Risk of Dysmetabolic Syndrome in Post-Acute COVID-19 Among Children and Adolescents: An EHR Cohort Study from the RECOVER Initiative

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Background

Amidst the global COVID-19 pandemic, a subset of patients experiencing acute SARS-CoV-2 infection is developing a diverse array of persistent symptoms beyond one month, diagnosed as Long COVID or post-acute sequelae of SARS-CoV-2 (PASC). Existing research has elucidated the presence of enduring metabolic alterations, including obesity and dyslipidemia, in association with COVID-19 infection. These metabolic changes are significant as they are linked to various health issues, such as coronary artery disease, type 2 diabetes[1], and nonalcoholic fatty liver disease[2].

Notably, a study by Xu et al. focused on dyslipidemia as a potential PASC risk, utilizing national health databases from the US Department of Veterans Affairs[3]. This investigation estimated higher risks and one-year burdens of incident dyslipidemia during the post-acute phase among COVID-19 infected survivors. However, there is a scarcity of data concerning lipid metabolism following COVID-19 infection in pediatric cohorts, and the risk of pediatric obesity during the post-acute phase of COVID-19 remains unclear. In addition, studies centered on pediatric patients often exhibit limitations such as short follow-up durations and restricted lipid laboratory results, contributing to a limited understanding of the clinical presentation of PASC in children and adolescents.

This study endeavors to address this gap by exploring the post-acute risk of metabolic dysfunctions, encompassing dyslipidemia and obesity, among children and adolescents following SARS-CoV-2 infection. Leveraging data from a pediatric cohort within the Researching COVID to Enhance Recovery (RECOVER) electronic health records (EHR) database, involving 25 children's hospitals and health institutions in the US, our investigation represents the first and largest study focused on the pediatric population. This study provides a comprehensive assessment of post-acute COVID-19 sequelae related to dyslipidemia and obesity, potentially offering valuable insights for future therapeutic approaches.

Defining Dyslipidemia Outcomes

These outcomes consisted of abnormal lipid laboratory results: Total cholesterol (TC) ≥ 200 mg/dL, Triglycerides (TG) ≥ 100 mg/dL (0-9 years); ≥ 130 mg/dL for (10-19 years); ≥ 150 mg/dL for (20-21 years), low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL, high-density lipoprotein (HDL) cholesterol < 40 mg/dL, non-HDL cholesterol ≥ 145 mg/dL, Apolipoprotein B ≥ 110 mg/dL [ref]; and incident lipid-lowering medications prescriptions, specifically statins. The incident of dyslipidemia outcomes in the post-acute

phase of COVID-19 were assessed in the follow-up period between 28 and 179 days after cohort entry in those without a history of dyslipidemia within two years before cohort entry. All abnormal lipid laboratory results were aggregated into composite outcomes called “any abnormal lipid laboratory result”. Additionally, the composite of any dyslipidemia outcome was specified as the initial incident occurrence of predefined dyslipidemia outcomes (abnormal lipid lab results or statin prescriptions) during the study.

Defining Obesity Outcomes

The obesity outcomes were defined by abnormal BMI/BMI z-score results, specifically BMI z-scores ≥ 95th percentile for (2-19 years); BMI ≥ 30 kg/m^2 for (19-21 years). The incidence of obesity outcomes in the post-acute phase of COVID-19 were assessed in the follow-up period between 28 and 179 days after cohort entry in those without a history of abnormal BMI results within two years before cohort entry.

Methods

In this cohort study, we analyzed data from the RECOVER datasets, which encompass information from 25 children's hospitals and health institutions in the United States, spanning March 2020 to September 2023. For dyslipidemia outcomes, the study included a contemporary non-infected control group of 384,289 patients and a COVID-infected group of 1,080,413 individuals. For obesity outcomes, the study analyzed a non-infected control group of 285,559 patients and a COVID-infected group of 817,315 individuals. Inclusion criteria were specified as individuals under 21 years of age for dyslipidemia analysis and 2 to 21 years of age for obesity analysis, with a minimum follow-up of six months. We applied inverse probability weighting with various predefined covariates to estimate the risks of five incident abnormal lipid outcomes. This included a composite abnormal lipid outcome (incidence of lipid-lowering medication, statins, and incidence of lipid lab test results) and an additional abnormal BMI outcome using a Poisson regression model. The measured risk was reported in terms of adjusted Relative Risk (aRR). We employed a cutoff incidence value of 0.1%[4,5] to prevent the implications of model overfitting for rare dyslipidemia outcomes. We further employed an empirical calibration approach using 37 negative control outcomes, which are known a priori to have no causal relationship with COVID-19 exposure, in order to mitigate the bias in the RR estimation[6,7].

Results

In the post-acute phase of SARS-CoV-2 infection, individuals in the COVID-19 group exhibited a higher risk of developing incident dyslipidemia compared to the non-infected contemporary control group. Detailed incidence rates of dysmetabolic outcomes are presented in **Table 1**, with adjusted relative risks (aRR) summarized in **Figure 1**. The composite measure of any dyslipidemia outcome, encompassing laboratory abnormalities or the use of lipid-lowering medications, yielded an aRR of 1.23 (95% CI 1.17-1.28). Additionally, the COVID-19 group demonstrated a higher risk of incident obesity, defined as BMI Z-scores greater than the 95th percentile for ages 2-19, or BMI greater than 30 for ages 19-21, with an aRR of 1.15 (95% CI 1.12-1.18). Importantly, our findings remained consistent and robust across sensitivity analysis designed to address residual confounding by negative control outcomes, yielding an aRR of 1.13 for the composite dyslipidemia outcomes and an aRR of 1.05 for obesity.

Dyslipidemia Outcomes	COVID-19-Positive (N=384,289)	COVID-19-Negative (N=1,080,413)
Incident abnormal lipid laboratory results		
HDL	0.576 (2,164/375,603)	0.414 (4,395/1,061,721)

LDL	0.197 (751/381,401)	0.149 (1,598/1,074,385)
Non-HDL	0.111 (425/382,449)	0.088 (946/1,077,298)
TC	0.268 (1,020/380,069)	0.211 (2,260/1,071,771)
TG	0.491 (1,851/376,655)	0.342 (3,639/1,064,911)
Incident lipid-lowering medications prescriptions		
Prescription of Statins	0.034 (132/383,678)	0.026 (282/1,079,285)
Composite dyslipidemia outcomes		
Any abnormal lipid lab results	0.945 (3,490/369,233)	0.691 (7,254/1,049,067)
Any dyslipidemia results	0.951 (3,510/368,987)	0.701 (7,348/1,048,547)
Obesity Outcomes	COVID-19-Positive (N=285,559)	COVID-19-Negative (N=817,315)
Abnormal BMI	5.954 (10,689/179,518)	4.743 (27,967/589,622)

Table 1. Raw incidence (in %, calculated as the absolute number of patients who suffered specific outcomes during the post-acute phase divided by the number of total patients that did not have the specific outcome during the baseline period) of individual

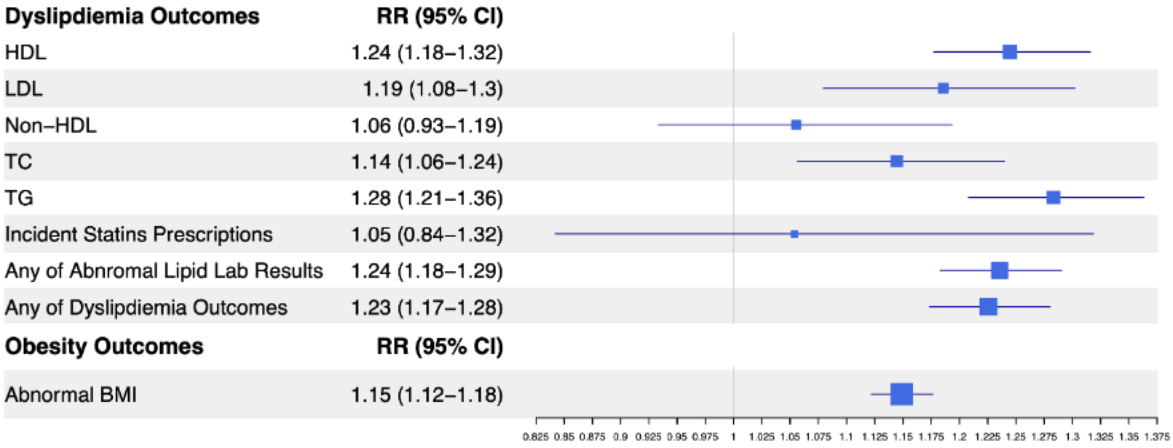

Figure 1. adjusted Relative Risk (RR) of incident post-acute COVID-19 dyslipidemia outcomes and obesity outcomes compared with the COVID-19-negative cohort.

Conclusion

The pediatric and adolescent patients had an increased risks of developing post-acute dysmetabolic outcomes, including dyslipidemia and abnormal BMI related outcomes. The findings informed the long-term impacts of COVID-19 on pediatric metabolic health and guided the development of effective interventions to mitigate these risks.

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