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Clinical Research Article

Accelerated Longitudinal Weight Gain Among Infants With In Utero COVID-19 Exposure

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Abstract

Context: Since the initial outbreak of coronavirus disease 2019 (COVID-19), a novel population of children with in utero exposure to maternal infection has emerged whose health outcomes are largely unknown.

Objective: To compare longitudinal growth trajectories among infants with vs without in utero COVID-19 exposure.

Methods: We conducted a longitudinal cohort study leveraging a prospectively enrolled perinatal biorepository among 149 infants with in utero COVID-19 exposure and 127 unexposed controls. Weight, length, and body mass index (BMI) were abstracted from health records at 0, 2, 6, and 12 months and standardized using World Health Organization growth charts. Analyses were adjusted for maternal age, ethnicity, parity, insurance, and BMI as well as infant sex, birthdate, and breastfeeding.

Results: Infants with in utero COVID-19 exposure vs controls exhibited differential trajectories of weight and BMI, but not length, z-score over the first year of life (study group × time interaction, $P < .0001$ for weight and BMI). Infants born to mothers with prenatal COVID-19 had lower BMI z-score at birth (effect size: −0.35, 95% CI −0.66 to −0.03) and greater gain in BMI z-score from birth to 12 months (effect size: 0.53, 95% CI 0.06 to 0.99). Birth weight z-score mediated a significant proportion of the relationship between COVID-19 exposure and postnatal growth (estimate ± SE, 32 ± 14%, $P = .02$).

Conclusion: Infants with in utero COVID-19 exposure exhibited lower birth weight and accelerated weight gain in the first year of life, which may be harbingers of downstream cardiometabolic pathology. Further studies are needed to delineate cardiometabolic sequelae among this emerging global population.

Key Words: COVID-19, in utero, fetal programming, growth, BMI

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; LBW, low birth weight; MGB, Mass General Brigham; MGH, Massachusetts General Hospital; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, small for gestational age.

Since its initial outbreak in 2019, coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to unprecedented morbidity and mortality worldwide. As pregnant women comprise 9% of reproductive-aged women with SARS-CoV-2 infection (1), a novel population of children with in utero exposure to maternal COVID-19 has emerged that is projected to span tens to hundreds of millions over the next 5 years (2). Importantly, the potential impact of maternal COVID-19 in pregnancy on the health of subsequent generations has received relatively little attention to date. Nonetheless, given that the intrauterine environment may modulate the health of offspring over the life course through effects on fetal programming (3), there is a pressing need to delineate differential growth patterns and associated cardiometabolic disease risk among the burgeoning population of children with in utero COVID-19 exposure.

Compared with nonpregnant females of similar age, pregnant women with COVID-19 are more likely to experience severe disease with increased risk of intensive care unit admission and mechanical ventilation (4). Furthermore, despite a low rate of vertical transmission (5, 6), pregnancies complicated by COVID-19 are more prone to preterm birth, gestational hypertension, and pre-eclampsia vs pregnancies uncomplicated by infection (7, 8). Hallmarks of SARS-CoV-2 infection including immune activation (9), hypercoagulability (10), and hypoxia (11) have been shown to impact fetoplacental development in diverse clinical contexts (9, 12, 13). Notably in

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contrast to common coronaviruses, immune alterations from SARS-CoV-2 infection may persist long after the virus has cleared (14, 15). Furthermore, placentas from pregnancies complicated by COVID-19 have demonstrated robust inflammation at the maternal–fetal interface characterized by enhanced infiltration of both maternal and fetal immune cells (16-18). While these data strongly suggest that SARS-CoV-2 infection confers a pathologic intrauterine environment that may alter the physiologic program of pregnancy, whether these disturbances translate to health consequences in offspring over the life course has yet to be established.

Longitudinal patterns of growth in early life may be influenced by fetal programming events (19), and have key prognostic relevance for obesity and cardiometabolic disease risk throughout childhood and adulthood (20, 21). In the current study, we leveraged a perinatal biorepository of well-phenotyped mothers with and without prenatal COVID-19 and their offspring to examine for the first time the association of in utero COVID-19 exposure with weight, length, and BMI z-score trajectories over the first year of life. Based on evidence that maternal SARS-CoV-2 infection confers a pathologic intrauterine state even in the absence of vertical transmission (9), we hypothesized that babies with in utero COVID-19 exposure would be smaller at birth, but would then exhibit steeper gains in weight and BMI z-score throughout infancy. Findings from this study emphasize the need for rigorous follow-up studies of the expanding global population of children with in utero COVID-19 exposure, particularly with regard to long-term cardiometabolic sequelae.

Materials and Methods

Study Participants

We utilized the Mass General Brigham (MGB) COVID-19 Perinatal Biorepository to compare longitudinal growth trajectories over the first 12 months of life among infants with vs without in utero exposure to maternal COVID-19. The MGB COVID-19 Perinatal Biorepository was rapidly established early in the pandemic to bank high-quality data and biospecimens with comprehensive clinical annotation from mothers with or at risk for SARS-CoV-2 infection and their neonates (2). Pregnant women who were at least 18 years of age and presented to Massachusetts General Hospital (MGH) for medical care were eligible for inclusion. Cases of maternal COVID-19 during pregnancy were diagnosed primarily (99%) by nasopharyngeal swab reverse transcription-polymerase chain reaction, though Food and Drug Administration–authorized antigen immunoassays were used in rare instances. Mothers with no known history of prenatal COVID-19 and a negative SARS-CoV-2 reverse transcription-polymerase chain reaction on universal screening at delivery comprised a comparator group.

In this analysis, we focused on the subset of infants born to mothers in the MGB COVID-19 Perinatal Biorepository who delivered prior to June 1, 2021, to ensure that all babies would be at least 12 months of age at the time of data collection and analysis (Fig. 1). To reduce variability within our sample before analysis, we excluded a small number of infants whose mothers received the SARS-CoV-2 vaccine during pregnancy (n = 5) or whose prenatal vaccination status was uncertain (n = 4). Infants who were from multiple gestations (n = 12), whose medical records were missing (n = 4), or whose mother was known professionally to the research team (n = 1) were additionally excluded.

Based on these criteria, 149 babies with in utero exposure to maternal COVID-19 and 127 babies without known exposure who were born from March 30, 2020, to May 30, 2021, were analyzed. Written informed consent was obtained from all mothers who enrolled in the MGB Perinatal COVID-19 Biorepository. The MGB Institutional Review Board approved both the parent biorepository study and the current extension analysis.

Data Collection

For the purposes of this analysis, we collected longitudinal anthropometric data on all eligible infants over the first year of life using the electronic medical record. Weight, length, and BMI were abstracted at birth, 2 months (±2 weeks), 6 months (±1 month), and 12 months (±1 month). We chose to assess BMI compared with other anthropometric constructs given its superior correlation in infancy with adiposity (22) and childhood obesity (23). Raw data were used to calculate age- and sex-adjusted z-scores based on growth charts from the World Health Organization (WHO) (24). Birth weight and length z-scores were also calculated based on Fenton growth charts, which are adjusted for gestational age at birth (25). Infants were classified as having low birth weight (LBW) based on birth weight <2.5 kg and small for gestational age (SGA) based on Fenton birth weight z-score <10th percentile.

In preparation for a sensitivity analysis, among babies born preterm, WHO BMI z-score at 2, 6, and 12 months were additionally calculated based on gestationally corrected age (ie, age from due date rather than date of birth). Anthropometric measures were also obtained from around each child's due date and used to ascertain WHO BMI z-score at a gestationally corrected age of 0 months. Using these data, a variable referred to as "corrected" BMI z-score was derived for each infant, which comprised BMI z-score adjusted for gestationally corrected age in babies born preterm when available, or otherwise BMI z-score adjusted for chronological age. A similar approach was used to calculate corrected length z-score.

In addition to anthropometric measures, data on sociodemographic, prenatal, and infant feeding parameters were abstracted from the MGB Perinatal COVID-19 Biorepository clinical annotation and the electronic medical record. For mothers with prenatal COVID-19, gestational age at time of infection and COVID-19 severity were additionally ascertained. Disease severity was categorized as asymptomatic, mild, moderate, severe, or critical per National Institutes of Health criteria (26).

Statistical Analysis

Based on our hypothesis that in utero COVID-19 exposure would be associated with accelerated growth over the first year of life, our prespecified primary endpoint was change in BMI z-score from birth to 12 months. With 276 infants identified as eligible for inclusion and assuming that 25% of participants would have data missing at random, we estimated 80% power to detect a difference between groups of at least 0.39 of the SD of this endpoint (α=.05, 2-sided).

To assess associations between in utero COVID-19 exposure status and longitudinal growth patterns, we used restricted maximum likelihood-based linear mixed effects models for individual anthropometric parameters (weight,

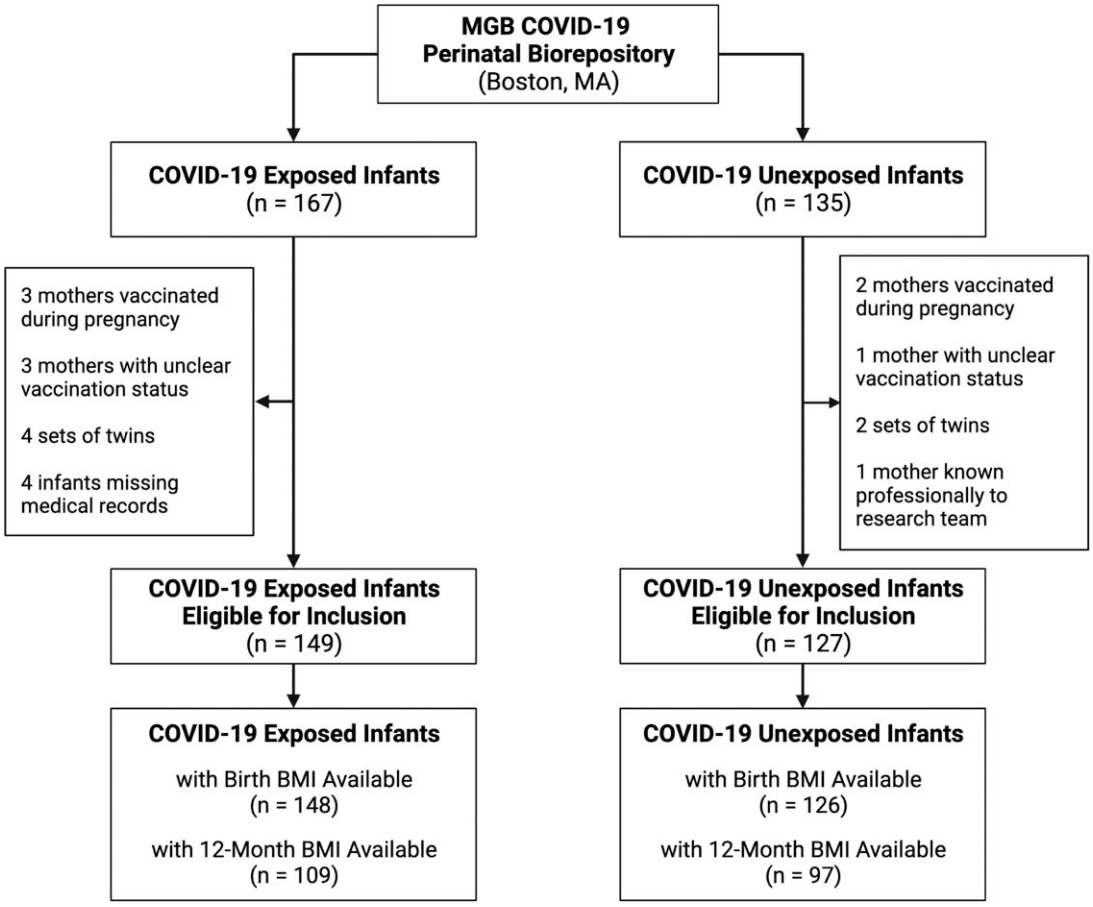

Figure 1. Participant selection. All infants in our study were born before June 1, 2021 to mothers with or at risk for prenatal COVID-19 who had participated in the MGB COVID-19 Perinatal Biorepository at MGH. Following the exclusion of individuals for the reasons delineated, a total of 149 infants with in utero COVID-19 exposure and 127 infants without known COVID-19 exposure were eligible for inclusion. Figure was created with BioRender.com.

length, or BMI z-score) with subject-level intercept treated as a random effect and study group, categorical time of measurement (0, 2, 6, and 12 months), and study group × time interaction treated as fixed effects. The model included both complete and incomplete longitudinal observations with variance components used as the specified covariance structure of the repeated measures. Anthropometric indices were further tested upon adjusting for the following covariates of interest: (1) maternal characteristics: age at delivery, ethnicity (Hispanic or Latina vs not Hispanic or Latina), parity (excluding index pregnancy), insurance status (public vs private), and earliest BMI during pregnancy; and (2) infant characteristics: sex, date of birth, and any history of breastfeeding. These covariates comprised the standard model for all multivariable analyses, except for comparisons of birth anthropometrics which did not adjust for breastfeeding since they were ascertained prior to initiation of infant feeding.

To further characterize differential growth patterns between the groups, we used 2-sample t-tests to compare anthropometric measures at birth and 12 months as well as changes in anthropometric measures from birth to 12 months. Outcomes found to differ by COVID-19 exposure status were further tested in linear regression models adjusting for the covariates listed above. We also performed stratified analyses to determine whether relationships of study group with change in BMI z-score differed by infant sex. In a sensitivity analysis, we examined the relationship of COVID-19 exposure status with our primary endpoint while adjusting for maternal race (Black vs non-Black) in addition to our standard covariates. In another sensitivity analysis, we repeated our analyses using BMI and length z-scores corrected for gestational age to take prematurity status into account. We further used within-group 1-sample t-tests to compare BMI z-score at birth and 12 months and change in BMI z-score from birth to 12 months to 0 as the WHO population average.

Subsequently, we examined birth weight z-score as a clinical predictor of longitudinal growth patterns over the first year of life. In this regard, we first assessed the association of birth weight z-score with change in BMI z-score from birth to 12 months using a linear regression model. We next performed a mediation analysis to assess whether birth weight z-score may underlie the relationship between in utero COVID-19 exposure and change in BMI z-score over time (27). Lastly, in an exploratory analysis, we examined associations of maternal COVID-19 severity and trimester of infection with anthropometric measures at birth and change in BMI z-score from birth to 12 months. Given that women with asymptomatic disease were most likely to be identified during the universal screening process at delivery, severity and timing of infection were considered to be interrelated in our sample. As such, both parameters were included in 1 model to distinguish their independent effects.

Table 1. Maternal, birth, and infant characteristics of overall sample

	Infants with COVID-19 exposure (n = 149)	Infants without COVID-19 exposure (n = 127)
Maternal prenatal characteristics		
Age at delivery, years	32 ± 6	34 ± 5
Gravidity	2.7 ± 1.7	2.4 ± 1.2
Parity (excluding index pregnancy)	1.2 ± 1.2	0.9 ± 0.9
Race		
Asian, n (%)	1 (1)	13 (10)
White, n (%)	60 (40)	85 (67)
Black/African American, n (%)	15 (10)	5 (4)
Native Hawaiian/Pacific Islander, n (%)	1 (1)	0 (0)
Unknown, n (%)	2 (1)	2 (2)
Other, n (%)	70 (47)	22 (17)
Ethnicity		
Hispanic or Latina, n (%)	75 (50)	29 (23)
Not Hispanic or Latina, n (%)	74 (50)	97 (77)
Insurance status		
Public insurance, n (%)	75 (50)	25 (20)
Private insurance, n (%)	74 (50)	102 (80)
Tobacco use in pregnancy, n (%)	3 (2)	7 (6)
BMI		
Earliest BMI during pregnancy (kg/m^2)	29 ± 7	26 ± 6
Obesity during pregnancy, n (%)	47 (32)	29 (23)
Gestational diabetes, n (%)	16 (11)	15 (12)
Preeclampsia or gestational hypertension, n (%)	24 (16)	21 (17)
Trimester of COVID-19 diagnosis		
First trimester, n (%)	10 (7)	—
Second trimester, n (%)	43 (29)	—
Third trimester, n (%)	96 (64)	—
COVID-19 severity		
Asymptomatic, n (%)	26 (17)	—
Mild, n (%)	79 (53)	—
Moderate, n (%)	32 (21)	—
Severe or critical, n (%)	12 (8)	—
Birth and infant characteristics		
Sex		
Male, n (%)	82 (55)	60 (47)
Female, n (%)	67 (45)	67 (53)
Gestational age at delivery, weeks	38.9 ± 1.9	39.3 ± 1.7
Full term, n (%)	136 (91)	123 (97)
Preterm, n (%)	13 (9)	4 (3)
Birth weight		
Low birth weight, n (%)	5 (3)	3 (2)
Small for gestational age, n (%)	8 (5)	3 (2)
Mode of delivery		
Cesarean section, n (%)	60 (40)	58 (46)
Vaginal delivery, n (%)	89 (60)	69 (54)
Ever breastfed, n (%)	134 (90)	114 (90)

Values are expressed as mean ± SD for continuous variables or n (%) for categorical variables. The following number of study participants had available data (infants with vs without COVID-19 exposure): age at delivery (149, 127); gravidity (149, 127); parity (149, 127); earliest BMI during pregnancy (145, 124); and gestational age at delivery (149, 127).

Continuous variables, categorical variables, and differences between groups were expressed as mean ± SD, frequency, and effect size (95% CI), respectively. All available data were analyzed. A critical value of $P < .05$ was used as the predefined threshold for statistical significance. Statistical analyses were performed using JMP 16.2 or SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Maternal and Infant Characteristics

Maternal, infant, and birth characteristics among study participants are shown in Table 1. Mothers with vs without prenatal COVID-19 demonstrated no clinically meaningful differences in prenatal age, tobacco use, obesity, gestational diabetes, or gestational hypertension. Nonetheless, higher rates of Hispanic or Latina ethnicity (50% vs 23%) and public insurance (50% vs 20%) were observed among mothers with SARS-CoV-2 infection, consistent with US population-based trends (28). Mothers with COVID-19 in our cohort most commonly had mild disease with a diagnosis in the third trimester.

Of the infants in our sample, approximately half in each group were male. Nearly all had a history of breastfeeding, irrespective of COVID-19 exposure status. While rates of cesarean section were similar between groups, infants born to mothers with COVID-19 tended toward a higher rate of prematurity (9% vs 3%). Rates of LBW and SGA were comparable between groups.

Birth Anthropometrics by In Utero COVID-19 Exposure Status

In our sample of infants with vs without in utero COVID-19 exposure, we first assessed for differences in weight, length, and BMI z-scores at birth. Infants born to mothers with prenatal COVID-19 exhibited lower birth weight z-score (−0.006 ± 1.07 vs 0.36 ± 1.08, $P = .006$) and BMI z-score (−0.19 ± 1.19 vs 0.22 ± 1.16, $P = .004$) compared with unexposed controls. The association of in utero COVID-19 exposure with lower weight and BMI z-scores at birth persisted in multivariable models adjusting for maternal age at delivery, ethnicity, parity, insurance status, and earliest BMI during pregnancy, in addition to infant sex and date of birth

Table 2. Anthropometric measures by in utero COVID-19 exposure status in the first year of life

Anthropometric parameter	Infants with COVID-19 exposure	Infants without COVID-19 Exposure	Unadjusted difference (95% CI)	Unadjusted *P* value	Adjusted difference (95% CI)[a]	Adjusted *P* value[a]
Birth (infants with COVID-19 exposure n = 149; infants without COVID-19 Exposure n = 127)						
Weight (g)	3311 ± 527	3480 ± 530	−169 (−295, −44)	**.009**	−145 (−285, −5)	**.04**
Weight z-score	−0.006 ± 1.07	0.36 ± 1.08	−0.36 (−0.62, −0.11)	**.006**	−0.30 (−0.59, −0.009)	**.04**
Length (cm)	50 ± 3	50 ± 3	0 (−1, 0)	.30	0 (−1, 0)	.49
Length z-score	0.21 ± 1.29	0.41 ± 1.40	−0.20 (−0.52, 0.12)	.22	−0.14 (−0.50, 0.22)	.45
BMI (kg/m^2)	13.2 ± 1.4	13.7 ± 1.5	−0.5 (−0.9, −0.2)	**.005**	−0.4 (−0.8, −0.1)	**.02**
BMI z-score	−0.19 ± 1.19	0.22 ± 1.16	−0.41 (−0.69, −0.13)	**.004**	−0.35 (−0.66, −0.03)	**.03**
12 Months (infants with COVID-19 exposure n = 119; infants without COVID-19 exposure n = 101)						
Weight z-score	0.79 ± 1.05	0.57 ± 1.10	0.22 (−0.06, 0.51)	.13	0.11 (−0.22, 0.45)	.51
Length z-score	0.87 ± 1.22	0.70 ± 1.10	0.16 (−0.16, 0.48)	.32	0.15 (−0.23, 0.53)	.45
BMI z-score	0.42 ± 1.13	0.20 ± 1.27	0.22 (−0.11, 0.55)	.20	0.03 (−0.36, 0.41)	.88
Change from birth to 12 months (infants with COVID-19 exposure n = 119; infants without COVID-19 exposure n = 101)						
Weight z-score	0.75 ± 1.27	0.20 ± 1.24	0.55 (0.22, 0.89)	**.001**	0.39 (0.007, 0.77)	**.05**
Length z-score	0.60 ± 1.69	0.31 ± 1.50	0.30 (−0.14, 0.74)	.19	0.17 (−0.35, 0.69)	.53
BMI z-score	0.62 ± 1.44	−0.05 ± 1.50	0.68 (0.27, 1.08)	**.001**	0.53 (0.06, 0.99)	**.03**

Anthropometric parameters are expressed as mean ± SD, whereas differences between groups (infants with vs without COVID-19 exposure) are expressed as effect size (95% CI). Unadjusted and adjusted differences were calculated using 2-sample t-tests and linear regression models, respectively. Bold text denotes $P < .05$.
[a]Analyses of birth anthropometric data are adjusted for *maternal covariates* (age at delivery, ethnicity, parity, insurance status, and earliest body mass index [BMI] during pregnancy) and *infant covariates* (sex and date of birth). Analyses of anthropometrics at 12 months and from birth to 12 months are additionally adjusted for any history of breastfeeding.

($P = .04$ for weight z-score; $P = .03$ for BMI z-score) (Table 2). In a sensitivity analysis, BMI z-score corrected for gestational age remained significantly lower among infants with vs without in utero COVID-19 exposure (−0.09 ± 1.08 vs 0.22 ± 1.13, $P = .02$), including in a model adjusting for the above covariates ($P = .05$) (Table S1 (29)). To contextualize our findings, we assessed whether cross-sectional BMI z-score at birth differed from 0 within each group as the WHO population average. BMI z-score at birth tended to be lower than 0 among infants with COVID-19 exposure ($P = .06$), whereas it significantly exceeded 0 among unexposed controls ($P = .03$). Notably, length z-score (Table 2) and corrected length z-score at birth (Table S1 (29)) were not found to differ between groups.

Longitudinal Growth Trajectories by In Utero COVID-19 Exposure Status

We next compared longitudinal growth patterns over the first year of life among infants with vs without in utero COVID-19 exposure. In linear mixed effects models, children born to mothers with prenatal COVID-19 exhibited substantially different trajectories in weight and BMI z-scores from birth to 12 months of age compared with unexposed controls (study group × time interaction, $P < .0001$ for each) (Fig. 2A; Fig. S1A) (29). These differences remained robust in multivariable models adjusting for the maternal and infant covariates included in our birth analyses (above) in addition to breastfeeding status ($P < .0001$ for each). In a sensitivity analysis, we similarly found differential trajectories in BMI z-score corrected for gestational age in unadjusted ($P = .0004$) and adjusted models ($P = .0005$). No difference was observed in length z-score trajectories by COVID-19 exposure status, including upon correction for gestational age, which was concordant with our observation that in utero COVID-19 exposure was unrelated to length at birth (Fig. S1B (29)).

We further characterized differences in growth patterns between COVID-19 exposure groups across infancy, focusing on BMI z-score as our main outcome of interest. As our primary endpoint, infants with in utero COVID-19 exposure had a significantly greater cumulative gain in BMI z-score vs unexposed controls from birth to 12 months (0.62 ± 1.44 vs −0.05 ± 1.50, $P = .001$) (Table 2 and Fig. 2B). This change remained significantly higher in infants born to mothers with prenatal COVID-19 than controls in an adjusted model (effect size: 0.53, 95% CI 0.06 to 0.99) (Table 2 and Fig. 2C). Furthermore, this difference between groups persisted in a model additionally adjusting for maternal race (effect size: 0.49, 95% CI 0.02 to 0.96). Comparable findings over 12 months were observed in a sensitivity analysis using BMI z-score corrected for gestational age in unadjusted ($P = .004$) and adjusted models ($P = .04$) (Table S1 (29)). Furthermore, similar trends in change in BMI z-score by COVID-19 exposure status were observed in analyses stratified by infant sex (Table S2 (29)). Like BMI z-score, weight z-score differentially increased from birth to 12 months among infants with vs without COVID-19 exposure, including in an adjusted model (effect size: 0.39, 95% CI 0.007 to 0.77) (Table 2).

Notably, though infants with in utero COVID-19 exposure exhibited a lower BMI z-score at birth, we found no difference in cross-sectional BMI z-score at 12 months (Table 2). Closure in the initial gap in BMI z-score over time aligns with the accelerated growth pattern observed in those with COVID-19 exposure. To strengthen our findings, we performed within-group comparisons to determine whether change in BMI z-score from birth to 12 months and cross-sectional BMI z-score at 12 months differed from 0 as the WHO population average. These parameters were both significantly

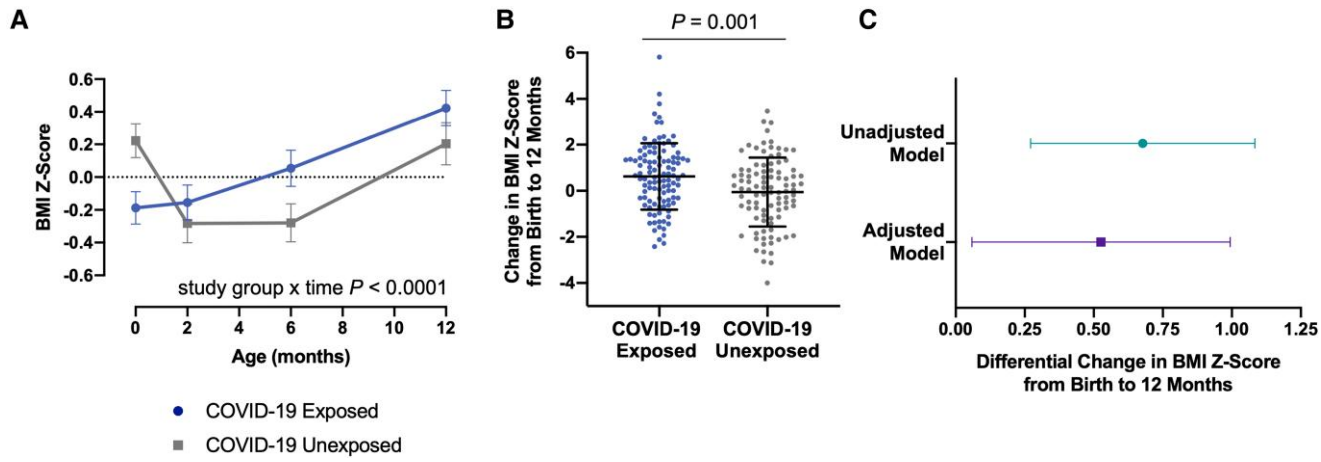

Figure 2. Longitudinal BMI z-score trajectories among infants with versus without in utero COVID-19 exposure. (A) Individuals born to mothers with vs without prenatal COVID-19 were found to have distinct BMI z-score trajectories over the first year of life with a linear mixed effects model. (B) As our primary endpoint, infants with in utero COVID-19 exposure demonstrated a greater change in BMI z-score from birth to 12 months than in unexposed controls using a 2-sample t-test. (C) The unadjusted differential change between groups in BMI z-score from birth to 12 months persisted in a linear regression model adjusting for maternal age at delivery, ethnicity, parity, insurance status, and earliest BMI during pregnancy as well as infant sex, date of birth, and any history of breastfeeding. Mean and SE of the mean (SEM), mean and SD, and effect size with 95% CI are shown in (A), (B), and (C), respectively.

greater than 0 among infants with COVID-19 exposure ($P < .0001$ and $P = .0002$, respectively), whereas no such differences were observed among unexposed controls.

Mediation of Relationship Between In Utero COVID-19 Exposure and Infant Longitudinal Growth by Birth Weight

Given that in utero COVID-19 exposure was associated with altered anthropometrics both at birth and over time, we next assessed the relationship between birth weight z-score and longitudinal growth. Among the overall sample, lower birth weight z-score was associated with a greater change in BMI z-score from birth to 12 months ($r = -0.49$, $P < .0001$), irrespective of study group (Fig. 3A). We then sought to evaluate whether lower birth weight z-score may underlie the link between in utero COVID-19 exposure and accelerated postnatal growth in infancy. In a mediation analysis, birth weight z-score was found to mediate a significant proportion (estimate ± SE: 32 ± 14%, $P = .02$) of the effect of COVID-19 exposure on change in BMI z-score from birth to 12 months (Fig. 3B), indicating a potential mechanistic role in this regard.

Exploratory Analysis of Maternal COVID-19 Timing and Severity in Relation to Infant Longitudinal Growth

Finally, among infants with in utero COVID-19 exposure, we assessed relationships of maternal COVID-19 severity and trimester of infection with anthropometric measures at birth in addition to change in BMI z-score from birth to 12 months. In models that included both severity and trimester of infection in addition to our standard covariates, there was no association of either parameter with weight, BMI, or length z-score at birth. In contrast, COVID-19 severity ($P = .008$), but not trimester of infection, was associated with change in BMI z-score from birth to 12 months. Specifically, individuals born to mothers with severe/critical illness during pregnancy had a greater gain in BMI z-score over time compared with those born to mothers with mild (effect size: 1.64, 95% CI 0.57 to 2.71) or moderate disease (effect size: 1.82, 95% CI 0.67 to 2.98). This analysis is regarded as exploratory given the limited number of participants in certain severity and trimester categories.

Discussion

In a longitudinal study leveraging a perinatal biorepository, we demonstrated that infants exposed in utero to maternal COVID-19 exhibited lower birth weight, lower birth BMI, and accelerated postnatal weight gain compared with their unexposed counterparts. Furthermore, birth weight z-score was found to partially mediate the relationship between in utero COVID-19 exposure and change in BMI z-score over the first year of life, suggesting that the exaggerated growth pattern observed among infants with COVID-19 exposure may in some cases be a catch-up response to a prenatal growth deficit. Given that lower birth weight and accelerated postnatal weight gain are risk factors for cardiometabolic disease, our findings point to a potentially increased cardiometabolic disease risk for the large global population of children with in utero COVID-19 exposure, and support the need for close long-term monitoring of these individuals over the life course.

In the current study, we found that infants born to mothers with prenatal COVID-19 had lower weight and BMI, but not length, at birth compared with babies without such exposure. The association of exposure status with birth anthropometrics persisted in multivariable models adjusting for key maternal and infant covariates, including sociodemographic factors known to distinguish populations most vulnerable to the COVID-19 pandemic (28). Notably, the absolute adjusted differences in birth weight and BMI between groups were relatively modest, amounting to less than 200 grams and 0.5 kg/m^2, respectively. These findings are consonant with previous studies, which have shown a small but significant decline in birth weight among babies born to mothers with vs without prenatal SARS-CoV-2 infection (7, 30). The current analysis extends these prior reports to demonstrate not only lower birth weight, but also lower birth BMI among infants with in utero

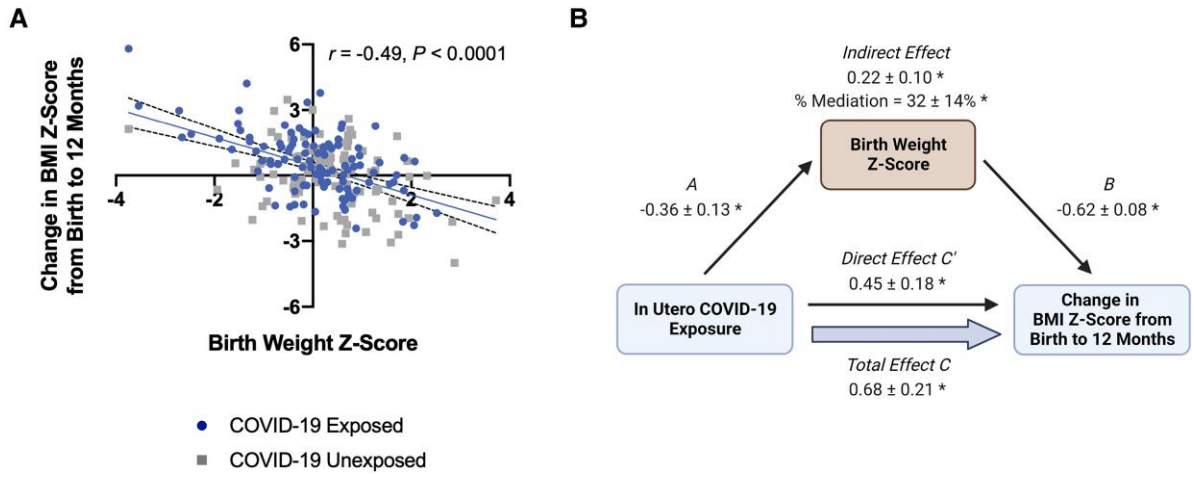

Figure 3. Birth weight z-score as a predictor of change in BMI z-score from birth to 12 months. (A) In the overall sample, birth weight z-score was inversely associated with change in BMI z-score over the first year of life, irrespective of study group. Linear regression with 95% confidence interval is shown. (B) A path model diagram depicts the results of a mediation analysis for the effect of in utero COVID-19 exposure on change in BMI z-score over 12 months as mediated by birth weight z-score. Total Effect C represents the effect of exposure status on change in BMI z-score with no mediators in the model. Direct Effect C′ represents the effect of exposure status on change in BMI z-score when birth weight z-score is included as a mediator in the model. Indirect Effect *AB* represents the effect of exposure status on change in BMI z-score through birth weight z-score. β-Coefficients are shown with asterisks used to denote $P < .05$. Figure was created with BioRender.com.

COVID-19 exposure. Of note, despite differences in absolute birth weight and BMI observed in our cohort, we did not find differences in the frequencies of the more severe phenotypes of LBW or SGA between groups.

As a novel aspect of our analysis, we examined longitudinal growth patterns over the first year of life among individuals with vs without in utero COVID-19 exposure. We found that individuals born to mothers with prenatal COVID-19 exhibited a steep, progressive rise in BMI z-score across infancy, in contrast to unexposed babies in whom the net change in BMI z-score over this period approximated 0. Importantly, the differential gain in BMI z-score from birth to 12 months among individuals with COVID-19 exposure persisted upon adjusting for maternal and infant characteristics, including breastfeeding status, such that the average adjusted change among babies born to mothers with prenatal COVID-19 exceeded that of controls by an estimated 0.5 z-score units. Notably, infants without COVID-19 exposure were found to exhibit a decline in BMI z-score in the first 6 months of life that rebounded back to baseline by 12 months. This growth pattern has been well described in other general population cohorts, including in 1 study that compared national growth references in 5 countries to WHO standards (31-33). WHO growth charts are intended to reflect ideal growth patterns in infants raised under optimal environmental conditions and breastfed through 1 year of life (34, 35). To bolster our findings, we performed within-group comparisons of change in BMI z-score from birth to 12 months and BMI z-score at 12 months to 0 as the WHO population average, which revealed significant differences among infants with but not without COVID-19 exposure.

A growing body of evidence has revealed that growth trajectories in early life are key predictors of long-term obesity and cardiometabolic disease. As an example, a large meta-analysis demonstrated J-shaped associations of birth weight with risk of type 2 diabetes mellitus and cardiovascular disease in adulthood, as well as an inverse relationship of birth weight with adult hypertension (36). Furthermore, irrespective of birth size, accelerated postnatal growth has been shown to correlate with obesity, abdominal adiposity, higher blood pressure, dyslipidemia, and vascular dysfunction in childhood and beyond (20, 21, 37-40). In addition, greater BMI velocity in early life was found to be a better predictor of later childhood adiposity than static BMI z-score (41). Taken together, the lower birth weight and accelerated gain in BMI that we observed among infants with in utero COVID-19 exposure may signal an increased risk of adverse cardiometabolic outcomes later in life. Our findings provide a compelling rationale for future research on health sequelae among children born to mothers with COVID-19, including prospective studies involving detailed cardiometabolic assessments.

In a formal mediation analysis, we found that birth weight z-score mediated a significant proportion of the relationship between in utero COVID-19 exposure and change in BMI z-score over the first year of life. This finding sheds light on a potential causal mechanism of accelerated weight gain among this population whereby maternal SARS-CoV-2 infection may impair the ability of a fetus to achieve its full growth potential in utero, in turn predisposing to "catch-up" growth postnatally. Catch-up growth is an evolutionarily conserved biologic response to a period of growth restriction that trades off improved short-term survival with heightened risk of chronic comorbidities (42, 43). Importantly, the sequence of reduced birth weight followed by accelerated weight gain in infants with in utero COVID-19 exposure may confer a "double hit" with respect to cardiometabolic disease risk (21, 44), suggesting that children exhibiting this growth pattern may require the most intensive long-term monitoring.

Notably, mounting evidence has linked acute and chronic maternal infections during pregnancy, even in the absence of vertical transmission, to long-term multisystemic morbidity in offspring with abnormalities first manifesting in early life (9). As an example, children and adolescents with perinatal HIV exposure without infection have been found to exhibit obesity, elevated blood pressure, dyslipidemia, cardiac mechanical dysfunction, and premature atherosclerosis compared

with their unexposed peers (45-48). Furthermore, lower maternal $CD4^+$ T cell count during pregnancy—a marker of HIV-related immune dysregulation—was associated with higher BMI z-score in offspring 18 years later on average (45). Similarly, studies of individuals born to mothers with influenza during pregnancy have revealed an increased likelihood of overweight at 30-80 months (49), as well as an elevated prevalence of heart disease in adulthood (50). These findings support an association between a pathologic intrauterine environment in the setting of maternal infection and downstream cardiometabolic pathology with key implications for the growing population of children born to mothers with prenatal COVID-19.

To our knowledge, this is the first study to assess longitudinal growth patterns among infants with vs without in utero COVID-19 exposure. As a strength of our study, we leveraged a rigorously phenotyped perinatal biorepository, in which the COVID-19 status of the mother in pregnancy was assured and all mothers were pregnant during the pandemic to control for the impact of pandemic-associated stress. As a limitation of the current analysis, sociodemographic differences were noted between groups that reflected population-level trends regarding the COVID-19 pandemic (28). Nonetheless, all mothers were treated during pregnancy within the same US academic healthcare system, and differences in growth patterns between groups persisted upon rigorous adjustment for potential confounders. Furthermore, by providing appropriate representation to ethnic groups most affected by the pandemic, our findings are generalizable to a broader population. Lastly, given that we relied on clinically available data, measures of body composition such as skinfold thicknesses were not available in the current study. However, since BMI z-score has been shown to correlate highly with infant adiposity (22), gains in BMI z-score in the first year of life are likely to reflect fat mass accrual.

The accelerated growth trajectory displayed by infants with fetal exposure to COVID-19 may be a harbinger for adverse cardiometabolic outcomes including obesity and heart disease later in life. Detailed physiologic studies are now needed to further delineate cardiometabolic disease risk among children born to mothers with prenatal COVID-19 as a key step toward optimizing the health and longevity of this expanding global population. In addition, while most infants in this cohort were exposed in utero to maternal COVID-19 prior to emergence of variants associated with more severe maternal and fetal/neonatal morbidity such as Alpha and Delta (51-53), future studies should explore differences in infant health outcomes by variant of exposure as the SARS-CoV-2 virus continues to evolve. Our data underscore the primacy of prevention with respect to prenatal SARS-CoV-2 infection including the need for widespread implementation of protective measures such as indoor masking and COVID-19 vaccination and boosting during or prior to pregnancy. Importantly, given the disproportionate impact that COVID-19 has had on historically marginalized populations, adverse health outcomes following in utero exposure to maternal COVID-19 may threaten to widen existing disparities in child health.

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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