

Decelerated Early Growth in Infants of Overweight and Obese Mothers

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## **Dedication**

This thesis is dedicated to my wonderful husband, Seth, without whom I would accomplish nothing, and to my wonderful children, Paul and Rebekah.

## Abstract

*Background:* Maternal obesity and overweight now affect a majority of US pregnancies. Evidence indicates that excess maternal weight increases offspring risk of obesity. Patterns of infant weight gain and growth also impact obesity risk; however, the effects of maternal pre-pregnancy BMI on early infant growth and body composition have not previously been well characterized.

*Objective:* To determine the relationship between maternal pre-pregnancy BMI category and infant growth and body composition.

*Methods:* Non-diabetic mothers with singleton pregnancies were recruited in pregnancy from an ongoing prospective cohort study and from the community. The mothers and their term, appropriate for gestational age (AGA), healthy infants were seen at 2 weeks and 3 months of age. Anthropometrics and body composition (fat mass, fat-free mass, and body fat percent) via air-displacement plethysmography were measured. Infant feeding information was collected. Maternal pre-pregnancy weight was collected via self-report and pregnancy glucose load results were obtained from the medical record. Results were analyzed by multiple-regression analysis controlling for known covariates that affect infant growth and body composition.

*Results:* Ninety-seven women/ infant pairs completed both study visits. Pre-pregnancy, 59 mothers were normal weight (BMI 18.5-24.99 kg/m<sup>2</sup>), 18 were overweight (BMI 25-29.99 kg/m<sup>2</sup>), and 20 were obese (BMI ≥ 30.00 kg/m<sup>2</sup>). At 2 weeks of age, infants did not differ in weight, length, fat free mass, fat mass, or body fat percent across maternal BMI groups. However, by 3 months of age, infants born to mothers with overweight or obese pre-pregnancy BMI had gained less weight, grew less in length, had a smaller increase in head circumference, and had smaller increases in body fat mass and body fat percentage (p= 0.01, 0.003, 0.005, 0.01, 0.01, respectively). The three groups had a similar gain in

fat free mass. Including maternal pregnancy glucose values and breastfeeding status in the models did not influence the outcomes.

*Conclusions:* Pre-pregnancy overweight and obesity were associated with reduced early infant linear growth and reduced accumulation of body fat mass, with preservation of increase in lean body mass. This “catch down” in growth and fat mass is a novel finding and may have implications for understanding infant growth, especially in the context of future metabolic risk.

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## **Background**

Maternal obesity is becoming increasingly common. In 1999-2004, 52% of US women of reproductive age were overweight or obese (1). Increasing evidence indicates that excess maternal weight prior to pregnancy increases offspring risk of obesity in childhood and tracking into adulthood (2, 3, 4, 5, 6, 7). The mechanisms behind this have not been fully elucidated, but pregnancy seems to be a critical window for the establishment of future metabolic patterns (8, 9).

Early infancy may also be a sensitive period for later obesity risk, because the patterns of weight gain and growth in infancy have significant relationships to long-term obesity and metabolic risk (10, 11, 12, 13, 14, 15). The rate of weight gain prior to 6 months of age seems to be especially pertinent (16, 17, 18, 19, 20). Despite this, few studies have characterized the growth of offspring of obese mothers in the first months of life.

In animal models (21, 22), maternal pre-pregnancy overweight has a negative impact on post-natal growth rates. In humans, however, the data that are available are contradictory (18, 23, 24, 25). This may be because studies have focused on infant weight without taking into account body composition. For example, a small infant with a significant amount of adipose tissue may weigh the same as a larger but more lean infant (26). Characterizing infants not only by weight, but by body composition may increase the specificity of our ability to determine obesity risk and may explain the differences found in the literature.

There is a paucity of data in the literature directly evaluating the effect of maternal pre-pregnancy weight status on the rate of change in body composition of infants. As both maternal pre-pregnancy weight status and early infant growth appear to be risk factors for obesity later in life, we sought to evaluate the relationship of maternal pre-pregnancy adiposity to early infant growth and body composition. These data may add to the understanding of the origins of obesity and provide possible targets for obesity prevention.

## **Materials and Methods**

*Subjects and Recruitment:* Women were recruited during pregnancy primarily from an ongoing prospective cohort study of the relationship between maternal diet and birth outcomes. Women were also recruited via fliers and word-of-mouth. The University of Minnesota's Institutional Review Board approved the study. All mothers provided verbal and written consent for themselves and their infants to participate in the study. Women were included if they were carrying an uncomplicated, singleton pregnancy and were excluded if they delivered prior to term (37.0 weeks), were underweight prior to pregnancy (BMI <18.5 kg/m<sup>2</sup>), or developed gestational diabetes mellitus (defined as a 1 hour glucose value following a 50g glucose load of  $\geq 130$ mg/dl (7.22 mmol/l) or glucose values during a 100g 3 hour oral glucose tolerance testing of fasting plasma glucose  $\geq 95$  mg/dl (5.28 mmol/l), 1 hr  $\geq 180$ mg/dl (10 mmol/l) or 2 hr  $\geq 140$  mg/dl (7.78 mmol/l) (27). Infants were excluded if they were small for gestational age (< 10<sup>th</sup> percentile for weight for gestational age as determined by plotting on the appropriate CDC growth charts), or if they had a health condition that would preclude them from safely being measured in the infant-sized air-displacement plethysmograph (PEA POD Infant Body Composition System) (Life Measurement Instruments, Concord CA).

*Study visits:* Mothers and infants were seen at the study site when the infant was two weeks of age and again at three months of age. At the two-week visit, demographic information and maternal and paternal self-reported height and weight were obtained by questionnaire. Maternal pre-pregnancy weight is routinely determined by self-report in the literature (28, 18, 29), and previous studies have shown acceptable agreement between maternal self-report and medical records from pregnancy (30, 31). At both the two-week and the three-month visit, the mother's standing height was obtained by wall-mounted stadiometer (SECA Hanover MD) and her weight by electronic scale (Health-O-Meter Professional Jarden Corporation Boca Raton, FL). Infant feeding and sleep behavior were assessed by a second questionnaire (adapted from 32). The infant's recumbent length was obtained by length board (Perspective Enterprises Portage, MI). Infant weight and length were used to calculate weight-for age and length-for-age z

scores, based on World Health Organization standards (33). Head circumference was obtained using standard techniques. All measurements were performed in duplicate and averaged. Body composition was assessed using air-displacement plethysmography (PeaPod, Life Measurement Instruments, Concord, CA). Quality control for the plethysmograph was performed at least once per visit day per manufacturer recommendations. Infant body composition was calculated from total body density using the Fomon prediction equation which also included gestational age, recumbent length, sex and age (34).

*Additional data collection:* With the written permission of study participants, prenatal records were extracted to verify self reported pre-pregnancy weight/BMI, infant birth weight, maternal weight at delivery, and glucose levels obtained during 50g glucose load and, if performed, 100g oral glucose tolerance tests for gestational diabetes mellitus.

*Statistical analysis:* Data analysis was performed using the Statistical Analysis Software version 9.2 (SAS institute, Cary NC, USA). All variables were assessed for normality of distribution. Maternal pre-pregnancy BMI was expressed as a categorical variable with normal BMI set at 18.5-24.9 kg /m<sup>2</sup>, overweight at 25.-29.9 kg/m<sup>2</sup> and obese as  $\geq 30.0$  kg/m<sup>2</sup>. The association of maternal BMI category with infant body composition, anthropometrics and infant and parental characteristics was first examined in unadjusted models using ANOVA for continuous variables and chi-square testing for categorical variables. Variables that were associated at  $p < 0.10$  in the unadjusted analysis were included as covariates in multiple linear regression models. Variables were retained in the multiple linear regression model if  $p < 0.05$ . Infant sex and gestational age were included in all models even when not significant by p value. A subgroup analysis was performed that included one-hour glucose value as an additional covariate.

## Results

### *Maternal and infant characteristics (table 1):*

One hundred and eighty-nine women without gestational diabetes were contacted: 20 could not be reached, 14 were ineligible (multiple gestation, miscarriage, would deliver after study close-out), 12 declined. One hundred and forty-three were recruited: 12 declined to schedule, 13 could not be contacted, 6 did not complete both visits, 1 moved out of state, 14 were excluded (7 delivered prematurely, 1 with intrauterine growth retardation, 1 with low maternal prepregnancy BMI, 1 who was already a month old, 1 with a heart defect and 3 with gestational diabetes which developed after initial recruitment).

Ninety-seven women and their infants completed both study visits. Fifty-nine women had a pre-pregnancy BMI in the normal range, 18 in the overweight range and 20 in the obese range. There were some notable differences in maternal and infant characteristics by study groups. Mothers who were overweight or obese prior to pregnancy had earlier onset of menarche ( $p=0.002$ ). When the groups were divided according to pregnancy weight gain categories per the criteria proposed by the Institute of Medicine (35), more women in the overweight group gained excessive weight during pregnancy than either the normal weight or the obese group, and no women in the overweight group gained too little ( $p=0.009$ ).

Gestational age of the infants did not differ across maternal BMI categories ( $p=0.95$ ). Birthweight was no different between infants born to mothers who were obese prior to pregnancy and those of normal weight ( $p=0.7$ ). However, infants born to mothers who were overweight but not obese prior to pregnancy had higher birthweights than infants of normal weight mothers ( $p=0.005$ ). Fewer of the infants born to overweight and obese weight mothers were classified as white (92% of normal weight vs. 78% of overweight and 60% of obese) ( $p=0.005$ ). Infants born to overweight or obese mothers were more likely to receive formula than infants born to normal weight mothers, and less likely to exclusively breastfeed ( $p=0.002$  for exclusive breastfeeding, 0.01 for initiation of supplemental or exclusive bottle feeding at 2 weeks and 0.0007 for initiation of supplemental or exclusive bottle feeding at 3 months). Infants of normal weight

mothers slept longer at night at 2 weeks and 3 months of age than infants of obese mothers (p=0.008, 0.03 respectively).

*Infant weight and length:* There was no difference in infant weight by maternal pre-pregnancy BMI category at 2 weeks of age. By three months of age, infants born to overweight or obese mothers weighed less than infants born to normal weight mothers (p=0.03)(table 1). At 2 weeks of age, infant length did not vary across the three BMI categories. At 3 months of age, infants born to obese mothers were significantly shorter than infants born to normal weight mothers (p= 0.01) (table 1).

*Infant head circumference:* There was no significant difference in infant head circumference by maternal BMI category at two weeks or three months of age (table 1).

**Table 1:** Characteristics of parents and infants (n=97) from the baseline questionnaire and measurements at the 2week and 3month study visits by maternal pre-pregnancy BMI category.

Maternal BMI Category	N	Normal N=59	Overweight N=18	Obese N=20	P value*
<b>Parental Characteristics</b>					
Maternal pre-pregnancy BMI (kg/m <sup>2</sup> )	97	21.8± 0.37	27.2± 0.67	36.7± 0.64	<0.0001
Maternal educational level (% with high school diploma or less)	97	17%	11%	15%	0.83
Maternal race (% white)	97	89.83%	83.33%	60%	0.01
Maternal ethnicity (% Hispanic)	97	3.39%	11.11%	0%	0.2
Maternal pre-pregnancy weight (kg)	97	60.41± 1.17	75.17± 2.12	96.18± 2.00	<0.0001
Maternal height (m)	97	1.66± 0.009	1.66± 0.017	1.62± 0.016	0.09
Maternal age (years)	97	30.73± 0.62	30.94± 1.14	32.45± 1.08	0.38
Maternal age at menarche (years)	96	13.1± 0.2	12.3± 0.3	12± 0.3	0.002
Maternal gestational weight gain (kg)	95	15.86± 0.75	16.38± 1.34	12.72± 1.27	0.07
Maternal gestational weight gain by IOM category	95				0.009
%inadequate		20.3%	0%	15%	

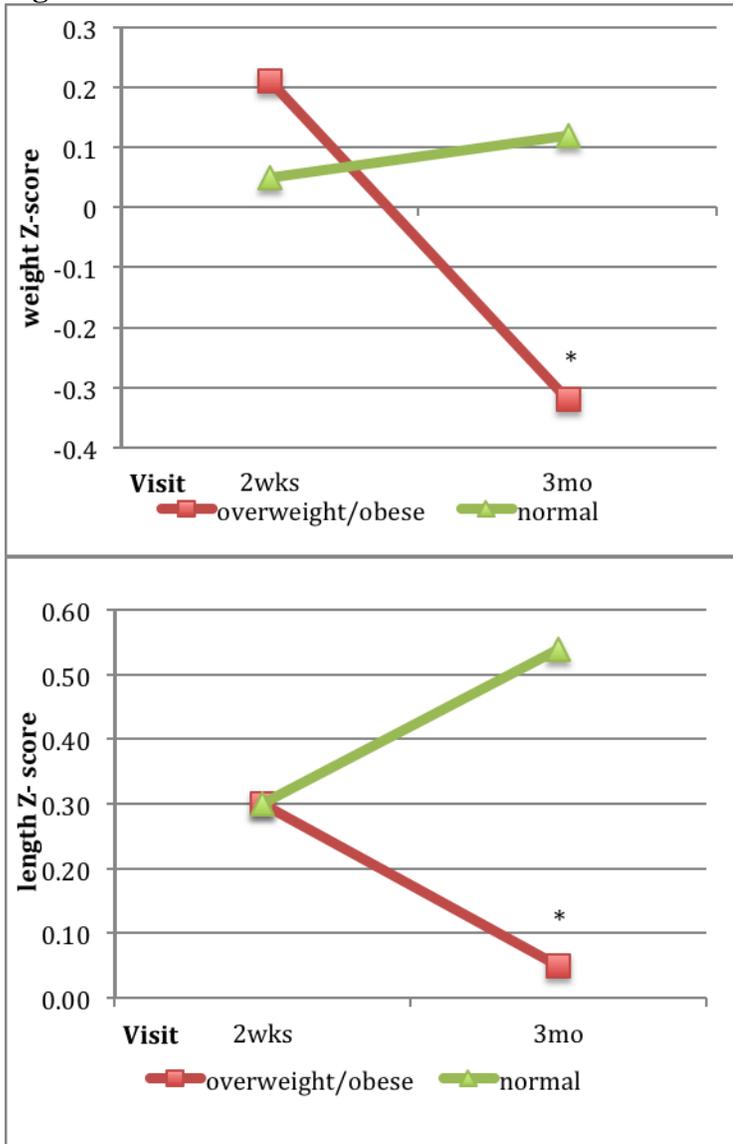
	%adequate	40%	11.1%	25%	
	%excessive	40.7%	88.9%	60%	
	Parity (% primiparous)	63%	50%	25%	0.01
	Paternal BMI (kg/m <sup>2</sup> )	96 26.37± 0.68	26.43± 1.22	31.54± 1.16	0.0007
	Paternal height (m)	97 1.80± 0.008	1.79± 0.02	1.79± 0.01	0.50
Infant characteristics					
	Gestational age (weeks)	97 39.77± 0.14	39.69± 0.25	39.79± 0.24	0.95
	Birth weight (g)	93 3467.21± 57.29	3812.24± 104.9	3510.92± 99.22	0.02
	Infant sex (% female)	97 45.8%	77.8%	35.0%	0.02
	Infant race (% white)	97 91.5%	77.8%	60.0%	0.005
	Infant ethnicity (% Hispanic)	97 8.5%	22.2%	5.0%	0.17
2 week visit					
	Infant weight (kg)	97 3.82± 0.05	4.03± 0.09	3.87± 0.09	0.15
	Infant weight Z score	97 0.05± 0.09	0.44± 0.17	0.009± 0.16	0.09
	Infant length (cm)	97 52.95± 0.23	53.41± 0.42	52.69± 0.4	0.42
	Infant length Z score	97 0.3± 0.11	0.59± 0.2	0.04± 0.19	0.14
	Infant head circumference (cm)	97 11.49± 0.1	11.91± 0.19	11.72± 0.18	0.33
	Infant fat mass (kg)	97 0.53± 0.02	0.64± 0.04	0.58± 0.04	0.17
	Infant fat free mass (kg)	97 3.29± 0.04	3.39± 0.08	3.29± 0.07	0.42
	Infant % body fat	97 13.8± 0.5	15.7± 0.9	14.9± 0.9	0.29
	Average nighttime sleep (hours)	97 8.0± 0.22	7.86± 0.4	7.38± 0.39	0.008
3 month visit					
	Infant weight (kg)	97 6.29± 0.09	5.85± 0.16	5.97± 0.15	0.03
	Infant weight Z score	97 0.12± 0.11	-0.27± 0.21	-0.36± 0.2	0.06
	Infant length (cm)	97 61.94± 0.27	61.23± 0.49	60.36± 0.46	0.01
	Infant length Z score	97 0.54± 0.12	0.43± 0.22	-0.29± 0.21	0.0009
	Infant head circumference (cm)	97 14.4± 0.15	14.26± 0.26	13.98± 0.25	0.8
	Infant fat mass (kg)	97 1.64± 0.06	1.37± 0.1	1.41± 0.1	0.02

Infant fat free mass (kg)	97	4.65± 0.06	4.47± 0.1	4.56± 0.1	0.34
Infant % body fat	97	25.7± 0.7	23.1± 1.2	23.5± 1.1	0.06
Average nighttime sleep (hours)	97	9.44± 0.25	8.66± 0.45	8.39± 0.42	0.03
% exclusive breastfeeding	97	69.5%	38.9%	30.0%	0.002
% initiating formula prior 2 weeks	97	18.6%	44.4%	50.0%	0.01
% initiating formula prior to 3 months	97	25.4%	55.6%	70.0%	0.0007

\*from ANOVA for continuous variables, from chi square for categorical variables, continuous variables expressed as mean ± standard error

At 2 weeks of age, there was no difference in weight-for-age or length-for-age z-scores across BMI categories. At 3 months of age, weight z score was still not significantly different across the three BMI categories ( $p=0.06$ ), but length z score for infants of overweight and obese mothers was significantly lower than that of infants of normal weight mothers ( $p=0.0009$ ). When expressed as a two level variable comparing infants of normal weight mothers versus overweight and obese mothers, infant weight for age and length for age z scores were no different at 2 weeks of age ( $p= 0.28, 0.97$  respectively), but were significantly different at 3 months ( $p= 0.02$  for both) (figure 1).

**Figure 1.**



**Legend:** Weight and length z-score by study visit for infants born to mothers with normal pre-pregnancy BMI (triangles) compared to infants born to mothers with overweight or obese pre-pregnancy BMI (squares). \*p=0.02 for t-test comparing infants of normal weight and overweight/obese mothers.

*Outcomes from the multivariate analysis (table 2):*

*Change in infant weight, length and head circumference (table 2):* When adjusted for infant sex, gestational age, and age at study visit, weight gain from 2weeks to 3 months of age

was significantly less in infants of overweight ( $p=0.0002$ ) and obese ( $p=0.01$ ) mothers than infants of normal weight mothers. Adjusted for infant sex, gestational age, age at study visit and maternal parity, infants of overweight and obese mothers also grew significantly less in length than infants of normal weight mothers ( $p=0.003$  for both). When adjusted for infant sex, gestational age, age at study visit and birthweight, increase in head size was significantly less in infants of obese mothers compared to infants of normal weight mothers ( $p=0.005$ ). Adjusting for maternal and paternal height did not affect the outcome (data not shown).

*Change in Infant body composition (table 2):* When adjusted for infant sex, gestational age and age at study visit, infants born to normal weight mothers gained significantly more fat mass from 2 weeks to 3 months of age than did infants born to overweight ( $p= 0.001$ ) and obese mothers ( $p=0.01$ ). Body fat percentage increased significantly more in infants of normal weight mothers as compared to infants born to both overweight ( $p= 0.0007$ ) and obese mothers ( $p= 0.01$ ), with infants of normal weight mothers increasing their percent body fat by 11.7% where infants born to overweight and obese mothers increased by 7.3 and 8.8%, respectively.

**Table 2:** Infant outcomes from multivariate model by maternal BMI category. Mean change from 2 weeks to 3 months of age, comparing infants of overweight and obese mothers to infants of normal weight mothers.

Maternal BMI Category	Normal	Overweight	Obese
Change in weight (kg)	2.45±0.07	1.89±0.12**	2.10±0.11*
Change in length (cm)	8.90±0.17	7.85±0.30*	7.84±0.30*
Change in head circumference (cm)	4.40±0.10	4.16±0.15	3.96±0.13*
Change in fat mass (kg)	1.09±0.05	0.75±0.09**	0.84±0.08*
Change in fat free mass (kg)	1.34±0.04	1.14±0.07*	1.26±0.07
Change in percent body fat (%)	11.79±0.60	7.30±1.12**	8.82±1.04*

Values expressed as least squared means ± standard error. All models controlled for infant sex, gestational age, and exact age between visits; model for change in length additionally controlled for maternal parity, model for change in infant head circumference additionally controlled for birthweight. \*p≤0.01, \*\*p≤0.001 for the comparison to infants of normal weight mothers.

*Subgroup analysis-- Maternal glucose values:* We were able to obtain and verify from the medical record values from glucose screening on 71 of the women included in the study. The population who had glucose values available differed from the population without glucose values available in rates of formula feeding at 3 months; 46% of those with glucose data were fed formula at 3 months compared to 22% in those without available glucose levels (p=0.04). Otherwise, there was no difference in maternal or infant characteristics. When the multivariate model was run on this sub-population both including and excluding this term, there was no significant difference in the outcomes (data not shown).

*Breastfeeding:* Although rates of exclusive breastfeeding and formula initiation differed across maternal BMI categories, these variables did not remain significant once included in the multivariate model (data not shown).

## **Discussion**

Maternal pre-pregnancy obesity is associated with increased offspring weight, height and fat mass (27, 24, 36), which has been suggested to occur both through prenatal epigenetic changes and postnatal behavioral differences. We hypothesized that maternal pre-pregnancy obesity would influence growth and body composition of offspring in early infancy. Previous literature on early infant growth has primarily examined infant weight (10, 25, 38, 39, 40). However, infant body composition may be a more sensitive and possibly specific indicator of long-term obesity risk. In later infancy and childhood, maternal obesity is associated with increased offspring fat mass and growth (3, 4, 6, 36, 37, 41). In contrast, our study demonstrated a reduction in linear growth and decrease in rate of accumulation of fat mass during early postnatal life.

By what mechanism might maternal overweight/obesity lead to slower growth in early infancy? A pattern of early growth deceleration in infancy followed by growth acceleration in later infancy and childhood has been seen in infants of diabetic mothers (42, 43), with Touger et al showing marked decline in weight z scores of infants of diabetic mothers from birth to 2 years of age with acceleration thereafter (42). In Regnault et al, who did not exclude mothers with gestational diabetes, infants of obese mothers were heavier and longer at birth, but had decreased weight and length-gain velocity such that by 3 months of age there was no difference in infant weight or length between infants of obese and normal weight mothers (23). Knight et al, who excluded maternal diabetes and controlled for maternal glycemia, had similar findings, showing a decline in weight and length standard deviation scores in infants of mothers in the highest weight tertile from birth to 3 months of age (25). The main difference between our study and those of Regnault and Knight is that in our study, the infants of obese mothers still experienced growth deceleration in the absence of elevated birthweights. This suggests that growth deceleration may be at least partially independent of birth size.

Neither Regnault nor Knight studied body composition in their populations, making it difficult to determine whether the decreased velocity of weight gain in their study can be attributed to decreased gain of fat mass, as in our population. One study that does provide data relating maternal prepregnancy BMI to infant body composition in

early infancy is Eriksson, Lof and Forsum, who found that maternal BMI correlated to infant birthweight and infant weight at 10 days, but did not correlate with any body composition findings or to any measurements at 3 months of age. However, their population, although similar in sample size to ours (108 vs 97), had a much lower rate of obesity (5% vs 21%), which may have resulted in reduced power to detect differences. They also did not comment on maternal diabetes status (44).

A possible explanation for this growth deceleration lies in the chronic inflammatory state associated with obesity, which has been shown to include increased free fatty acids, reactive oxygen species, inflammatory cells and markers of endothelial dysfunction in the mother (45, rev in 46). Increased reactive oxygen species and endothelial dysfunction would increase inflammation and decrease perfusion, thereby potentially restricting fetal growth. However, increased transfer free fatty acids may promote fetal growth and gain of fat mass (46, 44). One could hypothesize that while in utero, the deleterious effects of the inflammatory state are counterbalanced by excess nutrition, while in the early post-natal period, when excess nutrition is no longer available, growth would be relatively slower in these infants.

It has been shown that obese and overweight mothers who breastfeed produce less milk than normal weight mothers (48,49) and likewise in the present study, obese mothers were more likely to have fed their infants formula. Formula feeding is known to result in slower post-natal weight gain until approximately 3-6 months of age (50), when formula fed infants then begin to grow more rapidly, developing a greater risk for later obesity (51). We added infant feeding type (breast milk or formula at 2 weeks and at 3 months) in our multivariate model, but this did not appear to mediate the relationship between maternal obesity and infant growth. It is possible, however, that a more quantitative measure of breast milk and formula intake might have explained our findings.

The effects of maternal obesity and overweight must always be separated from the effects of gestational diabetes mellitus, which co-occurs with obesity. Our study is limited by the fact that glucose tolerance was determined from the medical chart, relying on diagnosis of GDM via standard screening, and that we were only able to obtain the

glucose screening results on 73% of women. Given that there are effects on infant outcomes of maternal glycemia in the absence of clinical diagnosis of GDM (25, 24), we cannot rule out that some of the effects found in our study derive from subclinical hyperglycemia. However, the lack of effect when controlling for glycemia in our subgroup analysis suggests that growth deceleration in infants of obese mothers is largely independent of maternal glycemia.

Our study provides novel data on the relation between early infant body composition and growth parameters and maternal pre-pregnancy overweight and obesity. It supports the notion that maternal obesity has a profound impact on infant metabolism as reflected in infant growth, and extends the evidence for this phenomenon to the earlier period of post-natal life. While mechanisms remain elusive, the findings of growth deceleration in the absence of the diagnosis of gestational diabetes mellitus and in the presence of normal birthweight suggests that these relationships are mediated by factors other than maternal glycemia .

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