

Impact of the COVID-19 pandemic on cardiometabolic health parameters in children with preexisting dyslipidemia



Juliette Schefelker, BA, Xiao Zhang, PhD, Ann Dodge, RN BSN APNP, Kristen Marten, DO, Greigory Dimailig, BS, Heather L. Bartlett, MD, Amy L. Peterson, MD MS*

Department of Pediatrics, Division of Pediatric Cardiology, University of Wisconsin School of Medicine and Public Health, USA

KEYWORDS

COVID-19;
Lipid clinic;
Cardiometabolic health;
Health behavior;
Lipid panel

Background: The COVID-19 pandemic has raised concerns for worsening cardiometabolic health in children.

Objective: This study evaluates the impact of the COVID-19 pandemic and subsequent social restrictions on pediatric cardiometabolic health factors.

Methods: Retrospective review of patients in a pediatric lipid clinic in the year prior to (3/18/2019-3/17/2020) and during (3/18/2020-3/17/2021) the COVID-19 pandemic was performed. Physical findings (body mass index [BMI], waist circumference [WC], and blood pressure), laboratory markers of cardiometabolic health (lipid panel, insulin resistance, and liver transaminases), self-reported exercise time, and lipid-lowering medications (metformin, statin, omega-3 fatty acids, fenofibrate) were compared.

Results: 297 subjects met inclusion criteria. Among subjects prescribed no medications or on stable medication doses (n=241), there were few changes in lipid panels. Among subjects with new or increased medication doses between pre-pandemic and pandemic intervals (n=62), there were increases in triglycerides (p= 0.019) and HgbA1c (p=0.046). There was no change in z-scores for both BMI and WC for either group.

Conclusion: We observed concerning trends in markers of cardiovascular disease health (dyslipidemia, insulin resistance, and diabetes), independent of changes in weight, in at-risk children during the recent COVID pandemic. Our findings suggest that this vulnerable population may benefit from more frequent monitoring and intense management during such events.

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Abbreviations : ALT, Alanine aminotransferase; ASCVD, Atherosclerotic cardiovascular disease; ASCVDRF, Atherosclerotic cardiovascular disease risk factor; BMI, Body Mass Index; BP, Blood pressure; DBP, Diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; HgbA1c, Hemoglobin A1c; LDL-C, Low-density lipoprotein cholesterol; LLM, Lipid Lowering Medication; Non-HDL-C, Non-high-density

lipoprotein cholesterol; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides; WC, Waist Circumference.

* Corresponding author at: Pediatric Cardiology, University of Wisconsin-Madison School of Medicine and Public Health, H6/516B CSC MC 4180, 600 Highland Ave, Madison, WI, 53792, USA.

E-mail address: apeterson@pediatrics.wisc.edu (A.L. Peterson).

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Introduction

Cardiovascular disease secondary to atherosclerosis begins in youth and tracks over a lifetime¹⁻⁵. Atherosclerotic cardiovascular disease (ASCVD) risk factors (RFs), such as dyslipidemia, elevated blood pressure (BP) and increased body mass index (BMI) in children correlate with increased ASCVD risk in adulthood⁴⁻⁸. Metabolic risk factors including increased insulin resistance and type 2 diabetes have also been associated with increased ASCVD risk⁹⁻¹².

Early treatment of ASCVDRFs has been shown to reduce risk of ASCVD events, such as stroke and myocardial infarction, in adulthood^{6,9}. Thus, early prevention, identification, and treatment of ASCVDRFs in children is essential to promote cardiometabolic health^{7,9,10}. Most treatments for ASCVDRFs in children are centered around lifestyle changes that encourage a diet with fruits and vegetables, limited sugared beverages and processed carbohydrates, regular physical activity, and maintenance of a healthy BMI^{9,10,13}.

Since the onset of the COVID-19 pandemic, subsequent social restrictions and school closures have subjected children to significant stressors, including restrictions from attending school and participation in regular physical activities, as well as changes in dietary patterns¹⁴⁻¹⁶. During the COVID-19 pandemic, many have observed an increase in lifestyle habits associated with risk of premature ASCVD, such as decreased physical activity, increases in screen time (both for school and leisure), increased and altered eating habits, and deviations from normal sleep patterns¹⁴⁻¹⁶. These changes all have the potential to worsen cardiometabolic health. Recent data have demonstrated an increased incidence and severity for new-onset type 2 diabetes¹⁷⁻¹⁹, an increase in pediatric BMI²⁰⁻²², and worsening exercise capacity^{22,23} during the pandemic. Furthermore, decreased socioeconomic status from unemployment or underemployment of parents may exacerbate existing disparities including food insecurity and access to care²⁴⁻²⁶. However, formal analysis of the impact the COVID-19 pandemic on pediatric cardiometabolic health has been limited.

The aim of this study was to investigate the impact of the COVID-19 pandemic on cardiometabolic health markers of children seen at a pediatric lipid clinic. These markers included physical exam findings, laboratory studies, self-reported exercise time, and medication prescription rates. We hypothesized that children with risk factors for premature ASCVD had worsening markers of cardiometabolic health during the COVID-19 pandemic compared to markers obtained in the year prior to the pandemic.

Methods

Study population

The institutional pediatric lipid clinic database was queried for all clinical encounters during two time intervals:

1) the year prior to the COVID-19 pandemic (March 18, 2019 to March 17, 2020) and 2) the year during the COVID-19 pandemic (March 18, 2020- March 17, 2021). Early in the pandemic, there were marked differences in the impact on children based on geographic area. Therefore, for the purposes of our study, March 18, 2020 was chosen as the start of the pandemic as this was the date schools in our state were required to stop in-person instruction under a statewide executive order²⁷. To qualify for inclusion, subjects needed at least one clinical encounter in both timeframes. Both in-person and virtual visits were included. Exclusion criteria included diagnosis of a genetic dyslipidemia syndrome or use of a medication which unpredictably alters the lipid panel (in this study, atypical antipsychotics, PEG-asparaginase, and isotretinoin). This study was deemed exempt by the institutional review board.

Measures

The following measures were analyzed: (1) physical exam findings including BMI, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP); (2) laboratory measures of cardiometabolic health: lipid panel (total cholesterol [TC], HDL-C, TG, LDL-C, non-HDL-C), markers of insulin resistance (fasting insulin, fasting glucose, and HgbA1c), and a marker of fatty liver disease (ALT); (3) self-reported hours of exercise; and (4) prescriptions of lipid-lowering medications (LLMs): statins, off-label metformin, fenofibrate, and omega-3 fatty acids. Although the effects of metformin on the lipid panel are indirect, it is commonly used to treat dyslipidemia due to insulin resistance in pediatrics, and so is included as a lipid-lowering medication here. Subjects were instructed to fast for at least 10 hours prior to collection of insulin, glucose, and lipid panels. Demographic information including sex and age were collected.

Statistical analysis

As dosing changes to LLMs is a significant confounder to evaluation of lipids and insulin resistance, we divided the subjects into two groups: those with (1) either no LLM prescriptions or with stable LLM dosages across both timeframes, and (2) those with LLM prescriptions which increased between the pre-pandemic and during-pandemic periods, or who were newly prescribed a LLM in the pandemic interval.

BMI and WC data were converted to standardized z-scores^{28,29}. Descriptive statistics were calculated, and average values for lab results, physical exam findings, and self-reported hours of exercise from each time period were compared between pre- and during-pandemic periods via paired t-tests. If a measurement was missing from a subject's paired data, then that subject was excluded from that particular analysis (i.e., if there was no WC measurement from during the pandemic, that subject was not used for a paired t-test for WC). Cohen's D was calculated to reflect effect size and a

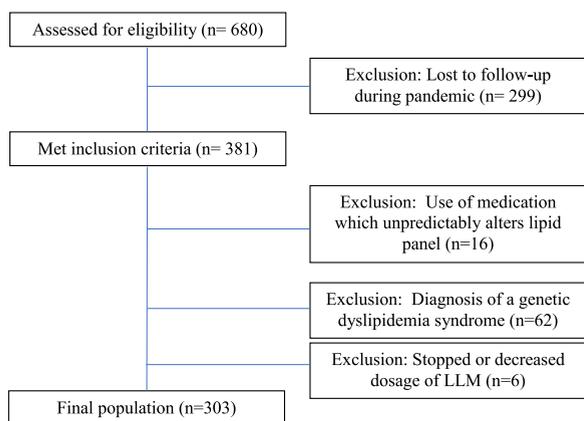


Fig. 1 illustrates the inclusion and exclusion criteria to select the final study sample.

corrected form was used to adjust for sample size to eliminate bias³⁰. As suggested by Cohen, $d = 0.2$ is considered a small effect size, $d = 0.5$ medium, and $d = 0.8$ large³¹. A value <0.05 was considered statistically significant. Analyses were performed with IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY).

Results

Subjects

Of the 608 subjects evaluated for inclusion in the lipid clinic between March 18, 2019 and March 17, 2021, 297 subjects met inclusion criteria (Fig. 1). Among excluded subjects, 299 were excluded because they did not have a visit during the pandemic, 62 were excluded because of a diagnosis of a primary genetic dyslipidemia syndrome (most commonly familial hypercholesterolemia), and 16 were excluded due to use of medications that unpredictably alter the lipid panel. Six subjects were excluded due to stopping or decreasing the dosage of an LLM.

A total of 245 subjects were either prescribed no LLM or had stable LLM dosages across both timeframes. In comparison, 52 subjects had increased LLM dosages or new LLM prescriptions in the pandemic timeframe (Table 1).

Physical exam, laboratory measures, and exercise

Table 2 shows the comparison of lab results and physical exam findings between the pre-pandemic and during-pandemic periods. Of all subjects, 98.5% reported fasting prior to having laboratory tests performed.

Among the 245 subjects prescribed no LLM or with stable LLM dose, there were no changes in z-scores for both BMI and WC. Of this group, 14.3% were classified as diabetic (defined as HgbA1c $>6.5\%$ at any time during the study); one subject had new-onset diabetes during the pandemic (Supplemental Figure 1b). There was no change in self-reported hours of exercise.

Among the 52 subjects with increased LLM dosages or new LLM prescriptions between the pre-pandemic and pandemic intervals, there were also no changes in z-scores for both BMI and WC. These subjects had significant changes in laboratory results including increases in TC (201.9 ± 38.95 vs 209.7 ± 38.95 mg/dL, $p=0.05$), non-HDL-C (157.7 ± 35.59 vs 165.4 ± 36.92 mg/dL, $p= 0.04$), TG (171.2 ± 98.45 mg/dL vs 196.3 ± 103.15 mg/dL, $p = 0.02$), HgbA1c ($6.9\% \pm 2.23$ vs $7.35\% \pm 2.60$, $p = 0.02$), and ALT (36.60 ± 38.92 vs 42.90 ± 58.60 , $p = 0.05$). There was also a trend towards increased fasting insulin (Table 2). Of these subjects, 39.1% were classified as diabetic; no subjects in this group were diagnosed with new-onset diabetes (Supplemental Figure 1b). There were no significant changes in LDL-C or HDL-C. There was a statistically significant decrease in hours of exercise (0.94 ± 0.94 hours vs. 0.58 ± 0.45 hours, $p = 0.05$).

Discussion

Pediatric patients in a subspecialty lipid clinic demonstrated no significant changes in z-scores for both BMI and WC in the year of the COVID-19 pandemic compared to the year prior. Among subjects with no changes in LLM, changes in the lipid panel were statistically, but not clinically, significant. However, there was subset of subjects who did have statistically and clinically significant changes in their lipid panel (including increased TC, non-HDL-C, and TG), In these sub-

Table 1 Baseline Demographics of Study Population

Measure	No LLM or Stable LLM (n=245)	New or increased LLM (n=52)	Total (n=297)
Age, mean (SD)	14.5 (3.0)	16.3 (3.4)	14.9 (3.12)
Female sex, n (%)	119 (48.6%)	26 (50%)	145 (48.8%)
Race, n (%)			
White	140 (57.1%)	34 (65.4%)	174 (58.6%)
Black/ African American	13 (5.3%)	2 (3.8%)	15 (5.1%)
Asian	7 (2.9%)	1 (1.9%)	8 (2.7%)
American Indian or Alaska Native	4 (1.6%)	0 (0%)	4 (1.3%)
Unavailable	81 (33.0%)	15 (28.8%)	96 (32.3%)

Table 2 Physical Exam, Laboratory, and Self-Reported Hours of Exercise Results

	No LLM or Stable LLM (n=245)					New LLM or Increased LLM (n=52)				
	Pre-Pandemic, Mean (SD)	During Pandemic, Mean (SD)	n	Cohen's d	P	Pre-Pandemic, Mean (SD)	During Pandemic, Mean (SD)	n	Cohen's d (Hedge's correction)	P
Physical Exam										
BMI z-score	1.54 (1.10)	1.53 (1.12)	88	0.37	0.73	1.33 (1.18)	1.31 (1.24)	18	0.09	0.70
Waist circumference z-score	1.30 (1.05)	1.37 (1.10)	75	0.14	.23	0.99 (1.31)	1.15 (1.15)	15	0.416	0.11
Systolic blood pressure (mmHg)	63.8 (29.70)	69.2 (25.48)	27	0.16	0.43	79.6 (10.08)	86.2 (15.97)	5	0.43	0.3
Diastolic blood pressure (mmHg)	52.4 (18.49)	60.9 (18.60)	27	0.38	0.06	61.5 (18.09)	71.0 (28.94)	5	0.23	0.56
Laboratory Markers										
TC (mg/dL)	188.7 (36.21)	184.6 (38.41)	213	0.16	0.024	201.9 (38.95)	209.7 (38.95)	50	0.28	0.05
HDL-C (mg/dL)	45.1 (13.07)	45.3 (14.09)	215	0.03	0.66	43.7 (11.20)	44.3 (10.99)	50	0.09	0.53
LDL-C (mg/dL)	114.6 (31.05)	109.0 (30.79)	210	0.24	< 0.001	126.0 (35.96)	129.2 (33.77)	49	0.13	0.34
Non-HDL-C (mg/dL)	143.28 (31.33)	139.2 (34.13)	213	0.17	0.016	157.7 (35.59)	165.4 (36.93)	50	0.29	0.04
Triglycerides (mg/dL)	153.4 (117.54)	158.10 (111.93)	214	0.07	0.34	171.2 (98.45)	196.3 (103.15)	50	0.35	0.02
Insulin (uIU/mL)	35.02 (21.35)	37.75 (20.19)	78	0.14	0.23	28.35 (14.78)	36.06 (16.67)	12	0.56	0.06
HgbA1c (%)	5.7 (1.18)	5.7 (1.12)	84	0.02	0.85	6.9 (2.23)	7.35 (2.60)	23	0.49	0.02
Glucose (mg/dL)	93.55 (14.80)	92.91 (22.58)	99	0.05	0.60	98.14 (27.28)	108.02 (58.14)	21	0.28	0.19
ALT (U/L)	42.60 (41.21)	41.21 (34.66)	99	0.05	0.60	36.70 (38.92)	42.90 (58.60)	30	0.37	0.05
Exercise										
Hours of Exercise	0.84 (0.64)	0.85 (1.04)	127	-0.07	0.14	0.94 (0.94)	0.58 (0.45)	29	0.37	0.05

ALT= Alanine aminotransferase; BMI= body mass index; HDL-C= high-density lipoprotein cholesterol; HgbA1c=hemoglobin A1c; LDL-C= low-density lipoprotein cholesterol; LLM= lipid-lowering medication; Non-HDL-C= non- high-density lipoprotein cholesterol; TG = triglycerides.

jects, increases in HgbA1c, fasting insulin, TC, TG, and ALT were indicative of worsening insulin resistance, dyslipidemia, and hepatic steatosis, respectively. These markers, particularly those indicating worsening insulin resistance (increased fasting insulin and HgbA1c), are consistent with reports of higher rates of pediatric type 2 diabetes during the pandemic¹⁷⁻¹⁹.

Notably, there was no increase in z-scores for both BMI and WC in the year of the COVID pandemic compared to the year prior in either group. As these scores are standardized and control for age and gender, in the group with no changes in LLM this may be a further indicator of minimal changes during this period. However, in the group of subjects with changes in LLM who demonstrated worsening insulin resistance and increasing TGs (as described above), we speculate

that the lack of change may indicate an increase in adiposity with corresponding decrease in lean muscle mass, or maintenance of a stable caloric intake with deterioration in diet quality. This is particularly noteworthy, as a clinician may be tempted to focus their monitoring efforts towards children and adolescents who have had significant increases in their BMI over the pandemic period. Our data would suggest that these children, who are already at high cardiometabolic risk, worsened their cardiometabolic parameters without significantly increasing their BMI. An approach that focuses solely on children with significant BMI increase may miss many children with worsening cardiometabolic health.

This study shows a decrease in hours of exercise only in subjects requiring a new or increased dose in LLM, suggesting that this change may have contributed to the worsening

of laboratory measures seen in this group. This is consistent with other reports of decreased physical activity in children during the pandemic^{14–16}.

There were 299 subjects who failed to seek care in the year of the pandemic. We speculate that some of these subjects may represent lower-risk or well-controlled patients, for whom missing a follow-up would not be detrimental to their care. In this light, our study population, subjects who sought care during the pandemic, may represent a higher-risk subgroup than initially thought. However, it is equally possible that some of these subjects may be at higher risk, as financial hardships, lack of access or desire to participate in a telemedicine encounter, parental illness or increased parental responsibilities could all be reasons for missing follow-up.

Limitations to this study include its observational and retrospective nature; while other studies have also reported unhealthy lifestyle changes in association with the pandemic, we cannot establish causality. Our study may have limited generalizability as this is a report from a single center. Furthermore, our study population included children previously diagnosed with dyslipidemia, and therefore had already been identified as a population at high risk for ASCVD. In our study, the population that continued to seek care during the pandemic year had higher TG and HgbA1c compared to the subjects that were excluded (Supplemental Table 1). Our study included both in-person and virtual visits. We were unable to collect all physical exam data during virtual visits, which decreased sample number for those results and may have made them less robust than desired. In addition, our measure of exercise was self-reported, which is a less reliable measure of physical activity.

Interestingly, our data suggest that there is a subset of children (i.e., the group with new or increased LLMs) who are particularly vulnerable from a cardiometabolic standpoint, as they experienced significant changes in laboratory markers, whereas most children in our study did not have significant changes in their laboratory markers. Future research to better characterize which children are particularly at risk for abrupt worsening of laboratory markers would help identify these children who could benefit from more frequent monitoring or earlier pharmacotherapy. Furthermore, future studies to investigate long-term impact of these changes via longitudinal follow-up would help to determine if the changes demonstrated in this study resolve or persist over time. Finally, previous studies suggested that social restrictions due to the pandemic had a greater impact on already vulnerable populations, such as families with lower socioeconomic status or children with pre-existing health conditions^{20,26}. Our data set did not include measures of socioeconomic status, making this a potential area for future investigation.

Conclusion

Our study shows concerning trends in markers of ASCVD health (dyslipidemia, insulin resistance, and diabetes), inde-

pendent of changes in weight, in at-risk children during the COVID-19 pandemic. The findings suggest that this vulnerable population may benefit from more frequent monitoring and intense management during such events.

Contributor's statement

Ms. Scheffelker collected data, carried out initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Zhang designed data collection instruments, coordinated and supervised data collection, and reviewed and revised the manuscript.

Ms. Dodge conceptualized and designed the study, reviewed and revised the manuscript.

Dr. Marten designed the data collection instruments, and reviewed and revised the manuscript.

Mr. Dimailig contributed to data interpretation and reviewed and revised the manuscript.

Dr. Bartlett contributed to data interpretation and reviewed and revised the manuscript.

Dr. Peterson conceptualized and designed the study, coordinated and supervised data collection, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

Ms. Dodge owns stock in Pfizer, Medtronic, Johnson and Johnson, and Merck. Ms. Scheffelker, Dr. Zhang, Dr. Marten, Mr. Demailig, Dr. Bartlett, and Dr. Peterson declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jacl.2022.06.006](https://doi.org/10.1016/j.jacl.2022.06.006).

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