The Long-Term Impact of Intrauterine Growth Restriction in a Diverse US Cohort of Children: The EPOCH Study

Objective: To explore the long-term impact of intrauterine growth restriction (IUGR) among a diverse, contemporary cohort of US children.

Design and Methods: A retrospective cohort of 42 children exposed to IUGR and 464 unexposed who were members of Kaiser Permanente of Colorado. Height and weight measurements since birth and measures of abdominal adiposity and insulin-resistance were measured at an average age of 10.6 (±1.3) years.

Results: Infants born IUGR experienced “catch-up growth” in the first 12 months of life at a rate of 3.58 kg/m² compared to 2.36 kg/m² in unexposed infants ($P = 0.01$). However, after 1 year of age, no differences in BMI growth velocity were observed. Nevertheless children exposed to IUGR had higher waist circumference (67.0 vs. 65.3 cm, $P = 0.03$), higher insulin (15.2 vs. 11.0 μU/ml, $P = 0.0002$), higher HOMA-IR (2.8 vs. 2.3, $P = 0.03$), and lower adiponectin levels (9.0 vs. 12.0 μg/ml, $P = 0.003$) in adolescence, independent of other childhood and maternal factors.

Conclusions: Our data from a contemporary US cohort suggests that children exposed to IUGR have increased abdominal fat and increased insulin resistance biomarkers despite no differences in BMI growth patterns beyond 12 months of age. These data provide further support for the fetal programming hypothesis.

Obesity (2014) 22, 608–615. doi:10.1002/oby.20565

Introduction

Between 1980 and 2002, the prevalence of childhood obesity in the US tripled in children and adolescents aged 6 to 19 (1), heralding an alarming forecast for the future burden of hypertension, diabetes, and cardiovascular disease. Since Barker et al. (2) first proposed the “thrifty phenotype hypothesis” suggesting that restricted fetal growth could represent an important contributor to the developmental origins of adult metabolic and cardiovascular disease, several studies have demonstrated significant associations between low birth weight and an elevated risk of type 2 diabetes, insulin resistance, and the metabolic syndrome in adult life (3-6). Previous studies have shown that IUGR infants undergo rapid catch-up growth during infancy (7) followed by higher levels of abdominal fat and increased centralized fat distribution in childhood and adulthood, independent of BMI (8). In the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), children born IUGR were found to be smaller than their peers through early childhood, with lower lean body mass but no reduction in fat mass, thus having a higher percent body fat (9). The effects of IUGR appear to be most prominent in a “mismatched” postnatal environment where the in utero nutritional restriction is followed by a postnatal environment characterized by over-nutrition (i.e., high fat Western diet and a sedentary lifestyle) (10). Dramatic long-term effects of IUGR have been seen in countries undergoing rapid westernization such as in Pune, India where low birth weight was associated with increased abdominal fat and higher fasting insulin at age 8 years among affluent urban children but not among poorer rural children (11). In a recent report by
Norris et al. (12) on 6,511 participants in a study from five developing countries including Brazil, Guatemala, India, the Philippines, and South Africa, birth weight was inversely associated with glucose and risk of impaired fasting glucose and type 2 diabetes in adulthood.

The majority of studies on the long-term impact of IUGR have been conducted in European populations born in the early part of the twentieth century (13,14) or among youth in developing countries undergoing rapid economic and lifestyle transitions (12,15,16). It remains unclear whether the long-term effects of IUGR, marked by a birth weight for gestational age $z$ score less than the fifth percentile, operate to the same extent in contemporary US childhood cohorts (17). In addition, previous studies on growth patterns have relied on cross-sectional comparisons of weight or BMI between two time periods and have not conducted a true longitudinal analysis to detect differences in the growth trajectories. The aim of this study was to investigate markers of adiposity, fat distribution patterns, and insulin resistance in a diverse cohort of predominantly pre-pubertal and early pubertal children from Colorado (average age 10.6 years) participating in the Exploring Perinatal Outcomes Among Children Study (EPOCH), who were exposed to IUGR and unexposed. In addition, we also sought to determine if differences exist in the overall and period-specific BMI growth trajectories between exposed and unexposed youth.

**Methods**

**Subjects**

This report utilizes data from a retrospective cohort study conducted in Colorado: the EPOCH Study. Participants were children age 10.6 (±1.3) years, offspring of singleton pregnancies, born at a single hospital in Denver between 1992 and 2002, whose biological mothers were members of the Kaiser Permanente of Colorado Health Plan (KPCO). Of the 1420 eligible children and their biological mothers that were invited to participate in a research visit between 2006 and 2009, a total of 601 agreed to participate. For this analysis, we excluded participants exposed to maternal diabetes in utero because of a hypothesized competing mechanism for increased obesity risk related to over-nutrition in utero, which we have previously described (18,19). The cohort for this analysis included 42 children exposed to IUGR, defined as birth weight for gestational age $z$ score (BWGA$z$) less than the fifth percentile, and a random sample of 464 children with BWGA$z$ above the fifth percentile (unexposed). The study was approved both by the Colorado Multiple Institutional Review Board and Human Participant Protection Program. All mothers provided written informed consent and youth provided written assent.

**Perinatal information**

The KPCO Perinatal database, an electronic database linking the neonatal and perinatal medical record, was used to collect birth weight (BW), gestational age, maternal age at birth, and maternal pre-pregnancy weight. Gestational age was measured as the time elapsed from the mothers’ last menstrual period birth to the birth date. Maternal pre-pregnancy BMI was calculated from the KPCO-measured weight before the last menstrual cycle preceding pregnancy and height collected at the in-person research visit. BWGA$z$ score was calculated with a method described by Oken et al. (20), adjusted by sex, birth order, and race/ethnicity using reference values of birth weight at gestational ages 22 through 44 weeks from all singleton births in the US Natality datasets from 1999 and 2000 (21).

**Childhood height and weight measurements**

Current height and weight were measured at the research visit in light clothing and without shoes. Weight was measured to the nearest 0.1 kg using an electronic scale. Height was measured to the nearest 0.1 cm using a portable stadiometer. Previously recorded measures of recumbent length (up to age 2 years), standing height (after the child was able to stand), and weight from pediatric office visits were abstracted from the KP CO medical record. For children with an enrollment gap, medical records from non-KPCO providers were obtained. The median number of BMI measurements for subjects was 10 (ranging from 3 to 34). BMI was calculated as kg/m$^2$ from weights and heights measured on the same day.

**Childhood adiposity and fat distribution**

Waist circumference and skinfolds were measured at the research visit. Waist circumference was measured to the nearest 1 mm at the mid-point between the lower ribs and pelvic bone with a fiberglass non-spring-loaded tape measure. Skinfolds were measured in triplicate using Holtain calipers and averaged; subscapular was measured 20 mm below the tip of the scapula and triceps measured halfway between the acromion process and the olecranon process. Magnetic resonance imaging (MRI) of the abdominal region was used to quantify visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) with a 3T HDx Imager (General Electric, Waukashau, WI) by a trained technician. Each study participant was placed supine and a series of T1 weighted coronal images were taken to locate the L4/L5 plane. One axial, 10 mm, T1-weighted image, at the umbilicus or L4/L5 vertebrae, was analyzed to determine subcutaneous and visceral adipose tissue content. The analysis technique used was a modification of that of Engelson where adipose tissue regions were differentiated by their signal intensity and location (i.e., not internal contents of bowel). Images were analyzed by a single reader, blinded to exposure status.

**Markers of insulin resistance and metabolic risk**

Blood samples were obtained at the EPOCH study visit after an overnight fast. Glucose, triglycerides (TG), and high density lipoprotein–cholesterol (HDL-c) were measured using the Olympus (Center Valley PA) AU400 advanced chemistry analyzer system. Insulin was measured by a radioimmunoassay method and adiponectin was measured by radioimmunoassay (Millipore, Billerica MA). HOMA-IR (fasting glucose (mmol/l) × fasting insulin (mU/ml)/22.5) and the TG:HDL-c ratio (22) were used as markers of insulin resistance.

**Other measurements**

Race/ethnicity was self-reported using 2000 US Census-based questions and categorized as Hispanic (any race), non-Hispanic white (NHW), non-Hispanic black, and non-Hispanic other race. Maternal level of education and total household income at the time of birth and smoking during pregnancy were self-reported during the research visit. Pubertal development at the time of EPOCH visit was assessed by self-report based on a diagrammatic representation of Tanner staging adapted from Marshall and Tanner (23) and youth were categorized as Tanner < 2 (pre-pubertal) and ≥ 2 (pubertal). Children’s total energy intake (kcal/day) was assessed using the Block Kid’s Food Questionnaire (24). Self-reported key activities,
both sedentary and non-sedentary, performed during the previous 3 days was queried using a 3-day Physical Activity Recall (3DPAR) questionnaire. Each 30-min block of activity was assigned a MET (metabolic equivalent) variable to accommodate the energy expenditure. Results were reported as the average number of 30 min blocks of moderate-to-vigorous activity per day.

**Statistical analysis**

Student’s t-tests were used to compare means and standard deviations of continuous variables and chi square tests were used to compare frequencies of categorical variables for youth exposed and not exposed to IUGR.

Mixed effects linear models were constructed to assess differences in average BMI and BMI growth velocity for subjects exposed and unexposed to IUGR. This modeling approach allows for intra-subject correlation of repeated measures on subjects and accounts for an unbalanced design in the number of BMI observations on each subject and the age (time) at which they were collected. Due to the change in use of recumbent length to standing height around the age of 2 years, two separate growth curves were developed to model the BMI trajectory over time. The first model was fit for the infancy period from birth through 26 months and a second model for the childhood period from 27 months through 13 years. An iterative process was used to determine the degree of polynomial in age for both its random and fixed effects. Both final models used a quadratic polynomial for the fixed effects of age on BMI and linear random effect. A spline with a single knot at 11 months was included in the infancy period model (from birth through 26 months) which allowed a quadratic function before and after the knot. The best fit was determined based on each model’s ability to predict BMI at specific ages (6 months, 1 year, 2 years, etc.) compared to a categorical linear effects model. Covariates for the model included exposure to IUGR, sex, and race/ethnicity as fixed effects. The average BMI during the infancy and childhood periods, as well as BMI growth velocity during specific age ranges were estimated for exposed and unexposed subjects from the models.

Multiple linear regression was used to examine the association of exposure to IUGR with measures of adiposity and fat distribution, and markers of insulin resistance and metabolic risk measured at the EPOCH study visit. Two multiple linear regression models were developed for each outcome. Model 1 adjusted for current childhood characteristics including age, sex, and race/ethnicity, Tanner stage, current BMI, and percent daily calories from fat. Model 2 included the variables from model 1 with additional adjustment for maternal characteristics during pregnancy including maternal age, level of education, total household income and smoking during the pregnancy. The analyses were performed using SAS 9.2 (SAS Institute Inc., NC) and the level of significance was set to <0.05.

**Results**

There were 42 subjects exposed to IUGR and 464 unexposed youth with complete data on variables of interest. Table 1 shows the characteristics of the study population. The mean birth weight of the IUGR exposed children was 2390.5 vs. 3238.9 grams in the unexposed (P < 0.0001); however, the mean gestational age did not differ significantly between the two groups, indicating that group assignment was likely driven by growth restriction rather than preterm birth. The IUGR exposed and unexposed groups were not significantly different in terms of age at the research visit, Tanner stage, sex, and racial/ethnic distribution, although the IUGR group tended to have a lower proportion of Hispanic and higher proportion of non-Hispanic-other racial/ethnic participants. Current physical activity levels, and total daily calories did not differ between the groups, however IUGR exposed children reported a higher average percent energy intake from fat compared to the unexposed (37.1% vs. 35.4%, P = 0.04). Finally, current BMI, weight and height tended to be somewhat lower in the IUGR group but there were no statistically significant differences. Maternal pre-pregnancy BMI and education level at the time of birth did not differ significantly by exposure group. Maternal age at birth was significantly lower (28.0 vs. 30.1 years, P = 0.03) and a higher proportion of mothers reported a total household income below $50,000/year (36.6% vs. 19.9%, P = 0.01) among the IUGR exposed subjects compared to the unexposed. Although the proportion of mothers who reported smoking during pregnancy was twice as high among the IUGR exposed children compared to the mothers of the unexposed, due to overall low numbers of smokers, the difference was not statistically significant (12.2 vs. 6.9%, P = 0.2).

The period-specific BMI growth velocity of IUGR exposed and unexposed youth as well as the number of BMI data points available in each period are shown in Table 2. Based on the quadratic spline model from birth through 26 months of age (adjusted for sex and race/ethnicity), we estimate that on average IUGR exposed infants gained significantly more in the first 12 months of life than unexposed infants (3.58 vs. 2.36 kg/m², P = 0.01). However, after 12 months of age and extending into childhood, there were no significant differences in the period-specific BMI growth velocities between IUGR exposed and unexposed youth. The overall BMI growth curve was significantly different for IUGR exposed versus unexposed youth during the infancy period from birth through 26 months of age (P = 0.0002). However, the overall growth trajectory and average BMI was not significantly different after 27 months and extending through 13 years of age (P = 0.3). Additional adjustment in the childhood model for Tanner stage, physical activity levels, total daily calories, and percent calories from fat did not alter the findings.

Table 3 shows measures of adiposity, fat distribution, markers of insulin resistance, and metabolic risk at the EPOCH study visit, according to exposure status. To explore potential differences between IUGR exposed and unexposed youth, independent of potential confounders, two sequentially adjusted models were used. Model 1 adjusted for current demographic and behavioral characteristics (age, sex, race/ethnicity, Tanner stage, BMI, physical activity levels, and percentage daily calories from fat), and Model 2 additionally adjusted for other perinatal exposures (maternal age at delivery, education and household income, and smoking during pregnancy). Results were similar in both models, with the magnitude of differences between exposed and unexposed youth and statistical significance being stronger in the fully adjusted model (Model 2). Our data (Model 2) show that exposed children had significantly higher waist circumference (67.1 vs. 65.3 cm, P = 0.02), a trend towards higher SAT (132.8 vs. 118.5 cm², P = 0.056), but no significant differences in skinfold thickness and VAT, compared to unexposed children. Exposed offspring also had higher fasting insulin (15.3 vs. 10.9 μU/ml, P = 0.0001) and lower glucose levels (76.5 vs. 82.6 mg/dl, P = 0.0001). In addition, they also had lower adiponectin levels (8.9 vs. 12.0 μg/ml, P = 0.003), and a trend towards higher TG levels (103.1 vs. 89.0 mg/dl, P = 0.07).
### TABLE 1 Characteristics of EPOCH study participants according to exposure to IUGR

|                          | IUGR exposed (n = 42) | Unexposed (n = 464) | P value |
|--------------------------|-----------------------|---------------------|---------|
|                          | Mean, SD or N (%)     | 95% C.I.            | Mean, SD or N (%) | 95% C.I. |
| **Offspring characteristics at birth** |                       |                     |                     |         |
| Birth weight (g)         | 2390.5 ± 327.0        | 2279.8, 2501.1      | 3238.9 ± 544.4      | 3189.2, 3288.6 | <0.0001 |
| Gestational age (weeks)  | 38.6 ± 1.4            | 38.1, 39.1          | 38.9 ± 2.1          | 38.7, 39.1 | 0.4     |
| Sex (% male)             | 24 (58.5%)            |                     | 224 (48.3%)         |         | 0.2     |
| **Race/ethnicity**       |                       |                     |                     |         |         |
| NHW                      | 20 (48.8%)            |                     | 209 (45.0%)         |         | 0.06    |
| Hispanic                 | 11 (26.8%)            |                     | 191 (41.2%)         |         |         |
| Other, non-Hispanic      | 10 (9.8%)             |                     | 64 (13.8%)          |         |         |
| **Offspring characteristics at EPOCH visit** |                       |                     |                     |         |
| Age (years)              | 10.9 ± 1.6            | 10.4, 11.4          | 10.6 ± 1.3          | 10.4, 10.7 | 0.2     |
| BMI (kg/m²)              | 18.6 ± 4.7            | 17.1, 20.1          | 18.9 ± 4.5          | 18.5, 19.4 | 0.6     |
| Height (cm)              | 143.1 ± 11.3          | 139.6, 146.7        | 144.5 ± 10.6        | 143.6, 145.5 | 0.4     |
| Weight (kg)              | 39.1 ± 15.0           | 34.4, 43.9          | 40.4 ± 13.7         | 39.1, 41.6 | 0.6     |
| Tanner stage             |                       |                     |                     |         |         |
| > 2                      | 23 (56.1%)            |                     | 238 (51.4%)         |         | 0.6     |
| ≥ 2                      | 18 (43.9%)            |                     | 225 (48.6%)         |         |         |
| Physical activity (blocks/day) | 4.9 ± 3.1            | 3.9, 5.9            | 4.2 ± 2.8           | 3.9, 4.5 | 0.2     |
| Total energy intake (kJ/day) | 1878.0 ± 686.9        | 1658.3, 2097.7      | 1791.1 ± 550.0      | 1740.9, 1841.4 | 0.3     |
| % energy intake from fat | 37.1 ± 4.3%           | 35.7, 38.4%         | 35.4 ± 5.0%         | 34.9, 35.8% | 0.04    |
| Maternal characteristics at birth |                       |                     |                     |         |         |
| Maternal age at birth    | 28.0 ± 6.9            | 25.7, 30.4          | 30.1 ± 5.4          | 29.6, 30.6 | 0.03    |
| Maternal education       |                       |                     |                     |         |         |
| < High school            | 0 (0.0%)              |                     | 4 (0.9%)            |         | 0.2     |
| High school              | 9 (21.9%)             |                     | 56 (12.1%)          |         |         |
| Any college              | 32 (78.1%)            |                     | 404 (87.1%)         |         |         |
| Total household income   |                       |                     |                     |         |         |
| <$50,000/year            | 15 (36.6%)            |                     | 92 (19.9%)          |         | 0.01    |
| >$50,000/year            | 26 (63.4%)            |                     | 371 (80.1%)         |         |         |
| Maternal pre-pregnancy BMI | 23.8 ± 5.2           | 21.9, 25.7          | 25.6 ± 6.1          | 24.9, 26.2 | 0.11    |
| Maternal smoking during pregnancy | 5 (12.2%)             |                     | 32 (6.9%)           |         | 0.2     |

**Adjusted for sex, race/ethnicity.**

### TABLE 2 Period specific BMI growth velocities of children exposed and unexposed to IUGR

| Age group               | # obs | IUGR exposed | Unexposed | Difference |
|-------------------------|-------|--------------|-----------|------------|
|                         |       | BMI change ± SE | 95%CI     | BMI change ± SE | 95%CI | BMI change ± SE  | 95%CI     | P-value |
| Birth-12 months         | 127   | 3.58 ± 0.48 | 2.64, 4.51 | 1355 | 2.36 ± 0.14 | 2.09, 2.63 | 1.22 ± 0.50 | 0.24, 2.19 | 0.01 |
| 12-27 months            | 120   | -1.13 ± 0.51 | -2.13, -0.13 | 1195 | 0.17 ± 0.16 | -0.49, 0.15 | -0.96 ± 0.53 | -2.01, 0.09 | 0.07 |
| 27 months-4 years       | 113   | -0.30 ± 0.19 | -0.67, 0.11 | 986  | -0.02 ± 0.06 | -0.14, 0.10 | -0.28 ± 0.20 | -0.67, 0.11 | 0.2  |
| 4-6 years               | 163   | 0.17 ± 0.18 | -0.18, 0.53 | 1420 | 0.38 ± 0.06 | 0.27, 0.49 | -0.21 ± 0.19 | -0.58, 0.16 | 0.2  |
| 6-9 years               | 204   | 1.28 ± 0.24 | 0.80, 1.75 | 1921 | 1.38 ± 0.07 | 1.24, 1.52 | -0.10 ± 0.25 | -0.60, 0.39 | 0.7  |
| 9-13 years              | 219   | 3.61 ± 0.40 | 2.83, 4.38 | 1921 | 3.35 ± 0.13 | 3.09, 3.61 | 0.26 ± 0.42 | -0.56, 1.07 | 0.5  |
| Total                   | 946   | 8796         |            |            |            |            |            |            |      |

Adjusted for sex, race/ethnicity.
|                          | IUGR exposed       | Unexposed       | P   | IUGR exposed       | Unexposed       | P   |
|--------------------------|--------------------|----------------|-----|--------------------|----------------|-----|
|                          | Mean ± SD (95% CI) | Mean ± SD (95% CI) |     | Mean ± SD (95% CI) | Mean ± SD (95% CI) |     |
| Waist circumference (cm) | 66.7 ± 0.7 (65.4, 68.1) | 65.4 ± 0.2 (65.0, 65.8) | 0.07 | 67.0 ± 0.7 (65.6, 68.5) | 65.3 ± 0.2 (64.9, 65.7) | 0.02 |
| Triceps skinfold (mm)    | 15.3 ± 0.7 (13.9, 16.7) | 16.3 ± 0.2 (15.9, 16.7) | 0.2  | 15.1 ± 0.8 (13.6, 16.6) | 16.3 ± 0.2 (15.8, 16.6) | 0.2  |
| Subscapular skinfold (mm)| 12.4 ± 0.7 (10.9, 13.8) | 12.8 ± 0.2 (12.4, 13.2) | 0.6  | 11.9 ± 0.8 (10.3, 13.4) | 12.7 ± 0.2 (12.3, 13.2) | 0.3  |
| Subscapular to triceps skinfold ratio | 0.078 ± 0.03 (0.072, 0.084) | 0.75 ± 0.009 (0.74, 0.77) | 0.4  | 0.77 ± 0.03 (0.73, 0.84) | 0.75 ± 0.009 (0.74, 0.77) | 0.6  |
| SAT (cm²)                | 128.7 ± 6.6 (115.7, 141.7) | 119.5 ± 1.9 (115.7, 123.3) | 0.2  | 132.8 ± 7.2 (118.7, 146.9) | 118.5 ± 1.9 (114.7, 122.2) | 0.056 |
| VAT (cm³)                | 21.5 ± 1.9 (17.9, 25.4) | 22.2 ± 0.6 (21.1, 23.3) | 0.7  | 22.4 ± 2.1 (18.2, 26.6) | 22.1 ± 0.6 (21.0, 23.2) | 0.9  |
| Insulin (uU/ml)          | 14.8 ± 1.0 (13.1, 17.0) | 11.0 ± 0.3 (10.4, 11.5) | 0.002 | 15.3 ± 1.1 (13.2, 17.5) | 10.9 ± 0.3 (10.4, 11.5) | 0.001 |
| Glucose (mmol/L)         | 4.25 ± 0.08 (4.1, 4.4) | 4.59 ± 0.02 (4.5, 4.6) | 0.0001 | 4.2 ± 0.09 (4.1, 4.4) | 4.58 ± 0.02 (4.5, 4.6) | 0.003 |
| HOMA-IR                  | 2.8 ± 0.2 (2.3, 3.2) | 2.3 ± 0.1 (2.1, 2.4) | 0.02  | 2.8 ± 0.2 (2.3, 3.2) | 2.3 ± 0.1 (2.1, 2.4) | 0.03  |
| Adiponectin (µg/ml)      | 8.9 ± 0.9 (7.1, 10.7) | 12.0 ± 0.3 (11.5, 12.5) | 0.001 | 8.9 ± 1.0 (7.0, 10.9) | 12.0 ± 0.3 (11.5, 12.5) | 0.003 |
| Triglycerides (mg/dl)    | 99.5 ± 6.8 (86.1, 113.0) | 89.2 ± 2.0 (85.2, 93.1) | 0.1  | 103.1 ± 7.5 (88.5, 117.9) | 89.0 ± 2.0 (85.0, 92.9) | 0.07  |
| HDL-c (mg/dl)            | 50.2 ± 1.8 (46.5, 53.9) | 49.5 ± 0.5 (48.5, 50.5) | 0.7  | 50.1 ± 1.9 (46.2, 53.8) | 49.6 ± 0.5 (48.6, 50.6) | 0.8  |
| Triglycerides:HDL-c ratio| 2.2 ± 0.2 (1.8, 2.6) | 1.9 ± 0.06 (1.8, 2.1) | 0.3  | 2.2 ± 0.2 (1.8, 2.6) | 1.9 ± 0.06 (1.8, 2.1) | 0.3  |

Model 1: Adjusted for childhood age, sex, race/ethnicity, Tanner stage, BMI, physical activity levels and % daily calories from fat.
Model 2: Model 1 + maternal smoking, age, education and household income.
Obesity

Discussion

In a contemporary, multiethnic cohort of healthy children from Colorado, IUGR exposed children experienced “catch-up growth” or higher growth velocity between birth and 12 months of age compared to unexposed children. However, no differences in period-specific BMI growth velocities were detected after the first year of life and the overall growth trajectories were not different beyond infancy. There were no long-term effects of IUGR on overall body size or growth velocity, but children exposed to IUGR had higher insulin, higher HOMA-IR, lower adiponectin levels, and a trend towards higher subcutaneous abdominal adipose tissue, independent of other perinatal exposures and current lifestyle and socioeconomic factors, suggesting a “programmed” propensity for development of insulin resistance. Our results are consistent with the “thrifty phenotype hypothesis” suggesting that fetuses make metabolic adaptations in response to nutritional deprivation in utero that benefit postnatal survival, but which also predisposes them, as children, to increased abdominal fat and an increased risk of developing insulin resistance.

We found higher waist circumference and lower adiponectin levels among children exposed to IUGR, independent of demographic characteristics, childhood lifestyle factors, including current BMI, and other perinatal exposures. This suggests the effects of under-nutrition in utero on later fat distribution and insulin resistance biomarkers are not mediated by postnatal growth or current BMI and lifestyle factors. Waist circumference is a marker of abdominal fat and a major determinant of insulin sensitivity (25). Indeed in this study, IUGR exposed children also had higher subcutaneous fat deposition (on average by 14.3 cm²), although, at least at this young age, similar visceral fat deposition. This may be due to the limited level of VAT accumulation in this early pubertal cohort with healthy BMI levels (26). Adiponectin, the most abundant adipose tissuespecific protein, exclusively expressed in, and secreted from adipose tissue, is decreased in obesity and insulin resistant states (27) and has been shown to play an important role in the development of impaired glucose regulation, insulin resistance and atherosclerosis in adults (28-30). A limited numbers of studies in children also support the findings in adults. Among youth from Pittsburgh, lower adiponectin was associated with greater peripheral insulin resistance (measured by hyperinsulinemic-euglycemic clamp), independent of current BMI (31). In another study from Yale, strong, inverse relationships were found between adiponectin and triglyceride levels and intramyocellular lipid accumulation (32). These data support the notion that adiponectin is related to insulin resistance, an effect that may be independent of total body size, even among children. Our study provides novel evidence that adiponectin levels are significantly lower among children growth restricted in utero, independent of their current BMI, suggesting a programmed increased propensity for development of insulin resistance.

Inconsistent findings of the effects of IUGR on adiposity and metabolic parameters in childhood have been reported in other studies. In a study of 55 SGA children who were age- and sex-matched to appropriate for gestational age (AGA) controls from Finland, Tenhola et al. (33) reported significantly lower BMI but no differences in adiponectin or estimated insulin resistance at a mean age of 12.2 years. Lopez-Bermejo et al. (34) reported that 32 SGA exposed children studied at a mean age 5.4 ± 2.9 years had higher levels of serum adiponectin than 37 AGA children, independent of current BMI. Consistent with our findings, a study by Ibanez et al. (35) on 64 children (32 age-matched pairs) from Spain found that at 6 years of age, children exposed to SGA had higher insulin levels, lower adiponectin and a shift from SAT to VAT deposition. Similarly, Cianfarani et al. (36) found lower adiponectin levels among SGA children who were attending an endocrinology clinic for short stature compared to short or obese AGA children. Veening et al. (37) in the Netherlands, found reduced insulin sensitivity (measured by hyperinsulinemic euglycemic clamp) among 29 SGA children compared to 24 AGA controls at a mean age of 9.0 ± 1.1 years. The reasons for differences across studies are not clear but they may be related to small sample sizes, different definitions of IUGR or SGA, different age-ranges and environments in which these children were studied.

Adding substantially to the current literature, our study utilized longitudinal analysis to examine both the short- and long-term effects of IUGR exposure, marked by SGA less than the fifth percentile, on BMI growth from birth through adolescence. Our study contributes the important observation that, despite a healthy childhood BMI and no differences in the BMI growth trajectory beyond 12 months of age, children exposed to IUGR have hyperinsulinemia, early indicators of insulin resistance and more centralized adiposity compared to those not exposed. Continued follow-up of this cohort is ongoing to determine if the associations of in utero and perinatal exposures with adiposity and metabolic parameters in childhood become more evident as the cohort transitions through puberty, another developmental period with increased obesogenic risk.

Our study has several limitations. The age range of this cohort was relatively large (6–13 years of age) and included both pre-, and early
pubertal children, therefore adjustment for age and Tanner stage was necessary. Traditionally, SGA below the 10th percentile or birth weight > 2 standard deviation scores below the respective mean for gestational age is used as a surrogage measure for IUGR (34,38,39). We used a BWGAz score below the fifth percentile in order to increase the likelihood that our sample reflected true physiologic growth rather than simply representing the lower tail of the birth weight distribution. However, given our lack of data on the underlying causes of growth restriction in our population (e.g., preclampsia, etc.) it is possible that our sample was contaminated with infants who were small at birth but attained their genetically-determined growth potential (40). The small sample size of children exposed to IUGR has likely limited our power to detect as statistically-significant more subtle differences in adiposity and insulin resistance related biomarkers. However, a clear tendency for exposed children to have higher TG levels and higher TG/HDL-c ratios, both markers of insulin resistance, was observed, despite lack of statistical significance. Furthermore, while we controlled for other perinatal exposures, current lifestyle and socioeconomic factors, the possibility of residual confounding is always present in an observational study. Our study also had important strengths including state of the art measures of abdominal adiposity measures and use of objective exposure assessment from medical records, assessed without concern for recall bias. The differences observed were not likely to have been confounded by differences in socioeconomic status because our cohort derived from a relatively affluent insured population and control for maternal education and income had no effect on observed associations. The longitudinal analysis of BMI growth trajectories made efficient use of the data and allowed us to explore more than just linear changes in BMI between different time periods. And, finally, our data extend the field of developmentally origins of chronic diseases to contemporary cohorts studied early in life.

In summary, our findings suggest that contemporary pre-pubertal and early pubertal children exposed to IUGR have increased abdominal fat and early signs of programmed insulin resistance, despite no differences in overall body size and growth trajectories. With additional follow-up, we will be able to better understand whether and how these programmed mechanisms are influenced by other developmentally sensitive periods and lifestyle choices.

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