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Infant psychomotor development after intrauterine exposure to hypertensive disorders of pregnancy: a P4 study

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Original Article

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Abstract

This study aimed to assess the impact of hypertensive disorders of pregnancy on infant neurodevelopment by comparing 6-month and 2-year psychomotor development outcomes of infants exposed to gestational hypertension (GH) or preeclampsia (PE) versus normotensive pregnancy (NTP). Participating infants were children of women enrolled in the Postpartum Physiology, Psychology and Paediatric (P4) cohort study who had NTPs, GH or PE. 6-month and 2-year Ages and Stages Questionnaires (ASQ-3) scores were categorised as passes or fails according to domain-specific values. For the 2-year Bayley Scales of Infant and Toddler Development (BSID-III) assessment, scores > 2 standard deviations below the mean in a domain were defined as developmental delay. Infants ($n = 369$, male = 190) exposed to PE ($n = 75$) versus GH ($n = 20$) and NTP ($n = 274$) were more likely to be born small for gestational age and premature. After adjustment, at 2 years, prematurity status was significantly associated with failing any domain of the ASQ-3 ($p = 0.015$), and maternal tertiary education with increased cognitive scores on the BSID-III ($p = 0.013$). However, PE and GH exposure were not associated with clinically significant risks of delayed infant neurodevelopment in this study. Larger, multicentre studies are required to further clarify early childhood neurodevelopmental outcomes following hypertensive pregnancies.

Introduction

Approximately 5%–8% of pregnancies worldwide are complicated by hypertensive disorders of pregnancy (HDP) including gestational hypertension (GH), characterised by new onset hypertension at or after 20 weeks' gestation, and preeclampsia (PE), characterised by hypertension with associated maternal organ dysfunction or fetal compromise.[1,2] Intrauterine exposure to HDP has been associated with long-term health implications for children including increased risks of mild cognitive impairment,[3] autism spectrum disorder and other neurodevelopmental disorders.[4] However, there is uncertainty regarding the impact of HDP on psychomotor development in infancy (birth to 2 years), a critical period of rapid development.

Studies have demonstrated increased risks, no difference, or even decreased risks of impaired motor or cognitive development after HDP exposure compared to infants of normotensive pregnancies (NTP).[5] These discrepant findings may be attributed to the non-standard adjustment of perinatal confounders, the differing use of developmental screening and assessment tools, and differing study cohorts, with some cohorts only including infants born small for gestational age (SGA) or preterm. SGA and preterm birth are independent risk factors for poor infant neurodevelopment that may confound the impacts of HDP exposure.[6]

Thus, this cohort study aimed to determine the impact of HDP exposure on infant neurodevelopment by comparing neurodevelopmental screening and assessment outcomes at 6 months and 2 years between infants exposed to PE or GH versus NTP. Furthermore, we aimed to assess whether any impacts of HDP exposure were independent of SGA or prematurity status, and sociodemographic characteristics including parental education levels. Understanding the

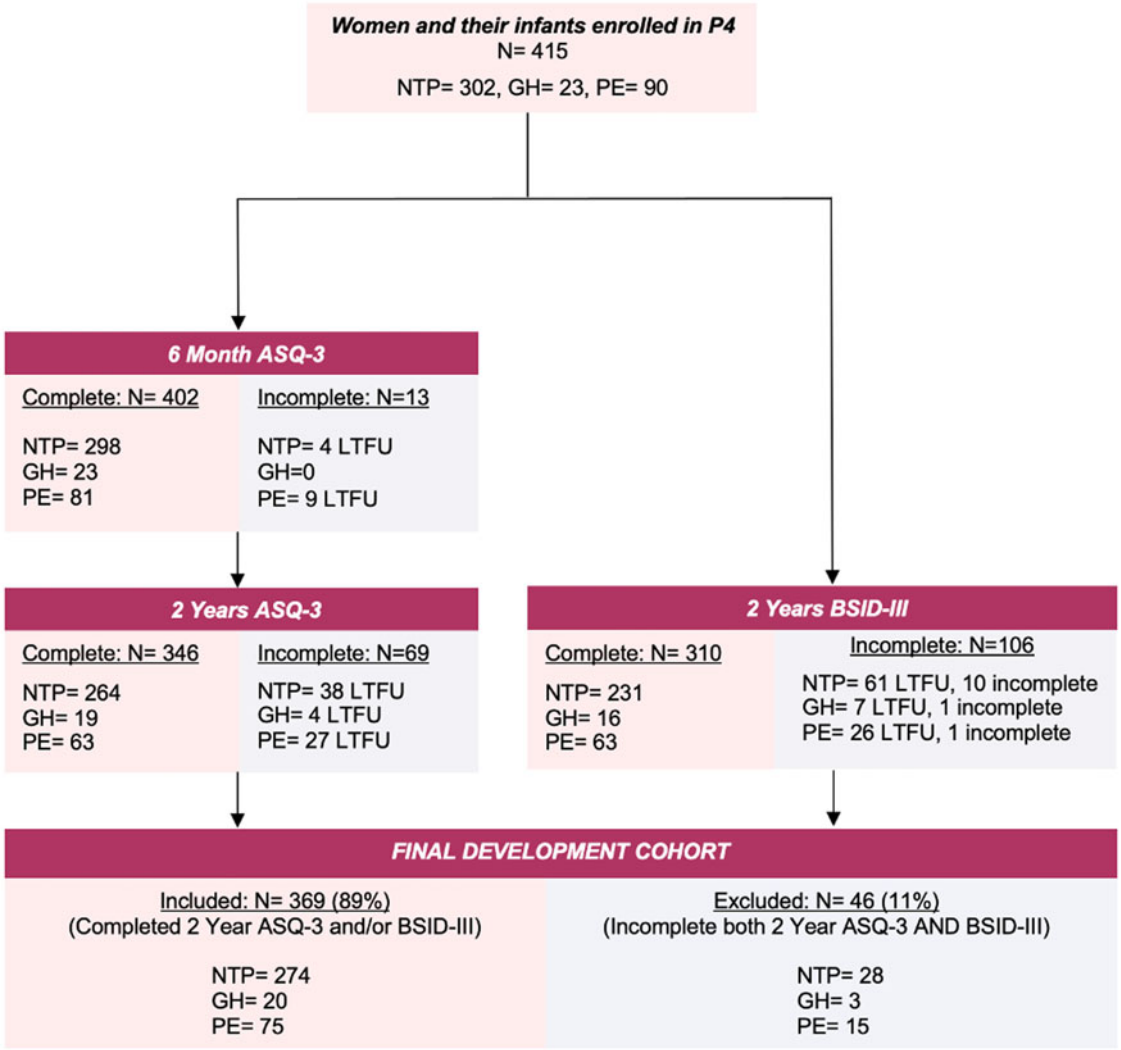

Figure 1. Flow diagram of study cohort. Abbreviations: ASQ-3, Ages and Stages Questionnaires, Third Edition[14]; BSID-III, Bayley Scales of Infant and Toddler Development, 3rd Edition[15]; GH, gestational hypertension; LTFU, loss to follow up; N, number; NTP, normotensive pregnancy; PE, preeclampsia.

early impacts of HDP exposure may highlight opportunities for early screening, intervention and optimisation of child neurodevelopment in these potentially at-risk populations.

Method

Study design and setting

This is a sub-study of the prospective, single-centre cohort study, the P4 (Postpartum Physiology, Psychology and Paediatric) follow-up Study at a metropolitan tertiary care hospital in Sydney, Australia. The study was approved by the South-Eastern Sydney Local Health District Human Research Ethics Committee (HREC/12/POWH395). A detailed study protocol has been published,[7] in addition to maternal physiological,[8,9] metabolic,[10] mental health[11] and infant growth[12,13] outcomes. This study was written with the STROBE reporting guidelines.

Participants

Study participants were infants of mothers in the P4 study. Mothers were eligible if they gave birth to a live singleton without major congenital abnormalities between January 2013 and December 2018, and had a good understanding of written and spoken English. Women were excluded if, prior to pregnancy, they had diabetes, hypertension, renal or other serious disease. Written informed consent for mother and baby was obtained at study enrolment by 6 months postpartum. The P4 study recruited 415 women who had either NTP ($n = 302$), PE ($n = 90$) or GH ($n = 23$), according to the International Society for the Study of Hypertension in Pregnancy Guidelines.[2] GH was defined as persistent, new onset hypertension (blood pressure $^{3}140$ mmHg systolic or $^{3}90$ mmHg diastolic) at or after 20 weeks' gestation without features of PE, while PE was GH accompanied by proteinuria or other maternal organ dysfunction including acute kidney injury, liver, neurological or haematological complications, or uteroplacental dysfunction.[2] This study includes infants exposed to NTP, GH or PE who had completed the 2-year Ages and Stages Questionnaires, Third Edition (ASQ-3)[14] or the 2-year Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III)[15] assessment (Fig. 1). Preterm birth was defined as < 37 weeks' gestation,[2] and SGA status as birthweight z-score corrected for sex and gestational age < -1.28, calculated for term infants using the World Health Organisation Child Growth Standards,[16] and for preterm infants using the INTERGROWTH-21st Preterm Postnatal Growth Standards.[17]

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Data collection

Maternal sociodemographic information, medical history and birth details were collected retrospectively from the mother's electronic medical record, and prospectively from P4 surveys (Supplementary Material S1) and study visits at 6 months and 2 years postpartum. Maternal blood pressure, body composition, and metabolic markers were also collected using standard methods at these study visits. Infant health details were collected by the paediatrician and parent surveys. Infant development was screened using the parent-completed ASQ-3 questionnaire at 6 months and 2 years (corrected for gestational age). Infant development was assessed by a child psychologist using the month-appropriate BSID-III assessment at approximately 2 years (corrected for gestational age). Testers were not blind to group status.

Outcomes

ASQ-3 scores at 6 months and 2 years were categorised as passes (development on schedule or close to cut-off requiring monitoring) or fails (indicating developmental risk and requiring formal developmental assessment) according to domain-specific cut-off values.[14] Primary ASQ-3 outcomes included the proportion of infants who failed each ASQ-3 domain (communication, gross motor, fine motor, problem solving, personal-social) and proportion of infants who failed any ASQ-3 domain overall. The presence of developmental delay in a BSID-III domain was defined as performance > 2 standard deviations (SD) below the mean,[18] corresponding to BSID-III scaled scores of ≤ 4, or performance ≤ 2nd percentile.[15] Primary BSID-III outcomes compared between exposure groups included BSID-III scaled scores in each domain, proportion of infants with developmental delay in each domain, and proportion of infants with developmental delay in any BSID-III domain overall.

Covariates

Maternal covariates considered in relation to HDP exposure and infant development included: age, parity, lifetime smoking history, maternal and paternal ethnicity (self-reported), tertiary education completion, first trimester weight and BMI, other pregnancy complications including medical, such as gestational diabetes mellitus, obstetric, such as antepartum haemorrhage, and fetal, such as reduced fetal movements, and at 6 months and 2 years; maternal blood pressure, alcohol consumption and Edinburgh Postnatal Depression Scale (EPDS) scores. Birth covariates included labour onset and mode of birth. Infant covariates included sex, birth gestation, prematurity status, SGA status, length of neonatal intensive care unit or special care nursery (NICU or SCN) stay, and total months breastfed in the first 2 years.

Statistical analysis

Descriptive statistics were used to summarise maternal, infant and birth covariates in each exposure group (NTP, GH or PE), as well as the excluded cohort. Developmental outcomes including ASQ-3 domains failed, BSID-III scaled scores and developmental delay in each BSID-III domain were compared between groups using independent samples T-tests and one-way ANOVA tests (parametric continuous data), Kruskal-Wallis tests (non-parametric continuous data), with Tukey post-hoc analysis to account for multiple comparisons, and Chi-Square or Fisher's exact tests (categorical data). Associations between infant psychomotor development and covariates were explored using multivariable linear regression and binary logistic regression, including adjustment for known determinants of infant neurodevelopment such as SGA status, prematurity status, maternal education, maternal employment, maternal EPDS scores and other pregnancy complications. Statistical analysis was performed using IBM SPSS Statistics, version 26.0 (Chicago, IL). A two-tailed p-value of 0.05 was considered statistically significant in univariate analyses. In logistic regression models, Bonferroni corrections were applied to correct for multiple comparisons.

Results

Of the 415 infants initially enrolled in the P4 study, 369 (NTP = 274, 91%; GH = 20, 87%; PE = 75, 83%) had completed at least one or both the 2-year ASQ-3 surveys ($n = 346$), or 2-year BSID-III assessments ($n = 310$) (Fig. 1).

Table 1 details the parental demographic, maternal health, birth and infant health information of included participants. There were no statistically significant differences in parental demographic, maternal health, birth and infant health outcomes between retained participants and those lost to follow up. Compared to the NTP group, GH and PE mothers had poorer measures of postpartum physical health including higher blood pressure and insulin resistance. Compared to the NTP group, GH and PE mothers were more likely to give birth via elective or emergency caesarean section and have been nulliparous in the index pregnancy. Compared to other groups, PE-exposed infants were more likely to be born preterm, SGA, be admitted to a NICU or SCN, and were breastfed for a shorter duration.

Univariate analyses

Table 2 details 6-month and 2-year ASQ-3 developmental outcomes. Compared to NTP or GH-exposed infants, a higher proportion of PE-exposed infants failed 4 of 5 domains, and at least 1 ASQ-3 domain at 6 months (NTP = 18%, GH = 5%, PE = 28%, $p = 0.07$), however this difference was not statistically significant.

Table 3 details 2-year BSID-III developmental outcomes. GH-exposed infants had on average lower BSID-III scaled scores in all domains, and although approaching significance in the expressive communication domain ($p = 0.053$), these differences were not statistically significant, and their scores were not indicative of developmental delay in any domain. There were no significant differences noted in the PE comparisons.

Multivariable analyses

Table 4 details binary logistic regression models exploring the association between PE and GH exposure compared to NTP exposure with 2-year ASQ-3 domain failure. When adjusting for prematurity status, SGA status, maternal tertiary education completion rates, maternal employment status, maternal EDPS scores at 2 years and other maternal pregnancy complications, GH was significantly associated with an increased risk of failing the problem-solving domain ($p = 0.048$). However, when corrected for multiple comparisons, this finding was no longer significant. Prematurity status was significantly associated with failing any domain (Exp(B) [95%CI]: 3.35 [1.27–8.88], $p = 0.015$).

Table 5 details multivariable linear regression models (same factors adjusted as for the 2-year ASQ-3) exploring the association between PE and GH exposure compared to NTP exposure with 2-year BSID-III scaled scores. Neither GH nor PE were significantly associated with lower BSID-III scaled scores at 2 years. Prematurity

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Table 1. Parental demographic, maternal health, birth and infant health details of infants with intrauterine exposure to a normotensive pregnancy, gestational hypertension or preeclampsia

Parental Demographic and Maternal Health Details	*NTP (n = 274)*	*GH (n = 20)*	*PE (n = 75)*	*P-value*	*Cohort LTFU (n = 46)*
			Mean (SD)		
Maternal age at birth	33 (4)	33 ± (4)	32 (5)	0.054	32 (6)
Average systolic BP, mmHg					
First trimester[a]	109 (11)	124 (6)	113 (11)	<**0.001**	107 (12)
6 months	104 (8)	117 (13)[x]	113 (9)[x]	<**0.001**	107 (10)
2 years[b]	103 (9)	118 (10)	111 (11)	<**0.001**	N/a
Average diastolic BP, mmHg					
First trimester[a]	67 (8)	77 (7)	71 (9)	<**0.001**	66 (7)
6 months	66 (6)	74 (9)[x]	72 (8)[x]	<**0.001**	68 (8)
2 years[b]	66 (7)	74 (7)[x]	72 (8)[x]	<**0.001**	N/a
			Median (IQR)		
Maternal weight, kg					
*Booking visit**	62 (16)	77 (36)	64 (18)	<**0.001**	65 (17)
6 months	65 (18)	81 (32)	69 (24)	<**0.001**	69 (18)
2 years[b]	63 (17)	79 (46)	67 (17)	<**0.001**	N/a
Maternal BMI, (kg/m^2)					
*Booking visit**	23 (5)	29 (10)	24 (6)	<**0.001**	25 (6)
6 months	24 (7)	30 (11)	27 (8)	<**0.001**	27 (7)
2 years[b]	23 (7)	30 (14)	27 (7)	<**0.001**	N/a
			N (%)		
Maternal ethnicity[e]					
White	154 (56)	15 (75)	42 (56)	0.415	15 (33)
Asian	57 (21)	1 (5)	15 (20)		13 (28)
European	38 (14)	4 (20)	10 (13)		4 (9)
Other	24 (9)	0 (0)	8 (11)		14 (30)
Paternal ethnicity[f]					
White	151 (56)	12 (63)	47 (63)	0.745	14 (30)
Asian	40 (15)	2 (11)	9 (12)		10 (22)
European	42 (16)	3 (16)	14 (19)		7 (15)
Other	36 (13)	2 (11)	5 (7)		14 (30)
Maternal tertiary education completed[e]	250 (92)	17 (85)	72 (96)	0.190	38 (83)
Paternal tertiary education completed[f]	240 (89)	17 (85)	66 (90)	0.681	34 (74)
Highest parental education level completed[e]				0.168	N/a
Secondary School	9 (3)	2 (10)	2 (2)		N/a
Trade/Certificate/Diploma	47 (17)	5 (25)	19 (25)		N/a
University Degree	217 (80)	13 (65)	54 (72)		N/a
Mum Unemployed, Second Edu Only[h]	2 (1)	2 (11)	0 (0)	0.018	N/a
Mum Unemployed[h]	13 (5)	2 (11)	2 (3)	0.345	N/a
Maternal ever smoked	76 (28)	5 (25)	25 (33)	0.602	17 (37)
Maternal alcohol consumption					
6 months	107 (39)	11 (55)	36 (48)	0.251	12 (26)
2 years	112 (41)	7 (35)	30 (40)	0.951	N/a
Gestational diabetes mellitus	31 (11)	5 (25)	10 (13)	0.181	7 (15)
EPDS Score diagnostic of depression					
Pregnancy[g]	3 (1)	1 (5)	4 (5)	0.086	5 (10)
6 months	6 (2)	0 (0)	6 (8)	0.150	3 (7)
2 years[h]	12 (4)	0 (0)	2 (3)	0.185	N/a
EPDS Question 10- non-0 score					
Pregnancy[g]	0 (0)	0 (0)	2 (3)	0.064	0 (0)
6 months	4 (2)	0 (0)	1 (1)	0.292	0 (0)
2 years[h]	3 (1)	0 (0)	0 (0)	1.000	N/a

(*Continued*)

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Table 1. (*Continued*)

Parental Demographic and Maternal Health Details	*NTP (n = 274)*	*GH (n = 20)*	*PE (n = 75)*	*P-value*	*Cohort LTFU (n = 46)*
Birth details					
			N (%)		
Labour onset					
Spontaneous labour	160 (58)	1 (5)	5 (7)	<**0.001**	20 (44)
Induction of labour	87 (32)	14 (70)	50 (67)		20 (44)
No labour	27 (10)	5 (25)	20 (27)		6 (13)
Mode of birth					
Normal vaginal	178 (65)	7 (35)	24 (32)	<**0.001**	26 (57)
Assisted vaginal	42 (15)	2 (10)	14 (19)		8 (17)
Elective caesarean section	21 (8)	4 (20)	7 (9)		5 (11)
Emergency caesarean section	33 (12)	7 (35)	30 (40)		7 (15)
Infant details					
			N (%)		
Male sex	143 (52)	9 (45)	38 (51)	0.829	17 (37)
Nulliparous pregnancy	135 (49)	12 (60)	56 (75)	<**0.001**	26 (57)
Premature birth	17 (6)	0 (0)	27 (35)	<**0.001**	6 (13)
Late preterm birth (34-36 weeks)	14 (5)	0 (0)	16 (21)		N/a
Early preterm birth (<34 weeks)	3 (1)	0 (0)	11 (15)		N/a
SGA birth	22 (8)	2 (10)	18 (24)	**0.002**	3 (7)
NICU/SCN Admission	36 (13)	1 (5)	39 (52)	<**0.001**	12 (26)
			Median (IQR)		
Birth gestation, week	39.6 (2.0)	39.1 (1.5)	37.6 (3.0)	<**0.001**	N/a
Months breastfed to 2 years[i]	12 (11)	6 (13)	8 (13)	**0.008**	N/a

Abbreviations: BMI, body mass index; BP, blood pressure; EPDS, Edinburgh Postnatal Depression Score; GH, gestational hypertension; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IQR, interquartile range; kg, kilograms; LTFU, loss to follow up (therefore excluded from further analyses); m, metres; mmHg, millimetres of mercury; N, number; N/a, not assessed due to lack of data/LTFU; NICU/SCN, neonatal intensive care unit/special care nursery; NTP, normotensive pregnancy; PE, preeclampsia; SD, standard deviation; SGA, small for gestational age. *Median (IQR) gestation of booking visit = 13 (3) weeks. [x]GH and PE groups did not significantly vary but were significantly greater than the NTP group. **Missing data:** [a]$n = 60$, [b]$n = 176$, [c]$n = 4$, [d]$n = 181$, [e]$n = 1$, [f]$n = 6$, [g]$n = 27$, [h]$n = 8$, [i]$n = 14$.

status was significantly associated with decreased scores in receptive communication (Exp(B) [95%CI]: −1.34[−2.63 - −0.04], $p = 0.043$) and cognitive domains (Exp(B) [95%CI]: −1.54[−2.90 - −0.19], $p = 0.026$) at 2 years. However, when corrected for multiple comparisons, this finding was no longer significant. Maternal tertiary education was significantly associated with increased scores in the cognitive domain at 2 years after correction (Exp(B) [95%CI]: 1.94 [0.42 - 3.46], $p = 0.013$).

Table 6 details a binary logistic regression model (same factors adjusted as for the 2-year ASQ-3) exploring the association between PE exposure compared to NTP exposure with the presence of developmental delay at 2-years, as assessed by the BSID-III. PE exposure was not associated with the presence of developmental delay in any domain at 2 years. No regression analysis was performed for the GH exposure group as no infants had scores indicative of developmental delay at 2 years in BSID-III domains (Table 3).

Discussion

In our population of 369 infants, PE-exposed infants were more likely to be born preterm, SGA, be admitted to a NICU or SCN, and breastfed for a shorter duration than infants born after NTP. After adjustment for confounders including SGA and prematurity status, we demonstrated no significant associations of PE or GH exposure with impaired or delayed psychomotor neurodevelopment at 6 months or 2 years. GH was only associated with a slightly increased risk of failing the problem-solving domain of the ASQ-3 screening tool at 2 years before corrections for multiple comparisons. However, this did not correlate to statistically significant differences in BSID-III scaled scores or the proportion of infants with developmental delay in problem-solving or other neurodevelopmental domains. Further, the small sample size of the GH group and the marginal significance of the non-corrected finding indicates a need to interpret this finding with caution.

This is one of the first studies to distinguish between PE and GH exposure when assessing infant neurodevelopment using the BSID-III and ASQ-3 tools. GH has been associated with decreased development quotient on social behaviour at 6 months[19] and increased risk of mild cognitive dysfunction in childhood[20] in children exposed to GH compared to NTP. This may be explained by factors associated with maternal GH such as an adverse genetic cardiometabolic profile, and postnatal lifestyle factors such as maternal socioeconomic status and mental health, associated with negative implications on infant neurodevelopment.[5,21,22] However, after adjustment for common confounders and multiple comparisons, we demonstrated GH was not associated with impaired psychomotor development at 6 months or 2 years on the ASQ-3, a parent-completed screening tool useful for indicating developmental risk but unable to diagnose developmental delay, nor the BSID-III, which is an objective developmental assessment tool used to diagnose developmental delay.[18]

PE exposure may have greater potential than GH to impair fetal neurodevelopment.[23] Proposed mechanisms associated with PE

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Table 2. Infant ASQ-3 outcomes after intrauterine exposure to a normotensive pregnancy, gestational hypertension or preeclampsia

ASQ-3 Developmental Outcomes	*NTP (n = 264)*	*GH (n = 19)*	*PE (n = 63)*	*P-value*
		Median (IQR)		
Age at developmental assessment, months				
6-month ASQ-3[a]	6.0 (1.0)	6.0 (0.5)	6.2 (1.0)	0.638
2-year ASQ-3[b]	24.0 (1.0)	24.3 (1.8)	24.0 (1.0)	0.487
		N (%)		
ASQ-3 Domain Failed at 6 months[c]				
Communication	5 (2)	0 (0)	2 (3)	0.256
Gross Motor	22 (8)	1 (5)	7 (11)	0.273
Fine Motor	17 (6)	1 (5)	6 (10)	0.255
Problem solving	11 (4)	1 (5)	3 (5)	0.300
Personal-social	15 (6)	0 (0)	3 (5)	0.337
Any domain	48 (18)	1 (5)	17 (28)	0.070
ASQ-3 Domain Failed at 2 years				
Communication	12 (5)	1 (5)	4 (6)	0.643
Gross Motor	7 (3)	0 (0)	2 (3)	0.812
Fine Motor	10 (4)	2 (11)	2 (3)	0.299
Problem solving	7 (3)	2 (11)	1 (2)	0.138
Personal-social	10 (04)	1 (5)	3 (5)	0.665
Any domain	31 (12)	4 (21)	8 (13)	0.418

Abbreviations: ASQ-3, Ages and Stages Questionnaires, Third Edition; GH, gestational hypertension; IQR, interquartile range; N, number; NTP, normotensive pregnancy; PE, preeclampsia. **Missing data:** [a]$n = 26$, [b]$n = 43$, [c]$n = 6$.

Table 3. Infant BSID-III outcomes after intrauterine exposure to a normotensive pregnancy, gestational hypertension or preeclampsia

BSID-III Developmental Outcomes	*NTP (n = 231)*	*GH (n = 15)*	*PE (n = 63)*	*P-value*
		Median (IQR)		
Age at 2-year BSID-III assessment, months	24.3 (1.1)	24.5 (1.2)	24.2 (1.0)	0.650
		Mean (SD)		
BSID-III Scaled Scores				
Expressive Communication	11 (3)	9 (2)	10 (2)	0.053
Receptive Communication	10 (3)	9 (2)	10 (3)	0.100
Gross Motor	11 (3)	9 (3)	10 (3)	0.095
Fine Motor	11 (3)	10 (3)	11 (3)	0.231
Cognitive	12 (3)	11 (4)	12 (4)	0.379
		N (%)		
BSID-III Presence of Developmental Delay				
Expressive Communication	3 (1)	0 (0)	0 (0)	1.000
Receptive Communication	8 (4)	0 (0)	4 (6)	0.514
Gross Motor	2 (1)	0 (0)	0 (0)	1.000
Fine Motor	1 (1)	0 (0)	2 (3)	0.240
Cognitive	4 (2)	0 (0)	2 (3)	0.713
Any domain	13 (6)	0 (0)	6 (10)	0.422

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, 3rd Edition; GH, gestational hypertension; IQR, interquartile range; N, number; NTP, normotensive pregnancy; PE, preeclampsia.

include early angiogenic imbalances, maternal inflammation, oxidative stress and uteroplacental insufficiency, which may cause fetal hypoxic-ischaemic brain injury and impair later neurodevelopment.[24] In addition, the Developmental Origins of Health and Disease hypothesis suggests the fetus undergoes 'developmental programming' as an adaptation to this adverse intrauterine environment, increasing their future risk of morbidity.[23] However, in our cohort neither PE nor GH exposure were associated with poorer BSID-III neurodevelopmental outcomes. Many studies that reported an increased risk of impaired cognitive functioning and neurodevelopment after HDP exposure,[3,4] and studies that reported no difference in motor, social, mental or cognitive development,[19,25,26] were conducted in SGA or very preterm (< 32 weeks) populations. PE is associated with fetal growth restriction and subsequent SGA birth, and as delivery is the only definitive treatment for PE, a higher proportion of neonates are born preterm.[24,27] SGA and preterm birth are comorbidities independently associated with poor neurodevelopment,[6] and subsequently, determining the impact of PE on neurodevelopment independent of these associations is difficult to discern. Importantly, our findings in a mixed cohort of gestations and birthweights, more reflective of the population distribution of HDP, with adjustment for SGA and prematurity status, add to two large prospective cohort studies in mixed populations that reported no significant differences in the proportion of infants with neurodevelopmental delay at 6 months,[19] or developmental risk on the ASQ-3 at 9 months[25] after PE exposure.

In infants exposed to severe PE, one study demonstrated no statistically significant differences in the proportion of infants with failed ASQ domains at 1 and 2 years, but greater failures by 3 years.[28] Although assessing neurodevelopmental outcomes later in life may be confounded by lifestyle and behavioural factors, continued follow-up of our cohort will assess whether 2-year trends such as greater proportions of developmental delay in the PE group, and lower BSID-III scaled scores in the GH group, may become statistically and clinically significant as developmental demands increase after infancy toward school age.

HDP exposure and SGA status were not significant predictors in our cohort, however preterm birth was an independent predictor of failing any ASQ-3 domain at 2 years. In preterm infants, PE has been reported as an independent risk factor for neurodevelopmental disability,[29] and preterm PE infants had poorer fine motor skills and visuo-auditory perception at 18 months than preterm NTP infants, while term infants had better motor skills, visuo-auditory perception, and social abilities.[30] HDP are clinically heterogenous, with early onset (< 34 weeks' gestation) or preterm PE (34–36 + 6 weeks' gestation), associated with more severe neurodevelopmental impacts than late-onset PE (≥37 weeks), more commonly experienced by our PE cohort.[31,32] This may reflect the greater uteroplacental insufficiency associated with early onset or more severe disease, or prolonged fetal exposure to the adverse intrauterine environment where delivery is delayed to avoid preterm birth.[24,27,32] However, it is impossible to exclude the influence of other complications of preterm birth including longer NICU or SCN stay and reduced breastfeeding rates at

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Table 4. Binary logistic regression: adjusted model of the associations between preeclampsia and gestational hypertension compared to normotensive pregnancy exposure versus 2-year ASQ-3 domain failure

2-Year ASQ-3 Domain Failure	*Model adjusted for: SGA status, prematurity status, maternal tertiary education, employment status, EPDS scores, other pregnancy complications*	
GH	***Exp(B) (95% CI)***	***P-value****
Communication	1.26 (0.15-10.42)	0.832
Gross Motor	0.00 (0.00)	0.998
Fine Motor	3.06 (0.58-16.20)	0.188
Problem-solving	5.71 (1.02-32.08)	0.048
Personal-social	2.06 (0.24-17.88)	0.511
Any domain	2.37 (0.72-7.72)	0.154
PE	***Exp(B) (95% CI)***	***P-value****
Communication	1.18 (0.32-4.35)	0.801
Gross Motor	0.25 (0.03-2.43)	0.232
Fine Motor	0.98 (0.19-5.02)	0.985
Problem-solving	0.57 (0.06-5.24)	0.621
Personal-social	1.03 (0.23-4.62)	0.972
Any domain	0.85 (0.33-2.21)	0.744

Abbreviations: ASQ-3, Ages and Stages Questionnaires, Third Edition; CI, confidence interval; Exp(B), exponent beta; GH, gestational hypertension; N, number; PE, preeclampsia, SGA, small for gestational age. Other pregnancy complications included gestational diabetes mellitus, preterm premature rupture of the membranes, antepartum haemorrhage, maternal infection, reduced fetal movements, polyhydramnios, oligohydramnios, exacerbation of Chron's disease, cholestasis, maternal surgery during pregnancy. $N = 346$ for all models.
*A p-value of 0.016 was considered statistically significant (Bonferroni correction).

discharge, which are independently associated with impaired neurodevelopment.[29] While PE was not associated with adverse neurodevelopmental outcomes in our cohort, we were unable to stratify PE exposure by onset or severity due to sample size. Subsequently, further studies with adjustment for prematurity and SGA status are indicated to further elucidate any independent impact of severe HDP exposure on infant neurodevelopment.

Strengths of this study include our recruitment of an ethnically diverse and mixed cohort of infants born at varying gestations and birthweights, with control for several known and proposed determinants of child neurodevelopment including preterm birth, SGA status, maternal education and employment, maternal postnatal mental health, and other maternal complications including gestational diabetes mellitus.[22,33] The validated developmental screening tool, the ASQ-3, is useful in primary care and general paediatric settings as it is readily available, quick to complete and parent-completed.[34] The BSID-III is a gold-standard developmental assessment tool for diagnosis of developmental delay.[35] Prior studies assessing the association of HDP with infant neurodevelopment have usually considered assessment and screening scores only, rather than clinically significant thresholds indicating future childhood cognitive and motor performance. Subsequently, our analyses of infants with failed ASQ-3 domains and developmental delay in BSID-III domains adds to the few studies assessing HDP and infant neurodevelopment with clinically significant outcomes rather than scores, using readily available and validated tools. However, we must note that the population from which the BSID-III was derived from included children with varied clinical conditions that may impact neurodevelopment, such as prenatal alcohol exposure and premature birth. Thus, the tool may underestimate the presence of delay, and not identify children with mild to moderate delay.[36,37] This may explain why on univariate analyses, GH-exposed infants had on average lower BSID-III scaled scores in all domains compared to NTP infants, however these scores did not cross the threshold for developmental delay in any domain.

Limitations include the single-centre nature of the P4 study, and that it was powered to detect differences in maternal rather than paediatric health outcomes specifically. The small sample size of GH-exposed infants reduced statistical power, and the moderately sized PE group prevented sub-analyses based on PE onset or severity. Although our final cohort was ethnically diverse, participants were excluded if they did not have a good understanding of written and spoken English, limiting the applicability of our findings to culturally and linguistically diverse populations. We also lacked data on other confounding factors that may influence infant development, including infant hospitalisations and comorbidities, parental prenatal mental health, paternal employment, and maternal alcohol consumption during pregnancy itself, despite no significant differences in maternal alcohol consumption between groups at 6 months and 2 years (Table 1). A high proportion of parents in our cohort completed tertiary education and we demonstrated that maternal tertiary education is associated with increased scores in the cognitive domain at 2 years. Parental education is an indicator of higher socioeconomic status, directly associated with early childhood neurodevelopment.[21] So, while HDP may not influence infant neurodevelopment in high income populations, our findings may not be generalisable to populations of lower socioeconomic status. Due to high-level, consistent HDP care in the study hospital, HDP-exposed mothers and children had additional antenatal and postnatal health visits and study participants likely had greater health awareness than the general population. Subsequently we cannot exclude the influence of healthy volunteer bias in our sample masking a negative influence of HDP on infant neurodevelopment.

Our findings are broadly reassuring regarding infant neurodevelopment after HDP, especially in populations with protective sociodemographic and clinical care factors. The comorbid complication of preterm birth in the PE group was associated with poorer neurodevelopment, highlighting the need for greater parental and physician awareness and early surveillance of neurodevelopment in HDP-exposed, premature infants. Early intervention may alter a child's neurodevelopmental trajectory before school age, where delay may confer more severe cognitive, psychosocial and behavioural consequences.[38] Our research also highlights opportunities to optimise breastfeeding duration in hypertensive groups, as breastfeeding is positively associated with cognitive development,[39] and promote key socioeconomic determinants of health like parental education and preschool attendance at individual, community and policy levels to optimise paediatric neurodevelopmental outcomes.

We demonstrated no strong association of PE or GH exposure, but a strong association of prematurity status, with abnormal psychomotor developmental outcomes in infants at 6 months or 2 years. Although reassuring, continued follow-up and further

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Table 5. Multivariable linear regression: adjusted model of the associations between preeclampsia and gestational hypertension compared to normotensive pregnancy exposure versus BSID-III scaled scores

BSID-III Scaled Scores	*Unadjusted*		*Model adjusted for: SGA status, prematurity status, maternal tertiary education, employment status, EPDS scores, other pregnancy complications*	
GH	***Regression coefficient B (95% CI)***	***P-value****	***Regression coefficient B (95% CI)***	***P-value****
Expressive Communication	−1.48 (−2.96- −0.004)	0.049	−1.41 (−2.90-0.08)	0.063
Receptive Communication	−1.73 (−3.46- −0.01)	0.049	−1.60 (−3.31-0.14)	0.072
Gross Motor	−1.64 (−3.46- 0.18)	0.077	−1.78 (−3.62- 0.06)	0.057
Fine Motor	−1.16 (−2.79-0.46)	0.160	−1.24 (−2.88-0.40)	0.139
Cognitive	−1.50 (−3.32-0.31)	0.104	−1.40 (−3.21-0.40)	0.126
PE	***Regression coefficient B (95% CI)***	***P-value****	***Regression coefficient B (95% CI)***	***P-value****
Expressive Communication	−0.70 (−1.50-0.11)	0.089	−0.34 (−1.24-0.57)	0.466
Receptive Communication	−0.47 (−1.40-0.47)	0.330	−0.11 (−1.16-0.93)	0.832
Gross Motor	−0.42 (−1.37-0.54)	0.393	−0.16 (−1.23-0.92)	0.776
Fine Motor	−0.36 (−1.25-0.52)	0.420	−0.15 (−1.14-0.85)	0.772
Cognitive	−0.14 (−1.12-0.85)	0.787	0.37 (−0.72-1.47)	0.506

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, 3rd Edition; CI, confidence interval; GH, gestational hypertension; N, number; PE, preeclampsia; SGA, small for gestational age. $N = 301$ for all models. *A p-value of 0.016 was considered statistically significant (Bonferroni correction).

Table 6. Binary logistic regression: adjusted model of the associations between preeclampsia compared to normotensive pregnancy exposure versus presence of developmental delay (BSID-III)

Presence of Developmental Delay (BSID-III)	*Model adjusted for: SGA status, prematurity status, maternal tertiary education, employment status, EPDS scores, other pregnancy complications*	
PE	***Exp(B) (95% CI)***	***P-value****
Expressive Communication	0.00 (0.00)	0.997
Receptive Communication	0.86 (0.16-4.46)	0.852
Gross Motor	0.00 (0.00)	0.997
Fine Motor	6.52 (0.09-38.50)	0.390
Cognitive	0.85 (0.06-12.19)	0.908
Any domain	0.92 (0.22-3.75)	0.903

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, 3rd Edition; CI, confidence interval; Exp(B), Exponent beta; N, number; PE, preeclampsia; SGA, small for gestational age. $N = 301$ for all models. *A p-value of 0.016 was considered statistically significant (Bonferroni correction).

research with larger samples and more term-born, non-SGA and socioeconomically diverse cohorts is necessary to elucidate the impacts of GH and PE exposure.

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Competing interests. The authors declare none.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the Australian National Statement on Ethical Conduct in Human Research of 2007, and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the South-Eastern Sydney Local Health District Human Research Ethics Committee (HREC/12/POWH395).

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