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Research Article

Maternal COVID-19 Infection during Pregnancy among Children Born between 3/2020 and 2/2023 and Potential Disparities

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Abstract

Purpose: This study aims to assess rates of COVID-19 exposure during pregnancy among children born during the original, Delta and Omicron waves, and to identify potential disparities. **Methods:** This birth cohort includes 125,152 children born from 3/1/2020 to 2/28/2023 in southern California. Data on maternal COVID-19 infection, demographics, and health status were extracted from electronic medical records. Rates were calculated for each wave and subgroup. Poisson regression tested trends over waves and compared rates within each subgroup. **Results:** A total of 20,187 (16.1%) children were born to mothers with COVID-19 during pregnancy. Rates were 2.8%, 13.6% and 26.5% during the original, Delta and Omicron waves respectively ($p<0.0001$). Younger mothers (age <25 and 25-35 years) had higher rates during the original and Delta waves but not during Omicron. Children of Black women had 47% higher rates during the original wave; and children of Hispanic women had 156% and 81% higher rates during the original and Delta waves, respectively. No significant differences were observed for Omicron. Higher neighbourhood deprivation index and Medicaid insurance had higher rates during the original and Delta waves. Higher maternal parity and obesity were associated with higher rates in all waves, with greater disparities during the original and Delta waves. Maternal diabetes, asthma or autoimmune disease were associated with higher rates during the Omicron wave. **Conclusion:** Substantial disparities exist for COVID-19 exposure during the original and Delta waves, but not for Omicron. These findings are important for public health and future research.

Keywords: Birth Cohort; Pregnancy; COVID-19; Disparities

Abbreviations: ACS: American Community Survey; API: Asian Pacific Islander; BMI: Body Mass Index; CDPH: California Department of Public Health; CDC: Centers for Disease Control and Prevention; CI: Confidence Interval; COVID-19: Coronavirus disease 2019; EMR: Electronic Medical Records; FDA: Food and Drug Administration; ICD-10: International Classification of Diseases, Tenth Revision (ICD-10); KPSC: Kaiser Permanente Southern California; NDI: Neighbourhood Deprivation Index; PHE: Public Health Emergency; RR: Rate Ratios; SES: Socioeconomic Status

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infection caused by the virus SARS-CoV-2 [1]. Since the beginning of the pandemic, COVID-19 exposures have been tracked by various organizations, including the United States Centers for Disease Control and Prevention (CDC) and the California Department

of Public Health (CDPH) [2,3]. However, little is known on how many children born during the major pandemic periods were exposed to maternal COVID-19 infection during pregnancy and potential disparities. SARS-CoV-2 infection could lead to an abnormal intrauterine environment, including inflammation and altered immune responses during this critical window for foetal development [4,5]. Recent studies found that exposure to maternal COVID-19 infection during pregnancy may be associated with future neuropsychiatric disorders in young children [5-7]. Moreover, there is increasing evidence that COVID-19 infection during pregnancy is associated with adverse pregnancy outcomes, including increased risk of preeclampsia, pre-term birth, and stillbirths [8,9]. Severe COVID-19 infection during pregnancy is associated with increased risk for gestational diabetes and low birth weight [10]. Adverse perinatal outcomes may later impact short and long-term health in childhood. For example, exposure to maternal preeclampsia is associated with the increased risk of autism spectrum disorders in children [11].

Previous studies on COVID-19 during pregnancy showed that pregnant women respond to infectious agents including COVID-19 differently than non-pregnant women due to the complexity of the immune system during pregnancy [12,13]. Obstetric studies earlier in the pandemic have suggested higher rates of COVID-19 infection and severe outcomes among pregnant women compared to non-pregnant women of the same age group [14]. A previous northern California study estimated that approximately 2.5% children born between January 1, 2020 to April 28, 2021 may have been exposed to COVID-19 during pregnancy [15]. Studies earlier in the pandemic also reported differences in COVID-19 transmission or disease severity by demographic, Socioeconomic Status (SES), and maternal health status [16-19]. Risk factors for COVID-19 infection among the obstetric population may include younger age, minority racial and ethnic groups, low SES, living with children, or with medical comorbidities [15,20-25]. While these studies have assessed potential disparities, significant knowledge gaps exist. Most studies were from earlier in the pandemic (original strain to early Delta variant), have small number of sample sizes, and have COVID-19 testing mostly around the time of labor and delivery.

The purpose of this study was to assess rates of COVID-19 exposure during pregnancy and potential disparities among children delivered in each of the three major pandemic waves (original, Delta and Omicron) between March 1, 2020 to February 28, 2023. The study population was derived from a large population-based multi-ethnic birth cohort from an integrated healthcare system within southern California. Standard care across the healthcare system and a well-established, integrated Electronic Medical Records (EMR) system with comprehensive information on demographic, SES, and health data made this study feasible. This study will help fill the knowledge gap and provide information about rates of exposure and potential disparities for children born across the major COVID-19 pandemic waves. Understanding the magnitude of children exposed across major COVID-19 pandemic waves and disparities will provide important data to help identify at risk children and develop prevention strategies to combat the long-term effects of COVID-19.

Materials and Methods

This is a population-based birth cohort study including 125,152 children delivered between March 1, 2020 and February 28, 2023 within Kaiser Permanente Southern California (KPSC) hospitals. KPSC is a large integrated healthcare system with over 4.6 million members, representative of southern California and regional diversity [26,27]. About 15.1% of these pregnant mothers had Medicaid or Medicare coverage at childbirth, with less than 1% having Medicare (Medicare is generally for those over 65 years of age, but people with certain disabilities under 65 years of age can have Medicare [28]). All data were extracted from the comprehensive and well-established KPSC EMR. This study was approved by KPSC Institutional Review Boards, with individual subject consent waived.

For each child delivered between 3/1/2020 to 2/28/2023, maternal pregnancy care and medical history from inception to delivery was used to identify potential COVID-19 infection during pregnancy. A positive COVID-19 exposure was indicated if mothers had positive SARS-CoV-2 labs or COVID-19 diagnosis codes (eTable 1) in maternal EMR during the pregnancy period. The codes captured both KPSC internal diagnosis and diagnosis made outside of KPSC facilities including self-reported antigen tests anytime during pregnancy (eTable 1).

	Lab Test	
KPSC	Polymerase Chain Reaction (PCR)	
	Detection of Antigen in Respiratory Specimens by Rapid Immunoassay	
	Detection of Antigen IgG Ab in Serum, Plasma, or Blood by Immunoassay	
	Antibody Nucleocapsid Total	
	Diagnosis Code	**Code Description**
KPSC	12459073	COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME
	12459074	COVID-19 PNEUMONIA
	12459075	COVID-19 ACUTE BRONCHITIS
	12459076	COVID-19 LOWER RESPIRATORY INFECTION
	12459077	ASYMPTOMATIC COVID-19
	12459078	CORONAVIRUS DISEASE 2019 (COVID-19)
	12459108	COVID-19
	12459208	COVID-19 TEST POSITIVE BY OUTSIDE LABORATORY
	12459285	COVID-19 DISEASE IN PREGNANCY, FIRST TRIMESTER
	12459286	COVID-19 DISEASE IN PREGNANCY, SECOND TRIMESTER
	12459287	COVID-19 DISEASE IN PREGNANCY, THIRD TRIMESTER
	12459288	COVID-19 DISEASE IN PREGNANCY, UNSPECIFIED TRIMESTER
	12459289	COVID-19 DISEASE IN CHILDBIRTH
	12459290	COVID-19 DISEASE, POSTPARTUM
	12459293	COVID-19 DISEASE IN PREGNANCY
	12459784	CONGENITAL COVID-19 DISEASE
	12461380	COVID-19 TEST POSITIVE BY HOME TEST
ICD-10	U07.1	
Abbreviations: KPSC: Kaiser Permanente Southern California		

eTable 1: COVID-19 Diagnosis Labs and Codes.

The subgroups we assessed include maternal demographic, SES, and health factors. Maternal age at delivery was categorized into <25, 25-35, and >35 years. Self-reported race and ethnicity was grouped into Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian Pacific Islander (API), and other. SES included Neighborhood Deprivation Index (NDI), and whether medical insurance was through Medicaid (Medicare was grouped into Medicaid since very few mothers had insurance through Medicare). NDI was estimated using residential birth address and data from the Census Bureau's American Community Survey (ACS) for 2020 [29]. The NDI is a z-score centered around 0 where higher values indicate more deprivation (lower SES area) [30]. NDI was categorized based on quintile distribution where quintile 1 was the least deprived and quintile 5 was the most deprived. Health factors included parity (0, 1, ≥2), pre-pregnancy obesity status (normal, overweight, obese), diabetes during pregnancy (yes, no), asthma (yes, no), and presence of any autoimmune diseases (yes, no). Pre-pregnancy obesity status was based on Body Mass Index (BMI) using weight and height data in EMR closest to the pregnancy start date where normal was defined as BMI<25 kg/m^2, overweight as 25≤BMI<30 kg/m^2, and obese as BMI≥30 kg/m^2. Pregnancy diabetes status included both gestational diabetes and pre-existing diabetes as previously described [31-33]. Mother's asthma status was identified based on ICD-10 codes (J45.2, J45.3, J45.4, J45.5, and J45.9) or prescription for asthma-specific medication 1 year before pregnancy until childbirth [34]. Autoimmune diseases were based on ICD-10 codes (see eTable 2) 1 year before pregnancy until childbirth or if the mother was identified as having type 1 diabetes, adapted from ICD-9 codes previously described [35].

Autoimmune Categories	ICD-10 codes
Autoimmune thyroid disease	E03.9, E05.00, E05.01, E05.90, E05.91, E06.3, E06.9
Idiopathic	D69.3, D69.41, D69.42, D69.49, D69.51, D69.6
Inflammatory bowel disease	K50.00, K50.011, K50.012, K50.013, K50.014, K50.018, K50.019, K50.10, K50.111, K50.112, K50.113, K50.114, K50.118, K50.119, K50.90, K50.911, K50.912, K50.913, K50.914, K50.918, K50.919, K51.50, K51.511, K51.512, K51.513, K51.514, K51.518, K51.519, K51.80, K51.90, K51.911, K51.912, K51.913, K51.914, K51.918, K51.919, K52.0, K52.1, K52.21, K52.22, K52.29, K52.3, K52.81, K52.82, K52.831, K52.832, K52.838, K52.839, K52.89, K52.9, K59.31
All other auto-immune disease	A52.15, D59.0, D59.1, D60.0, D60.1, D60.8, D60.9, D61.01, D61.09, D61.1, D61.2, D61.3, D61.810, D61.811, D61.818, D61.82, D61.89, D61.9, D68.51, D68.52, D68.59, D68.61, D68.62, D69.0, D86.0, D86.1, D86.2, D86.3, D86.81, D86.82, D86.83, D86.84, D86.85, D86.86, D86.87, D86.89, D86.9, D89.1, D89.82, D89.89, E27.1, E27.2, E27.3, E27.40, E27.49, E89.6, G13.0, G13.1, G35, G61.0, G61.1, G61.81, G61.82, G61.89, G61.9, G62.0, G62.1, G62.2, G62.81, G62.82, G62.89, G62.9, G63, G64, G65.0, G65.1, G65.2, G70.00, G70.01, G70.1, G70.2, G70.80, G70.81, G70.89, G70.9, G73.1, G73.3, H20.00, H20.9, H30.891, H30.892, H30.893, H30.899, H30.90, H30.91, H30.92, H30.93, H44.111, H44.112, H44.113, H44.119, H46.8, H46.9, H81.01, H81.02, H81.03, H81.09, I00, I01.0, I01.1, I01.2, I01.8, I01.9, I02.0, I02.9, I05.0, I05.1, I05.2, I05.8, I05.9, I06.0, I06.1, I06.2, I06.8, I06.9, I07.0, I07.1, I07.2, I07.8, I07.9, I08.0, I08.1, I08.2, I08.3, I08.8, I08.9, I09.0, I09.1, I09.2, I09.81, I09.89, I09.9, I12.0, I12.9, I67.0, I67.7, I68.2, I73.00, I73.01, I73.1, I73.81, I73.89, I73.9, I77.3, I77.6, I77.70, I77.71, I77.72, I77.73, I77.74, I77.75, I77.76, I77.77, I77.79, I77.89, I77.9, I79.1, I79.8, J84.111, J84.112, J84.113, J84.114, J84.115, J84.116, J84.117, J84.2, J99, K71.0, K71.10, K71.11, K71.2, K71.3, K71.4, K71.50, K71.51, K71.6, K71.7, K71.8, K71.9, K73.1, K73.2, K73.8, K74.3, K74.4, K74.5, K75.2, K75.3, K75.81, K75.89, K75.9, K76.4, K90.0, K90.1, K90.2, K90.3, K90.41, K90.49, K90.89, K90.9, K91.2, L10.0, L10.1, L10.2, L10.3, L10.4, L10.5, L10.81, L10.89, L10.9, L12.0, L12.30, L12.31, L12.35, L12.8, L12.9, L13.0, L13.9, L40.0, L40.1, L40.2, L40.3, L40.4, L40.50, L40.51, L40.52, L40.53, L40.54, L40.59, L40.8, L40.9, L43.0, L43.1, L43.2, L43.3, L43.8, L43.9, L44.1, L44.2, L44.3, L44.9, L51.0, L51.1, L51.2, L51.3, L51.8, L51.9, L63.2, L63.8, L63.9, L64.9, L65.9, L66.1, L80, L93.0, L93.1, L93.2, M01.X0, M02.30, M02.311, M02.312, M02.319, M02.321, M02.322, M02.329, 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M12.021, M12.022, M12.029, M12.031, M12.032, M12.039, M12.041, M12.042, M12.049, M12.051, M12.052, M12.059, M12.061, M12.062, M12.069, M12.071, M12.072, M12.079, M12.08, M12.09, M30.0, M30.1, M30.2, M30.3, M30.8, M31.0, M31.1, M31.30, M31.31, M31.4, M31.5, M31.6, M31.7, M32.0, M32.10, M32.11, M32.12, M32.13, M32.14, M32.15, M32.19, M32.8, M32.9, M33.00, M33.01, M33.02, M33.03, M33.09, M33.10, M33.11, M33.12, M33.13, M33.19, M33.20, M33.21, M33.22, M33.29, M33.90, M33.91, M33.92, M33.93, M33.99, M34.0, M34.1, M34.2, M34.81, M34.82, M34.83, M34.89, M34.9, M35.00, M35.01, M35.02, M35.03, M35.04, M35.09, M35.2, M35.3, M35.9, M36.0, M36.8, M45.0, M45.1, M45.2, M45.3, M45.4, M45.5, M45.6, M45.7, M45.8, M45.9, M46.90, M46.91, M46.92, M46.93, M46.94, M46.95, M46.96, M46.97, M46.98, M46.99, M48.8X1, M48.8X2, M48.8X3, M48.8X4, M48.8X5, M48.8X6, M48.8X7, M48.8X8, M48.8X9, M84.80, M84.811, M84.812, M84.819, M84.821, M84.822, M84.829, M84.831, M84.832, M84.833, M84.834, M84.839, M84.841, M84.842, 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M89.369, M89.371, M89.372, M89.379, M89.38, M89.39, M89.50, M89.511, M89.512, M89.519, M89.521, M89.522, M89.529, M89.531, M89.532, M89.539, M89.541, M89.542, M89.549, M89.551, M89.552, M89.559, M89.561, M89.562, M89.569, M89.571, M89.572, M89.579, M89.58, M89.59, M89.8X0, M89.8X1, M89.8X2, M89.8X3, M89.8X4, M89.8X5, M89.8X6, M89.8X7, M89.8X8, M89.8X9, M94.1, M94.351, M94.352, M94.359, M94.8X0, M94.8X1, M94.8X2, M94.8X3, M94.8X4, M94.8X5, M94.8X6, M94.8X7, M94.8X8, M94.8X9, N05.0, N05.1, N05.6, N05.7, N05.8, N06.0, N06.1, N06.6, N06.7, N06.8, N07.0, N07.1, N07.6, N07.7, N07.8, N08, N14.0, N14.1, N14.2, N14.3, N14.4, N15.0, N15.8, N16, Q68.8, Q79.8, Q79.9

eTable 2: ICD-10 Codes for Autoimmune Disease.

The rates of COVID-19 exposure were calculated as the number of children with maternal record indicating COVID-19 exposure during pregnancy divided by the total number of children delivered during the same time period, expressed as per 100 deliveries. The rates were separately calculated for each pandemic wave, defined as original (March 1, 2020-November 30, 2020), Delta (December 1, 2020-November 30, 2021) and Omicron (December 1, 2021-February 28, 2023), and stratified by subgroups of demographic, SES, and health status factors.

Poisson regression was performed to assess time trends across pandemic waves overall and by each subgroup. P-values <0.05 was considered statistically significant. To assess differences within subgroups, Poisson regression was used to estimate Rate Ratios (RRs) and 95% CIs for each subgroup. All analyses were performed using SAS Enterprise Guide 8.3 (SAS Institute).

Results

Among the cohort, children were predominately born to mothers aged 25-35 years at delivery (61.3%) and Hispanic ethnicity (55.1%), 15.1% of mothers had Medicaid insurance, 33.1% were nulliparous and 26.6% had parity ≥2, 64.2% had overweight or obesity status pre-pregnancy, 14.6% had diabetes during pregnancy, 13.7% had asthma, and 12.7% had autoimmune diseases (Table 1). A total of 20,187 (16.1%) children were exposed to maternal COVID-19 infection during pregnancy for the entire study period. Overall, the infection rates were higher for mothers with Hispanic ethnicity, living in higher NDI areas, having Medicaid insurance, parity ≥2, and with obesity, diabetes, asthma, or autoimmune diseases (Table 1).

		COVID-19 Exposure during Pregnancy	
Characteristics	**Total (N=125152)**	**Yes (N=20187)**	**No (N=104965)**
Mother's Age at Delivery Categories, in years			
<25 years	13906 (11.1%)	2245 (11.1%)	11661 (11.1%)
25-35 years	76703 (61.3%)	12604 (62.4%)	64099 (61.1%)
>35 years	34543 (27.6%)	5338 (26.4%)	29205 (27.8%)
Mother's Race and Ethnicity			
API	17810 (14.4%)	2301 (11.5%)	15509 (14.9%)
Black	8744 (7.1%)	1232 (6.2%)	7512 (7.2%)
Hispanic	68203 (55.1%)	12310 (61.6%)	55893 (53.8%)
White	26880 (21.7%)	3822 (19.1%)	23058 (22.2%)
Other	2240 (1.8%)	308 (1.5%)	1932 (1.9%)
Missing	1275	214	1061
NDI Quintiles			
Quintile 1	25029 (20%)	3587 (17.8%)	21442 (20.4%)
Quintile 2	24988 (20%)	3837 (19%)	21151 (20.2%)
Quintile 3	25051 (20%)	4246 (21%)	20805 (19.8%)
Quintile 4	24997 (20%)	4200 (20.8%)	20797 (19.8%)
Quintile 5	24991 (20%)	4311 (21.4%)	20680 (19.7%)
Missing	96	6	90
Medicaid Insurance			
Yes	18887 (15.1%)	3479 (17.2%)	15408 (14.7%)
Mother's Parity			
0	34996 (33.1%)	5391 (31%)	29605 (33.6%)
1	42523 (40.3%)	6969 (40%)	35554 (40.3%)
≥2	28055 (26.6%)	5042 (29%)	23013 (26.1%)
Missing	19578	2785	16793
Mother's Pre-pregnancy Obesity			
Normal (BMI<25)	42672 (35.7%)	5886 (30.7%)	36786 (36.7%)
Overweight (25≤BMI<30)	35485 (29.7%)	5833 (30.5%)	29652 (29.6%)
Obese (BMI≥30)	41242 (34.5%)	7423 (38.8%)	33819 (33.7%)
Missing	5753	1045	4708
Mother's Diabetes in Pregnancy Status			

		COVID-19 Exposure during Pregnancy	
Characteristics	**Total (N=125152)**	**Yes (N=20187)**	**No (N=104965)**
Yes	18279 (14.6%)	3125 (15.5%)	15154 (14.4%)
Mother's Asthma Status			
Yes	17104 (13.7%)	2985 (14.8%)	14119 (13.5%)
Mother's Autoimmune Disease Status			
Yes	15900 (12.7%)	2721 (13.5%)	13179 (12.6%)
Abbreviations: API: Asian Pacific Islander; BMI: Body Mass Index; NDI: Neighborhood Deprivation Index			

Table 1: Birth cohort characteristics among children born between 3/1/2020 and 2/28/2023.

When stratified by pandemic waves, exposure to maternal COVID-19 during pregnancy increased with rates of 2.83%, 13.61% and 26.54% among children delivered during the original, Delta, and Omicron waves respectively (p<0.0001 for trend; Figure 1A, eTable 3). The increase in rates over the pandemic waves were observed across all demographics, socioeconomic, and health status subgroups (p-value for trend <0.0001 for each subgroup; Figure 1, Figure 2, eTable 3). For children delivered during the original wave, the exposure rate was highest for those born to mothers age <25 years, Hispanic ethnicity, living in neighborhoods with highest NDI, with Medicaid insurance, parity ≥2, with pre-pregnancy overweight or obesity. For children delivered during the Delta wave, these subgroups continued to have highest rates; in addition, children born to mothers with asthma or autoimmune disease also showed having higher rate of exposure. For children delivered during the Omicron wave, the rate pattern reversed for mother's age group and NDI, with higher rates for children born to mothers age ≥25 years and living in neighborhoods with lower NDI; the pattern remained similar to the Delta wave regarding maternal race and ethnicity, Medicaid insurance, and health factors except that diabetes in pregnancy showed having higher rate exposure than no diabetes for the Omicron wave.

	Original COVID-19 Wave			**Delta Wave**			**Omicron Wave**			**Time Trend**
	COVID-19, N	**Total, N**	**COVID-19, %**	**COVID-19, N**	**Total, N**	**COVID-19, %**	**COVID-19, N**	**Total, N**	**COVID-19, %**	**P-value**
All Participants	903	31896	2.83	5747	42241	13.61	13537	51015	26.54	<0.0001
Mother's Age <25 years	160	3883	4.12	840	4773	17.60	1245	5250	23.71	<0.0001
Mother's Age 25-35 years	556	19482	2.85	3746	26168	14.32	8302	31053	26.73	<0.0001
Mother's Age >35 years	187	8531	2.19	1161	11300	10.27	3990	14712	27.12	<0.0001
API Mothers	57	4583	1.24	430	5953	7.22	1814	7274	24.94	<0.0001
Black Mothers	50	2248	2.22	314	3062	10.25	868	3434	25.28	<0.0001
Hispanic Mothers	669	17330	3.86	4027	22978	17.53	7614	27895	27.30	<0.0001
White Mothers	105	6962	1.51	899	9260	9.71	2818	10658	26.44	<0.0001
Other Race and Ethnicity Mothers	12	548	2.19	51	704	7.24	245	988	24.80	<0.0001

	Original COVID-19 Wave			Delta Wave			Omicron Wave			Time Trend
	CO-VID-19, N	Total, N	CO-VID-19, %	CO-VID-19, N	Total, N	CO-VID-19, %	CO-VID-19, N	Total, N	CO-VID-19, %	P-value
NDI Quintile 1	108	6325	1.71	767	8566	8.95	2712	10138	26.75	<0.0001
NDI Quintile 2	130	6341	2.05	949	8459	11.22	2758	10188	27.07	<0.0001
NDI Quintile 3	168	6367	2.64	1332	8457	15.75	2746	10227	26.85	<0.0001
NDI Quintile 4	235	6484	3.62	1265	8311	15.22	2700	10202	26.47	<0.0001
NDI Quintile 5	262	6363	4.12	1433	8424	17.01	2616	10204	25.64	<0.0001
Medicaid or Medicare	174	4294	4.05	1017	6189	16.43	2288	8404	27.23	<0.0001
No Medicaid or Medicare	729	27602	2.64	4730	36052	13.12	11249	42611	26.4	<0.0001
Parity 0	229	9273	2.47	1441	11639	12.38	3721	14084	26.42	<0.0001
Parity 1	309	10860	2.85	1976	14465	13.66	4684	17198	27.24	<0.0001
Parity ≥2	251	6991	3.59	1544	9493	16.26	3247	11571	28.06	<0.0001
Normal Weight	242	11924	2.03	1590	15208	10.46	4054	15540	26.09	<0.0001
Overweight	297	9459	3.14	1747	12534	13.94	3789	13492	28.08	<0.0001
Obese	360	10377	3.47	2397	14329	16.73	4666	16536	28.22	<0.0001
No Diabetes	771	27670	2.79	4896	35885	13.64	11395	43318	26.31	<0.0001
With Diabetes	132	4226	3.12	851	6356	13.39	2142	7697	27.83	<0.0001
No Asthma	781	27578	2.83	4906	36484	13.45	11515	43986	26.18	<0.0001
With Asthma	122	4318	2.83	841	5757	14.61	2022	7029	28.77	<0.0001
No Autoimmune Disease	781	27552	2.83	5003	37100	13.49	11682	44600	26.19	<0.0001
With Autoimmune Disease	122	4344	2.81	744	5141	14.47	1855	6415	28.92	<0.0001

Abbreviations: API: Asian Pacific Islander; BMI: Body Mass Index; NDI: Neighborhood Deprivation Index

eTable 3: Rates of COVID-19 exposure during pregnancy by major COVID-19 waves and by maternal demographic, socioeconomic, and health factors.

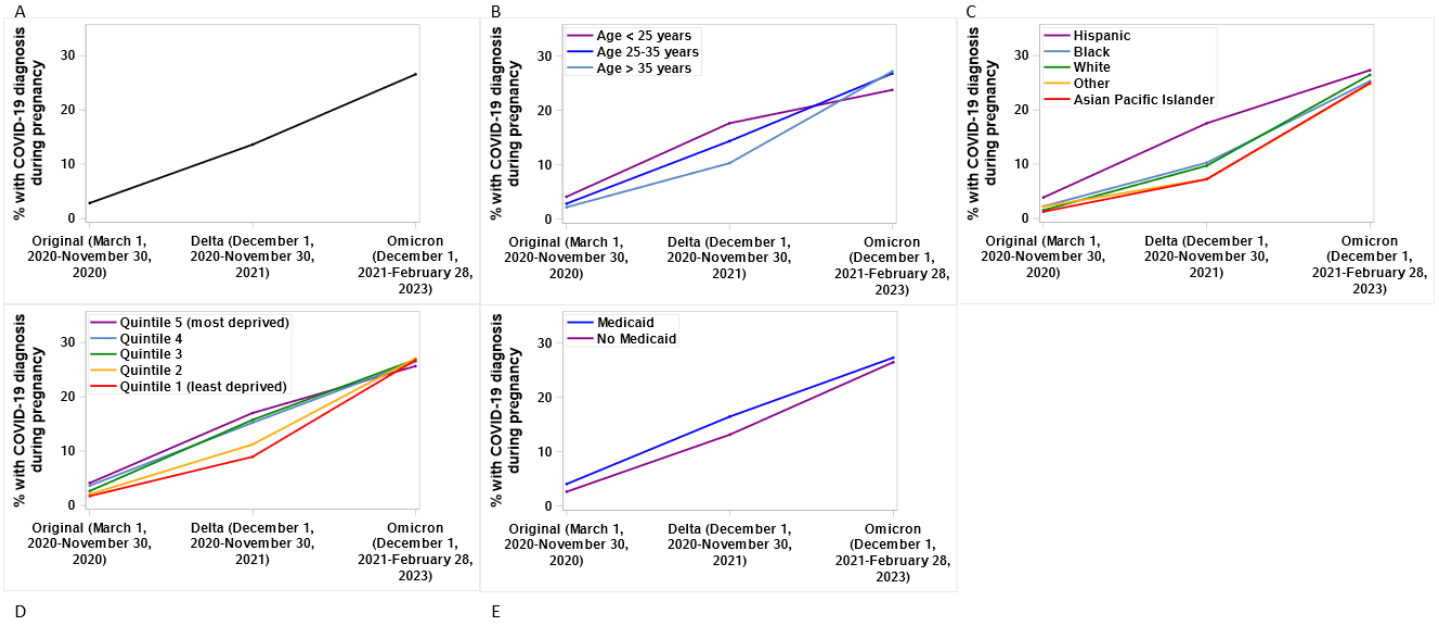

Figure 1: Rates of COVID-19 exposure during pregnancy by major COVID-19 waves and by demographic and socioeconomic status.

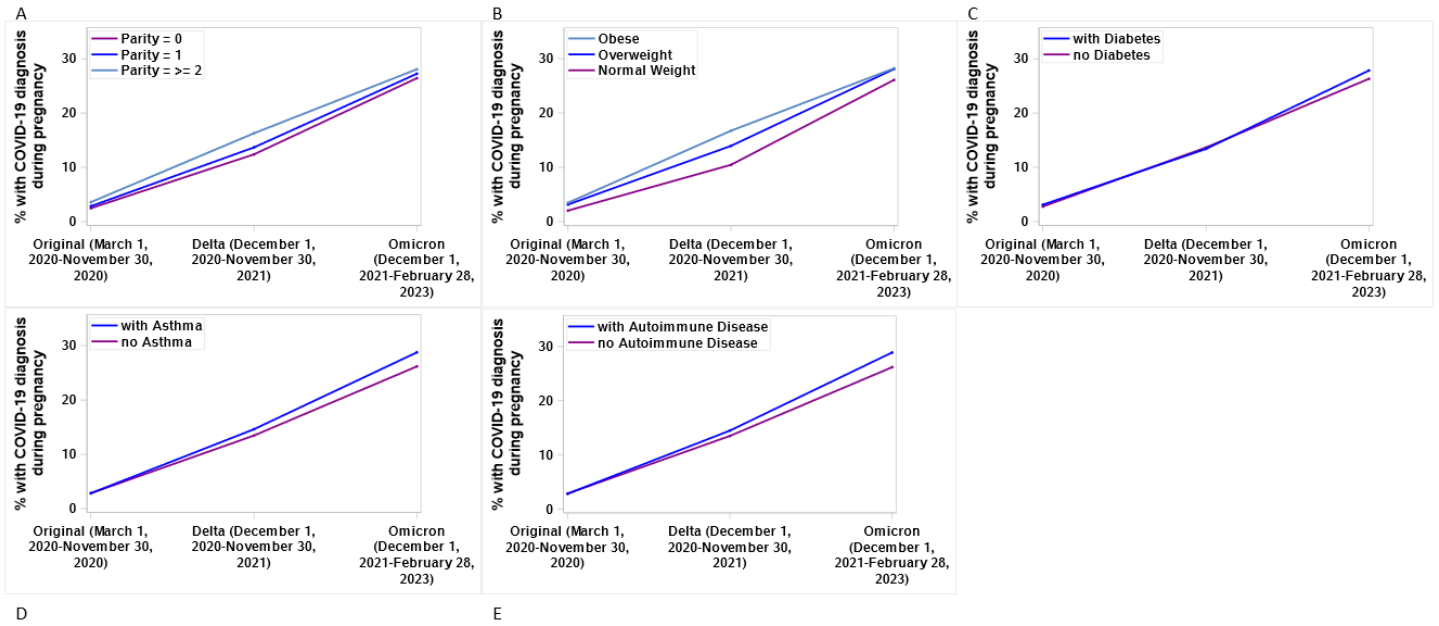

Figure 2: Rates of COVID-19 exposure during pregnancy by major COVID-19 waves and maternal health factors.

Table 2 presents RRs within each subgroup by pandemic waves. The exposure rate was 88% higher for children born to mothers age <25 years (RR, 1.88; 95% CI, 1.52-2.32) and 30% higher for children born to mothers age 25-35 years (RR, 1.30; 95% CI, 1.10-1.54) compared to those born to mothers age >35 years during the original wave. Similar RR were observed during the Delta wave. However, no elevated risks were observed for younger age mothers for the Omicron wave. Compared to children born to White women, rates were 47% higher for children born to Black women (RR, 1.47; 95% CI, 1.05-2.07) for the original wave, 156% (RR, 2.56; 95% CI, 2.08-3.14) and 81%

(RR, 1.81; 95% CI, 1.68-1.94) higher for children born to Hispanic women in the original and Delta waves; no significant differences were observed for the Omicron wave. Living in areas with higher NDI or with Medicaid insurance had higher rates for the original and Delta waves, but no differences were observed during Omicron. Higher maternal parity and obesity were associated with higher rates for all waves and the rate ratios were greater during original and Delta waves. Maternal diabetes, asthma or autoimmune disease were not associated with higher rates for the original wave; but were associated with higher rates of exposure for the Omicron waves.

		Pandemic Waves		
		Original	**Delta**	**Omicron**
Characteristic Level	**Reference Level**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Mother's Age				
<25 years	>35 years	**1.88 (1.52-2.32)**	**1.71 (1.57-1.87)**	**0.87 (0.82-0.93)**
25-35 years	>35 years	**1.30 (1.10-1.54)**	**1.39 (1.30-1.49)**	0.99 (0.95-1.02)
Mother's Race and Ethnicity				
API	White	0.82 (0.60-1.14)	**0.74 (0.66-0.83)**	0.94 (0.89-1.00)
Black	White	**1.47 (1.05-2.07)**	1.06 (0.93-1.20)	0.96 (0.89-1.03)
Hispanic	White	**2.56 (2.08-3.14)**	**1.81 (1.68-1.94)**	1.03 (0.99-1.08)
Other	White	1.45 (0.80-2.64)	**0.75 (0.56-0.99)**	0.94 (0.82-1.07)
NDI Quintile				
Quintile 2	Quintile 1 (least deprived)	1.20 (0.93-1.55)	**1.25 (1.14-1.38)**	1.01 (0.96-1.07)
Quintile 3	Quintile 1 (least deprived)	**1.55 (1.21-1.97)**	**1.76 (1.61-1.92)**	1.00 (0.95-1.06)
Quintile 4	Quintile 1 (least deprived)	**2.12 (1.69-2.67)**	**1.70 (1.55-1.86)**	0.99 (0.94-1.04)
Quintile 5	Quintile 1 (least deprived)	**2.41 (1.93-3.02)**	**1.90 (1.74-2.07)**	0.96 (0.91-1.01)
Medicaid Insurance				
Yes	No	**1.53 (1.30-1.81)**	**1.25 (1.17-1.34)**	1.03 (0.99-1.08)
Mother's Parity				
1	0	1.15 (0.97-1.37)	**1.10 (1.03-1.18)**	1.03 (0.99-1.08)
≥2	0	**1.45 (1.22-1.74)**	**1.31 (1.22-1.41)**	**1.06 (1.01-1.11)**
Mother's Pre-pregnancy Obesity				
Overweight (25≤BMI<30)	Normal (BMI<25)	**1.55 (1.31-1.83)**	**1.33 (1.25-1.43)**	**1.08 (1.03-1.13)**
Obese (BMI≥30)	Normal (BMI<25)	**1.71 (1.45-2.01)**	**1.60 (1.50-1.70)**	**1.08 (1.04-1.13)**
Mother's Diabetes in Pregnancy Status				
Yes	No	1.12 (0.93-1.35)	0.98 (0.91-1.06)	**1.06 (1.01-1.11)**
Mother's Asthma Status				
Yes	No	1.00 (0.82-1.21)	**1.09 (1.01-1.17)**	**1.10 (1.05-1.15)**
Mother's Autoimmune Disease Status				
Yes	No	0.99 (0.82-1.20)	1.07 (0.99-1.16)	**1.10 (1.05-1.16)**

Abbreviations: API: Asian Pacific Islander; BMI: Body Mass Index; NDI: Neighborhood Deprivation Index; RR: Rate Ratio

Table 2: Crude rate ratios (RRs) of COVID-19 exposure during pregnancy for each demographic, socioeconomic status, and health factors for each pandemic waves (Original, Delta, Omicron).

Discussion

For children born during the pandemic time, the rates of maternal exposure to COVID-19 infection during pregnancy significantly increased across the pandemic waves. This was observed overall and by maternal demographics, socioeconomic, and health factor subgroups. Disparities by subgroups were observed. The disparities in exposure by maternal demographic and socioeconomic variables were most evident for children born during the original wave and persisted into the Delta wave, but no apparent disparities were observed for children born during the Omicron wave. The exposure rates were highest for children born during the original and Delta waves to younger mothers (<25 years), mothers with Hispanic ethnicity, mothers living in more deprived neighborhoods and mothers with Medicaid insurance. Children born to mothers with parity ≥2, overweight or obesity had elevated exposure rate throughout all pandemic waves. Maternal diabetes, asthma, and autoimmune diseases are associated with elevated maternal COVID-19 exposure during pregnancy for children born during the Omicron waves.

Our estimated overall rate of 2.83% COVID-19 exposure during pregnancy for children born during the original wave is in line with the 2.5% reported by a previous study in northern California [15]. The slightly elevated rate in our study may be that our population has a higher proportion of Hispanic ethnicity and the exposure rate appeared higher for Hispanic ethnicity throughout the pandemic, with the highest rates earlier in the pandemic wave [36,37]. Additionally, our study showed that about 13% of children born during the Delta variant period (December 2020 to November 2021) were exposed to maternal COVID-19 infection during pregnancy, a period with vaccine implementation across different populations. Furthermore, our study showed that the exposure rate was doubled to 26% during the major Omicron variant period (December 2021 to February 2023) when vaccination was widely available free of charge. The Food and Drug Administration (FDA) issued an emergency use authorization for COVID-19 vaccines in December 2020. By March 2021, over 100 million covid-19 vaccine doses had been given in the US. In California, by June 2023, 81.4% of Californians had received at least one dose of the vaccine [38]. COVID-19 vaccines were provided free, regardless of health insurance status, during the federal Public Health Emergency (PHE) for COVID-19 which expired on May 11, 2023 [39]. Since then, COVID-19 vaccines in California have remained free. However, the uninsured population has until December 31, 2024, to receive free vaccines through the CDC Bridge Access Program [40].

Our results by demographic and socioeconomic status subgroups for the early pandemic waves were generally consistent with prior reports. A previous study of COVID-19 exposure in pregnant women reported a higher rate among younger women (<25 years) compared to older women during the original and early Delta waves [15]. However, we observed reversed pattern for the Omicron wave where children born to younger mothers had slightly lower rate of exposure during pregnancy. Our higher exposure rates for Hispanic mothers for the original and Delta waves were also reported by other studies [15,21,24,25]; however, in this study we saw that the rates were similar across all race and ethnic groups for children born during the Omicron wave. Similar to previously reported [15], COVID-19 exposure in pregnancy was highest among mothers living in the most deprived areas during the original and delta waves; however, we found that NDI was not associated with COVID-19 exposure during pregnancy for children born during the Omicron wave. The similar rates of exposures by demographic and socioeconomic status during the Omicron wave may be due to the reopening of California in June 2021.

Our results by maternal health status were also generally consistent with previous reports. Previous study of COVID-19 in pregnant women reported women with living children having higher risk of severe COVID-19 [21], and COVID-19 in pregnancy was higher among women with pre-pregnancy overweight and obesity in the original wave [25] as well as in the Omicron and Delta waves. The attenuated rate ratios may suggest a lessening of this disparity with time. Pre-existing comorbidities are known to be risk factors for both contracting COVID-19 and experiencing worse outcomes [41,42]. Differences in COVID-19 exposure rates during pregnancy by maternal health factors, especially later in the pandemic, may be due to the re-opening of California, including relaxing of face mask recommendations and changes to isolation guidance. Increasing in exposure sample size for later pandemic will also enhance the study power to detect small differences.

Our results provide important data to guide future research to assess the long-term effects of maternal COVID-19 exposure during pregnancy on her child's long-term health. This may include neuro and cognitive development, growth and cardiometabolic risk and other diseases after some follow-up years of these children.

Strengths of this study include its large sample size, availability of health data from EMR collected prospectively (and thus eliminating recall bias), and the availability of pregnancy information with or without COVID-19 infection during entire pregnancy. This study reports rates across three major pandemic waves where the impact of the exposures to human health changes over the waves due to the development of vaccines and the development of immunity over time. We also assess potential disparities by demographics, SES, and many health factors.

Limitations for this study include potential underreporting of COVID-19, particularly at the beginning of the pandemic. Rates of COVID-19 in pregnancy may also be lower earlier in the pandemic

since the entire duration of these pregnancies would not have fallen within the pandemic (for instance, the pregnancy of women giving birth in March 2020 would have been largely unexposed during pregnancy). However, our rate appears comparable to previously reported rate in the obstetric population. This study used EMR data, and certain variables were unavailable, including loss of job or occupation type. Lastly, while our study population may represent the residence of southern California, it may not completely reflect the exposure patterns for the entire state of California, other states, or the United States overall.

Conclusion

For children born during March 2020 to February 2023, a significant number were born to mothers with COVID-19 infection during pregnancy. The rates were substantially increased from the original to Delta to Omicron waves both overall and across all subgroups. Significant disparities by demographics and SES were observed during the original and Delta waves, but the disparities were diminished by the Omicron wave. Maternal health factors remained as important risk factors associated with COVID-19 exposure during pregnancy for the Delta and Omicron waves. These findings provide important data to help public health efforts in identifying at risk children and develop prevention strategies to combat long-term COVID-19 effects.

Declarations

Ethics Approval and Consent to Participate: This study was approved by the Kaiser Permanente Southern California (KPSC) Institutional Review Board, with individual subject consent waived.

Consent for Publication: Not applicable

Availability of Data and Materials: The datasets analyzed during the current study are not publicly available due the data originating from electronic medical records.

Competing Interests: The authors declare that they have no competing interests.

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Author's Contributions

F.D.G, Z.C., and A.H.X. were responsible for the study concept and design. A.H.X. and Z.C. obtained funding. A.H.X., Z.C, F.D.G., S.A.C., M.P.M., and T.C., conducted the study. S.A.C, T.C., M.P.M., and A.H.X., acquired data. T.C., and A.H.X. analyzed data. T.C., M.P.M., S.A.C., and A.H.X. drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final version to be published.

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