Impact of hypertensive disorders of pregnancy on respiratory outcomes in extremely and very preterm infants: A population-based study in Japan

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Shortened running title: HDP and offspring respiratory outcomes

Abstract

Objectives: We aimed to evaluate the impact of hypertensive disorders of pregnancy (HDP) on short- and medium-term respiratory outcomes in extremely and very preterm infants using the Neonatal Research Network of Japan database.

Study design: This was a population-based retrospective study of preterm infants weighing ≤ 1,500 g born between 22 and 31 weeks of gestation between 2003 and 2017. After 1:1 stratification matching by four factors (maternal age, gestational age, parity, and year of delivery), a total of 5,137 infants in each group (HDP and non-HDP groups) were selected.

Main outcome measures: The association between HDP and various respiratory outcomes was evaluated using univariate and multivariate logistic regression analyses.

Results: In the multivariate analyses, HDP was associated with higher odds for respiratory distress syndrome (RDS) (odds ratio 1.83, 95% confidence interval [1.65–2.03]), but reduced odds of persistent pulmonary hypertension of the newborn (PPHN) (0.34 [0.26–0.46]) and inhaled nitric oxide use (0.43 [0.33–0.55]). Although HDP was associated with an increased risk of chronic lung disease (CLD) in the univariate analysis, this association was not significant after adjustment for covariates (0.94 [0.83–1.07]). No significant association was found between HDP and home oxygen therapy (HOT) and medium-term oxygen use.

Conclusion: The impact of maternal HDP largely differed depending on respiratory disorders and respiratory support. HDP was associated with higher odds of RDS but reduced odds of PPHN. The risks for CLD, HOT, and medium-term respiratory outcomes in the HDP group were comparable to those in the non-HDP group.

Keywords: hypertensive disorders of pregnancy, preterm infant, respiratory outcomes,

Abbreviation

ACS, antenatal corticosteroid; CAM, chorioamnionitis; CLD, chronic lung disease; HDP, hypertensive disorders of pregnancy; HFOV, high-frequency oscillatory ventilation; HOT, home oxygen therapy; inhaled nitric oxide, iNO; NRNJ, Neonatal Research Network of

Japan; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; SGA, small for gestational age; VEGF, vascular endothelial growth factor

Introduction

Hypertensive disorders of pregnancy (HDP), including preeclampsia and gestational hypertension, is one of the most common pregnancy complications, affecting 5%–10% of all pregnancies worldwide [1]. Although the precise pathophysiology of HDP, especially preeclampsia, has not been fully elucidated, abnormal placental implantation and impaired uterine spiral artery remodeling lead to placental ischemia and imbalanced angiogenic profiles, promoting a cascade of endothelial damage and maternal multi-organ dysfunction [1, 2]. HDP contributes to various adverse consequences in both affected mothers and their infants for a long period of time [3, 4]. At present, due to the absence of curative treatment except for delivery, iatrogenic preterm delivery cannot be avoided in cases of severe early onset HDP due to risks to both maternal and fetal health. Therefore, both the iatrogenic preterm birth and intrauterine adverse environments (e.g., hypoxia, adverse inflammation, and excessive oxidative stress) in cases of early onset HDP are potentially associated with increased risks for neonatal morbidities and mortality, as well as for various long-term disabilities [3, 4].

To date, there is no consensus regarding the impact of HDP on respiratory outcomes in preterm infants, especially in extremely and very preterm infants. Comparatively speaking, there are more reports that demonstrated an increased risk of chronic lung disease (CLD)

(odds ratios [ORs] 1.16–1.64) in very preterm infants born to mothers with HDP [5-7]. However, several reports demonstrated no causal association between HDP and CLD [8, 9]. In addition, little evidence is available regarding the causal link between HDP and other respiratory disorders (e.g., respiratory distress syndrome [RDS] and persistent pulmonary hypertension of the newborn [PPHN]), the use of respiratory support (e.g., surfactant use and inhaled nitric oxide [iNO] use), and medium- or long-term respiratory outcomes.

Small for gestational age (SGA) is a well-known contributing factor for CLD (ORs 2.7–4.4) [10, 11]. Approximately 30%–50% of early onset HDP is accompanied by fetal growth restriction, which is attributed to placental insufficiency in the early stages of pregnancy. Therefore, a higher prevalence of CLD is expected in cases of HDP; however, whether this is solely due to increased prevalence of SGA or due to HDP itself, regardless of SGA, remains uncertain. In addition, a recent meta-analysis by Razak *et al.* demonstrated that the increased risk of CLD in preterm infants born to mothers with HDP was limited exclusively among infants born at < 28 gestational weeks [12].

Thus, we sought to investigate the impact of HDP on short- and medium-term respiratory outcomes in extremely and very preterm infants using a population-based neonatal database in Japan. Additionally, we performed two subgroup analyses to examine

whether the link between HDP and respiratory outcomes depends on the presence or absence of SGA and if it depends on gestational age. This study may allow neonatologists and obstetricians to better understand the mechanisms of respiratory disorders and improve the early identification of at-risk preterm infants, enabling timely diagnosis and prevention of respiratory disorders.

Materials and methods

Study population and data source

This retrospective population-based study included a total of 50,599 infants born alive between 22 and 31 gestational weeks from the Neonatal Research Network of Japan database (NRNJ). The NRNJ is a nationwide prospective registry of very low birth weight infants (≤ 1,500 g) that was created for the promotion of neonatal research; it consists of approximately 200 facilities throughout Japan, consisting of mainly level II/III neonatal intensive care units (NICUs). Infants born to multiple pregnancies, those with major congenital abnormalities, those transferred from other facilities, those with in-hospital mortality, and those with incomplete maternal or neonatal medical records were excluded from this study (Figure 1). The NRNJ registry was approved by the institutional ethics committee at each participating facility, and informed consent was obtained from all parents of infants at each facility. This study was approved by the Institutional Ethics Committee at Nagoya University Hospital (approval

number: 2018–0026), and the data were approved by the NRNJ Executive Committee.

Definition and diagnosis

HDP was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg occurring after 20 weeks of gestation [13]. SGA infants were defined as having a birth weight below the 10^{th} percentile for gestational age based on the sex-specific Japanese neonatal anthropometric chart in 2000 [14]. RDS was diagnosed by neonatologists based on a combination of clinical manifestations (e.g., signs of respiratory distress [tachypnea, nasal flaring, expiratory grunting, and cyanosis] and increased oxygen requirement), microbubble test results, and chest radiography imaging [15]. CLD was defined when oxygen was needed at 36 weeks' postmenstrual age [16]. The diagnosis of PPHN was confirmed by echocardiography after differentiating cyanotic congenital heart disease from PPHN [17]. High-frequency oscillatory ventilation (HFOV) was used to reduce the stress caused by trauma and barotrauma. Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that is used for a short period of time to decrease pulmonary hypertension in neonates with hypoxic respiratory failure associated with PPHN. The definitions and diagnosis of other outcomes, including intraventricular hemorrhage grade III/IV, periventricular leukomalacia, sepsis, necrotizing enterocolitis, patent ductus arteriosus banding, and late-onset circulatory collapse, have been previously described [18].

The outcome measurements were as follows: (short-term) oxygen use at birth, intubation at birth, surfactant use, RDS, artificial ventilation use, HFOV use, iNO use, PPHN, CLD, and home oxygen therapy (HOT) at NICU discharge; and (medium-term) oxygen use at 1.5 and 3 years of age.

Stratification matching and statistical analyses

The detailed method of stratification matching has been described previously [19]. A total of 24,373 eligible infants were randomly assigned to two groups (HDP and non-HDP groups) at a ratio of 1:1 after stratification by four factors: gestational weeks at delivery (10 categories: 22, 23, 24, 25, 26, 27, 28, 29, 30, and 31 weeks), maternal age at delivery (7 categories: –19, 20–24, 25–29, 30–34, 35–39, 40–44, and 45–), parity (two categories: primipara and multipara), and years of delivery (two categories: 2003–2010 and 2011–2017) (Figure 1). A total of 5,137 infants in each group were selected after 1:1 stratification matching. Associations between HDP and short- and medium-term respiratory outcomes were evaluated using univariate and multivariate logistic regression analyses. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were evaluated after adjustment for 11 covariates including maternal age, gestational age, parity, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis (CAM), antenatal corticosteroid (ACS) treatment, HDP, year of

delivery, infant sex, and birth weight. The variance inflation factor, which is used to calculate the degree of multicollinearity, was less than three (data not shown). We then performed two subgroup analyses to evaluate whether our results were consistent within the different subgroups of infants (subgroup analysis #1: SGA and non-SGA, subgroup analysis #2: < 28 gestational age and ≥ 28 gestational age). In the subgroup analyses, adjusted ORs for respiratory outcomes were evaluated after adjustment for the same 11 covariates. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, 50,599 infants were born alive at the participating facilities and were registered in the NRNJ database. A total of 26,226 infants met the exclusion criteria and were excluded from this study. Clinical data of the remaining 24,373 eligible infants (HDP: n = 5,258, non-HDP: n = 19,115) were obtained, and baseline characteristics are shown in Supplementary Table 1. After 1:1 stratification matching by four factors, a total of 5,137 infants in each group (HDP and non-HDP groups) were selected. As shown in Table 1, women in the HDP group were more likely to deliver by cesarean section and less likely to be complicated with histological CAM and to receive ACS treatment. Infants in the HDP group were more likely to be female, have lower birth weights, and were of SGAs compared to those in the non-HDP

group. Table 2 shows the short- and medium-term respiratory outcomes and other major neonatal outcomes between the two groups. Table 3 shows the crude and adjusted ORs for each respiratory outcome in the univariate and multivariate logistic regression analyses. Although HDP was associated with an increased risk of CLD in the univariate analysis, this association was not significant after adjustment for covariates. In the multivariate analyses, HDP increased the risks of surfactant use, RDS, and artificial ventilator use; on the other hand, HDP decreased the risks for HFOV use, iNO use, and PPHN. We found that HDP was not associated with HOT or medium-term oxygen use.

The first subgroup analysis was performed to evaluate whether the results were consistent with those of infants with and without SGA. We found that the HDP had a similar impact on respiratory manifestations between infants with and without SGA (Table 4). The second subgroup analysis was performed to evaluate whether the results were consistent with infants born at 22–27 and 28–31 weeks of gestation. Although adjusted ORs of surfactant use and RDS in infants younger than 28 weeks of gestation were higher than those older than 28 weeks of gestation, we found that the crude and adjusted ORs for each outcome were similar between the two groups (Table 5).

Discussion

In this study, we evaluated the impact of maternal HDP on respiratory manifestations in extremely and very preterm infants using a population-based neonatal database in Japan. The main finding of this study is that the effects of maternal HDP largely differed depending on respiratory disorders and respiratory support. We also demonstrated that the results were consistent within the different subgroups of infants (#1 with and without SGA, #2 born at 22–27 and 28–31 gestational weeks). Our study is unique in that we focused on various short- and medium-term respiratory outcomes and respiratory support in detail, enabling a better understanding of the pathophysiology of neonatal respiratory disorders attributed to maternal HDP.

To date, conflicting results exist regarding the causal link between maternal HDP and offspring risk for CLD. The pathophysiology of CLD is multifactorial and is associated with various antenatal factors (e.g., gestational age, fetal growth restriction, antenatal corticosteroid treatment, impaired angiogenesis, and inflammation) and postnatal factors (e.g., mechanical ventilation, oxygen toxicity, sepsis, and patent ductus arteriosus) [16, 20]. These factors are intricately involved in the disruption of lung development and injury of vulnerable premature lungs. It is conceivable that maternal angiogenic imbalance impairs vasculogenesis and alveolarization in fetal lungs; therefore, maternal HDP is expected to predispose infants to CLD due to abnormal angiogenesis, which is one of the leading pathophysiologies in the

development of HDP [2]. In fact, several previous studies demonstrated that maternal HDP increased CLD risk in very preterm infants (adjusted ORs 1.64 [1.12–2.40], 1.47 [1.03–2.12], and 1.16 [1.05–1.27]) [5-7]. In this study, a higher prevalence of CLD was observed in the HDP group, as in previous studies; however, no significant association was found after adjustment for several covariates. This is consistent with the two subgroup analyses and is in agreement with previous studies that demonstrated no significant relationships (adjusted ORs 1.14 [0.71–1.81] and 1.10 [0.85–1.44]) [8, 9]. Although the underlying mechanism behind the lack of association between HDP and CLD is unclear, the impact of intrauterine impaired angiogenesis on offspring CLD might be limited compared with other risk factors. Another possibility is that there may have been more high-risk infants for CLD in the non-HDP group (e.g., infants exposed to oligohydramnios in utero, and spontaneous preterm infants with fetal inflammatory response syndrome without histological CAM).

Possible explanations for the conflicting data on the association between HDP and CLD based on the literature are as follows: (1) the association may differ depending on gestational age at birth. According to a previous meta-analysis, the causal association between HDP and CLD was observed exclusively in preterm infants born at ≤ 28 weeks' gestation, and the authors suggested that this may be explained by the relatively low prevalence of CLD in infants born at higher gestational ages [12]. However, our subgroup analysis demonstrated that

247 the adjusted ORs for CLD were similar between infants born at < 28 weeks' gestation and ≥
248 28 weeks' gestation. (2) Conflicting results can be accounted for in part by the inconsistency
249 of the covariates incorporated into the multivariate analyses. In several reports, postnatal
250 factors (e.g., duration of ventilation, RDS, sepsis, and patent ductus arteriosus) were included
251 as covariates in the multivariate models, despite the fact that these factors could be involved in
252 the causal pathway [5, 6, 21]. In several reports, birth weight or SGA, which are major
253 contributing factors for respiratory outcomes, were not included in the models, and multivariate
254 analyses were not conducted [22, 23]. (3) The issues of small sample size (< 300) and different
255 outcome measures regarding CLD (e.g., CLD or severe CLD [need for ≥ 30% oxygen]) may
256 affect the results.
257
258 The relationship between HDP and RDS is controversial because of contradictory
259 findings. We showed that maternal HDP significantly increased the risk of RDS, especially in
260 extremely preterm infants. This is backed by data of increased adjusted OR of surfactant use
261 in the HDP group; in addition, this is in agreement with several reports (adjusted ORs 2.44
262 [1.22–4.90], 2.40 [1.76–3.29], and 1.5 [1.1–2.2]) [5, 22, 24]. On the other hand, TA Yen *et al*.
263 and YH Wen *et a*l. demonstrated no association (adjusted ORs 1.07 [0.87–1.32] and 1.12
264 [0.98–1.29]) [21, 25], and Langenveld J *et al*. demonstrated that HDP reduced the risk for RDS
265 (adjusted OR 0.81 [0.64–1.00]) in infants born at 34–36 weeks of gestation [26]. These authors

hypothesized a protective effect of maternal HDP on offspring respiratory systems because intrauterine fetal stress that occurs due to the maternal hostile environment may produce endogenous corticosteroids, accelerating lung maturation and producing surfactant, similar to in ACS treatment. However, according to an animal experiment demonstrating increased surfactant production in the vascular endothelial growth factor (VEGF)-rich intrauterine environment [27], HDP, especially preeclampsia, could impair surfactant production and function due to increased anti-VEGF (e.g., soluble fms-like tyrosine kinase-1 and soluble endoglin) concentrations in the umbilical cord and amniotic fluid. Another possible explanation for this increased risk for RDS in the HDP group is that almost all women in the HDP group likely delivered by cesarean section before the onset of labor. It is well known that surfactants are secreted into the fetal lung fluid during labor, and the presence of labor significantly reduces approximately 20–30% OR for RDS [26, 28, 29]. There is a possibility that the rate of women who experienced labor before cesarean section was higher in the non-HDP group. However, data on the presence of labor were not documented in the NRNJ database.

With regard to PPHN, we showed a decreased risk in the HDP group. This is reasonable because of the decreased odds of iNO, which is mainly used for PPHN treatment. The established risk factors of PPHN in preterm infants are male infants, infection, gestational diabetes mellitus, perinatal asphyxia, maternal smoking, and antenatal drug exposure (e.g.,

SSRI-type antidepressants and NSAIDs) [30, 31]. According to a previous review, preeclampsia is listed as a risk factor for PPHN [31]; however, a recent meta-analysis demonstrated no significant association between HDP and PPHN (adjusted OR 2.42 [0.73–8.05]) [30].

In this study, we evaluated the risk for HOT at NICU discharge and oxygen requirement at 1.5 and 3 years of age in the HDP group. We could not find any significant association between HDP and HOT or medium-term outcomes. These results were understandable because the odds for these outcomes in the HDP group were similar to those of CLD, which is the main contributing factor for HOT and oxygen requirement in the medium-term [32, 33].

The strengths of this study are as follows: First, the sample size of this study was large, with sufficient statistical power; in addition, the clinical data were derived from multiple centers, improving the generalizability of the study. Second, our study is unique in that various respiratory outcomes, including medium-term outcomes at 3 years of age, were evaluated. Finally, we conducted two subgroup analyses to confirm the consistency within the different subgroups.

304 This study has several limitations. First, we could not collect clinical data on the
305 severity and type of HDP and use of antihypertensive agents and magnesium sulphate; therefore,
306 we could not investigate the association between severity or type of HDP and respiratory
307 outcomes. A meta-analysis demonstrated that the risks for several neonatal outcomes increased
308 in cases of severe HDP or preeclampsia [12]. Second, infants with in-hospital deaths were
309 excluded from the analyses. Therefore, we could not consider the most severe cases of early
310 lethal CLD who died before reaching 36 weeks' postmenstrual age, generating a survival bias.
311 Third, the maternal and neonatal characteristics were not matched between infants with and
312 without SGA in the subgroup analysis because the SGA ratio was different in the HDP and
313 non-HDP groups. Finally, several unmeasured covariates associated with offspring respiratory
314 outcomes (e.g., maternal smoking status, drug use, and the presence of labor before delivery)
315 may exist but were not documented in this database.
316
317 ***Conclusion***
318 We evaluated the impact of HDP on short- and medium-term respiratory outcomes in extremely
319 and very preterm infants. HDP was associated with higher odds for RDS and artificial ventilator
320 use, but reduced odds of PPHN. The risks for CLD, HOT, and medium-term respiratory
321 outcomes in the HDP group were comparable to those in the non-HDP group.
322

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The authors have no potential conflicts of interest to disclose.

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Data availability

Data that support the findings of this study are available from the corresponding author (TU) upon reasonable request and with permission from the Neonatal Research Network of Japan.

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Figure legend

Figure 1. Flow diagram of the study population

The clinical data of 50,599 infants weighing ≤ 1,500 g, at 22–31 weeks of gestation, and born between 2003 and 2017 were collected. After excluding 26,226 infants, 24,373 infants were eligible for this study. After 1:1 stratification matching, 5,137 infants in each group were selected to analyze the impact of maternal HDP on short- and medium-term respiratory outcomes. HDP, hypertensive disorders of pregnancy.

Table 1. Maternal and neonatal baseline characteristics between the HDP and non-HDP groups.

Variables	HDP (n = 5,137)	Non-HDP (n = 5,137)	*p*-value
Maternal characteristics			
Maternal age (years)	34 (30–38)	34 (30–37)	
–19 years	24 (0.5)	24 (0.5)	1.00
20–29 years	983 (19.1)	983 (19.1)	
30–39 years	3,511 (68.3)	3,511 (68.3)	
40– years	619 (12.1)	619 (12.1)	
Gestational age (weeks)	29.3 (27.4–30.7)	29.2 (27.4–30.6)	
22–23 weeks	57 (1.1)	57 (1.1)	1.00
24–25 weeks	481 (9.4)	481 (9.4)	
26–27 weeks	1,020 (19.9)	1,020 (19.9)	
28–29 weeks	1,597 (31.1)	1,597 (31.1)	
30–31 weeks	1,982 (38.6)	1,982 (38.6)	
Primiparity	2,953 (57.5)	2,953 (57.5)	1.00
Cesarean section	4,944 (96.2)	3,750 (73.0)	<0.01
GDM or DM	243 (4.7)	236 (4.6)	0.74
Histological CAM	709 (13.8)	2,222 (43.3)	<0.01
ACS treatment	2,834 (55.2)	3,101 (60.4)	<0.01
Year of delivery			1.00
2003–2010	1,903 (37.0)	1,903 (37.0)	
2011–2017	3,234 (63.0)	3,234 (63.0)	
Neonatal characteristics			
Male	2,410 (46.9)	2,696 (52.5)	<0.01
Birth weight (g)	932 (704–1,143)	1,142 (900–1,346)	<0.01
Birth height (cm)	34.6 (31.5–37.0)	36.5 (34.0–38.5)	<0.01
SGA	3,757 (73.1)	1,296 (25.2)	<0.01

Data are presented as medians (interquartile range) or numbers (%). P-values were calculated using the chi-squared test or Student's *t*-test. HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; DM, diabetes mellitus; CAM, chorioamnionitis; ACS, antenatal corticosteroid; SGA, small for gestational age.

Table 2. Short- and medium-term offspring outcomes between the HDP and non-HDP groups.

Variables	HDP (n = 5,137)	Non-HDP (n = 5,137)	*p*-value
Short-term respiratory outcomes			
Oxygen use at birth	4,564/5,108 (89.4)	4,471/5,112 (87.5)	<0.01
Intubation at birth	2,898/5,119 (56.6)	2,837/5,123 (55.4)	0.21
Surfactant use	3,459/5,115 (67.6)	2,825/5,104 (55.3)	<0.01
Respiratory distress syndrome	3,564/5,135 (69.4)	2,851/5,130 (55.6)	<0.01
Artificial ventilator use	3,918/5,073 (77.2)	3,620/5,063 (71.5)	<0.01
HFOV use	1,462/5,056 (28.9)	1,278/5,043 (25.3)	<0.01
Inhaled nitric oxide use	129/5,014 (2.6)	261/5,015 (5.2)	<0.01
PPHN	86/5,117 (1.7)	234/5,112 (4.6)	<0.01
Chronic lung disease	1,241/4,947 (25.1)	1,000/4,922 (20.3)	<0.01
HOT at discharge from NICU	301/5,087 (5.9)	271/5,081 (5.3)	0.20
Medium-term respiratory outcomes			
Oxygen use at 1.5 years of age	47/1,993 (2.4)	40/1,872 (2.1)	0.64
Oxygen use at 3 years of age	31/1,943 (1.6)	21/1,782 (1.2)	0.28
Short-term other outcomes			
IVH (III or IV)	78/5,118 (1.5)	148/5,115 (2.9)	<0.01
Periventricular leukomalacia	121/5,119 (2.4)	167/5,121 (3.3)	<0.01
Sepsis	294/5,119 (5.7)	294/5,121 (5.7)	1.00
Necrotizing enterocolitis	45/5,130 (0.9)	55/5,127 (1.1)	0.31
Patent ductus arteriosus banding	196/5,119 (3.8)	210/5,128 (4.1)	0.49
Late-onset circulatory collapse	472/5,080 (9.3)	344/5,065 (6.8)	<0.01

Data are presented as medians (interquartile range) or numbers (%). P-values were calculated using the chi-squared test. HDP, hypertensive disorders of pregnancy; HFOV, high-frequency oscillatory ventilation; PPHN, persistent pulmonary hypertension of the newborn; HOT, home oxygen therapy; NICU, neonatal intensive care unit; IVH, intraventricular hemorrhage.

Table 3. Impact of maternal HDP on offspring respiratory outcomes in the univariate and multivariate logistic regression analyses.

	Univariate	Multivariate
	Crude OR (95% CI)	Adjusted OR (95% CI)
Oxygen use at birth	**1.20 (1.07–1.36)**	1.04 (0.90–1.20)
Intubation at birth	1.05 (0.97–1.14)	**0.80 (0.72–0.88)**
Surfactant use	**1.69 (1.56–1.83)**	**1.69 (1.52–1.87)**
Respiratory distress syndrome	**1.81 (1.67–1.97)**	**1.83 (1.65–2.03)**
Artificial ventilator use	**1.35 (1.24–1.48)**	**1.19 (1.06–1.34)**
HFOV use	**1.20 (1.10–1.31)**	**0.87 (0.77–0.98)**
Inhaled nitric oxide use	**0.48 (0.39–0.60)**	**0.43 (0.33–0.55)**
PPHN	**0.36 (0.28–0.46)**	**0.34 (0.26–0.46)**
Chronic lung disease	**1.31 (1.20–1.44)**	0.94 (0.83–1.07)
HOT at discharge from NICU	1.12 (0.94–1.32)	0.82 (0.66–1.01)
Oxygen use at 1.5 years of age	1.11 (0.72–1.69)	0.81 (0.47–1.39)
Oxygen use at 3 years of age	1.36 (0.78–2.38)	1.01 (0.52–1.93)

The impact of HDP on offspring respiratory outcomes was evaluated using univariate and multivariate logistic regression analyses. The multivariate analyses were adjusted for each covariate as follows: maternal age, gestational age, parity, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis, antenatal corticosteroid treatment, HDP, year of delivery, infant sex, and birth weight.

HDP, hypertensive disorders of pregnancy; HFOV, high-frequency oscillatory ventilation; PPHN, persistent pulmonary hypertension of the newborn; HOT, home oxygen therapy; NICU, neonatal intensive care unit; OR, odds ratio; CI, confidence interval.

Table 4. Impact of maternal HDP on offspring respiratory outcomes stratified by the presence of small for gestational age.

	SGA infants		Non-SGA infants	
	Univariate	Multivariate	Univariate	Multivariate
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Oxygen use at birth	**1.23 (1.01–1.49)**	0.99 (0.81–1.22)	1.18 (0.97–1.44)	1.13 (0.91–1.41)
Intubation at birth	**1.20 (1.05–1.36)**	**0.73 (0.63–0.85)**	0.95 (0.84–1.07)	0.86 (0.73–1.01)
Surfactant use	**1.97 (1.73–2.24)**	**1.35 (1.16–1.57)**	**2.01 (1.76–2.31)**	**1.76 (1.50–2.07)**
Respiratory distress syndrome	**2.01 (1.77–2.29)**	**1.41 (1.22–1.64)**	**2.33 (2.03–2.67)**	**1.97 (1.68–2.32)**
Artificial ventilator use	**1.64 (1.43–1.89)**	1.03 (0.88–1.22)	**1.43 (1.23–1.66)**	**1.29 (1.08–1.56)**
HFOV use	**1.43 (1.23–1.66)**	0.86 (0.72–1.02)	0.91 (0.78–1.05)	0.87 (0.72–1.04)
Inhaled nitric oxide use	**0.54 (0.39–0.74)**	**0.43 (0.31–0.61)**	**0.41 (0.28–0.60)**	**0.50 (0.33–0.76)**
PPHN	**0.48 (0.33–0.70)**	**0.36 (0.24–0.54)**	**0.30 (0.19–0.47)**	**0.37 (0.23–0.60)**
Chronic lung disease	**1.40 (1.20–1.63)**	0.98 (0.81–1.18)	**0.79 (0.67–0.94)**	0.88 (0.72–1.09)
HOT at discharge from NICU	**1.34 (1.01–1.78)**	0.91 (0.67–1.24)	**0.74 (0.55–1.00)**	0.91 (0.64–1.29)
Oxygen use at 1.5 years of age	2.08 (0.87–4.96)	1.55 (0.61–3.95)	0.77 (0.38–1.57)	0.76 (0.34–1.73)
Oxygen use at 3 years of age	2.06 (0.71–5.94)	1.80 (0.58–5.59)	0.90 (0.35–2.30)	1.17 (0.41–3.30)

The impact of HDP on offspring respiratory outcomes was evaluated using univariate and multivariate logistic regression analyses stratified by the presence of small for gestational age (HDP group: SGA, n = 3,757; non-SGA, n = 1,380; non-HDP group, n = 1,296; non-SGA, n = 3,841). The multivariate analyses were adjusted for each covariate as follows: maternal age, gestational age, parity, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis, antenatal corticosteroid treatment, HDP, year of delivery, infant sex, and birth weight.

HDP, hypertensive disorders of pregnancy; SGA, small for gestational age; HFOV, high-frequency oscillatory ventilation; PPHN, persistent pulmonary hypertension of the newborn; HOT, home oxygen therapy; NICU, neonatal intensive care unit; OR, odds ratio; CI, confidence interval.

Table 5. Impact of maternal HDP on offspring respiratory outcomes stratified by gestational age.

	< 28 gestational weeks		≥ 28 gestational weeks	
	Univariate	Multivariate	Univariate	Multivariate
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Oxygen use at birth	0.97 (0.74–1.28)	0.82 (0.57–1.17)	**1.27 (1.11–1.46)**	1.08 (0.93–1.27)
Intubation at birth	**1.31 (1.07–1.59)**	0.79 (0.60–1.04)	1.01 (0.92–1.11)	**0.78 (0.70–0.88)**
Surfactant use	**2.96 (2.41–3.62)**	**2.06 (1.58–2.69)**	**1.57 (1.43–1.73)**	**1.59 (1.41–1.78)**
Respiratory distress syndrome	**3.61 (2.96–4.39)**	**2.65 (2.06–3.43)**	**1.61 (1.46–1.77)**	**1.65 (1.47–1.85)**
Artificial ventilator use	**2.58 (1.81–3.68)**	1.43 (0.90–2.28)	**1.33 (1.20–1.46)**	**1.16 (1.02–1.30)**
HFOV use	**1.45 (1.25–1.67)**	0.91 (0.75–1.12)	1.10 (0.97–1.26)	**0.81 (0.69–0.94)**
Inhaled nitric oxide use	**0.47 (0.34–0.64)**	**0.43 (0.29–0.64)**	**0.49 (0.36–0.66)**	**0.43 (0.31–0.59)**
PPHN	**0.41 (0.30–0.57)**	**0.43 (0.29–0.65)**	**0.28 (0.18–0.42)**	**0.26 (0.16–0.40)**
Chronic lung disease	**1.48 (1.28–1.71)**	0.84 (0.69–1.02)	**1.28 (1.10–1.49)**	0.96 (0.80–1.14)
HOT at discharge from NICU	1.22 (0.99–1.50)	0.79 (0.60–1.05)	0.94 (0.68–1.28)	0.76 (0.53–1.09)
Oxygen use at 1.5 years of age	1.07 (0.66–1.73)	0.76 (0.40–1.44)	1.08 (0.42–2.81)	0.88 (0.30–2.58)
Oxygen use at 3 years of age	1.36 (0.68–2.69)	0.77 (0.33–1.76)	1.33 (0.50–3.50)	1.56 (0.49–4.97)

The impact of HDP on offspring respiratory outcomes was evaluated using univariate and multivariate logistic regression analyses stratified by gestational age (HDP group: < 28 gestational weeks n = 1,558, ≥ 28 gestational weeks n = 3,579, non-HDP group: < 28 gestational weeks n = 1,558, ≥ 28 gestational weeks n = 3,579). The multivariate analyses were adjusted for each covariate as follows: maternal age, gestational age, parity, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis, antenatal corticosteroid treatment, HDP, year of delivery, infant sex, and birth weight.

HDP, hypertensive disorders of pregnancy; HFOV, high-frequency oscillatory ventilation; PPHN, persistent pulmonary hypertension of the newborn; HOT, home oxygen therapy; NICU, neonatal intensive care unit; OR, odds ratio; CI, confidence interval.

Supplementary Table 1. Maternal and neonatal baseline characteristics between the HDP and non-HDP groups before 1:1 stratification matching.

Variables	HDP (n = 5,258)	Non-HDP (n = 19,115)	*p*-value
Maternal characteristics			
Maternal age (years)	34 (31–38)	31 (28–35)	<0.01
–10 years	24 (0.5)	360 (1.9)	
20–29 years	983 (18.7)	6,517 (34.1)	
30–39 years	3,574 (68.0)	11,141 (58.3)	
40– years	677 (12.9)	1,097 (5.7)	
Gestational age (weeks)	29.3 (27.6–30.7)	27.7 (25.6–29.4)	
22–23 weeks	58 (1.1)	1,517 (7.9)	<0.01
24–25 weeks	483 (9.2)	3,915 (20.5)	
26–27 weeks	1,023 (19.5)	4,800 (25.1)	
28–29 weeks	1,601 (30.4)	5,385 (28.2)	
30–31 weeks	2,093 (39.8)	3,498 (18.3)	
Primiparity	3,008 (57.2)	9,072 (47.5)	<0.01
Cesarean section	5,061 (96.3)	13,358 (69.9)	<0.01
GDM or DM	252 (4.8)	607 (3.2)	<0.01
Histological CAM	725 (13.8)	9,608 (50.3)	<0.01
ACS treatment	2,896 (55.1)	11,411 (59.7)	<0.01
Year of delivery			
2003–2010	1,939 (36.9)	7,971 (41.7)	<0.01
2011–2017	3,319 (63.1)	11,144 (58.3)	
Neonatal characteristics			
Male	2,461 (46.8)	10,222 (53.5)	<0.01
Birth weight (g)	938 (708–1,150)	976 (740–1,234)	<0.01
Birth height (cm)	34.8 (31.7–37.0)	35.0 (32.0–37.5)	<0.01
SGA	3,844 (73.1)	3,257 (17.0)	<0.01

Data are presented as medians (interquartile range) or numbers (%). *P*-values were calculated using the chi-squared test or Student's *t*-test. HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; DM, diabetes mellitus; CAM, chorioamnionitis; ACS, antenatal corticosteroid; SGA, small for gestational age.