Original Investigation

Preeclampsia, Placental Insufficiency, and Autism Spectrum Disorder or Developmental Delay

Cheryl K. Walker, MD; Paula Krakowiak, PhD; Alice Baker, MPH; Robin L. Hansen, MD; Sally Ozonoff, PhD; Irva Hertz-Picciotto, PhD

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 Childhood Autism Risks from Genetics and the Environment (CHARGE) study is a population-based, case-control investigation of ASD and/or DD origins. Children from 20 California counties aged 24 to 60 months at the time of recruitment and living in catchment areas with a biological 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) (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.

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

MAIN OUTCOMES AND MEASURES 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, $P = .02$). 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.

JAMA Pediatr. 2015;169(2):154-162. doi:10.1001/jamapediatrics.2014.2645
Published online December 8, 2014.

Supplemental content at jamapediatrics.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Cheryl K. Walker, MD, Medical Investigation of Neurodevelopmental Disorders (MIND) Institute and Department of Obstetrics and Gynecology, School of Medicine, University of California, Davis, 4869 Y St, Ste 2500, Sacramento, CA 95817 (ckwalker@ucdavis.edu).

Autism spectrum disorder (ASD) is a neurobehavioral condition identified in 1 in 68 US children and is part of a broader group of developmental disabilities that affect 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, hypoxic-ischemic 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 hypoperfusion 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 (although 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. A meta-analysis[7] of 17 studies of variable quality published before 2007 that examined preeclampsia in association with autism found substantial unexplained heterogeneity of effect estimates. 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 were 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 3 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 of 24 to 60 months, (2) residence with at least one biological 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 from 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 written 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 inconsis-

tencies 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 nonreassuring 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 from 823 (77.6%), and data from both in 764 (72.0%); agreement was substantial (κ = 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 preeclamsia 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), healthy 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 above 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 than 15, 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 in the Supplement). 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 $P < .20$ as a threshold for selection as a potential confounder.[39] Categorical variables were analyzed using likelihood ratio χ^2 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 data set) 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 education, 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 birth weight 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[40]; 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 documenta-

Table 1. Characteristics of the CHARGE Study Participants by Diagnostic Group

Characteristic	No. (%) of Participants (N = 1061)		
	ASD (n = 517)	DD (n = 194)	TD (n = 350)
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)
Multiracial	18 (3.5)	10 (5.1)	17 (4.8)
Maternal educational level			
Less than high school	20 (3.9)	29 (14.9)	18 (5.1)
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's degree	150 (29.0)	43 (22.2)	123 (35.1)
Graduate or professional degree	83 (16.1)	12 (6.2)	55 (15.7)
Missing	1 (0.2)	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 (0.2)	0	1 (0.3)
All births/parity (including 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	29 (5.7)	27 (14.4)	18 (5.2)
Appropriate	383 (74.9)	138 (73.4)	273 (79.1)
Large	99 (19.4)	23 (12.2)	54 (15.7)
Missing	6 (1.2)	6 (3.1)	5 (1.4)
Known chromosomal, genetic, or mitochondrial disorder			
Yes	10 (2.1)	62 (33.2)	0
No	470 (97.9)	125 (66.8)	341 (100.0)
Missing	37 (7.2)	7 (3.6)	9 (2.6)
Catchment regional centers			
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, and Golden Gate	90 (17.4)	19 (9.8)	68 (19.4)
Valley Mountain, Central Valley, and Kern	91 (17.6)	46 (23.7)	52 (14.9)
Los Angeles, Orange County, San Diego, Tri-Counties district, and 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.

tion, 27 women with preeclampsia (54.0%) received magnesium sulfate during labor for seizure prophylaxis, and 5 women without preeclampsia (0.6%) 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

Table 2. Exposures, Pregnancy Complications, and Delivery Characteristics of the CHARGE Study Participants by Diagnostic Group

Characteristic	No. (%) of Participants (N = 1061)		
	ASD (n = 517)	DD (n = 194)	TD (n = 350)
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 (6.2)	15 (7.7)	21 (6.0)
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 (7.2)	24 (12.4)	41 (11.7)
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 (7.0)	16 (8.2)	13 (3.7)
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 (13.9)	16 (8.2)	13 (3.7)
Body mass index[a]			
<18.5 (underweight)	18 (3.6)	5 (2.7)	9 (2.7)
18.5-24.99 (healthy 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 (1.5)	5 (2.6)	4 (1.1)
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 (1.4)	2 (1.0)	3 (0.9)
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).

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 in the Supplement). 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 in the Supplement). 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 (ie, 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 = .02) and a threshold effect in the DD vs TD analysis (P = .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.

Table 3. Preeclampsia Characteristics of the CHARGE Study Participants With Medical Records Only by Diagnostic Group

Characteristic	No. (%) of Participants (n = 823)		
	ASD (n = 408)	DD (n = 138)	TD (n = 277)
Preeclampsia severity (without placental insufficiency)			
None	377 (92.4)	128 (92.8)	267 (96.4)
Mild	25 (6.1)	6 (4.3)	9 (3.2)
Severe[a]	6 (1.5)	4 (2.9)	1 (0.4)
Preeclampsia severity (with placental insufficiency)			
None	359 (88.0)	117 (84.8)	261 (94.2)
Mild	23 (5.6)	5 (3.6)	9 (3.3)
Severe	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
Missing	0	0	1 (0.4)
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 (0.5)	0	0

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

[a] Includes nonreassuring fetal test results, intrauterine growth restriction, or oligohydramnios.

[b] For the 5 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 Data Set[a] Interview With or Without Medical Records	Limited to Those With Medical Records Only[b]: Placental Insufficiency Included[c]		Full Data Set[a] Interview With or Without Medical Records	Limited to Those With 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 educational level						
No bachelor's 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's degree or higher	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [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	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [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; BMI, body mass index; 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 = 1027).

[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 data set, 796 women with medical records and data on preeclampsia severity were included.

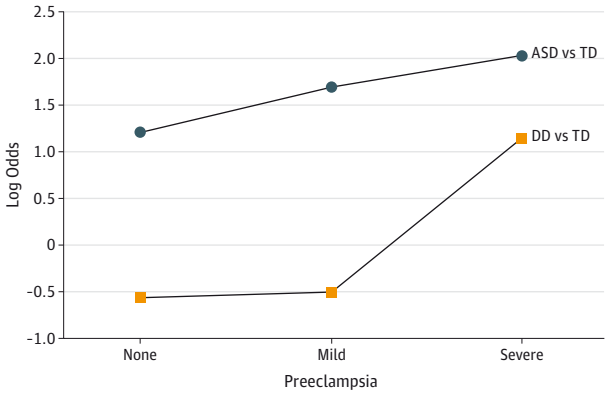
[c] For this analysis using the limited medical record data set, the definition of severe preeclampsia (and thus preeclampsia) included placental insufficiency.

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

Figure. 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).

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 birth weight, both of which commonly result from these conditions.[4,5,22,30,31]

Other recent population-based epidemiologic studies[8-11] that, similar to our CHARGE study, also had reasonably high statistical power and tended to use objective 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. 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 nongenetic 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.[41]

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.[42] 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,[43] 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 stud-

ies 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.[44] 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.

ARTICLE INFORMATION

Accepted for Publication: September 18, 2014.

Published Online: December 8, 2014. doi:10.1001/jamapediatrics.2014.2645.

Author Affiliations: Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, School of Medicine, University of California, Davis (Walker); Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California, Davis (Walker, Krakowiak, Hansen, Ozonoff, Hertz-Picciotto); Department of Public Health Sciences, School of Medicine, University of California, Davis (Krakowiak, Baker, Hertz-Picciotto); Department of Pediatrics, School of Medicine, University of California, Davis (Hansen); Department of Psychiatry and Behavioral Sciences, School of Medicine, University of California, Davis (Ozonoff).

Author Contributions: Dr Walker had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Walker, Krakowiak, Hertz-Picciotto.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Walker.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Walker, Krakowiak, Hertz-Picciotto.
Obtained funding: Hertz-Picciotto.
Administrative, technical, or material support: Walker, Baker, Hansen, Hertz-Picciotto.
Study supervision: Walker, Ozonoff, Hertz-Picciotto.

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.

Funding/Support: This publication was made possible by grants 1P01ES11269 and R01ES015359 from the National Institute of Environmental Health Sciences and grant 1U54HD079125 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health; grants R82938801 and R83329201 from the US Environmental Protection Agency through the Science to Achieve Results program; and the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute at the University of California, Davis.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Disclaimer: The contents of this publication are solely the responsibility of the grantee and do not necessarily represent the official views of the funding agencies. Furthermore, the funders do not endorse the purchase of any commercial products mentioned in the publication.

Additional Contributions: We thank the CHARGE study families for their participation and commitment to understanding the environmental and genetic causes of ASD and the staff and investigators of the CHARGE study, the Medical Records Unit staff and interns, and the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute at the University of California, Davis, for their assistance. Written informed consent was required for participation in the CHARGE study under institutional review board approval 226028.

REFERENCES

1. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators; Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2010. *MMWR Surveill Summ*. 2014;63(2):1-21.

2. Hallmayer J, Cleveland S, Torres A, et al. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry*. 2011;68(11):1095-1102.

3. Stoner R, Chow ML, Boyle MP, et al. Patches of disorganization in the neocortex of children with autism. *N Engl J Med*. 2014;370(13):1209-1219.

4. Hultman CM, Sparén P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology*. 2002;13(4):417-423.

5. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. *Arch Gen Psychiatry*. 2004;61(6):618-627.

6. Brimacombe M, Ming X, Lamendola M. Prenatal and birth complications in autism. *Matern Child Health J*. 2007;11(1):73-79.

7. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. *Br J Psychiatry*. 2009;195(1):7-14.

8. Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparén P, Cnattingius S. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? *Pediatrics*. 2009;124(5):e817-e825.

9. Mann JR, McDermott S, Bao H, Hardin J, Gregg A. Pre-eclampsia, birth weight, and autism spectrum disorders. *J Autism Dev Disord*. 2010;40(5):548-554.

10. Burstyn I, Sithole F, Zwaigenbaum L. Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. *Chronic Dis Can*. 2010;30(4):125-134.

11. Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson S. The role of prenatal, obstetric and neonatal factors in the development of autism. *J Autism Dev Disord*. 2011;41(7):891-902.

12. Atladóttir HO, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. *Pediatrics*. 2012;130(6):e1447-e1454.

13. Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci*. 2003;23(1):297-302.

14. Zerbo O, Iosif AM, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) study. *J Autism Dev Disord*. 2013;43(1):25-33.

15. Goines PE, Croen LA, Braunschweig D, et al. Increased midgestational IFN-γ, IL-4 and IL-5 in women bearing a child with autism: a case-control study. *Mol Autism*. 2011;2:13.

16. Giulivi C, Zhang YF, Omanska-Klusek A, et al. Mitochondrial dysfunction in autism. *JAMA*. 2010;304(21):2389-2396.

17. Burstyn I, Wang X, Yasui Y, Sithole F, Zwaigenbaum L. Autism spectrum disorders and fetal hypoxia in a population-based cohort: accounting for missing exposures via Estimation-Maximization algorithm. *BMC Med Res Methodol*. 2011;11:2.

18. Lyall K, Schmidt RJ, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. *Int J Epidemiol*. 2014;43(2):443-464.

19. Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics*. 2012;129(5):e1121-e1128.

20. Shevell M. Global developmental delay and mental retardation or intellectual disability: conceptualization, evaluation, and etiology. *Pediatr Clin North Am*. 2008;55(5):1071-1084, xi.

21. Srour M, Shevell M. Genetics and the investigation of developmental delay/intellectual disability. *Arch Dis Child*. 2014;99(4):386-389.

22. Thomaidis L, Zantopoulos GZ, Fouzas S, Mantagou L, Bakoula C, Konstantopoulos A. Predictors of severity and outcome of global

developmental delay without definitive etiologic yield: a prospective observational study. *BMC Pediatr*. 2014;14:40.

23. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ*. 2013; 347:f6564.

24. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta*. 2009;30(suppl A):S32-S37.

25. Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. *Nat Med*. 2012;18(12):1754-1767.

26. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005;308 (5728):1592-1594.

27. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy, American College of Obstetricians and Gynecologists. *Hypertension in Pregnancy*. Washington, DC: American College of Obstetricians and Gynecologists; 2013.

28. Neerhof MG, Thaete LG. The fetal response to chronic placental insufficiency. *Semin Perinatol*. 2008;32(3):201-205.

29. Triunfo S, Lobmaier S, Parra-Saavedra M, et al. Angiogenic factors at diagnosis of late-onset small-for-gestational age and histological placental underperfusion. *Placenta*. 2014;35(6):398-403.

30. Moore GS, Kneitel AW, Walker CK, Gilbert WM, Xing G. Autism risk in small- and large-for-gestational-age infants. *Am J Obstet Gynecol*. 2012; 206(4):314.e1-314.e9.

31. Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. *Pediatrics*. 2011;128(5):883-891.

32. Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. *Environ Health Perspect*. 2006;114(7):1119-1125.

33. Bodnar LM, Tang G, Ness RB, Harger G, Roberts JM. Periconceptional multivitamin use reduces the risk of preeclampsia. *Am J Epidemiol*. 2006;164 (5):470-477.

34. Zhang J, Klebanoff MA, Levine RJ, Puri M, Moyer P. The puzzling association between smoking and hypertension during pregnancy. *Am J Obstet Gynecol*. 1999;181(6):1407-1413.

35. Kalkbrenner AE, Braun JM, Durkin MS, et al. Maternal smoking during pregnancy and the prevalence of autism spectrum disorders, using data from the Autism and Developmental Disabilities Monitoring Network. *Environ Health Perspect*. 2012;120(7):1042-1048.

36. Palmsten K, Setoguchi S, Margulis AV, Patrick AR, Hernández-Díaz S. Elevated risk of preeclampsia in pregnant women with depression: depression or antidepressants? *Am J Epidemiol*. 2012;175(10):988-997.

37. Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics*. 2014;133(5): e1241-e1248.

38. Pedersen M, Stayner L, Slama R, et al. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. *Hypertension*. 2014;64(3):494-500.

39. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health*. 1989;79 (3):340-349.

40. Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics*. 2014;133(5): e1241-e1248.

41. Walker CK, Anderson KW, Milano KM, et al. Trophoblast inclusions are significantly increased in the placentas of children in families at risk for autism. *Biol Psychiatry*. 2013;74(3):204-211.

42. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. *Arch Pediatr Adolesc Med*. 2007;161(4):326-333.

43. Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Arch Pediatr Adolesc Med*. 2005;159(2):151-157.

44. Costantine MM, Cleary K; Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network. Pravastatin for the prevention of preeclampsia in high-risk pregnant women. *Obstet Gynecol*. 2013;121(2, pt 1): 349-353.