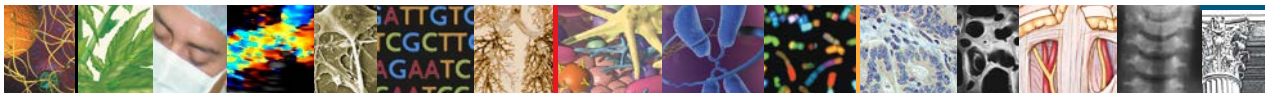

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Perspective

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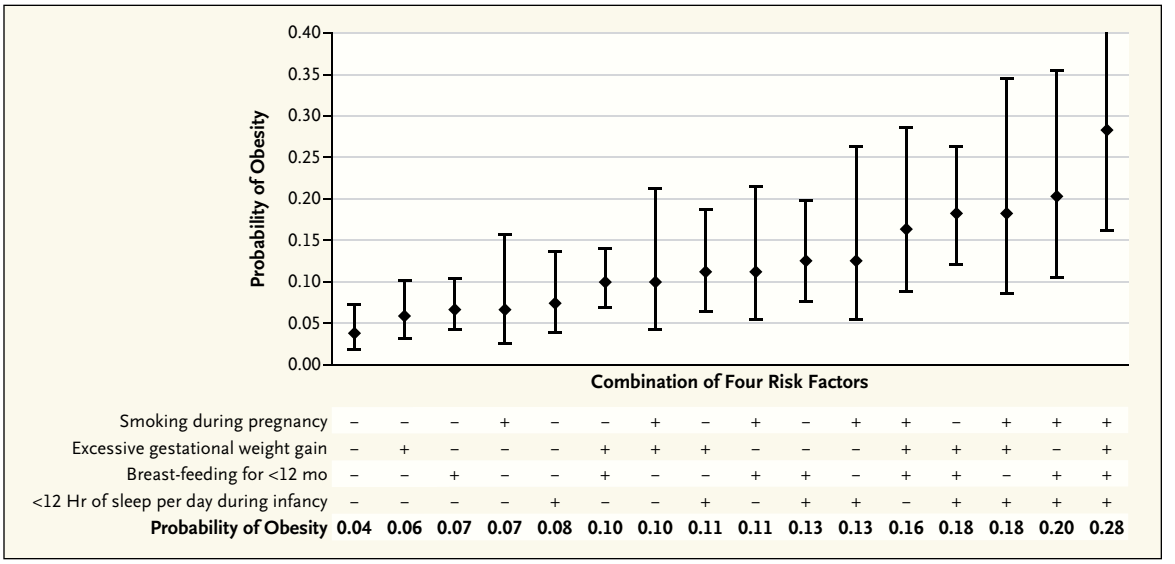
How Early Should Obesity Prevention Start?

Matthew W. Gillman, M.D., and David S. Ludwig, M.D., Ph.D.

Obesity has pervaded the United States and is spreading throughout the world. Following in its wake is type 2 diabetes, which will affect at least half a billion people worldwide by 2030. A majority of U.S. women of childbearing age are overweight or obese (as defined by a body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] >25). These women are likely to gain excessive weight when they're pregnant, making it harder for them to return to their prepregnancy weight after delivery. Postpartum weight retention not only portends increased lifelong risks for obesity-related complications but also an increased BMI at the inception of future pregnancies. During pregnancy, excessive weight gain, along with other risk factors such as gestational diabetes, can alter fetal growth and metabolism, leading to higher adiposity in the offspring. If the child is female, grows up obese, and becomes pregnant, the cycle begins again. It is time to interrupt this vicious cycle to prevent obesity and chronic diseases in mothers and children.

Once obesity is present, it is challenging to treat because of multiple physiological, behavioral, and cultural feedback loops. The good news is that the prenatal period and the first postnatal year hold critical clues that may lead to interventions to reduce obesity in women and prevent it in children. In a range of animal models (from rodents to nonhuman primates), dietary, hormonal, mechanical, and other perturbations that occur prenatally and during infancy induce lifelong, often irreversible derangements in the offspring's adiposity and metabolism. These changes involve the environmental alteration of genetic expression, in part through epigenetic mechanisms, rather than changes in the genome itself. Thus, timely intervention during the early, plastic phases of development — unlike corrective efforts made later in life — may lead to improved lifelong health trajectories.

Because of challenges in measuring fetal exposures and the long latency between initial determinants and salient health outcomes, however, it is difficult to translate such proofs of principle in animals to human populations. The first generation of developmental-origins studies in humans linked birth weight to adult obesity-related morbidity and mortality. We now recognize that birth weight and each of its compo-



Predicted Probability of Obesity at 7 to 10 Years of Age for 16 Combinations of Four Modifiable Prenatal and Postnatal Risk Factors.

Data are from 1110 mother–child pairs participating in Project Viva. Estimates are adjusted for the mother's educational level and body-mass index (BMI), household income, and the child's race or ethnic group. Obesity was defined as a BMI above the 95th percentile for age and sex. Excessive gestational weight gain was defined according to the 2009 recommendations of the Institute of Medicine. Plus signs indicate the presence of the risk factor, and minus signs the absence of the risk factor. I bars indicate 95% confidence intervals.

nents, gestational duration and fetal growth, are low-resolution, momentary markers for myriad prenatal and perinatal influences. In the past decade, many such influences have been identified and quantified in epidemiologic studies that have involved the period before birth, used modern methods to mitigate confounding, and incorporated biomarkers. These studies have identified prenatal risk factors for obesity ranging from lifestyle factors such as the mother's smoking status to psychosocial factors including antepartum depression, medical conditions such as gestational diabetes, physiological stress as reflected by fetal exposure to glucocorticoids, and epigenetic markers such as gene-specific DNA methylation levels in umbilical-cord tissue.

After birth, rapid weight gain in the first 3 to 6 months of life is a potent predictor of later obesity and cardiometabolic risk. Lactation cannot be the entire explanation, because breast-fed babies tend to gain more weight than formula-fed babies in the first few months of life. The perinatal hormonal milieu may very well be a contributing factor. In one study, higher leptin levels in umbilical-cord blood, chiefly reflecting placental production, were associated with slower gain in infant weight-for-length and lower adiposity at the ages of 3 years and 7 years. In contrast, higher leptin levels at 3 years of age were associated with faster gains in BMI from 3 to 7 years, suggesting that leptin resistance develops between birth and 3 years of age.[1] These findings are consistent with studies in animals showing a critical period of perinatal leptin exposure that allows normal maturation of appetite-regulating neurons in the hypothalamus. Features of infant feeding other than breast versus bottle may also play a role. Among formula-fed infants, the introduction of solids before 4 months was associated with a sixfold increase in the odds of obesity 3 years later.[2]

Emerging risk factors for obesity include exposure to endocrine disruptors, which appear to do the most damage during times of maximum developmental plasticity, and the gut microbiota. Our bodies contain about 10^{13} cells but as many as 10^{14} microorganisms. Certain modifications in the number and type of microorganisms during infancy are associated with excess weight gain, at least in rodents. The infant gut is normally colonized during transit through the birth canal, which could be one reason why children delivered by cesarean section appear to be at elevated risk for obesity.[3]

Given obesity's numerous developmental determinants, it is logical that effective prevention

would target multiple modifiable factors. In combination, two well-studied prenatal risk factors, excessive gestational weight gain and maternal smoking during pregnancy, and two postnatal factors, fewer months of breast-feeding and a shorter duration of daily sleep during infancy, are associated with wide variation in childhood obesity. In one study, preschool-age children whose mothers did not smoke or gain excessive weight during pregnancy and who were breast-fed for at least 12 months and slept for at least 12 hours per day during infancy had a predicted obesity prevalence of 6%, as compared with 29% among children for whom the opposite was true for all four risk factors[4]; the rates were similar (4% and 28%, respectively) when the children reached 7 to 10 years of age (see graph). These observational data raise the possibility that avoiding some or all of these risk factors could substantially reduce the proportion of childhood obesity.

Preventing racial and ethnic disparities in obesity risk will also require a developmental approach. By school age, rates of obesity among black and Hispanic children in the United States are higher than the rates among white children, even after adjustment for socioeconomic circumstances. Many of the risk factors during pregnancy and early childhood are more prevalent among nonwhite persons, and they explain a substantial proportion of racial and ethnic differences in obesity in mid-childhood.[5]

Several features of pregnancy and infancy make the prenatal and postnatal periods conducive to behavior change to reduce the risk of obesity and its complications. First, women appear especially willing to modify their behavior during these periods to benefit their children. Second, since pregnant women and infants receive frequent routine medical care, interventions involving improved health care delivery have great potential. Third, these periods are relatively brief, and we know that behavior-change interventions are typically most successful in the short term. Fourth, if effective interventions begun during pregnancy are maintained after birth, they will reduce the risk of maternal obesity for future pregnancies and thus help to interrupt the intergenerational cycle.

Ongoing intervention studies promise to inform medical practice and public health. Many current trials target excessive gestational weight gain, including seven randomized, controlled trials funded by the National Institutes of Health that will together include more than 1000 overweight or obese women and follow infants through at least 1 year of age. It remains to be proven, however, that reducing gestational weight gain reduces the obesity risk in offspring. An alternative approach focuses on dietary quality, independent of calorie content, to ameliorate maternal insulin resistance and excessive placental nutrient transfer. Pilot studies have suggested that a multiple-risk-factor approach during infancy, targeting mothers as conduits for changes in their infants, can improve sleep duration and delay the introduction of solid foods.

But even as we await the results of obesity-prevention trials, some recommendations are warranted because of their beneficial effects on other health outcomes. Pregnant women should not smoke. Treatment of gestational diabetes reduces macrosomia at birth, although such treatment hasn't been proven to prevent obesity. U.S. rates of elective cesarean sections have apparently leveled off, but reducing these rates, especially of cesarean sections performed before 39 weeks of gestation, is a public health goal. Simple sleep-hygiene measures are worth trying, even in early infancy. The ideal age, in terms of allergy prevention, for introducing solid foods appears to be 4 to 6 months, and further research may show that the same is true in terms of obesity prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute (M.W.G.), the New Balance Foundation Obesity Prevention Center, Boston Children's Hospital (D.S.L.), and the Department of Nutrition, Harvard School of Public Health (M.W.G., D.S.L.) — all in Boston.

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