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SARS-CoV-2 infection during pregnancy and neurodevelopmental outcomes in early childhood

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SARS-CoV-2 infection in pregnancy has become common, yet very little is known about the impact of prenatal exposure on child development. Our objective was to examine the impact of infection with SARS-CoV-2 during pregnancy on child neurodevelopment in the first years of life. We conducted a longitudinal prospective cohort study among a diverse population of 69,987 children born January 2020-September 2021 in Northern California to members of an integrated healthcare system. Maternal SARS-CoV-2 infection during pregnancy was confirmed by polymerase chain reaction (PCR) test. All neurodevelopmental disorders (NDD) diagnosed in children by December 2023 were identified, including autism spectrum disorder (ASD), speech/language delay, and motor delay. Cox proportional hazards regression models estimated hazard ratios (HR) and 95% confidence intervals (CIs), with adjustment for maternal sociodemographic and clinical characteristics, SARS-CoV-2 vaccination status during pregnancy, and child sex. A total of 2777 (3.97%) pregnant individuals had PCR-confirmed SARS-CoV-2 infection during pregnancy. Among 69,987 children aged 27–48 months, 12,006 (17.15%) were diagnosed with NDD; 2724 (3.89%) with ASD, 10,047 (14.36%) with speech/language delay, and 2716 (3.88%) with motor delay. Maternal infection with SARS-CoV-2 during pregnancy was not associated with an increased risk of speech/language delay or motor delay but was associated with an elevated risk of ASD among females (aHR = 1.44, 95% CI 1.05–1.97) but not males (aHR = 1.04, 95% CI 0.83–1.31). Prenatal exposure to SARS-CoV-2 infection may increase risk for autism spectrum disorders among females. Future studies are needed to confirm and extend these findings.

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INTRODUCTION

Very little is known about the impact of SARS-CoV-2 infection during pregnancy on offspring neurodevelopmental outcomes. Preliminary evidence suggests that SARS-CoV-2 can infect and alter the physiology of the placenta, raising the possibility of impacts on fetal development [1–3]. However, early studies examining association have had mixed results [4–9]. While some studies reported neurodevelopmental risks measured with various screening tools [8, 9] or diagnoses in young infants [6, 7], no studies have evaluated associations with neurodevelopmental disorder (NDD) diagnoses in children older than 18 months of age which is well before the median age of diagnosis of autism spectrum disorder (ASD) in U.S [10].

Prenatal infections with viruses and other infectious agents have been linked to increased risk of NDD [11–14] and are hypothesized to impact fetal brain development via maternal immune activation (MIA) [15]. Although in some cases direct fetal infection with a viral pathogen, such as Zika virus [16], may lead to the development of NDD, MIA resulting from maternal viral infection or other immune insult during pregnancy may have detrimental effects on child neurodevelopment [17–21]. Further, studies have demonstrated that risks of adverse neurodevelopmental outcomes associated with maternal prenatal infection differ by trimester of exposure [22]. The known differences in maternal immune system function by fetal sex [23–25] may play a role in the noted sex differences in prevalence and symptomatology of NDD [26, 27]. However, only one study to date has examined sex-specific associations between prenatal SARS-CoV-2 infection and offspring NDDs [6].

In the current study, we examined the impact of infection with SARS-CoV-2 during pregnancy on child neurodevelopment in the first four years. We linked electronic health records (EHR) of all individuals who received healthcare from a large integrated healthcare system and were pregnant early in the COVID-19 pandemic to their child's EHR to investigate risks of specific neurodevelopmental outcomes by timing of SARS-CoV-2 infection during pregnancy and child sex.

MATERIALS AND METHODS

Participants

This longitudinal prospective cohort study was set within Kaiser Permanente Northern California (KPNC), an integrated health care system serving over 4.5 million health plan members living in the San Francisco and Sacramento metropolitan areas and surrounding counties. The sociodemographic profile of the KPNC membership is similar to the local and state-wide California population, though the extremes of the income distribution are underrepresented [28]. The study population was selected from all individuals who were members of KPNC, in any stage of pregnancy

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in 2020, and delivered a liveborn baby at a KPNC hospital who had KPNC membership after 3 months of age (N = 69,987). This study was approved by the KPNC Institutional Review Board, which waived the requirement for informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

SARS-CoV-2 infection

SARS-CoV-2 infection during pregnancy was ascertained from the SARS-CoV-2 polymerase chain reaction (PCR) test results recorded in the maternal KPNC EHR during pregnancy. Pregnant individuals with a positive SARS-CoV-2 PCR test anytime between the last menstrual period and the date of delivery were considered to have been infected with SARS-CoV-2. At KPNC, SARS-CoV-2 PCR testing started in March 2020 but was limited to symptomatic individuals. Testing was expanded to asymptomatic individuals in April 2020, and to all individuals who were admitted for delivery beginning December 1, 2020. PCR-testing was recommended for all patients who tested positive using home rapid antigen test kits. Pregnant individuals who did not have a positive SARS-CoV-2 PCR test recorded in their EHR during pregnancy were considered COVID-19 negative. This included individuals who had a negative SARS-CoV-2 PCR test (N = 33,793) and those who were never tested (N = 33,417).

Child neurodevelopmental disorders

All children with the following International Classification of Diseases 10th Revision (ICD-10) [29] diagnoses recorded in their EHR from 3 months after birth through December 2023 were considered to have a NDD: intellectual disability (F70-F79), speech/language delay (F80), learning disorder (F81), motor delay (F82), autism spectrum disorder (ASD) (F84.0, F84.5, F84.8, F84.9), and other developmental disorders (F84.2, F84.3, F88, F89). As standard of care, KPNC implements a universal child developmental screening program using the Developmental Milestones Questionnaire from the validated Survey of Well-Being of Young Children (SWYC) [30] at the 18-month well-child visit and The Parent's Observation of Social Interactions (POSI) [31] at the 18- and 24-month well-child visit. Most children who screen positive for developmental or ASD concerns undergo a secondary screening using the Ages and Stages Questionnaire (ASQ) [32] and the Modified Checklist for Autism in Toddlers—Revised with Follow-up (MCHAT-R/F) [33]. Children with developmental concerns following screening are referred to Developmental Behavioral Pediatrics or an ASD Evaluation Center for further assessment and diagnosis. Children referred to a KPNC ASD evaluation center are assessed by a multidisciplinary team using a standardized protocol, including the Autism Diagnostic Observation Schedule [34]. At the time of child outcome data extraction (December 31, 2023), children were between 27–48 months of age.

Covariates

We considered factors shown in previous studies to be significantly associated with SARS-CoV-2 infection or NDD risk as potential covariates. These included maternal age at delivery, parity, race, ethnicity, type of health insurance, non-COVID-19 infection, asthma, allergy, autoimmune disease, gestational diabetes (GDM), obesity, hypertension, preeclampsia, and depression which were identified from maternal inpatient and outpatient EHR. Child characteristics were extracted from the child EHR and included child sex, birthweight, gestational age, plurality, Apgar score, number of well-child visits, and month and year of birth (Table 1). We also extracted information on maternal COVID-19 vaccination status during pregnancy from the maternal EHR, which integrated information from vaccinations received inside as well as outside the health plan.

Statistical analyses

We compared maternal and child characteristics between SARS-CoV-2 positive and negative pregnancies, and between children with and without NDD using chi-square statistics for categorical variables and t-tests for continuous variables. We ran Cox proportional hazards regression models to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for any NDD and separately for ASD, speech/language delay, and motor delay, associated with maternal SARS-CoV-2 infection during pregnancy. Outcome groups were not mutually exclusive. Children were followed from 3 months of age until the date of the first NDD diagnosis (or first ASD, speech/language delay, or motor delay diagnosis for each outcome specific model), the date they left the KPNC health system, death, or December 31, 2023, whichever occurred first. Marginal Cox models with a cluster term at the maternal level and robust standard errors were used to account for correlated observations (i.e., multiple births per pregnancy). To evaluate the association between maternal SARS-CoV-2 infection in pregnancy and child NDD, a series of multivariable models were run for each outcome. Model 1 included adjustment for sociodemographic characteristics (maternal age, race/ethnicity, insurance type; and child sex). Model 2 included additional adjustment for maternal clinical conditions during pregnancy (asthma, allergy, autoimmune disease, depression, GDM, non-COVID infection, preeclampsia, hypertension, pre-pregnancy obesity). Model 3 included additional adjustment for maternal COVID-19 immunization during pregnancy. Since child birthweight and gestational age may be on the causal pathway between maternal SARS-CoV-2 infection and child NDD, we conducted a mediation analysis to estimate the proportion of the association of SARS-CoV-2 infection mediated by child birthweight and gestational age [35]. We applied the SAS %MEDIATE macro which uses the difference method to compute the mediation proportion in a Cox model, where the mediation proportion is defined as the natural indirect effect divided by the total effect [36].

To assess whether associations between maternal COVID-19 infection during pregnancy and child outcomes differed by child sex or timing of infection, we conducted the same series of multivariable Cox regression analyses stratified by 1) child sex, and 2) trimester of SARS-CoV-2 infection (Trimester 1[T1] = LMP–90 days; T2 = 91–180 days; T3 = 181–delivery date). To test for effect modification by child sex or trimester of infection, we included two-way interaction terms. As sensitivity analyses, we repeated the above analyses after excluding mothers who, a) received any COVID-19 immunization during pregnancy (N = 8722), and b) did not have a COVID PCR test during pregnancy (N = 33,417). To address a potential bias in the ascertainment of NDDs resulting from confounding by healthcare seeking behavior, we conducted additional sensitivity analyses adding the Kotelchuck index, a standard measure of the adequacy of prenatal care utilization, to the fully adjusted models [37]. All P values were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

The study population was diverse with respect to maternal age (11.1% <25, 63.9% 25–34, 24.9% 35 +), maternal race/ethnicity (25.6% Asian, 6.5% Black, 27.3% Hispanic, 34.6% White, 6% Other/Unknown), type of insurance (86.7% commercial, 11.3% government, 2% unknown), and parity (40% primiparous, 60% multiparous) (Table 1). A total of 2777 (3.97%) pregnant individuals had a PCR-confirmed SARS-CoV-2 infection during pregnancy (20% first trimester, 29% second trimester, 51% third trimester). Most infections occurred when the Wuhan strain was dominant in the US population (Mar 2020-May 2021) (90.3%). Only 12.5% of pregnant individuals received the COVID-19 vaccine during pregnancy. Compared with uninfected individuals, those with SARS-CoV-2 infection during pregnancy were more likely to be <25 years of age at delivery, Hispanic, on government health insurance, and multiparous. COVID-19 infected individuals were also more likely to have been diagnosed during pregnancy with pre-eclampsia, pre-pregnancy obesity, hypertension, asthma, infections other than COVID-19, and depression. Children born to COVID-19 positive individuals were more likely to have low birthweight and be born from December 2020-September 2021 (Table 1). The ratio of well-child visits to years of follow-up was similar between children with and without prenatal exposure to COVID-19 (Mean (SD): 5.97 (3.21) vs. 5.87 (3.19), $P = 0.09$).

A total of 12,006 (17.15%) children were diagnosed with NDD; 2724 (3.89%) with ASD (83% at a KPNC ASD Evaluation Center), 10,047 (14.36%) with speech/language delay, 2716 (3.88%) with motor delay, 736 (1%) with other developmental disorders, and 3084 (4.41%) with more than one diagnosis (Table 2). The age at first diagnosis for each outcome is shown in Fig. 1.

Compared to children without NDD, children with NDD were more likely to have a mother who was > = 35 years at delivery, non-White, primiparous, and have government health insurance (eTable 1). All recorded maternal medical conditions during pregnancy were significantly more common among children with NDD.

SARS-CoV-2 infection during pregnancy was not associated with increased risk for all NDD diagnoses combined after adjustment

Table 1. Characteristics of study population by maternal SARS-CoV-2 infection status during pregnancy, children born January 2020-September 2021 at Kaiser Permanente Northern California.

Characteristic	All (N = 69987) n (%)	SARS-CoV-2 Infection during pregnancy (N = 2777) n (%)	No SARS-CoV-2 Infection during pregnancy (N = 67210) n (%)	P-Value
Maternal age, mean (SD), y	31.40 (5.10)	29.70 (5.31)	31.47 (5.08)	<0.0001
Maternal age				<0.0001
<20	1153 (1.65)	78 (2.81)	1075 (1.60)	
20–24	6645 (9.49)	458 (16.49)	6187 (9.21)	
25–29	18209 (26.02)	917 (33.02)	17292 (25.73)	
30–34	26546 (37.93)	834 (30.03)	25712 (38.26)	
35–39	14771 (21.11)	421 (15.16)	14350 (21.35)	
40+	2663 (3.80)	69 (2.48)	2594 (3.86)	
Maternal Race				<0.0001
Asian	17916 (25.60)	401 (14.44)	17515 (26.06)	
Black	4524 (6.46)	225 (8.10)	4299 (6.40)	
Hispanic	19091 (27.28)	1287 (46.34)	17804 (26.49)	
Other	2659 (3.80)	88 (3.17)	2571 (3.83)	
White	24244 (34.64)	738 (26.58)	23506 (34.97)	
Unknown	1553 (2.22)	38 (1.37)	1515 (2.25)	
Maternal Insurance Type				<0.0001
Commercial	60653 (86.66)	2205 (79.40)	58448 (86.96)	
Government	7922 (11.32)	504 (18.15)	7418 (11.04)	
Unknown	1412 (2.02)	68 (2.45)	1344 (2.00)	
Parity				<0.0001
0	28061 (40.09)	979 (35.25)	27082 (40.29)	
1	24575 (35.11)	946 (34.07)	23629 (35.16)	
2	9492 (13.56)	493 (17.75)	8999 (13.39)	
3	3065 (4.38)	182 (6.55)	2883 (4.29)	
4+	1469 (2.10)	82 (2.95)	1387 (2.06)	
Unknown	3325 (4.75)	95 (3.42)	3230 (4.81)	
Maternal conditions during pregnancy				
Gestational Diabetes	7366 (10.52)	311 (11.20)	7055 (10.50)	0.2373
Preeclampsia	7761 (11.09)	343 (12.35)	7418 (11.04)	0.0306
Pre-pregnancy obesity	17762 (25.38)	1011 (36.41)	16751 (24.92)	<0.0001
Hypertension	1463 (2.09)	87 (3.13)	1376 (2.05)	<0.0001
Asthma	9321 (13.32)	440 (15.84)	8881 (13.21)	<0.0001
Allergy	13028 (18.61)	533 (19.19)	12495 (18.59)	0.4242
Autoimmune disorder	6068 (8.67)	269 (9.69)	5799 (8.63)	0.0521
Infection (other than COVID)	41584 (59.42)	1862 (67.05)	39722 (59.10)	<0.0001
Depression	7646 (10.92)	345 (12.42)	7301 (10.86)	0.0098
Plurality				0.7500
Singleton	68131 (97.35)	2706 (97.44)	65425 (97.34)	
Multiple[a]	1856 (2.65)	71 (2.56)	1785 (2.66)	
Gestational age, mean (SD), weeks	39.08 (1.75)	38.92 (1.79)	39.09 (1.75)	<0.0001
Gestational Age				0.0798
<35 weeks (early preterm)	888 (1.27)	43 (1.55)	845 (1.26)	
35–37 weeks (preterm)	4476 (6.40)	205 (7.38)	4271 (6.35)	
>=38 weeks (term)	64621 (92.33)	2529 (91.07)	62092 (92.39)	
Missing	2 (0.00)	0 (0.00)	2 (0.00)	
Birthweight, mean (SD), g	3329.1 (551.2)	3322.7 (564.8)	3329.4 (550.7)	0.5358
Birthweight				0.0392
<1500 gm (very low bwt)	505 (0.72)	20 (0.72)	485 (0.72)	

Table 1. continued

Characteristic	All (N = 69987) n (%)	SARS-CoV-2 Infection during pregnancy (N = 2777) n (%)	No SARS-CoV-2 Infection during pregnancy (N = 67210) n (%)	P-Value
1500–2499 gm (low bwt)	3638 (5.20)	177 (6.37)	3461 (5.15)	
2500+gm (normal bwt)	65838 (94.07)	2580 (92.91)	63258 (94.12)	
missing	6 (0.01)	0 (0.00)	6 (0.01)	
APGAR score under 7				
1 min	5026 (7.18)	185 (6.66)	4841 (7.20)	0.4893
5 min	759 (1.08)	36 (1.30)	723 (1.08)	0.5091
Child Sex				0.8809
Female	34203 (48.87)	1361 (49.01)	32842 (48.86)	
Male	35784 (51.13)	1416 (50.99)	34368 (51.14)	
Child Month of Birth				<0.0001
January 2020	3109 (4.44)	0 (0.00)	3109 (4.63)	
February 2020	3051 (4.36)	0 (0.00)	3051 (4.54)	
March 2020	3322 (4.75)	0 (0.00)	3322 (4.94)	
April 2020	3235 (4.62)	10 (0.36)	3225 (4.80)	
May 2020	3353 (4.79)	6 (0.22)	3347 (4.98)	
June 2020	3313 (4.73)	12 (0.43)	3301 (4.91)	
July 2020	3687 (5.27)	45 (1.62)	3642 (5.42)	
August 2020	3517 (5.03)	54 (1.94)	3463 (5.15)	
September 2020	3462 (4.95)	73 (2.63)	3389 (5.04)	
October 2020	3526 (5.04)	69 (2.48)	3457 (5.14)	
November 2020	3237 (4.63)	105 (3.78)	3132 (4.66)	
December 2020	3086 (4.41)	198 (7.13)	2888 (4.30)	
January 2021	3139 (4.49)	241 (8.68)	2898 (4.31)	
February 2021	2950 (4.22)	247 (8.89)	2703 (4.02)	
March 2021	3419 (4.89)	271 (9.76)	3148 (4.68)	
April 2021	3308 (4.73)	257 (9.25)	3051 (4.54)	
May 2021	3517 (5.03)	251 (9.04)	3266 (4.86)	
June 2021	3480 (4.97)	231 (8.32)	3249 (4.83)	
Child Month of Birth				<0.0001
July 2021	3512 (5.02)	228 (8.21)	3284 (4.89)	
August 2021	3597 (5.14)	275 (9.90)	3322 (4.94)	
September 2021	3167 (4.53)	204 (7.35)	2963 (4.41)	

Table 2. Distribution of child neurodevelopmental outcomes.

Child Neurodevelopment Status	All (N = 69987) n (%)
Any Neurodevelopmental Disorder	12006 (17.15)
Autism Spectrum Disorder	2724 (3.89)
Speech/language Delay	10047 (14.36)
Motor Delay	2716 (3.88)
Learning Disorder	12 (0.02)
Intellectual Disability	8 (0.01)
Other Developmental Disorder	716 (1.02)
More than one (ASD, S/L, Motor)	3084 (4.41)

for maternal sociodemographic characteristics (Model 1: aHR = 1.03 (95% CI 0.94–1.13)). Additional adjustment for maternal clinical conditions during pregnancy (Model 2: aHR = 1.01 (0.92–1.11)) plus maternal COVID-19 vaccination during pregnancy (Model 3: aHR = 1.01 (0.92–1.11)) yielded similar null results (Table 3, Fig. 2). Null associations were also observed across all models for Speech/Language Delay and Motor Delay (Table 3, Fig. 2). In contrast, we observed a borderline significantly elevated HR for ASD in all models (Model 3: aHR = 1.15 (0.96–1.39)) (Table 3, Fig. 2).

Sex differences

Prenatal exposure to SARS-CoV-2 infection was associated with significantly elevated risk for ASD among females (aHR = 1.44 (1.05–1.97)) but not males (aHR = 1.04 (0.83–1.31)), interaction $P = 0.10$, and a significantly lower risk for motor delay in males (aHR = 0.73 (0.53–1.00)) than in females (aHR = 1.11 (0.84–1.45)), interaction $P < 0.05$). Prenatal exposure was not associated with risk for Speech/Language Delay in either sex (Fig. 2, eTable 2.)

Trimester of infection

A suggested elevated risk for ASD was associated with maternal SARS-CoV-2 infection in the first (aHR = 1.45 (0.99–2.12)) and second (aHR = 1.29 (0.93–1.79)) but not third (aHR = 0.98 (0.75–1.29)) trimester, but there was no evidence that trimester-specific risk estimates were significantly different (interaction $P = 0.25$). Risk for motor delay differed by trimester of infection (interaction $P = 0.05$), with a suggestive elevation for first trimester exposure (aHR = 1.35

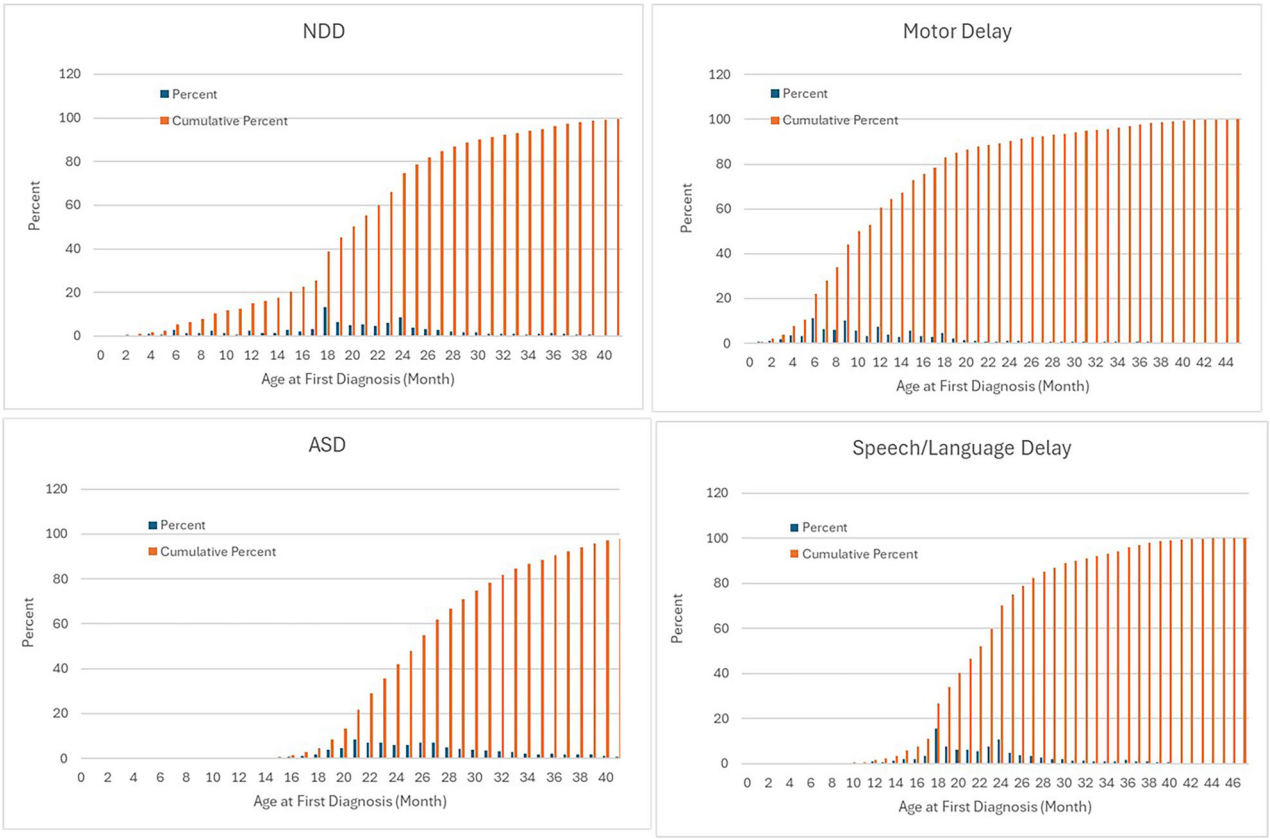

Fig. 1 Age in Months at First Diagnosis of Neurodevelopmental Disorders. NDD Neurodevelopmental disorders; ASD Autism Spectrum Disorder.

Table 3. Cox regression model results estimating adjusted associations between maternal COVID-19 infection during pregnancy in 2020 and child neurodevelopmental disorders diagnosed by Dec 31, 2023.

Child Outcome	Maternal Infection n (%)	No maternal infection n (%)	Model 1 [1] HR (95% CI)	Model 2 [2] HR (95% CI)	Model 3 [3] HR (95% CI)
No NDD	2306	55675	Ref	Ref	Ref
Any NDD	471 (16.96)	11535 (17.16)	1.03 (0.94–1.13)	1.01 (0.92–1.11)	1.01 (0.92–1.11)
ASD	119 (4.91)	2605 (4.47)	1.20 (1.0–1.45)	1.15 (0.96–1.39)	1.15 (0.96–1.39)
Speech/Language Delay	397 (14.69)	9650 (14.77)	1.03 (0.93–1.14)	1.01 (0.91–1.12)	1.01 (0.91–1.12)
Motor delay	95 (3.96)	2621 (4.50)	0.92 (0.75–1.13)	0.91 (0.74–1.12)	0.91 (0.74–1.12)

HR Hazard ratio, *CI* Confidence interval, *NDD* Neurodevelopmental Disorder, *ASD* Autism Spectrum Disorder
[1]Model 1: Adjusted for maternal age, maternal race/ethnicity, maternal insurance type, child sex.
[2]Model 2: Adjusted for all variables in Model 1plus maternal asthma, allergy, autoimmune, depression, GDM, non-COVID infection, preeclampsia, hypertension, pre-pregnant obesity.
[3]Model 3: Adjusted for all variables in Model 2 plus maternal COVID vaccine status during pregnancy.

(0.94–1.94) and suggestive inverse associations for second (aHR = 0.78 (0.51–1.17)) and third trimester exposure (aHR = 0.81 (0.59–1.09). Speech delay was not associated with infection in any trimester of pregnancy (interaction $P = 0.66$) (Fig. 3 and eTable 3**)**.

Sensitivity analyses

Analyses excluding participants who received a COVID-19 immunization during pregnancy (eTables 4–6, eFigures 1–2) or did not receive a COVID-19 PCR test during pregnancy **(**eTables 7–9, eFigures 3–4) yielded results materially identical to the main models. There was no evidence of mediation by gestational age or birthweight (eTable 10), nor of confounding by healthcare seeking behavior (eTables 11–13).

DISCUSSION

In this large and diverse Northern California study population with child follow-up to age 4, PCR-confirmed SARS-CoV-2 infection during pregnancy was differentially associated with ASD and motor delay in a sex- and trimester-specific manner. We observed an increased risk of ASD only among females, and a decreased risk of motor delay only among males. For both conditions, we observed an increased risk associated with exposure in the first trimester. In contrast, Speech/Language delay was not associated with maternal infection with SARS-CoV-2 in sex- or trimester-stratified models.

Our finding that maternal SARS-CoV-2 infection during pregnancy was not associated with all NDD combined is consistent

	COVID, n(%)	No COVID, n(%)	aHR (95% CI)
Any NDD			
All	471 (16.96)	11535 (17.16)	1.01 (0.92–1.11)
Male	291 (20.55)	7364 (21.43)	0.98 (0.87–1.11)
Female	180 (13.23)	4171 (12.70)	1.06 (0.91–1.23)
ASD			
All	119 (4.91)	2605 (4.47)	1.15 (0.96–1.39)
Male	77 (6.41)	1894 (6.55)	1.04 (0.83–1.31)
Female	42 (3.09)	711 (2.16)	1.44 (1.05–1.97)
Speech & Language Delay			
All	397 (14.69)	9650 (14.77)	1.01 (0.91–1.12)
Male	258 (18.66)	6425 (19.22)	0.99 (0.87–1.12)
Female	139 (10.53)	3224 (10.11)	1.05 (0.89–1.24)
Motor Delay			
All	95 (3.96)	2621 (4.50)	0.91 (0.74–1.12)
Male	40 (3.43)	1403 (4.94)	0.73 (0.53–1.00)
Female	55 (4.45)	1218 (4.08)	1.11 (0.84–1.45)

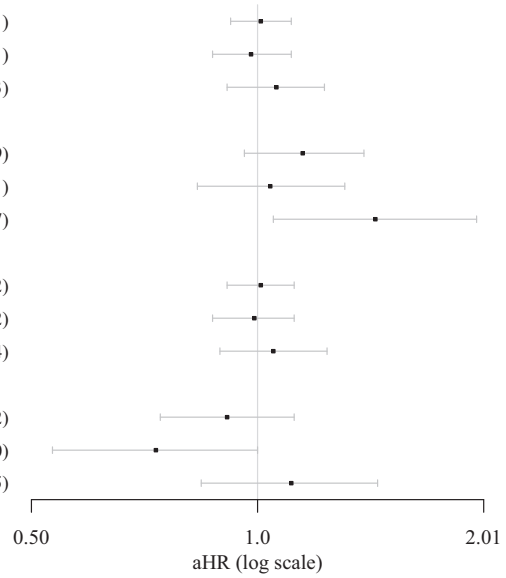

Fig. 2 Adjusted Hazard Ratios for the Association between Maternal SARS-CoV-2 Infection in Pregnancy and Neurodevelopmental Disorders by Sex of Child. NDD Neurodevelopmental disorders; ASD Autism Spectrum Disorder; COVID = SARS-CoV-2 infection during pregnancy; aHR adjusted Hazard Ratio; CI Confidence Interval. %=frequency of child outcome among COVID-19 exposed pregnancies. All models adjusted for maternal: age, race/ethnicity, insurance type, asthma, allergy, autoimmune disease, depression, GDM, non-COVID infection, preeclampsia, hypertension, pre-pregnancy obesity, and maternal COVID vaccine status during pregnancy. Models labeled 'All' additionally adjusted for sex of child.

	COVID, n(%)	No COVID, n(%)	aHR (95% CI)
Any NDD			
All	471 (16.96)	11535 (17.16)	1.01 (0.92–1.11)
T1	107 (19.18)	11535 (17.16)	1.13 (0.94–1.37)
T2	134 (16.88)	11535 (17.16)	1.01 (0.85–1.20)
T3	230 (16.14)	11535 (17.16)	0.96 (0.85–1.10)
ASD			
All	119 (4.91)	2605 (3.88)	1.15 (0.96–1.39)
T1	27 (5.65)	2605 (3.88)	1.45 (0.99–2.12)
T2	37 (5.31)	2605 (3.88)	1.29 (0.93–1.79)
T3	55 (4.40)	2605 (3.88)	0.98 (0.75–1.29)
Speech & Language Delay			
All	397 (14.69)	9650 (14.77)	1.01 (0.91–1.12)
T1	86 (16.01)	9650 (14.77)	1.09 (0.88–1.35)
T2	114 (14.73)	9650 (14.77)	1.02 (0.85–1.23)
T3	197 (14.15)	9650 (14.77)	0.97 (0.84–1.12)
Motor Delay			
All	95 (3.96)	2621 (4.50)	0.91 (0.74–1.12)
T1	30 (6.24)	2621 (4.50)	1.35 (0.94–1.94)
T2	23 (3.37)	2621 (4.50)	0.78 (0.51–1.17)
T3	42 (3.40)	2621 (4.50)	0.81 (0.59–1.09)

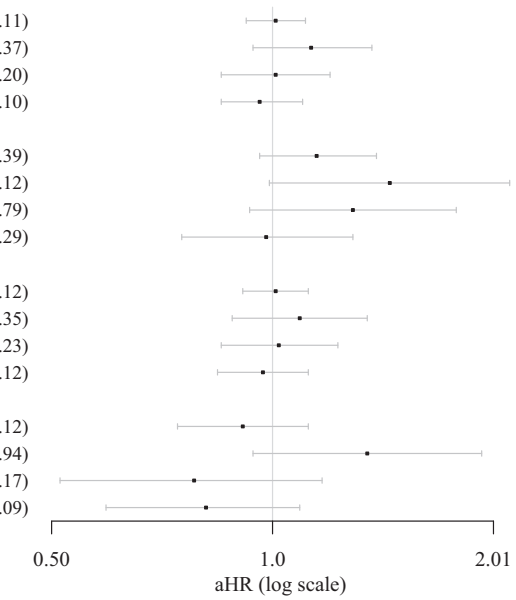

Fig. 3 Adjusted Hazard Ratios for the Association between Maternal SARS-CoV-2 Infection in Pregnancy and Neurodevelopmental Disorders in Child by Trimester of Infection. NDD Neurodevelopmental disorders; ASD Autism Spectrum Disorder; COVID = SARS-CoV-2 infection during pregnancy; aHR adjusted Hazard Ratio; CI Confidence Interval. %=frequency of child outcome among COVID-19 exposed pregnancies. All models adjusted for maternal age, maternal race/ethnicity, maternal insurance type, child sex, maternal asthma, allergy, autoimmune disease, depression, GDM, non-COVID infection, preeclampsia, hypertension, pre-pregnancy obesity, and maternal COVID vaccine status during pregnancy.

with most previous studies examining child outcomes in the first two years of life. A 2022 meta-analysis of studies of prenatally exposed children born and screened for developmental delay during the pandemic found no association with neurodevelopmental impairment at 3–12 months of age [38]. One study of 255 children born in New York City reported that scores on the ASQ-3, a general neurodevelopmental screener, at 6 months of age did not differ between those with and without

prenatal SARS-CoV-2 exposure regardless of the severity or timing of the infection during pregnancy [8]. In a study of 135 mother-infant pairs in China, late pregnancy SARS-CoV-2 was not associated with developmental delay in infants at 3 months as measured by the ASQ-3 [39]. In a study of 403 pregnancies in 3 US states, maternal SARS-CoV-2 infection during pregnancy was not associated with differences in any subdomain of infant neurodevelopment between 5–11 months of age as measured by the Developmental Assessment of Young Children, second edition (DAYC-2), a telehealth adapted observational neurodevelopmental assessment [40]. Findings were consistent across trimester and severity of maternal infection. In a cohort study of approximately 1500 children born during the pandemic, maternal SARS-CoV-2 infection during pregnancy was not associated with a positive screen on the MCHAT-R between 16–30 months [41].

By contrast, a cohort study of 7772 live births in Massachusetts found that maternal SARS-CoV-2 infection in pregnancy increased odds of NDD diagnoses recorded in child EHR by 12 months of age (aOR = 1.86, 1.03–3.36), with higher odds associated with third trimester SARS-CoV-2 infection (aOR, 2.34 [95% CI, 1.23–4.44] [7]. A subsequent study of over 18,000 livebirths confirmed this finding at 12 months (aOR = 1.94, 95% C.I. 1.12–3.17) and 18 months (aOR = 1.42, 95% CI 0.92–2.11), but only among males [6].

That risk of ASD was increased only among females in our study is consistent with our previous findings of ASD risk associated with maternal obesity and asthma during pregnancy, conditions also associated with heightened maternal inflammation [42]. In the general pregnant population, individuals carrying female fetuses exhibit increased cytokine production throughout pregnancy compared to those carrying males [23]. Such cytokines can mediate signals between the immune and nervous systems that help shape early brain development and subsequent behaviors. In the case of increased levels of inflammatory cytokines during pregnancy, studies have shown an elevated risk of ASD or other NDD outcome in children [43–45].

Sexually-dimorphic effects of gestational SARS-CoV-2 infection on immune molecules in the placenta has also been demonstrated with significant upregulation of the interferon signaling pathways in the placenta of male fetuses and downregulation of these viral protection molecules in the female placentas [46]. Sex-specific differences in genetic susceptibility to ASD have also been documented. Findings from a large study of sex differences in the heritability of autism suggest that a relatively larger portion of ASD diagnoses can be explained by additive genetic sources in males compared to females, suggesting that females could be more vulnerable to other risk factors, such as *in utero* exposure to infection and inflammation [47]. Pre-clinical animal models have also demonstrated sex-specific effects of gestational exposure to infection and inflammation on behavior and development [17, 48]. Our finding that female fetuses are more susceptible to ASD risk, and male fetuses protected from motor delay, following *in utero* exposure to SARS-CoV-2 requires replication and exploration in future studies.

Our results suggest that SARS-CoV-2 infection in early to mid-pregnancy may pose the greatest risk for adverse fetal brain development, consistent with some research prior to the COVID-19 pandemic demonstrating increased risk for ASD associated with maternal infection in the second trimester requiring hospitalization [11] or accompanied by fever [49]. However, findings across studies have been inconsistent [22], and future studies examining risk across developmentally vulnerable time periods are needed.

This study has many strengths. No cohort of this size has previously been leveraged to address the impact of COVID-19 during pregnancy on child NDD. We had comprehensive longitudinal clinical information on mothers during pregnancy and children up to four years of age, enabling examination of a range of reliably diagnosed neurodevelopmental outcomes. Information on SARS-CoV-2 infection status and child outcomes was based on objective measures recorded prospectively in EHR. This is the first study to examine impacts of *in utero* exposure to SARS-CoV-2 by child sex and trimester of infection while controlling for COVID-19 vaccination status. To our knowledge, no previous studies have followed children beyond 18 months, the earliest age at which ASD-specific screening is recommended, and ASD can be reliably diagnosed [50].

Several limitations deserve mention. Our findings could be confounded by unmeasured socioeconomic factors, such as maternal education, as well as maternal pandemic related stress. In a previous study, children born during the pandemic had significantly higher rates of neurodevelopmental delays at 6 months compared with children born before the pandemic [8]. The authors hypothesized that increased parental stress due to the pandemic might account for these findings. Our findings could also be confounded by unobserved familial factors (e.g., genetic factors or shared environment) [14, 51]. We were unable to evaluate risks for other NDD outcomes that are not reliably diagnosed by 4 years of age (e.g., attention-deficit/hyperactivity disorder; subtle delays not reaching a diagnostic threshold). We had no information on the severity of maternal infection nor on other potential prenatal inflammatory exposures such as maternal smoking or trauma. Given the lack of universal screening and testing for COVID-19, we may have under-ascertained maternal infection, however results were unchanged after removing untested individuals from analyses. Given the timing of the study, we were unable to examine risks associated with the Delta variant. Recent studies indicated the Delta variant may be more strongly associated with severe illness [52, 53]. Studies have also indicated that the Delta variant is more likely to damage the placenta and is associated with a much higher risk of stillbirth compared with other variants [54, 55]. It is possible our findings were explained by postnatal exposures, such as child SARS-CoV-2 infection or pandemic-related disruptions. Child neurodevelopmental outcomes could be influenced by early exposure to altered family social behavior during lockdown, pandemic-related social isolation, and masking. In a study of over 50,000 children visiting primary care practices in the US during the pandemic, developmental ASQ screening scores were lower than before the pandemic [56]. It is possible that prenatally exposed children were more socially isolated than unexposed children, which could explain our observed associations. Finally, due to the exploratory nature of the study, we did not correct for multiple comparisons.

CONCLUSION

Maternal SARS-CoV-2 infection during pregnancy, especially in the first or second trimester, may increase risk of ASD among female offspring. Future research, including study designs assessing familial confounding, is needed to evaluate impacts of prenatal SARS CoV-2 infection severity, SARS-CoV-2 vaccination, and SARS-CoV-2 variants, as well as pandemic related stress on neurodevelopmental outcomes including those that emerge later in childhood.

SUMMARY

In this observational study of 69,987 children aged 27 to 48 months, maternal SARS-CoV-2 infection in pregnancy was associated with increased risk of autism spectrum disorder in girls.

What's Known on This Subject:

- Very little is currently known about the impact of SARS-CoV-2 infection during pregnancy on offspring neurodevelopmental outcomes. Early studies examining the association have had mixed results, and no studies have evaluated associations in children older than 18 months of age.

What This Study Adds:

- Children with *in utero* exposure to SARS-CoV-2 may be at an increased risk of autism spectrum disorder. Future studies are needed to confirm and extend these findings.

DATA AVAILABILITY

Deidentified individual participant data will not be made available.

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AUTHOR CONTRIBUTIONS

Drs. Lisa Croen and Robert Yolken conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr. Judy Van de Water conceptualized and designed the study, critically reviewed and revised the manuscript. Dr. Yinge Qian carried out data analysis, critically reviewed and revised the manuscript. Drs. Luke Grosvenor, Stacey Alexeeff, Jennifer Ames, Paul Ashwood, and Danielle Kim critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors have indicated they have no potential conflicts of interest relevant to this article to disclose.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. This data-only study was approved by the KPNC Institutional Review Board (Protocol #1674365), which waived the requirement for informed consent from participants.

ADDITIONAL INFORMATION

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