EMERGING INFECTIOUS DISEASES®

U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

Infection-Associated Chronic Conditions and Illnesses

Winter 2025 Supplement

Patrick Mead, *Untitled*, 2016. Digital mosaic. Image courtesy of the artist.

EMERGING INFECTIOUS DISEASES®

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Infection-Associated Chronic Conditions and Illnesses **Winter 2025**

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Patrick Mead, *Untitled*, 2016. Digital mosaic. Image courtesy of the artist.

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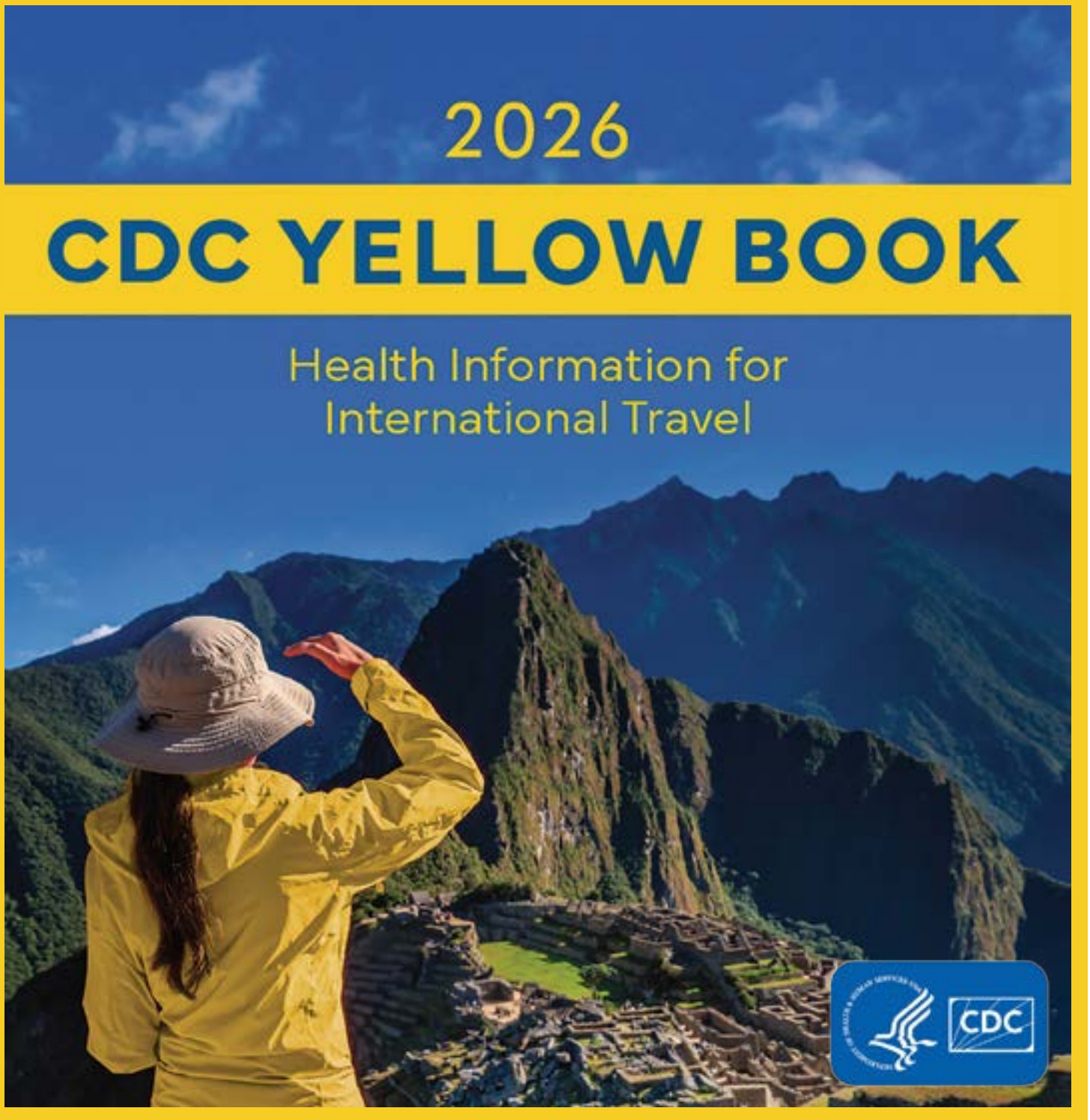

Launch of CDC Yellow Book 2026– A Trusted Travel Medicine Resource

CDC is pleased to announce the launch of the **CDC Yellow Book 2026**. The CDC Yellow Book is a resource containing the U.S. government's travel medicine recommendations and has been trusted by the travel medicine community for over 50 years. Healthcare professionals can use the print and digital versions to find the most up-to-date travel medicine information to better serve their patients' healthcare needs.

The CDC Yellow Book is available online now at www.cdc.gov/yellowbook and in print starting in June 2025 through Oxford University Press and other major online booksellers.

Progress Toward Understanding Infection-Associated Chronic Conditions and Illnesses

Anthony E. Fiore

Infection-associated chronic conditions and illnesses (IACCIs) are a variety of health consequences that occur after an acute infection (*1*). Chronic sequelae considered IACCIs include various combinations of infection-associated organ damage, autoimmune conditions, and persistent unexplained systemic symptoms, such as debilitating fatigue, postexertional malaise, cognitive impairment, musculoskeletal pain, and sleep disorders (*1*). The health and societal impact of long COVID over the past 5 years, and recognition of long COVID as an IACCI, has reinvigorated the study of these poorly understood disorders (*2*–*7*).

This supplement of *Emerging Infectious Diseases* features a series of studies undertaken by the Centers for Disease Control and Prevention to increase awareness and understanding of IACCIs and to highlight available prevention and treatment resources for public health practitioners, healthcare providers, and the public. The supplement includes research regarding IACCIs occurring after infections caused by SARS-CoV-2 (COVID-19), respiratory syncytial virus, *Giardia lamblia*, *Coccidioides immitis*, *Borrelia burgdorferi* and other *Borrelia* species (Lyme disease), and West Nile virus. The studies describe various approaches to characterizing IACCIs, which include measuring prevalence, persistence, management, and duration of a defined syndrome; assessing absenteeism attributable to an IACCI; and estimating risk for life-threatening sequalae, such as increased thrombotic events.

IACCIs can emerge with a heterogenous range of signs, symptoms, and laboratory results and are not consistent in duration, presentation, or severity, even when grouped according to the known or suspected previous infection, suggesting that multiple underlying mechanisms could be responsible for illness (*1*,*2*). Suspected mechanisms include continued immune stimulation from antigens or continued infection in a sequestered body site that cannot be sampled, reactivation of latent viruses, autoimmune responses, microbiome dysbiosis, persistent tissue damage, disordered coagulation, and disrupted nerve signaling (*1*,*2*). IACCIs cause marked disruption to a patient's ability to return to work or school or to resume their life as it was before the inciting infection. Complicating the frustrated patient's predicament, clinicians attempting unproven treatments (e.g., repeated antibiotic courses) might exacerbate illness by introducing additional risks or temporarily masking potentially treatable causes.

The medical community now has a framework for how research on IACCIs should be developed. In 2024, the National Academies of Science, Engineering, and Medicine (NASEM) proposed a definition to harmonize terminology and measurement approaches and to formulate a research agenda for "infection-associated chronic illnesses" (authors in this supplement have used the term IACCI to also include health conditions that also are debilitating) (*2*). In terms of IACCIs attributable to COVID-19, NASEM proposed a long COVID definition, and the American Academy of Physical Medicine and Rehabilitation established the Multi-Disciplinary Post-Acute Sequelae of SARS-CoV-2 Infection Collaborative to develop multidisciplinary guidance on clinical management (*8*). Of note, many of the IACCIs discussed in this supplement have similarities to or include myalgia encephalomyelitis and chronic fatigue syndrome in their definition. Although questions remain regarding the pathophysiology of each, adapting clinical management of such syndromes to IACCIs may be useful (*9*,*10*).

Patients suffering with IACCIs often receive misdiagnoses or become stigmatized, both of which impede potentially beneficial clinical management strategies. Without an understanding of pathophysiology, diagnosis, treatment, and care for patients with

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IACCIs, healthcare providers will continue struggling to provide patients with accurate diagnoses and potentially effective treatment and support. This supplement aims to provide additional insights into several IACCIs and focus more attention on these poorly understood conditions.

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References

1. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med. 2022;28:911–23. https://doi.org/10.1038/s41591-022-01810-6
2. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Board on Global Health; Forum on Neuroscience and Nervous System Disorders; Forum on Microbial Threats. Toward a common research agenda in infection-associated chronic illnesses: proceedings of a workshop. Snair M, Liao J, Ashby E, Biffl C, editors. Washington: National Academies Press [cited 2025 Aug 5]. https://doi.org/10.17226/27462
3. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Global Health; Board on Health Sciences Policy; Committee on Examining the Working Definition for Long COVID. A long COVID definition: a chronic, systemic disease state with profound consequences. Goldowitz I, Worku T, Brown L, Fineberg HV, editors. Washington: National Academies Press [cited 2025 Aug 5]. https://doi.org/10.17226/27768
4. Ewing AG, Salamon S, Pretorius E, Joffe D, Fox G, Bilodeau S, et al. Review of organ damage from COVID and long COVID: a disease with a spectrum of pathology. Med Rev (Berl). 2024;5:66–75. https://doi.org/10.1515/mr-2024-0030
5. Vahratian A, Saydah S, Bertolli J, Unger ER, Gregory CO. Prevalence of post-COVID-19 and activity-limiting post-COVID-19 condition among adults. JAMA Netw Open. 2025; 7:e2451151. https://doi.org/10.1001/jamanetworkopen.2024.51151
6. Perlis RH, Lunz Trujillo K, Safarpour A, Santillana M, Ognyanova K, Druckman J, et al. Association of post–COVID-19 condition symptoms and employment status. JAMA Netw Open. 2023;6:e2256152. https://doi.org/10.1001/jamanetworkopen.2022.56152
7. Department of Health and Human Services, Office of the Assistant Secretary for Health. National Research Action Plan on Long COVID. 2022 [cited 2025 Sept 4]. https://www.autoimmuneinstitute.org/wp-content/uploads/2025/03/The-National-Research-Action-Plan-on-Long-COVID.pdf
8. Cheng AL, Herman E, Abramoff B, Anderson JR, Azola A, Baratta JM, et al. Multidisciplinary collaborative guidance on the assessment and treatment of patients with long COVID: A compendium statement. PM R. 2025;17:684–708. https://doi.org/10.1002/pmrj.13397
9. Unger ER, Lin JS, Brimmer DJ, Lapp CW, Komaroff AL, Nath A, et al. CDC Grand Rounds: chronic fatigue syndrome—advancing research and clinical education. MMWR Morb Mortal Wkly Rep. 2016;65:1434–8. https://doi.org/10.15585/mmwr.mm655051a4
10. Centers for Disease Control and Prevention. Myalgic encephalomyelitis/chronic fatigue syndrome healthcare provider toolkit, May 13, 2024 [cited 2025 Aug 5] https://www.cdc.gov/me-cfs/hcp/toolkit/index.html

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Thrombotic Events and Stroke in the Year After COVID-19 or Other Acute Respiratory Infection

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Previous studies have documented an increased risk for thrombotic events 30 days after COVID-19 infection, but less is known about this risk beyond 30 days or compared with risk after other infectious acute respiratory illnesses (ARIs). By using PCORnet data from April 1, 2022–April 30, 2023, we compared the incidences of thrombotic events in the year after COVID-19 illness with other ARI diagnoses in hospitalized and nonhospitalized patients. Overall, the risk for any thrombotic event was higher among patients with COVID-19 compared with patients with other ARIs (incidence ratio 1.63; p<0.05). Nonhospitalized patients with COVID-19 had a 73% increased risk for a thrombotic event in the year after acute illness compared with nonhospitalized patients with ARI (p<0.05). The increased risk for thrombotic events in the year after COVID-19 emphasizes the need for stroke awareness for patients and healthcare professionals.

Stroke and thrombotic events are known sequelae of respiratory viral illnesses, including influenza and COVID-19 (*1*–*5*). Since the onset of the COVID-19 pandemic, studies have documented an increased risk for embolic events, including ischemic stroke, in the first 30 days after a COVID-19 infection, with a ≥2-fold greater risk compared with people without COVID-19 (*6*,*7*). Several studies have found the risk for ischemic stroke is higher in those with severe acute illness (*8*,*9*). Among children, who have fewer strokes and thromboembolic events, 2 studies found an increased risk for stroke after COVID-19 (*10*,*11*). Although the mechanisms remain under investigation, the hypothesized pathophysiology that leads to increased stroke and thromboembolic events among patients with COVID-19 include endothelial cell damage (*12*,*13*), a viral-triggered exaggerated immune response and cytokine storm (*14*), and persistent microthrombi formation and fibrin amyloid microclots (*15*,*16*).

Limited information exists on stroke and thrombotic events in the postillness period beyond 30 days after COVID-19 infection. Many patients with risk factors for stroke, such as hypertension, high cholesterol, and smoking, might recover from COVID-19 but experience an elevated risk for thrombotic events beyond 30 days. In addition, whether the risk for stroke and thrombotic events in the months after SARS-CoV-2 infections is similar to that for other respiratory viruses (e.g., influenza) is unknown (*17*,*18*). Further, previous studies have focused on earlier SARS-CoV-2 variants (*19*,*20*), some of which were conducted before recommendations for thromboprophylaxis during hospitalization for COVID-19 (*21*), widespread use of COVID-19 treatments, or COVID-19 vaccination (*19*,*22*). Determining the incidence of stroke and thrombotic events in patients with COVID-19 or acute respiratory illnesses (ARI) in the 31–365 days after illness could help clarify long-term risk among patients with COVID-19 and point to possible interventions for prevention. We investigated incidence of thromboembolic events and stroke in the 31–365 days after COVID-19 diagnosis, both overall and by patient hospitalization status.

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Methods

We used data from the National Patient-Centered Clinical Research Network (PCORnet), a national research network containing comprehensive electronic health record data from healthcare systems across the United States (*23*). We examined the overall incidence of thromboembolic events and stroke, as well as the specific incidence of ischemic stroke, deep vein thrombosis (DVT), hemorrhagic stroke, transient ischemic attack (TIA), and cerebral venous sinus thrombosis (CVST), in the 31–365 days after COVID-19 diagnosis, overall and by patient hospitalization status, for the period April 1, 2022–April 30, 2023. We then used the incidences after an acute respiratory illness (ARI) in the same period as a comparison group. Because of a nonbillable diagnosis code being mistakenly used in the initial data pull, pulmonary embolism (PE) was not included in the analysis. Therefore, a patient with only a PE and no DVT diagnosed in the electronic health record (EHR) would not have been included in this analysis.

PCORnet provides data infrastructure to support distributed research across participating healthcare systems (*24*). PCORnet uses a Common Data Model to enable data interoperability and centralized querying of longitudinal EHR data by using modular statistical programs. Queries were performed at each participating healthcare system by using patient-level EHR data; results were transmitted to investigators in aggregated tabular format. Patient-level data were stored behind institutional firewalls.

This activity was included in a larger surveillance program funded through a cooperative agreement by the Centers for Disease Control and Prevention (CDC) and was deemed exempt from review under the public health surveillance provision of the Common Rule by the Harvard Pilgrim Health Care institutional review board. The design and analysis adhere to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (*25*). This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy (See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq).

We selected the period April 1, 2022–April 30, 2023, to account for potential temporal confounding caused by changing treatment and prevention availability and changing predominant SARS-CoV-2 variants. We included patients who were ≥5 years of age; had COVID-19 or other ARI during April 1, 2022–April 30, 2023; had no evidence of pregnancy in the prior year; and had evidence of an encounter in the healthcare system in the 30–540 days before the COVID-19 or ARI diagnosis. An encounter with the healthcare system from 30–540 days prior was required to attempt to capture patient medical history, including prior strokes or thrombotic events. We stratified data by age, sex, race (American Indian or Alaska Native, Asian or Native Hawaiian or Pacific Islander, Black or African American, multiple races or other, White, or missing), and ethnicity (Hispanic, non-Hispanic, unknown, other, or missing).

Patients with COVID-19 were identified by a positive antigen or PCR laboratory record with a positive, detected, or presumptive positive result; receipt of a COVID-19 medication (monoclonal antibodies, nirmatrelvir/ritonavir, molnupiravir, or remdesivir); or COVID-19 diagnostic codes U07.1 or U07.2 from the International Classification of Diseases, 10th Revision, Clinical Modification. Patients with ARI were identified by an ARI or influenza diagnostic code (Appendix Table 1, http://wwwnc.cdc.gov/EID/article/32/1/25-0630-App1.pdf), receipt of oseltamivir or baloxavir, and no COVID-19 diagnosis from 365 days prior through 14 days after ARI diagnosis. Patients diagnosed with ischemic stroke, DVT, hemorrhagic stroke, TIA, or CVST in the 18 months before COVID-19 or ARI diagnosis were excluded from the cohorts when measuring the respective outcomes to better capture incident cases rather than prevalence or recurrent cases (*26*,*27*).

Among COVID-19 and ARI patients, cohorts were created on the basis of hospitalization status, whether or not a stroke or thrombotic event occurred, and the postacute period of focus. We calculated the incidence of any stroke or thrombotic event and the disaggregated categories of ischemic stroke, DVT, hemorrhagic stroke, TIA, or CVST in the time intervals after COVID-19 or ARI diagnosis: 31–90 days, 91–180 days, 181–365 days, and 31–365 days. Results were stratified according to patient hospitalization status (hospitalized vs. nonhospitalized from 1 day before through 16 days after COVID-19 or ARI diagnosis to reflect the period of acute illness). We chose those time intervals to characterize the postacute phase of illness (31–90 days), to remain consistent with the definition of long COVID (having symptoms for ≥90 days after COVID-19 diagnosis) (*28*), and to determine when events are most likely to occur (e.g., 91–180 days vs. 181–365 days). We used χ^2 testing to assess significant differences at $p<0.05$.

We calculated the incidence of any event per 10,000 patients. We calculated each ischemic stroke, DVT, hemorrhagic stroke, TIA, and CVST event among patients with COVID-19 or ARI and

stratified by hospitalization status and time from acute COVID-19 or ARI diagnosis. Within each period, we calculated the 30-day incidence. We calculated incidence ratios and 95% CIs on the basis of the normal distribution to compare the risk for stroke or TIA after COVID-19 versus ARI. We indicated significance at $p<0.05$ by using *Z*-test to assess the differences of proportions.

Results

A total of 1,132,355 patients were diagnosed with COVID-19 and 2,301,209 patients with ARI (Appendix Table 2) during the study period. A higher proportion of patients who had COVID-19 were in older age groups ($p<0.0001$ by χ^2 test) and had more chronic conditions ($p<0.0001$ by χ^2 test) compared with patients who had ARI. Among patients diagnosed with COVID-19, the most common age groups were 50–64 (25.8%) and ≥65 years (32.5%); 5–17 years (34.0%) was the largest age group among patients with ARI. There was a greater percentage of females in both the COVID-19 (60.4% vs. 39.6% male) and ARI (59.8% vs. 40.2% male) cohorts. The most common race among patients with COVID-19 and ARI was White (COVID-19, 70.7%; ARI, 69.3%), followed by Black or African American (COVID-19, 14.5%; ARI, 15.1%). Most patients were non-Hispanic (COVID-19, 73.6%; ARI, 71.1%). The most common conditions in both COVID-19 and ARI patients in the 18 months before diagnosis were hypertension (COVID-19, 38.6%; ARI, 23.2%), hyperlipidemia (COVID-19, 30.2%; ARI, 17.4%), and diabetes (COVID-19, 16.8%; ARI, 10.4%) (Appendix Table 2).

A total of 17,606 patients with COVID-19 and 21,871 patients with ARI experienced an event (ischemic stroke, DVT, hemorrhagic stroke, TIA, or CVST) in the 31–365 days after COVID-19 or ARI diagnosis (Appendix Table 3). Adults ≥50 years of age were most of the patients with COVID-19 (88.2%). There was no significant difference between hospitalized (88.4%) and nonhospitalized (88.1%) COVID-19 patients ≥50 years of age ($p = 0.63$). Adults ≥50 years of age were most of the patients with ARI (83.5%), and this age group also represented most hospitalized patients (85.4%) ($p<0.0001$). Combining hospitalized and nonhospitalized patients, patients ≥50 years of age made up a greater percentage of COVID-19 patients (88.2%) than ARI patients (83.5%) in the same age group ($p<0.0001$).

Among both COVID-19 and ARI hospitalized patients who experienced an event in the 31–365 days after acute illness, underlying hypertension (COVID-19, 82.1%; ARI, 81.8%), hyperlipidemia (COVID-19, 60.0%; ARI, 60.1%), diabetes (COVID-19, 45.6%; ARI, 43.2%), coronary artery disease (COVID-19, 41.6%; ARI, 42.1%), and chronic kidney disease (COVID-19, 46.3%; ARI, 41.7%) were all more common than among nonhospitalized patients ($p<0.0001$) (Appendix Table 3). When comparing all COVID-19 patients who experienced an event in the 31–365 days after acute illness to all ARI patients who experienced a stroke or thrombotic event within 31–365 days after acute illness, a history of chronic kidney disease ($p<0.0001$), hyperlipidemia ($p = 0.0019$), and alcohol abuse ($p = 0.0103$) were statistically more common among COVID-19 patients. We found no significant difference between the percentage of COVID-19 and ARI patients with a history of coronary artery disease ($p = 0.6835$), diabetes ($p = 0.9171$), or hypertension ($p = 0.2757$).

Among COVID-19 patients, hospitalized patients were also more likely to have received anticoagulants in the prior 18 months (16.8%) than were nonhospitalized patients (10.7%) ($p<0.0001$). Among ARI patients, hospitalized patients were more likely to have received anticoagulants (16.4%) than were nonhospitalized patients (10.0%) ($p<0.0001$). When comparing all COVID-19 patients to all ARI patients, more COVID-19 patients had received antiplatelet medications in the 18 months prior (COVID-19, 9.1%; ARI, 8.1%) ($p = 0.0009$), but there was no statistical difference in the percentage of patients previously having received anticoagulants (COVID-19, 11.9%; ARI, 11.4%) ($p = 0.124$).

Overall, incidence of all events decreased as time increased after acute illness: 31–90 days, 20 events/10,000 COVID-19 patients and 13 events/10,000 ARI patients; 91–180 days, 19 events/10,000 COVID-19 patients and 12 events/10,000 ARI patients; 181–365 days, 16 events/10,000 COVID-19 patients and 10 events/10,000 ARI patients (Figure; Appendix Table 4). For all time intervals, incidence of all events was higher among patients who were hospitalized than patients who were nonhospitalized, and higher among patients with COVID-19 than patients with ARI. DVT and ischemic stroke were the most common events diagnosed in the year after acute illness for both COVID-19 (4 DVT/10,000 patients and 6 ischemic strokes/10,000 patients) and ARI (3 DVT/10,000 patients and 3 ischemic strokes/10,000 patients) (Appendix Table 2). DVT and ischemic stroke incidence was also higher among patients hospitalized with COVID-19 versus patients who were nonhospitalized and patients diagnosed with ARI; rates for those events decreased farther out from the acute illness (Appendix Table 4).

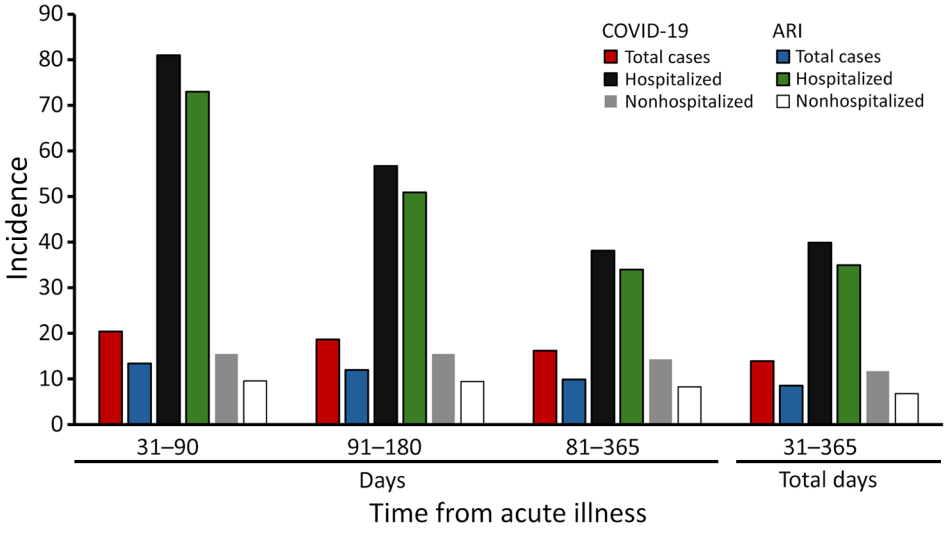

Figure. Thirty-day incidence of all events per 10,000 patients by acute illness, hospitalization status, and time from acute illness in a study of thrombotic events and stroke in the year after COVID-19 or other acute respiratory infection. We defined events as cerebral venous sinus thrombosis, deep vein thrombosis, hemorrhagic stroke, ischemic stroke, or transient ischemic attack.

The unadjusted risk for any event was higher among patients with COVID-19 compared with patients with ARI regardless of hospitalization status or time interval after acute illness (hospitalized patient incidence ratio 1.11 for 31–90 days and 91–180 days, 1.12 for 181–365 days; nonhospitalized patient incidence ratio 1.62 for 31–90 days, 1.64 for 91–180 days, 1.73 for 181–365 days) (p<0.0001) (Table). The unadjusted risk for ischemic stroke was higher among patients with COVID-19 compared with patients with ARI in every time interval and among both hospitalized and nonhospitalized patients (hospitalized patient incidence ratio 1.13 for 31–90 days, 1.26 for 91–180 days, 1.12 for 181–365 days; nonhospitalized patient incidence ratio 1.65 for 31–90 days, 1.68 for 91–180 days, 1.77 for 181–365 days) (p<0.0001). Hospitalized patients with COVID-19 had a 14% increased crude risk for any event measured in the 31–365 days after acute illness compared with patients with ARI (p<0.0001) (Table). Although the overall incidence of all events for nonhospitalized patients compared with hospitalized patients was lower for both COVID-19 and ARI (Appendix Table 3), nonhospitalized patients with COVID-19 had a 73% increased crude risk for any event in the year after acute illness compared with nonhospitalized patients with ARI (p<0.0001) (Table). Among hospitalized patients, when comparing risk by specific outcomes, there was an increased risk for DVT (11%, p<0.0001), ischemic stroke (20%, p<0.0001), and TIA (27%, p<0.0001) among COVID-19 versus ARI patients but no significant difference for CVST or hemorrhagic stroke.

Discussion

Among patients with COVID-19 and ARI illness, the greatest risk for incident thrombotic events, including stroke, occurred within 31–90 days after acute illness. Incident thrombotic events continued up to a year after acute illness. Overall, hospitalized patients had the highest incidence of postillness events, and patients with COVID-19 had higher incidence of thrombotic events compared with patients with ARI, regardless of hospitalization status.

Although the incidence of all events decreased as the time from acute illness increased, overall, increased awareness of risk for such events in COVID-19 patients is justified well past 1 month after acute infection. It is critical that healthcare providers maintain awareness of the risk for stroke and thromboembolic events in patients even after recovery from acute COVID-19 infection and monitor those at risk, particularly patients with known risk factors such as hypertension, high cholesterol, diabetes, obesity, smoking, sedentary lifestyle, or previous venous thromboembolisms. Current clinical guidelines recommend thromboprophylaxis during hospitalization for many adults hospitalized with COVID-19 but not after discharge or for those treated in outpatient settings (*29*). A small trial in 2021 showed improved clinical outcomes with thromboprophylaxis after hospital discharge in high-risk patients (*30*), whereas another trial published in 2023 showed no significant difference in outcomes between COVID-19 outpatients who did and did not receive thromboprophylaxis and was stopped early because of low thromboembolic incidence rates (*31*). The risk of bleeding from anticoagulation would ideally be balanced with thromboembolic event prevention. However, this study was not designed to determine the usefulness of thromboprophylaxis or other risk modifications after hospital discharge or in outpatient settings; further study is needed to inform that determination.

Rates for all events we tracked—DVT, hemorrhagic stroke, ischemic stroke, and TIA—were higher among hospitalized than nonhospitalized patients with COVID-19 across all time intervals. The higher rates likely reflect the higher hospitalization rates among patients at greater risk for severe COVID-19, such as those ≥50 years of age or with multiple comorbidities. In addition, the higher rates for all events suggest an increased risk for stroke and thromboembolic events associated with more severe acute illness (*8*,*9*,*32*,*33*). Determining the biological mechanisms driving the increased incidence of stroke and thromboembolic events after COVID-19 infection could help identify patients at higher risk and inform prevention strategies. Current thromboprophylaxis recommendations in patients with COVID-19 are limited to select hospitalized patients (*34*–*37*).

Of note, the risk ratios for all events in COVID-19 versus ARI patients were higher among the nonhospitalized group in this analysis, with a risk ratio of 1.73 (95% CI 1.71–1.76) for 31–365 days among nonhospitalized patients versus 1.14 (95% CI 1.10–1.18) in hospitalized patients. Many earlier studies focused on the initial phases of the COVID-19 pandemic, primarily during the pre-Delta and Delta variant periods (*19*,*20*). In contrast, this study provides more recent data from the Omicron-dominant period, characterized by high population immunity because of extensive vaccination and prior infections. Those updated findings could provide valuable insights for future studies and enhance early recognition and effective management of DVT and stroke, while informing the long-term cardiovascular consequences of COVID-19.

This study underscores the importance of COVID-19 vaccination and other prevention and treatment efforts to reduce risk for severe illness and subsequent adverse outcomes and conditions (*38*). In addition, given the higher risk for post-COVID conditions with more severe COVID-19 acute illness (*39*,*40*), our data provide yet another reason to increase efforts targeted at prevention and improved management of chronic conditions that increase the risk for severe COVID-19, stroke, and thrombotic complications. Comprehensive chronic disease management, combined with COVID-19 and ARI prevention strategies, can help reduce the incidence of postillness DVT and stroke, ultimately benefiting those most vulnerable to complications. Patient education is also crucial, particularly an emphasis on the benefits of vaccinations for those with underlying risk factors or comorbidities.

The first limitation of this study is that this analysis does not include biological measurements or pathophysiology information to assign direct causation of SARS-CoV-2 infection to stroke incidence. Second, because of the aggregated data for this analysis, we could not adjust for patient level potential confounders. Compared with patients with ARI, COVID-19

Table. Unadjusted incidence ratios of stroke and thrombotic events for patients with COVID-19 compared with ARI by hospitalization status and days from acute illness*

	Unadjusted ratio of COVID-19 to ARI (95% CI)		
All events	All patients	Hospitalized	Nonhospitalized
All events 31–90 d and no record in 18 mo prior	**1.52 (1.48–1.56)**	**1.11 (1.04–1.18)**	**1.62 (1.58–1.67)**
Ischemic stroke	**1.55 (1.49–1.61)**	**1.13 (1.02–1.25)**	**1.65 (1.58–1.73)**
Deep vein thrombosis	**1.51 (1.44–1.57)**	**1.12 (1.01–1.23)**	**1.62 (1.53–1.7)**
Hemorrhagic stroke	**1.47 (1.36–1.58)**	0.99 (0.81–1.16)	**1.71 (1.57–1.85)**
Transient ischemic attack	**1.56 (1.47–1.65)**	1.2 (0.99–1.41)	**1.6 (1.51–1.7)**
Cerebral venous sinus thrombosis	1.09 (0.72–1.45)	0.92 (0.31–1.53)	1.09 (0.63–1.54)
All events 91–180 d and no record in 18 mo prior	**1.55 (1.52–1.59)**	**1.11 (1.04–1.18)**	**1.64 (1.61–1.68)**
Ischemic stroke	**1.63 (1.58–1.68)**	**1.26 (1.16–1.37)**	**1.68 (1.62–1.74)**
Deep vein thrombosis	**1.5 (1.44–1.56)**	1.08 (0.97–1.19)	**1.6 (1.53–1.66)**
Hemorrhagic stroke	**1.43 (1.34–1.53)**	0.91 (0.73–1.09)	**1.62 (1.51–1.73)**
Transient ischemic attack	**1.56 (1.49–1.64)**	1.15 (0.94–1.35)	**1.61 (1.53–1.69)**
Cerebral venous sinus thrombosis	**1.35 (1.03–1.66)**	0.87 (0.24–1.49)	**1.49 (1.12–1.85)**
All events 181–365 d and no record in 18 mo prior	**1.64 (1.62–1.66)**	**1.12 (1.07–1.18)**	**1.73 (1.71–1.76)**
Ischemic stroke	**1.68 (1.64–1.72)**	**1.16 (1.07–1.25)**	**1.77 (1.73–1.82)**
Deep vein thrombosis	**1.62 (1.57–1.66)**	1.08 (0.98–1.19)	**1.73 (1.68–1.78)**
Hemorrhagic stroke	**1.58 (1.51–1.65)**	0.92 (0.77–1.08)	**1.79 (1.7–1.87)**
Transient ischemic attack	**1.69 (1.63–1.74)**	**1.34 (1.18–1.49)**	**1.72 (1.66–1.77)**
Cerebral venous sinus thrombosis	**1.38 (1.16–1.6)**	1.13 (0.6–1.66)	**1.4 (1.15–1.65)**
All events 31–365 d and no record in 18 mo prior	**1.63 (1.61–1.65)**	**1.14 (1.1–1.18)**	**1.73 (1.71–1.76)**
Ischemic stroke	**1.67 (1.64–1.7)**	**1.2 (1.14–1.27)**	**1.76 (1.73–1.8)**
Deep vein thrombosis	**1.59 (1.55–1.62)**	**1.11 (1.04–1.18)**	**1.7 (1.66–1.74)**
Hemorrhagic stroke	**1.56 (1.51–1.62)**	0.98 (0.87–1.09)	**1.77 (1.7–1.84)**
Transient ischemic attack	**1.42 (1.37–1.46)**	**1.27 (1.16–1.39)**	**1.42 (1.37–1.46)**
Cerebral venous sinus thrombosis	**1.36 (1.18–1.55)**	0.95 (0.53–1.37)	**1.44 (1.23–1.65)**

*Bold indicates statistically significant ratios. ARI, acute respiratory illness

patients were in older age groups and had more chronic conditions; adjusting for those potential confounders might attenuate the differences across the groups. Although unadjusted risk ratios for all events in COVID-19 versus ARI patients were higher among the nonhospitalized group, those are relative risks, and the difference in risks might be influenced by selection bias. Hospitalized patients are more likely to get virus-specific testing to guide therapy, and patients with mild illness might have visited a provider for a diagnosis, but those with mild illness are less likely to get tested with a virus-specific test compared with those with moderate symptoms (*41*,*42*). Therefore, it is possible that hospitalized patients were more likely to be correctly categorized between COVID-19 and other ARIs, compared with those who were only seen as outpatients and might not have had definitive testing. The nonhospitalized ARI cohort was younger and healthier than the nonhospitalized COVID-19 cohort, suggesting a lower baseline risk of thromboembolism and stroke. That age difference might have led to an overestimation of the effect of COVID-19 on the thromboembolic and stroke risk. Third, only patients who had access to and sought clinical care for their acute COVID-19 or ARI illness or subsequent event were included, likely leading to the exclusion of some people with mild or asymptomatic infections and persons who never received laboratory testing for COVID-19 or ARI. Fourth, persons with mild DVT or TIA who did not seek care were also not included. Fifth, because of a coding error identified that could not be corrected after the data was received, this analysis also did not include PE as an outcome. Patients with DVT who only saw a provider after a PE developed might have been diagnosed with PE alone, leading to potential undercount of DVT cases. Sixth, excluding persons with a prior history of events (DVT, ischemic stroke, hemorrhagic stroke, PE, or TIA) limits the representativeness of the analytic sample and therefore limits the generalizability of our findings to the US population. Finally, the study period (April 1, 2022–April 30, 2023) includes various Omicron sublineages but was not designed to align with specific sublineage periods.

Future analyses with line level data available could control for patients' chronic conditions to better identify thrombotic events attributable to viral infection. Separating out specific pathogens, such as influenza, from other ARI could also help quantify the risks of specific viruses.

In conclusion, this study identified a possible elevated risk for thrombotic events, including stroke, up to a year after COVID-19, especially among patients hospitalized with COVID-19. This risk appears to remain higher for patients with COVID-19 than for those with ARI. Future multivariate analysis with adjustments for demographic and medical differences is needed. Continued surveillance and epidemiologic studies are essential to monitor these long-term risks and assess mitigation strategies. This study also underscores the importance of stroke awareness. By recognizing stroke signs and symptoms, such as by using the FAST acronym (*43*), patients and providers can help ensure timely intervention, potentially improving recovery outcomes and reducing disability and mortality (*44*).

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References

1. Bahouth MN, Venkatesan A. Acute viral illnesses and ischemic stroke: pathophysiological considerations in the era of the COVID-19 pandemic. Stroke. 2021;52:1885–94. https://doi.org/10.1161/STROKEAHA.120.030630
2. Nguyen TQ, Vlasenko D, Shetty AN, Reid CM, Clothier HJ, Buttery JP. Laboratory-confirmed respiratory viral infection triggers for acute myocardial infarction and stroke: systematic review protocol. PLoS One. 2024;19:e0302748. https://doi.org/10.1371/journal.pone.0302748
3. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004;351:2611–8. https://doi.org/10.1056/NEJMoa041747
4. Babkina AS, Pisarev MV, Grechko AV, Golubev AM. Arterial thrombosis in acute respiratory infections: an underestimated but clinically relevant problem. J Clin Med. 2024;13:6007. https://doi.org/10.3390/jcm13196007
5. Ward A, Sarraju A, Lee D, Bhasin K, Gad S, Beetel R, et al. COVID-19 is associated with higher risk of venous thrombosis, but not arterial thrombosis, compared with influenza: insights from a large US cohort. PLoS One. 2022; 17:e0261786. https://doi.org/10.1371/journal.pone.0261786
6. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly AM. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in

Sweden: a self-controlled case series and matched cohort study. Lancet. 2021;398:599–607. https://doi.org/10.1016/S0140-6736(21)00896-5
7. Tu TM, Seet CYH, Koh JS, Tham CH, Chiew HJ, De Leon JA, et al. Acute ischemic stroke during the convalescent phase of asymptomatic COVID-2019 infection in men. JAMA Netw Open. 2021;4:e217498. https://doi.org/10.1001/jamanetworkopen.2021.7498
8. Siepmann T, Sedghi A, Simon E, Winzer S, Barlinn J, de With K, et al. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. Eur J Neurol. 2021;28:238–47. https://doi.org/10.1111/ene.14535
9. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: a systematic review and meta-analysis. Int J Stroke. 2021;16:137–49. https://doi.org/10.1177/17474930 20972922
10. Kompaniyets L, Bull-Otterson L, Boehmer TK, Baca S, Alvarez P, Hong K, et al. Post-COVID-19 symptoms and conditions among children and adolescents—United States, March 1, 2020–January 31, 2022. MMWR Morb Mortal Wkly Rep. 2022;71:993–9. https://doi.org/10.15585/mmwr.mm7131a3
11. Vielleux MJ, Swartwood S, Nguyen D, James KE, Barbeau B, Bonkowsky JL. SARS-CoV-2 infection and increased risk for pediatric stroke. Pediatr Neurol. 2023;142:89–94. https://doi.org/10.1016/j.pediatrneurol.2022.10.003
12. Koyama AK, Imperatore G, Rolka DB, Lundeen E, Rutkowski RE, Jackson SL, et al. Risk of cardiovascular disease after COVID-19 diagnosis among adults with and without diabetes. J Am Heart Assoc. 2023;12:e029696. https://doi.org/10.1161/JAHA.123.029696
13. Ackermann M, Mentzer SJ, Kolb M, Jonigk D. Inflammation and intussusceptive angiogenesis in COVID-19: everything in and out of flow. Eur Respir J. 2020;56:2003147. https://doi.org/10.1183/13993003.03147-2020
14. Silva Andrade B, Siqueira S, de Assis Soares WR, de Souza Rangel F, Santos NO, Dos Santos Freitas A, et al. Long-COVID and post-COVID health complications: an up-to-date review on clinical conditions and their possible molecular mechanisms. Viruses. 2021;13:700. https://doi.org/10.3390/v13040700
15. Ranucci M, Baryshnikova E, Anguissola M, Pugliese S, Falco M, Menicanti L. The long term residual effects of COVID-associated coagulopathy. Int J Mol Sci. 2023;24:5514. https://doi.org/10.3390/ijms24065514
16. Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem J. 2022;479:537–59. https://doi.org/10.1042/BCJ20220016
17. Kulick ER, Alvord T, Canning M, Elkind MSV, Chang BP, Boehme AK. Risk of stroke and myocardial infarction after influenza-like illness in New York State. BMC Public Health. 2021;21:864. https://doi.org/10.1186/s12889-021-10916-4
18. Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MSV. Influenza-like illness as a trigger for ischemic stroke. Ann Clin Transl Neurol. 2018;5:456–63. https://doi.org/10.1002/acn3.545
19. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28:583–90. https://doi.org/10.1038/s41591-022-01689-3
20. Yang Q, Chang A, Tong X, Jackson SL, Merritt RK. Long-term cardiovascular disease outcomes in non-hospitalized Medicare beneficiaries diagnosed with COVID-19: population-based matched cohort study. PLoS One. 2024;19:e0302593. https://doi.org/10.1371/journal.pone.0302593
21. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. N Engl J Med. 2021;385:790–802. https://doi.org/10.1056/NEJMoa2105911
22. Yang Q, Tong X, George MG, Chang A, Merritt RK. COVID-19 and risk of acute ischemic stroke among medicare beneficiaries aged 65 years or older: self-controlled case series study. Neurology. 2022;98:e778–89. https://doi.org/10.1212/WNL.0000000000013184
23. Ghildayal N, Nagavedu K, Wiltz JL, Back S, Boehmer TK, Draper C, et al. Public health surveillance in electronic health records: lessons from PCORnet. Prev Chronic Dis. 2024;21:E51. https://doi.org/10.5888/pcd21.230417
24. Forrest CB, McTigue KM, Hernandez AF, Cohen LW, Cruz H, Haynes K, et al. PCORnet® 2020: current state, accomplishments, and future directions. J Clin Epidemiol. 2021;129:60–7. https://doi.org/10.1016/j.jclinepi.2020.09.036
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–9. https://doi.org/10.1016/j.jclinepi.2007.11.008
26. Kolmos M, Christoffersen L, Kruuse C. Recurrent ischemic stroke—a systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2021;30:105935. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105935
27. Verburgt E, Hilkens NA, Ekker MS, Schellekens MMI, Boot EM, Immens MHM, et al. Short-term and long-term risk of recurrent vascular event by cause after ischemic stroke in young adults. JAMA Netw Open. 2024;7:e240054. https://doi.org/10.1001/jamanetworkopen.2024.0054
28. Committee on Examining the Working Definition for Long COVID, Board on Health Sciences Policy, Board on Global Health, Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine. A long COVID definition: a chronic, systemic disease state with profound consequences. Fineberg HV, Brown L, Worku T, Goldowitz I, editors. Washington: National Academies Press; 2024.
29. Cuker A. COVID-19: hypercoagulability. 2024 [cited 2024 Oct 31]. https://www.uptodate.com/contents/covid-19-hypercoagulability#H3177214199
30. Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, et al.; MICHELLE investigators. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet. 2022;399:50–9. https://doi.org/10.1016/S0140-6736(21)02392-8
31. Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, et al. ACTIV-4B Investigators. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. JAMA. 2021;326:1703–12. https://doi.org/10.1001/jama.2021.17272
32. Luo W, Liu X, Bao K, Huang C. Ischemic stroke associated with COVID-19: a systematic review and meta-analysis. J Neurol. 2022;269:1731–40. https://doi.org/10.1007/s00415-021-10837-7
33. Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute cerebrovascular events in hospitalized COVID-19 patients. Stroke. 2020;51:e219–22. https://doi.org/10.1161/STROKEAHA.120.030995

34. Centers for Disease Control and Prevention. COVID-19 clinical treatment clinical care for outpatients. 2024 [cited 2024 Nov 1]. https://www.cdc.gov/covid/hcp/clinical-care/outpatient-treatment.html
35. Centers for Disease Control and Prevention. Benefits of getting vaccinated. 2024 [cited 2024 Nov 1]. https://www.cdc.gov/covid/vaccines/benefits.html
36. Mercadé-Besora N, Li X, Kolde R, Trinh NT, Sanchez-Santos MT, Man WY, et al. The role of COVID-19 vaccines in preventing post-COVID-19 thromboembolic and cardiovascular complications. Heart. 2024;110:635–43. https://doi.org/10.1136/heartjnl-2023-323483
37. Payne AB, Novosad S, Wiegand RE, Najdowski M, Gomes DJ, Wallace M, et al. Effectiveness of bivalent mRNA COVID-19 vaccines in preventing COVID-19-related thromboembolic events among medicare enrollees aged ≥65 years and those with end stage renal disease—United States, September 2022–March 2023. MMWR Morb Mortal Wkly Rep. 2024;73:16–23. https://doi.org/10.15585/mmwr.mm7301a4
38. Romero-Rodríguez E, Pérula-de Torres LÁ, Castro-Jiménez R, González-Lama J, Jiménez-García C, González-Bernal JJ, et al. Hospital admission and vaccination as predictive factors of long COVID-19 symptoms. Front Med (Lausanne). 2022;9:1016013. https://doi.org/10.3389/fmed.2022.1016013
39. Hastie CE, Lowe DJ, McAuley A, Winter AJ, Mills NL, Black C, et al. Outcomes among confirmed cases and a matched comparison group in the long-COVID in Scotland study. Nat Commun. 2022;13:5663. https://doi.org/10.1038/s41467-022-33415-5
40. Centers for Disease Control and Prevention. Long COVID basics. 2025 [cited 2025 Apr 29]. https://www.cdc.gov/covid/long-term-effects/index.html
41. Heikkinen T, Järvinen A. The common cold. Lancet. 2003;361:51–9. https://doi.org/10.1016/S0140-6736(03)12162-9
42. Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. Clin Infect Dis. 2001;33:757–62. https://doi.org/10.1086/322627
43. Centers for Disease Control and Prevention. Signs and symptoms of stroke [cited 2024 Oct 24]. https://www.cdc.gov/stroke/signs-symptoms/index.html
44. Chen X, Zhao X, Xu F, Guo M, Yang Y, Zhong L, et al. A systematic review and meta-analysis comparing FAST and BEFAST in acute stroke patients. Front Neurol. 2022;12:765069. https://doi.org/10.3389/fneur.2021.765069

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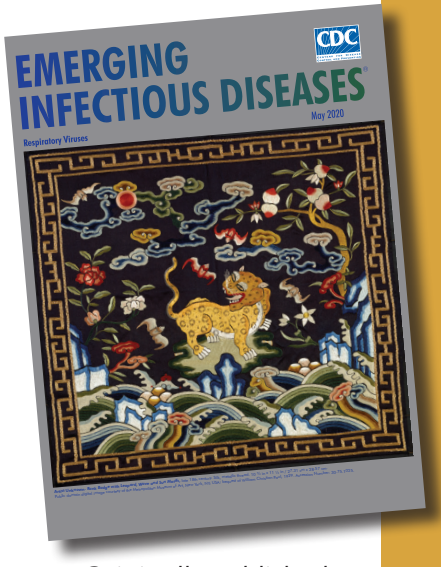

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etymologia revisited

Coronavirus

The first coronavirus, avian infectious bronchitis virus, was discovered in 1937 by Fred Beaudette and Charles Hudson. In 1967, June Almeida and David Tyrrell performed electron microscopy on specimens from cultures of viruses known to cause colds in humans and identified particles that resembled avian infectious bronchitis virus. Almeida coined the term "coronavirus," from the Latin corona ("crown"), because the glycoprotein spikes of these viruses created an image similar to a solar corona. Strains that infect humans generally cause mild symptoms. However, more recently, animal coronaviruses have caused outbreaks of severe respiratory disease in humans, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and 2019 novel coronavirus disease (COVID-19).

References

1. Almeida JD, Tyrrell DA. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. J Gen Virol. 1967;1:175–8. https://doi.org/10.1099/0022-1317-1-2-175
2. Beaudette FR, Hudson CB. Cultivation of the virus of infectious bronchitis. J Am Vet Med Assoc. 1937;90:51–8.
3. Estola T. Coronaviruses, a new group of animal RNA viruses. Avian Dis. 1970;14:330–6. https://doi.org/10.2307/1588476
4. Groupe V. Demonstration of an interference phenomenon associated with infectious bronchitis virus of chickens. J Bacteriol. 1949;58:23–32. https://doi.org/10.1128/JB.58.1.23-32.1949

https://wwwnc.cdc.gov/eid/article/26/5/et-2605_article

Functional Limitations and Illness-Related Absenteeism among School-Aged Children with and without Long COVID, United States, 2022–2023

Nicole D. Ford, Regina M. Simeone, Caroline Pratt, Sharon Saydah

We examined functional limitations and illness-related chronic absenteeism (i.e., missing ≥18 days of school for health reasons) in a cross-sectional nationally representative sample of 11,057 US children 5–17 years of age who ever or never had long COVID (i.e., symptoms lasting ≥3 months after COVID-19 illness). Among 4,587 children with prior COVID-19, we estimated whether long COVID was associated with increased illness-related chronic absenteeism by using logistic regression. Our analysis showed that ≈1.4% of school-aged children had long COVID at some point. Among children with prior COVID-19, those who had long COVID at some point more frequently reported functional limitations, such as difficulty with memory, than those who did not have long COVID (18.3% vs. 8.6%). Having long COVID was associated with higher odds of illness-related chronic absenteeism. Children who had long COVID could experience functional limitations and absenteeism. School accommodations might be an option to improve functional limitations.

Long COVID is a chronic condition that includes a wide range of symptoms and conditions lasting ≥3 months after SARS-CoV-2 infection (*1*). Long COVID can affect multiple body systems, including cardiovascular, respiratory, and musculoskeletal. Commonly reported symptoms include fatigue, difficulty thinking or concentrating, and cough (*2*). In the 2023 US National Health Interview Survey (NHIS), 1.0% of children 6–11 years of age and 2.3% of children 12–17 years of age reported having long COVID at some point (*3*). Long COVID symptoms can limit a person's ability to carry out day-to-day activities and affect functioning at school or work. In 2023, eight in 10 children with long COVID had activity limitation compared with before their COVID-19 illness (*3*).

Studies quantifying illness-related absenteeism in children by long COVID status are lacking, and few studies have examined functional limitations among children with long COVID. A qualitative study of UK children with long COVID reported that those children found attending school difficult, and even a gradual return required balancing the effects of missing school with preventing relapse (*4*). The larger societal effects of long COVID could be far-reaching if US school-aged children are unable to maintain school attendance, gain educational advancement, or engage in recreational activities vital to social and emotional development. We assessed whether functional limitations and illness-related absenteeism were more common among US school-aged children and adolescents who ever had long COVID compared with those who never had long COVID.

Methods

We used data from the 2022 and 2023 NHIS, a large, nationally representative cross-sectional household survey of the civilian noninstitutionalized population of the United States (*5*,*6*). NHIS uses geographically clustered sampling techniques to select household units. One child 0–17 years of age is then sampled from each selected household. Interviewers collect information from the sample child's parent or a knowledgeable adult during interviews. The sample child response rates for the overall surveys were 45.8% in 2022 and 44.9% in 2023 (*5*,*6*). We limited the analytic sample to school-aged children 5–17 years of age.

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Study Definition of Long COVID

Prior COVID-19 was determined by an affirmative response to NHIS survey questions about SARS-CoV-2 infection. In 2022, questions were "Has a doctor or other health professional ever told you that [NAME] had or likely had coronavirus or COVID-19?" and "Did [NAME] ever take a test that showed he or she had coronavirus or COVID-19?" and in 2023 "Has [NAME] ever had COVID-19?" In 2022, the survey ascertained ongoing COVID-19 symptoms among children with symptomatic mild, moderate, or severe COVID-19 and those who had unknown symptom severity. In 2023, the survey ascertained ongoing COVID-19 symptoms among all children with prior COVID-19 irrespective of symptom severity during acute illness. NHIS classified children as having long COVID when they had any symptoms lasting ≥3 months that they did not have before having COVID-19. NHIS classified children as never having long COVID if they never had COVID-19 or had COVID-19 at some point but never had ongoing symptoms.

Functional Limitations

NHIS administers the Washington Group/UNICEF Child Functioning Module to identify the subpopulation of children who are at greater risk of experiencing limited participation in an unaccommodating environment (*7*). The 24-question module for children 5–17 years of age was designed and validated for use in censuses and population-based surveys (*7*). Functional domains of the module were vision, hearing, mobility, self-care, communication, learning, cognition, accepting change, behavior, relationships, and psychosocial. Because of the small number of children with vision, hearing, mobility, self-care, and communication limitations in the sample when stratified by long COVID status, we did not include those estimates because they did not meet National Center for Health Statistics (NCHS) data presentation standards on the basis of effective sample size, confidence interval width, number of events, and degrees of freedom (*8*). We classified indicators in the learning, cognition, accepting change, behavior, and relationships domains as binary yes/no variables where yes indicated children with any difficulty. In the psychosocial domain, we classified both the frequency of seeming very anxious, nervous, or worried and the frequency of seeming very sad or depressed as never, a few times per year, monthly, or weekly/daily.

Illness-Related Absenteeism

Parents reported days of school the sample child missed because of illness or injury during the 12 months preceding the survey. We classified illness-related chronic absenteeism according to the US Department of Education's definition of chronic absenteeism (*9*), which is missing ≥18 days of school (yes/no).

Sociodemographic and Health Characteristics

Parents reported child-level sociodemographic characteristics including age (5–11 years or 12–17 years), sex (male or female), private health insurance (yes/no), and race and Hispanic ethnicity (Hispanic, non-Hispanic White, or other single or multiple races). Other single or multiple races included non-Hispanic Asian, non-Hispanic American Indian/Alaska Native, non-Hispanic Black, and other single and multiple races, which we aggregated to meet NCHS presentation standards because of small numbers. We included race and Hispanic ethnicity in this study to account for documented racial and ethnic differences in parent-reported long COVID in US children (*10*). Household-level characteristics included region (Northeast, Midwest, South, West), urban–rural classification (metropolitan, nonmetropolitan), and parental education (high school diploma or less, some college or associate's degree, bachelor's degree or higher). NCHS classifies region and urban–rural on the basis of household location (*11*).

Parent-reported child health characteristics were 12-month recall of COVID-19 vaccine receipt and use of prescription medication for emotions, concentration, behavior, or mental health (yes/no). NHIS did not collect information about prescription medication use for other conditions. Co-occurring conditions included chronic health conditions (i.e., asthma, prediabetes, diabetes) and neurodevelopmental conditions (i.e., attention-deficit/hyperactivity disorder [ADHD], autism, developmental delay, intellectual disability, and learning disability), coded yes/no.

Statistical Analyses

We estimated the weighted prevalence (Clopper-Pearson 95% CI) of ever experiencing long COVID among the cohort. We then estimated weighted prevalences and 95% CIs of sociodemographic and health indicators, functional limitations, and sick days by long COVID status. For all indicators, we used Rao-Scott χ^2 tests to examine differences by long COVID status.

During the COVID-19 pandemic, the Centers for Disease Control and Prevention published guidance on isolation following a positive SARS-CoV-2 test and quarantine following exposure (*12*). Because COVID-19 illness is associated with sick days, irrespective of whether long COVID develops, we created a restricted subsample of 4,587 children with prior COVID-19. That design helped control for

confounding by acute COVID-19 effects, which might otherwise bias estimates in the full sample. We used logistic regression to estimate whether ever having long COVID was associated with increased occurrence of illness-related chronic absenteeism among children with prior COVID-19. We first ran an unadjusted model including only long COVID as the exposure. We then tested various adjusted models. We identified age, sex, race and Hispanic ethnicity, and parental education as potential confounders and assessed our study population by examining differences in unadjusted and adjusted estimates of association and model goodness of fit, favoring parsimony. We used Harrell's C statistic to assess goodness of fit.

Because chronic health conditions and neurodevelopmental conditions can develop as the result of a SARS-CoV-2 infection, we did not consider those conditions for the primary models. However, those conditions potentially could confound the relationship between long COVID and illness-related chronic absenteeism. For example, diabetes might be associated with risk of developing long COVID and with missing days from school. To examine confounders, we conducted sensitivity analyses. First, we added chronic health conditions (any vs. none) to the final adjusted model, then we added neurodevelopmental conditions (any vs. none) to the model. We compared the estimates of association for long COVID in the final adjusted model to those in the models containing chronic health conditions and neurodevelopmental conditions.

We used SAS version 9.4 (SAS Institute, Inc., https://www.sas.com) to conduct analyses. We obtained weighted estimates by using SAS-callable SUDAAN (RTI International, https://www.rti.org), applying survey weights generated by NHIS (*5*,*6*) and accounting for complex sampling. We considered 2-sided $p<0.05$ statistically significant.

Results

In total, NHIS surveyed 5,498 children 5–17 years of age in 2022 and 5,676 in 2023. We excluded 106 (0.9%) children missing information on prior COVID-19 and 11 (0.1%) missing information on ongoing symptoms following COVID-19. The final unweighted analytic sample included 11,057 children with a weighted value of 106,793,000.

On the basis of the weighted samples, we estimated 1,538,000 (1.4%) school-aged children had long COVID at some point (Table 1). Among those children, 69.7% were 12–17 years of age, 59.4% were female and 40.6% were male, and 35.2% were experiencing long COVID symptoms at time of survey. We found statistically significant differences by long COVID status for age group, sex, race and ethnicity, parental education, co-occurring chronic health conditions, neurodevelopmental conditions, learning disability, and use of prescription medication for emotions, concentration, behavior, or mental health.

Compared with children who never had long COVID, children who had long COVID had a higher prevalence of functional limitations across 5 of the 6 functional domains (Table 2). Within the cognition domain, compared with children who never had long COVID, children who ever had long COVID had approximately double the prevalence of difficulty with memory (18.3% vs. 8.6%) and difficulty concentrating (14.3% vs. 7.7%) ($p<0.01$ for both comparisons). Prevalence of learning difficulty was also roughly double among children who had long COVID at some point compared with those who had not (19.8% vs. 10.4%).

In the relationship domain, children who had long COVID had a higher prevalence of difficulty making friends than children who never had long COVID (18.4% vs. 11.3%) ($p = 0.008$). Children who had long COVID also had more difficulty accepting changes in routine than children who never had long COVID (37.8% vs. 23.0%) ($p<0.001$). In the psychosocial domain, children who had experienced long COVID had higher prevalence of anxiety than children who never had long COVID (31.3% vs. 17.5% for weekly or daily anxiety) and for depression (18.9% vs. 6.2% for weekly or daily depression) ($p<0.001$ for both comparisons).

Among children who had experienced long COVID, 10.7% missed ≥30 days of school for health reasons during the year preceding the survey (Table 3). In both the full analytic sample and restricted subsample of children with prior COVID-19 illness, 13.9% of children who had experienced long COVID were chronically absent (i.e., missed ≥18 days). Among children who never had long COVID, 3.5% in the full analytic sample and 4.9% in the restricted subsample of children with prior COVID-19 were chronically absent for health reasons.

In the unadjusted model, long COVID was associated with 3.1 (95% CI 1.8–5.3; Harrell's C statistic = 0.53) times the odds of illness-related chronic absenteeism (Figure; Appendix Table, https://wwwnc.cdc.gov/EID/article/31/14/25-1035-App1.pdf). In the adjusted multivariable model accounting for race and Hispanic ethnicity and parental education, having long COVID at some point was associated with 2.5 (95% CI 1.5–4.3; Harrell's C statistic = 0.63) times the odds of illness-related chronic absenteeism compared with never having long COVID. In the sensitivity analyses, the effect sizes for long COVID were attenuated slightly after additionally controlling for chronic

health conditions (adjusted odds ratio 2.4, 95% CI 1.4–4.2; Harrell's C statistic = 0.64) and neurodevelopmental conditions (adjusted odds ratio 2.3, 95% CI 1.4–4.0; Harrell's C statistic = 0.65) (Figure; Appendix Table).

Discussion

In this nationally representative sample of US school-aged children during 2022–2023, 1.4% had experienced long COVID at some point, and long COVID disproportionately affected older and female children. We found approximately double the prevalence of functional limitations in the learning, cognition, relationships, accepting change, and psychosocial domains among children who had experienced long COVID compared with those who never had long COVID. In the absence of appropriate supports, those functional limitations could make academic achievement and engagement in social activities challenging. Nearly 14% of children who experienced long COVID were chronically absent from school for health reasons, and >1 in 10 missed ≥6 weeks during the 12 months preceding the survey. After controlling for sociodemographic and health characteristics, children who experienced long COVID had 2.3 times the adjusted odds of illness-related chronic absenteeism compared with those who never had long COVID.

Table 1. Sociodemographic and health characteristics of children in a study of functional limitations and illness-related chronic absenteeism among school-aged children with or without long COVID, United States, 2022–2023*

Characteristic	Weighted no. (%) [95% CI]		p value†
	Had long COVID	Never had long COVID	
Total no.	1,538,000 (1.4) [1.2–1.7]	105,255,000 (98.6) [98.3–98.8]	
Age group, y			<0.001
5–11	467,000 (30.3) [22.9–38.6]	55,319,000 (52.6) [51.5–53.6]	
12–17	1,072,000 (69.7) [61.4–77.1]	49,936,000 (47.4) [46.4–48.5]	
Sex			0.02
M	625,000 (40.6) [32.1–49.5]	53,925,000 (51.3) [50.2–52.3]	
F	914,000 (59.4) [50.5–67.9]	51,274,000 (48.7) [47.7–49.8]	
Race and Hispanic ethnicity‡			0.002
Hispanic	494,000 (32.1) [24.4–40.6]	27,188,000 (25.8) [24.0–27.7]	
Non-Hispanic White	874,000 (56.8) [48.2–65.1]	53,633,000 (51.0) [49.1–52.8]	
Another single or multiple races	171,000 (11.1) [6.6–17.3]	24,433,000 (23.2) [21.9–24.6]	
Private health insurance§	745,000 (48.4) [39.7–57.2]	58,410,000 (55.7) [54.2–57.2]	0.09
Region			0.87
Northeast	221,000 (14.4) [8.8–21.7]	16,382,000 (15.6) [14.3–16.9]	
Midwest	344,000 (22.4) [16.1–29.7]	21,691,000 (20.6) [19.2–22.1]	
South	571,000 (37.1) [29.1–45.7]	41,589,000 (39.5) [37.5–41.6]	
West	402,000 (26.1) [19.2–34.0]	25,593,000 (24.3) [22.5–26.3]	
Urban classification¶			0.35
Metropolitan	1,289,000 (83.8) [76.2–89.8]	91,184,000 (86.6) [85.2–88.0]	
Nonmetropolitan	249,000 (16.2) [10.2–23.8]	14,071,000 (13.4) [12.0–14.8]	
Parental education			<0.001
High school diploma, GED, or less	367,000 (24.8) [17.8–32.9]	27,649,000 (27.0) [25.7–28.3]	
Some college or associate's degree	576,000 (38.9) [30.5–47.8]	25,446,000 (24.8) [23.8–25.9]	
Bachelor's degree or higher	538,000 (36.3) [28.1–45.1]	49,447,000 (48.2) [46.7–49.8]	
Received COVID-19 vaccine ≤12 mo	280,000 (18.2) [11.9–26.1]	22,232,000 (21.1) [20.1–22.2]	0.43
Ever had COVID-19	1,538,000 (100.00) [NA]	41,511,000 (39.4) [38.3–40.6]	NA
Current long COVID	542,000 (35.2) [27.1–44.1]	NA	NA
Chronic health condition#	261,000 (17.0) [11.2–24.1]	9,131,000 (8.7) [8.1–9.3]	<0.001
Neurodevelopmental condition**	432,000 (28.1) [20.5–36.7]	18,584,000 (17.7) [16.8–18.6]	0.002
Intellectual disability	25,000 (1.7) [0.3–5.1]	1,581,000 (1.5) [1.2–1.8]	0.88
Learning disability	225,000 (14.6) [8.8–22.3]	8,238,000 (7.8) [7.2–8.5]	0.007
Prescription medication for emotions, concentration, behavior, or mental health ≤12 mo	382,000 (24.8) [17.6–33.3]	10,196,000 (9.7) [9.1–10.5]	<0.001

*Data are from the National Health Interview Survey (*5*,*6*). Numbers are weighted, are rounded to the nearest thousand, and might vary because of missing data. All estimates are weighted, account for complex sampling, and meet National Center for Health Statistics data standards. Parents of children with prior COVID-19 (mild, moderate, or severe symptoms or unknown symptom severity during acute illness [2022] and all children with prior COVID-19 irrespective of acute illness symptom severity [2023]) were asked about ongoing symptoms using the question "Did [NAME] have any symptoms lasting 3 months or longer that [she/he] did not have prior to having COVID-19?" Children with an affirmative response were classified as having long COVID. Children who never had COVID-19 and those who had COVID-19 but never had ongoing symptoms were classified as never having long COVID. NA, not applicable.
†p values are for Rao-Scott χ^2 tests for sociodemographic and health characteristics comparing children who ever and never had long COVID.
‡Another single or multiple race(s) were non-Hispanic Asian, non-Hispanic American Indian/Alaska Native, non-Hispanic Black, and other single race and multiple races.
§Private health insurance compared to Medicaid, other public coverage, and no insurance.
¶Urban–rural classification defined according to the 2013 National Center for Health Statistics Urban-Rural Classification Scheme for Counties (https://www.cdc.gov/nchs/data/series/sr_02/sr02_166.pdf).
#Current asthma, prediabetes, or diabetes.
**Current autism, attention-deficit hyperactivity disorder, developmental delay, intellectual disability, or learning disability.

Table 2. Functional domains of children in a study of functional limitations and illness-related chronic absenteeism among school-aged children with and without long COVID, United States, 2022–2023*

Functional domain	Weighted no. (%) [95% CI]		p value†
	Had long COVID	Never had long COVID	
Learning difficulty	305,000 (19.8) [13.2–27.9]	10,929,000 (10.4) [9.7–11.1]	<0.001
Cognition			
Difficulty concentration	220,000 (14.3) [8.7–21.7]	8,120,000 (7.7) [7.1–8.3]	0.006
Difficulty remembering	282,000 (18.3) [11.6–26.7]	9,069,000 (8.6) [8.0–9.3]	<0.001
Behavior, difficulty controlling	282,000 (18.3) [12.1–26.0]	16,732,000 (15.9) [15.0–16.8]	0.45
Relationships, difficulty making friends	281,000 (18.4) [12.4–25.7]	11,852,000 (11.3) [10.6–12.0]	0.008
Difficulty accepting changes in routine	582,000 (37.8) [30.1–46.1]	24,173,000 (23.0) [22.0–24.0]	<0.001
Psychosocial			
Frequency of seeming anxious, nervous, or worried			<0.001
Never	437,000 (28.7) [21.4–36.8]	50,235,000 (47.8) [46.4–49.2]	
A few times per year	368,000 (24.2) [17.4–32.0]	25,437,000 (24.2) [23.2–25.3]	
Monthly	243,000 (15.9) [9.8–23.9]	10,994,000 (10.5) [9.8–11.2]	
Weekly or daily	477,000 (31.3) [23.6–39.8]	18,387,000 (17.5) [16.6–18.4]	
Frequency of seeming very sad or depressed			<0.001
Never	765,000 (49.8) [41.0–58.5]	70,865,000 (67.5) [66.2–68.7]	
A few times per year	286,000 (18.6) [12.8–25.7]	20,760,000 (19.8) [18.8–20.7]	
Monthly	195,000 (12.7) [7.7–19.4]	6,811,000 (6.5) [5.9–7.1]	
Weekly or daily	291,000 (18.9) [12.6–26.8]	6,552,000 (6.2) [5.7–6.8]	

*Data are from the National Health Interview Survey (*5*,*6*). Numbers are weighted, are rounded to the nearest thousand, and might vary because of missing data. All estimates are weighted, account for complex sampling, and meet National Center for Health Statistics data standards. Parents of children with prior COVID-19 (mild, moderate, or severe symptoms or unknown symptom severity during acute illness [2022] and all children with prior COVID-19 irrespective of acute illness symptom severity [2023]) were asked about ongoing symptoms using the question "Did [NAME] have any symptoms lasting 3 months or longer that [she/he] did not have prior to having COVID-19?" Children with an affirmative response were classified as having long COVID. Children who never had COVID-19 and those who had COVID-19 but never had ongoing symptoms were classified as never having long COVID. NA, not applicable.
†p values are for Rao-Scott χ^2 tests for sociodemographic and health characteristics comparing children who ever and never had long COVID.

Together, our findings suggest that long COVID has a potentially large impact on US school-aged children. Parents, caregivers, teachers, and schools may consider that children with long COVID disproportionately experience both functional limitations and sick days off from school. School accommodations, such as reduced workload and rest periods that are recommended for other conditions affecting cognitive and academic functioning, such as concussion or ADHD, could be options to improve outcomes (*13*,*14*).

Little information about functional limitation, sick days off, and long COVID in US children is available to put our study findings into context. Most of the available literature on long COVID in children was reported from medical records, convenience samples, and small case-based studies (*15*,*16*). However, studies of pediatric populations have described symptoms or conditions in long COVID, such as autonomic dysfunction (*17*), abnormalities in brain metabolism (*18*), and exercise intolerance (*19*). In 2023, 80.0% of children who had long COVID at the time of NHIS had ≥1 long COVID-associated activity limitation; however, the study did not examine specific functional limitations (*3*). Our findings are consistent with studies reporting positive associations between other chronic health conditions, such as type 1 diabetes and asthma, and school absence in children (*20*,*21*). For example, a study of asthma in urban US schools found that asthma explained 14%–18% of student absenteeism, after accounting for sociodemographic and health characteristics (*20*).

Cognitive, learning, relationship, accepting changes, and psychosocial functional limitations were roughly twice as common among children who had long COVID at some point compared with those who never had long COVID. In the absence of appropriate supports or accommodations, functional limitations might affect academic performance and social development. Neuropsychiatric symptoms, such as impairment to memory recall, executive dysfunction, and depression, are commonly reported postacute sequelae of SARS-CoV-2 infection (*22*,*23*). The prevalence of childhood mental, behavioral, and developmental disorders (MBDD) in the United States has increased broadly over time; data from the National Survey of Children's Health showed MBDD prevalence among children 3–17 years of age increased from 25.3% to 27.7% during 2016–2021, with increases specific to learning disability, developmental delay, speech or language disorder, anxiety, and depression (*24*).

The association between COVID-19 and MBDD could be bidirectional. COVID-19 might influence MBDD prevalence indirectly through social determinants of health (e.g., social isolation), directly through infection (e.g., long COVID–associated cognitive impairment), or both (*25*). Conversely, chronic health, mental health, and neurodevelopmental conditions might be associated with long COVID because they increase the risk for SARS-CoV-2 infection, severe COVID-19 illness, and symptoms and conditions consistent with long COVID (*26*–*28*). For example, a study

using 2022 National Survey on Health and Disability data found the prevalence of long COVID was higher among persons with preexisting disabilities compared with the general population (40.6% vs. 18.9%) (*29*). Furthermore, a 2023 systematic review and meta-analysis found that poor mental health increased the likelihood of developing long COVID in pediatric populations (*30*). Symptoms and conditions might develop, or underlying conditions might worsen after SARS-CoV-2 infection (*31*). Our study is cross-sectional and does not provide information regarding the onset of co-occurring conditions relative to the development of long COVID. Thus, our findings cannot be used to examine the direction of the effects. However, our findings highlight that children with long COVID could have complex needs.

Prescription medication use for emotions, concentration, behavior, or mental health were common among children in our study who had experienced long COVID; 1 in 4 reportedly used those medications during the 12 months preceding the survey. That finding might represent increased risk for long COVID among children with underlying psychological or neurodevelopmental health conditions or new onset long COVID–associated conditions requiring medication. Studies have reported increased use of those types of prescription medications since the pandemic, specifically in adults and school-aged girls. For example, a study of commercial healthcare claims found that the percentage of girls receiving stimulants, primarily those used to treat ADHD, increased by 8.3% for girls 10–15 years of age and 15.1% of those 15–19 years of age from 2020 to 2021 (*32*). In our study, long COVID was more prevalent in adolescents and girls. Similarly, the monthly rate of antidepressant dispensing to adolescents and young adults increased during 2016–2020, and the rate of change increased by 63.5% beginning March 2020 (*33*). Although those findings might reflect secular trends, studies have also shown differences in receipt of some medications by long COVID status. For example, adult patients with long COVID–associated fatigue and concentration problems were twice as likely to receive a stimulant prescription than patients with only acute COVID-19 illness, suggesting potential off-label use of stimulants to treat long COVID (*34*). Furthermore, stimulants can be prescribed to treat myalgic encephalomyelitis/chronic fatigue syndrome, a common postacute sequelae of SARS-CoV-2 infection (*35*,*36*).

Chronic absenteeism is a primary cause of poor academic achievement (*37*). Missing school makes keeping pace with schoolwork difficult, increases the likelihood of dropping out, and reduces opportunities to build relationships with peers (*37*). From 2018–19 to 2021–22 enrollment-weighted prevalence of chronic absenteeism in the United States increased from 14.8% to 28.3%, a 91% increase relative to the prepandemic timeframe (*38*). In our study, 1 in 7 children who experienced long COVID were chronically absent from school for health reasons, more than double the odds of children with only acute COVID-19 illness. That finding is consistent with literature on

Table 3. Illness-related absenteeism among children in a study of functional limitations and illness-related absenteeism among school-aged children with and without long COVID, United States, 2022–2023*

Absenteeism	Weighted no. (%) [95% CI]		p value†
	Had long COVID	Never had long COVID	
Total analytic sample	1,538,000	105,255,000	
No. sick days			<0.001
0	311,000 (20.3) [13.5–28.5]	33,808,000 (32.4) [31.3–33.6]	
1–5	421,000 (27.4) [20.4–35.4]	47,782,000 (45.9) [44.8–47.0]	
6–17	588,000 (38.3) [29.7–47.6]	18,873,000 (18.1) [17.2–19.0]	
18–29	49,000 (3.2) [1.1–7.1]	2,203,000 (2.1) [1.8–2.5]	
≥30	165,000 (10.7) [5.7–18.0]	1,530,000 (1.5) [1.2–1.8]	
Chronic absence‡	214,000 (13.9) [8.5–21.1]	3,733,000 (3.5) [3.1–4.0]	<0.001
Subsample of children with prior COVID-19	1,538,000	41,511,000	
No. sick days			<0.001
0	311,000 (20.3) [13.5–28.5]	9,473,000 (23.0) [21.6–24.6]	
1–5	421,000 (27.4) [20.4–35.4]	18,950,000 (46.1) [44.3–47.8]	
6–17	588,000 (38.3) [29.7–47.6]	10,659,000 (25.9) [24.4–27.5]	
18–29	49,000 (3.2) [1.1–7.1]	1,201,000 (2.9) [2.4–3.6]	
≥30	165,000 (10.7) [5.7–18.0]	844,000 (2.1) [1.6–2.6]	
Chronic absence‡	214,000 (13.9) [8.5–21.1]	2,045,000 (4.9) [4.2–5.7]	<0.001

*Data are from the National Health Interview Survey (*5*,*6*). Numbers are weighted, are rounded to the nearest thousand, and might vary because of missing data. All estimates are weighted, account for complex sampling, and meet National Center for Health Statistics data standards. Parents of children with prior COVID-19 (mild, moderate, or severe symptoms or unknown symptom severity during acute illness [2022] and all children with prior COVID-19 irrespective of acute illness symptom severity [2023]) were asked about ongoing symptoms using the question "Did [NAME] have any symptoms lasting 3 months or longer that [she/he] did not have prior to having COVID-19?" Children with an affirmative response were classified as having long COVID. Children who never had COVID-19 and those who had COVID-19 but never had ongoing symptoms were classified as never having long COVID. NA, not applicable.

†p values are for Rao-Scott χ^2 tests for sociodemographic and health characteristics comparing children who ever and never had long COVID.

‡Chronic absence from school for health reasons was defined as missing ≥18 days of school due to illness or injury during the 12 months preceding the survey.

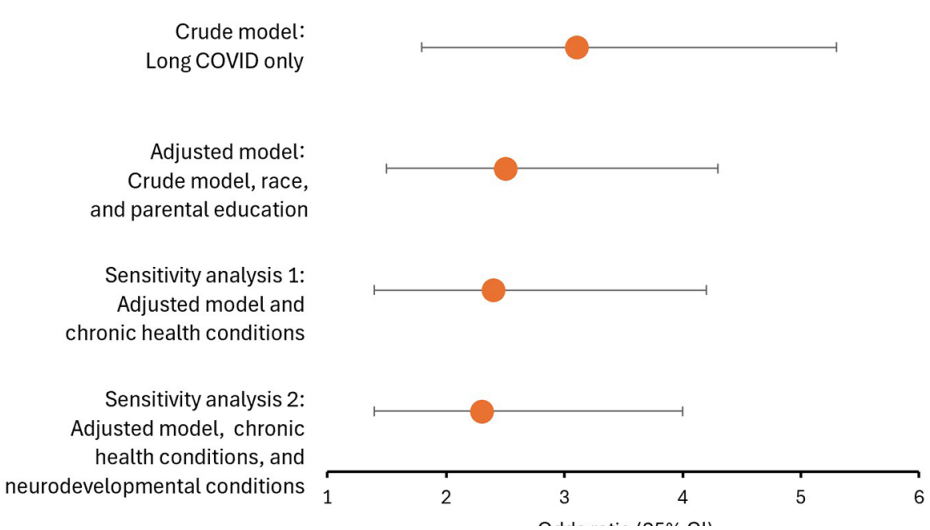

Figure. Adjusted odds ratios from a study of functional limitations and illness-related chronic absenteeism among school-aged children with and without long COVID, United States, 2022–2023. Graph shows adjusted odds ratios (dots) and 95% CIs (whiskers) for chronic absence from school for health reasons among children with prior COVID-19 illness comparing children who did and did not have long COVID. The study examined 4,587 school-aged children (5–17 years) who had COVID-19 illness identified through the National Health Interview Survey, 2022–2023 (*5*,*6*). Chronic absence from school for health reasons was defined as missing ≥18 days of school because of illness or injury (compared with 0–17 days) during the 12 months preceding the survey. The minimally adjusted model controls for race and Hispanic ethnicity and parental education. Chronic health conditions included asthma, prediabetes, and diabetes. Neurodevelopmental conditions include autism, attention-deficit hyperactivity disorder, intellectual disability, learning disability, and developmental delay.

disability and chronic absenteeism in US children wherein children with disabilities more frequently experienced ≥15 missed days of school compared with children without disabilities (14.8% vs. 4.4%) (*39*). Moreover, having long COVID at any point was significantly associated with parental education level ($p<0.001$), and previous literature found that socioeconomic factors can affect the association of chronic health conditions and absenteeism (*40*). Schools might consider health-related factors in their ongoing efforts to improve school attendance (*41*) and could collaborate with healthcare systems to provide integrated systems of support to address complex needs for children with disabilities and health concerns (*42*).

Limited guidance exists to address long COVID–associated functional limitations or chronic absence resulting from long COVID in US school-aged children (*43*). Guidance related to return-to-work and reasonable accommodations for adults affected by long COVID (*44*) might not be applicable to children. The National Academies of Sciences, Engineering, and Medicine's report on long COVID and disability highlight that long COVID could greatly affect disability and functioning in children and that long COVID is poorly understood in that population (*1*). Appropriate diagnosis and treatment of symptoms could improve functional limitations among children with long COVID. In addition, long COVID can be relapsing and remitting, so children might require flexible accommodations to meet changing needs. Furthermore, inadequate rest and pushing beyond functional limitations can worsen long COVID symptoms (*45*,*46*). Healthcare providers can collaborate with parents, caregivers, and schools to develop educational intervention and support for children with special educational needs (*47*).

Strengths of this study include a large, nationally representative sample of children with detailed information about sociodemographic and health characteristics. In addition, the tool used to measure functional limitations was specifically designed for population-based surveys and validated (*7*).

The first limitation of this study was that long COVID and illness-related chronic absenteeism were based on parental report and could be subject to recall bias and misclassification. Second, identification of COVID-19 history varied slightly between survey years. In 2022, ongoing symptoms were not ascertained among children with asymptomatic COVID-19. In 2023, ongoing symptoms were ascertained among all children with prior COVID-19. Thus, children with asymptomatic COVID-19 or those with undetected COVID-19 might have been misclassified in the group without long COVID. In that case, our results might have been biased toward the null. Third, younger children have difficulty expressing ongoing symptoms, potentially leading to underreporting of long COVID. The Child Functioning Module was designed to be administered to caregivers in surveys so functional limitations could be less subject to misclassification. Fourth, missed days of school for health reasons was not specific to long COVID. Because acute COVID-19 illness is associated with missed time from school, we limited the modeling to the subsample

of children who had prior COVID-19 illness to isolate the effect of long COVID on illness-related chronic absenteeism beyond acute illness. Fifth, the NHIS is cross sectional, so we did not have information about the timing of long COVID relative to chronic health or neurodevelopmental conditions, functional limitations, or absence from school. Long COVID–associated activity limitation was added to the 2023 survey but was not available for 2022. Finally, because of low prevalence of long COVID in children, stratified estimates for some chronic health and neurodevelopmental conditions did not comply with NCHS reporting standards. We combined response options for some sociodemographic characteristics to comply with reporting standards.

In summary, long COVID remains a public health concern in US school-aged children. Because children who had long COVID experienced a disproportionate burden of functional limitations compared with their peers, educational institutions need to recognize the potential for accommodations that support learning goals and social development. Because having long COVID at any point was strongly associated with illness-related chronic absenteeism among children with prior COVID-19, healthcare providers and schools could collaborate to recognize and support children experiencing long COVID to minimize effects on learning and development.

This activity was reviewed by the US Centers for Disease Control and Prevention (CDC)'s Human Research Protection Office, deemed not research but rather public health surveillance, and was conducted consistent with applicable federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

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About the Author

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References

1. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on the Long-Term Health Effects Stemming from COVID-19 and Implications for the Social Security Administration. Long-term health effects of COVID-19: disability and function following SARS-CoV-2 infection. Spicer CM, Chu BX, Volberding PA, editors. Washington: National Academies Press; 2024.
2. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Global Health; Board on Health Sciences Policy; Committee on Examining the Working Definition for Long COVID. A long COVID definition: a chronic, systemic disease state with profound consequences. Goldowitz I, Worku T, Brown L, Fineberg HV, editors. Washington: National Academies Press; 2024.
3. Ford ND, Vahratian A, Pratt CQ, Yousaf AR, Gregory CO, Saydah S. Long COVID prevalence and associated activity limitation in US children. JAMA Pediatr. 2025;179:471–3.
4. MacLean A, Wild C, Hunt K, Nettleton S, Skea ZC, Ziebland S. Impact of long Covid on the school experiences of children and young people: a qualitative study. BMJ Open. 2023;13:e075756.
5. National Center for Health Statistics. National Health Interview Survey 2022 survey description. Hyattsville (MD): National Center for Health Statistics; 2023.
6. National Center for Health Statistics. National Health Interview Survey 2023 survey description. Hyattsville (MD): National Center for Health Statistics; 2024.
7. Washington Group on Disability Statistics. The Washington Group/UNICEF child functioning module (CFM)—ages 5–17 years [cited 2024 Aug 19]. https://nhis.ipums.org/nhis/resources/Washington_Group_Questionnaire__5_-_WG-UNICEF_Child_Functioning_Module__ages_5-17_.pdf
8. Parker JD, Talih M, Malec DJ, Beresovsky V, Carroll M, Gonzalez JF Jr, et al. National Center for Health Statistics data presentation standards for proportions; vital statistics series 2, no. 175. Hyattsville (MD): National Center for Health Statistics: 2017.
9. US Department of Education. Chronic absenteeism [cited 2025 June 2]. https://www.ed.gov/teaching-and-administration/supporting-students/chronic-absenteeism
10. Vahratian A, Adjaye-Gbewonyo D, Lin JMS, Saydah S. Long COVID in children: United States, 2022; NCHS data brief no. 479. Hyattsville (MD): National Center for Health Statistics; 2023.
11. Ingram D, Franco S. 2013 NCHS urban-rural classification scheme for counties; vital health statistics, series 2, no. 166. Hyattsville (MD): National Center for Health Statistics; 2014.
12. Centers for Disease Control and Prevention. Isolation and precautions for people with COVID-19 [cited 2024 Nov 27]. https://archive.cdc.gov/www_cdc_gov/coronavirus/2019-ncov/your-health/isolation.html
13. Popoli DM, Burns TG, Meehan WP III, Reisner A. CHOA concussion consensus: establishing a uniform policy for academic accommodations. Clin Pediatr (Phila). 2014; 53:217–24.
14. Wolraich ML, Hagan JF Jr, Allan C, Chan E, Davison D, Earls M, et al.; Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactive Disorder. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2019;144:e20192528.
15. Rao S, Gross RS, Mohandas S, Stein CR, Case A, Dreyer B, et al. Postacute sequelae of SARS-CoV-2 in children. Pediatrics. 2024;153:e2023062570.

16. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, Perelman C, Sepulveda R, Rebolledo PA, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. Sci Rep. 2022;12:9950.
17. Delogu AB, Aliberti C, Birritella L, De Rosa G, De Rose C, Morello R, et al. Autonomic cardiac function in children and adolescents with long COVID: a case-controlled study. Eur J Pediatr. 2024;183:2375–82.
18. Cocciolillo F, Di Giuda D, Morello R, De Rose C, Valentini P, Buonsenso D. Orbito-frontal cortex hypometabolism in children with post-COVID condition (long COVID): a preliminary experience. Pediatr Infect Dis J. 2022;41:663–5.
19. Baldi F, De Rose C, Mariani F, Morello R, Raffaelli F, Valentini P, et al. Cardiopulmonary exercise testing in children with long COVID: a case-controlled study. Pediatr Infect Dis J. 2024;43:795–802.
20. Johnson SB, Spin P, Connolly F, Stein M, Cheng TL, Connor K. Asthma and attendance in urban schools. Prev Chronic Dis. 2019;16:E148.
21. Glaab LA, Brown R, Daneman D. School attendance in children with type 1 diabetes. Diabet Med. 2005;22:421–6.
22. Badenoch JB, Rengasamy ER, Watson C, Jansen K, Chakraborty S, Sundaram RD, et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. Brain Commun. 2022;4:fcab297.
23. Becker JH, Lin JJ, Doernberg M, Stone K, Navis A, Festa JR, et al. Assessment of cognitive function in patients after COVID-19 infection. JAMA Netw Open. 2021;4:e2130645.
24. Leeb RT, Danielson ML, Claussen AH, Robinson LR, Lebrun-Harris LA, Ghandour R, et al. Trends in mental, behavioral, and developmental disorders among children and adolescents in the US, 2016–2021. Prev Chronic Dis. 2024;21:E96.
25. Substance Abuse and Mental Health Services Administration. Identification and management of mental health symptoms and conditions associated with long COVID. Publication no. PEP23-06-05-007. Rockville (MD): The Administration; 2023.
26. Camporesi A, Morello R, La Rocca A, Zampino G, Vezzulli F, Munblit D, et al. Characteristics and predictors of long Covid in children: a 3-year prospective cohort study. EClinicalMedicine. 2024;76:102815.
27. Heslin KP, Haruna A, George RA, Chen S, Nobel I, Anderson KB, et al. Association between ADHD and COVID-19 infection and clinical outcomes: a retrospective cohort study from electronic medical records. J Atten Disord. 2023;27:169–81.
28. Centers for Disease Control and Prevention. People with certain medical conditions and COVID-19 risk factors [cited 2024 May 14]. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
29. Hall JP, Kurth NK, McCorkell L, Goddard KS. Long COVID among people with preexisting disabilities. Am J Public Health. 2024;114:1261–4.
30. Zheng YB, Zeng N, Yuan K, Tian SS, Yang YB, Gao N, et al. Prevalence and risk factor for long COVID in children and adolescents: a meta-analysis and systematic review. J Infect Public Health. 2023;16:660–72.
31. Kompaniyets L, Bull-Otterson L, Boehmer TK, Baca S, Alvarez P, Hong K, et al. Post–COVID-19 symptoms and conditions among children and adolescents—United States, March 1, 2020–January 31, 2022. MMWR Morb Mortal Wkly Rep. 2022;71:993–9.
32. Danielson ML, Bohm MK, Newsome K, Claussen AH, Kaminski JW, Grosse SD, et al. Trends in stimulant prescription fills among commercially insured children and adults—United States, 2016–2021. MMWR Morb Mortal Wkly Rep. 2023;72:327–32.
33. Chua KP, Volerman A, Zhang J, Hua J, Conti RM. Antidepressant dispensing to US adolescents and young adults: 2016–2022. Pediatrics. 2024;153:e2023064245.
34. Koonce RM, Martin BC. The association between suspected long-COVID and stimulant prescribing in the United States. Psychiatry Res. 2024;331:115686.
35. Vernon SD, Zheng T, Do H, Marconi VC, Jason LA, Singer NG, et al.; NIH Researching COVID to Enhance Recovery (RECOVER) Consortium. Incidence and prevalence of post-COVID-19 myalgic encephalomyelitis: a report from the observational RECOVER-Adult study. J Gen Intern Med. 2025;40:1085–94.
36. Grach SL, Seltzer J, Chon TY, Ganesh R. Diagnosis and management of myalgic encephalomyelitis/chronic fatigue syndrome. Mayo Clin Proc. 2023;98:1544–51.
37. American Federation of Teachers. Chronic absenteeism 2016 [cited 2024 Nov 25]. https://www.aft.org/childrens-health-safety-and-well-being/childrens-access-care/chronic-absenteeism
38. Dee TS. Higher chronic absenteeism threatens academic recovery from the COVID-19 pandemic. Proc Natl Acad Sci U S A. 2024;121:e2312249121.
39. Black LI, Elgaddal N. Chronic school absenteeism for health-related reasons among children ages 5–17 years: United States, 2022. NCHS data brief, no. 498. Hyattsville (MD): National Center for Health Statistics; 2024.
40. Wikel K, Markelz AM. Chronic health conditions, school attendance, and socioeconomic factors: a literature review. J Spec Educ Apprenticeship. 2023;12:9. https://doi.org/10.58729/2167-3454.1173
41. Attendance Works. Chronic absence: 3 tiers of intervention [cited 2025 Feb 19]. https://www.attendanceworks.org/chronic-absence/addressing-chronic-absence/3-tiers-of-intervention/
42. Kearney CA, Dupont R, Fensken M, Gonzálvez C. School attendance problems and absenteeism as early warning signals: review and implications for health-based protocols and school-based practices. Front Educ (Lausanne). 2023;8:1253595. https://doi.org/10.3389/feduc.2023.1253595
43. Malone LA, Morrow A, Chen Y, Curtis D, de Ferranti SD, Desai M, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of postacute sequelae of SARS-CoV-2 infection (PASC) in children and adolescents. PM R. 2022;14:1241–69.
44. Howard J, Cloeren M, Vanichkachorn G. Long COVID and occupational medicine practice. J Occup Environ Med. 2024;66:1–5.
45. Ziauddeen N, Gurdasani D, O'Hara ME, Hastie C, Roderick P, Yao G, et al. Characteristics and impact of long Covid: findings from an online survey. PLoS One. 2022;17:e0264331.
46. Appelman B, Charlton BT, Goulding RP, Kerkhoff TJ, Breedveld EA, Noort W, et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. Nat Commun. 2024;15:17.
47. Lipkin PH, Okamoto J; Council on Children with Disabilities; Council on School Health. The Individuals With Disabilities Education Act (IDEA) for children with special educational needs. Pediatrics. 2015;136:e1650–62.

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Long-Term Illness in Adults Hospitalized for Respiratory Syncytial Virus Disease, United States, February 2022–September 2023

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Respiratory syncytial virus (RSV) can cause severe illness, but little is known about long-term consequences in hospitalized adults. We surveyed adults (≥18 years of age) who survived hospitalization for RSV or COVID-19 during February 2022–September 2023 about physical functioning and quality of life; surveys were conducted 6–12 months after hospitalization. We compared outcomes after RSV hospitalization by age (<60 vs. ≥60 years) and to those hospitalized for COVID-19 by using multivariable regression models. Among 146 adults hospitalized with RSV, 27.4% reported severe breathlessness and 21.9% poor quality of life at follow-up. Few differences were seen in posthospital illness by age. After adjustment, participants with RSV had 1.81 (95% CI 1.08–3.04) times increased odds of worse dyspnea than did those with COVID-19. Participants reported functional and quality of life impairments after RSV hospitalization, regardless of age, and a postdischarge sequelae constellation similar to that for those hospitalized for COVID-19.

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[1]A full list of collaborators in the IVY Network is provided in Appendix 1 (https://wwwnc.cdc.gov/EID/article/31/14/24-1982-App1.pdf).

Respiratory syncytial virus (RSV) can cause severe acute respiratory illness, especially in older adults. In the United States, RSV infections are responsible for ≈100,000–150,000 hospitalizations annually in persons ≥60 years of age (*1*) and an estimated economic burden of ≥$1.5 billion annually (*2*). RSV infections in older adults comprise 11% of hospital admissions for pneumonia and chronic obstructive pulmonary disease, 7% for acute heart failure, and 5% for asthma exacerbation (*3*). Compared with adults hospitalized and vaccinated for influenza and COVID-19 in 2022–23, those hospitalized with RSV were more likely to be in the intensive care unit (ICU) and receive mechanical ventilation and are at higher risk for death in the hospital and by 1 year after hospitalization (*4*–*6*).

The COVID-19 pandemic highlighted the long-term sequelae associated with severe acute respiratory viral infection. Survivors of moderate-to-severe COVID-19 have substantial and persistent impairments in cognitive and physical function and mental health, leading to loss of independence and health-related quality of life (*7*–*9*) similar to those after other critical illnesses (*10*–*13*). Less is known about recovery after hospitalization with RSV. A previous report found that 10% of adults hospitalized with RSV continue to have moderate-to-severe dyspnea, fatigue, or sleep disruption 3 months after discharge (*14*). One quarter of patients ≥60 years of age may have worsening dyspnea, and one third experience worsening functional impairment 6 months after hospitalization (*15*). However, those studies were limited by narrow capture of outcomes (*14*), focusing only on older cohorts (*15*), and limiting follow-up to 6 months (*14*,*15*).

Substantial gaps remain in determining the long-term consequences of hospitalization with RSV. The primary objective of the prospective multicenter Surveillance of Respiratory Infections' Sequelae (SunRISE) program is to describe posthospital functional, physical, symptom, and quality of life outcomes of patients hospitalized with acute RSV and other acute respiratory infections (ARI) up to 1 year after index hospitalization. The objectives of this analysis are to characterize patients in the SunRISE program and describe the burden of physical disability, loss of independence, persistent symptoms, and poor quality of life outcomes 6–12 months after hospitalization with RSV; examine those outcomes after hospitalization for RSV among adults ≥60 years versus those <60 years of age, given RSV vaccination recommendations for those ≥60 years of age starting in June 2023 (*16*); and compare 6–12-month outcomes to outcomes among persons hospitalized with COVID-19.

Methods

Study Design and Setting

SunRISE is a nested posthospitalization surveillance project involving adult patients hospitalized in 26 hospitals in 20 US states participating in the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network, funded by the Centers for Disease Control and Prevention. Full IVY methods can be found elsewhere (*17*–*19*). In brief, IVY enrolls adults (≥18 years of age) admitted to participating hospitals with a clinical syndrome consistent with acute respiratory illness (≥1 signs and symptoms of fever, cough, shortness of breath, hypoxemia, or new pulmonary findings on chest imaging consistent with pneumonia). Enrolled participants are systematically tested for RSV, SARS-CoV-2, and influenza by laboratory-based PCR on a nasal swab sample within 10 days of symptom onset (*17*–*19*).

Selection of Participants

Patients were eligible for SunRISE if they survived to hospital discharge. Patients were ineligible if the patient or their surrogate was unable to communicate in English or Spanish or if they had no reliable telephone access. This analysis includes patients enrolled in SunRISE after hospitalization with either RSV (primary analytic cohort) or COVID-19 (comparator cohort) during February 2022–September 2023. For this analysis, we excluded patients who tested positive for multiple viruses (RSV, SARS-CoV-2, or influenza) during the index hospitalization and those in hospice care at hospital admission or discharge.

SunRISE telephone survey attempts began on April 26, 2023, and contact occurred up to 14 months after discharge. We recontacted patients who were still in the hospital at the time of initial contact after discharge. Eligible patients were approached at 6, 9, or 12 months after hospital admission at the earliest survey window in which they were eligible (Appendix 2 Figure 1, https://wwwnc.cdc.gov/EID/article/31/14/24-1982-App2.pdf), enabling entry at any follow-up time point; we recontacted participants who were unable to be reached at the next open survey window. We prioritized patients hospitalized with RSV for contact because the primary goal was to study RSV-related sequelae. We matched hospitalized RSV patients with COVID-19 patients 1:1 by admission date (within 30 days where possible) and site; not all RSV participants were matched (n = 1 in current analysis). We approached both IVY participants and proxies; whenever possible, we prioritized collecting data directly from the participant.

To maximize survey completion, we offered surveys by telephone, email link, or postal mail, based on respondent preference; we offered a Spanish-language version of the survey in all forms. We collected data using Research Electronic Data Capture (REDCap) (*20*,*21*). If the patient had multiple surveys completed (e.g., 6 and 9 months), we used the earliest follow-up timepoint with completed data because most participants had 6-month data.

Primary Outcomes

The primary outcomes for this analysis were physical function; degree of dyspnea; ability to perform basic activities of daily living (ADLs), such as bathing, feeding, and dressing, and instrumental ADLs, such as shopping, managing finances, or making telephone calls; self-rated health; and quality of life (Appendix 2 Table 1). We characterized physical function by using the physical functioning subscale of the RAND 36-Item Health Survey 1.0 (SF-36 Physical Functional Subscale), which ranges from 0 to 100, with higher scores indicating better physical functioning (*22*); its overall population mean (±SD) is 70.6 (±27.4) (*23*). At the first survey contact, we asked patients to rate physical function 2 weeks before the acute illness using the SF-36 Physical Function Subscale. We characterized the degree of dyspnea using a modified Medical Research Council (MRC) dyspnea scale (*24*), for which scores range from grade 0 (only gets breathless during strenuous exercise) to grade 4 (gets too breathless to leave the house).

The Katz Index of Independence in ADLs characterized the patient's ability to perform basic ADLs (*25*). Scores range from 0 to 6, and higher scores indicate greater independence in performing basic ADLs (*25*). The Lawton Instrumental Activities of Daily Living characterized the patient's ability to perform instrumental ADLs (*26*). Scores range from 0 to 8, and higher scores indicate greater independence in performing instrumental ADLs (*26*). At the first contact, we asked patients to rate their ability to perform their basic and instrumental ADLs 2 weeks before the acute illness, using both scales to establish a baseline. We considered a decrease of ≥1 point compared with baseline on the Katz or Lawton scale a loss of 1 basic or instrumental ADL, respectively.

We assessed quality of life by using the EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L), which uses 5 questions to characterize impairments in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression to calculate utility index values validated for the US population (*27*). A utility index value of 1.0 indicates perfect health, 0.0 represents death, and <0.0 indicates quality of life worse than death. The EQ-5D-5L's population mean (±SD) is 0.85 (±0.21) (*28*). An EQ-5D-5L score <0.632 indicates fair quality of life, and a score <0.338 indicates poor quality of life (*28*). We also asked patients to report self-rated health on a scale from 0 (the worst health) to 100 (the best health). The self-rated health rating's overall population mean (±SD) is 80.4 (±15.6) (*28*).

Secondary and Exploratory Outcomes

We characterized sleep, cognition, and involvement with social activities by using the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance (4 items) (*29*,*30*), Cognitive Function Abilities Subset (6 items) (*31*), and Social Roles and Activities (4 items) (*32*), respectively. We scored PROMIS scales by using the online HealthMeasures service, with default populations selected. The population means for all PROMIS scales are standardized to 50 (SD ±10). Higher scores represent poorer sleep quality for the PROMIS Sleep Disturbance, and lower scores represent worse cognitive functioning for the PROMIS Cognitive Function Abilities subset and decreased involvement in social activities for the Social Roles and Activities subset. We assessed symptoms using a modified 15-item version of the Community-Acquired Pneumonia Symptoms Survey (*33*) (CAP-Sym), scored 0–75, with each symptom rated on a scale of 0 (no symptom presence) to 5 (severe) and higher scores indicating greater symptom severity burden. Participants with missing data for a given symptom in the CAP-Sym score were imputed to not have that symptom. Symptoms were severe if rated 4 or 5 in severity.

We also assessed exploratory outcomes. Those outcomes included the use of home help and living in a long-term care facility or skilled nursing facility (LTCF/SNF), 2 items about missed work or school for patients and caregivers, new or worsened home oxygen use, and new or worsened continuous positive airway pressure or other breathing machine use compared with 1 month before hospitalization.

Data Collected during Acute Hospitalization

Data collected from the index hospitalization included ICU admission; discharge location, such as home or skilled nursing facility; and length of stay. Severe in-hospital outcomes were any of the following events: deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, high-flow nasal cannula

oxygen, noninvasive or invasive mechanical ventilation, new tracheostomy, new renal replacement therapy, use of vasopressors, or use of extracorporeal membrane oxygenation.

Statistical Analysis

We computed descriptive statistics, including frequencies and percentages, means with SDs, or medians with interquartile ranges (IQR), for demographic data and outcome variables. We calculated p values for comparisons between adults <60 years versus ≥60 years of age and between patients with RSV versus those with COVID-19 by using χ^2 or Fisher exact tests for categorical variables and independent *t* or Wilcoxon signed-rank tests for continuous variables, as appropriate.

We constructed multivariable regression models separately for each primary and secondary outcome of interest to compare age <60 years versus ≥60 years among patients hospitalized with RSV, as well as to compare patients hospitalized with RSV to those hospitalized with COVID-19, adjusting for potential confounders. Model forms included linear, logistic, and ordinal regression, as appropriate; model construction was based on sample size and number of outcomes to avoid the overfitting of models. We used firth correction for rare outcomes, where appropriate. We adjusted all models for age, sex, race and ethnicity, smoking status at index hospitalization, number of organ systems affected by chronic disease, and baseline physical functioning limitations (defined as requiring home care help or unable to walk independently) and additionally adjusted dyspnea models for chronic pulmonary disease as a sensitivity analysis. Models comparing persons hospitalized with RSV to those hospitalized with COVID-19 included a virus variable. For outcome models with baseline Katz, Lawton, and SF-36 Physical Functional Subscale data available, we included the matching retrospective baseline variable. We assessed collinearity between selected variables before final model construction. Results are presented following STROBE guidelines; odds ratios (ORs), proportional odds, or β coefficients with 95% CIs are reported for comparator groups, as appropriate, based on model form.

We used complete case analysis and conducted all analyses using SAS version 9.4 (SAS Institute Inc., https://www.sas.com). We considered $p<0.05$ to be statistically significant for all analyses conducted.

Results

During February 2022–September 2023, a total of 21,611 patients were enrolled in IVY during acute hospitalization. Of those, 610 were hospitalized with RSV, and 465 were eligible and approached for long-term outcome assessment (Appendix 2 Figure 2). Sixty-two patients had co-detection of influenza or COVID-19 and were excluded from the analysis. Of the remaining 403 patients, 146 completed surveys included in the analysis at the earliest of 6 (n = 84), 9 (n = 34), or 12 (n = 28) months. Patients hospitalized with RSV participating in SunRISE were largely similar to nonparticipants, although nonparticipants were older and more often discharged to LTCFs (Appendix 2 Table 2). An additional 118 patients hospitalized with COVID-19 (of 8,715 hospitalized) were able to be matched to RSV cases and included as a comparator cohort. The median time of survey follow-up was ≈6.5 (IQR 5.2–9.8) months for those hospitalized with RSV and 6.7 (IQR 5.6–9) months for those hospitalized with COVID-19.

Characteristics of RSV-Positive Participants

Median age of participating RSV patients was 60.5 (IQR 49.0–70.0) years; 88 (60.3%) were female and 58 (39.7%) male, 43 (29.5%) were non-Hispanic Black, and 22 (15.1%) were of Hispanic ethnicity (Table 1). Most (67.8%) patients had cardiovascular disease before hospitalization with RSV; other common underlying conditions included pulmonary disease (45.9%), endocrine disease (36.3%), and immunocompromised status (30.1%). Forty-four (30.1%) patients had baseline physical functioning limitations. During hospitalization with RSV, 25% were admitted to an ICU, and 36% had severe in-hospital outcomes; median hospital length of stay was 5 (IQR 3–9) days.

Long-Term Outcomes after RSV Hospitalization

Compared with preillness baseline, 28% of patients had a decrease of ≥5 points in their SF-36 Physical Function Subscale scores 6–12 months after hospitalization, indicating a significant loss of physical function after acute RSV illness (Table 2; Appendix 2 Table 3); 48% reported similar physical functioning, and 12% reported improvement. In addition, 11.6% had a loss in instrumental and 11.0% in basic ADL; 71% (instrumental) and 76% (basic) reported the same ADLs as baseline, and ≈10% showed improvement. More than 25% reported that they got breathless when dressing, talking, or at rest. The RSV cohort had a median (IQR) self-rated health of 60 (IQR 50–80), indicating moderate health. Last, 21.9% indicated that they had poor quality of life as characterized by the EQ-5D-5L.

Table 1. Characteristics of patients in a study of long-term illness in adults hospitalized for respiratory syncytial virus disease or COVID-19, United States, February 2022–September 2023*

Category	Primary RSV cohort			COVID-19, n = 118
	Overall, n = 146	Age <60, n = 71	Age ≥60, n = 75	
Demographics				
Age at admission, y (IQR)	60.5 (49.0–70.0)	49.0 (35.0–54.0)	70.0 (65.0–75.0)	64.5 (52.0–75.0)
Sex				
F	88 (60.3)	39 (54.9)	49 (65.3)	60 (50.9)
M	58 (39.7)	32 (45.1)	26 (34.7)	57 (48.3)
Race/ethnicity				
Non-Hispanic White	68 (46.6)	22 (31.0)	46 (61.3)	73 (61.9)
Non-Hispanic Black	43 (29.5)	26 (36.6)	17 (22.7)	27 (22.9)
Hispanic	22 (15.1)	15 (21.1)	7 (9.3)	11 (9.3)
Other	8 (5.5)	4 (5.6)	4 (5.3)	5 (4.2)
Unknown	5 (3.4)	4 (5.6)	1 (1.3)	2 (1.7)
Current/former smoker	22 (15.1)	12 (16.9)	10 (13.3)	21 (18.8)
Long-term care facility at admission†	4 (2.7)	1 (1.4)	3 (4.0)	5 (4.2)
Baseline characteristics at hospital admission				
Immunocompromised status	44 (30.1)	28 (39.4)	16 (21.3)	39 (33.1)
Cardiovascular disease	99 (67.8)	40 (56.3)	59 (78.7)	82 (69.5)
Neurologic disease	9 (6.2)	8 (11.3)	1 (1.3)	19 (16.1)
Pulmonary disease	67 (45.9)	25 (35.2)	42 (56.0)	38 (32.2)
Gastrointestinal disease	6 (4.1)	6 (8.5)	0 (0.0)	7 (5.9)
Endocrine disease	53 (36.3)	23 (32.4)	30 (40.0)	51 (43.2)
Renal disease	40 (27.4)	15 (21.1)	25 (33.3)	34 (28.8)
Hematologic disease	24 (16.4)	9 (12.7)	15 (20.0)	16 (13.6)
Autoimmune/inflammatory disease	13 (8.9)	8 (11.3)	5 (6.7)	9 (7.6)
Psychiatric disorders	32 (21.9)	18 (25.4)	14 (18.7)	32 (27.1)
No. organ systems with chronic disease (IQR)‡	2.0 (2.0–3.0)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	2.0 (1.0–3.0)
Baseline physical functioning limitations§	44 (30.1)	18 (25.4)	26 (34.7)	50 (42.4)
COVID-19 vaccination, current season¶	50 (34.2)	16 (22.5)	34 (45.3)	36 (30.5)
Characteristics of hospital course				
Intensive care unit admission	36 (24.7)	19 (26.8)	17 (22.7)	15 (12.7)
Severe hospital outcomes#	53 (36.3)	24 (33.8)	29 (38.7)	20 (17.0)
Hospital length of stay, d (IQR)**	5.0 (3.0–9.0)	4.0 (3.0–8.0)	5.0 (3.0–10.0)	4.0 (2.0–7.0)
Discharged to long-term care facility	10 (6.9)	4 (5.6)	6 (8.0)	15 (12.7)

*Values are no. (%) except as indicated. Percentages for fields with missing values are computed based on the full column value. For those with RSV, variables missing data were current/former smoker (n = 12), long-term care facility at admission (n = 2), COVID-19 vaccination status (n = 2), and discharged to long-term care facility (n = 6). For those with COVID-19, variables missing data were sex (n = 1), current/former smoker (n = 6), long-term care facility at admission (n = 4), COVID-19 vaccination status (n = 4), and discharged to long-term care facility (n = 1). IQR, interquartile range; RSV, respiratory syncytial virus.
†Including nursing homes, assisted living homes, and rehabilitation hospital or other subacute or chronic facility.
‡Organ systems affected by chronic disease: cardiovascular disease, neurologic disease, pulmonary disease, gastrointestinal disease, endocrine disease, kidney disease, hematologic disease, autoimmune disease, and immunocompromising conditions.
§Baseline physical functioning limitations are defined as receiving home care help or unable to walk.
¶Defined for those hospitalized before September 1, 2022, as completion of a primary series plus 1 or 2 monovalent (original) boosters and for those hospitalized after September 1, 2022, as receipt of ≥1 bivalent vaccine doses
#Defined as any of the following events during the acute illness hospitalization: deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, high-flow nasal cannula oxygen, noninvasive or invasive mechanical ventilation, new tracheostomy, new renal replacement therapy, use of vasopressors, or extracorporeal membrane oxygenation.
**Those hospitalized >28 d had length of stay truncated at 28 d.

Among the RSV cohort, 26.7% of participants reported PROMIS Sleep Disturbances ≥1 SD above the standardized mean of 50, 13.7% reported PROMIS Cognitive scores ≥1 SD below the standardized mean of 50, and 24.0% reported PROMIS Social Activities ≥1 SD below the standardized mean of 50. The total median modified CAP-Sym score was 13 (IQR 5–23), with a median of 1 (IQR 0–3) severe symptom reported (Appendix 2 Table 4).

Almost half (44%) of RSV participants reported receiving home care help for medical care or activities of daily living at the time of the survey. Of those currently working (n = 27), 59% reported missing ≥1 day of work or school because of illness after hospitalization.

Comparing 6–12-Month Outcomes for Patients <60 and ≥60 Years of Age in Adults Hospitalized for RSV

The loss of ability to perform ≥1 basic ADL, decreased physical function (SF-36 Physical Function Subscale decrease ≥5 points), extreme dyspnea, self-rated health, and poor quality of life were similar between younger (<60 years) and older (≥60 years) patients with RSV at 6–12 months postillness. Cognitive function, social function, and CAP-Sym scores were additionally similar. However, younger adults had lower odds of a loss in ability to perform 1 instrumental ADL (4.2% vs. 18.7%; adjusted OR [aOR] 0.24, 95% CI 0.07–0.83) (Figure 1) and higher odds of having sleep disturbances ≥1 SD above the mean

Table 2. Six- to 12-mo outcomes in a study of long-term illness in adults hospitalized for respiratory syncytial virus disease or COVID-19, United States, February 2022–September 2023*

Category	RSV only			RSV versus COVID-19		
	Age <60, n = 71	Age ≥60, n = 75	p value†	RSV positive, n = 146	SARS-CoV-2 positive, n = 118	p value†
Primary outcomes‡						
SF36-PF, median (IQR)	47.5 (20.0–80.0)	20.0 (10.0–60.0)	0.008	40.0 (15.0–75.0)	42.5 (10.0–80.0)	0.799
Change from baseline, median (IQR)	0.0 (–5.0 to 0.0)	0.0 (–10.0 to 0.0)	0.087	0.0 (–5.0 to 0.0)	0.0 (–10.0 to 0.0)	0.462
Katz ADLs,§ median (IQR)	6.0 (6.0–6.0)	6.0 (5.0–6.0)	0.053	6.0 (5.0–8.0)	6.0 (5.0–6.0)	0.854
Decrease from baseline ≥1 point	7 (9.9)	9 (12.0)	0.682	16 (11.0)	12 (10.2)	0.858
Lawton instrumental ADLs,§ median (IQR)	8.0 (6.0–8.0)	7.0 (3.0–8.0)	0.077	8.0 (5.0–8.0)	8.0 (5.0–8.0)	0.802
Decrease from baseline ≥1 point	3 (4.2)	14 (18.7)	0.005	17 (11.6)	17 (14.4)	0.519
Dyspnea			0.558			0.104
Grade 0/1	21 (29.6)	22 (29.3)		43 (29.5)	49 (41.5)	
Grade 2	9 (12.7)	6 (8.0)		15 (10.3)	7 (5.9)	
Grade 3	19 (26.8)	18 (24.0)		37 (25.3)	26 (22.0)	
Grade 4	16 (22.5)	24 (32.0)		40 (27.4)	23 (19.5)	
Self-rated health, median (IQR)	62.5 (50.0–80.0)	60.0 (50.0–80.0)	0.222	60.0 (50.0–80.0)	70.0 (50.0–80.0)	0.678
EQ-5D-5L, median (IQR)	0.712 (0.394–0.926)	0.687 (0.363–0.883)	0.551	0.705 (0.338–0.902)	0.719 (0.458–0.904)	0.481
Good, >0.632	39 (54.9)	39 (52.0)		78 (53.4)	67 (56.8)	
Fair, 0.338–0.632	13 (18.3)	15 (20.0)		28 (19.2)	24 (20.3)	
Poor, <0.338	16 (22.5)	16 (21.3)		32 (21.9)	22 (18.6)	
Secondary outcomes						
PROMIS Sleep Disturbances						
Median (IQR)	53.9 (41.2–63.8)	51.4 (41.2–57.2)	0.219	51.7 (41.2–61.1)	50.0 (42.1–57.7)	0.606
≥1 SD >50	25 (35.2)	14 (18.7)	0.023	39 (26.7)	23 (19.5)	0.189
PROMIS Cognitive Function						
Median (IQR)	50.8 (43.4–66.2)	52.7 (43.4–66.2)	0.931	51.4 (43.4–66.2)	51.7 (43.9–66.2)	0.880
≥1 SD <50	8 (11.3)	12 (16.0)	0.333	20 (13.7)	16 (13.6)	0.963
PROMIS Social Activities						
Median (IQR)	51.8 (37.2–64.2)	49.9 (40.2–58.1)	0.489	51.5 (37.9–64.2)	51.8 (40.3–64.2)	0.423
≥1 SD <50	19 (26.8)	16 (21.3)	0.626	35 (24.0)	26 (22.0)	0.666
CAP-Sym Score						
Total score	14.0 (3.0–24.0)	12.0 (6.0–20.0)	0.533	13.0 (5.0–23.0)	9.0 (3.0–20.0)	0.161
Total no. severe symptoms	1.0 (0.0–3.0)	1.0 (0.0–2.0)	0.269	1.0 (0.0–3.0)	1.0 (0.0–2.0)	0.430
Exploratory outcomes§						
Receives regular help at home with medical care or ADL	27 (38.0)	38 (50.7)	0.125	65 (44.5)	53 (44.9)	0.900
New receipt of home health care from hospitalization	10 (14.1)	17 (22.7)	0.195	27 (18.5)	10 (8.5)	0.019
SNF/LTCF at survey timepoint	2 (2.8)	7 (9.3)	0.094	9 (6.2)	7 (5.9)	0.784
New SNF/LTCF compared with hospitalization	1 (1.4)	5 (6.7)	0.099	6 (4.1)	2 (1.7)	0.263
Patient missed work or school¶	12/18 (66.7)	4/9 (44.4)	0.411	16/27 (59.3)	11/19 (57.9)	0.926
Caregiver missed work or school	31 (43.7)	18 (24.0)	0.016	49 (34.5)	29 (24.6)	0.196
New/worsened home oxygen use#	19 (26.9)	17 (22.7)	0.566	36 (24.7)	19 (16.1)	0.110
New/worsened CPAP/other breathing machine use#	6 (8.5)	5 (6.7)	0.683	11 (7.5)	5 (4.2)	0.287

*Values are no. (%) except as indicated. Earliest completed survey from 6, 9, or 12 mo was used. Percentages for fields with missing values are computed based on the full column. Details on each testing scale are provided in the text. For those with RSV, variables missing data were SF36-PF (n = 9), baseline SF-36 PF comparison (n = 17), Katz (n = 5), baseline Katz comparison (n = 6), Lawton (n = 4), baseline Lawton comparison (n = 11), dyspnea (n = 11), self-rated health (n = 9), EQ-5D-5L (n = 8), PROMIS sleep disturbance (n = 4), PROMIS cognitive function (n = 8), PROMIS social activities (n = 14), new home care help (n = 3), new LTCF (n = 3), and caregiver time off (n = 4). For those with COVID-19, variables missing data were SF36-PF (n = 8), baseline SF-36 PF comparison (n = 12), Katz (n = 5), baseline Katz comparison (n = 6), Lawton (n = 5), baseline Lawton comparison (n = 8), dyspnea (n = 13), self-rated health (n = 4), EQ-5D-5L (n = 5), PROMIS sleep disturbance (n = 5), PROMIS cognitive function (n = 6), PROMIS social activities (n = 10), home care help (n = 1), new home care help (n = 2), new LTCF (n = 4), caregiver time off (n = 10), new home oxygen use (n = 3), and new home CPAP use (n = 3). Of those with RSV, 94 (64%) had nonmissing data for the survey components, and of those with COVID-19, 76 (64%) had nonmissing data for the survey components; missing data was imputed to 0/no for symptoms, so those missing individual symptoms are not included. ADL, activity of daily living; CPAP, continuous positive airway pressure; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; IQR, interquartile range; LTCF, long-term care facility; RSV, respiratory syncytial virus; SF-36 PF, Short Form-36 Physical Function Subscale score; SNF, skilled nursing facility.
†p values compare persons <60 y of age to those ≥60 y of age and patients with RSV versus those with COVID-19 and were computed using χ^2 or Fisher exact tests for categorical variables or Wilcoxon signed-rank tests for continuous variables, as appropriate.
‡Change from baseline calculated for those surveys with nonmissing data.
§Basic ADLs include bathing, feeding, and dressing; instrumental ADLs include shopping, managing finances, or making telephone calls
¶Column percentages computed for those who reported being employed or in school at time of hospitalization.
¶Compared with 1 mo before hospitalization.

(35.2% vs 18.7%; aOR 2.61, 95% CI 1.11–6.12) compared with older patients.

Comparing 6–12-Month Outcomes for Adults Hospitalized with RSV Versus COVID-19

Compared with COVID-19 patients and similar to the larger IVY cohort (*4*), patients hospitalized with RSV in SunRISE were slightly younger (median age 60.5 [IQR 49.0–70.0] years vs. 64.5 [IQR 52.0–75.0] years) and had higher proportions of preillness pulmonary disease (45.9% vs. 32.2%). Those with RSV additionally had more frequent ICU admission (24.7% vs. 12.7%), and severe in-hospital outcomes (36.3% vs. 17.0%) than those with COVID-19. Patients hospitalized with COVID-19 reported a higher rate of baseline physical functioning limitations (42.4% vs. 30.1%). Unadjusted outcomes were largely similar for patients with COVID-19 and those with RSV (Table 2). After adjusting for demographics and covariates, those hospitalized with RSV had 1.90 (95% CI 1.14–3.16) times higher proportional odds of more severe dyspnea than those hospitalized with COVID-19 (Figure 2; Appendix 2 Table 5); results were similar when adjusting for pulmonary disease. We found no other statistically significant differences between outcomes.

Discussion

In this multicenter analysis of adults hospitalized with RSV in 20 US states, patients exhibited significant impairments in physical function and abilities to perform ADLs, significant dyspnea, poor self-rated health, and poor quality of life at 6–12 months after hospitalization. Of note, almost half of SunRISE participants were <60 years of age, the minimum age recommended for RSV vaccination by the Advisory Committee on Immunization Practices starting in June 2023 (*16*). However, our cohort showed significant and persistent functional and quality of life impacts after RSV hospitalization regardless of age. In addition, those hospitalized with RSV suffered a constellation of postdischarge sequelae of similar breadth and severity to that described by patients hospitalized with COVID-19, with the exception of more severe dyspnea in those with RSV. Together, those results suggest the potential for substantial and lingering harm from severe RSV illness across the entire adult age spectrum.

Our findings document long-term sequelae after hospitalization with RSV. One potential additional benefit of RSV vaccination may be prevention of adverse long-term outcomes. This information can be used by clinicians and public health practitioners who monitor at-risk patients after hospitalization, and to inform efforts to prevent and reduce the severity of these hospitalizations through targeted vaccination campaigns and other measures (*34*).

Few studies have evaluated the effect of severe RSV illness on physical function, which can deteriorate even before any impairments in performing activities of daily living are appreciated. We found that the median SF-36 Physical Function Subscale score at the time of the 6–12 month follow-up survey was 40, and >25% of all participants reported a decrease of ≥5 points (≥10 points for those ≥60 years of age) from baseline, indicating substantial physical long-term impairment after hospitalization with RSV. That

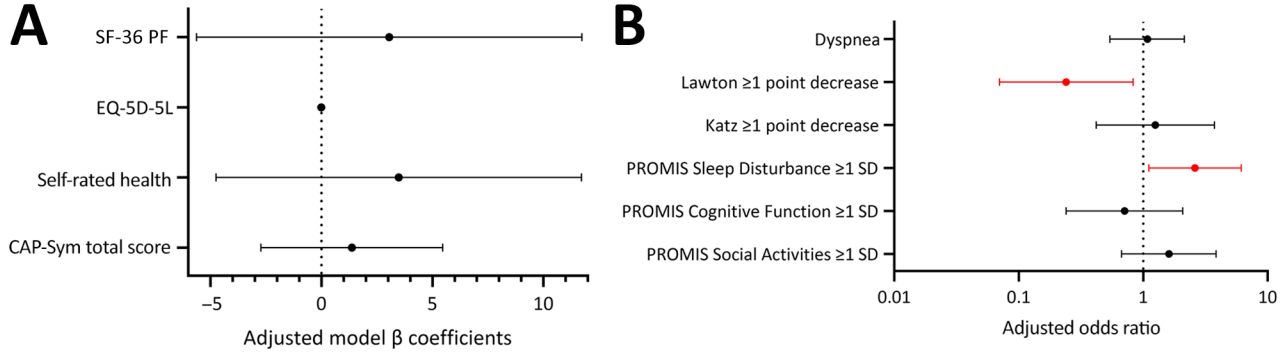

Figure 1. Multivariable model results for 6- to 12-month primary and secondary outcomes for patients hospitalized with respiratory syncytial virus by age in a study of long-term illness in adults hospitalized for respiratory syncytial virus disease or COVID-19, United States, February 2022–September 2023. Models compared persons <60 years of age to those ≥60 years of age. Results are presented separately for continuous (A) and binary or ordinal (dyspnea) (B) outcomes. The earliest completed survey from 6, 9, or 12 months was included. Models were additionally adjusted for sex, race/ethnicity, smoking status, baseline functional limitations, and number of organ systems affected by chronic disease. For outcome models with baseline data available (Katz, Lawton, and SF-36 PF), the matching retrospective baseline variable was included. Red indicates statistically significant effects. Error bars indicate 95% CIs. Vertical dotted lines indicate a null result value for that model type. Outcomes where higher values indicate worse illness for those <60 years of age: CAP-Sym total score, dyspnea, Lawton ≥1 point decrease, Katz ≥1 point decrease, and PROMIS Sleep Disturbance ≥1 SD. Details on each testing scale are provided in the text.

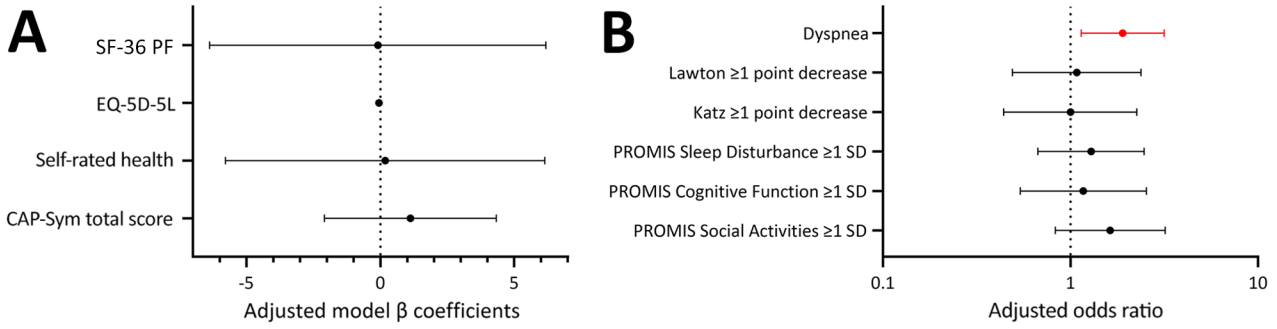

Figure 2. Multivariable model results for 6- to 12-month primary and secondary outcomes for patients in a study of long-term illness in adults hospitalized for respiratory syncytial virus disease or COVID-19, United States, February 2022–September 2023. The earliest completed survey from 6, 9, or 12 months was included. Results are presented separately for continuous (A) and binary or ordinal (dyspnea) (B) outcomes. Models were additionally adjusted for sex, race/ethnicity, smoking status, baseline functional limitations, number of organ systems affected by chronic disease. For outcome models with baseline data available (Katz, Lawton, and SF-36 PF), the matching retrospective baseline variable was included. Red indicates statistically significant effects. Error bars indicate 95% CIs. Vertical dotted lines indicate a null result value for that model type. The following are those outcomes where higher values indicate worse illness for those with respiratory syncytial virus: CAP-Sym total score, dyspnea, Lawton ≥1 point decrease, Katz ≥1 point decrease, and PROMIS Sleep Disturbance ≥1 SD. Details on each testing scale are provided in the text.

loss in physical function could be driven by persistent symptoms; 63% of patients reported moderate or worse dyspnea at the time of the survey. We also observed that 11% of our cohort had lost the ability to perform 1 basic ADL and 12% lost the ability to perform 1 instrumental ADL at 6-months. Those percentages are lower than those observed in a previous study that reported 33% lost the ability to perform 1 basic ADL and 32% lost the ability to perform 1 instrument ADL at 6 months after RSV hospitalization (*15*). However, those differences are likely because of different patient characteristics; our cohort was younger (median age 60.5 vs. 74 years), and fewer resided in a skilled nursing facility (3% vs. 8%).

Given the degree of functional impairment, disability, and persistent symptoms, that SunRISE participants reported poor self-rated health and quality of life is not surprising. Several studies have evaluated health-related quality of life after RSV illness. A study in Europe observed a median (IQR) EQ-5D-5L index score of 0.85 (0.81–0.94) in community-dwelling older patients with RSV illness at 1 week after acute illness, but index scores improved to baseline 4 weeks postinfection (*35*). However, that cohort enrolled nonhospitalized RSV patients, who likely had better baseline quality of life and health than those in our study; health-related quality of life and self-rated health are moderately correlated with lower respiratory tract symptoms (*14*). Another study collected EQ-5D-5L scores at 3 months after hospitalization with RSV from 238 patients; the authors did not report summary EQ-5D-5L index scores, but the mean self-rated health was slightly higher than that observed in SunRISE (*14*). Our study extends the findings to a younger cohort with longer duration of follow-up and strengthens evidence for potential significant long-term sequelae after RSV hospitalization, regardless of age. Additional studies are needed to determine how severe RSV illness affects quality of life.

This study has several strengths, most notably that the underlying patient population is drawn from a large nationwide public health surveillance network for ARI, making the cohort more generalizable to those experiencing severe RSV illness. Robust data collection, including surveys in both English and Spanish, increase the generalizability of the SunRISE cohort. Surveys included both single-item questions and validated questionnaires, enabling robust data capture and comparison to other critical care and ARI cohorts.

The first limitation of our study is that, as for many prospective studies, the included population may represent a relatively healthier population; survival to hospital discharge was required for participation, so results may underestimate RSV and COVID-19 posthospitalization sequelae. In addition, given the broad range of underlying conditions in this population, fully separating changes occurring as part of the natural history of those conditions versus the effects of hospitalization for acute viral illness may be difficult. That difference could potentially overestimate the degree of long-term sequelae caused by the acute viral disease. However, adjustment for functional limitations collected at hospitalization, number of organ systems affected by a chronic disease, and pulmonary disease status (for dyspnea) reduced that risk. Retrospective recall of preillness health status is

imprecise because of time elapsed and other factors, and is potentially biased in either direction. Further, prehospitalization baseline data were limited and not collected on all outcomes, potentially biasing results in either direction. Finally, the sample size for this study did not allow for the robust examination of risk factors or protective factors, such as vaccination, for long-term sequelae after hospitalization with RSV; those considerations will be the focus of subsequent analyses of the SunRISE program.

In this first analysis of the SunRISE program, many patients who were hospitalized with RSV had poor physical functioning (median SF-36 Physical Function Subscale score of 40 out of 100), functional impairment (19% reporting new receipt of home help after hospitalization), and persistent symptoms including dyspnea (63% reporting grade 2 or higher dyspnea) at 6–12 months after hospitalization, regardless of age. A substantial proportion of participants also reported poor quality of life (41% reporting fair or poor EQ-5D-5L scores) and poor self-rated health (median 60 out of 100) up to 1 year after hospitalization with RSV. Such long-term effects appear similar to those occurring after hospitalization with COVID-19, another acute respiratory illness associated with adverse long-term outcomes in adults. Data from this analysis can inform risk communication about RSV in adults and the potential benefits of RSV prevention through vaccination.

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This activity was reviewed by CDC and each participating institution (https://www.cdc.gov/flu-vaccines-work/php/vaccine-effectiveness/ivy.html), deemed not research, and conducted consistent with applicable federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq). All participants provided oral consent.

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References

1. Havers FP, Whitaker M, Melgar M, Pham H, Chai SJ, Austin E, et al. Burden of respiratory syncytial virus–associated hospitalizations in US adults, October 2016 to September 2023. JAMA Netw Open. 2024;7:e2444756. https://doi.org/10.1001/jamanetworkopen.2024.44756
2. Grace M, Colosia A, Wolowacz S, Panozzo C, Ghaswalla P. Economic burden of respiratory syncytial virus infection in adults: a systematic literature review. J Med Econ. 2023; 26:742–59. https://doi.org/10.1080/13696998.2023.2213125
3. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005;352:1749–59. https://doi.org/10.1056/NEJMoa043951
4. Surie D, Yuengling KA, DeCuir J, Zhu Y, Lauring AS, Gaglani M, et al.; Investigating Respiratory Viruses in the Acutely Ill (IVY) Network. Severity of respiratory syncytial virus vs COVID-19 and influenza among hospitalized US adults. JAMA Netw Open. 2024;7:e244954. https://doi.org/10.1001/jamanetworkopen.2024.4954
5. Begley KM, Monto AS, Lamerato LE, Malani AN, Lauring AS, Talbot HK, et al. Prevalence and clinical outcomes of respiratory syncytial virus vs influenza in adults hospitalized with acute respiratory illness from a prospective multicenter study. Clin Infect Dis. 2023;76:1980–8. https://doi.org/10.1093/cid/ciad031
6. Tseng HF, Sy LS, Ackerson B, Solano Z, Slezak J, Luo Y, et al. Severe morbidity and short- and mid- to long-term mortality in older adults hospitalized with respiratory syncytial virus infection. J Infect Dis. 2020;222:1298–310. https://doi.org/10.1093/infdis/jiaa361
7. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. Brain Behav Immun. 2022;101:93–135. https://doi.org/10.1016/j.bbi.2021.12.020
8. Marchi M, Grenzi P, Serafini V, Capoccia F, Rossi F, Marrino P, et al. Psychiatric symptoms in long-COVID patients: a systematic review. Front Psychiatry. 2023;14:1138389. https://doi.org/10.3389/fpsyt.2023.1138389
9. Tabacof L, Tosto-Mancuso J, Wood J, Cortes M, Kontorovich A, McCarthy D, et al. Post-acute COVID-19 syndrome negatively impacts physical function, cognitive function, health-related quality of life, and participation. Am J Phys Med Rehabil. 2022;101:48–52. https://doi.org/10.1097/PHM.0000000000001910
10. Ehlenbach WJ, Hough CL, Crane PK, Haneuse SJ, Carson SS, Curtis JR, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA. 2010;303:763–70. https://doi.org/10.1001/jama.2010.167
11. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304:1787–94. https://doi.org/10.1001/jama.2010.1553
12. Weinert C, Meller W. Epidemiology of depression and antidepressant therapy after acute respiratory failure. Psychosomatics. 2006;47:399–407. https://doi.org/10.1176/appi.psy.47.5.399

13. Feemster LC, Cooke CR, Rubenfeld GD, Hough CL, Ehlenbach WJ, Au DH, et al. The influence of hospitalization or intensive care unit admission on declines in health-related quality of life. Ann Am Thorac Soc. 2015;12:35–45. https://doi.org/10.1513/AnnalsATS.201404-172OC
14. Falsey AR, Walsh EE, Osborne RH, Vandendijck Y, Ren X, Witek J, et al. Comparative assessment of reported symptoms of influenza, respiratory syncytial virus, and human metapneumovirus infection during hospitalization and post-discharge assessed by Respiratory Intensity and Impact Questionnaire. Influenza Other Respir Viruses. 2022;16:79–89. https://doi.org/10.1111/irv.12903
15. Branche AR, Saiman L, Walsh EE, Falsey AR, Jia H, Barrett A, et al. Change in functional status associated with respiratory syncytial virus infection in hospitalized older adults. Influenza Other Respir Viruses. 2022;16:1151–60. https://doi.org/10.1111/irv.13043
16. Centers for Disease Control and Prevention. RSV vaccine guidance for adults. 2024 [cited 2024 Oct 14]. https://www.cdc.gov/rsv/hcp/vaccine-clinical-guidance/older-adults.html
17. Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, et al.; Influenza and Other Viruses in the Acutely Ill (IVY) Network. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ. 2022;376:e069761. https://doi.org/10.1136/bmj-2021-069761
18. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al.; Influenza and Other Viruses in the Acutely Ill (IVY) Network. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA. 2021;326:2043–54. https://doi.org/10.1001/jama.2021.19499
19. Tenforde MW, Patel MM, Ginde AA, Douin DJ, Talbot HK, Casey JD, et al.; Influenza and Other Viruses in the Acutely Ill (IVY) Network. Effectiveness of severe acute respiratory syndrome coronavirus 2 messenger RNA vaccines for preventing coronavirus disease 2019 hospitalizations in the United States. Clin Infect Dis. 2022;74:1515–24. https://doi.org/10.1093/cid/ciab687
20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81. https://doi.org/10.1016/j.jbi.2008.08.010
21. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al.; REDCap Consortium. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208
22. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473–83. https://doi.org/10.1097/00005650-199206000-00002
23. Rand Corporation. 36-Item Short Form Survey (SF-36) scoring instructions [cited 2021 Feb 3]. https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html
24. Tong A, Baumgart A, Evangelidis N, Viecelli AK, Carter SA, Azevedo LC, et al.; COVID-19-Core Outcomes Set Investigators. Core outcome measures for trials in people with coronavirus disease 2019: respiratory failure, multiorgan failure, shortness of breath, and recovery. Crit Care Med. 2021;49:503–16. https://doi.org/10.1097/CCM.0000000000004817
25. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc. 1983;31:721–7. https://doi.org/10.1111/j.1532-5415.1983.tb03391.x
26. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86. https://doi.org/10.1093/geront/9.3_Part_1.179
27. Pickard AS, Law EH, Jiang R, Pullenayegum E, Shaw JW, Xie F, et al. United States valuation of EQ-5D-5L health states using an international protocol. Value Health. 2019;22:931–41. https://doi.org/10.1016/j.jval.2019.02.009
28. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. Qual Life Res. 2021;30:803–16. https://doi.org/10.1007/s11136-020-02650-y
29. Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep. 2010;33:781–92. https://doi.org/10.1093/sleep/33.6.781
30. Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, et al. Development of short forms from the PROMIS™ Sleep Disturbance and Sleep-Related Impairment item banks. Behav Sleep Med. 2011;10:6–24. https://doi.org/10.1080/15402002.2012.636266
31. Lai JS, Wagner LI, Jacobsen PB, Cella D. Self-reported cognitive concerns and abilities: two sides of one coin? Psychooncology. 2014;23:1133–41. https://doi.org/10.1002/pon.3522
32. Hahn EA, DeWalt DA, Bode RK, Garcia SF, DeVellis RF, Correia H, et al.; PROMIS Cooperative Group. New English and Spanish social health measures will facilitate evaluating health determinants. Health Psychol. 2014;33:490–9. https://doi.org/10.1037/hea0000055
33. Lamping DL, Schroter S, Marquis P, Marrel A, Duprat-Lomon I, Sagnier PP. The community-acquired pneumonia symptom questionnaire: a new, patient-based outcome measure to evaluate symptoms in patients with community-acquired pneumonia. Chest. 2002;122:920–9. https://doi.org/10.1378/chest.122.3.920
34. Payne AB, Watts JA, Mitchell PK, Dascomb K, Irving SA, Klein NP, et al. Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis. Lancet. 2024;404:1547–59. https://doi.org/10.1016/S0140-6736(24)01738-0
35. Mao Z, Li X, Korsten K, Bont L, Butler C, Wildenbeest J, et al.; RESCEU Investigators. Economic burden and health-related quality of life of respiratory syncytial virus and influenza infection in European community-dwelling older adults. J Infect Dis. 2022;226(Suppl 1):S87–94. https://doi.org/10.1093/infdis/jiac069

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Nonspecific Symptoms Attributable to Lyme Disease in High-Incidence Areas, United States, 2017–2021

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For some patients who have Lyme disease (LD), nonspecific symptoms can persist after treatment and impair quality of life. Estimating the frequency and duration of such symptoms is challenging. Using commercial insurance claims data from 2017–2021 for enrollees residing in states where LD is common, we identified 24,503 case-patients with LD and matched them (1:5) with 122,095 control-patients with other diagnoses by demographics, medical service date, and inpatient/outpatient setting. We compared relative frequencies of diagnosis codes for pain, fatigue, and cognitive difficulties between case-patients and control-patients in the year after diagnosis. Those symptom codes occurred 5.0% more frequently among case-patients than among control-patients and comprised »11.0% of the total symptom codes among case-patients. Symptom code frequency among case-patients declined significantly in the 6–12 months after LD diagnosis and reached levels similar to control-patients by the end of the year, with the exception of fatigue.

Lyme disease (LD) is a tickborne illness caused in North America by the bacteria Borrelia burgdorferi and B. mayonii. Human cases occur primarily in the northeastern and upper midwestern United States (1). Most patients recover completely when treated with appropriate antimicrobial drugs (2–4); however, some report prolonged nonspecific symptoms of pain, fatigue, or cognitive difficulties (5–12). Those prolonged symptoms are often referred to as post-treatment Lyme disease syndrome (PTLDS) and can occur in the absence of objective chronic sequelae such as facial palsy or recurrent arthritis. Persistence of similar nonspecific symptoms has been reported after other infections, including COVID-19, which suggests a common mechanism underlying such infection-associated chronic conditions and illnesses (13).

Published studies describing the frequency and duration of nonspecific symptoms after acute LD have several limitations. Some have lacked a control group. Because symptoms of pain, fatigue, and cognitive difficulties are commonly experienced by the general population, inclusion of a control group is essential to determine the fraction of symptoms specifically attributable to LD. Other studies have been challenging to contextualize because of variations in methodology, patient groups, and timing of assessment (*4*,*14*–*18*). Among recent studies that are methodologically similar and include controls, 5 have reported on the frequency of nonspecific symptoms at 6 and 12 months after treatment for patients with early localized LD (i.e., erythema migrans rash). Two studies (*16*,*18*) reported elevated frequencies 6 months after treatment for ≥2 symptom types among case-patients compared with control-patients; 3 other studies reported no notable differences in relative frequencies for the symptom types of pain, fatigue, or cognitive difficulties (*11*,*14*,*19*). One of the 5 studies reported significantly elevated symptom frequencies among case-patients at 12 months posttreatment (*16*). Nevertheless, most of those recent studies identified a small subset of patients having prolonged symptoms consistent with PTLDS during 12 months of follow-up (*11*,*16*,*18*).

Large health record databases, such as those containing electronic health records or insurance claims records, have been used to identify and evaluate LD diagnoses, including the frequency of nonspecific symptom diagnosis codes suggestive of PTLDS in the year after LD diagnosis (*20*,*21*). In this study, we used a large insurance claims database to determine the frequency and risk for nonspecific symptom codes

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suggestive of PTLDS that were attributable to LD during the 12 months after diagnosis.

Methods

Data Source

In this matched cohort study, we used 2017–2021 data from the Merative MarketScan Commercial Claims and Encounters Databases (*22*), which contains annual insurance claims information for >25 million US residents ≤65 years of age with employer-sponsored health insurance and their dependents. We restricted the eligible patient population for this study to those who resided in states with a high incidence of LD (defined as ≥10 confirmed cases of LD per 100,000 population for 3 years) (*23*). Centers for Disease Control and Prevention human subjects review determined that this project did not involve human subjects. Thus, Institutional Review Board approval was not required.

Identification of LD Case-Patients

To identify LD case-patients, we used a previously developed algorithm (*23*) based on International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), codes for LD (A69.2x) and a prescription claim for ≥7 days of treatment with a recommended first-line drug for LD within 14 days before or after the date of the the ICD-10-CM code. We identified inpatient diagnoses solely on the basis of whether an ICD-10-CM code for LD was listed as the primary or secondary diagnosis code.

We excluded case-patients with <365 days of continuous health plan enrollment immediately before and after their LD diagnosis date. To increase the probability that we included only new LD diagnoses, we also excluded patients with an LD ICD-10-CM code in the 365 days before they met LD case-patient criteria. Patients could meet LD diagnosis criteria multiple times in the 5-year study period, but we included only the first instance per calendar year.

Selection of Matched Control-Patients

We identified a 5% random sample of all eligible MarketScan enrollees each year during the 5-year study period. We then matched the potential control-patients individually to case-patients without replacement on age group (0–17, 18–34, 35–44, 45–54, 55–64 years), sex, and inpatient versus outpatient diagnosis. Of the potential control-patients meeting the matching criteria for a case-patient, we considered for selection only those having a healthcare visit within ±14 days of the case-patient's LD diagnosis date. All potential control-patients had to have ≥365 days of continuous enrollment immediately before and after their matched date. We required ≥1 control-patient per case-patient to a maximum of 5. Persons who met case-patient criteria in a given year were ineligible to be control-patients in that year.

Identification of Nonspecific Symptom Codes

We identified nonspecific symptoms suggestive of PTLDS by specific healthcare encounter-associated ICD-10-CM diagnosis codes in case-patient and control-patient claims occurring 365 days before to 365 days after the matched diagnosis date. We noted such symptoms in the categories of pain, fatigue, and cognitive difficulties (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/31/14/25-0459-App1.pdf).

Analysis

We calculated weighting for each observation (Appendix) and incorporated it into all point and variance estimates. We compared the weighted proportion of symptom codes among case-patients and control-patients by month and symptom category (pain, fatigue, cognitive difficulties) in the 2–12 months (hereafter referred to as the year) before and after diagnosis. The 30 days before and after the diagnosis date were the wash-out period, in which we considered any symptom codes to be likely attributable to acute illness rather than persistent symptoms. To evaluate associations between having a diagnosis of LD and nonspecific symptom codes in the year before and after diagnosis, we calculated risk ratios (RRs) and attributable risk percents (i.e., the percentage of incidence of disease in exposed persons that is a result of the exposure), as well as 95% CIs around differences and ratios. We report observed frequencies but weighted proportions throughout. We extracted data using SAS version 9.4 (SAS Institute Inc., https://www.sas.com) and performed analyses in R version 4.4.0 or 4.4.1 (The R Project for Statistical Computing, https://www.r-project.org).

Results

A total of 24,503 LD diagnoses (24,197 unique persons) met case-patient criteria during 2017–2021. The highest number of case-patients was 6,550 in 2017 and the lowest was 3,668 in 2020 (Table 1). Nearly all (99.1%) case-patients had 5 matched control-patients.

Nonspecific Symptom Prevalence and Risk Ratios in the Postdiagnosis Year

Approximately 46% of case-patients and 41% of control-patients had ≥1 diagnosis code for any nonspecific

Table 1. Distribution of characteristics of among Lyme disease case-patients and matched control-patients in in study of nonspecific symptoms attributable to Lyme disease in high-incidence areas, United States, 2017–2021*

Characteristic	No. (%) Case-patients, n = 24,503†	No. (%) Control-patients, n = 122,095
Year		
2017	6,550 (22.7)	32,632 (22.7)
2018	5,257 (23.2)	26,140 (23.1)
2019	5,303 (22.5)	26,472 (22.5)
2020	3,668 (17.5)	18,267 (17.5)
2021	3,725 (14.2)	18,584 (14.2)
Age group, y		
0–17	6,101 (23.7)	30,681 (23.8)
18–34	3,587 (22.5)	18,170 (22.8)
35–44	3,398 (15.0)	17,075 (15.1)
45–54	5,582 (18.9)	27,671 (18.8)
55–64	5,835 (19.9)	28,498 (19.5)
Sex		
F	11,088 (44.5)	55,316 (44.6)
M	13,415 (55.5)	66,779 (55.4)
Season of onset		
Winter, Dec–Feb	1,670 (6.9)	8,311 (6.9)
Spring, Mar–May	4,316 (17.4)	21,498 (17.4)
Summer, Jun–Aug	13,704 (56.1)	68,307 (56.1)
Fall, Sep–Nov	4,813 (19.6)	23,979 (19.6)
Diagnosis encounter type		
Outpatient	24,241 (98.9)	120,978 (99.1)
Inpatient	262 (1.1)	1,117 (0.9)

*Case-patients and control-patients were matched on age group, sex, Lyme disease diagnosis or healthcare visit date, and inpatient vs. outpatient status.
†Unweighted frequencies reflect distributions of variables in the sample; weighted percents reflect distributions of variables in MarketScan database.

symptoms related to pain, fatigue, or cognitive difficulties in the postdiagnosis year, representing an absolute difference of 5% (Figure 1). Upon calculating attributable risk percent, an estimated 11.0% of symptom codes among case-patients were a result of their LD diagnosis (Table 2). Pain was the most common symptom code category among both groups, followed by fatigue, then cognitive difficulties. Although less common than pain, fatigue was the symptom code category with the highest relative risk for case-patients compared with control-patients in the postdiagnosis year (RR = 1.67 [95% CI 1.61–1.72]) (Table 2).

Changes in Relative Frequency of Nonspecific Symptoms during the Postdiagnosis Year

The relative frequency of any symptom code among case-patients declined statistically during the year after LD diagnosis, becoming similar to control-patients by the end of the year (Figure 2). The average percent of excess symptom codes among case-patients compared with control-patients declined from 2.5% in the 2nd month to 0.5% in the 6th month (difference = 2.1% [95% CI 1.5%–2.6%) and 1.0% in the 12th month (difference = 1.6% [95% CI 1.0%–2.2%]) postdiagnosis (Table 3). Of the 3 symptom categories, pain declined most precipitously in relative frequency among case-patients, becoming similar to that of control-patients at ≈6 months (Figure 3, Table 3). Similarly, we observed fatigue symptom codes more often among case-patients than control-patients in the first 6 months postdiagnosis; however, relative frequency among case-patients stabilized and remained slightly elevated (≈1.0%) over that reported for control-patients during the remaining 6 months of the postdiagnosis year. The relative frequency of codes for cognitive difficulties was extremely low (≤0.1%) for both case-patients and control-patients and varied little in the postdiagnosis year.

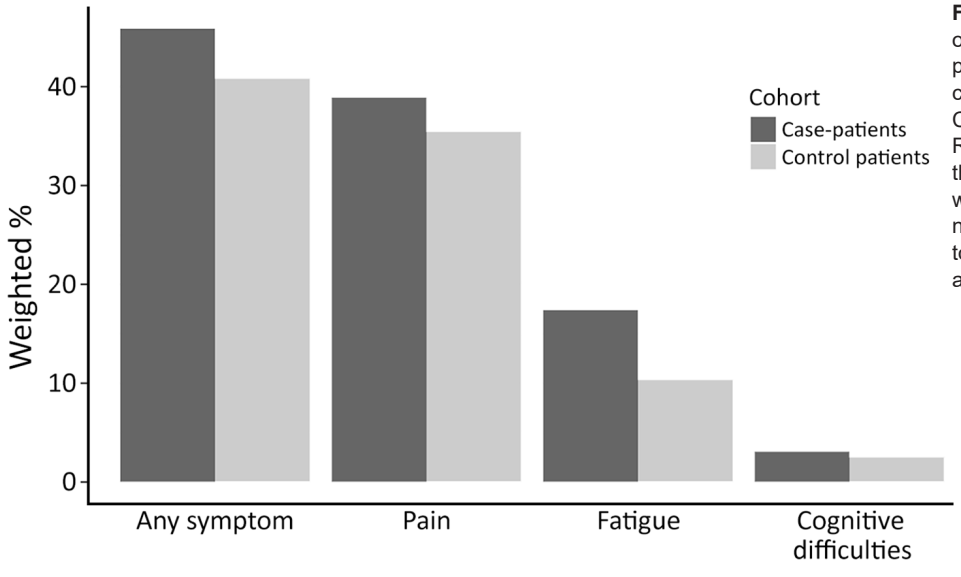

Figure 1. Weighted percentages of case-patients and control-patients with nonspecific symptom codes from the International Classification of Diseases, 10th Revision, Clinical Modification, in the year postdiagnosis excluding wash-out period in study of nonspecific symptoms attributable to Lyme disease in high-incidence areas, United States.

Table 2. Risk for nonspecific symptom codes among case-patients and control-patients in the prediagnosis and postdiagnosis years in study of nonspecific symptoms attributable to Lyme disease in high-incidence areas, United States, 2017–2021*

Measure	Any symptom	Pain	Fatigue	Cognitive difficulties
Risk ratio prediagnosis (95% CI)	1.05 (1.03–1.07)	1.03 (1.01–1.05)	1.35 (1.29–1.41)	0.91 (0.81–1.01)
Risk ratio postdiagnosis (95% CI)	1.12 (1.11–1.14)	1.10 (1.08–1.12)	1.67 (1.61–1.72)	1.18 (1.08–1.28)
Ratio of relative risks (95% CI)	1.07 (1.05–1.10)	1.07 (1.04–1.10)	1.24 (1.17–1.30)	1.30 (1.13–1.49)
Attributable risk postdiagnosis, %	10.9	8.7	40.2	16.1

*Symptom codes from the International Classification of Diseases, 10th Revision, Clinical Modification.

Comparing Symptom Prevalence and Risk Ratios in the Prediagnosis Versus Postdiagnosis Year

Approximately 33% of case-patients and 32% of control-patients had ≥1 code for a nonspecific symptom in the same category in both the year before and year after diagnosis date. When we evaluated by specific symptom category, we found proportions of symptom codes in the prediagnosis year were similar for case-patients and control-patients for all conditions. When we compared the relative risk for symptom codes in the prediagnosis year to the relative risk for symptom codes in the postdiagnosis year (Table 2), the relative risk for pain among case-patients was 1.07 times as high in the postdiagnosis year (95% CI 1.04–1.10), fatigue was 1.24 times as high (95% CI 1.17–1.30), and cognitive difficulties was 1.30 times as high (95% CI 1.13–1.49).

Discussion

In this investigation of a large commercial insurance claims dataset, we observed that 5% more LD case-patients had a code for a nonspecific symptom in the categories of pain, fatigue, or cognitive difficulties than did control-patients in the year after their diagnosis. The relative risk of experiencing nonspecific symptoms at any point in the postdiagnosis year was statistically higher for case-patients (Table 2) but varied substantially based on postdiagnosis month, symptom category, and whether those symptom category codes also occurred in the year before LD diagnosis. The frequency of symptom codes among case-patients declined statistically over the 6 months after LD diagnosis and treatment (Table 3); codes for pain and cognitive difficulties reached proportions that were not statistically different from those of control-patients by the end of the postdiagnosis year. Although the frequency of fatigue codes also diminished significantly (Table 3; Figure 3) over time among case-patients, it was still slightly elevated (≈1%) compared to controls at 12 months postdiagnosis among LD case-patients. Our findings are consistent with several previous clinical studies (*3*,*11*,*18*) identifying similar persisting symptoms of unclear pathogenesis among a subset of persons who received diagnosis and treatment for LD.

Symptoms of pain, fatigue, and cognitive difficulties are common in the general population and have many causes. We observed a 5% excess of nonspecific symptom codes among case-patients amid an overall high background prevalence of those same codes. On that basis, we calculated that ≈11% of those nonspecific symptoms experienced by case-patients were attributable to having had LD, meaning that 89% were likely from other causes. That situation might explain some of the difficulty in identifying effective treatments for PTLDS (*24*–*27*). In addition, ≥30% of both case-patients and control-patients had ≥1 of these symptom category codes in the year before diagnosis. For case-patients, it is possible that some of those preexisting codes represented symptoms indicative of LD that were not recognized, diagnosed, or treated until a later clinical visit (our assigned diagnosis date). Studies have consistently reported on higher rates of prolonged symptoms among patients with disseminated manifestations or longer durations of disease before effective treatment (*16*,*28*–*32*). However, severe fatigue, cognitive impairment, or pain before diagnosis has also been shown to be a determinant of persistent symptoms after LD diagnosis and treatment. In a previous study (*33*), the main

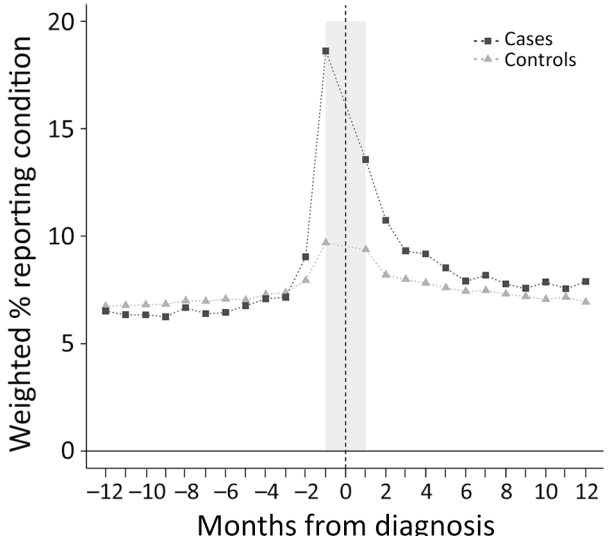

Figure 2. Weighted percentages of case-patients and control-patients with any nonspecific symptom code from the International Classification of Diseases, 10th Revision, Clinical Modification, by month in the year prediagnosis and postdiagnosis, in study of nonspecific symptoms attributable to Lyme disease in high-incidence areas, United States.

Table 3. Average percentage difference in relative frequency of nonspecific symptoms between Lyme disease case-patients and control-patients over the postdiagnosis year in study of nonspecific symptoms attributable to Lyme disease in high-incidence areas, United States, 2017–2021

Symptom	2 mo postdiagnosis	6 mo postdiagnosis	12 mo postdiagnosis	% Difference (95% CI) between 2 and 12 mo	% Difference (95% CI) between 6 and 12 mo
Any symptom	2.5	0.5	1.0	1.6 (1.0–2.2)	−0.5 (−1.0 to 0.06)
Pain	1.2	0.0	0.4	0.8 (0.3–1.3)	−0.4 (−1.0 to −0.1)
Fatigue	2.3	0.8	0.9	1.4 (1.1–1.7)	−0.1 (−0.4 to 0.2)
Cognitive difficulties	0.3	0.0	0.1	0.2 (0.0–0.3)	−0.06 (−0.2 to 0.1)

predictors of persistent symptoms were lower social and physical functioning, negative illness perceptions, and anxiety and depression, factors that we could not assess in this claims-based study. It is also possible that these codes might have been assigned, both before and after the diagnosis date, for symptoms unrelated to a LD diagnosis.

The excess frequency of nonspecific symptom codes observed for case-patients is similar to that reported in 2021 in the largest prospective study of clinically confirmed LD patients published as of March 2025 (*16*), which reported a prevalence of persistent symptoms that was 3.9%–6.0% higher than that of controls over the postdiagnosis year. That study actively and systematically collected information on occurrence of all symptoms at regular intervals from all study participants and further identified participants who had symptoms that began within 6 months of a LD diagnosis and persisted for ≥6 months. Although our study involved data collected for billing purposes and thus our methodology is notably different from theirs, we expect that both the persistent-symptoms group from Ursinus et al. (*16*) and the healthcare-seeking patients in our study represent persons with more severe or unusual symptoms. Ursinus et al. (*16*) also observed a higher proportion of patients with disseminated LD (e.g., Lyme arthritis or cranial neuritis) experienced persistent symptoms of fatigue and pain compared with those with early localized disease (i.e., erythema migrans rash); resolution of symptoms over time occurred primarily for the patient group having disseminated manifestations. Given the limitations of claims data analyses, we were not able to evaluate in our study the effects of specific LD manifestations.

The excess 5% of nonspecific symptoms observed for case-patients in our study was somewhat lower than that reported in other recent evaluations of large health databases. Although we used methodology similar to that of Moon et al. (*21*), those authors found a 9% difference between case-patients and control-patients for symptoms occurring anytime in the postdiagnosis year in an evaluation of electronic health records from a Pennsylvania health system. The diagnosis codes we used to identify nonspecific symptoms were converted from the ICD-9-CM codes used in that previous study (*21*) to ICD-10-CM, because ICD-9-CM codes were phased out and replaced by ICD-10-CM codes in 2015. Although it is possible that we missed some relevant codes in the conversion and thus did not include them in our study, our symptom code list was also somewhat broader; we included additional codes for specific joint and limb pain, consistent with other past clinical studies of subjective symptoms after LD (*31*,*34*). Last, our estimate is much lower than the 35.3% difference in relative frequency of symptom codes occurring over the postdiagnosis year between case-patients and control-patients as reported previously

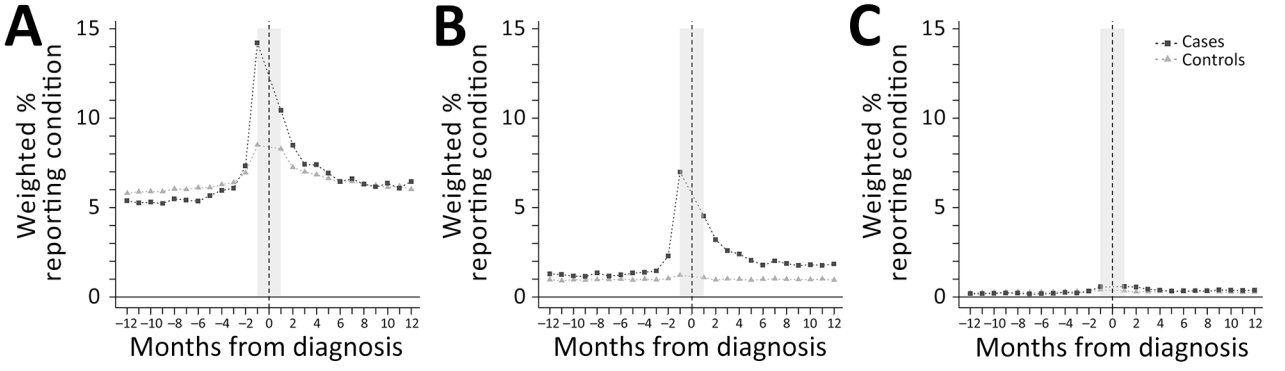

Figure 3. Weighted percentages of case-patients and control-patients with codes from the International Classification of Diseases, 10th Revision, Clinical Modification, in each nonspecific-symptom category, by month in the year prediagnosis and postdiagnosis, in study of nonspecific symptoms attributable to Lyme disease in high-incidence areas, United States. A) Pain; B) fatigue; C) cognitive difficulties.

(*20*). The primary difference between that study and ours was that the previous study (*20*) included codes during the 1 month immediately after LD diagnosis, whereas we did not include codes during that period because they would likely represent symptoms associated with acute LD.

The first limitation of this study is that we relied on observational claims data for information on patient care-seeking and were unable to verify those data by medical record review. We interpreted ICD-10-CM codes as provider diagnoses, but such codes are assigned primarily for billing purposes and thus may not accurately reflect actual diagnosis or the reason for seeking care. In addition, ICD-10-CM codes are subject to varying provider coding practices, leading to the potential for both overestimation and underestimation of the true prevalence of nonspecific symptoms among our study population and potential misclassification of LD case-patients and control-patients. Second, we were unable to assess symptom severity. Clinical studies have found that greater symptom severity at time of LD treatment increases risk of experiencing prolonged symptoms (*8*,*35*). Although information on severity is not available in claims data, we might expect that most of the codes recorded in claims were the result of complaints that warranted care-seeking and were not those experienced more regularly by a substantial portion of the population (*36*). Nevertheless, ability to assess symptom severity would have lent additional confidence to the identification of potential PTLDS symptoms and provided the opportunity to evaluate qualitative improvement of symptoms over time. Third, we did not evaluate LD case-patients for potential co-infections or underlying conditions that could have caused prolonged symptoms, leading to possible overestimation of LD-associated symptoms among case-patients. However, in a sensitivity analysis in which we removed case-patients with diagnosis codes for pain, fatigue, or cognitive difficulties in the year before diagnosis to control for preexisting conditions, we found minimal changes to observed symptom trends (Appendix Figures 1, 2). Fourth, we conducted this analysis among residents of high-incidence states, where healthcare providers are more experienced with diagnosing LD. The relative frequency of symptoms after LD diagnoses in emerging or low-incidence areas might be different because of variation in ascertainment or coding practices. Fifth, although a very large convenience sample, MarketScan lacks data on persons who are uninsured, ≥65 years of age, or military personnel, and it is not nationally or otherwise representative. Last, the observed decrease in LD case-patients during the study period coincides with an overall decrease in MarketScan enrollees during that time because of changing data contributors. On the basis of past evaluations of LD diagnoses in MarketScan (*37*) and our use of weighting, we do not expect that the decrease affected our results.

Certain biases may have also affected our study results. Misinformation, coupled with limited diagnostic testing, has contributed to confusion and controversy about LD (*38*,*39*). It is possible that observed patterns were influenced by patient or healthcare provider beliefs about the disease. For example, some patients with a recent LD diagnosis might expect to have long-term, nonspecific symptoms and would therefore be more likely to report or seek healthcare for those symptoms. Similarly, healthcare providers might be more likely to ask about or record symptoms for patients having had LD (*40*,*41*). A second potential bias is our selection of controls from among a care-seeking population that could potentially overrepresent generally sicker persons (*21*,*42*). If that is the case for those claims data, we might have overestimated the baseline frequency of pain, fatigue, and cognitive difficulties and underestimated the proportion of symptoms attributable to LD diagnoses.

Ultimately, this analysis of a large commercial claims dataset supports observations made in past clinical and epidemiologic studies that a minority of patients with LD diagnosis will experience symptoms of pain, fatigue, or cognitive difficulties for months beyond the acute illness period. Although it appears that most of those symptoms will improve or resolve in the 6 months after diagnosis, a smaller subset of patients might continue to experience persistent symptoms that affect their daily quality of life. More studies are needed to understand the underlying factors associated with occurrence and persistence of such symptoms to inform appropriate treatment and care. Until more is known, guidance on caring for patients with clinically similar infection-associated chronic conditions and illnesses, such as long COVID, will be useful.

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References

1. Schwartz AM, Hinckley AF, Mead PS, Hook SA, Kugeler KJ. Surveillance for Lyme disease— United States, 2008–2015. MMWR Surveill Summ. 2017;66:1–12. https://doi.org/10.15585/mmwr.ss6622a1
2. Dersch R, Sommer H, Rauer S, Meerpohl JJ. Prevalence and spectrum of residual symptoms in Lyme neuroborreliosis after pharmacological treatment: a systematic review. J Neurol. 2016;263:17–24. https://doi.org/10.1007/s00415-015-7923-0
3. Ljøstad U, Mygland A. Remaining complaints 1 year after treatment for acute Lyme neuroborreliosis; frequency, pattern and risk factors. Eur J Neurol. 2010;17:118–23. https://doi.org/10.1111/j.1468-1331.2009.02756.x
4. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43:1089–134. https://doi.org/10.1086/508667
5. Eikeland R, Mygland A, Herlofson K, Ljøstad U. Risk factors for a non-favorable outcome after treated European neuroborreliosis. Acta Neurol Scand. 2013;127:154–60. https://doi.org/10.1111/j.1600-0404.2012.01690.x
6. Eliassen KE, Hjetland R, Reiso H, Lindbaek M, Tschudi-Madsen H. Symptom load and general function among patients with erythema migrans: a prospective study with a 1-year follow-up after antibiotic treatment in Norwegian general practice. Scand J Prim Health Care. 2017;35:75–83. https://doi.org/10.1080/02813432.2017.1288812
7. Mac S, Bahia S, Simbulan F, Pullenayegum EM, Evans GA, Patel SN, et al. Long-term sequelae and health-related quality of life associated with Lyme disease: a systematic review. Clin Infect Dis. 2020;71:440–52. https://doi.org/10.1093/cid/ciz1158
8. Nowakowski J, Nadelman RB, Sell R, McKenna D, Cavaliere LF, Holmgren D, et al. Long-term follow-up of patients with culture-confirmed Lyme disease. Am J Med. 2003; 115:91–6. https://doi.org/10.1016/S0002-9343(03)00308-5
9. Tibbles CD, Edlow JA. Does this patient have erythema migrans? JAMA. 2007;297:2617–27. https://doi.org/10.1001/jama.297.23.2617
10. Weitzner E, McKenna D, Nowakowski J, Scavarda C, Dornbush R, Bittker S, et al. Long-term assessment of post-treatment symptoms in patients with culture-confirmed early Lyme disease. Clin Infect Dis. 2015;61:1800–6. https://doi.org/10.1093/cid/civ735
11. Wormser GP, McKenna D, Karmen CL, Shaffer KD, Silverman JH, Nowakowski J, et al. Prospective evaluation of the frequency and severity of symptoms in Lyme disease patients with erythema migrans compared with matched controls at baseline, 6 months, and 12 months. Clin Infect Dis. 2020;71:3118–24. https://doi.org/10.1093/cid/ciz1215
12. Wormser GP, Weitzner E, McKenna D, Nadelman RB, Scavarda C, Nowakowski J. Long-term assessment of fatigue in patients with culture-confirmed Lyme disease. Am J Med. 2015;128:181–4. https://doi.org/10.1016/j.amjmed.2014.09.022
13. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med. 2022;28:911–23. https://doi.org/10.1038/s41591-022-01810-6
14. Cerar D, Cerar T, Ruzić-Sabljić E, Wormser GP, Strle F. Subjective symptoms after treatment of early Lyme disease. Am J Med. 2010;123:79–86. https://doi.org/10.1016/j.amjmed.2009.05.011
15. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2023;401:e21–33. https://doi.org/10.1016/S0140-6736(23)00810-3
16. Ursinus J, Vrijmoeth HD, Harms MG, Tulen AD, Knoop H, Gauw SA, et al. Prevalence of persistent symptoms after treatment for Lyme borreliosis: a prospective observational cohort study. Lancet Reg Health Eur. 2021;6:100142. https://doi.org/10.1016/j.lanepe.2021.100142
17. Dattwyler RJ, Wormser GP, Rush TJ, Finkel MF, Schoen RT, Grunwaldt E, et al. A comparison of two treatment regimens of ceftriaxone in late Lyme disease. Wien Klin Wochenschr. 2005;117:393–7. https://doi.org/10.1007/s00508-005-0361-8
18. Geebelen L, Lernout T, Devleesschauwer B, Kabamba-Mukadi B, Saegeman V, Belkhir L, et al. Non-specific symptoms and post-treatment Lyme disease syndrome in patients with Lyme borreliosis: a prospective cohort study in Belgium (2016–2020). BMC Infect Dis. 2022;22:756. https://doi.org/10.1186/s12879-022-07686-8
19. Stupica D, Maraspin V, Bogovic P, Ogrinc K, Blagus R, Cerar T, et al. Comparison of clinical course and treatment outcome for patients with early disseminated or early localized Lyme borreliosis. JAMA Dermatol. 2018; 154:1050–6. https://doi.org/10.1001/jamadermatol. 2018.2306
20. Adrion ER, Aucott J, Lemke KW, Weiner JP. Health care costs, utilization and patterns of care following Lyme disease. PLoS One. 2015;10:e0116767. https://doi.org/10.1371/journal.pone.0116767
21. Moon KA, Pollak J, Hirsch AG, Aucott JN, Nordberg C, Heaney CD, et al. Epidemiology of Lyme disease in Pennsylvania 2006–2014 using electronic health records. Ticks Tick Borne Dis. 2019;10:241–50. https://doi.org/10.1016/j.ttbdis.2018.10.010
22. Merative. Merative Marketscan Research Databases 2025 [cited 2024 Nov 25]. https://www.merative.com/documents/brief/marketscan-explainer-general
23. Nawrocki CC, Earley AR, Hook SA, Hinckley AF, Kugeler KJ. Optimizing identification of Lyme disease diagnoses in commercial insurance claims data, United States. BMC Infect Dis. 2024;24:1322. https://doi.org/10.1186/s12879-024-10195-5
24. Berende A, ter Hofstede HJ, Vos FJ, van Middendorp H, Vogelaar ML, Tromp M, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. N Engl J Med. 2016;374:1209–20. https://doi.org/10.1056/NEJMoa1505425
25. Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008;70:992–1003. https://doi.org/10.1212/01.WNL.0000284604.61160.2d
26. Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001;345:85–92. https://doi.org/10.1056/NEJM200107123450202
27. Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post Lyme disease (STOP-LD). Neurology. 2003;60:1923–30. https://doi.org/10.1212/01.WNL.0000071227.23769.9E

28. Asch ES, Bujak DI, Weiss M, Peterson MG, Weinstein A. Lyme disease: an infectious and postinfectious syndrome. J Rheumatol. 1994;21:454–61.
29. Aucott JN, Crowder LA, Kortte KB. Development of a foundation for a case definition of post-treatment Lyme disease syndrome. Int J Infect Dis. 2013;17:e443–9. https://doi.org/10.1016/j.ijid.2013.01.008
30. Hirsch AG, Poulsen MN, Nordberg C, Moon KA, Rebman AW, Aucott JN, et al. Risk factors and outcomes of treatment delays in Lyme disease: a population-based retrospective cohort study. Front Med (Lausanne). 2020;7:560018. https://doi.org/10.3389/fmed.2020.560018
31. Shadick NA, Phillips CB, Logigian EL, Steere AC, Kaplan RF, Berardi VP, et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Intern Med. 1994;121:560–7. https://doi.org/10.7326/0003-4819-121-8-199410150-00002
32. Shadick NA, Phillips CB, Sangha O, Logigian EL, Kaplan RF, Wright EA, et al. Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. Ann Intern Med. 1999;131:919–26. https://doi.org/10.7326/0003-4819-131-12-199912210-00003
33. Vrijmoeth HD, Ursinus J, Harms MG, Tulen AD, Baarsma ME, van de Schoor FR, et al. Determinants of persistent symptoms after treatment for Lyme borreliosis: a prospective observational cohort study. EBioMedicine. 2023;98:104825. https://doi.org/10.1016/j.ebiom.2023.104825
34. Seltzer EG, Gerber MA, Cartter ML, Freudigman K, Shapiro ED. Long-term outcomes of persons with Lyme disease. JAMA. 2000;283:609–16. https://doi.org/10.1001/jama.283.5.609
35. Steere AC, Hutchinson GJ, Rahn DW, Sigal LH, Craft JE, DeSanna ET, et al. Treatment of the early manifestations of Lyme disease. Ann Intern Med. 1983;99:22–6. https://doi.org/10.7326/0003-4819-99-1-22
36. Yoon JH, Park NH, Kang YE, Ahn YC, Lee EJ, Son CG. The demographic features of fatigue in the general population worldwide: a systematic review and meta-analysis. Front Public Health. 2023;11:1192121. https://doi.org/10.3389/fpubh.2023.1192121
37. Schwartz AM, Kugeler KJ, Nelson CA, Marx GE, Hinckley AF. Use of commercial claims data for evaluating trends in Lyme disease diagnoses, United States, 2010–2018. Emerg Infect Dis. 2021;27:499–507. https://doi.org/10.3201/eid2702.202728
38. Aguero-Rosenfeld ME, Wormser GP. Lyme disease: diagnostic issues and controversies. Expert Rev Mol Diagn. 2015;15:1–4. https://doi.org/10.1586/14737159.2015.989837
39. Nesgos AT, Harrington LC, Mader EM. Experience and knowledge of Lyme disease: a scoping review of patient-provider communication. Ticks Tick Borne Dis. 2021;12:101714. https://doi.org/10.1016/j.ttbdis.2021.101714
40. Aucott JN. Posttreatment Lyme disease syndrome. Infect Dis Clin North Am. 2015;29:309–23. https://doi.org/10.1016/j.idc.2015.02.012
41. Halperin JJ. Lyme disease: neurology, neurobiology, and behavior. Clin Infect Dis. 2014;58:1267–72. https://doi.org/10.1093/cid/ciu106
42. Klompas M, Cocoros NM, Menchaca JT, Erani D, Hafer E, Herrick B, et al. State and local chronic disease surveillance using electronic health record systems. Am J Public Health. 2017;107:1406–12. https://doi.org/10.2105/AJPH.2017.303874

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Persistence of Symptoms among Commercially Insured Patients with Coccidioidomycosis, United States, 2017–2023

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Some patients with coccidioidomycosis experience prolonged respiratory and systemic symptoms. However, data on prevalence and persistence of most symptoms are lacking. Using an insurance claims database, we identified patients with coccidioidomycosis diagnoses in the United States during 2017–2023. We assessed prevalence of associated symptoms from 6 months before to 1 year after first diagnosis code (index date) and compared post–index date prevalence to baseline (within 6 to 4 months before index date). Among 2,640 patients, cough (20.8%), dyspnea (13.0%), and fatigue (8.8%) were the most common symptoms at index date. Dyspnea and erythema nodosum were elevated 3–6 months post–index date ($p<0.03$), and fatigue, headache, joint pain, and weakness were elevated 9–12 months post–index date compared with baseline ($p<0.05$).These findings demonstrate that symptoms can persist in coccidioidomycosis patients, which could help inform clinical management and refine estimates of the health and economic burden of coccidioidomycosis.

Coccidioidomycosis is a fungal infection that often presents as acute pulmonary infection; symptoms include cough, fatigue, dyspnea, and fever (*1*–*3*). A small percentage of those affected experience chronic pulmonary or disseminated disease (*4*).

Although coccidioidomycosis symptoms are often self-limited, some might persist for months or years (*5*). In previous studies, patients have self-reported median symptom duration of 60–120 days (*1*,*2*). Fatigue can be particularly long-lasting and can persist after all other evidence of the infection has resolved (*3*,*4*,*6*,*7*). Prolonged symptoms of coccidioidomycosis can cause substantial negative effects; evidence suggests that nearly three-quarters of patients are limited in their ability to perform usual daily activities for a median of 40–47 days during their illness (*1*,*2*).

Although chronic fatigue is increasingly recognized as a characteristic feature of coccidioidomycosis (*6*), data on the persistence of other symptoms are limited. Such information could help inform clinical management and refine estimates of the health and economic burden of coccidioidomycosis. We describe the prevalence and persistence of symptoms among patients with coccidioidomycosis by using a large US health insurance claims database.

Methods

We used the Merative MarketScan Commercial/Medicare Database (https://www.merative.com/documents/brief/marketscan-explainer-general), which includes health insurance claims data for >48 million patients with employer-sponsored plans, including Medicare Supplemental and Medicare Advantage plans, throughout the United States during July 31, 2017–January 31, 2023. We identified patients with coccidioidomycosis diagnoses using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/31/14/25-0022-App1.pdf). Included patients had continuous insurance enrollment in the 180 days before and 365 days after the date the coccidioidomycosis diagnosis code was first used (index date) during the study window. We excluded patients for whom the coccidioidomycosis diagnosis code was listed on a laboratory or imaging claim alone, to minimize diagnoses recorded because the healthcare provider was

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attempting to rule out coccidioidomycosis. To capture incident diagnoses, we excluded patients with a coccidioidomycosis diagnosis code within the 6 months before the index date.

We assessed the prevalence of symptoms associated with coccidioidomycosis, which include abnormal weight loss, chest pain, chills without fever, cough, erythema nodosum or multiforme, fatigue or malaise, fever, generalized hyperhidrosis, headache, myalgia, joint pain, dyspnea, and weakness (*4*,*8*). We also examined the prevalence of a subset of symptoms and conditions associated with other infection-associated chronic illnesses and conditions (IACCIs): depression, dizziness, general paresis, generalized anxiety disorder, hypoactive sexual desire, insomnia, irritable bowel syndrome, palpitations, sleep apnea, and tinnitus (https://www.cdc.gov/chronic-symptoms-following-infections/about/index.html). We assessed the period prevalence of each symptom and condition (for brevity, hereafter referred to as symptoms) during nonoverlapping 30-day periods, from 6 months before to 1 year after index date.

To evaluate the persistence of symptoms, we next used log-binomial regression to compare the prevalence of each symptom within a baseline period before coccidioidomycosis illness (180–121 days before the index date) with the prevalence of symptoms within 4 consecutive 3-month follow-up periods after the index date: 0–89 days (0–3 months), 90–179 days (3–6 months), 180–269 days (6–9 months), and 270–365 days (9–12 months). We selected the baseline period on the basis of previous data indicating that in >90% of patients with coccidioidomycosis, the disease is diagnosed within 120–180 days of illness onset (*9*,*10*).

Finally, we assessed potential factors associated with symptom trends in patients with coccidioidomycosis: presence of underlying medical conditions (asthma or chronic obstructive pulmonary disease, diabetes, or immunosuppression), sex, age group (<18, 18–44, 45–64, or ≥65 years of age), receipt of fluconazole (≥30-day supply, representing a clinically significant duration), and coccidioidomycosis diagnosis type (pulmonary, extrapulmonary, other, or unspecified). We used log-binomial regression to compare symptom prevalence across the levels of each factor (e.g., comparing patients with underlying conditions to patients without) within baseline and the 4 follow-up periods as described. We calculated p values by using the Wald test. We conducted analyses using the Merative MarketScan Treatment Pathways analysis tool (Merative) and R version 4.4.0 (The R Project for Statistical Computing, https://www.r-project.org).

This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.). Because MarketScan data are fully deidentified, this analysis was not subject to review by the CDC institutional review board.

Results

Among 6,062 patients with coccidioidomycosis during the study window, we identified 3,113 (51%) who met the continuous insurance enrollment criteria. We excluded 474 (15%) persons who had a previous coccidioidomycosis diagnosis in the 6 months before the index date, leaving 2,640 coccidioidomycosis patients in the analytic cohort (Table 1). Among all patients, 52% were male and 48% were female, most were between the ages of 18–44 (30%) or 45–64 (50%), and most lived in the West (78%) and in nonrural areas

Table 1. Demographic characteristics, underlying conditions, and coccidioidomycosis type among 2,640 commercially insured patients with coccidioidomycosis, United States, July 2017–January 2023*

Characteristic	No. (%)
Sex	
M	1,363 (52)
F	1,277 (48)
Median age, y (IQR)	51.0 (39.0–60.0)
Age group, y	
<18	123 (5)
18–44	803 (30)
45–64	1,326 (50)
≥65	388 (15)
US Census region of primary beneficiary's residence†	
Northeast	80 (3)
Midwest	219 (8)
South	266 (10)
West	2,047 (78)
Rural status‡	
Rural	123 (5)
Nonrural	2,304 (95)
Underlying conditions	898 (66)
Asthma or COPD	633 (24)
Diabetes	426 (18)
Hypertension	850 (35)
Immunosuppression§	971 (40)
Coccidioidomycosis type on index date	
Pulmonary	1,336 (51)
Cutaneous	52 (2)
Disseminated	118 (4)
Other or unspecified	1,277 (48)

*Values are no. (%) except as indicated. COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
†Regions were derived from US Census regions (https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf).
‡Rural versus nonrural status were based on US Census metropolitan statistical area designation.
§Immunosuppression related to autoimmune disease, cancer, HIV, solid organ transplant, immunosuppressive medication, or a combination of those factors.

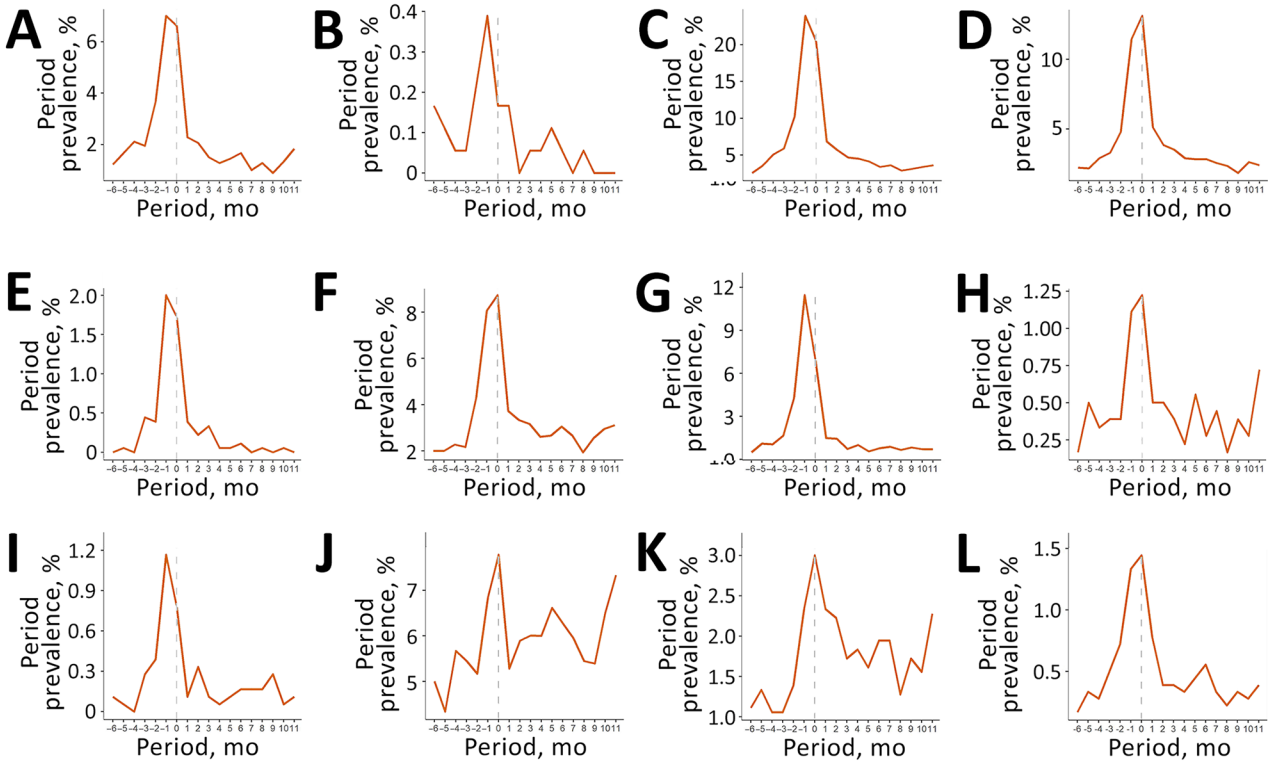

Figure 1. Period prevalence of selected coccidioidomycosis symptoms among commercially insured patients with coccidioidomycosis, United States, July 2017–January 2023. Prevalence is shown for chest pain (A), chills (B), cough (C), dyspnea (D), erythema nodosum or multiforme (E), fatigue (F), fever (G), headache (H), hyperhidrosis (I), joint pain (J), weakness (K), and weight loss (L). The index period (0–29 days after index date) is shown with a dotted line. Data for myalgia are not shown because period prevalence was <1%. X-axis labels represent the beginning of 1-month follow-up periods relative to the index date (e.g., –6 refers to the period of 6–5 months before the index date).

(95%). Approximately 66% had documented underlying conditions. Pulmonary coccidioidomycosis (51%) and other or unspecified coccidioidomycosis (48%) were the most common coccidioidomycosis diagnoses on the index date.

Period Prevalence of Symptoms

Among patients in the cohort, most symptoms increased in the months preceding the index date and peaked during the index period (0–29 days after index date) (Figure 1). During the index period, cough (20.8%), dyspnea (13.0%), and fatigue (8.8%) were the most prevalent coccidioidomycosis-associated symptoms. Most IACCI-associated symptoms also increased in the months preceding the index date and peaked during the index period, although anxiety continued to increase after the index date (Figure 2; Appendix Tables 2, 3). Sleep apnea was the most common IACCI-associated symptom at index date (8%).

The period prevalence of almost every symptom was higher at 0–3 months after the index date than at baseline (Table 2). Most symptoms then declined in the following periods (Figures 1, 2), although many remained elevated compared with baseline levels. Dyspnea and erythema nodosum or multiforme remained elevated 3–6 months after index date ($p<0.03$) (Table 2). Fatigue, joint pain, and weakness were elevated in all follow-up periods and remained higher 9–12 months after the index date than at baseline ($p<0.05$). Headache was also higher at 0–3 months and 9–12 months after index date than at baseline ($p<0.03$). The prevalence of most IACCI-related symptoms was similar to baseline by 3–6 months after index date, but dizziness was marginally higher among patients 9–12 months post–index date compared with baseline ($p<0.10$). Anxiety prevalence was not significantly different from baseline at 0–3 months post–index date but was marginally elevated 6–9 months and 9–12 months post–index date compared with baseline ($p<0.08$).

Factors Associated with Period Prevalence of Symptoms

Patients with underlying conditions had higher prevalence of symptoms during baseline and across each follow-up period compared with patients without underlying conditions (Appendix Table 2, Figures 1,

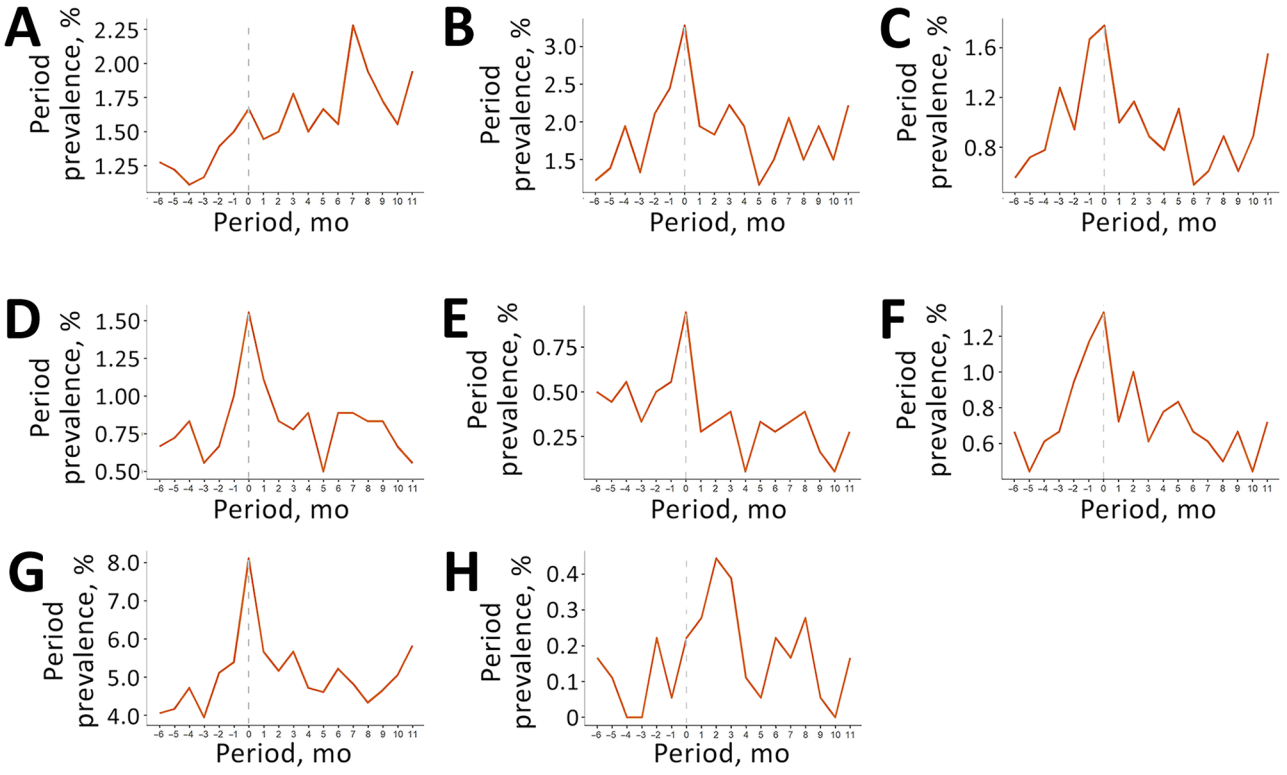

Figure 2. Period prevalence of selected symptoms from infection-associated chronic conditions and illnesses among commercially insured patients with coccidioidomycosis, United States, July 2017–January 2023. Prevalence is shown for anxiety (A), depression (B), dizziness (C), insomnia (D), irritable bowel syndrome (E), palpitations (F), sleep apnea (G), and tinnitus (H). The index period (0–29 days after index date) is shown with a dotted line. Anger, hypoactive sexual desire disorder, and paresis are not shown because prevalence was <0.1% in all periods. X-axis labels represent the beginning of 1-month follow-up periods relative to the index date (e.g., –6 refers to the period of 6–5 months before the index date).

2). Women had higher prevalence of several symptoms (e.g., joint pain and myalgia) than men at baseline and throughout most follow-up periods. Prevalence of erythema nodosum or multiforme, fatigue, and anxiety were similar among women and men at baseline but were higher among women in the periods after index date (Appendix Table 3, Figures 3, 4).

Compared with patients in other age groups, patients ≥65 years of age had higher prevalence of many symptoms, including weakness, dyspnea, and joint pain, at baseline and during most follow-up periods but had lower prevalence of fever and erythema nodosum or multiforme 0–3 months after index date (Appendix Table 4, Figure 5, 6). Compared with patients who did not receive fluconazole, patients who received fluconazole generally had similar prevalence of symptoms, such as chest pain, dyspnea, fatigue, and fever, at baseline but had higher prevalence during follow-up periods (Appendix Table 5, Figures 7, 8). Approximately 4% of patients who did not receive fluconazole received a ≥30-day supply of another azole medication (data not shown). Compared with patients with pulmonary or other or unspecified coccidioidomycosis types, patients with extrapulmonary disease had lower prevalence of respiratory symptoms (e.g., cough and dyspnea) and higher prevalence of headache 0–3 months after index date and higher prevalence of weakness, weight loss, fever, and tinnitus 9–12 months after index date (Appendix Table 6, Figures 9, 10).

Discussion

In this claims-based analysis of patients with commercial health insurance or Medicare, the period prevalence of several coccidioidomycosis-associated symptoms, such as fatigue, joint pain, and weakness, remained significantly elevated for up to 12 months after coccidioidomycosis index date compared with baseline. Most IACCI symptoms were less persistent in patients with coccidioidomycosis, although dizziness and anxiety were marginally elevated at 9–12 months post–index date compared with baseline, and anxiety appeared to increase over time. In addition, the actual duration of many symptoms is

likely longer than estimated in our study, because most patients experience substantial delays between symptom onset and coccidioidomycosis index date (*1*,*10*). Our findings corroborate previous data about long-term persistence of symptoms, such as fatigue (*6*), and suggest that the spectrum of long-term symptoms in patients with coccidioidomycosis might be broader and more persistent for some patients than previously recognized (*11*,*12*). Coccidioidomycosis symptoms can be debilitating and can result in lost work and school attendance (*1*,*6*,*7*), making clinical and public health efforts to better characterize and address those symptoms a priority.

Period prevalence of most symptoms was higher in patients with underlying conditions during baseline and most follow-up periods, likely reflecting higher baseline rates of some symptoms and higher rates of severe coccidioidomycosis in this patient population (*4*). Similarly, higher prevalence of symptoms in older patients might reflect differences in baseline health status and the possibility of more severe infections because of higher rates of underlying conditions (*13*). Although male sex is considered a risk factor for susceptibility to *Coccidioides* infection and severe disease (*14*,*15*), we found higher prevalence of several symptoms in women. Higher baseline prevalence of symptoms in women might be attributable to differences in healthcare use or self-reporting of symptoms (*16*,*17*), whereas higher post–index date prevalence of erythema nodosum or multiforme and fatigue in women could also reflect sex-related differences in the immune response to infection (*18*). Patients who received fluconazole generally had higher post–index date prevalence of many symptoms than patients who did not receive fluconazole, as has been observed previously (*3*). That finding likely reflects increased severity of illness in patients who are prescribed antifungal medications for coccidioidomycosis or fluconazole-related side effects (*5*,*19*).

Although the physiologic underpinnings of chronic coccidioidomycosis-related fatigue are not well understood, some studies have pointed to the possible role of diminished aerobic capacity or postinfectious mitochondrial dysfunction (*20*,*21*).

Table 2. Prevalence ratios of symptoms among commercially insured patients with coccidioidomycosis during 4 follow-up periods after index date compared with baseline, United States, July 2017–January 2023*

	0–3 months		3–6 months		6–9 months		9–12 months	
Characteristic	PR (95% CI)	p value	PR (95% CI)	p value	PR (95% CI)	p value	PR (95% CI)	p value
Coccidioidomycosis-associated symptoms								
Abnormal weight loss	3.64 (2.08–6.82)	<0.001	1.29 (0.64–2.63)	0.5	1.21 (0.60– 2.50)	0.6	1.29 (0.64– 2.63)	0.5
Chest pain	2.10 (1.71–2.60)	<0.001	0.92 (0.71–1.18)	0.5	0.69 (0.53– 0.91)	0.009	0.83 (0.64– 1.07)	0.15
Cough	2.83 (2.48–3.24)	<0.001	1.16 (0.99–1.37)	0.063	0.89 (0.75–1.06)	0.2	0.92 (0.77–1.09)	0.3
Dyspnea	3.05 (2.56–3.67)	<0.001	1.29 (1.05–1.59)	0.018	1.10 (0.89–1.37)	0.4	0.90 (0.72–1.14)	0.4
Erythema nodosum or multiforme	28.6 (6.97–117)	<0.001	5.50 (1.48–35.5)	0.026	2.50 (0.54–17.4)	0.3	1.50 (0.25–11.4)	0.7
Fatigue or malaise	2.48 (2.06–3.00)	<0.001	1.31 (1.06–1.62)	0.012	1.33 (1.08–1.65)	0.008	1.29 (1.04–1.60)	0.019
Fever	3.28 (2.56–4.24)	<0.001	0.88 (0.64–1.22)	0.4	0.67 (0.47–0.95)	0.026	0.76 (0.54– 1.07)	0.12
Generalized hyperhidrosis	4.43 (2.07–10.9)	<0.001	1.57 (0.62– 4.26)	0.3	1.00 (0.34– 2.92)	>0.9	1.00 (0.34– 2.92)	>0.9
Headache	2.55 (1.58–4.24)	<0.001	1.50 (0.88– 2.60)	0.14	1.14 (0.64– 2.03)	0.7	1.82 (1.09– 3.10)	0.024
Myalgia	2.42 (1.27–4.91)	0.010	1.25 (0.59– 2.72)	0.6	1.00 (0.45– 2.25)	>0.9	0.50 (0.17– 1.29)	0.2
Pain in joint	1.28 (1.10–1.50)	0.001	1.19 (1.02– 1.40)	0.027	1.17 (1.00– 1.37)	0.050	1.25 (1.07– 1.46)	0.005
Weakness	2.53 (1.85–3.51)	<0.001	1.49 (1.05– 2.13)	0.026	1.71 (1.22– 2.42)	0.002	1.86 (1.34– 2.62)	<0.001
IACCI symptoms								
Depression	1.59 (1.22–2.07)	<0.001	1.17 (0.89–1.56)	0.3	1.18 (0.90–1.57)	0.2	1.15 (0.87–1.53)	0.3
Dizziness	1.73 (1.23–2.47)	0.002	1.10 (0.75–1.62)	0.6	0.96 (0.64–1.43)	0.8	1.37 (0.95–1.98)	0.092
Generalized anxiety disorder	1.26 (0.93–1.74)	0.14	1.18 (0.86–1.62)	0.3	1.32 (0.97–1.81)	0.077	1.32 (0.97–1.81)	0.077
Insomnia	1.60 (1.12–2.30)	0.011	1.13 (0.76–1.67)	0.5	0.98 (0.65–1.47)	>0.9	0.98 (0.65–1.47)	>0.9
Irritable bowel syndrome	1.23 (0.77–1.98)	0.4	0.61 (0.34–1.07)	0.091	0.74 (0.43–1.26)	0.3	0.52 (0.28–0.93)	0.031
Palpitations	1.47 (1.02–2.13)	0.040	0.96 (0.64–1.44)	0.8	0.91 (0.61–1.38)	0.7	0.89 (0.59–1.35)	0.6
Sleep apnea	1.47 (1.23–1.77)	<0.001	1.13 (0.93–1.38)	0.2	1.14 (0.94–1.38)	0.2	1.14 (0.94–1.38)	0.2
Tinnitus	2.56 (1.23–5.82)	0.017	1.33 (0.57–3.26)	0.5	1.33 (0.57–3.26)	0.5	0.89 (0.33–2.32)	0.8

*Baseline was 180–121 days before the index date. The 3-month follow-up periods were nonoverlapping periods after the index date: 0–89 days (0–3 months), 90–179 days (3–6 months), 180–269 days (6–9 months), and 270–365 days (9–12 months). Because of insufficient cell size, prevalence ratios were not calculated for chills, intracranial abscess, meningitis, irritability or anger, general paresis, or hypoactive sexual desire disorder. IACCI, infection-associated chronic conditions and illnesses; PR, prevalence ratio.

Deconditioning could also play a role in chronic fatigue, and referral to physical therapists might be necessary (*21*). Some symptoms, such as persistent joint pain, might be related to patients' immune response to infection, rather than the infection itself (*22*).

The mechanisms that might explain the marginal post–index date increases in anxiety that we observed are unclear; few studies have investigated the psychological effects of coccidioidomycosis (*11*,*12*). Data from patients with IACCIs point toward illness-related physical and psychological stress, social and economic effects, or immune response dysregulation as possible drivers for postinfection anxiety, which can persist or emerge months after infection (*23*). Further clinical investigations could shed light on the prevalence, persistence, and causes of anxiety or other psychological symptoms in patients with coccidioidomycosis. Future work could also address the effects of persistent coccidioidomycosis symptoms on patient quality of life (*24*).

The first limitation of this study was our reliance on ICD-10-CM codes, which are inherently subject to misclassification and undercoding. Patients were not actively followed, and we relied on diagnosis codes to assess the presence of symptoms during visits; however, providers might not code all associated symptoms during coccidioidomycosis-related visits (*25*). Thus, our symptom prevalence estimates likely underestimate the true prevalence in patients with coccidioidomycosis. Absolute symptom prevalence was substantially higher in a prospective study of 36 patients with pulmonary coccidioidomycosis in which symptom presence was directly evaluated every 4 weeks for 24 weeks (*3*). However, the relative trends appeared similar to those observed in our study, which lend credence to our results. Administrative datasets also offer unique opportunities to study large patient populations, which are difficult to achieve with other sources of fungal disease data, and several studies have similarly assessed coccidioidomycosis symptoms using ICD-10-CM codes (*8*,*9*). Additional large-scale studies with direct patient follow-up or medical chart review could validate our findings by directly measuring symptom prevalence and persistence over longer periods. Second, some symptoms coded in claims data could also have been unrelated to coccidioidomycosis. The substantial increase in symptoms in the months around the index date suggests the observed trends were largely related to coccidioidomycosis, but follow-up case–control studies could help corroborate those findings by comparing symptom trends between patient populations with and without coccidioidomycosis. Third, only patients with commercial health insurance were included in our analysis, meaning our results might not represent the illness experience of those with other insurance types or without health insurance. Fourth, we also lacked data on socioeconomic status and race/ethnicity, which limited our ability to assess potential social determinants of health in symptom prevalence and trends. Finally, the high proportion of patients with unspecified coccidioidomycosis ICD-10-CM codes limited our ability to directly compare symptom trends in patients with pulmonary disease with those of patients with extrapulmonary disease.

In conclusion, our findings provide evidence about the long-term duration of selected symptoms in patients with coccidioidomycosis, which could help clinicians manage patient symptoms long after initial diagnosis and provide information to counsel patients during follow-up evaluation. In addition, these findings can help inform estimates of the overall health and economic burden of coccidioidomycosis to inform related public health interventions and provide additional rationale for ongoing efforts to develop a vaccine against coccidioidomycosis.

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References

1. Benedict K, Ireland M, Weinberg MP, Gruninger RJ, Weigand J, Chen L, et al. Enhanced surveillance for coccidioidomycosis, 14 US States, 2016. Emerg Infect Dis. 2018;24:1444–52. https://doi.org/10.3201/eid2408.171595
2. Tsang CA, Anderson SM, Imholte SB, Erhart LM, Chen S, Park BJ, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007–2008. Emerg Infect Dis. 2010;16:1738–44. https://doi.org/10.3201/eid1611.100475
3. Blair JE, Chang Y-HH, Cheng M-R, Vaszar LT, Vikram HR, Orenstein R, et al. Characteristics of patients with mild to moderate primary pulmonary coccidioidomycosis. Emerg Infect Dis. 2014;20:983–90. https://doi.org/10.3201/eid2006.131842
4. Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Geertsma F, Hoover SE, et al. Executive summary: 2016 Infectious Diseases Society of America (IDSA) clinical practice

guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016;63:717–22. https://doi.org/10.1093/cid/ciw538
5. Ampel NM, Giblin A, Mourani JP, Galgiani JN. Factors and outcomes associated with the decision to treat primary pulmonary coccidioidomycosis. Clin Infect Dis. 2009;48:172–8. https://doi.org/10.1086/595687
6. Garrett AL, Chang Y-HH, Ganley K, Blair JE. Uphill both ways: fatigue and quality of life in Valley fever. Med Mycol. 2016;54:310–7. https://doi.org/10.1093/mmy/myv097
7. Muir Bowers J, Mourani JP, Ampel NM. Fatigue in coccidioidomycosis. Quantification and correlation with clinical, immunological, and nutritional factors. Med Mycol. 2006;44:585–90. https://doi.org/10.1080/13693780600794533
8. Benedict K, Kobayashi M, Garg S, Chiller T, Jackson BR. Symptoms in blastomycosis, coccidioidomycosis, and histoplasmosis versus other respiratory illnesses in commercially insured adult outpatients—United States, 2016–2017. Clin Infect Dis. 2021;73:e4336–44. https://doi.org/10.1093/cid/ciaa1554
9. Ginn R, Mohty R, Bollmann K, Goodsell J, Mendez G, Bradley B, et al. Delays in coccidioidomycosis diagnosis and relationship to healthcare utilization, Phoenix, Arizona, USA. Emerg Infect Dis. 2019;25:1742–4. https://doi.org/10.3201/eid2509.190019
10. Donovan FM, Wightman P, Zong Y, Gabe L, Majeed A, Ynosencio T, et al. Delays in coccidioidomycosis diagnosis and associated healthcare utilization, Tucson, Arizona, USA. Emerg Infect Dis. 2019;25:1745–7. https://doi.org/10.3201/eid2509.190023
11. Gaab EM, Naeem F. Pediatric coccidioidomycosis patients: perceptions, quality of life and psychosocial factors. Healthcare (Basel). 2015;3:775–95. https://doi.org/10.3390/healthcare3030775
12. Fayed MA, Evans TM, Almasri E, Bilello KL, Libke R, Peterson MW. Overview of the current challenges in pulmonary coccidioidomycosis. J Fungi (Basel). 2024;10:724. https://doi.org/10.3390/jof10100724
13. Blair JE, Mayer AP, Currier J, Files JA, Wu Q. Coccidioidomycosis in elderly persons. Clin Infect Dis. 2008;47:1513–8. https://doi.org/10.1086/593192
14. Egger M, Hoenigl M, Thompson GR III, Carvalho A, Jenks JD. Let's talk about sex characteristics as a risk factor for invasive fungal diseases. Mycoses. 2022;65:599–612. https://doi.org/10.1111/myc.13449
15. McHardy I, Reagan KL, Sebastian JF, Barker B, Bays DJ, Dandekar S, et al. Sex differences in susceptibility to coccidioidomycosis. Open Forum Infect Dis. 2022;9:ofab543. https://doi.org/10.1093/ofid/ofab543
16. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs. 2005;49:616–23. https://doi.org/10.1111/j.1365-2648.2004.03331.x
17. Molarius A, Janson S. Self-rated health, chronic diseases, and symptoms among middle-aged and elderly men and women. J Clin Epidemiol. 2002;55:364–70. https://doi.org/10.1016/S0895-4356(01)00491-7
18. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626–38. https://doi.org/10.1038/nri.2016.90
19. Davis MR, Nguyen MH, Donnelley MA, Thompson GR III. Tolerability of long-term fluconazole therapy. J Antimicrob Chemother. 2019;74:768–71. https://doi.org/10.1093/jac/dky501
20. Ganley KJ, Bosch PR, Blair JE, Rischard F, Galgiani JN. Oxygen consumption deficits in patients with residual fatigue after primary coccidioidomycosis. Open Forum Infect Dis. 2017;4:ofx136. https://doi.org/10.1093/ofid/ofx136
21. Galgiani JN, Blair JE, Ampel NM, Thompson GR. Treatment for early, uncomplicated coccidioidomycosis: what is success? Clin Infect Dis. 2020;70:2008–12. https://doi.org/10.1093/cid/ciz933
22. Cox RA, Pope RM, Stevens DA. Immune complexes in coccidioidomycosis. Correlation with disease involvement. Am Rev Respir Dis. 1982;126:439–43.
23. Seighali N, Abdollahi A, Shafiee A, Amini MJ, Teymouri Athar MM, Safari O, et al. The global prevalence of depression, anxiety, and sleep disorder among patients coping with post COVID-19 syndrome (long COVID): a systematic review and meta-analysis. BMC Psychiatry. 2024;24:105. https://doi.org/10.1186/s12888-023-05481-6
24. Harvey E, Clegg J, Bresnik M, Blatt E, Hughes S, Umanzor-Figueroa C, et al. Development of a novel patient-reported outcome measure for disseminated coccidioidomycosis (Valley fever). J Antimicrob Chemother. 2025;80:657–65. https://doi.org/10.1093/jac/dkae453
25. Centers for Medicare and Medicaid Services (CMS); National Center for Health Statistics (NCHS). ICD-10-CM official guidelines for coding and reporting 2019 [cited 2025 Mar 5]. https://www.cms.gov/Medicare/Coding/ICD10/Downloads/2019-ICD10-Coding-Guidelines-.pdf

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Postinfectious Syndromes and Long-Term Sequelae after *Giardia* Infections

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Giardiasis, caused by the parasite *Giardia duodenalis*, is a common infection throughout the world. Acute infections can be asymptomatic, cause mild gastrointestinal symptoms, or be associated with severe, prolonged diarrhea. Most *Giardia* infections are self-limiting; however, a subset of symptomatic and asymptomatic persons experience infection-associated chronic conditions that can affect multiple body systems. Those conditions include stunting and impaired cognitive function in children, irritable bowel syndrome, chronic fatigue, arthritis, and fibromyalgia, all of which can persist for months or years. Such conditions can impair daily functioning and quality of life; however, research has yet to fully elucidate underlying mechanisms, describe the prevalence, identify persons at increased risk, and develop effective treatment strategies. We synthesized what is known about giardiasis-associated chronic conditions and illnesses to improve recognition of those complications and ensure appropriate management that can improve the well-being of persons affected.

Infection with the parasite *Giardia duodenalis*, known as giardiasis, is reported throughout the world, including in the United States (https://www.cdc.gov/giardia). *G. duodenalis* infection is endemic in many regions, and prevalence estimates range from 3%–10% in high-income countries to 20%–35% in low-income countries (*1*,*2*). In the United States, *G. duodenalis* is the most common intestinal parasitic infection among humans (*3*). The pathogen is transmissible through multiple pathways, including contaminated water or through the fecal–oral route. Infections are associated with poor sanitation, human-to-human or animal-to-human spread, and exposure to untreated or inadequately treated fresh water by drinking or swimming (*2*). Acute giardiasis symptoms vary across world regions and include severe, prolonged diarrhea, mild or intermittent gastrointestinal illness, and extraintestinal manifestations, whereas some infections can be asymptomatic (*2*). Asymptomatic infections in children of endemic areas can be a major contributor to complications later in life (*4*,*5*). Most *G. duodenalis* infections are self-limiting, but some symptomatic and asymptomatic persons experience infection-associated chronic conditions and illnesses (IACCIs). IACCIs can affect multiple body systems and persist for months or years, resulting in a disease burden that greatly reduces daily functioning and quality of life (*2*,*6*,*7*).

Some IACCIs, such as functional gastrointestinal disorders (FGIDs) and myalgic encephalomyelitis or chronic fatigue syndrome, may be reported after infections including, but not limited to, COVID-19, Lyme disease, campylobacteriosis, and giardiasis (*7*) (https://www.cdc.gov/chronic-symptoms-following-infections). Data collection for IACCIs remains challenging, given the multiple pathophysiologic mechanisms, varied symptomatology, and wide-ranging period of syndrome onset and duration. Therefore, prevalence and risk factors for the conditions are not fully understood (*7*). Giardiasis increases intestinal epithelial permeability, resulting in malabsorption and mucus depletion, and may induce intestinal dysbiosis. This intestinal barrier disruption is believed to be associated with some IACCIs (*2*,*8*). Early diagnosis could mitigate the most severe disability symptoms and optimize outcomes among patients (*7*,*9*).

We have synthesized what is known about the clinical manifestations of IACCIs after giardiasis. We focused on IACCIs most often reported in the literature, including FGIDs, musculoskeletal and neuromuscular syndromes, and pediatric implications such as stunting and cognitive impairment (Figure). We then identified knowledge gaps in the epidemiology of IACCIs after giardiasis in the United States,

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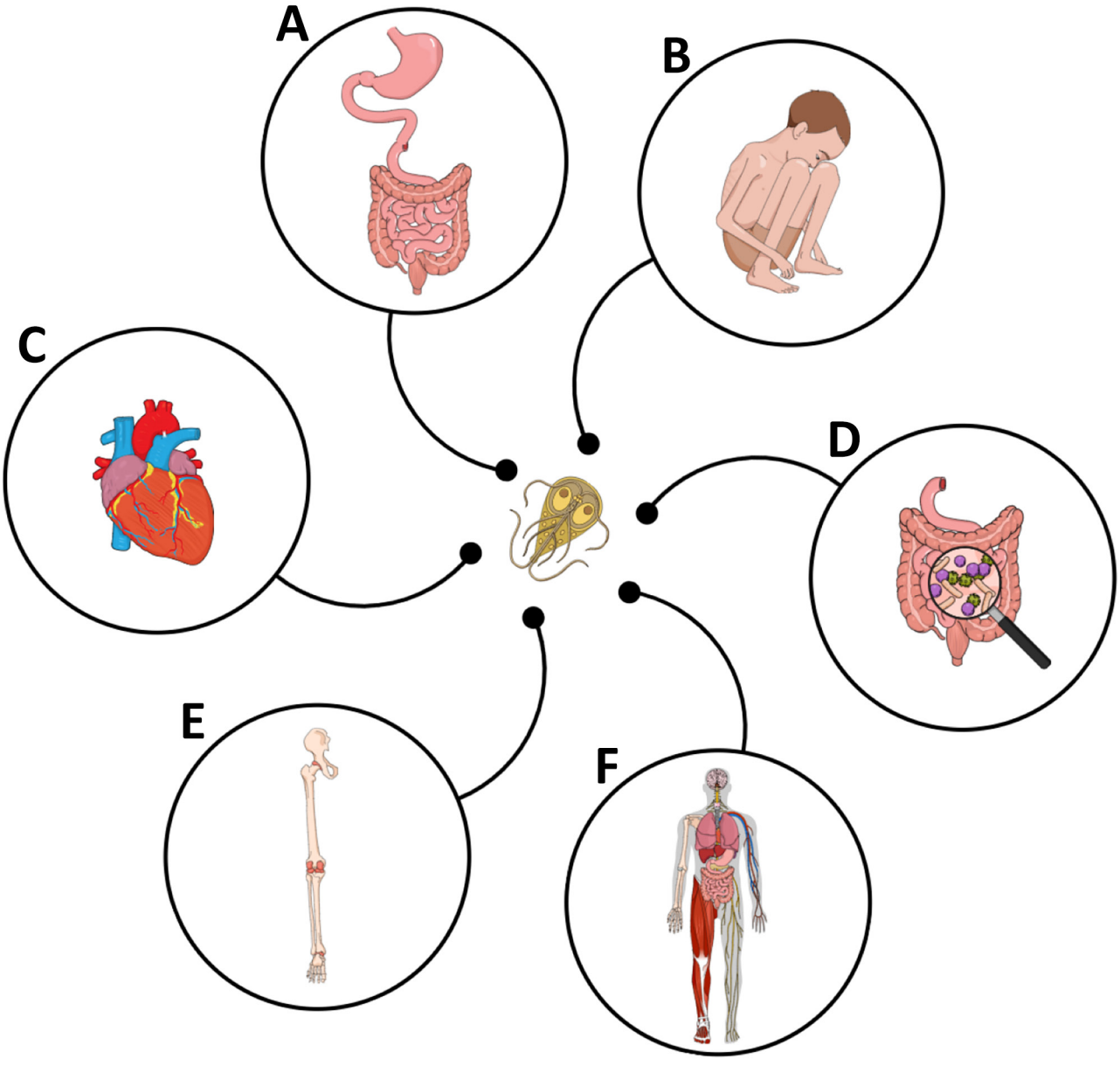

Figure. Clinical manifestations of infection-associated chronic conditions and illnesses most often reported after giardiasis. A) Postinfectious irritable bowel syndrome, postinfectious functional dyspepsia, gastresophageal reflux, bloating, and nausea. B) Cognitive impairment, failure to thrive, and stunting. C) Myocarditis. D) Treatment-refractory giardiasis. E) Arthridites. F) Fibromyalgia, and myalgic encephalomyelitits/chronic fatigue syndrome.

including the defining of high-risk populations. We explored potential approaches to expand our understanding of these IACCIs through routine analyses of national hospitalization databases, insurance claims databases, and active surveillance programs. Our discussion aims to support public health efforts around IACCIs after giardiasis and contribute to an increased understanding of these conditions more broadly. Increasing healthcare provider (HCP) awareness around IACCIs is essential in providing timely and targeted treatment and improving patient outcomes.

Approach to Summarizing the Literature

We reviewed Ovid and Scopus databases in May 2024 to identify studies in English without date restrictions. We used Medical Subject Headings terms alone or in combination to capture complications of giardiasis infections in humans, including persistent and chronic infections, chronic symptoms, postinfectious

syndromes, and long-term sequelae. We included articles if the research or report involved human subjects, were published in peer-reviewed journals, had a full text or abstract in English, and included evidence of postgiardiasis chronic sequelae. We excluded articles if they were written without original peer-reviewed data, written in languages other than English, or involved animal models. We identified duplicates by using the Endnote (https://web.endnote.com) automated "find duplicates" function, set preferences to match on title, author, and year, and removed duplicates from the Endnote library. Of the 3,135 initial records, we removed 1,542 (49%) duplicate results, 842 (27%) publications that excluded postgiardiasis chronic sequelae, 375 (12%) studies not written in English, and 194 (6%) animal model studies, leaving 182 publications. Although the quality of data among the articles varied, we attempted to include publications about all proposed IACCIs to describe the breadth of IACCIs that may be associated with giardiasis. We also summarized studies and reviews identified in the search but not included in this article (Appendix, https://wwwnc.cdc.gov/EID/article/31/14/24-1793-App1.pdf).

Postinfectious FGIDs

Chronic gastrointestinal symptoms associated with giardiasis are most often described in the literature. Postinfectious FGIDs (PI-FGIDs) involve recurring or chronic gastrointestinal symptoms without other known disease processes. They are frequently classified by using Rome criteria for FGIDs, which do not necessarily occur after infections (*10*,*11*). The Rome IV criteria consists of 33 adult and 20 pediatric FGIDs, defined on the basis of the type, duration, and frequency of gastrointestinal symptoms (https://theromefoundation.org/rome-iv/rome-iv-criteria). Two frequently diagnosed giardiasis-associated PI-FGIDs are postinfectious irritable bowel syndrome, often clinically indistinguishable from irritable bowel syndrome (IBS) not associated with infection, and postinfectious functional dyspepsia (*10*).

Postinfectious IBS

Postinfectious IBS (PI-IBS) symptoms commonly include diarrhea or diarrhea alternating with constipation, bloating, and recurring abdominal discomfort for >6 months (*8*,*11*,*12*). Reports highlight bloating, diarrhea, nausea, and abdominal pain as the most severe symptoms (*11*,*13*). In a study of 82 persons with giardiasis-associated PI-FGIDs (81% of whom had PI-IBS), symptom exacerbation was related to specific foods (58% of cases) and physical or mental stress (45% of cases) (*11*). The foods associated with the most complications included dairy products, vegetables, fruit, alcohol, and foods from fermentable oligosaccharides, disaccharides, and monosaccharides and polyols subgroup polyols (i.e., sugar alcohols) (*14*). Other PI-IBS symptoms included gastric hypersensitivity, decreased drinking capacity, and reduced gastric emptying (*15*). Regardless of symptoms, many persons with giardiasis-associated PI-IBS reported a negative effect on their quality of life associated with the IBS and fatigue symptoms (*6*).

Robust evidence supporting the relationship between giardiasis and PI-IBS comes from studies regarding 2 separate drinking water contamination events in northern Europe. The research demonstrated an increased risk for IBS symptoms after giardiasis or cryptosporidiosis, on the basis of Rome criteria, at 3 (adjusted risk ratio [aRR] 3.4; 95% CI 2.9–3.8) (*16*), 6 (aRR 3.4; 95% C: 2.9–3.9) (*17*), and 10-year intervals postinfection (adjusted odds ratio 4.7; 95% CI 3.6–6.2) (*18*). Follow-up studies noted a small but significant decrease in the prevalence of PI-IBS from 3 to 6 years but no change from 6 to 10 years, indicating that symptoms may improve for some patients but can have long-lasting effects for others (*17*,*18*). Another drinking water contamination event further demonstrated this association; persons who were affected by giardiasis, campylobacteriosis, or norovirus had a nearly 3-fold (odds ratio [OR] 2.6; 95% CI 1.4–1.7) increase in the odds of IBS onset 1 year later compared with persons who were not infected (*19*).

PI-IBS is the most common PI-FGID, occurring in an estimated 10%–20% of persons after gastrointestinal infection (*8*,*10*–*12*,*20*–*23*). A previously healthy person recovering from an acute gastrointestinal infection, regardless of pathogen type (e.g., viral, bacterial, or parasitic infection), has a 3- to 4-fold increase in risk for IBS symptom onset compared with unexposed persons (*8*,*24*). One study analyzed data from a commercial insurance database and reported that the 1-year incidence of IBS was higher in persons with previous giardiasis (37.7/1,000 person-years) compared with persons without a documented *G. duodenalis* infection diagnosis (4.4/1,000 person-years) (*23*). After adjusting for anxiety, depression, and healthcare use, the adjusted hazard ratio was 3.9 (95% CI 2.9–5.4) (*23*). Similar outcomes were observed in a pooled analysis of several cohort studies, where documented giardiasis infection increased the odds for developing IBS >5-fold (OR 5.5; 95% CI 4.2–7.1) compared with uninfected persons (*25*).

Factors associated with a higher risk for PI-IBS onset include younger age (*8*), female sex (*8*,*12*,*25*,*26*),

antibiotic exposure (*25*), severity of initial infection (*8*), prior mental health diagnosis (*8*,*12*,*18*,*19*,*25*), somatization (*19*), and giardiasis infections that require >1 treatment course (i.e., treatment-refractory giardiasis) (*26*). Moreover, data suggest protozoal infections such as giardiasis and blastocystosis carry a higher risk for PI-IBS onset (*16*,*27*) compared with bacterial and viral gastrointestinal infections (*8*,*21*,*25*).

Postinfectious Functional Dyspepsia

Postinfectious functional dyspepsia (PI-FD) is characterized as an onset of new dyspeptic symptoms after an acute gastrointestinal infection (*10*). Symptoms can include constipation, epigastric pain, severe bloating, gastric hypersensitivity, decreased drinking capacity, and reduced gastric emptying (*11*,*15*). Independent factors associated with a higher risk for PI-FD include younger age, somatization (*19*), and prior mental health diagnosis (*27*). Considerable overlap seems to exist between PI-IBS and PI-FD. Some studies note that, among participants meeting the Rome criteria for PI-IBS, a subset (15%–44%) also met criteria for PI-FD (*11*,*13*). Likewise, ≈85% of participants with PI-FD also met Rome criteria for PI-IBS in another study (*13*).

An estimated 10% of persons with gastrointestinal infections might have onset of PI-FD (*23*). A systematic review described increased odds of PI-FD onset 6 months after a gastrointestinal infection (OR 2.5; 95% CI 1.8–3.7) compared with a control population (*23*). Further, some large cohort studies indicated that ≈25% of persons with giardiasis had onset of PI-FD (*11*,*13*). Another cohort study examining active-duty military personnel with prior giardiasis documented an increased risk for PI-FD (risk ratio 3.2; 95% CI 1.2–8.9) compared with controls (*27*).

Other Gastrointestinal Symptoms

Giardiasis is also a risk factor for developing chronic gastrointestinal symptoms that do not meet PI-IBS or PI-FD criteria. One cohort study described prior giardiasis associated with an increased risk (risk ratio 4.0; 95% CI 2.9–5.6) of gastroesophageal reflux (*27*). Another study reported an increase in the prevalence of bloating (aRR 1.8) and nausea (aRR 3.0) compared with persons without prior giardiasis (*13*).

Postinfectious Musculoskeletal and Neuromuscular Syndromes

An estimated 30% of persons with prior giardiasis experience long-term extraintestinal symptoms (*28*). Many of those symptoms are expressed as joint or fatigue syndromes, but some persons report a wide variety of symptoms that often overlap with diagnostic criteria for other extraintestinal syndromes. Frequent manifestations include a decrease in daily functional status, exertion intolerance, unrelieved fatigue despite rest or sleep, neurocognitive and sensory impairments, and musculoskeletal complaints. Although some of these symptoms occur in the absence of gastrointestinal symptoms, many co-occur with PI-IBS (*7*,*29*).

Postinfectious Arthritis

Case reports of postinfectious joint pain and arthritis were once rare; however, since the 2010s, studies increasingly report arthritides after giardiasis (*30*–*34*). Still, the pathogenesis remains unclear, and no standardized timeframe is used to diagnose the condition (*30*,*33*). Studies use wide-ranging definitions for symptom onset, ranging from ≥4 days to ≤3 months after giardiasis and an average duration in joint symptoms of 3 months; however, symptoms can last years (*33*). Postgiardiasis arthritis can manifest in ≥1 joint, often in the knee, ankle, hip, and wrist (*34*). Research is sparse on identifying risk factors, although a higher risk among children has been reported. One study demonstrated an association between arthritis and previous *G. duodenalis* infection among children 0–19 years of age and adults 20–64 years of age (*33*), and a systematic review reported that the prevalence of postgiardiasis arthritis was higher among children <18 years of age compared with adults (*34*).

An analysis of healthcare encounters and insurance claims in the United States described the odds of arthritis or joint pain within 6 months of giardiasis as 51% higher compared with controls (adjusted odds ratio 1.5; 95% CI 1.3–1.8) (*33*). Despite the high prevalence of giardiasis globally, postgiardiasis arthritis is not diagnosed as frequently as arthritis after other gastrointestinal infections such as *Campylobacter jejuni* (*30*).

Myalgic Encephalomyelitis or Chronic Fatigue Syndrome

Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) is characterized by waxing and waning physical, cognitive, or emotional exertion intolerance that is not relieved by sleep or rest (*7*). Its pathogenesis remains unclear, and the time to onset varies, but the trajectory is similar. A prodromal phase progresses to a nadir, with some level of improvement (*35*), followed by a chronic phase in which preillness health and abilities are not regained (*9*). Impairments often are associated with extended leave from work and school (*9*,*26*,*36*). Regardless of symptoms, persons with giardiasis-associated ME/

CFS report a negative impact on their quality of life associated with disabilities and disruptions of activities of daily living (*6*).

Giardiasis-associated ME/CFS was first reported after a 1986 California water contamination event (*37*). It was again documented after a 2004 water contamination event in Norway (*31*), when ≈5% of persons developed ME/CFS-like symptoms after giardiasis resolution (*36*). Two years after the event in Norway, questionnaire respondents reported more fatigue symptoms than gastrointestinal symptoms (*31*). A follow-up study 3 years postexposure validated the symptoms and identified persons with history of giardiasis as having an increased risk for ME/CFS compared with controls (aRR 4.0; 95% CI 3.5–4.5) (*16*). At 6 years, the fatigue risk decreased slightly but remained higher compared with unexposed persons (aRR 2.9; 95% CI 2.3–3.4) (*17*).

The severity of the giardiasis and having ≥1 treatment course are associated with ME/CFS (*26*). Chronic fatigue syndrome may also be associated with overactive bladder in both giardiasis-exposed and unexposed persons (OR 2.73, 95% CI 1.85–4.02 in exposed persons; OR 2.79, 95% CI 1.69–4.62 in unexposed persons) (*38*). Throughout follow-up studies, ME/CFS symptoms are associated with IBS symptoms across all age and sex groups (*16*,*17*,*39*).

Fibromyalgia

Evidence of postinfectious fibromyalgia after giardiasis is emerging. Symptoms of fibromyalgia include chronic generalized pain accompanied with chronic fatigue, disrupted sleep patterns, headache, cognitive dysfunction, and gastrointestinal symptoms (*40*).

A study after a drinking water contamination event in Finland associated with several types of gastrointestinal infections (including giardiasis) described postinfectious complex regional pain syndrome and fibromyalgia in 4% of study participants (*32*). However, the report did not describe associations specifically among persons with giardiasis (*32*). A study from a separate outbreak in Norway detailed a higher prevalence of fibromyalgia (9%) 10 years postgiardiasis compared with persons who had no prior giardiasis (3%) (*29*). The report also described the odds of fibromyalgia were nearly 3-fold among case-patients compared with controls (OR 2.9; 95% CI 1.7–4.9) (*29*).

At the time of this publication, studies have not demonstrated sex or age as risk factors for postinfectious fibromyalgia. However, some analyses reveal that diagnosis often is concomitant with IBS or ME/CFS status after giardiasis (*29*).

Pediatric Implications

Despite the reduction of intestinal infectious diseases such as giardiasis as leading causes of death in children ≤5 years of age, they remain a leading cause of disease burden and disability-adjusted life-years globally (*41*). Diarrheal illness in early childhood has been linked not only to impairments in hand–eye coordination, physical fitness, information processing, and cognitive function (*42*,*43*) but also to growth disorders. A study from Ethiopia of 224 children 2–5 years of age demonstrated increased odds of stunting among children infected with ≥1 intestinal parasites compared with those without (*44*). Furthermore, research shows that giardiasis, even when asymptomatic, is a major contributor to stunting in children (*4*,*5*). Given that a recent study of >11,000 children in low-resource settings identified *G. duodenalis* parasites in stool samples of 35% of asymptomatic children, millions of children worldwide may be at risk for giardiasis-associated stunting (*2*).

Although *G. duodenalis* infections can cause nutrient malabsorption and malnutrition in any human host if not adequately treated, such infections can contribute to IACCIs in children who are still growing and developing (*30*). Persistent giardiasis within the first 6 months of life is associated with deficits in both weight and length at 24 months of age in a large study of children from several countries (*5*). Fecal presence of *G. duodenalis* parasites in 3–6-month-old infants ($p = 0.012$) and 9-month-old infants ($p = 0.006$) was associated with a mean difference of ≈0.3 SD in height-for-age *Z*-score at 2 years of age in a study conducted in Pakistan (*45*). Any giardiasis before 2 years of age was a predictor of lower social and intelligence quotients and poorer growth at 3 years of age compared with children without giardiasis in a study from southern India (*42*). Moreover, giardiasis during a child's first 2 years is associated with cognitive impairment up to 7 years later, independent of physical growth (*43*). Furthermore, a longitudinal study in Peru following ≈140 children from birth to age 9 years describes lower intelligence quotient scores in children with ≥1 episode of giardiasis annually, compared with children with 1 or no infection (*43*). Of note, most studies examining the association between giardiasis and long-term pediatric implications including stunting, failure to thrive, and cognitive impairment are conducted in low-income or lower middle-income countries, highlighting an important potential health disparity. Higher *G. duodenalis* infection endemicity in lower-resource settings may be contributing to the higher prevalence of stunting and other developmental conditions in these areas.

Other Complications of Giardiasis

We also surveyed research on additional complications of giardiasis. Those include rarely described complications (e.g., myocarditis and pancreatic neoplasms) and treatment-refractory giardiasis (Appendix).

Future Directions

The body of literature on giardiasis-associated postinfection sequelae is growing. However, this information largely has been gathered within the context of focal epidemiologic studies or as a follow-up to outbreak investigations, having limited sample sizes, varying clinical criteria, and varying methodologic approaches. Several open areas of research exist to guide giardiasis-associated postinfection sequelae strategies and actions at a national level for the United States.

Of note, a gap exists in research to elucidate the pathophysiology and establish specific diagnostic criteria for IACCIs after giardiasis. Variation in the definitions used to characterize IACCIs complicate the ability to draw definitive conclusions across studies or generate accurate prevalence estimates. Furthermore, given the differences between adult and pediatric clinical manifestations, characterizing the mechanisms of illness at different stages of life may be useful. From the studies we described, we observed a high number of reports of IACCIs after giardiasis based in resource-limited countries. We have an opportunity to understand the biology of how underlying health status, including nutritional, chronic stress, and immunologic profiles, may predispose populations to IACCIs after giardiasis.

In the United States, national-level epidemiologic data on IACCIs after giardiasis are lacking. Routine longitudinal analyses of national hospitalization and insurance claims databases, such as studies presented by Nakao et al. (*22*) and Painter et al. (*33*), may help to identify temporal or regional patterns of IACCIs after giardiasis, including the characterization of high-risk populations by age, sex, race/ethnicity, and insurance type (*22*,*33*). Separately, surveillance activities such as the Foodborne Diseases Active Surveillance Network offer opportunities for state health departments to identify and recruit persons with giardiasis into a prospective cohort study to detect postinfection sequelae and understand risk factors in nonoutbreak settings. As of 2024, however, giardiasis is not among the 8 enteric diseases included in the system. The lack of exposure and symptomatologic data within national surveillance systems contributes to gaps in epidemiologic knowledge for giardiasis. Increasing the robustness of this data collection would enhance our understanding of disease risk factors and clinical manifestations, in turn supporting national prevention and mitigation strategies, identifying populations for targeted outreach, and identifying opportunities for HCP education (*46*).

Finally, research describing HCP awareness and practice regarding IACCIs after giardiasis is lacking, and studies suggest that limited knowledge of giardiasis may be a contributor to illness burden in the United States. Two studies reported gaps in HCP knowledge of giardiasis as a source of childhood diarrhea in the United States (*47*,*48*). Another study found that less than half of surveyed HCPs considered postinfectious IBS as a diagnosis in patients with recent gastrointestinal infections (*49*). With respect to case management, 1 study reported 20% of persons with giardiasis had not received appropriate treatment (*28*), whereas another found that adults often had ≥3 visits to an HCP before giardiasis diagnosis, were less likely to have a *Giardia*-specific test, and were more likely to receive only antibiotics as treatment (*50*). Those knowledge gaps among HCPs suggest IACCIs after giardiasis probably are underdiagnosed. Resource development to enhance HCP knowledge and aid diagnosis and treatment strategies may help improve case management of affected persons, thereby minimizing the burden of IACCIs and enhancing patient outcomes.

Conclusions

G. duodenalis IACCIs negatively affect the health and quality of life of those in endemic and nonendemic countries (*2*,*6*,*7*). Some priority areas for future progress include creating a consensus around clinical criteria and definitions for IACCIs after giardiasis and increasing data collection through surveillance systems for robust epidemiologic studies. In addition, research is needed to fully understand the underlying mechanisms, national prevalence, populations at increased risk, and specific knowledge gaps for HCPs that may result in delayed diagnosis or misdiagnosis of IACCIs after giardiasis. Ultimately, increased epidemiologic knowledge and educational resources for IACCIs after giardiasis among HCPs may guide public health efforts and contribute to an increased understanding of IACCIs more broadly.

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References

1. Marcenac P, Traoré A, Kim S, Prentice-Mott G, Berendes DM, Powell H, et al. *Giardia* detection and codetection with other enteric pathogens in young children in the vaccine impact on diarrhea in Africa (VIDA) case-control study: 2015–2018. Clin Infect Dis. 2023;76(Suppl1):S106–13. https://doi.org/10.1093/cid/ciac940
2. Allain T, Buret AG. Pathogenesis and post-infectious complications in giardiasis. Adv Parasitol. 2020;107:173–99. https://doi.org/10.1016/bs.apar.2019.12.001
3. Collier SA, Deng L, Adam EA, Benedict KM, Beshearse EM, Blackstock AJ, et al. Estimate of burden and direct healthcare cost of infectious waterborne disease in the United States. Emerg Infect Dis. 2021;27:140–9. https://doi.org/10.3201/eid2701.190676
4. MAL-ED Network Investigators. Relationship between growth and illness, enteropathogens and dietary intakes in the first 2 years of life: findings from the MAL-ED birth cohort study. BMJ Glob Health. 2017;2:e000370. https://doi.org/10.1136/bmjgh-2017-000370
5. Rogawski ET, Bartelt LA, Platts-Mills JA, Seidman JC, Samie A, Havt A, et al.; MAL-ED Network Investigators. Determinants and impact of *Giardia* infection in the first 2 years of life in the MAL-ED birth cohort. J Pediatric Infect Dis Soc. 2017;6:153–60. https://dx.doi.org/10.1093/jpids/piw082
6. Litleskare S, Rortveit G, Eide GE, Emberland KE, Hanevik K, Langeland N, et al. Quality of life and its association with irritable bowel syndrome and fatigue ten years after giardiasis. Neurogastroenterol Motil. 2019;31:e13559. https://doi.org/10.1111/nmo.13559
7. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med. 2022;28:911–23. https://doi.org/10.1038/s41591-022-01810-6
8. Berumen A, Edwinson AL, Grover M. Post-infection irritable bowel syndrome. Gastroenterol Clin North Am. 2021;50:445–61. https://doi.org/10.1016/j.gtc.2021.02.007
9. Stormorken E, Jason LA, Kirkevold M. From good health to illness with post-infectious fatigue syndrome: a qualitative study of adults' experiences of the illness trajectory. BMC Fam Pract. 2017;18:49. https://doi.org/10.1186/s12875-017-0614-4
10. Mearin F. Postinfectious functional gastrointestinal disorders. J Clin Gastroenterol. 2011;45(Suppl):S102–5. https://doi.org/10.1097/mcg.0b013e31821fbf58
11. Hanevik K, Dizdar V, Langeland N, Hausken T. Development of functional gastrointestinal disorders after *Giardia lamblia* infection. BMC Gastroenterol. 2009;9:27. https://doi.org/10.1186/1471-230x-9-27
12. Spiller R, Lam C. An update on post-infectious irritable bowel syndrome: role of genetics, immune activation, serotonin and altered microbiome. J Neurogastroenterol Motil. 2012;18:258–68. https://doi.org/10.5056/jnm.2012.18.3.258
13. Wensaas KA, Hanevik K, Hausken T, Eide GE, Langeland N, Mørch K, et al. Postinfectious and sporadic functional gastrointestinal disorders have different prevalences and rates of overlap: results from a controlled cohort study 3 years after acute giardiasis. Neurogastroenterol Motil. 2016;28:1561–9. https://doi.org/10.1111/nmo.12856
14. Litleskare S, Wensaas KA, Eide GE, Hanevik K, Kahrs GE, Langeland N, et al. Perceived food intolerance and irritable bowel syndrome in a population 3 years after a giardiasis-outbreak: a historical cohort study. BMC Gastroenterol. 2015;15:164. https://doi.org/10.1186/s12876-015-0393-0
15. Dizdar V, Gilja OH, Hausken T. Increased visceral sensitivity in *Giardia*-induced postinfectious irritable bowel syndrome and functional dyspepsia. Effect of the 5HT3-antagonist ondansetron. Neurogastroenterol Motil. 2007;19:977–82. https://doi.org/10.1111/j.1365-2982.2007.00988.x
16. Wensaas KA, Langeland N, Hanevik K, Mørch K, Eide GE, Rortveit G. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. Gut. 2012;61:214–9. https://doi.org/10.1136/gutjnl-2011-300220
17. Hanevik K, Wensaas K-A, Rortveit G, Eide GE, Mørch K, Langeland N. Irritable bowel syndrome and chronic fatigue 6 years after *Giardia* infection: a controlled prospective cohort study. Clin Infect Dis. 2014;59:1394–400. https://doi.org/10.1093/cid/ciu629
18. Litleskare S, Rortveit G, Eide GE, Hanevik K, Langeland N, Wensaas K-A. Prevalence of irritable bowel syndrome and chronic fatigue 10 years after *Giardia* infection. Clin Gastroenterol Hepatol. 2018;16:1064–1072.e4. https://doi.org/10.1016/j.cgh.2018.01.022
19. Wouters MM, Van Wanrooij S, Nguyen A, Dooley J, Aguilera-Lizarraga J, Van Brabant W, et al. Psychological comorbidity increases the risk for postinfectious IBS partly by enhanced susceptibility to develop infectious gastroenteritis. Gut. 2016;65:1279–88. https://dx.doi.org/10.1136/gutjnl-2015-309460
20. Svendsen AT, Bytzer P, Engsbro AL. Systematic review with meta-analyses: does the pathogen matter in post-infectious irritable bowel syndrome? Scand J Gastroenterol. 2019;54:546–62. https://doi.org/10.1080/00365521.2019.1607897
21. España-Cueto S, Oliveira-Souto I, Salvador F, Goterris L, Treviño B, Sánchez-Montalvá A, et al. Post-infectious irritable bowel syndrome following a diagnosis of traveller's diarrhoea: a comprehensive characterization of clinical and laboratory parameters. J Travel Med. 2023;30:31. https://doi.org/10.1093/jtm/taad030
22. Nakao JH, Collier SA, Gargano JW. Giardiasis and subsequent irritable bowel syndrome: a longitudinal cohort study using health insurance data. J Infect Dis. 2017;215:798–805. https://doi.org/10.1093/infdis/jiw621
23. Futagami S, Itoh T, Sakamoto C. Systematic review with meta-analysis: post-infectious functional dyspepsia. Aliment Pharmacol Ther. 2015;41:177–88. https://doi.org/10.1111/apt.13006
24. Abedi SH, Fazlzadeh A, Mollalo A, Sartip B, Mahjour S, Bahadory S, et al. The neglected role of *Blastocystis* sp. and *Giardia lamblia* in development of irritable bowel syndrome: a systematic review and meta-analysis. Microb Pathog. 2022;162:105215. https://doi.org/10.1016/j.micpath.2021.105215
25. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. Gastroenterology. 2017;152:1042–1054.e1. https://doi.org/10.1053/j.gastro.2016.12.039
26. Mørch K, Hanevik K, Rortveit G, Wensaas K-A, Eide GE, Hausken T, et al. Severity of *Giardia* infection associated with post-infectious fatigue and abdominal symptoms two years after. BMC Infect Dis. 2009;9:206. https://doi.org/10.1186/1471-2334-9-206
27. Dormond M, Gutierrez RL, Porter CK. *Giardia lamblia* infection increases risk of chronic gastrointestinal disorders.

Trop Dis Travel Med Vaccines. 2016;2:17. https://doi.org/10.1186/s40794-016-0030-0
28. Cantey PT, Roy S, Lee B, Cronquist A, Smith K, Liang J, et al. Study of nonoutbreak giardiasis: novel findings and implications for research. Am J Med. 2011;124:1175.e1–8. https://doi.org/10.1016/j.amjmed.2011.06.012
29. Hunskar GS, Rortveit G, Litleskare S, Eide GE, Hanevik K, Langeland N, et al. Prevalence of fibromyalgia 10 years after infection with *Giardia lamblia*: a controlled prospective cohort study. Scand J Pain. 2021;22:348–55. https://doi.org/10.1515/sjpain-2021-0122
30. Halliez MC, Buret AG. Extra-intestinal and long term consequences of *Giardia duodenalis* infections. World J Gastroenterol. 2013;19:8974–85. https://doi.org/10.3748/wjg.v19.i47.8974
31. Hanevik K. Long-term consequences of *Cryptosporidium* and *Giardia* gastroenteritis. Curr Trop Med Rep. 2016;3:89–93. https://doi.org/10.1007/s40475-016-0078-y
32. Uotila T, Antonen J, Laine J, Kujansuu E, Haapala A-M, Lumio J, et al.; Pirkanmaa Waterborne Outbreak Study Group. Reactive arthritis in a population exposed to an extensive waterborne gastroenteritis outbreak after sewage contamination n Pirkanmaa, Finland. Scand J Rheumatol. 2011;40:358–62. https://doi.org/10.3109/03009742.2011.562533
33. Painter JE, Collier SA, Gargano JW. Association between *Giardia* and arthritis or joint pain in a large health insurance cohort: could it be reactive arthritis? Epidemiol Infect. 2017;145:471–7. https://doi.org/10.1017/s0950268816002120
34. Mahdavi J, Motavallihaghi S, Ghasemikhah R. Evaluation of clinical and paraclinical findings in patients with reactive arthritis caused by giardiasis: a systematic review. Semin Arthritis Rheum. 2022;57:152094. https://doi.org/10.1016/j.semarthrit.2022.152094
35. Mørch K, Hanevik K, Rivenes AC, Bødtker JE, Næss H, Stubhaug B, et al. Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course. BMC Gastroenterol. 2013;13:28. https://doi.org/10.1186/1471-230X-13-28
36. Naess H, Nyland M, Hausken T, Follestad I, Nyland HI. Chronic fatigue syndrome after *Giardia enteritis*: clinical characteristics, disability and long-term sickness absence. BMC Gastroenterol. 2012;12:13. https://doi.org/10.1186/1471-230X-12-13
37. Levine PH, Jacobson S, Pocinki AG, Cheney P, Peterson D, Connelly RR, et al. Clinical, epidemiologic, and virologic studies in four clusters of the chronic fatigue syndrome. Arch Intern Med. 1992;152:1611–6. https://doi.org/10.1001/archinte.1992.00400200049009
38. Persson R, Wensaas KA, Hanevik K, Eide GE, Langeland N, Rortveit G. The relationship between irritable bowel syndrome, functional dyspepsia, chronic fatigue and overactive bladder syndrome: a controlled study 6 years after acute gastrointestinal infection. BMC Gastroenterol. 2015;15:66. https://doi.org/10.1186/s12876-015-0296-0
39. Mørch K, Hanevik K, Rortveit G, Wensaas KA, Langeland N. High rate of fatigue and abdominal symptoms 2 years after an outbreak of giardiasis. Trans R Soc Trop Med Hyg. 2009;103:530–2. https://doi.org/10.1016/j.trstmh.2009.01.010
40. Slim M, Calandre EP, Rico-Villademoros F. An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms. Rheumatol Int. 2015;35:433–44. https://doi.org/10.1007/s00296-014-3109-9
41. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability, disability-adjusted life-years, and healthy life expectancy for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403:2133–61. https://doi.org/10.1016/S0140-6736(24)00757-8
42. Ajjampur SS, Koshy B, Venkataramani M, Sarkar R, Joseph AA, Jacob KS, et al. Effect of cryptosporidial and giardial diarrhoea on social maturity, intelligence and physical growth in children in a semi-urban slum in south India. Ann Trop Paediatr. 2011;31:205–12. https://doi.org/10.1179/1465328111Y.0000000003
43. Berkman DS, Lescano AG, Gilman RH, Lopez SL, Black MM. Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study. Lancet. 2002;359:564–71. https://doi.org/10.1016/S0140-6736(02)07744-9
44. Gizaw Z, Yalew AW, Bitew BD, Lee J, Bisesi M. Stunting among children aged 24–59 months and associations with sanitation, enteric infections, and environmental enteric dysfunction in rural northwest Ethiopia. Sci Rep. 2022;12:19293. https://doi.org/10.1038/s41598-022-23981-5
45. Kabir F, Iqbal J, Janil Z, Iqbal NT, Mallawaarachchi I, Aziz F, et al. Impact of enteropathogens on faltering growth in a resource-limited setting. Front Nutr. 2022;9:1081833. https://doi.org/10.3389/fnut.2022.1081833
46. Coffey CM, Collier SA, Gleason ME, Yoder JS, Kirk MD, Richardson AM, et al. Evolving epidemiology of reported giardiasis cases in the United States, 1995–2016. Clin Infect Dis. 2021;72:764–70. https://doi.org/10.1093/cid/ciaa128
47. Munoz FM, Attias E, Czinn SJ, Black J; Persistent Diarrhea Working Group. Paediatrician and caregiver awareness of cryptosporidiosis and giardiasis in children: US survey responses. Zoonoses Public Health. 2016;63:410–9. https://doi.org/10.1111/zph.12246
48. Barry MA, Weatherhead JE, Hotez PJ, Woc-Colburn L. Childhood parasitic infections endemic to the United States. Pediatr Clin North Am. 2013;60:471–85. https://doi.org/10.1016/j.pcl.2012.12.011
49. Austhof E, Schaefer K, Faulkner J, Bach L, Riddle M, Pogreba-Brown K. Knowledge and practices of primary care physicians or general practitioners treating post-infectious irritable bowel syndrome. BMC Gastroenterol. 2020;20:159. https://doi.org/10.1186/s12876-020-01305-z
50. Beer KD, Collier SA, Du F, Gargano JW. Giardiasis diagnosis and treatment practices among commercially insured persons in the United States. Clin Infect Dis. 2017;64:1244–50. https://doi.org/10.1093/cid/cix138

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Patrick Mead, *Untitled*, 2016 (detail). Digital mosaic. Image courtesy of the artist.

A Tangle of Curious Forms

Lesli Mitchell

> I love forms beyond my own /
> and regret the borders between us
> —Loren Eiseley (*1*)

The untitled cover art for this supplement issue of *Emerging Infectious Diseases* was created by Patrick Mead in 2016. Mead's first experience creating art came at the age of 15, when his parents gave him a digital camera. The artist describes it as his first experience of feeling creative (pers. comm., email, 2025 Dec 9). Initially, his photographic subjects were abandoned structures, such as the Great Western Sugar Company mills found along the Front Range of the Rocky Mountains in Colorado, but his attention turned more toward nature as he grew older.

Mead's digital image is a mosaic he created in Adobe Photoshop from a single photograph he took of an Eastern cottonwood tree. "The tree was at the intersection of College and Vine in Fort Collins," said Mead (pers. comm., email, 2026 Jan 8). "I chose it somewhat at random, but also because, like all old cottonwoods, it has this semblance of being a protrusion or extension of the earth beneath it rather than something that rests atop it."

At the time Mead was creating this piece, he was fascinated by fractal patterns found in the growth of trees and the promise of underlying order and unity that they offered. A fractal is a mathematical equation that describes a complex geometric shape characterized by self-similarity, meaning that it exhibits a similar pattern regardless of scale (*2*). This pattern is also found in nature. A tree is a good example of a fractal pattern: as it grows it repeats the same pattern; each branch has a similar structure to that of the original tree, as illustrated in the Figure.

Fractals are a newer discovery, the term introduced in 1975 by mathematician Benoît Mandelbrot. Fractals quickly captured the attention of the general public, and the "Mandelbrot set" was featured on the cover of *Scientific American* in 1985 (*3*). Over the course of 50 years, fractals have moved from the realm of mathematics to art and the popular imagination (*4*).

Mead (pers. comm., email, 2025 Dec 9) describes his personal experience of solace in exploring nature's connectedness:

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I found my love for the natural world, of which this image is an early example, grew from my attempts to establish connections with my environment by naming and befriending its nonhuman inhabitants. Isolation can be a pernicious and, at times, self-inflicted condition, independent from one's social surroundings. Knowing the local flora and fauna proved an effective way for me to combat this. To see the trees you pass every day on your way through the world as fellow inhabitants and companions, friends even, offered me a sense of comfort when it was otherwise lacking.

The series from which this piece originates was inspired by the art of Karl Blossfeldt, a German photographer and key figure in Germany's Neue Sachlichkeit (New Objectivity) movement, a post–World War I style emphasizing objective, factual representation. Best known for his close-up photography of plants, Blossfeldt, like Mead, was inspired by and spent much time in nature in his youth. Over 30 years, Blossfeldt produced 6,000 photographs using a homemade camera and lens that could magnify up to 30 times (*5*,*6*). The microcosmic aesthetic of his botanical photographs reflected his enduring interest in the repetitive patterns found in nature's textures and forms, a fascination also shared by Mead. Mead was also inspired at the time the work was created by the writing of Loren Eiseley, a naturalist, anthropologist, writer, and poet. Eiseley's writings helped inspire the modern environmental movement, and his work explores humanity's relationship with the natural world.

The artist recognizes that his analysis, while accurate, is one only afforded to him in retrospect. Mead acknowledges that his early interest in the underlying order and unity in patterns found in the growth of trees, and his fuller understanding of the natural world now, are not so different. Mead still practices photography for self-enrichment but says most of his time now is dedicated to his career as an art teacher and to designing board games. He currently resides in Colorado.

This supplemental issue of *Emerging Infectious Diseases* contains articles describing the prolonged, often nonspecific symptoms that arise in some patients after different infections. Collectively, such symptoms fall under the rubric of Infection-Associated Chronic Conditions and Illnesses (IACCIs). In addition to the suffering they cause patients, IACCIs pose a frequent conundrum for healthcare providers. They are familiar in some respects, yet their pathogenesis and full nature are obscure, and their overlap with other diseases fosters misdiagnosis and frustration.

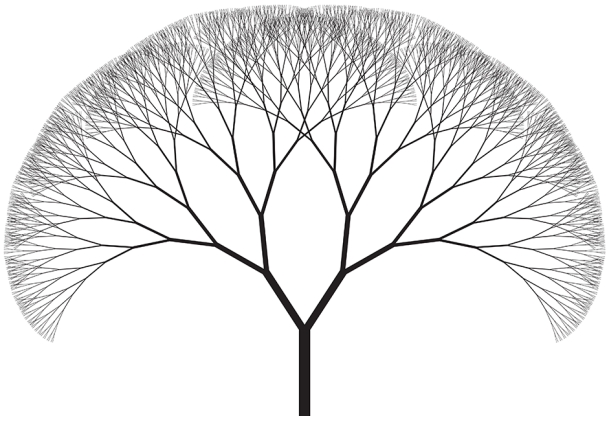

Figure. Symmetric fractal binary tree silhouette. Image by synthetick. Source: Adobe Stock (https://stock.adobe.com/1569039416).

Mead's cover image is based on reflections and permutations of a single tree. Although the original object is familiar, the viewer's orientation is upended and confused. What begins as recognizable tree branches overlap and blend into a tangle of curious forms in which different viewers may imagine a host of entities—creatures, faces, capillaries, phantoms—reflecting the multitude of challenges posed by IACCI.

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References

1. Eiseley L. Magic. In: Notes of an alchemist: poems by Loren Eiseley. New York: Charles Scribner's Sons; 1972. p. 56.
2. Lee S. The ultimate guide to fractals [cited 2026 Jan 9]. https://www.numberanalytics.com/blog/ultimate-guide-to-fractals
3. Dewdney AK. Computer recreations. Sci Am. 1985;253 [cited 2026 Jan 7]. https://www.scientificamerican.com/issue/sa/1985/08-01
4. Robb D. Fifty years of fractals. JSTOR [cited 2026 Jan 7]. https://daily.jstor.org/fifty-years-of-fractals
5. Blossfeldt K. Art forms in nature. Southbank Centre [cited 2026 Jan 9]. https://web.archive.org/web/20131122075826/http://www.southbankcentre.co.uk/find/hayward-gallery-and-visual-arts/hayward-touring/future/karl-blossfeldt-%E2%80%93-art-forms-in-nature-0
6. WSJ Gallery. Karl Blossfelt [cited 2025 Dec 19]. https://www.wsjgallery.com/artists/112-karl-blossfeldt/overview

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