

Language development and pro-inflammatory IL-6/IL-10 imbalance in SARS-CoV-2-exposed pregnancies

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Highlights:

- **Pandemic-born infants converged at sub-normative CDI percentiles in several domains regardless of infection status.**
- **In exposed infants, IL-6/IL-10 balance predicted Difficult Verbs; counterregulation outperforms magnitude as immune index.**
- **IL-6/IL-10 tentatively associated with reduced Vocalizations in exposed girls; subgroup size limits inference.**
- **Within-group immune-language gradients without case-control differences support probabilistic over deterministic MIA effects on early language.**

Abstract

Background: Prenatal SARS-CoV-2 infection may influence early development through maternal immune activation (MIA), but its relevance for language remains unclear because pandemic-born children developed within altered communicative ecologies.

Methods: We examined parent-reported language at 18 months in 87 mother–infant dyads from a pandemic-born cohort in Cantabria, Spain (51 exposed, 36 non-exposed; child age: M = 564.5 days, SD = 31.9; 49 boys, 38 girls). MacArthur–Bates CDI percentiles were compared across six domains, and maternal log10 IL-6/IL-10 indexed pro-/anti-inflammatory balance.

Results: Exposure was not associated with global language delay after covariate adjustment, and cytokine balance did not differ by exposure status. Within exposed pregnancies, higher IL-6/IL-10 showed a correction-sensitive, model-convergent association with lower Difficult Verbs percentiles (GAM F ≈ 3.54, p

$\leq .05$; adj. $R^2 = .115$). Among exposed girls, higher IL-6/IL-10 was also associated with lower Vocalizations (GAM $F \approx 4.33$, $p \leq .05$; adj. $R^2 = .368$), although subgroup size and multiple-testing correction warrant cautious interpretation.

Conclusions: Findings do not support a uniform exposure-related language effect. Instead, prenatal immune balance may mark one conditional pathway through which early neurodevelopmental variation could become more evident under greater inflammatory burden or in interaction with susceptibility and postnatal ecology.

Keywords: Maternal Immune Activation (MIA), SARS-CoV-2, Neurodevelopment, Language Acquisition, MacArthur-Bates Communicative Development Inventory CDI.

1. Introduction

Prenatal exposure to infection has long been implicated in the etiology of neurodevelopmental disorders (NDD). Ongoing epidemiological, clinical, and preclinical evidence has increasingly supported the hypothesis that these associations are mediated not solely by the pathogen itself, but by the maternal immune response it elicits. This framework, formally articulated by Gilmore and Jarskog (1997), proposed maternal immune activation (MIA) as a cytokine-mediated pathway through which prenatal inflammatory signals may disrupt fetal brain development and confer vulnerability to later neuropsychiatric outcomes, including autism spectrum disorder (ASD) and schizophrenia spectrum disorders (SSD) ¹⁻⁹. Several viral infections, including influenza, cytomegalovirus, and Zika virus, have demonstrated clear and, in some cases, severe neurodevelopmental consequences when occurring during pregnancy. In contrast, the neurodevelopmental impact of maternal infection with SARS-CoV-2 remains incompletely understood ¹⁰⁻¹². This uncertainty reflects both the biological heterogeneity of immune responses to SARS-CoV-2 and the relatively recent onset of the COVID-19 pandemic, which has limited the availability of long-term developmental follow-up data.

The plausibility of SARS-CoV-2-related MIA influencing fetal neurodevelopment is supported by extensive evidence implicating cytokine signaling in neuronal migration, synaptogenesis, and circuit formation ¹³. Although elevated interleukin-6 (IL-6) has been linked to altered connectivity and atypical developmental trajectories, neurodevelopmental risk is unlikely to be driven by IL-6 (or any single cytokine) in isolation, particularly in the context of predominantly mild-to-moderate infection ^{14,15}. Rather, risk appears to emerge from the balance between pro- and anti-inflammatory signaling ¹⁶⁻¹⁸, with interleukin-10 (IL-10) playing a key regulatory role in constraining inflammation and maintaining immune homeostasis ^{16,17}. Accordingly, even modest inflammatory exposures may become biologically consequential when anti-inflammatory capacity is insufficient. Reflecting this perspective, recent work has emphasized the limitations of single-biomarker approaches and the value of balance- or composite-based indices that better capture the integrated gestational immune milieu ^{19,20}. Within this framework, the IL-6/IL-10 ratio provides a parsimonious, mechanistically interpretable index of cytokine balance, that has been used to characterize SARS-CoV-2 severity, and may index immune states relevant to fetal neurodevelopment ^{14,15,17}. However, biomarker-based definitions may preferentially reflect chronic or low-grade inflammation rather than acute pathogen-specific responses, a limitation heightened in viral, time-dependent immune processes where cytokine kinetics make inference highly contingent on biospecimen timing: a requirement difficult to meet in most pregnancy cohorts ²¹. The developmental impact of SARS-CoV-2-related MIA therefore remains uncertain and likely moderated by inter-individual susceptibility, including sex: males appear more vulnerable to prenatal inflammatory perturbations, whereas effects in females may be subtler or atypical and less readily detected ²²⁻²⁷. Consistent with this complexity, evidence from later developmental stages has been heterogeneous, with large longitudinal studies reporting null associations between prenatal inflammation and brain outcomes in childhood and adolescence, raising the possibility that early MIA-related alterations may partially normalize over time through developmental “catch-up” processes ^{19,21}. Rather than refuting the MIA hypothesis, these findings highlight the importance of developmental timing, measurement sensitivity, and domain-resolved developmental assessment ⁸. If MIA-related effects are most pronounced during early sensitive periods, they may be detectable only transiently or in domains that are particularly vulnerable during infancy and toddlerhood.

Language acquisition represents one such domain. As a core neurodevelopmental milestone with few viable preclinical analogues, early language development provides a uniquely informative window into emerging cognitive function ²⁸. Early linguistic abilities are robust predictors of later cognitive, social, and academic outcomes ^{29,30}. The vocabulary explosion, typically occurring between 18 and 24 months of age, marks a period of rapid representational growth and neural reorganization. Disruptions prior to or during this phase may signal underlying neurodevelopmental vulnerability ³¹. Across theoretical frameworks—including innatist, cognitivist, social-interactionist, behaviorist, statistical learning, and functionalist perspectives—language acquisition depends on the integrity of distributed neural systems supporting auditory processing, symbolic representation, social communication, and the extraction of statistical regularities from input. MIA-related perturbations could plausibly bias language development by subtly altering the maturation or coordination of these systems, even in the absence of gross structural abnormalities ³⁰. At the same time, language emergence is fundamentally experience-dependent: biologically prepared neural circuits are tuned by the quantity and quality of linguistic input during critical

and sensitive periods ^{32–37}. As a result, postnatal environmental factors may either buffer prenatal vulnerabilities or exacerbate them, constraining the degree to which typical language trajectories can be recovered when early development is disrupted ^{38–40}. Attending language is partly an unfolding biological capacity and partly a product of communicative input, SARS-CoV-2 pregnancy cohorts require a specifically ecological interpretation. Children born during the pandemic were not only potentially exposed to prenatal immune perturbation; they also acquired language within a period of altered interactional conditions as pandemic restrictions and their social consequences affected daily activities and the diversity of social and linguistic input.

Given the relatively short interval since the onset of the COVID-19 pandemic, empirical evidence on early language outcomes following prenatal SARS-CoV-2 exposure remains limited and mixed. While some studies report no significant developmental differences, others suggest subtle cognitive effects or mild delays that may not meet clinical thresholds but nonetheless reflect meaningful variation in early development ^{34,41–44}. A recent scoping review of 94 studies concluded that young children’s language-learning environments were substantially affected by COVID-19 and that studies reporting language outcomes most often converged on lower-than-expected performance across communication, vocabulary, morphosyntax, literacy-related skills, school readiness, and academic progress ³⁶. This broader pattern is also supported by early-childhood studies reporting lower vocabulary and morphosyntactic scores among pandemic-born toddlers in Spain ⁴⁵, persistent differences in word segmentation, word learning, and lexical/language-communication development through 30 months ³⁵, and links between reduced interlocutor variability and expressive vocabulary in post-pandemic children ⁴⁶. Thus, pandemic-era language ecology is not simply a background confounder; it is part of the developmental context in which prenatal immune variation may become visible—or be masked. Shared postnatal pressures could depress or reshape language trajectories in both exposed and non-exposed children, making simple case–control contrasts relatively insensitive to subtle infection-specific effects. These inconsistencies further motivate approaches that move beyond binary exposure models and instead examine developmental outcomes along continuous dimensions of immune variation. This dimensional approach is also strengthened by evidence that early language development is sex-sensitive and context-dependent. Large CDI-based cross-linguistic data show a modest female advantage in communicative gestures, productive vocabulary, and word combinations, whereas review evidence indicates that this advantage is usually small, age-dependent, and shaped by interacting biological and environmental factors ^{47,48}. During the pandemic, sex may also have operated as a marker of differential sensitivity to altered language ecology: a large Japanese study of 18-month-old children reported pandemic-associated language-development effects that were more pronounced among girls and children cared for at home ⁴⁹. This supports testing whether sex modifies the association between prenatal immune balance and early language in a disrupted communicative environment. In this context, human cohort studies focusing on early-emerging, developmentally sensitive domains are essential for clarifying the potential impact of SARS-CoV-2-related MIA. Considering the unprecedented scale of prenatal exposure during the COVID-19 pandemic, continued monitoring is warranted even following mild-to-moderate maternal infection ⁵⁰.

The present study extends our prior work with this cohort ^{51–53} by examining whether MIA related SARS-CoV-2 infection is associated with early language outcomes at 18 months of age. Adopting a dimensional framework, we investigate whether language development varies as a function of fetal sex and the gestational inflammatory milieu within this shared pandemic-era communicative context. We hypothesize that (i) children exposed to MIA due to SARS-CoV-2 will exhibit a delayed language explosion relative to non-exposed children with specific sex effects, and (ii) language-score distributions will vary with the gestational inflammatory milieu along a continuum from predominantly anti-inflammatory to predominantly pro-inflammatory, with peak performance occurring a near-equilibrium inflammatory profile.

2. Methods

2.1. Study design and participants

The COGESTCOV-19 study (INNAL20/02) recruited a total of 117 mother-infant dyads at baseline between December 1, 2020, and February 28, 2022, in Cantabria, Spain, with cases and controls matched for maternal age, parity, and estimated delivery date ^{52,53}. Participant recruitment was facilitated through the voluntary collaboration of midwives and obstetricians from the Marqués de Valdecilla University Hospital

(HUMV) and various primary care canterers across Cantabria, who informed eligible pregnant women about the study. Additional outreach was conducted via social media platforms. Inclusion criteria required that all pregnancies were singleton and resulted in live births, with no history of severe perinatal complications. Women in the exposed group had confirmed SARS-CoV-2 infection during pregnancy, verified via polymerase chain reaction (PCR) testing. The study was approved by the HUMV Review Board (approval code 2020.190) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

At 18 months of age, mothers were invited to participate in the follow-up. This study analyzed data from 87 dyads who continued participation between June 2022 and March 2024, comprising 51 infants born to SARS-CoV-2-exposed mothers (cases) and 36 to unexposed mothers (controls) (**Figure 1**).

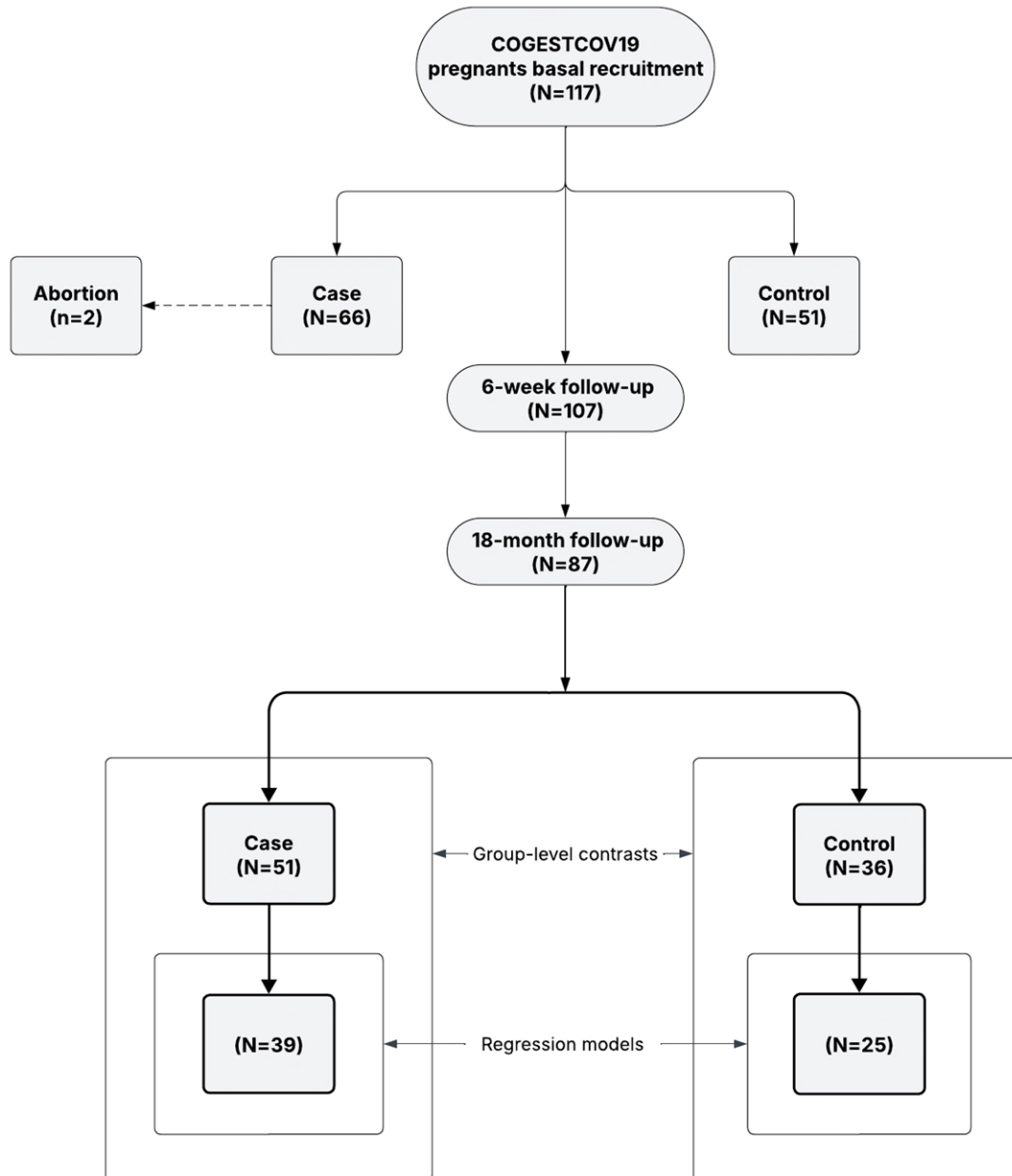


Figure 1. Flow diagram of the COGESTCOV19 cohort. At baseline, 117 pregnant women were enrolled (66 cases, 51 controls), with follow-up at 6 weeks postpartum ($n = 107$) and at child age 18 months ($n = 87$). Two analytic samples were defined at the current analytic time point: (i) a case-control comparison (51 cases, 36 controls); and (ii) a regression subset including participants with maternal blood drawn ≤ 9 weeks from the index event (SARS-CoV-2 infection for cases, $n = 39$; COVID-19 vaccination for controls, $n = 25$), with unvaccinated controls additionally included as not anchored to a specific index event.

2.2. Interviews and data collection

Maternal sociodemographic, psychological, and medical information was collected through semi-structured interviews conducted by trained clinical psychologists. Psychological assessments included: Anxiety: State-Trait Anxiety Inventory (STAI) ⁵⁴, Prenatal Stress: Prenatal Distress Questionnaire (PDQ) ⁵⁵, Life Stressors: Social Readjustment Rating Scale (SRSS) ⁵⁶, Relationship Quality: Couple Relationship Scale (CRP) ⁵⁷, Sleep Quality: Oviedo Sleep Questionnaire (COS) ⁵⁸, Pandemic-Related Anxiety: Fear of COVID-19 Scale. Postnatally ⁵⁹, Postpartum depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) ⁶⁰. Clinical data evaluated cases for symptom presence (yes/no)—including fever, cough, fatigue, myalgia, diarrhea, headache, and others—and Infection severity was classified using standard clinical criteria, distinguishing between mild cases managed at home and moderate-severe cases requiring hospitalization ⁶¹. Data on delivery outcomes, neonatal health, and birth parameters, including gestational age, Apgar scores, and birth weight and length, were retrieved from medical records.

2.3. Cytokines

Maternal venous blood was drawn at enrolment during the first prenatal interview, following confirmation of no recent non-steroidal anti-inflammatory or systemic corticosteroid use. Plasma was obtained by double centrifugation (1,500 g for 10 min at 4 °C, followed by 2,500 g for 15 min at 4 °C). Plasma aliquots were then stored at -80 °C in the Valdecilla Biobank until analysis. Interleukin-6 (IL-6) and Interleukin-10 (IL-10) concentrations were quantified using high-sensitivity ELISA kits from Enzo Life Sciences (IL-6: ENZ-KIT178-0001; IL-10: ADI-900-036), following the manufacturer's instructions. Concentrations were log-transformed prior to statistical analysis ^{52,53}.

2.4. Language assessment

At 18 months, children's language development was assessed using an online adaptation of the MacArthur-Bates Communicative Development Inventories (CDI) ^{62,63}, a parent-report instrument widely used in neurodevelopmental research. Mothers reported their child's language abilities using a structured checklist, classifying words as "understood" or "understood and spoken." CDI percentile scores were calculated based on age- and sex-normative data. Six core language measures are analyzed: *Vocabulary* (lexicon size), *MLU* (utterance length as a proxy for syntax), *Complexity* (diversity and structure of word combinations), *Vocalizations* (preverbal phonological and speech motor output), *Inflections* (morphological endings and articulation), and *Difficult Verbs* (use of higher order action verbs).

2.5. Statistical analysis

Analyses were conducted in R 4.3.2. Categorical variables were compared using Pearson's χ^2 or Fisher's exact tests and continuous variables using t tests (Welch's when appropriate), Mann-Whitney U tests, ANOVA, or ANCOVA, testing maternal-infant covariate sets (education, income; gestational age, birth weight) and, given consistent results, reporting the least-missing models to maximize sample size. Group equivalence was assessed with two one-sided tests (TOST; bounds 0.5–1.5 SD). Associations between $\log_{10}(\text{IL-6/IL-10})$ and language percentiles were modeled using GAMs and spline-based linear models. Model support was compared using AIC, BIC, RMSE, adjusted R^2 , and deviance explained ($\Delta\text{AIC} < 2$). Exploratory regression models, we report unadjusted p and increasingly stringent multiple-comparison control: false discovery rate (FDR)—the expected false-positive proportion among significant results—and family-wise error rate—the chance of ≥ 1 false positive across tests (Bonferroni); all tests were two-sided with $p < 0.05$ considered statistically significant.

3. Results

3.1. Sociodemographic, clinical and physiological characteristics

No significant differences were found between the case and control groups in maternal age, parity, or marital status. However, a significantly higher proportion of mothers in the case group had an annual income below €20,000 (64.6% vs. 25.7%, $\chi^2=12.25$, $p<0.001$), and a trend toward lower education levels was observed

($p < 0.1$). Cytokine balance concentrations showed no significant differences (**Figure 2**). Newborns exhibited optimal and comparable neonatal health parameters, with no statistical differences observed (5th-minute APGAR scores: 9.8 vs. 9.5). A trend toward higher gestational age was noted in the case group (40.18 vs. 39.59 weeks, $p < 0.1$). All case–control comparisons are presented in **Table 1**, with sex-stratified results provided in **Supplementary Table 1**.

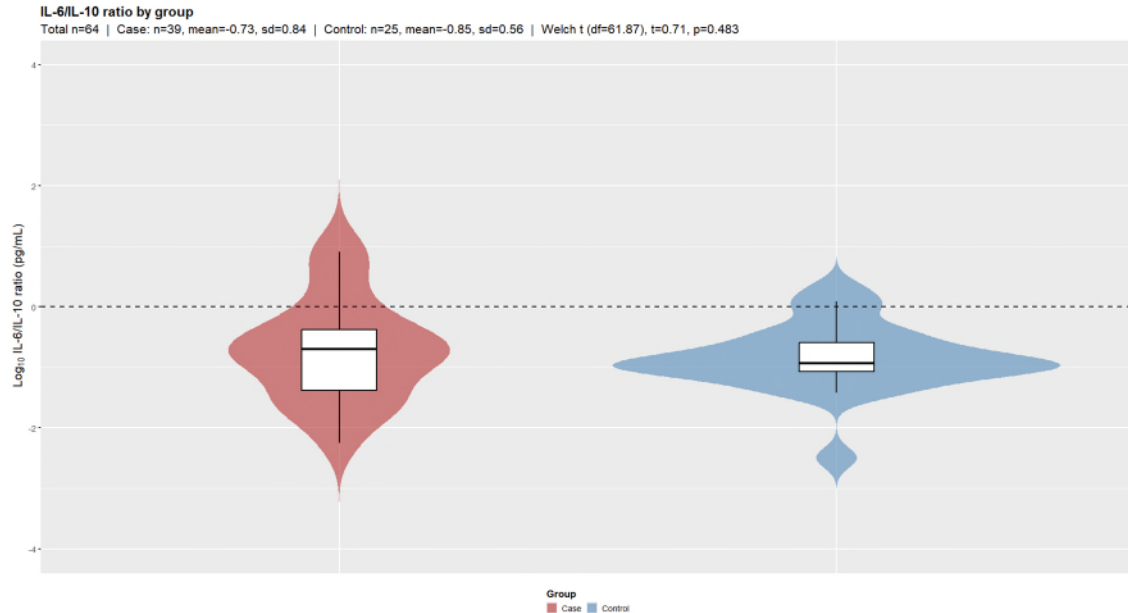


Figure 2. Violin/box plots of $\log_{10}$ IL-6/IL-10 ratio in cases ($n=39$) and controls ($n=25$), showing no significant group difference (Welch t-test $p = 0.48$). Because the ratio is plotted on a $\log_{10}$ scale, cytokine balance (raw IL-6/IL-10=1, i.e., IL-6=IL-10) corresponds to 0 on the y-axis (dashed line); values >0 indicate relative IL-6 predominance (pro-inflammatory), and values <0 indicate relative IL-10 predominance (anti-inflammatory).

Table 1. Sociodemographic, clinical and physiological baseline data comparisons from COGESTCOV19 case-control maternal-newborn dyads

	Case N = 51			Control N = 36					
	n	Mean	SD	n	Mean	SD	Statistic(df)	Value	p-value
Sociodemographic									
<i>Mother</i>									
Age (years)	51	33,69	3,72	36	34,47	3,73	t(85)	-0,969	0,335
Years of education	51	15,71	4,80	36	17,50	4,42	t(85)	-1,774	0,080
	N	n	(%)	N	n	(%)			
Married or with parther	51	49	96,1	36	34	94,4	Fisher	0,000	1,000
Anual salary (<€20k)	48	31	64,6	35	9	25,7	$\chi^2(1)$	12,248	<0.001***
Primiparous (Yes)	51	29	56,9	36	20	55,6	$\chi^2(1)$	0,015	0,904
Alcohol (Yes)	51	3	5,9	35	1	2,9	Fisher	0,018	0,643
Tabaco (Yes)	51	3	5,9	36	1	2,8	Fisher	0,026	0,639
Trimester of infection	51								
1 st	-	11	21,6	-	-	-	-	-	-
2 nd	-	25	49,0	-	-	-	-	-	-
3 rd	-	15	29,4	-	-	-	-	-	-
<i>Newborn</i>									
	n	Mean	SD	n	Mean	SD			
Gestational age (weeks)	51	40,18	0,94	36	39,59	1,75	W	1116,5	0,088
Age (days)	51	566,1	36,3	36	562,3	24,7	W	1080,5	0,162
	N	n	(%)	N	n	(%)			
Sex (male)	51	30	58,8	36	19	52,8	$\chi^2(1)$	0,314	0,662
Full term (Full term)	48	48	100,0	35	35	100,0	-	-	-
Natural birth (Yes)	48	32	66,7	35	18	51,4	$\chi^2(1)$	1,962	0,161
Clinical									
	n	Mean	SD	n	Mean	SD			
PDQ	51	22,3	8,1	36	24,7	8,5	t(85)	-1,328	0,188
SRRS	51	156,7	85,3	36	144,6	71,0	t(85)	0,698	0,487
CRP Anxiety	51	51,0	16,0	36	54,1	14,3	t(85)	-0,945	0,348
STAI-E	51	11,3	6,6	36	10,7	6,8	t(85)	0,366	0,715
COS	51	32,6	8,0	36	33,7	8,9	t(85)	-0,578	0,565
PSS	51	21,3	6,5	36	19,1	7,0	t(85)	1,503	0,136
Fear to COVID-19 scale	51	13,4	4,1	36	13,9	5,5	W	897,0	0,859
EPDS	51	5,5	3,4	36	5,2	3,1	t(85)	0,412	0,681
	N	n	(%)	N	n	(%)			
Hospitalization (yes)	51	1	1,97	-	-	-	-	-	-
Symptoms during COVID-19 (yes)	50	48	96,0	-	-	-	-	-	-

Fever (yes)	48	27	56,3	-	-	-	-	-	-
Cough (yes)	48	30	62,5	-	-	-	-	-	-
Fatigue (yes)	48	23	47,9	-	-	-	-	-	-
Muscle pain (yes)	48	23	47,9	-	-	-	-	-	-
Diarrhea (yes)	48	8	16,7	-	-	-	-	-	-
Headache (yes)	48	25	52,1	-	-	-	-	-	-
Others (yes)	48	44	91,7	-	-	-	-	-	-
Physiological	n	Mean	SD	N	Mean	SD			
<i>Mother</i>									
Weight (kg)	51	72,55	11,88	36	73,03	12,95	t(85)	-0,179	0,859
Length (cm)	51	164,00	5,92	36	164,78	6,87	t(85)	-0,565	0,574
BMI	51	27,01	4,51	36	26,89	4,39	t(85)	0,121	0,904
Postpartum systolic blood pressure	44	111,61	12,30	29	112,31	10,58	t(71)	-0,250	0,803
Postpartum diastolic blood pressure	44	68,43	8,21	29	67,14	7,57	t(71)	0,679	0,499
IL-6 (log10(pg/mL))	39	0.71	0.87	25	0.89	0.65	t W(60)	-0.904	0.370
IL-10 (log10(pg/mL))	39	1.44	1.07	25	1.74	0.3	t W(60)	-1.240	0.220
IL-6/IL-10 ratio (log10(pg/mL))	39	-0.73	0.84	25	-0.85	0.56	t W(62)	0.707	0.483
<i>Newborn</i>									
Weight (g)	48	3388.29	466.7	35	3411.57	479.33	t(81)	-0.222	0.825
Length (cm)	47	50.2447	1.757	35	50.4	2.0715	t(80)	-0.367	0.715
1st minute APGAR score	50	8,4	1,4	35	8,4	1,1	W	920,0	0,605
5th minute APGAR score	50	9,4	1,1	35	9,5	0,8	W	903,0	0,771
10th minute APGAR score	50	10	0	35	10	0	-	-	-

3.2. Early language development outcomes

CDI percentile scores were examined for six core language measures (*Vocabulary*, *LME*, *Complexity*, *Vocalizations*, *Inflections*, and *Difficult Verbs*) in case–control comparisons (**Table 2**), with additional analyses stratified by sex (**Supplementary Table 1**).

Unadjusted analyses revealed no significant case–control differences in early language development, except for *Difficult Verbs* in sex-stratified comparisons. For this measure, both case and control females outperformed case males (all $p < 0.05$). In addition, case females also outperformed control males ($M = 67.3$, $SD = 12.5$, $p < 0.05$). However, after adjustment for covariates, none of these differences remained significant. Supplementary TOST analyses reinforced statistical equivalence (**Supplementary Table 1** and **Supplementary Figure 1**).

Table 2. MacArthur CDI percentile scores: unadjusted and adjusted case–control comparisons at 18 months in the COGESTCOV19 cohort.

	Case N = 51			Control N = 36			Unadjusted		Adjusted (years of education & gestational age)		
	n	Mean	SD	n	Mean	SD	Statistic (df)	Value	p-value	Statistic (df)	p-value
<i>Vocabulary</i>	51	35,3	29,5	36	28,3	24,8	t(85)	1,155	0,251	F(1)	0,282
<i>MLU</i>	51	32,3	37,5	36	23,8	33,3	t(85)	1,078	0,284	F(1)	0,238
<i>Complexity</i>	51	32,7	26,8	36	26,5	25,0	t(85)	1,098	0,275	F(1)	0,239
<i>Vocalizations</i>	51	75,6	23,7	36	80,6	18,7	W	820,0	0,388	F(1)	0,501
<i>Inflections</i>	51	38,7	13,5	36	36,3	12,1	t(85)	0,880	0,382	F(1)	0,395
<i>Difficult Verbs</i>	51	70,4	13,8	36	67,6	10,3	W	1027,5	0,323	F(1)	0,486

3.3. Maternal immune–language associations

We modelled 18-month CDI percentiles as a function of maternal $\log_{10}(\text{IL-6/IL-10})$ using GAMs and spline-based linear models adjusted for exposure, maternal education, vaccination, and age, with comparable fit across approaches ($\Delta\text{AIC} < 2$). Most immune effects were non-significant after correction, with signal limited to two patterns: an exposure-specific non-linear association between higher IL-6/IL-10 and lower *Difficult Verbs*, and a female-specific association with lower *Vocalizations* among exposed girls, alongside a maternal-age effect. No robust IL-6/IL-10 associations were observed for *Vocabulary*, *MLU*, or *Inflections*, and IL-6/IL-10-independent case–control differences were small (**Supplementary Table 1**).

For *Difficult Verbs*, the main immune-related signal was an exposure-specific association with maternal IL-6/IL-10. In pooled case control models, the exposed group showed a nonlinear effect in the GAM ($F \approx 3.54$, $p \leq 0.05$) mirrored by the spline-based LM ($t \approx -2.52$, $p \leq 0.05$), such that higher IL-6/IL-10 in exposed pregnancies was associated with lower *Difficult Verbs* percentiles, with no comparable pattern in controls. However, these effects did not survive FDR correction (all $p > 0.05$). In sex stratified analyses, the effect was weaker but directionally consistent in girls, with an exposed specific GAM smooth ($F \approx 3.05$, $p \leq 0.05$) and only a trend in the corresponding LM ($t \approx -2.05$, $p > 0.05$), again not surviving FDR correction (**Figure 3**).

For *Vocalizations*, the main immune-related pattern suggested a female-specific vulnerability among exposed girls. In females, the GAM showed an exposed-specific IL-6/IL-10 smooth ($F \approx 4.33$, $p \leq 0.05$) indicating lower *Vocalization* percentiles at higher maternal IL-6/IL-10, although this did not survive FDR correction ($p > 0.05$) (**Figure 4**). In contrast, the spline-based LM showed an IL-6/IL-10 spline term that remained FDR significant ($t \approx -3.01$, $p \leq 0.01$; $p(\text{FDR}) \leq 0.05$), and a maternal age spline term that was also FDR significant ($t \approx 2.91$, $p \leq 0.01$; $p(\text{FDR}) \leq 0.05$).

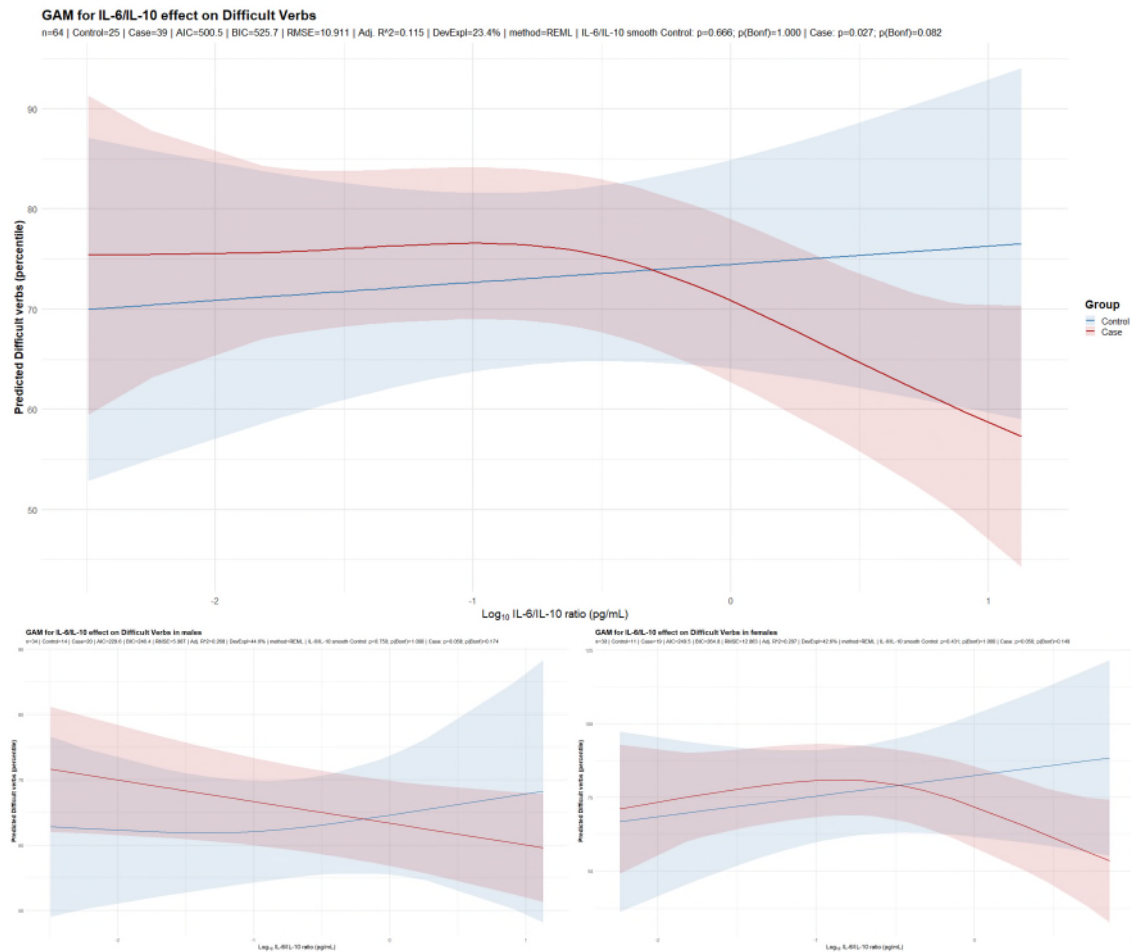


Figure 3. GAMs of *Difficult Verbs* percentile scores by $\log_{10}$ IL-6/IL-10 for cases vs controls (top) and by sex (bottom). Lines and shaded areas show fitted means and 95% CIs. Header model performance metrics: n =sample size; AIC/BIC=model fit (lower=better); RMSE=average prediction error (percentile points); adj. R² and deviance explained=variance accounted for; method=REML=estimation method. For each group, the smooth-term p tests the association between IL-6/IL-10 and *Difficult Verbs*; Bonferroni p is the multiple-comparison-adjusted value.

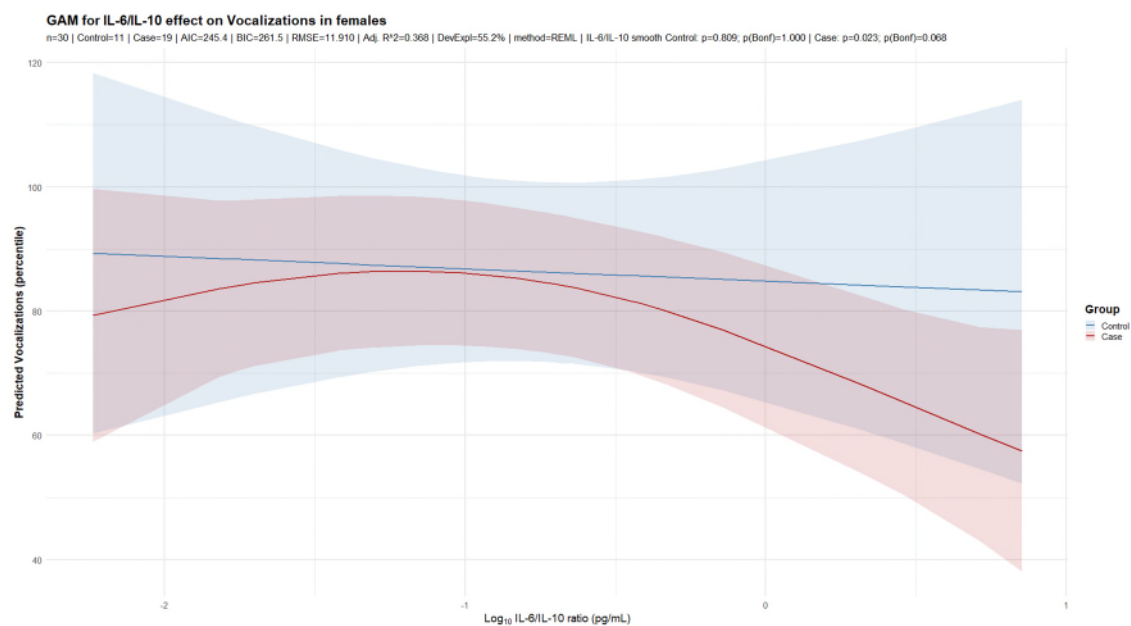


Figure 4. GAM of *Vocalizations* percentile scores by $\log_{10}$ IL-6/IL-10 ratio in females, for case and control groups. Lines and shaded areas show predicted means and 95% CIs. Model performance metrics in the header (n , AIC, BIC, RMSE, adj. R^2 , deviance explained, estimation method, and smooth-term p and Bonferroni- p values) are interpreted as in **Figure 3**.

To describe the internal structure of language skills in the regression sample, we estimated case- and control-specific partial correlations among MacArthur CDI percentiles adjusting for maternal age and education (**Figure 5**). *Vocabulary*, *MLU*, and *Complexity* formed a moderately to strongly intercorrelated cluster in both groups ($r \approx 0.38$ – 0.74 ; mostly $p \leq 0.05$), with *Vocalizations* showing modest-to-moderate correlations with this cluster ($r \approx 0.35$ – 0.60 ; often $p \leq 0.05$). Inflections correlated moderately with *Vocabulary*/*MLU*/*Complexity* in cases ($r = 0.44$ – 0.62 ; $p \leq 0.01$) but were weak and non-significant in controls ($|r| \leq 0.19$). *Difficult Verbs* showed the weakest connectivity, with only small-to-moderate associations (cases: $r = 0.34$ – 0.39 with *Vocabulary*/*Complexity*/*Vocalizations*; controls: $r = 0.40$ – 0.48 with *MLU*/*Complexity*; other pairs generally non-significant).

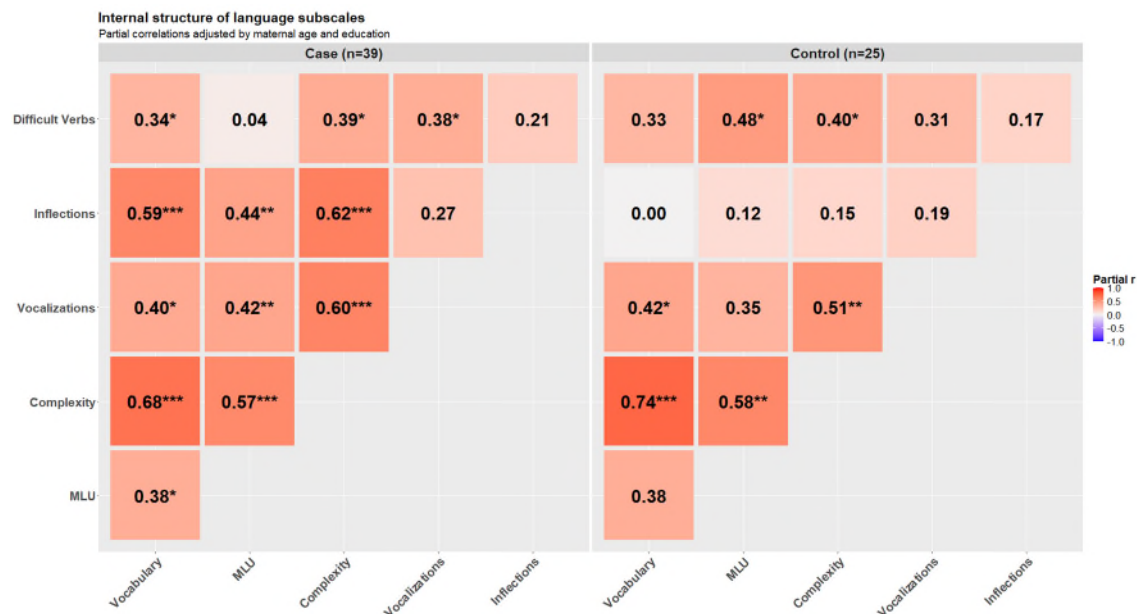


Figure 5. Partial correlations among language subscales in cases (left) and controls (right), adjusted for maternal age and education. Color indicates partial r ; asterisks denote significance ($p < .05$, $.01$, $.001$).

4. Discussion

Taken together, the findings from this study do not support a model in which mild-to-moderate maternal SARS-CoV-2 infection produces uniform, detectable language delay at 18 months. Rather, they point toward a more conditional account: one in which developmental relevance depends on the regulatory balance of the gestational immune response, the specific linguistic domain under examination, fetal sex, and the broader communicative ecology in which language emerges. The null case-control contrast and the within-group immune-language associations are not contradictory, they reflect two different levels of resolution applied to the same developmental system, and interpreting them together is necessary to extract the signal that neither alone can provide.

4.1. Early Language Development at 18 Months

Case-control differences across all six CDI domains were small, non-significant after covariate adjustment, and not sustained in sex-stratified analyses. Equivalence testing further confirmed that the null contrasts reflect genuine absence of a large group-level effect rather than insufficient statistical power to detect one. This pattern aligns with large-scale pandemic-era cohort studies reporting no substantial impact of prenatal SARS-CoV-2 exposure on early neurodevelopmental outcomes under mild infection conditions^{34,43}, and contrasts with reports of broader delays in cohorts with more severe or third-trimester-concentrated infections, or with greater sociodemographic risk^{64,65}. Overall, prenatal SARS-CoV-2 exposure, when mild

to moderate, does not produce a detectable uniform language delay assessable by parent-reported CDI at 18 months.

However, given the broader developmental context, it could be premature to infer that pandemic-era language development was unaffected solely from the absence of case-control differences. Both exposed and non-exposed children in our sample scored comparatively low percentiles for several CDI subscales relative to pre-pandemic normative expectations^{36,45}. This convergence at the lower end of the normative distribution is consistent with broader pandemic-era sociocultural factors (such as reduced opportunities for social interaction, altered caregiving routines, and changes in healthcare access) exerting diffuse pressure on early communicative environments, regardless of their prenatal infection history^{32,33,35–37,45,49,66–68}. The floor-level percentile distribution observed across both groups in this study is consistent with this shared ecological pressure and underscores that the pandemic communicative environment was not merely a background covariate but an active developmental context that may have shaped language outcomes in both groups simultaneously.

This caution also applies to sex-stratified null-findings. Under normative developmental conditions, girls show a modest but consistent early advantage in communicative gestures, productive vocabulary, and early word combinations, documented cross-linguistically across ten language communities^{47,48}. Therefore, the absence of boy-girl differences in our pandemic-born cohort should not automatically be interpreted as sex-equivalent development. It may instead reflect attenuation of an expected female advantage within a shared pandemic ecology, a possibility supported by evidence that pandemic-related language effects are stronger in girls and in children cared for exclusively at home^{46,48,49,69}. Without comparison to pre-pandemic cohorts or population-based normative benchmarks from the same geographic and socioeconomic context, sex-stratified null findings cannot be interpreted at face value.

4.2. IL-6/IL-10 balance, domain-specific vulnerability, and sex modulation

The observed immune-language associations were not distributed uniformly across CDI domains. Higher IL-6/IL-10 balance predicted lower Difficult Verbs percentiles across the Casse group, and lower Vocalizations percentiles specifically among exposed girls. Vocabulary, MLU, Complexity, and Inflections showed no comparable associations. This selectivity argues against generalized language depression and toward circuit-specific vulnerability.

That the ratio (rather than either cytokine alone) carries the signal is consistent with regulatory balance, not inflammatory magnitude, being the developmentally relevant dimension. Preclinical work has shown that insufficiently counter-regulated IL-6 signaling alters glutamatergic synapse density, disrupts microglial pruning, and perturbs frontolimbic connectivity even at moderate levels^{17,70–72}, and human neuroimaging studies link gestational IL-6 to frontolimbic white matter organization and newborn brain connectivity predictive of later working memory^{73,74}. IL-10 is not merely an attenuating marker: it actively constrains the duration and amplitude of IL-6-driven neuroinflammatory effects, and insufficient counterregulation may allow cytokine-mediated circuit perturbation to persist beyond the acute infectious period^{16,17}. One caveat applies: equivalent ratio values in exposed and unexposed pregnancies may reflect qualitatively different immune milieus. SARS-CoV-2 activates immune-programming pathways (interferon signaling, complement, placental remodeling) well beyond the IL-6/IL-10 axis^{75–77}, and the ratio should be understood as a parsimonious index within a specific infectious context, not a context-free inflammatory measure.

The two affected domains share a structural feature: both showed weak-to-moderate connectivity with the core CDI cluster of Vocabulary, MLU, and Complexity ($r \approx 0.34$ – 0.39 for Difficult Verbs in cases), consistent with indexing neurally distinct expressive systems. Difficult Verbs taps argument structure, flexible predicate use, and emerging morphosyntactic integration, capacities linked to frontotemporal and frontoparietal circuits supporting expressive syntax⁷⁸. Vocalizations indexes preverbal phonological and speech-motor output, dependent on auditory-motor and subcortical-cortical circuits involved in early phonetic tuning^{79,80}. The specificity of the immune signal to these peripheral, neurally distinct domains is interpretable as differential cytokine sensitivity of frontotemporal expressive and auditory-motor circuitry during the gestational windows represented in this cohort^{77,81}.

The female specificity of the Vocalizations finding should not be read as generalized female vulnerability, a framing inconsistent with evidence that males generally show greater susceptibility to gross MIA-related neurodevelopmental outcomes^{23,26,82,82}. It is more precisely consistent with qualitatively different susceptibility profiles by sex: males tend to show pronounced microglial activation and sensorimotor deficits following prenatal immune challenge, while females show alterations in social behavior and myelinated axon contacts, pointing to distinct target circuits rather than equivalent outcomes at different severity^{22,26,27}. In girls, the auditory-motor and socio-communicative circuitry underlying early vocalization may be specifically sensitive to the convergence of prenatal cytokine imbalance and reduced postnatal interactional input, a possibility consistent with evidence that pandemic-related language effects were stronger in girls and in home-care contexts^{46,49}, and with established context-sensitivity of early language sex differences to input diversity and interlocutor variability^{47,48}. Whether the underlying mechanism involves sex-differentiated placental immune responses⁷⁵ sex differences in microglial activation in auditory-motor circuits^{82,83}, or sex-linked timing of circuits supporting early vocal production cannot be determined from these data. Given that the effect was based on a small subgroup and was significant in only one of two statistical models, it must be treated as hypothesis-generating, but its neurobiological specificity warrants direct replication.

4.3. Implications for understanding MIA and pandemic-era influences

The null case-control contrast and the within-group immune-language associations are not inconsistent findings: they operate at different levels of resolution. Binary exposure status captures whether an infection occurred; it does not capture the regulatory quality of the immune response it triggered. That the ratio, not exposure per se, predicts domain-specific language variation is itself a finding as it indicates that one developmentally relevant dimension is the degree to which the pro-inflammatory response was counter-regulated, not the occurrence of infection. Pandemic-era controls share the postnatal communicative ecology with exposed children, which necessarily compresses between-group variance and could make binary contrasts an insufficient sensitive instrument for detecting effects that operate through immune variation within the exposed group^{43,84}. Null group contrasts should therefore not be read as refutation of MIA-related relevance, but as a methodological floor that dimensional immune analyses are designed to go below.

The specificity of the effect to exposed girls within a communicative environment that may independently reduce early vocal output in that group^{46,49}, invites a cautious interpretation grounded in developmental equifinality and risk co-occurrence. From this perspective, early language variation associated with neurodevelopmental risk may arise from distinct etiological configurations, including the possible convergence of sub-threshold prenatal immune imbalance and postnatal communicative constraints, where neither pressure would necessarily produce a detectable effect in isolation^{85–87}. Given the present sample, this interpretation should remain tentative; nevertheless, the framework may be useful for guiding future follow-up of this cohort and for evaluating whether subtle early deviations persist, resolve, or shift across developmental domains.

The broader theoretical implication is that mild gestational immune activation is unlikely to function as an independent sufficient cause of early language variation. Under the Developmental Origins of Health and Diseases framework, mild prenatal perturbations adjust developmental probabilities and circuit-level constraints rather than determining outcomes⁸⁸. The question is not whether such perturbations produce measurable deficits at 18 months (they may not) but whether they shift the probability distribution of later trajectories in ways that become visible only when environmental scaffolding is reduced, representational demands increase, or sensitive-period dynamics amplify existing biases^{89,90}. The present stage cannot resolve which trajectory is operating. At this stage, the data cannot determine which developmental trajectory is unfolding. They do, however, identify a biologically detectable signal in a theoretically coherent domain, within a cohort that remains under follow-up. Whether this signal marks the beginning of a cascade or the ceiling of the observable effect is a question for the next developmental window.

Strengths and limitations

This study has several strengths. It draws on a clinically characterized pregnancy cohort with confirmed maternal SARS-CoV-2 exposure, maternal cytokine data, and domain-resolved language assessment at a

developmentally sensitive age. By combining case-control contrasts with dimensional immune models, we were able to distinguish the absence of global exposure-related effects from more specific immune-language associations. Equivalence testing strengthened interpretation of null group contrasts, while pandemic-era controls reduced confounding by broad historical context.

Several limitations should also be acknowledged. The sample size was modest, particularly for sex-stratified models. The immune-language associations should therefore be interpreted as preliminary, especially when they did not consistently survive stringent multiple-comparison correction. Most infections were mild-to-moderate (representative of the predominant COVID-19 exposure profile) limiting generalization to severe maternal illness or other viral infections. Cytokines were measured at a single time point and were restricted to IL-6 and IL-10, providing only a partial snapshot of a dynamic gestational immune process. Because cytokine kinetics are time-sensitive, the biological meaning of the IL-6/IL-10 ratio may depend on the interval between infection, vaccination, biospecimen collection, and fetal developmental stage. Language was assessed through parent-report CDI measures at a single age. Although the CDI is widely used and developmentally appropriate, it may not capture all relevant aspects of communicative competence, especially pragmatic, phonological, or interactional features. Postnatal environmental variables central to the pandemic-language literature—such as childcare attendance, household confinement intensity, screen exposure, caregiver sensitivity, interlocutor diversity, and frequency of shared reading—were not directly modeled. This limits our ability to distinguish prenatal immune mechanisms from postnatal ecological moderation. Finally, socioeconomic differences between groups, particularly income and maternal education trends, remain relevant potential confounders despite covariate adjustment.

Future directions

Future work should determine whether the domain- and sex-specific IL-6/IL-10 associations observed at 18 months persist, normalize, or shift toward later language, cognitive, socio-emotional, or motor outcomes. Higher-resolution developmental assessment, combining digital precise domain-specific behavioral measures with functional neurophysiological indices where feasible, may help distinguish persistent developmental delay from compensatory performance or alternative developmental trajectories. Critically, comparison with harmonized pre-pandemic cohorts and clinically characterized neurodevelopmental samples will be needed to separate shared pandemic-era effects from SARS-CoV-2-specific MIA signals and to evaluate whether different combinations of prenatal immune activation, sex-linked timing, postnatal communicative ecology, transient developmental variation, and compensatory processes converge on similar domain-specific developmental outcomes.

5. Conclusions

In this pandemic-born cohort, mild-to-moderate maternal SARS-CoV-2 infection during pregnancy was not associated with global parent-reported language delay at 18 months. However, higher pro-inflammatory IL-6/IL-10 balance was linked to subtle, domain-specific reductions in expressive skills, suggesting graded, sex-modulated immune-language associations rather than a generalized MIA-related effect. These findings support a view of prenatal immune activation as a probabilistic context-dependent influence embedded within broader pandemic-related environments. Longitudinal, mechanistically oriented follow-up is needed before drawing firm conclusions about the persistence or long-term neurodevelopmental significance of these associations.

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Availability of Data

Due to ethical and privacy restrictions involving pediatric participants, the dataset is not publicly available. De-identified data may be available from the corresponding author upon reasonable request and subject to institutional and ethical approval.

Availability of Methods/material

All methodological details necessary to reproduce the study are described in the manuscript. Additional information may be obtained from the corresponding author upon reasonable request.

Competing Interests statement

The authors declare no competing interests.

Authorship contribution statement

A.D.-P. and R.A.-A. conceptualized the study. A.D.-P., C.M.-A., V.O.-G.d.l.F., and R.A.-A. curated the data. A.D.-P., S.C.-C., C.M.-A., and V.O.-G.d.l.F. developed and implemented the analytical software, performed the formal analyses, and prepared the visualizations and figures. S.C.-C. contributed to validation of the analytical approach. R.A.-A. acquired funding, provided resources, supervised the study, and administered the project. A.D.-P., S.C.-C., C.P., A.Y.-R., S.I., and R.A.-A. wrote the original manuscript draft. All authors reviewed and edited the manuscript, approved the final version, and agreed to be accountable for the content of the work.

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

During the preparation of this manuscript, the authors used ChatGPT-5 to improve the readability and language of the text. The authors subsequently reviewed and edited the resulting content and take full responsibility for the final content of the manuscript.

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