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Authors

Lyall, Kristen

Ning, Xuejuan

Aschner, Judy L

et al.

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Original Contribution

Cardiometabolic Pregnancy Complications in Association With Autism-Related Traits as Measured by the Social Responsiveness Scale in ECHO

Kristen Lyall*, Xuejuan Ning, Judy L. Aschner, Lyndsay A. Avalos, Deborah H. Bennett, Deborah A. Bilder, Nicole R. Bush, Kecia N. Carroll, Su H. Chu, Lisa A. Croen, Dana Dabelea, Julie L. Daniels, Christiane Duarte, Amy J. Elliott, M. Daniele Fallin, Assiamira Ferrara, Irva Hertz-Picciotto, Alison E. Hipwell, Elizabeth T. Jensen, Susan L. Johnson, Robert M. Joseph, Margaret Karagas, Rachel S. Kelly, Barry M. Lester, Amy Margolis, Cindy T. McEvoy, Daniel Messinger, Jenae M. Neiderhiser, Thomas G. O'Connor, Emily Oken, Sheela Sathyanarayana, Rebecca J. Schmidt, Stephen J. Sheinkopf, Nicole M. Talge, Kedir N. Turi, Rosalind J. Wright, Qi Zhao, Craig Newschaffer, Heather E. Volk, and Christine Ladd-Acosta, on behalf of program collaborators for Environmental Influences on Child Health Outcomes

* Correspondence to Dr. Kristen Lyall, 3020 Market Street, Suite 560, Philadelphia, PA 19104 (e-mail: kld98@drexel.edu).

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Prior work has examined associations between cardiometabolic pregnancy complications and autism spectrum disorder (ASD) but not how these complications may relate to social communication traits more broadly. We addressed this question within the Environmental Influences on Child Health Outcomes program, with 6,778 participants from 40 cohorts conducted from 1998–2021 with information on ASD-related traits via the Social Responsiveness Scale. Four metabolic pregnancy complications were examined individually, and combined, in association with Social Responsiveness Scale scores, using crude and adjusted linear regression as well as quantile regression analyses. We also examined associations stratified by ASD diagnosis, and potential mediation by preterm birth and low birth weight, and modification by child sex and enriched risk of ASD. Increases in ASD-related traits were associated with obesity ($\beta = 4.64$, 95% confidence interval: 3.27, 6.01) and gestational diabetes ($\beta = 5.21$, 95% confidence interval: 2.41, 8.02), specifically, but not with hypertension or preeclampsia. Results among children without ASD were similar to main analyses, but weaker among ASD cases. There was not strong evidence for mediation or modification. Results suggest that common cardiometabolic pregnancy complications may influence child ASD-related traits, not only above a diagnostic threshold relevant to ASD but also across the population.

autism; cardiometabolic complications; obesity; pregnancy complications; Social Responsiveness Scale

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; ECHO, Environmental Influences on Child Health Outcomes; SRS, Social Responsiveness Scale.

Autism spectrum disorder (ASD) is a neurodevelopmental condition that presents along a continuum of deficits in social communication and presence of restricted repetitive behaviors. Evidence suggests a complex etiology that includes prenatal origins (1). Multiple meta-analyses have supported a link between pregnancy complications and ASD (2–6). Early studies investigating this relationship yielded conflicting findings with regard to the specific complications linked with ASD, although obstetric suboptimality in general was associated with increased risk (2, 6). More recently, a number of studies have suggested an increased ASD risk with the class of cardiometabolic pregnancy complications, including gestational diabetes, preeclampsia, gestational hypertension, and obesity (7–13). In addition, preterm birth and low birth weight, which have been fairly consistently associated with increased risk of ASD (14–18), are consequences of cardiometabolic pregnancy complications and may be on the pathway linking cardiometabolic

complications and neurodevelopmental outcomes, but they have not been examined as potential mediators on the causal pathway (19). Given the high prevalence of these cardiometabolic complications in the United States and worldwide (20–25), and concurrent increases in prevalence of these conditions, understanding the potential pathways of these factors and clarifying their associations with neurodevelopmental outcomes is of high public health relevance.

Existing work examining cardiometabolic pregnancy complications in association with ASD has focused almost uniformly on ASD defined as a binary outcome. It is not clear how these pregnancy complications may relate to autistic traits when considered along a continuum across the population. Examining associations with continuously measured ASD-related traits may help to clarify the extent to which such complications influence underlying latent traits across the spectrum.

We used data from the Environmental Influences on Child Health Outcomes (ECHO) program to address these research gaps and examine how cardiometabolic pregnancy complications relate to offspring ASD traits as assessed quantitatively by scores on the Social Responsiveness Scale (SRS), a widely used, validated measure of ASD-related traits. In addition, as secondary goals, we considered mediation by preterm birth and low birth weight, as common sequalae of these complications, as well as potential modification of these associations by child's sex and enrichment for ASD risk.

METHODS

Study population

ECHO is a large collaborative project focused on environmental factors that affect child health. Detailed methods have been previously published (26). Briefly, ECHO is composed of 69 individual cohorts across the United States, whose participants follow a common protocol to assess a range of exposures in relation to child-focused outcomes, including neurodevelopment. Here, we used previously collected data from individual cohorts. We excluded participants who were missing >15% of items on the primary outcome measure (the SRS (27, 28)), missing information on child sex, had the SRS collected outside of recommended age range (<2.5 years old), and those without information on at least 1 of the 4 pregnancy complications under study. The analytical data set included 6,778 participants from 40 ECHO cohorts (Web Figure 1 and Web Table 1, available at https://doi.org/10.1093/aje/kwac061). Eight cohorts enrolled participants who may be defined as at higher risk for ASD given known risk factors for ASD (29, 30), including premature birth or younger siblings of children with ASD ("enriched risk cohorts"), while remaining cohorts were broadly drawn from the general population or otherwise nonenriched for ASD ("nonenriched risk cohorts").

Cardiometabolic pregnancy complications

Four cardiometabolic pregnancy complications were examined. These were defined according to data collected and provided by individual cohorts by January 2021 and harmonized across these studies for use in these analyses (see also Web Table 2): prepregnancy obesity, gestational diabetes, hypertension during pregnancy, and preeclampsia. Prepregnancy obesity was defined as body mass index (BMI, calculated as weight (kg)/height $(m)^2$) ≥30 using measured or self-reported height and weight from 12 months prior to conception through the first trimester. Gestational diabetes was defined as new-onset diabetes during pregnancy based on self-report or as indicated in medical records. Hypertension during pregnancy was self-reported or extracted from the medical records with documentation of high blood pressure or antihypertensive medication use during pregnancy. These indications were as described/defined by individual cohorts or as reported in records; we did not have further information on blood pressure levels. Preeclampsia was determined by self-report or medical record diagnosis. For analyses of individual complications, we included all participants with data, and missing data resulted in varying sample size across models of individual complications. We also created an indicator for whether individuals had any of these 4 cardiometabolic complications. Approximately 36% of included participants had information on at least 1 condition according to medical record data and/or as measured by study staff (weight/height) (referred to hereafter as "objective measures"), while data for the remainder relied on self-report.

ASD outcomes

Social Responsiveness Scale. Our primary outcome measure was the SRS (27, 28), a 65-item informant-report tool and one of the most widely used quantitative measures of ASD-related phenotype, capable of capturing traits both in ASD-affected and unaffected individuals. Item scores (ranging from 0 to 3) are summed to yield a total score ranging from 0 to 195, with higher scores indicating greater expression of the ASD-related phenotype and greater social communication deficits. Per publisher guidelines (31), missing values on individual SRS items for those with <15% missing were imputed with population median values. Sex-normed T-scores, which convert raw scores into units with a mean of 50 (standard deviation, 10), can also be obtained according to publisher guidelines to facilitate clinical interpretation. The SRS has well-established psychometric properties in both in the general population and in clinical settings (31, 32), with high internal validity, reliability, and reproducibility (31, 33, 34). Validation against a "gold standard'" diagnostic interview, the Autism Diagnostic Interview–Revised (ADI-R), has also provided strong results ($r = 0.7$ for SRS scores and ADI-R algorithm scores for *Diagnostic and Statistical Manual of Mental Disorders IV* criteria) (33, 34). For this analysis, SRS forms were collected at ages 2.5–18 years via parent/caregiver reports. Prior work supports stability of SRS scores over these ages, particularly for the school-aged form (31, 35).

ASD diagnosis. ASD diagnosis was defined based on parent/caregiver report of physician-diagnosed ASD (in

approximately 80% of cases) and/or gold-standard clinical assessment (in approximately 20% of cases). Further details on ASD assessment are provided in Web Table 2. Individuals missing information on ASD diagnosis were assumed not to have ASD; sensitivity analyses were conducted to ensure that this did not influence results.

Statistical analyses

Descriptive statistics were examined, including the individual and combined frequency of the defined cardiometabolic pregnancy complications. Associations between SRS scores and the complications were examined in multiple ways to more fully understand potential associations. First, we used linear regression to examine associations between these complications and raw total SRS scores. In addition, we used quantile regression (36, 37) to assess whether associations differed across quantiles of SRS scores, which may help to inform whether complications influence social communication deficits only at higher quantiles of scores typically consistent with an ASD diagnosis, or rather, across the continuum of SRS scores. We also performed these same analyses stratified by ASD diagnostic status in order to examine whether the pregnancy complications influenced ASD severity (within those with an ASD diagnosis) and, separately, whether the complications related to social deficits in unaffected individuals (within those without an ASD diagnosis). In addition, as a secondary analysis for purposes of comparison with primary analyses, and to confirm associations between these risk factors and ASD in our study population, we also conducted parallel analyses using logistic regression models examining relationships with ASD diagnosis as the outcome.

Covariates included in final models were selected a priori based on previously reported associations with ASD and the complications under study; they included maternal age (continuous); maternal race/ethnicity as a proxy for unmeasured structural factors that may have an impact on pregnancy, such as access to health care; maternal education level, as potentially related to interpretation of social communication questions; child age at SRS administration (continuous); and child's sex (defined as male or female), due to the known male sex bias in ASD diagnosis and differences in SRS raw score distributions by sex. Study type/source population (as defined above according to ASD-enriched risk or not) was also included in model adjustments for those analyses not stratified by this factor. Individuals with missing covariate values had median values imputed using simple imputation; sensitivity analyses were also performed using multiple imputation as a comparison. We fitted a series of nested models to examine percent change in estimates according to covariate adjustment.

To examine mediation by preterm birth and, separately, low birth weight, we used 4-way effect decomposition methods as described by VanderWeele et al. (38); both the binary variables and their continuous counterparts (e.g., gestational age and birth weight) were examined as mediators. Mediation analyses were performed using Stata (StataCorp LLC, College Station, Texas) with the Med4way package (https://github.com/anddis/med4way). Modification by child sex, as well as study type according to enriched and nonenriched risk studies, was examined using stratified models, as representing groups whose background risk for ASD—and SRS distributions—are expected to differ (39–41).

A series of sensitivity analyses were performed to test robustness of results. We tested additional adjustment, to extend the primary models, for income as an additional sociodemographic factor that may influence relationships (but with a relatively high degree of missing data in our study), as well as an indicator for cohort (cohorts with n of <50 were collapsed within enriched and nonenriched groupings) and for gestational age and birth weight, to evaluate whether associations remained after adjustment. We also tested co-adjustment of other pregnancy complications for obesity. To address potential impacts of missing data, we examined whether associations changed when using a complete-case approach, including only those individuals with information on all 4 complications under study (n = 2,685), and we examined results using multiple imputation for missing complication information. We also conducted analyses restricted to cohorts with a low degree of missingness (<10%) on confounders. Secondary meta-analyses were conducted to assess variability in associations across individual cohorts. In order to test whether potential misclassification due to self-report may have influenced results, we conducted analyses using complications as defined only according to medical records/objectively collected data. As noted, we also examined analyses of ASD diagnosis excluding those missing this information. Finally, given challenges in assessing ASD at younger ages (42), we also conducted analyses among individuals with school-aged (4–18 years) SRS forms only (n = 5,283).

RESULTS

Basic characteristics of our study population, overall and by study type, are shown in Table 1. Approximately 17% of the study population was drawn from an ASD-enriched risk study. Prevalence of complications in our overall study population was similar to national averages and/or those reported in prior research studies for time periods overlapping pregnancies in this study population (22, 23, 43, 44). The majority of participant mothers were non-Hispanic White (63%) and had a post–high-school degree (66%), although educational, racial, and ethnic diversity were somewhat greater in the enriched risk group. Sociodemographic characteristics were broadly comparable across those with and without pregnancy complications, although some variability, particularly with lower education being more common among those with obesity, was noted (Web Table 3). Nearly 80% of child SRS data was obtained using the school-age SRS-2 form. The overall prevalence of ASD in the study population was just under 5% (higher than the general population rate of 1%–2% owing to the inclusion of enriched risk cohorts and a large case-control study). The distribution of SRS scores in the study population is shown in Web Figure 2 (median raw score = 28; interquartile range, 18,43).

Table 1. Basic Characteristics (Study Population Drawn From 40 Cohorts), Environmental Influences on Child Health Outcomes Participants, United States, 1998–2021[a]

Characteristic	Total Study Population (*n* = 6,778)		Nonenriched Risk Participants[b] (*n* = 5,600)		ASD-Enriched Risk Participants[c] (*n* = 1,178)	
	No.	%	No.	%	No.	%
Maternal race/ethnicity						
Non-Hispanic White	4,262	62.9	3,600	64.3	662	56.2
Non-Hispanic Black	823	12.1	577	10.3	246	20.9
Non-Hispanic Asian	292	4.3	236	4.2	56	4.8
Non-Hispanic, other race	266	3.9	203	3.6	63	5.3
Hispanic	830	12.2	706	12.6	124	10.5
Missing	305	4.5	278	5.0	27	2.3
Maternal education						
Less than high school	291	4.3	179	3.2	112	9.5
High-school degree, GED, or equivalent	691	10.2	420	7.5	271	23.0
Some college, no degree	1,397	20.6	1,070	19.1	327	27.8
Bachelor's degree	1,663	24.5	1,396	24.9	267	22.7
Master's, professional, or doctoral degree	1,404	20.7	1,223	21.8	181	15.4
Missing	1,332	19.7	1,312	23.4	20	1.7
Household income, $						
<30,000	612	9.0	546	9.8	66	5.6
≥30,000	3,561	52.5	3,244	57.9	317	26.9
Missing	2,605	38.4	1,810	32.3	795	67.5
Child's sex						
Male	3,456	51.0	2,839	50.7	617	52.4
Female	3,322	49.0	2,761	49.3	561	47.6
SRS version						
Preschool	1,495	22.1	1,368	24.4	127	10.8
School-age	5,283	77.9	4,233	75.6	1,051	89.2
Child ASD diagnosis						
No	3,564	52.6	3,010	53.8	554	47.0
Yes	326	4.8	220	3.9	106	9.0
Missing	2,888	42.6	2,370	42.3	518[d]	44.0
Preterm birth						
No	5,227	77.1	5,044	90.1	183	15.5
Yes	1,500	22.1	510	9.1	990	84.0
Missing	51	0.8	46	0.8	5	0.4
Low birth weight, <2,500 g						
No	4,487	66.2	4,309	77.0	178	15.0
Yes	1,272	18.8	294	5.3	978	83.0
Missing	1,019	15	997	17.8	22	1.9
Metabolic pregnancy complication, any the 4 defined below						
No	4,763	70.3	4,001	71.4	762	64.7
Yes	2015	29.7	1,599	28.6	416	35.3
Prepregnancy obesity						
No	4,605	67.9	3,794	67.8	811	68.8
Yes	1,470	21.7	1,117	19.9	353	30.0
Missing	703	10.4	689	12.3	14	1.2

Table continues

Table 1. Continued

Characteristic	Total Study Population (*n* = 6,778)		Nonenriched Risk Participants[b] (*n* = 5,600)		ASD-Enriched Risk Participants[c] (*n* = 1,178)	
	No.	%	No.	%	No.	%
Gestational diabetes						
No	3,696	54.5	3,307	59.1	389	33.0
Yes	278	4.1	233	4.2	45	3.8
Missing	2,804	41.4	2,060	36.8	744	63.2
Hypertension during pregnancy/delivery						
No	3,968	58.5	3,728	66.6	240	20.4
Yes	486	7.2	400	7.1	86	7.3
Missing	2,324	34.3	1,472	26.3	852	72.3
Preeclampsia during pregnancy/delivery						
No	3,914	57.7	3,538	63.2	376	31.9
Yes	245	3.6	188	3.4	57	4.8
Missing	2,619	38.6	1,874	33.5	745	63.2
≥2 pregnancy complications[e]						
No	6,403	94.5	5,311	94.8	1,092	92.7
Yes	375	5.5	289	5.2	86	7.3
Maternal age, years[f]	30.4 (5.7)		30.3 (5.6)		30.3 (5.6)	
Child age, years[f]	8.0 (4.5)		8.0 (4.8)		8.0 (4.8)	

Abbreviations: ASD, autism spectrum disorder; GED, General Educational Development; SRS, Social Responsiveness Scale.

[a] Study dates provided represent range from earliest year of enrollment to latest year of SRS administration across participants drawn from the Environmental Influences on Child Health Outcomes cohorts.

[b] Defined as cohorts who enrolled from the general population and/or in samples not enriched for ASD risk.

[c] Defined as cohorts enrolling preterm births or based on having an older sibling with ASD (enriched familial risk).

[d] Missingness in this category was due lack of data in preterm birth cohorts at the time of this analysis (all enriched familial risk cohorts have this information; see Web Table 2 for further information).

[e] The largest degree of overlap was prepregnancy obesity and hypertension; among those with obesity, 17% also had hypertension.

[f] Values are expressed as mean (standard deviation).

In adjusted analyses examining associations between the pregnancy complications and SRS scores, we observed elevations in scores (increases in ASD-related traits) among children whose mothers had prepregnancy obesity (β = 4.64, 95% confidence interval (CI): 3.27, 6.01), gestational diabetes (β = 5.21, 95% CI: 2.41, 8.02), or any of the metabolic pregnancy complications (β = 3.65, 95% CI: 2.43, 4.86) (Table 2). These estimates are consistent with approximately a 1/5–1/6 standard deviation increase in raw SRS score, or approximately a 2-point change in SRS T-score (Web Table 4). Analyses of SRS scores using quantile regression also supported associations with obesity, any metabolic complication, and (less uniformly across SRS quantiles) gestational diabetes (Figure 1). Associations above the 60th or 70th percentile appeared stronger, although a positive, generally linear, association was observed across quantiles for these conditions. Confidence bands crossed the null for all quantiles for preeclampsia and hypertension, again consistent with linear regression results. In analyses stratified by ASD diagnostic status (Table 3), obesity, gestational diabetes, and any metabolic pregnancy complication were associated with increases in SRS scores among those without an ASD diagnosis, suggesting increases in subclinical deficits. Associations between complications and SRS scores were attenuated among individuals with an ASD diagnosis, suggesting little impact on ASD trait severity among those above the threshold for clinical impairment, but were estimated with low precision.

Analyses examining ASD diagnosis as the outcome yielded results consistent with those of SRS scores, suggesting modest increases in odds of ASD with any cardiometabolic complication, and with obesity specifically (adjusted odds ratio = 1.48, 95% CI: 1.12, 1.96; Table 4). Odds of ASD were also elevated and suggested a similar relationship, although estimated with less precision, in association with maternal gestational diabetes. As with analyses of SRS scores, increases in risk were not observed with maternal hypertension, although there was a stronger association with preeclampsia in the nonenriched group.

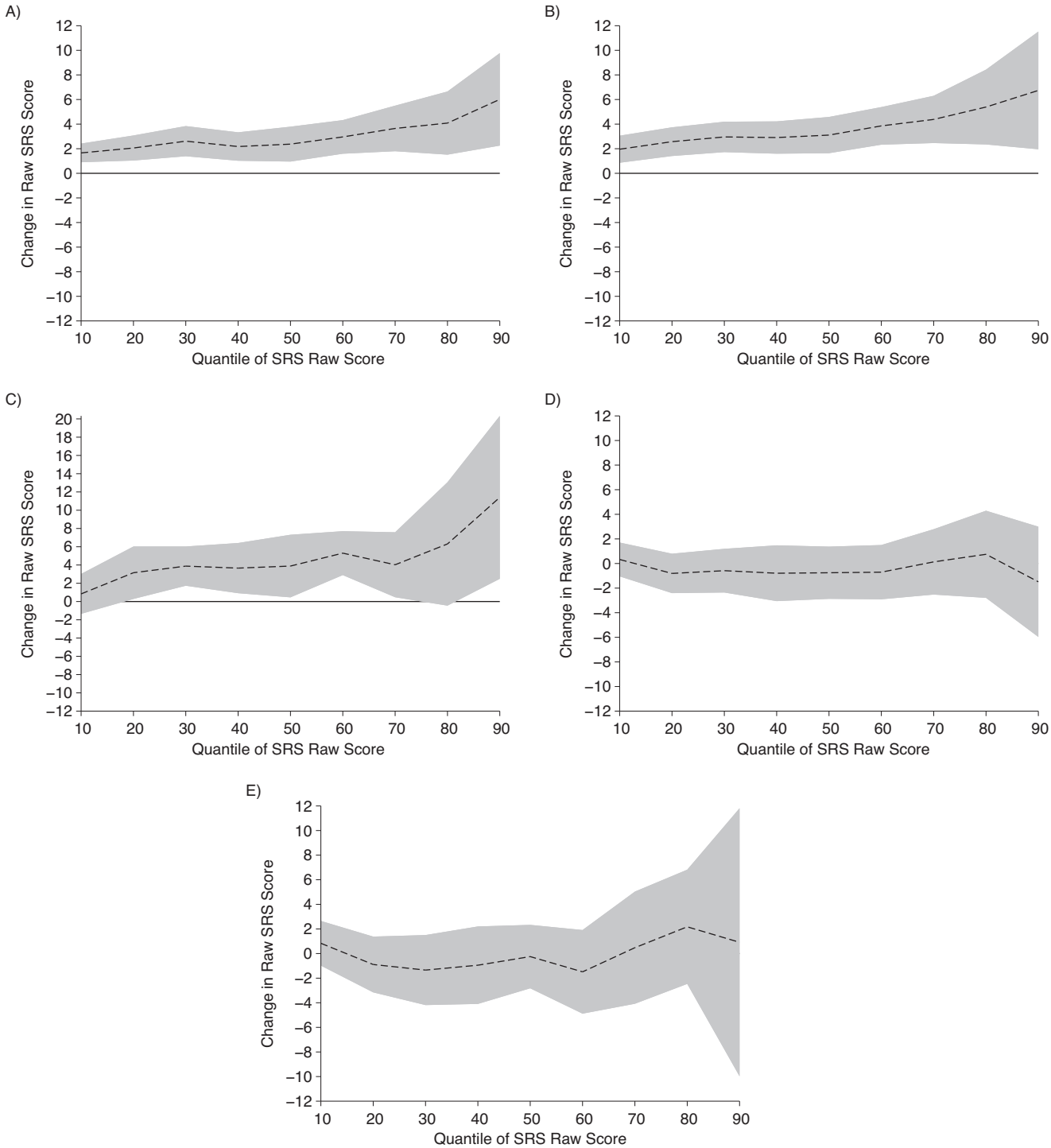

Figure 1. Associations between cardiometabolic pregnancy complications and Social Responsiveness Scale (SRS) scores according to quantile regression in the Environmental Influences on Child Health Outcomes study population (participants from 40 cohorts, United States, 1998–2021). Quantile regression models adjusted for maternal age, race, ethnicity, and education as well as child's sex, child's age at SRS, and study type (general population or high-risk cohort). Plots show the change in raw SRS score (*y*-axis) according to the following: A) any maternal metabolic condition (defined as any of prepregnancy obesity, gestational diabetes, hypertension, or preeclampsia), B) prepregnancy obesity (defined as body mass index, calculated as weight (kg)/height $(m)^2$, of 30 or higher in the 12 months preceding pregnancy), C) gestational diabetes, D) hypertension, and E) preeclampsia, across percentiles of SRS score (*x*-axis). For example, results suggest there is approximately a 6-point increase in raw SRS score in association with any pregnancy complication among those in the highest percentile (90th) of SRS scores, but this association is weaker, suggesting only a 2-point increase, for those in the lowest (10th) percentile of SRS scores. Gray shaded regions indicate 95% confidence intervals. Null association indicated by the horizontal line at the *y*-axis value of 0. Association line indicated by the dotted line; a relatively flat line/consistent slope across the *x*-axis is indicative of consistent association across all quantiles of SRS scores.

Table 2. Associations Between Cardiometabolic Pregnancy Complications and Child Social Responsiveness Scale Scores in the Environmental Influences on Child Health Outcomes Study Population (Participants From 40 Cohorts), United States, 1998–2021[a]

Pregnancy Complication	Total No.[b]	Exposed No.[c]	Crude		Adjusted[d]	
			β	95% CI	β	95% CI
Metabolic pregnancy complications, any	6,778	2015	5.73	4.49, 6.97	3.65	2.43, 4.86
Obesity	6,075	1,470	7.19	5.80, 8.59	4.64	3.27, 6.01
Gestational diabetes	3,974	278	7.06	4.16, 9.97	5.21	2.41, 8.02
Hypertension	4,454	486	1.85	−0.28, 3.98	−1.16	−3.24, 0.92
Preeclampsia	4,159	245	1.77	−1.35, 4.89	0.00	−2.99, 2.99

Abbreviation: CI, confidence interval.
[a] Table displays results of linear regression analyses.
[b] Number in column represents total *n* included in analyses.
[c] Number in column represents exposed *n*.
[d] Adjusted for maternal age, race/ethnicity, education level, child age at Social Responsiveness Scale scoring, child's sex, and study type (enriched risk status, as described in text).

Stratified by cohort type, associations were similar to primary results for SRS and ASD (Web Tables 5 and 6). Results were somewhat stronger for SRS scores in the enriched risk cohorts, although confidence intervals were wider in this smaller subset. In analyses stratified by child's sex, we did not observe strong evidence

Table 3. Associations Between Metabolic Pregnancy Conditions and Child Social Responsiveness Scale Scores, Stratified by Autism Spectrum Disorder Diagnosis in the Environmental Influences on Child Health Outcomes Study Population (Participants From 40 Cohorts), United States, 1998–2021[a]

Pregnancy Complication	Total No.[b]	Exposed No.[c]	Crude		Adjusted[d]	
			β	95% CI	β	95% CI
		ASD Cases				
Metabolic pregnancy complications, any	326	131	−0.36	−8.02, 7.31	1.38	−6.57, 9.34
Obesity	273	87	0.23	−8.62, 9.09	2.14	−7.22, 11.49
Gestational diabetes	231	23	−4.21	−19.67, 11.25	0.06	−16.11, 16.24
Hypertension	196	30	−4.17	−17.70, 9.36	−3.89	−18.30, 10.53
Preeclampsia	254	25	−14.57	−29.30, 0.16	−10.21	−25.39, 4.97
		Noncases				
Metabolic pregnancy complications, any	3,564	1,063	4.57	3.14, 6.00	2.15	0.75, 3.55
Obesity	3,174	742	6.65	5.01, 8.30	3.74	2.13, 5.36
Gestational diabetes	2,199	133	6.27	2.70, 9.84	4.90	1.48, 8.32
Hypertension	2,500	316	1.69	−0.65, 4.03	−1.68	−3.96, 0.60
Preeclampsia	2,151	144	3.40	−0.04, 6.83	1.48	−1.85, 4.82

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval.
[a] Table displays results of linear regression analyses within ASD cases (top rows) and noncases (bottom rows). As described in the text, ASD diagnosis was determined separately from SRS scores, according to parent report of a clinical diagnosis or clinical determination from diagnostic evaluations. Analyses in ASD cases inform on associations with severity of traits among those with a diagnosis, while analyses in noncases inform on associations with subclinical traits.
[b] Number in column represents total *n* included in analyses.
[c] Number in column represents exposed *n*.
[d] Adjusted for maternal age, race/ethnicity, and education level as well as child age at Social Responsiveness Scale, child's sex, and study type (for models not stratified by this factor).

Table 4. Associations Between Metabolic Pregnancy Conditions and Autism Spectrum Disorder Diagnosis in the Environmental Influences on Child Health Outcomes Study Population (Participants from 40 Cohorts), United States, 1998–2021[a]

Pregnancy Complication	Total No.[b]	Exposed No.[c]	Crude		Adjusted[d]	
			OR	95% CI	OR	95% CI
Metabolic pregnancy complication, any	6,778	131	1.63	1.30, 2.05	1.70	1.34, 2.17
Obesity	6,075	87	1.49	1.15, 1.94	1.48	1.12, 1.96
Gestational diabetes	3,974	23	1.51	0.97, 2.37	1.42	0.87, 2.32
Hypertension	4,454	30	1.51	1.01, 2.25	1.10	0.72, 1.70
Preeclampsia	4,159	25	1.83	1.18, 2.82	1.66	1.03, 2.66

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio.
[a] Table displays results of logistic regression analyses.
[b] Number in column represents total *n* included in analyses.
[c] Number in column represents exposed ASD cases.
[d] Adjusted for maternal age, race/ethnicity, and education level as well as child age, child's sex, and study type (enriched risk status, as described in text).

for effect modification by this factor (Web Tables 7 and 8).

In mediation analyses, preterm birth and low birth weight assessed as binary factors were not found to mediate the association between cardiometabolic pregnancy complications and ASD outcomes (Web Tables 9 and 10). Some evidence for mediation by continuous gestational age and birth weight was suggested (with proportions mediated of 23% and 14% respectively), although estimates included the null in these analyses as well (Web Tables 11 and 12).

In sensitivity analyses, additional adjustment for household income, cohort, gestational age, or birth weight did not alter results; in addition, co-adjustment of other complications for obesity yielded similar estimates (Web Table 13). Associations with any cardiometabolic pregnancy complication and SRS scores and ASD diagnosis were somewhat attenuated in the subsample that had information on all 4 pregnancy complications (Web Tables 14 and 15). However, findings remained consistent in suggesting modest increases in ASD-related outcomes among children whose mothers had any of the complications, with stronger associations with maternal prepregnancy obesity in particular. Results for additional missing-data strategies and analyses in subsets of cohorts were also similar (Web Table 16), although meta-analyses did demonstrate some variability across cohorts (Web Figure 3). When examining complications defined according to objectively collected data (medical record or measured), which included approximately 35% of the total study sample, estimates were attenuated for any complication and obesity, although still suggestive of modest increases in SRS scores for the latter. Estimates remained similar and suggestive of increases in scores for gestational diabetes and mainly null for hypertension and preeclampsia (Web Table 17). No differences in results from primary analyses were observed in the subset using only SRS-2 school-age forms (Web Table 18). Results were also similar when examining relationships with ASD diagnosis when excluding those participants missing this information (Web Table 19). Thus, findings were robust across sensitivity analyses.

DISCUSSION

In this study from the ECHO program, including data from 40 cohorts, we observed positive associations between cardiometabolic pregnancy complications and child ASD-related traits captured by the SRS. These findings, which are broadly consistent with prior studies reporting associations with ASD diagnosis, provide new information to demonstrate the influence of these complications on social communication traits across the spectrum of values. Results also support the utility of continuous trait measures in estimating associations with ASD risk factors. Of the conditions examined, the strongest signals observed were with maternal obesity and gestational diabetes. We also found that these complications were associated not only with scores above a threshold consistent with ASD diagnosis but also with more modest trait shifts across the population, which may be relevant in capturing influences on subclinical deficits in social communication and behavioral characteristics associated with ASD. Thus, results suggest a larger public health impact on child social communication functioning not previously considered when focusing on ASD as a binary diagnostic outcome alone.

An extensive literature has examined associations with pregnancy complications and ASD (7). Our focus was on associations between cardiometabolic conditions specifically and continuous measures of ASD-related traits. While most prior studies have examined associations with ASD diagnosis, some have included analyses with scores capturing aspects of the ASD-related phenotype. In the Childhood Risks for Autism from Genetics and the Environment (CHARGE) study (one of the cohorts included in this analysis), metabolic conditions (as a group) were associated not only with ASD diagnosis but also, within ASD cases, lower

cognitive and adaptive functioning scores (10). Another study reported increases in ASD-related traits as captured by the Autism-Spectrum Quotient in children without ASD according to maternal obesity at conception (45). Here, we were able to assess both ASD-related traits and diagnosis in a relatively large sample as compared with case-control studies and clinical samples. Results supported overall consistency in associations across these outcomes, which could relate to the fact that these cardiometabolic conditions have been associated with a broader range of neurodevelopmental outcomes and conditions. However, our results suggesting increases in scores according to cardiometabolic complications across SRS quantiles and among those without ASD also speak to the broader impact of conditions like maternal obesity on child social communication traits across the population. This is an important consideration given that social communication skills have been linked with academic performance, adaptive function, and psychological health across the life course (46, 47).

We observed increases in ASD-related outcomes according to obesity and gestational diabetes. These results are consistent with a number of prior large studies and meta-analyses (3, 4, 7, 8, 11, 48–50). However, our results stand in contrast to some prior work suggesting stronger associations with hypertensive conditions (2, 7, 10, 51–54). Some of this work has suggested differences by timing of onset or severity of preeclampsia (51, 52), which we did not have the ability to examine. We also lacked medical-record confirmation of these conditions, which may be less prone to misreporting, for a majority of participants (55). Inconsistency in results across published studies examining associations with pregnancy complications may relate to underlying differences in study populations, differences in adjustment factors, classification of complications under study, or simply the possibility that overall obstetric suboptimality and combinations of various factors (pregnancy complications and other) may contribute to estimated risk. We did not examine potential combined effects of multiple metabolic pregnancy complications, as indicated in some prior work to increase risk of ASD diagnosis further (12). Future work should consider whether combined effects of complications (or increasing obstetric suboptimality) are associated with larger increases in SRS scores than we observed.

We observed an overall lack of mediation in associations by preterm birth and low birth weight defined according to standard cutoffs, although mediation by continuously assessed gestational age and low birth weight suggests these factors could play modest roles in observed relationships. It is likely that the relative effects of downstream factors differ for the individual complications studied here, although those with the positive associations observed in our work (namely, obesity and gestational diabetes) may have overlapping pathways. Larger studies may be needed to more fully consider mediation and interaction.

Mechanisms underlying associations between cardiometabolic pregnancy complications and ASD have not been determined, but several potential pathways may link these conditions. Broad biological mechanisms suggested in animal models and some human studies include potential impacts of hypoglycemia (for gestational diabetes) (56); oxidative stress (57), alterations in the microbiome, and epigenetic changes (for gestational diabetes and obesity) (19); placental thickening (for gestational diabetes) (58) or decreased placental vascularization (for preeclampsia and hypertensive disorders) (51, 52); and inflammation or other immune-mediated pathways (across cardiometabolic conditions) (59, 60). In addition, social factors related to environmental exposures and psychosocial stress may also link obesity and risk of adverse neurodevelopmental outcomes (61, 62) and could have played into our findings; this represents an area of need for continued study.

It has also been posited that pregnancy complications in general may be a consequence rather than a cause of ASD, due to shared familial or genetic factors (63). A few prior studies have addressed this question by considering the role of enrichment for ASD risk in these associations. One study (9) observed weaker associations with pregnancy weight gain in those with familial ASD risk. Another found evidence that increases in ASD-related traits in family members influenced the observed relationship between pregnancy complications and ASD in the child, and suggested that the associations observed were therefore not causal (64). In our work, results were generally consistent across cohorts drawn from nonenriched and enriched risk settings. However, the latter group was composed of a high proportion of preterm birth cohort participants, which could represent a different relationship (e.g., potential mediation rather than modification; potential for collider stratification bias suggesting the need for caution in interpretation) than that due to enriched familial risk. We did not have the sample size to permit analyses among familial-enriched studies alone, which may provide further information as to the role of background risk in these associations. In addition to future work addressing these questions and focused on mechanisms of action related to dysregulated metabolic states in pregnancy in order to clarify causal relationships, future work should also assess specificity of relationships to ASD-related outcomes. These complications have been linked with related developmental outcomes, including attention-deficit/hyperactivity disorder, developmental delays, and intellectual disability as well as poorer scores on cognitive and behavioral tests (19, 48, 65–69). Comparing associations not only across commonly co-occurring diagnostic categories but also across their underlying, quantitatively assessed latent traits may help to better understand relationships—causal or not.

Key strengths of this work include a relatively large sample size for ASD research, ability to examine associations across multiple source populations within the ECHO framework, including comparisons across enriched risk and general population groups, and use of a comparative outcome approach enabling new questions to be addressed about how risk across a hypothesized latent trait distribution may compare to risk above a diagnostic threshold.

Despite these strengths, several limitations should also be noted in framing our findings and directing continued study of this topic. We did not have medical-record confirmation of conditions for all participants included, and misclassification is possible. Missing data was also relatively high for

some covariates, including maternal age and some complications. Sensitivity analyses using a complete-case approach or relying on conditions defined according to objectively collected measures yielded findings that were somewhat attenuated but were generally similar to the results of our primary analyses. In addition, prior work has supported the validity of women self-reporting pregnancy complications, with somewhat weaker support for gestational hypertension (55, 70, 71). Likewise, we cannot rule out potential outcome misclassification, although prior work has supported stability and validity of SRS scores (32–34). We did not have diagnostic confirmation of ASD for all cases, although analyses examining ASD as the outcome were conducted for comparative purposes, and results for associations with ASD were generally similar in enriched risk cohorts, which utilized gold-standard research measures for ASD diagnosis. Finally, we had a high degree of missingness on income, which plays a substantial role in health in the United States, and our proxies for sociodemographic factors may have been relatively crude indicators of actual social confounders, such as neighborhood deprivation and access to health care. We cannot rule out potential residual confounding by such constructs, or other social factors that may influence complications and ASD. Focus on reported ASD-related traits may have helped to reduce residual confounding by social factors closely tied to access to health care and diagnosis, but these topics warrant further consideration.

In sum, our results suggest that obesity and gestational diabetes, 2 common cardiometabolic complications, are associated with increased risk of broader social communication deficits. These findings complement previously observed associations between cardiometabolic complications and ASD diagnosis, but they suggest broader public health impact across the population. Such phenotypic links reiterate the need for careful early detection and treatment for women who experience these pregnancy complications, and follow-up of their children, in order to optimize outcomes.

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Author affiliations: AJ Drexel Autism Institute, Drexel University, Philadelphia, Pennsylvania, United States (Kristen Lyall); Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, United States (Xuejuan Ning, Christine Ladd-Acosta); Department of Pediatrics, Hackensack Meridian School of Medicine, Nutley, New Jersey, United States (Judy L. Aschner); Department of Pediatrics, Albert Einstein College of Medicine, the Bronx, New York, United States (Judy L. Aschner); Division of Research, Kaiser Permanente Northern California, Oakland, California, United States (Lyndsay A. Avalos, Lisa A. Croen, Assiamira Ferrara); Department of Public Health Sciences, School of Medicine, University of California Davis, Davis, California, United States (Deborah H. Bennett); Huntsman Mental Health Institute, University of Utah, Salt Lake City, Utah, United States (Deborah A. Bilder); Department of Psychiatry, University of California San Francisco, California, United States (Nicole R. Bush); Department of Pediatrics, University of California San Francisco, California, United States (Nicole R. Bush); Kravis Children's Hospital, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, New York, United States (Kecia N. Carroll, Rosalind J. Wright); Institute for Exposomic Research, Icahn School of Medicine at Mount Sinai, New York, New York, United States (Kecia N. Carroll, Rosalind J. Wright); Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston Massachusetts, United States (Su H. Chu, Rachel S. Kelly); Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Denver, Colorado, United States (Dana Dabelea); Department of Pediatrics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Denver, Colorado, United States (Dana Dabelea); Department of Maternal and Child Health, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (Julie L. Daniels); Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (Julie L. Daniels); Division of Child and Adolescent Psychiatry, Columbia University, New York, New York, United States (Christiane Duarte, Amy Margolis); Avera Research Institute, University of South Dakota School of Medicine, Sioux Falls, South Dakota, United States (Amy J. Elliott); Department of Pediatrics, University of South Dakota School of Medicine, Sioux Falls, South Dakota, United States (Amy J. Elliott); Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, United States (M. Daniele Fallin, Heather E. Volk); Department of Public Health Sciences, School of Medicine, University of California Davis, Davis, California, United States (Irva Hertz-Picciotto, Rebecca J. Schmidt); MIND Institute, School of Medicine, University of California Davis, Davis, California, United States (Irva Hertz-Picciotto, Rebecca J. Schmidt); Department of Psychiatry and Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States (Alison E. Hipwell); Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States (Elizabeth T. Jensen); Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, Colorado, United States (Susan L. Johnson); Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, Massachusetts, United States (Robert M. Joseph); Department of Epidemiology, Geisel School of Medicine, Dartmouth University, Hanover, New Hampshire, United States (Margaret Karagas); Department of Pediatrics, Warren Alpert Medical School of Brown University and Women and Infants Hospital, Providence, Rhode Island, United States (Barry M. Lester); Brown Center for the Study of Children at Risk and Women and Infants Hospital, Providence, Rhode Island, United States (Barry M. Lester);

Department of Pediatrics, Oregon Health & Science University, Portland, Oregon, United States (Cindy T. McEvoy); Department of Psychology, University of Miami, Coral Gables, Florida, United States (Daniel Messinger); Department of Pediatrics, University of Miami, Coral Gables, Florida, United States (Daniel Messinger); Department of Psychology, Pennsylvania State University, University Park, Pennsylvania, United States (Jenae M. Neiderhiser); Department of Psychiatry, University of Rochester, Rochester, New York, United States (Thomas G. O'Connor); Departments of Obstetrics and Gynecology, University of Rochester, Rochester, New York, United States (Thomas G. O'Connor); Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, United States (Emily Oken); Department of Pediatrics, UW Medicine, University of Washington, Seattle, Washington, United States (Sheela Sathyanarayana); Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, Seattle, Washington, United States (Sheela Sathyanarayana); Seattle Children's Research Institute, Seattle, Washington, United States (Sheela Sathyanarayana); Department of Psychiatry, Warren Alpert Medical School of Brown University, Providence, Rhode Island, United States (Stephen J. Sheinkopf); Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, Rhode Island, United States (Stephen J. Sheinkopf); Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, Rhode Island, United States (Stephen J. Sheinkopf); Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, Michigan, United States (Nicole M. Talge); Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, United States (Kedir N. Turi); Department of Preventive Medicine, College of Medicine, University of Tennessee, Memphis, Tennessee, United States (Qi Zhao); and College of Health and Human Development, Pennsylvania State University, State College, Pennsylvania, United States (Craig Newschaffer).

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