Original Investigation

Preterm Birth and Random Plasma Insulin Levels at Birth and in Early Childhood

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IMPORTANCE Although previous reports have linked preterm birth with insulin resistance in children and adults, it is not known whether altered insulin homeostasis is detectable at birth and tracks from birth through childhood.

OBJECTIVE To investigate whether preterm birth is associated with elevated plasma insulin levels at birth and whether this association persists into early childhood.

DESIGN, SETTING, AND PARTICIPANTS A prospective birth cohort of 1358 children recruited at birth from 1998 to 2010 and followed-up with prospectively from 2005 to 2012 at the Boston Medical Center in Massachusetts.

MAIN OUTCOMES AND MEASURES Random plasma insulin levels were measured at 2 time points: at birth (cord blood) and in early childhood (venous blood). The median age was 1.4 years (interquartile range [IQR], 0.8-3.3) among 4 gestational age groups: full term (≥39 wk), early term (37-38 wk), late preterm (34-36 wk), and early preterm (<34 wk).

RESULTS The geometric mean of insulin levels at birth were 9.2 μIU/mL (95% CI, 8.4-10.0) for full term; 10.3 μIU/mL (95% CI, 9.3-11.5) for early term; 13.2 μIU/mL (95% CI, 11.8-14.8) for late preterm; and 18.9 μIU/mL (95% CI, 16.6-21.4) for early preterm. In early childhood, these levels were 11.2 μIU/mL (95% CI, 10.3-12.0) for full term; 12.4 μIU/mL (95% CI, 11.3-13.6) for early term; 13.3 μIU/mL (95% CI, 11.9-14.8) for late preterm; and 14.6 μIU/mL (95% CI, 12.6-16.9) for early preterm. Insulin levels at birth were higher by 1.13-fold (95% CI, 0.97-1.28) for early term, 1.45-fold (95% CI, 1.25-1.65) for late preterm, and 2.05-fold (95% CI, 1.69-2.42) for early preterm than for those born full term. In early childhood, random plasma insulin levels were 1.12-fold (95% CI, 0.99-1.25) higher for early term, 1.19-fold (95% CI, 1.02-1.35) for late preterm, and 1.31-fold (95% CI, 1.10-1.52) for early preterm than those born full term. The association was attenuated after adjustment for postnatal weight gain and was not significant after adjustment for insulin levels at birth. Infants ranked in the top insulin tertile at birth were more likely to remain in the top tertile (41.2%) compared with children ranked in the lowest tertile (28.6%) in early childhood.

CONCLUSIONS AND RELEVANCE There was an inverse association between gestational age and elevated plasma insulin levels at birth and in early childhood. The implications for future development of insulin resistance and type 2 diabetes warrant further investigation.

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In the United States, preterm birth affects 1 in 9 live births and 1 in 5 live births among African Americans.[1] In contrast to the well-established association between term low birthweight and adult diseases, much less is known about the role of preterm birth in the later development of chronic diseases. Such information is needed in light of the persistently high rates of incidence of preterm birth and survival among those born preterm in the United States.[2] Available studies have linked preterm birth to insulin resistance[3-7] and type 2 diabetes in childhood,[3] young adulthood,[4,5] and middle-adulthood.[6,8]

Our study intends to fill the knowledge gap on preterm birth and metabolic risk during early developmental periods. The in utero and early childhood periods are critical windows for growth, development, imprinting, and the establishment of an epigenome and are highly sensitive to environmental perturbation. There is growing evidence that fetal and early life events may result in permanent metabolic alterations, such as type 2 diabetes and metabolic syndrome.[9-12] Although available studies in children and adults support the hypothesis that preterm birth may result in adverse metabolic alterations, it is unclear whether the observed association between preterm birth, later insulin resistance, and type 2 diabetes stems from alterations in insulin metabolism during the in utero period or in early childhood.

Our study used a prospective birth cohort enriched by a spectrum of preterm births and tested the hypothesis that preterm birth is associated with elevated plasma insulin levels (indirect evidence of insulin resistance) at birth that persist into early childhood, defined as the period from birth to age 6.5 years.

Methods

The study protocol was approved by the institutional review boards of Boston University Medical Center, the Ann & Robert H. Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital of Chicago), and the Johns Hopkins Bloomberg School of Public Health. Written informed consent was obtained from the mothers. As illustrated in **Figure 1**, this study included 1358 children from the Boston Birth Cohort who were recruited at birth (from 1998 to 2010), followed-up prospectively from 2005 to 2012, and had plasma insulin measurement at birth or during postnatal follow-up (age range, 0.5-6.5 years); median age, 1.4 years (interquartile range [IQR], 0.8-3.3). As detailed in our previous report,[13] a rolling enrollment was initiated in 1998 and targeted all mothers who delivered singleton live preterm (<37 wk) or low-birthweight (<2500 g) infants and matched term (≥37 wk) normal birthweight (>2500 g) controls by maternal age and parity, with a case to control ratio of 1:2. The exclusion criteria for initial enrollment included multiple-gestation pregnancies (eg, twins and triplets) and newborns with major birth defects. Since 2003, the subset that continued to receive pediatric care at the Boston Medical Center has been followed-up from birth onwards. The exclusion criteria for the follow-up included not being enrolled in the original birth cohort or not planning to receive pediatric care at Boston Medical Center. The cohort participation rate was more than 90% for initial enrollment and postnatal follow-up among eligible participants approached by the research staff. Of 2870 children who were eligible for postnatal follow-up, 1512 were excluded from this analysis for the following reasons: 228 refused to participate in the follow-up study; 1183 had insufficient blood samples; 101 had insulin measured at older than 6.5 years (to eliminate potential confounding due to adrenarche or puberty). This study included 1358 children. Maternal demographic characteristics and birth outcomes were comparable with the total eligible for postnatal follow-up, as well as to the entire Boston Birth Cohort (eTable 1 in the Supplement).

Definition of Maternal and Perinatal Characteristics

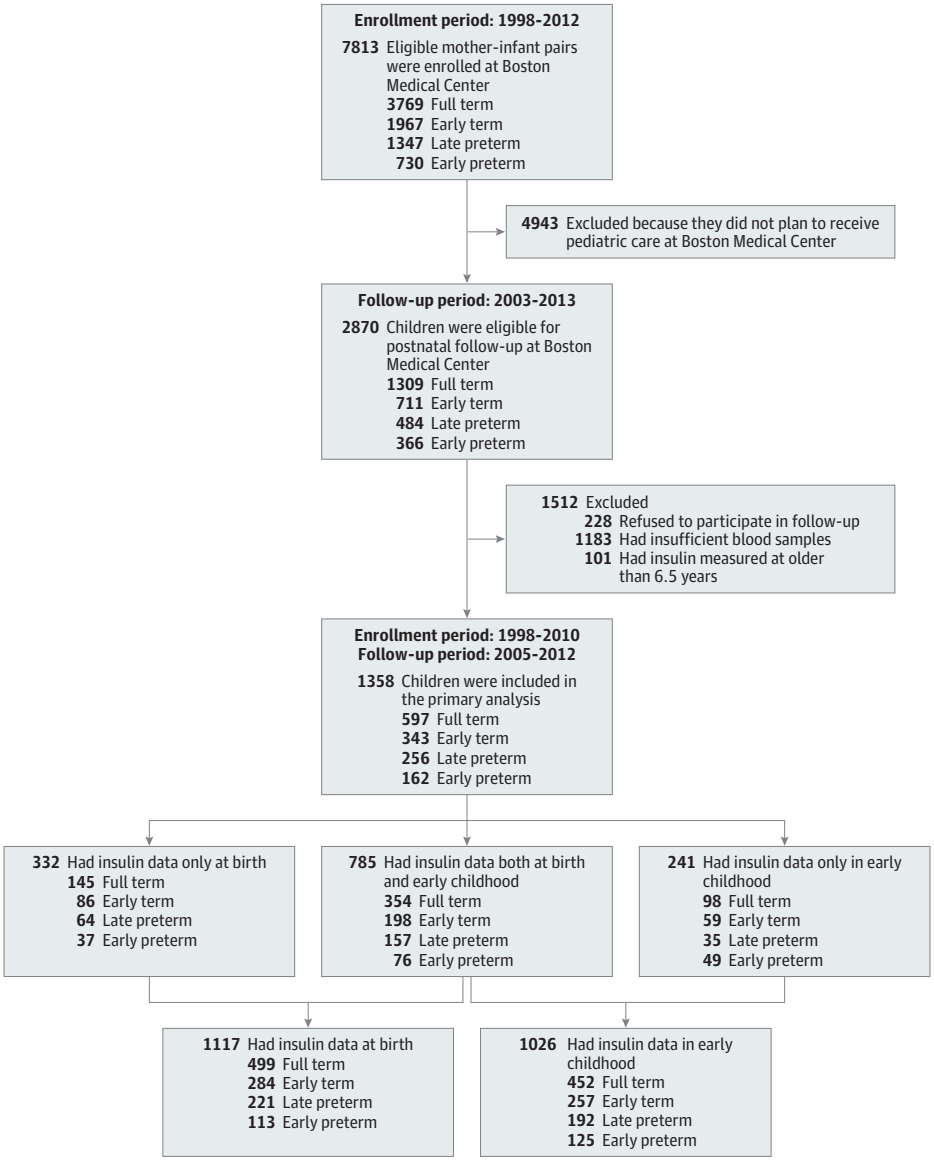
Maternal variables were defined based on a standard maternal questionnaire interview. Race/ethnicity was based on maternal response to fixed categories in the questionnaire and classified as black, Hispanic, white, or other. Race/ethnicity was treated as a confounder due to a well-observed racial disparity in preterm births and diabetes (black populations have higher rates of preterm birth and diabetes in the United States).[1,14] Prepregnancy body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was calculated based on prepregnancy height and weight.[15] Maternal smoking during pregnancy was classified into 3 groups: never smoker (did not smoke cigarettes throughout index pregnancy), quitter (only smoked in the 3 months before pregnancy or during the first trimester), or continuous smoker (smoked continuously from prepregnancy to delivery).[13] Perceived stress during pregnancy was defined based on the responses to the following question: "How would you characterize the amount of stress in your life during pregnancy?" Answers of "not stressful" and "average stressful" were coded as low stress, and "very stressful" was coded as high stress.[16]

The following maternal variables were defined based on maternal medical records: *maternal diabetes* was defined as having either gestational or pregestational diabetes[17] and *hypertensive disorders* as 1 or more of the following during pregnancy: preeclampsia, eclampsia, chronic hypertension, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.[16] Mode of delivery was categorized into cesarean or vaginal delivery.

Definition of Gestational Age, Birthweight for Gestational Age, and Apgar Scores

All the following variables are based on medical records. Gestational age was assessed based on both the first day of the last menstrual period and using early prenatal ultrasonographic results, as described previously.[13] Preterm birth is defined as gestational age less than 37 weeks, and further grouped into late preterm (34-36 wk) and early preterm (<34 wk). To improve health outcomes for newborns and limit unnecessary early deliveries, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recently revised the classification system for term birth.[18] Accordingly,

Figure 1. Flowchart of Initial Enrollment and Postnatal Follow-up of the Boston Birth Cohort and the Sample Included in the Analysis



Eligible mother-infant pairs were those who delivered a singleton live birth at the Boston Medical Center. Multiple-gestation pregnancies (eg, twins or triplets) or newborns with major birth defects were excluded. Early childhood age range was 0.5 to 6.5 years; median age was 1.4 years (interquartile range, 0.8-3.3). The Boston Birth Cohort initiated a rolling enrollment in 1998. The follow-up was initiated in 2003. Our study participants were a subset of the Boston Birth Cohort, thus the enrollment and follow-up are different than the Boston Birth Cohort.

term birth is defined as 37 weeks or more of gestation, and further grouped into early term (37-38 wk) and full term (≥39 wk).

Birthweight for gestational age is categorized into 3 groups: small for gestational age (<10th percentile), large for gestational age (>90th percentile), and appropriate for gestational age (10th-90th percentile) according to an established local sex- and race-specific reference population.[19] Apgar scores at 1 and 5 minutes were both coded into 3 groups: 0 through 4, 5 through 7, and 8 through 10.[20] Antenatal steroid intake was coded as none vs at least 1 dose.[21]

Assessment of Postnatal Growth, Adiposity, and Breastfeeding

Height, length, and weight were abstracted from the childrens' medical records. The BMI was calculated based on weight and height/length, and converted to age- and sex-specific BMI *z* scores based on the World Health Organization's growth chart[22] for children younger than 2 years. The BMI *z* scores for children older than 2 years and weight-for-age *z* scores were calculated using US national reference data.[23] *Weight gain in the first year of life* was defined as the change in weight-for-age *z* scores between birth and the first year of life and then categorized into 2 groups: rapid weight gain (change in *z* score, >0.67) and nonrapid weight gain (change in *z* score, ≤0.67).[24] Plasma leptin levels were used as a proxy for total body adiposity.[25-27] Information on infant feeding was obtained using a standardized postnatal follow-up questionnaire and categorized into 3 groups: (1) exclusively formula fed, (2) exclusively breastfed, or (3) both.[28]

Assays of Plasma Insulin and Leptin

Umbilical cord blood was collected at delivery, and postnatal venous blood was collected at follow-up visits. Plasma was stored in a −80°C freezer. Plasma insulin levels were measured in cord blood at birth and in the first available postnatal venous blood sample (age range, 0.5-6.5 years; median, 1.4 years [IQR, 0.8-3.3]). Plasma insulin and leptin levels were measured using a sandwich immunoassay (Luminex multianalyte profiling system, Luminex Corp) with an interassay coefficient of variation of 4.0% for plasma insulin and 4.5% for leptin. The immunoassay kit was obtained commercially from Millipore Corp. Each sample was run in duplicate, and the intraassay coefficients of variation for insulin and leptin were 4.3%.

Statistical Analysis

The primary outcomes of interest were plasma insulin levels at birth and in early childhood. We used locally weighted regression smoothing plots (PROC LOESS) to explore the relationship between gestational age and plasma insulin levels at birth as well as tracking of plasma insulin levels from birth to early childhood. Linear regression models were applied to estimate the crude and adjusted associations between gestational age groups (*X*, independent variables) and log-transformed insulin levels at birth and in early childhood (*Y*, dependent variables). To make the results easy to interpret, all of the regression coefficients were exponentiated (exp[β]), and represent the point estimate of the fold change of *Y* on the original scale, for the specific gestational age groups (early term, late preterm, and early preterm) compared with the full-term group (reference group). The variance and standard deviation of the fold change of *Y* were calculated based on Delta methods[29] and the 95% CI of the fold change of *Y* were calculated with the following equation: exp(β) +/− 1.96 × SD. Both exp(β) and the corresponding 95% CI were reported. All *P* values for linear trend were based on models using gestational age as a continuous variable. Those associations with *P* values (2-sided tests) less than .05 were regarded as statistically significant. The adjusted models included pertinent covariables (including maternal race, parity, smoking, antenatal steroid use, gestational or pregestational diabetes), child's sex, Apgar score at 1 minute, birthweight for gestational age, hour of day at the study visit, plasma leptin (at the same time point as insulin), age at measurement, rapid weight gain in the first year of life, and insulin level at birth. These covariables were chosen based on previous literature and multiple stepwise regression analysis (entry criteria: if the *P* value of the *F* test was <.05; removal criteria: if the *P* value of the *F* test was >.10). All statistical analyses were performed using SAS (SAS Institute), version 9.3.

Results

Of the 1358 children included in the analysis, 418 were born preterm (162 early preterm, 256 late preterm), and 940 were born at term (343 early term and 597 full term). As illustrated in Figure 1, of 1358 children, 1117 had insulin measured at birth, 1026 in early childhood, and 785 at both time points. Maternal and infant characteristics by gestational age groups are presented in **Table 1** and **Table 2**. Maternal smoking, diabetes, hypertensive disorders, cesarean delivery, and antenatal steroid use were more prevalent in preterm births. At birth, the geometric mean of insulin levels were 9.2 µIU/mL (95% CI, 8.4-10.0) for full term, 10.3 µIU/mL (95% CI, 9.3-11.5) for early term, 13.2 µIU/mL (95% CI, 11.8-14.8) for late preterm, and 18.9 µIU/mL (95% CI, 16.6-21.4) for early preterm births (to convert insulin to pmol/mL, multiply by 6.945). In early childhood, these levels were 11.2 µIU/mL (95% CI, 10.3-12.0) for full term, 12.4 µIU/mL (95% CI, 11.3-13.6) for early term, 13.3 µIU/mL (95% CI, 11.9-14.8) for late preterm, and 14.6 µIU/mL (95% CI, 12.6-16.9) for early preterm births.

Association Between Gestational Age and Plasma Insulin Levels at Birth

As shown in **Figure 2**, cord blood insulin levels were inversely associated with gestational age, regardless of birthweight for gestational age. This association was further quantified by regression models (**Table 3**): cord blood insulin levels were 1.13-fold (95% CI, 0.97-1.28) higher for early term, 1.45-fold (95% CI, 1.25-1.65) for late preterm, and 2.05-fold (95% CI, 1.69-2.42) for early preterm than full term (*P* value for linear trend <.001; crude model). This association remained after adjustment for pertinent covariables. Pertinent covariables included maternal race, cigarette smoking, parity, diabetes status, antenatal steroid use, infant's sex, Apgar score at 1 minute, birthweight for gestational age, and leptin levels at birth. We performed additional analyses by restricting the sample to children with insulin measured both at birth and in early childhood (n = 785) and found similar results (eTable 2 in the Supplement).

Association Between Preterm Birth and Plasma Insulin Levels in Early Childhood

As shown in Table 3, plasma insulin levels in early childhood were also inversely associated with gestational age. Plasma insulin levels were higher by 1.12-fold (95% CI, 0.99-1.25) for early term, 1.19-fold (95% CI, 1.02-1.35) for late preterm, and 1.31-fold (95% CI, 1.10-1.52) for early preterm than for children born full term (*P* value for linear trend <.001). This association remained significant after adjusting for other covariables, including maternal race, parity, smoking, infant's sex, birthweight for gestational age, age at measurement, hour of day of study visit, and plasma leptin (measured at the same time as insulin) (model 1). We found that a much higher proportion of early preterm infants experienced rapid weight gain in the first year of life than did full-term infants (84.8% in early preterm vs 27.6% in full term). As a result, the association between gestational age groups and plasma insulin was substantially attenuated after adjustment for rapid weight gain in the first year of life (model 2). The association was no longer significant after adjusting for cord blood insulin levels (model 3) due to a strong tracking of plasma insulin from birth to early childhood, which is discussed in the following section. Similar results were found when the above analyses were restricted to children with insulin levels measured both at birth and in early childhood (n = 785; eTable 3 in the Supplement).

Table 1. Characteristics of Study Participants Stratified by Gestational Age Groups (N=1358)

Variable, No. (%)	Gestational Age Group[a]				*P* Value
	Full Term, ≥39 wk	Early Term, 37-38 wk	Late Preterm, 34-36 wk	Early Preterm, 34 wk	
Maternal characteristics					
No.	597	343	256	162	
Age at enrollment, y					
≤20	57 (9.5)	31 (9.1)	22 (8.6)	12 (7.4)	.39
21-30	321 (53.8)	161 (46.9)	126 (49.2)	82 (50.6)	
>30	219 (36.7)	151 (44.0)	108 (42.2)	68 (42.0)	
Prepregnancy BMI, mean (SD)	26.5 (6.2)	26.3 (6.3)	26.7 (6.5)	26.9 (6.4)	.70
Education					
High school and lower	396 (66.3)	208 (60.6)	173 (67.6)	110 (67.9)	.20
≥ College degree	201 (33.7)	135 (39.4)	83 (32.4)	52 (32.1)	
Race					
Black	344 (57.6)	213 (62.1)	151 (59.0)	103 (63.6)	.47
Hispanic	127 (21.3)	72 (21.0)	62 (24.2)	34 (21.0)	
White	39 (6.5)	19 (5.5)	19 (7.4)	7 (4.3)	
Other	87 (14.6)	39 (11.4)	24 (9.4)	18 (11.1)	
Parity					
Nulliparous	264 (44.2)	126 (36.7)	101 (39.4)	61 (37.6)	.11
Multiparous	333 (55.8)	217 (63.3)	155 (60.6)	101 (62.4)	
Perceived pregnancy stress					
Low	494 (82.7)	269 (78.4)	198 (77.3)	127 (78.4)	.19
High	103 (17.3)	74 (21.6)	58 (22.7)	35 (21.6)	
Smoking					
Never	509 (85.3)	290 (84.6)	195 (76.2)	128 (79.0)	.02
Quitter	40 (6.7)	20 (5.8)	22 (8.6)	15 (9.3)	
Continuous	48 (8.0)	33 (9.6)	39 (15.2)	19 (11.7)	
Antenatal steroids use					
None	586 (98.2)	332 (96.8)	221 (86.3)	28 (17.3)	<.001
≥1 Dose	11 (1.8)	11 (3.2)	35 (13.7)	134 (82.7)	
Pregestational/gestational diabetes					
No	567 (95.0)	310 (90.4)	223 (87.1)	146 (90.1)	.001
Yes	30 (5.0)	33 (9.6)	33 (12.9)	16 (9.9)	
Hypertensive disorder					
No	565 (94.6)	293 (85.4)	200 (78.1)	103 (63.6)	<.001
Yes	32 (5.4)	50 (14.6)	56 (21.9)	59 (36.4)	
Child birth characteristics					
Sex					
Male	301 (50.4)	168 (49.0)	140 (54.7)	74 (45.7)	.31
Female	296 (49.6)	175 (51.0)	116 (45.3)	88 (54.3)	
Mode of delivery					
Vaginal	423 (70.9)	221 (64.4)	164 (64.1)	73 (45.1)	<.001
Cesarean	174 (29.1)	122 (35.6)	92 (35.9)	89 (54.9)	
Gestational age at birth, mean (SD), wk	40.2 (0.8)	38.0 (0.6)	35.7 (0.9)	30.0 (3.0)	<.001
Birthweight, mean (SD), g	3414 (478)	2962 (503)	2588 (511)	1430 (552)	<.001
Apgar score at 1 min					
0-4	24 (4.0)	17 (5.0)	14 (5.5)	45 (27.8)	<.001
5-7	77 (12.9)	45 (13.1)	60 (23.4)	76 (46.9)	
8-10	476 (79.7)	272 (79.3)	180 (70.3)	41 (25.3)	
Missing data	20 (3.4)	9 (2.6)	2 (0.8)	0 (0.0)	
Apgar score at 5 min					
0-4	1 (0.2)	2 (0.6)	3 (1.2)	8 (4.9)	<.001
5-7	14 (2.4)	10 (2.9)	19 (7.4)	62 (38.3)	
8-10	562 (94.1)	322 (93.9)	232 (90.6)	92 (56.8)	
Missing data	20 (3.3)	9 (2.6)	2 (0.8)	0 (0.0)	

(continued)

Table 1. Characteristics of Study Participants Stratified by Gestational Age Groups (N=1358) (continued)

Variable, No. (%)	Gestational Age Group[a] Full Term, ≥39 wk	Early Term, 37-38 wk	Late Preterm, 34-36 wk	Early Preterm, 34 wk	*P* Value
Child birth characteristics (continued)					
Birthweight for gestational age					
SGA	79 (13.2)	89 (25.9)	42 (16.4)	19 (11.7)	<.001
AGA	465 (77.9)	231 (67.4)	195 (76.2)	138 (85.2)	
LGA	53 (8.9)	23 (6.7)	19 (7.4)	5 (3.1)	
Cord blood biomarker, geometric mean (95% CI)[b]					
Insulin, μIU/mL	9.2 (8.4-10.0)	10.3 (9.3-11.5)	13.2 (11.8-14.8)	18.9 (16.6-21.4)	<.001
Leptin, ng/mL	26.8 (24.3-29.6)	22.2 (19.5-25.3)	13.3 (11.4-15.5)	4.4 (3.4-5.7)	<.001

Abbreviations: AGA, appropriate for gestational age; BMI; body mass index (calculated as weight in kilograms divided by height in meters squared); LGA, large for gestational age; SGA, small for gestational age.

SI conversion factor: To convert insulin to pmol/mL, multiply by 6.945.

[a] Gestational age groups were based on the classification of American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.

[b] For child birth characteristics, n = 1117.

Table 2. Infant Characteristics Stratified by Gestational Age Groups

Variable, No. (%)	Gestational Age Group[a] Full Term, ≥39 wk	Early Term, 37-38 wk	Late Preterm, 34-36 wk	Early Preterm, 34 wk	*P* Value
Child characteristics					
No.	452	257	192	125	
Age at follow-up, mean (SD), y	2.2 (1.7)	2.1 (1.7)	2.2 (1.6)	2.2 (1.7)	.78
Breastfed					
Exclusively formula	102 (22.6)	60 (23.3)	55 (28.6)	37 (29.6)	.30
Exclusively breastfed	12 (2.6)	3 (1.2)	4 (2.1)	1 (0.8)	
Both	338 (74.8)	194 (75.5)	133 (69.3)	87 (69.6)	
Monthly weight gain in the first year, mean (SD), kg	0.59 (0.13)	0.60 (0.20)	0.66 (0.18)	0.65 (0.12)	<.001
Weight gain in the first year, mean (SD), *z* score[b]	0.10 (1.11)	0.61 (1.34)	1.27 (1.45)	1.99 (1.15)	<.001
Rapid weight gain in first year[b]					
Nonrapid	296 (65.5)	138 (53.7)	59 (30.7)	13 (10.4)	<.001
Rapid	125 (27.6)	108 (42.0)	117 (61.0)	106 (84.8)	
Missing data	31 (6.9)	11 (4.3)	16 (8.3)	6 (4.8)	
BMI, mean (SD)	17.2 (2.2)	17.2 (2.5)	17.1 (2.2)	16.8 (1.9)	.32
BMI, mean (SD), *z* score[c]	0.51 (1.25)	0.44 (1.36)	0.42 (1.32)	0.24 (1.27)	.26
Hour of day at the study visit					
Before 9:00 AM	22 (4.9)	9 (3.5)	7 (3.7)	10 (8.0)	.21
9:01 AM-12:00 PM	195 (43.1)	106 (41.3)	91 (47.4)	62 (49.6)	
12:01 PM-2:00 PM	66 (14.6)	45 (17.5)	40 (20.8)	15 (12.0)	
2:01 PM-4:00 PM	147 (32.5)	80 (31.1)	48 (25.0)	32 (25.6)	
After 4:00 PM	19 (4.2)	16 (6.2)	6 (3.1)	6 (4.8)	
Missing data	3 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	
Venous blood biomarker, geometric mean (95% CI)[d]					
Insulin, μIU/mL	11.2 (10.3-12.0)	12.4 (11.3-13.6)	13.3 (11.9-14.8)	14.6 (12.6-16.9)	.003
Leptin, ng/mL	2.2 (2.0-2.4)	2.3 (2.0-2.6)	2.1 (1.8-2.5)	2.3 (1.9-2.8)	.81

Abbreviations: BMI; body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factor: To convert insulin to pmol/mL, multiply by 6.945.

[a] Gestational age groups were based on the classification of American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.

[b] Weight gain *z* score in the first year of life was defined as the change in weight for age *z* score from birth to during first year of life; rapid weight gain was defined as weight gain *z* score of more than 0.67.

[c] BMI *z* score was calculated to correct for child's age and sex, and 14 were missing.

[d] For infant characteristics, n = 1026.

In addition, we performed age subgroup analyses and found that the preterm birth-insulin association was consistently observed in infancy (aged ≤12 months) and early childhood (1-6.5 years) (eTable 4 in the Supplement).

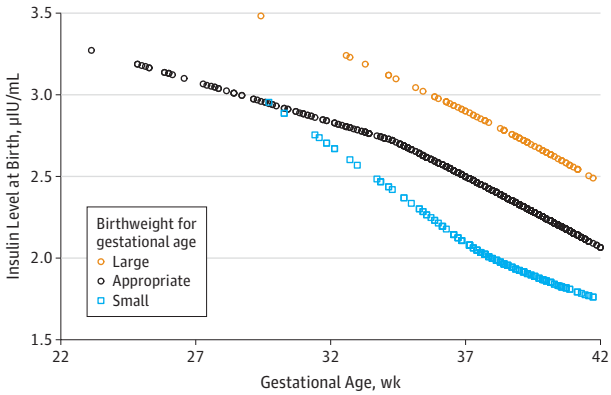
Tracking of Insulin Levels From Birth to Early Childhood

As illustrated in **Figure 3**, among children ranked in low, middle, and high tertiles based on cord blood insulin levels at birth, there were clear group differences in plasma insulin levels in early childhood. In regression analysis (Table 3, Model 3), cord blood insulin levels were a significant predictor of insulin levels in early childhood. Finally, children who ranked in the top tertile for cord blood insulin levels at birth were more likely to remain in the top tertile (41.2%) than were children ranked in the lowest tertile (28.6%) in early childhood.

Discussion

To our knowledge, this is the first study to investigate the association between preterm birth and random plasma insulin levels at birth and in early childhood in a large, prospective, US birth cohort. We found that plasma insulin levels at birth were inversely associated with gestational age in a dose-response fashion, even after adjustment for birthweight for gestational age and other measured prenatal and perinatal variables. This association was also observed in early childhood. Furthermore, our data are consistent with the tracking of plasma insulin levels from birth into early childhood (≤6.5 years). This study lends further support to previous studies that have reported relationships between preterm birth and altered insulin homeostasis manifested by increased insulin resistance in childhood,[3] young adulthood,[4,5] and middle adulthood.[8] This study fills a gap in the knowledge base regarding insulin levels during early developmental periods in children born preterm. Our findings suggest that insulin resistance exhibited by adolescents and adults born preterm may

Figure 2. Association of Plasma Insulin Levels at Birth With Gestational Age, Stratified by Birthweight for Gestational Age Category (n=1117)



To convert insulin to pmol/mL, multiply by 6.945.
The y-axis is the mean of logarithmically transformed insulin levels. Birthweight for gestational age was categorized into 3 groups: small for gestational age (birthweight, <10th percentile; n=174), large for gestational age (birthweight, ≥90th percentile; n=89), and appropriate for gestational age (birthweight, 10th-90th percentile; n=854) according to the local reference population.

Table 3. Association of Gestational Age Groups With Plasma Insulin Levels at Birth and in Early Childhood in the Boston Birth Cohort

	Gestational Age Group[a]						
	Early Term, 37-38 wk		Late Preterm, 34-36 wk		Early Preterm, <34 wk		
Model	exp(β) (95% CI)	*P* Value	exp(β) (95% CI)	*P* Value	exp(β) (95% CI)	*P* Value	*P* for Trend
At birth[b]							
Crude	1.13 (0.97-1.28)	.07	1.45 (1.25-1.65)	<.001	2.05 (1.69-2.42)	<.001	<.001
Adjusted[c]	1.16 (1.03-1.30)	.01	1.60 (1.38-1.82)	<.001	2.51 (1.87-3.15)	<.001	<.001
In early childhood[d]							
Crude	1.12 (0.99-1.25)	.08	1.19 (1.02-1.35)	.01	1.31 (1.10-1.52)	.001	<.001
Adjusted[e]							
1	1.08 (0.96-1.21)	.17	1.16 (1.00-1.32)	.03	1.22 (1.03-1.41)	.02	.007
2	1.08 (0.96-1.21)	.20	1.14 (0.98-1.30)	.07	1.19 (0.98-1.39)	.05	.03
3	1.06 (0.92-1.21)	.34	1.14 (0.98-1.30)	.07	1.12 (0.90-1.34)	.29	.07

[a] Gestational age groups were based on the classification of American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine. Full-term group was the reference. *P* values for linear trend were based on models using gestational age as a continuous variable.

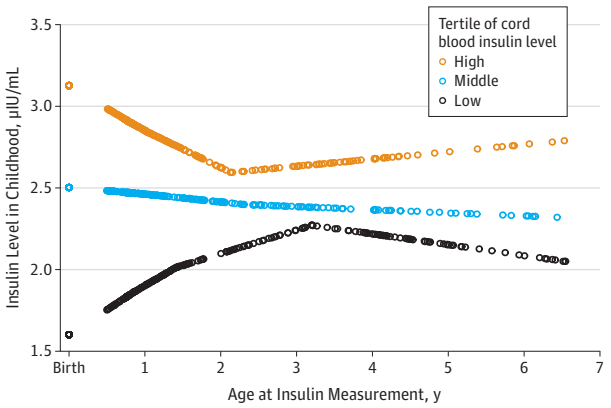
[b] At birth (n = 1117), full term = 499, early term = 284, late preterm = 221, early preterm = 113; adjusted R^2 = 0.25.

[c] At birth, the model adjusted for maternal race, parity, smoking status, gestational and pregestational diabetes, antenatal steroids use; also infant sex, birthweight for gestational age, Apgar score at 1 minute, and leptin levels in cord blood.

[d] In early childhood (n = 1026), full term = 452, early term = 257, late preterm = 192, early preterm = 125; adjusted R^2 = 0.11.

[e] In early childhood, model 1 adjusted for maternal race, parity, smoking status; also infant sex, birthweight for gestational age, Apgar score at 1 minute, leptin levels at the same time point of postnatal insulin measurement, age at the insulin measurement, and the hour of day at the study visit. Model 2: model 1 adjustments plus rapid weight gain in the first year of life. Model 3 (n = 785): model 1 adjustments plus insulin levels at birth.

Figure 3. Tracking of Plasma Insulin Levels From Birth to Early Childhood (n=785)



To convert insulin to pmol/mL, multiply by 6.945.
The y-axis is the mean of logarithmically transformed insulin levels. Age at insulin measurement was the age when the blood sample was obtained for the insulin measurement. Early childhood age range was 0.5 to 6.5 years; median, 1.4 years (interquartile range [IQR], 0.8-3.3). The participants were grouped as low, middle, and high tertile based on cord blood insulin levels. The median cord blood insulin levels were 4.8 µIU/mL (IQR, 2.9-6.9) for low tertile (n=261); 12.0 µIU/mL (IQR, 10.4-13.7) for middle tertile (n=260); and 24.0 µIU/mL (IQR, 18.6-33.8) for high tertile (n=264).

originate in utero and that the developmental programming that occurs in small-for-gestational-age births may also occur in preterm births, irrespective of whether they are small or appropriate for gestational age. These findings provide additional evidence that preterm birth (and perhaps early term birth as well) may be a risk factor for the future development of insulin resistance and type 2 diabetes.

The major strength of this study is that plasma insulin levels were measured 2 times (at birth and in early childhood) in a large prospective birth cohort. Major limitations of this study include the use of nonfasting insulin in early childhood and the lack of blood glucose measurements. Although we do not have the postprandial time for each participant, we found that the distributions of the hour of day at the study visit were similar among the 4 groups (the Kolmogorov-Smirnov test, *P* value = .12). Additionally, the association between gestational age groups and insulin levels in early childhood was not significantly altered when further adjusting for the hour of day at the study visit. Hence, the observed association between preterm birth and childhood insulin levels was not due to differential timing of blood sampling among the 4 groups.

There are no standard approaches for defining insulin resistance in children.[30] In large-scale epidemiological studies, it is challenging in adults, and even more so in children, to estimate insulin sensitivity by hyperglycemic-euglycemic clamp, regarded as the gold standard for determining insulin sensitivity. Although a fasting insulin level is regarded as an adequate proxy for insulin sensitivity in children in epidemiological studies,[31] it has a low to moderate correlation with gold standard indices obtained from clamp studies, and the correlation is even lower in black patients,[32] who comprised 60% of our sample. Moreover, fasting levels best reflect hepatic insulin sensitivity rather than peripheral insulin sensitivity (better quantified by hyperglycemic-euglycemic clamps). In children and adults who were born preterm, discordance in peripheral and hepatic insulin sensitivity was reported by at least 2 research groups who found that preterm survivors showed abnormalities in peripheral insulin sensitivity, but no association was found with fasting insulin (or hepatic insulin sensitivity).[3,33] Thus, fasting insulin may not be a sensitive enough indicator to detect differences in insulin homeostasis across gestational groups.

In this study, we observed random insulin levels at birth and in early childhood. These should not be regarded as fasting, nor postprandial insulin levels. Presently, there are no data comparing postprandial or fasting insulin levels with those obtained with a hyperglycemic-euglycemic clamp in young children. Moreover, there are no extant data on the implications of using these different methods in children to assess later disease risk. However, available data provide some support for the use of random insulin levels relative to metabolic and cardiovascular disease outcomes in adults. Random insulin levels have been correlated with the risk of cardiovascular diseases in men,[34] stroke,[35] type 2 diabetes,[36] and hypertension.[37] Findings from these adult studies are similar to findings in subsequent studies using fasting insulin as the index for insulin/glucose homeostasis.[38] In light of the ongoing debate on fasting vs nonfasting levels in serum lipid testing,[39-41] our study findings establish a foundation upon which to develop additional research questions regarding the use of random insulin measures and their interpretation. Although we cannot directly address the hypothesis that peripheral insulin sensitivity is more likely affected in preterm birth, it is consistent with previous reports on lower insulin sensitivity in preterm birth.[3,33]

The biological mechanisms underlying the association between preterm birth and elevated insulin at birth and in early childhood are not well understood. As shown in Table 3, the observed preterm-insulin association at birth and in early childhood could not be explained by prenatal and perinatal variables known or suspected to be associated with preterm birth or metabolic risk. In contrast, adjusting for insulin levels at birth, the preterm-insulin association in early childhood was no longer significant, suggesting a strong tracking of insulin levels from birth to early childhood. The observed preterm-insulin association in early childhood was substantially attenuated after adjustment for rapid weight gain in the first year of life because those born preterm experienced an accelerated weight gain in the first year of life compared with those born at term, and children with rapid weight gain in the first year of life had higher insulin levels than those who did not in early childhood.

Conclusions

In this prospective, predominantly urban minority birth cohort, plasma insulin levels were inversely associated with gestational age at birth and in early childhood. The implications for early prevention of insulin resistance and type 2 diabetes warrant further investigation.

ARTICLE INFORMATION

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