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The association between antenatal SARS-CoV-2 exposure and infant neurodevelopment at four months of age: A prospective multicenter cohort survey within the COPE study

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ABSTRACT

Objectives: It remains unclear whether antenatal SARS-CoV-2 exposure affects subsequent infant neurodevelopment. We aimed to investigate the association between antenatal maternal SARS-CoV-2 infection and neurodevelopment in four-month-old infants.

Methods: Data was collected within the prospective multicenter COVID-19 during pregnancy and early childhood study, COPE (NCT04433364). Infants exposed to maternal SARS-CoV-2 infection from conception until two days postpartum and unexposed controls were included June 2020-December 2022.

Primary outcome: four-month-old infant neurodevelopment, measured using the Ages and Stages Questionnaire 3rd Edition (ASQ) total mean scores. Secondary outcomes: Scores below cutoff for total ASQ or the ASQ domains.

Results: Of 2453 enrolled infants, 1446 (555 exposed and 891 unexposed) had available ASQ data. In adjusted regression models, there was no group difference in ASQ total mean scores. Exposed infants had lower risk of fine motor domain scores below cutoff (exposed: 4.0% vs. unexposed: 6.6%; adjusted odds ratio (aOR), 0.55; 95% CI, 0.33-0.92). Infants exposed to severe maternal COVID-19 had increased risk of total ASQ scores below cutoff (exposed: 16.0% vs. unexposed: 6.1%; aOR, 3.57; 95% CI, 1.14-11.24).

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Conclusions: Antenatal maternal SARS-CoV-2 infection was not associated with overall impaired four-month infant neurodevelopmental screening. In exploratory analyses, severe maternal COVID-19 was associated with abnormal screening results.

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Introduction

The emergence of SARS-CoV-2 has raised new concerns about the potential effects of antenatal viral exposure on infant development [1]. SARS-CoV-2 infection during pregnancy has been associated with increased risk of severe maternal disease, preterm birth, and admission of the infant to the neonatal intensive care unit [2,3]. The virus could potentially harm the fetal brain through placental compromise, severe maternal infection, and by induction of maternal or fetal immune and inflammatory response [1,4]. Transplacental SARS-CoV-2 infection is rare but has been reported to occur in some pregnancies [5]. Altogether, this raises the concern that SARS-CoV-2 infection, similarly to other infectious and inflammatory conditions, may lead to long-term neurological adverse outcomes in the offspring [1,4].

It remains unclear if antenatal maternal SARS-CoV-2 exposure affects subsequent infant neurodevelopment. Even if most studies failed to establish a link [6–9], some reported an association [10–12]. However, many studies had small sample sizes, and some lacked well-defined data on maternal SARS-CoV-2 infection. Furthermore, two large retrospective cohort studies found an association between antenatal SARS-CoV-2 exposure and increased incidence of neurodevelopmental diagnosis, particularly in male infants at 12 months of age [13,14].

Given the conflicting results in previous studies, we aimed to investigate the association between antenatal maternal SARS-CoV-2 infection and neurodevelopment in four-month-old infants using well-defined prospectively collected data.

Methods

We employed a prospective cohort study design. Data was collected within the Swedish national multicenter COVID-19 during pregnancy and early childhood study (COPE, NCT04433364). The COPE study investigates how COVID-19 impacts pregnancy outcomes and long-term maternal and child health in Sweden [15].

Study participants

Pregnant women aged 18 years or more receiving antenatal care or giving birth at the participating hospitals were eligible for the COPE study. They were recruited by health care personnel at clinical visits during pregnancy between June 1, 2020, and December 12, 2022.

Additional eligibility criteria for this study were: 1) infants had to be liveborn and 2) the neurodevelopmental screening questionnaire had to be completed within the correct time frame specified in the manual [16]. Twenty-four Swedish maternity units and their corresponding neonatal care units participated in the recruitment for the present study (Supplementary Figure S1). Data were linked to national quality registers using Swedish personal identification numbers. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed (https://www.strobe-statement.org/, Supplementary Table S1).

Exposure definition

Infants were classified as exposed if there was a documented maternal SARS-CoV-2 infection during pregnancy. This exposure was defined by 1) either a positive SARS-CoV-2 test result (using polymerase chain reaction analysis (PCR) or antigen testing) recorded in the Swedish Register for Mandatory Registration for Notifiable Diseases (SmiNet) [15] or 2) the presence of specific diagnostic codes according to the Swedish version of the International Classifications of Diseases tenth edition (ICD-10); U07.1 or U07.2 in the Swedish Pregnancy Register [17], the National Patient Register [18] or the Swedish Intensive Care Register [15]. The timeframe for potential exposure began at the estimated conception date until two days after birth to cover the shortest mean incubation period [19]. Infants without a documented maternal infection during this time frame were classified as unexposed.

Sweden's antenatal care program achieves near-universal participation. As a high-risk group, pregnant women were advised to test and report COVID-19 symptoms to their midwife throughout the pandemic. Reporting of positive PCR and, from early 2021, antigen tests to Sminet was mandatory under the Swedish Communicable Disease Act. Testing scaled up rapidly and was widely available by June-July 2020. Hospital admission screening was introduced in early 2021 [15,20,21]. Further details on the Swedish testing strategy during the COVID-19 pandemic are available in the study protocol [15].

The severity of maternal SARS-CoV-2 infection was categorized as mild/asymptomatic vs. severe. Severe infection was defined as a cutoff score of four or above (SARS-CoV-2 infection requiring hospitalization and oxygen therapy) using the World Health Organization's seven-point ordinal scale [22]. Scores between one and three were classified as mild/asymptomatic infection. We determined trimester at onset of infection by comparing the date of infection with the gestational age (GA). Trimesters were categorized as: first trimester, from conception to less than 12 weeks; second trimester, GA 12 weeks 0 days to less than 28 weeks; third trimester, GA 28 weeks 0 days and above.

Outcomes and covariates

The primary outcome was infant neurodevelopment assessed at four months of age (between three months, zero days and four months, 30 days) by the Ages and Stages Questionnaire third edition (ASQ) and presented with mean total score with 95% confidence intervals (CI). The secondary outcomes were rates of cutoff scores 2 SD below the mean (indicating need for further assessment for neurodevelopmental impairment, please see below) for ASQ total score and in any domain.

The ASQ is a series of parent-reported developmental screening questionnaires that assess five domains: communication, gross motor, fine motor, problem solving, and personal-social, with each domain having a maximum score of 60. The cutoff score in each ASQ domain categorizes the participant as 1) "low risk," 2) "monitor" (a cutoff score more than 1 standard deviation (SD) and less than or equal to 2 SD below the mean), and 3) "refer" (a cutoff score more than 2 SD below the mean) [16]. In addition, we calculated the overall ASQ score by combining the individual domain scores

to a maximum score of 300 and established a "refer" threshold at 2 SD below the total mean score. All cutoff scores were derived using ASQ data from more than 6000 four-month-old typically developing infants from the Northern Sweden Population Health Study [23].

A web-based version of the ASQ in Swedish, English, Somali, or Arabic was sent to the birthing mother but both parents were encouraged to complete the questionnaire together. The questionnaires were distributed at four months after the expected date of birth rather than the actual date of birth. To determine if the questionnaires were completed within the eligibility window, the ASQ manual was consulted [16].

The Swedish version was created by translating the English version to Swedish and then back-translating it to English. Translations were crosschecked by a native English speaker fluent in Swedish. The ASQ is widely used globally as a developmental screening tool, has been used in several studies to assess neurodevelopment during the pandemic [24] and has previously been used in Sweden [25].

Covariates were collected from Swedish national quality registers: the Swedish Pregnancy Register and the Swedish Neonatal Quality Register [26], including maternal age, educational attainment, mother's country of birth, parity, body mass index (BMI) in early pregnancy and prepregnancy comorbidity, infant's age at ASQ completion, gestational age, APGAR score less than seven at five minutes, mode of birth, breastfeeding at four weeks, small for gestational age (Supplementary Table S2).

Study size

The size of this study was dependent on the overarching COPE study [15]. An a priori study size analysis was performed based on the ASQ four-month total mean scores from a previous Swedish cohort study [25]. The calculation assumed a two-tailed test with 80% power and a significance level of $\alpha = 0.05$. We hypothesized that antenatal SARS-CoV-2 exposure would be present in 17% of the study population as the recruitment goal for the COPE study was 200 in the SARS-CoV-2 infected and 1000 uninfected mothers. To detect a reasonable clinically relevant effect, we choose a difference of ten points in the ASQ total score between infants exposed and unexposed to this risk factor. With an assumed SD of 30, the analysis indicated a required sample size of 87 vs. 421 infants in the SARS-CoV2 exposed and unexposed groups, respectively.

Statistical methods

Group comparisons for demographic and health outcome differences were analyzed by Student's t-test, Mann Whitney U-test, or Chi-Square test, as appropriate. Means and SDs were used for normally distributed variables, medians and ranges for skewed variables, and numbers and percentages for categorical variables.

Unadjusted and adjusted mean difference (aMD) were calculated using linear regression analysis for the primary outcome ASQ total mean score. Unadjusted and adjusted odds ratios (aOR) were calculated using logistic regression for the secondary outcomes a cutoff score 2 SD below the mean for ASQ total score and in any ASQ domain.

Covariates were chosen a priori based on the available literature. The same adjusted regression models were used for all analyses. Two sets of adjusted models were presented 1) model one included infant's age at ASQ completion and demographic confounders: maternal age, educational attainment, country of birth, and parity, 2) model two additionally added maternal health-related factors: BMI in early pregnancy and prepregnancy comorbidity (any of hypertension; cardiovascular disease; pre-gestational diabetes; lung disease; and kidney disease).

A missing category was added for all covariates when missingness was greater than 2%. We assessed representativeness of those included in the analysis population by comparing clinical characteristics of mothers who completed the ASQ versus those who did not. Significance was set at $P < 0.05$. The data were analyzed using IBM SPSS Statistics (Version 29).

Exploratory analyses

For hypothesis generating purposes, we analyzed if severity and trimester of SARS-CoV-2 infection were associated with the outcomes using the same adjusted regression models as described above.

We introduced outcomes with increased sensitivity by setting cutoff points to 1 SD below the mean for ASQ total score and any domain. This approach has been suggested by the ASQ developers [27].

An interaction analysis was conducted based on the exposure and the primary outcome separated by sex of the infant.

A third regression model, model three, was created by adding covariates related to birth outcome and breastfeeding to model two described above. Model three was used in all regression analyses and additionally included gestational age, Apgar score <7 at five minutes, Cesarean section, small for gestational age, and breastfeeding at four weeks (Supplementary Table S2).

Results

Of 2,449 infants whose mothers were invited to complete the ASQ at age four months, 1446 (555 vs. 891 in the exposed vs. unexposed group) met the inclusion criteria and were included in the final analysis (Figure 1). The ASQ was completed between three months, 0 days and four months, 30 days (mean (SD) 4.06 (0.30) months, age adjusted for prematurity).

Table 1 shows demographic and health variables by study group. Infected mothers were younger (32.2 vs. 32.7 years, $P = 0.02$), more often obese (BMI ≥30: 20.0% vs. 14.3%, $P = 0.006$) and multiparous (54.2% vs. 48.5%, $P = 0.04$), had lower education level (education >12 years: 78.2% vs. 85.8%, $P < 0.001$), and were more likely to be born outside the Nordic countries (89.9% vs. 93.3%, $P = 0.03$) than uninfected mothers. There were no differences in infant birth outcomes between groups (Table 1).

Antenatal SARS-CoV-2 exposure was not significantly associated with mean total ASQ score: adjusted mean difference (aMD) for SARS-CoV-2 exposed vs. unexposed group; 2.70; 95% CI −0.44 to 5.84 (model one in Table 2). In the secondary analyses, antenatal SARS-CoV-2 exposure was associated with lower risk of having a score 2 SD below mean for fine motor function (exposed 4.0% vs. unexposed 6.6%; aOR 0.55; 95% CI 0.33 to 0.92, model one in Table 3). There were no other differences in scores 2 SD below mean observed between groups for the ASQ total score or in the remaining domains (model one in Table 3). Adding maternal health-related factors did not change the conclusions of the primary and secondary outcomes (model two in Table 2–3)

Exploratory analyses

As for the primary and secondary outcomes, the unexposed group served as the reference group for all subgroup comparisons below.

The small subgroup of infants exposed to severe maternal SARS-CoV-2 infection ($n = 25$) had higher risk of scoring 2 SD below mean for ASQ total score (exposed 16.0% vs. unexposed 6.1%; aOR 3.57; 95% CI 1.14-11.24) and in the gross motor domain (exposed 24.0% vs. unexposed 7.1%; aOR 3.82; 95% CI 1.42-10.27). In contrast,

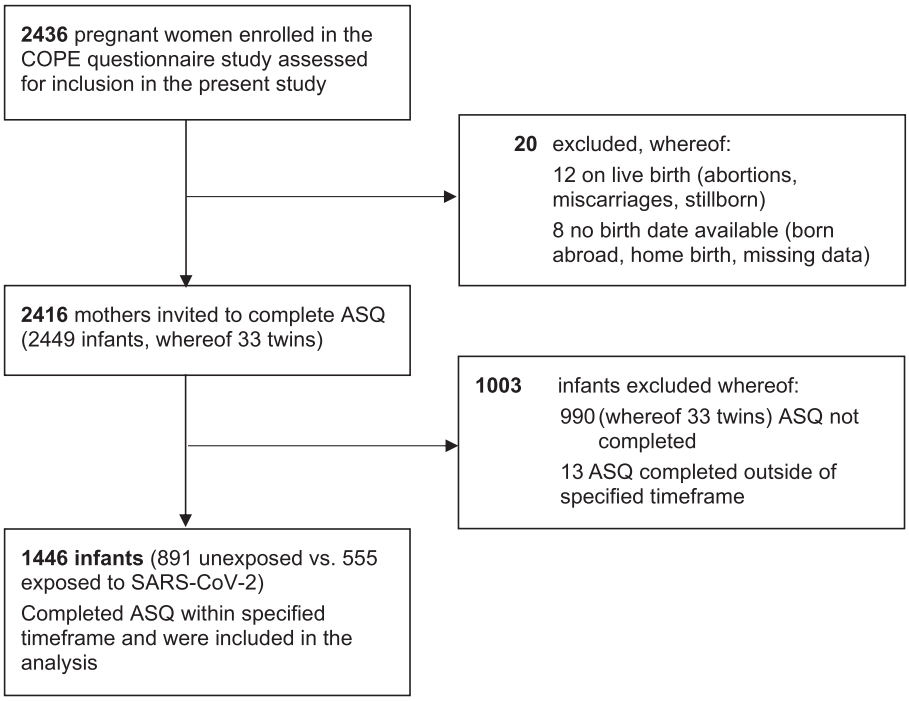

Figure 1. Flow diagram of the study population.
Abbreviations: ASQ, ages and stages questionnaire 3rd edition; COPE study, COVID-19 during pregnancy and early childhood study.

those exposed to mild or asymptomatic infection had lower risk of below-cutoff fine motor scores (exposed 3.6% vs. unexposed 6.6%; aOR 0.50; 95% CI 0.29-0.85), similar to the full group of exposed infants. Severe infection exposure was not associated with fine motor scores 2 SD below mean (exposed 12.0% vs. unexposed 6.6%; aOR 1.92; 95% CI 0.53-6.93, model two in Supplementary Table S5).

There were no associations between trimester of SARS-CoV-2 exposure and the primary and secondary outcomes (Supplementary Table S6).

Table 1
Clinical and sociodemographic characteristics and health outcomes of included mothers and infants.

Characteristics	Maternal SARS-CoV-2 status during pregnancy		*p* value
	Negative	Positive	
Mother	*n* = 891	*n* = 555	
Age at birth, y			
Mean (SD)	32.7 (4.0)	32.2 (4.0)	0.02
No. (%)			
<20	0 (0)	0 (0)	0.15
20-34	629 (70.6)	422 (76.0)	
35-39	217 (24.4)	115 (20.7)	
≥40	35 (3.9)	18 (3.2)	
Missing data	10	0	
Education >12 y, No. (%)	626 (85.8)	366 (78.2)	<0.001
Missing data	161	87	
Parity, No. (%)			
Multiparous	427 (48.5)	301 (54.2)	0.04
Multiparous with previous CS	58 (6.5)	43 (7.7)	0.83
Missing data	10	0	
Birth country, No. (%)			
Nordic	789 (93.3)	473 (89.9)	0.03
Non-Nordic Europe	30 (3.5)	21 (4.0)	
Middle East or Africa	9 (1.1)	17 (3.2)	
Other	18 (2.1)	15 (2.9)	
Missing data	45	29	
Pre-pregnancy comorbidity, No. (%)[a]	99 (11.7)	59 (11.1)	0.80
Missing data	48	24	
BMI at start of pregnancy			
Mean (SD)	25.1 (4.9)	25.9 (5.3)	0.008
No. (%)			
<18.5	12 (1.4)	8 (1.5)	0.06
18.5-<25	492 (57.9)	281 (52.9)	
25-<30	225 (26.5)	136 (25.6)	
30-<40	105 (12.4)	96 (18.1)	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Maternal SARS-CoV-2 status during pregnancy		*p* value
	Negative	Positive	
≥40	16 (1.9)	10 (1.9)	
Missing data	41	24	
Smoking at gestational week 32, No. (%)	<5 (<0.5)	0 (0.0)	0.30
Missing data	84	68	
Mode of birth, No. (%)			
Vaginal, non-instrumental	688 (78.1)	431 (77.7)	0.85
Vaginal, Instrumental	56 (6.4)	37 (6.7)	0.83
CS	137 (15.6)	87 (15.7)	0.95
Emergency CS rate, No. (% of all CS)	*98 (71.5)*	*51 (58.6)*	*0.06*
Missing data	10	0	
Breastfeeding at 4 weeks, No. (%)			
No	72 (9.2)	53 (11.2)	0.36
Partly	117 (14.9)	61 (12.9)	
Exclusively	596 (75.9)	359 (75.9)	
Missing data	106	82	
Breastfeeding at 4 months, No. (%)			
No	44 (6.0)	33 (6.7)	0.80
Previously, but not anymore	101 (13.8)	63 (12.9)	
Yes	585 (80.1)	394 (80.4)	
Missing data	161	65	
COVID-19 severity No. (%)			
Mild/asymptomatic[b]	-	530 (95.5)	
Severe[b]	-	25 (4.5)	25 (4.5)
SARS-CoV-2 infection by trimester			
Trimester 1	-	63 (11.4)	
Trimester 2	-	278 (50.1)	
Trimester 3	-	214 (38.6)	
Single parent during early pregnancy	13 (1.5)	5 (1.0)	0.47
Missing data	47	54	
Infant	$n = 891$	$n = 555$	
Sex, No. (%)			
Female	433 (49.1)	264 (47.7)	0.63
Male	448 (50.9)	289 (52.3)	
Unknown/Missing data	10	2	
Gestational age, weeks			
Mean (SD)	39.8 (1.6)	39.7(1.8)	0.43
No. (%)			
<32	<5 (<0.5)	5 (0.9)	0.26
32-<37	41 (4.6)	18 (3.2)	
≥37	847 (95.1)	532 (95.9)	
Missing data	0	0	
Birth weight g, mean (SD)	3612 (515.3)	3569 (543.1)	0.13
Large for gestational age, No. (%)	49 (5.5)	31 (5.6)	>0.99
Small for gestational age, No. (%)	23 (2.6)	11 (2.0)	0.48
Missing data	11	1	
Apgar score, median (min-max)			
1 min	9 (0-10)	9 (1-10)	0.55
5 min	10 (3-10)	10 (5-10)	0.28
10 min	10 (7-10)	10 (6-10)	0.6
Apgar score <7 at 5 min, No. (%)	7 (0.8)	7 (1.3)	0.42
Missing data	20	5	
Age at completion of ASQ, m, mean (SD)	4.05 (0.3)	4.08 (0.3)	0.05

Group comparisons analyzed by T-test, Mann-Whitney U-test or Chi2 test, as appropriate.
ASQ, ages and stages questionnaire 3rd version; BMI, body mass index; CS, cesarean section; m, months; No, number; SD, standard deviation; y, years.
[a] Pre-pregnancy comorbidity included diabetes, hypertension, cardiovascular disease, kidney disease, and lung disease.
[b] Mild/asymptomatic vs. severe maternal infection was defined as a positive SARS-CoV-2 test with vs. without inpatient care and oxygen therapy.

Additionally adjusting for birth outcomes and breastfeeding: gestational age, Apgar score, small for gestational age, cesarean section, and breastfeeding rates did not decisively change the association between prenatal SARS-CoV-2 exposure and the ASQ measures (model three in Supplementary Table S2-5).

Sex specific analyses

SARS-CoV-2 exposed female infants had higher mean ASQ total scores compared to unexposed female infants (aMD 4.50; 95% CI 0.11-8.89). There was no significant difference in ASQ total scores between exposed and unexposed male infants (aMD 0.88; 95% CI −3.65 to 5.41, model two in Supplementary Table S7).

Assessment of analysis population representativeness

We compared demographic and health variables between mothers who completed the ASQ and those who did not. SARS-CoV-2 infection rates were similar. Mothers who completed the ASQ were slightly older, more often primiparous, born in Nordic countries, had higher education level, lower Cesarean section rate, breastfed to a higher degree at four weeks postpartum, had infants with slightly higher gestational age, and fewer Apgar score <4 at five

Table 2
The association of Antenatal SARS-CoV-2 exposure with ASQ mean total scores in four-month-old infants, including stratification for severity and timing of maternal infection.

Type of maternal SARS-CoV-2 exposure	Unexposed	Exposed	Linear regression analysis: Unadjusted		Adjusted: Model 1 (adjusted for demographics)[a]		Adjusted: Model 2 (adjusted for demographics and maternal morbidity)[b]	
	Number (n) ASQ total mean score (SD)		mean difference (95% CL)	*p* value	mean difference (95% CL)	*p* value	mean difference (95% CL)	*p* value
Any infection	n=891	n=555						
	255.0 (29.7)	258.5 (29.4)	3.45 (0.32, 6.59)	0.03*	2.70 (-0.44, 5.84)	0.09	2.67 (-0.48, 5.81)	0.10
Mild or asymptomatic infection[c]		n=530						
		258.4 (28.7)	3.42 (0.34, 6.60)	0.04*	2.72 (-0.46, 5.90)	0.09	2.69 (-0.50, 5.87)	0.10
Severe infection[c]		n=25						
		259.2 (42.3)	4.23 (-7.52, 16.00)	0.48	2.22 (-9.51, 13.96)	0.71	2.17 (-9.57, 13.91)	0.72
First trimester Infection		n=63						
		258.1 (27.2)	3.09 (-4.47, 10.65)	0.42	3.49 (-3.99, 10.97)	0.36	3.27 (-4.21, 10.75)	0.39
Second trimester infection		n=278						
		259.2 (28.1)	4.23 (0.25, 8.22)	0.04*	3.18 (-0.81, 7.16)	0.12	3.17 (-0.83, 7.16)	0.12
Third trimester infection		n=214						
		257.6 (31.6)	2.55 (-1.87, 6.96)	0.26	1.85 (-2.55, 6.24)	0.41	1.84 (-2.55, 6.24)	0.41

ASQ, ages and stages questionnaire 3rd version; CL, confidence limit; No, number; SD, standard deviation.
[a] Model 1 includes maternal age, educational attainment, mother's country of birth, parity and age at ASQ completion.
[b] Model 2 includes maternal age, educational attainment, mother's country of birth, parity and age at ASQ completion, BMI in early pregnancy and pre-pregnancy comorbidity, (any of hypertension; cardiovascular disease; pre-gestational diabetes; lung disease; and kidney disease).
[c] Mild/asymptomatic vs. severe maternal infection was defined as a positive SARS-CoV-2 test with vs. without inpatient care and oxygen therapy.
* $=P < 0.05$.

Table 3
The association of antenatal SARS-CoV-2 exposure with ASQ scores 2 SD below mean in four-month-old infants.

	Antenatal exposure to maternal SARS-CoV-2		Logistic regression analysis: Unadjusted		Adjusted: Model 1 (adjusted for demographics)[a]		Adjusted: Model 2 (adjusted for demographics and maternal morbidity)[b]	
	Unexposed (n=891)	Exposed (n=555)						
ASQ domain	Scores 2 SD below mean[c], No. (%)		*Odds ratio (95% CL)*	*p* value	*Odds ratio (95% CL)*	*p* value	*Odds ratio (95% CL)*	*p* value
Communication (<36.1)	56 (6.3)	27 (4.9)	0.76 (0.48, 1.22)	0.26	0.80 (0.49, 1.29)	0.35	0.78 (0.48, 1.26)	0.31
Gross Motor (<41.6)	63 (7.1)	44 (7.9)	1.13 (0.76 1.69)	0.55	1.15 (0.76, 1.74)	0.50	1.15 (0.76, 1.73)	0.51
Fine Motor (<29.8)	59 (6.6)	22 (4.0)	0.58 (0.35, 0.96)	0.03*	0.55 0.33, 0.92)	0.02*	0.55 (0.33, 0.92)	0.02*
Problem Solving (<40.4)	78 (8.8)	42 (7.6)	0.85 (0.58, 1.26)	0.43	0.87 (0.58, 1.30)	0.49	0.87 (0.58, 1.29)	0.48
Personal Social (<32.1)	52 (5.8)	23 (4.1)	0.70 (0.42, 1.15)	0.16	0.70 (0.42, 1.16)	0.17	0.70 (0.42, 1.16)	0.17
Total score (<204.1)	54 (6.1)	29 (5.2)	0.86 (0.54, 1.36)	0.51	0.88 (0.55, 1.41)	0.60	0.87 (0.54, 1.14)	0.56

ASQ, ages and stages questionnaire 3rd version; CL, confidence limit; No, number; SD, standard deviation.
[a] Model 1 includes maternal age, educational attainment, mother's country of birth, parity and age at ASQ completion.
[b] Model 2 includes maternal age, educational attainment, mother's country of birth, parity and age at ASQ completion, BMI in early pregnancy and prepregnancy comorbidity, (any of hypertension; cardiovascular disease; pre-gestational diabetes; lung disease; and kidney disease).
[c] Indicating need for further assessment for neurodevelopmental impairment according to the ASQ manual.

minutes compared to those who did not complete it (Supplementary Table S8). These factors were all used as covariates in the regression models.

Discussion

To the best of our knowledge, this is the largest study group of infants antenatally exposed to SARS-CoV-2 that has undergone prospective neurodevelopmental follow-up. There was no difference in ASQ total mean scores in exposed compared to unexposed infants. This suggests that antenatal SARS-CoV-2 exposure was not associated with overall early infant neurodevelopmental impairment.

Our findings add to the increasing body of evidence showing no association between antenatal SARS-CoV-2 exposure and impaired neurodevelopment across the first two years of life [6–9].

In contrast, other studies have reported associations with neurodevelopmental delay [11,12], greater rate of neurodevelopmental diagnoses [14] and suboptimal neuromotor development [10] in exposed compared to unexposed infants, all at different time points during the first year of life. Some studies were limited by small sample sizes [7,10,12]. Others relied on serology or self-reporting for SARS-CoV-2 infection in some mothers [8,9] or used controls born before the pandemic [11], which might have affected data reliability.

Although most studies did not find associations with overall neurodevelopment, sex-specific differences might exist. In a retrospective cohort study of 18,335 infants, Edlow et al. found increased occurrence of neurodevelopmental diagnoses in exposed males at age 12 months. The difference persisted but was smaller and no longer significant at age 18 months [13]. The authors proposed that the sex-specific effect could be explained by higher sensitivity to maternal immune activation in the male fetal brain and by stronger immune response to SARS-CoV-2 in male placentas [13]. In our study, there was no difference in ASQ total mean scores between exposed and unexposed male infants. Instead, we found that exposed female infants had higher scores than those unexposed. Given the absence of a clear biological explanation for the improved neurodevelopmental outcome observed in exposed female infants, we consider residual confounding to be the most probable explanation. It is possible that the results of the aforementioned study diverged from ours because of differences between the study populations.

Exposure to maternal SARS-CoV-2 was associated with decreased risk of having a score below 2 SD from mean in the fine motor domain compared to unexposed infants. This finding was unexpected and might also be due to self-selection bias or residual confounding. A possible explanation is that maternal self-efficacy and mother-infant-bonding could serve as protective factors. Recent studies demonstrated that mothers with high self-efficacy who also expressed increased concerns about COVID-19-related health risks, experienced enhanced mother-infant bonding [28] and had infants with better neurodevelopmental outcome [29]. The researchers suggested that these health-related concerns might have led to greater maternal attentiveness, thereby promoting infant neurodevelopment [29]. Contrary to our results, a metanalysis by Hessami et al. found that exposed infants were at increased risk of having ASQ scores below 2 SD from mean in the fine motor domain at age three to six months [24]. The finding was based on two smaller studies with a total sample size of 390 infants, of whom 171 were exposed. Also, neurodevelopment was assessed at different time points, which might limit the interpretation. Interestingly, Firestein et al. found an association with slightly higher gross motor domain neurodevelopmental scores at age five to 11 months in infants exposed to mild maternal SARS-CoV-2 during pregnancy compared to unexposed infants [6].

Exposure to severe maternal SARS-CoV-2 infection was associated with increased risk of scoring 2 SD below mean for ASQ total score and in the gross motor domain compared to unexposed infants. This could be explained by that severe SARS-CoV-2 infection in pregnancy induces a particularly strong immune response in the pregnant woman and the offspring, which can increase the risk of long-term infant neurodevelopmental impairment even without vertical viral transmission [1,30]. Two studies reported associations between antenatal exposure to severe maternal SARS-CoV-2 infection and impaired infant neurodevelopment [11,31], whereas Shuffrey et al. did not find an association [7]. Interestingly, Hill et al. reported that elevated levels of IL-6 in mothers with severe SARS-CoV-2 infection correlated to lower communication and problem-solving scores in the infants. In the same study, infants exposed to severe maternal SARS-CoV-2 had distinct differences in DNA methylation profiles, including for genes relevant to autism and synaptic pathways [31]. All the studies above were limited by small sample sizes, which could explain the divergence in results. It is important to note that our results should be interpreted with caution since the analysis was exploratory.

Strengths and limitations

The study's strengths include its large population size, multicenter nationwide design, prospective approach, and early start of recruitment during the pandemic, which likely captured many first-time SARS-CoV-2 infections. We had access to health data from Swedish national health and quality registers, which encompass the entire pregnancy and neonatal period, with minimal loss to follow-up. This rendered the possibility to assess and control for a wide range of confounders. It also made it possible to perform robust dropout analyses. The access to the SmiNet database where all laboratory-confirmed SARS-CoV-2 cases in Sweden are reported, gave us reliable data on exposure.

This study had some limitations. First, the response rate was 60%. Mothers who completed the ASQ were more often born in Nordic countries, had higher education levels, breastfed more, had lower Cesarean section rates, and infants with better Apgar scores. These trends were observed both compared to mothers who did not complete the ASQ and compared to a nearly population-based Swedish register study conducted during the pandemic by Norman et al. [21]. This could reflect that we analyzed a healthier and more resourceful study population with better infant neurodevelopmental outcome than in the general population. Consequently, a true difference between groups might be concealed limiting the generalizability of our results. There was no difference in SARS-CoV-2 infection rates between mothers who completed vs. did not complete the ASQ. Among mothers who completed the ASQ, SARS-CoV-2–positive and –negative groups differed in BMI, education, country of origin, and maternal age. Even if we adjusted for these factors, the interplay between them and developmental outcome might be masked or confounded in the analyses, and additional unmeasured confounders might exist. It is worth noting that the differences followed a similar pattern as in other comparable studies [7–9]. Second, data that are associated with stigma, such as maternal substance abuse, risk being underreported [32] which increases the risk of residual confounding. Third, infant neurodevelopment assessed by parent-reported survey data may be subjected to bias and should not be misinterpreted as diagnostic. Still, ASQ is a widely used screening instrument with acceptable psychometric properties [11,33], and has been frequently utilized for studying infant neurodevelopment during the pandemic [24]. Fourth, there were few mothers with severe SARS-CoV-2 infection and during our study's 2.5-year recruitment period SARS-CoV-2 became less virulent and vaccines became more available. Fifth, some study participants might have been misclassified as un-

exposed, especially 1) asymptomatic mothers that might not have tested themselves or 2) the few participants recruited early and late in the study period when screening was less available. This could have attenuated a true association between maternal SARS-CoV-2 infection and subsequent infant neurodevelopment. Even so, because pregnant women were considered high risk, they were likely tested more frequently than the general population, even when screening was less available. Although maternal vaccination status was not available in our data set, Jaswa et al. found no difference in neurodevelopmental outcomes between children exposed to breakthrough infections vs. primary infections [8].

Clinical impact

The lack of group difference in ASQ total scores in the adjusted models indicates that there are no clinically important effects of antenatal SARS-CoV-2 exposure on overall early infant neurodevelopment. These reassuring results are important for the affected families as well as for clinicians and health authorities.

Our exploratory analyses suggest possible associations between antenatal exposure to severe maternal SARS-CoV-2 infection and increased risk of adverse neurodevelopmental outcome, particularly in the gross motor domain. Further studies are needed to evaluate if these infants constitute a risk group for neurodevelopmental impairment.

Finally, our results should again be interpreted with caution, since neurodevelopmental milestone assessments at four months of age are limited predictors of subsequent cognitive function [27,34]. To validate and extend our findings, large-scale prospective follow-up studies at later developmental stages are necessary. Such studies are currently planned for our study population.

Conclusion

Antenatal exposure to maternal SARS-CoV-2 infection was not associated with impaired infant neurodevelopmental screening at four months of age compared to unexposed infants.

In exploratory analysis, there was increased risk for abnormal neurodevelopmental screening scores in infants exposed to severe maternal SARS-CoV-2 infection. However, no firm conclusions can be drawn for the latter finding due to low case numbers, multiple comparisons, and the early age at which the evaluation was conducted. Follow-up studies at older ages are planned for this study population.

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Ethical approval

Before inclusion, participating pregnant women and their partners received oral and written information about the study before and provided written consent. The principles of the Declaration of Helsinki were followed, and ethical approval was obtained by the Swedish Ethical Review Authority, Sweden (Decision date: May 13, 2020; dnr 2020-02189 and amendments 2020-02848, 2020-05016, 2020-06696, 2021-00870, 2022-00260-02, 2022-01231-02).

Author contributions

VS, LB, OA and KL conceived and designed the study. All authors planned the statistical analyses. JB performed the analyses. All authors participated in interpreting the results. JB wrote the first draft of the manuscript together with MZ, KL, SA, VS and OA. All authors critically revised the manuscript for important intellectual content and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Availability of data and materials

The data underlying this article cannot be shared publicly owing to restrictions by law. The use of microdata from the national registers follows the rules and regulations of the Swedish General Data Protection Regulation (GDPR) agency. Due to data protection and privacy legislations no individual data are available.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used PerplexityAI. (2023. [Large language model] https://www.perplexity.ai) in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107973.

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