Impact of Preterm Birth and Post-Discharge Growth on Cardiometabolic Outcomes at School Age: A Case Control Study

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Abstract

Background: Adverse metabolic outcomes later in life have been reported among children or young adults who were born small for gestational age. This study was conducted to examine the impact of preterm birth and subsequent growth after hospital discharge on cardiometabolic risks among early school-aged children.

Methods: This case-control study included school-aged children born prematurely (n = 60) and at term (n = 110). Body size, fat mass, blood pressure (BP), glucose, insulin, leptin, adiponectin, and lipid profiles were measured. Weight z-score changes between discharge and early school-age period were also calculated, and factors associated with BP and insulin resistance were analyzed.

Results: Early school-aged children who were born preterm had lower fat masses, higher systolic BP and diastolic BP, and higher values of fasting glucose, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR), compared to children born at term. Preterm birth was correlated with HOMA-IR and BPs after adjusting for various factors, including fat mass index and weight z-score changes. Weight z-score changes were associated with HOMA-IR, but not with BPs.

Conclusions: Although early school-aged children born prematurely showed lower weight and fat mass, they had higher BPs, fasting glucose, HOMA-IR, and leptin levels. The associations of preterm birth with cardiometabolic factors were independent of weight, fat mass and weight gain velocity.

Background

Prematurity accounts for almost 10% of births. Despite improvements in the overall survival of preterm infants in recent decades [1–3], health inequalities emerge later in life in this population. Since the term “thrift phenomenon” was coined by Barker and colleagues [4], an association between low birth weight or small for gestational age (SGA) and cardiometabolic diseases, such as insulin resistance and increased blood pressure (BP), has been consistently demonstrated by many prospective and cohort studies [5–7]. As for preterm births, the association between cardiovascular diseases and metabolic syndrome in later life has also been demonstrated in a number of studies [8]. These cardiometabolic changes typically begin during infancy or school age [9–11].

A cohort study from New Zealand reported that extreme prematurity and high body mass index (BMI) at age 7–8 years were significant predictors of metabolic syndrome in young adulthood [5]. Obesity and accelerated postnatal growth during childhood were also suggested as risk factors for adverse cardiometabolic outcomes in children born preterm [12, 13]. However, it is not typical for children who were born prematurely to be fat or obese during childhood, even though they have cardiometabolic risks during this period [14, 15]. So far, the association between preterm birth and cardiometabolic risks at early school age, considering adiposity and growth velocity, has been scarcely studied.

This study aimed to investigate whether there are differences in the cardiometabolic factors in early school-aged children born prematurely, compared to term infants and whether these adverse cardiometabolic findings are associated with preterm birth and growth velocity.

Methods

Study design

This was a case-control study evaluating early school-aged children born as preterm and term infants. Preterm infants with gestational age (GA) < 32 weeks or birth weight < 1,500 g born between 2008 and 2009 in Seoul National University Hospital were screened and enrolled as the preterm group, if informed consent was received. Children with congenital anomalies and chromosomal abnormalities were excluded from the study. Children born in 2009 at term and enrolled in the healthy children cohort were included as the term group. This study was approved by the Institution of Review Board of Seoul National University Hospital (IRB No. H1509-030-702).

Data collection and laboratory analysis

Perinatal factors, including birth weight, GA, delivery mode, and sex were reviewed. SGA was defined as birth weight < 10th percentile for age. At 6 to 8 years of age, body measurements, including weight, height, and waist circumference were measured and BMI was calculated. Fat mass and fat free mass were measured using the InBody Test (BIA; InBody 770, Biospace Co., Seoul, Korea). BP was measured around the left upper arm using an appropriately sized cuff and an automated blood pressure measuring device, and the average of two blood pressure readings was calculated. Questionnaires, completed by the parents, were used to assess recent daily intakes of total energy and physical activity. The BMI of the parents was also collected at the time of evaluation.

Blood was obtained by venipuncture after fasting for at least 8 hours. Fasting glucose, insulin, lipid profile, leptin (Human Leptin RIA kit, LINCO Research, Inc., St. Charles., U.S.A.) and adiponectin (Human Adiponectin ELISA, Biovendor, Czech Republic) were measured. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), which was calculated as the product of the fasting plasma insulin level multiplied by the fasting plasma glucose level [HOMA-IR = (fasting plasma insulin [U/mL] × fasting plasma glucose [mg/dL])/(22.5 × 18.182)] [16]. To estimate the partial correlation coefficient for HOMA-IR, preterm birth, age, gender, SGA, mode of delivery, lean mass index, fat mass index, any breast milk feeding > 6 months, and weight z-score change were included.

To measure growth velocity in the study population, the change in weight z-score between discharge at term equivalent age from the neonatal intensive care unit and early school age was taken as a variable for preterm infants. For the term group, change in weight z-score between birth and early school age was calculated because preterm infants experience postnatal growth restriction during their stay in the neonatal intensive care unit. Preterm infants were further categorized according to their growth velocity between discharge at term equivalent age and school age. Those with a z-score change > 0 were defined

as preterm infants with positive growth and those with a z-score change ≤ 0 were defined as preterm infants with negative growth for the subgroup analysis of HOMA-IR, fasting glucose, systolic and diastolic BP at school age.

Statistical analysis

Data analysis was performed using STATA 12.0 for Windows (Stata Corp, College Station, TX, USA). The Wilcoxon rank sum test was used for the comparison of continuous variables, and Fisher's exact test was used for categorical variables. HOMA-IR, leptin, and adiponectin-leptin ratios were skewed and transformed onto a logarithmic scale before analysis. Correlations between variables and cardiometabolic outcomes such as HOMR-IR, systolic and diastolic BP at school age were evaluated using Pearson's correlation coefficient and regression analyses. P-values < 0.05 were considered statistically significant. Data are presented as the median (interquartile range) or rates. Listwise deletion was used to handle missing data.

Results

Demographic findings of the study population

Sixty preterm and 110 term infants were included in the study. GA and birth weight were 28.4 weeks (interquartile range, 26.3–30.5 weeks) and 935 g (790-1,220 g) in the preterm group and 39.6 weeks (38.4–40.3 weeks) and 3,240 g (2,970-3,500 g) in the term group (Table 1). Postmenstrual age and weight at discharge were 37.9 weeks (36.1–40.6 weeks) and 2,300 g (1,960-2,580 g) in the preterm infants. SGA infants and Cesarean sections were more prevalent in the preterm group. The incidence of breastmilk feeding at > 6 months of age was observed more frequently in the term group. There were no differences in parental education level and parental BMI between the two groups.

Table 1. Demographic and parental information of the study population

	Preterm (n = 60)	Term (n = 110)	p-value
GA at birth (weeks)	28.4 (26.3–30.5)	39.6 (38.4–40.3)	< 0.001
Birth weight (g)	935 (790–1220)	3240 (2970–3500)	< 0.001
Birth weight z-score	-0.2 (-1.3-0.3)	-0.2 (-0.9-0.2)	0.388
SGA	15 (25)	9 (8.2)	0.005
Female	28 (46.7)	57 (51.8)	0.630
Cesarean section	41 (68.3)	35 (31.8)	< 0.001
PMA at discharge (weeks)	37.9 (36.1–40.6)	-	-
Weight at discharge (g)	2300 (1960–2580)	-	-
Weight z-score at discharge	-1.7 (-3.3–1)	-	-
Any breastmilk feeding > 6 months	24 (46.2)	67 (77)	< 0.001
Paternal education college or above	48 (80)	87 (79.1)	1.000
Maternal education college or above	48 (80)	90 (81.8)	0.838
Paternal BMI (kg/m^2)	24.8 (22.1–25.9)	24.4 (22.8–26.4)	0.573
Maternal BMI (kg/m^2)	21.1 (19.1–22.6)	21.5 (19.7–24)	0.146

Values are expressed as n (%) or median (interquartile range).

GA gestational age, *SGA* small for gestational age, *BMI* body mass index, *PMA* postmenstrual age.

Body measurements at early school age

The average age at evaluation was 7.2 years (6.8–7.5 years) in the preterm group and 7.8 years (6-7.9 years) in the term group (p = 0.801) (Table 2). We found the z-scores for weight and height were significantly lower in the preterm group. Although BMI was lower in the preterm group (15.0 vs. 15.5 kg/m^2, p = 0.003), BMI z-scores were comparable between the two groups (-0.5 vs. -0.3, p = 0.07). Lean body mass (18.4 vs. 19.2 kg, p = 0.18) and lean mass index (12.6 vs. 12.9 kg/m^2, p = 0.09) were also comparable between the two groups. Fat mass (3.1 vs. 4.1 kg, p = 0.002) and fat mass index (2.1 vs. 2.8 kg/m^2, p = 0.002) were lower in the preterm group. Daily caloric intake, weekly physical activity, and walk hours were comparable between the two groups.

Table 2. Body measurements in early school-aged children

	Preterm (n = 60)	Term (n = 110)	p-value
Age (year)	7.2 (6.8–7.5)	7.8 (6-7.9)	0.801
Weight (kg)	20.8 (19.5–24.8)	23 (19.9–26.9)	0.028
Weight z-score	-0.8 (-1.3-0.1)	0 (-0.8-0.9)	0.001
Change in weight z-score	1.4 (0.2–2.8)	0.2 (-0.4-0.9)	< 0.001
Height z-score	-0.3 (-1-0.1)	0.2 (-0.2-0.9)	< 0.001
BMI (kg/m^2)	15 (13.9–15.9)	15.5 (14.6–16.9)	0.003
BMI z-score	-0.5 (-1.5-0.2)	-0.3 (-1-0.5)	0.072
Lean body mass (kg)	18.4 (16.9–20.2)	19.2 (17.1–21.2)	0.180
Lean mass index (kg/m^2)	12.6 (12-13.1)	12.9 (12.3–13.4)	0.091
Fat mass (kg)	3.1 (2.1–4.1)	4.1 (2.8–5.8)	0.002
Fat mass index (kg/m^2)	2.1 (1.6–2.9)	2.8 (1.9–3.9)	0.002
Waist circumference (cm)	51.6 (49-54.3)	53.8 (50–57)	0.013
Calorie intake (Kcal/day)	1537 (1345.9-1709.4)	1441.4 (1299.4-1588.1)	0.114
Moderate or more activity[a]	120 (20–320)	180 (70–300)	0.140
Walking time[a]	120 (30–210)	120 (60–210)	0.403

Values are expressed as the median (interquartile range).

BMI body mass index, *BP* blood pressure.

[a]values expressed as hours/week

Blood pressures and laboratory findings

Systolic and diastolic BPs were higher in the preterm group (107 vs 97.5 mmHg, p < 0.001, and 64 vs 59 mmHg, p < 001, respectively) (Table 3). In comparison to children born at term, children born prematurely had significantly higher high-density lipoprotein (HDL) cholesterol, fasting glucose, and HOMA-IR. Leptin was also higher in the preterm group, while adiponectin was comparable between the two groups.

Table 3. Blood pressures and laboratory findings of metabolic syndrome

	Preterm (n = 60)	Term (n = 110)	p-value
Systolic BP (mmHg)	107 (102.5–111)	97.5 (93–102)	< 0.001
Diastolic BP (mmHg)	64 (59.3–68.5)	59 (54.5–64)	< 0.001
HDL-Cholesterol (mg/dl)	69 (61–79)	64 (55–73)	0.010
TG (mg/dl)	60 (46–74)	57.5 (48–74)	0.844
Fasting glucose (mg/dl)	96 (93–101)	93 (88–97)	< 0.001
Fasting insulin (mU/ml)	4.4 (3.4–5.9)	3.7 (2.6–5.8)	0.053
HOMA-IR	1.05 (0.81–1.49)	0.84 (0.58–1.35)	0.017
Leptin (ng/ml)	6.4 (5.1–10)	5.8 (4-9.3)	0.040
Adiponectin (µg/mL)	9.7 (7.2–11.5)	8.9 (6.6–10.9)	0.297

Values are expressed as the median (interquartile range).

BP blood pressure. *HDL-Cholesterol* high-density lipoprotein cholesterol, *TG* triglyceride, *HOMA-IR* Homeostasis model assessment of insulin resistance.

Factors related to HOMA-IR, systolic and diastolic blood pressures

In a simple regression analysis, preterm birth, age, lean mass index, fat mass index, and weight z-score change were related to HOMA-IR (Table 4). Partial correlation analysis showed that preterm birth, as well as age, fat mass index and weight z-score change had a positive correlation.

Table 4
Partial correlation analysis for HOMA-IR and systolic and diastolic BP

	HOMA-IR*		Systolic BP		Diastolic BP	
	Simple coef	Partial beta	Simple coef	Partial beta	Simple coef	Partial beta
Preterm birth	0.282§	0.203¶	9.173§	0.471§	4.459§	0.340§
Age (year)	0.201§	0.209§	2.020¶	0.118	2.906§	0.201¶
Female	0.103	-0.025	1.482	0.120	0.429	0.017
LMI (kg/m^2)	0.165§	-0.172	0.126	-0.072	1.172	-0.008
FMI (kg/m^2)	0.130§	0.224¶	0.548	0.139	1.108§	0.385§
Weight z-score change	0.216§	0.374§	2.239§	0.094	1.082¶	-0.127

Adjusted for preterm birth, age, sex, small for gestational age, mode of delivery, lean mass index, fat mass index, any breastmilk feeding > 6 months and weight z-score change. * Transformed onto a logarithmic scale.

HOMA-IR Homeostatic model assessment- insulin resistance, *LMI* lean mass index, *BMI* body mass index. $p < 0.05$ and § $p < 0.01$

Simple regression analysis showed that preterm birth, age, and weight z-score change had a positive correlation with systolic BP (Table 4). In the partial correlation analysis, preterm birth was the only factor associated with higher systolic BP. Diastolic BP was related to preterm birth, age, fat mass index, and weight z-score change in the simple regression. Preterm birth, as well as age and fat mass index, had positive correlations with diastolic BP in partial correlation analysis.

Cardiometabolic findings among preterm and term infants according to growth velocity

When preterm infants were further categorized into those with positive growth or negative growth, we found that preterm infants with positive growth showed higher HOMA-IR, fasting glucose, and systolic and diastolic BPs than term infants (Fig. 1). However, preterm infants with negative growth showed no differences in HOMA-IR and fasting glucose, compared to term infants. Systolic BP was higher in preterm infants than term infants, irrespective of their post-discharge growth velocity. Systolic and diastolic BPs were comparable between the two preterm groups, while fasting glucose was higher in preterm infants with positive growth than those with negative growth.

Discussion

In this case-control study, preterm infants were compared with term infants in the cardiometabolic outcomes at school age, and important factors associated with outcomes such as post-discharge growth, weight, lean body mass and fat mass were considered and adjusted. Early school-aged children who were born preterm had higher BP, more insulin resistance, and higher fasting glucose than those who were term infants, while weight and fat mass were lower in the preterm group. Insulin resistance and BPs were associated with preterm birth, independent of lean mass index and fat mass index. The weight z-score change from the neonatal period to school age was not associated with BPs but had a correlation with insulin resistance in the multivariate analysis.

Patterns of growth, as well as alterations in adipose tissue, were different between SGA infants and preterm infants. Previous SGA studies reported that they had less adipose tissue at birth, becoming similar after the neonatal period [17], and a higher fat distribution was observed in childhood and adolescence [18, 19]. However, for the preterm infants, lower BMI and fat mass were frequently seen compared with term infants until infancy and school age [20, 21], even though they had higher BMIs and fat mass with adverse cardiometabolic outcomes in adulthood [22–25].

Although the interaction between obesity and insulin resistance is a key pathogenesis factor in the development of metabolic syndrome [26], cardiometabolic problems in preterm infants at school age have been reported, despite a lower BMI during this period [10, 27]. In the present study, to elucidate the effect of body composition more clearly, fat mass and lean body mass were measured and adjusted, and the results showed that preterm birth was independently associated with increased BP and HOMA-IR.

Moreover, as catch-up growth is an important factor in the development of insulin resistance [28], weight z-score change until school age was considered and adjusted, and it was found to be associated with insulin resistance. The weight z-score was much lower in preterm infants at discharge compared to term infants, with a subsequent increase by early school age, resulting in a higher weight gain velocity in preterm infants in this study, even though the weight z-score was still lower than that of term infants. As with SGA infants [29, 30], preterm infants experienced the development of insulin resistance during rapid weight gain [31].

On the other hand, while BPs were associated with preterm, weight z-score change was not associated with BPs at school age. Although the mechanisms of elevated BP in children born prematurely are not fully understood, impaired development of the glomeruli with decreased nephrons, microvascular growth arrest, and sympathoadrenal overactivity might be contributing factors [9, 32, 33]. These conditions were associated with preterm birth and related morbidities during a neonatal intensive care unit stay, rather than the pattern of growth beyond the neonatal period. However, the influence of weight gain velocity on increased BP should not be ignored because a longitudinal cohort study from the UK showed that growth gain velocity from 1 year of age until adolescence was correlated with systolic and diastolic BP [34].

When preterm infants were further categorized according to their growth velocity, cardiometabolic factors were consistently higher in the preterm infants with improved growth group, compared to term infants. However, there were no differences in the HOMA-IR and fasting glucose between term infants and preterm

infants with negative growth, and HOMA-IR was even lower in the preterm infants with negative growth group than in the group with positive growth. Interestingly, systolic BP was higher in both preterm infant groups, regardless of growth velocity after discharge, and there were no differences in the systolic and diastolic BPs between the two preterm groups. Notwithstanding the small sample sizes used for these subgroup analyses, they did demonstrate an impact of the growth pattern in preterm infants on adverse cardiometabolic findings, as shown in the multivariate analysis.

There are several limitations to our study. A relatively small patient population was analyzed, and the growth velocity of the early post-discharge period, such as the time between discharge and one year of age, was not compared. Also, the fat mass was not measured by dual energy X-ray absorptiometry (DEXA). However, bioelectrical impedance analysis is a useful method for estimating body composition and has been used in both clinical and research fields in the pediatric population [35, 36]. The aforementioned New Zealand Very Low Birth Weight Study also used bioelectrical impedance as a method to measure fat mass [5].

Conclusions

In this study, preterm birth was found to represent an important risk factor for elevated BP, independent of weight, fat mass and growth velocity after discharge. Preterm birth, as well as growth velocity, was also related to increased insulin resistance. Despite the low weight and low fat mass, children born prematurely may be at a higher risk for increased BP, and preterm infants with better weight gain after discharge may be at risk of insulin resistance during early school age. Further studies are required to investigate the growth pattern of preterm infants, including detailed fat distribution, to determine an appropriate growth in this population to minimize the risk of adverse cardiometabolic outcomes.

Abbreviations

BMI
body mass index; BP:blood pressure; HOMA-IR:Homeostatic Model Assessment of Insulin Resistance; SGA:small for gestational age; GA gestational age; PMA:postmenstrual age; HDL:high-density lipoprotein; DEXA:dual energy X-ray absorptiometry; TG:triglyceride

Declarations

Ethics approval and consent to participate

This study was approved by the Institution of Review Board of Seoul National University Hospital (IRB No. H1509-030-702) and written consents were obtained from parents or guardians on behalf of participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Each author has met the authorship requirements. YHJ and JY conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; SHS contributed to the conceptualization and design of the study, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; YAL, IGS, CHS, E-K K, and H-S K critically reviewed the manuscript for important intellectual content; all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

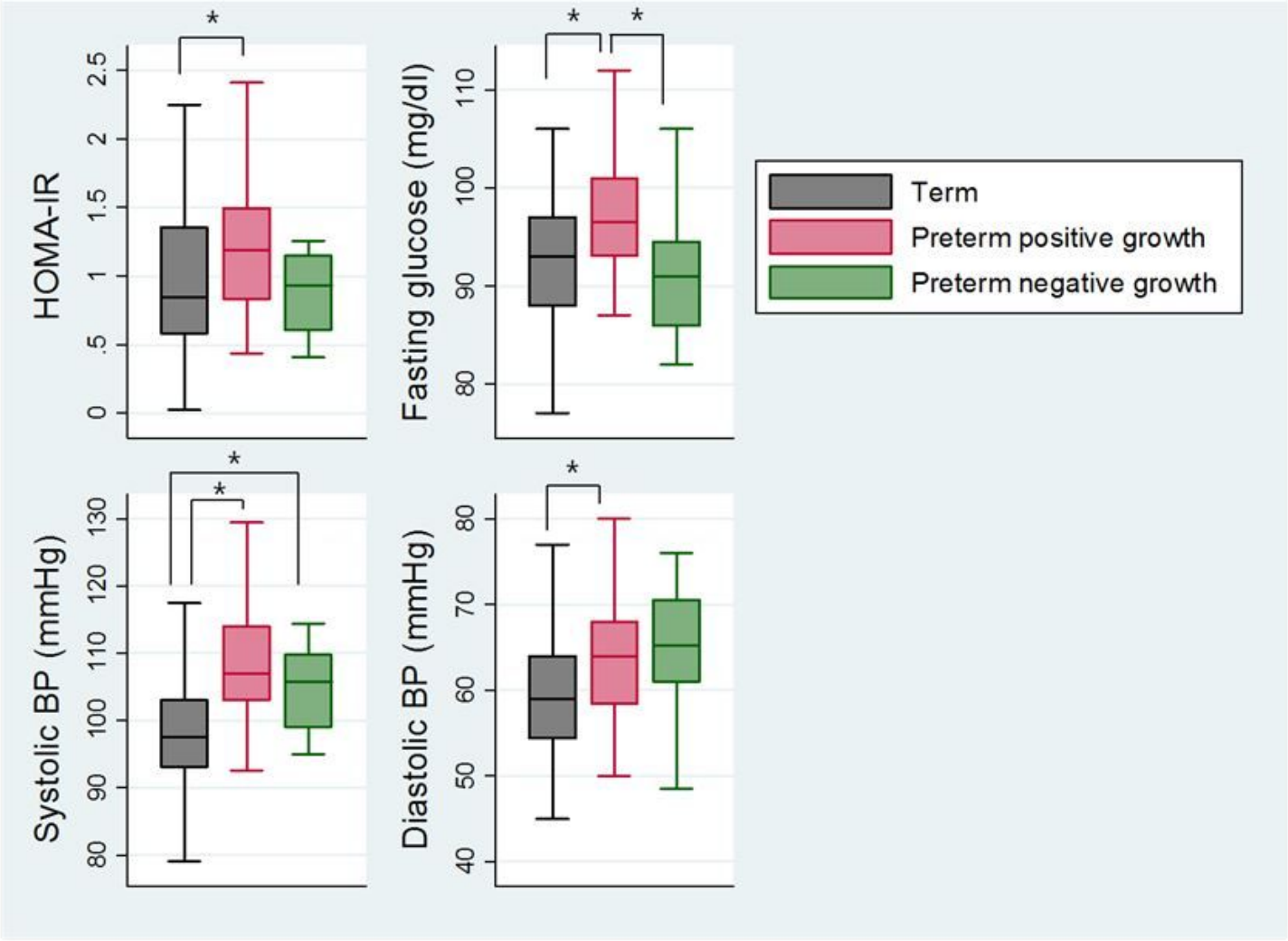
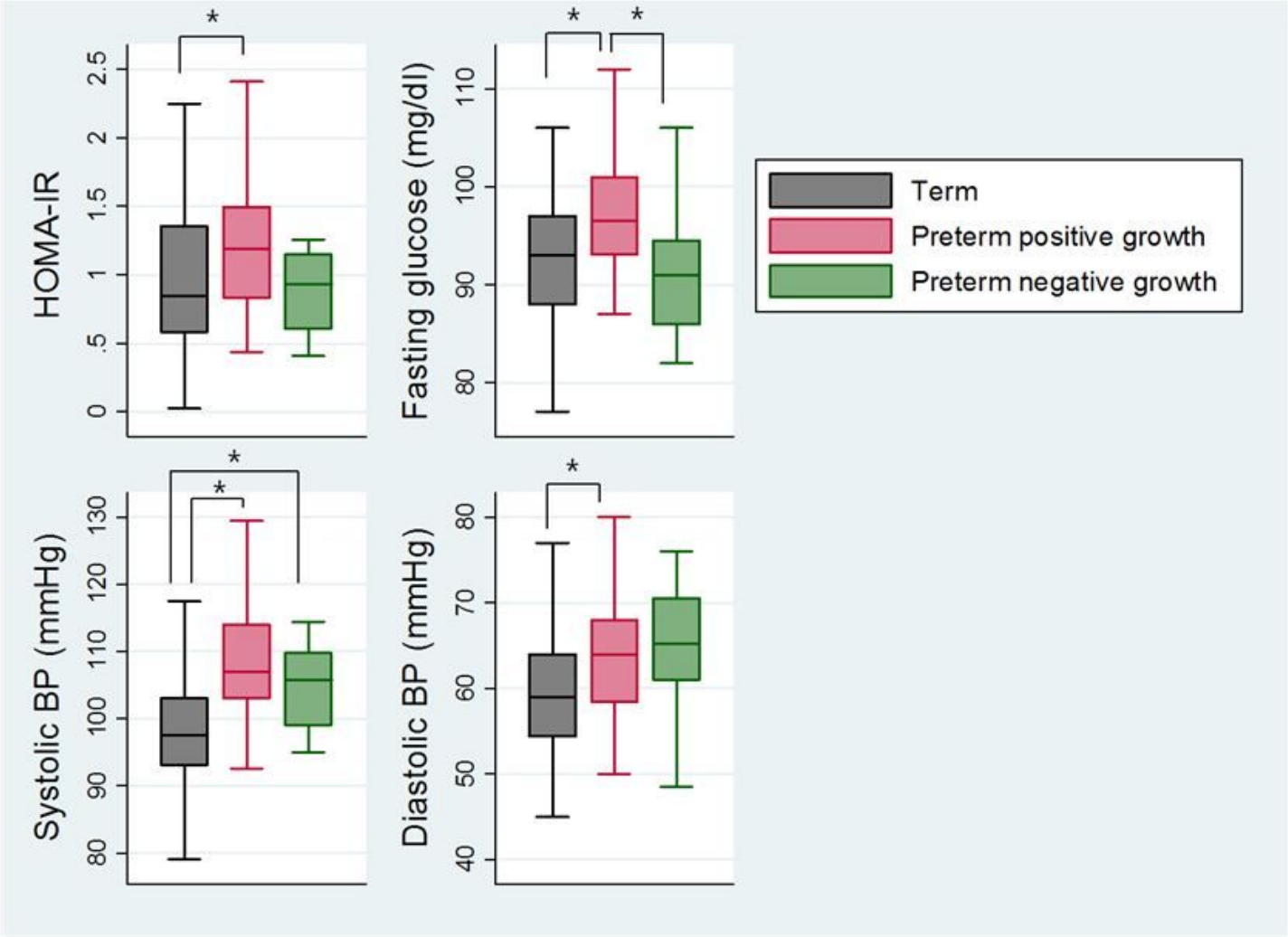


Figure 1

Cardiometabolic findings of preterm infants according to growth pattern and term infants. Preterm infants with improved growth showed higher HOMA-IR, fasting glucose, and systolic and diastolic BPs than term infants. Preterm infants with negative growth had a higher systolic BP than term infants but showed lower fasting glucose than preterm infants with positive growth. HOMA-IR homeostasis model assessment of insulin resistance, BP blood pressure.



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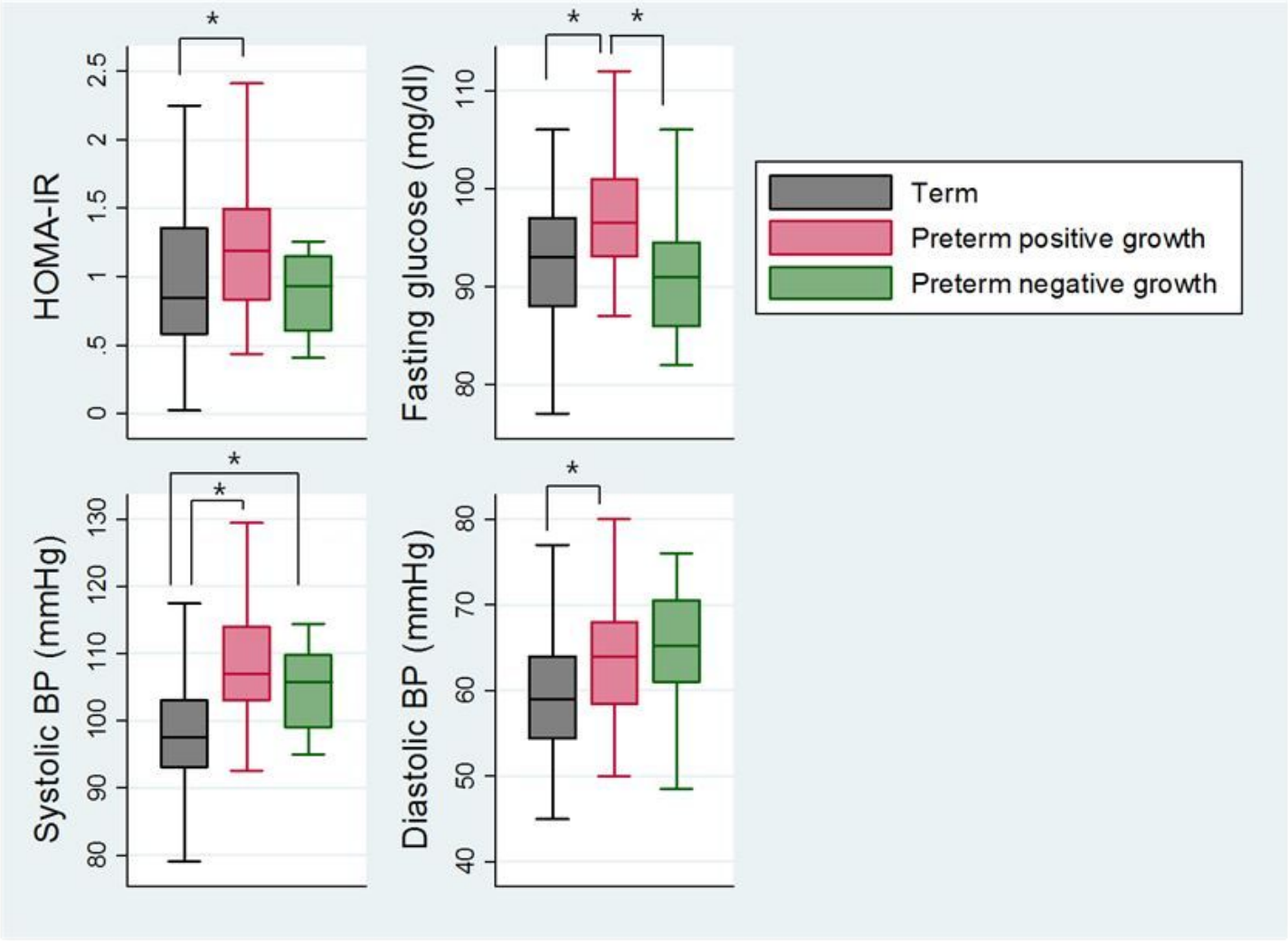

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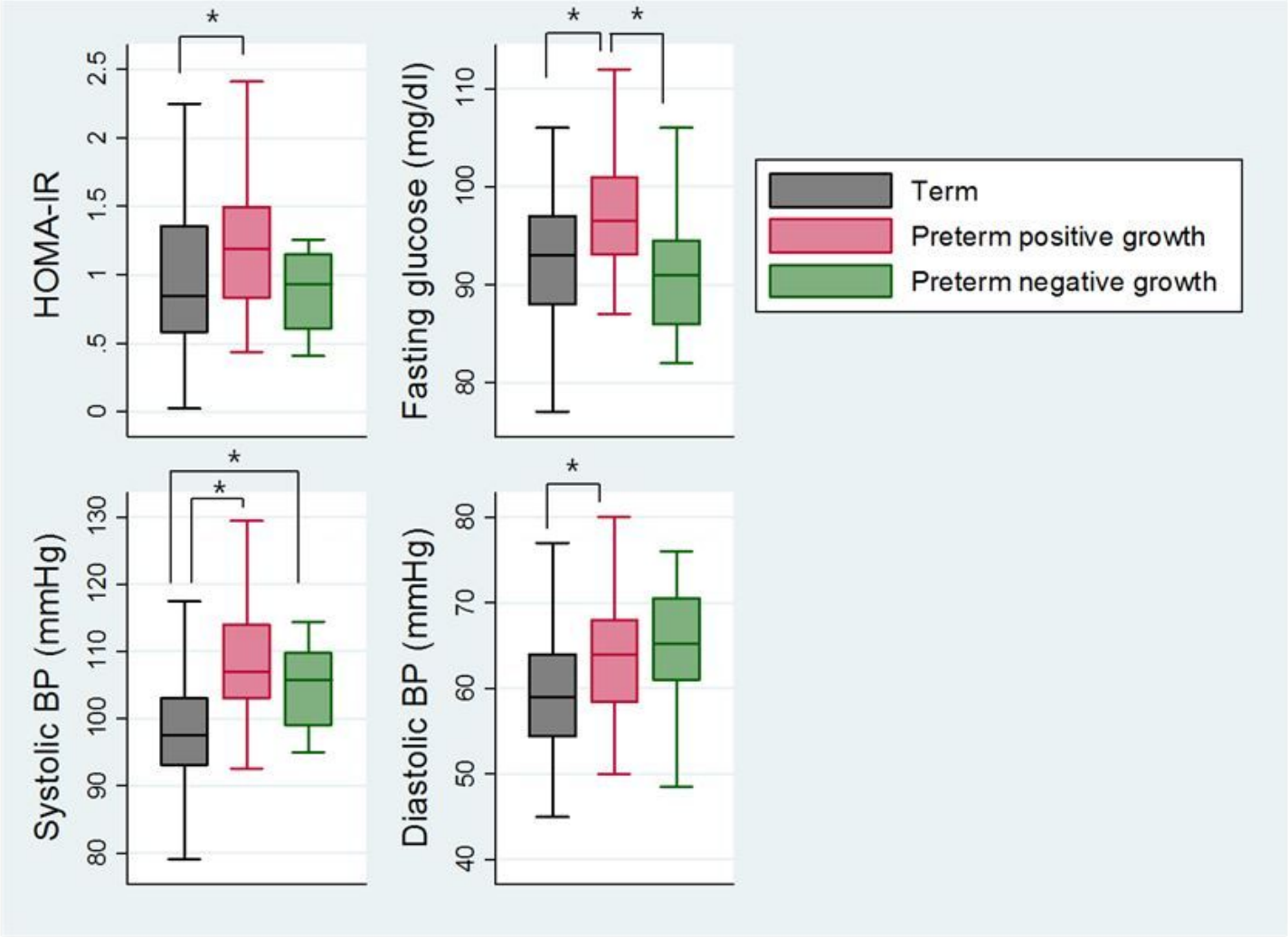

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