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Original Article: Preeclampsia, Placental Insufficiency and Autism Spectrum Disorder or Developmental Delay

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Abstract

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Study concept and design: Walker, Krakowiak,Hertz-Picciotto.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Walker.
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Conflict of Interest Disclosures: Dr. Walker reported serving on the Speaker's Bureau for Merck & Co, Inc. This work pertains neither to preeclampsia nor to neurodevelopment. Dr Hertz-Picciotto reported serving on the Scientific Advisory Committee of Autism Speaks and receiving reimbursement for travel to in-person meetings and in-kind meals. She also reported receiving honoraria and/or travel reimbursements for speaking engagements on the topic of autism and environment at academic institutions and to professional societies or child advocacy organizations. None of these activities pertained to preeclampsia. No other disclosures were reported.

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Importance—Increasing evidence suggests that autism spectrum disorder (ASD) and many forms of developmental delay (DD) originate during fetal development. Preeclampsia may trigger aberrant neurodevelopment through placental, maternal and fetal physiologic mechanisms.

Objective—To determine whether preeclampsia is associated with ASD and/or DD.

Design, Setting and Participants—The *CH*ildhhood *A*utism *R*isks from *G*enetics and the *E*nvironment (CHARGE) Study is a population-based case-control investigation of ASD and/or DD origins. Children from 20 California counties aged 24-60 months at the time of recruitment, and living in catchment areas with a biologic parent fluent in English or Spanish were enrolled from January 29, 2003 through April 7, 2011. Children with ASD (n=517) and DD (n=194) were recruited through the California Department of Developmental Services, the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute and referrals. Controls with typical development (TD) controls (n=350) were randomly selected from birth records and frequency-matched on age, sex, and broad geographic region. Physicians diagnosing preeclampsia were masked to neurodevelopmental outcome, and those assessing neurodevelopmental function were masked to preeclampsia status.

Exposure—Preeclampsia and placental insufficiency were self-reported and abstracted from medical records.

Main Outcome Measure—The Autism Diagnostic Observation Schedule and Autism Diagnostic Interview–Revised were used to confirm ASD, whereas children with DD and TD were confirmed by Mullen Scales of Early Learning and Vineland Adaptive Behavior Scales and were free of autistic symptoms. Hypotheses were formulated before data collection.

Results—Children with ASD were twice as likely to have been exposed in utero to preeclampsia as controls with TD after adjustment for maternal educational level, parity, and prepregnancy obesity (adjusted odds ratio, 2.36; 95% CI, 1.18-4.68); risk increased with greater preeclampsia severity (test for trend p=0.02). Placental insufficiency appeared responsible for the increase in DD risk associated with severe preeclampsia (adjusted odds ratio, 5.49; 95% CI, 2.06-14.64).

Conclusions and Relevance—Preeclampsia, particularly severe disease, is associated with ASD and DD. Faulty placentation manifests in the mother as preeclampsia with vascular damage, enhanced systemic inflammation and insulin resistance; in the placenta as oxygen and nutrient transfer restriction and oxidative stress; and in the fetus as growth restriction and progressive hypoxemia. All are potential mechanisms for neurodevelopmental compromise.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurobehavioral condition identified in 1 in 68 U.S. children and is part of a broader group of developmental disabilities that affects 1 in 6 children.[1] In the prevailing etiologic theory for ASD, environmental influences factor prominently in mechanisms for neurodevelopmental programming during critical periods in genetically-susceptible individuals.[2] Physiologic and architectural changes identified in the brains of children and adults with ASD indicate that its pathophysiologic mechanism likely originates during fetal development.[3] Gestational conditions and obstetric complications have been linked to ASD, [4-11] but research on mechanisms that might explain the associations is still lacking. Neuropathogenic processes in the gestational environment,

including infection,[12-14] inflammation,[15] oxidative stress,[16] fetal hypoxia,[17] micronutrient insufficiency,[18] and metabolic dysfunction,[19] have been proposed to play some role in the etiology of ASD.

Developmental delay (DD) is a diagnosis applied to young children who have low cognitive function in addition to significant limitations in at least 2 other developmental domains.[20] Etiologic paradigms for DD are as diverse as the component conditions, and although genetic and congenital causes are implicated in up to 50% of affected children, environmental exposures (including antenatal toxin exposure, central nervous system infections, hypoxicischemic encephalopathy, cerebral dysgenesis, and early severe psychosocial deprivation) likely enhance risk during critical fetal and postnatal periods.[21] Maternal prepregnancy obesity, diabetes mellitus and chronic hypertension during pregnancy have been associated with DD and specific impairments in visual reception, motor skills, receptive and expressive language, adaptive communication and socialization.[19] Prematurity and fetal growth restriction, both commonly associated with severe preeclampsia, are significantly and independently related to DD severity.[22]

Preeclampsia is a complex multisystem disorder unique to the latter half of pregnancy that can lead to severe maternal and fetal morbidity and even mortality. The condition is more common in first pregnancies and maternal age extremes,[23] and risk appears to be modulated considerably by underlying maternal metabolic and cardiovascular health.[24] The most prominent causal paradigm for preeclampsia is predicated on a model of shallow placentation[25] marked by hypo-perfusion that reduces concentrations of angiogenic growth factors and increases placental debris in the maternal circulation, culminating in a robust maternal immune response and damage to the maternal, placental and fetal circulatory systems.[26] Classic features of preeclampsia include progressive hypertension, edema, and proteinuria (though new guidelines no longer require proteinuria for diagnosis),[27] and severe variants manifest evidence of maternal brain, liver or kidney deterioration and/or placental insufficiency, a clinical syndrome characterized by fetal growth restriction, reduced amniotic fluid, and suboptimal fetal oxygenation.[28] Although placental insufficiency may arise without maternal hypertension, failed placental vascular remodeling appears to be a unifying mechanism for both conditions.[29] Women with preeclampsia are more likely to deliver early, either spontaneously or by elective intervention to prevent complications from maternal and/or fetal deterioration.[26]

Preeclampsia has been examined as a risk factor for ASD in multiple investigations with mixed results. Seventeen studies of variable quality published before 2007 that examined preeclampsia in association with autism had substantial unexplained heterogeneity of effect estimates.[7] Four large population-based case-control studies[8-11] reported statistically significant increased adjusted odds of ASD after pregnancies complicated by preeclampsia. Fetal growth restriction and premature delivery occur more commonly with preeclampsia, and are associated with DD[22] and ASD.[4,5,30,31]

The first objective of this study was to examine the association between preeclampsia and ASD or DD in a population-based case-control study with confirmed diagnoses. The second aim was to explore whether preeclampsia severity and/or placental insufficiency increased

the odds of ASD or DD. Given the co-occurrence of intellectual impairments among many individuals with ASD, we included the DD group in our analyses to examine whether findings were specific to ASD or rather associated with cognitive delays in general.

METHODS

The CHildhood Autism Risks from Genetics and the Environment (CHARGE) study is a population-based case-control study of children from three groups: children with ASD, children with DD without ASD, and children with typical development (TD).[32] Children with ASD and DD were recruited from lists provided by the California Department of Developmental Services; referred from the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California, Davis, local physicians, or regional centers that contracted with the California Department of Developmental Services; or self-referred after public outreach efforts. Population controls were selected randomly from California birth files with a male-to-female ratio of 4:1 and frequency-matched for age and broad geographic regions within the study catchment areas.

Inclusion criteria were: (1) age 24 to 60 months, (2) residence with at least one biologic parent, (3) English or Spanish spoken by at least one parent, (4) birth in California, and (5) living within specified catchment areas in California. Children with severe visual, hearing or motor impairments that precluded standardized developmental assessment were excluded. Participants in this analysis were enrolled between January 29, 2003 through April 7, 2011. The institutional review boards at the University of California, Davis, and the University of California, Los Angeles, and the State of California Committee for the Protection of Human Subjects approved this study, and informed consent was obtained.

We used 2 sources of data to establish our exposure variable and covariates. We abstracted diagnoses and supporting information from medical records when available. Records were reviewed multiple times by trained staff and inconsistencies were resolved. Mild preeclampsia and pregnancy-induced hypertension were combined, and severe preeclampsia included HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome. We considered women with preeclampsia to have severe disease if it was documented in their record or if they had preeclampsia with evidence of placental insufficiency, a composite that involved intrauterine growth restriction, oligohydramnios and/or non-reassuring fetal test results. In the absence of medical records, we relied on maternal self-report in a telephone interview conducted in English or Spanish.[32] Mothers were asked whether a medical professional had told them they had preeclampsia or toxemia during their pregnancy. We had self-report data from 1002 participants (94.4%), maternal records from823 (77.6%), and data from both in 764 (72.0%); agreementwas substantial ($\kappa = 0.66$, 95% CI, 0.55-0.77).

We examined demographic factors and pregnancy outcomes. All federally, state, or locally funded programs, except for military insurance, were included under government payer; military programs were categorized as private because they function as employer-sponsored health insurances. Maternal factors examined as potential confounders of the associations between preeclampsia and child's diagnosis were: periconceptional folic acid intake,[18,33]

smoking and selective serotonin reuptake inhibitor (SSRI) use during pregnancy,[34-37] residential air pollution exposure,[18,38] and prepregnancy obesity, diabetes or chronic hypertension,[19,24] were evaluated for their influence as confounders. We merged pregestational (types 1 and 2) and gestational diabetes mellitus into a diabetes variable and calculated the prepregnancy body mass index (BMI) as maternal self-reported weight in kilograms divided by the square of height in meters and categorized women as obese (BMI≥ 30), overweight (BMI 25-29.9), health weight (BMI 18.5-24.9), or underweight (BMI<18.5).

Our outcome was child developmental status, categorized as ASD, DD, and TD. Highly trained research-reliable health care professionals administered standardized assessments to establish developmental diagnosis and functional level. Bilingual, bicultural health care professionals evaluated children from Spanish-speaking families. Outcome determination has been described previously.[19] Briefly, children with a previous ASD diagnosis were examined using the Autism Diagnostic Observation Schedule and the primary caregiver was administered the Autism Diagnostic Interview–Revised. Diagnostic confirmation required scores over established cutoffs on both instruments. Children with DD and population controls were screened for ASD using the Social Communication Questionnaire; those with scores above the cutoff (score of ≥15) were assessed using the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview–Revised and reclassified to the ASD group if they met the criteria. Adaptive function was evaluated on all children using the Vineland Adaptive Behavior Scales and cognitive function was measured with the Mullen Scales of Early Learning. Inclusion criteria for the TD group were population control with a composite Mullen Scales of Early Learning standard score of 70 or higher, an overall Vineland Adaptive Behavior Scales score of 70 or higher, and a Social Communication Questionnaire score less than15, whereas DD inclusion criteria were a Mullen Scales of Early Learning score less than 70 and / or a Vineland Adaptive Behavior Scales score less than 70 and a Social Communication Questionnaire score less than 15.

We studied 1061 children from singleton pregnancies with a confirmed diagnosis and preeclampsia status (517 children with ASD, 350 children with TD, and 194 children with DD). Seven women had 2 index pregnancies, leaving 1054 distinct mothers.

We generated a conceptual framework in the form of a Directed Acyclic Graph to guide our analysis of underlying causal relationships (eFigure 1). Analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc). Box plots were generated with GraphPad Prism software, version 5.00 for Windows (GraphPad Software Inc). We screened covariates for association with exposure and outcome, using $p<0.20$ as a threshold for selection as a potential confounder.[39] Categorical variables were analyzed using likelihood-ratio Chi-square tests and continuous variables were compared using analysis of variance. Multinomial logistic regression models that controlled for maternal factors were developed to examine the association between preeclampsia (complete dataset) and preeclampsia severity (medical-record subset) with developmental outcomes. We compared these with parallel models adjusted for differential self-selection bias by weighting to the inverse probability of participation based on maternal educational level, insurance status at delivery, and child's recruitment case group. The potential for exposure misclassification was

assessed. Final models were not restricted to mothers with complete data on all covariates considered.

RESULTS

No differences were found between children with ASD and population controls with respect to race/ethnicity, parity, gestational length, or birthweight extremes (Table 1 and eFigure 2 in the Supplement). Mothers of children with DD were more likely to be of minority ethnic or racial status, not to have received a bachelor's degree, to have had a government payer for delivery, to have high parity and to have delivered prematurely. Children with DD were born a week earlier compared with children with ASD or TD. Control children were more likely to have resided in Northern California, an effect of recruitment efforts. A total of 62 children with DD (33.2%), 10 children with ASD (2.1%), and none of the children with TD had a known chromosomal, genetic or mitochondrial disorder.

As has been reported previously, mothers of children with ASD or DD were less likely than mothers of children with TD to have taken periconceptional folic acid supplementation (Table 2).[18] Other factors previously reported from the CHARGE study (prepregnancy obesity, diabetes, and hypertension,[19] gestational SSRI use,[37] and residence near a freeway at delivery[18]) were more common in this sample of mothers of children with ASD and DD. Among those with medical record documentation, 27 (54%) of women with preeclampsia received magnesium sulfate during labor for seizure prophylaxis and 5 (0.6%) of women without preeclampsia received magnesium sulfate to treat preterm labor (Table 3).

Preeclampsia complicated the gestations of children with ASD more than twice as often as those of children with TD (Table 3). Among participants with medical records, mothers of children with ASD and DD were significantly more likely to have had placental insufficiency, severe preeclampsia or both compared with mothers of children with TD. In final models adjusted for confounding by maternal educational level, prepregnancy obesity and parity; women with preeclampsia had more than double the risk of having a child with ASD compared with women without this condition (adjusted odds ratio, 2.36; 95% CI, 1.18-4.68) (Table 4). Combining placental insufficiency and/or preeclampsia into one variable did not appear to confer additional risk in the ASD analysis, although a substantial number of women had placental insufficiency without preeclampsia; in contrast, DD was substantially more likely when placental compromise was identified. In subset analyses that explored cognitive function among children with ASD, preeclampsia was associated with low-functioning ASD compared with children with TD; the numbers were too small in the high-functioning ASD group for further analyses. Multinomial logistic regression model results were not demonstrably affected by most candidate confounders (eTable 1). Weighted and unweighted analyses were not materially different, suggesting minimal influence from participation (selection) bias.

Comparison of exposure source in various models revealed important distinctions (eTable 2). Recall bias was evident in the subset of women whose preeclampsia status could be determined by both medical record and self-report, with estimated odds 40% higher for ASD and 30% higher for DD when preeclampsia was defined using self-report (ignoring the

medical record). These differences suggest that case mothers were overreporting preeclampsia in the interview, control mothers were underreporting or a mix of both (i.e., differential misclassification).

In models restricted to medical record data, substantial ASD (adjusted odds ratio, 2.29; 95% CI, 0.97-5.43) and DD risk (adjusted odds ratio, 5.49; 95% CI, 2.06-14.64) was found among mothers with severe preeclampsia (Figure). Trend analysis was significant in both models, with a dose-response effect in the ASD vs TD comparison ($p = 0.02$) and a threshold effect in the DD vs TD analysis ($p = 0.004$), likely reflecting the strong influence of placental insufficiency in the DD model. These dose-response results must be viewed with caution because only 7 of 270 women with children with TD experienced severe preeclampsia and/or placental insufficiency.

DISCUSSION

Fetal exposure to preeclampsia was associated significantly with development of ASD in children from the CHARGE study, and the association was more robust in those pregnancies complicated by severe disease. Preeclampsia was associated with DD primarily in severe presentations that involved placental insufficiency.

The literature is inconsistent with respect to preeclampsia and ASD. In older studies designed to identify multiple gestational risk factors for ASD, one study[4] found no association for hypertensive disorders in general, another study[5] found no association for preeclampsia, and yet another study[6] noted that their preeclampsia prevalence of 3.9% among cases was consistent with the general population rate. Exposure and outcome ascertainment was suboptimal in these analyses, which controlled for a set of intrapartum and neonatal factors that may have biased the results. We measured exposures and outcomes objectively and our analysis plan assessed covariates according to principles of confounding that take into account causal pathways.[39] Specifically, because our overarching aim was to estimate the total effect on risk for ASD or DD from preeclampsia or the combination of preeclampsia and placental insufficiency, it was critical *not* to adjust for pathway intermediates such as preterm birth or low birthweight, both of which commonly result from these conditions.[4,5,22,30,31]

Other population-based epidemiologic studies that had greater statistical power and used more objective administrative data sources to identify preeclampsia and neurodevelopmental outcome have found an increased risk of ASD among children exposed to preeclampsia, with point estimates ranging from 1.24 to 1.85. [8-11] Higher odds in the current study may reflect the fact that enhanced ASD risk primarily involved severe preeclampsia and placental insufficiency identified from medical records that would not as easily have been captured from administrative sources or self-report.

The enhanced odds of DD in women with severe preeclampsia presentations that involved placental insufficiency parallels the literature of non-genetic DD causes which now include fetal growth restriction and prematurity in addition to classic traumatic insults to the fetal brain in the form of hypoxia, infection or toxin exposure.[22]

There are several mechanisms by which preeclampsia may affect the developing brain. Suboptimal uteroplacental perfusion arises from abnormal trophoblast differentiation during embryogenesis[28] and the effects of vascular compromise progress at a variable rate through gestation. Abnormal trophoblast bilayer foldings have been associated with ASD.[40]

For the fetus, limitations in nutrient and oxygen availability cause progressive oxidative stress, prompting syncytiotrophoblast release of proteins into the maternal bloodstream in an effort to improve circulation. These proteins promote maternal vascular and immune responses that greatly exaggerate baseline systemic inflammation, insulin resistance and vascular endothelial changes.[24]

Although difficult to measure retrospectively and outside the scope of the current investigation, acute and chronic fetal hypoxia and resulting oxidative stress have been implicated in the pathophysiology of preeclampsia and as risks for ASD. Nonspecific surrogates, such as low Apgar scores, fetal distress, cesarean delivery, and bleeding during pregnancy, have been associated with ASD.[41] Umbilical blood pH at birth is a more precise measure of acute hypoxia and was weakly associated with ASD in one study.[17]

An etiologic role for heightened maternal systemic inflammation in autism is highly plausible. Fetal exposure to maternal allergies, autoimmune diseases[42] and maternal infections[12-14] have also been associated with ASD. Although direct fetal brain infection is possible, untreated maternal fever[14] and the proinflammatory milieu accompanying systemic infection[13] may compromise the placenta and fetal compartments, predisposing patients to ASD. Some maternal cytokines, most notably interleukin 6, appear able to cross the placenta and enter fetal circulation where they have the potential to modulate neuronal proliferation, survival, differentiation and function.

Maternal metabolic dysregulation, systemic inflammation and insulin resistance are prominent features of obesity, diabetes and chronic hypertension, which are associated with preeclampsia[24] and ASD.[19] Women with preeclampsia are twice as likely to be obese, and increasing obesity prevalence has paralleled the increase in preeclampsia in the United States[23] Markers of increased insulin resistance are apparent in the first trimesters of preeclamptic pregnancies and persist after birth, suggesting baseline maternal metabolic derangements not unique to gestation.[24] Excess weight and other maternal metabolic conditions have been associated with ASD in multiple populations.[11,19]

There is substantial strength in this case-control study. Our population-based sampling and large sample size enabled examination of rare exposures. We explored information bias in our exposure extensively by comparing self-report across subsets of the data and validating with objective clinical sources. Medical record availability for a large subset of participants allowed us to better ascertain mild and severe preeclampsia variants and placental insufficiency using confirmatory physical findings and test results; such details are not accessed commonly by researchers. Case status was confirmed with rigorous neurodevelopmental and behavioral assessment by trained and reliability-tested staff. The level of detail obtained by the CHARGE study on predictors, confounders, and outcomes enabled a comprehensive exploration of this topic.

CONCLUSIONS

We found significant associations between preeclampsia and ASD that increased with presentation severity; we also observed a significant association between severe preeclampsia and/or placental insufficiency and DD. Although single studies cannot establish causality, the cumulative evidence supports efforts to reduce preeclampsia and diminish severity to improve neonatal outcomes. Optimization of metabolic health before and throughout gestation may improve placental perfusion and should be investigated. Maternal administration of low-dose aspirin has shown modest benefit, and use of statins shows promise given their ability to diminish angiogenic signaling, endothelial injury, oxidative stress, and inflammation pathways implicated in preeclampsia's pathogenesis.[43] Finally, a deeper understanding of these complex etiologic pathways will be of clinical utility in managing pregnancies and timing the deliveries of women with preeclampsia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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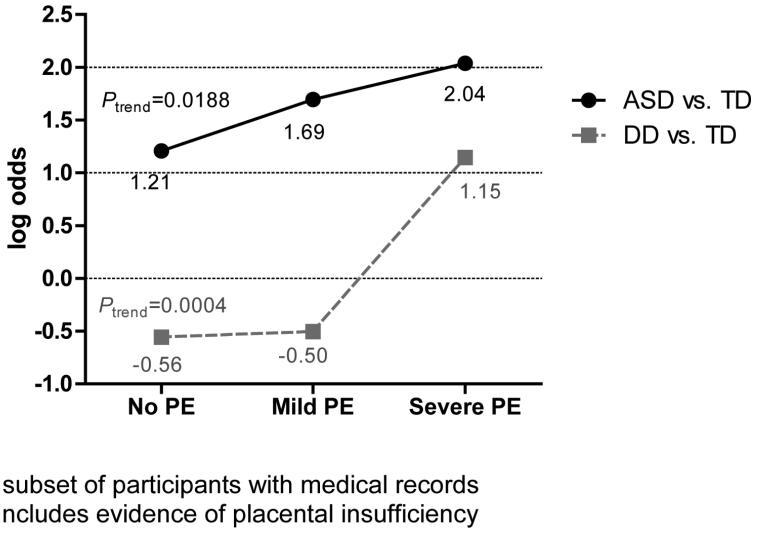

+ subset of participants with medical records
[a] Includes evidence of placental insufficiency

Figure 1. Log odds of Autism Spectrum Disorder (ASD) and Developmental Delay (DD) Relative to Typical Development (TD) in Relation to Preeclampsia Severity

In models restricted to medical record data, substantial ASD and DD risk was found among mothers with severe preeclampsia. Trend analysis was significant in both models (*P* for trend = .02 for ASD vs TD and <.001 for DD vs TD).

Table 1

Characteristics of CHARGE Study Participants by Diagnostic Group, (N=1,061)

	ASD (n=517)		DD (n=194)		TD (n=350)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Maternal race/ethnicity						
White	304	58.8	93	47.9	221	63.1
Black	17	3.3	15	7.7	10	2.9
American Indian/Alaska native	2	0.4	0		1	0.3
Asian / Pacific Islander	43	8.3	4	2.1	24	6.9
Hispanic	133	25.7	72	37.2	77	22.0
Multi-racial	18	3.5	10	5.1	17	4.8
Maternal educational level						
Less than High school	20	3.9	29	14.9	18	5.2
High school	51	9.9	34	17.5	38	10.9
Some post-high school education	212	41.1	76	39.2	116	33.1
Bachelor degree	150	29.0	43	22.2	123	35.1
Graduate/Professional degree	83	16.1	12	6.2	55	15.7
Missing	*1*		*0*		*0*	
Delivery payer						
Government program	88	17.1	62	32.0	47	13.5
Private insurance	428	82.9	132	68.0	302	86.5
Missing	*1*		*0*		*1*	
All births/Parity (incl. index child)						
1	243	47.0	72	37.1	152	43.4
2	196	37.9	65	33.5	122	34.9
3	52	10.1	32	16.6	53	15.1
4	15	2.9	14	7.2	14	4.0
≥5	11	2.1	11	5.6	9	2.6
Child's sex[a]						
Male	439	84.9	128	66.0	289	82.6
Female	78	15.1	66	34.0	61	17.4
Size for gestational age						
Small-for-GA (SGA)	29	5.7	27	14.4	18	5.2
Appropriate-for-GA (AGA)	383	74.9	138	73.4	273	79.1
Large-for-GA (LGA)	99	19.4	23	12.2	54	15.7
Missing	*6*		*6*		*5*	
Known chromosomal, genetic, or mitochondrial disorder						
Yes	10	2.1	62	33.2	0	0.0
No	470	97.9	125	66.8	341	100.0
Missing	*37*		*7*		*9*	
Catchment Regional Centers						

	ASD (n=517)		DD (n=194)		TD (n=350)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Alta, Far Northern, and Redwood Coast	180	34.8	95	49.0	154	44.0
North Bay	70	13.6	22	11.3	58	16.6
East Bay, San Andreas, Golden Gate	90	17.4	19	9.8	68	19.4
Valley Mountain, Central Valley, Kern	91	17.6	46	23.7	52	14.9
Los Angeles County, Orange County, San Diego County, Tri-Counties, Inland	86	16.6	12	6.2	18	5.1

Abbreviations: ASD, autism spectrum disorder; CHARGE, Childhood Autism Risks from Genetics and the environment; DD, developmental delay; TD, typical Development.

[a]Controls were frequency-matched to patients with ASD.

Table 2

Exposures, Pregnancy Complications and Delivery Characteristics of the CHARGE Study Participants by Diagnostic Group, (N=1,061)

	ASD (n=517)		DD (n=194)		TD (n=350)	
Characteristic	**n**	**%**	**N**	**%**	**n**	**%**
Folic acid supplementation[a]						
Yes	251	51.7	86	47.5	206	59.1
No	234	48.3	95	52.5	130	40.9
Missing	*32*		*15*		*21*	
SSRI use[b]						
Yes	26	5.4	9	5.3	10	3.2
No	454	94.6	161	94.7	299	96.8
Missing	*37*		*24*		*41*	
Maternal smoking[b]						
Yes	49	10.2	12	6.7	19	6.5
No	432	89.8	166	93.3	318	93.5
Missing	*36*		*16*		*13*	
Maternal residence near a freeway[b]						
Yes	55	12.4	24	16.3	22	10.1
No	390	87.6	123	83.7	239	89.9
Missing	*72*		*16*		*13*	
Body mass index[2a]						
<18.5 (underweight)	18	3.6	5	2.7	9	2.7
18.5-24.99 (health weight)	267	53.5	72	38.7	197	55.8
25-29.99 (overweight)	112	22.4	65	34.9	87	25.8
30-34.9 (obese)	102	20.5	44	23.7	50	15.7
Missing	*18*		*7*		*8*	
Diabetes, any type[a,b]						
Yes	44	8.6	24	12.7	19	5.4
No	465	91.4	165	87.3	327	94.6
Missing	*8*		*5*		*4*	
Chronic hypertension[a]						
Yes	17	3.3	6	3.1	4	1.1
No	493	96.7	186	96.9	343	98.9
Missing	*7*		*2*		*3*	
Preeclampsia[c]						
Yes	40	7.7	10	5.1	11	3.7
No	477	92.3	184	94.9	339	96.3

Abbreviations: ASD, autism spectrum disorder; CHARGE, Childhood Autism Risks from Genetics and the Environment; DD, developmental delay; SSRI, selective serotonin reuptake inhibitor; TD, typical development.

[a] In the period anytime between 3 months before pregnancy through the first month of pregnancy (periconceptional)

[b] Any time during pregnancy (gestational)

[c] At the time of delivery (peripartum)

Table 3

Preeclampsia Characteristics of the CHARGE Study Participants with Medical Records Only by Diagnostic Group (N=823)

Characteristic	ASD (n=408)		DD (n=138)		TD (n=277)	
	N	%	n	%	n	%
Preeclampsia severity (w/o placental insufficiency)						
No preeclampsia	377	92.4	128	92.8	267	96.4
Mild preeclampsia	25	6.1	6	4.3	9	3.2
Severe preeclampsia[a]	6	1.5	4	2.9	1	0.4
Preeclampsia severity (with placental insufficiency)						
No preeclampsia	359	88.0	117	84.8	261	94.2
Mild preeclampsia	23	5.6	5	3.6	9	3.3
Severe preeclampsia	26	6.4	16	11.6	7	2.5
Preeclampsia or placental insufficiency						
No preeclampsia or placental insufficiency	359	88.0	117	84.8	261	94.6
Preeclampsia only	25	6.1	8	5.8	9	3.2
Placental insufficiency only	17	4.2	11	8.0	6	2.2
Preeclampsia and placental insufficiency	7	1.7	2	1.4	0	0.0
Missing	*0*		*0*		*1*	
Magnesium Sulfate administration[b]						
Yes	18	4.4	8	5.8	6	2.2
No	388	95.6	130	94.2	271	97.8
Missing	*2*		*0*		*0*	

Abbreviations: ASD, autism spectrum disorder; CHARGE, Childhood Autism Risks from Genetics and the Environment; DD, developmental delay; TD, typical development.

[a] Includes non-reassuring fetal test results, intrauterine growth restriction or oligohydramnios

[b] For the 4 women without preeclampsia who received this medication, all had preterm labor as the indication.

Table 4

Adjusted Odds Ratios (95% Cis) from Logistic Regression Models for Preeclampsia and ASD or DD for CHARGE Study Participants

	Children with ASD vs TD			Children with DD vs TD		
	Full Dataset[a] Interview +/− Medical Records	Limited Dataset Medical Records Only[b] Placental Insufficiency Included[c]		Full Dataset[a] Interview +/− Medical Records	Limited Dataset Medical Records Only[b] Placental Insufficiency Included[c]	
		No	Yes		No	Yes
Preeclampsia	**2.36 (1.18, 4.68)**	**2.00 (0.96, 4.16)**	**1.92 (1.06, 3.50)**	**1.44 (0.59, 3.53)**	**1.82 (0.72, 4.64)**	**2.80 (1.34, 5.88)**
Mother's education level						
No Bachelor degree	1.28 (0.96, 1.70)	1.41 (1.02, 1.95)	1.43 (1.03, 1.98)	2.42 (1.63, 3.58)	2.75 (1.72, 4.41)	2.75 (1.72, 4.41)
Bachelor degree or higher	Reference	Reference	Reference	Reference	Reference	Reference
BMI						
<18.5	1.37 (0.60, 3.12)	2.01 (0.71, 5.65)	1.80 (0.63, 5.14)	1.39 (0.44, 4.42)	2.86 (0.76, 10.86)	2.34 (0.61, 8.99)
18.5-24.9	Reference	Reference	Reference	Reference	Reference	Reference
25-29.9	0.96 (0.68, 1.36)	0.95 (0.65, 1.40)	0.95 (0.65, 1.40)	2.02 (1.31, 3.11)	1.71 (1.03, 2.85)	1.67 (1.00, 2.80)
≥30	1.43 (0.96, 2.13)	1.25 (0.81, 1.93)	1.23 (0.79, 1.90)	2.10 (1.29, 3.43)	1.83 (1.04, 3.23)	1.74 (0.99, 3.07)
Parity	0.89 (0.77, 1.02)	0.84 (0.71, 0.99)	0.84 (0.71, 1.00)	1.10 (0.94, 1.29)	1.18 (0.97, 1.42)	1.20 (0.99, 1.44)

Abbreviations: ASD, autism spectrum disorder; CHARGE, Childhood Autism Risks from Genetics and the Environment; DD, developmental delay; TD, typical development.

[a] Mothers with interview or medical record data and the 3 covariates (N=1,027)

[b] Mothers with medical record data (N=807); A total of 11 of 807 women did not have data on preeclampsia severity; therefore, in analyses using the limited dataset, 796 women with medical records and data on preeclampsia severity were included.

[c] For this analysis using the limited medical record dataset, the definition of severe preeclampsia (and thus preeclampsia) included placental insufficiency.