

SUPPLEMENTARY INFORMATION

Inflammatory Conditions During Pregnancy and Risk of Autism and Other Neurodevelopmental Disorders

Croen et al.

Supplementary Methods for Sample Collection and Genotyping

Genetic Sample Collection

Maternal blood and serum specimens were deidentified and aliquoted into 2D barcoded storage vials using robotic liquid handlers (Tecan EVO 150, Fluent 780). DNA was extracted from blood/buffy coat using Life Technologies MAGMAX/MAGJET DNA ULTRA 2.0 reagents. DNA quantity was measured by Infinity M200, M-NANO multimode detectors or Qubit fluorometers. DNA specimens were normalized and aliquoted using Tecan Fluent 780/1080 robots in standard 96 well PCR plates or Micronic tubes for distribution.

Genotyping

Samples were genotyped using the Axiom Precision Medicine Research Array (PMRA) by the Genomics Core Facility at UCSF. The PMRA assays approximately 800,000 markers across the genome and is optimized for imputation in five ancestral population groups [African (AFR), admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) ancestry]. Genotype calling and quality control were carried out as in Tsang et al., 2013 (1). We performed genotyping on DNA from 2561 IMPaCT samples in two batches.

Among all the samples, 4 (0.16%) were excluded due to Dish QC less than 0.82, 14 (0.55%) were excluded for having a call rate per SNP less than 97%, 21 (0.82%) were excluded for having missingness per individual larger than 97%. After quality control 2522 samples remained. We then used PLINK (2) to calculate pairwise genetic relatedness between individuals, excluding those that were estimated to be first-, second-, or third-degree relatives (85 individuals, 3.37% of QC passing samples). We filtered markers following the process outlined in Tsang et

al., 2013 (1) resulting in 727,655 markers. Genomes were then imputed using the Michigan Imputation Server (3) with the 1000 Genomes Reference panel (4). After imputation the number of markers was increased to 30,969,804.

1. Tsang KM, Croen LA, Torres AR, Kharrazi M, Delorenze GN, Windham GC, et al. (2013): A genome-wide survey of transgenerational genetic effects in autism. *PLoS One*. 8:e76978.
2. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015): Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*. 4:7.
3. Das S, Forer L, Schonherr S, Sidore C, Locke AE, Kwong A, et al. (2016): Next-generation genotype imputation service and methods. *Nat Genet*. 48:1284-1287.
4. Fairley S, Lowy-Gallego E, Perry E, Flicek P (2020): The International Genome Sample Resource (IGSR) collection of open human genomic variation resources. *Nucleic Acids Res*. 48:D941-D947.

Table S1: Definitions of child neurodevelopmental disorders and maternal immune-mediated and cardiometabolic conditions

Condition	ICD codes		Definition
Child conditions			
ASD	ICD-9	299.0, 299.8, 299.9	>=1 dx
	ICD-10	F84.0, F84.5, F84.8, F84.9	
DD		Any ID, CP, Language Delay, Motor Disorder, Global Delay, or Learning Disorder diagnosis as defined below	>=1 dx
ID	ICD-9	317-319	>=1 dx
	ICD-10	F70-F73, F78, F79	
CP	ICD-9	333.71, 342.1, 342.8, 342.9, 343.0-343.9, 344.0, 344.1, 344.30, 344.31, 344.32, 344.5	>=1 dx
	ICD-10	G04.1, G80.0 - G80.4, G80.8, G80.9, G81.1, G81.9, G82.20-G82.22, G82.5, G83.10 - G83.14, G83.30 - G83.34, R25.8	
Language Delay	ICD-9	315.3	>=1 dx
	ICD-10	F80.0-F80.2, F80.4, F80.82, F80.89, F80.9, H93.25	
Motor Disorder	ICD-9	315.4	>=1 dx
	ICD-10	F82	
Global Delay	ICD-9	315.5, 315.8, 315.9	>=1 in this group or >=1 dx in any two of the following (language delay, motor disorder, learning disorder)
	ICD-10	F81.9, F88, F89	
Learning Disorder	ICD-9	315.0, 315.1, 315.2	>=1 dx
	ICD-10	F81.0, F81.2, F81.81, F81.89, R48.0	
Maternal conditions			
Allergy	ICD-9	279, 287.0, 322.8, 323.8, 381.04-381.06, 372.0, 372.10-372.14, 372.2, 372.3, 373.32, 380.22, 381.3, 381.4, 477, 495.0-495.7, 495.9, 518.3, 518.6, 530.19, 558.3, 691, 692.0-692.6, 692.70-692.72, 692.76, 692.79, 692.81, 692.83, 692.89, 692.9, 695.1, 692.3, 693.1, 708.0, 708.1, 708.9, 716.2, 727.3, 780.63, 989.82, 995.0-995.4, 995.6, 999.4, 999.39, V14.0-V14.9, V15.0, V64.04	>=1 dx during pregnancy

Condition	ICD codes		Definition
	ICD-10	B44.81, D69.0, D80, D81.0, D81.1, D81.2, D81.4, D81.6-D81.9, D82, D83, D84, D89.8, D89.3, D89.89, D89.9, G04.81, G04.89, H01.11, H10, H16.26, H60.5, H65.11, H65.4, H65.9, J30, J67.0-J67.7, J67.9, J82, K20.8, K52.2, L12.3, L20, L22-L25, L27.2, L30.0, L30.2, L30.8, L30.9, L50.0, L50.1, L50.9, L51, L55.0, L55.1, L55.9, L56.0-L56.3, L56.8, L56.9, M13.8, M35.9, M71.1, M71.5, N98.0, R50.83, T36-T50, T65.81, T78.0, T78.2, T78.3, T78.4, T80.5, T80.29, T88.0, T88.2, T88.52, T88.59, T88.6, Z28.04, Z88, Z91.0	
Asthma	ICD-9	493, 495.8, 518.3, 518.6, 518.81-518.84, 519.11, 786.07	>=2dx during pregnancy, or Rx during pregnancy w/ asthma history
	ICD-10	B44.81, J44, J45, J67.8, J80, J82, J96.00, J96.90, J96.10-J96.12, J96.20-J96.22, J98.01, R06.03, R06.2	
Autoimmune	ICD-9	099.3, 135, 136.1, 242.0, 242.2, 242.4, 242.8, 242.9, 245.2, 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93, 255.4, 258.1, 273.2, 279.0-279.5, 279.8, 279.9, 283.0, 286.52, 287.31, 287.32, 287.4, 287.5, 321.4, 323.51, 323.52, 340, 358.1, 357.0, 357.81, 358.0, 359.71, 360.11, 360.12, 362.18, 363.2, 364.3, 695.4, 373.34, 376.12, 377.30, 377.31, 377.39, 386.0, 390-398, 443.0, 446.0, 446.1, 446.20, 446.21, 446.29, 446.4-446.7, 447.6, 447.8, 516.3, 517.2, 517.8, 555, 556, 558, 571.42, 571.49, 571.6, 573.3, 576.1, 579.0-579.4, 579.8, 579.9, 583.89, 583.9, 694.4, 694.5, 694.9, 695.13, 695.14, 696, 697, 701.0, 704.0, 709, 710.0-710.4, 710.8, 710.9, 711.1, 711.2, 711.9, 714.0-714.3, 714.9, 720.0, 720.9, 725, 728.11, 728.81, 733.99, 775.2, V12.3	>=1 dx during pregnancy
Autoimmune	ICD-10	D59.0, D59.1, D68.311, D69.3, D69.41, D69.5, D69.6, D80, D81.0, D81.1, D81.2, D81.4, D81.6, D81.7, D81.89, D81.9, D82, D83, D84, D86, D89.1, D89.3, D89.81, D89.82, D89.89, D89.9, E05.0, E05.2, E05.3, E05.4, E05.8, E05.9, E06.3, E08.628, E09.628, E10, E27.1-E27.4, E31.0, E89.6, G02, G04.02, G04.32, G61.0, G61.81, G35, G70.0, G72.41, G73.3, H01.12, H05.12, H20.9, H30.2, H30.8, H30.9, H35.06, H44.11, H44.13, H46.0, H46.8, H46.9, H81.0, I00-I09, I73.0, I77.3, I77.6, I77.89, J84.11, J84.2, J99, K50, K51.919, K52, K71, K73.1, K73.2, K73.8, K74.3, K74.4, K74.5, K75.2, K75.3, K75.4, K75.8, K75.9, K76.4, K80.3, K83.0, K90, K91.2, L10, L12.0, L12.8, L12.9, L13.9, L30.5, L40-L43, L44.0-L44.3, L44.8, L44.9, L45, L51.1, L51.3, L57.3, L63, L64, L65, L66.0-L66.2, L66.8, L66.9, L80, L81, L90.0, L90.5, L92.1, L92.3, L93, L94.0, L94.1, L94.2, L94.3, L94.4, L94.5, L94.8, L95.0, L95.8, L95.9, L98.8, L98.9, L99, M01, M02.3, M05.0, M05.2, M05.3, M05.4, M05.5, M05.6, M05.7, M05.8, M06, M08, M30, , M31.0, M31.1, M31.3-M31.7, M32-M34, M35.0-M35.3, M35.5, M35.8, M35.9, M36.0, M36.8, M45, M46.9, M48.8, M60.1, M61.1, M84.8, M84.9, M85.1, M85.8, M89.2, M89.3, M89.5, M89.8, M94.1, M94.35, M94.8, N05.0, N05.1, N05.6-N05.9, N06.0, N06.1, N06.6-N06.9, N07.0, N07.1, N07.6-N07.9, N14, N15.0, N15.8, N15.9, P94.0, Z86.2	

Condition	ICD codes		Definition
Infection	ICD-9	001-018, 020-027, 030-039, 040-042, 045-066, 070-088, 090-104, 110-112, 114-118, 136, 289.1, 289.2, 289.3, 320-322, 323.0-323.6, 323.8, 323.9, 324-326, 357.0, 357.4, 360.0, 360.12, 360.13, 360.19, 363.0-363.2, 364.0-364.3, 370.32, 372.00-372.05, 372.10-372.13, 372.15, 372.2, 372.30, 372.31, 372.33, 372.39, 373.0, 373.1, 373.4-373.9, 380.0-380.2, 381.0-381.5, 382, 383, 384.0, 384.1, 385, 386.0-386.3, 387, 388.0, 388.2, 388.3, 388.40, 388.41, 388.5, 388.8, 388.9, 389-392, 420-422, 424.9, 460-466, 472, 473, 476, 480-488, 490, 517.1, 522.5-522.7, 527.2, 527.3, 528.00, 528.1, 528.3, 535.0-535.2, 535.4-535.6, 540, 567.0-567.3, 567.8, 567.9, 573.1, 577.0, 583.0, 583.4, 583.9, 590, 595, 597, 599.0, 599.2, 601, 604, 608.81, 614-616, 658.4, 680-686, 711.4-711.9, 713.5, 730.81, 730.88, 762.7, 770.0, 771, 785.6, 790.7, 790.8, 795.71, 995.91, V04.82, V08, V65.44	>=1 dx during pregnancy
	ICD-10	A00-A09, A15, A17, A18, A19, A20-A28, A30-A33, A35-A44, A45.86, A46, A48-A58, A60, A63-A71, A74, A75, A77-A96, A98, A99, B00-B10, B15-B20, B25-B27, B28.85, B30, B33-B43, B44.0-B44.2, B44.7, B44.89, B44.9, B45-B55, B57, B60.0, B60.12, B60.8, B64, B77.81, B78.1, B95-B97, E83.2, G00-G03, G04.0, G04.2-G04.9, G05-G09, G37.4, G61.0, H00.0, H01.0, H01.8, H01.9, H10.0, H10.1, H10.22, H10.23, H10.3, H10.40, H10.42-H10.44, H10.5, H10.8, H10.9, H16.26, H20, H21.33, H30, H32, H33.12, H40.40X0, H44.0, H44.11, H44.12, H44.19, H60.0-H60.4, H60.6-H60.9, H61.0, H61.9, H62.4, H62.8, H65-H67, H68.0, H70, H71, H73.0-H73.2, H74, H75, H80, H81.0-H81.4, H83.0, H90, H91, H93.0, H93.1, H93.22, H93.24, H93.29, H93.3, H93.8, H93.9, H94.0, H94.8, H95.0, H95.1, I00-I02, I30, I32, I33.9, I38-I41, I67.3, I88, J00-J17, J18.0, J18.1, J18.8, J18.9, J20, J21, J31, J32, J37, J40, K04.5, K04.6, K04.7, K11.2, K12.2, K29, N34.1, K35, K65, K66.8, K67, K68.12, K68.19, K68.9, K77, K90.81, L01-L08, L44.4, L88, L92.8, L98.0, L98.3, M00.0-M00.2, M00.8, M01, M02.3, M02.80-M02.89, M32.11, M32.12, M60.009, M90.81, M90.88, N10-N12, N13.6, N15.1, N15.9, N16, N28.84, N28.85, N28.86, N30.0, N30.2, N30.3, N30.8, N30.9, N34, N36.1, N39.0, N41, N45, N51, N70-N77, O41.1, P02.7, P23, P35-P39, R11.11, R59, R75, R78.81, Z21, Z23, Z71.7	
Gestational Diabetes	ICD-9	648.8	>=1 dx & >=1 Lab glucose abnormal results during pregnancy, or Carpenter and Coustan (C&C) criteria
	ICD-10	O24.4	
Diabetes	ICD-9	250	>=2 dx, or >=2 Lab abnormal results, or >=1 Rx before/during pregnancy
	ICD-10	E10, E11, E13, O24.0, O24.1, O24.3, O24.8, O24.9	

Condition	ICD codes		Definition
Obesity Obesity Class I Obesity Class II Obesity Class III	ICD-9	278.00-278.03, 783.22	≥1 dx or BMI recorded just before pregnancy Class I: 30 ≤ BMI < 35 Class II: 35 ≤ BMI < 40 Class III: BMI ≥ 40
	ICD-10	E66.01, E66.2, E66.3, E66.9, R63.6	
Preeclampsia	ICD-9	642.4, 642.5, 642.7	≥2 dx during pregnancy
	ICD-10	O11, O14, O15.2	
Hypertension Chronic HTN Gestational HTN	ICD-9	Chronic: 401-405 Gestational: 642.3	Chronic: ≥2 dx, or ≥1 dx & rx during pregnancy. Gestational: ≥1 dx during pregnancy
	ICD-10	Chronic: I10-I13, I15 Gestational: O13	

ASD=Autism Spectrum Disorder; ID=Intellectual Disability; CP=Cerebral Palsy; DD=Neurodevelopmental Disorder; ICD=International Classification of Diseases; HTN=Hypertension

Table S2. Associations of maternal asthma and obesity with child neurodevelopmental outcomes by race/ethnicity

	ASD	DD	GP	ASD vs GP		DD vs GP	
	n (%) in race group	n (%) in race group	n (%) in race group	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
Asthma							
Asian	5 (7.81)	28 (10.53)	18 (8.82)	0.88 (0.31-2.46)	0.75 (0.26-2.18)	1.22 (0.65-2.27)	1.13 (0.59-2.15)
Black	3 (15.00)	18 (22.50)	8 (16.67)	0.88 (0.21-3.74)	0.75 (0.11-4.97)*	1.45 (0.58-3.65)	1.55 (0.58-4.14)
Hispanic	15 (21.74)	73 (22.60)	31 (13.66)	1.76 (0.88-3.49)	1.74 (0.82-3.70)	1.85 (1.17-2.92)	1.99 (1.23-3.21)
Other	3 (21.43)	8 (13.11)	14 (29.17)	0.66 (0.16-2.74)	0.50 (0.11-2.42)*	0.37 (0.14-0.97)	0.24 (0.08-0.72)
White	38 (26.39)	96 (17.11)	65 (14.77)	2.07 (1.31-3.26)	2.21 (1.37-3.55)	1.19 (0.85-1.68)	1.22 (0.87-1.73)
Obesity							
Asian	5 (7.81)	24 (9.02)	22 (10.78)	0.72 (0.25-2.01)	0.84 (0.28-2.51)	0.83 (0.44-1.54)	0.91 (0.47-1.74)
Black	11 (55.00)	34 (42.50)	18 (37.50)	2.75 (0.74-10.27)	0.93 (0.18-4.90)*	1.89 (0.79-4.50)	1.54 (0.57-4.18)
Hispanic	26 (37.58)	127 (39.32)	83 (36.56)	1.18 (0.60-2.34)	1.22 (0.59-2.54)	1.16 (0.76-1.76)	1.29 (0.83-2.02)
Other	5 (35.71)	20 (32.79)	11 (22.92)	1.36 (0.35-5.31)	1.33 (0.25-7.26)*	1.66 (0.65-4.27)	1.46 (0.50-4.29)
White	50 (34.72)	151 (26.92)	99 (22.50)	2.01 (1.27-3.17)	1.98 (1.23-3.19)	1.21 (0.88-1.65)	1.24 (0.90-1.70)

ASD=Autism Spectrum Disorder; DD=Neurodevelopmental Disorders; GP=General Population controls; OR=Odds Ratio; CI=Confidence Interval;

^aAdjusted models include child sex, birth year, maternal age, and maternal education. Reference group for each condition is absence of the condition.

Table S3. Associations of treated and untreated maternal asthma with child neurodevelopmental outcomes

	ASD	DD	POP	ASD vs POP		DD vs POP	
	(N=311) N (%)	(N=1291) N (%)	(N=967) N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Asthma with RX during pregnancy	31 (9.97)	114 (8.83)	70 (7.24)	1.49 (0.95 - 2.33)	1.58 (0.98 - 2.54)	1.27 (0.93 - 1.73)	1.27 (0.92 - 1.74)
Asthma without Rx during pregnancy	33 (10.61)	109 (8.44)	66 (6.83)	1.68 (1.08 - 2.62)	1.68 (1.05 - 2.67)	1.29 (0.93 - 1.77)	1.34 (0.97 - 1.85)

ASD=Autism Spectrum Disorder; DD=Neurodevelopmental Disorders; GP=General Population controls; OR=Odds Ratio; CI=Confidence Interval;RX=asthma medication

Adjusted models include child sex, birth year, maternal age, maternal race, and maternal education. Reference group for each condition is absence of the condition.

Table S4. Joint effects of maternal asthma during pregnancy, gestational diabetes, and pre-pregnancy obesity on child neurodevelopmental outcomes

ASD vs GP						
	GDM				P int	RERI (95% CI)
	No GDM		GDM			
Asthma	N (%)*	OR (95% CI) ^a	N (%)*	OR (95% CI) ^a		
No Asthma	214 (68.81)	1.0 (ref)	33 (10.61)	1.14 (0.73 - 1.80)		
Asthma	58 (18.65)	1.82 (1.26 - 2.64)	6 (1.93)	0.84 (0.32 - 2.20)	0.11	-1.12 (-2.29, 0.05)
DD vs GP						
	GDM				P int	RERI (95% CI)
	No GDM		GDM			
Asthma	N (%)*	OR (95% CI) ^a	N (%)*	OR (95% CI) ^a		
No Asthma	904 (70.02)	1.0 (ref)	164 (12.70)	1.46 (1.10 - 1.95)		
Asthma	185 (14.33)	1.36 (1.05 - 1.76)	38 (2.94)	1.34 (0.78 - 2.31)	0.21	-0.51 (-1.39, 0.37)
ASD vs GP						
	GDM				P int	RERI (95% CI)
	No GDM		GDM			
Obesity Class	N (%)*	OR (95% CI) ^a	N (%)*	OR (95% CI) ^a		
Not Obese	196 (63.02)	1.0 (ref)	18 (5.79)	0.81 (0.45 - 1.43)		
Obese all Classes	76 (24.44)	1.38 (0.99 - 1.94)	21 (6.75)	1.49 (0.83 - 2.66)	0.54	0.28 (-0.75, 1.30)
Obese Class I	38 (12.22)	1.21 (0.79 - 1.86)	12 (3.86)	1.35 (0.64 - 2.87)	0.52	0.34 (-0.85, 1.53)
Obese Class II	20 (6.43)	1.24 (0.68 - 2.23)	6 (1.93)	1.69 (0.56 - 5.06)	0.44	0.66 (-1.38, 2.70)
Obese Class III	18 (5.79)	2.43 (1.25 - 4.72)	3 (0.96)	1.52 (0.38 - 6.08)	0.74	-0.76 (-3.38, 1.86)
DD vs GP						
	GDM				P int	RERI (95% CI)
	No GDM		GDM			
Obesity Class	N (%)*	OR (95% CI) ^a	N (%)*	OR (95% CI) ^a		
Not Obese	826 (63.98)	1.0 (ref)	109 (8.44)	1.29 (0.92 - 1.82)		
Obese all Classes	263 (20.37)	1.14 (0.91 - 1.42)	93 (7.20)	1.46 (0.99 - 2.14)	0.94	0.07 (-0.66, 0.81)
Obese Class I	145 (11.23)	1.11 (0.84 - 1.47)	41 (3.18)	1.06 (0.64 - 1.75)	0.36	-0.34 (-1.09, 0.40)
Obese Class II	73 (5.65)	1.15 (0.78 - 1.69)	29 (2.25)	2.35 (1.09 - 5.08)	0.30	0.99 (-0.98, 2.95)
Obese Class III	45 (3.49)	1.19 (0.72 - 1.95)	23 (1.78)	1.90 (0.86 - 4.22)	0.65	0.45 (-1.23, 2.13)

ASD=Autism Spectrum Disorder; DD=Neurodevelopmental Disorders; GP=General Population controls; OR=Odds Ratio; CI=Confidence Interval; GDM=Gestational Diabetes

^aAdjusted models include child sex, birth year, and maternal age, race, and education. For each combination of maternal conditions, both conditions (i.e., GDM and Asthma, GDM and Obesity) were both included in the model simultaneously.

*N represents counts for ASD or DD.