figure S.D.3.c. The logit structure exhibited non-parallelism with multiple crossing slopes. The probit model exhibited a parallel ordinal structure in the lower values discontinuously with the upper values, treating the middle value (4) as centroid. The clog-log linking function exhibited a parallel structure, but large distances between low levels and diminishing distances between higher levels.

Ordinal factor level slopes for logit, probit, and c-log-log link functions

Link function	Level of impairment	Slope
logit	2	-4.44

logit	3	-4.67
logit	4	-2.56
logit	5	-3.02
logit	6	-4.02
logit	7	-5.6
probit	2	-2.55
probit	3	-2.36
probit	4	-0.99
probit	5	-1.06
probit	6	-1.22
probit	7	-1.47
cloglog	2	-2.38
cloglog	3	-1.8
cloglog	4	-0.59
cloglog	5	-0.59
cloglog	6	-0.6
cloglog	7	-0.65

Proportional odds and parallelism assumptions

Y component correlations with different scores for Re-evaluation

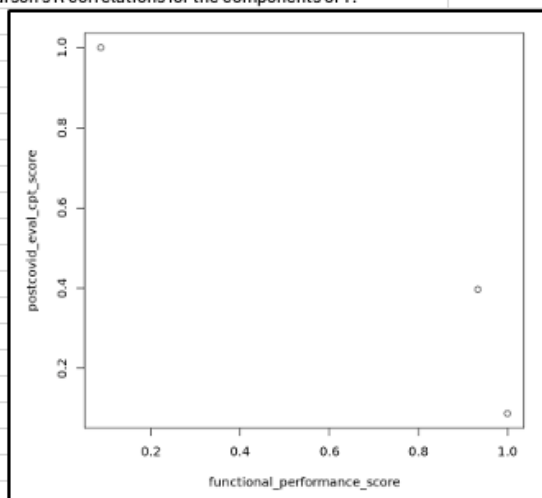
Approach 1: Re-eval as level 2 (between low and moderate complexity)

	function	eval cpt	Y(function + eval cpt)
functional_performance_score	1	0.06272065	0.8595293
postcovid_eval_cpt_score	0.06272065	1	0.5639905
postcovid_functional_score	0.85952926	0.5639905	1

Approach 2: Re-eval collapsed with moderate complexity eval

	function	eval cpt	Y(function + eval cpt)
functional_performance_score	1	0.08691601	0.9331793
postcovid_eval_cpt_score	0.08691601	1	0.3964496
postcovid_functional_score	0.93317932	0.39644956	1

Plot of Pearson's R correlations for the components of Y:



Aim 2 Corrections: Steps above were repeated with revised eval CPT scoring.

Revised continuous variable spline reductions:

Model	R2	LR X2	df	p	Δ BIC	Decision
Initial full	0.227					
Age knot changes and linearity						
Age 4 knots	0.227				14.630	Superior to starting model
Age 6 knots	0.227				-14.800	Inferior to starting model
Age linear	0.226	43.8	6.0	8.010116e-08	16.079	There is very strong evidence that age has a linear relationship with decreasing functional status. The reduction in R2 value is relatively small. Compare 4-knot model with linear model for age.
Age 4 knots - Age linear		38.49	4.0	8.891920e-08	1.448	There is strong evidence that the linear fit for age is slightly better than the 4-knot fit for age. Retain a linear fit for age.
Total number of symptoms: splines versus linearity (starting model), compared to linear fit for age.						
Sx 3 knots	0.277	60.65	2	6.750156e-14	40.685	Superior to initial model
Sx 4 knots	0.227	74.59	4	2.442491e-15	34.653	Superior to initial model
Sx 5 knots	0.227	85.61	6	2.220446e-16	25.709	Superior to initial model. There is very strong evidence that all spline fits for pre-infection symptoms are superior to the linear fit for symptoms. A 4-knot spline function shows the best balance between higher R2 and lower BIC. Retain 3 knot spline for pre-infection symptom total.

Updated working model:

```
aim2_sx3 <- orm(postcovid_functional_score ~
  group +
  variant +
  age+
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  pre_functional_performance_level +
  precovid_eval_cpt +
  rcs(pre_infection_sx_total,3) +
  group:rcs(pre_infection_sx_total,3) +
  group:age +
  group:race,
  data = temp2, y=TRUE, x=TRUE, family=probit)
```

Interaction terms vs. additive fits: Checking fit of interaction terms

Testing dropped interaction terms:

Model	R2	LR X2	df	p	Δ BIC	Decision
Working model: 3 knots for pre-infection sx, linear fit for age	0.227					
Removal of interaction terms singly						
A) No interactions	0.225	95.09	7	0.00000	-25.199	Inferior to reference model
B) Drop group:pre-infection sx	0.226	60.38	2	7.738254e-14	-40.413	Inferior to reference model
C) Drop group:age	0.226	27.28	1	1.757541e-07	-17.299	Inferior to reference model
D) Drop group:race	0.227	0.61	4	0.9621039	39.327	Superior to reference model.
E) Keep group:sx only	0.226	28.75	5	2.599843e-05	21.173	Superior to reference model
F) Keep group:age only	0.226	60.93	6	2.919043e-11	-1.023	Inferior to reference model
G) Keep group:race only	0.225	93.94	3	0.00000	-63.939	Inferior to reference model. Compare the two superior models, D and E.
D - E		28.14	1	1.129663e-07	-18.15	Retain model D, interaction terms for group:pre-infection symptoms and group:age. Remove interaction term for group:race.

Updated working model:

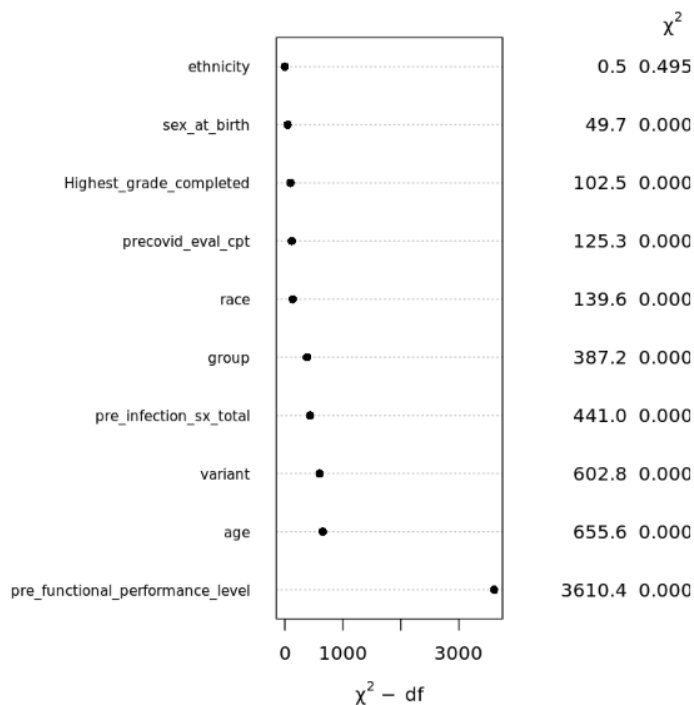
```
initial_full14 <- orm(postcovid_functional_score ~
  group +
  variant +
  age+
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  pre_functional_performance_level +
  precovid_eval_cpt +
  rcs(pre_infection_sx_total,3) +
  group:rcs(pre_infection_sx_total,3) +
  group:age,
  data = temp2, y=TRUE, x=TRUE, family=probit)
```

Tests for main effects

Table. ANOVA for omnibus test of main effects:

	Chi-Square	d.f.	P
group (Factor+Higher Order Factors)	387.1959022	4	0.00000
All Interactions	91.4111135	3	0.00000
variant	602.8423192	5	0.00000
age (Factor+Higher Order Factors)	655.5834171	2	0.00000
All Interactions	27.5188613	1	0.00000
sex_at_birth	49.7071047	1	0.00000
race	139.6198776	4	0.00000
ethnicity	0.4647575	1	0.49541
Highest_grade_completed	102.4576338	4	0.00000
pre_functional_performance_level	3610.444541	2	0.00000
precovid_eval_cpt	125.2557289	4	0.00000
pre_infection_sx_total (Factor+Higher Order Factors)	440.9543006	4	0.00000
All Interactions	59.1378487	2	0.00000
Nonlinear (Factor+Higher Order Factors)	58.6603361	2	0.00000
group * pre_infection_sx_total (Factor+Higher Order Factors)	59.1378487	2	0.00000
Nonlinear	58.0444781	1	0.00000
Nonlinear Interaction : f(A,B) vs. AB	58.0444781	1	0.00000
group * age (Factor+Higher Order Factors)	27.5188613	1	0.00000
TOTAL NONLINEAR	58.6603361	2	0.00000
TOTAL INTERACTION	91.4111135	3	0.00000
TOTAL NONLINEAR + INTERACTION	92.7698488	4	0.00000
TOTAL	9401.654956	28	0.00000

Figure. Importance of single predictors in the full model



Computed by partial Wald χ^2 minus the predictor degrees of freedom Wald χ^2 values, including contributions from all higher-order effects.

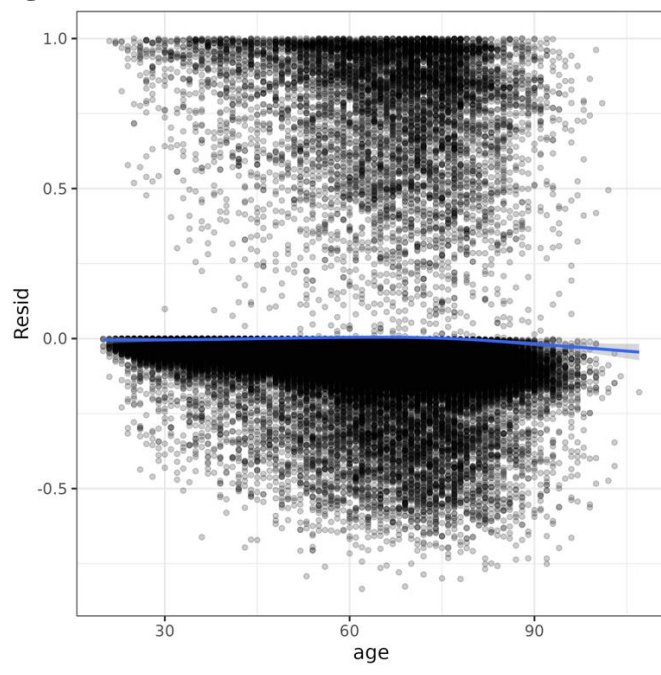
Alternative models with main effects were fitted for the five largest contributors from this omnibus test: Pre-infection functional performance level, age, variant at first infection, pre-infection symptom total, and group (case vs. control). We found no evidence for main effects for groupings of similar variables, so proceeded to model assumption tests with initial_full4 (model D).

Model	R ²	Δ BIC	Decision
Model D, 3 knots for pre-infection sx, linear fit for age	0.229		
Main effects models compared to working model			
Demographic main effects	0.227	-0.0599	Slightly inferior to reference model
Disease and pre-infection sx main effects	0.229	-46.546	Inferior to reference model
Pre-infection functional status	0.227	-64.979	Inferior to reference model. Test model assumptions on model D.

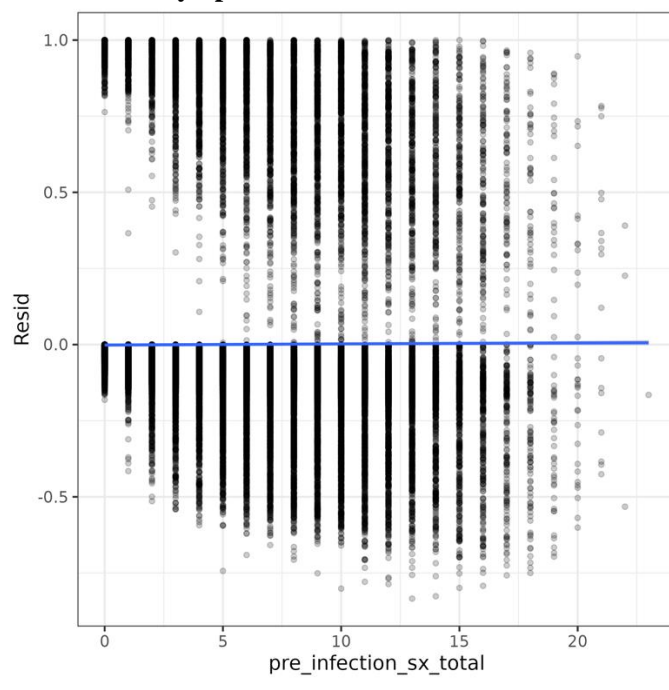
3. Check model assumptions

Residual plots vs. fitted values and individual predictors

Age:



Pre-infection symptoms:



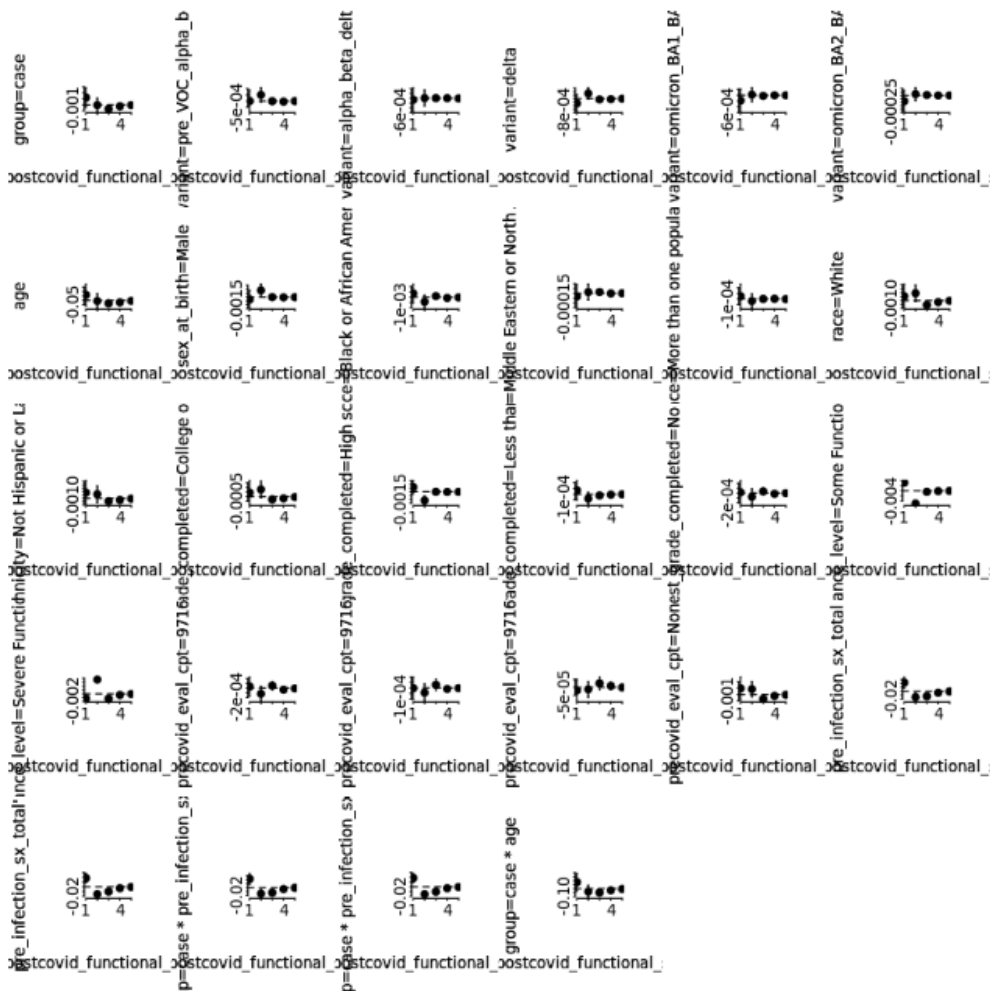
Ordinal structure of the outcome “postcovid_functional_score”

We explored the outcome variable fitted as a proportional odds model (logit link function), probit ordinal model (probit link function) and a cumulative odds model (log-log link function) by comparing the slope at each ordinal level (Table S.D.#, Figure S.D.#). The logit structure again exhibited non-parallelism. The probit model exhibited a parallel ordinal structure for all but the highest level of severity. The clog-log linking function exhibited a parallel structure, again with large distances between low levels, and diminishing distances plus some overlap between higher levels.

Ordinal factor level slopes for logit, probit, and c-log-log link functions

Link function	Level of impairment	Slope
logit	2	-4.48
logit	3	-4.72
logit	4	-3.27
logit	5	-3.85
logit	6	-5.68
probit	2	-2.57
probit	3	-2.39
probit	4	-1.19
probit	5	-1.17
probit	6	-1.49
cloglog	2	-2.42
cloglog	3	-1.82
cloglog	4	-0.68
cloglog	5	-0.58
cloglog	6	-0.66

Figure S.D.D. Proportional odds and parallelism assumptions



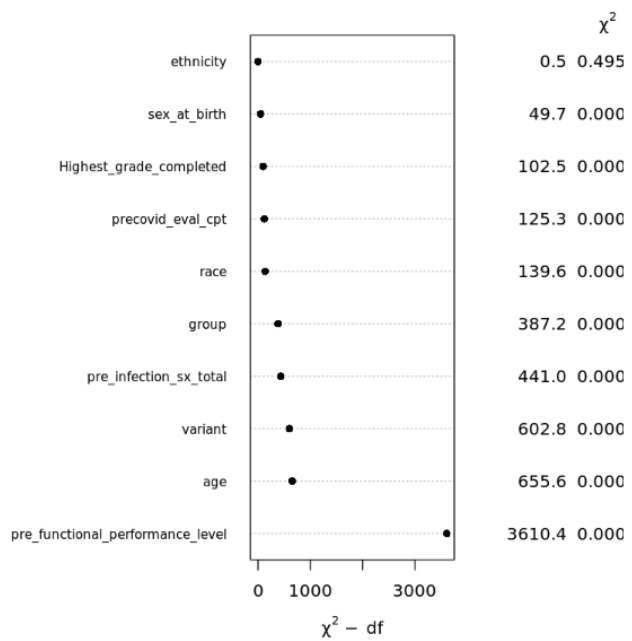
Compared to the previous model, this second Aim 2 model with recalculated outcome levels has a higher R2, improved metrics of parallelism, and a slightly higher omnibus X2 value for main effects. We note that parallelism continues to be elusive for some levels of the outcome. The trend in middle levels towards 0 may be an indicator of noise in the middle level of either contributing variable – the eval CPT with both moderate and re-evaluation complexity codes, and the functional status finding with a wide potential range of actual daily activity impairment which we cannot disambiguate from the available data. This is an important consideration in the use of EMR-based proxy indicators - it gets us in the neighborhood, but not to a precise address. Additional attempts to improve the model's fit to these data could include transformations of the outcome for constant variance, or fitting more specific models for non-constant variance. These were not attempted. This was adopted as the final model as the best-fitting attempt.

Aim 2 Final Model Fit Indices

Probit Ordinal Regression Model

```
orm(formula = postcovid_functional_score ~ group + variant +
  age + sex_at_birth + race + ethnicity + Highest_grade_completed +
  pre_functional_performance_level + precovid_eval_cpt + rcs(pre_infection_sx_total,
  3) + group:rcs(pre_infection_sx_total, 3) + group:age, data = temp2,
  x = TRUE, y = TRUE, family = probit)
```

Frequencies of Responses



Computed by partial Wald X2 minus the predictor degrees of freedom Wald X2 values, including contributions from all higher-order effects.

Appendix D. Model fitting notes (cont.)

Aim 3.

Summary of final model:

Probit Ordinal Regression Model

```
orm(formula = postcovid_functional_score ~ group + variant +
    age + sex_at_birth + race + ethnicity + Highest_grade_completed +
    pre_functional_performance_level + precovid_eval_cpt + pre_infection_sx_total +
    age:group + age:pre_infection_sx_total, data = temp2, x = TRUE,
    y = TRUE, family = probit)
```

Frequencies of Responses

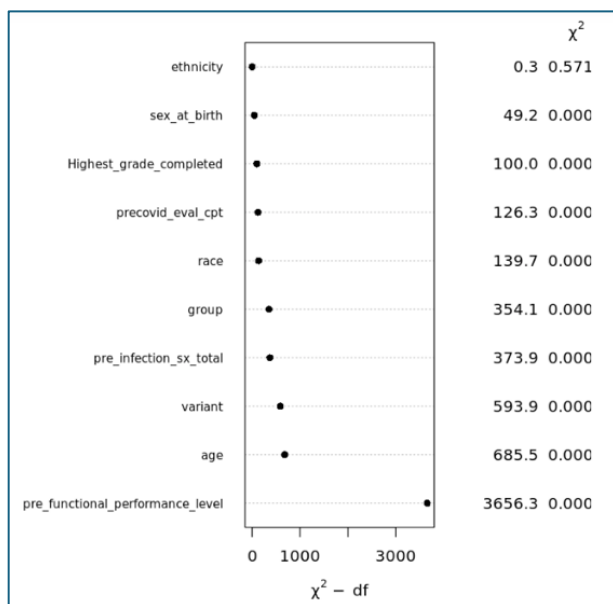
	0	1	2	3	4
	75823	4767	2952	204	40

	Model Likelihood	Discrimination	Rank Discrim.
	Ratio Test	Indexes	Indexes
Obs	83786	LR chi2	10936.75
Distinct Y	5	d.f.	26
Median Y	1	Pr(> chi2)	<0.0001
max deriv	0.01	Score chi2	10441.16
		R2	0.226
		R2(26,83786)	0.122
		R2(26,21671.4)	0.396
		Pr(Y>=median)-0.5	0.409
		rho	0.322

Table S.C.3. ANOVA Ominbus test for main effects

	Chi-Square	d.f.	P
group (Factor+Higher Order Factors)	353.3241362	2	0.00E+00
All Interactions	16.027218	1	6.24E-05
variant	596.6582331	5	0.00E+00
age (Factor+Higher Order Factors)	675.6251241	3	0.00E+00
All Interactions	50.3965182	2	1.14E-11
sex_at_birth	49.7459816	1	1.75E-12
race	140.8009372	4	0.00E+00
ethnicity	0.3484231	1	5.55E-01
Highest_grade_completed	101.5273826	4	0.00E+00
pre_functional_performance_level	3637.874228	2	0.00E+00
precovid_eval_cpt	126.337028	4	0.00E+00
pre_infection_sx_total (Factor+Higher Order Factors)	395.5065605	2	0.00E+00
All Interactions	17.317028	1	3.16E-05
group * age (Factor+Higher Order Factors)	16.027218	1	6.24E-05
age * pre_infection_sx_total (Factor+Higher Order Factors)	17.317028	1	3.16E-05
TOTAL INTERACTION	50.3965182	2	1.14E-11
TOTAL	9396.457913	26	0.00E+00

Figure S.C.1. Importance of single predictors in the full model



Computed by partial Wald X2 minus the predictor degrees of freedom Wald X2 values, including contributions from all higher-order effects.

S.C.1. Model fitting procedure

We followed model fitting processes recommended by Harrell (2001) for a main effects model using an ordinal probit regression for the odds of levels of post-infection functional status (OT evaluation CPT level + inferred level from EMR code “Finding of functional performance and activity”). We fitted two main effects models; one among the entire sample, and one among only cases that explored symptom clusters as a covariate). The first was fitted with natural (restricted) cubic spline functions for continuous variables, and interaction terms for age with long covid status, pre-infection functioning score, and pre-infection number of long COVID symptoms. Modelling and hypothesis testing was completed using the R package rms (Harrell, 2024). For use of the Bayesian Information Criterion in model fitting, the effective sample size given by:

$$N - 1/N^2 * (n_1^3 + n_2^3 + n_3^3 \dots n_k^3),$$

with $n \sim$ number of people in each category of the Y outcome variable functional impairment score. For this sample, this is

$$83786 - 1/83786^2 * (75823^3 + 4767^3 + 2952^3 + 204^3 + 40^3) = 21,671$$

1. Variables of interest

Aim 3 Variables for model 1: Full sample post-infection functional status

Type	Covariate	Sources	Modifier, mediator, or confounder?
Demographics	Age Sex at birth Race Ethnicity	Self-reported “Basics” survey responses at enrollment EMR	

Acquired demographics/SDH	Education (highest level completed)	Self-reported “Basics” survey responses	
SARS-CoV-2 Variant	The calendar period between the starts of major variants of concern in which the first infection occurred.	Self-report of symptoms on the COPE surveys EMR condition and measurement codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Pre-infection indicators of daily functioning	Occupational therapy evaluation code, level of complexity (0 = no evaluation, 4 = high complexity). Incidences of at least one pre-infection functional performance finding diagnostic codes*, collapsed into three levels (0 = No difficulty, 1 = Some difficulty, 2 = Severe difficulty). Pre-COVID functional performance score (sum of above two variables, analogous score to the outcome variable)	EMR condition and procedure codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Note. * = Entered in EMR between January 1, 2020 and four weeks before first infection date.			

Covariate variables for model 2: Cases’ post-infection functional status

Type	Covariate	Sources	Confounder, mediator, or moderator?
Demographics	Age Sex at birth Race Ethnicity	Self-reported “Basics” survey responses at enrollment EMR	
Acquired demographics/SDH	Education (highest level completed)	Self-reported “Basics” survey responses	

SARS-CoV-2 Variant	The calendar period between the starts of major variants of concern in which the first infection occurred.	Self-report of symptoms on the COPE surveys EMR condition and measurement codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Pre-infection indicators of daily functioning	Occupational therapy evaluation code, level of complexity (0 = no evaluation, 4 = high complexity). Incidences of at least one pre-infection functional performance finding diagnostic codes*, collapsed into three levels (0 = No difficulty, 1 = Some difficulty, 2 = Severe difficulty). Pre-COVID functional performance score (sum of above two variables, analogous score to the outcome variable)	EMR condition and procedure codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Symptoms	Pre-infection number of long COVID symptoms Post-infection number of long COVID symptoms Hierarchical cluster of symptoms	EMR condition and measurement codes (SNOMED, OMOP, and ICD-10 vocabularies).	
Note. * = Entered in EMR between January 1, 2020 and four weeks before first infection date.			

Primary demographics

Included were age, sex assigned at birth, race, and ethnicity. Older age is an independent risk factor for SARS-CoV-2 infection, as well as severe illness which confers additional risk for long COVID (Tana et al., 2023). However, the evidence concerning functional status is relatively mixed for this age group. Studies on long COVID's effect on functioning in middle-aged adults is plentiful, but many use assessment of employment status (Jaywant et al., 2024), absenteeism, or sick leave (Nielsen et al., 2022), precluding inclusion of older adults. An analysis of the Household Pulse survey data counterintuitively found that prevalence of self-reported significant activity limitations was lower in older compared to middle-aged adults (Ford et al., 2023), which the authors postulate may be due in part to selection bias. In hospitalized older adults, lower baseline functional status increased the odds of post-discharge functional limitations (Izaguirre et al., 2023) and functional limitations were associated with lower health-related quality of life (Shanbehzadeh et al., 2023). Female sex appears to increase risk. Most observational studies' samples are approximately 60-70%

female, and female sex has been identified as both an independent risk factor (Jacobs et al., 2023) and interacting with age to increase risk (Vasilevskaya et al., 2023). Black and Hispanic respondents have been shown to have higher burdens of SARS-CoV-2 infection and illness severity (Mackey et al., 2021), long COVID symptoms and conditions (Jacobs et al., 2023; Khullar et al., 2023), and lower access to health services post-hospitalization (Cañas et al., 2024). This reiterates the need for higher inclusion of people of color in COVID-19 clinical research overall (Gilmore-Bykovskyi et al., 2021). The evidence suggests that these demographics all may moderate long COVID risk, thus we have included them in our model.

Upon running X2 analyses on all variables in the model, correlation matrices on the functional variables, and the initial full model on all variables, there were nine warnings for sparse diagonal matrices. By process of single-variable elimination, the pre-covid functional performance score was accountable for these errors. This summed score was removed but its component variables were retained (OT evaluation CPT codes and approximate functional level). Finally the highest levels of impairment in the outcome variable were collapsed into one due to the highest level of impairment having only 5 individuals.

Aim 3 Model fitting process

Initial full model

We began with a model fitting age with 5-knot restricted (natural) cubic splines to allow for non-linear effects, and a less-flexible fit for pre-infection symptom totals due to the small range of values in this variable (0-23). We included interaction terms for age with variables we found were related to development of long COVID symptoms in a previous analysis. These were: long COVID status, pre-infection functional performance level (computed as the outcome but prior to infection) and the number of pre-infection incidences of long COVID symptoms/conditions. We also included an interaction term for group with race as a potential modifier of group membership per prior literature findings of increased prevalence and risk for long COVID among some racial groups.

Starting model:

```
initial_full <- orm(postcovid_functional_score ~
  group +
  variant +
  rcs(age, 6)+
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  precovid_functional_score +
  pre_infection_sx_total +
  rcs(age, 6):group +
  rcs(age, 6):precovid_functional_score +
  rcs(age, 6):pre_infection_sx_total,
  data = temp2, y=TRUE, x=TRUE, family=probit)
```

Structured model tests of complexity

We tested the initial full model against models with reduced or increased spline knots and linear fits for age and pre-infection symptom incidences. Because we had a lower number of covariates and larger sample size for this analysis, we computed both Akaike and Bayesian Information Criteria (AIC and BIC, resp) as estimators of error, prioritizing the BIC for decisions at the above-computed effective sample size of 21,671. All deltas were computed following the convention “starting model fit – revised model fit”; negative delta values indicated that the starting fit was favorable, and positive values that the revised fit was favorable.

Continuous variable spline reductions:

Model	R2	LR X2	df	p	Δ BIC	Δ AIC	Decision (per BIC)
Initial_full Age 6 knots	0.227				0	0	Working model
Age knot reductions and linearity							
Age 5 knots	0.227	5.36	5	0.3728922	44.553	4.635	Superior to BIC to 6-knot fit, non-significant
Age 4 knots	0.227	20.57	10	0.02431437	79.269	-0.568	Superior BIC to 6-knot fit, non-significant
Age linear	0.226	57.05	20	2.018505e-05	142.627	-17.048	Superior BIC to 6-knot fit, reduced R2 by 0.001. Because age is an important variable in the present analysis, I will absorb the loss of R2 predictive value to give it more flexibility. Retain a linear fit for age.
Total number of symptoms: splines versus linearity (starting model)							
Sx 3 knots	0.228	4.50	6	0.6087582	-55.40	-7.50	Inferior to linear fit
Sx 4 knots	0.228	10.84	12	0.5429363	-108.97	-13.16	Inferior to linear fit
Sx 5 knots	0.228	22.69	18	0.2027991	-157.02	-13.31	Inferior to linear fit. Retain linear fit for pre-infection symptoms.

Updated working model:

```
Initial_full12 <- orm(postcovid_functional_score ~
  group +
  variant +
  age+
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  pre_functional_performance_level +
  precovid_eval_cpt +
  pre_infection_sx_total +
  age:group +
  age:pre_functional_performance_level +
  age:pre_infection_sx_total,
  data = temp2, y=TRUE, x=TRUE, family=probit)
```

Interaction terms vs. additive fits: Checking fit of interaction terms

Table S.C.5. Testing dropped interaction terms:

Model	R2				Δ BIC	Δ AIC	Decision
Initial full2	0.226				0	0	Working model
Removal or inclusion of interaction terms singly							
A) No interactions	0.225	64.02	4.00	4.131140e-13	-24.09	-56.02	Inferior to working model
B) Drop age:group	0.226	1.81	10.00	2.082877e-05	-8.13	-16.11	Inferior to working model
C) Drop age:prior functioning	0.226	12.58	2.00	0.00185652	7.39	-8.59	Slightly better than working model
D) Drop age:prior symptoms	0.226	5.72	1.00	0.01678475	4.26	-3.72	Slightly better than working model, non-significant
E) Keep only age:group	0.223	181.14	4.00	0.0000	-141.21	-173.14	Inferior to working model
F) Keep only age:prior functioning	NA	NA	NA	NA	-180.34	-180.34	Inferior to working model
G) Keep only age:prior symptoms	NA	NA	NA	NA	-142.60	-174.54	Inferior to working model. There is strong evidence that interactions between age and group & prior symptoms are appropriate to include in this model. Remove age:prior functioning interaction.
Note: NA for non-nested models							

Updated working model:

```
Initial_full13 <- orm(postcovid_functional_score ~
  group +
  variant +
  age+
  sex_at_birth +
  race +
  ethnicity +
  Highest_grade_completed +
  pre_functional_performance_level +
  precovid_eval_cpt +
```

```

pre_infection_sx_total +
  age:group +
  age:pre_infection_sx_total,
data = temp2, y=TRUE, x=TRUE, family=probit)

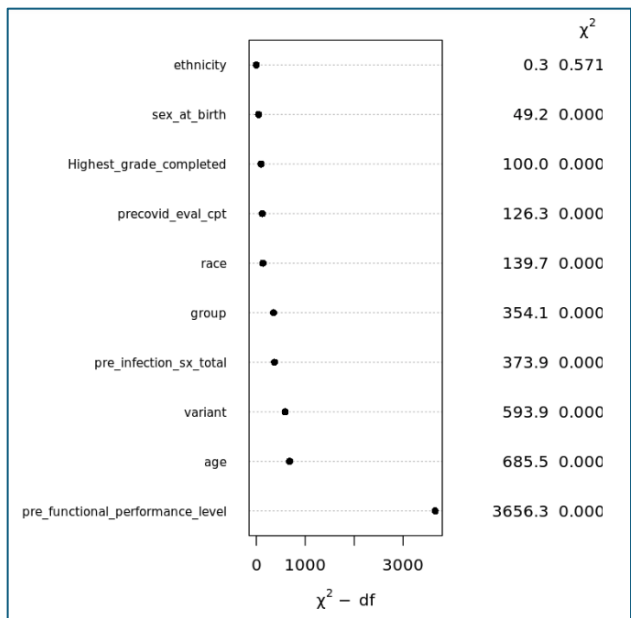
```

Test for main effects

ANOVA Ominbus test for main effects

	Chi-Square	d.f.	P
group (Factor+Higher Order Factors)	353.3241362	2	0.00E+00
All Interactions	16.027218	1	6.24E-05
variant	596.6582331	5	0.00E+00
age (Factor+Higher Order Factors)	675.6251241	3	0.00E+00
All Interactions	50.3965182	2	1.14E-11
sex_at_birth	49.7459816	1	1.75E-12
race	140.8009372	4	0.00E+00
ethnicity	0.3484231	1	5.55E-01
Highest_grade_completed	101.5273826	4	0.00E+00
pre_functional_performance_level	3637.874228	2	0.00E+00
precovid_eval_cpt	126.337028	4	0.00E+00
pre_infection_sx_total (Factor+Higher Order Factors)	395.5065605	2	0.00E+00
All Interactions	17.317028	1	3.16E-05
group * age (Factor+Higher Order Factors)	16.027218	1	6.24E-05
age * pre_infection_sx_total (Factor+Higher Order Factors)	17.317028	1	3.16E-05
TOTAL INTERACTION	50.3965182	2	1.14E-11
TOTAL	9396.457913	26	0.00E+00

Figure S.C.1. Importance of single predictors in the full model



Computed by partial Wald X2 minus the predictor degrees of freedom Wald X2 values, including contributions from all higher-order effects.

We fitted alternative models with main effects for the five largest contributors from this omnibus test: Pre-infection functional performance level, age, variant at first infection, pre-infection symptom total, and group (case vs. control).

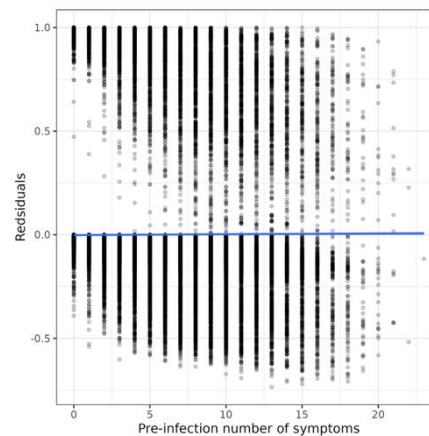
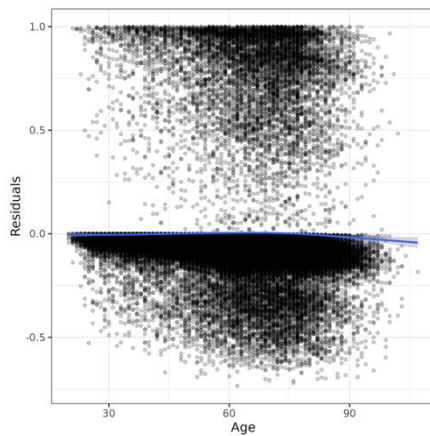
Model	R2	Δ BIC	Δ AIC	Decision
Working model	0.226	0		
Main effects models:				
For prior functioning	0.223	-144.07	-152.05	
For age	0.223	-144.07	-152.05	
For variant	0.226	0	0	
For prior symptoms	0.226	0	0	
For long COVID case/control	0.226	0	0	We did not find evidence of a main effect as a modeling parameter. Test model assumptions with current model.

Check model assumptions

Residual plots vs. fitted values and individual predictors

Figure S.C.2. Age

Figure S.C.3. Pre-infection symptoms



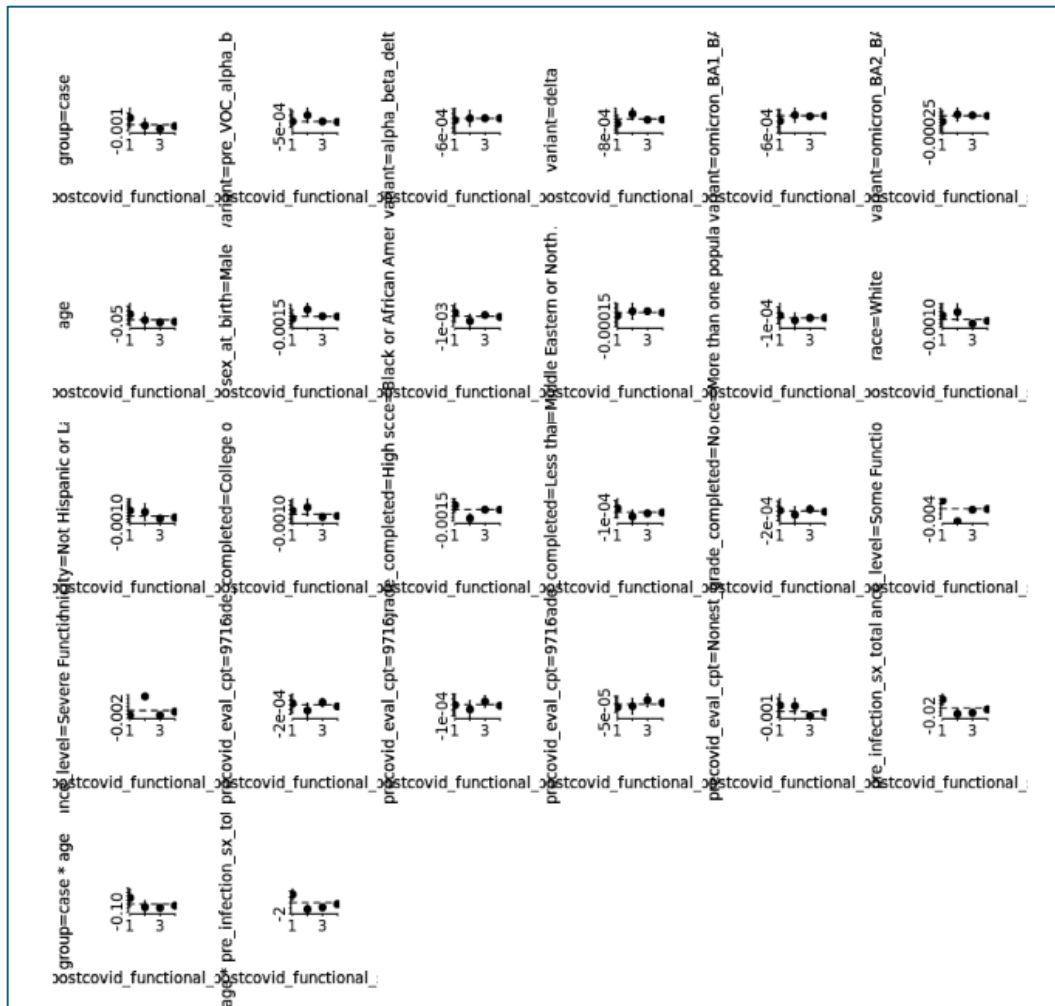
Ordinal structure of the outcome “`postcovid_functional_score`”

We explored the outcome variable fitted as a proportional odds model (logit link function), probit ordinal model (probit link function) and a cumulative odds model (log-log link function) by comparing the slope at each ordinal level using `rms:poma` (Table S.C.#, Figure S.C.F). The logit structure exhibited non-parallelism with multiple crossing slopes. The probit model exhibited a grossly parallel relationship between levels of the outcome. The clog-log linking function also exhibited a parallel structure, with large distances between low levels and diminishing distances between higher levels. All link functions resulted in slightly lower slopes at the highest level than the second-highest level, which may have been due to low counts in the highest level of severity. An alternative fitting approach may be to assess unequal variances and use weighted least squares if variances are not found to be independent and identically-distributed.

Ordinal factor level slopes for logit, probit, and c-log-log link functions

Link	Level of impairment	Slope (compared to 0=no impairment)
logit	1	-4.5
logit	2	-4.78
logit	3	-3.32
logit	4	-3.92
probit	1	-2.59
probit	2	-2.42
probit	3	-1.2
probit	4	-1.19
c log-log	1	-2.44
c log-log	2	-1.84
c log-log	3	-0.68
c log-log	5	-0.59

Proportional odds cut points of covariates at each level of outcome



Final model:

Probit Ordinal Regression Model

```
orm(formula = postcovid_functional_score ~ group + variant +
age + sex_at_birth + race + ethnicity + Highest_grade_completed +
pre_functional_performance_level + precovid_eval_cpt + pre_infection_sx_total +
age:group + age:pre_infection_sx_total, data = temp2, x = TRUE,
y = TRUE, family = probit)
```

Frequencies of Responses

	0	1	2	3	4
	75823	4767	2952	204	40

	Model Likelihood Ratio Test	Discrimination Indexes	Rank Discrim. Indexes
Obs	LR chi2 10936.75	R2 0.226	rho 0.322
Distinct Y	d.f. 26	R2(26,83786) 0.122	
Median Y	Pr(> chi2) <0.0001	R2(26,21671.4) 0.396	
max deriv	Score chi2 10441.16	Pr(Y>=median)-0.5 0.409	
	Pr(> chi2) <0.0001		

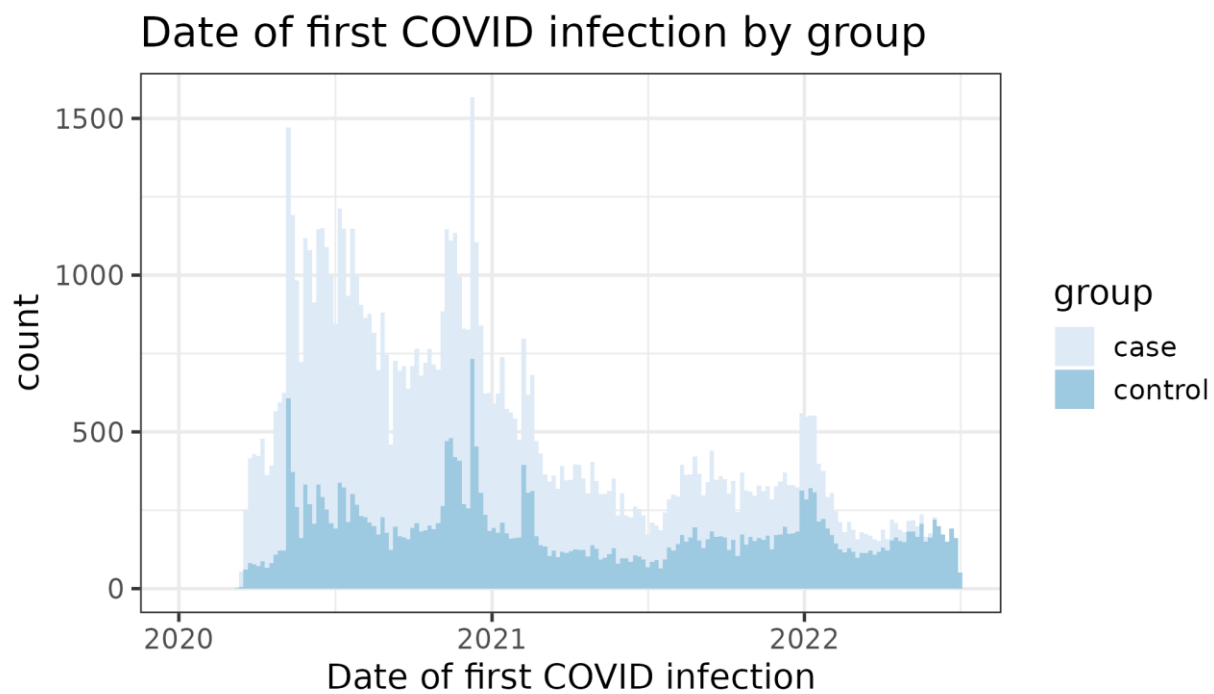
Appendix E. Expanded results.**Figure S.E.1.**
Infections over time, by long COVID group.

Table S.E.1.
Correlation matrix of pre-infection symptoms

	abdominal	anxiety	chestpain	cough	depressor	diarrhea	dizziness	dyspnea	fatigue	fever	headache	cognition	joint_pain	me_cfs	menstruat	muscle_pi	msk_chest	palpitation	paraesthe	sexual_fur	rash	sleep	tachycardia
abdominal	1.00	0.25	0.32	0.23	0.25	0.32	0.22	0.25	0.23	0.19	0.27	0.13	0.24	0.09	0.16	0.19	0.14	0.15	0.14	0.07	0.18	0.20	0.17
anxiety	0.25	1.00	0.24	0.18	0.53	0.20	0.19	0.19	0.22	0.12	0.24	0.22	0.21	0.09	0.13	0.16	0.12	0.14	0.12	0.07	0.17	0.29	0.16
chestpain	0.32	0.24	1.00	0.29	0.23	0.22	0.27	0.40	0.24	0.18	0.28	0.16	0.28	0.09	0.05	0.20	0.33	0.22	0.16	0.04	0.16	0.25	0.21
cough	0.23	0.18	0.29	1.00	0.19	0.20	0.20	0.33	0.22	0.24	0.22	0.12	0.26	0.08	0.04	0.17	0.11	0.13	0.12	0.03	0.18	0.21	0.16
depression	0.25	0.53	0.23	0.19	1.00	0.20	0.19	0.20	0.23	0.12	0.24	0.26	0.23	0.10	0.11	0.16	0.11	0.10	0.12	0.06	0.16	0.31	0.15
diarrhea	0.32	0.20	0.22	0.20	0.20	1.00	0.20	0.21	0.21	0.20	0.21	0.12	0.18	0.08	0.06	0.15	0.11	0.11	0.11	0.04	0.16	0.18	0.17
dizziness	0.22	0.19	0.27	0.20	0.19	0.20	1.00	0.25	0.26	0.14	0.27	0.15	0.21	0.10	0.04	0.16	0.10	0.21	0.15	0.04	0.14	0.20	0.16
dyspnea	0.25	0.19	0.40	0.33	0.20	0.21	0.25	1.00	0.26	0.20	0.23	0.14	0.22	0.09	0.00	0.17	0.12	0.21	0.13	0.01	0.14	0.27	0.24
fatigue	0.23	0.22	0.24	0.22	0.23	0.21	0.26	0.26	1.00	0.17	0.22	0.16	0.24	0.34	0.07	0.21	0.12	0.17	0.17	0.05	0.18	0.26	0.14
fever	0.19	0.12	0.18	0.24	0.12	0.20	0.14	0.20	0.17	1.00	0.17	0.09	0.12	0.05	0.04	0.12	0.08	0.09	0.07	0.02	0.12	0.12	0.20
headache	0.27	0.24	0.28	0.22	0.24	0.21	0.27	0.23	0.22	0.17	1.00	0.17	0.21	0.08	0.12	0.21	0.13	0.15	0.16	0.06	0.16	0.20	0.17
cognition	0.13	0.22	0.16	0.12	0.26	0.12	0.15	0.14	0.16	0.09	0.17	1.00	0.13	0.07	0.01	0.10	0.06	0.06	0.09	0.02	0.09	0.17	0.11
joint_pain	0.24	0.21	0.28	0.26	0.23	0.18	0.21	0.22	0.24	0.12	0.21	0.13	1.00	0.10	0.04	0.23	0.15	0.14	0.17	0.05	0.19	0.28	0.11
me_cfs	0.09	0.09	0.09	0.08	0.10	0.08	0.10	0.09	0.34	0.05	0.08	0.07	0.10	1.00	0.05	0.11	0.06	0.07	0.09	0.03	0.08	0.13	0.04
menstruation	0.16	0.13	0.05	0.04	0.11	0.06	0.04	0.00	0.07	0.04	0.12	0.01	0.04	0.05	1.00	0.05	0.04	0.05	0.05	0.10	0.11	0.02	0.06
muscle_pain	0.19	0.16	0.20	0.17	0.16	0.15	0.16	0.17	0.21	0.12	0.21	0.10	0.23	0.11	0.05	1.00	0.16	0.11	0.16	0.06	0.14	0.18	0.10
msk_chest_pain	0.14	0.12	0.33	0.11	0.11	0.11	0.10	0.12	0.12	0.08	0.13	0.06	0.15	0.06	0.04	0.16	1.00	0.08	0.10	0.03	0.10	0.12	0.08
palpitations	0.15	0.14	0.22	0.13	0.10	0.11	0.21	0.21	0.17	0.09	0.15	0.06	0.14	0.07	0.05	0.11	0.08	1.00	0.10	0.03	0.10	0.13	0.18
paraesthesia	0.14	0.12	0.16	0.12	0.12	0.11	0.15	0.13	0.17	0.07	0.16	0.09	0.17	0.09	0.05	0.16	0.10	0.10	1.00	0.03	0.11	0.14	0.07
sexual_function	0.07	0.07	0.04	0.03	0.06	0.04	0.04	0.01	0.05	0.02	0.06	0.02	0.05	0.03	0.10	0.06	0.03	0.03	0.03	1.00	0.05	0.04	0.02
rash	0.18	0.17	0.16	0.18	0.16	0.16	0.14	0.14	0.18	0.12	0.16	0.09	0.19	0.08	0.11	0.14	0.10	0.10	0.11	0.05	1.00	0.15	0.10
sleep	0.20	0.29	0.25	0.21	0.31	0.18	0.20	0.27	0.26	0.12	0.20	0.17	0.28	0.13	0.02	0.18	0.12	0.13	0.14	0.04	0.15	1.00	0.12
tachycardia	0.17	0.16	0.21	0.16	0.15	0.17	0.16	0.24	0.14	0.20	0.17	0.11	0.11	0.04	0.06	0.10	0.08	0.18	0.07	0.02	0.10	0.12	1.00

Table S.E.2.
Aim 1 Full adjusted odds

	Contrast	Lower	Upper	Z	Pr(> z)	yhat	lower	upper
Age								
25	0.72	0.67	0.77	-13.49	<0.000	0.79	0.77	0.81
35	0.79	0.75	0.82	-13.49	<0.000	0.80	0.79	0.82
45	0.86	0.83	0.88	-13.49	<0.000	0.82	0.80	0.83
55	0.94	0.93	0.95	-13.49	<0.000	0.83	0.82	0.84
62	1.00	1.00	1.00			0.84	0.83	0.85
75	1.12	1.10	1.15	13.49	<0.000	0.85	0.84	0.86
85	1.23	1.18	1.28	13.49	<0.000	0.86	0.85	0.88
Race								
White	1.00	1.00	1.00			0.84	0.83	0.85
Black of african American	1.06	0.99	1.14	2.25	0.02	0.85	0.83	0.86
Asian	0.90	0.78	1.04	-1.85	0.06	0.82	0.80	0.85
Middle Eastern or North African	1.00	0.74	1.36	0.01	0.99	0.84	0.79	0.88
More than one population	0.98	0.81	1.18	-0.27	0.79	0.84	0.81	0.86
Sex assigned at birth								
Female or Intersex	1.00	1.00	1.00			0.84	0.83	0.85

Male	0.95	0.89	1.00	-2.65	0.01	0.83	0.82	0.84
Ethnicity								
Not Hispanic or Latino	1.00	1.00	1.00			0.84	0.83	0.85
Hispanic or Latino	0.85	0.72	1.00	-2.65	0.01	0.81	0.79	0.84
Variant								
pre_VOC	1.00	1.00	1.00			0.84	0.83	0.85
pre_VOC_alpha_beta	0.61	0.57	0.65	-19.54	<0.000	0.76	0.74	0.78
alpha_beta_delta	0.48	0.44	0.53	-19.32	<0.000	0.72	0.69	0.74
delta	0.33	0.30	0.36	-32.74	<0.000	0.63	0.61	0.66
omicron_BA1_BA2	0.17	0.16	0.19	-50.91	<0.000	0.47	0.45	0.50
omicron_BA2_BA5	0.02	0.02	0.03	-61.11	<0.000	0.10	0.09	0.12
Approximate functional level based on "Finding of Functional Performance or Activity" code								
No Functional Performance Difficulty	1.00	1.00	1.00			0.84	0.83	0.85
Some Functional Performance Difficulty	0.93	0.82	1.04	-1.66	0.10	0.83	0.81	0.85
Dependent on Others for Care	1.51	1.28	1.79	6.42	0.00	0.89	0.87	0.90
Number of long COVID symptoms/conditions present prior to infection (Quartiles)								
0	0.08	0.07	0.08	-82.83	<0.000	0.29	0.27	0.31
1	0.19	0.18	0.20	-91.66	<0.000	0.50	0.48	0.52
4	1.00	1.00	1.00			0.84	0.83	0.85
7	1.73	1.65	1.80	24.80	<0.000	0.90	0.89	0.91
23	34.62	24.93	48.09	21.14	<0.000	0.99	0.99	1.00

Self-rated ability to complete physical daily activities								
Completely	1.00	1.00	1.00			0.84	0.83	0.85
Mostly	1.04	0.97	1.12	1.51	0.13	0.84	0.83	0.86
Moderately	1.03	0.94	1.13	0.87	0.39	0.84	0.83	0.86
A little	0.95	0.84	1.06	-1.23	0.22	0.83	0.81	0.85
Not at all	0.81	0.63	1.04	-2.21	0.03	0.81	0.77	0.85
No Answer	1.02	0.73	1.44	0.17	0.86	0.84	0.79	0.88
Self-rated social role performance and satisfaction (composite)								
2	1.04	0.95	1.15	1.15	0.25	0.84	0.83	0.86
3	1.03	0.94	1.12	0.77	0.44	0.84	0.83	0.85
4	1.00	1.00	1.00			0.84	0.83	0.85
5	1.06	0.97	1.15	1.68	0.09	0.85	0.83	0.86
6	1.00	0.91	1.10	0.11	0.91	0.84	0.82	0.85
7	0.96	0.85	1.08	-0.88	0.38	0.83	0.81	0.85
8	1.03	0.90	1.19	0.58	0.56	0.84	0.82	0.86
9	0.95	0.77	1.16	-0.70	0.49	0.83	0.80	0.86
10	0.81	0.62	1.06	-1.98	0.05	0.81	0.76	0.85
Self-rated mental health (mood and cognitive function)								
Excellent	1.00	1.00	1.00			0.83	0.82	0.84
Very Good	1.06	0.98	1.15	2.04	0.04	0.84	0.83	0.85
Good	1.19	1.09	1.31	4.98	<0.000	0.85	0.84	0.87
Fair	1.11	0.99	1.25	2.29	0.02	0.84	0.83	0.86
Poor	1.23	1.00	1.50	2.62	0.01	0.86	0.83	0.88
Pre-infection total CPU's billed								
0	1.00	1.00	1.00			0.84	0.83	0.85
5	1.00	0.99	1.01	0.76	0.45	0.84	0.83	0.85
20	1.01	0.97	1.05	0.76	0.45	0.84	0.83	0.85

80	1.05	0.89	1.24	0.76	0.45	0.85	0.82	0.87
700	1.53	0.36	6.39	0.76	0.45	0.89	0.66	0.97

S.E.3. Unadjusted odds of developing long COVID given self-rated functional performance

Table S.B.3 shows pre-COVID self-reported functional and health status of the two groups, and the odds of developing at least one long COVID symptom after infection. There were significant differences between groups in all questions, with participants' odds of developing PASC symptoms generally increasing as their ratings of overall health and daily functioning decreased. The largest difference was in those who selected lower ratings of their ability to perform their social roles (twice as likely, $X^2=632.5$, $p < 0.001$). In carrying out daily physically demanding daily activities, compared to those who said they could "Completely" carry out these activities, participants who rated their pre-infection ability any less than "Completely" were about 2 times more likely to develop long COVID symptoms ($X^2=1383.1$, $p < 0.001$). Participants were more likely to develop post-acute conditions who selected lower rating of social role satisfaction (10-89% more likely, $X^2=418.5$, $p < 0.001$), and mental health, mood and cognition (13-100% more likely, $X^2=522.5$, $p < 0.001$).

Table S.E.3. Pre-infection self-rated health and daily functioning – Unadjusted odds

Question & response				OR			P-values		
In general, please rate how well you carry out your usual social roles*.									$X^2 = 632.5$
	control	case	Total	estimate	lower	upper	Mid point	Fisher MLE	Wald X2
Excellent	7735	10178	17913	1.00					
Very Well	9413	14267	23680	1.15	1.10	1.21	0.000	0.000	0.000
Well	5302	10611	15913	1.52	1.44	1.60	0.000	0.000	0.000
Fair	2054	4884	6938	1.81	1.68	1.94	0.000	0.000	0.000
Poorly	468	1088	1556	1.77	1.55	2.02	0.000	0.000	0.000
No Answer	360	611	971	1.29	1.10	1.51	0.000	0.000	0.000
In general, how would you rate your satisfaction with your social activities and relationships?									$X^2 = 418.5$
	control	case	Total	estimate	lower	upper	Mid point	Fisher MLE	Wald X2
Excellent	5402	7670	13072	1.00					
Very Well	9255	13362	22617	1.02	0.97	1.07	0.454	0.454	0.454
Well	6579	11710	18289	1.25	1.19	1.32	0.000	0.000	0.000
Fair	2925	6251	9176	1.51	1.41	1.61	0.000	0.000	0.000
Poorly	846	2048	2894	1.70	1.54	1.89	0.000	0.000	0.000
No Answer	325	598	923	1.30	1.10	1.53	0.000	0.000	0.000

To what extent are you able to carry out your everyday physical activities?									X2 = 1383.1
	control	case	Total	estimate	lower	upper	Mid point	Fisher MLE	Wald X2
Completely	16773	21740	38513	1.00					
Mostly	3902	7860	11762	1.55	1.48	1.64	0.000	0.000	0.000
Moderately	2594	6572	9166	1.95	1.84	2.07	0.000	0.000	0.000
A little	1488	4237	5725	2.20	2.04	2.37	0.000	0.000	0.000
Not at all	263	692	955	2.03	1.71	2.41	0.000	0.000	0.000
No Answer	312	538	850	1.33	1.13	1.57	0.000	0.000	0.000
In general, how would you rate your mental health, including your mood and your ability to think?									X2 = 522.5
	control	case	Total	estimate	lower	upper	Mid point	Fisher MLE	Wald X2
Excellent	16773	21740	38513	1.00					
Very Good	3902	7860	11762	1.11	1.05	1.16	0.000	0.000	0.000
Good	2594	6572	9166	1.43	1.35	1.51	0.000	0.000	0.000
Fair	1488	4237	5725	1.64	1.53	1.75	0.000	0.000	0.000
Poor	263	692	955	1.79	1.58	2.02	0.000	0.000	0.000
No Answer	312	538	850	1.33	1.13	1.57	0.000	0.000	0.000
Note. Odds ratios were computed with mid-point median-unbiased estimation (midpoint) and maximum likelihood estimation (Fisher MLE), and unconditional maximum likelihood estimation (Wald Chi-squared). Confidence intervals were calculated using exact methods for midpoint and Fisher estimates, and normal approximation for the Wald X2. For each baseline survey response level, the odds and OR's of later having ≥ 1 long COVID symptom/condition/squelum after COVID-19 infection. Reference levels are the group with the most participants unless otherwise noted. All computations were rounded to three digits.									

A sub-cohort of this study's sample enrolled in the study after questions were added to the survey regarding ability to perform complex daily routines (Table S.B.4). Among those who were administered this survey, the odds of developing post-acute symptoms increased for those with difficulty performing basic self care (OR 1.48-2.12, $X^2=288.2$, $p < 0.001$), doing errands in the community alone (OR 1.47-1.94, $X^2=311.6$, $p < 0.001$), and cognitive difficulty (OR 1.48-1.88, $X^2=332.5$, $p < 0.001$). The majority of non-respondents in these items represent participants who enrolled and took this survey prior to the addition of these questions. This timing reflects potential differences between these two groups, with eventual cases making up a higher proportion of the non-responders.

Table S.B.4. Pre-infection self-rated activities of daily living (when available) – Unadjusted odds.

Question & response			OR			P-values		
Because of a physical, mental, or emotional condition, do you have difficulty dressing or bathing?								
								X2 = 288.2

	control	case	Total	estimate	lower	upper	Mid point	Fisher MLE	Wald X2
No	7167	9406	16573	1.00					
Yes	252	587	839	1.77	1.48	2.12	0.000	0.000	0.000
Survey not administered	17913	31646	49559	1.35	1.29	1.40	0.000	0.000	0.000
Total	25332	41639	66971						
Because of a physical, mental, or emotional condition, do you have difficulty doing errands alone such as visiting doctor's office or shopping?									X2 = 311.6
	control	case	Total	estimate	lower	upper	Mid point	Fisher MLE	Wald X2
No Difficulty	6978	9034	16012	1.00					
Have Difficulty	430	939	1369	1.69	1.47	1.94	0.000	0.000	0.000
Survey not administered	17924	31666	49590	1.36	1.31	1.42	0.000	0.000	0.000
Because of a physical, mental, or emotional condition, do you have serious difficulty concentrating, remembering or making decisions?									X2 = 332.5
	control	case	Total	estimate	lower	upper	Mid point	Fisher MLE	Wald X2
No	6745	8598	15343	1.00					
Yes	612	1303	1915	1.67	1.48	1.88	0.000	0.000	0.000
Survey not administered	17975	31738	49713	1.39	1.33	1.45	0.000	0.000	0.000

S.E.4. Post-infection long COVID symptom groupings: Data reduction approaches

To explore symptom groupings in cases, several data reduction techniques were tested: exploratory factor analysis (EFA), first principle components analysis (PCA) and hierarchical cluster analysis (HCA). The symptoms/conditions with no observations were first removed: these were loss of smell, loss of taste, muscle fatigue, positional orthostatic tachycardia syndrome (POTS), and post-viral fatigue syndrome (PVFS). Then a correlation matrix was computed using Spearman's ρ . From this, EFA procedures were run for three, four, and five factor loadings, based on similar k symptom clusters found in prior literature. All models tested were found to have negative eigenvalues for multiple variables, suggesting that EFA was not suitable to these data. PCA was then computed on Pearson's R correlation coefficients using `stats::princomp` and plotted with `corrplot`. Figure S.A.1 exhibits the low to moderate range and relatively weak groupings of PCA correlations from this matrix. Finally, all symptom observations were converted to binary (1=any observation, 0=no observation) values, and ran a hierarchical cluster analysis on the squared correlations, using Spearman's ρ as the similarity measure (Figure S.A.2.). The resulting clusters were then grouped based first on their primary branching, then large clusters were split by similar Spearman's ρ values (Table S.A.2). The final clusters are

similar to clinical presentations known to the authors, and overlapped with previously found symptom groups using clustering methods. Based on this concurrence, this was the grouping used in subsequent modeling.

Figure S.E.2. Distribution of number of long COVID symptoms in the symptomatic group.

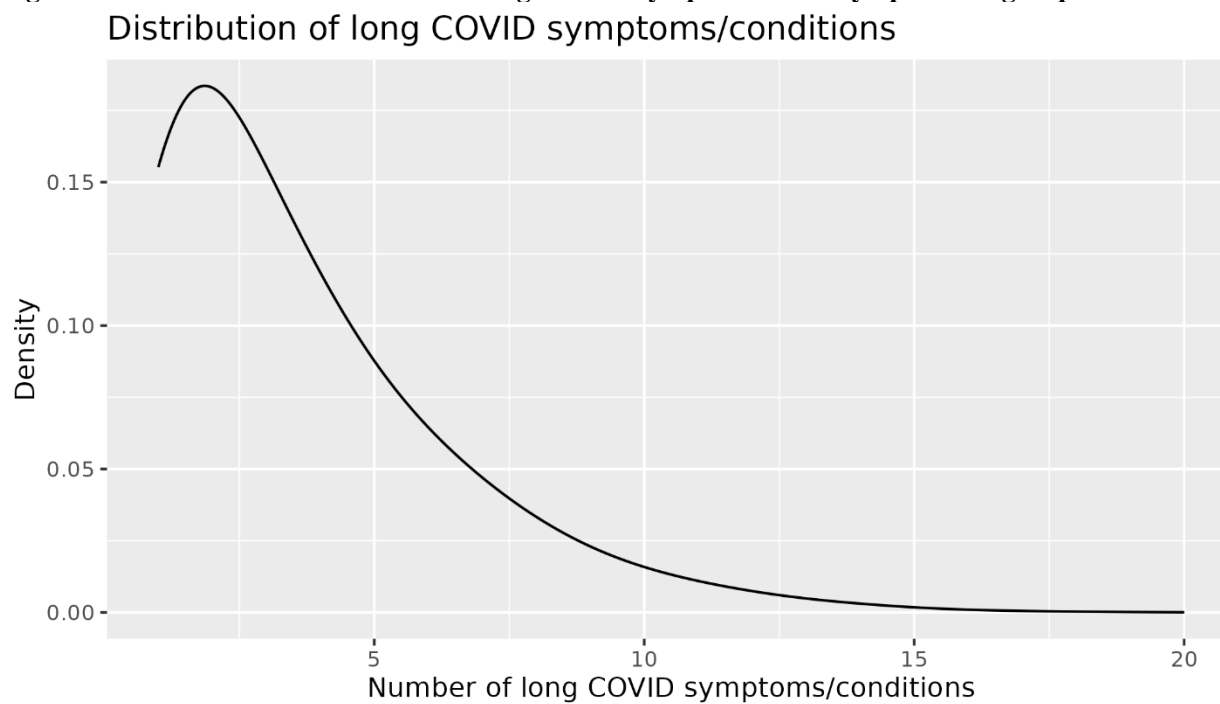


Figure S.E.3. Correlogram of first principal components analysis using Pearson's R correlation coefficient.

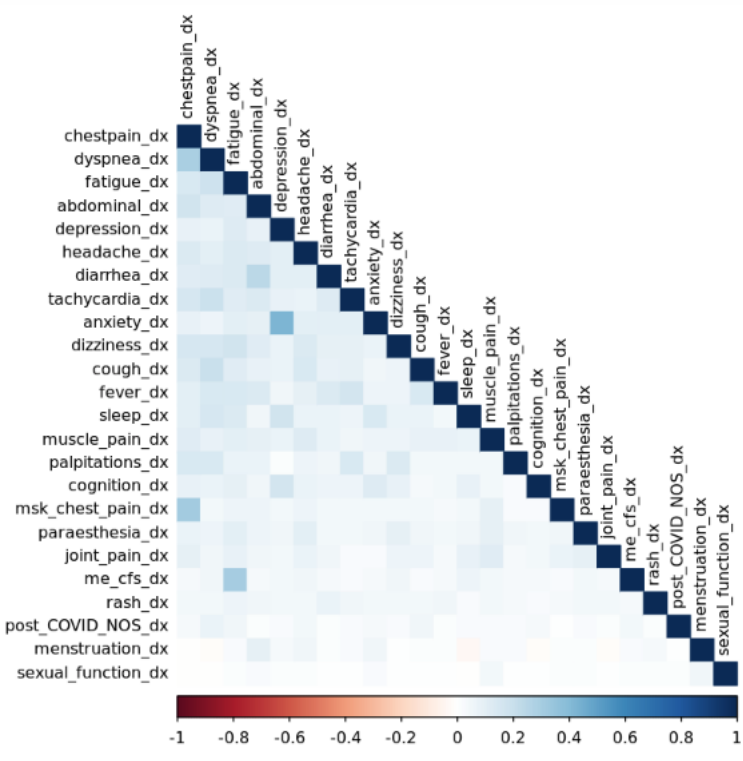


Figure S.E.4. Hierarchical clusters of post-infection symptoms

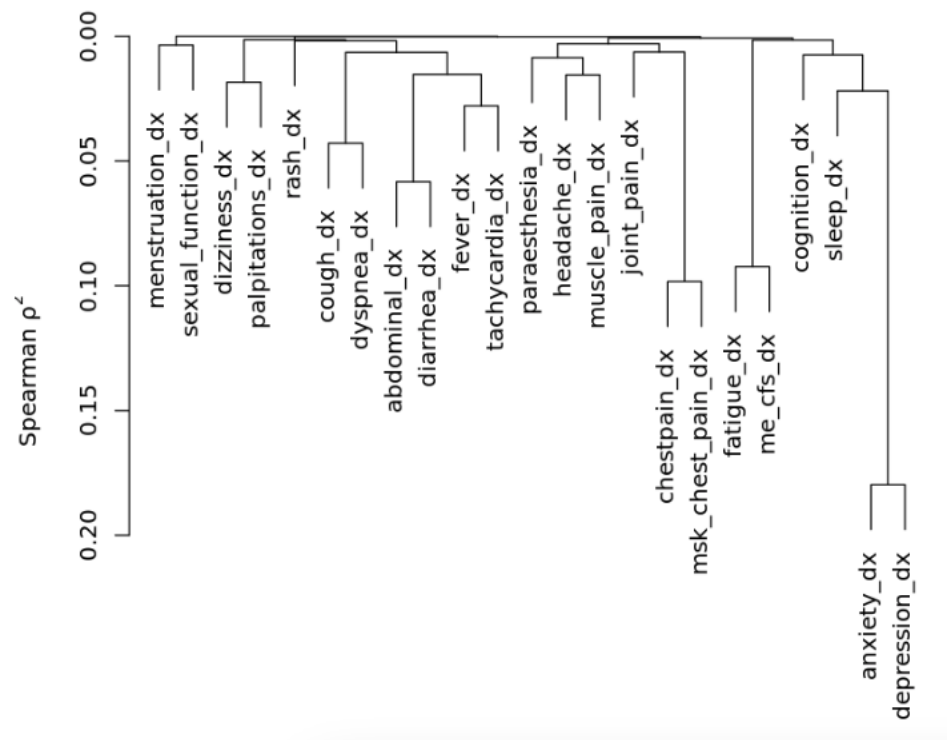


Table S.B.5. Selected clusters based on hierarchical cluster analysis dendrogram.

Cluster	Variables	Score (sum of observations within the cluster)
Reproductive	Sexual dysfunction + Menstrual dysfunction	0-2
Dizzy_palp_skin	Dizziness + Palpitations + Rash	0-3
Resp_abd_fever_tachy	Cough + Dyspnea + Abdominal pain + Diarrhea + Fever + tachycardia	0-6
paraesthesia_ha_pain_chest	Paraesthesias + Headache + Muscle pain + Joint pain + Chest pain + Musculoskeletal chest pain	0-6
fatigue_cog_sleep_mood	Fatigue + ME/CFS/Chronic fatigue syndrome + Cognitive dysfunction + Sleep dysfunction + Anxiety + Depression	0-6

References

- 29 USC Ch. 28: Family and Medical Leave Act, § §2612(a)(1)(D) (1993).
<https://uscode.house.gov/view.xhtml?path=/prelim@title29/chapter28&edition=prelim>
- Ahmed, M. U., Hanif, M., Ali, M. J., Haider, M. A., Kherani, D., Memon, G. M., Karim, A. H., & Sattar, A. (2020). Neurological Manifestations of COVID-19 (SARS-CoV-2): A Review. *Front Neurol*, *11*, 518. <https://doi.org/10.3389/fneur.2020.00518>
- Ajčević, M., Iskra, K., Furlanis, G., Michelutti, M., Miladinović, A., Buoite Stella, A., Ukmar, M., Cova, M. A., Accardo, A., & Manganotti, P. (2023). Cerebral hypoperfusion in post-COVID-19 cognitively impaired subjects revealed by arterial spin labeling MRI. *Sci Rep*, *13*(1), 5808. <https://doi.org/10.1038/s41598-023-32275-3>
- Akbarian, S., Beerli, M. S., & Haroutunian, V. (2013). Epigenetic determinants of healthy and diseased brain aging and cognition. *JAMA Neurol*, *70*(6), 711-718.
<https://doi.org/10.1001/jamaneurol.2013.1459>
- Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nat Med*, *30*(8), 2148-2164.
<https://doi.org/10.1038/s41591-024-03173-6>
- Al-Aly, Z., Xie, Y., & Bowe, B. (2021). High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*, *594*(7862), 259-264. <https://doi.org/10.1038/s41586-021-03553-9>
- Alim-Marvasti, A., Ciocca, M., Kuleindiren, N., Lin, A., Selim, H., & Mahmud, M. (2024). Subjective brain fog: a four-dimensional characterization in 25,796 participants. *Front Hum Neurosci*, *18*, 1409250. <https://doi.org/10.3389/fnhum.2024.1409250>
- Almeria, M., Cejudo, J. C., Sotoca, J., Deus, J., & Krupinski, J. (2020). Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. *Brain Behav Immun Health*, *9*, 100163.
<https://doi.org/10.1016/j.bbih.2020.100163>
- Alosco, M. L., Spitznagel, M. B., Cohen, R., Sweet, L. H., Colbert, L. H., Josephson, R., Waechter, D., Hughes, J., Rosneck, J., & Gunstad, J. (2012). Cognitive impairment is independently associated with reduced instrumental activities of daily living in persons with heart failure. *J Cardiovasc Nurs*, *27*(1), 44-50.
<https://doi.org/10.1097/JCN.0b013e318216a6cd>
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders : DSM-5*. American Psychiatric Association.
<https://search.library.wisc.edu/catalog/9910135447902121>
<https://id.loc.gov/authorities/names/n79049301.html>
- Andersen, P. K., & Skovgaard, L. T. (2010). *Regression with Linear Predictors*. Springer.
<https://doi.org/10.1007/978-1-4419-7170-8>
- AOTA. (2020). Occupational Therapy Practice Framework: Domain and Process-Fourth Edition. *Am J Occup Ther*, *74*(Supplement_2), 7412410010p7412410011-7412410010p7412410087. <https://doi.org/10.5014/ajot.2020.74S2001>
- Arevalo-Rodriguez, I., Smailagic, N., Roqué-Figuls, M., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., Pedraza, O. L., Bonfill Cosp, X., & Cullum, S. (2021). Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*, *7*(7), Cd010783.
<https://doi.org/10.1002/14651858.CD010783.pub3>

- Austin, P. C. (2011). An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research*, 46(3), 399-424, Article Pii 938470000. <https://doi.org/10.1080/00273171.2011.568786>
- Badinlou, F., Forsström, D., Jansson-Fröjmark, M., Abzhandadze, T., & Lundgren, T. (2023). Impairments following COVID-19 infection: manifestations and investigations of related factors. *Sci Rep*, 13(1), 6564. <https://doi.org/10.1038/s41598-023-33810-y>
- Baig, A. M. (2021). Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. *J Med Virol*, 93(5), 2555-2556. <https://doi.org/10.1002/jmv.26624>
- Baltes, P. B., & Smith, J. (2004). Lifespan psychology: From developmental contextualism to developmental biocultural co-constructivism. *Research in Human Development*, 1(3), 123-144. https://doi.org/10.1207/s15427617rhd0103_1
- Banic, M., Jankovic Makek, M., Samarzija, M., Mursic, D., Boras, Z., Trkes, V., Baricevic, D., Korsic, M., Basara, L., Jalusic Gluncic, T., & Vukic Dugac, A. (2022). Risk factors and severity of functional impairment in long COVID: a single-center experience in Croatia. *Croat Med J*, 63(1), 27-35. <https://doi.org/10.3325/cmj.2022.27>
- Baum, C. M., Connor, L. T., Morrison, T., Hahn, M., Dromerick, A. W., & Edwards, D. F. (2008). Reliability, validity, and clinical utility of the Executive Function Performance Test: a measure of executive function in a sample of people with stroke. *Am J Occup Ther*, 62(4), 446-455. <https://doi.org/10.5014/ajot.62.4.446>
- Bergamaschi, G., Barteselli, C., Calabretta, F., Lenti, V. M., Merli, S., Rossi, M. C., & Sabatino, D. A. (2024). Haematological sequelae in the post-acute phase of symptomatic SARS-CoV-2 infection. *Internal and Emergency Medicine*, 19(1), 125-133. <https://doi.org/10.1007/s11739-023-03459-6>
- Bowe, B., Xie, Y., & Al-Aly, Z. (2023). Postacute sequelae of COVID-19 at 2 years. *Nat Med*. <https://doi.org/10.1038/s41591-023-02521-2>
- Brannock, D. M., Chew, F. R., Preiss, J. A., Hadley, C. E., McMurry, A. J., Leese, J. P., Girvin, T. A., Crosskey, M., Zhou, G. A., Moffitt, A. R., Funk, J. M., Pfaff, R. E., Haendel, A. M., & Chute, G. C. (2022). Long COVID risk and pre-COVID vaccination: An EHR-based cohort study from the RECOVER program. In *medRxiv* (20221007 ed.).
- Brehon, K., Niemeläinen, R., Hall, M., Bostick, G. P., Brown, C. A., Wieler, M., & Gross, D. P. (2022). Return-to-Work Following Occupational Rehabilitation for Long COVID: Descriptive Cohort Study. *JMIR Rehabilitation and Assistive Technologies*, 9(3), e39883. <https://doi.org/10.2196/39883>
- Brugliera, L., Spina, A., Castellazzi, P., Cimino, P., Tettamanti, A., Houdayer, E., Arcuri, P., Alemanno, F., Mortini, P., & Iannaccone, S. (2020). Rehabilitation of COVID-19 patients. *J Rehabil Med*, 52(4), jrm00046. <https://doi.org/10.2340/16501977-2678>
- Cahan, J., Finley, J. A., Cotton, E., Orban, Z. S., Jimenez, M., Weintraub, S., Sorets, T., & Koralnik, I. J. (2024). Cognitive functioning in patients with neuro-PASC: the role of fatigue, mood, and hospitalization status. *Front Neurol*, 15, 1401796. <https://doi.org/10.3389/fneur.2024.1401796>
- Callard, F., & Perego, E. (2021). How and why patients made Long Covid. *Soc Sci Med*, 268, 113426. <https://doi.org/10.1016/j.socscimed.2020.113426>
- Cañas, A., Wolf, A., Chen, E. C., Ruddy, J., El-Sadek, S., Gomez, L., Furfaro, D., Fullilove, R., Burkart, K. M., Zelnick, J., & O'Donnell, M. R. (2024). Racial and ethnic disparities post-hospitalization for COVID-19: barriers to access to care for survivors of COVID-19

- acute respiratory distress syndrome. *Sci Rep*, 14(1), 11556.
<https://doi.org/10.1038/s41598-024-61097-0>
- Carter, S. J., Baranauskas, M. N., Raglin, J. S., Pescosolido, B. A., & Perry, B. L. (2022). Functional Status, Mood State, and Physical Activity Among Women With Post-Acute COVID-19 Syndrome. *Int J Public Health*, 67, 1604589.
<https://doi.org/10.3389/ijph.2022.1604589>
- Case, K. R., Wang, C. P., Hosek, M. G., Lill, S. F., Howell, A. B., Taylor, B. S., Bridges, J., MacCarthy, D. J., Winkler, P., & Tsevat, J. (2022). Health-related quality of life and social determinants of health following COVID-19 infection in a predominantly Latino population. *J Patient Rep Outcomes*, 6(1), 72. <https://doi.org/10.1186/s41687-022-00473-8>
- Centers for Disease Control and Prevention. (2023). *Long COVID or Post-COVID Conditions*. https://www.cdc.gov/covid/long-term-effects/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/
- Centers for Medicare and Medicaid Services. (2020). *Billing and Coding: Therapy Evaluation, Re-Evaluation and Formal Testing. A53309*. DHHS, CMS. Retrieved 10/3/2024 from <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53309>
- Ceravolo, M. G., de Sire, A., Andrenelli, E., Negrini, F., & Negrini, S. (2020). Systematic rapid "living" review on rehabilitation needs due to COVID-19: update to March 31st, 2020. *Eur J Phys Rehabil Med*, 56(3), 347-353. <https://doi.org/10.23736/s1973-9087.20.06329-7>
- Chuang, H. J., Lin, C. W., Hsiao, M. Y., Wang, T. G., & Liang, H. W. (2023). Long COVID and rehabilitation. *J Formos Med Assoc*. <https://doi.org/10.1016/j.jfma.2023.03.022>
- Costa, A., Martins, T. F., da Silva, V. Z. M., Leite, C. F., Castro, S. S., Cipriano, G., Jr., & Cipriano, G. F. B. (2024). Standardization use of the international classification of functioning, disability and health in the determination of health status in patients with post-acute COVID-19 syndrome. *Disabil Rehabil*, 1-13.
<https://doi.org/10.1080/09638288.2024.2358897>
- Crook, H., Raza, S., Nowell, J., Young, M., & Edison, P. (2021). Long covid—mechanisms, risk factors, and management. *Bmj*, 374, n1648. <https://doi.org/10.1136/bmj.n1648>
- Cutler, D. M. (2022). The Costs of Long COVID. *JAMA Health Forum*, 3(5), e221809.
<https://doi.org/10.1001/jamahealthforum.2022.1809>
- da Costa, J. P., Vitorino, R., Silva, G. M., Vogel, C., Duarte, A. C., & Rocha-Santos, T. (2016). A synopsis on aging-Theories, mechanisms and future prospects. *Ageing Res Rev*, 29, 90-112. <https://doi.org/10.1016/j.arr.2016.06.005>
- Davis, E. H., Assaf, S. G., Mccorkell, L., Wei, H., Low, J. R., Re'Em, Y., Redfield, S., Austin, P. J., & Akrami, A. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*, 38, 101019.
<https://doi.org/10.1016/j.eclinm.2021.101019> (EClinicalMedicine)
- Davis, E. H., Mccorkell, L., Vogel, M. J., & Topol, J. E. (2023). Long COVID: major findings, mechanisms and recommendations. *Nature Reviews Microbiology*, 21(3), 133-146.
<https://doi.org/10.1038/s41579-022-00846-2>
- de Sire, A., Andrenelli, E., Negrini, F., Lazzarini, S. G., Cordani, C., & Ceravolo, M. G. (2022). Rehabilitation and COVID-19: update of the rapid living systematic review by Cochrane

- Rehabilitation Field as of February 28th, 2022. *Eur J Phys Rehabil Med*, 58(3), 498-501. <https://doi.org/10.23736/s1973-9087.22.07593-1>
- Deer, R. R., Rock, A. M., Vasilevsky, N., Carmody, L., Rando, H., Anzalone, J. A., Basson, D. M., Bennett, D. T., Bergquist, T., Boudreau, A. E., Bramante, T. C., Byrd, B. J., Callahan, J. T., Chan, E. L., Chu, H., Chute, G. C., Coleman, D. B., Davis, E. H., Gagnier, J.,...Robinson, N. P. (2021). Characterizing Long COVID: Deep Phenotype of a Complex Condition. *EBioMedicine*, 74, 103722. <https://doi.org/10.1016/j.ebiom.2021.103722>
- Di Primio, C., Quaranta, P., Mignanelli, M., Siano, G., Bimbati, M., Scarlatti, A., Piazza, C. R., Spezia, P. G., Perrera, P., Basolo, F., Poma, A. M., Costa, M., Pistello, M., & Cattaneo, A. (2023). Severe acute respiratory syndrome coronavirus 2 infection leads to Tau pathological signature in neurons. *PNAS Nexus*, 2(9), pgad282. <https://doi.org/10.1093/pnasnexus/pgad282>
- Diar Bakerly, N., Smith, N., Darbyshire, J. L., Kwon, J., Bullock, E., Baley, S., Sivan, M., & Delaney, B. (2024). Pathophysiological Mechanisms in Long COVID: A Mixed Method Systematic Review. *Int J Environ Res Public Health*, 21(4). <https://doi.org/10.3390/ijerph21040473>
- Durfey, S. N. M., Kind, A. J. H., Buckingham, W. R., DuGoff, E. H., & Trivedi, A. N. (2019). Neighborhood disadvantage and chronic disease management. *Health Serv Res*, 54 Suppl 1(Suppl 1), 206-216. <https://doi.org/10.1111/1475-6773.13092>
- Eligulashvili, A., Darrell, M., Gordon, M., Jerome, W., Fiori, K. P., Congdon, S., & Duong, T. Q. (2024). Patients with unmet social needs are at higher risks of developing severe long COVID-19 symptoms and neuropsychiatric sequela. *Sci Rep*, 14(1), 7743. <https://doi.org/10.1038/s41598-024-58430-y>
- Erlandson, K. M., Geng, L. N., Selvaggi, C. A., Thaweethai, T., Chen, P., Erdmann, N. B., Goldman, J. D., Henrich, T. J., Hornig, M., Karlson, E. W., Katz, S. D., Kim, C., Cribbs, S. K., Laiyemo, A. O., Letts, R., Lin, J. Y., Marathe, J., Parthasarathy, S., Patterson, T. F.,...McComsey, G. A. (2024). Differentiation of Prior SARS-CoV-2 Infection and Postacute Sequelae by Standard Clinical Laboratory Measurements in the RECOVER Cohort. *Ann Intern Med*, 177(9), 1209-1221. <https://doi.org/10.7326/m24-0737>
- Fekete, M., Lehoczki, A., Szappanos, Á., Toth, A., Mahdi, M., Sótonyi, P., Benyó, Z., Yabluchanskiy, A., Tarantini, S., & Ungvari, Z. (2025). Cerebromicrovascular mechanisms contributing to long COVID: implications for neurocognitive health. *Geroscience*. <https://doi.org/10.1007/s11357-024-01487-4> (Geroscience)
- Ford, N. D., Slaughter, D., Edwards, D., Dalton, A., Perrine, C., Vahratian, A., & Saydah, S. (2023). Long COVID and Significant Activity Limitation Among Adults, by Age — United States, June 1–13, 2022, to June 7–19, 2023. *MMWR Morb Mortal Wkly Rep* 2023, 72, 866-970. <https://doi.org/http://dx.doi.org/10.15585/mmwr.mm7232a3>
- Gell, N. M., Rosenberg, D. E., Carlson, J., Kerr, J., & Belza, B. (2015). Built environment attributes related to GPS measured active trips in mid-life and older adults with mobility disabilities. *Disabil Health J*, 8(2), 290-295. <https://doi.org/10.1016/j.dhjo.2014.12.002>
- Gentilotti, E., Górska, A., Tami, A., Gusinow, R., Mirandola, M., Rodríguez Baño, J., Palacios Baena, Z. R., Rossi, E., Hasenauer, J., Lopes-Rafegas, I., Righi, E., Caroccia, N., Cataudella, S., Pasquini, Z., Osmo, T., Del Piccolo, L., Savoldi, A., Kumar-Singh, S., Mazzaferri, F.,...Tacconelli, E. (2023). Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective

- ORCHESTRA cohort. *EClinicalMedicine*, 62, 102107.
<https://doi.org/10.1016/j.eclinm.2023.102107>
- Gilmore-Bykovskiy, A., Jackson, J. D., & Wilkins, C. H. (2021). The Urgency of Justice in Research: Beyond COVID-19. *Trends Mol Med*, 27(2), 97-100.
<https://doi.org/10.1016/j.molmed.2020.11.004>
- Goërtz, Y. M. J., Van Herck, M., Delbressine, J. M., Vaes, A. W., Meys, R., Machado, F. V. C., Houben-Wilke, S., Burtin, C., Posthuma, R., Franssen, F. M. E., Van Loon, N., Hajian, B., Spies, Y., Vijlbrief, H., Van 'T Hul, A. J., Janssen, D. J. A., & Spruit, M. A. (2020). Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Research*, 6(4), 00542-02020.
<https://doi.org/10.1183/23120541.00542-2020>
- Gonzalez Aleman, G., Vavougiou, G. D., Tartaglia, C., Uvais, N. A., Guekht, A., Hosseini, A. A., Lo Re, V., Ferreccio, C., D'Avossa, G., Zamponi, H. P., Figueredo Aguiar, M., Yecora, A., Ul Haq Katshu, M. Z., Stavrou, V. T., Boutlas, S., Gourgoulisanis, K. I., Botero, C., González Insúa, F., Perez-Lloret, S.,...de Erausquin, G. A. (2024). Age-dependent phenotypes of cognitive impairment as sequelae of SARS-CoV-2 infection. *Front Aging Neurosci*, 16, 1432357. <https://doi.org/10.3389/fnagi.2024.1432357>
- Grimmer, K., Beaton, K., & Hendry, K. (2013). Identifying functional decline: a methodological challenge. *Patient Related Outcome Measures*, 4, 37-48.
<https://doi.org/10.2147/PROM.S42474>
- Groff, D., Sun, A., Ssentongo, A. E., Ba, D. M., Parsons, N., Poudel, G. R., Lekoubou, A., Oh, J. S., Ericson, J. E., Ssentongo, P., & Chinchilli, V. M. (2021). Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA Network Open*, 4(10), e2128568. <https://doi.org/10.1001/jamanetworkopen.2021.28568>
- Guenther, S. P. W., Cheaban, R., Hoepner, L., Weinrautner, N., Kirschning, T., Al-Khalil, R., Bruenger, F., Serrano, M. R., Barndt, I., Wiemer, M., Niedermeyer, J., Rudloff, M., Helms, S., Schramm, R., & Gummert, J. F. (2023). Functional Status and Quality of Life 6 Months After Extracorporeal Membrane Oxygenation Therapy for COVID-19-Related Pulmonary Failure. *Asaio j*. <https://doi.org/10.1097/mat.0000000000001993>
- Gutzeit, J., Weiß, M., Nürnberger, C., Lemhöfer, C., Appel, K. S., Pracht, E., Reese, J. P., Lehmann, C., Polidori, M. C., Hein, G., & Deckert, J. (2024). Definitions and symptoms of the post-COVID syndrome: an updated systematic umbrella review. *Eur Arch Psychiatry Clin Neurosci*. <https://doi.org/10.1007/s00406-024-01868-y>
- Hadley Wickham, M. A., Jennifer Bryan, Winston Chang, Lucy D'Agostino McGowan, Romain François, Garrett Golemund, Alex Hayes, Lionel Henry, Jim Hester, Max Kuhn, Thomas Lin Pedersen, Evan Miller, Stephan Milton Bache, Kirill Müller, Jeroen Ooms, David Robinson, Dana Paige Seidel, Vitalie Spinu, Kohske Takahashi, Davis Vaughan, Claus Wilke, Kara Woo, Hiroaki Yutani. (2019). *Welcome to the tidyverse*. In (Version 2.0.0) R Foundation for Statistical Computing. <https://tidyverse.tidyverse.org>, <https://github.com/tidyverse/tidyverse>
- Hall, J. P., Kurth, N. K., McCorkell, L., & Goddard, K. S. (2024). Long COVID Among People With Preexisting Disabilities. *Am J Public Health*, 114(11), 1261-1264.
<https://doi.org/10.2105/ajph.2024.307794>
- Harrell, F. E. (2001). *Regression Modeling Strategies* (2nd ed.). Springer.
- Harrell, F. E. (2024). *Regression Modeling Strategies*. In (Vol. 6.8-2): CRAN.

- Haunhorst, S., Dudziak, D., Scheibenbogen, C., Seifert, M., Sotzny, F., Finke, C., Behrends, U., Aden, K., Schreiber, S., Brockmann, D., Burggraf, P., Bloch, W., Ellert, C., Ramoji, A., Popp, J., Reuken, P., Walter, M., Stallmach, A., & Puta, C. (2024). Towards an understanding of physical activity-induced post-exertional malaise: Insights into microvascular alterations and immunometabolic interactions in post-COVID condition and myalgic encephalomyelitis/chronic fatigue syndrome. *Infection*. <https://doi.org/10.1007/s15010-024-02386-8>
- Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., Collange, O., Boulay, C., Fafi-Kremer, S., Ohana, M., Anheim, M., & Meziani, F. (2020). Neurologic Features in Severe SARS-CoV-2 Infection. *New England Journal of Medicine*, 382(23), 2268-2270. <https://doi.org/10.1056/nejmc2008597>
- Helms, J., Kremer, S., Merdji, H., Schenck, M., Severac, F., Clere-Jehl, R., Studer, A., Radosavljevic, M., Kummerlen, C., Monnier, A., Boulay, C., Fafi-Kremer, S., Castelain, V., Ohana, M., Anheim, M., Schneider, F., & Meziani, F. (2020). Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care*, 24(1), 491. <https://doi.org/10.1186/s13054-020-03200-1>
- Higgins, V., Sohaei, D., Diamandis, E. P., & Prassas, I. (2020). COVID-19: from an acute to chronic disease? Potential long-term health consequences. *Crit Rev Clin Lab Sci*, 1-23. <https://doi.org/10.1080/10408363.2020.1860895>
- Ho, D. E., Imai, K., King, G., & Stuart, E. A. (2007). Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political Analysis*, 15(3), 199-236. <https://doi.org/10.1093/pan/mp1013>
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2), 271-280.e278. <https://doi.org/10.1016/j.cell.2020.02.052>
- Hou, Y., Gu, T., Ni, Z., Shi, X., Ranney, M. L., & Mukherjee, B. (2025). Global Prevalence of Long COVID, its Subtypes and Risk factors: An Updated Systematic Review and Meta-Analysis. *medRxiv*. <https://doi.org/10.1101/2025.01.01.24319384>
- Iqbal, F. M., Lam, K., Sounderajah, V., Clarke, J. M., Ashrafian, H., & Darzi, A. (2021). Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EClinicalMedicine*, 36, 100899. <https://doi.org/10.1016/j.eclinm.2021.100899>
- Izaguirre, P., Arakaki, É., Boero, J. V., Zalazar, Á., Ghirlanda, M., & Caruso, D. (2023). Functional Status in Older Adults Following Hospitalization for Covid-19: A Cohort Study. *Ann Geriatr Med Res*. <https://doi.org/10.4235/agmr.23.0071>
- Jacobs, M. M., Evans, E., & Ellis, C. (2023). Racial, ethnic, and sex disparities in the incidence and cognitive symptomology of long COVID-19. *J Natl Med Assoc*, 115(2), 233-243. <https://doi.org/10.1016/j.jnma.2023.01.016>
- Jacobson, K. B., Rao, M., Bonilla, H., Subramanian, A., Hack, I., Madrigal, M., Singh, U., Jagannathan, P., & Grant, P. (2021). Patients With Uncomplicated Coronavirus Disease 2019 (COVID-19) Have Long-Term Persistent Symptoms and Functional Impairment Similar to Patients with Severe COVID-19: A Cautionary Tale During a Global Pandemic. *Clinical Infectious Diseases*, 73(3), e826-e829. <https://doi.org/10.1093/cid/ciab103>

- Jaywant, A., Gunning, F. M., Oberlin, L. E., Santillana, M., Ognyanova, K., Druckman, J. N., Baum, M. A., Lazer, D., & Perlis, R. H. (2024). Cognitive Symptoms of Post-COVID-19 Condition and Daily Functioning. *JAMA Netw Open*, 7(2), e2356098. <https://doi.org/10.1001/jamanetworkopen.2023.56098>
- Khullar, D., Zhang, Y., Zang, C., Xu, Z., Wang, F., Weiner, M. G., Carton, T. W., Rothman, R. L., Block, J. P., & Kaushal, R. (2023). Racial/ethnic disparities in post-acute sequelae of SARS-CoV-2 infection in New York: an EHR-based cohort study from the RECOVER program. *J Gen Intern Med*, 38(5), 1127-1136. <https://doi.org/10.1007/s11606-022-07997-1>
- Kind, A. J. H., & Buckingham, W. R. (2018). Making Neighborhood-Disadvantage Metrics Accessible - The Neighborhood Atlas. *N Engl J Med*, 378(26), 2456-2458. <https://doi.org/10.1056/NEJMp1802313>
- Kirchberger, I., Peilstöcker, D., Warm, T. D., Linseisen, J., Hyhlik-Dürr, A., Meisinger, C., & Goßlau, Y. (2023). Subjective and Objective Cognitive Impairments in Non-Hospitalized Persons 9 Months after SARS-CoV-2 Infection. *Viruses*, 15(1). <https://doi.org/10.3390/v15010256>
- Kitsios, G. D., Blacka, S., Jacobs, J. J., Mirza, T., Naqvi, A., Gentry, H., Murray, C., Wang, X., Golubykh, K., Qurashi, H., Dodia, A., Risbano, M., Benigno, M., Emir, B., Weinstein, E., Bramson, C., Jiang, L., Dai, F., Szigethy, E.,...Morris, A. (2024). Subphenotypes of self-reported symptoms and outcomes in long COVID: a prospective cohort study with latent class analysis. *BMJ open*, 14(3), e077869. <https://doi.org/10.1136/bmjopen-2023-077869>
- Köseoğlu, B. F., Sonel Tur, B., Kutay Ordu Gökkaya, N., Güneş Gökmen, İ., Nur Kesiktaş, F., Bilir Kaya, B., Önal, R., Tuncay, F., Genç, A., Findikoglu, G., Koldaş Doğan, Ş., Tomruk Sütbeyaz, S., Sarıkaya, S., Tıkız, C., Özdemir, H., Demirbağ Kabayel, D., Örucü Atar, M., Atan, T., & Yüksel, S. (2023). Applying the WHO ICF framework to long COVID patients with persistent respiratory symptoms. *Turk J Phys Med Rehabil*, 69(4), 410-423. <https://doi.org/10.5606/tftrd.2023.13455>
- Ladds, E., Rushforth, A., Wieringa, S., Taylor, S., Rayner, C., Husain, L., & Greenhalgh, T. (2020). Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Serv Res*, 20(1), 1144. <https://doi.org/10.1186/s12913-020-06001-y>
- Law, M., Cooper, B., Strong, S., Stewart, D., Rigby, P., & Letts, L. (1996). The Person-Environment-Occupation Model: A transactive approach to occupational performance. *Canadian Journal of Occupational Therapy*, 63(1), 9-23. <https://doi.org/10.1177/000841749606300103>
- Lemhöfer, C., Appel, S. K., Häuser, W., Hettich, N., Kohls, M., & Polidori, C. M. (2022). Post-COVID: Alles eine Frage der Definition? *DMW - Deutsche Medizinische Wochenschrift*, 147(21), 1391-1397. <https://doi.org/10.1055/a-1940-1222> (Post-COVID: Alles eine Frage der Definition?)
- Liew, F., Efstathiou, C., Fontanella, S., Richardson, M., Saunders, R., Swieboda, D., Sidhu, J. K., Ascough, S., Moore, S. C., Mohamed, N., Nunag, J., King, C., Leavy, O. C., Elneima, O., McAuley, H. J. C., Shikotra, A., Singapuri, A., Sereno, M., Harris, V. C.,...Openshaw, P. J. M. (2024). Large-scale phenotyping of patients with long COVID post-hospitalization reveals mechanistic subtypes of disease. *Nat Immunol*, 25(4), 607-621. <https://doi.org/10.1038/s41590-024-01778-0>

- Lorman, V., Razzaghi, H., Song, X., Morse, K., Utidjian, L., Allen, A. J., Rao, S., Rogerson, C., Bennett, T. D., Morizono, H., Eckrich, D., Jhaveri, R., Huang, Y., Ranade, D., Pajor, N., Lee, G. M., Forrest, C. B., & Bailey, L. C. (2023). A machine learning-based phenotype for long COVID in children: An EHR-based study from the RECOVER program. *PloS one*, *18*(8), e0289774. <https://doi.org/10.1371/journal.pone.0289774>
- Mackey, K., Ayers, C. K., Kondo, K. K., Saha, S., Advani, S. M., Young, S., Spencer, H., Rusek, M., Anderson, J., Veazie, S., Smith, M., & Kansagara, D. (2021). Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. *Ann Intern Med*, *174*(3), 362-373. <https://doi.org/10.7326/m20-6306>
- Markov, P. V., Ghafari, M., Beer, M., Lythgoe, K., Simmonds, P., Stilianakis, N. I., & Katzourakis, A. (2023). The evolution of SARS-CoV-2. *Nat Rev Microbiol*, *21*(6), 361-379. <https://doi.org/10.1038/s41579-023-00878-2>
- Marks, T. S., Giles, G. M., Al-Heizan, M. O., & Edwards, D. F. (2020). Can Brief Cognitive or Medication Management Tasks Identify the Potential for Dependence in Instrumental Activities of Daily Living? *Front Aging Neurosci*, *12*, 33. <https://doi.org/10.3389/fnagi.2020.00033>
- Marks, T. S., Giles, G. M., Al-Heizan, M. O., & Edwards, D. F. (2021a). How Well Does the Brief Interview for Mental Status Identify Risk for Cognition Mediated Functional Impairment in a Community Sample? *Arch Rehabil Res Clin Transl*, *3*(1), 100102. <https://doi.org/10.1016/j.arrct.2021.100102>
- Marks, T. S., Giles, G. M., Al-Heizan, M. O., & Edwards, D. F. (2021b). Screening to Assessment Pathways in Evaluating Functional Cognition in Older Adults. *OTJR (Thorofare N J)*, *41*(4), 275-284. <https://doi.org/10.1177/15394492211021851>
- Marks, T. S., Giles, G. M., Kehl-Floberg, K. E., & Edwards, D. F. (2023). Screening older adults for potential deficits in IADL using the Menu Task and Medi-Cog-R [Conference abstract]. *Alzheimer's & Dementia*, *19*(S19). <https://doi.org/doi.org/10.1002/alz.079778>
- McCorkell, L., G, S. A., H, E. D., Wei, H., & Akrami, A. (2021). Patient-Led Research Collaborative: embedding patients in the Long COVID narrative. *Pain Rep*, *6*(1), e913. <https://doi.org/10.1097/pr9.0000000000000913>
- Mendelson, M., Nel, J., Blumberg, L., Madhi, S. A., Dryden, M., Stevens, W., & Venter, F. W. D. (2020). Long-COVID: An evolving problem with an extensive impact. *S Afr Med J*, *111*(1), 10-12. <https://doi.org/10.7196/SAMJ.2020.v111i11.15433>
- Mina, Y., Enose-Akahata, Y., Hammoud, D. A., Videckis, A. J., Narpala, S. R., O'Connell, S. E., Carroll, R., Lin, B. C., McMahan, C. C., Nair, G., Reoma, L. B., McDermott, A. B., Walitt, B., Jacobson, S., Goldstein, D. S., Smith, B. R., & Nath, A. (2023). Deep Phenotyping of Neurologic Postacute Sequelae of SARS-CoV-2 Infection. *Neurol Neuroimmunol Neuroinflamm*, *10*(4). <https://doi.org/10.1212/nxi.0000000000200097>
- Molnar, T., Lehoczki, A., Fekete, M., Varnai, R., Zavori, L., Erdo-Bonyar, S., Simon, D., Berki, T., Csecsei, P., & Ezer, E. (2024). Mitochondrial dysfunction in long COVID: mechanisms, consequences, and potential therapeutic approaches. *Geroscience*. <https://doi.org/10.1007/s11357-024-01165-5> (Geroscience)
- Monteiro, P. I., Appelt, A. P., Sisconetto, T. A., Sucupira, B. M. S. K., Bazan, R., Luvizutto, J. G., & Souza, D. S. P. A. L. (2023). Post-coronavirus disease 2019 functional impairments, limitations, and restrictions: A prospective cohort study based on the international classification of functioning, disability, and health. *Journal of Central*

- Nervous System Disease*, 15, 11795735231195759.
<https://doi.org/10.1177/11795735231195759>
- Mujahid, M. S., Gao, X., Tabb, L. P., Morris, C., & Lewis, T. T. (2021). Historical redlining and cardiovascular health: The Multi-Ethnic Study of Atherosclerosis. *Proc Natl Acad Sci U S A*, 118(51). <https://doi.org/10.1073/pnas.2110986118>
- Nakamura, T., Lapiere, M. H., & Lipton, S. A. (2017). The Neurobiology of aging: Free radical stress and metabolic pathways. In *Brocklehurst's Textbook of Geriatric Medicine and Gerontology* (8th ed., pp. 61-69). Elsevier. <https://www-clinicalkey-com.ezproxy.library.wisc.edu/#!/content/book/3-s2.0-B9780702061851000119>
- Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., Cook, J. R., Nordvig, A. S., Shalev, D., Sehrawat, T. S., Ahluwalia, N., Bikdeli, B., Dietz, D., Der-Nigoghossian, C., Liyanage-Don, N., Rosner, G. F., Bernstein, E. J., Mohan, S., Beckley, A. A.,... Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nat Med*, 27(4), 601-615. <https://doi.org/10.1038/s41591-021-01283-z> (Nat Med)
- National Academies of Sciences Engineering and Medicine. (2024). *A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences*. The National Academies Press. <https://doi.org/10.17226/27768>
- National Center for Health Statistics, U. S. C. B. (2024). *Household Pulse Survey - Long COVID*. <https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm>
- National institutes of Health. (2022-2025). *All of Us, Curated data repository version 7, Controlled Tier C2022Q4R9* (National Institutes of Health). https://docs.google.com/document/d/1tr-WqIUsJicbF9QeCkvhvQmMiSivEg4vSLiQ0A5zR_4/edit?tab=t.0#heading=h.e7ppu6uf0bea
- Newton, K. M., Peissig, P. L., Kho, A. N., Bielinski, S. J., Berg, R. L., Choudhary, V., Basford, M., Chute, C. G., Kullo, I. J., Li, R., Pacheco, J. A., Rasmussen, L. V., Spangler, L., & Denny, J. C. (2013). Validation of electronic medical record-based phenotyping algorithms: results and lessons learned from the eMERGE network. *J Am Med Inform Assoc*, 20(e1), e147-154. <https://doi.org/10.1136/amiajnl-2012-000896>
- Nielsen, T. B., Leth, S., Pedersen, M., Harbo, H. D., Nielsen, C. V., Laursen, C. H., Schiøttz-Christensen, B., & Oestergaard, L. G. (2022). Mental Fatigue, Activities of Daily Living, Sick Leave and Functional Status among Patients with Long COVID: A Cross-Sectional Study. *Int J Environ Res Public Health*, 19(22). <https://doi.org/10.3390/ijerph192214739>
- Observational Health Data Sciences and Informatics. (2024). *Standardized Data: The OMOP Common Data Model*. <https://www.ohdsi.org/data-standardization/>
- Occupational Therapy practice framework: Domain and process (4th ed.). (2020). *The American Journal of Occupational Therapy*, 74(Supplement_2), 7412410010p7412410011-7412410074. <https://doi.org/10.5014/ajot.2020.74S2001>
- Odysseus Data Services, I. (2023). ATHENA - OHDSI Vocabularies Repository. In (Vol. Version 1.13.0.23.230616.0657).
- Organization, W. H. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Bulletin of the World Health Organization*, 85(11), 867-872. <https://doi.org/10.2471/blt.07.045120>
- Owen, R., Ashton, R. E., Bewick, T., Copeland, R. J., Ferraro, F. V., Kennerley, C., Phillips, B. E., Maden-Wilkinson, T., Parkington, T., Skipper, L., Thomas, C., Arena, R., Formenti,

- F., Ozemek, C., Veluswamy, S. K., Gururaj, R., & Faghy, M. A. (2025). Profiling the persistent and episodic nature of long COVID symptoms and the impact on quality of life and functional status: a cohort observation study. *J Glob Health*, *15*, 04006. <https://doi.org/10.7189/jogh.15.04006>
- Pattanayak, C. W., Rubin, D. B., & Zell, E. R. (2011). [Propensity score methods for creating covariate balance in observational studies]. *Rev Esp Cardiol*, *64*(10), 897-903. <https://doi.org/10.1016/j.recesp.2011.06.008> (Métodos de puntuación de propensión para crear una distribución equilibrada de las covariables en los estudios observacionales.)
- Paul, K. C., Haan, M., Mayeda, E. R., & Ritz, B. R. (2019). Ambient Air Pollution, Noise, and Late-Life Cognitive Decline and Dementia Risk. *Annu Rev Public Health*, *40*, 203-220. <https://doi.org/10.1146/annurev-publhealth-040218-044058>
- Peluso, M. J., Kelly, J. D., Lu, S., Goldberg, S. A., Davidson, M. C., Mathur, S., Durstenfeld, M. S., Spinelli, M. A., Hoh, R., Tai, V., Fehrman, E. A., Torres, L., Hernandez, Y., Williams, M. C., Arreguin, M. I., Bautista, J. A., Ngo, L. H., Deswal, M., Munter, S. E.,...Martin, J. N. (2021). Rapid implementation of a cohort for the study of post-acute sequelae of SARS-CoV-2 infection/COVID-19. *medRxiv*. <https://doi.org/10.1101/2021.03.11.21252311>
- Perry, B. L., McConnell, W. R., Coleman, M. E., Roth, A. R., Peng, S., & Apostolova, L. G. (2021). Why the cognitive "fountain of youth" may be upstream: Pathways to dementia risk and resilience through social connectedness. *Alzheimers Dement*. <https://doi.org/10.1002/alz.12443>
- Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*(3), 183-194. <https://doi.org/10.1111/j.1365-2796.2004.01388.x>
- Petersen, R. C., Lopez, O., Armstrong, M. J., Getchius, T. S. D., Ganguli, M., Gloss, D., Gronseth, G. S., Marson, D., Pringsheim, T., Day, G. S., Sager, M., Stevens, J., & Rae-Grant, A. (2018). Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*, *90*(3), 126-135. <https://doi.org/10.1212/wnl.00000000000004826>
- Prabhakaran, D., Day, G., Munipalli, B., Rush, B., Pudalov, L., Niazi, S., Brennan, E., Powers, H., Durvasula, R., Athreya, A., & Blackmon, K. (2022). Neurophenotypes of COVID-19: risk factors and recovery trajectories. *Brain Behav Immun Health*. <https://doi.org/10.21203/rs.3.rs-2363210/v1>
- Prevention, C. f. D. C. a. (2021). *New ICD-10-CM code for Post-COVID Conditions, following the 2019 Novel Coronavirus (COVID-19)*. Retrieved from <https://www.cdc.gov/nchs/data/icd/announcement-new-icd-code-for-post-covid-condition-april-2022-final.pdf>
- Puente, A. N., Terry, D. P., Faraco, C. C., Brown, C. L., & Miller, L. S. (2014). Functional impairment in mild cognitive impairment evidenced using performance-based measurement. *J Geriatr Psychiatry Neurol*, *27*(4), 253-258. <https://doi.org/10.1177/0891988714532016>
- R Core Team. (2022). R: A language and environment for statistical computing. In. Vienna, Austria: R Foundation for Statistical Computing.
- R Core Team and contributors worldwide. (2025). *The R Stats Package*. In (Version 4.3.0-4.4.3) R Foundation for Statistical Computing.

- Ramirez, A. H., Sulieman, L., Schlueter, D. J., Halvorson, A., Qian, J., Ratsimbazafy, F., Loperena, R., Mayo, K., Basford, M., Deflaux, N., Muthuraman, K. N., Natarajan, K., Kho, A., Xu, H., Wilkins, C., Anton-Culver, H., Boerwinkle, E., Cicek, M., Clark, C. R.,...Roden, D. M. (2022). The All of Us Research Program: Data quality, utility, and diversity. *Patterns (N Y)*, 3(8), 100570. <https://doi.org/10.1016/j.patter.2022.100570>
- Rando, H. M., Bennett, T. D., Byrd, J. B., Bramante, C., Callahan, T. J., Chute, C. G., Davis, H. E., Deer, R., Gagnier, J., Korashy, F. M., Liu, F., McMurry, J. A., Moffitt, R. A., Pfaff, E. R., Reese, J. T., Relevo, R., Robinson, P. N., Saltz, J. H., Solomonides, A.,...Haendel, M. A. (2021). Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. *medRxiv*. <https://doi.org/10.1101/2021.03.20.21253896> (medRxiv)
- Reese, J. T., Blau, H., Casiraghi, E., Bergquist, T., Loomba, J. J., Callahan, T. J., Laraway, B., Antonescu, C., Coleman, B., Gargano, M., Wilkins, K. J., Cappelletti, L., Fontana, T., Ammar, N., Antony, B., Murali, T. M., Caufield, J. H., Karlebach, G., McMurry, J. A.,...Robinson, P. N. (2023). Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes. *EBioMedicine*, 87, 104413. <https://doi.org/10.1016/j.ebiom.2022.104413>
- Robinson, P. N. (2012). Deep phenotyping for precision medicine. *Hum Mutat*, 33(5), 777-780. <https://doi.org/10.1002/humu.22080>
- Rolin, S., Chakales, A., & Verduzco-Gutierrez, M. (2022). Rehabilitation Strategies for Cognitive and Neuropsychiatric Manifestations of COVID-19. *Curr Phys Med Rehabil Rep*, 10(3), 182-187. <https://doi.org/10.1007/s40141-022-00352-9>
- Schaap, G., Wensink, M., Doggen, C. J. M., Van Der Palen, J., Vonkeman, H. E., & Bode, C. (2022). “It Really Is an Elusive Illness”—Post-COVID-19 Illness Perceptions and Recovery Strategies: A Thematic Analysis. *Int J Environ Res Public Health*, 19(20), 13003. <https://doi.org/10.3390/ijerph192013003>
- Schild, A. K., Scharfenberg, D., Regorius, A., Klein, K., Kirchner, L., Yasemin, G., Lülling, J., Meiberth, D., Schweitzer, F., Fink, G. R., Jessen, F., Franke, C., Onur, O. A., Jost, S. T., Warnke, C., & Maier, F. (2024). Six-month follow-up of multidomain cognitive impairment in non-hospitalized individuals with post-COVID-19 syndrome. *Eur Arch Psychiatry Clin Neurosci*. <https://doi.org/10.1007/s00406-024-01863-3>
- Shabani, Z., Liu, J., & Su, H. (2023). Vascular dysfunctions contribute to the long-term cognitive deficits following COVID-19. *Biology (Basel)*, 12(8). <https://doi.org/10.3390/biology12081106>
- Shanbehzadeh, S., Zanjari, N., Yassin, M., Yassin, Z., & Tavahomi, M. (2023). Association between long COVID, functional activity, and health-related quality of life in older adults. *BMC Geriatr*, 23(1), 40. <https://doi.org/10.1186/s12877-023-03757-w>
- Soriano, J. B., Murthy, S., Marshall, J. C., Relan, P., & Diaz, J. V. (2022). A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*, 22(4), e102-e107. [https://doi.org/10.1016/s1473-3099\(21\)00703-9](https://doi.org/10.1016/s1473-3099(21)00703-9)
- Stuart, E. A. (2010). Matching Methods for Causal Inference: A Review and a Look Forward. *Statistical Science*, 25(1), 1-21. <https://doi.org/10.1214/09-sts313>
- Tana, C., Moffa, L., Falasca, K., Vecchiet, J., Tana, M., Mantini, C., Ricci, F., Ticinesi, A., Meschi, T., Cipollone, F., & Giamberardino, M. A. (2023). Approach to COVID-19 in older adults and indications for improving the outcomes. *Ann Med*, 55(2), 2265298. <https://doi.org/10.1080/07853890.2023.2265298>

- Tenforde, M. W., Kim, S. S., Lindsell, C. J., Billig Rose, E., Shapiro, N. I., Files, D. C., Gibbs, K. W., Erickson, H. L., Steingrub, J. S., Smithline, H. A., Gong, M. N., Aboodi, M. S., Exline, M. C., Henning, D. J., Wilson, J. G., Khan, A., Qadir, N., Brown, S. M., Peltan, I. D.,...Feldstein, L. R. (2020). Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep*, 69(30), 993-998. <https://doi.org/10.15585/mmwr.mm6930e1>
- Thaweethai, T., Jolley, E. S., Karlson, W. E., Levitan, B. E., Levy, B., Mccomsey, A. G., Mccorkell, L., Nadkarni, N. G., Parthasarathy, S., Singh, U., Walker, A. T., Selvaggi, A. C., Shinnick, J. D., Schulte, M. C. C., Atchley-Challenner, R., Horwitz, I. L., Foulkes, S. A., Aberg, A. J., Adolph, L. N.,...Zisis, S. (2023). Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *Jama*, 329(22), 1934. <https://doi.org/10.1001/jama.2023.8823>
- The Lancet. (2020). Facing up to long COVID. *Lancet*, 396(10266), 1861. [https://doi.org/10.1016/s0140-6736\(20\)32662-3](https://doi.org/10.1016/s0140-6736(20)32662-3)
- U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion. (2025). *Healthy People 2030: Social Determinants of Health*. Retrieved April 15 from <https://odphp.health.gov/healthypeople/priority-areas/social-determinants-health/literature-summaries>
- Ursescu, C., Teodoru, G., Bucurica, S., Nica, R. I., Lazăr Ş, D., Popescu, M. N., Ciobanu, I., & Berteanu, M. (2024). Using the ClinFIT COVID-19 Instrument to Assess the Functional Impairments Specific to Post-COVID-19 Patients in Romania. *Diagnostics (Basel)*, 14(14). <https://doi.org/10.3390/diagnostics14141540>
- Vanichkachorn, G., Newcomb, R., Cowl, C. T., Murad, M. H., Breeher, L., Miller, S., Trenary, M., Neveau, D., & Higgins, S. (2021). Post-COVID-19 syndrome (long haul syndrome): Description of a multidisciplinary clinic at Mayo Clinic and characteristics of the initial patient cohort. *Mayo Clin Proc*, 96(7), 1782-1791. <https://doi.org/10.1016/j.mayocp.2021.04.024>
- Vasilevskaya, A., Mushtaque, A., Tsang, M. Y., Alwazan, B., Herridge, M., Cheung, A. M., & Tartaglia, M. C. (2023). Sex and age affect acute and persisting COVID-19 illness. *Sci Rep*, 13(1), 6029. <https://doi.org/10.1038/s41598-023-33150-x>
- Venkatesan, P. (2021). NICE guideline on long COVID. *Lancet Respir Med*, 9(2), 129. [https://doi.org/10.1016/s2213-2600\(21\)00031-x](https://doi.org/10.1016/s2213-2600(21)00031-x)
- Verveen, A., Verfaillie, S. C. J., Visser, D., Koch, D. W., Verwijk, E., Geurtsen, G. J., Roor, J., Appelman, B., Boellaard, R., van Heugten, C. M., Horn, J., Hulst, H. E., de Jong, M. D., Kuut, T. A., van der Maaden, T., van Os, Y. M. G., Prins, M., Visser-Meily, J. M. A., van Vugt, M.,...Knoop, H. (2024). Neuropsychological functioning after COVID-19: minor differences between individuals with and without persistent complaints after SARS-CoV-2 infection. *Clin Neuropsychol*, 1-16. <https://doi.org/10.1080/13854046.2024.2379508>
- Watters, K., Marks, T. S., Edwards, D. F., Skidmore, E. R., & Giles, G. M. (2021). A framework for addressing clients' functional cognitive deficits after COVID-19. *Am J Occup Ther*, 75(Supplement_1), 7511347010p7511347011-7511347010p7511347017. <https://doi.org/10.5014/ajot.2021.049308>
- Wei, T. (2021). *Visualization of a Correlation Matrix (corrplot)*. In (Version 0.92) R Foundation for Statistical Computing.

- Wilson, R. S., & Bennett, D. A. (2017). How Does Psychosocial Behavior Contribute to Cognitive Health in Old Age? *Brain Sci*, 7(6). <https://doi.org/10.3390/brainsci7060056>
- World Health Organization. *Coronavirus disease (COVID-19) pandemic*. Retrieved February 1, 2025 from <https://www.who.int/europe/emergencies/situations/covid-19>
- World Health Organization. (2001). *International Classification of Functioning, Disability and Health (ICF)*. WHO. <https://www.who.int/classifications/icf/en/>
- World Health Organization. (2025a). *Post COVID-19 condition (Long COVID)*. Retrieved February 1, 2025 from <https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition>
- World Health Organization. (2025b). *WHO Coronavirus (COVID-19) Dashboard*. Retrieved January 31, 2025 from <https://covid19.who.int/>
- Zeng, C., Schlueter, D. J., Tran, T. C., Babbar, A., Cassini, T., Bastarache, L. A., & Denny, J. C. (2024). Comparison of phenomic profiles in the All of Us Research Program against the US general population and the UK Biobank. *J Am Med Inform Assoc*, 31(4), 846-854. <https://doi.org/10.1093/jamia/ocad260>
- Zhang, H., Zang, C., Xu, Z., Zhang, Y., Xu, J., Bian, J., Morozyuk, D., Khullar, D., Zhang, Y., Nordvig, A. S., Schenck, E. J., Shenkman, E. A., Rothman, R. L., Block, J. P., Lyman, K., Weiner, M. G., Carton, T. W., Wang, F., & Kaushal, R. (2023). Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med*, 29(1), 226-235. <https://doi.org/10.1038/s41591-022-02116-3>