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Maternal-infant immune signatures in infants at risk for SARS-CoV-2-associated neurodevelopmental disorders

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Maternal immune activation during pregnancy has been associated with abnormal infant neurodevelopment. During the COVID-19 pandemic, we enrolled pregnant individuals with laboratory-confirmed SARS-CoV-2 infection into a cohort study conducted in Los Angeles, United States, and Rio de Janeiro, Brazil, and monitored their infants for neurodevelopmental outcomes. We reported a ten-fold higher rate of developmental delay in 172 SARS-CoV-2-exposed children (11.6%) compared to 128 pre-pandemic controls (1.6%) and a nearly 2-fold higher frequency of positive screens for autism spectrum disorder (ASD) in 218 SARS-CoV-2-exposed (10.1%) children as compared to 527 unexposed control children (5.7%) evaluated through standardized developmental tools. To identify potential biomarkers of SARS-CoV-2-associated risk of abnormal infant neurodevelopment, we evaluated the serum immunoprofiles of a subset of mother-infant dyads from this cohort. Serum proteomics profiling of 34 newborns (27 SARS-CoV-2-exposed and 7 controls) revealed 62 biomarkers dysregulated in SARS-CoV-2-exposed children at risk for neurodevelopmental disorders, including activation of nicotinamide biosynthesis, microglial cells, and neutrophil extravasation. Maternal serum profiling of 51 women (33 SARS-CoV-2-positive and 18 controls) identified 34 biomarkers associated with upregulated apoptosis signaling in COVID-19 affected pregnancies. Our findings suggest prenatal SARS-CoV-2 infection is potentially associated with dysregulation of maternal-infant peripheral immunity profiles reportedly associated with neurodevelopmental disorders.

The repercussions of SARS-CoV-2 infection during pregnancy on the developing fetal brain are yet to be determined. Converging epidemiological studies corroborated by mouse models over the past decades have implicated an interaction between maternal immune activation (MIA) and increased risk for neurodevelopmental disorders in the offspring[1–10]. Infections during pregnancy can alter brain structure and function via a direct mechanism of pathogen transfer across the placenta, causing direct injury to fetal brain cells, as seen with congenital TORCH and Zika virus pathogens. Another potential pathogenetic mechanism of brain injury would be through an indirect route, with MIA triggering an inflammatory response in the fetus, thus affecting normal brain development through the dysregulation of cytokines, triggering cellular apoptosis, and cellular damage[11]. While estimates of vertical transmission of SARS-CoV-2 are overall low[12–14], the virus has been shown to trigger a systemic inflammatory response not only in the mother but also in the fetus in our prior studies and that of others[15–17] leading to growing concerns for long-term consequences.

Although maternal immune responses are essential in fighting infections, aberrant activation of the maternal immune system can interfere with fetal central nervous system development and regulation[16,18]. Our prior analysis suggests that prenatal exposure to SARS-CoV-2 activates an inflammatory cascade in the newborn that regulates Wnt signaling expression, which is essential for brain development and function[15]. Recent studies in our cohort of mother-infant dyads and other similar cohorts have demonstrated the potential effect of SARS-CoV-2 on the development of prenatally exposed infants, with higher rates of developmental delay identified, particularly in language and motor domains[19–22].

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MIA has been associated with a potentially higher risk of neuropsychiatric conditions[23,24]. Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent impairment in social interactions and the presence of restricted, repetitive patterns of behaviors, interests, or activities (DSM-5)[25]. Maternal infection was one of the earliest suggested non-genetic risk factors for ASD[26]. The prevalence of ASD varies within and across different regions of the world; however, the global median prevalence is reported to be 100/10,000 or 1%[27]. In the US, when both term and preterm children are included, the prevalence of ASD is 1 in 36 children, or 2.8% in 2020, according to the U.S. Centers for Disease Control and Prevention[28]. The American Academy of Pediatrics (AAP) recommends universal screening for autism at 18 and 24 months of age using standardized autism-specific screening tools[29]. The most studied and widely used questionnaire-based screening tool is the Modified Checklist for Autism in Toddlers-Revised, with Follow-Up (MCHAT-R/F)[30,31].

In the present study, we investigated potential mechanistic explanations for ASD risk and developmental delay through serum proteomic signature analysis in serum specimens of patients with SARS-CoV-2 in pregnancy and their infants, prospectively evaluated for developmental delay and ASD risk[19,20]. Serum specimens were obtained from pregnant mothers and infants exposed to SARS-CoV-2 infection during pregnancy, enrolled in our COVID-19 Outcomes in Mother-Infant Pairs Study (COMP) and control unexposed children. We hypothesize that among children with developmental delay and/or positive ASD screens, proteomic markers associated with brain development are potentially altered, with changes possibly present in maternal markers, due to MIA triggered by SARS-CoV-2.

Results

Participant characteristics

Participating mother-child dyads were enrolled in the COVID-19 Outcomes in Mother-Infant Pairs (COMP) Study between March 2020 and August 2022[15,17,19,20]. As part of routine pediatric care, between January 2021 and August 2024, 218 children exposed to laboratory-confirmed maternal SARS-CoV-2 in pregnancy enrolled in the COMP study underwent screening for ASD using the MCHAT-R/F[30]. Many of these children were also previously screened for developmental delay using standardized instruments such as Bayley-III and Ages and Stages Questionnaires as previously reported[20]. MCHAT-R/F results for the SARS-CoV-2-exposed cohort were compared to those of unexposed children born between January 2016 and March 2020. These children, born before the pandemic initiated, had also undergone screening for ASD using the MCHAT-R/F as part of routine pediatric care. MCHAT screening was performed between the ages of 18 and 32 months in all children. Children with a positive screen at 18 months had repeat screening with MCHAT-R/Fon or after 24 months of age according to testing guidelines. All children with a positive screen were referred to ASD specialized diagnostic early intervention services. Among 218 SARS-CoV-2-exposed children, 22 (10.1%) had a positive score for potential ASD, while 30 (5.7%) of 527 pre-pandemic control children screened positive for ASD using MCHAT-R/F (Fig. 1). Table 1 compares clinical and demographic parameters of mother-infant pairs in the COMP study cohort to pre-pandemic control children. Children with antenatal exposure to SARS-CoV-2 were nearly twice as likely to screen positive for ASD compared to unexposed controls (10.1% vs. 5.7%, $p = 0.03$). None of the exposed infants in our study tested positive for SARS-CoV-2 at birth.

Positive MCHAT-R/F screens in antenatally exposed SARS-CoV-2 infants were associated with preterm birth (adjusted odds ratio [aOR]:1.18; 95%CI:1.02–1.37, $p = 0.03$) and being born to unvaccinated mothers prior to delivery (adjusted odds ratio [aOR]:0.92;95%CI:0.84–0.99, $p = 0.04$) as seen in Table 2. There was no significant difference in positive ASD screens among infants born to pregnant women with pre-existing maternal comorbidities, Hypertensive disorders of pregnancy (HDP), Diabetes Mellitus (DM), pre-pregnancy obesity and mental health disorders (Table 2 and Supplementary Tables 1 and 3). We did not observe an association between positive ASD screens and trimester of maternal SARS-CoV-2 infection during pregnancy, nor reported fever during pregnancy (Supplementary Table 2). In total, 95 women received COVID-19 vaccines prior to delivery of their infants, 41 were vaccinated prior to the pregnancy, and 54 during pregnancy; the vast majority received mRNA vaccines. We did not observe any differences in the frequency of maternal vaccination status when we performed a stratified analysis in infants with normal or failed MCHAT results (Supplementary Table 2), yet in the adjusted analysis, maternal vaccination prior to delivery was protective against a failed MCHAT result as seen in Table 2. Among pre-pandemic controls, the only

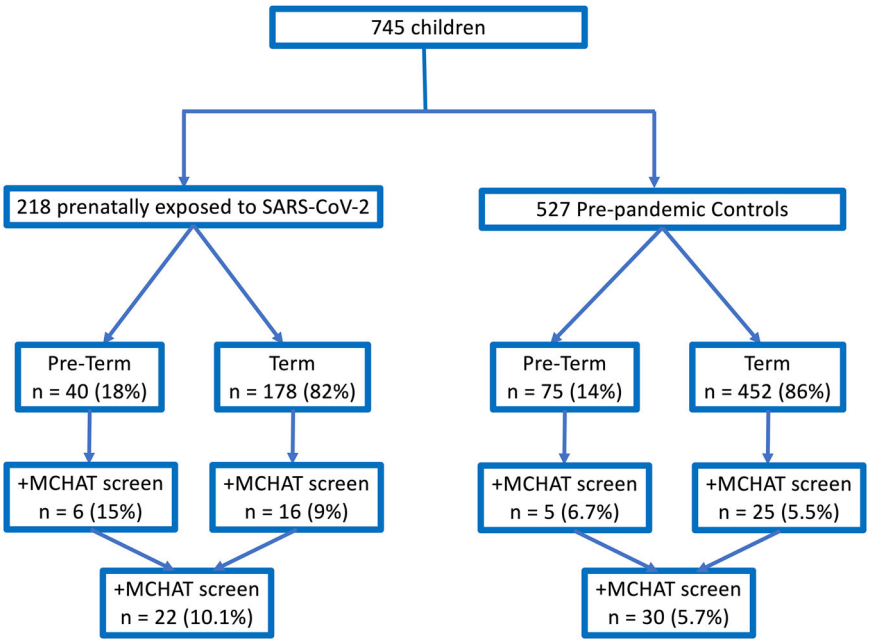

Fig. 1 | Flowchart of autism spectrum disorder (ASD) assessment in children prenatally exposed to SARS-CoV-2. Prospective cohort of infants prenatally exposed to SARS-CoV-2 ($n = 218$) underwent screening for autism spectrum disorder (ASD) using the Modified Checklist for Autism in Toddlers Revised and Revised Follow-up (MCHAT-R/F) compared to pre-pandemic control children ($n = 527$).

Table 1 | Maternal sociodemographic and clinical characteristics between cases and pre-pandemic controls

	Exposed Infants (N = 218)		Pre-pandemic Control Infants (N = 527)		P-value
	N	%	N	%	
Positive MCHAT-R/F screens or ASD diagnosis ≤3 years of age	22	10%	30	6%	0.03
Caesarean delivery	90	41%	124	24%	<0.001
Comorbidities[a]	123	56%	75	14%	<0.001
• HDP	51	23%	28	5%	<0.001
• Diabetes Mellitus (DM)	23	11%	31	6%	0.02
• Pre-pregnancy Obesity	37	17%	10	2%	<0.001
• Mental Health Disorders	34	16%	16	3%	<0.001
Maternal Age (Years) (Mean/SD)	31.1	6.3	34.0	4.6	<0.001
Infant BW (Mean/SD)	3121.3	605.5	3205.6	600.0	0.10
Low birth weight	29	13%	47	9%	0.07
Male infant	110	50%	290	55%	0.26
Preterm	40	18%	75	14%	0.16
Small for gestational age (SGA)	6	3%	16	3%	0.84
Head Circumference (HC) at birth					
• Microcephaly	24	11%	46	9%	0.01
• Normal	178	82%	466	88%	
• Macrocephaly	16	7%	15	3%	

[a]Hypertensive Disorders of Pregnancy (HDP), Diabetes Mellitus (DM) (including Gestational DM), pre-pregnancy obesity, or mental health disorders (depression, anxiety, or substance use).

non-COVID-19 risk factor associated with a positive MCHAT-R/F screen was a normal spontaneous vaginal delivery, which was protective against the outcome (adjusted OR: 0.89 (0.85, 0.93), $p < 0.001$. (Supplementary Table 1). Among infants with antenatal exposure to SARS-CoV-2, in the adjusted regression analysis, we saw that being male was associated with a slightly higher risk of a failed MCHAT-R/F result [aOR: 1.12 (95%CI:1.03, 1.22), p = 0.01], and that maternal SARS-CoV-2 vaccination prior to delivery was associated with a lower likelihood of a failed MCHAT-R/F result [aOR: 0.89 (95%CI: 0.82, 0.98), $p = 0.02$] (Table 2). Maternal comorbidities during pregnancy were not associated with a greater or lower likelihood of having a failed MCHAT screen result, with the exception of mental health disorders, which were more likely associated with a failed MCHAT-R/F screen only in the pre-pandemic control group in both the crude and adjusted regression analysis [cOR: 1.14 (95%CI:1.02, 1.28), $p = 0.02$; aOR: 1.13 (95%CI: 1.00, 1.26, $p = 0.04$], but not in the SARS-CoV-2 exposed cohort [cOR: 1.02 (95%CI:0.91, 1.14), $p = 0.73$; aOR: 1.03 (95%CI: 0.92, 1.15), $p = 0.64$]. (Supplementary Tables 1 and 2).

Serum proteomic signatures in antenatally SARS-CoV-2-exposed children with and without ASD

We examined the potential impact of antenatal SARS-CoV-2 exposure on children by profiling systemic serum cytokine levels using a multiplex assay in specimens of 34 newborn children. A subset of 27 SARS-CoV-2-exposed children, 4 of whom screened positive for ASD was matched to 7 children born from pregnancies without SARS-CoV-2 infection (Fig. 2A). Comparative proteomic profiles revealed sixty-two significantly altered serum biomarkers among SARS-CoV-2-exposed-children with a positive ASD screen relative to healthy controls (Fig. 2B, C). Enrichment analysis also demonstrated that the most involved biological pathways in children exposed to SARS-CoV-2 *in utero*, who later screened positive by MCHAT-R/F, were nicotinamide biosynthesis, neutrophil extravasation, and microglial cell activation (Fig. 2D, H). In contrast, biological processes related to chemotactic responses were significantly downregulated (Fig. 2E). Among nicotinamide biosynthesis-related genes, we identified NMNAT1 and NADK differentially abundant in the sera of the SARS-CoV-2-exposed cohort (Fig. 2F), while genes associated with microglial cell activation, MMP8, ITGAM, AZU1, and AIF1, were also significantly expressed systemically (Fig. 2G). Interestingly, genes involved in the neutrophil extravasation pathway, such as SERPINB1, PRTN3, LBR, and NCF2, were found to be significantly upregulated (Fig. 2I).

In utero SARS-CoV-2 infection with altered hematopoietic and apoptotic biomarkers is associated with positive MCHAT-R/F screens

We explored the antenatal impact of SARS-CoV-2 infection in 33 mothers of children with and without a positive ASD screen and 18 mothers with healthy pregnancies without SARS-CoV-2 exposure using similar serum proteomics profiling (Fig. 3A). Compared to healthy pregnancies, SARS-CoV-2-infected mothers with children with positive MCHAT-R/F screens showed 34 significantly altered genes ($P < 0.05$) (Fig. 3B, C), with the majority of apoptosis signaling pathways being significantly upregulated (Fig. 3D). Maternal serum cytokine analysis showed significantly elevated CD34 levels (Fig. 3E) and upregulation of key apoptosis-related genes, such as CASP2, MAP3K5, FHIT, BIRC2, and BAX, among pregnant persons with SARS-CoV-2 infection in pregnancy compared to healthy pregnant persons without SARS-CoV-2 infection (Fig. 3F). Intriguingly, while we observed different subsets of biomarkers elevated in maternal and infant serum specimens, correlation analyses performed between maternal and infant serum proteomics across all 3 groups – (i) Healthy, (ii) SARS-CoV-2 (-)ASD and (ii) SARS-CoV-2 (+) ASD revealed a similar trend of an overall positive correlation (Supplementary Fig. 1), hence, suggesting that maternal immune status is closely associated with offspring immunity, especially during infancy.

Discussion

In our evaluation of 745 children, positive MCHAT-R/F screens occurred in 10.1% of infants born to pregnant women with SARS-CoV-2 infection at any point during pregnancy, and in 5.7% of pre-pandemic controls, a difference that was statistically significant. In earlier evaluations of our longitudinal cohort using General Movements Assessment (GMA)[31] for early neuromotor development in 239 children, between cases and controls, we observed a higher frequency of abnormal endogenous movement patterns at 3 to 5 months of age in 14% of cases. This was a sign of sub-optimal nervous system functioning[19] present in none of the pre-pandemic controls in our earlier study, which were matched for age (at the time of GMA performance), gender, and gestational age[19]. Twelve percent of exposed children in this study had delayed developmental milestones at 6 to 8 months of age[19]. In a subsequent study of 300 children, we observed a 10-fold higher developmental delay risk in infants exposed antenatally to maternal SARS-CoV-2 between 5 and 30 months of age when compared to unexposed pre-pandemic controls of the same sex and similar age using the gold standard Bayley-III assessment[20]. In total, 9.4% of children exposed to maternal SARS-CoV-2 infections had developmental delay, compared to 1.6% of pre-pandemic control children from the same environment, a statistically significant finding[20]. When the analysis included Ages and Stages Questionnaires as an alternative neurodevelopmental assessment, this difference further expanded 10-fold to 11.6% in cases and 1.6% in controls[20]. These findings are consistent with Motta et al., who followed a prospective cohort of 269 infants from a single site in Brasília, Brazil, and reported neurodevelopmental delays in 26% of exposed children, particularly in the language domain, based on Bayley-III assessments at 6 and

Table 2 | Risk factors for MCHAT-R/F ≥ 3 in *in-utero* exposed SARS-CoV-2 infants

	Crude OR[a]	p	Adjusted OR (95% CI)[b]	p
NSVD	1.06 (0.98, 1.16)	0.14	1.06 (0.97, 1.16)	0.22
Comorbidities	1.00 (0.92, 1.09)	0.95	0.99 (0.89, 1.09)	0.83
Mental Health Comorbidities	1.02 (0.91, 1.14)	0.35	1.11 (0.98, 1.26)	0.09
Fever During Pregnancy	0.96 (0.88, 1.05)	0.37	0.98 (0.88, 1.09)	0.69
Maternal Age ≥ 35	0.98 (0.89, 1.07)	0.66	0.95 (0.86, 1.05)	0.32
Maternal COVID-19 severity				
Mild/Moderate vs. Asymptomatic	1.08 (0.95, 1.22)	0.22	1.11 (0.96, 1.27)	0.15
Severe/Critical vs. Asymptomatic	1.03 (0.88, 1.21)	0.71	1.03 (0.85, 1.25)	0.78
Male infant	1.05 (0.98, 1.14)	0.19	**1.12 (1.03, 1.22)**	0.01
Low Birth Weight	0.96 (0.85, 1.08)	0.54	0.91 (0.76, 1.09)	0.31
Preterm Birth	1.06 (0.96, 1.17)	0.26	1.13 (0.97, 1.32)	0.12
Small for gestational age (SGA)	0.90 (0.70, 1.15)	0.41	0.95 (0.70, 1.30)	0.75
Trimester of maternal COVID-19				
Second vs. first	1.03 (0.91, 1.17)	0.66	0.98 (0.86, 1.12)	0.76
Third vs. first	1.00 (0.89, 1.13)	0.94	1.01 (0.89, 1.14)	0.85
Maternal SARS- CoV-2 vaccination prior to delivery	0.94 (0.86, 1.01)	0.11	**0.89 (0.82, 0.98)**	0.02
Macrocephaly vs Normal* (at 6 months)	0.97 (0.85, 1.11)	0.66	0.96 (0.83, 1.10)	0.54
Microcephaly vs Normal* (at 6 months)	1.06 (0.96, 1.31)	0.60	1.04 (0.83, 1.30)	0.76

[a]The unadjusted odds ratio was calculated with a univariate model.

[b]The adjusted odds ratio was calculated with a multivariate model, adjusted for comorbidities (HDP, DM, and pre pregnancy obesity), mental health comorbidities (history of anxiety, depression, or substance abuse) fever, maternal age, COVID-19 severity, sex, low birth weight preterm, SGA, trimester of infection, vaccination status, and head circumference score at 6 months.

12 months of age[32]. While Motta et al. observed an association with third-trimester exposure, we did not detect differences by trimester of maternal infection. Despite these methodological differences, both studies converge in demonstrating an increased risk of neurodevelopmental delay following *in utero* exposure to maternal SARS-CoV-2 infection. In contrast, Jaswa et al. followed a large prospective cohort of 2003 pregnant individuals recruited online across the United States, with offspring neurodevelopment assessed remotely using parent-completed Ages and Stages Questionnaires (ASQ-3) at 12, 18, and 24 months of age[33]. The cohort was predominantly highly educated, with 87% of mothers holding a college-level degree. No differences in neurodevelopmental outcomes were observed between exposed and unexposed children, and multivariable analyses showed no associations by trimester of infection, maternal fever, or vaccination status. Differences across studies likely reflect variation in study design, population characteristics, severity of maternal illness, and the use of screening tools such as ASQ-3 versus gold-standard developmental assessments, such as Bayley-III.

In the present ASD screen analysis, our findings cannot be explained by prematurity alone, as positive MCHAT-R/F screens were also identified at a higher frequency in term children, albeit at a lower rate. Eighteen percent of exposed preterm infants in our cohort screened positive for ASD as compared to 9% term infants. Among unexposed controls, 6.7% of preterm infants and 5.5% term infants screened positive, which underscores a statistically higher rate of positive screens in both preterm and term infants among cases, as opposed to controls[30]. Exposed children had surprisingly higher rates of positive MCHAT-R/F screens, far beyond what has been reported in the general population[28,32] and also higher than pre-pandemic control children. Children born to mothers who had at least one COVID-19 vaccine prior to delivery were 8% less likely to fail the MCHAT-R/F screen. Vaccination during pregnancy has been shown to be protective against adverse maternal pregnancy and clinical outcomes in several studies[28,33–35]. This data suggests another beneficial effect of maternal immunization regarding infant outcomes, while other groups have also demonstrated protection against other adverse neonatal outcomes through maternal immunization against COVID-19[36,37]. Maternal comorbidities in the COVID-19-exposed cohort were not associated with a higher likelihood of a failed MCHAT-R/F screen in our study. Interestingly, mental health disorders in the pre-pandemic cohort were slightly more likely to be associated with a failed MCHAT-R/F screen.

In the cohort of SARS-CoV-2-exposed children, the significant upregulation of proteomic pathways related to nicotinamide biosynthesis, neutrophil extravasation, and microglial cell activation in children at birth offers a potential link between *in utero* SARS-CoV-2 exposure and increased risk of neurodevelopmental disorders, such as ASD. The distinct nicotinamide biosynthesis-related proteins we identified, such as NMNAT1 and NADK, are implicated in cellular energy homeostasis and redox balance and critical for fetal neurodevelopment[38]. Nicotinamide is a vital precursor of nicotinamide adenine dinucleotide (NAD +) and is essential in neuronal survival and function[9,39]. Although decreased levels of NAD+ have been observed in children with ASD[36,40–43], the upregulation of this pathway in this study may reflect a compensatory response to metabolic and oxidative stress due to *in utero* SARS-CoV-2 exposure.

It is known that the risk of ASD development in children increases by 13 ~ 15% after exposure to antenatal maternal viral infections such as rubella, cytomegalovirus, and influenza A, among others[36,37,43,44]. Children with ASD risk showed enhanced neuroinflammation in cerebrospinal fluid (CSF) and various brain regions involving microglial action[45,46]. Interestingly, in this study, we observed significantly elevated levels of proteins related to microglial cell activation, such as MMP8, ITGAM, AZU1, and AIF1, in the SARS-CoV-2-exposed children, suggestive of heightened microglial activation in these children during infancy. Additionally, elevated levels of SERPINB1, PRTN3, LBR, and NCF2, were biomarkers of neutrophil activation[47], thus suggestive of a sustained and dysregulated immune response during fetal development in the SARS-CoV-2-exposed children. Our findings suggest that persistent inflammatory signaling, immune dysregulation, and metabolic stress resulting from SARS-CoV-2 infection in pregnancy are associated with a potential risk of poor neurodevelopmental outcomes in children.

In our study, elevated CD34 levels in pregnant mothers infected with SARS-CoV-2 suggest a heightened state of vascular response during pregnancy, such as endothelial damage[17,48–52]. Increased mobilization of these circulating progenitor cells may also reflect an inflammatory adaptation to

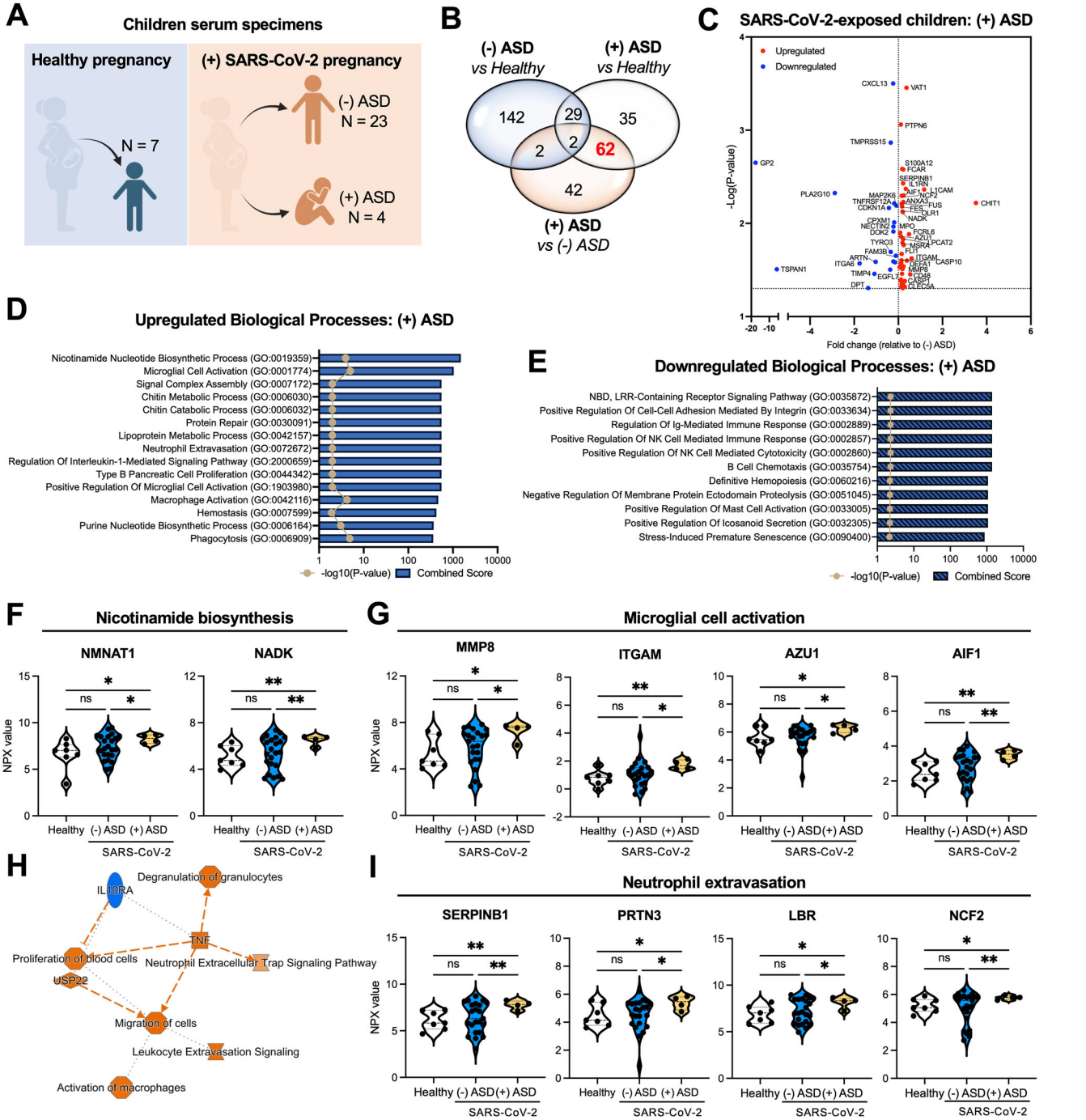

Fig. 2 | SARS-CoV-2-exposed children with a positive ASD screen exhibit elevated expressions of biomarkers related to immune and microglial cell activation at birth. A Schematic representation of serum proteome multiplexing among SARS-CoV-2-exposed children. Serum specimens were collected at birth from children born to healthy mothers ($n = 7$) and SARS-CoV-2-exposed mothers ($n = 27$). SARS-CoV-2-exposed children were clustered according to positive (n = 4) and negative ($n = 23$) ASD screens. Figure was created using Biorender.com, and all icons were sourced in Biorender.com (https://BioRender.com/lp9p53o)(**B**). Venn diagram summarizing the overlapping differentially expressed and significantly altered serum biomarkers among children with positive or negative ASD screens relative to healthy controls ($P < 0.05$). **C** Volcano plot illustrating the significantly upregulated (red) and downregulated (blue) serum cytokines ($P < 0.05$, Unpaired t-test with Welch correction test) among SARS-CoV-2-exposed children with (+)ASD screening relative to (-)ASD screening. Gene ontology enrichment analysis of biological processes for up- (**D**) and downregulated (**E**) biomarkers exclusive for SARS-CoV-2-exposed children who screened positive for ASD. All the pathways shown in (D-E) are statistically significant ($P < 0.05$). Proteins upregulated in SARS-CoV-2-exposed children with a positive ASD screen were related to (**F**) nicotinamide biosynthesis, (**G**) microglial cell activation, and (**I**) neutrophil extravasation. Welch's ANOVA test, $^{*}P < 0.05$, $^{**}P < 0.01$. **H** Graphical representation of biological pathways and upstream regulators enriched in SARS-CoV-2-exposed children with a positive ASD screen.

repair potential damages to tissue injury in the context of a viral infection breaching tissue barriers[51]. The placenta is an essential organ in fetal development; changes in its vascular integrity may affect the oxygen and nutrient delivery to the fetus; hence, disruptions in these processes may contribute to neuroinflammation and are linked to ASD[46,52]. Our study also revealed the activation of five apoptosis-related biomarkers (CASP2, MAP3K5, FHIT, BIRC2, and BAX) in SARS-CoV-2-positive mothers who had children who screened positive for ASD, suggestive of oxidative stress

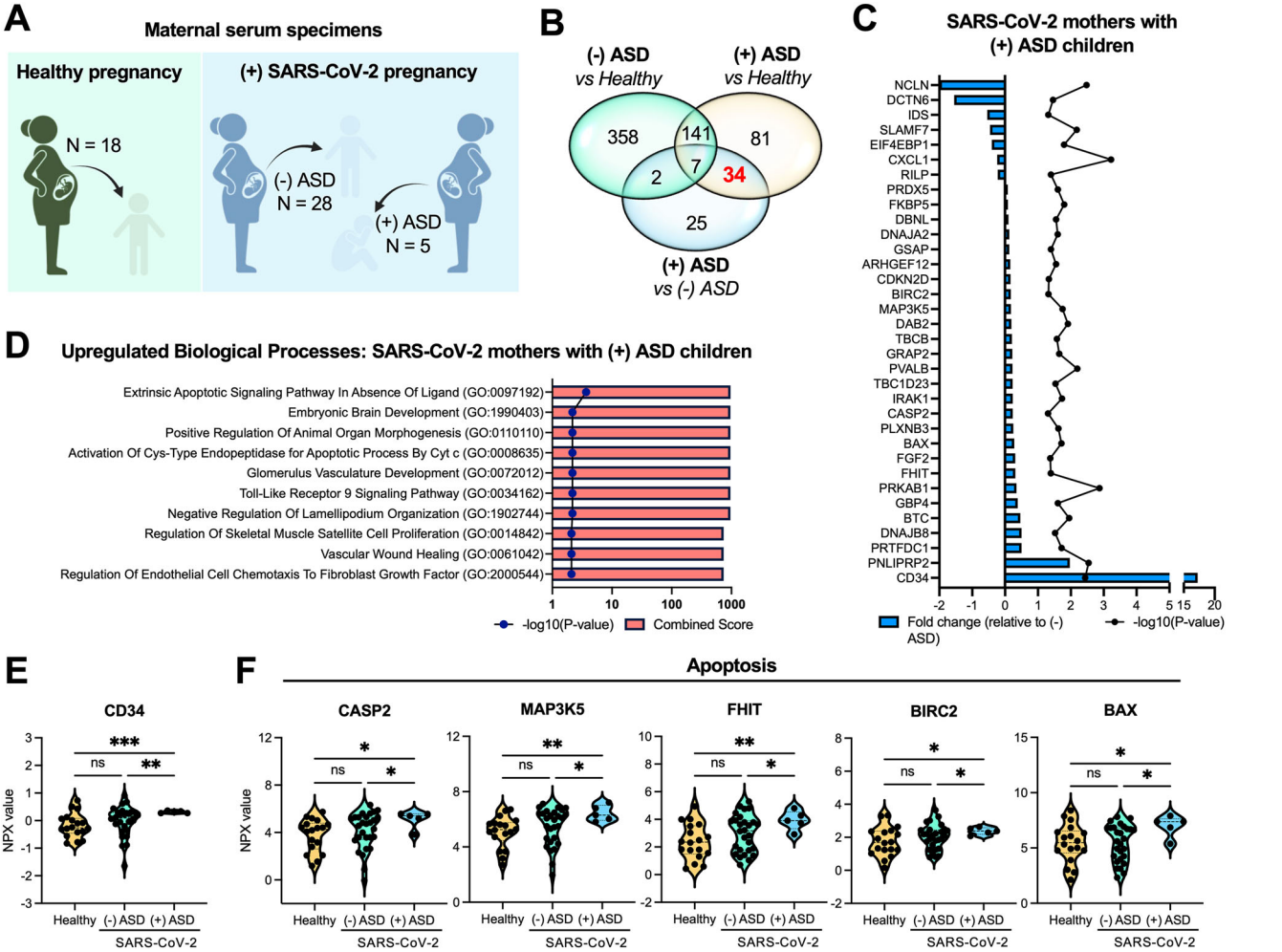

Fig. 3 | SARS-CoV-2-positive mothers with positive ASD screened children exhibit elevated circulating levels of CD34 and apoptosis-related biomarkers during prenatal proteomics profiling. A Schematic overview of patient specimens used for prenatal proteomics profiling. Maternal serum specimens were collected from healthy pregnant women ($n = 18$) or SARS-CoV-2-infected women ($n = 33$). SARS-CoV-2 pregnancies were clustered according to positive ($n = 5$) and negative ($n = 28$) ASD screened children. Figure was created in Biorender.com and all icons were sourced from Biorender.com (https://BioRender.com/xjr3wck)(**B**) Venn diagram summarizing the overlapping differentially expressed and significantly altered genes among SARS-CoV-2 pregnancies with positive or negative ASD screened children relative to healthy controls ($P < 0.05$). **C** Bar plot illustrating the cytokines specifically altered in SARS-CoV-2-infected mothers with (+)ASD screened children and are presented as a mean fold change relative to cytokines present in SARS-CoV-2-infected mothers with (-) ASD screened children. **D** Gene ontology enrichment analysis of biological processes for upregulated genes exclusive for SARS-CoV-2-infected women with (+)ASD screened children. Expressions of the (**E**) hematopoietic stem and progenitor cell marker, CD34, as well as (**F**) apoptotic serum biomarkers are shown. Welch's ANOVA test, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***} < P < 0.001$).

due to SARS-CoV-2 infection[46,48,53]. Oxidative stress and neuroinflammation drive apoptosis in maternal and fetal tissues, consistent with recent work[54] and the MIA hypotheses (MIA)[55–57], supporting a potential association between prenatal SARS-CoV-2 infection and a higher ASD risk. Interestingly, we also report elevated levels of BIRC2, known to inhibit apoptosis, which may be a compensatory mechanism in response to dysregulated apoptotic activity induced during viral infection.

There are study limitations that should be acknowledged. First, although the MCHAT-R/F is a validated screening tool for autism spectrum disorder (ASD), it is not diagnostic and may yield false positives or miss subtler ASD traits, particularly in children assessed before the age of 24 months. Confirmation of an ASD diagnosis may take several years, and very frequently is performed after 36 months of age, which surpassed our study follow-up period. For this reason, a positive ASD screen was the clinical outcome used to identify potential candidates for the proteomic analysis. Another study limitation was that proteomic analyses were limited to a relatively small subset of the cohort, potentially limiting the generalizability of mechanistic findings. Nevertheless, our pilot data provide insight into biological pathways that corroborate clinical observations. Our findings highlight the need for close neurodevelopmental follow-up of children born to mothers with COVID-19 during pregnancy for neurodevelopmental outcomes. Causal links should be confirmed in studies of larger independent cohorts with longer follow-up periods to enable confirmation of an ASD diagnosis and further evaluate potential mechanistic/ experimental associations.

Methods

Study site, population, and study design

The COMP study was approved by the institutional review boards of the University of California, Los Angeles (UCLA), USA, and the Fundação Oswaldo Cruz (Fiocruz) in Rio de Janeiro, Brazil. The study was carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from patients at enrollment. All ethical regulations relevant to human research participants were followed.

Briefly, pregnant women, 16 years or older, with confirmed SARS-CoV-2 infection by nasopharyngeal RT-PCR during gestation were eligible

for enrollment, regardless of pre-existing conditions[15]. Participants were primarily recruited from the outpatient obstetric clinic and labor and delivery unit at the University of California, Los Angeles (UCLA), and from a maternity hospital in Caxias, Rio de Janeiro, Brazil, from April 2020 to December 2022. Beginning of April 2020, all women admitted to participating sites for labor and delivery were screened for SARS-CoV-2 by nasopharyngeal swab. Infants were similarly screened for SARS-CoV-2 within 48 hours of life if the mother tested positive at delivery. Exposed children were excluded if mothers had no laboratory documentation of SARS-CoV-2 infection during pregnancy, had congenital birth defects, or if parents were unwilling to bring infants to study visits for the length of the study (from birth to 3 years of age). Exposed infants were recruited in LA and Rio from 2020 to 2022 and followed from birth and every 6 months thereafter with in-person visits to our clinics at both sites.

SARS-CoV-2 unexposed control children were selected through retrospective chart review of medical records, and were born between January 2016 and March 2020, being between the ages of 3 weeks and 4 years of age at the start of the COVID-19 pandemic. Controls were chosen based on the availability of MCHAT- R/F results between 18 and 32 months of age performed in general pediatric clinics during routine pediatric care.

Proteomic profiling analysis

Proteomic analysis was performed following previously described methodology[15]. Briefly, serum protein levels were measured using the Olink Explore 1536 protein biomarker platform, employing Proximity Extension Assay (PEA) technology in tandem with next-generation sequencing (NGS) readout. Comparative protein profiling was conducted among SARS-CoV-2-exposed children with and without ASD pathologies and age-matched healthy controls (Fig. 2a) or SARS-CoV-2-infected mothers and healthy unexposed, healthy pregnant women (Fig. 3a). Controls were determined from convenience sampling of healthy mothers without SARS-CoV-2 infection and gestational age-matched healthy children. All maternal-infant specimens used in the proteomic analysis came from patients enrolled at UCLA.

The proteomics data utilized in this study was re-analyzed from a dataset previously published by our group[15]. Herein, using a proteomics data from a subset of mother-infant dyads: (i) 33 SARS-CoV-2-positive pregnant women (28 mothers of ASD-positive children, 5 mothers of ASD-negative children) and 18 mothers with healthy pregnancies without SARS-CoV-2 exposure; and (ii) 27 SARS-CoV-2-exposed children (4 ASD-positive, 23 ASD-negative) and 7 children born from pregnancies without SARS-CoV-2 infection (controls), we explored the associations of serum biomarkers profiles to ASD outcomes in COVID-19 pregnancies. Peripheral infant blood specimens were collected between 24 and 48 h of life. This timeframe was selected to coincide with routine bilirubin checks in order to minimize blood draws. Significantly differentially expressed proteins between controls and SARS-CoV-2 (with ASD or without ASD) groups were determined by Unpaired t-test with Welch correction using GraphPad Prism v10. The pathway analysis was performed using EnrichR, which utilized a combined score computed by integrating both statistical significance (p-value) and the magnitude of enrichment (z-score). The combined score is calculated based on the formula of log(P-value) x z-score.

Sampling, variables, and definitions

MCHAT-R/F was utilized as a validated screening tool for ASD, with a positive screen defined as a score ≥3 at 18 months, with a subsequent score of ≥2 on follow-up at or after 24 months. MCHAT-R/F is a validated tool across nations to screen for the risk of ASD. Infants were considered premature if they were born at a gestational age less than 37 + 0 weeks. Children were enrolled as cases if their mothers had a positive RT-PCR for SARS-CoV-2. Maternal COVID severity was determined by NIH classification, as done by Thompson et al.[13]. Control children were unexposed to SARS-CoV-2 by definition and were enrolled based on the availability of MCHAT- R/F results in the four years preceding the SARS CoV-2 pandemic in general pediatric clinics. Control children were overall healthy children without genetic disorders and known co-morbidities. ASD screening data were analyzed as a dichotomous value (yes or no).

Statistics and reproducibility

Proteomics profiling was performed on maternal and infant specimens derived from the same COVID-19 mother-infant dyad cohort[15]. The exact sample numbers evaluated are indicated in the figure legends. Statistical analyses using Welch's ANOVA test (*$P < 0.05$, **$P < 0.01$, ***$< P < 0.001$) were performed in Figs. 2 and 3. For clinical data analysis performed for Tables 1 and 2, we compared the demographics of exposed infants to pre-pandemic control children using Chi-square or Fisher's exact test when appropriate and conducted a logistic regression multivariable analysis in *in-utero* exposed SARS-CoV-2 children who screened positive for ASD. Analysis was done with simple logistic regression for each predictor variable including delivery mode, comorbidities (HDP, diabetes, and prepregnancy obesity), mental health comorbidities (history of depression, anxiety, or substance absuse), maternal age, low birthweight, sex, preterm, and head circumference at birth, and additional variables in the exposed group, including maternal vaccination, trimester of infection, disease severity, maternal fever, and head circumference at six months). Subsequently, all variables were included in a multi-variable logistic model for potential confounding effects.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availabilty

The data that support the findings of this study are available under restricted access due to the sensitivity of the information and patient confidentiality. The raw data are protected and not available due to data privacy laws. Access to processed deidentified data may be available upon reasonable request to the corresponding authors. The raw data used for the proteomic profiling analysis were published previously[15] and are publicly available (https://doi.org/10.17632/mdnb359tp9.1). Data are located in a controlled-access electronic storage managed by the University of California Los Angeles Health System. Source data for Figs. 2 and 3 are presented in Supplementary Data 1 and 2, respectively.

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Competing interests

The authors declare the following competing interests: Suan-Sin Foo is an Editorial Board Member for *Communications Biology*, but was not involved in the editorial review of, nor the decision to publish this article. The remaining authors declare no competing interests.

Additional information

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