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Fetal Programming of Children's Obesity Risk

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Abstract

OBJECTIVE—Childhood obesity affects nearly 17% of children and adolescents in the United States. Increasing evidence indicates that prenatal maternal stress signals influence fetal growth, child obesity, and metabolic risk. Children exhibiting catch-up growth, a rapid and dramatic increase in body size, within the first two years of life are also at an increased risk for developing metabolic disorder and obesity. We evaluate the potential role of the maternal hypothalamic-pituitary-adrenal (HPA) and placental axis in programming risk for child obesity.

METHOD—This prospective longitudinal study measured placental corticotropin-releasing hormone (pCRH) and maternal plasma cortisol at 15, 19, 25, 30, and 37 gestational weeks and collected child body mass index (BMI) at birth, 3, 6, 12, and 24 months. Participants included 246 mothers and their healthy children born full term. Each child's BMI percentile (BMIP) was determined using World Health Organization (WHO) standards based on age and sex. Child BMIP profiles from birth to two years of age were characterized using General Growth Mixture

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Conflict of Interest.

None of the authors have any financial interests to disclose.

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Study concept and design: EPD, CAS, LMG. Acquisition of data: EPD, CAS, LMG. Analysis and interpretation of data: SAS, EVE, EPD, CAS, LMG. Drafting of the manuscript: SAS. Critical revision of the manuscript for important intellectual content: EPD, CAS, LMG, EVE. Obtained funding: EPD, CAS, LMG.

Modeling (GGMM). We evaluated whether fetal exposure to placental CRH and maternal cortisol are associated with BMIP profiles.

RESULTS—Placental CRH at 30 gestational weeks was highly associated with both BMIP ($p < .05$) and weight ($p < .05$) at birth when accounting for gestational age at birth and used as a predictor in modeling BMIP profiles. Maternal cortisol was not associated with child BMIP. GGMM analyses identified four distinct BMIP profiles: Typical, Rapid Increase, Delayed Increase, and Decreasing (See Figure 2). The Typical profile comprised the majority of the sample and maintained BMIP across the first two years. The Rapid and Delayed Increase profiles each exhibit a period of reduced body size followed by BMI catch-up growth. The Rapid Increase profile exhibited catch-up within the first 3 months while the Delayed group showed an initial decrease in BMIP at 3 months and a dramatic increase from 12 to 24 months. The Decreasing profile exhibited normal birth weight and BMIP followed by persisting, low BMIP. The members of the Rapid and Delayed Increase profiles were exposed to the highest concentrations of placental CRH at 30 gestational weeks compared to those in the Typical profile group (Figure 3).

CONCLUSIONS—Exposure to elevated placental CRH concentrations during the third trimester is associated with catch up growth. An early period of small body size followed by rapid catch-up growth is a profile associated with increased metabolic risk and increased obesity risk. Our findings suggest that placental CRH exposure makes a unique contribution to fetal programming of obesity risk.

Keywords

obesity; fetal programming; BMI; early childhood; CRH; prenatal

1. Introduction

Childhood obesity in the United States is a growing problem, affecting nearly 17% of children ages 2–19 (Ogden et al., 2012). Obese children are at risk for developing cardiovascular disease, pulmonary problems, and metabolic disorders, as well as numerous psychological consequences (Daniels et al., 2005). Propensity to accrue fat mass, and thus susceptibility to obesity, is determined by both genetic and environmental risk factors (Choquet and Meyre, 2011). Increasing evidence suggests that exposure to stress and stress hormones during the fetal period have a long-term influence on metabolic health and obesity risk (Gangestad et al., 2012). We evaluate the role of maternal-placental stress responsive systems in prenatal programming of obesity risk.

The Fetal Programming (Barker, 1998) and Developmental Origins of Disease (Gluckman et al., 2008) models posit that during periods of rapid development, such as prenatal life and early infancy, the organism is susceptible to environmental factors that have a persisting influence on disease risk. Size at birth is a phenotypic link between prenatal experiences and postnatal outcomes, providing information about the quality of the prenatal environment and predicting later health outcomes. Small size at birth is an indicator of exposure to prenatal perturbations, which affect physical development and metabolic function (Gangestad et al., 2012). Compelling evidence from epidemiological studies indicates that small size at birth is a risk factor for a range of metabolic problems including high adult body mass index (BMI),

insulin resistance, increased visceral adiposity, and impaired glucose tolerance (Calkins and Devaskar, 2011).

More recent data suggest that it is not size at birth alone that best predicts disease risk. Rather, the combination of small size at birth and rapid weight gain during the first two postnatal years (known as catch-up growth) is the strongest predictor of risk for later obesity and metabolic disease (Cianfarani et al., 1999; Nobili et al., 2008; Calkins and Devaskar, 2011). Children who experience catch-up growth, regardless of birth weight, are at an increased risk of developing obesity in childhood and into adulthood (Ong and Loos, 2006). However, children born smaller are more likely to experience catch-up growth than children born larger (Ong et al, 2000), suggesting that infants born small may experience even greater levels of increased risk for developing obesity. This suggests that evaluation of early life growth profiles can contribute to understanding the early origins of obesity risk.

The hypothalamic-pituitary-adrenocortical (HPA) and placental axis represents one of the major pathways by which gestational experiences may exert lifelong influences on development. The maternal HPA axis changes dramatically during the prenatal period. By seven gestational weeks the human placenta begins synthesizing corticotropin-releasing hormone (CRH), which is released into the maternal and fetal compartments (Goland et al., 1988). Concentrations of placental CRH (pCRH) increase dramatically over pregnancy reaching levels only present in the hypothalamic portal system during stress (Lowry, 1993). In contrast to the negative feedback loop whereby cortisol inhibits hypothalamic CRH production, maternal cortisol stimulates the increased production of CRH from the placenta (Robinson et al., 1988; Sandman et al., 2006). Levels of maternal cortisol, ACTH and pCRH increase normatively over the course of gestation (Sandman and Davis, 2012). Fetal exposure to increasing stress hormones is one of the primary mechanisms proposed to underlie fetal programming of adult obesity and disease (Entringer, 2013).

Most of the literature examining the role of prenatal stress hormone exposures on early physical development has focused on glucocorticoids (GCs). Fetal exposure to elevated synthetic and endogenous GCs is associated with reduced birth size (Davis et al., 2009; Duthie and Reynolds, 2013), and increased weight gain during early childhood (Street et al., 2011). However, not all studies demonstrate an association between fetal GC exposure and growth outcomes (Khan et al., 2011; Duthie and Reynolds, 2013). These inconsistencies suggest that we must consider other programming influences on fetal growth.

We propose that prenatal exposure to pCRH will contribute to fetal outcomes that are strongly associated with growth profiles and obesity risk. Because pCRH is produced by the placenta and thus is of fetal origin, it may more accurately reflect fetal responses to stress signals than maternal markers such as cortisol. A critical function of the human placenta is to incorporate information from the maternal host environment into the fetal developmental program. There is evidence from in vivo and in vitro studies that pCRH levels are responsive to many major biological stress signals including cortisol, catecholamines, and pro-inflammatory signals (Petraglia et al., 1987; Petraglia et al., 1989; Petraglia, 1990; Cheng et al., 2000; Sandman et al., 2006). Detection of stress signals by the fetal-placental unit primes the “placental clock” by increasing the synthesis of the CRH gene product

(McLean et al., 1995). The resulting acceleration of pCRH production stimulates a cascade of events leading to shortened gestation or preterm birth (Sandman et al., 2006), reduced fetal growth (Wadhwa et al., 2004), and maturational delays (Ellman et al., 2008). Experimental rodent models provide compelling evidence that CRH programs growth profiles. Prenatal CRH administration is associated with decreased birth weight (Williams et al., 1995) and early rapid postnatal growth (Zadina et al., 1985). The existing animal and human literature strongly supports a contribution of pCRH to the programming of fetal development and birth outcomes.

To our knowledge only two human studies have evaluated the persisting consequences of pCRH for postnatal growth and metabolic functioning. These studies find elevated pCRH is associated with childhood outcomes such as increased adiponectin levels, a potential indicator of increased insulin sensitivity (Fasting et al., 2009), and increased central adiposity (Gillman et al., 2006).

The goal of the present investigation is to prospectively evaluate pCRH and maternal cortisol as plausible biological mechanisms underlying fetal programming of birth weight and postnatal growth profiles. Growth profiles were characterized using standardized child BMI from birth to two years of age because BMI is a valid, reliable measure of body composition (Gray and Fujioka, 1991) and is more accurate than weight as a measure of adiposity (Cole et al., 2005). We test the hypothesis that prenatal exposure to elevated stress hormones is associated with growth profiles characterized by low birth BMI and accelerated postnatal BMI increases (e.g. catch-up growth), which are associated with obesity and metabolic risk.

2. Method

2.1 Study Overview

Participants included mother-child dyads from a prospective longitudinal study investigating prenatal environment and child development. Women with singleton pregnancies less than 16 weeks gestational age were recruited from obstetric clinics in southern California. Mothers were assessed longitudinally at 15, 19, 25, 30, and 37 gestational weeks. Mothers and their children were also assessed at birth and when the child reached 3, 6, 12, and 24 months of age.

2.2 Participants

The study sample consisted of 246 mothers and their term born (> 37 weeks) children (126 male, 120 female). The additional 26 mothers who delivered preterm were not included in the present study. Initial prenatal recruitment criteria were as follows: participants were English-speaking, over the age of 18 and with a singleton intrauterine pregnancy. Exclusionary criteria for mothers included alcohol, tobacco, and drug use, cervical or uterine abnormalities, use of corticosteroid-based medication, and presence of diseases affecting neuroendocrine function. Pregnant women were enrolled in the study at ~15 gestational weeks and were invited to participate in a longitudinal study that would continue through the first 2 years postpartum. Descriptive information for the maternal and child samples is

provided in Table 1. All children included in the current investigation were full term at birth ($M = 39.51$ gestational weeks, $SD = 1.09$), had a stable neonatal course (5 minute Apgar scores > 8), and did not present with congenital, neurological, or genetic disorders. All mothers provided informed, written consent as approved by the Institutional Review Board for Protection of Human Subjects.

Of the 246 mother-child pairs included in this study, 68 pairs (27.6%) were missing height and/or weight data at two or more postnatal visits. Those participants missing data were on average younger mothers ($p < .01$), but did not differ on other demographic variables (all $p > .05$). Given that maternal age was not associated with our predictor or outcomes of interest (all p 's $> .10$), mother-infant pairs missing data were *included* in subsequent analyses and any relevant missing data was estimated as part of the General Growth Mixture Modeling analyses (see Section 3.3).

2.3 Procedures

2.3.1 Maternal plasma collection—Maternal blood samples were collected at five gestational intervals to assess placental CRH and plasma (total) cortisol concentrations – 15 ($15.2 \pm .9$), 19 (19.4 ± 1.0), 25 ($25.4 \pm .9$), 31 ($30.8 \pm .7$), and 37 ($36.6 \pm .8$) gestational weeks. All maternal blood samples were collected at least one hour after the participant had eaten (time of day $M = 13:34 \pm 1:33$). A 20-ml blood sample was drawn using antecubital venipuncture into EDTA vacutainers. Aprotinin (500 KIU/ml; Sigma Chemical Company, St. Louis, Mo., USA) was added to each sample before being chilled at approximately 6°C until processing. All samples were centrifuged at $2000 \times g$ for 15 minutes; plasma was then extracted and stored in polypropylene tubes at -70°C until assayed.

2.3.1.1 Placental CRH concentrations: Placental CRH concentrations were measured using radioimmunoassay (Bachem Peninsula Laboratories LLC, San Carlos, CA). Plasma samples of 1–2 ml were extracted with three volumes of ice-cold methanol, mixed, and allowed to stand for 10 min at 4°C before centrifugation (1700 g, 20 min, 4°C) using a modified method (Linton et al., 1995). Pellets were washed with .5 ml methanol, and the supernatants dried down (Savant SpeedVac concentrator). Samples were reconstituted in assay buffer and incubated with anti-CRH serum (human) for 48 hours at 4°C before a 48 hour incubation in ^{125}I -CRH. After a 90-min incubation, labeled and unlabeled CRH were collected by immunoprecipitation with goat anti-rabbit IgG serum and normal rabbit serum. Samples were centrifuged again (1700 g, 20 min, 4°C) and the pellets were aspirated and quantified with a gamma scintillation counter. Data reduction for the RIA was conducted with a computer-assisted four-parameter logistics program (Rodbard et al., 1973). Values exhibiting greater than 25% error (deviation from the standard curve) were not included in the analyses. A subset of samples ($n = 60$) were sent to a clinical laboratory (Quest Diagnostics) for further validation. The correlation between the two sets of data was .87 ($p < .01$). The intra- and inter-assay coefficient of variance ranged from 5% to 15% respectively. The minimum detectable pCRH concentration in the assay is 2.04 pg/ml (95% confidence interval). Samples were assayed in duplicate and averaged. Placental CRH concentrations were not significantly associated with time of sample collection (all r 's $< .14$).

2.3.1.2 Plasma cortisol concentrations: Plasma cortisol levels were determined with a competitive binding, solid-phase, enzyme-linked immunosorbent assay (IBL America, Minneapolis, MN). Plasma samples (20 μ l) and enzyme conjugate (200 μ l) were added to the antibody-coated microtiter wells, thoroughly mixed, and incubated for 60 min at room temperature. Each well was washed three times with wash solution (400 μ l per well) and struck to remove residual droplets. Substrate solution (100 μ l) was added to each well and incubated for 15 min at room temperature. The absorbance units were measured at 450 nm within 10 min after the stop solution (100 μ l) had been added. The assay has less than 9% crossreactivity with progesterone and less than 2% cross-reactivity with five other naturally occurring steroids. The interassay and intra-assay coefficients of variance are reported as less than 8%, and the minimum detectable level of the assay was 0.25 μ g/dL. Plasma cortisol concentrations were significantly associated with the time of sample collection at 15, 19, and 25 gestational weeks (*range r*: -.19 to -.23; all *p*'s < .01) but not at 31 (*r* = -.13; *p* > .05) and 37 gestational weeks (*r* = -.02; *p* > .10). Therefore, time of sample collection was used as a covariate in analyses involving cortisol.

2.4 Pregnancy and birth outcomes

Gestational age (GA) at each prenatal collection and at birth was determined using standard ACOG guidelines (2009) with a combination of last menstrual period and an ultrasound conducted prior to 20 gestational weeks. Medical record review was conducted to assess birth outcomes, including birth weight and Apgar scores.

2.5 Child measures

Child weight and height/length were collected five times throughout the first two postnatal years: at birth, 3, 6, 12, and 24 months (Table 2). Measures were collected using a standardized procedure; the mother undressed the child, and weight was recorded using a digital infant scale (Midmark, Versailles, OH). At birth through 12 months of age, child length was measured in the supine position on a pediatric exam table. Child height was measured at two years using a standard sliding height rod. Body composition was assessed using body mass index (BMI; weight kg/height m²) at each postnatal assessment.

Child BMI and weight were converted to standardized percentiles accounting for age and sex using the LMS model (Cole and Green, 1992) for child growth standards provided by the World Health Organization (WHO), which is used to assess relative weight, height, and BMI among children through 2 years of age (WHO Multicentre Growth Reference Study Group, 2006). Unstandardized BMI and weights were highly correlated with the calculated percentiles across all assessments (all *r*'s > 0.86; all *p*'s < .001). BMI percentile (BMIP) and weight percentile were significantly intercorrelated (all *r*'s < .66, all *p*'s < .001). Mean BMI and weight and corresponding percentiles are presented in Table 2.

2.6 Maternal and demographic factors

Maternal pre-pregnancy BMI was computed based on pre-pregnancy weight extracted from medical charts and maternal height measured at the research laboratory during the first visit. Maternal weight was then measured in the research laboratory at 37 gestational weeks. Total gestational weight gain was calculated by subtracting pre-pregnancy weight from maternal

weight at 37 gestational weeks. Maternal demographic information including age, ethnicity/race, parity, marital and cohabitation status, household income, and education was obtained using structured interview. Breastfeeding status was assessed at each postpartum visit.

2.7 Statistical Analyses

We first assessed how gestational pCRH and cortisol concentrations were associated with one another and how they changed across gestation. We then evaluated the relation between each hormone concentration across gestation and standardized BMI and weight at birth to determine which exposure period best predicted fetal growth. The hormone and related exposure period most highly associated with these growth outcomes was then used as a predictor in the modeling of BMIP profiles. Once BMIP profiles were established, we assessed profile group differences in relevant maternal and demographic factors. The details of these steps are outlined in the following sections.

2.7.1 Preliminary analyses—Repeated measures ANOVA was used to characterize changes in maternal cortisol and pCRH across gestation and to assess changes in child BMIP. The interrelations between maternal cortisol and pCRH concentrations at different gestational intervals were assessed using bivariate correlations. Bivariate correlations were also performed to examine the association between anthropometric measures at birth (standardized weight and BMIP) and later measures at 3, 6, 12, and 24 months. Given that previous work has found that fetal stress hormone exposure is associated with gestational age at birth (GAB) and therefore size at birth (Wadhwa et al., 2004), GAB was tested as a covariate. An alpha level of .05 was used for all statistical tests.

2.7.2. Birth outcomes and gestational timing—Strong evidence from our work and others' demonstrates that timing of exposure to placental CRH and cortisol are critical factors in determining developmental outcomes (Davis and Sandman, 2010; Duthie and Reynolds, 2013). Before evaluating whether maternal cortisol or pCRH predicted early changes in body composition, operationalized as BMIP profiles, we evaluated whether there was a gestational time point at which cortisol or pCRH was associated with fetal development as indicated by birth outcome. Time points of exposure significantly associated with BMIP and weight at birth were used as a predictor in a model assessing BMIP profiles over the first two postnatal years.

2.7.3 General growth mixture model (GGMM)—General growth mixture modeling (GGMM) was conducted using MPlus software (Muthén and Muthén, 2012) to identify divergent BMIP profiles of children from birth to 24 months of age. The pCRH and/or maternal cortisol time point most strongly associated with size at birth was used in GGMM as a predictor of BMIP changes over the first two postnatal years. BMIP profile differences in the predictor at this designated time point were evaluated as part of the GGMM analysis. Details of the GGMM and subsequent analyses are discussed in the results.

2.7.4 BMIP Profile group differences—Based on individuals' most probable profile membership as determined by the GGMM analyses, differences in BMIP at each postnatal time point were evaluated in SPSS using one-way ANOVA with post-hoc Dunnett tests.

Group differences in birth weight percentile were assessed using ANOVA with post-hoc Dunnett tests to compare with previous literature asserting that catch-up growth is more likely among those infants who are born at a lower birth weight (Cianfarani et al., 1999).

To rule out alternative explanations for group differences in BMIP, we evaluated whether BMIP groups differed systematically in factors that might affect child BMIP. We assessed whether groups differed in gestational maternal factors (parity, maternal prepregnancy BMI, maternal weight gain during pregnancy), maternal sociodemographic factors (race/ethnicity, age, cohabitation with baby's father, and household income as an indicator of SES), and child factors (sex, child's duration of breastfeeding, gestational age at birth). Analyses were conducted in SPSS using One-way ANOVA with post-hoc Dunnett, t-tests, and chi-square where applicable.

3. Results

3.1 Preliminary Analyses

As expected, pCRH increased significantly throughout gestation ($F(1.7, 194.9) = 804.36; p < .001$) (See Figure 1a). Placental CRH levels across gestation were positively correlated with one another (range $r: .18$ to $.69$; all $p's < .05$) with the exception of pCRH at 15 and 37 weeks ($r = .12, p = .14$). Cortisol also increased significantly across gestation ($F(3.5, 691.1) = 284.53; p < .001$) (See Figure 1b). Plasma cortisol levels also were intercorrelated across gestation (range $r: .22$ to $.49$; all $p's < .001$).

Placental CRH and cortisol levels were positively associated with one another at 19 weeks ($r = .25, p < .01$) and 25 weeks ($r = .15, p < .05$) gestational age, but were not significantly correlated at any other time (all $r's < .13$, all $p's > .05$).

As expected based on previous research with children from a U.S. sample (Mei, Grummer-Strawn, Thompson, & Dietz, 2004), BMIP increased significantly across time ($F(3.2, 416.0) = 14.97, p < .001$), with a mean 53.7% at birth and rising to 67.7% by 24 months.

Child BMIP at birth was significantly associated with BMIP at 3, 6, and 12 months (range $r: .16$ to $.24$; all $p's < .05$), but was not associated with BMIP at 24 months ($r = .15, p > .05$). Similarly, birth weight percentile was associated with BMIP at birth, 3, 6, and 12 months (range $r: .19$ to $.25$, all $p's < .05$), but was not associated with BMIP at 24 months ($r = .12, p = .14$).

Consistent with previous work, GAB was negatively associated with placental CRH exposure at 25 ($r = -.16; p < .05$), 31 ($r = -.23; p < .001$), and 37 ($r = -.30; p < .001$) gestational weeks, but not earlier in gestation (all $r's < .09$; all $p's > .20$). GAB was also negatively associated with cortisol levels at 31 ($r = -.20; p < .01$) and 37 ($r = -.16; p < .05$) gestational weeks but not earlier in gestation all $r's < .05$; all $p's > .50$). GAB was therefore used as a covariate in the gestational timing analyses.

3.2 Gestational Timing

After covarying GAB and time of collection, plasma cortisol during pregnancy was not significantly associated with child BMIP or weight percentile at birth (all *partial r*'s < .10, all *p*'s > .10) or birth weight percentile (all *partial r*'s < .11, all *p*'s > .10). Therefore, plasma cortisol was not considered in any subsequent analyses.

When covarying for GAB, BMIP at birth was significantly negatively associated with pCRH at 30 gestational weeks (*partial r* = -.16, *p* < .05), but was not associated with pCRH at any other gestational time point (all *p*'s > .10). Partial correlations covarying for GAB additionally revealed that higher pCRH at 25 weeks (*partial r* = -.16, *p* < .05), 30 weeks (*partial r* = -.24, *p* < .001), and 37 weeks (*partial r* = -.13, *p* < .05) gestation was significantly associated with lower weight percentile at birth. There was no significant association between pCRH at 15 or 19 weeks and size at birth (*partial r*'s < .10, all *p*'s > .20).

Placental CRH at 30 gestational weeks was used as a predictor in GGMM analyses because of its strong associations with both BMIP and weight at birth, which is consistent with previous work suggesting there is a sensitive period around 30 gestational weeks for the effects of CRH on birth outcomes and fetal development (Sandman et al., 2006; Wadhwa et al., 2004).

3.3 Classification of BMIP Profiles

GGMM was used to evaluate divergent profiles of BMI percentile using pCRH at 30 gestational weeks as a predictor. Of the 246 mother-child dyads, 16 were missing data for this predictor. Therefore, 230 dyads were included in GGMM analyses. The models allowed for quadratic growth. The optimal number of classes for BMI percentile profiles was determined by the Bayesian and Akaike Information Criterion (BIC and AIC, respectively) as well as the *p*-value for the Parametric Bootstrapped Likelihood Ratio Test (BLRT) (McLachlan and Peel, 2000; See Table 3). When an additional class is added to the model, a decreased value of BIC and AIC from *k* to *k*+1 classes indicates improved model fit. The BLRT compares a model with *k* versus *k*-1 classes, testing the fit of *k* (alternative hypothesis) classes over *k*-1 (null hypothesis) classes; therefore a significant BLRT indicates *k* classes as a better fit for the given data. Quadratic variance of the model was constrained to zero. To avoid listwise deletion of data for subjects with missing values, Full Information Maximal Likelihood (FIML) was used in these analyses to interpolate missing values. Based on the fit parameters (BIC, AIC, BLRT), the 4-group model was selected for BMIP profiles. Despite the increase in BIC from the 3- to 4-group model, this increase was minor and other measures of fit, including AIC and BLRT, indicate improvement from the 3- to 4-group model.

This model supported the division of the 230 subjects into four distinct BMI percentile trajectories: Typical (*n* = 111, 48.3% of subjects), Rapid Increase (*n* = 54, 23.5%), Delayed Increase (*n* = 43, 18.7%), and Decreasing (*n* = 22, 9.6%) (Figure 2). The latent class probabilities (Typical - .86, Rapid Increase - .82, Delayed Increase - .79, Decreasing - .82) indicated good model fit (Nagin, 2005). GGMM calculates the probability that a subject

belongs to each of the four trajectory groups. Subjects were categorized into the trajectory group for which they had the highest probability of belonging. Notably, BMIP profile groups did not differ by child (sex, child's duration of breastfeeding, gestational age at birth), maternal (parity, maternal prepregnancy BMI, maternal weight gain during pregnancy), or sociodemographic factors (race/ethnicity, age, cohabitation with baby's father, and household income) (all p 's > .10). Although all children were full term at birth, the members of the Rapid Increase group were born earlier ($M=39.2$, $SD=1.1$) than those in the Typical group ($M=39.7$, $SD=1.1$; $p = .008$).

3.4 Group Differences in BMI Percentile

Groups differed significantly in BMIP at birth ($F(3,225) = 8.20$; $p < .001$), 3 months ($F(3,187)=15.83$; $p < .001$), 6 months ($F(3,186)=38.0$; $p<.001$), 12 months ($F(3,172)=114.96$; $p<.001$), 24 months ($F(3,146)=39.094$; $p<.001$). The Typical group was defined as the group including the greatest number of children (48.5%). This profile had a moderate mean BMIP at birth, remained stable over the first three months, increased marginally from three to 12 months, and remained stable thereafter (Figure 2).

As shown in Figure 2, the members of the Rapid Increase group exhibited lower BMIP at birth ($M = 39.8\%$, $SD = 31.2$; $p < .001$), 3 months ($M = 44.6\%$, $SD = 30.3$; $p = .001$), and 6 months ($M = 60.4\%$, $SD = 25.7$; $p < .05$) than the Typical group, but did not differ from the Typical group at 12 and 24 months (all p 's > .10).

The Delayed Increase group ($M = 52\%$, $SD = 30$) did not significantly differ in BMIP at birth from the Typical group ($p = .12$). This group then showed a decrease in BMIP, remaining significantly lower than the Typical group at 3 ($M = 31.1\%$, $SD = 25.4$; $p < .001$), 6 ($M = 27.7\%$, $SD = 20.5$; $p < .001$), and 12 months ($M = 32.7\%$, $SD = 16.3$; $p < .001$). By 24 months of age, however, the Delayed Increase group ($M = 67.7\%$, $SD = 21.7$) no longer differed from the Typical group at 24 months ($p > .10$).

The Decreasing group ($M = 47.7\%$, $SD = 29.1$) did not differ significantly from the Typical group in BMIP at birth ($p > .80$). However, this group showed a steady decrease in BMIP and remained significantly lower than the Typical BMIP group at 3 ($M = 33.1\%$, $SD = 23.7$; $p < .001$), 6 ($M = 33.3\%$, $SD = 19.8$; $p < .001$), 12 ($M = 31.7\%$, $SD = 15.6$; $p < .001$), and 24 months ($M = 19.6\%$, $SD = 13.1$; $p < .001$).

3.5 Group Differences in Birth Weight Percentile for Gestational Age

Birth weight percentile differed significantly across the BMIP profile groups ($F(3, 226) = 11.601$, $p < .001$). Post-hoc tests show that the Rapid Increase group ($M = 44.2\%$, $SD = 26.5$; $p < .001$) and the Delayed Increase group ($M = 55.2\%$, $SD = 27.3$; $p < .05$) exhibited low birth weight percentile compared to the Typical BMIP group ($M = 67.6\%$, $SD = 22.4$; $p < .05$), while the Decreasing group ($M = 56.6\%$, $SD = 27.2$) did not differ from the Typical group ($p > .10$).

3.6 Group Differences in Prenatal Hormone Exposure

Gestational exposure to pCRH at 30 weeks differed significantly across the BMIP profile groups (See Figure 3). The Rapid Increase group ($M = 445.8$ pg/ml, $SD = 161.7$) was exposed to significantly higher pCRH at 30 gestational weeks compared to the other three groups (all $p < .046$). The Delayed Increase group ($M = 295.6$, $SD = 105.7$) exhibited significantly higher pCRH as compared to the Typical group ($M = 148.7$, $SD = 56.0$; $p < .01$). The Decreasing group ($M = 140.8$, $SD = 61.8$) did not differ significantly from the Typical group in pCRH exposure ($p > .10$). BMIP trajectory groups did not differ significantly based on prenatal cortisol levels (all F 's $> .55$; p 's $> .10$).

4. Discussion

The current study provides new evidence that pCRH may be a mechanism of fetal metabolic programming and contribute to long-term obesity and disease risk. This longitudinal, prospective study documents that fetal exposure to higher concentrations of pCRH is associated with reduced birth weight, reduced BMI, and a period of rapid postnatal increase in BMI. These characteristics constitute a profile, described as catch-up growth, which is associated with heightened risk for obesity and metabolic disorders (Nobili et al., 2008).

We identified four distinct BMIP profiles in our sample. The Typical group comprised the majority of the sample and displayed a generally stable BMIP that is typical of U.S. samples (Mei et al., 2004). Compared to the Typical group, the Rapid Increase group had low birth BMIP and low birth weight as well as accelerated postnatal BMIP increase across the first 12 months. The Delayed Increase group exhibited low birth weight and a reduction in BMIP throughout the first year followed by accelerated BMIP increase between 12 and 24 months. Smaller body size followed by catch-up growth, as displayed by the Rapid and Delayed Increase groups, is a well-supported indicator of increased risk for obesity and metabolic disease (Cianfarani et al., 1999; Nobili et al., 2008). The Decreasing group exhibited an early decrease in BMIP and maintained a low BMIP compared to the Typical group from three to 24 months. Infants that experience reduced weight gain and stay small through the first two years also are at an increased risk for developing diabetes and impaired glucose tolerance (Eriksson et al., 2006). Importantly, the four groups did not differ on any of the maternal, child, or sociodemographic confounding factors, including sex of the child, and thus it is unlikely that such potential confounding factors account for these group differences.

Prenatal exposure to pCRH was highest among the Rapid and Delayed Increase groups exhibiting a pattern of BMI change associated with high obesity and metabolic risk. This corroborates previous human (Wadhwa et al., 2004; Fasting et al., 2009) and experimental animal (Williams et al., 1995) research concluding that CRH is associated with lower birth weight, indicating reduced fetal growth. The present findings provide new evidence that the consequences of pCRH extend beyond birth outcomes and are associated with postnatal growth profiles characterized by catch-up growth. Consistent with our findings, recent work with the Project Viva cohort finds that elevated pCRH exposure is associated with increased central adiposity and reduced BMI z-score at 3 years of age (Gillman et al., 2006; Fasting et al., 2009). Furthermore, experimental rodent research suggests that pCRH may play a causal

role in fetal programming of body composition. Zadina and colleagues (1985) found that pregnant dams receiving daily CRH injections during late pregnancy had offspring with exaggerated weight increases across the first postnatal week, similar to catch-up growth.

Our findings add to previous research that suggests there is a sensitive period for the effects of pCRH during the early third trimester. Placental CRH production begins to increase dramatically at about 25 gestational weeks with a 40-fold increase from the first through third trimesters (Sandman et al., 2006). A number of studies have documented that pCRH concentrations, specifically during this period of rapid increase in the early third trimester, are associated with fetal growth restriction (Wadhwa et al., 2004) and physical maturation (Ellman et al., 2008), and neurodevelopment (Davis et al., 2005). Furthermore, even though the current sample consisted of only full-term infants, the Rapid Increase group was born, on average, four days earlier than the Typical group consistent with previous research which has found a link between increased pCRH exposure and shortened gestational length (Sandman et al., 2006; Fasting et al., 2009). We find, that pCRH affects fetal growth and is associated with birth weight and BMIP independent of gestational length.

The mechanism by which pCRH influences early growth and development during this sensitive period is not well understood. CRH is released from the placenta into the maternal and fetal compartments. Maternal and fetal pCRH levels are positively correlated (Gitau et al., 2004). There are several plausible pathways by which pCRH may affect fetal growth and body composition. Placental CRH may program nutrition uptake and allocation. As a key regulating factor in nutritional exchange between the maternal and fetal systems (Gangestad et al., 2012), it is plausible that elevated pCRH either leads to or signals fetal nutrient restriction. Prenatal nutrient restriction stunts fetal growth, which is reflected in low birth weight, and prepares the fetus for a nutrient-deprived postnatal environment, in part, by adopting a 'thrifty' phenotype programmed to preserve excess nutrients. Although a thrifty phenotype is adaptive under conditions of scarcity, in conditions where postnatal food is plentiful the propensity to store nutrients leads to risk for obesity and metabolic disease (Dulloo et al., 2006; Gluckman et al., 2008). Another possibility is that elevated exposure to pCRH programs the fetal insulin system directly. Placental CRH, via CRH receptors in fetal insulin-producing pancreatic cells, modulates insulin secretion and glucose uptake (Schmid et al., 2011). CRH-stimulated insulin secretion may lead to increased fatty acid storage and therefore increased adipose tissue density (Frayn et al., 2006). Alternatively, elevated levels of pCRH may program the fetal HPA-axis (Mastorakos and Ilias, 2003) leading to a hypersecretion of cortisol, which is associated with increased blood glucose and insulin resistance (Reynolds and Walker, 2003) as well as increased visceral fat (Drapeau et al., 2003).

We did not observe an association between prenatal cortisol and weight or BMI at birth. There are significant inconsistencies in the existing literature evaluating endogenous maternal cortisol. Although some studies find that elevated maternal cortisol is associated with suppressed fetal growth (Duthie and Reynolds, 2013), others do not show this association (Khan et al., 2011). Discrepancies in these studies may be due to a variety of methodological differences including variation in the gestational age at assessment, type of cortisol collected (free versus total), ethnic diversity of the sample, and the inclusion of both

term and preterm infants. Our data indicate that in a low-risk sample of children who were born full term, maternal plasma (total) cortisol levels are not associated with body composition within the first two postnatal years.

4.1 Strengths and Limitations

The current study has several methodological strengths. First, it is one of the few to implement a prospective, longitudinal design to investigate the link between prenatal stress hormone exposure and postnatal growth patterns. Second, this study examines early changes in body composition using BMI, which provides a more accurate measure of adiposity than weight alone (Cole et al., 2005). Third, the BMI trajectories assessed in the present investigation are likely stronger predictors of risk for obesity compared to assessment of body composition at a single time point (Wen et al., 2012). Finally, this study includes only full term infants, and thus can identify the consequences of fetal hormone exposure independent of the well-documented effects of premature delivery. Furthermore, the effects found in this study are present even after considering the role of socio-demographic factors, which are known to affect child BMI.

A limitation of this study is that it did not include direct measures of maternal and infant nutrition, which may contribute to the patterns of fetal and infant development characterized in this study. Notably, neither maternal prepregnancy BMI nor maternal weight gain during gestation accounted for the study findings. Additionally, we are unable to infer any causal relations in this study because we did not implement an experimental design. It is plausible that pCRH is not in the causal pathway, but is a biomarker that is correlated with the biological processes regulating fetal growth. However, experimental animal research supports a causal role for CRH in programming body composition.

4.2 Implications

The early rapid increases in BMI observed among infants exposed to higher levels of pCRH during fetal development may be indicative of metabolic dysregulation. Childhood changes in BMI, such as the ones observed here, predict cardiovascular and pulmonary health in early adulthood (Ziyab et al., 2014). It is plausible that prenatal exposure to maternal stress signals has long-term implications for how offspring utilize and conserve energy, leading to a 'thrifty' phenotype associated with higher risk for obesity. Recent studies have concluded that prenatal exposure to maternal bereavement stress is associated with increased likelihood of becoming overweight as early as 10 years old (Li et al., 2010) as well as a two-fold risk of obesity at age 18 among men (Hohwü et al., 2014). The present findings indicate that fetal exposure to pCRH is a plausible mechanism underlying programming of obesity risk. Follow-up of the current cohort into middle childhood will shed light on the long-term health consequences associated with the distinct BMI trajectory groups observed in the current study.

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ACRONYMS

BMI	body mass index
BMIP	BMI percentile
HPA axis	hypothalamic-pituitary-adrenal axis
CRH	corticotropin-releasing hormone
pCRH	placental corticotropin-releasing hormone
WHO	World Health Organization
GC	glucocorticoid

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Highlights

- A prospective, longitudinal study identified four child profiles of BMI change.
- Elevated placental CRH exposure was associated with reduced birth weight and BMI.
- Children exposed to elevated placental CRH *in utero* exhibited catch-up growth in BMI.
- Placental CRH is a plausible mechanism for prenatal programming of obesity.

Figure 1. Hormone Concentrations Across Pregnancy

Levels of placental CRH (**A**) increased significantly across gestation from 15 weeks ($M = 36.91$, $SD = 18.97$), 19 weeks ($M = 50.32$, $SD = 32.37$), 25 weeks ($M = 126.12$, $SD = 90.21$), 30 weeks ($M = 245.23$, $SD = 159.66$), and through 37 weeks ($M = 763.97$, $SD = 286.35$).

Levels of plasma cortisol (**B**) increased significantly across gestation from 15 weeks ($M = 10.73$, $SD = 3.71$), 19 weeks ($M = 14.79$, $SD = 5.00$), 25 weeks ($M = 19.29$, $SD = 6.18$), 30 weeks ($M = 21.54$, $SD = 5.75$), and through 37 weeks ($M = 24.69$, $SD = 6.66$).

Figure 2. BMIP Profiles

Colored asterisks (*) refer to significant ($p < .05$) differences in the corresponding colored lines relative to the Typical BMIP group.

Figure 3. Placental CRH at 30 Weeks GA by BMIP Profile

Groups with different letters (e.g. **a** vs **b** vs **c**) differ significantly. The Rapid BMIP Increase group had significantly higher placental CRH at 30 gestational weeks than all other groups. The Delayed BMIP Increase group had significantly higher placental CRH at 30 gestational weeks than the Typical and Decreasing BMIP groups, which did not differ from one another.

Table 1

Descriptives

	Study Sample (N=246 pairs)
Maternal	
Age at Delivery (Mean $\pm$ SD)	29.7 $\pm$ 5.4
Cohabiting with Child's Father (%)	88.2
Primiparous (%)	41.0
Ethnicity (%)	
Non-Hispanic White	45.7
Hispanic	29.4
Asian	13.1
Multi-Ethnic	9
Other	2.7
Household Income (%)	
\$0–\$30,000	23.5
\$30,001–\$60,000	25.5
\$60,001–\$100,000	30
Over \$100,000	21
Education (%)	
High School or Less	17.2
Some College	42.5
College Graduate	40.3
CESD (Mean $\pm$ SD)	1.49 $\pm$.44
Child	
Sex (% Male)	51.2
Apgar Score (5 min)	9.0 $\pm$ 0.3; Range: 8–10
Gestational Age at Birth	39.5 $\pm$ 1.1

Table 2

Child Body Composition Measures

	n	Age	BMI	BMI (percentile)	Weight (kg)	Weight (percentile)
Birth	246	-	13.56±1.39	53.7±29	3.44±.43	58.6 ± 26
3 mos	201	3.06±.26	16.70±1.73	49.2 ± 29	6.18±.82	49.0 ± 27
6 mos	196	6.04±.28	17.55±1.69	55.7 ± 29	7.85±1.00	54.4 ± 27
12 mos	184	12.19±.29	17.41±1.57	64.6 ± 26	9.75±1.24	58.1 ± 27
24 mos	153	24.14±.39	16.73±1.31	67.7 ± 26	13.02±1.44	70.9 ± 24

This modeled BMIP trajectories across the first two years of life using pCRH as a predictor. The four-class model had the best fit and was used to define BMIP profile membership.

Table 3

General Growth Mixture Modeling

	Log Likelihood	# of Parameters	BIC	AIC	BLRT p-value
2 classes	-35.5	16	158.1	103.1	<.001
3 classes	-20.6	21	155.4	83.2	<.001
4 classes	-10.7	26	162.8	73.4	.04
5 classes	-5.8	31	180.2	73.6	1

BLRT = Bootstrapped Likelihood Ratio Test