Long COVID associated with SARS-CoV-2 reinfection among children and adolescents in the omicron era (RECOVER-EHR): a retrospective cohort study

*Bingyu Zhang, Qiong Wu, Ravi Jhaveri, Ting Zhou, Michael J Becich, Yuriy Bisyuk, Frank Blancerό, Elizabeth A Chrischilles, Cynthia H Chuang, Lindsay G Cowell, Daniel Fort, Carol R Horowitz, Susan Kim, Nathalia Ladino, David M Liebovitz, Mei Liu, Abu S M Mosa, Hayden T Schwenk, Srinivasan Suresh, Bradley W Taylor, David A Williams, Jeffrey S Morris, Christopher B Forrest, Yong Chen, on behalf of the RECOVER Consortium**

Summary

Background Post-acute sequelae of SARS-CoV-2 infection (PASC) remain a major public health challenge. Although previous studies have focused on characterising PASC in children and adolescents after an initial infection, the risks of PASC after reinfection with the omicron variant remain unclear. We aimed to assess the risk of PASC diagnosis (U09.9) and symptoms and conditions potentially related to PASC in children and adolescents after a SARS-CoV-2 reinfection during the omicron period.

Methods This retrospective cohort study used data from 40 children's hospitals and health institutions in the USA participating in the Researching COVID to Enhance Recovery (RECOVER) Initiative. We included patients younger than 21 years at the time of cohort entry; with documented SARS-CoV-2 infection after Jan 1, 2022; and who had at least one health-care visit within 24 months to 7 days before the first infection. The second SARS-CoV-2 infection was confirmed by positive PCR, antigen tests, or a diagnosis of COVID-19 that occurred at least 60 days after the first infection. The primary endpoint was a clinician-documented diagnosis of PASC (U09.9). Secondary endpoints were 24 symptoms and conditions previously identified as being potentially related to PASC. We used the modified Poisson regression model to estimate the relative risk (RR) between the second and first infection episodes, adjusted for demographic, clinical, and health-care utilisation factors using exact and propensity-score matching.

Findings We identified 407 300 (87·5%) of 465 717 eligible children and adolescents with a first infection episode and 58 417 (12·5%) with a second infection episode from Jan 1, 2022, to Oct 13, 2023, in the RECOVER database. 233 842 (50·2%) patients were male and 231 875 (49·8%) were female. The mean age was 8·17 years (SD 6·58). The incident rate of PASC diagnosis (U09.9) per million people per 6 months was 903·7 (95% CI 780·9–1026·5) in the first infection group and 1883·7 (1565·1–2202·3) in the second infection group. Reinfection was associated with a significantly increased risk of an overall PASC diagnosis (U09.9) (RR 2·08 [1·68–2·59]) and a range of symptoms and conditions potentially related to PASC (RR range 1·15–3·60), including myocarditis, changes in taste and smell, thrombophlebitis and thromboembolism, heart disease, acute kidney injury, fluid and electrolyte disturbance, generalised pain, arrhythmias, abnormal liver enzymes, chest pain, fatigue and malaise, headache, musculoskeletal pain, abdominal pain, mental ill health, POTS or dysautonomia, cognitive impairment, skin conditions, fever and chills, respiratory signs and symptoms, and cardiovascular signs and symptoms.

Interpretation Children and adolescents face a significantly higher risk of various PASC outcomes after reinfection with SARS-CoV-2. These findings add to previous evidence linking paediatric long COVID to multisystem effects and highlight the need to promote vaccination in younger populations and support ongoing research to better understand PASC, identify high-risk subgroups, and improve prevention and care strategies.

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*Collaborators listed in the appendix (pp 49–52)

Center for Health AI and Synthesis of Evidence (B Zhang MS, Q Wu PhD, T Zhou MD PhD, Prof Y Chen PhD), **Graduate Group in Applied Mathematics and Computational Science, School of Arts and Sciences** (B Zhang, Prof Y Chen), **and Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine** (Q Wu, T Zhou, Prof J S Morris PhD, Prof Y Chen), **University of Pennsylvania, Philadelphia, PA, USA; Department of Biostatistics and Health Data Science** (Q Wu) **and Department of Biomedical Informatics** (Prof M J Becich MD PhD), **University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; Division of Pediatric Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA** (Prof R Jhaveri MD); **University Medical Center New Orleans, New Orleans, LA, USA** (Y Bisyuk MD PhD); **RECOVER Patient, Caregiver, or Community Advocate Representative, New York, NY, USA** (F Blancerό BA); **Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA** (Prof E A Chrischilles PhD); **Penn State College of Medicine, Hershey, PA, USA** (Prof C H Chuang MD MSc); **O'Donnell School of Public Health, UT Southwestern Medical Center, Dallas, TX, USA** (Prof L G Cowell MS PhD); **Center**

Introduction

Since the onset of the COVID-19 pandemic, post-acute sequelae of SARS-CoV-2 infection (PASC, also known as long COVID) has emerged as a pronounced global concern with substantial long-term health effects in adults and children. Defined by the US National Institutes of Health (NIH)[1] and Centers for Disease Control and Prevention (CDC)[2] as new or ongoing health problems persisting at least 4 weeks after infection, PASC spans a wide range of symptoms and syndromes affecting multiple organ systems.

Although existing research has characterised the clinical features and burden of PASC in adults and children,[3–7] the clinical presentation differs markedly between these populations. In adults, PASC often includes respiratory, cardiovascular, and neurocognitive

for Outcomes Research, Ochsner Health, New Orleans, LA, USA (D Fort PhD MPH); Institute for Health Equity Research, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Prof C R Horowitz MD MPH); Department of Pediatrics, Division of Pediatric Rheumatology, Benioff Children's Hospital, University of California San Francisco, San Francisco, CA, USA (S Kim MD MMSc); NYU Langone Health, New York, NY, USA (N Ladino MS); Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (D M Liebovitz MD); Department of Health Outcomes and Biomedical Informatics, University of Florida, College of Medicine, FL, USA (M Liu PhD); Department of Biomedical Informatics, Biostatistics, and Medical Epidemiology, University of Missouri School of Medicine, Columbia, MO, USA (A S M Mosa PhD); Department of Biomedical Informatics and Data Science, University of Alabama at Birmingham, Birmingham, AL, USA (A S M Mosa); Stanford School of Medicine, Division of Pediatric Infectious Diseases, Stanford, CA, USA (H T Schwenk MD MPH); Department of Pediatrics, University of Pittsburgh, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA (Prof S Suresh MD MBA); Clinical and Translational Science Institute, Medical College of Wisconsin, Milwaukee, WI, USA (B W Taylor MBA FAMIA); Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA (Prof D A Williams PhD); Applied Clinical Research Center, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA (Prof C B Forrest MD PhD); Leonard Davis Institute of Health Economics, Philadelphia, PA, USA (Prof Y Chen, Prof C B Forrest); Penn Medicine Center for Evidence-based Practice, Philadelphia, PA, USA (Prof Y Chen); Penn Institute for Biomedical Informatics, Philadelphia, PA, USA (Prof Y Chen)

Research in context

Evidence before this study

We searched PubMed for articles published in English up to July 15, 2025, using the terms ("SARS-CoV-2" or "COVID-19") AND ("reinfection" or "reinfections") AND ("PASC" or "post-acute sequelae" or "long COVID" or "post-COVID-19 condition"). This search yielded nine studies examining the association between SARS-CoV-2 reinfection and the development of post-acute sequelae of SARS-CoV-2 (PASC). Most studies focused on adult populations, with few addressing paediatric cohorts. Several studies suggested that repeated SARS-CoV-2 infections might increase the risk of long-term health complications, including PASC, particularly in older adults and those with comorbidities. However, data on the paediatric population remain scarce. The identified studies often faced limitations such as small sample sizes, reliance on self-reported data, and short follow-up, which hinder the ability to draw definitive conclusions about the risk of PASC after reinfection in children and adolescents. Furthermore, variations in PASC definitions and diagnostic criteria across studies contribute to inconsistencies in the reported outcomes.

Added value of this study

To our knowledge, this study is the first and largest electronic health record (EHR)-based cohort to comprehensively evaluate the risk of PASC after SARS-CoV-2 reinfection with the omicron variant (B.1.1.529) among children and adolescents. By leveraging EHR data from the National Institutes of Health Researching COVID to Enhance Recovery Initiative across 40 paediatric institutions, we were able to assess the PASC diagnosis (ICD-10-CM code U09.9) and a broad variety of potential post-acute symptoms and conditions. Using a second versus first infection design, we aligned calendar time and time from infection and adjusted for confounding with propensity score matching. This study extends the literature on PASC symptom development beyond the early pandemic period (March, 2020 to December, 2021).

Implications of all the available evidence

The growing frequency of SARS-CoV-2 reinfections in the omicron era underscores the need to understand their long-term consequences. Our findings indicate that PASC risk persists after reinfection in children and adolescents, although the magnitude might vary by previous infection history, severity, and vaccination status. These results suggest that reinfections might contribute to cumulative morbidity. Ongoing long-term follow-up is essential for informing clinical care and public health strategies to mitigate the paediatric burden of long COVID.

sequelae,[3,4] whereas children and adolescents tend to have more heterogeneous and non-specific symptoms, such as fatigue, mood changes, dizziness, and abdominal pain.[5,6,8,9] Understanding how PASC manifests in children is crucial for improving diagnosis, treatment, and long-term monitoring.

With the emergence of omicron (B.1.1.529) variants, SARS-CoV-2 reinfections have markedly increased, likely due to the immune-evasive and fast-spreading nature of omicron variants, the generally milder acute presentation compared with earlier variants,[10–12] and a declining booster uptake in the UK and USA.[13,14] This shift in the pandemic landscape has led to uncertainties regarding the risk of PASC after reinfection, particularly by omicron. Understanding the long-term consequences of reinfection is crucial, as even mild or asymptomatic cases could contribute to substantial morbidity.

In adult populations, several observational studies have investigated the risk of PASC after reinfection.[15–19] Most found that individuals with reinfection had a higher risk of developing PASC compared with those with a single infection, and that the risk increased with the number of infections. Evidence on the effect of reinfection on PASC risk in paediatric populations remains scarce. Five studies focused on children and adolescents, most of which relied on survey data with small sample sizes and insufficient adjustment for confounding factors.[18,20–23] Notably, three of those studies focused on the omicron period[20–22] but were based on self-reported outcomes and did not have clinically verified diagnoses or detailed information on comorbidities or health-care utilisation. These studies generally reported no significant difference in risk of PASC between children with reinfection and those with only one infection, but the interpretation of these findings could be restricted by the small sample size and insufficient statistical power.

To our knowledge, this study is the first and largest investigation based on longitudinal electronic health records (EHRs) of PASC after SARS-CoV-2 reinfection in children and adolescents, using data from institutions participating in the NIH-funded Researching COVID to Enhance Recovery (RECOVER) Initiative. We aimed to assess the risk of PASC diagnosis (ICD-10-CM code U09.9) and symptoms and conditions potentially related to PASC using definitions established in paediatric literature.[6–9,24–28] The studies investigating risk of PASC after reinfection in adult populations used two main analytical approaches. One approach compared individuals with a second infection to those without a second infection (second *vs* no second infection), aiming to estimate the effect of reinfection on PASC with the counterfactual scenario in which no reinfection occurred.[15–17] The second approach compared individuals after their second infection to those after their first infection during the same calendar period (second *vs* first infection), isolating reinfection-specific risk within a similar follow-up timeframe.[18,19] In this study, we adopt the second approach to enable comparability in calendar time and time since infection.

Methods

Study design

This retrospective cohort study included 40 children's hospitals and health institutions in the USA (appendix pp 3–4). We included patients younger than 21 years at the time of cohort entry, consistent with the paediatric definition used by the US Department of Health and Human Services and the American Academy of Pediatrics.[29] Eligible participants had a documented SARS-CoV-2 infection after Jan 1, 2022, which is when omicron variants were considered to have completely displaced earlier variants and at least one health-care visit within the baseline period (defined as 24 months to 7 days before the first infection) to ensure active interaction with the health-care system. For the first infection group, the infection had to occur on or after Jan 1, 2022. For the second infection group, the second infection had to occur after Jan 1, 2022, and the first infection could have occurred during earlier variant phases. Individuals could contribute to both first and second infection groups if they independently met the eligibility criteria for each infection episode.

The first documented SARS-CoV-2 infection was defined by positive PCR, serology, antigen tests, or diagnoses of COVID-19 (appendix pp 5–6). The index date for the first infection was set as the earliest date of positive tests or COVID-19 diagnoses. The second SARS-CoV-2 infection was identified by positive PCR, antigen tests, or diagnoses of COVID-19 that occurred at least 60 days after the first infection. Patients whose second infection was within 60 days of the first were put in the first infection group. The index date for the second infection was set as the earliest date of positive tests and COVID-19 diagnoses for the second infection. A visual schematic of the cohort design and timelines is shown in the appendix (p 5). Institutional Review Board approval was obtained at the Biomedical Research Alliance of New York (BRANY; New York, NY, USA; protocol number 21–08–508), and the protocol was reviewed in accordance with institutional guidelines. The study protocol and statistical analysis plan are available in the appendix (pp 42–48). BRANY waived the need for informed consent and HIPAA authorisation.

Covariates

A comprehensive set of patient characteristics collected during the baseline period (24 months to 7 days before the first infection) and before the index date were considered as confounders and adjusted for using exact and propensity-score matching to balance first and second infection episodes between study groups, which was based on previous literature and clinical and epidemiological knowledge.[6,30] These characteristics included demographic factors (age at index date, sex [female or male] as recorded in the EHR, and race and ethnicity [Hispanic, non-Hispanic White, non-Hispanic Black, Asian American and Pacific Islander, multiple, or other and unknown]), clinical factors (obesity status [latest measure before the index date, yes, no, or unknown; appendix p 7], a chronic condition indicator defined by the Pediatric Medical Complexity Algorithm[31] [PMCA; no chronic condition, non-complex chronic condition, or complex chronic condition], and a list of pre-existing chronic conditions), health-care utilisation factors (the number of inpatient, outpatient, and emergency department visits, unique medications or prescriptions, and negative COVID-19 tests [0, 1, 2, or ≥3]), vaccine information (dose of COVID-19 vaccine before the index date [0, 1–2, or ≥3] and interval since the last COVID-19 immunisation [no vaccine, <4 months, or ≥4 months]), the severity of acute COVID-19 (non-severe, including asymptomatic and mild or severe, including moderate and severe), year–month of cohort entry (from January, 2022, to October, 2023), and an indicator variable for each participating site to account for differences in patient characteristics and health-care delivery.

Outcomes

The primary endpoint was a clinician-documented diagnosis of PASC (U09.9), which has been increasingly adopted in clinical settings as a marker for post-COVID conditions. Secondary endpoints were a set of 24 symptoms and conditions possibly associated with paediatric PASC, based on recommendations from paediatric physicians and previously published literature.[6–9,24–28] The symptoms and conditions included abdominal pain, abnormal liver enzymes, acute kidney injury, acute respiratory distress syndrome, arrhythmias, cardiovascular signs and symptoms, changes in taste and smell, chest pain, cognitive impairment, fatigue and malaise, fever and chills, fluid and electrolyte disturbance, generalised pain, hair loss, headache, heart disease, mental ill health, musculoskeletal pain, myocarditis, myositis, postural orthostatic tachycardia syndrome (POTS) or dysautonomia, respiratory signs and symptoms, skin conditions, and thrombophlebitis and thromboembolism.

Symptoms and conditions potentially related to PASC were assessed during 28–179 days after cohort entry in patients without a history of the specific condition from 24 months to 7 days before the index date, thereby capturing new-onset or incident cases. We used validated diagnostic codes (ICD-10-CM) confirmed by board-certified paediatricians (appendix pp 3–8).

Statistical analysis

Follow-up for each participant ended at the next documented SARS-CoV-2 infection, the next documented SARS-CoV-2 infection of the matched patient, 179 days after the index date, or at the end of the study period, whichever occurred first. This pairwise censoring approach ensured that both individuals in a matched pair contributed equal follow-up time, thereby preventing

Correspondence to:
Prof Yong Chen, Center for Health AI and Synthesis of Evidence, University of Pennsylvania, Philadelphia, PA 19104, USA
ychen123@pennmedicine.upenn.edu

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differential exposure to outcome ascertainment. This design aligns with a per-protocol framework commonly used in target trial emulation studies,[32,33] in which individuals are censored upon deviating from the assigned exposure group (second *vs* first infection).

We calculated the incidence of PASC outcomes in the first and second infection episode groups. For each PASC-related symptom and condition outcome, incidence rates were calculated by dividing new diagnoses of the symptom or condition during the follow-up period by the total number of patients without any diagnoses at baseline.

We used exact matching and propensity score matching to adjust for confounders. First, we performed exact matching using age group (0–4, 5–11, or 12–20 years), sex, race and ethnicity, indicator for each participating site, vaccine doses, and year–month of cohort entry. Age was calculated in years and floored (eg, 20·9 years was recorded as 20 years). Within each exact-matched stratum, propensity scores of patients were estimated by fitting a logistic regression model that included all other covariates, including age in years. Propensity-score matching was then performed within each exact-matched stratum without replacement (1:5 ratio, where 1 is the second infection group and 5 is the first infection group). The balance of baseline characteristics was assessed by calculating standardised mean differences between study groups, with a standardised mean difference of 0·1 or less indicating an acceptable balance.

We used the modified Poisson regression model for binary outcomes to estimate the relative risk (RR) for each outcome between study groups, which is a popular and effective alternative to traditional logistic regression.[34] RR is a collapsible measure, meaning the measure of association conditional on some factors remains consistent with the marginal measure collapsed over strata. The odds ratio (OR) or hazard ratio (HR) is non-collapsible, which can lead to discrepancies between marginal and conditional estimates, even in the absence of confounding. This property makes RR more suitable for accurate interpretation in clinical research.[35,36]

Given that vaccine status and severity of acute COVID-19 might be effect modifiers, we performed stratified analyses by vaccine status (vaccinated or unvaccinated) and COVID-19 severity (severe or non-severe) to examine how these factors might influence the observed associations.

We conducted several sensitivity analyses to examine the robustness of our findings. Although we attempted to balance a comprehensive list of potential confounders using exact and propensity-score matching, residual study bias from unmeasured and systematic sources could still exist. To address this potential bias, we

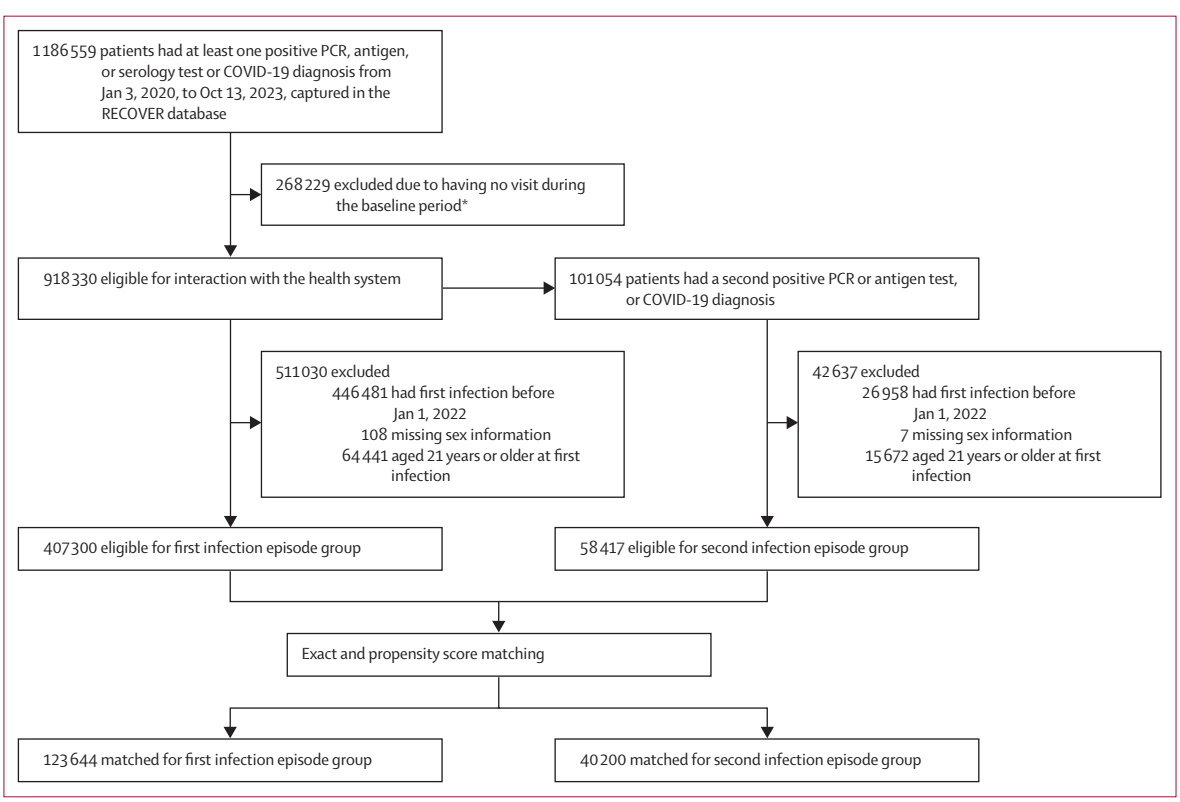


Figure 1: **Participant selection**
RECOVER=Researching COVID to Enhance Recovery. *Baseline period from 24 months to 7 days before the first infection.

performed negative-control outcome experiments,[37,38] leveraging a predefined set of 36 negative-control outcomes identified by board-certified paediatricians with the assumption of a true null effect (appendix p 15). In another sensitivity analysis, to ensure continuity of follow-up within the health-care system, we restricted the analysis to patients who had at least one visit during the follow-up period (28–179 days after the index date). To better align with the WHO definition of the post-COVID condition,[39] we conducted a sensitivity analysis restricting the outcome window to 90–179 days after infection. Additionally, we conducted subgroup analyses by stratifying the cohort based on key demographic and clinical factors, including age (0–4, 5–11, or 12–20 years), sex (male or female), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or Asian American and Pacific Islander), and obesity status (obesity or no obesity). RRs were estimated within each stratum by comparing second versus first infections. Interaction tests were also performed to assess effect modification.

All analyses were performed using R (version 4.4.0). Statistical significance was set at p<0·05 (two-tailed).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 1 186 559 children and adolescents who had at least one positive SARS-CoV-2 PCR, antigen, or serology test or a COVID-19 diagnosis recorded in the RECOVER database between March 1, 2020, and Oct 13, 2023. After exclusions, 465 717 children and adolescents were eligible for inclusion, of whom 407 300 (87·5%) contributed to the first infection episode and 58 417 (12·5%) to the second infection episode from Jan 1, 2022, to Oct 13, 2023 (figure 1). 233 842 (50·2%) patients were male and 231 875 (49·8%) were female (table 1). The mean age was 8·17 years (SD 6·58).

In the first infection episode group, 170 911 (42·0%) patients were non-Hispanic White, 62 128 (15·3%) were non-Hispanic Black, 97 994 (24·1%) were Hispanic, 22 149 (5·4%) were Asian American and Pacific Islanders, 7357 (1·8%) were classified as multiple race and ethnicity, and 46 761 (11·5%) were classified as other or unknown. In the second infection episode group, 26 545 (45·4%) patients were non-Hispanic White, 9199 (15·7%) were non-Hispanic Black, 14 869 (25·5%) were Hispanic, 2238 (3·8%) were Asian American and Pacific Islanders, 929 (1·6%) were classified as multiple race and ethnicity, and 4637 (7·9%) were classified as other or unknown. Patients with second infection episodes tended to be older, were more often female, had obesity, had a higher PMCA index indicative of complex chronic conditions, and showed greater health-care utilisation, including more

	First infection (n=407 300)	Second infection (n=58 417)	Overall (n=465 717)
Age			
Mean	7·98 (6·56)	9·45 (6·59)	8·17 (6·58)
Age category			
0–4 years	164 310 (40·3%)	18 854 (32·3%)	183 164 (39·3%)
5–11 years	106 894 (26·2%)	15 026 (25·7%)	121 920 (26·2%)
12–20 years	136 096 (33·4%)	24 537 (42·0%)	160 633 (34·5%)
Sex			
Female	202 402 (49·7%)	29 473 (50·5%)	231 875 (49·8%)
Male	204 898 (50·3%)	28 944 (49·5%)	233 842 (50·2%)
Race and ethnicity			
Non-Hispanic White	170 911 (42·0%)	26 545 (45·4%)	197 456 (42·4%)
Non-Hispanic Black	62 128 (15·3%)	9199 (15·7%)	71 327 (15·3%)
Hispanic	97 994 (24·1%)	14 869 (25·5%)	112 863 (24·2%)
Asian American and Pacific Islanders	22 149 (5·4%)	2238 (3·8%)	24 387 (5·2%)
Multiple*	7357 (1·8%)	929 (1·6%)	8286 (1·8%)
Other or unknown†	46 761 (11·5%)	4637 (7·9%)	51 398 (11·0%)
Obesity			
No	171 700 (42·2%)	21 434 (36·7%)	193 134 (41·5%)
Yes	155 893 (38·3%)	24 568 (42·1%)	180 461 (38·7%)
Unknown	79 707 (19·6%)	12 415 (21·3%)	92 122 (19·8%)
Paediatric Medical Complexity Algorithm			
No chronic condition	303 053 (74·4%)	37 461 (64·1%)	340 514 (73·1%)
Non-complex chronic condition	58 747 (14·4%)	9486 (16·2%)	68 233 (14·7%)
Complex chronic condition	45 500 (11·2%)	11 470 (19·6%)	56 970 (12·2%)
Number of inpatient visits			
0	348 613 (85·6%)	45 707 (78·2%)	394 320 (84·7%)
1	44 026 (10·8%)	7797 (13·3%)	51 823 (11·1%)
2	7383 (1·8%)	1922 (3·3%)	9305 (2·0%)
≥3	7278 (1·8%)	2991 (5·1%)	10 269 (2·2%)
Number of outpatient visits			
0	69 705 (17·1%)	8386 (14·4%)	78 091 (16·8%)
1	52 174 (12·8%)	6379 (10·9%)	58 553 (12·6%)
2	41 989 (10·3%)	5326 (9·1%)	47 315 (10·2%)
≥3	243 432 (59·8%)	38 326 (65·6%)	281 758 (60·5%)
Number of emergency department visits			
0	293 010 (71·9%)	37 282 (63·8%)	330 292 (70·9%)
1	62 722 (15·4%)	10 074 (17·2%)	72 796 (15·6%)
2	24 404 (6·0%)	4550 (7·8%)	28 954 (6·2%)
≥3	27 164 (6·7%)	6511 (11·1%)	33 675 (7·2%)
Number of unique medications or prescriptions			
0	86 417 (21·2%)	9264 (15·9%)	95 681 (20·5%)
1	48 894 (12·0%)	5431 (9·3%)	54 325 (11·7%)
2	41 014 (10·1%)	4896 (8·4%)	45 910 (9·9%)
≥3	230 975 (56·7%)	38 826 (66·5%)	269 801 (57·9%)
Number of negative COVID-19 tests			
0	217 327 (53·4%)	21 830 (37·4%)	239 157 (51·4%)
1	94 054 (23·1%)	13 670 (23·4%)	107 724 (23·1%)
2	42 757 (10·5%)	8289 (14·2%)	51 046 (11·0%)
≥3	53 162 (13·1%)	14 628 (25·0%)	67 790 (14·6%)

(Table 1 continues on the next page)

	First infection (n=407 300)	Second infection (n=58 417)	Overall (n=465 717)
(Continued from previous page)			
Dose of COVID-19 vaccine			
0	318 702 (78·2%)	43 209 (74·0%)	361 911 (77·7%)
1–2	71 645 (17·6%)	11 637 (19·9%)	83 282 (17·9%)
≥3	16 953 (4·2%)	3571 (6·1%)	20 524 (4·4%)
Interval since the last COVID-19 immunisation			
No vaccine	318 702 (78·2%)	43 209 (74·0%)	361 911 (77·7%)
≥4 months	60 771 (14·9%)	11 886 (20·3%)	72 657 (15·6%)
<4 months	27 827 (6·8%)	3322 (5·7%)	31 149 (6·7%)
Acute COVID-19 severity			
Asymptomatic	225 525 (55·4%)	31 365 (53·7%)	256 890 (55·2%)
Mild	149 902 (36·8%)	17 061 (29·2%)	166 963 (35·9%)
Moderate	22 447 (5·5%)	6976 (11·9%)	29 423 (6·3%)
Severe	9426 (2·3%)	3015 (5·2%)	12 441 (2·7%)
Pre-existing chronic conditions (top 10)			
Allergies	76 149 (18·7%)	12 065 (20·7%)	88 214 (18·9%)
Asthma	39 753 (9·8%)	7950 (13·6%)	47 703 (10·2%)
Anxiety disorder	28 403 (7·0%)	5510 (9·4%)	33 913 (7·3%)
Oesophageal disorder	24 986 (6·1%)	5496 (9·4%)	30 482 (6·5%)
Cornea and external disease	24 232 (5·9%)	3976 (6·8%)	28 208 (6·1%)
Implant, device, or graft related encounter	21 929 (5·4%)	5916 (10·1%)	27 845 (6·0%)
Sleep–wake disorder	21 813 (5·4%)	5016 (8·6%)	26 829 (5·8%)
Musculoskeletal congenital conditions	21 190 (5·2%)	3832 (6·6%)	25 022 (5·4%)
Communication and motor disorders	20 877 (5·1%)	3473 (5·9%)	24 350 (5·2%)
Mental health treatment	17 434 (4·3%)	2158 (3·7%)	19 592 (4·2%)

Data are mean (SD) or n (%). *Multiple refers to patients with multiple race and ethnicity categories. †Other includes American Indian/Alaska Native, Middle Eastern or North African, and Other; unknown refers to instances where patients gave no answer.

Table 1: **Baseline characteristics of patients**

frequent inpatient, outpatient, and emergency department visits and a higher proportion of negative COVID-19 tests and medications or prescriptions. Descriptive data of the first infection in the second infection group are shown in the appendix (pp 12–13), including time between infections, dominant phase, acute COVID-19 severity, and vaccine status.

The characteristics of the first and second infection episode groups were well balanced after exact matching and propensity score matching (appendix pp 9–12). Individuals with a second infection episode generally have higher incidence rates per million people per 6 months of PASC outcomes than those with a first infection episode after matching (table 2). The PASC diagnosis (U09.9) showed 903·7 (95% CI 780·9–1026·5) incidence rate per million people per 6 months in the first infection group and 1883·7 (1565·1–2202·3) in the second infection group. The highest incidence rate observed was for respiratory signs and symptoms (61 008·2 [60 030·4–61 986·0] per million people per 6 months in the first infection group *vs* 78 342·3 [76 367·6–80 317·0] in the second infection group).

There was a significantly higher risk of PASC across multiple outcomes among patients with second infection episodes than those with first infection episodes (figure 2). Reinfection was associated with a significantly increased risk of an overall PASC diagnosis (U09.9; RR 2·08 [95% CI 1·68–2·59]). Several potential PASC-related symptoms and conditions also showed increased risks including myocarditis (3·60 [1·46–8·86]); changes in taste and smell (2·83 [1·41–5·67]); thrombophlebitis and thromboembolism (2·28 [1·71–3·04]); heart disease (1·96 [1·69–2·28]); acute kidney injury (1·90 [1·38–2·61]); fluid and electrolyte disturbance (1·89 [1·62–2·20]); generalised pain (1·70 [1·48–1·95]); arrhythmias (1·59 [1·45–1·74]); abnormal liver enzymes (1·56 [1·24–1·96]); chest pain (1·53 [1·39–1·69]); fatigue and malaise (1·50 [1·38–1·64]); headache (1·46 [1·36–1·57]); musculoskeletal pain (1·45 [1·37–1·54]); abdominal pain (1·42 [1·34–1·50]); mental ill health (1·38 [1·33–1·43]); POTS or dysautonomia (1·35 [1·20–1·51]); cognitive impairment (1·32 [1·15–1·50]); skin conditions (1·29 [1·22–1·37]); fever and chills (1·29 [1·22–1·36]); respiratory signs and symptoms (1·29 [1·25–1·33]); and cardiovascular signs and symptoms (1·15 [1·02–1·29]).

The increased risk of PASC after a second infection persists across subgroups defined by vaccination status and acute phase severity, indicating that the heightened risk is consistent regardless of these factors (figure 3). Vaccinated and unvaccinated individuals and those with severe and non-severe acute COVID-19 showed higher risks of PASC after reinfection. This analysis does not directly compare vaccinated versus unvaccinated patients or severe versus non-severe COVID-19. Instead, subgroup analyses within each group assess whether the overall conclusion holds.

A prespecified sensitivity analysis of negative control outcome experiments indicated a slight systematic error, as shown by a minor shift in point estimates with wider CIs (appendix pp 15–16). As a result, some associations became non-significant, including those for POTS or dysautonomia, cognitive impairment, skin conditions, fever and chills, respiratory signs and symptoms, and cardiovascular signs and symptoms. Analysis restricted to patients who had at least one visit during the post-acute phase (appendix pp 17–18) and follow-up during 90–179 days post-infection (appendix pp 19–20) showed similar results to the primary analyses.

Subgroup analyses (appendix pp 21–33) show RRs for PASC diagnosis (U09.9) and PASC-related symptoms and conditions comparing the second infection to the first infection within each subgroup. In age-stratified analyses (appendix pp 21–24), adolescents aged 12–20 and children aged 5–11 years had higher RRs of PASC diagnosis after reinfection, whereas children aged 0–4 years had higher RRs of thrombophlebitis and thromboembolism and abnormal liver enzymes. In sex-stratified analyses (appendix pp 25–27), both males and females showed consistently elevated RRs for PASC

	Number of events		Incidence rate per million people per 6 months (95% CI)	
	First infection	Second infection	First infection	Second infection
Primary endpoint				
Post-acute sequelae of SARS-CoV-2 diagnosis (U09.9)	208	134	903·7 (780·9–1026·5)	1883·7 (1565·1–2202·3)
Secondary endpoints				
Acute kidney injury	102	60	443·2 (357·2–529·2)	843·4 (630·1–1056·7)
Abdominal pain	3700	1626	16 075·4 (15 561·6–16 589·2)	22 857·4 (21 759·1–23 955·7)
Acute respiratory distress syndrome	17	8	73·9 (38·8–109·0)	112·5 (34·5–190·5)
Heart disease	457	277	1985·5 (1803·6–2167·4)	3893·9 (3436·2–4351·6)
Skin conditions	3726	1483	16 188·3 (15 672·7–16 703·9)	20 847·2 (19 797·3–21 897·1)
Cognitive impairment	747	305	3245·5 (3013·1–3477·9)	4287·5 (3807·3–4767·7)
Thrombophlebitis and thromboembolism	112	79	486·6 (396·5–576·7)	1110·5 (865·8–1355·2)
Cardiovascular signs and symptoms	1102	390	4787·9 (4505·9–5069·9)	5482·4 (4939·8–6025·0)
Mental ill health	9498	4046	41 265·9 (40 453·3–42 078·5)	56 876·5 (55 174·5–58 578·5)
Arrythmias	1345	662	5843·6 (5532·2–6155·0)	9306·0 (8600·4–10 011·6)
Postural orthostatic tachycardia syndrome or dysautonomia	965	412	4192·6 (3928·6–4456·6)	5791·7 (5234·1–6349·3)
Abnormal liver enzymes	224	108	973·2 (845·8–1100·6)	1518·2 (1232·1–1804·3)
Musculoskeletal pain	3617	1627	15 714·8 (15 206·7–16 222·9)	22 871·5 (21 772·9–23 970·1)
Fatigue and malaise	1715	798	7451·2 (7099·9–7802·5)	11 217·9 (10 443·9–11 991·9)
Myositis	16	6	69·5 (35·4–103·6)	84·3 (16·8–151·8)
Myocarditis	9	10	39·1 (13·6–64·6)	140·6 (53·5–227·7)
Changes in taste and smell	17	15	73·9 (38·8–109·0)	210·9 (104·2–317·6)
Generalised pain	583	308	2533·0 (2327·6–2738·4)	4329·7 (3847·2–4812·2)
Fluid and electrolyte disturbance	456	266	1981·2 (1799·5–2162·9)	3739·3 (3290·8–4187·8)
Hair loss	211	66	916·7 (793·1–1040·3)	927·8 (704·1–1151·5)
Chest pain	1226	580	5326·6 (5029·2–5624·0)	8153·3 (7492·5–8814·1)
Fever and chills	4194	1715	18 221·7 (17 675·3–18 768·1)	24 108·6 (22 981·4–25 235·8)
Headache	2248	1023	9766·9 (9365·1–10 168·7)	14 380·8 (13 505·9–15 255·7)
Respiratory signs and symptoms	14 042	5573	61 008·2 (60 030·4–61 986·0)	78 342·3 (76 367·6–80 317·0)

Calculated after exact and propensity score matching.

Table 2: **Number of events and incidence rate of patients after first and second infection episodes**

outcomes after reinfection. Racial and ethnic subgroup analysis (appendix pp 28–32) showed that non-Hispanic White patients had the highest RR of PASC diagnosis after reinfection, followed by Hispanic patients. In obesity stratified analysis (appendix pp 33–35), reinfection was associated with an increased PASC risk regardless of obesity status. The results of interaction tests are reported in the appendix (pp 40–41).

Discussion

In this study involving 465 717 individuals, we observed an increased risk of PASC across multiple organ systems after SARS-CoV-2 reinfection, reinforcing concerns about the long-term consequences of reinfection. These findings emphasise the ongoing risk of PASC with reinfection, regardless of severity, and suggest that the risk of PASC might be cumulative with each successive infection.

Our large and diverse cohort enables clinically verified outcomes, detailed covariate data, and extended follow-up. Using a second versus first infection design, within the omicron-dominant period, we aligned calendar time and time from infection and adjusted for confounding using propensity score matching. This approach allowed us to isolate reinfection-specific risk and extends the literature on PASC development beyond the early pandemic period, which has been the primary focus of most paediatric studies to date.

Our findings align with emerging evidence on immune waning post-infection. Although T-cell responses remain stable, neutralising antibody concentrations decline over time, possibly compromising immunity upon reinfection.[40] During the omicron era, protection from natural infection diminished more rapidly,[41] with reinfections becoming more common, especially among younger adults aged 18–49 years.[42] These dynamics elevate the need to understand reinfection risks in children, a group increasingly affected yet understudied in this context.

Previous paediatric studies further support the clinical relevance of our findings. Long COVID in paediatric populations has been associated with proteomic

biosignatures,[43] POTS,[44] exercise intolerance,[45] vascular problems,[46] and CNS issues.[47,48] Our real-world data add to this literature by showing that post-acute sequelae persist across reinfections and continue to impose a measurable clinical burden.

Our paediatric findings also align with adult studies. Research in adults shows that long COVID symptoms often worsen with repeated infections, suggesting potential shared mechanisms across age groups. These cross-population findings collectively emphasise the importance of ongoing clinical vigilance, mechanistic research, and strategies to mitigate reinfection-related risk.

A previous study shows that immunisation can reduce PASC risk by preventing infections.[49] Persistently low paediatric vaccination rates, due to milder omicron symptoms, delayed vaccine availability for those younger than 5 years, low booster uptake among older children,[14] and public COVID-19 fatigue, remain a challenge. Strengthening public health messaging and expanding access to vaccination might help to reduce the burden of PASC in children.

Our study has several strengths. First, we leveraged the RECOVER EHR database to construct a large paediatric cohort with longitudinal follow-up after first and second SARS-COV-2 infections, enhancing statistical power and generalisability. The RECOVER EHR data infrastructure was specifically designed to support COVID-19 research and includes dedicated fields for laboratory testing, vaccinations, clinical diagnoses, and health-care encounters. All participating sites contribute data that are standardised and undergo rigorous data quality assessments to ensure completeness, consistency, and harmonisation. Comorbidities and PASC outcomes were based on medically documented diagnoses, which offer greater specificity and reproducibility than the survey based data used in most paediatric PASC literature. Second, propensity score matching with hundreds of covariates helped to balance study groups and better control for confounders and reduced the influence of non-linear confounder effects compared with traditional regression methods.[50] Third, we used RR as the comparative measure, which provides a more intuitive and clinically interpretable estimate of relative risk, unlike OR or HR which are affected by non-collapsibility. Fourth, we conducted extensive sensitivity analyses, including negative control experiments[37,38] to address systematic bias and control unmeasured confounders, analyses across different selected populations, and a series of subgroup analyses to examine the robustness of our findings.

This study has several limitations. First, although SARS-CoV-2 testing was broadly accessible in the USA during the study period, with costs typically covered by insurance or federal programmes, results from at-home testing were not systematically captured in EHRs; therefore, some infections might be misclassified or missed, particularly for asymptomatic or mild cases. In paediatric populations, test results are more likely to be documented during a clinical encounter or due to school and day care requirements. We mitigated this limitation by using PCR, antigen tests, and diagnosis codes, although some underdiagnosis might remain and could possibly bias estimates toward the null, making our findings more conservative. Previous methods have been developed to address exposure misclassification when not highly differential.[36] Second, the timing of infection (index date) might be less accurate, especially when diagnosis codes are recorded after symptom onset. We defined index date as the earliest available test or

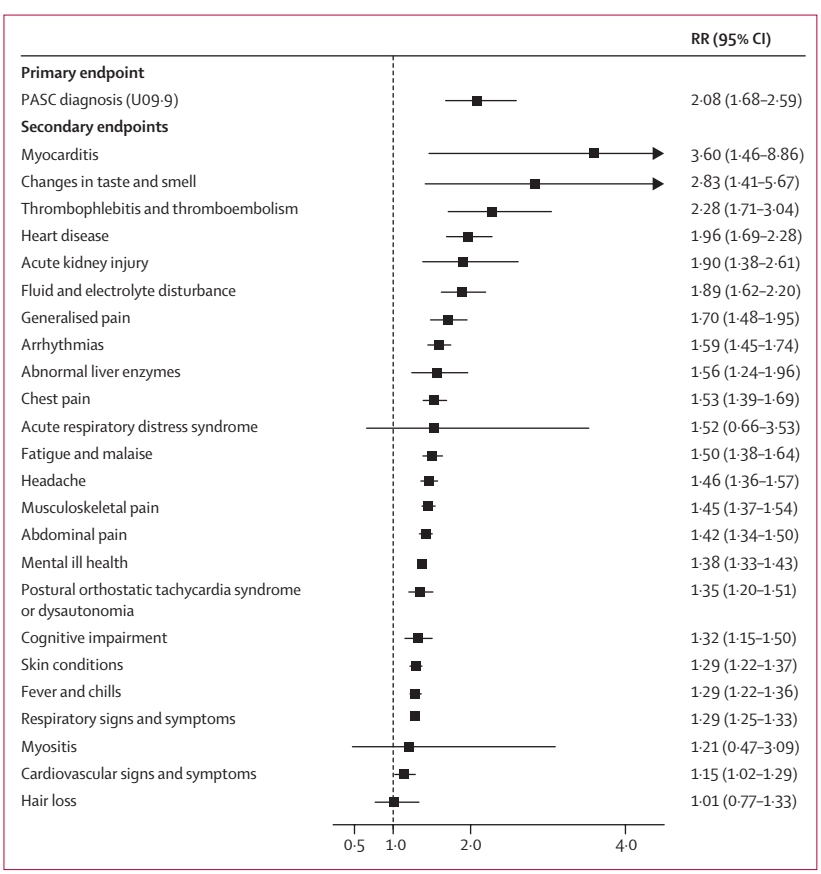
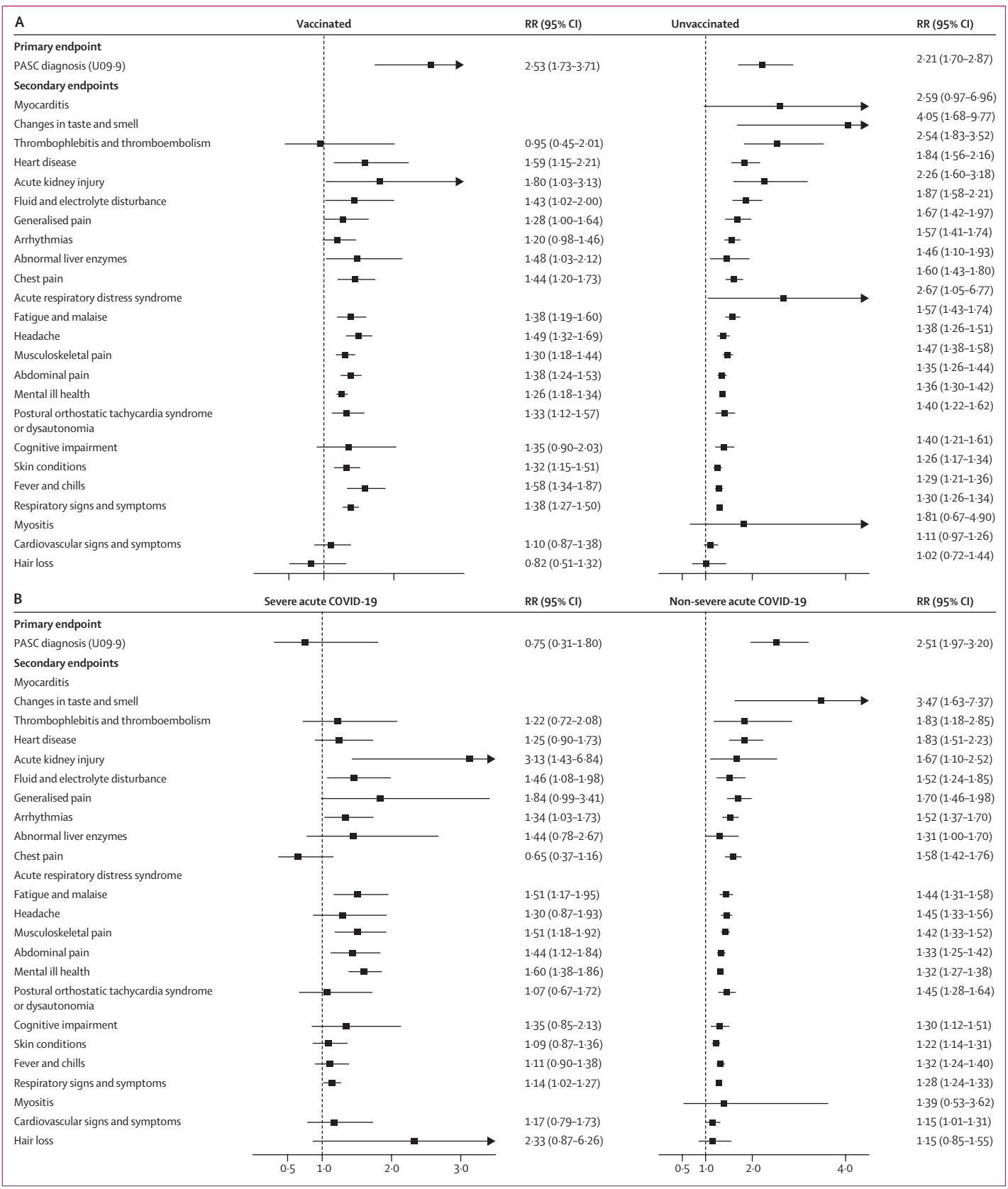


Figure 2: **Incident PASC outcomes after the second versus first infection**
Error bars show 95% CI of estimated RR. After matching, 123 644 patients were included in the first infection group and 40 200 in the second infection group. PASC=post-acute sequelae of SARS-CoV-2. RR=relative risk.

Figure 3: **Stratified incident PASC outcomes after the second versus first infection**
Stratified by vaccine status (A) and severity of acute COVID-19 (B). Error bars show 95% CI of estimated RR. Estimates are not shown for some conditions when the number of events was insufficient (<6) to support reliable RR estimation. After matching, 26 923 vaccinated, 100 130 unvaccinated, 5760 with severe infection, and 104 916 with non-severe infection were included in the first infection group and 9751 vaccinated, 31 450 unvaccinated, 3208 with severe infection, and 33 723 with non-severe infection were included in the second infection group. PASC=post-acute sequelae of SARS-CoV-2. RR=relative risk.


A
Vaccinated
RR (95% CI)
Unvaccinated
RR (95% CI)
Primary endpoint
PASC diagnosis (U09·9)
2·53 (1·73–3·71)
2·21 (1·70–2·87)
Secondary endpoints
Myocarditis
2·59 (0·97–6·96)
Changes in taste and smell
4·05 (1·68–9·77)
Thrombophlebitis and thromboembolism
0·95 (0·45–2·01)
2·54 (1·83–3·52)
Heart disease
1·59 (1·15–2·21)
1·84 (1·56–2·16)
Acute kidney injury
1·80 (1·03–3·13)
2·26 (1·60–3·18)
Fluid and electrolyte disturbance
1·43 (1·02–2·00)
1·87 (1·58–2·21)
Generalised pain
1·28 (1·00–1·64)
1·67 (1·42–1·97)
Arrhythmias
1·20 (0·98–1·46)
1·57 (1·41–1·74)
Abnormal liver enzymes
1·48 (1·03–2·12)
1·46 (1·10–1·93)
Chest pain
1·44 (1·20–1·73)
1·60 (1·43–1·80)
Acute respiratory distress syndrome
2·67 (1·05–6·77)
Fatigue and malaise
1·38 (1·19–1·60)
1·57 (1·43–1·74)
Headache
1·49 (1·32–1·69)
1·38 (1·26–1·51)
Musculoskeletal pain
1·30 (1·18–1·44)
1·47 (1·38–1·58)
Abdominal pain
1·38 (1·24–1·53)
1·35 (1·26–1·44)
Mental ill health
1·26 (1·18–1·34)
1·36 (1·30–1·42)
Postural orthostatic tachycardia syndrome or dysautonomia
1·33 (1·12–1·57)
1·40 (1·22–1·62)
Cognitive impairment
1·35 (0·90–2·03)
1·40 (1·21–1·61)
Skin conditions
1·32 (1·15–1·51)
1·26 (1·17–1·34)
Fever and chills
1·58 (1·34–1·87)
1·29 (1·21–1·36)
Respiratory signs and symptoms
1·38 (1·27–1·50)
1·30 (1·26–1·34)
Myositis
1·81 (0·67–4·90)
Cardiovascular signs and symptoms
1·10 (0·87–1·38)
1·11 (0·97–1·26)
Hair loss
0·82 (0·51–1·32)
1·02 (0·72–1·44)
B
Severe acute COVID-19
RR (95% CI)
Non-severe acute COVID-19
RR (95% CI)
Primary endpoint
PASC diagnosis (U09·9)
0·75 (0·31–1·80)
2·51 (1·97–3·20)
Secondary endpoints
Myocarditis
Changes in taste and smell
3·47 (1·63–7·37)
Thrombophlebitis and thromboembolism
1·22 (0·72–2·08)
1·83 (1·18–2·85)
Heart disease
1·25 (0·90–1·73)
1·83 (1·51–2·23)
Acute kidney injury
3·13 (1·43–6·84)
1·67 (1·10–2·52)
Fluid and electrolyte disturbance
1·46 (1·08–1·98)
1·52 (1·24–1·85)
Generalised pain
1·84 (0·99–3·41)
1·70 (1·46–1·98)
Arrhythmias
1·34 (1·03–1·73)
1·52 (1·37–1·70)
Abnormal liver enzymes
1·44 (0·78–2·67)
1·31 (1·00–1·70)
Chest pain
0·65 (0·37–1·16)
1·58 (1·42–1·76)
Acute respiratory distress syndrome
Fatigue and malaise
1·51 (1·17–1·95)
1·44 (1·31–1·58)
Headache
1·30 (0·87–1·93)
1·45 (1·33–1·56)
Musculoskeletal pain
1·51 (1·18–1·92)
1·42 (1·33–1·52)
Abdominal pain
1·44 (1·12–1·84)
1·33 (1·25–1·42)
Mental ill health
1·60 (1·38–1·86)
1·32 (1·27–1·38)
Postural orthostatic tachycardia syndrome or dysautonomia
1·07 (0·67–1·72)
1·45 (1·28–1·64)
Cognitive impairment
1·35 (0·85–2·13)
1·30 (1·12–1·51)
Skin conditions
1·09 (0·87–1·36)
1·22 (1·14–1·31)
Fever and chills
1·11 (0·90–1·38)
1·32 (1·24–1·40)
Respiratory signs and symptoms
1·14 (1·02–1·27)
1·28 (1·24–1·33)
Myositis
1·39 (0·53–3·62)
Cardiovascular signs and symptoms
1·17 (0·79–1·73)
1·15 (1·01–1·31)
Hair loss
2·33 (0·87–6·26)
1·15 (0·85–1·55)
0·5
1·0
2·0
3·0
0·5
1·0
2·0
4·0

diagnosis date, consistent with practices in similar EHR-based studies. For reinfections, a minimum 60-day interval was required to reduce misclassification due to overlapping infections. Third, the timing of PASC diagnosis might vary across providers depending on individual clinical judgment, which is a common limitation when using structured EHR data and ICD codes. However, previous studies have shown that the U09.9 code has reasonable validity in identifying PASC cases in clinical settings. Fourth, the second infection group had generally higher pre-existing chronic conditions and health-care utilisation than the first infection group before matching. These differences might affect the observed outcomes, as reinfected patients could have had more clinical encounters, increasing the likelihood of PASC documentation. We adjusted for multiple health-care utilisation factors, including hospital visits, diagnostic tests, and medication use, as confounders in our models, and we did not observe strong evidence of systematic differences in data availability between groups. Fifth, the absence of a concurrent uninfected control group reduces the interpretation of absolute incidence rates of PASC-related symptoms and conditions. However, the selected outcomes were based on previous studies that compared infected and uninfected children with adolescents,[6,7] adopted in subsequent studies,[24,28] and supported by organ-specific research showing increased post-COVID-19 incidence in infected versus uninfected children and adolescents.[8,9,25,26] We also used a prespecified washout period and excluded individuals with pre-existing conditions, ensuring that PASC-related symptoms and conditions reflected new-onset diagnoses. Sixth, the under-representation of some racial and ethnic groups and patients without obesity might limit the generalisability of our findings. Seventh, we also did not assess differences in the timing, persistence, or resolution of PASC outcomes between first and second infections. Notably, the second infection group includes individuals with omicron and pre-omicron first infections, which is a distinction that might influence immune priming,[17] acute disease severity, and subsequent risk of PASC.

Subgroup analyses in our study suggested potential differences in PASC risk by age, sex, and race and ethnicity. These signals, combined with previous evidence of disparities in PASC incidence by socioeconomic and demographic factors,[28] highlight the need for future studies to explore how reinfection risk interacts with social determinants of health. Additional research is also needed to assess whether updated vaccine formulations offer protection against PASC and whether the cumulative burden of repeated infections compounds long-term health outcomes. Understanding these patterns will be essential for tailoring prevention and care strategies in clinically vulnerable paediatric populations.

In summary, this study shows an increased risk of PASC in children and adolescents after SARS-CoV-2 reinfection. These findings add to previous evidence linking paediatric long COVID to multisystem effects and highlight the need to promote vaccination in younger populations and support ongoing research to better understand PASC, identify high-risk subgroups, and improve prevention and care strategies.

Contributors

The study was conceptualised by BZ, QW, RJ, TZ, JSM, CBF, and YC. BZ, QW, RJ, TZ, JSM, and YC contributed to the statistical methodology. Data analysis was carried out by BZ, QW, and TZ. Data was accessed by BZ, QW, TZ, RJ, MJB, YB, EAC, CHC, LGC, DF, CRH, SK, NL, DML, ML, ASMM, HTS, SS, BWT, DAW, CBF, and YC. Data curation was done by MJB, YB, EAC, CHC, LGC, DF, CRH, SK, NL, DML, ML, ASMM, HTS, SS, BWT, DAW, and CBF. CBF and YC have accessed and verified all the data. BZ, QW, RJ, TZ, JSM, and YC wrote the first draft of the manuscript. All authors (including FB) reviewed, edited, gave final approval of the manuscript, and had final responsibility for the decision to submit for publication. Supervision was provided by RJ, JSM, CBF, and YC. Project administration was done by BZ and YC. Funding was acquired by CBF and YC.

Declaration of interests

RJ is a consultant for AstraZeneca, Seqirus, Gilead, and Sanofi; receives an editorial stipend from the Pediatric Infectious Diseases Society; research support from GSK; and royalties from Up To Date (Wolters Kluwer). DML received institutional funding from the National Institutes of Health (NIH) Researching COVID to Enhance Recovery (RECOVER) Initiative via a subcontract from Joan and Sanford I Weill Medical College of Cornell University (grants office ID SP0072825). ASMM received institutional funding from Patient-Centered Outcomes Research Institute (PCORI) for PCORnet Common Data Model creation, and from the NIH RECOVER Initiative through the University of Missouri as site principal investigator and serves as a board member of the i2b2 tranSMART Foundation, a non-profit organisation supporting the development of the i2b2 informatics platform. All other authors declare no competing interests.

Data sharing

Results reported in this manuscript are based on detailed individual level patient data compiled as part of the RECOVER programme. Due to the high risk of reidentification based on the number of unique patterns in the data, patient privacy regulations prohibit us from releasing the data publicly. The data are maintained in a secure enclave, with access managed by the programme coordinating centre to remain compliant with regulatory and programme requirements. Requests to access data should be directed to the RECOVER electronic health records Pediatric Coordinating Center (recover@chop.edu).

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