Obesity: Common Symptom of Diverse Gene-Based Metabolic Dysregulations

Periods of Risk in Childhood for the Development of Adult Obesity—What Do We Need to Learn?[1]

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ABSTRACT The prenatal period, the period of adiposity rebound and adolescence appear to represent critical periods for the development of obesity that persists into adulthood. Nonetheless, relatively little is known about the extent to which incident obesity at each of these intervals contributes to the prevalence of adult obesity. Similarly, little is known about the mechanisms that operate at each of these critical periods to entrain adult obesity. J. Nutr. 127: 1884S–1886S, 1997

KEY WORDS: • *obesity* • *childhood* • *adolescence* • *critical periods*

The focus of this brief review is on the critical periods in childhood related to the development of subsequent obesity. A critical period refers to a developmental stage in which physiologic alterations increase the risk of later obesity. A number of critical periods exist for the development of behavior or function, particularly in fetal life. For example, intrauterine exposure to rubella in the first trimester of pregnancy leads to blindness and deafness, whereas exposure to rubella at later periods of fetal life has no adverse effect whatever. Similarly, exposure to sex hormones in utero may alter either the expression of gender or gender-related behaviors.

Postnatally, critical periods also exist. Iron deficiency in young children may have permanent effects on cognition. When young children are artificially fed for any period of time, eating behaviors are lost and must be relearned. These observations emphasize that there are both physiologic and behavioral alterations that occur in response to specific interventions or exposures at critical periods during development.

David Barker has repeatedly shown effects of birth weight on the prevalence of the Syndrome X–associated symptoms of hypertension, glucose intolerance and cardiovascular disease (Barker et al. 1993). Although Barker's work infers that low birth weight is associated with both syndrome X and obesity (Law et al. 1992), several sources of data suggest that increased rather than decreased birthweight is associated with later obesity, whereas low birth weight is associated with reduced subsequent growth and possibly leanness (Curhan et al 1996, Gallaher et al 1991, Strauss and Dietz 1997).

CRITICAL PERIODS FOR THE DEVELOPMENT OF OBESITY

The prenatal period. There appear to be at least three critical periods for the development of childhood obesity (Dietz 1994). These include the following: fetal life; the period of adiposity rebound between ages 4 and 6 in which body mass index, after a rise in infancy and subsequent decline begins to increase again; and finally, the period of adolescence.

The earliest data relate to the Dutch famine study (Ravelli et al. 1976). The Dutch famine was a natural experiment that occurred near the end of World War II, beginning in October 1944, as retribution for subversive activities, as the Germans put it. The Germans began to restrict food for most of the population in Northern Holland; over about a 6-mo period, food intake declined from ~1500 kcal to ~1000 kcal in January 1945, to ~500 kcal per person in April 1945, until the famine ended promptly with the liberation of Holland by the allies in May 1945. This exposure to famine was thus quite defined, and caloric intake could at least be estimated.

On the basis of the timing of their intrauterine exposure to famine, a number of cohorts were constituted. The cohort exposed to famine in the last trimester were found to have a reduced prevalence of obesity at age 18 y at the time of their induction into the Dutch army. Because the last trimester of fetal life represents a period of adipocyte replication and rapid increases in body fat, these results suggest that reduced fetal fat deposition late in pregnancy may lead to subsequent leanness. These data are quite consistent with our observations that intrauterine growth retardation is associated with reduced weight and height until at least 3 y of age (Strauss and Dietz 1997), and possibly longer.

In contrast, an increased prevalence of obesity was observed among individuals exposed to famine in the first two trimesters of pregnancy who were examined at age 18 y (Ravelli et al. 1976). The first two trimesters of pregnancy are when the hypothalamus begins to organize. Therefore, responsiveness to caloric clues or caloric intake might well be set by the

[1] Presented as part of a symposium Obesity: Common Symptom of Diverse Gene-Based Metabolic Dysregulations, Little Rock, Arkansas, March 4, 1997. This conference was co-sponsored by the National Center for Toxicological Research/Food and Drug Administration and the University of Arkansas for Medical Sciences. It was supported by generous grants from The Jane B. Mendel Family Trust, Amgen, Wyeth-Ayerst Laboratories Division of American Home Products and The Governor Winthrop Rockefeller Memorial Lecture Series-University of Arkansas. Guest editor for this symposium was George L. Wolff, Division of Biochemical Toxicology, National Center for Toxicological Research/FDA, Jefferson, AR 72079.

responsiveness of the hypothalamus and sympathetic nervous system to intrauterine substrate availability on the famine cohort.

The lack of birth weight measurements suggests that birth weight may confound these associations, because low birth weight may be more likely with late intrauterine exposure to undernutrition. The other inference is that the effects of maternal exposure to famine on fetal growth reflect a nutritional effect. However, women who supported a term pregnancy after exposure to famine may have differed substantially in other respects from other individuals who did not become pregnant, or who aborted before term. Nonetheless, these data suggest that some factors operate during gestation that may affect subsequent adiposity.

Much stronger data derive from studies that have examined the effect of birth weight on later weight (Whitaker and Dietz, in press). Roughly a dozen studies have examined the effect of birth weight on weight from ages 15 through 70. Virtually all of these studies demonstrate a clear, direct association of birth weight with subsequent adiposity, depending on how adiposity is measured. For example (Seidman et al. 1991), 17-y-old individuals with birth weights >4500 g compared with a birth weight of 3000–3499 g have a fourfold greater risk of severe overweight, defined as a BMI (body mass index) > 27.8 kg/m^2 for males and BMI > 27.7 kg/m^2 for females. The relationship of increased birth weight to increased adult adiposity contradicts the implication that low birth weight infants develop obesity and subsequent Syndrome X morbidity.

Infants of mothers with diabetes represent an important variant of the effect of birth weight on subsequent adiposity. Perhaps the best-known study is that of Pima Indian infants who were exposed to diabetes during gestation, and whose subsequent weights were dramatically increased compared with infants whose mothers were prediabetic, or infants whose mothers did not have and did not develop diabetes (Pettit et al. 1983). Not only are infants of diabetic mothers fatter at birth but they are also fatter at 5–9, 10–14 and 15–19 y of age.

The effects of insulin-requiring diabetes have rarely been distinguished from noninsulin-requiring gestational diabetes. A recent study by Whitaker et al. (1996) examined the prevalence of obesity at age 7 y among infants of mothers with gestational diabetes. Infants of mothers who required insulin had an increased prevalence of obesity, whereas there was no significant increase in obesity among 7-y-old children whose mothers had glucose intolerance or gestational diabetes by common criteria, but did not require insulin. These data suggest that either the severity of glucose intolerance or the use of insulin during pregnancy may represent the more important risk factors for subsequent adiposity.

A number of potential mechanisms can account for the effect of prenatal growth on subsequent adiposity. How the metabolic memory incorporated by fetal exposure to these factors is stored and how it is subsequently expressed represent fascinating challenges for research. For example, either adipocyte synthesis of leptin or central responsiveness to leptin may become entrained in utero, particularly during maximal adipocyte replication in the last trimester of pregnancy. Similarly, hypothalamic responsiveness to leptin might begin during the same period. Alterations in either process might be expected to influence the long-term regulation of adiposity. Insulin sensitivity, the regulation of lipoprotein lipase activity or the capacity for fat oxidation may also entrain prenatally.

Adiposity rebound. The second critical period in childhood for the development of obesity appears to be the period known as the adiposity rebound. Rolland-Cachera et al. (1987) observed that BMI rose during infancy, then declined to a nadir at ~6–8 y of age, and then began to accelerate again. Two confirmatory studies have now been published from the United States (Siervogel et al. 1991) and Czechoslovakia (Prokopec and Bellisle 1993).

At least three potential mechanisms may explain why adiposity rebound may contribute to subsequent obesity. The period of adiposity rebound may be the period in which behaviors related to food intake or activity, acquired in early childhood, begin to be expressed. For example, Johnson and Birch (1994) have shown clearly that the capacity of infants or young children to regulate their food intake is affected by maternal restraint and maternal control of eating. Young children whose mothers exert an increased control of food intake are less capable of regulating their own food intake. When such children become more autonomous and assume more control of their food intake, their capacity to regulate energy balance may be impaired, and increased adiposity may result. Alternatively, at least one study suggests that infants with early adiposity rebound may be those infants who were exposed to gestational diabetes. The final possibility is that early rebound may reflect early maturation. Among adolescents, accelerated maturation is associated with increased adiposity in adulthood (Garn et al. 1986, van Lenthe et al. 1996). For example, one study demonstrated a 6-kg increase in weight among 34-y-old women who had early menarche (Garn et al. 1986).

Adolescence. The final critical period of childhood is adolescence. Adolescence represents a period of increased risk for the development of obesity in girls, but it is also the period in which the location of body fat changes, and thereby may entrain the subsequent risks associated with obesity. Longitudinal data from England have examined the prevalence of earlier obesity among 36-y-old women and men (Braddon et al. 1986). In men, ~10% of adult obesity began in early adolescence, whereas in females this proportion was ~30%. However, the same study demonstrated that only 30% of adult obesity began at adolescence.

Some time ago we had the opportunity to reexamine individuals originally studied in the Third Harvard growth study (Must et al. 1992), performed in three communities north of Boston between 1922 and 1935 by the Harvard School of Education. The study enrolled all children entering elementary school and collected careful annual measurements of height and weight through childhood and adolescence. We subsequently tracked the effects of adolescent obesity on morbidity and mortality of the same individuals 55 y after they graduated from high school. To provide a sufficient sample for later follow-up, we defined obesity as a BMI > the 75th percentile for individuals of the same age and sex at two or more intervals throughout adolescence. The subsequent morbidity and mortality of obese adolescents was compared with that of lean individuals, defined as a BMI between the 25th and 50th percentile for that same period of time.

In males, but not in females, the mortality curves associated with adolescent weight were shifted to the left by about 10 y. Mortality from coronary heart disease, ischemic heart disease, cerebrovascular accident and colorectal cancer were all increased. One of the fortuitous characteristics of this study was that a mid-life follow-up had been conducted when these individuals were 55 y of age. The mid-life follow-up survey included questions about self-reported weight and cigarette smoking, which enabled us to correct the effects of adolescent obesity on morbidity and mortality for adult BMI and cigarette smoking. Adjustment for adult BMI only mildly attenuated these risks. These findings suggested that the effects of obesity present in adolescence on adult mortality were not mediated

by the effect of adolescent obesity on adult weight. Among women, as well as men, there was also an increase in obesity-related co-morbidities such as coronary heart disease, diabetes and atherosclerosis.

The two potentially premorbid effects that begin to operate during adolescence are changes in the quantity and location of body fat (Mueller 1982). In girls, body fat changes from ~17% of body mass to ~24% of body mass over the period of adolescence (Cheek 1968). In contrast, in boys, body fat decreases over this same period. In girls, increases in body fat that occur at adolescence may have a profound effect on the quantity or persistence of obesity. In contrast to girls, boys lose body fat, but the central deposition of body fat increases almost fivefold, whereas this increase in females is only approximately threefold (Goran et al. 1995).

A variety of factors affect the deposition of body fat. As Bouchard and others have shown (Bouchard et al. 1988), hereditary influences constitute a major factor. Furthermore, puberty, and perhaps the androgenic effects of puberty, predispose to central adiposity, particularly in males. Nonetheless, because androgens are increased among girls during puberty, the sexual dimorphism in central fat deposition remains unclear. Stress (Bjorntorp 1990), tobacco (Shimokata et al. 1989), and alcohol (Troisi et al. 1991) represent environmental factors that predispose to central fat deposition, whereas activity appears to reduce visceral fat (Tremblay et al. 1990). How these factors interact and operate may further entrain the potential morbidity and mortality of obesity present during adolescence.

The relative contribution of each of these critical periods to the prevalence, morbidity and mortality of adult obesity remains uncertain. Few longitudinal studies have carefully examined the tracking of obesity from childhood into adulthood. One of the few exceptions is a study published by Guo and her colleagues at the Fels Institute (Guo et al. 1994). In this study, the odds ratio for the persistence of obesity into early adulthood appeared to rise linearly throughout childhood. One of the difficulties with data expressed in this fashion is that they do not indicate the contribution of incident obesity at each of these ages. Therefore, one of many challenges is to examine the effects of incident obesity at each of these critical periods to determine the magnitude of its subsequent effect on the prevalence of adult obesity. Similarly, the effect of incident obesity on subsequent morbidity and mortality may be quite different.

To summarize, a number of very interesting research questions relate to the existence of critical periods. What are the mechanisms that promote total and regional fat depositions at these intervals? Does the locus of fat deposition in infants who develop subsequent obesity differ from that in individuals whose obesity appears at a period of adiposity rebound or adolescence? What is the contribution of incident obesity at these intervals to adulthood obesity and its morbidities? Finally, what biologic or behavioral mechanisms entrain the persistence of obesity?

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