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The role of prenatal exposures on body fat patterns at 7 years: Intrauterine programming or birthweight effects?

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Abstract *Background and aims:* It remains unknown whether the effects of prenatal exposures on child's adiposity reflect entirely intrauterine programming. We aimed to assess the effects of maternal gestational weight gain, diabetes and smoking on the child's body fat patterns, disentangling the direct (through intrauterine programming) and indirect (through birthweight) effects.
Methods and results: We included 4747 singleton 7-year-old children from the Generation XXI birth cohort (Porto, Portugal). At birth, maternal and newborn's characteristics were obtained. Anthropometrics were measured at age 7 years and body fat patterns were identified by principal component analysis. Path analysis was used to quantify direct, indirect and total effects of gestational weight gain, diabetes and smoking on body fat patterns. Pattern 1 was characterized by strong factor loadings with body mass index, fat mass index and waist-to-height ratio (fat quantity) and pattern 2 with waist-to-hip ratio, waist-to-thigh ratio, and waist-to-weight ratio (fat distribution). The positive total effect of maternal gestational weight gain and diabetes on the child's fat quantity was mainly through a direct pathway, responsible for 91.7% and 83.7% of total effects, respectively ($\beta = 0.022$; 95% Confidence Interval (CI): 0.017, 0.027; $\beta = 0.041$; 95% CI: −0.011, 0.093). No effects on fat distribution were found. Maternal prenatal smoking had a positive direct effect on patterns 1 and 2, explaining 94.9% and 76.1% of total effects, respectively.
Conclusion: The effects of maternal gestational weight gain, diabetes and smoking on a child's fat quantity seem to be mainly through intrauterine programming. Maternal smoking also showed a positive direct effect on child's fat distribution.

Introduction

Intrauterine programming has been pointed out, along with genetic predisposition, as a major cause of childhood obesity [1]. A large body of evidence has focused on adiposity programming by maternal under- or over-nutrition, weight gain, diabetes and smoking during pregnancy [2]. These exposures are likely to affect the development of adipocytes and their capacity to expand or contract, the appetite control system and the energy metabolism in later life [3]. However, it remains unknown whether the observed effects in these previous studies reflect entirely intrauterine programming. Confounding by

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lifestyles or genetics and the possibility of pathways mediated by other exposures might still be an issue.

Previous studies have addressed the effect of prenatal exposures on the risk of childhood obesity with and without adjustment for birthweight [4–7]. Since birthweight may be a mediator in these associations, the adjustment for birthweight might be inappropriate. First, the effect estimate obtained from a model adjusted for birth weight does no longer correspond to the total effect. Secondly, the approach of simply adjusting for mediators in the regression models is prone to bias and may produce flawed conclusions [8]. To our knowledge, no study has discussed separately the intrauterine programming effects from those mediated by birthweight. Assessing these effects separately will help to get further insight into the paths and mechanisms involved and their specific contributions to the associations between prenatal exposures and adiposity in later life.

Most studies looking at the relation between prenatal exposures and later adiposity have used proxies and have relied on single measures for defining adiposity, which might have limited their ability to detect associations [9]. The combination of anthropometric indices according to their inter-correlations into robust and uncorrelated patterns of body fat could be a more accurate and yet simple approach of evaluating childhood adiposity.

The present study aimed to assess the effects of prenatal exposures (gestational weight gain, diabetes and smoking) on body fat patterns of 7-year-old children. A path analysis helped to understand whether these effects are mainly explained by a direct (through intrauterine programming) or indirect pathway (through birthweight).

Methods

Study population

This study included participants from Generation XXI – a population-based birth cohort assembled during 2005–2006 at all public maternity units of Porto, Portugal. Of the invited mothers, 91.4% accepted to participate, corresponding to 8647 newborns. A detailed description of the cohort methodology was previously reported [10]. At the age of 7 years (2012–2014), 6889 children were re-evaluated (79.7% of the entire cohort), of which 5849 provided data by face-to-face interviews.

For the definition of body fat patterns, of 5849 children who attended the face-to-face interviews at 7 years old, we excluded 130 children with missing information on anthropometrics and/or tetra-polar bioelectric impedance, yielding a total of 5719 children (48.5% females). Further, we excluded 212 twins and 760 children who lacked data on selected variables of interest. The final study sample included 4747 children (48.6% females). The comparison between participants (n = 4747) and non-participants (excluding twins, n = 3604) showed that mothers in this study were slightly older [mean (standard deviation, SD) = 29.6 (5.30) vs. 28.1 (5.94) years old] and higher educated [mean (SD) = 11.1 (4.27) vs. 9.5 (4.04) years] than mothers who were not included in this study. However, the magnitude of the differences was not high (Cohen's effect size values [11] of 0.27 and 0.38 for maternal age and education, respectively), suggesting that the differences were mostly due to the large sample size rather than due to large differences between participants' characteristics.

Data collection

Baseline evaluation

Data on maternal characteristics were collected in face-to-face interviews, within 72 h after delivery, during the hospital stay. Maternal age and educational level at birth were recorded as completed years of aging and schooling. Information on prenatal smoking habits was collected and mothers were grouped into never or ever smokers during pregnancy. Pre-pregnancy weight was obtained through recall. Maternal height was measured by interviewers, and, when not possible, was abstracted from the national identity card. Pre-pregnancy body mass index (kg/m^2, BMI) was calculated. Maternal gestational weight gain was calculated as the difference between the final pre-delivery weight, reported by mothers, and the pre-pregnancy weight. Personal history of diabetes mellitus was considered present when participants reported a medical diagnosis of this condition before the current pregnancy. Gestational diabetes was considered present when recorded on obstetrical records as a diagnosis during the current pregnancy. Mothers were grouped into never or ever had a diagnosis of type 1 or type 2 diabetes mellitus or gestational diabetes. Clinical records were reviewed at birth to retrieve data on gestational age and birthweight. Gestational age was estimated by ultrasound and, when it was missing, it was estimated based on the last menstrual period. The z-scores of birthweight for gestational age were calculated according to a sex-specific, population-based Canadian reference [12].

Re-evaluation at 7 years old

Anthropometrics were obtained by trained personnel with children in underwear and barefoot, according to standard procedures. Body weight and height were measured using a digital scale (TANITA®) and a wall stadiometer (SECA®), respectively. Waist circumference was measured at the umbilicus level, with abdomen relaxed and hip circumference was measured at the level of the greatest posterior protuberance of the buttocks. Thigh circumference was measured at the position around the mid-thigh and perpendicular to the long axis of the thigh, with the leg slightly flexed. All anthropometrics were measured to the nearest 0.1 kg or cm. Body mass index was calculated (kg/m^2). The waist-to-height, waist-to-hip and waist-to-thigh ratios were calculated as waist circumference divided by height, hip circumference and thigh circumference, respectively. The relationship between waist circumference and weight was assessed using a log–log regression analysis. Log-waist circumference was regressed on log-weight. The gradient of the regression line was approximately 0.5,

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