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Hypertensive disorders of pregnancy, preterm prelabour rupture of membranes and placental abruption differentially shape neonatal morbidity phenotypes in preterm infants: a retrospective cohort study

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Abstract

Background

Preterm birth is a syndrome driven by distinct upstream pathological processes, yet most studies examine a single maternal complication against a single neonatal endpoint, so that the resulting phenotypes cannot be compared within one population. We compared, in parallel within one cohort, the neonatal morbidity phenotypes associated with placental abruption, hypertensive disorders of pregnancy (HDP) and preterm prelabour rupture of membranes (PPROM).

Methods

In one tertiary maternity hospital we conducted a retrospective cohort study of 14,690 hospitalised preterm infants (gestational age below 37 weeks) born between November 2013 and December 2022. Maternal exposures were assigned hierarchically and mutually exclusively as placental abruption, HDP, PPROM or none of the above (reference). The primary outcome was a composite of severe neonatal morbidity. Associations were estimated by multivariable logistic regression in three incremental models, with cluster-robust standard errors clustered on maternal hospital number.

Results

Of 16,081 records screened, 14,690 infants were analysed: 8,232 (56.0%) had no major complication, 3,591 (24.4%) PPROM, 1,929 (13.1%) HDP and 938 (6.4%) placental abruption; 40.0% reached the composite outcome. Placental abruption raised composite risk (adjusted odds ratio 1.69, 95% CI 1.46–1.96) but not after adjustment for gestational age and birth weight (0.97, 0.82–1.14), indicating mediation by earlier gestation and lower birth weight. HDP independently increased very low birth weight (1.97, 1.75–2.23) and small-for-gestational-age birth (2.38, 2.03–2.78), yet lowered respiratory distress syndrome risk at the same gestation and weight (0.79, 0.68–0.91). PPROM increased very preterm birth (1.32, 1.18–1.48) and sepsis (1.20, 1.02–1.40) while reducing small-for-gestational-age risk (0.31, 0.23–0.41). The interaction between gestational age and maternal complication was significant (P = 0.001), and the findings were robust in four pre-specified sensitivity analyses.

Conclusions

Three canonical maternal pathways to preterm delivery map onto three distinguishable neonatal morbidity phenotypes: a gestation-and-weight-mediated phenotype (placental abruption), a growth-restriction phenotype (HDP) and an infection–preterm-birth phenotype (PPROM). Maternal complications shape not merely whether a preterm infant becomes ill but which phenotype emerges.

Background

Preterm birth — delivery before 37 completed weeks of gestation — remains the leading cause of neonatal and under-five mortality. In 2015, complications of preterm birth accounted for an estimated 1.05 million deaths among children under 5 years of age, more than any other single cause.[1] An estimated 13.4 million infants were born preterm in 2020 (9.9% of all live births), and the global preterm birth rate showed no measurable decline between 2010 and 2020.[2] Preterm birth and small-for-gestational-age (SGA) birth are the two principal pathways to “small vulnerable newborn” status; together they accounted for more than half of the 2.4 million neonatal deaths worldwide in 2020.[3] For those who survive, the burden is lifelong: a meta-analysis of 71 studies comprising 7,752 extremely or very preterm children found a mean IQ deficit of 0.86 standard deviations relative to term-born controls, a gap that did not narrow between 1990 and 2008.[4] Identifying modifiable maternal determinants and explaining heterogeneity in neonatal outcome therefore remain central problems in perinatal and neonatal medicine.

Preterm birth is not a single disease but a syndrome driven by several distinct upstream pathological processes. Obstetric practice has long recognised canonical pathways: iatrogenic or fetal-compromise delivery driven by maternal vascular–placental disease such as pre-eclampsia and placental abruption; spontaneous preterm labour initiated by intrauterine infection and inflammation, of which preterm prelabour rupture of membranes (PPROM) is the archetype; and idiopathic preterm labour without an identified trigger.[5, 6] These pathways differ not only in the timing of delivery and the resulting distribution of gestational age but also, plausibly, in the mechanisms through which they harm the newborn: vascular–placental disease is characterised by impaired placental perfusion and fetal growth restriction, whereas intrauterine infection–inflammation involves chorioamnionitis, cytokine activation and neonatal infection.[7]

However, most previous studies have treated preterm birth as a single outcome defined by gestational age or birth weight, or have examined one maternal complication against one neonatal endpoint. Research on placental abruption has focused largely on perinatal mortality and suggests that its excess mortality is mediated predominantly by early delivery;[8, 9] work on pre-eclampsia has centred on fetal growth restriction;[10, 11] and work on intrauterine infection has concentrated on spontaneous preterm labour and neonatal infection.[7] This “one complication, one endpoint” design makes it difficult to compare, within a single population and care setting, the severity of prematurity and the neonatal morbidity phenotypes associated with different complications. The relationship between pre-eclampsia and neonatal respiratory distress syndrome (RDS) illustrates the problem: some studies report a lower incidence of RDS among infants of pre-eclamptic mothers, yet this apparent protection attenuates or reverses after adjustment for gestational age and birth weight.[12, 13] Unless effects mediated through earlier gestation and lower birth weight are separated from disease-specific effects operating independently of both, the true direction of a maternal complication’s influence may be masked or misattributed.

To address this gap, we conducted a retrospective cohort study of 14,690 hospitalised preterm infants delivered between November 2013 and December 2022 in a tertiary maternity hospital, comparing in parallel the severity of prematurity and the neonatal morbidity phenotypes associated with three maternal pregnancy complications: placental abruption, hypertensive disorders of pregnancy (HDP) and PPROM. Exposures were assigned hierarchically and mutually exclusively to prevent multiple attribution when complications coexisted. Three incremental multivariable logistic regression models (Model 1, crude; Model 2, adjusted for maternal and obstetric covariates; Model 3, further adjusted for gestational age and birth weight) were used to separate effects mediated by earlier gestation and lower birth weight from disease-specific effects independent of both, with cluster-robust standard errors clustered on maternal hospital number. The primary outcome was a composite of severe neonatal morbidity (any of RDS, bronchopulmonary dysplasia, intracranial haemorrhage/periventricular leucomalacia, necrotising enterocolitis, sepsis or retinopathy of prematurity). We hypothesised that the three complications map onto three distinguishable neonatal morbidity phenotypes. Distinguishing which phenotype a maternal complication produces, rather than merely whether a preterm infant becomes ill, has direct implications for antenatal decision-making and postnatal surveillance.

Methods

Study design and data sources

This was a single-centre retrospective cohort study, reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Additional file 1). The data were derived from the legacy inpatient information system of the Women's Hospital, School of Medicine, Zhejiang University, a tertiary obstetrics and gynaecology hospital in Hangzhou, China, and covered all neonatal inpatient records from November 2013 to December 2022 (n = 16,081). Each record contained four groups of variables: (i) neonatal demographics and clinical data (sex, date and time of birth, gestational age, birth weight, birth length and mode of delivery); (ii) neonatal ICD-10 diagnosis codes and diagnosis text, comprising 69,574 diagnosis entries with 1,689 distinct labels; (iii) maternal demographics, obstetric history and pregnancy-complication diagnoses, comprising 101,520 entries with 8,189 distinct labels; and (iv) admission and discharge times together with hospitalisation charges. No large language model was used at any stage of data extraction, statistical analysis or interpretation.

Study population

Records were eligible if gestational age could be parsed and fell within the plausible range of 20–45 weeks. Of 16,081 records, 40 were excluded for missing or uninterpretable gestational age (16,041 remained), and a further 1,351 infants born at or after 37 weeks were excluded, leaving 14,690 hospitalised preterm infants (gestational age below 37 weeks) for analysis (Fig. 1). Births spanned 2013–2022; 259 infants (1.8%) were born before 28 weeks, 3,404 (23.2%) at 28–31^{+6} weeks and 11,027 (75.1%) at 32–36^{+6} weeks. The cohort comprised 12,282 mothers; 4,771 records (32.5%) shared a

maternal identifier because of multiple gestation or multiple deliveries within a single admission. No a priori sample size calculation was performed: all eligible records in the study period were included, and the analysable sample size was determined by the size of the source database.

Exposure definition

Maternal exposures were assigned hierarchically and mutually exclusively from ICD-10 codes and Chinese diagnosis text: (i) placental abruption (diagnosis text containing the term for placental abruption); (ii) hypertensive disorders of pregnancy (pre-eclampsia, severe pre-eclampsia, gestational hypertension or eclampsia); (iii) preterm prelabour rupture of membranes (prelabour rupture of membranes, necessarily preterm within this cohort); and (iv) none of the above (reference group). The hierarchy abruption > HDP > PPROM was chosen because abruption carries the highest clinical acuity and frequently co-occurs with hypertensive disease, while mutual exclusivity ensures that each effect estimate is interpretable against the complication-free reference rather than being confounded by overlapping indications.

Outcome definitions

Neonatal diagnoses were extracted by matching ICD-10 codes and Chinese diagnosis-text keywords: respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), non-traumatic intracranial/intraventricular haemorrhage, periventricular leucomalacia (PVL), necrotising enterocolitis (NEC), neonatal sepsis, retinopathy of prematurity (ROP), neonatal hypoglycaemia, neonatal hyperbilirubinaemia and small-for-gestational-age birth (SGA, clinically diagnosed). The primary composite outcome was the occurrence of any of RDS, BPD, intracranial haemorrhage/PVL, NEC, sepsis or ROP.

Covariates

Based on prior literature and directed acyclic graph reasoning, Model 2 adjusted for maternal age (continuous, years), maternal education (junior high or below / senior high or technical / college / bachelor or above), parity, gravidity, multiple gestation, mode of delivery (caesarean versus vaginal), neonatal sex and birth year (continuous, to capture secular trends). Paternal age and in-vitro fertilisation were compared descriptively but excluded from the main model because of collinearity with the exposure. Missingness was minimal (maternal education 45 records, 0.3%; maternal age 71 records, 0.5%; all other covariates below 0.2%), and complete-case analysis was used.

Statistical analysis

Continuous variables were summarised as mean ± standard deviation (SD) and compared across groups by one-way analysis of variance; categorical variables were reported as counts (percentages) and

compared by the χ^2 test. Multivariable logistic regression estimated odds ratios (ORs) with 95% confidence intervals (CIs) in three incremental models: Model 1, exposure only (crude OR); Model 2, adjusted for the maternal and obstetric covariates listed above; and Model 3, further adjusted for gestational age and birth weight, to quantify how much of each effect is mediated by earlier delivery and lower birth weight. When an outcome was itself defined by gestational age (very preterm birth) or by birth weight (very low birth weight), the defining variable was omitted from Model 3 to avoid circular adjustment. Because a single maternal hospital number could correspond to more than one infant, all models used cluster-robust standard errors clustered on maternal hospital number (sandwich estimator). The dose–response relation between gestational age and severe neonatal morbidity was modelled with a restricted cubic spline (4 knots at the 5th, 35th, 65th and 95th percentiles) interacting with exposure group, and the overall interaction was assessed by a Wald test. All tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed with Python 3.13 (pandas 2.x, statsmodels 0.14, scipy 1.x); the analysis scripts and intermediate datasets are available from the corresponding author on reasonable request.

Sensitivity analyses

Four pre-specified sensitivity analyses tested the robustness of the main findings: (i) singleton births only (n = 9,015), removing the influence of multiple gestation on the gestational age and birth-weight distributions; (ii) exclusion of periviable infants (gestational age below 28 weeks) to avoid selection driven by the very high mortality at the lowest gestations; (iii) the complete-case dataset; and (iv) stratification by birth era (2013–2017 versus 2018–2022) to assess temporal stability of the estimates.

Results

Study flow and cohort composition

Of 16,081 neonatal records screened, 40 were excluded for missing or uninterpretable gestational age (16,041 remained) and a further 1,351 term infants (at or after 37 weeks) were excluded, leaving 14,690 preterm infants for analysis (Fig. 1). The cohort comprised 12,282 mothers; 4,771 records (32.5%) shared a maternal identifier owing to multiple gestation or multiple deliveries within one admission. By maternal complication, 8,232 infants (56.0%) had no major complication, 3,591 (24.4%) were born after PPROM, 1,929 (13.1%) to mothers with HDP, and 938 (6.4%) after placental abruption. Births spanned 2013–2022; 259 infants (1.8%) were born before 28 weeks, 3,404 (23.2%) at 28–31^{+6} weeks and 11,027 (75.1%) at 32–36^{+6} weeks. Median length of stay was 6.8 days (interquartile range 4.9–10.8), with a mean of 4.5 neonatal diagnosis entries per infant (median 4).

Baseline characteristics

Baseline characteristics differed significantly across groups (Table 1). Infants born after placental abruption had the lowest gestational age (32.15 ± 2.57 weeks) and those born to mothers with HDP the

lowest birth weight (1,795 ± 547 g). The PPROM group had the lowest rates of multiple gestation (30.8%) and caesarean delivery (50.3%), consistent with a spontaneous-labour pathway; conversely, 95.1% of HDP infants were delivered by caesarean section, in keeping with iatrogenic delivery dominating this group. Mean maternal age exceeded 30 years in every group and was highest for HDP (32.0 ± 5.0 years), matching the well-described association between advanced maternal age and pre-eclampsia.

Table 1
Baseline characteristics of mothers and infants by maternal pregnancy complication group

Characteristic	None of the above (n = 8,232)	Hypertensive disorders (n = 1,929)	PPROM (n = 3,591)	Placental abruption (n = 938)	P value
Gestational age, weeks	33.64 ± 2.36	33.44 ± 2.26	33.01 ± 2.49	32.15 ± 2.57	< 0.001
Birth weight, g	2,045 ± 559	1,795 ± 547	2,000 ± 561	1,821 ± 537	< 0.001
Maternal age, years	31.0 ± 4.6	32.0 ± 5.0	30.9 ± 4.5	31.1 ± 4.6	< 0.001
Paternal age, years	32.8 ± 5.4	33.8 ± 5.7	32.7 ± 5.2	32.8 ± 5.3	< 0.001
Parity	0.5 ± 0.6	0.4 ± 0.6	0.4 ± 0.6	0.5 ± 0.6	< 0.001
Gravidity	2.3 ± 1.4	2.3 ± 1.4	2.2 ± 1.4	2.3 ± 1.4	< 0.001
Female sex	3,882 (47.2)	1,003 (52.0)	1,582 (44.1)	389 (41.5)	< 0.001
Multiple gestation	3,620 (44.0)	760 (39.4)	1,105 (30.8)	160 (17.1)	< 0.001
Caesarean delivery	6,759 (82.1)	1,835 (95.1)	1,807 (50.3)	574 (61.2)	< 0.001
Assisted reproduction (IVF)	1,147 (13.9)	336 (17.4)	501 (14.0)	101 (10.8)	< 0.001
Maternal education					< 0.001
Bachelor or above	4,119 (50.0)	878 (45.5)	1,866 (52.0)	478 (51.0)	
College	1,334 (16.2)	300 (15.6)	570 (15.9)	153 (16.3)	
High school or vocational	2,499 (30.4)	676 (35.0)	1,026 (28.6)	267 (28.5)	
Junior high school or below	194 (2.4)	64 (3.3)	77 (2.1)	29 (3.1)	

Data are presented as mean ± SD for continuous variables and n (%) for categorical variables. P values were derived from one-way analysis of variance for continuous variables and the χ^2 test for categorical variables. PPROM, preterm prelabour rupture of membranes; SD, standard deviation; IVF, in vitro fertilisation.

Distribution of neonatal outcomes

All 12 neonatal outcomes differed significantly across the four groups (Table 2). Overall, the composite severe-morbidity outcome occurred in 40.0% of infants (5,871/14,690), very preterm birth in 24.9%, very low birth weight (VLBW) in 20.7%, RDS in 26.9%, intracranial haemorrhage in 13.4% and sepsis in 8.4%. The morbidity phenotypes diverged clearly (Fig. 2). The HDP group was characterised by SGA (16.5%) and hypoglycaemia (15.7%), roughly 2.4-fold and 1.3-fold the reference rates. The PPROM group showed high very-preterm (29.4%), sepsis (10.6%) and hyperbilirubinaemia (17.9%) rates together with the lowest SGA of any group (1.7%). The placental-abruption group carried the heaviest burden on nearly every endpoint, with the highest rates of the composite outcome (53.2%), very preterm birth (41.6%), RDS (38.1%) and VLBW (30.0%). BPD, NEC and ROP were infrequent in absolute terms (1.5%, 1.3% and 2.2%), reflecting the relatively short length of stay and the limited proportion of extremely low gestations.

Table 2
Distribution of neonatal outcomes by maternal pregnancy complication group

Neonatal outcome	None of the above (n = 8,232)	Hypertensive disorders (n = 1,929)	PPROM (n = 3,591)	Placental abruption (n = 938)	P value
Severe neonatal morbidity (composite)	3,183 (38.7)	774 (40.1)	1,415 (39.4)	499 (53.2)	< 0.001
Very preterm birth (< 32 weeks)	1,772 (21.5)	444 (23.0)	1,057 (29.4)	390 (41.6)	< 0.001
Very low birth weight (< 1500 g)	1,450 (17.6)	569 (29.5)	739 (20.6)	281 (30.0)	< 0.001
Respiratory distress syndrome	2,223 (27.0)	505 (26.2)	861 (24.0)	357 (38.1)	< 0.001
Intraventricular/intracranial haemorrhage	999 (12.1)	296 (15.3)	512 (14.3)	158 (16.8)	< 0.001
Neonatal sepsis	621 (7.5)	127 (6.6)	381 (10.6)	106 (11.3)	< 0.001
Neonatal hypoglycaemia	965 (11.7)	302 (15.7)	230 (6.4)	69 (7.4)	< 0.001
Neonatal hyperbilirubinaemia	1,084 (13.2)	214 (11.1)	644 (17.9)	106 (11.3)	< 0.001
Small for gestational age	556 (6.8)	319 (16.5)	62 (1.7)	35 (3.7)	< 0.001

Data are presented as n (%). P values were derived from the χ^2 test. Severe neonatal morbidity (composite) was defined as the presence of at least one of respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular/intracranial haemorrhage, periventricular leukomalacia, necrotising enterocolitis, neonatal sepsis or retinopathy of prematurity. PPROM, preterm prelabour rupture of membranes; SGA, small for gestational age.

Multivariable logistic regression

Table 3 reports the full set of odds ratios across the three incremental models. Three key findings emerge.

Table 3
Association between maternal pregnancy complications and neonatal outcomes

Outcome and exposure group	Crude OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Severe neonatal morbidity (composite)			
Hypertensive disorders	1.06 (0.95–1.18)	1.04 (0.93–1.16)	0.90 (0.79–1.02)
PPROM	1.03 (0.94–1.12)	1.04 (0.94–1.14)	0.83 (0.75–0.92)***
Placental abruption	1.80 (1.56–2.08)***	1.69 (1.46–1.96)***	0.97 (0.82–1.14)
Very preterm birth (< 32 weeks)			
Hypertensive disorders	1.09 (0.96–1.25)	1.14 (1.00–1.31)	0.25 (0.20–0.31)***
PPROM	1.52 (1.37–1.68)***	1.32 (1.18–1.48)***	1.47 (1.25–1.73)***
Placental abruption	2.60 (2.23–3.02)***	2.42 (2.06–2.83)***	1.61 (1.26–2.04)***
Very low birth weight (< 1500 g)			
Hypertensive disorders	1.97 (1.74–2.22)***	1.97 (1.75–2.23)***	3.37 (2.81–4.04)***
PPROM	1.22 (1.09–1.36)***	1.13 (1.00–1.27)	0.71 (0.61–0.83)***
Placental abruption	2.01 (1.71–2.35)***	1.95 (1.65–2.29)***	0.70 (0.56–0.89)**
Respiratory distress syndrome			
Hypertensive disorders	0.96 (0.85–1.08)	0.91 (0.80–1.03)	0.79 (0.68–0.91)**
PPROM	0.85 (0.77–0.94)**	0.91 (0.82–1.01)	0.64 (0.56–0.72)***

*Values are odds ratios (95% confidence intervals) derived from multivariable logistic regression with cluster-robust standard errors to account for multiple gestations from the same mother. The reference group comprised infants of mothers without any of the three complications. Model 1, unadjusted (crude OR); Model 2, adjusted for maternal age, maternal education, parity, gravidity, multiple gestation, mode of delivery, infant sex and birth year; Model 3, Model 2 additionally adjusted for gestational age and birth weight. For outcomes defined by gestational age (very preterm birth) or birth weight (very low birth weight), the corresponding variable was not included in Model 3 to avoid over-adjustment. *P < 0.05, **P < 0.01, ***P < 0.001. PPROM, preterm prelabour rupture of membranes; OR, odds ratio; CI, confidence interval; SGA, small for gestational age.*

Outcome and exposure group	Crude OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Placental abruption	1.66 (1.43–1.92)***	1.61 (1.38–1.88)***	0.81 (0.68–0.97)*
Intraventricular/intracranial haemorrhage			
Hypertensive disorders	1.32 (1.14–1.53)***	1.29 (1.11–1.50)***	1.18 (1.01–1.38)*
PPROM	1.21 (1.08–1.37)**	1.16 (1.02–1.31)*	1.11 (0.98–1.26)
Placental abruption	1.46 (1.21–1.77)***	1.28 (1.06–1.56)*	1.08 (0.89–1.32)
Neonatal sepsis			
Hypertensive disorders	0.87 (0.71–1.06)	0.93 (0.75–1.14)	0.80 (0.65–1.00)*
PPROM	1.45 (1.26–1.67)***	1.20 (1.02–1.40)*	1.14 (0.98–1.32)
Placental abruption	1.57 (1.26–1.97)***	1.32 (1.05–1.66)*	0.96 (0.76–1.22)
Neonatal hypoglycaemia			
Hypertensive disorders	1.40 (1.21–1.62)***	1.28 (1.10–1.49)**	1.32 (1.13–1.55)***
PPROM	0.52 (0.44–0.60)***	0.66 (0.56–0.77)***	0.70 (0.59–0.82)***
Placental abruption	0.60 (0.46–0.78)***	0.70 (0.54–0.92)**	0.80 (0.61–1.04)
Neonatal hyperbilirubinaemia			
Hypertensive disorders	0.82 (0.69–0.97)*	0.86 (0.72–1.02)	1.24 (1.02–1.50)*
PPROM	1.44 (1.29–1.61)***	1.10 (0.98–1.23)	1.36 (1.18–1.56)***

*Values are odds ratios (95% confidence intervals) derived from multivariable logistic regression with cluster-robust standard errors to account for multiple gestations from the same mother. The reference group comprised infants of mothers without any of the three complications. Model 1, unadjusted (crude OR); Model 2, adjusted for maternal age, maternal education, parity, gravidity, multiple gestation, mode of delivery, infant sex and birth year; Model 3, Model 2 additionally adjusted for gestational age and birth weight. For outcomes defined by gestational age (very preterm birth) or birth weight (very low birth weight), the corresponding variable was not included in Model 3 to avoid over-adjustment. *P < 0.05, **P < 0.01, ***P < 0.001. PPROM, preterm prelabour rupture of membranes; OR, odds ratio; CI, confidence interval; SGA, small for gestational age.*

Outcome and exposure group	Crude OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Placental abruption	0.83 (0.67–1.03)	0.62 (0.50–0.77)***	1.41 (1.09–1.81)**
Small for gestational age			
Hypertensive disorders	2.73 (2.35–3.17)***	2.38 (2.03–2.78)***	1.15 (0.92–1.44)
PPROM	0.24 (0.18–0.32)***	0.31 (0.23–0.41)***	0.68 (0.48–0.97)*
Placental abruption	0.54 (0.38–0.77)***	0.60 (0.42–0.86)**	0.86 (0.54–1.35)

*Values are odds ratios (95% confidence intervals) derived from multivariable logistic regression with cluster-robust standard errors to account for multiple gestations from the same mother. The reference group comprised infants of mothers without any of the three complications. Model 1, unadjusted (crude OR); Model 2, adjusted for maternal age, maternal education, parity, gravidity, multiple gestation, mode of delivery, infant sex and birth year; Model 3, Model 2 additionally adjusted for gestational age and birth weight. For outcomes defined by gestational age (very preterm birth) or birth weight (very low birth weight), the corresponding variable was not included in Model 3 to avoid over-adjustment. *P < 0.05, **P < 0.01, ***P < 0.001. PPROM, preterm prelabour rupture of membranes; OR, odds ratio; CI, confidence interval; SGA, small for gestational age.*

(1) The effect of placental abruption is largely mediated by gestation and birth weight. Abruption raised the risk of the composite outcome by 69% (Model 2 OR 1.69, 95% CI 1.46–1.96), an association that was no longer statistically significant once gestational age and birth weight were added (Model 3 OR 0.97, 95% CI 0.82–1.14). The same pattern held for RDS (1.61 → 0.81) and VLBW (1.95 → 0.70), indicating that the neonatal impact of abruption operates almost entirely through earlier delivery and lower birth weight.

(2) HDP defines an independent growth-restriction phenotype. HDP nearly doubled the risk of VLBW (Model 2 OR 1.97, 95% CI 1.75–2.23), raised the risk of SGA about 1.4-fold (OR 2.38, 95% CI 2.03–2.78) and that of hypoglycaemia by 28% (OR 1.28, 95% CI 1.10–1.49); yet at identical gestational age and birth weight, HDP was associated with a lower risk of RDS (Model 3 OR 0.79, 95% CI 0.68–0.91), reproducing the classic observation that pre-eclampsia accelerates fetal lung maturation.

(3) PPROM defines an independent infection–preterm-birth phenotype. PPROM independently increased the risk of very preterm birth (Model 2 OR 1.32, 95% CI 1.18–1.48) and sepsis (OR 1.20, 95% CI 1.02–1.40), while markedly lowering the risk of SGA (OR 0.31, 95% CI 0.23–0.41) and hypoglycaemia (OR 0.66); at the same gestational age and birth weight its infants had lower RDS risk (Model 3 OR 0.64, 95% CI 0.56–0.72), consistent with the hypothesis that intrauterine inflammation promotes pulmonary maturation.

Dose–response relationship and interaction

The restricted cubic spline showed a monotonic rise in the predicted probability of severe neonatal morbidity with decreasing gestational age: approximately 0.95 at 24 weeks, 0.55 at 28 weeks, 0.28 at 32 weeks and below 0.10 after 36 weeks (Fig. 4). At a given gestational age the four group-specific curves nearly overlapped, diverging only mildly below 28 and above 35 weeks. The interaction between gestational age and maternal complication was significant overall (Wald $\chi^2 = 27.8$, df = 9, P = 0.001), indicating modest differences in the gestational age–risk slope across pathways, although these differences were small relative to the effect of gestational age itself.

Sensitivity analyses

Table 4 summarises the sensitivity analyses. In the singleton-only cohort, the effect of placental abruption on the composite outcome persisted (OR 1.57, 95% CI 1.34–1.84), the SGA effect of HDP was amplified (OR 3.28, 95% CI 2.69–4.01), and the protective association between PPROM and SGA was maintained (OR 0.23). Excluding periviable infants (below 28 weeks) left the abruption effect intact (OR 1.67, 95% CI 1.44–1.94), and stratifying by birth era preserved both the direction and the magnitude of all estimates. Taken together, the sensitivity analyses support the robustness of the main findings.

Table 4
Sensitivity analyses of the association between maternal pregnancy complications and neonatal outcomes

Analysis	n	Events, n	HDP OR (95% CI)	PPROM OR (95% CI)	Placental abruption OR (95% CI)
Main analysis — Severe composite	14,690	5,871	1.04 (0.93–1.16)	1.04 (0.94–1.14)	1.69 (1.46–1.96)
S1 Singleton-only — Severe composite	9,015	3,819	1.09 (0.96–1.25)	0.90 (0.81–1.01)	1.57 (1.34–1.84)
S1 Singleton-only — Very preterm birth	9,015	2,449	1.53 (1.32–1.77)	1.29 (1.14–1.46)	2.43 (2.06–2.86)
S1 Singleton-only — SGA	9,015	566	3.28 (2.69–4.01)	0.23 (0.15–0.34)	0.61 (0.41–0.92)
S2 GA 28–36 weeks — Severe composite	14,377	5,630	1.05 (0.94–1.17)	1.05 (0.95–1.15)	1.67 (1.44–1.94)
S3 Complete cases — Severe composite	14,636	5,849	1.04 (0.93–1.16)	1.04 (0.95–1.14)	1.69 (1.46–1.96)
S4 Birth era 2013–2017 — Severe composite	6,633	2,364	0.97 (0.82–1.15)	1.01 (0.88–1.16)	1.78 (1.43–2.23)
S4 Birth era 2018–2022 — Severe composite	8,003	3,485	1.08 (0.94–1.25)	1.05 (0.93–1.20)	1.66 (1.37–2.01)

All models were adjusted as for Model 2 (maternal age, maternal education, parity, gravidity, multiple gestation, mode of delivery, infant sex and birth year) with cluster-robust standard errors. The reference group in all models was no major maternal pregnancy complication. S1, singleton pregnancies only; S2, restricted to infants born at 28–36 weeks of gestation; S3, complete cases with available maternal education; S4, stratified by birth era. HDP, hypertensive disorders of pregnancy; PPROM, preterm prelabour rupture of membranes; OR, odds ratio; CI, confidence interval.

Discussion

Principal findings

In a large single-centre cohort of 14,690 hospitalised preterm infants we quantified, in parallel and within one cohort, the neonatal phenotypes associated with three canonical maternal pathways to preterm delivery. The central finding is that maternal complications shape which morbidity phenotype a preterm infant develops, not merely whether the infant becomes ill. Placental abruption corresponds to a

gestation-and-weight-mediated injury; HDP to placental-insufficiency growth restriction; PPROM to an inflammation–infection phenotype. The three differ not only in overall morbidity burden but also in the direction in which their effects change once gestational age and birth weight are taken into account — the key message distinguishing this work from previous single-outcome studies.

Comparison with previous studies

Placental abruption. Using US birth records, abruption has been shown to be associated with an approximately 3-fold increase in preterm delivery and a 2-fold increase in fetal growth restriction,[15] while about 55% of the excess perinatal mortality is attributable to early delivery.[8] Subsequent cohort work confirmed a higher overall morbidity burden among abruption-affected infants that attenuates substantially after adjustment for gestational age and birth weight.[9] Our findings align closely: the abruption effect on severe neonatal morbidity (Model 2 OR 1.69, 95% CI 1.46–1.96) essentially disappeared after adjustment for gestational age and birth weight (Model 3 OR 0.97, 95% CI 0.82–1.14), indicating that abruption acts mainly through earlier delivery and lower birth weight rather than through an independent inflammatory injury. That this mediation pattern reproduces for a morbidity — not mortality — endpoint strengthens the “abruption as a delivery-mediated injury” framework.

Hypertensive disorders of pregnancy. The causal link between pre-eclampsia, impaired placental perfusion and fetal growth restriction is well established,[10, 11] and early- versus late-onset pre-eclampsia differ in risk factors and outcomes and should be regarded as distinct clinical entities.[16] Our SGA estimate (Model 2 OR 2.38, 95% CI 2.03–2.78) falls within the 2–3-fold range reported previously. Evidence on the “pre-eclampsia accelerates lung maturation” hypothesis is mixed: some studies report higher RDS rates and greater respiratory-support needs among infants of mothers with severe pre-eclampsia, others report protection.[12, 13] Our incremental design offers a sharper view — at identical gestational age and birth weight, HDP was associated with lower RDS risk (Model 3 OR 0.79, 95% CI 0.68–0.91), suggesting a genuine protective effect that is masked by the earlier gestation and lower birth weight characteristic of this group. This apparent cancellation is precisely why stratified adjustment such as Model 3 is needed to recover the underlying pathophysiological direction.

PPROM. Intrauterine infection and inflammation are central mechanisms of spontaneous preterm birth.[5, 7] The independent associations we observed between PPROM and sepsis (OR 1.20, 95% CI 1.02–1.40) and very preterm birth (OR 1.32, 95% CI 1.18–1.48) are consistent with this, and the antenatal antibiotic trial ORACLE I — in which antibiotic treatment for PPROM reduced neonatal sepsis and respiratory morbidity — provides interventional support for the role of infection in this phenotype.[18] The markedly lower SGA risk in the PPROM group (OR 0.31, 95% CI 0.23–0.41) requires careful interpretation: while some prospective studies suggest that fetal growth restriction may be more common after PPROM,[17] our PPROM definition was based on maternal diagnosis text and may have included cases whose primary indication was membrane rupture while excluding those with coexisting growth restriction who were preferentially delivered by induction — an indication-related selection bias. This “protective” association should therefore be treated as an observation requiring further verification rather than a definitive causal effect.

Pathophysiological interpretation

The phenotype differences can be unified within two intrauterine pathways. The vascular–placental pathway (HDP, placental abruption) shares impaired placental perfusion as its common starting point. HDP acts mainly through shallow placentation and an anti-angiogenic state (raised circulating sFlt-1 with reduced free PlGF/VEGF), producing chronic placental insufficiency manifest as growth restriction and neonatal hypoglycaemia (limited glycogen stores),[19, 20] while chronic fetal stress raises cortisol exposure and relatively accelerates lung maturation. Placental abruption, by contrast, is an acute placental separation in which fetal haemorrhage and hypoxia force emergency delivery; it therefore presents as a wholesale shift toward earlier gestation and lower birth weight rather than as a disease-specific injury.[8, 15] The infection–inflammation pathway (PPROM) starts from chorioamnionitis and cytokine activation: prostaglandin-mediated uterine activation drives very preterm birth and neonatal sepsis,[5, 7] while the same inflammatory exposure may promote surfactant maturation,[21, 22] yielding lower RDS risk at a given gestation. This “inflammation-induced maturation” mechanism also explains why intrauterine inflammatory exposure that lowers RDS may nonetheless increase susceptibility to later bronchopulmonary dysplasia.[22]

Clinical and public health implications

Our findings argue for antenatal phenotype stratification in postnatal management. For placental abruption the emphasis is antenatal: prolonging gestation as far as safely possible and completing antenatal corticosteroid courses, rather than expecting postnatal disease-specific therapy.[14] For HDP, blood glucose should be screened routinely in the first hours of life and intrauterine growth formally assessed, with vigilance for hypoglycaemia and feeding intolerance;[24] where neurodevelopmental risk is present, the neuroprotective benefit of antenatal magnesium sulfate is supported by high-quality evidence.[23] For PPROM, infection surveillance should be intensified (a lower threshold for blood counts, C-reactive protein and blood cultures) and antibiotics given where indicated by guidelines,[18], without over-interference in growth and nutrition. Across all groups, gestational age remains the strongest determinant of severe morbidity, so preterm classification should treat gestational age as the first axis and maternal complication as the second.

Strengths

The strengths of this study are its large sample (14,690 infants over nearly a decade), among the larger single-centre cohorts of its kind; the parallel comparison of three complications within one cohort, which avoids confounding by cross-study differences in population and care standards; the hierarchical, mutually exclusive exposure assignment, which yields clearly interpretable estimates; the use of cluster-robust standard errors clustered on maternal hospital number, which handles the intra-cluster correlation introduced by multiples and repeat admissions; and the three incremental models, which identify the gestation-and-weight mediation pathway, supported by four pre-specified sensitivity analyses.

Limitations

This study has several limitations. First, it was a single-centre retrospective design; exposures and outcomes were derived from inpatient diagnosis text, with possible coding and transcription bias, and the accuracy of ICD-based definitions varies across conditions.[25] Second, SGA was a clinical diagnosis rather than one derived from standardised growth curves, which probably underestimates its true prevalence and cannot distinguish symmetric from asymmetric growth restriction; standardised charts such as Fenton or INTERGROWTH-21st should be applied in future work.[26, 27] Third, we had no mother–infant-linked long-term follow-up (cerebral palsy, neurodevelopment) and no data on perinatal interventions (antenatal corticosteroids, magnesium sulfate, antibiotics), which precludes direct assessment of intervention effects within the mediation pathway. Fourth, multiple gestation accounted for 38.4%; although this was adjusted for and handled with cluster-robust standard errors, residual confounding remains possible. Fifth, selection bias in a hospital-based cohort may over-represent severe disease and limits generalisation to population-level preterm infants. Sixth, missing latency from membrane rupture to delivery and the absence of microbiological evidence of chorioamnionitis restrict finer phenotyping of PPROM. Finally, the mutually exclusive hierarchical exposure assignment precludes assessment of interaction between complications (for example, pre-eclampsia plus abruption).

Future directions

Future work should proceed along four lines: first, recompute SGA and fetal growth restriction using standardised charts (Fenton, INTERGROWTH-21st) and refine outcomes into symmetric versus asymmetric restriction;[26, 27] second, link maternal–infant follow-up to test whether the three phenotypes differentially predict neurodevelopmental outcomes at 18–24 months; third, incorporate records of antenatal interventions (timing and course of corticosteroids, magnesium sulfate, antibiotics) into formal mediation analyses that decompose gestation-and-weight-mediated from disease-specific effects;[14, 23] and fourth, undertake multicentre external validation to assess the transferability of the three-phenotype framework across care settings.

Conclusions

In a large hospital-based preterm cohort spanning nearly a decade, three maternal pregnancy complications mapped onto three distinguishable neonatal morbidity phenotypes. Placental abruption was characterised by a broad morbidity burden mediated by earlier gestation and lower birth weight; hypertensive disorders of pregnancy by independent growth restriction and hypoglycaemia, yet lower respiratory-distress risk at the same gestation and weight; and preterm prelabour rupture of membranes by very preterm birth and sepsis with the lowest growth-restriction risk. Maternal complications shape not only whether a preterm infant becomes ill but which phenotype emerges — a framework with direct implications for antenatal decision-making and postnatal surveillance, and a rationale for stratifying preterm infants by maternal pathway in future cohort studies.

Abbreviations

BPD

bronchopulmonary dysplasia
CI
confidence interval
CRP
C-reactive protein
HDP
hypertensive disorders of pregnancy
ICD-10
International Classification of Diseases,Tenth Revision
IVF
in vitro fertilisation
NEC
necrotising enterocolitis
OR
odds ratio
PlGF
placental growth factor
PPROM
preterm prelabour rupture of membranes
PVL
periventricular leucomalacia
RDS
respiratory distress syndrome
ROP
retinopathy of prematurity
SD
standard deviation
sFlt-1
soluble fms-like tyrosine kinase 1
SGA
small for gestational age
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
VEGF
vascular endothelial growth factor
VLBW
very low birth weight.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Women's Hospital, School of Medicine, Zhejiang University (approval number IRB-20240135-R), which waived the requirement for individual informed consent because the analysis used de-identified retrospective records.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Clinical trial number:

not applicable

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Author Contribution

All authors contributed to the study conception and design, data acquisition, analysis and interpretation, and critically revised the manuscript. XZ: conceptualisation, methodology, writing — original draft, writing — review and editing. SQ: data curation, formal analysis, methodology. YC: conceptualisation, data curation, methodology, project administration, supervision, writing — original draft, writing — review and editing, visualisation. WL: conceptualisation, data curation, methodology, project administration, supervision, writing — original draft, writing — review and editing, visualisation. All authors read and approved the final manuscript.

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Availability of data and materials

The de-identified datasets generated and analysed during the current study are not publicly available because of institutional data-governance restrictions, but are available from the corresponding author on reasonable request and subject to institutional approval. The analysis code is available from the corresponding author on reasonable request.

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Figures

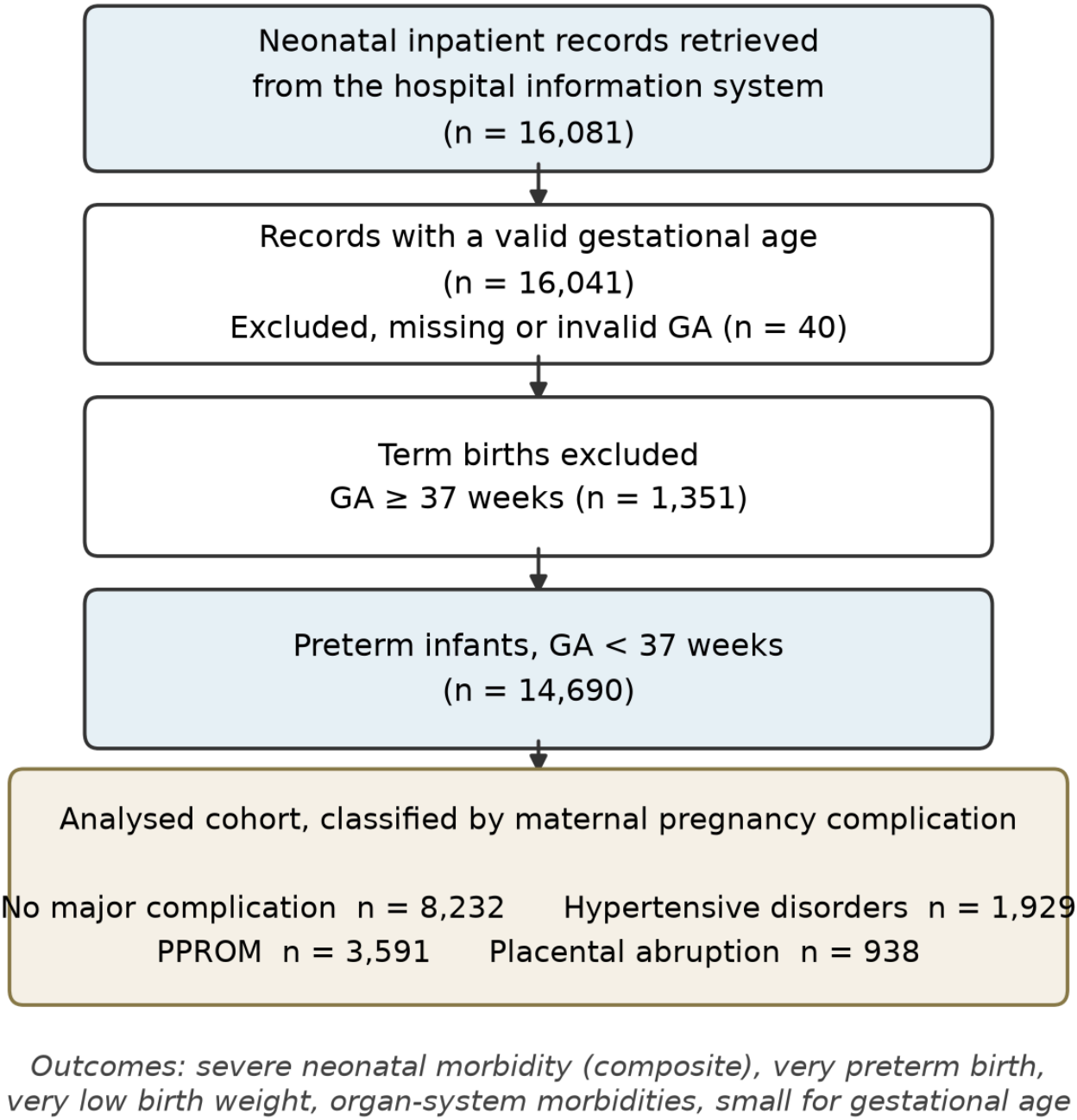


Figure 1

Study flow diagram. Of 16,081 neonatal inpatient records screened, 40 records with missing or invalid gestational age and 1,351 term infants (at or after 37 weeks) were excluded, leaving 14,690 hospitalised preterm infants (gestational age below 37 weeks). These were stratified by maternal pregnancy complication into four mutually exclusive groups: none of the above (n = 8,232), hypertensive disorders of pregnancy (n = 1,929), preterm prelabour rupture of membranes (n = 3,591) and placental abruption (n = 938).

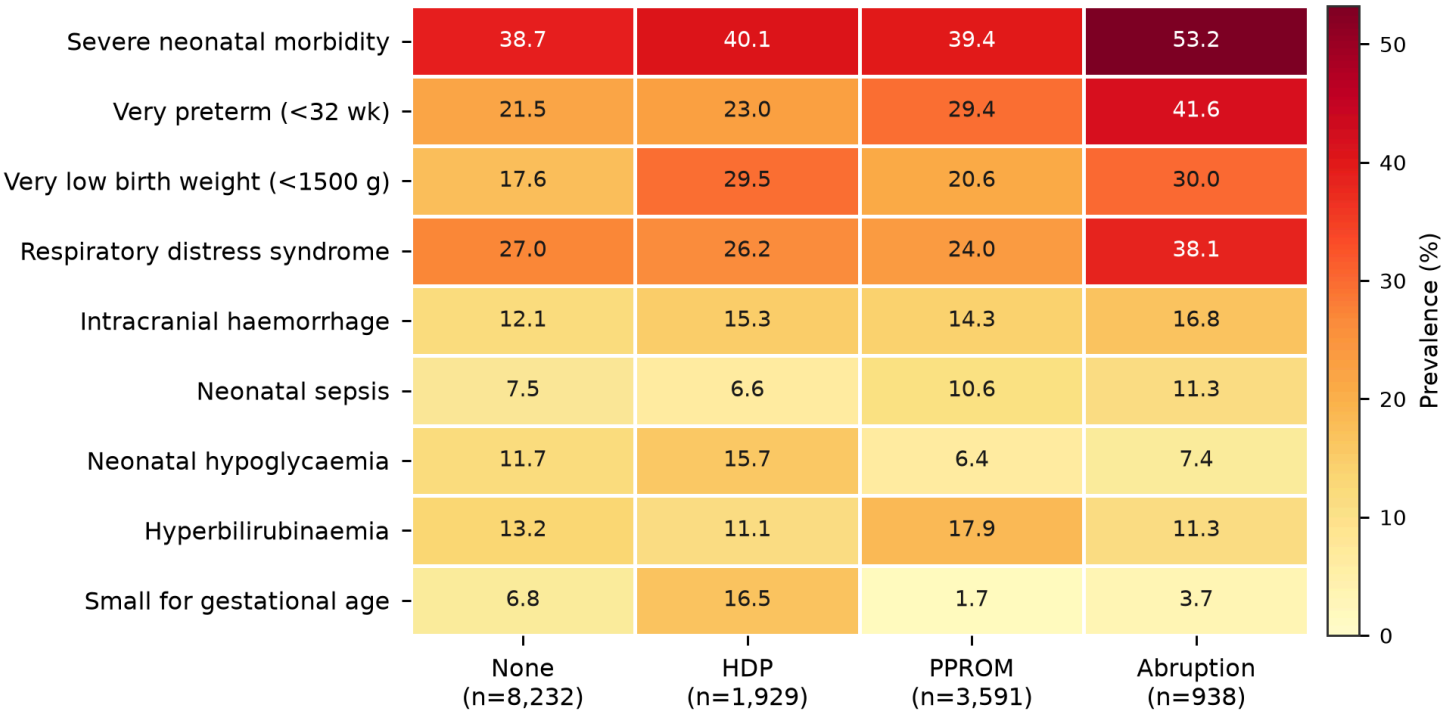


Figure 2

Prevalence of neonatal outcomes by maternal complication group. Heat map of the prevalence of neonatal outcomes by maternal pregnancy complication group. Rows represent neonatal outcomes and columns the four mutually exclusive maternal-complication groups; each cell shows the prevalence (%) and the colour scale encodes its magnitude, with darker shading indicating higher prevalence. The composite outcome comprised any of respiratory distress syndrome, bronchopulmonary dysplasia, intracranial haemorrhage/periventricular leucomalacia, necrotising enterocolitis, sepsis or retinopathy of prematurity. PPROM, preterm prelabour rupture of membranes; SGA, small for gestational age.

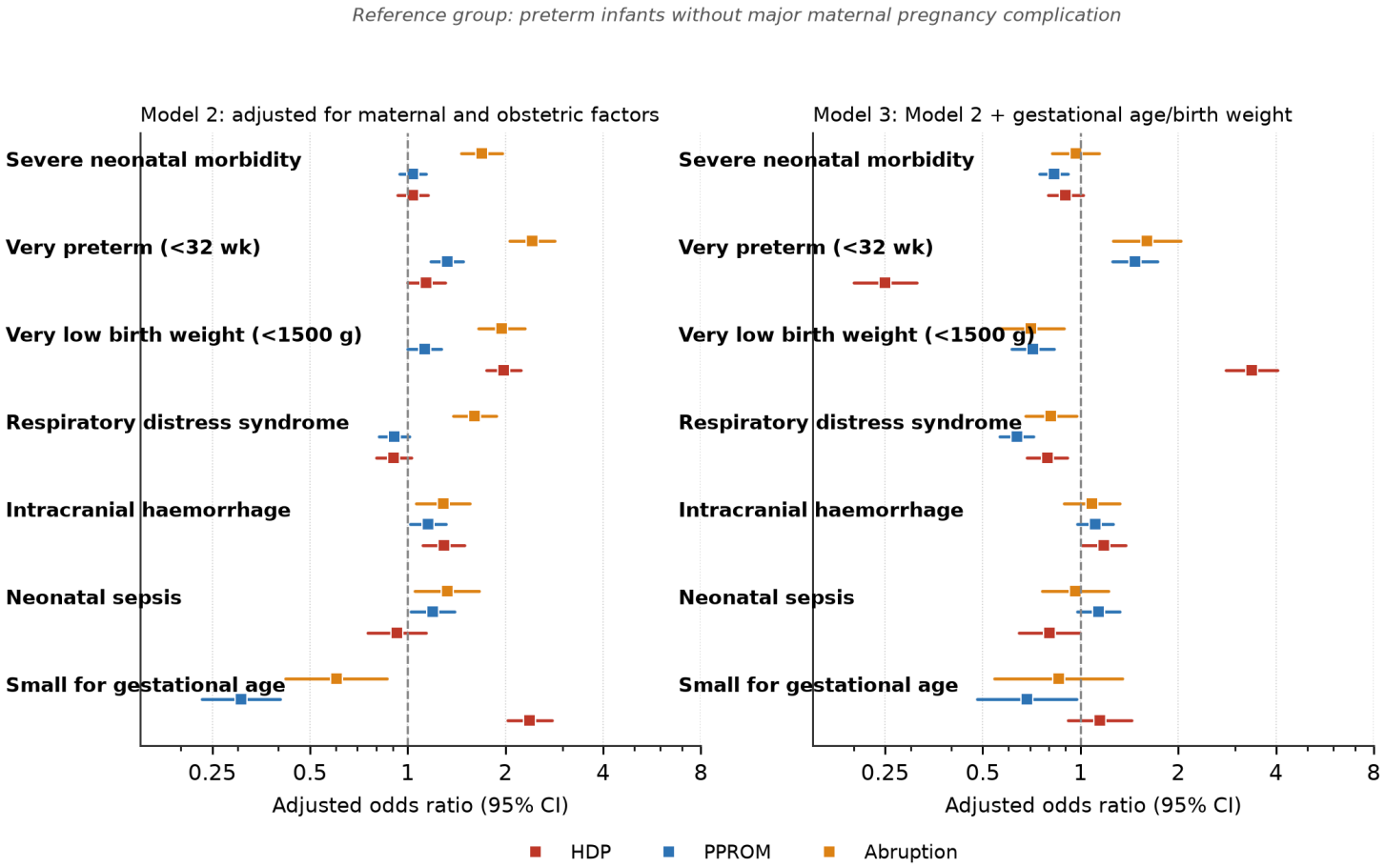


Figure 3

Forest plot of adjusted odds ratios. Forest plot of adjusted odds ratios (log scale) for the association between maternal pregnancy complications and neonatal outcomes. The left panel shows Model 2 (adjusted for maternal and obstetric factors) and the right panel Model 3 (additionally adjusted for gestational age and birth weight, with the outcome-defining variable omitted for very preterm birth and very low birth weight). Squares represent point estimates and horizontal lines 95% confidence intervals; the dashed vertical line marks the null value of 1. The reference group comprised preterm infants without any of the three maternal complications. PPROM, preterm prelabour rupture of membranes; SGA, small for gestational age.

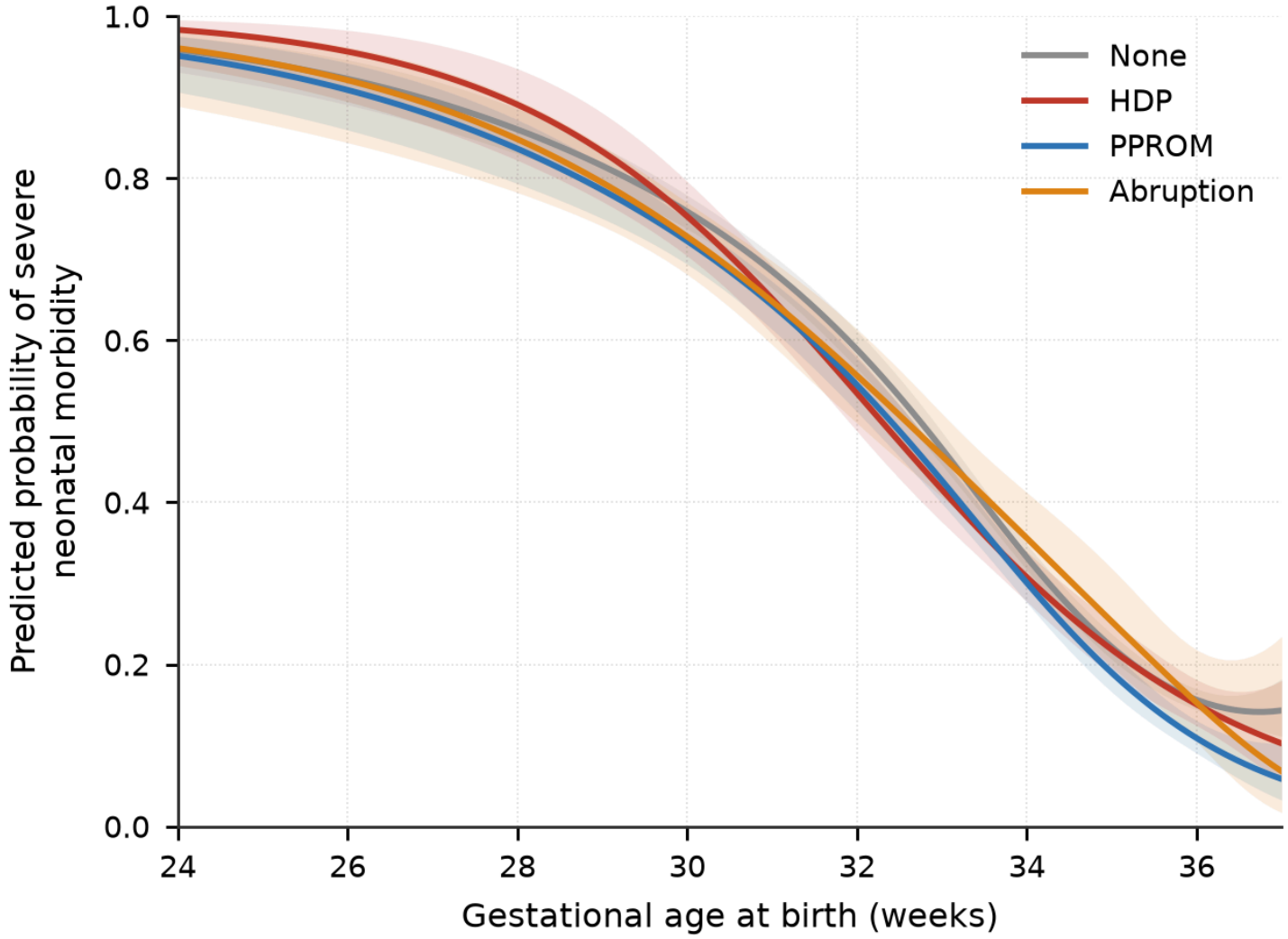


Figure 4

Predicted morbidity probability by gestational age. Predicted probability of severe neonatal morbidity as a function of gestational age, by maternal pregnancy complication group. Curves were derived from a multivariable logistic model incorporating a restricted cubic spline for gestational age (4 knots at the 5th, 35th, 65th and 95th percentiles) interacting with exposure group and adjusted for maternal and obstetric covariates; shaded bands represent 95% confidence intervals. PPROM, preterm prelabour rupture of membranes.