HHS Public Access

Author manuscript

Autism Res. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Autism Res. 2019 June ; 12(6): 967–975. doi:10.1002/aur.2105.

Maternal Diabetes and Hypertensive Disorders in Association with Autism Spectrum Disorder

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Abstract

Background: Previous studies have shown complications of pregnancy, often examined in aggregate, to be associated with autism spectrum disorder (ASD). Results for specific complications such as maternal diabetes and hypertension have not been uniformly consistent and should be investigated independently in relation to ASD in a large community-based sample.

Methods: The Study to Explore Early Development (SEED), a U.S. multisite case-control study, enrolled children born in 2003–2006 at 2–5 years of age. Children were classified into three groups based on confirmation of ASD (n=698), non-ASD developmental delay (DD; n= 887), or controls drawn from the general population (POP; n=979). Diagnoses of any diabetes or hypertensive disorder during pregnancy were identified from prenatal medical records and maternal self-report. Logistic regression models estimated adjusted odds ratios (aOR) and confidence intervals (CI) adjusting for maternal age, race/ethnicity, education, smoking during pregnancy, and study site. Models for hypertension were additionally adjusted for parity and plurality.

Results: Among 2,564 mothers, we identified 246 (9.6%) with any diabetes and 386 (15.1%) with any hypertension in pregnancy. After adjustment for covariates, any diabetes during

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The authors do not have any conflicts of interest to report.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease and Control and Prevention, nor of the California Department of Public Health.

This work was completed while the corresponding author was the University of North Carolina Chapel Hill, she is now located at the University of Miami.

pregnancy was not associated with ASD (aOR=1.10 [95% CI 0.77, 1.56]), but any hypertension was associated with ASD (aOR=1.69 [95% CI 1.26, 2.26]). Results were similar for DD, and any diabetes (aOR=1.29 [95% CI 0.94 1.78]) or any hypertension (aOR=1.71 [95% CI 1.30, 2.25]).

Conclusions: Some pregnancy complications, such as hypertension, may play a role in autism etiology and can possibly serve as a prompt for more vigilant ASD screening efforts.

Lay Summary

We studied if common complications in pregnancy are associated with autism spectrum disorder (ASD) in a large sample of mothers and children. Our results show an association between conditions marked by high blood pressure and ASD, but no association with conditions marked by high blood sugar and ASD. Associations were similar for children who had a developmental disorder that was not ASD, suggesting that this relationship may not be specific to ASD.

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders characterized by deficits in social interaction and communication, as well as restrictive and repetitive patterns of behaviors or interests [APA, 2013]. While the documented prevalence of ASD has steadily increased [Baio et al., 2018], the complex etiology of ASD remains largely unknown and suspected to involve both genetic and environmental factors [Hallmayer et al., 2011; Sandin et al., 2014]. Several studies implicate the prenatal period as a sensitive time window for the development of ASD [Willsey et al., 2013; Stoner et al., 2014; Ben-Ari, 2015].

Pregnancy complications have been frequently reported in association with the development of ASD [Gardener et al., 2009]. Maternal diabetes and hypertension are the most common complications of pregnancy and have increased over recent decades in the United States due to trends in increasing maternal age and obesity [Wallis et al., 2008; Albrecht et al., 2010]. It is possible that both conditions affect fetal brain development through pathways involving altered nutrient delivery [Harding, 2001] and inflammation [Jonakait, 2007]. Some previous studies have shown positive associations between maternal diabetes and ASD [Leonard et al., 2006; Lyall et al., 2012; Gregory et al., 2013; Xiang et al., 2015; Connolly et al., 2016] and maternal hypertension and ASD [Mann et al., 2010; Langridge et al., 2013; Polo-Kantola et al., 2014; Walker et al., 2015]; yet others did not strongly implicate these conditions [Juul-Dam et al., 2001; Hultman et al., 2002; Krakowiak et al., 2012; Li et al., 2016]. Some inconsistencies may be attributable to variable study designs, the use of administrative data, and limited sample size. In this analysis, we use rich data from the Study to Explore Early Development [Schendel et al., 2012] to examine the association between maternal diabetes and hypertension and ASD.

METHODS

Study Population

The Study to Explore Early Development (SEED) is a U.S. multisite case-control study with multiple-source ascertainment of children with ASD, children with developmental delays

other than ASD (DD), and children sampled from the general population [POP; Schendel et al., 2012]. Children in the ASD and DD groups were ascertained through multiple agencies and clinical settings that evaluate or serve children with developmental challenges. This broad diagnostic net for ascertainment better captures ASD among both previously diagnosed and undiagnosed children [Schendel et al., 2012]. State birth records were randomly sampled to identify children from the general population (POP group) who were born in the same time period and catchment area.

Children eligible for SEED were required to have been born and currently reside in one of six multi-county catchment areas in California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania [Schendel et al., 2012]. Children also had to be between the ages of 30 and 68 months of age at the time of in-person assessment, born between September 1, 2003 and August 31, 2006, and live with a knowledgeable caregiver who was at least 18 years of age, spoke English (all sites) or Spanish (California and Colorado), and was able to provide legal consent. This analysis was restricted to participants who completed the developmental assessment, had a final outcome classification of ASD, DD, or POP, and had data available on pregnancy complications.

Data Collection

The SEED data collection protocol is detailed elsewhere [Schendel et al., 2012]. SEED collected data on family medical history, maternal reproductive health and pregnancy outcomes, and child development and behavioral characteristics through telephone interviews, self-administered forms, an in-person child developmental assessment, collection of biosamples, and abstraction of maternal and child medical records. Limited birth certificate data were also obtained for all enrolled participants; however, information on pregnancy complications was not abstracted from the birth certificate. Data collection was standardized across sites and subject to uniform standards for quality data checks.

Outcome Assessment

All children enrolled in the study were initially screened for autism symptoms using the Social Communication Questionnaire [SCQ; Rutter et al., 2003]. As part of the data collection protocol, children were administered developmental assessments in-person by a trained clinician and were given a more extensive assessment if they screened positive for possible ASD (SCQ score >11), were determined to have a previous ASD diagnosis, or were suspected to have ASD based on the study clinician's direct observation. The more extensive assessment of the child included the Autism Diagnostic Observation Schedule [ADOS; Gotham et al., 2007]. Additionally, their caregivers completed the Autism Diagnostic Interview-Revised [ADI-R; Lord et al., 1994]. Final classification of ASD (yes or no) was based on the findings from these two developmental assessments [Wiggins et al., 2015]. Children who were suspected to have ASD but screened negative on the SCQ or did not meet ADOS and ADI-R criteria for ASD were classified as DD. Children with DD who had some ASD characteristics were excluded from this analysis. Children who screened negative on the SCQ and were sampled from birth records were classified as POP. More detail about the SEED outcome assessment is described elsewhere [Schendel et al., 2012; Wiggins et al., 2015].

Ascertainment of Maternal Hypertension and Diabetes

Multiple SEED instruments included information on any hypertension and diabetes during pregnancy: 1) prenatal care records; 2) telephone interview administered to the caregiver that included questions on her health during pregnancy; and 3) self-administered checklists of the mother's medical history both before and during pregnancy, used specifically for diabetes. Overall, prenatal medical record data were available for 67.3% of our study sample, and maternal self-report data were available for 99.5%. Among the 1,711 participants who had both medical record and self-reported data available, we found substantial to high agreement for both maternal diabetes (κ=0.85 95% CI 0.80, 0.89) and maternal hypertension (κ=0.66 95% CI 0.61, 0.71), based on Landis and Koch criteria [Landis & Koch, 1977]. Thus, the mother was classified as having the condition if it was reported in the prenatal medical record or by maternal self-report (either telephone interview or on self-checklist). Additionally, if the condition was reported by both medical record and self-report, the mother was further classified as having a 'Confirmed' condition (see below).

Maternal diabetes was further classified as gestational diabetes (GDM) or pre-existing diabetes (including Type 1 and Type 2 Diabetes Mellitus). These sub-classifications are mutually exclusive. In addition to reported diagnoses of GDM, results from oral glucose tolerance tests (OGTT) in the prenatal medical record were used to classify GDM. Clinical guidelines by Carpenter and Coustan requiring two elevated measurements in the OGTT were used [Coustan et al., 1989]. Four mothers were classified as having diabetes only by OGTT criteria. Mothers were classified as having 'Confirmed' diabetes if they met criteria on the OGTT or if the condition was reported by both medical record and self-report. If only one data source specified a diabetes type but the other confirmed a non-specified type of diabetes or use of antidiabetic medications (Insulin, Glyburide, or Metformin), then the mother was also classified as having 'Confirmed' diabetes through both sources. We defined 'No Diabetes' as not having a diagnosis in the medical record and no maternal report of diabetes.

Additionally, using any data source, 386 mothers (15.1%) were classified as having any hypertensive disorder during pregnancy (maternal hypertension). Mothers in the hypertension group were classified as having pre-existing chronic hypertension, pregnancy induced hypertension (PIH), or a more severe hypertensive disorder of pregnancy, including preeclampsia, eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Sub-classifications were not mutually exclusive as mothers may have pre-existing chronic hypertension and then go on to develop preeclampsia, eclampsia, or HELLP syndrome in pregnancy. In addition to reported diagnoses, serial blood pressure measurements from clinic and hospital visits were used to classify a woman as having a hypertensive disorder, depending on the timing of these measurements. Clinical guidelines requiring two separate elevated measurements (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) were used to classify the mother as having pre-existing chronic hypertension (if <20 weeks gestational age), PIH (if >20 weeks gestational age), or preeclampsia (if ≥20 weeks gestational age and accompanied by use of Magnesium) [American College of et al., 2013]. Forty-one mothers were classified as having hypertension only by blood pressure measurement criteria. Mothers were classified as

having ‘Confirmed’ hypertension if they met the blood pressure measurement or reported a hypertensive disorder through both self-report and medical record. We defined ‘No Hypertension’ as not having a diagnosis for a hypertensive disorder in the medical record and no maternal report of a hypertensive disorder.

Covariates

We conducted a thorough literature search to identify covariates that may be potential confounders in the association of these maternal conditions with ASD or broader developmental delays. For each condition, a Directed Acyclic Graph was used to identify potential confounders in order to obtain the least biased estimates [Shrier & Platt, 2008]. Data from birth certificates, prenatal medical records, and caregiver phone interview were used to define covariates. Odds ratios and 95% confidence intervals were obtained for the effect of each covariate on both the maternal condition and the outcome.

Confounders included maternal age at conception (continuous variable), maternal race/ethnicity (white non-Hispanic [referent] vs. other race/ethnicity), maternal education (high school degree or less vs. some college or more [referent]), maternal smoking during pregnancy (any vs. none [referent]), and study site (Georgia as referent). Hypertension and diabetes were more prevalent among non-Hispanic Black and Hispanic women, but neither group was of sufficient size to further refine racial categories. For hypertension models, parity (categorized as first birth [referent], second birth, third or more) and plurality (dichotomized as singleton [referent] vs. multiple) were included as additional confounders. For both maternal conditions, other potential confounders included having the other condition (diabetes or hypertension) and pre-pregnancy body mass index (BMI), categorized using World Health Organizations levels for low or normal BMI (referent; <25 kg/m^2), overweight ($\geq 25 – 30$ kg/m^2), and obese (≥ 30 kg/m^2). However, because the exact onset of the maternal condition is unknown, it is possible that one maternal condition could affect or be affected by the occurrence of the other condition; therefore, we treated the other condition and BMI as potential confounders (added separately in the adjustment set), also as potential mediators (excluded from the adjustment set), and evaluated for statistical interaction. Preterm birth, defined as a gestational age <37 weeks, is also an important mediator in this association. We therefore evaluated if associations remained among infants born at term.

Statistical Analysis

We calculated distributions of maternal characteristics by child outcome and maternal condition. We evaluated differences in maternal characteristics across study groups using Chi-square tests based on alpha=0.05. Multivariable logistic regression models estimated odds ratios (OR) and 95% confidence intervals (CI) for the association between maternal conditions and either ASD (vs. POP) or DD (vs. POP), adjusting for all confounders. We further adjusted for pre-pregnancy BMI and presence of other condition in separate models. In unadjusted models, we used the Breslow-Day test for homogeneity of the odds ratio with an alpha level $\alpha=0.10$ for interaction. In adjusted models, we obtained stratum-specific effect estimates by BMI category and preterm birth (<37 weeks gestation) for diabetes and

hypertension in association with ASD and DD, and tested the assumption of a multiplicative model.

Analyses were replicated in separate samples including only those with a confirmed condition and also for sub-classifications of the condition. Effect estimates were also obtained for ASD with and without intellectual disability (ID) vs. POP, as previous studies have concluded that they may be etiologically distinct [Li et al., 2016]. A Mullen Early Learning Composite Standard Score of <70 was used to identify ASD children with ID [Mullen, 1995]. All analyses were conducted using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

This analysis comprises a sample of 2,564 mother-child pairs enrolled in SEED. The study sample included 698 children with ASD, 887 with a non-ASD DD, and 979 from the POP group. Compared to our analytic sample, the excluded subset (n=1,205) was less likely to be non-White and less likely to have attained a higher education (data not shown). Mothers of children with ASD and DD were less likely to be White, less educated, and more likely to smoke during pregnancy, have higher pre-pregnancy BMI, or deliver a multiple birth, compared with POP mothers (Table 1). They were also more likely to have a hypertensive disorder, compared with POP mothers.

There were 246 mothers (10%) with any report of diabetes during pregnancy; 65 (3%) were classified with pre-existing diabetes and 181 (7 %) with GDM (Table 1). Among mothers with any diabetes, 151 (61%) had confirmed diabetes (i.e. record in both medical record and self-report), 33 (13%) were classified by only maternal report and 14 (6%) by only prenatal medical record. Hypertensive disorders were present during pregnancy for 386 mothers (15%), with 89 (3%) classified with pre-existing chronic hypertension, 282 (11%) with PIH, and 164 (6 %) with more severe hypertensive disorders of pregnancy such as preeclampsia, eclampsia, and HELLP syndrome (Table 1). Among mothers with any hypertensive disorder during pregnancy, 195 (51%) conditions were confirmed, 78 (20%) were classified as having a hypertensive disorder only by maternal report and 64 (17%) only by prenatal medical record.

In unadjusted analyses, we did not observe an association between any diabetes and ASD (OR=1.24 [0.89, 1.75]) (Table 2). In contrast, any diabetes was associated with DD (OR=1.47 [1.07, 2.00]). Adjustment for confounders attenuated the effect estimates in both groups (ASD aOR=1.10 [0.77, 1.56]; DD aOR= 1.29 [0.94, 1.78]). Additional adjustment for BMI and/or hypertensive disorders further attenuated the effect estimates, but did not materially alter the results (Table 2). In subgroup analyses, a stronger association was observed with ‘Confirmed’ diabetes, particularly in the DD group. Additionally, while stronger associations with ASD and DD were observed for mothers with GDM versus pre-existing diabetes, estimates were imprecise, with few mothers having pre-existing diabetes.

Hypertensive disorders in pregnancy were associated with both ASD (OR=1.78 [1.35, 2.35]) and DD (OR=1.67 [1.28, 2.18]) in unadjusted analyses (Table 2). After adjustment for

confounders, effect estimates both remained elevated (ASD aOR=1.69 [1.26, 2.26]; DD aOR=1.71 [1.30, 2.25]). Additional adjustment for BMI and diabetes did not notably alter effect estimates. In subgroup analyses, stronger associations were observed with 'Confirmed' hypertension. A stronger association was also observed for pre-existing chronic hypertension and DD, but not for other sub-classifications of hypertensive disorders.

Associations were generally similar for any diabetes or any hypertensive disorder and ASD with ID (vs. POP) compared to ASD without ID (vs. POP) (Table 3), though confidence intervals were imprecise due to smaller samples in each sub-group. In one model, however, the association with preeclampsia, eclampsia, HELLP syndrome and ASD without ID was stronger compared to the ASD with ID group. We did not find any evidence of interaction between BMI and diabetes or hypertensive disorders in association with ASD and DD (Table 4). Sample sizes were insufficient to evaluate the effect through the causal pathway of preterm birth. However, associations were attenuated but remained between hypertensive disorders and ASD (aOR=1.46 [1.04, 2.04]) or DD (aOR=1.40 [1.01, 1.94)] in children born at term (≥37 weeks).

DISCUSSION

We did not observe an association between any diabetes in pregnancy and ASD, but there was some suggestion of an association between any diabetes and DD. We observed that any hypertensive disorders during pregnancy were associated with ASD in the child. Similar associations were also observed between any hypertensive disorders and DD, suggesting a more general effect on neurodevelopment rather than specific to ASD processes. Further adjustment for BMI and diabetes did not materially alter these associations for hypertensive disorders. Overall, stronger associations were seen in mothers with a 'Confirmed' condition (reported in both the medical record and through maternal report, or in a diagnostic test). This may reflect better exposure classification among those with two sources. Confirmed conditions may also reflect more severe conditions in pregnancy.

There are several hypotheses regarding how maternal hypertension may affect fetal neurodevelopment. Previous studies have established an association between inflammation and oxidative stress and hypertensive disorders [Dinh et al., 2014], including those in pregnancy [Ferguson et al., 2017]. Oxidative stress and inflammation have also been associated with changes in neurodevelopment [Jonakait, 2007; Rose et al., 2012]. Oxidative stress may bring about cell necrosis or changes to the epigenome, affecting DNA methylation and gene expression [Rose et al., 2012; Main et al., 2013]. Additionally, some markers of inflammation are known to cross the blood brain barrier [Jonakait, 2007; Zerbo et al., 2013]. Hypertensive disorders are also associated with altered fetal nutrient delivery and intrauterine growth restriction [Long et al., 1980]. Changes in nutrient delivery may alter fetal metabolism and how the fetus grows and develops in utero, thereby affecting brain development.

We observed stronger associations with pre-existing hypertension, specifically with DD. This may be related to the timing of the condition during pregnancy and fetal brain development, or the association may operate through an alternate pathway involving

different metabolic and vascular factors. However, this group may be composed of mothers who had a more severe condition throughout pregnancy. Further study with a larger sample of mothers with pre-existing chronic hypertension is needed to explore this association. Unlike previous studies suggesting etiologically distinct pathways between ASD with and without ID [Li et al., 2016], we did not observe differences in the associations for ASD with ID versus ASD without ID, with an exception in mothers with preeclampsia, eclampsia, and HELLP syndrome.

Previous studies have reported an interaction with high BMI and both maternal diabetes and hypertension in association with ASD [Krakowiak et al., 2012; Connolly et al., 2016; Li et al., 2016]. Comparing BMI stratum-specific estimates, we did not observe differences in the association among mothers with low/normal pre-pregnancy BMI, overweight BMI, or obese BMI. Aside from the influence of BMI on development of hypertension, our results suggest that BMI may not play a role in the association between maternal hypertension and ASD. Sample sizes were insufficient to evaluate the causal pathway through preterm birth, which is more common among mothers with hypertensive disorders [Magnussen et al., 2011] and among children with ASD [Buchmayer et al., 2009]. However, an association between hypertensive disorders and ASD and DD did remain when we restricted the sample to terms births only, although it was attenuated. Further investigation on the added effect of preterm birth is warranted in a larger sample.

Our results are generally in agreement with other case-control studies that found associations between hypertensive disorders and ASD [Buchmayer et al., 2009; Mann et al., 2010; Walker et al., 2015], but there are subtle differences that may be due to the study population and sample size, with SEED having the largest number of affected children over multiple sites in the United States. While our results were similar to some studies, they differed from others, particularly those reporting a positive association between maternal diabetes and ASD [Burstyn et al., 2010; Gregory et al., 2013; Connolly et al., 2016; Li et al., 2016]. Compared to SEED, most large cohort studies used less detailed data from administrative datasets [Burstyn et al., 2010; Connolly et al., 2016] and/or birth certificates [Gregory et al., 2013; Connolly et al., 2016], and the somewhat rare exposures limited power in smaller studies [Connolly et al., 2016; Li et al., 2016]. Additionally, SEED confirmed ASD through a standardized, direct evaluation, instead of relying on ICD-9 codes [Burstyn et al., 2010; Connolly et al., 2016; Li et al., 2016] or school records [Gregory et al., 2013] that may instead be used to refer the child for further testing and not as a final diagnosis. In contrast, all children enrolled in SEED received an in-person evaluation to confirm ASD diagnosis with the gold standard instruments, the ADOS and ADI-R. Children in the DD and POP group were also screened, reducing outcome misclassification.

The SEED population-based study design is specifically designed to identify etiologic factors contributing to ASD. Data regarding risk factors are collected in great detail and from multiple sources, including mailed-in questionnaires, telephone interviews, birth certificates, and medical records, ensuring that pregnancy conditions are well-captured. For this study, we had results from diagnostic tests and clinic and hospital blood pressure measurements. These additional data allowed us to include mothers who met diagnostic criteria but were missing diagnosis codes in their medical record.

Although there are many strengths of this study, some limitations exist. Limited data were available to characterize the potential for sample selectivity, especially for the POP controls sampled from birth records. While a number of families of potentially-eligible children did not respond to the SEED invitation letter, analyses of data from one SEED site with the most complete data available to assess non-response indicated that maternal age and education were associated with participation in the POP group and maternal education was associated with participation in the ASD group [Schieve et al., 2018]. However, no differences were observed between participants and non-participants for measured pregnancy-related or other demographic variables. While we could not fully account for sample selectivity due to limited data from non-responders, our analyses adjusted for the aforementioned demographic factors known to be associated with participation [Schieve et al., 2018] and we have no reason to suspect participation was related to having pregnancy complications 3–5 years prior to study enrollment.

We aimed to obtain least-biased estimates of the association between maternal conditions and child development. We conducted a thorough literature review and used directed acyclic graphs to confirm the role of specific variables as confounders, rather than mediators or colliders. While our final adjustment set was comparable to or more extensive than previous studies, we cannot rule out the possibility that the observed associations resulted from residual confounding by an unknown and unmeasured variable, such as a genetic predisposition associated with both the maternal pregnancy condition and child brain development.

Diabetes and hypertension are among the most common complications of pregnancy; still SEED is one of the few studies with the detailed data necessary to investigate these conditions. The level of agreement among the caregiver interview and medical record was substantial, however there may be some exposure misclassification due to poor maternal recall or incomplete data in the medical record. The availability of medical record data was similar for participants in the ASD (69%) and POP (67%) groups, tempering concern about the potential for differential misclassification of prenatal health conditions in these groups. However, medical record availability was slightly lower for those with DD (62%). Analyses that required both caregiver interview and medical record to characterize the condition produced effect estimates of greater magnitude. This observation could reflect a better/confirmed exposure characterization or a more severe condition; while the observed weaker associations when maternal report and medical record data were discordant could reflect exposure misclassification or a less severe condition. We were unable to fully assess heterogeneity in either the severity or timing of maternal hypertension and diabetes during pregnancy. Vulnerable periods for fetal brain development are largely unknown and our ability to explore critical time windows of exposure to maternal conditions was limited by data availability reflecting the presence of these conditions during unique time windows of pregnancy and the generally small number of women with these conditions.

In summary, while we did not find an association between maternal diabetes and ASD, we did observe an association with maternal hypertensive disorders and both ASD and DD. This complements earlier reports among mothers with preeclampsia [Mann et al., 2010; Langridge et al., 2013; Walker et al., 2015] and extending them by identifying associations

between hypertension diagnosed previous to pregnancy and PIH and both ASD and DD. These results contribute to our understanding that maternal conditions during pregnancy and altered gestational environment are involved in autism etiology, warranting further investigation into the biological mechanism behind associations. Existence of prenatal risk factors for ASD may prove to be useful markers to prompt earlier developmental screening.

Acknowledgements

Dr. Cordero was supported by a training grant from the National Institute of Child Health and Human Development (5T32HD052468–07) and by The Study to Explore Early Development. The Study to Explore Early Development is funded by the Centers for Disease Control and Prevention: Cooperative Agreement Number U10DD000180, Colorado Department of Public Health; Cooperative Agreement Number U10DD000181, Kaiser Foundation Research Institute (CA); Cooperative Agreement Number U10DD000182, University of Pennsylvania; Cooperative Agreement Number U10DD000183, Johns Hopkins University; Cooperative Agreement Number U10DD000184, University of North Carolina at Chapel Hill; and Cooperative Agreement Number U10DD000498, Michigan State University.

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Table 1.

Distribution of maternal characteristics during pregnancy with index child born September 2003-August 2006, by child outcome classification in SEED (N=2,564)

Maternal Characteristics	Total Population (N=2,564)	Column percent by child outcome				
		ASD (n=698)	DD (n=887)	POP (n=979)	ASD vs. POP p-value	DD vs. POP p-value
Maternal Age at Conception (mean=31.03, SD= 5.53)					0.3399	0.6185
< 35 years	1911 (75)	525 (76)	655 (74)	731 (75)		
≥ 35 years	636 (25)	167 (24)	227 (26)	242 (25)		
Maternal Race/Ethnicity					<0.0001	<0.0001
White, non-Hispanic	1614 (63)	288 (56)	541 (61)	685 (70)		
Other	935 (37)	308 (44)	337 (38)	290 (30)		
Maternal Education					0.0002	<0.0001
High school degree or less	372 (15)	113 (16)	160 (18)	99 (10)		
Some college or more	2191 (85)	584 (84)	727 (82)	880 (90)		
Maternal Smoking					0.0003	0.0111
Yes	338 (13)	113 (16)	125 (14)	100 (10)		
No	2206 (86)	578 (83)	757 (85)	871 (89)		
Pre-pregnancy Body Mass Index					0.0003	0.0004
<25 kg/m^2 (Low/Normal)	1492 (58)	382 (55)	483 (54)	627 (64)		
25-<30 kg/m^2 (High)	603 (24)	171 (25)	221 (25)	211 (22)		
≥30 kg/m^2 (Obese)	419 (16)	132 (19)	158 (18)	129 (13)		
Parity					0.7378	0.0093
First birth	1113 (43)	325 (47)	345 (39)	443 (45)		
Second	908 (35)	231 (33)	327 (37)	350 (36)		
Third or more	510 (20)	129 (18)	204 (23)	177 (18)		
Plurality					0.0003	0.0078
Singleton	9410 (94)	641 (92)	828 (93)	941 (96)		
Multiple	154 (6)	57 (8)	59 (7)	38 (4)		
Study Site					0.6116	0.0065
California	392 (15)	107 (15)	133 (15)	152 (16)		
Colorado	496 (19)	141 (20)	157 (18)	198 (20)		
Georgia	508 (20)	137 (20)	192 (22)	179 (18)		
Maryland	370 (14)	108 (15)	118 (13)	144 (15)		
North Carolina	457 (18)	103 (15)	182 (21)	172 (18)		
Pennsylvania	341 (13)	102 (15)	105 (12)	134 (14)		
Diabetes in pregnancy						
No diabetes	2315 (90)	630 (90)	786 (89)	899 (92)		
Any diabetes	246 (10)	68 (10)	100 (11)	78 (8)	0.2091	0.0161
Confirmed	151 (6)	43 (6)	69 (8)	39 (4)	0.0460	0.0006
Not confirmed	95 (4)	25 (4)	31 (3)	39 (4)	0.3434	0.6996
GDM	181 (7)	52 (7)	74 (8)	55 (6)	0.1348	0.0195

Maternal Characteristics	Total Population (N=2,564)	Column percent by child outcome				
		ASD (n=698)	DD (n=887)	POP (n=979)	ASD vs. POP p-value	DD vs. POP p-value
Pre-existing diabetes	65 (3)	16 (2)	26 (3)	23 (2)	0.9822	0.3750
Hypertension in pregnancy						
No hypertensive disorder	2177 (85)	571 (82)	735 (83)	871 (89)		
Any hypertensive disorder	386 (15)	126 (18)	152 (17)	108 (11)	<0.0001	0.0001
Confirmed	195 (8)	68 (10)	76 (9)	51 (5)	0.0002	0.0025
Not confirmed	191 (7)	58 (8)	76 (9)	57 (6)	0.0409	0.0206
Pre-existing hypertension	89 (3)	26 (4)	44 (5)	19 (2)	0.0273	0.0005
PIH	282 (11)	99 (14)	98 (11)	85 (9)	0.0003	0.0633
Preeclampsia, eclampsia, HELLP syndrome	164 (6)	55 (8)	62 (7)	47 (5)	0.0095	0.0493

Table 2.

Associations between maternal diabetes or hypertensive disorders and ASD or DD in SEED

	Exposed *n* (Column %)			ASD vs. POP	DD vs. POP
Model	**ASD**	**DD**	**POP**	**OR (95%CI)**	**OR (95% CI)**
Maternal Diabetes					
Diabetes unadjusted	68 (10)	100 (11)	78 (8)	1.24 [0.89, 1.75]	1.47 [1.07, 2.00]
Diabetes adjusted[a]	65 (10)	96 (11)	78 (8)	1.10 [0.77, 1.56]	1.29 [0.94, 1.78]
Diabetes adjusted[a] + BMI, HTN	65 (10)	96 (11)	78 (8)	0.96 [0.67, 1.38]	1.16 [0.84, 1.61]
Confirmed diabetes[a]	42 (6)	68 (8)	39 (4)	1.45 [0.91, 2.29]	1.80 [1.19, 2.72]
Pre-existing diabetes[a]	15 (2)	24 (3)	23 (2)	0.88 [0.45, 1.73]	1.06 [0.59, 1.91]
GDM[a]	50 (7)	72 (8)	55 (6)	1.20 [0.80, 1.80]	1.41 [0.97, 2.04]
Maternal Hypertensive Disorders					
Hypertension unadjusted	126 (18)	152 (17)	108 (11)	1.78 [1.35, 2.35]	1.67 [1.28, 2.18]
Hypertension adjusted[b]	123 (18)	150 (17)	106 (11)	1.69 [1.26, 2.26]	1.71 [1.30, 2.25]
Hypertension adjusted[b] + BMI, DM	123 (18)	150 (17)	106 (11)	1.58 [1.17, 2.13]	1.61 [1.21, 2.14]
Confirmed hypertension[b]	67 (10)	74 (9)	51 (5)	1.84 [1.24, 2.73]	1.79 [1.22, 2.62]
Pre-existing hypertension[b]	26 (4)	44 (5)	19 (2)	1.67 [0.90, 3.11]	2.53 [1.44, 4.42]
PIH[b]	96 (14)	96 (11)	84 (9)	1.71 [1.24, 2.37]	1.36 [0.99, 1.87]
Preeclampsia, eclampsia, and HELLP[b]	54 (8)	60 (7)	46 (5)	1.69 [1.11, 2.57]	1.56 [1.03, 2.34]

[a.] Adjusted for maternal age, maternal race/ethnicity, maternal education, maternal smoking, and study site.

[b.] Adjusted for above (a.) plus plurality and parity.

Table 3.

Associations between maternal diabetes or hypertensive disorders and ASD with (*n*=258) and without (*n*=429) intellectual disabilities (ID) in SEED

Model	Exposed *n* (Column %)			ASD with ID vs. POP aOR (95% CI)	ASD without ID vs. POP aOR (95% CI)
	ASD with ID	ASD without ID	POP		
Maternal Diabetes					
Diabetes[a]	44 (10)	21 (8)	78 (8)	1.23 [0.82, 1.85]	0.98 [0.59, 1.63]
Pre-existing diabetes[a]	10 (2)	5 (2)	23 (2)	0.92 [0.42, 2.03]	0.83 [0.31, 2.22]
GDM[a]	34 (8)	16 (6)	55 (6)	1.37 [0.87, 2.17]	1.05 [0.58, 1.87]
Maternal Hypertensive Disorders					
Hypertension[b]	74 (18)	45 (18)	106 (11)	1.68 [1.20, 2.37]	1.64 [1.11, 2.42]
Pre-existing hypertension[b]	18 (4)	7 (3)	19 (2)	1.72 [0.86, 3.45]	1.52 [0.63, 3.70]
PIH[b]	56 (13)	37 (15)	84 (9)	1.73 [1.18, 2.52]	1.67 [1.09, 2.55]
Preeclampsia, eclampsia, HELLP[b]	27 (7)	24 (10)	46 (5)	1.37 [0.81, 2.29]	1.90 [1.12, 3.21]

[a.] Adjusted for maternal age, race/ethnicity, maternal education, maternal smoking, and study site.

[b.] Adjusted for above (a.) plus plurality and parity.

Table 4.

Stratum-specific effect estimates for maternal diabetes and hypertensive disorders for three strata of maternal pre-pregnancy BMI in SEED

***Model* / Strata**	**ASD vs. POP aOR (95% CI)**	**p-value for interaction**	**DD vs. POP aOR (95% CI)**	**p-value for interaction**
Maternal Diabetes				
BMI: low, normal (<25 kg/m^2)[a]	0.95 [0.71, 1.27]	Reference	1.23 [0.97, 1.57]	Reference
BMI: overweight (25-<30 kg/m^2)[a]	0.99 [0.71, 1.37]	0.874	0.94 [0.69, 1.28]	0.1833
BMI: obese (≥30 kg/m^2)[a]	1.10 [0.80, 1.52]	0.523	1.08 [0.79, 1.57]	0.522
Maternal Hypertensive Disorders				
BMI: low, normal (<25 kg/m^2) [b]	1.33 [1.06, 1.67]	Reference	1.36 [1.10, 1.68]	Reference
BMI: overweight (25-<30 kg/m^2)[b]	1.23 [0.93, 1.64]	0.687	1.31 [1.00, 1.72]	0.840
BMI: obese (≥30 kg/m^2)[b]	1.17 [0.89, 1.53]	0.479	1.12 [0.86, 1.46]	0.263

[a.] Adjusted for maternal age, race/ethnicity, maternal education, maternal smoking, and study site.

[b.] Adjusted for above (a.) plus plurality and parity.