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# Developmental Origins of Childhood Overweight: Potential Public Health Impact

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# Abstract

Several modifiable pre- and postnatal determinants of childhood overweight are known, but no one has examined how they influence risk of overweight in combination. We estimated the risk of overweight at age 3 years according to levels of maternal smoking during pregnancy, gestational weight gain, breastfeeding duration, and infant sleep duration. We studied 1,110 mother-child pairs in Project Viva, a prospective prebirth cohort study. The main outcome measure was child overweight (BMI for age and sex  $\geq$ 95th percentile) at age 3. We ran logistic regression models with all four modifiable risk factors as well as the covariates maternal BMI and education, child race/ethnicity, and household income. From the model, we obtained the estimated probability of overweight for each of the 16 combinations of the four risk factors. During pregnancy, 9.8% of mothers smoked and 50% gained excessive weight. In infancy, 73% mother-child pairs breastfed for <12 m, and 31% of infants slept <12 h/day. Among the 3-year-old children in the cohort, 9.5% were overweight. In the prediction model, the estimated probability of overweight ranged from 0.06 among children exposed to favorable levels of all four risk factors, to 0.29 with adverse levels of all four. Healthful levels of four behaviors during early development predicted much lower probability of overweight at age 3 than adverse levels. Interventions to modify several factors during pregnancy and infancy could have substantial impact on prevention of childhood overweight.

# INTRODUCTION

The obesity epidemic has spared no age group, even young infants (1). The implication is that prevention of childhood obesity should begin at the earliest stages of human development. In recent years, investigators have identified several potentially modifiable factors in the prenatal and early postnatal periods that increase the risk of overweight in childhood. These include maternal smoking during pregnancy (2-5), excessive gestational weight gain (6-10), reduced breastfeeding duration (11), rapid weight gain during the first few months of life (12-15), and short sleep duration (16,17).

Although studies have reported independent associations of each of these factors individually with later overweight, no previous study has assessed their combined impact. Such an

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DISCLOSURE

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The purpose of this study was to estimate the probability of overweight at age 3 years for different combinations of four modifiable risk factors occurring prenatally and during the first year of life.

# METHODS OF PROCEDURES

#### **Participants**

The subjects for this study were participants in Project Viva, a prospective, observational cohort study of gestational factors, pregnancy outcomes, and offspring health. We recruited women who were attending their initial prenatal visit at eight urban and suburban obstetrical offices of a multispecialty group practice in eastern Massachusetts. Eligibility criteria included fluency in English, gestational age <22 weeks at the initial prenatal clinical appointment, and singleton pregnancy. Details of recruitment and retention procedures are available elsewhere (18).

Of the 2,128 women who delivered a live infant, 1,579 were eligible for 3-year follow-up by virtue of having completed prenatal nutritional assessments and consenting for their children to be followed up. We collected follow-up information on 1,397 (88% of 1579), including inperson examinations on 1,283 (81%). For this analysis, we excluded 20 of the 1,283 participants whose gestational age at birth was <34 weeks, 28 participants missing height or weight at 3 years, and 125 participants missing values for any of the four risk factors, leaving a cohort for analysis of 1,110 mother–child pairs.

After obtaining informed consent, we performed in-person study visits with the mother at the end of the first and second trimesters of pregnancy, and with both mother and child immediately after delivery and at 6 months and 3 years after birth. Mothers completed mailed questionnaires at 1 and 2 years after birth. We also obtained information from medical records. Institutional review boards of participating institutions approved the study. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.

Comparison of the 1,110 participants in this analysis with the 1,579 who were eligible for 3year follow-up showed a higher proportion of maternal white race (76% vs. 69%), college or graduate education (74% vs. 68%), and annual household income exceeding \$70,000 (66 vs. 62%), and slightly lower smoking rates during pregnancy (10% vs. 12%) but did not differ on mean maternal prepregnancy BMI, gestational weight gain, or infant birth weight.

#### Measurements

**Risk factors**—We focused on factors during the prenatal period and infancy that have been associated with childhood overweight, are likely to be causal, and are potentially modifiable. Foregoing nuance for simplicity, we elected to use each of the four risk factors in dichotomous form. That decision limited the estimated probabilities to a tractable 16 combinations of the four risk factors.

**Smoking during pregnancy**—We asked mothers at both first and second trimester visits about their cigarette smoking habits before and during pregnancy. In Project Viva (2) and other cohort studies (3-5), smoking during pregnancy is associated with increased risk of overweight during childhood. A meta-analysis of 14 studies shows that the adjusted odds ratio for overweight among children of women who smoked during pregnancy was 1.50 (95%)

confidence interval (CI) 1.36–1.65) (19). In this analysis, we compared women who smoked during pregnancy with those who never smoked or quit before becoming pregnant.

Gestational weight gain—At the first trimester study visit, we asked mothers to report their weights just before they became pregnant. From medical records, we collected all weights measured during prenatal visits. We calculated total weight gain by subtracting pre-pregnancy weight from the last prenatal weight. In the Project Viva cohort, we have recently shown that excessive weight gain during pregnancy is associated with increased risk of overweight at age 3; compared with inadequate gain, the odds ratio for BMI exceeding the 95th percentile (vs. <50th percentile) was 4.35 (95% CI 1.69, 11.24) (7). Other preliminary data support this association (6,8-10). In this analysis, we expressed gestational weight gain in categories based on the 1990 recommendations of the Institute of Medicine (20), which advise less weight gain for mothers with higher pre-pregnancy BMI. For example, for a woman of normal weight BMI (19.8–26.0 kg/m<sup>2</sup>), the Institute of Medicine guidelines recommend a total weight gain during pregnancy of 11.5–16 kg, whereas for a woman with high BMI (26.1–29.0 kg/m<sup>2</sup>) the recommended gain is 7–11.5 kg. We used this same range, 7–11.5 kg, for obese women (>29.0  $kg/m^2$ ). In this analysis, we compared excessive maternal weight gain with adequate or inadequate gain, and to be consistent across all variables we defined normal childhood weight as BMI 5th–85th percentile rather than <50th percentile.

**Breastfeeding duration**—At 6, 12, and 24 months, we asked mothers whether they were still breastfeeding at all. If they had stopped, we asked them the children's age at cessation. Although the magnitude of the association between breastfeeding and later overweight is still controversial (21-23), the only meta-analysis examining duration of breastfeeding demonstrated a substantial decrease in odds (4% (95% CI 2–6%)) of later overweight for each additional month of breastfeeding (11). In this analysis, we compared any breastfeeding duration of <12 months with at least 12 months, which is recommended by the American Academy of Pediatrics (24).

**Daily sleep during infancy**—At 6 and 12 months postpartum, we asked mothers to quantify the average amount of daily sleep their children obtained over the past month. The questions prompted them to include morning and afternoon naps in addition to nighttime sleep. Using these questions, we have recently shown in the Project Viva cohort that average daily sleep duration from 6 to 24 months is inversely associated with overweight at 3 years (16). In that analysis, comparing average daily sleep duration of <12 with at least 12 h/day, the odds ratio for overweight was 2.04 (95% CI 1.07, 3.91). Here, we limited the sleep variable to 6 and 12 months because we were interested in the first year after birth. We used the mean of 6-month and 12-month sleep among the 914 participants with data at both time-points; in the remainder of participants one time point was missing, so we used the nonmissing value to represent the mean. In this analysis, we compared daily sleep duration of <12 h with at least 12 h, as in our published work (16).

**Outcome measures**—At 3 years, we measured weight using a calibrated scale (Seca model 881; Seca, Hanover, MD) and length using a calibrated stadiometer (Shorr Productions, Olney, MD), and we calculated age- and sex-specific BMI z-scores using US national reference data (25). We defined overweight as BMI ≥95th percentile for age and sex, and used BMI 5th–85th percentile as the comparison.

**Other measures**—Using a combination of self-administered questionnaires and interviews, we collected information about maternal pre-pregnancy weight, height, age, education, and parity, father's weight and height, child's age, sex, and race/ethnicity, and household income. We calculated birth weight for gestational age z-score as a measure of fetal growth (26). As a

measure of infant weight gain, we calculated the difference between weight-for-age z-scores at 6 months and at birth (25). Both fetal growth and rapid early infancy weight gain are directly associated with later BMI in childhood or adulthood (12-15,27). In this analysis, we considered fetal growth and infant weight gain to be "nonmodifiable" factors that might be intermediates in the causal pathways between the four risk factors and childhood obesity. At age 3, we estimated energy intake from a validated food frequency questionnaire (28), a weighted average of hours of television watched on weekdays and weekend days, and physical activity by asking mothers to report whether their children were less active, more active, or about the same as other children. As these three variables reflect energy intake and expenditure, we also considered them to be potential mediators.

#### **Statistical analysis**

To obtain estimates of the independent association of each risk factor with the outcome, we used logistic regression models that included all four modifiable risk factors as well as the four "nonmodifiable" determinants maternal prepregnancy BMI and education, child race/ ethnicity, and household income. Here, we consider these four factors nonmodifiable because usually they are fixed from the few months before pregnancy through 1 year after pregnancy. In preliminary modeling, we also included six additional potential confounding variables, namely maternal age and parity, paternal BMI, duration of gestation, and child sex and exact age. Because their inclusion did not materially change the effect estimates for the four risk factors, we left them out of the final model. Note that child age and sex are *de facto* in the final model because the BMI percentile calculation includes them.

Using parameter estimates from the multivariate logistic models, we estimated the predicted probability of overweight for each of the 16 combinations of the four risk factor variables. To estimate predicted probabilities, we needed to choose fixed values for the nonmodifiable determinants, and we selected a "typical" participant. By typical, we mean an individual with the modal values of race/ethnicity, education, and income, and the mean value of BMI, *i.e.*, one who was white, and who had a mother with a bachelor's degree and a BMI of 24.5 kg/m<sup>2</sup>, and a household income between \$40,000 and \$70,000. In this article, we show estimates for the 16 combinations of the four risk factors. In secondary analyses, we additionally adjusted for the two potentially mediating variables fetal growth and infant weight gain from birth to 6 months. We conducted all analyses using SAS, version 9.1 (Cary, NC).

# RESULTS

At age 3, mean (s.d.) for BMI *z*-score was 0.46(1.0) and 9.5% were overweight. The proportion of mothers who smoked during pregnancy was 9.8%; 50% experienced excessive weight gain. Seventy-three percent of infants were breastfed for <12 months, and 31% slept an average of <12 h/day. Table 1 shows the extent to which adverse levels of each of the four risk factors were independently associated with overweight at 3 years. The four factors were associated with odds ratios in the 1.3–1.8 range, some with wider CIs than others.

We next modeled the covariate-adjusted predicted probability of 3-year overweight for varying combinations of the four modifiable risk factors. In Figure 1, we show predicted probabilities for the 16 combinations of the four factors. Participants with favorable levels of all four risk factors had a predicted probability of 3-year overweight of 6%, whereas those with adverse levels of all four had a probability of 29%. Mixtures of favorable and adverse risk factor levels resulted in probabilities between these extremes.

In additional models that included the potentially mediating variables fetal growth and infant weight gain, the range of probabilities for the 16 combinations of the four risk factors was from 0.04 to 0.20, which is slightly lower and narrower than the main result of 0.06–0.29. With these

additional variables in the model, odds ratios for the four risk factors were not much changed: 1.6 instead of 1.7 for maternal smoking, 1.2 vs. 1.3 for gestational weight gain, 1.8 vs. 1.5 for breastfeeding, and 1.9 vs. 1.8 for infant sleep duration. A similar mediation analysis with 3-year energy intake, television watching, and physical activity showed similar results, *i.e.*, a range of probabilities of 0.04–0.20.

#### DISCUSSION

In this study, the predicted probability of overweight in childhood varied from 6 to 29%, depending on the levels of four potentially modifiable risk factors in pregnancy and infancy maternal smoking during pregnancy, gestational weight gain, breastfeeding duration, and daily sleep duration during infancy. This wide range of risk of childhood overweight implies that developmentally appropriate interventions to modify these factors may have substantial impact on preventing childhood obesity and its consequences.

Research into developmental origins of health and disease suggests that factors operating before and soon after birth can alter occurrence of chronic disease throughout the lifecourse (29). Some critics, however, have questioned the magnitude of public health impact of modifying the pre- and postnatal environment. A previous attempt at quantifying long-term effects invoked birth weight as the single perinatal factor (30). But birth weight, though easily measured, is unfortunately a poor proxy for true etiologic factors operating before and after birth (31). Likewise, although several studies implicate rapid infant weight gain in the genesis of later obesity (12-15), its modifiability is debatable beyond the potential effect of infant feeding, which we included as a risk factor in our analysis. In this study, we focused on four factors that are likely to be causal and potentially modifiable through clinical or public health interventions.

In most populations, the number of children with extreme risk factor profiles, e.g., those resulting in a 29% risk in this study, is likely to be small. Nevertheless, many mother–infant pairs in the intermediate categories would have room for substantial risk reduction. Consider, for example, a 3-year-old whose mother had smoked and gained an excessive amount of weight during pregnancy, and who had been breastfed for <12 months, but slept for at least 12 h/day during infancy. The estimated probability of overweight for such a child would be 19% (Figure 1), which is likely to approximate the prevalence of overweight in US children by 2010 (32). If the mother had not smoked or gained excessive weight during pregnancy and had breastfed for at least 12 months, the probability of overweight at 3 would be only 6%, assuming sleep duration did not change.

These are potentially achievable changes. In the developed world, smoking rates among pregnant women have risen and then declined in the past several decades (33), and smoking cessation before or even during pregnancy is attainable (34). Although no randomized controlled trials exist to show that moderating gestational weight gain is feasible, one trial with historical controls showed reduction in risk of excessive weight gain among low-income women (35). In addition, wide fluctuations have occurred over the past 50 years in the amount of weight women gain during pregnancy, likely due to health professionals changing their recommendations over time (36). After falling in the early to mid 20th century, breastfeeding rates have now risen from their nadir >30 years ago (37), and a large randomized trial of breastfeeding promotion resulted in substantial increases in duration and exclusivity of breastfeeding (38). Sleep duration during infancy appears modifiable as well (39).

This study has several strengths. They include prospective data collection and the ability to adjust for several important confounding factors. The study also has several potential limitations. Gestational diabetes is associated with offspring overweight in some studies (40),

but was not prevalent enough in our cohort (n = 42, 3.8%) to include as a risk factor. Including gestational diabetes status as a covariate hardly changed the estimated range of probabilities (from 0.06–0.29 to 0.06–0.30). Our main outcome was overweight at age 3. Overweight at this age does not predict adult consequences as well as overweight later in childhood (41) but can nevertheless presage serious adverse health consequences in childhood itself (42).

Some of our exposure–outcome associations were not "statistically significant" according to the common but arbitrary standard of a *P* value <0.05. Nonetheless, as detailed in the Methods and Procedures section, other studies and meta-analyses have shown similar magnitudes of association with more precision than was possible in our single study, and the imprecision of our estimates is manifest in the width of the CIs (Figure 1). As in other studies (43), maternal BMI was a strong predictor of childhood obesity. Prevention of maternal obesity entering pregnancy is a public health priority, but was not the focus of this study, in which we evaluated modifiable factors once pregnancy begins.

Most measures were from self-report, including prepregnancy weight, smoking, breastfeeding, and infant sleep, and loss to follow-up was not random. These factors could have introduced bias. We obtained results from one cohort of mothers and children from Massachusetts. The quantitative results may not be directly applicable to other populations, chiefly because the frequencies of risk factors or overweight may differ. That is not a true limitation of the study, rather just a reminder that absolute risks differ across populations as covariate frequencies do. For example, in our calcuations of predicted probabilities if we had chosen as a "typical" participant, a woman with BMI of 30 instead of the sample population mean of 24.5 kg/ m<sup>2</sup>, the range of predicted probabilities would have been 0.11-0.43 instead of 0.06-0.29. Regardless, more important than the exact probabilities is the message that varying levels of potentially modifiable early developmental factors predict a wide range of probabilities of childhood overweight.

In summary, we found that combinations of four modifiable factors in pregnancy and infancy can predict quite low or quite high risk of childhood overweight, in this cohort from well under 10 to almost 30%. Given the short- and long-term adverse consequences of childhood obesity, these findings suggest how crucial early developmental factors may be in determining obesity-related consequences across the life course. They also provide a strong rationale for testing developmentally appropriate pre- and postnatal interventions to prevent childhood overweight.

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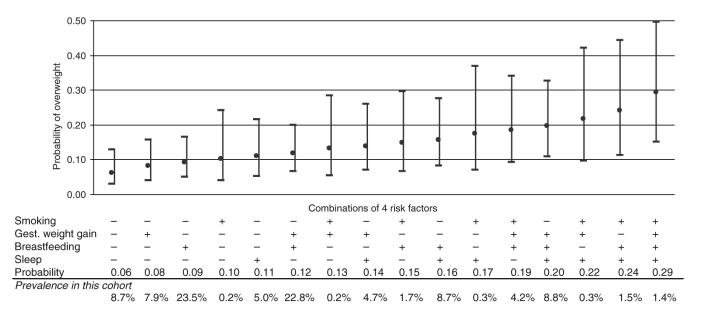
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#### Figure 1.

Predicted probability of overweight at 3 years for 16 combinations of four modifiable risk factors during pregnancy and infancy. Bars show 95% confidence limits. Also shown is prevalence in this cohort for each depicted combination of factors. Data from 1,110 mother–child pairs participating in Project Viva. Probabilities are adjusted for maternal education and BMI, household income, and child race/ethnicity.

+	_
Yes	No
"Excessive"	"Adequate or inadequate"
<12	≥12
<12	≥12
	Yes "Excessive" <12

 $\overline{a}$ Gestational weight gain categories according to 1990 recommendations of Institute of Medicine (19).

#### Table 1

Prevalence of four modifiable and several nonmodifiable factors during pregnancy and infancy, and adjusted odds of overweight at 3 years of age

	Overweight at age 3 years		
	No (BMI 5th—8th percentile) <i>n</i> = 791	Yes (BMI > 95th percentile) <i>n</i> = 105	Adjusted <sup>a</sup> odds of overweight
Modifiable risk factors	N (% of	subjects)	
Prenatal smoking			
No	725 (92)	88 (84)	1.0 (Ref)
Yes	66 (8)	17 (16)	1.71 (0.90, 3.25)
Gestational weight gain <sup>b</sup>			
Inadequate or adequate	407 (51)	45 (43)	1.0 (Ref)
Excessive	384 (49)	60 (57)	1.32 (0.85, 2.03)
Breastfeeding duration (m)			
>12	222 (28)	18 (17)	1.0 (Ref)
<12	569 (72)	87 (83)	1.50 (0.86, 2.64)
Infant sleep (h/day)			
>12	563 (71)	60 (57)	1.0 (Ref)
<12	228 (29)	45 (43)	1.83 (1.17, 2.85)
Nonmodifiable factors included in multivariate model			
Maternal education			
Some college or less	198 (25)	37 (35)	1.27 (0.66, 2.43)
BA or BS	301 (38)	43 (41)	1.41 (0.82, 2.42)
Graduate degree	292 (37)	25 (24)	1.0 (Ref)
Household income			
Don't know or missing	57 (7)	10 (10)	1.32 (0.61, 2.87)
<\$40,000	86 (11)	15 (14)	0.73 (0.32, 1.66)
\$40,000-\$70,000	144 (18)	25 (24)	1.07 (0.61, 1.89)
>\$70,000	504 (64)	55 (52)	1.0 (Ref)
Child race/ethnicity			
White	571 (72)	68 (65)	1.0 (Ref)
Black	81 (10)	15 (14)	1.02 (0.49, 2.13)
Hispanic	27 (3)	8 (8)	1.86 (0.72, 4.78)
Other	112 (14)	14 (13)	0.91 (0.48, 1.74)
	Mean	a (s.d.)	
Maternal pre-pregnancy BMI (kg/m <sup>2</sup> )	24.0 (4.7)	27.5 (6.4)	1.11 (1.07, 1.15)
Other non-modifiable factors			
	N (% of	subjects)	
Nulliparous	386 (49)	39 (37)	
Child sex (F)	407 (51)	42 (40)	
Weight gain birth to 6 m			
Quartile 1–3	602 (81)	51 (52)	
Quartile 4	144 (19)	48 (48)	

	Overweight at age 3 years			
	No (BMI 5th—8th percentile) <i>n</i> = 791	Yes (BMI > 95th percentile) <i>n</i> = 105	Adjusted <sup><i>a</i></sup> odds of overweight	
	Mean	e (s.d.)		
Maternal age at enrolment (y)	32.6 (5.0)	33.0 (4.7)		
Paternal BMI (kg/m <sup>2</sup> )	26.1 (3.6)	28.6 (4.8)		
Gestation length (weeks)	39.6 (1.4)	39.5 (1.4)		
Fetal growth (birth weight/gestational age z score)	0.13 (0.93)	0.53 (0.84)		
Child age at outcome measurement (y)	3.3 (0.3)	3.3 (0.3)		

Data from 1,110 mother-infant pairs participating in Project Viva.

<sup>a</sup>Model covariates include all four modifiable risk factors and the four "nonmodifiable" variables maternal education and BMI, household income, and child race/ethnicity.

 $^{b}$  Gestational weight gain categories according to 1990 recommendations of the Institute of Medicine (19).