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Association of Birth During the COVID-19 Pandemic With Neurodevelopmental Status at 6 Months in Infants With and Without In Utero Exposure to Maternal SARS-CoV-2 Infection

Lauren C. Shuffrey, PhD; Morgan R. Firestein, PhD; Margaret H. Kyle, BA; Andrea Fields, MA; Carmela Alcántara, PhD; Dima Amso, PhD; Judy Austin, PhD; Jennifer M. Bain, MD, PhD; Jennifer Barbosa, MA; Mary Bence, BA; Catherine Bianco, BA; Cristina R. Fernández, MD, MPH; Sylvie Goldman, PhD; Cynthia Gyamfi-Bannerman, MD, MS; Violet Hott, BA; Yunzhe Hu, BA; Maha Hussain, MS; Pam Factor-Litvak, PhD; Maristella Lucchini, PhD; Arthur Mandel, MD, PhD; Rachel Marsh, PhD; Danielle McBrian, MD; Mirella Mourad, MD; Rebecca Muhle, MD, PhD; Kimberly G. Noble, MD, PhD; Anna A. Penn, MD, PhD; Cynthia Rodriguez, BA; Ayesha Sania, ScD; Wendy G. Silver, MD, MA; Kally C. O'Reilly, PhD; Melissa Stockwell, MD; Nim Tottenham, PhD; Martha G. Welch, MD; Noelia Zork, MD; William P. Fifer, PhD; Catherine Monk, PhD; Dani Dumitriu, MD, PhD

IMPORTANCE Associations between in utero exposure to maternal SARS-CoV-2 infection and neurodevelopment are speculated, but currently unknown.

OBJECTIVE To examine the associations between maternal SARS-CoV-2 infection during pregnancy, being born during the COVID-19 pandemic regardless of maternal SARS-CoV-2 status, and neurodevelopment at age 6 months.

DESIGN, SETTING, AND PARTICIPANTS A cohort of infants exposed to maternal SARS-CoV-2 infection during pregnancy and unexposed controls was enrolled in the COVID-19 Mother Baby Outcomes Initiative at Columbia University Irving Medical Center in New York City. All women who delivered at Columbia University Irving Medical Center with a SARS-CoV-2 infection during pregnancy were approached. Women with unexposed infants were approached based on similar gestational age at birth, date of birth, sex, and mode of delivery. Neurodevelopment was assessed using the Ages & Stages Questionnaire, 3rd Edition (ASQ-3) at age 6 months. A historical cohort of infants born before the pandemic who had completed the 6-month ASQ-3 were included in secondary analyses.

EXPOSURES Maternal SARS-CoV-2 infection during pregnancy and birth during the COVID-19 pandemic.

MAIN OUTCOMES AND MEASURES Outcomes were scores on the 5 ASQ-3 subdomains, with the hypothesis that maternal SARS-CoV-2 infection during pregnancy would be associated with decrements in social and motor development at age 6 months.

RESULTS Of 1706 women approached, 596 enrolled; 385 women were invited to a 6-month assessment, of whom 272 (70.6%) completed the ASQ-3. Data were available for 255 infants enrolled in the COVID-19 Mother Baby Outcomes Initiative (114 in utero exposed, 141 unexposed to SARS-CoV-2; median maternal age at delivery, 32.0 [IQR, 19.0-45.0] years). Data were also available from a historical cohort of 62 infants born before the pandemic. In utero exposure to maternal SARS-CoV-2 infection was not associated with significant differences on any ASQ-3 subdomain, regardless of infection timing or severity. However, compared with the historical cohort, infants born during the pandemic had significantly lower scores on gross motor (mean difference, −5.63; 95% CI, −8.75 to −2.51; $F_{1,267}$ = 12.63; P<.005), fine motor (mean difference, −6.61; 95% CI, −10.00 to −3.21; $F_{1,267}$ = 14.71; P < .005), and personal-social (mean difference, −3.71; 95% CI, −6.61 to −0.82; $F_{1,267}$ = 6.37; P<.05) subdomains in fully adjusted models.

CONCLUSIONS AND RELEVANCE In this study, birth during the pandemic, but not in utero exposure to maternal SARS-CoV-2 infection, was associated with differences in neurodevelopment at age 6 months. These early findings support the need for long-term monitoring of children born during the COVID-19 pandemic.

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Supplemental content
Editorial

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Dani Dumitriu, MD, PhD, Departments of Pediatrics and Psychiatry, Columbia University Irving Medical Center, 1051 Riverside Dr, Ste 4807, New York, NY 10032 (dani.dumitriu@columbia.edu).

Globally, more than 200 million infants have been born since the onset of the COVID-19 pandemic.[66] During the first 2 weeks of universal testing at the height of the pandemic in New York City (spring of 2020), 14% of laboring women in the Columbia University Irving Medical Center hospital system tested positive for SARS-CoV-2 by nasopharyngeal polymerase chain reaction.[1] To date, 2% of the world's population has been infected at some point during the pandemic. Although impossible to precisely quantify, even the most conservative estimates of the total number of infants worldwide with in utero exposures to maternal SARS-CoV-2 infection range in the millions.[66]

Fetal exposure to perturbations of the intrauterine environment is implicated in altered brain development and long-term offspring vulnerability for neurodevelopmental and psychiatric sequelae.[2-15] Although vertical transmission of SARS-CoV-2 from mother to fetus is rare,[16-20] data from prior human coronavirus outbreaks (SARS and Middle East respiratory syndrome) suggest that severe infection during pregnancy may be associated with both maternal health[21] and increased risk for several adverse infant outcomes through mechanisms related to maternal immune activation.[22] Other viral illnesses during pregnancy are associated with higher risk for neurodevelopmental deficits, including motor delays,[23] as in the case of in utero HIV-exposed uninfected infants.[5-15] Additional epidemiological support for this association comes from naturalistic studies of viral epidemics that identified population-level associations. Cohort studies of the generation born during the 1918 influenza A virus subtype H1N1 pandemic found lower child educational level attainment and adult socioeconomic status.[24] The 1964 rubella pandemic led to a 10- to 15-fold increase in autism spectrum disorder or schizophrenia in offspring.[25,26] There is a need to determine the associations between fetal exposure to maternal SARS-CoV-2 infection and child neurodevelopmental status,[27-31] especially given the well-established benefits of early identification of at-risk children.[32-34]

The COVID-19 Mother Baby Outcomes (COMBO) Initiative[35] is a prospective cohort study established at Columbia University Irving Medical Center in Spring 2020 to examine associations between in utero exposure to maternal SARS-CoV-2 infection and the health and well-being of both mother and children living in New York City, the first US pandemic epicenter. Based on evidence from prior studies,[23,36,37] we hypothesized that maternal SARS-CoV-2 infection during pregnancy would be associated with delays in social and motor development at age 6 months. In addition, we compared infants born during the COVID-19 pandemic with a historical cohort born at the same medical center using the same neurodevelopmental assessment.

Key Points

Question Is maternal SARS-CoV-2 infection during pregnancy associated with infant neurobehavioral development at age 6 months?

Findings In this cohort study of 255 infants born between March and December 2020, exposure to maternal SARS-CoV-2 infection was not associated with differences on any Ages & Stages Questionnaire, 3rd Edition, subdomain at age 6 months, regardless of infection timing or severity. However, both exposed and unexposed infants born during that period had significantly lower scores on gross motor, fine motor, and personal-social subdomains compared with a historical cohort of infants born before the onset of the COVID-19 pandemic.

Meaning These findings suggest that birth during the COVID-19 pandemic, but not maternal SARS-CoV-2 infection, is associated with differences in neurodevelopment at age 6 months.

Participants and Methods

Study Design and Participants

Analyses included infants enrolled in COMBO and born between March (oldest enrolled infants) and December 2020 (eFigure, eTable 1 in the Supplement). All mother-infant dyads participating in COMBO receive prenatal care and deliver at the Columbia University Irving Medical Center–affiliated NewYork-Presbyterian Morgan Stanley Children's Hospital or NewYork-Presbyterian Allen Pavilion Hospital. All dyads with a documented SARS-CoV-2 infection during pregnancy (exposed cohort) according to the electronic health record (EHR) were invited to participate. Dyads were enrolled during pregnancy or in the first few months postpartum. For each exposed dyad, 1 to 3 unexposed dyads, defined as the absence of EHR documentation of maternal SARS-CoV-2 infection during pregnancy and at delivery, were selected and invited to participate based on infant sex, gestational age (GA) at birth, mode of delivery, and date of birth within a 2-week window. Self-reported race and ethnicity were collected from the EHR and 6-month surveys. Race and ethnicity are reported given known COVID-19 racial and ethnic disparities; however, race and ethnicity were not used for inclusion criteria or as a selection strategy. Study procedures were approved by the Columbia University Irving Medical Center Institutional Review Board for the COMBO cohort and by the New York State Psychiatric Institute Institutional Review Board for the historical cohort and written informed consent was obtained from all participants. Participants in both cohorts received financial compensation for their participation. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Infants included in the historical cohort were recruited from the Well Baby Nursery at Morgan Stanley Children's Hospital as part of a separate protocol to examine the association between gestational diabetes, newborn neurophysiologic status, and 6-month neurodevelopment, and were born between November 2017 and January 2020. There were no significant group differences between infants exposed and those not exposed to gestational diabetes on any Ages & Stages Questionnaire, 3rd Edition (ASQ-3) subdomain; therefore, all historical infants were combined into a single cohort. Given that this cohort was recruited from the same medical center and that the same 6-month neurodevelopmental measure was

used, this situation presented a unique opportunity to examine the association between the COVID-19 pandemic and infant neurodevelopment.

A total of 596 of 1706 women who were approached to participate enrolled in the COMBO Study; 385 women were invited to participate in the 6-month assessment, of whom 272 (70.6%) completed the ASQ-3. Data at age 6 months were available for 272 infants in the pandemic cohort and 71 infants in the historical cohort. Data from 17 pandemic cohort and 9 historical cohort infants were excluded owing to completion of the neurodevelopmental assessment outside of the eligibility window. The final sample included data from 317 infants: 255 in the pandemic cohort (n = 114 exposed, n = 141 unexposed) and 62 in the historical cohort.

Determination of SARS-CoV-2 Infection Status

The hospital practices of NewYork-Presbyterian during the COVID-19 pandemic have been published[38] and a detailed account of the classification and potential for misclassification is included in eMethods 1 in the Supplement. Mother-infant separation, which is known to affect neurodevelopmental outcomes,[39] was never implemented. The labor and delivery units of the NewYork-Presbyterian hospital system implemented universal SARS-CoV-2 testing of all delivering mothers by nasopharyngeal polymerase chain reaction on March 22, 2020, and by serological testing for antibodies on July 20, 2020. Additional symptom-based testing occurred throughout pregnancy and results obtained from external testing sites were recorded in the EHR when possible. Mothers in the exposed group were identified by automated EHR extraction defined as a positive SARS-CoV-2 polymerase chain reaction and/or serology test during pregnancy (based on conception date calculated from automated extraction of delivery date and GA at birth). For each mother identified by automated extraction, a careful EHR review was conducted to determine the date of symptom onset, which was then referenced to the infant's GA to determine the trimester of in utero exposure. Exact exposure timing was determined for 85 of 114 mothers (75%) included in this analysis. For 29 of 39 (74%) asymptomatic mothers with positive serologic testing, an exact date of symptom onset could not be determined, so the date with the peak number of SARS-CoV-2 infections during the first wave of the pandemic in New York City (April 6, 2020) was used to impute the trimester of exposure. SARS-CoV-2 infection severity was categorized as previously described[16] and is included in eMethods 1 in the Supplement.

Based on EHR and/or maternal report, 5 infants in the pandemic cohort and no infants in the historical cohort were infected with SARS-CoV-2 between birth and the neurodevelopmental assessment.

Assessment of Neurodevelopment

Between 5 months, 0 days, and 6 months, 30 days (mean [SD], 185 [9.97] days, age-adjusted for preterm infants), neurodevelopment was assessed by maternal report using the ASQ-3 in English or Spanish via secure REDCap survey. The ASQ-3 was completed between October 7, 2020, and June 17, 2021, for the pandemic cohort and between May 24, 2018, and July 22, 2020, for the historical cohort. The ASQ-3 is a validated, widely used, standardized, level 1 screening tool based on parental report that reliably assesses 5 key developmental domains: communication, fine and gross motor, problem solving, and personal-social skills. The ASQ-3 has strong concurrent validity (r = 0.85), 2-week test-retest reliability (r = 0.75-0.82), interobserver reliability (r = 0.43-0.69), and internal consistency (α = 0.51-0.87). The ASQ-3 provides cutoff scores to indicate possible delay as follows: communication, 29.65; gross motor, 22.25; fine motor, 25.14; problem solving, 27.72; and personal-social, 25.34.[40,41]

Statistical Analysis

Statistical analyses were conducted in R, version 4.0.2 (R Foundation for Statistical Computing). The experimental design (forced-choice online survey and EHR review) resulted in no missingness. Power analyses were based on the primary outcome investigating mean differences in ASQ-3 subdomain scores between infants with and without in utero exposure to maternal SARS-CoV-2 infection using analyses of covariance, for which we had 90% power to detect a 0.5-SD difference in each subdomain using a 2-sided test with α<.05 (eMethods 2 in the Supplement). Within the exposed subset, we also examined associations between SARS-CoV-2 timing and severity and ASQ-3 subdomains via analysis of covariance. For secondary analyses, preterm infants (n = 17) and term infants admitted to the neonatal intensive care unit (n = 11) were excluded to match the sample characteristics of the historical cohort. Analyses of covariance were used to determine mean differences in ASQ-3 subdomains between the pandemic (n = 227) and historical (n = 62) cohorts.

To examine potential demographic differences between groups, comparisons were performed using the χ^2 test for binomial variables and Wilcoxon rank sum test for continuous variables. For both primary and secondary analyses, we implemented minimally adjusted (GA at birth, infant sex, and infant age at assessment) and fully adjusted (additionally controlled for maternal race, ethnicity, age at delivery, educational level, parity, and mode of delivery) models. Neonatal intensive care unit admission was additionally included in fully adjusted models only for pandemic cohort analyses. Percentages of infants screening below cutoff levels indicative of delays per ASQ-3 developers[40] were computed for each subdomain and for overall ASQ-3 outcome. The Fisher exact test was used to examine group differences in screening positive for delays between the pandemic and historical cohorts. For ASQ-3 subdomains in which a significant main effect was identified, tertiary analyses examined scores in relation to trimester of pregnancy during the peak New York City SARS-CoV-2 cases (April 6, 2020) using fully adjusted analysis of covariance models with general linear hypothesis testing using Tukey pairwise contrasts. Mean differences with 95% CIs are reported for all significant main outcomes. Estimated marginal means are reported in eTable 7 and eTable 12 in the Supplement. All sensitivity analyses used fully adjusted models. Significance was set at $P < .05$.

Table 1. Cohort Characteristics

Variable	Pandemic cohort, No. (%)					ASQ-3 cohort, No. (%)			
	Overall	SARS-CoV-2 unexposed	SARS-CoV-2 exposed	*P* value	χ^2 or Wilcoxon rank sum test[a]	Historical	Pandemic[b]	*P* value	χ^2 or Wilcoxon rank sum test[a]
No.	255	141	114			62	227		
Maternal characteristics									
Age at delivery, median (IQR), y	32.0 (19.0-45.0)	32.0 (19.0-45.0)	31.0 (19.0-44.0)	.08	7021.5	32.0 (18.0-46.0)	32.0 (19.0-45.0)	.25	6364
Race									
Asian or Asian American	15 (5.9)	13 (9.2)	2 (1.8)	<.01	16.82	2 (3.2)	13 (5.7)	<.01	49.04
Black or African American	32 (12.5)	17 (12.1)	15 (13.2)			12 (19.4)	29 (12.8)		
Native American or Alaskan Native	2 (0.8)	1 (0.7)	1 (0.9)			4 (6.5)	2 (0.9)		
Native Hawaiian or Other Pacific Islander	3 (1.2)	2 (1.4)	1 (0.9)			0 (0)	3 (1.3)		
White	99 (38.8)	64 (45.4)	35 (30.7)			13 (21.0)	87 (38.3)		
Other or mixed	69 (27.1)	29 (20.6)	40 (35.1)			31 (50.0)	64 (28.2)		
Declined or unknown	35 (13.7)	15 (10.6)	20 (17.5)			0 (0)	29 (12.8)		
Ethnicity									
Hispanic or Latino/a/x or Spanish	128 (50.2)	55 (39.0)	73 (64.0)	<.01	19.54	48 (77.4)	118 (52.0)	<.01	36.82
Not Hispanic or Latino/a/x or Spanish	108 (42.4)	77 (54.6)	31 (27.2)			14 (22.6)	95 (41.9)		
Declined or unknown	19 (7.5)	9 (6.4)	10 (8.8)			0 (0)	14 (6.2)		
Educational level									
Some high school	18 (7.1)	9 (6.4)	9 (7.9)	<.01	18.87	11 (17.7)	16 (7.0)	<.01	32.72
High school degree/GED/trade school	32 (12.5)	11 (7.8)	21 (18.4)			13 (21.0)	28 (12.3)		
Some college	25 (9.8)	12 (8.5)	13 (11.4)			8 (12.9)	21 (9.3)		
College degree									
2 y	30 (11.8)	12 (8.5)	18 (15.8)			5 (8.1)	27 (11.9)		
4 y	70 (27.5)	39 (27.7)	31 (27.2)			12 (19.4)	64 (28.2)		
Graduate	77 (30.2)	56 (39.7)	21 (18.4)			12 (19.4)	68 (30.0)		
Declined or unknown	3 (1.2)	2 (1.4)	1 (0.9)			1 (1.6)	3 (1.3)		
Infant characteristics									
Vaginal delivery	166 (65.1)	84 (59.6)	82 (71.9)	.05	3.71	26 (41.9)	154 (67.8)	<.01	17.10
Primiparous	127 (49.8)	76 (53.9)	51 (44.7)	.18	1.77	23 (37.1)	113 (49.8)	.23	0.63
Gestational age at birth, median (IQR), wk	39.1 (30.1-41.6)	39.1 (34.1-41.6)	39.1 (30.1-41.1)	.45	8478.5	39.1 (37.0-41.0)	39.1 (37.0-41.6)	.18	7825
Full-term	39.1 (37.0-41.6)	39.1 (37.0-41.6)	39.1 (37.0-41.1)	.46	7396	NA	NA	NA	NA
Preterm	35.9 (30.1-36.9)	36.5 (34.1-36.9)	35.6 (30.1-36.7)	.03	12.5	NA	NA	NA	NA
Preterm <37 wk	17 (6.7)	10 (7.1)	7 (6.1)	.10	0.003	0	0	NA	NA
Sex									
Female	111 (43.5)	53 (37.6)	58 (50.9)	.04	4.00	26 (41.9)	100 (44.1)	.21	3.16
Male	144 (56.5)	88 (62.4)	56 (49.1)			36 (58.1)	127 (55.9)		

Abbreviations: NA, not applicable; NICU, neonatal intensive care unit.

[a] Comparisons performed using the χ^2 test for binomial variables and Wilcoxon rank sum test for continuous variables. All statistical tests were 2-sided.

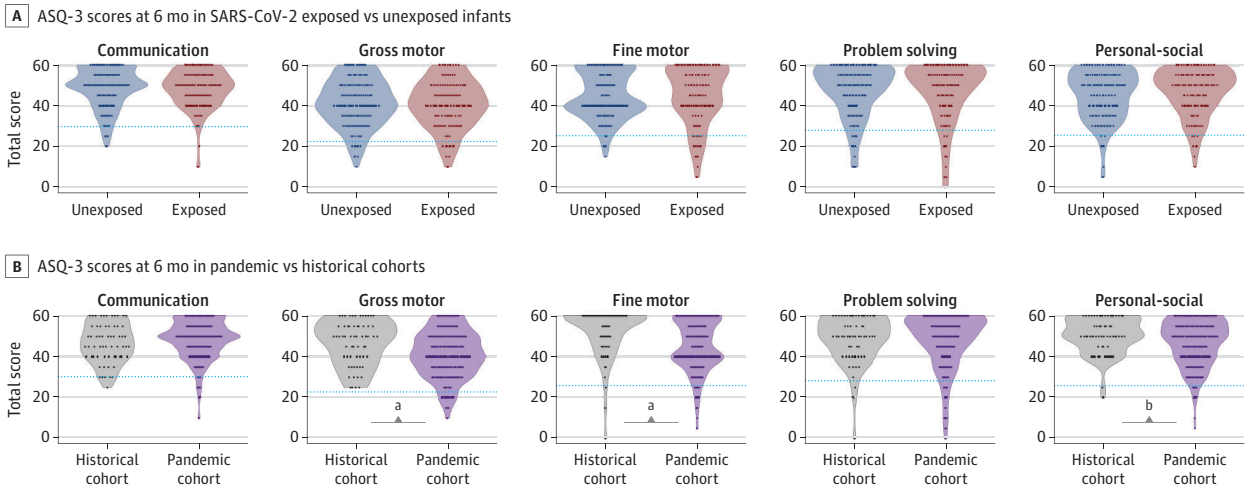
[b] Infants born preterm or who were hospitalized in the NICU were removed for comparisons of the pandemic and historical cohorts.

Results

Cohort Characteristics

Median age at delivery of the 255 women in the pandemic cohort was 32.0 (IQR, 19.0-45.0) years. Highlighting the disproportionate predilection of COVID-19 in already medically disadvantaged groups, mothers with SARS-CoV-2 infection (n = 114) significantly differed from noninfected mothers (n = 141) in their self-reported race (χ^2 = 16.82; *P* < .01), ethnicity (χ^2 = 19.54; *P* < .01), and educational level (χ^2 = 18.87; *P* < .01), with a higher proportion of mothers with SARS-CoV-2 infection identifying as other or mixed race (40 [35.1%] vs 29 [20.6%]) and Hispanic or Latino/a/x or Spanish ethnicity (73 [64.0%] vs 55 [39.0%]) and a lower proportion reporting a graduate degree (21 [18.4%] vs 56 [39.7%]) (**Table 1**). Compared with the healthy, full-term pandemic cohort (n = 227), the historical cohort (n = 62) significantly differed in race

Figure 1. Ages & Stages Questionnaire, 3rd Edition (ASQ-3) Scores at Age 6 Months



A, Total raw scores on each ASQ-3 domain for infants with in utero exposure to maternal SARS-CoV-2 infection vs unexposed infants. No significant group differences were identified on any of the ASQ-3 domains in either minimally or fully adjusted models. B, Total raw scores on each ASQ-3 domain for infants born during the pandemic vs a historical cohort born at the same hospital. Blue dashed horizontal lines represent the cutoff indicating possible delay on each subscale (communication, 29.65; gross motor, 22.25; fine motor, 25.14; problem solving, 27.72; personal-social, 25.34). Analyses performed on fully adjusted models.

[a] $P < .001$.

[b] $P = .01$.

($\chi^2 = 49.04$; $P < .01$), ethnicity ($\chi^2 = 36.82$; $P < .01$), educational level ($\chi^2 = 32.72$; $P < .01$), and mode of delivery ($\chi^2 = 17.10$; $P < .01$). Group differences were accounted for in all fully adjusted models.

ASQ-3 Evaluation at Age 6 Months

There were no significant group differences between exposed and unexposed infants on any of the 5 ASQ-3 subdomain scores (communication, gross motor, fine motor, problem solving, or personal-social skills) at age 6 months (**Figure 1**A) in either minimally or fully adjusted models (**Table 2**). Most mothers experienced asymptomatic (39 [34%]) or mild (71 [62%]) disease and were infected in the second (54 [47%]) or third (35 [31%]) trimester (eTable 2 in the Supplement). A small proportion of mothers had severe disease (4 [4%]) and 25 (22%) were infected in the first trimester. Neither symptom severity nor timing of infection showed an association with any ASQ-3 subdomain score in either minimally or fully adjusted models (eTable 3 and eTable 4 in the Supplement). For example, personal-social ASQ-3 subdomain scores were not associated with maternal SARS-CoV-2 severity ($F_{2,106} = 1.09$; $P = .34$) or maternal SARS-CoV-2 trimester of infection ($F_{2,106} = 1.21$; $P = .30$). Results remained nonsignificant after sensitivity analyses were conducted removing asymptomatic women with positive serologic test results with imputed gestational timing (n = 29) (eTable 5 in the Supplement). For example, personal-social ASQ-3 subdomain scores were not associated with maternal SARS-CoV-2 severity ($F_{1,51} = 0.12$; $P = .74$), even after excluding the 29 infants exposed to asymptomatic maternal SARS-CoV-2 with imputed gestational timing. Sensitivity analyses removing preterm infants and those admitted to the neonatal intensive care unit (n = 28) also yielded nonsignificant results (eTable 6 in the Supplement). For example, personal-social ASQ-3 subdomain scores were not associated with maternal SARS-CoV-2 infection ($F_{1,205} = 0.47$; $P = .49$), even after excluding the 28 infants born preterm and/or admitted to the neonatal intensive care unit.

Our primary analysis revealed no associations between SARS-CoV-2 status, timing, or severity and ASQ-3 scores. Therefore, exposed and unexposed healthy, term infants with no neonatal intensive care unit admissions in the pandemic cohort were pooled (n = 227) and compared with infants in the historical cohort. Compared with those in the historical cohort, infants in the pandemic cohort had significantly lower mean scores on the gross motor (mean difference, −5.63; 95% CI, −8.74 to −2.52; $F_{1,284} = 12.68$; $P < .001$; $n^2 = 0.016$), fine motor (mean difference, −6.61; 95% CI, −10.04 to −3.18; $F_{1,284} = 14.38$; $P < .001$, $n^2 = 0.016$), and personal-social (mean difference, −3.71; 95% CI, −6.61 to −0.82; $F_{1,284} = 6.39$; $P = .01$; $n^2 = 0.005$) subdomains in the minimally adjusted models (**Table 3**; eTable 7 in the Supplement). These group differences persisted in the fully adjusted models: gross motor (mean difference, −5.63; 95% CI, −8.75 to −2.51; $F_{1,267} = 12.63$; $P<.001$; $n^2 = 0.018$), fine motor (mean difference, −6.61; 95% CI, −10.00 to 3.22; $F_{1,267} = 14.71$; $P < .001$; $n^2 = 0.015$), and personal-social (mean difference, −3.71; 95% CI, −6.61 to −0.82; $F_{1267} = 6.37$; $P = .01$; $n^2 = 0.004$) (Figure 1B). Sensitivity analyses excluding 1 exposed and 4 unexposed infants diagnosed with COVID-19 between birth and ASQ-3 assessments did not alter the findings (eTable 8 in the Supplement). Sensitivity analyses excluding 15 infants in the historical cohort who were assessed during the pandemic did not alter the findings on fine and gross motor scores, but personal-social scores no longer differed significantly between cohorts (eTable 9 in the Supplement). Although not specifically powered to detect differences in the proportion of infants who met screening cutoffs

Table 2. Comparison of 6-Month ASQ-3 Scores Between SARS-CoV-2 Exposed and Unexposed Infants in the Pandemic Cohort

ASQ-3 subdomain	Overall pandemic cohort	SARS-CoV-2		Adjusted			
				Minimally[a]		Fully[b]	
		Unexposed	Exposed	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value
No.	255	141	114				
Score, mean (SD)[c]							
Communication	48.1 (9.75)	48.2 (9.84)	48.0 (9.68)	−0.17 (−2.57 to 2.24)	.89	−0.17 (−2.58 to 2.25)	.89
Gross motor	41.0 (11.8)	41.3 (11.7)	40.6 (12.0)	−0.70 (−3.56 to 2.16)	.63	−0.70 (−3.55 to 2.16)	.63
Fine motor	44.9 (12.7)	44.9 (11.3)	44.9 (14.3)	0.01 (−3.04 to 3.06)	>.99	0.01 (−2.98 to 3.00)	.99
Problem solving	47.1 (13.7)	47.2 (12.8)	46.8 (14.8)	−0.39 (−3.65 to 2.86)	.81	−0.39 (−3.64 to 2.85)	.81
Personal-social	45.9 (11.9)	45.3 (12.2)	46.7 (11.6)	1.35 (−1.48 to 4.17)	.35	1.35 (−1.42 to 4.12)	.34
Below cutoff, No. (%)							
Communication	9 (3.5)	6 (4.3)	3 (2.6)	NA	NA	NA	NA
Gross motor	21 (8.2)	10 (7.1)	11 (9.6)	NA	NA	NA	NA
Fine motor	23 (9.0)	7 (5.0)	16 (14.0)	NA	NA	NA	NA
Problem solving	25 (9.8)	13 (9.2)	12 (10.5)	NA	NA	NA	NA
Personal-social	16 (6.3)	8 (5.7)	8 (7.0)	NA	NA	NA	NA
Any domain	53 (20.8)	27 (19.1)	26 (22.8)	NA	NA	NA	NA

Abbreviations: ASQ-3, Ages & Stages Questionnaire, 3rd Edition; NA, not applicable.

[a] Minimally adjusted models include gestational age at birth, infant sex, and infant age at assessment.

[b] Fully adjusted models include gestational age at birth, infant sex, infant age at assessment, maternal race, maternal ethnicity, maternal age at delivery, maternal educational level, parity, mode of delivery, and neonatal intensive care unit admission status.

[c] ASQ-3 scores in each subdomain can range from 0 to 60, with lower scores indicating greater delay and higher scores indicating greater competence.

Table 3. Comparison of 6-Month ASQ-3 Scores Between the Pandemic and Historical Cohorts

ASQ-3 subdomain	Pandemic cohort and historical cohort[a]	Cohort		Minimally adjusted[b]		Fully adjusted[c]		Fisher exact test *P* value[d]
		Historical	Pandemic[a]	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value	
No.	289	62	227					
Score, mean (SD)[e]								
Communication	47.9 (9.49)	46.8 (9.54)	48.2 (9.48)	1.42 (−1.26 to 4.09)	.30	1.42 (−1.23 to 4.07)	.29	NA
Gross motor	42.4 (11.5)	46.8 (10.8)	41.1 (11.5)	−5.63 (−8.74 to 2.52)	<.001	−5.63 (−8.75 to −2.51)	<.001	NA
Fine motor	46.7 (12.6)	51.9 (12.1)	45.2 (12.4)	−6.61 (−10.04 to −3.18)	<.001	−6.61 (−10.00 to −3.22)	<.001	NA
Problem solving	48.0 (13.0)	48.6 (11.6)	47.8 (13.4)	−0.79 (−4.37 to 2.80)	.67	−0.79 (−4.40 to 2.83)	.67	NA
Personal-social	47.6 (10.7)	50.6 (8.78)	46.9 (11.0)	−3.71 (−6.61 to −0.82)	.01	−3.71 (−6.61 to −0.82)	.01	NA
Below cutoff, No. (%)								
Communication	9 (3.1)	1 (1.6)	8 (3.5)	NA	NA	NA	NA	.39
Gross motor	17 (5.9)	0 (0)	17 (7.5)	NA	NA	NA	NA	.01
Fine motor	20 (6.9)	3 (4.8)	17 (7.5)	NA	NA	NA	NA	.34
Problem solving	22 (7.6)	3 (4.8)	19 (8.4)	NA	NA	NA	NA	.26
Personal-social	12 (4.2)	2 (3.2)	10 (4.4)	NA	NA	NA	NA	.51
Any domain	47 (16.3)	7 (11.3)	40 (17.6)	NA	NA	NA	NA	.16

Abbreviations: ASQ-3, Ages & Stages Questionnaire, 3rd Edition; NA, not applicable.

[a] Subset excludes preterm infants (7 exposed, 10 unexposed) and full-term infants admitted to the neonatal intensive care unit (6 exposed, 5 unexposed).

[b] Minimally adjusted models include gestational age at birth, infant sex, and infant age at assessment.

[c] Fully adjusted models include gestational age at birth, infant sex, infant age at assessment, maternal race, maternal ethnicity, maternal age at delivery, maternal educational attainment, parity, and mode of delivery.

[d] Fisher exact tests were 1-sided to test whether a greater proportion of infants in the pandemic cohort met the ASQ-3 cutoffs compared with infants in the historical cohort.

[e] ASQ-3 scores in each subdomain can range from 0 to 60, with lower scores indicating greater delay and higher scores indicating greater competence.

for delay, a greater proportion of infants in the pandemic cohort met the gross motor cutoff (1-sided Fisher exact test, $P = .01$) (Table 3).

As a post hoc analysis, we investigated whether the timing of pregnancy relative to the peak of the pandemic in New York City was associated with scores on the ASQ-3 subdomains that were identified as different between the pandemic and historical cohorts using fully adjusted models. There was a significant association between trimester of pregnancy on infant gross motor ($F_{3,265} = 5.56$; $P < .01$; $n^2 = 0.022$), fine motor ($F_{3,265} = 6.16$; $P < .005$; $n^2 = 0.021$), and personal-social scores ($F_{3,266} = 4.96$; $P < .01$; $n^2 = 0.036$). Compared with the historical control cohort, infants born to mothers who were in their first trimester of pregnancy during the peak of the pandemic had a significant reduction in gross motor (mean difference, −5.70; 95% CI, −11.89 to 0.49; $P < .05$), fine motor (mean difference, −5.60; 95% CI, −12.33 to 1.14; $P < .05$), and personal-social (mean difference, −6.32; 95% CI, −11.53 to −1.11; $P < .005$) scores, and these results were consistent across peak pandemic imputation dates ranging from March 7 to April 6, 2020 (**Figure 2**; eTables 10-12 in the Supplement). Sensitivity analyses using fully adjusted models excluding 15 infants in the historical cohort who were assessed during the pandemic did not alter findings on personal-social scores. Pairwise comparisons for gross motor and fine motor skills also continued to show decrements in the pandemic cohort but were no longer significant (eTable 13 in the Supplement).

Discussion

The clinical and research communities have emphasized the need for information regarding the associations between fetal exposure to maternal SARS-CoV-2 infection and neurodevelopmental outcomes.[27-31] Prior studies of the association between fetal exposure to maternal viral infections and atypical child neurodevelopment have led to the speculation that maternal SARS-CoV-2 infection during pregnancy may be associated with global developmental delays or specific neurodevelopmental disorders.[27-31] To our knowledge, our analysis is the first to examine this association and, contrary to the proposed hypothesis, we did not find an association between maternal SARS-CoV-2 infection status, timing, or severity and infant neurodevelopment at age 6 months as measured using a standardized screener. However, infants born during the pandemic, regardless of maternal SARS-CoV-2 status, scored significantly lower on the gross motor, fine motor, and personal-social subdomains of the ASQ-3 compared with a historical cohort of infants born at the same institution. Fifteen infants in the historical cohort had postnatal exposure to the pandemic environment before being assessed. Sensitivity analyses excluding these infants did not alter the main findings, suggesting a relatively greater association between neurodevelopment and in utero exposure to the pandemic than postnatal pandemic exposure. Furthermore, early gestation at the peak of the pandemic in New York City was associated with the lowest scores on these subdomains compared with the historic controls. Taken together, these findings suggest the potential for a significant public health crisis for the generation born during the COVID-19 pandemic, necessitating further investigation.

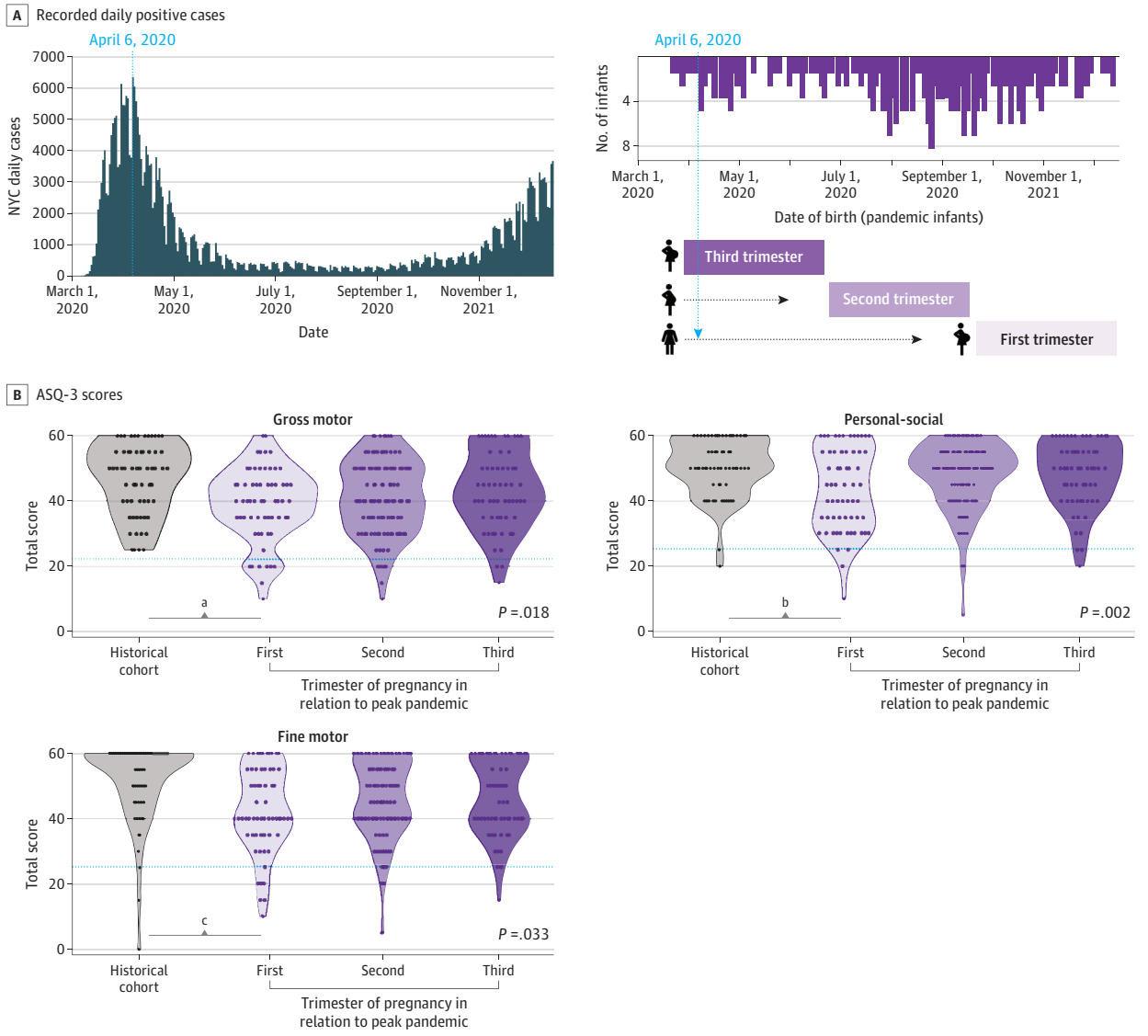
Despite little evidence that coronaviruses, such as SARS-CoV, Middle East respiratory syndrome CoV, and now SARS-CoV-2, can cross the placenta,[42,43] the speculation that in utero SARS-CoV-2 exposure may be associated with infant neurobehavior was based on the established role of maternal immune activation on fetal brain development and supported by recent findings of increased interleukin 6 levels in pregnant women with SARS-CoV-2 infection.[44] In animal models of maternal immune activation, both viral exposure and direct injection of interleukin-6 led to dose-dependent atypical behavior in offspring.[45,46] Although the severity of SARS-CoV-2 infection during pregnancy is correlated with interleukin 6 levels,[44] our analysis did not reveal an association between severity and ASQ-3 scores. Most of our participants experienced an asymptomatic or mild SARS-CoV-2 infection; therefore, infants exposed to greater levels of maternal immune activation may not be represented in our data. Similarly, early gestational exposure is most likely to be associated with adverse neurodevelopmental outcomes.[47-49] Given that only 25 maternal SARS-Cov-2 infections (8 imputed) in our sample occurred in the first trimester, our results provide limited power for detecting an association between infection at this early time point and neurodevelopment.

Together, the lack of neurodevelopmental differences between infants with and without in utero SARS-CoV-2 exposure and the observed group differences between the historical and pandemic cohorts suggest COVID-19–related stress should be considered as a potential underlying mechanism. Reported stressors have included job loss, food insecurity, and loss of housing,[50] and the pandemic has resulted in significant increases in symptoms of anxiety and depression.[51] Consistent with our finding that infants born to women who were in the first trimester of pregnancy during the pandemic peak had the lowest scores in gross motor, fine motor, and personal-social subdomains, data from numerous cohort studies have demonstrated that prenatal perceived stress, loneliness, and objective stress, especially during early gestation, are associated with an increased risk for adverse neurodevelopment in children.[3,52-60]

Strengths and Limitations

The study has several limitations. The data included in this analysis represent a single site from the first hard-hit COVID-19 epicenter in the US, which may limit generalizability. It is also possible that different developmental patterns will emerge beyond age 6 months, as this is a relatively early time point. The ASQ-3 has modest agreement with objective measures of development[61,62] and is often used by general pediatricians.[63] As a parent-report measure, it is possible that our results are a reflection of parental-perception of—rather than objective differences in—infant neurodevelopment. Nonetheless, parental perception of development also has implications for long-term child outcomes.[64] In addition, an analysis of 8507 mother-child dyads revealed minimal associations between maternal psychopathologic conditions and maternal-reported child emo-

Figure 2. Association Between Gestational Trimester at Pandemic Peak and Ages & Stages Questionnaire, 3rd Edition (ASQ-3) Scores at Age 6 Months



A, Representation of the COVID-19 pandemic in New York City during the time infants in the cohort were born and the gestational timing assignment for the trimester of pregnancy during which the mother experienced the peak of the pandemic. The histogram in black represents the number of recorded daily SARS-CoV-2–positive cases in New York City between March and December 2020. The histogram in purple represents the dates of birth in 2-day bins of infants enrolled in the pandemic cohort. For meaningful comparison with the historical cohort (n = 62), only full-term infants admitted to the Well Baby Nursery were included in the pandemic cohort (n = 227). Gestational timing at the peak of the COVID-19 pandemic in New York City, defined as April 6, 2020 (the date with the highest number of SARS-CoV-2–positive cases), was computed using date of birth and gestational age at birth. The diagram below depicts the trimester of pregnancy corresponding to the dates of birth of infants in the pandemic cohort. Infants with third trimester pandemic exposure were born between March and June 2020, infants with second trimester pandemic exposure were born between June and October 2020, and infants with first trimester pandemic exposure were born between October and December 2020. B, ASQ-3 gross motor, fine motor, and personal-social scores for infants in the historical cohort vs infants in the pandemic cohort by maternal trimester of pregnancy at the peak of the pandemic in New York City. Gray horizontal lines represent the cutoff indicating possible delay on each subscale (gross motor, 22.25; fine motor, 25.14; and personal-social, 25.34). Analyses performed on fully adjusted models.

[a] $P = .02$.

[b] $P = .002$.

[c] $P = .03$.

tional and behavioral problems.[65] Although we used fully adjusted models and conducted a number of sensitivity analyses to check the robustness of our results, additional unmeasured confounders and modifiers might have been present. Observed differences in the characteristics of approached vs enrolled participants are suggestive of such potential biases, pointing to the need for additional research. Notable strengths of our study include detailed medical records on maternal SARS-CoV-2 status, timing, and severity that minimize potential misclassification, and availability of a historical comparison group from the same hospital center using the same neurodevelopmental assessment.

Conclusions

The findings of this analysis of the neurodevelopmental status of infants born during the COVID-19 pandemic support the need for long-term monitoring of these children to mitigate substantial sequelae similar to those observed in generations born during previous pandemics. The observed association between birth during the pandemic and neurodevelopmental status, regardless of maternal SARS-CoV-2 status, suggests a potential pathway involving maternal pandemic-related distress that warrants future investigation.

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Author Affiliations: Department of Psychiatry, Columbia University Irving Medical Center, New York, New York (Shuffrey, Firestein, Barbosa, Hu, Lucchini, Marsh, Muhle, Sania, O'Reilly, Welch, Fifer, Monk, Dumitriu); Department of Pediatrics, Columbia University Irving Medical Center, New York, New York (Kyle, Bence, Fernández, Hott, Hussain, Penn, Stockwell, Welch, Fifer, Dumitriu); Department of Psychology, Columbia University, New York, New York (Fields, Amso, Bianco, Tottenham); School of Social Work, Columbia University, New York, New York (Alcántara); Heilbrunn Department of Population and Family Health, Columbia University Irving Medical Center, New York, New York (Austin); Department of Neurology, Division of Child Neurology, Columbia University Irving Medical Center, New York, New York (Bain, Goldman, Mandel, McBrian, Silver); Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Diego, La Jolla (Gyamfi-Bannerman); Department of Epidemiology, Mailman School of Public Health, Columbia University Irving Medical Center, New York, New York (Factor-Litvak); Department of Obstetrics and Gynecology, Columbia University Irving Medical Center New York, New York (Mourad, Zork, Monk); Department of Neuroscience and Education, Teachers College, Columbia University, New York, New York (Noble); New York State Psychiatric Institute, New York (Rodriguez, O'Reilly); Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, New York (Welch).

Author Contributions: Dr Dumitriu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Shuffrey and Firestein contributed equally as co-first authors.
Concept and design: Shuffrey, Firestein, Kyle, Fields, Amso, Goldman, Gyamfi-Bannerman, Hussain, Factor-Litvak, Lucchini, Mandel, Penn, Silver, Tottenham, Welch, Monk, Dumitriu.
Acquisition, analysis, or interpretation of data: Shuffrey, Firestein, Kyle, Alcántara, Austin, Bain, Barbosa, Bence, Bianco, Fernandez, Hott, Hu, Hussain, Factor-Litvak, Lucchini, Marsh, McBrian, Mourad, Muhle, Noble, Rodriguez, Sania, O'Reilly, Stockwell, Zork, Fifer, Monk, Dumitriu.
Drafting of the manuscript: Shuffrey, Firestein, Kyle, Fields, Barbosa, Hu, Marsh, Dumitriu.
Critical revision of the manuscript for important intellectual content: Shuffrey, Firestein, Kyle, Alcántara, Amso, Austin, Bain, Bence, Bianco, Fernandez, Goldman, Gyamfi-Bannerman, Hott, Hussain, Factor-Litvak, Lucchini, Mandel, Marsh, McBrian, Mourad, Muhle, Noble, Penn, Rodriguez, Sania, Silver, O'Reilly, Stockwell, Tottenham, Welch, Zork, Fifer, Monk, Dumitriu.
Statistical analysis: Shuffrey, Firestein, Kyle, Austin, Factor-Litvak, Lucchini, Sania.
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Supervision: Amso, Bain, Goldman, Hussain, Factor-Litvak, Lucchini, Penn, Fifer, Dumitriu.

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