

Overweight in Childhood and Adolescence

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The prevalence of overweight doubled among children 6 to 11 years of age and tripled among those 12 to 17 years of age between the second National Health and Nutrition Examination Survey, conducted between 1976 and 1980, and the most recent such survey, conducted in 1999 and 2000. Overweight in children and adolescents, defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) at or above the 95th percentile for children of the same age and sex, is epidemic. Black and Mexican-American children and adolescents are disproportionately affected. Although only 25 to 30 percent of obesity in U.S. adults begins during childhood or adolescence, early childhood overweight that persists into adulthood is associated with more severe obesity among adults.

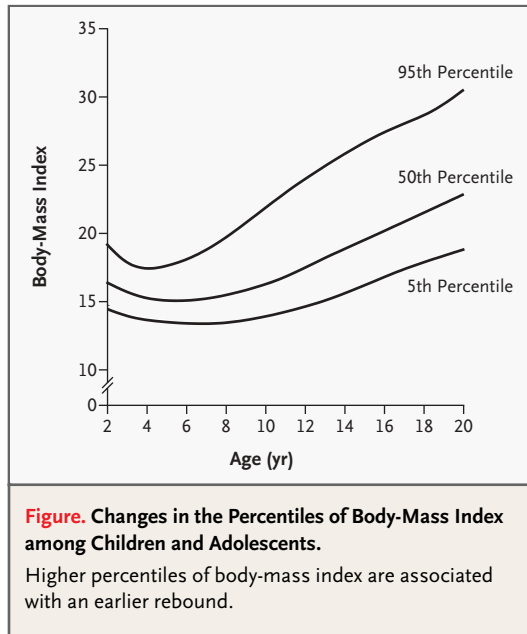
A critical period for overweight or obesity is defined as a time when the risk of onset, complications, or persistence of overweight or obesity is increased. The rapid increases in the prevalence of childhood overweight and its potential effect on morbidity and mortality in childhood and adulthood emphasize the importance of identifying critical periods for the prevention of overweight in vulnerable populations and of understanding the factors that cause excess weight gain.

Overweight in childhood can no longer be considered a benign condition or one related only to appearance. Between 1979 and 1999, the rates of obesity and obesity-associated hospital-discharge diagnoses, such as sleep apnea and gallbladder disease, and the costs of hospitalizations tripled among children 6 to 17 years of age. Approximately 60 percent of overweight children and adolescents have at least one additional risk factor for cardiovascular disease, such as elevated blood pressure, hyperlipidemia, or hyperinsulinemia. More than 25 percent have two or more of these risk factors. Type 2 diabe-

tes mellitus has been estimated to account for anywhere from 8 percent to 45 percent of all new cases of diabetes in children and adolescents. Even if the evolution of complications of type 2 diabetes in adolescents is similar to that in adults, the longer duration of complications will add considerably to the burden and costs associated with the disease.

Two critical periods in the development and persistence of overweight in the pediatric age group are the prenatal period and adolescence. The period of "adiposity rebound" may constitute a third. Both low and high body mass appear to arise during the prenatal period.¹ Infants with low birth weights for gestational age appear to remain smaller than their peers whose birth weights are in the normal range. Nonetheless, low birth weight for gestational age has been associated with an increased risk of diseases such as diabetes or cardiovascular disease in adulthood. Infants with high birth weights appear to have an increased risk of subsequent overweight. Effects of the intrauterine environment on cell numbers, satiety centers in the brain, and endocrine function represent mechanisms that may logically account for the apparent prenatal channeling of either restricted or exuberant growth. Whether the effects of low birth weight on the risk of illness in adulthood are independent of growth during early childhood remains uncertain.

The period when the body-mass index begins to increase after reaching a nadir in early childhood has been called adiposity rebound (see Figure). Rebound of the body-mass index may be a more appropriate term to describe this phenomenon, because it has not yet been demonstrated that changes in adiposity are responsible for the increase in the body-mass index that occurs. Several studies have suggested that early rebound of the body-mass index is associated with an increased risk of high body-mass



index in adulthood, although this association may not be independent of the body-mass index in early childhood. These observations have also focused attention on the potential interaction between birth weight and early growth as determinants of later body-mass index and the risk of obesity-associated illness. In this issue of the *Journal*, Bhargava and colleagues (pages 865–875) link glucose intolerance and diabetes in Indian adults to early rebound of the body-mass index. Although the growth of children with early rebound was below U.S. standards, both at the time of rebound and at 12 years of age, children with an early rebound had a higher body-mass index at 12 years of age than children with a later rebound.

These observations raise several important issues. First, the absence of overweight among children with early rebound in this study does not rule out an effect of early rebound on abdominal fat deposition, either at the time of rebound or later. Increased abdominal fat deposition would be expected to increase the risk of subsequent glucose intolerance and diabetes. The questions of whether and how early rebound leads to these sequelae provide rich possibilities for a generation of investigators. Second, whether body-mass index at the time of rebound is more important than the time at which the rebound occurs remains uncertain. Third, the rela-

tive contribution of physiological and environmental factors to early rebound remains to be delineated. Finally, early rebound of the body-mass index can be recognized only in retrospect. Therefore, it is unclear whether or how one could delay the rebound and whether such a delay would alter or reverse the effects of early rebound.

Adolescence represents a third critical period when overweight may occur and may increase the risks of the sequelae of obesity in adulthood. The risk of becoming overweight during adolescence appears to be higher among girls than among boys, perhaps because adolescence in girls is characterized by a relative increase in fatness. Several studies have suggested that up to 80 percent of overweight adolescents will become obese adults. Furthermore, obesity that was present in adolescence has been shown to increase mortality among adult men and to increase the risks of cardiovascular disease and diabetes in adult men and women. Opinion is divided on whether the increased risks of these diseases are mediated through their effect on adult weight. The changes in body composition that occur during adolescence have been well described. In boys, fat-free mass tends to increase, body fat as a percentage of body weight decreases, and fat tends to be deposited abdominally. In girls, both fat and fat-free mass increase, fat-free mass as a percentage of body weight decreases, and fat tends to be deposited in the buttocks. In both sexes, factors that contribute to the quantity of body fat and abdominal fat distribution appear to increase the risk of subsequent complications.

Observations during these three periods emphasize the need to identify the factors that contribute to the onset and persistence of childhood overweight. The association of adult obesity and its complications with birth weight, rebound of the body-mass index, and overweight during adolescence suggests that these periods may prove critical for the prevention of early overweight and its effects on adult disease. Effective prevention will require efforts to understand why these periods are fraught with risk and the identification of the critical shifts in dietary intake, physical activity, or both that contribute to becoming overweight and having associated complications.

Various ethnic groups have rarely been systematically compared in terms of longitudinal changes in growth, nor have linkages been established be-

tween changes in food intake or physical activity and changes in growth. Other studies of children and adolescents have demonstrated that the upper tail of the distribution of body-mass index has increased more than the median. This observation suggests that half the members of the population harbor genes that make them more susceptible to increased weight gain, that half are exposed to more environmental factors that promote weight gain, or that there is some interaction of the two factors. The increased rates of weight gain among black and Mex-

ican-American children and adolescents indicate that the interactions between people and their environment that account for overweight and its complications probably vary according to ethnic background. Effective prevention may therefore require strategies specific to each ethnic group.

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1. Strauss RS, Dietz WH. Growth and development of term children born with low birth weight: effects of genetic and environmental factors. *J Pediatr* 1998;133:67-72.

Pulmonary Hypertension in Sickle Cell Disease

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Sickle cell disease was first described in 1910 by Herrick and Irons. The irregularly shaped blood cells observed by Irons were those of Walter Clement Noel, a dental student with symptoms that included joint pain and shortness of breath. After graduation, Dr. Noel returned to his native Grenada, where he died suddenly at 32 years of age. Although the cause of death was recorded as pneumonia, his death was most likely the result of sudden, undetected pulmonary hypertension.

Today, we know that pulmonary hypertension and chronic lung disease are two of the most common causes of death among patients with sickle cell disease. Autopsy studies reveal clinically unsuspected obliterative pulmonary vasculopathy with signs of pulmonary hypertension in a third of all patients with sickle cell disease (see Figure), although the true frequency of pulmonary hypertension is unknown. Retrospective studies have shown that as many as 60 percent of patients with sickle cell disease are affected by pulmonary hypertension, and similar frequencies are now being observed among patients with many other hemolytic anemias, including congenital spherocytosis, thalassemia, and paroxysmal nocturnal hemoglobinuria. Chronic hemolysis and asplenia are the pathologic links between hemolytic anemia and pulmonary hypertension.

Hemolysis results in the release of free hemoglobin, which scavenges nitric oxide and catalyzes the formation of reactive oxygen species. Cell breakdown also releases red-cell arginase, which limits the availability of arginine to nitric oxide synthetase, resulting in a deficiency of nitric oxide. Asplenia increases the circulation of platelet-derived mediators, which promotes pulmonary microthrombosis and the adhesion of red cells to endothelium.

More is known about the pathophysiology of pulmonary hypertension in sickle cell disease than about that of pulmonary hypertension complicating any other hemolytic anemia. The catalysts of lung injury in patients with sickle cell disease include infection, bronchoreactive lung disease, and fat embolism. However, mild, undetected episodes of regional pulmonary hypoxia may be more important in the development of pulmonary hypertension and sudden death syndrome. These subclinical hypoxic events would explain the high rate of pulmonary hypertension in patients who do not have repeated episodes of acute chest syndrome.

Episodes of regional pulmonary hypoxia result in sickling, increased vascular adhesion, and the production of vasoactive substances. Repeated episodes of these hypoxic events, followed by reoxygenation, cause ischemia (i.e., reperfusion injury) with progressive tissue damage, altered pulmonary vascular