Does the SARS-CoV-2 Infection Increase the Risk of Mental Health Disorder? Findings from Difference-in-Differences Analyses Using an EHR-Based Cohort from the RECOVER Program

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Background

By December 2023, the global impact of COVID-19, as reported by the World Health Organization (WHO), affected over 772 million individuals and resulted in more than 6 million deaths.(1) While the immediate consequences have been extensively documented, WHO defines Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) as symptoms persisting or emerging beyond 30 days post-infection, highlighting the need for long-term effect research.(2) Significant research exists on PASC in adults(3–6), but there is a notable gap in pediatric studies. Children and adolescents, who typically exhibit milder symptoms and lower risk of severe outcomes, need comprehensive investigation into PASC due to distinct symptoms and prevalence differences compared to adults.(7–9) PASC impacts various organ systems, including mental health, with increased risks of anxiety, depression, and other mental health disorders documented in adults.(10) Children and adolescents are also susceptible to mental health issues post-infection and are more affected by quarantine and isolation, increasing their mental health risks.(11–13) This study aims to examine the disparity in mental health disorder risks post-pandemic in children and adolescents who tested positive for COVID-19 versus those who tested negative, using EHR data from 25 children's hospitals in the U.S. The study uses interrupted time series analysis to assess if COVID-19 infection heightens mental health disorder risks and account for pandemic-related factors.

Methods

This study used electronic health record (EHR) data from RECOVER, a national healthcare consortium established by the National Institutes of Health (NIH). It aims to enhance our capacity to forecast, address, and mitigate post-acute sequelae of SARS-CoV-2 (PASC) including Long COVID.

We constructed our COVID-19 positive cohort by identifying individuals who tested positive from March 1, 2020, to December 3, 2022, filtered those with at least one medical visit 28-179 days after and within 7 days to 24 months before the index date, and included only patients with complete records aged 5-20 at the study's start, resulting in children (aged 5-11) and adolescents (aged 12-20) cohorts. For the control cohort, we selected individuals who tested negative within the same period, imputed index dates according to the COVID-19 cohort, ensured similar follow-up times, required at least one visit in the same timeframes, and included only those with complete records, resulting in similarly stratified cohorts.

The outcomes were predetermined based on our prior research on systematically characterizing the post-acute effects of SARS-CoV-2 infection. We specified our outcomes using the Systematized Nomenclature of Medicine (SNOMED)(14), including 49 prespecified mental health outcomes within 28 to 179 days after SARS-CoV-2 infection, along with a composite outcome of any mental health disorder.

In this research, we utilized high-dimensional covariates chosen with predefined, all assessed within two years before the follow-up period finished. The predefined covariates were determined based on prior knowledge.(15–18) The predefined covariates include age, race (Asian/PI, black/AA, Hispanic, white, multiple, and other), gender (male, female, and other), hospital, body mass index, and hospital utilization including number of ED visits, number of inpatient and outpatient encounters, PMCA index, number of negative tests prior to the entry of cohorts, and medical history.

To assess differences in the prevalence of mental health conditions between COVID-19 positive and negative patients, we conducted an interrupted time-series analysis using a two-sample proportion test with stratified cohorts of children and adolescents. To mitigate the potential impact of measured confounding factors, we employed a propensity score matching method with the covariates outlined in

the Covariates section. After matching, we assessed the standardized mean difference (SMD) for each covariate, employing a cutoff value of 0.1. Subsequently, we compared the risk difference in mental health conditions between the COVID-19 positive cohort and the contemporary negative control cohort.

Results

After propensity score matching and interrupted time analysis, both the children and adolescents COVID-19 positive group persisted significant positive risk difference compared to negative group in the composite outcome (children: 0.96%, 95% CI [0.75%, 1.16%]; adolescents: 0.84%, [0.53%, 1.15%]). The children COVID-19 positive group also exhibited significant positive risk differences in anxiety disorder (0.26%, [0.19%, 0.33%]), OCD (0.02%, [0.00%, 0.04%]), somatoform disorder (0.03%, [0.00%, 0.05%]), and stress disorder (0.08%, [0.02%, 0.14%]) in anxiety disorders category, avoidant/restrictive food intake (0.07%, [0.03%, 0.11%]) in eating and feeding disorders, bipolar disorder (0.01%, [0.00%, 0.02%]) in mood disorders, delirium (0.04%, [0.02%, 0.06%]) in neurocognitive disorders, ADHD (0.11%, [0.02%, 0.21%]), autism spectrum disorder (0.10%, [0.02%, 0.18%]), communication/motor disorder (0.38%, [0.25%, 0.52%]), and intellectual disability (0.12%, [0.05%, 0.20%]) in neurodevelopmental disorders, and tic disorder (0.05%, [0.02%, 0.08%]) in tic disorders category.

For adolescents cohorts, the COVID-19 positive group had significant positive risk difference in anxiety disorder (0.26%, [0.05%, 0.48%]) in anxiety disorders category, suicidality (0.11%, [0.02%, 0.19%]) in intentional self-harm/suicidality, minor depression (0.21%, [0.05%, 0.37%]) in mood disorders, delirium (0.08%, [0.03%, 0.14%]) in neurocognitive disorders, intellectual disability (0.09%, [0.01%, 0.17%]) in neurodevelopmental disorders, insomnia (0.13%, [0.06%, 0.21%]) in sleep/wake disorders, and anxiety symptoms (0.05%, [0.00%, 0.10%]), attention symptoms (0.08%, [0.03%, 0.14%]), depressive symptoms (0.02%, [0.00%, 0.04%]) in standalone symptoms category.

Conclusion

This study reveals an increased risk of mental health disorders in children and adolescents following SARS-CoV-2 infection. Awareness of mental health complications in the post-acute phase of COVID-19 infection will enhance the timely diagnosis and treatment of these conditions.

Figure 1. Risk difference of Covid-19 positive group vs. control group in prespecified mental health outcomes

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