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Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring
A Systematic Review and Meta-analysis

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IMPORTANCE Although research suggests an association between hypertensive disorders of pregnancy (HDP) and autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and other neurodevelopmental disorders in offspring, consensus is lacking. Given the increasing prevalence of hypertension in pregnancy, it is important to examine the association of HDP with neurodevelopmental outcome.

OBJECTIVE To synthesize the published literature on the association between HDP and risk of neurodevelopmental disorders in offspring in a systematic review and meta-analysis.

DATA SOURCES On the basis of a preprepared protocol, a systematic search of PubMed, CINAHL, Embase, PsycINFO, and Web of Science was performed from inception through June 7, 2017, supplemented by hand searching of reference lists.

STUDY SELECTION Two investigators independently reviewed titles, abstracts, and full-text articles. English-language cohort and case-control studies were included in which HDP and neurodevelopmental disorders were reported.

DATA EXTRACTION AND SYNTHESIS Data extraction and quality appraisal were performed independently by 2 reviewers. Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed throughout.

MAIN OUTCOMES AND MEASURES Random-effects meta-analyses of estimated pooled odds ratios (ORs) for HDP and ASD and for HDP and ADHD. Stand-alone estimates were reported for all other neurodevelopmental disorders.

RESULTS Of 1166 studies identified, 61 unique articles met inclusion criteria. Twenty studies reported estimates for ASD. Eleven of these (including 777 518 participants) reported adjusted estimates, with a pooled adjusted OR of 1.35 (95% CI, 1.11-1.64). Ten studies reported estimates for ADHD. Six of these (including 1 395 605 participants) reported adjusted estimates, with a pooled adjusted OR of 1.29 (95% CI, 1.22-1.36). Subgroup analyses according to type of exposure (ie, preeclampsia or other HDP) showed no statistically significant differences for ASD or ADHD. Thirty-one studies met inclusion criteria for all other neurodevelopmental disorders. Individual estimates reported for these were largely inconsistent, with few patterns of association observed.

CONCLUSIONS AND RELEVANCE Exposure to HDP may be associated with an increase in the risk of ASD and ADHD. These findings highlight the need for greater pediatric surveillance of infants exposed to HDP to allow early intervention that may improve neurodevelopmental outcome.

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Supplemental content

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The International Society for the Study of Hypertension in Pregnancy classifies hypertensive disorders of pregnancy (HDP) into the following categories: chronic hypertension (essential/secondary), white-coat hypertension, masked hypertension, transient gestational hypertension, gestational hypertension, and preeclampsia (de novo or superimposed on chronic hypertension).[1] Hypertensive disorders of pregnancy affect 5% to 15% of all pregnancies and therefore are among the most common prenatal complications.[2,3] Hypertensive disorders of pregnancy create adverse in utero conditions that can alter fetal development and may increase the risk of long-term vascular, cognitive, and psychiatric sequelae in offspring.[4-7] Neurodevelopmental disorders, including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), are a group of conditions with onset during the developmental period that can impair personal, social, academic, or occupational functioning.[8,9] Genetics are widely accepted to play a key role.[10,11] Familial coaggregation implies shared genetic risk factors,[12] but environmental factors may contribute to their etiology.[13-15] A study conducted using Swedish National Registries estimated that environmental contribution of ASD ranges from 17% to 50%,[10,16] highlighting the importance of identifying the environmental factors that contribute to the risk of neurodevelopmental disorders in offspring.

Overall, epidemiologic evidence examining the association between HDP and neurodevelopmental disorders remains largely inconsistent,[17-22] and residual or unmeasured confounding is of particular concern in the literature.[23-28] Given the increasing prevalence of HDP, partially owing to increasing levels of obesity, metabolic syndrome, and advanced maternal age,[3,4] collating the existing evidence of the association of HDP with neurodevelopmental outcome is timely. The objective of this study was to synthesize the available published literature on the association between HDP and the risk of neurodevelopmental disorders in offspring in a systematic review and meta-analysis.

Key Points

Question What are the pooled estimates from existing literature examining the association between hypertensive disorders of pregnancy and neurodevelopmental disorders in offspring?

Findings Pooled estimates from this systematic review and meta-analysis of 61 studies suggest that exposure to hypertensive disorders of pregnancy is associated with a small yet statistically significant increase in the odds of autism spectrum disorder and attention-deficit/hyperactivity disorder in offspring compared with no exposure.

Meaning Increased developmental screening of infants exposed to hypertensive disorders of pregnancy could allow for early intervention, which in turn may improve neurodevelopmental outcome.

Methods

Data Sources and Search Strategy

The systematic review required studies with the following: a population of pregnant women and their children, exposure to HDP, a comparison group with no HDP, and primary outcome of ASD or ADHD, with secondary outcomes consisting of neurodevelopmental and other behavioral or cognitive outcomes. The protocol for this systematic review and meta-analysis was registered on PROSPERO, the international prospective register of systematic reviews (CRD42017068258), and subsequently published.[29]

In accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,[30] one of us (G.M.M.) conducted a systematic literature search in PubMed, CINAHL, Embase, PsycINFO, and Web of Science electronic databases from inception through June 7, 2017. Search terms relating to HDP, ASD, ADHD, and other neurodevelopmental disorders were combined according to the principles of Boolean logic (using AND, OR, or NOT) and using Medical Subject Headings, for example, (*preeclampsia* OR *gestational hypertension*) AND (*autism spectrum disorder* OR *attention-deficit/hyperactivity disorder* OR *neurodevelopmental disorder*). The full search strategy is included in eTable 1 in the Supplement. Results were limited to English-language studies with human participants. No restrictions were placed on publication date, location of study, or age of participants. Searches of the electronic databases were supplemented by hand searching the reference lists of included studies for further potentially eligible studies, and authors were contacted when a conference proceeding only was located. We also conducted a post hoc search of PubMed adding the keywords *perinatal complication* OR *prenatal complication* OR *obstetric* complication* to the search strategy.

Study Selection

Two of us (G.M.M. and A.S.K.) independently reviewed the titles and abstracts of all studies, obtaining full texts when necessary. When consensus on eligibility could not be achieved, a third reviewer (G.W.O.K.) was involved in the discussion. Eligibility criteria for inclusion in the systematic review included the following: cohort, case-control, or cross-sectional studies in which a diagnosis of HDP was reported and neurodevelopmental disorders were the outcome of interest; the association between HDP and neurodevelopmental disorders were part of the main objective of the study (including studies that investigated other perinatal risk factors in addition to HDP); data were from an original study and HDP was confirmed through medical records and/or physician-diagnosed self-reporting; peer-reviewed literature only; and neurodevelopmental and other behavioral or cognitive outcomes only (motor disorders were included in the search strategy to capture studies that include these outcomes).

Data Extraction

Two reviewers (G.M.M. and G.W.O.K.) independently extracted data from eligible studies using a standardized data collection form. Information extracted included author, year of publication, study design, definition of exposure and outcome used, sample size, confounders adjusted for (if any), and

crude and adjusted estimates. Any discrepancies were resolved by consensus with a third reviewer (A.S.K.). Authors of 2 studies were contacted for further information, with a reply received from one.

Bias and Quality Assessment

Publication bias was evaluated by visually assessing a funnel plot and Egger test for asymmetry of the funnel plot, by which 10 or more studies were included in the meta-analysis.[31] Quality assessment of included studies was conducted by 2 reviewers (G.M.M. and M.M.) independently using an appropriate quality assessment tool and agreed on subsequently. Any discrepancies were resolved by a third reviewer (A.S.K.). We used a bias classification tool[32] consisting of a checklist to assess 6 types of bias most often associated with observational studies (selection, exposure, outcome, confounding, analytic, and attrition). Study bias was classified as minimal, low, moderate, high, or not reported for each type of bias. An overall likelihood of bias based on the total of the 6 types of bias was then measured and reported. For example, selection bias was minimized if the sample was taken from a "consecutive unselected population," whereas selection bias was categorized as high if "sample selection was ambiguous and the sample was not likely representative."[32(p146)]

Statistical Analysis

Data were analyzed using Review Manager software (version 5.3; http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download), and the Egger test was conducted in Stata/MP software (version 14.2; StataCorp). Random-effects meta-analyses were performed to calculate overall pooled estimates of the association between combined HDP, preeclampsia, and HDP excluding preeclampsia and the outcomes of ASD and ADHD using the generic inverse variance method. The generic inverse variance method allowed studies that do not report raw data to be included in the meta-analyses.[33] Partially adjusted estimates, as a result of matching, were included as crude results, and studies that adjusted for confounders in the analysis phase were included as adjusted results. Forest plots were used to display crude and adjusted estimates, with adjustment based on the definition outlined in each identified study. Studies that provided a crude and adjusted estimate and studies that adjusted for similar variables were analyzed separately (eFigures 1-4 in the Supplement).

The following subgroup and sensitivity analyses were decided a priori: type of HDP (preeclampsia and other HDP), study design, location, income level of country, study quality, and measurement of exposure and outcome data. A post hoc subgroup analysis was performed according to length of follow-up.

Results

Search Results

The original search produced 796 unique results after removal of duplicates (**Figure 1**). Of these, 33 full-text articles were reviewed after screening of titles and abstracts. Eleven articles were excluded because they did not meet the inclusion criteria. Reasons for exclusion are outlined in Figure 1. This process resulted in 22 eligible articles. After reviewing reference lists, 38 additional articles were identified. One additional study of ASD was subsequently published and included in the review. A total of 61 unique articles were included in the systematic review, including 20 for ASD[20,21,26-28,34-48] (8 identified from the original search, 11 from reference lists, and 1 subsequently published), 10 for ADHD[17-19,23-25,49-52] (4 identified from the original search and 6 from reference lists), and 31 for other neurodevelopmental outcomes[53-83] (10 identified from the original search and 21 from reference lists).

Characteristics of Studies Included in the Systematic Review

A summary of included studies that report ASD and ADHD is available in eTables 2 and 3 in the Supplement. A summary of studies that report other neurodevelopmental outcomes (including cognitive functioning/developmental delay, behavioral outcomes, and intellectual disability), along with main findings, is available in eTable 4 in the Supplement.

Results of the Meta-analyses

ASD: Primary Analysis

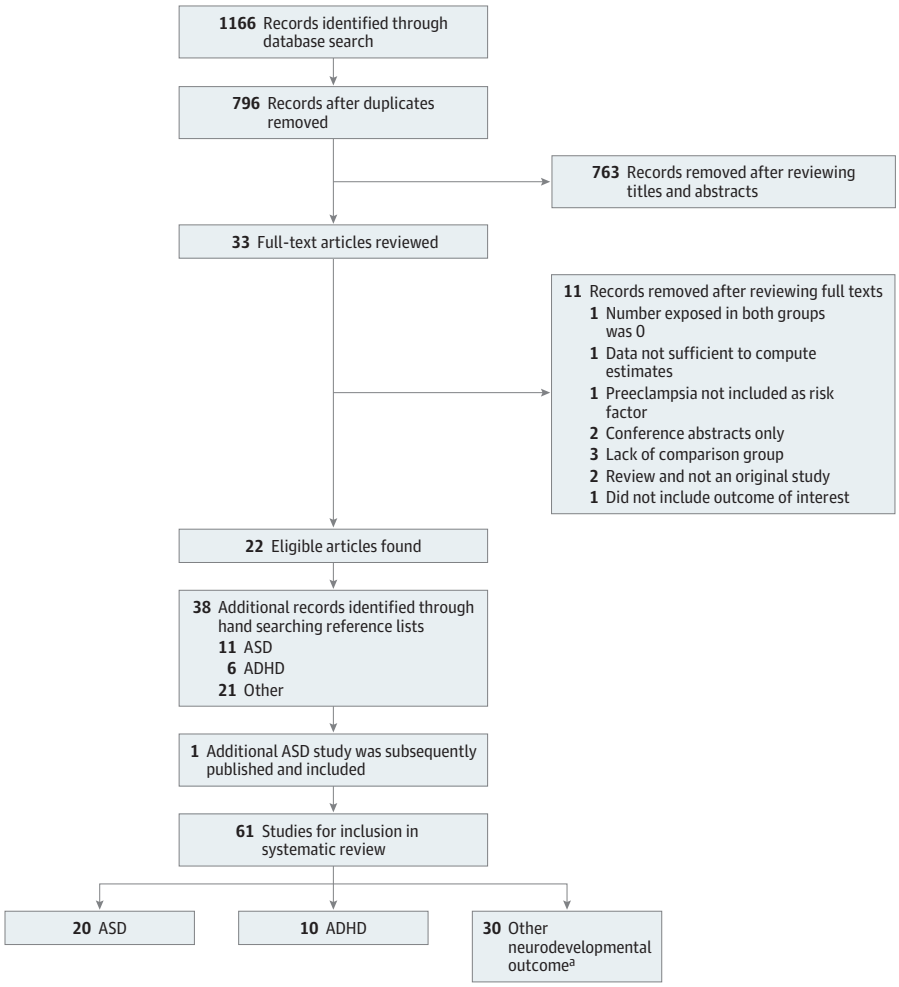
A total of 20 studies[20,21,26-28,34-48] were identified in which a diagnosis of HDP was reported and ASD was the outcome of interest. The prevalence of HDP among cohort studies of ASD ranged from 1.3% to 9.1% (mean, 6.2%; median, 6.9%; interquartile range [IQR], 3.6%-8.9%). Twenty-three estimates from 19 unique studies[20,21,26-28,34-36,38-48] included crude estimates, and 13 estimates from 11 unique studies[20,21,34,35,38,41-46] included adjusted estimates and were included in the meta-analysis (including 777 518 participants). **Figure 2**A displays crude and partially adjusted estimates (as a result of matching), producing a pooled odds ratio (OR) of 1.41 (95% CI, 1.22-1.64). A subgroup analysis examining the association of preeclampsia with ASD and other HDP with ASD separately resulted in ORs of 1.37 (95% CI, 1.07-1.75) and 1.43 (95% CI, 1.17-1.73), respectively (test for subgroup differences, $P = .80$).

Adjusted estimates reduced the overall HDP-ASD estimate to 1.35 (95% CI, 1.11-1.64) (Figure 2B). Subgroup analysis examining the association of preeclampsia with ASD resulted in an OR of 1.50 (95% CI, 1.26-1.78), whereas the association of other HDP with ASD produced a nonsignificant OR of 1.25 (95% CI, 0.90-1.73). However, the test for subgroup differences does not indicate a statistically significant difference ($P = .33$).

ADHD: Primary Analysis

Ten studies[17-19,23-25,49-52] were identified in which a diagnosis of HDP was reported and ADHD was the outcome of interest. The prevalence of HDP among cohort studies of ADHD ranged from 0.1% to 20.8%, (mean, 7.8%; median, 5.5%; IQR, 2.4%-15.1%). Twelve estimates from 9 unique studies[17-19,23-25,49-51] included crude results examining the association of HDP with ADHD, and 8 estimates from 6 unique studies[17-19,49,50,52] included adjusted estimates (including 1 395 605 participants) (**Figure 3**A). Crude pooled estimates produced an OR of 1.32 (95% CI, 1.20-1.45). In subgroup analysis examining the association of preeclampsia with ADHD only, the OR was 1.31 (95% CI, 1.19-1.44), and the OR for the association between other HDP and ADHD was 1.62 (95% CI, 1.07-2.47) ($P = .33$).

Figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review



ADHD indicates attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

[a] An additional 6 studies are also included for ASD and 1 for ADHD.

Adjusted estimates remained relatively unchanged (Figure 3B) (overall pooled OR, 1.29; 95% CI, 1.22-1.36). Results of the subgroup analysis examining the association of preeclampsia with ADHD (OR, 1.28; 95% CI, 1.22-1.36), and of other HDP with ADHD (OR, 1.70; 95% CI, 1.06-2.72) were not significantly different (P = .24).

Other Neurodevelopmental Outcomes

Owing to varying outcome measures, assessment methods, and summary scales used, pooling results of these studies was not appropriate. Therefore, we reported stand-alone estimates for 31 unique studies (plus 7 studies that were also included as ASD or ADHD outcomes) examining the association between HDP and neurodevelopmental, cognitive, or behavioral outcomes. A summary of the main findings of these studies is available in eTable 4 in the Supplement. Overall, results were largely inconsistent; however, a few patterns of association emerged. For example, 6 of 10 studies[53-58] suggest a positive association between preeclampsia and cognitive impairment within specific populations, whereas 4 of 5 studies[37,42,59,60] suggest a potential association between HDP and intellectual disability.

Bias and Heterogeneity

Visual inspection of the funnel plot including adjusted studies only did not indicate publication bias (eFigure 5 in the Supplement) (Egger test, P = .43; 95% CI, −1.8 to 4.0). Moderate heterogeneity for ASD (I^2 = 63%) and low heterogeneity for ADHD (I^2 = 0) were found on the basis of adjusted estimates. Heterogeneity among ASD studies was possibly attributable to differences in confounder adjustments, because heterogeneity reduced to 0 when studies that adjusted for maternal age, maternal smoking, and parity and/or birth order were analyzed separately (eFigure 3 in the Supplement). Most studies were classified as having low or moderate risk of bias (eTables 5-7 in the Supplement).

ASD: Subgroup/Sensitivity Analysis

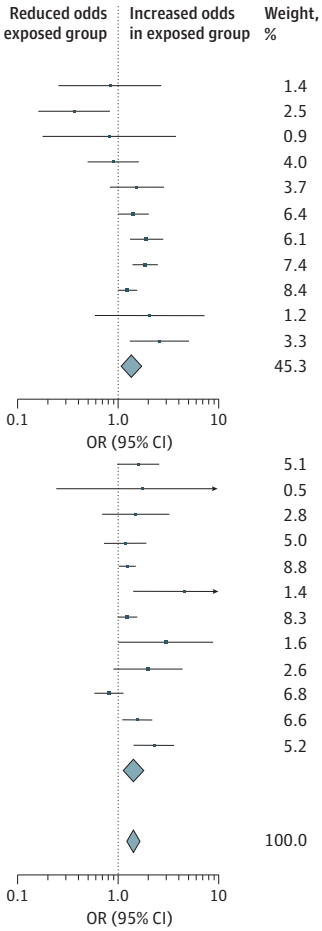
The **Table** shows pooled estimates for all studies that reported crude estimates, adjusted estimates, and adjusted estimates according to the category of HDP for ASD and ADHD. Results of the following subgroup analysis are also outlined in the Table.

Six case-control studies[20,35,38,41,44,46] (7 estimates) resulted in a pooled OR of 1.47 (95% CI, 1.18-1.84). Five cohort

Figure 2. Forest Plot for Studies of the Association of Hypertensive Disorders of Pregnancy (HDP) With Autism Spectrum Disorder (ASD)

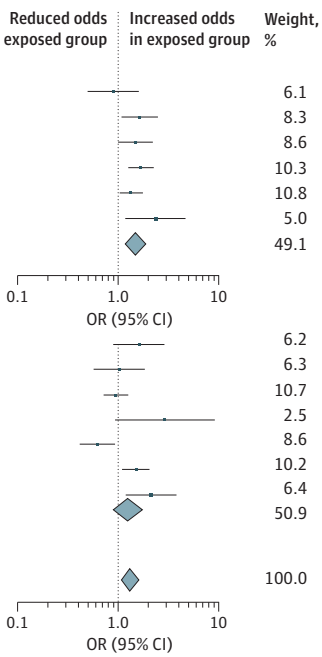
A Crude and partially adjusted estimates

Source (HDP)	log OR (SE)	OR (95% CI)	Weight, %
Preeclampsia only and ASD			
Deykin and MacMahon,[35] 1980 (toxemia)	-0.19 (0.60)	0.83 (0.25-2.70)	1.4
Mason-Brothers et al,[40] 1990 (toxemia)	-1.01 (0.42)	0.36 (0.16-0.83)	2.5
Matsuishi et al,[28] 1999 (toxemia)	-0.19 (0.78)	0.82 (0.18-3.79)	0.9
Glasson et al,[27] 2004 (preeclampsia)	-0.11 (0.30)	0.90 (0.50-1.62)	4.0
Larsson et al,[39] 2005 (preeclampsia)	0.43 (0.32)	1.54 (0.83-2.86)	3.7
Buchmayer et al,[41] 2009 (preeclampsia)	0.34 (0.19)	1.41 (0.98-2.03)	6.4
Burstyn et al,[34] 2010 (preeclampsia)	0.65 (0.20)	1.91 (1.30-2.81)	6.1
Mann et al,[21] 2010 (preeclampsia)	0.62 (0.15)	1.85 (1.38-2.48)	7.4
Lyall et al,[43] 2012 (toxemia)	0.21 (0.12)	1.24 (0.99-1.55)	8.4
Mrozek-Budzyn et al,[47] 2013 (preeclampsia)	0.72 (0.65)	2.05 (0.58-7.28)	1.2
Walker et al,[44] 2015 (preeclampsia)	0.95 (0.35)	2.58 (1.31-5.11)	3.3
Subtotal		1.37 (1.07-1.75)	45.3
Heterogeneity: $\tau^2=0.08$, $\chi^2_{10}=24.42$ ($P=.007$); $I^2=59\%$ Test for overall effect: $z=2.47$ ($P=.01$)			
Other HDP and ASD			
Hultman et al,[38] 2002 (hypertensive diseases)	0.47 (0.24)	1.60 (1.00-2.56)	5.1
Bilder et al,[26] 2009 (chronic hypertension)	0.56 (1.01)	1.75 (0.24-12.74)	0.5
Bilder et al,[26] 2009 (pregnancy-induced hypertension)	0.40 (0.39)	1.50 (0.70-3.23)	2.8
Buchmayer et al,[41] 2009 (gestational hypertension)	0.17 (0.25)	1.18 (0.73-1.91)	5.0
Dodds et al,[36] 2011 (pregnancy-induced hypertension)	0.22 (0.10)	1.24 (1.02-1.51)	8.8
Nath et al,[48] 2012 (pregnancy-induced hypertension)	1.52 (0.60)	4.57 (1.41-14.85)	1.4
Lyall et al,[43] 2012 (pregnancy-related HBP)	0.21 (0.12)	1.24 (0.99-1.55)	8.3
Krakowiak et al,[20] 2012 (hypertension)	1.09 (0.56)	2.97 (1.00-8.82)	1.6
Mrozek-Budzyn et al,[47] 2013 (chronic hypertension)	0.69 (0.41)	1.99 (0.90-4.43)	2.6
Langridge et al,[42] 2013 (pregnancy hypertension)	-0.21 (0.17)	0.81 (0.58-1.13)	6.8
Polo-Kantola et al,[46] 2014 (maternal hypertension)	0.44 (0.18)	1.56 (1.10-2.21)	6.6
Curran et al,[45] 2017 (HDP)	0.82 (0.24)	2.27 (1.43-3.60)	5.2
Subtotal		1.43 (1.17-1.73)	
Heterogeneity: $\tau^2=0.05$, $\chi^2_{11}=23.51$ ($P=.01$); $I^2=53\%$ Test for overall effect: $z=3.57$ ($P<.001$)			
Total		1.41 (1.22-1.64)	100.0
Heterogeneity: $\tau^2=0.06$, $\chi^2_{22}=48.74$ ($P<.001$); $I^2=55\%$ Test for overall effect: $z=4.52$ ($P<.001$) Test for subgroup differences: $\chi^2_1=0.07$ ($P=.80$); $I^2=0\%$			



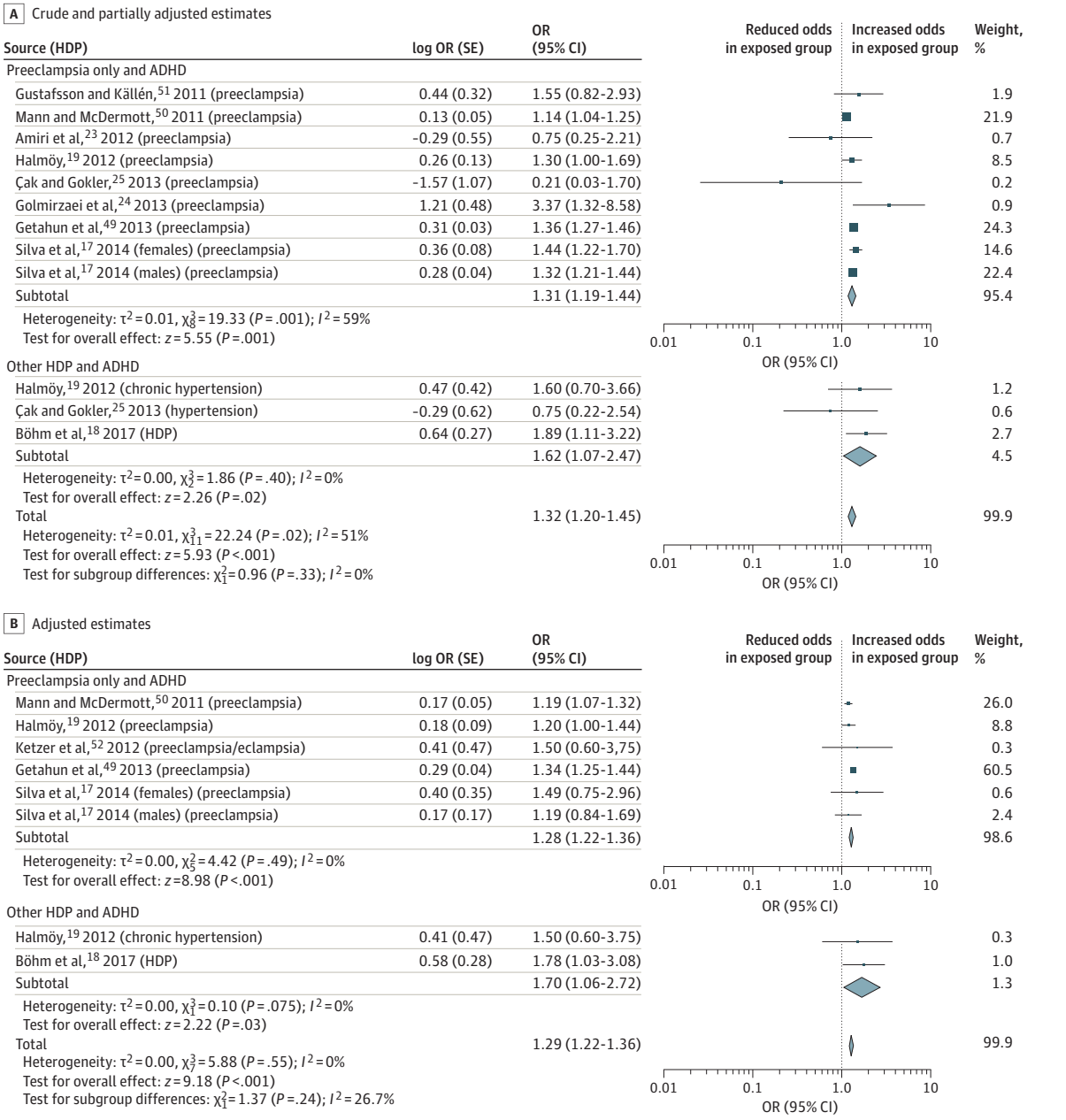
B Adjusted estimates

Source (HDP)	log OR (SE)	OR (95% CI)	Weight, %
Preeclampsia only and ASD			
Deykin and MacMahon,[35] 1980 (toxemia)	-0.11 (0.30)	0.90 (0.50-1.62)	6.1
Buchmayer et al,[41] 2009 (preeclampsia)	0.49 (0.21)	1.64 (1.08-2.49)	8.3
Burstyn et al,[34] 2010 (preeclampsia)	0.40 (0.20)	1.49 (1.00-2.22)	8.6
Mann et al,[21] 2010 (preeclampsia)	0.52 (0.15)	1.69 (1.26-2.27)	10.3
Lyall et al,[43] 2012 (toxemia)	0.31 (0.14)	1.36 (1.04-1.78)	10.8
Walker et al,[44] 2015 (preeclampsia)	0.86 (0.35)	2.36 (1.18-4.72)	5.0
Subtotal		1.50 (1.26-1.78)	49.1
Heterogeneity: $\tau^2=0.01$, $\chi^2_5=5.87$ ($P=.32$); $I^2=15\%$ Test for overall effect: $z=4.64$ ($P<.001$)			
Other HDP and ASD			
Hultman et al,[38] 2002 (hypertensive diseases)	0.47 (0.29)	1.60 (0.90-2.84)	6.2
Buchmayer et al,[41] 2009 (gestational hypertension)	0.04 (0.29)	1.04 (0.59-1.83)	6.3
Lyall et al,[43] 2012 (pregnancy-related HBP)	-0.04 (0.14)	0.96 (0.73-1.26)	10.7
Krakowiak et al,[20] 2012 (hypertension)	1.04 (0.56)	2.84 (0.94-8.58)	2.5
Langridge et al,[42] 2013 (pregnancy hypertension)	-0.45 (0.20)	0.64 (0.43-0.95)	8.6
Polo-Kantola et al,[46] 2014 (maternal hypertension)	0.40 (0.15)	1.49 (1.10-2.02)	10.2
Curran et al,[45] 2017 (HDP)	0.74 (0.29)	2.10 (1.20-3.67)	6.4
Subtotal		1.25 (0.90-1.73)	50.9
Heterogeneity: $\tau^2=0.13$, $\chi^2_6=21.22$ ($P=.002$); $I^2=72\%$ Test for overall effect: $z=1.34$ ($P=.18$)			
Total		1.35 (1.11-1.64)	100.0
Heterogeneity: $\tau^2=0.07$, $\chi^2_{12}=32.63$ ($P=.001$); $I^2=63\%$ Test for overall effect: $z=3.05$ ($P=.002$) Test for subgroup differences: $\chi^2_1=0.95$ ($P=.33$); $I^2=0\%$			



Odds ratios (ORs) are calculated using random-effects analysis. The generic inverse variance method was used to include studies that do not report raw data. Diamonds indicate effect size; size of markers, 95% CI. HBP indicates high blood pressure.

Figure 3. Forest Plot for Studies of the Association of Hypertensive Disorders of Pregnancy (HDP) With Attention-Deficit/Hyperactivity Disorder (ADHD)



Odds ratios (ORs) are calculated using random-effects analysis. The generic inverse variance method was used to include studies that do not report raw data. Diamonds indicate effect size; size of markers, 95% CI.

studies[21,34,42,43,45] (6 estimates) provided an overall nonsignificant OR of 1.26 (95% CI, 0.93-1.70) (*P* = .41). Six studies[20,21,34,35,43,44] (7 adjusted estimates) were from North America (OR, 1.39; 95% CI, 1.09-1.77), 4 studies[38,41,45,46] were from Europe (5 estimates) (OR, 1.53; 95% CI, 1.26-1.87), and 1 study[42] was from Australia (OR, 0.64; 95% CI, 0.43-0.95) (*P* < .001). All ASD studies were conducted in high-income countries. Fourteen studies[20,21,26-28,34,36,38,39,41,42,44-46] (16 estimates) were assessed as having minimal to low risk of bias, resulting in a significant OR of 1.39 (95% CI, 1.17-1.65). Five studies[35,40,43,47,48] (7 estimates) were assessed as having moderate to high risk of bias, resulting in a nonsignificant OR of 1.18 (95% CI, 0.81-1.74) (*P* = .46). Four studies[20,43-45] that relied on self-reported measurements of HDP produced 5 adjusted estimates, resulting in a pooled OR of 1.54 (95% CI, 1.07-2.22). The pooled OR observed among the 7 studies[21,34,35,38,41,42,46] (with 8 estimates) that relied on medical records for confirmation of HDP was 1.27 (95% CI, 0.99-

Table. Subgroup Meta-analyses for HDP-ASD and HDP-ADHD Associations

Variable	No. of Studies (No. of Estimates)	No. of Participants	No. of Outcomes	OR (95% CI)	I^2, %	Test for Subgroup Differences *P* Value
Autism Spectrum Disorder						
Overall unadjusted	19 (23)	941 285	9331	1.41 (1.22-1.64)	55	.80[a]
Overall adjusted[b]	11 (13)	777 518	6866	1.35 (1.11-1.64)	63	.33[a]
Category of HDP[b]						
Preeclampsia	6 (6)	378 991	4254	1.50 (1.26-1.78)	15	.33
Other	7 (7)	472 268	4621	1.25 (0.90-1.73)	72	
Study design[b]						
Case-control	6 (7)	16 975	3812	1.47 (1.18-1.84)	21	.41
Cohort	5 (6)	760 543	3054	1.26 (0.93-1.70)	78	
Location[b]						
North America	6 (7)	372 527	3555	1.39 (1.09-1.77)	59	<.001
Europe	4 (5)	28 010	2859	1.53 (1.26-1.87)	0	
Australia	1 (1)	376 981	452	0.64 (0.43-0.95)	NA	
Study quality[c]						
Minimal to low risk of bias	14 (16)	873 772	8041	1.39 (1.17-1.65)	47	.46
Moderate to high risk of bias	5 (7)	67 513	1263	1.18 (0.81-1.74)	69	
Exposure measurement[b]						
Self-reported	4 (5)	81 242	2026	1.54 (1.07-2.22)	68	.39
Medical records	7 (8)	696 276	4840	1.27 (0.99-1.64)	65	
Outcome measurement[b]						
Maternal-reported	2 (3)	79 543	992	1.32 (0.91-1.91)	72	.86
Medical records	9 (10)	697 975	5874	1.37 (1.07-1.75)	63	
Length of follow-up, y[b]						
≤7	5 (5)	102 838	1823	1.71 (1.23-2.38)	41	.09
≤21	6 (8)	674 680	5043	1.22 (0.98-1.52)	64	
Attention-Deficit/Hyperactivity Disorder						
Overall unadjusted	9 (12)	1 428 209	37 635	1.32 (1.20-1.45)	48	.33[a]
Overall adjusted[b]	6 (8)	1 395 605	37 128	1.29 (1.22-1.36)	0	.24[a]
Category of HDP[b]						
Preeclampsia	5 (6)	1 382 105	36 962	1.28 (1.22-1.36)	0	.24
Other	2 (2)	1 185 896	2489	1.70 (1.06-2.72)	0	
Study design[b]						
Case-control	3 (4)	124 988	26 728	1.34 (1.25-1.43)	0	.08
Cohort	3 (4)	1 270 617	10 400	1.21 (1.10-1.32)	0	
Location[b]						
North America	2 (2)	166 399	21 524	1.27 (1.13-1.43)	70	.99
Europe	2 (3)	1 185 896	2489	1.26 (1.06-1.49)	0	
Other	2 (3)	43 310	13 115	1.27 (0.95-1.70)	0	
Study quality[c]						
Minimal to low risk of bias	7 (9)	1 427 617	37 365	1.29 (1.22-1.36)	0	.57
Moderate to high risk of bias	3 (4)	840	394	0.95 (0.32-2.76)	67	
Exposure measurement[b]						
Self-reported	2 (2)	13 748	290	1.70 (1.06-2.72)	0	.24
Medical records	4 (6)	1 381 857	36 838	1.28 (1.22-1.36)	0	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; HDP, hypertensive disorders of pregnancy; NA, not applicable; OR, odds ratio.

[a] Calculated using test for subgroup differences between preeclampsia and other HDP.

[b] Includes all studies that adjusted for confounders in the analysis phase.

[c] Includes all studies.

1.64) (*P* = .39). Two studies[43,45] (with 3 adjusted estimates) used maternal reporting of ASD and resulted in an OR of 1.32 (95% CI, 0.91-1.91). However, individual point estimates for these studies ranged from 0.96 to 2.10. Pooled results were similar among the 9 studies[20,21,34,35,38,41,42,44,46] (10 estimates) that used medical records to determine ASD status in the off-

spring, with an OR of 1.37 (95% CI, 1.07-1.75) (*P* = .86). Five studies[20,21,35,44,45] had a potential 2 to 7 years of follow-up with a pooled OR of 1.71 (95% CI, 1.23-2.38), and 6 studies[34,38,41-43,46] (8 estimates) had a potential 2 to 21 years follow-up with a pooled OR of 1.22 (95% CI, 0.98-1.52) (*P* = .09).

ADHD: Subgroup/Sensitivity Analysis

Three case-control studies[17,49,52] (with 4 adjusted estimates) were identified with a pooled OR of 1.34 (95% CI, 1.25-1.43), whereas 3 cohort studies[18,19,50] (4 adjusted estimates) resulted in a pooled OR of 1.21 (95% CI, 1.10-1.32) (*P* = .08). Two studies[49,50] (2 estimates) were from North America (OR, 1.27; 95% CI, 1.13-1.43), 2 studies[18,19] (3 estimates) were from Europe (OR, 1.26; 95% CI, 1.06-1.49), and 2 studies[17,52] (3 estimates) were from other locations (OR, 1.27; 95% CI, 0.95-1.70) (*P* = .99). Five studies[17-19,49,50] (7 adjusted estimates) were conducted in high-income countries compared with 1 study conducted in an upper- to middle-income country.[52] Results of a sensitivity analysis including results from high-income countries only did not change the pooled results (OR, 1.29; 95% CI, 1.22-1.36). Seven studies[17-19,49-52] (9 estimates) were assessed as having minimal or low risk of bias. The pooled estimate for these studies was significant (OR, 1.29; 95% CI, 1.22-1.36). A pooled estimate for the 3 studies[23-25] (4 estimates) assessed as having moderate to high risk of bias was nonsignificant (OR, 0.95; 95% CI, 0.32-2.76) (*P* = .57). Two studies[18,52] (2 estimates) used self-reporting of HDP status, resulting in a pooled OR of 1.70 (95% CI, 1.06-2.72), whereas pooled results of 4 studies[17,19,49,50] (6 estimates) using medical records to obtain exposure status resulted in a pooled estimate of 1.28 (95% CI, 1.22-1.36) (*P* = .24).

Five studies[17,19,49,50,52] (7 adjusted estimates) used medical records to measure ADHD status in offspring, and 1 study[18] used maternal reporting. However, results of a sensitivity analysis (including medical records only) did not change pooled results (OR, 1.28; 95% CI, 1.22-1.36).

Discussion

The aim of this systematic review and meta-analysis was to synthesize the published literature on the association between HDP and the risk of neurodevelopmental disorders in offspring. Three principal findings resulted. First, our adjusted pooled results indicate that exposure to HDP was associated with a 35% increased odds of ASD compared with nonexposure. Results of a subgroup analysis examining an association between preeclampsia and ASD in isolation provided an OR of 1.50, whereas the association between other HDP and ASDwas nonsignificant, with an OR of 1.25. Although subgroup analysis may suggest that the type of HDP may play a role in determining the association with neurodevelopmental outcome, subgroup differences were not statistically significant.

Second, adjusted pooled results suggest that offspring exposed to HDP in utero were 30% more likely to have ADHD compared with unexposed offspring. Examination of an association between preeclampsia and ADHD in isolation did not change the estimate, whereas the odds of ADHD was increased by 70% in association with other HDP. However, this subgroup difference was not statistically significant.

These reported effect sizes are similar to those of other obstetric risk factors for ASD. For example, cesarean delivery is associated with a 23% to 26% increased odds of ASD, and advancing maternal age (>35 years) is associated with a 30% increased odds of ASD[84-86];breech presentation and Apgar score of less than 7 may increase the risk of ADHD by 14% and 30%, respectively.[87]

Third, literature examining the association between HDP and other neurodevelopmental, cognitive, or behavioral outcomes remains inconsistent (eTable 4 in the Supplement). Some patterns of association were observed between preeclampsia and cognitive impairment when confined to specific populations, such as infants with growth restriction, preterm birth, and low birth weight.[53-58] Similarly, the epidemiologic evidence examined suggests a potential association between HDP and intellectual disability.[37,42,59,60] However, methodologic differences among studies, particularly differences in population and outcome assessment methods, may partially explain the overall lack of consistent findings.

Although this study is suggestive of an association between HDP and neurodevelopmental disorders in offspring, it is difficult to rule out the possibility that antihypertensive medication used during pregnancy may be associated with adverse effects in offspring.[88] However, several potential mechanisms have been proposed in attempts to explain the association between HDP and neurodevelopmental outcome. For example, placental dysfunction, associated with HDP, may result in reduced placental perfusion and oxidative stress.[89] In turn, suboptimal nutrient and oxygen availability for the fetus, attributable to placental insufficiency, may affect the developing brain, increasing the risk of a poor neurodevelopmental outcome.[6,7,21,44]

Maternal inflammation may also play a key role. Results of a population-based study in Finland[90,91] with data from more than 1 million pregnancies showed that increased levels of the inflammatory biomarker C-reactive protein associated with preeclampsia was significantly associated with a 43% increased risk of autism in offspring when maternal C-reactive protein levels in the highest and lowest quintiles were compared. Fewer hypotheses have been suggested that address the biological mechanisms of ADHD specifically; however, similar mechanisms may be involved.[18,92,93]

The literature examining HDP and ASD is suggestive of a small increase in the risk of ASD in offspring exposed to HDP[21,36,41,43-46,48]; however, some studies[20,26,34,38,39,41,47] fail to meet statistical significance. In contrast, other studies[27,28,35,37,43] suggest a protective association between HDP and ASD, with only 2 of these[40,42] reaching statistical significance. Similarly, the literature alludes to a positive association between HDP and ADHD, with some studies[18,24,49,50] indicating significant associations and others[17,19,51,52] producing nonsignificant positive estimates. In comparison, 2 HDP-ADHD studies[23,25] suggest reduced odds of ADHD in HDP-exposed offspring. However, neither study reached statistical significance or controlled for potential confounders.

Strengths and Limitations

This systematic review had several strengths. It was based on a preprepared protocol, and MOOSE guidelines were followed throughout.[30] It included a comprehensive search of 5 relevant databases, supplemented by hand searching the reference lists of included studies for additional potentially eligible studies.

However, several limitations, including those of the current literature, should be noted. Results were limited to English-language studies, potentially leading to relevant, non-English language studies being overlooked. Although the full search strategy was published along with the protocol, it may have been lacking in keywords, such as *perinatal complication* OR *prenatal complication* OR *obstetric* complication*, because hand searching the reference lists identified a larger number of relevant studies compared with searching the electronic databases. Therefore, we conducted a post hoc search of PubMed, adding these words to the search strategy. Although this search increased the number of hits retrieved 5-fold, identifying more eligible studies than the original search strategy, no new studies were identified in the process.

Sample size calculations are lacking in the literature examining the associations of HDP with ASD and ADHD, and therefore the studies may lack statistical power. For example, 5 of 20 studies of ASD[26,28,35,47,48] and 3 of 10 studies of ADHD[19,23,25] had fewer than 10 exposed cases. Validated questionnaires were not always used to obtain exposure and outcome status, potentially introducing misclassification bias,[18,20,43-45,52] whereas varying HDP and ASD or ADHD diagnostic criteria may increase clinical heterogeneity between studies.[94]

Finally, residual or unmeasured confounding is of particular concern in observational studies, and therefore important confounding factors may not always be considered or available.[95] Most of the studies included in our meta-analyses identified potential confounders a priori on the basis of previous literature, and only 2 studies[20,44] appear to have aided this method with directed acyclic graphs to evaluate and assess suspected confounding.[96] Other studies in our review, however, failed to control for confounding or did not provide justification for included confounders. Only 1 study of ASD[45] and 1 study of ADHD[49] controlled for a combination of key variables, such as maternal age, socioeconomic status, ethnic origin, and family history of mental illness. Separately, only 3 studies of ASD[34,38,42] and 1 study of ADHD[17] adjusted for gestational age and birthweight, all of which attenuated toward the null after adjustment. Therefore, although an apparent association exists between HDP and ASD and between HDP and ADHD, future research examining the association between HDP and neurodevelopmental outcomes needs to identify a comprehensive set of confounders to assess whether this association is causal or attributable to residual or unmeasured confounding. Furthermore, this research focused specifically on ASD, ADHD, and other neurodevelopmental, behavioral, or cognitive outcomes. Future research could explore the association between HDP and mental disorders not included in this review to gain a greater understanding of the specificity of the effects of HDP.

Conclusions

Our systematic review indicates that exposure to HDP may be associated with an increase in the risk of ASD and ADHD. If the observed associations are causal, they highlight the potential need for increased developmental screening of HDP-exposed infants to allow early intervention, which may improve neurodevelopmental outcome. However, before more definitive conclusions can be reached, more robust research is needed that addresses key limitations in the literature.

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