Intrauterine exposure to hypertensive disorders of pregnancy and postnatal growth in extremely and very preterm infants

Takafumi Ushida[1,2], Tomomi Kotani[1,2], Masahiro Nakatochi[3], Yumiko Kobayashi[4], Noriyuki Nakamura[1], Kenji Imai[1], Yukako Iitani[1], Tomoko Nakano-Kobayashi[1], Masahiro Hayakawa[5], Hiroaki Kajiyama[1], for the Neonatal Research Network of Japan.

[1]Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[2]Division of Perinatology, Center for Maternal-Neonatal Care, Nagoya University Hospital, Nagoya, Japan

[3]Public Health Informatics Unit, Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan

[4]Data Science Division, Data Coordinating Center, Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan

[5]Division of Neonatology, Center for Maternal-Neonatal Care, Nagoya University Hospital, Nagoya, Japan

[*]Corresponding author:

Takafumi Ushida, M.D., Ph.D.

Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine,

65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan,

Tel: +81-52-744-2261

Fax: +81-52-744-2268

E-mail: u-taka23@med.nagoya-u.ac.jp

Abstract

Objectives: There is growing evidence regarding the association between rapid growth during infancy and metabolic and cardiovascular diseases later in life. We aimed to evaluate postnatal growth trajectories in extremely and very preterm infants exposed to hypertensive disorders of pregnancy (HDP) in utero.

Study design: This multicenter retrospective study used a nationwide database of preterm infants weighing ≤1,500 g born between 22 and 31 weeks of gestation between 2003 and 2015.

Main outcome measures: The Z-scores for height and weight were evaluated at three time points (at birth, corrected age of 1.5 years, and chronological age of 3 years) in 5,144 infants (HDP, n=1,188; non-HDP, n=3,956). Univariate and multivariate regression analyses were performed to investigate the associations between HDP exposure and accelerated postnatal growth.

Results: Male and female infants in the HDP group showed increased mean Z-scores for height and weight, whereas those in the non-HDP group showed decreased mean Z-scores. Multivariate analyses showed that HDP were associated with accelerated postnatal growth (Δ Z-scores) in weight in both male and female infants (β coefficient [95% CI]; male 0.17 [0.05 to 0.30], female 0.27 [0.14 to 0.39]), but not in height (male 0.02 [−0.09 to 0.13], female 0.04 [−0.06 to 0.15]). An interaction analysis revealed no significant differences in the effects of HDP on postnatal growth between male and female infants.

Conclusions: Intrauterine exposure to HDP contributes to accelerated postnatal weight growth in extremely and very preterm infants during early childhood. In addition, no sex differences were observed in postnatal growth.

Keywords: catch-up growth, DOHaD, fetal programming, hypertensive disorders of pregnancy, small for gestational age

Abbreviation

CAM, chorioamnionitis; DM, diabetes mellitus; DOHaD, Developmental Origins of Health and Disease; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; IVH, intraventricular hemorrhage; LCC, late-onset circulatory collapse; NICU, neonatal intensive care unit; NRNJ, Neonatal Research Network of Japan; PDA, patent ductus

58 arteriosus; SGA, small for gestational age.

59

60 ***Introduction***

61 Hypertensive disorders of pregnancy (HDP), including preeclampsia and gestational
62 hypertension, are common complications that affect 5%–10% of all pregnancies worldwide
63 (1). Recently, increasing evidence has demonstrated elevated lifetime risks for metabolic and
64 cardiovascular diseases in infants born to mothers with HDP (2-6). Long-term
65 epidemiological studies have demonstrated that infants exposed to preeclampsia in utero are
66 at a higher risk of developing endocrine or metabolic diseases (7) and have a two-to three-
67 fold increased risk of hypertension and obesity at a young adult age (4). The underlying
68 mechanism linking HDP and infants' subsequent metabolic and cardiovascular disease risks
69 has yet to be fully elucidated; however, these alterations in cardiometabolism may be
70 attributed to various factors, such as fetal programming by exposure to HDP in utero, shared
71 genetic susceptibility to such diseases, and postnatal lifestyle factors (e.g., dietary patterns,
72 smoking, alcohol, stress, and physical activity) (2).

73

74 In cases of pregnancies complicated by HDP, particularly preeclampsia, fetuses are
75 exposed to various insults in utero, such as hypoxia, undernutrition, oxidative stress, and
76 inflammatory cytokines (e.g., interleukin-6 and tumor necrosis factor-α) attributed to

abnormal placentation in the early stages of pregnancy (8). Thus, fetal growth restrictions, which are often accompanied by abnormal umbilical arterial blood flow and a non-reassuring fetal status pattern in cardiotocography, occur in approximately 30%–50% cases of early onset HDP (9). According to the Developmental Origins of Health and Disease (DOHaD) hypothesis advocated by David Baker, fetuses exposed to various insults in utero undergo adaptive responses to hostile environments, resulting in the development of a “thrifty phenotype” to conserve energy for postnatal life (10). In cases of a greater mismatch between intra- and extra-uterine environments, these adaptive responses may cause negative consequences, such as life-long susceptibility to non-communicable diseases such as diabetes mellitus and hypertension (11). As evidence of the DOHaD hypothesis, some epidemiological studies have demonstrated that growth-restricted infants are more likely to show catch-up and accelerated growth in early childhood and that these infants have increased risks for obesity and diabetes and show cardiovascular alterations during adolescence or young adulthood (12, 13).

Several studies have demonstrated that intrauterine exposure to HDP accelerates postnatal growth in late preterm and term infants (14-18); however, little is known regarding the effect of maternal HDP on postnatal growth in extremely or very preterm infants. To date, only a few case-control studies with small sample sizes (n=80–135) have been conducted on

this issue (19, 20); however, no large cohort study focusing on very preterm infants has been conducted. In addition, most reports did not properly consider covariates that could affect postnatal growth in statistical analysis (16, 17, 20). Thus, in this study, we sought to investigate the postnatal growth trajectories in extremely and very preterm infants exposed to maternal HDP using a nationwide neonatal database in Japan and to evaluate the accelerated growth attributed to HDP using multivariate analyses.

Methods

This multicenter retrospective study used a nationwide database of extremely and very preterm infants weighing ≤1,500 g born at 22–31 weeks of gestational age between 2003 and 2015. Approximately 200 facilities in Japan, mainly neonatal intensive care units (NICUs) of levels II and III, participate in the Neonatal Research Network of Japan (NRNJ), and more than 4,000 infants are registered in this database each year, covering approximately 70% of very low birth weight neonates born in Japan (21). This database provides maternal and neonatal information, including prenatal obstetric factors and short-term (at NICU) and long-term (3 years of age) infant outcomes, along with physical assessment at birth, corrected age of 1.5 years, and chronological age of 3 years. The maternal and neonatal clinical information obtained from the medical records at the participating institutions was anonymized and sent to the NRNJ database center on a yearly basis. Informed consent was obtained from the

caregivers of the infants at each facility. This study was approved by the Institutional Ethics Committee of Nagoya University Hospital (approval number: 2018–0026), and the data use was approved by the Japan Neonatal Network Executive Committee.

A total of 44,657 infants weighing ≤1,500 g, born at a gestational age of 22–31 weeks, were included in the NRNJ database during the study period. The following cases were excluded from this study: those involving multiple pregnancies, major congenital and chromosomal abnormalities, out-of-hospital births, in-hospital mortality, and incomplete medical records on maternal characteristics and neonatal outcomes. The Z-scores of body weight and height at birth, corrected age of 1.5 years, and chronological age of 3 years were calculated using the software provided by the Japanese Society for Pediatric Endocrinology based on the Japanese neonatal anthropometric chart in 2000 (22). This software was developed based on the LMS method (23). The formula for the Z-scores is as follows: Z-scores = $[(X/M)^{L} - 1]/(L \times S)$, where X: measured values (weight or height); M: median; L (Lambda): asymmetry value; and S (Sigma): variation coefficient. Z-scores permit a more precise assessment of infant growth compared with percentiles (24).

Small for gestational age (SGA) infant was defined if both body weight and height were below the 10^{th} percentile for the gestational age, based on the sex-specific Japanese

neonatal anthropometric chart in 2000 (22). HDP were defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg during pregnancy (25). Neonatal complications were defined as previously described (26).

All statistical analyses were performed using the SPSS 27 software (SPSS Inc., Chicago, IL, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Differences between the two groups were assessed using the Mann–Whitney *U* test for continuous variables and chi-squared test for categorical variables. Statistical significance for all analyses was set at $p<0.05$. Multivariate regression analyses were performed to evaluate the association between exposure to HDP and accelerated postnatal growth during the first 3 years from birth after adjustment of the potential variables recognized as clinically important based on the literature (27-29). In this study, two types of covariates (#1 [prenatal and early postnatal factors] and #2 [prenatal, early postnatal, and late postnatal factors at NICU discharge]) were used for adjustment in multivariate analyses: prenatal and early postnatal factors, including maternal age, parity, gestational age at delivery, mode of delivery, gestational diabetes mellitus (GDM)/diabetes mellitus (DM), histological chorioamnionitis (CAM), antenatal corticosteroid treatment, infant sex, and birth weight (or height) Z-scores; and postnatal factors at NICU discharge, including chronic lung disease, intraventricular hemorrhage (IVH) (grade III/IV), periventricular leukomalacia, sepsis, necrotizing enterocolitis, patent ductus arteriosus (PDA)

153 banding, late-onset circulatory collapse (LCC), and total parenteral nutrition. The magnitude
154 of the difference in the Δ Z-scores of height (or weight) from the reference (non-HDP group)
155 was expressed as a β coefficient. To investigate whether the effect of HDP on postpartum
156 accelerated growth varies across infant sex, we assessed the interaction between infant sex and
157 HDP in the multivariate models. A *p*-value <0.05 for the interaction indicated a significant
158 difference in the effect of HDP on accelerated growth between male and female infants.
159
160 ***Results***
161 Among 44,657 infants weighing ≤1,500 g born at 22–31 weeks of gestational age, 19,331
162 (HDP, n=4,258 [22.0%]; non-HDP, n=15,073 [78.0%]) were eligible for this study after
163 excluding 25,326 infants (Figure 1). Among 19,331 infants discharged from NICUs, 5,144
164 infants (HDP, n=1,188; non-HDP, n=3,956) underwent physical assessment at corrected age
165 of 1.5 years and chronological age of 3 years. These accounted for 26.6% of the infants
166 discharged from the NICUs. A total of 14,187 infants were not followed up because they
167 were transferred to other hospitals or were lost to follow-up.
168
169 Table 1 shows the maternal and neonatal characteristics, including short-term
170 neonatal morbidities, of the two groups. The mothers in the HDP group were older and more
171 likely to be primiparous, delivered at a slightly later gestational age, and had a higher rate of

cesarean sections than those in the non-HDP group. The mothers in the non-HDP group had higher rates of antenatal corticosteroid treatment and histological CAM. The infants in the HDP group had a lower birth weight and were more likely to be female and SGA than those in the non-HDP group. Infants born to mothers with HDP showed a significantly lower incidence of respiratory distress, persistent pulmonary hypertension of the newborn, IVH (grade III/IV), sepsis, PDA banding, and LCC.

Figure 2 shows the trajectories of the mean Z-scores for height and weight with 95% confidence intervals (CIs) at three different time points (at birth, corrected age of 1.5 years, and chronological age of 3 years) in the HDP and non-HDP groups stratified according to infant sex. Overall, male and female infants in the HDP group showed increased mean Z-scores for height and weight, mainly between birth and corrected age of 1.5 years (Figure 2A–D). On the other hand, both male and female infants in the non-HDP group showed decreased mean Z-scores for height and weight during the first 3 years. Supplementary Table 1 shows the physical assessments and Z-scores at birth, corrected age of 1.5 years, and chronological age of 3 years.

Figure 3 presents a graph showing Z-scores at birth plotted against Δ Z-scores between birth and 3 years of age to depict the distribution. We found a negative correlation between Z-scores at birth and the Δ Z-scores for height and weight during the first 3 years in both groups.

Both male and female infants in the HDP group showed significantly lower Z-scores at birth and increased Δ Z-scores than those in the non-HDP group.

To eliminate the possibility that the increased mean Z-scores of height and weight in the HDP group (Figure 2A–D) were simply a result of the increased rate of infants with SGA in the HDP group, we performed univariate and multivariate regression analyses to evaluate the effect of intrauterine exposure to HDP on the Δ Z-scores for height and weight during the first 3 years after birth, after adjusting for eight covariates including Z-scores at birth (Table 2). In the univariate analysis, the HDP group showed accelerated postnatal growth (increased Δ Z-scores) in height and weight in both male and female infants. However, the multivariate analysis, which incorporated eight prenatal and early postnatal covariates (#1), demonstrated that HDP were associated with accelerated postnatal growth (Δ Z-scores) in weight in both male and female infants (β coefficient [95% CI]: male, 0.17 [0.05 to 0.30], female, 0.27 [0.14 to 0.39]), but not with height (male, 0.02 [−0.09 to 0.13]; female 0.04 [−0.06 to 0.15]). These results were consistent with another multivariate analysis that was adjusted for 16 covariates (#2), including prenatal, early postnatal, and late postnatal factors (β coefficient [95% CI]: male, 0.17 [0.05 to 0.30]; female, 0.27 [0.15 to 0.39]), but not in height (male, 0.03 [−0.08 to 0.13]; female, 0.05 [−0.05 to 0.15]).

It was observed that the β coefficient of female body weight was larger than that of male body weight by both types of multivariate analyses; thus, we performed an additional analysis to investigate whether the effect of HDP on postpartum accelerated growth varies according to infant sex. In this interaction analysis, we observed no significant difference in the effect of HDP on accelerated postnatal growth (Δ Z-scores of body weight) between male and female infants after adjusting for the two types of covariates (#1 and #2) (Table 3).

Discussion

In this multicenter retrospective study, we demonstrated the postnatal growth trajectories of extremely and very preterm infants born to mothers with HDP and evaluated the effect of HDP on postnatal growth using a nationwide Japanese neonatal database. The main finding of this study was that HDP contributed to accelerated postnatal growth of weight, but not height, during the first 3 years after birth in both male and female infants. In addition, in this study, we found no significant association between infant sex and accelerated postnatal growth in infants born to mothers with HDP.

Our findings are consistent with those of previous studies showing accelerated postnatal growth in term infants exposed to preeclampsia (16, 18, 19). Vatten et al. demonstrated that maternal preeclampsia was associated with increased weight and body mass

index (BMI) in female infants (preeclampsia, n=243; control, n=3,853) (18). A Swedish cohort study demonstrated accelerated height gain in early childhood due to prenatal exposure to preeclampsia (preeclampsia, n=865; control, n=22,898) (16). Beukers et al. demonstrated that the majority of growth-restricted children born to mothers with HDP underwent caught-up growth within the normal range at 4.5 years of age (HDP: n=135) (19). However, a consensus regarding whether accelerated growth occurs in terms of both height and weight, or either height or weight, in infants born to mothers with HDP has not been reached. At first glance, infants exposed to HDP showed accelerated growth in both weight and height (Figure 2); however, multivariate analyses revealed that HDP were associated with accelerated growth of weight alone, considering the effect of Z-scores at birth and the maternal and neonatal characteristics that can affect postnatal growth (Table 2). These conflicting results between the univariate and multivariate analyses could be explained by the difference in the distribution of Z-scores at birth between the HDP and non-HDP groups (Figure 3). The negative correlations between Z-scores at birth and postnatal growth were similar between the two groups. Clinically, the results of this study suggest that infants born to mothers with HDP may have an increased risk of obesity, diabetes, and cardiovascular disease later in life based on the association between rapid weight gain in infancy and metabolic disturbances and cardiovascular alterations (30, 31).

248 The issue of sex differences in postnatal growth patterns following in utero exposure
249 to HDP remains controversial. A previous cohort study by Seidman et al. demonstrated that
250 male term infants exposed to preeclampsia showed higher body weight and BMI at 17 years of
251 age (preeclampsia, n=145; control, n=12,701), whereas there was no significant difference in
252 female infants between the two groups (15). Mitsui et al. reported a higher incidence of catch-
253 up growth during the first 3 years after birth in female term infants (male: n=13, female: n=16)
254 (32). Furthermore, Byberg et al. showed a positive association between exposure to
255 preeclampsia and higher weight and BMI after preschool age in female infants (male, n=230;
256 female, n=238) (33). This discrepancy in sex differences may result from a complex
257 combination of factors, such as the intrauterine environment (e.g., severity and type of HDP),
258 degree of prematurity (term of preterm), neonatal adverse morbidities, postnatal treatments and
259 nutrients (e.g., type and period of lactation), and various postnatal environments. In this study,
260 we found no significant differences between the sexes in terms of postnatal growth in the HDP
261 group. This could be explained by the fact that the factors that can affect postnatal growth in
262 very preterm infants are more likely to be severe and complex than those affecting postnatal
263 growth in term infants, suggesting that the sex differences may be underestimated due to
264 various other factors. Furthermore, several studies have not performed an interaction analysis
265 to demonstrate sex differences in postnatal growth (15, 32).
266

The underlying mechanism linking maternal HDP to accelerated postnatal growth remains to be completely elucidated; however, the DOHaD hypothesis is widely accepted (34). Many studies have focused on the association between low birth weight and increased insulin levels, insulin resistance, and abdominal obesity (33, 35). Furthermore, in the last decade, the mechanisms for increased risk of subsequent metabolic syndrome and cardiovascular disease have been found to be associated with epigenetic alterations (e.g., DNA methylation and histone modifications) or cardiovascular remodeling caused by exposure to adverse intrauterine environments (12, 34, 36).

The strength of this study lies in its examination of postnatal growth trajectories, specifically in extremely and very preterm infants born to mothers with HDP. Few studies have been conducted on this topic thus far. In addition, the number of participants was larger than that those in previous reports (14, 19, 32). Second, we focused on extremely and very preterm infants to eliminate the influence of differences in gestational age on the results. Several studies did not match the gestational age or percentage of preterm neonates between the HDP and control groups (16). Third, we performed multivariate analyses to evaluate the effect of HDP on postnatal growth across the infant sex; most previous studies did not consider the effect of covariates (e.g., Z-scores at birth, maternal characteristics, and neonatal complications) on postnatal growth (20, 37, 38). In addition, we performed an interaction analysis to investigate

the sex differences in postnatal growth.

Our study has several limitations. First, the NRNJ database does not include certain perinatal information, including the type and severity of HDP, causes of preterm birth, and potentially confounding variables such as early aggressive nutrition management, period of breastfeeding, and maternal and paternal physical data. Byberg et al. showed that postnatal growth differed according to preeclampsia severity only in male infants (14). Beukers et al. evaluated the catch-up growth rate of height by adjusting for maternal and paternal height to consider parental contribution to child growth (19). Finally, among 19,331 neonates discharged from NICUs in the NRNJ database, only one-fourth of the infants were followed up at 3 years of age. Thus, we cannot exclude the possibility of a selection bias in participation.

Conclusion

Intrauterine exposure to early onset HDP contributes to accelerated postnatal growth of weight but not height in extremely and very preterm infants during early childhood. In addition, no significant association was found between infant sex and accelerated postnatal growth in infants born to mothers with HDP. Our results indicate that extremely and very preterm infants born to mothers with HDP may be at high risk of developing metabolic and cardiovascular

diseases later in life. Therefore, these infants require particular attention to postnatal growth, and regular physical assessment throughout adolescence and young adulthood may be important to prevent such diseases.

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Disclosures

The authors have no potential conflicts of interest to disclose.

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Figure legends

Figure 1. Flow diagram of this study population.

Data on 44,657 infants registered in the NRNJ database from 2003 to 2015 were available. Physical assessment was performed at birth, corrected age of 1.5 years, and chronological age of 3 years. HDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit

Figure 2. The trajectories of mean Z-scores for height and weight in the HDP and non-HDP groups.

The mean Z-scores for height and weight with 95% confidence intervals in the HDP and non-HDP groups were evaluated (2A, male height; 2B, male weight; 2C, female height; 2D, female weight). HDP, hypertensive disorders of pregnancy; *p <0.05, **p <0.01

Figure 3. Relationships between the Z-scores at birth and Δ the Z-scores during the first 3 years in the HDP and non-HDP groups

Z-scores at birth (X-axis) vs. Δ Z-scores (Y-axis) in the HDP (red) and non-HDP (blue) groups are presented to depict the distribution (3A, male height; 3B, male weight; 3C, female height; and 3D, female weight). HDP: hypertensive disorders of pregnancy

Table 1 Maternal and neonatal characteristics in the HDP and non-HDP groups

Variables	HDP (n = 1,188)	Non-HDP (n = 3,956)	*p*-value
Maternal characteristics			
Maternal age (years)	34 (31–38)	32 (28–35)	<0.01
Gestational age (weeks)	29.1 (27.4–30.6)	27.4 (25.6–29.3)	<0.01
Primiparity	692 (58.2)	1,917 (48.5)	<0.01
Cesarean section	1,143 (96.2)	2,821 (71.3)	<0.01
GDM or DM	52 (4.4)	122 (3.1)	0.03
Histological CAM	151 (12.7)	1,960 (49.5)	<0.01
PROM	44 (3.7)	1,866 (47.2)	<0.01
NRFS	456 (38.4)	1,030 (26,0)	<0.01
ACS treatment	657 (55.3)	2,400 (60.7)	<0.01
Neonatal characteristics			
Male	538 (45.3)	2,097 (53.0)	<0.01
Birth height (cm)	34.5 (31.5–37.0)	34.5 (31.8–37.1)	0.07
Birth weight (g)	926 (697–1,126)	960 (740–1,207)	<0.01
Head circumference (cm)	25.5 (23.2–27.0)	25.0 (23.0–26.8)	<0.01
Small for gestational age	648 (54.5)	495 (12.5)	<0.01
RDS	812 (68.4)	2,530 (64.0)	<0.01
Chronic lung disease	313 (26.3)	1,075 (27.2)	0.57
PPHN	19 (1.6)	236 (6.0)	<0.01
IVH (III or IV)	17 (1.4)	160 (4.0)	<0.01
PVL	28 (2.4)	129 (3.3)	0.11
Sepsis	71 (6.0)	339 (8.6)	<0.01
Necrotizing enterocolitis	8 (0.7)	50 (1.3)	0.09
PDA banding	49 (4.1)	335 (8.5)	<0.01
LCC	125 (10.5)	508 (12.8)	0.03
Total parenteral nutrition	986 (83.0)	3,364 (85.0)	0.09

HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; DM, diabetes mellitus; CAM, chorioamnionitis; PROM, premature rupture of the membranes ; NRFS, non-reassuring fetal status; ACS, antenatal corticosteroid; RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the newborn; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; PDA, patent ductus arteriosus; LCC, late-onset circulatory collapse. Data are presented as the median (interquartile range) or n (%).

Table 2. Effect of intrauterine exposure to HDP on postnatal growth during the first 3 years after birth in the univariate and multivariate regression analyses

	Univariate	Multivariate #1	Multivariate #2
	β coefficient (95% CI)	β coefficient (95% CI)	β coefficient (95% CI)
Male height Δ Z-score	1.10 (0.97 to 1.23)	0.02 (−0.09 to 0.13)	0.03 (−0.08 to 0.13)
Male weight Δ Z-score	1.26 (1.13 to 1.39)	0.17 (0.05 to 0.30)	0.17 (0.05 to 0.30)
Female height Δ Z-score	0.92 (0.80 to 1.04)	0.04 (−0.06 to 0.15)	0.05 (−0.05 to 0.15)
Female weight Δ Z-score	1.17 (1.04 to 1.29)	0.27 (0.14 to 0.39)	0.27 (0.15 to 0.39)

The effect of HDP on the Δ Z-scores for height and weight between birth and 3 years of age in the HDP and non-HDP groups was evaluated using univariate and multivariate regression analyses. Multivariate analyses (#1 and #2) were adjusted for each covariate as follows:

#1 (prenatal and early postnatal factors): maternal age, parity, gestational age, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis, antenatal corticosteroid treatment, and Z-score of birth height (or weight).

#2 (prenatal, early postnatal, and postnatal factors at NICU discharge): maternal age, parity, gestational age, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis, antenatal corticosteroid treatment, Z-score of birth height (or weight), chronic lung disease, intraventricular hemorrhage (grade III/IV), periventricular leukomalacia, sepsis, necrotizing enterocolitis, patent ductus arteriosus banding, late-onset circulatory collapse, and total parenteral nutrition. Data are presented as β coefficients (95% confidence interval [CI]).

HDP, hypertensive disorders of pregnancy; CI, confidence interval

Table 3. Interaction between infant sex and HDP on postnatal body weight during the first 3 years

	Multivariate #1		Multivariate #2	
	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value
Infant sex × HDP	0.04 (−0.1 to 0.19)	0.55	0.12 (−0.03 to 0.27)	0.13

The interaction between infant sex and HDP on the Δ Z-score of body weight between birth and 3 years of age was evaluated using multivariate analyses. Multivariate analyses (#1 and #2) were adjusted for covariates, as follows:

#1 (prenatal and early postnatal factors): maternal age, parity, gestational age, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis, antenatal corticosteroid treatment, infant sex, Z-score of birth weight, and infant sex × HDP.

#2 (prenatal, early postnatal, and postnatal factors at NICU discharge): maternal age, parity, gestational age, mode of delivery, gestational diabetes mellitus/diabetes mellitus, histological chorioamnionitis, antenatal corticosteroid treatment, infant sex, Z-score of birth weight, chronic lung disease, intraventricular hemorrhage (grade III/IV), periventricular leukomalacia, sepsis, necrotizing enterocolitis, patent ductus arteriosus banding, late-onset circulatory collapse, total parenteral nutrition, and infant sex × HDP. Data are presented as β coefficients (95% confidence interval [CI]).

HDP, hypertensive disorders of pregnancy; CI, confidence interval