Association between hypertensive disorders of pregnancy and long-term neurodevelopmental outcomes in the offspring

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Abstract

Objective: The long-term impact of hypertensive disorders of pregnancy (HDP) exposure on offspring health is an emerging research area. The objective of this study was to evaluate the association between a maternal diagnosis of HDP (gestational hypertension and preeclampsia) and adverse neurodevelopmental outcomes in the offspring.

Study Design: This was a secondary analysis of two parallel multicenter clinical trials of thyroxine therapy for subclinical hypothyroid disorders in pregnancy. Women with singleton non-anomalous gestations diagnosed with subclinical hypothyroidism or hypothyroxinemia were randomized to thyroxine therapy or placebo. The primary outcome was child intelligence quotient (IQ) at 5 years of age. Secondary outcomes included several neurodevelopmental measures, including Bayley-III cognitive, motor, and language scores at 12- and 24- months, DAS-II scores at 36 months, the Conners' Rating Scales-Revised at 48 months, and scores from the Child Behavior Checklist at 36 and 60 months. Thyroxine therapy did not influence neurodevelopment in either of the primary studies. Associations between neurodevelopment outcomes and maternal HDP were examined using univariable and multivariable analyses.

Results: A total of 112 woman-child dyads with HDP were compared with 1067 woman-child dyads without HDP. In univariable analysis, mean maternal age (26.7±5.9 vs. 27.8±5.7 years, p=0.032) and the frequency of nulliparity (45.5% vs. 31.0%, p=0.002) differed significantly between the two groups. Maternal socioeconomic characteristics did not differ between the groups. After adjusting for potential confounders, there were no significant differences in any primary or secondary neurodevelopment outcome between offspring exposed to HDP and those unexposed. However, when dichotomized as low or high scores, we found higher rates of language delay (language scores <85: −1 standard deviation) at two years of age among offspring exposed to HDP compared with those unexposed (46.5% versus 30.5%, adjusted odds ratio 2.22, 95% CI 1.44 - 3.42).

Conclusions: In this cohort of pregnant women, HDP diagnosis was associated with language delay at 2 years of age. However, other long-term neurodevelopmental outcomes in offspring were not associated with HDP.

Introduction

Hypertensive disorders of pregnancy (HDP) affect about 7%-10% of pregnancies worldwide.[1] Pregnancies complicated by HDP are at increased risk for maternal and/or fetal

mortality or serious morbidity.[2-4] Lifelong consequences of HDP affect the maternal-child dyad with increased risk of developing cardiovascular disease.[3, 5-8] Moreover, new evidence is emerging that in utero exposure to HDP may be an independent risk factor for adverse neurologic outcomes in the offspring.[9-13]

Recent studies investigating long-term effects of HDP on offspring health suggest that maternal HDP may be associated with lower cognitive ability of the offspring.[10-14] Several studies have suggested that HDP may adversely affect neurodevelopment during childhood and into early adulthood, including intelligence quotient (IQ) scores.[14-16] Mechanisms proposed to explain this association include genetic components that may predispose to HDP, as well as cardiovascular and neurodevelopment diseases in later life, which may be inherited by the offspring, as well as inflammatory components that are present in preeclampsia and may disrupt placental signaling and/or cross to the fetal circulation to alter fetal neurodevelopment trajectories. Other studies, however, did not confirm the association between HDP and offspring neurodevelopment.[17-19]

In 2017, two parallel multicenter randomized placebo-controlled trials were published examining the effect of treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy on cognitive function in offspring.[20] The study followed 1,179 children up to 5 years of age and reported several neurodevelopmental outcome measures including IQ. Therefore, we proposed to use this unique long-term data base to examine the association between maternal diagnosis of HDP and offspring neurodevelopment. The objective of this study was to compare full-scale intelligence quotient assessed with the use of the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) at 5 years of age, or with the overall score from the Differential Ability Scales–II at 3 years of age between offspring of women with and without diagnosis of HDP. Our hypothesis was that offspring of women with diagnosis of HDP will have lower full-scale intelligence quotient at 5 years of age or lower overall score from Differential Ability Scales–II at 3 years of age.

Methods

This was a secondary analysis of two multicenter randomized placebo-controlled trials of thyroxine therapy for hypothyroid disorders in pregnancy.[20] The trials were conducted in 15 centers within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Women with a singleton pregnancy who were diagnosed with subclinical hypothyroidism or hypothyroxinemia at a gestational age between 8 weeks 0 days and 20 weeks 6 days were included in separate but parallel trials . These women were randomized to receive thyroxine therapy or placebo. Apart from the underlying condition of the participants (subclinical hypothyroidism versus hypothyroxinemia) and dosing for the active and placebo groups, the trials were identical. For the purposes of this analysis they are combined and designated as the parent study. The primary outcome in the original trial was the full-scale intelligence quotient (IQ) assessed with the use of the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) at 5 years of age, or with the overall (General Conceptual Ability) score from the Differential Ability Scales–II (DAS) at 3 years of age if the WPPSI-III score was not available, or death before 3 years of age (because it was a competing event for IQ score). The primary outcome

for this analysis was child intelligence quotient (IQ) at 5 years of age. We did not include deaths in this analysis since the primary outcome for this analysis was looking at IQ at five years of age. The number of deaths were low and occurred mainly before hospital discharge. Secondary outcomes included several neurodevelopmental measures, including Bayley-III cognitive, motor, and language scores at 12- and 24-months, DAS-II scores at 36 months, the Conners' Rating Scales-Revised at 48 months, and scores from the Child Behavior Checklist at 36 and 60 months. Composite scores are derived for cognitive, language, and motor development and scaled to a metric, with a mean of 100, standard deviation of 15, and range of 40 to 160.[21] There was no specific language assessment done at 5 years, nor the WPPSI-III receptive or expressive tests. For the Child intelligence quotient at the age of 5, if there was an impairment, they were assigned a score less than 50 (N=5). The score of 50 was the lower limit of the test score and it was given instead of having a missing score. The impairment could have been a visual, hearing, or motor impairment severe enough that the test could not be administered. For other assessments, only valid non-missing values were included. Of note, in the parent study thyroxine therapy did not influence neurodevelopment.

We applied the following exclusion criteria to this analysis: miscarriage, stillbirth or neonatal death. Maternal diagnosis of HDP was abstracted in the parent study from the electronic health records and included gestational hypertension and preeclampsia. In the original study, preeclampsia was defined as hypertension (defined as a systolic blood pressure of 140 mm Hg or a diastolic blood pressure of 90 mm Hg on 2 occasions 4 hours apart) plus proteinuria (either 300 mg per 24 hours or 2+ or more by dipstick on 2 or more occasions 4 hours apart). Women with chronic hypertension were not included in the diagnosis of HDP. The primary and secondary neurodevelopmental and behavior outcomes from the parent study were compared between women with and without diagnosis of HDP.

Maternal baseline characteristics including demographic characteristics (maternal age, marital status, education, body mass index (BMI), insurance type), clinical characteristics (parity, smoking during pregnancy, alcohol use during pregnancy, thyroid status (subclinical hypothyroidism vs. hypothyroxinemia), treatment group (levothyroxine vs. placebo), and neonatal sex were compared between those with and without HDP. Maternal baseline characteristics were compared using the Wilcoxon rank sum, chi-square, or Fisher exact test, as appropriate. Differences between HDP groups for the primary and secondary outcomes were analyzed using Wilcoxon rank sum test, Fisher exact, or chi-square tests, as appropriate. Multivariable quantile regression was used to assess differences in scores adjusting for potential confounders. Multivariable logistic regression was used to evaluate dichotomized outcomes. Baseline characteristics that were found to be different between HDP groups at a level $p < .0.05$ in univariable analysis were included in the models. In addition, the original trial treatment group assignment and maternal baseline thyroid status were included in the models. .Adjusted beta coefficients (demonstrating differences in scores) and adjusted odds ratios with 95% confidence intervals were reported. Additional analyses stratifying by preterm (less than 37 weeks) and term (greater than or equal to 37 weeks) deliveries were performed. The rationale behind stratifying by preterm delivery is the inverse relationship between gestational age and risk for developmental impairment as preterm delivery can predispose the offspring to neurodevelopmental delays.[22] Since gestational age at birth could be in the causal pathway for the association between

HDP and offspring's neurodevelopment we did not adjust for it in the regression model but examined term and preterm groups, separately. A p-value <0.05 was considered statistically significant. No imputation for missing data was performed. Statistical analysis was performed using SAS 9.4 statistical software (SAS Institute Inc., Cary, NC). The parent study was approved by the Institutional Review Board at each center prior to trial initiation. All STROBE checklist items were followed when planning, conducting and reporting the original RCT which this secondary analysis is based on.

Results

A total of 1,179 women-children dyads were included in the analysis (Figure 1). Of these, 112 (9.5%) were exposed to HDP. Table 1 describes baseline demographic and clinical characteristics of the cohort. Women who developed HDP were younger, more likely to be nulliparous, have higher BMI and higher rates of preterm delivery. Marital status, insurance type, substance abuse, maternal education and receipt of levothyroxine treatment did not differ between women with and without a diagnosis of HDP.

Table 2 describes neurodevelopmental outcomes among offspring by diagnosis of HDP. The full-scale IQ assessed with the use of the WPPSI-III at 5 years of age, both as continuous outcome and as IQ< 85 (one standard deviation below the mean), did not differ between children exposed to HDP and those unexposed. Median scores were 94 [interquartile range: (IQR): 85 – 101.5] and 95 [IQR: 84-104] for those exposed to HDP versus unexposed to HDP, respectively (p=0.75). Similarly, there were no significant differences between the two groups, for a low WPPSI-III score, 22.2% of HDP group and 25.3% of the non-HDP group had an IQ < 85 (p=0.48). Among secondary outcomes, both groups were similar with the exception of the Bayley-III language assessment at two years of age. Children exposed to HDP had higher rates of language score <85 at two years of age, indicating language delay (46.5% versus 30.5%, p=0.001).

Multivariable regression analyses were performed and showed similar findings. Regression models were adjusted for baseline maternal age, parity and BMI, since these were significantly different between the two groups, and for the original trial treatment group assignment and baseline thyroid status. The adjusted difference in medians between the two groups for the WPPSI-III IQ was –0.82, 95% CI: –4.31 to 2.67. The adjusted odds ratio for the HDP group compared with the non-HDP group for low WPPSI-III score was 0.80, 95% CI: 0.50 to 1.31. The adjusted odds ratio for the HDP group compared with the non-HDP group for low Bayley-III language score at two years was significant (aOR 2.22, 95%CI 1.44 to 3.42). In addition, median language scores were lower among children exposed to HDP compared with the non-HDP group. No other secondary outcomes were significantly different in the adjusted analyses.

Analysis stratified by preterm delivery (<37 weeks) was conducted and described in Tables 3 and 4. The results confirmed the finding of higher rates of language score <85, both in preterm and term groups. In addition, median language scores were lower in the preterm group among children exposed to HDP compared with the non-HDP group.

Discussion

In this study, we found that maternal diagnosis of HDP was associated with higher rates of language delay in the offspring at the age of 2 but did not have an effect on any other neurodevelopmental measures at the age of 2 or at the age of 5. The results did not differ when analysis was stratified by preterm birth.

Our findings of language delay were similar to the study by Whitehouse et al that found lower verbal ability in offspring exposed to HDP.[16] Whitehouse et al examined verbal ability in 1,389 children at age 10 using the "Peabody Picture Vocabulary Test – Revised" and found that exposure to preeclampsia or gestational hypertension was associated with 1.83 (95% Confidence Interval –3.48 - –0.17) points lower score.[16] This study controlled for birthweight and gestational age which suggested that reduced verbal ability cannot be attributed solely to immaturity or intrauterine growth restriction. In contrast, Sverrisson et al analyzed nationwide data from the Icelandic registries and reported no difference in language art scores among children age 9 to 15 years old.[18] This study, however, lacked information about maternal smoking status, maternal BMI and maternal medical co-morbidities, such as diabetes, all of which have been associated with child cognitive development.[22-24]

In regard to the rest of the neurodevelopmental outcomes, including child IQ assessed at the age of 5, our study did not find an association between offspring exposure to HDP and long-term neurodevelopmental concerns. This conflicts with prior studies reporting positive association.[10, 11, 13] Spinillo et al found that infants delivering preterm secondary to HDP compared to spontaneous preterm birth, had higher rates of minor neurodevelopmental impairment.[13] Cheng et al followed infants born at <32 weeks with and without an exposure to preeclampsia up to 2 years of age and found that preeclampsia was associated with a significantly lower score on the mental development index of the Bayley Scales of Infant Development.[10] Other studies that included full term deliveries found an association between exposure to HDP and childhood behavioral issues and mild lower cognitive ability in the offspring.[14, 15, 19, 25] A recent systematic review showed that exposure to HDP was associated with a 35% increase in the odds of Autism Spectrum Disorder (ASD) when compared to those unexposed to HDP.[11] Another recent study from Norway using medical birth registry of term deliveries found that offspring from preeclampsia had higher odds ratio of attention-deficit/hyperactivity disorder, ASD, epilepsy and intellectual disability.[26] The limitation of that study included lack of information on maternal smoking status and overall, as this was a registry ascertainment of exposures and outcomes may have been limited to more severe cases.[26] It is important to note, that other studies that found a positive association between preeclampsia and neurodevelopmental outcomes in the offspring did not control for certain key variables such as maternal age, socio-economic status, ethnic origin and maternal depression, calling into question the validity of findings.[11,19] Other studies focused on preterm population,[10,13] a factor that by itself can predispose the offspring to neurodevelopmental delays.[27] Finally, other long cohort studies did not support the association between exposure to HDP and impaired neurodevelopment in the offspring.[17, 18, 25]

Given the epidemiologic evidence for an association between exposure to HDP and offspring's language delay, confirmed by our study, the question arise what could be the mechanisms that mediate this association. These include a genetic component that may predispose to preeclampsia, cardiovascular and neurodevelopment diseases in later life and may be inherited by offspring.[1] Another mechanism is inflammation. Inflammation is recognized as a core clinical feature in preeclampsia.[2] The decrease in placental perfusion in preeclampsia leads to an increased production of pro-inflammatory cytokines such as IL-6 and TNF-α. These cytokines may disrupt placenta signaling and/or cross to the fetal circulation to alter fetal neurodevelopment trajectories, which may increase the risk of suboptimal neurodevelopmental outcomes, including verbal ability, in offspring exposed to pre-eclampsia. The potential effect of these mechanisms on neurologic pathways related to language and verbal ability is intriguing and deserves further elucidation.

The limitations of this study should be noted. First, this analysis is limited to the population included in the parent study and sample size used for our analysis was fixed. Moreover, all women in the parent study had a diagnosis of subclinical thyroid disease. There has been a controversy surrounding the contribution of untreated maternal subclinical thyroid disease in pregnancy towards offspring long-term cognitive development.[20, 28-34] However recent large randomized controlled trials, including the parent trial[20] and the Controlled Antenatal Thyroid Screening study[30] with a follow-up up to 9.5 years of age[35] did not show that levothyroxine in pregnancy improves child cognitive scores. The IQ scores were similar across the groups and within the general population range. Furthermore, studies investigating maternal thyroid dysfunction did not find an association between thyroid function tests and offspring language ability.[32, 33] This supports that our findings are not related to maternal diagnosis of subclinical thyroid disease. Second limitation included lack of information whether women with HDP required antihypertensive medication, and if so, what type of medication. Therefore, we are unable to control our results for antihypertensive medication exposure or the severity of maternal HDP disease. Third, we analyzed both gestational hypertension and preeclampsia in the same group of HDP as a separate analysis for each of these disease stages was not feasible due to limited sample size. Fourth, it should be emphasized that the language delay was detected at the age of 2. There was no specific language assessment done at 5 years; therefore, we are unable to assess whether the language delay persisted. It is possible that the language difference was a type 1 error due to comparison of multiple neurodevelopment measures in this analysis, Furthermore, we did not account for an important confounder when assessing offspring language, and that is the primary language of the parents. Finally, it is important to note that while missing data for the primary outcome of this analysis, WPPSI-III, was missing in only 5.8% of participants, some of the data for secondary outcomes was missing in up to 10%.

In contrast, our study has several strengths. First, our analysis stands apart from other studies as it is based on the only prospective cohort of women-children dyads assessing long-term neurodevelopmental outcomes of the offspring and collecting a detailed maternal information on prenatal clinical, social and demographic variables. Second, the association between offspring language delay and HDP exposure was significant both in the entire cohort as well as in the sub-group analysis limited to term deliveries. Therefore, this is less likely to represent a random association.

In conclusion, in this secondary analysis, diagnosis of maternal HDP was associated with language score <85 at 2 years of age but not with any other long-term neurodevelopmental outcomes in offspring.

Appendix A

In addition to the authors, other members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows:

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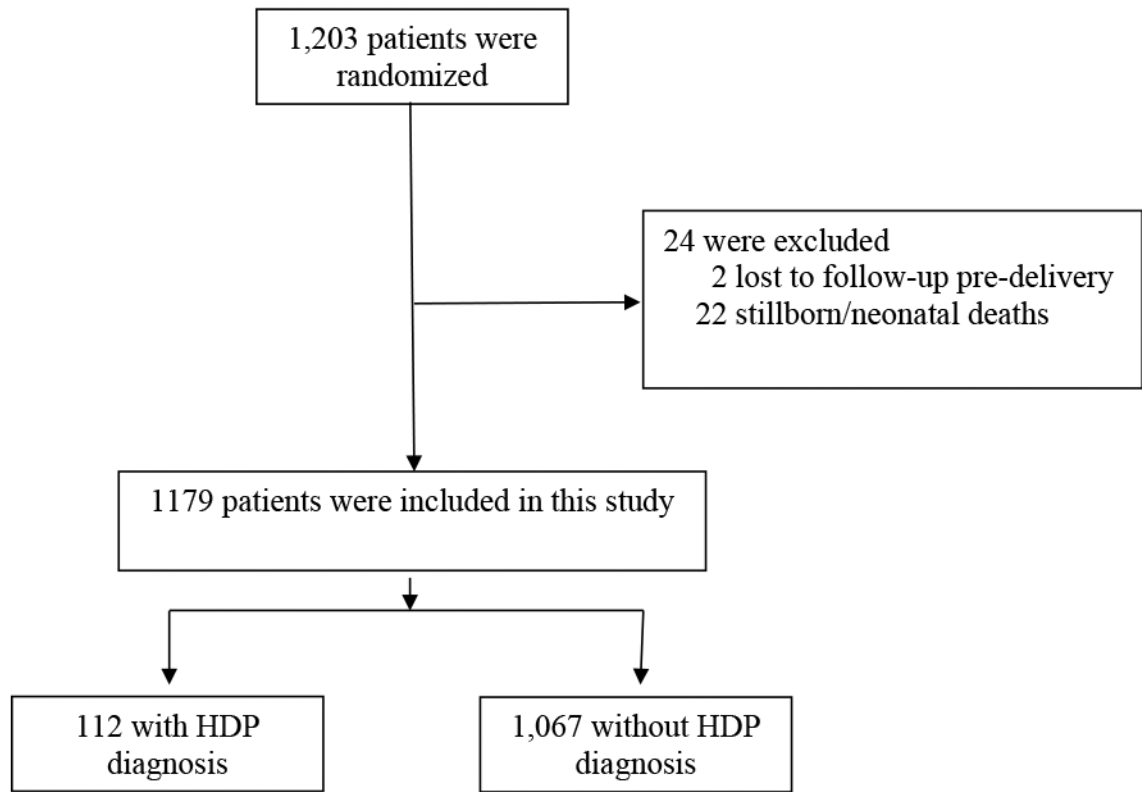
Figure 1.
Study flowchart.

Table 1.

Comparison of neurodevelopment outcomes among offspring by maternal diagnosis of hypertensive disorders of pregnancy.

Outcome	HDP diagnosis (N=112)	No HDP diagnosis (N=1067)	P-value
Maternal age (years)	26.7 ± 5.9	27.8 ± 5.7	0.03
Marital status			0.27
Married / living with partner	76 (67.9)	795 (74.5)	
Divorced / widowed / separated	6 (5.4)	41 (3.8)	
Never married	30 (26.8)	231 (21.6)	
BMI kg/m2	31.8 ± 7.8	28.8 ±6.4	<0.001
Preterm delivery < 37 weeks	25 (22.3)	76 (7.1)	<0.001
Smoking during pregnancy	8 (7.1)	83 (7.8)	0.81
Alcohol during pregnancy	4 (3.6)	61 (5.7)	0.34
Insurance type			0.22
Government assisted	73 (65.2)	610 (57.2)	
Private	28 (25.0)	304 (28.5)	
Self-pay	11 (9.8)	153 (14.3)	
Maternal education			0.52
Less than High School graduate	51 (45.5)	478 (44.8)	
High school graduate	42 (37.5)	362 (33.9)	
College graduate and higher	19 (17.0)	227 (21.3)	
Parity			0.002
Nulliparous	51 (45.5)	331 (31.0)	
Multiparous	61 (54.5)	736 (69.0)	
Levothyroxine treatment group	53 (47.3)	542 (50.8)	0.48
Thyroid status			0.24
Subclinical hypothyroidism	69 (61.6)	595 (55.8)	
Subclinical hypothyroxinemia	43 (38.4)	472 (44.2)	
Infant male sex	64 (57.1)	545 (51.1)	0.22

Data displayed as mean ± SD or n (%).

Table 2.

Comparison of neurodevelopmental outcomes among offspring by maternal diagnosis of hypertensive disorders of pregnancy.

Outcome	HDP diagnosis (N=112)	No HDP diagnosis (N=1067)	Adjusted Difference in Medians or Adjusted Odds Ratio (95% CI)
WPPSI-III IQ at 5y	94 [85–101.5]	95 [84–104]	−0.82 (−4.31 to 2.67)
WPPSI-III IQ<85 (n, %)	24 (22.2)	254 (25.3)	0.80 (0.50 to 1.31)
Bayley-III assessment at 1y:			
Cognitive	100 [95-110]	100 [90-110]	0 (−2.58 to 2.58)
Cognitive <85 (n, %)	7 (6.6)	90 (9.0)	0.76 (0.34 to 1.70)
Motor	97 [91-107]	97 [91-103]	0 (−1.56 to 1.56)
Motor <85 (n, %)	8 (7.5)	98 (9.8)	0.79 (0.37 to 1.70)
Language	95.5 [89-103]	94 [86-103]	1.84 (−0.90 to 4.58)
Language<85 (n, %) (indicating language delay)	17 (16.0)	181 (18.1)	0.93 (0.54 to 1.62)
Bayley-III assessment at 2y:			
Cognitive	90 [85-95]	90 [85-100]	−0.39 (−3.03 to 2.25)
Cognitive <85 (n, %)	19 (18.8)	235 (24.0)	0.73 (0.43 to 1.25)
Motor	97 [91-103]	97 [91-103]	0.47 (−2.23 to 3.16)
Motor <85 (n, %)	8 (7.9)	96 (9.9)	0.74 (0.34 to 1.60)
Language	86 [79-97]	91 [83-97]	−4.63 (−9.09 to −0.17)
Language<85 (n, %) (indicating language delay)	47 (46.5)	292 (30.5)	2.22 (1.44 to 3.42)
DAS-II General Conceptual Ability score (GCA)at 3y	89 [79-97]	90 [81-100]	−1.04 (−6.01 to 3.93)
DAS-II (GCA) at 3y <85	39 (37.9)	348 (35.2)	1.11 (0.72 to 1.72)
CBCL T score at 3y	46.5 [41-57]	46.5 [40-54]	0.21 (−3.21 to 3.63)
CBCL T score at 3y >60	12 (11.5)	97 (9.8)	1.32 (0.68 to 2.53)
Conners' Rating Scale-Revised ADHD score at 4y	48.5 [44-57.5]	49 [44-57]	−0.48 (−3.55 to 2.59)
Conners' Rating Scale-Revised ADHD T score > 60	17 (16.3)	160 (16.5)	0.92 (0.53 to 1.61)
CBCL T score at 5y	44.5 [37-53]	44.5 [37-53]	0.02 (−3.05 to 3.10)
CBCL T score at 5y >60	10 (9.3)	105 (10.4)	0.87 (0.43 to 1.75)

Data displayed as median and interquartile range unless otherwise indicated.

WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence-III; DAS-II, Differential Ability Scales-II; Bayley, Bayley Scales of Infant Development-III; Conners, Conners' Rating Scales-Revised, for assessment of attention; CBCL, Child Behavior Checklist, for behavioral and social competency

Number of participants in each outcome: WPPSI-III: 1111; 12 month Bayley cognitive: 1111; 12 month Bayley motor: 1108; 12 month Bayley language: 1104; 24 month Bayley cognitive: 1080; 24 month Bayley motor: 1069; 24 month Bayley language: 1057; DAS II: 1091; 36 month CBCL: 1096; Conners: 1071; 60 month CBCL: 1114.

Quantile regression model adjusters included parity, maternal age, maternal BMI, treatment group, and baseline thyroid status.

Table 3.

Comparison of neurodevelopmental outcomes among offspring stratified by maternal diagnosis of hypertensive disorders of pregnancy for women who delivered preterm (<37 weeks).

Outcome	HDP diagnosis (N=25)	No HDP diagnosis (N=76)	Adjusted Difference in Medians or Adjusted Odds Ratio (95% CI)
WPPSI-III IQ at 5y	89 [81 – 103]	90.5 [80 -102]	1.13 (−11.33 to 13.59)
WPPSI-III IQ<85 (n, %)	7 (29.2)	24 (34.3)	0.63 (0.21 to 1.94)
Bayley-III assessment at 1y			
Cognitive	100 [95-110]	100[95-110]	2.89 (−4.93 to 10.70)
Cognitive <85 (n, %)	1 (4.5)	3 (4.3)	0.69 (0.06 to 8.57)
Motor	97 [91-100]	100 [91-110]	−3.81 (−9.82 to 2.21)
Motor < 85 (n, %)	4 (18.2)	6 (8.7)	2.03 (0.48 to 8.64)
Language	97 [89-109]	94 [89-106]	−3.05 (−13.64 to 7.53)
Language <85 (n, %)	4 (18.2)	13 (18.8)	0.81 (0.21 to 3.11)
Bayley-III assessment at 2y			
Cognitive	90 [85-95]	90 [80-100]	1.22 (−6.03 to 8.47)
Cognitive <85 (n, %)	3 (13.6)	17 (25.8)	0.54 (0.13 to 2.29)
Motor	94 [91-107]	97 [91-107]	0.00 (−7.39 to 7.39)
Motor < 85 (n, %)	2 (9.1)	5 (7.7)	1.17 (0.16 to 8.41)
Language	83 [77-94]	91 [83-97]	−6.52 (−14.53 to −1.50)
Language <85 (n, %)	12 (54.5)	17 (26.6)	3.32 (1.12 to 9.84)
DAS-II General Conceptual Ability score at 3y	82 [78-95]	87 [77-96]	−1.32 (−13.43 to 10.79)
DAS II (GCA) at 3y < 85	12 (54.5)	30 (43.5)	1.73 (0.60 to 4.96)
CBCL T score at 3y	48 [41-59]	47 [39-58]	3.14 (−3.01 to 9.30)
CBCL T score at 3y >60	4 (18.2)	13 (8.8)	0.62 (0.14 to 2.83)
Conners' Rating Scale-Revised ADHD score at 4y	50 [44-58])	49.5 [44-57]	−0.34 (−7.00 to 6.32)
Conners' Rating Scale-Revised ADHD T score >60	5 (22.7)	12 (19.4)	2.61 (0.57 to 12.02)
CBCL T score at 5y	51 [45-55.5]	46 [39-54]	5.55 (−0.74 to 11.85)
CBCL T score at 5y >60	3 (12.5)	10 (14.3)	0.55 (0.12 to 2.67)

Data displayed as median and interquartile range.

WPPS III, Wechsler Preschool and Primary Scale of Intelligence-III; DAS II, Differential Ability Scales-II; Bayley, Bayley Scales of Infant Development; Conners, Conners' Rating Scales-Revised, for assessment of attention; CBCL, Child Behavior Checklist, for behavioral and social competency

Number of participants in each outcome: WPPS III: 94; 12 month Bayley cognitive: 92; 12 month Bayley motor: 91; 12 month Bayley language: 91; 24 month Bayley cognitive: 88; 24 month Bayley motor: 87; 24 month Bayley language: 86; DAS II: 91; 36 month CBCL: 91; Conners: 84; 60 month CBCL: 94.

Quantile regression models included parity, maternal age, maternal BMI, treatment group, and baseline thyroid status.

Table 4.

Comparison of neurodevelopmental outcomes among offspring stratified by diagnosis of HDP for women who delivered at term (>=37 weeks)

Outcome	HDP diagnosis (N=87)	No HDP diagnosis (N=991)	Adjusted Difference in Medians or Adjusted Odds Ratio (95% CI)
Primary outcome			
WPPSI-III IQ at 5y	94.5 [86-101]	95 [85 -104]	−1.12 (−4.70 to 2.46)
WPPSI-III IQ<85 (n, %)	17 (20.2)	230 (24.7)	0.73 (0.42 to 1.30)
Secondary outcomes			
Bayley-III assessment at 1y:			
Cognitive	100 [92.5-110]	100 [90-110]	0.87 (−1.97 to 3.71)
Cognitive <85 (n, %)	6 (7.1)	87 (9.3)	0.81 (0.34 to 1.94)
Motor	97 [92.5-110]	97 [91-103]	0.00 (−2.78 to 2.78)
Motor <85 (n, %)	4 [4.8]	92 (9.9)	0.50 (0.18 to 1.40)
Language	94 [89-103]	94 [86-103]	1.82 (−1.07 to 4.71)
Language<85 (n, %) (indicating language delay)	13 (15.5)	168 (18.1)	0.92 (0.49 to 1.71)
Bayley-III assessment at 2y:			
Cognitive	90 [85-95]	90 [85-95]	−0.30 (−3.65 to 3.05)
Cognitive <85 (n, %)	16 (20.3)	218 (23.9)	0.79 (0.44 to 1.42)
Motor	97 [91-103]	97 [91-103]	0.56 (−1.68 to 2.80)
Motor <85 (n, %)	6 (7.6)	91 (10.1)	0.70 (0.29 to 1.68)
Language median	86 [79-100]	90 [83-98.5]	−2.91 (−7.40 to 1.58)
Language<85 (n, %) (indicating language delay)	35 (44.3)	275 (30.8)	2.01 (1.24 to 3.25)
DAS-II General Conceptual Ability score (GCA) at 3y	89 [80-97]	90 [81-100]	−0.62 (−5.40 to 4.15)
DAS-II (GCA)<85	27 (33.3)	318 (34.6)	0.92 (0.56 to 1.52)
CBCL T score at 3y	46 [41-56]	46 [40-54]	−0.61 (−4.71 to 3.48)
CBCL T score at 3y >60	8 (9.8)	84 (9.1)	1.24 (0.57 to 2.70)
Conners' Rating Scale-Revised ADHD score at 4y	47.5 [44-57])	49 [44-56]	−0.30 (−3.90 to 3.30)
Conners' Rating Scale-R >60 ADHD T score > 60	12 (14.6)	148 (16.4)	0.80 (0.42 to 1.52)
CBCL T score at 5y	42 [37-51]	44.0 [37-53]	−1.57 (−4.58 to 1.45)
CBCL T score at 5y >60	7 (8.3)	95 (10.1)	0.82 (0.36 to 1.86)

Data displayed as median and interquartile range.

WPPS III, Wechsler Preschool and Primary Scale of Intelligence-III; DAS II, Differential Ability Scales-II; Bayley, Bayley Scales of Infant Development; Conners, Conners' Rating Scales-Revised, for assessment of attention; CBCL, Child Behavior Checklist, for behavioral and social competency

Number of participants in each outcome: WPPS III: 1017; 12 month Bayley cognitive: 1019; 12 month Bayley motor: 1017; 12 month Bayley language: 1013; 24 month Bayley cognitive: 982; 24 month Bayley motor: 982; 24 month Bayley language: 971; DAS II: 1000; 36 month CBCL: 1005; Conners: 987; 60 month CBCL: 1114.

Quantile regression model adjusters included parity, maternal age, maternal BMI, treatment group, and baseline thyroid status.