Review

Fetal Origins of Obesity

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Abstract

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The worldwide epidemic of obesity continues unabated. Obesity is notoriously difficult to treat, and, thus, prevention is critical. A new paradigm for prevention, which evolved from the notion that environmental factors in utero may influence lifelong health, has emerged in recent years. A large number of epidemiological studies have demonstrated a direct relationship between birth weight and BMI attained in later life. Although the data are limited by lack of information on potential confounders, these associations seem robust. Possible mechanisms include lasting changes in proportions of fat and lean body mass, central nervous system appetite control, and pancreatic structure and function. Additionally, lower birth weight seems to be associated with later risk for central obesity, which also confers increased cardiovascular risk. This association may be mediated through changes in the hypothalamic pituitary axis, insulin secretion and sensing, and vascular responsiveness. The combination of lower birth weight and higher attained BMI is most strongly associated with later disease risk. We are faced with the seeming paradox of increased adiposity at both ends of the birth weight spectrum—higher BMI with higher birth weight and increased central obesity with lower birth weight. Future research on molecular genetics, intrauterine growth, growth trajectories after birth, and relationships of fat and lean mass will elucidate relationships between early life experiences and later body proportions. Prevention of obesity starting in childhood is critical and can have lifelong, perhaps multigenerational, impact.

Key words: **birth weight, body mass index, diabetes, insulin resistance, prenatal influences**

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Introduction

Obesity is a growing concern worldwide. The prevalence of obesity has risen dramatically in developed countries over the past 2 to 3 decades (1,2). In developing countries, the transition from rural agrarian to urban economies has accelerated the appearance of obesity (3), which is accompanied by a shift in overall health burden from infectious diseases and undernutrition to Western chronic diseases such as cardiovascular disease, cancer, and diabetes (Figure 1) (4). The rise in obesity, thus, portends a worldwide increase in those chronic conditions associated with obesity (5,6), most importantly, ischemic heart disease, whose mortality rate has otherwise declined in developed countries during the late 20th century (7). Prevention is critical because obesity is notoriously difficult to treat.

A new paradigm for prevention has emerged in recent years, evolved from the notion that environmental factors in early life and in utero can have profound influence on lifelong health. A large number of studies have demonstrated relationships between fetal experiences and later risk for adult chronic disease, including cardiovascular disease and its risk factors, cancer, osteoporosis, diabetes, neuropsychiatric outcomes, and respiratory diseases (8–12). Information regarding the fetal origins of obesity, however, is emerging more slowly.

The purpose of this paper is to review the epidemiological evidence relating fetal exposures to later obesity, including central obesity and associated morbidities; to highlight potential mechanisms underlying the epidemiological associations; to underscore areas for further research; and to comment on the public health implications of current knowledge.

Birth Weight Is Directly Associated with Later Body Mass Index

Most investigations into the relationship between prenatal exposures and later obesity have studied associations between birth weight and attained BMI. Birth weight can be easily measured, has reference norms, is part of the routine medical record, and may be available historically. Variation in weight at birth serves as a surrogate to reflect underlying mechanisms influencing growth.

BMI (kilograms per meter squared), a gauge of weight for height, is the most common measure of obesity in child and

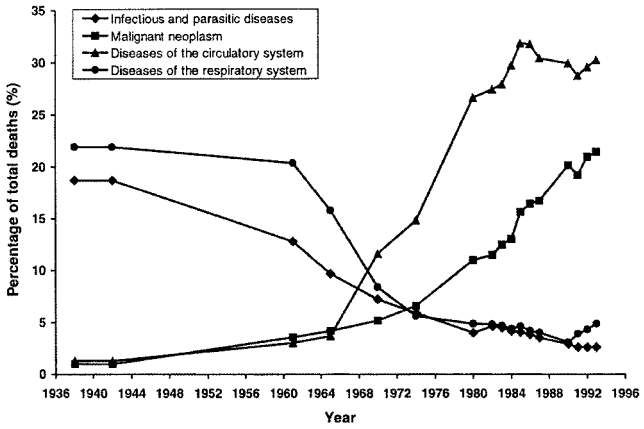

Figure 1: Trends in cause of death in South Korea, 1938–1993, showing the "epidemiologic transition" from respiratory and infectious diseases to cardiovascular diseases and cancer (4). Reproduced with permission by the *American Journal of Clinical Nutrition*. © American Society for Clinical Nutrition.

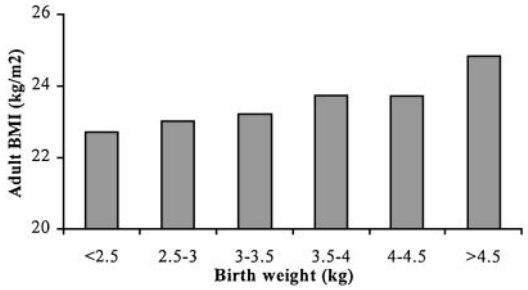

Figure 2: BMI at ages 18 to 26 years in Danish military conscripts by birth weight. Estimates are adjusted for gestational age, birth length, birth order, mother's marital status, age, and occupation. Adult BMI rises monotonically with birth weight (20).

adult epidemiological studies. One attraction is its simplicity of measurement; even self-report of BMI can be quite accurate (13,14). BMI predicts morbidity and mortality in a strong, graded relationship (15,16). BMI has been used in many populations worldwide, allowing comparison among study results. Nevertheless, the use of BMI as a proxy for adiposity has recognized limitations (17).

More than two dozen studies have addressed the association between birth weight and attained BMI. Most have measured the outcome in childhood, but several have examined adult BMI (18). Almost all of the studies have found direct associations, i.e., that higher birth weight is associated with higher attained BMI (19–26). Some of the smaller studies have found no association (27,28); none have found an inverse association. The typical magnitude ranges from 0.5 to 0.7 kg/m^2 for each 1-kg increment in birth weight (20,29).

Limitations of most of these studies have included incomplete data on gestational age, birth length, parental body size, tobacco use, and socioeconomic factors. Disentangling prematurity from impaired fetal growth is important, because the two may have different determinants and different sequelae (30). Whereas many published data emanate from an era when few premature babies survived until adulthood (9,22), a few more recent studies of children and adolescents have found that the relationship between birth weight and obesity persists after adjustment for gestational age (31). In a study of Danish military conscripts, BMI at ages 18 to 26 years rose monotonically over the range of birth weight, after controlling for gestational age, birth length, and maternal factors (Figure 2) (20).

Maternal and paternal body habitus predict offspring fatness, particularly fatness during childhood (32–34). A combination of genetic and both pre- and postnatal environmental causes is likely. In addition, parental adiposity is directly associated with offspring birth weight, with stronger associations for the mother than for the father (35,36), which implicates prenatal environmental factors. Associations of maternal and paternal birth weight with offspring birth weight also suggest genetic or intergenerational environmental influences (37,38). Thus, one needs to interpret results after adjustment for maternal BMI carefully. Empirically, where data have been available, the relationship between birth weight and later BMI tends to be attenuated after control for maternal BMI (24,34,39). In the U.S. Growing Up Today Study, a cohort study of over 14,000 adolescents, a 1-kg increment in birth weight among full-term infants was associated with an ~50% increase in the risk of overweight at ages 9 to 14 years (40). The increase in risk was ~30% after adjustment for maternal BMI, with no further attenuation after control for additional social and economic factors.

Cigarette smoking may confound the relationship between birth weight and later body size. Mothers who smoke during pregnancy have infants with lower birth weight (41,42). As smoking behavior often runs in families, and adults who smoke tend to have lower BMI, intergenerational smoking behavior would lower the apparent association between birth weight and adult BMI. Alternatively, maternal smoking during gestation may cause lower birth weight through mechanisms that do not have lasting impact on later body size. In this case, observed associations would seem weaker than the true relationship. Maternal smoking status has been unavailable in many previous studies of birth weight and adult disease, although it is unlikely that many mothers smoked before the late 20th century (43). Several recent cohort studies have not demonstrated a clear relationship between maternal smoking and childhood weight (23,44), although one study suggested an increased risk of later obesity among offspring of mothers who smoked during pregnancy (45).

Similarly, social and economic factors may confound the relationship between birth weight and later adiposity. Low

socioeconomic status was associated with obesity in children and adults during the late 20th century (46,47). Babies born to women with lower social status have lower birth weights in some recent studies (48), although not in studies using data from the early part of the century (49). Thus, the direction of confounding may differ depending on the era of data collection. More appropriate strategies to control for social status, such as information on diet and household crowding (50), are needed to minimize residual confounding of the birth weight–obesity relationship.

Several investigators have used twin registries to address some of these confounding issues, because twin pairs share gestational age, similar (or identical) genes, and similar postnatal environments. Identical twins are no more similar in birth weight than nonidentical twins, emphasizing the role of the prenatal environment in determining birth weight (51). Allison et al. noted that differences in birth weight between 2880 identical twin pairs directly correlated with adult height and weight, but did not significantly correlate with BMI (51). Baird et al. reported a similar lack of association between birth weight differences and adult BMI differences in mono-and dizygous twin pairs from Birmingham (52). However, in twin studies performed by Loos et al., higher birth weight did predict higher BMI, although birth weight more strongly predicted height and weight alone (29,53). Null or small effects in twin studies may reflect limited variability in variables of interest; similar genetics and pre- and postnatal influences for twins could overwhelm our ability to detect prenatal tendencies for different adult outcomes.

Overall, the preponderance of epidemiological evidence indicates that higher birth weight is associated with increased risk of adiposity in childhood and adulthood, as reflected by BMI. One explanation is that a postnatal environment that includes adverse eating and activity habits shared by family members is related to both higher birth weight and later adiposity. Another is that genes shared between parents and child entrain both birth weight and later obesity. In the few studies that have been able to control for possible confounders, the birth weight–obesity relationship remains, suggesting a persistent impact of the fetal environment.

Possible Mechanisms for an Association Between Birth Weight and Later Adiposity

Research into the fetal origins of adult diseases generally relies on the assumption of programming, the process wherein a stimulus occurring at a critical period of development has lasting effect (54). Evidence abounds to indicate that programming occurs in animals (55,56). Accumulating evidence from human randomized trials adds support that the programming phenomenon also occurs in humans, particularly as a result of influences in pregnancy or early infancy (57–59).

Figure 3: Symmetry Index (SI, mean ± SEM) in offspring of diabetic mothers from birth to 8 years of age. SI = (weight/National Center for Health Statistics median weight for age)/(height/National Center for Health Statistics median height for age). SI is greater than expected (1.0) at all ages except 12 months (62). Reproduced with permission of the journal *Diabetes*. © American Diabetes Association.

Most evidence to date for human programming of offspring obesity comes from the special circumstance of diabetes during pregnancy. Whereas maternal glucose is freely transferred to the fetus, maternal insulin does not cross the placenta (60). The developing fetal pancreas responds to a glucose load by producing insulin, which acts as a fetal growth hormone in addition to its hypoglycemic effects. Almost 50 years ago, Pederson proposed a "hyperglycemia-hyperinsulinism" pathway to explain the observation that offspring of diabetic mothers demonstrate relatively higher birth weights (61). Frienkel more recently broadened this theory to include the possibility that other fuels, including free fatty acids, ketone bodies, and amino acids, also contribute to fetal insulin hypersecretion (60).

Human studies have addressed the lasting influence of this "fuel-mediated teratogenesis" by examining offspring of diabetic mothers. Silverman et al. found that at ages 14 to 17 years, offspring of mothers with gestational diabetes had a mean BMI of 26.0 kg/m^2 compared with 20.9 kg/m^2 in control subjects (28). Interestingly, the increased adiposity was apparent at birth and progressively after the age of 4 years, but not at ages 1 to 3 years (Figure 3) (62). In this study population, amniotic fluid insulin levels, which reflect fetal pancreatic insulin production, correlated with obesity during adolescence (28).

In a study among Pima Indians, Dabelea et al. examined BMI among siblings ages 9 to 24 whose fetal lives were discordant for the presence of maternal diabetes (63). Offspring exposed to diabetes in utero had higher BMI than their unexposed siblings (Figure 4). These results mitigate the roles of both shared genes and postnatal environment, emphasizing the potential role of the fetal environment.

Other studies, however, have not found that milder gestational diabetes confers a risk of offspring obesity. Whitaker et al. (64) found no increase in BMI among young adult offspring of mothers with mild, diet-treated gestational diabetes. Data from the Growing Up Today Study

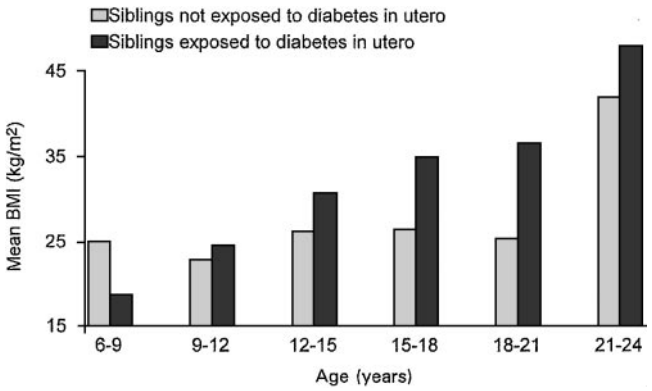

Figure 4: Mean BMI in Pima Indian siblings exposed and not exposed to diabetic intrauterine environment, separated into 3-year age intervals. Siblings exposed have a higher BMI than those unexposed ($p = 0.003$, controlled for sibship by ANOVA) (63). Reproduced with permission of the journal *Diabetes*. © American Diabetes Association.

showed a moderate increase in risk of adolescent overweight among offspring of diabetic mothers, but the risk was attenuated after adjustment for maternal BMI (40). These studies do not refute the possibility that more severe fetal hyperinsulinemia, or the presence of "a second hit," may be required for the fetus to manifest programming for later obesity.

If fetal hyperinsulinemia is involved in the fetal origins of later obesity, how does it participate in programming? In particular, why would the effects persist after birth, when the stimulus for excess insulin recedes?

Intrauterine exposures may have lasting influence by determining body composition, i.e., fat cell size or number, in early life. Large for gestational age infants have higher proportions of total body fat and relatively lower lean body mass than infants who are appropriate for gestational age (65,66). These changes may be exaggerated in infants exposed to diabetic intrauterine environments (65). However, in other studies, both infant and adult lean body mass, rather than body fat, increased with increasing birth weight (25,29,53,67).

Other investigators have studied the effects of early overnutrition on pancreatic function. Newborn rats given formula extremely high in carbohydrates demonstrate hyperinsulinemia despite normoglycemia, which persists into adulthood in association with obesity (68). The hyperinsulinemia is sustained by a variety of biochemical, molecular, and cellular adaptations in the pancreatic islet cells.

Other animal models suggest that perinatal nutrition may induce permanent change in structure and function of the appetite regulation centers of the brain. Plagemann et al. have used several rat models to understand the mechanisms by which experiences in the perinatal period may result in adult obesity. In adulthood, these animals demonstrate hyperphagia, hyperinsulinemia, impaired glucose tolerance, and overweight (69). Through a hypothesized mechanism of induced hypothalamic insulin resistance, these authors have described several potential pathways, including increased levels of orexigenic neurotransmitters, increased sensitivity to orexigenic neurotransmitters, and decreased levels of satiety signals (70–72). While animals in most studies have demonstrated hyperphagia, some have not (73), supporting the suggestion that peripheral as well as central nervous system changes may occur (74).

These studies support epidemiological observations that influences in fetal or early postnatal life, specifically nutrient excess and insulin exposure, can have long-term impact on body weight regulation. It remains to be determined whether the influence of prenatal nutrition is mediated through changes in the central nervous system affecting appetite and the satiety set point, permanent changes in the ratio of fat to lean body mass, or alterations in insulin metabolism, and whether the same pathways mediate associations in offspring of mothers with and without clinically evident diabetes.

Reduced Size at Birth and Central Obesity

Adverse distribution of body fat may carry risk for morbidity as great as or greater than total amount of body fat. Central or truncal obesity, often measured by the waist-to-hip ratio or the subscapular to triceps skinfold ratio, has gained attention as an indicator of cardiovascular risk. Central obesity is associated with a constellation of problems, including hypertension, dyslipidemia, hyperinsulinemia, impaired glucose tolerance or frank diabetes, and an increased risk for ischemic cardiovascular disease, which has been called the insulin resistance syndrome, the metabolic syndrome, or "Syndrome X" (75).

Several studies have addressed the association of small size at birth with measures of later central obesity (19,29,53,76–80), insulin resistance, and the metabolic syndrome (22,81–84). Tables 1–3 display results for central obesity, insulin resistance, and Syndrome X from studies that have presented them in terms of a 1-kg increment of birth weight. In general, they are consistent in showing that, after adjustment for attained BMI, birth weight is inversely associated with these outcomes. Associations of low birth weight seem stronger with the subscapular/triceps skinfold ratio than with the waist-to-hip ratio (Table 1), although this observation is limited by the fact that skinfold measurements tend to be used more for children and adolescents and the waist-to-hip ratio for adults.

These associations seem to be independent of gestational age (81), although length of gestation has not reliably been available for all studies. While not all investigators have found this relationship between lower birth weight and abdominal obesity or metabolic syndrome (52,85–87),

Table 1. Measures of central obesity per 1-kg increase in birth weight

Measure	Percent change in estimate per 1-kg increase in birth weight	95% CI
Subscapular:triceps skinfold ratio (78)	−6.0%	−12, 0
Log subscapular:triceps skinfold ratio (82)	−4.8%	−8.7, −0.7
Waist-to-hip ratio (76)	−1.2%	−2.5, 0
Waist-to-hip ratio (126)	−0.8%	(not available)
Waist-to-hip ratio (29)	−1.2%	(not available)

some twin studies have supported the relationship (29), and a recent review confirms these findings in most populations (88).

The mechanisms of these associations of lower birth weight with central obesity and the metabolic syndrome remain unknown. Genetic differences affecting insulin regulation may play a role as a "thrifty genotype" (89,90). This genetic predisposition to nutritional thrift may provide a survival advantage for individuals born at lower birth weight. However, no candidate genes have been described that are common enough to explain the modern epidemic of obesity. Populations with putative higher "genetic" risks, such as African Americans and Native Americans, also may experience poorer social status and worse nutrition during pregnancy. Furthermore, shifts in prevalence of obesity and non–insulin-dependent diabetes have occurred within a generation, particularly in populations that experienced famine in early life and a change in diet associated with sedentary habits in later life (91). Emerging data suggest that associations between lower birth weight and central obesity or metabolic syndrome may occur independently of a predisposing genotype (92).

Table 2. Measures of insulin resistance per 1-kg increase in birth weight

Measure	Change in estimate per 1-kg increase in birth weight	95% CI
Insulin sensitivity (81) (glucose infusion rate during euglycemic hyperinsulinemic clamp)	0.7 g/kg/min	0.1, 1.2
Fasting glucose (83)	−2.4%	−0.1, −4.7
2-hour postload glucose	−5.1%	−0.7, −9.3
Fasting insulin	−9.7%	−2.5, −16.5
2-hour postload insulin	−14.0%	−2.4, −24.2
Log HOMA-IR (82) (homeostasis model assessment)	−9.7%	−18.6, 0.2
Fasting glucose (84)	−0.021mM	−0.077, 0.035
30-minute postload glucose	0.115mM	−0.131, 0.355
Fasting insulin	−16.9%	−25.8, −7.1
30-minute postload insulin	−11.6%	−19.1, −3.5

Table 3. Odds ratios for developing metabolic syndrome (Syndrome X) in later life per 1-kg increase in birth weight

Measure of metabolic syndrome	Odds ratio per 1-kg increase in birth weight	95% CI
Dyslipidemia + impaired glucose tolerance + hypertension (127)	0.61	0.38,0.97
Hypertension + impaired glucose tolerance or insulin resistance + subscapular:triceps skinfold ratio (126)	0.46	0.30,0.69

Alternatively, intrauterine exposures may lead to persistent changes in gene *expression*, resulting in a "thrifty phenotype" (93). The theory that individuals who experience fetal undernutrition may be programmed to stockpile nutrients originated more than 20 years ago from ecological observations that risk for coronary heart disease followed regional low birth weight and poor living conditions in early life (94). Ravelli et al. observed that males in The Netherlands exposed to famine during the first trimester of gestation had higher weights at age 18 (95). Fetal undernutrition in mid-to-late gestation may particularly predispose to central obesity and related metabolic changes (43).

Recent research has focused on several possible intrauterine mechanisms that may program the infant for later central obesity and metabolic syndrome. A first potential pathway suggests that inadequate maternal nutrient intake and low availability of protein cause permanent changes in pancreatic vascularity, structure, and function (93,96). Amino acids determine growth and development of pancreatic islet

beta cells in the fetus; in turn, the insulin produced by these beta cells acts as a fetal growth factor.

Laboratory scientists have extensively studied animal models of low protein intake during gestation, demonstrating long-term changes in pancreatic islet β cells and insulin secretion (97), as well as offspring obesity (98). In one rat model, offspring whose mothers had been protein restricted during gestation, but who were then nursed by mothers fed a full protein diet, grew fatter than those that had never been protein restricted (99). In another series of experiments, offspring of protein malnourished rats demonstrated low birth weight and later glucose intolerance in association with changes in hypothalamic appetite control centers (100,101).

Another possibility is that long-term changes in the activation of the hypothalamic-pituitary-adrenal axis mediate associations between birth weight and later body proportions and metabolic syndrome. Phillips et al. have shown that among 370 men ages 59 to 70 years, morning cortisol levels were lower by 26.2 nM (95% CI, 7.2–45.1 nM) for every 1-kg increment in birth weight (102). Similarly, among a cohort of 20-year-old South Africans, basal and adrenocorticotropic hormone-stimulated morning cortisol levels were higher in individuals born at weights below the 10th percentile for gestational age compared with those born appropriate for gestational age (103). Others have suggested that alterations in growth hormone (104), insulin-like growth factors (105), or the sympathetic nervous system (106) may also mediate associations between lower birth weight and later central obesity.

It remains to be determined whether abdominal obesity is itself the "generator" of the metabolic syndrome (107), because abdominal fat may alter glucose and lipid metabolism, or whether as-yet unknown mechanisms determine both body habitus and risk profile. Higher adult BMI in men with higher weight for length at birth may not confer elevated risk of cardiovascular disease (108), supporting the possibility that "metabolically normal" (109–111) obesity could have different fetal origins than central obesity. In one of the few studies focused on body composition, Gale et al. examined the relationship between birth weight and adult fat and lean body mass, ascertained by DXA (25). In this study of 143 septuagenarians, after adjustment for adult height and weight, birth weight was inversely associated with total body fat. Further research is needed to understand the different pathways by which individuals achieve a given birth weight, the ways that birth weight is associated with later body composition, and whether knowledge of the underlying mechanisms may inform risk equations in later life.

"Trouble on Both Ends of the Birth Weight Spectrum"

In summary, evidence indicates that birth weight is directly associated with later BMI. Larger babies are at greater risk for eventual obesity and its comorbidities, such as type 2 diabetes. In contrast, after adjustment for BMI, birth weight is inversely associated with central obesity, insulin resistance, and the accompanying metabolic syndrome that confers elevated cardiovascular risk. Insulin may mediate both outcomes, in conjunction with other neurological, endocrine, and vascular changes. One study showed such a U-shaped relationship between birth weight and incident type 2 diabetes (22), which became linear after adjustment for BMI and family history of diabetes. These findings suggest the presence of two different mechanisms for development of glucose intolerance: one at the higher end of the birth weight spectrum, perhaps associated with maternal hyperglycemia, and another at the lower end, likely caused by different mechanisms. These results have implications for research and public health interventions.

Areas for Research

Because BMI is an indirect measure of fatness, more information is needed on the relationships of fat and lean mass (25). The fact that newborns small for gestational age tend to preserve body fat at the expense of lean body mass (67), whereas large newborns also may have relatively increased body fat (65), suggests that associations between fetal growth and later adiposity are complex.

Birth weight is an amalgam of multiple determinants. On the simplest level, both gestational age and fetal growth contribute to size at birth. Size at birth is only a proxy for the many different processes that occur in the months preceding delivery. Thus, it is crucial for investigators to go "beyond birth weight" and work to refine descriptions of prenatal predictors of postnatal outcomes. It is likely, for example, that the determinants underlying the direct association between birth weight and BMI are different from those that explain the inverse association of birth weight with central obesity and associated adverse cardiovascular outcomes. Until more is known about these determinants, therefore, adjusting for attained BMI remains a useful analytic step (22,112).

Fetal life is an important period, but more complete answers regarding risk for obesity will come from a life course approach (113). Many studies of birth weight and later obesity, for example, have measures of obesity at only one point in time. Numerous growth trajectories can result in the same attained level of adiposity (26). For example, the interactions of the fetal environment with catch-up growth in infancy (49,114), the period of adiposity rebound (115), and obesity during childhood or adolescence (24,85,86) require further investigation. Infant feeding mode may influence later development of obesity (116) and may modify the relationship between birth weight and obesity (117). Careful adjustment for parental body habitus, socioeconomic status, and smoking is also necessary.

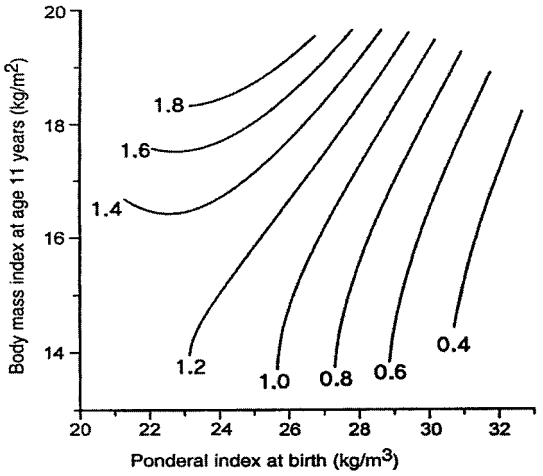

Figure 5: Risk ratios for coronary heart disease in Finnish men born 1924 to 1933, according to ponderal index (kg/m^3) at birth and BMI in childhood. The highest risk ratios are in men who were thin at birth but attained high BMI at age 11 years. In general, men who had a higher ponderal index at birth had low-to-moderate risk of disease no matter what their attained BMI at age 11. This suggests an interaction between intrauterine growth and attained weight influencing later disease risk (128). Reproduced with permission from the *British Medical Journal.* © BMJ Publishing Group.

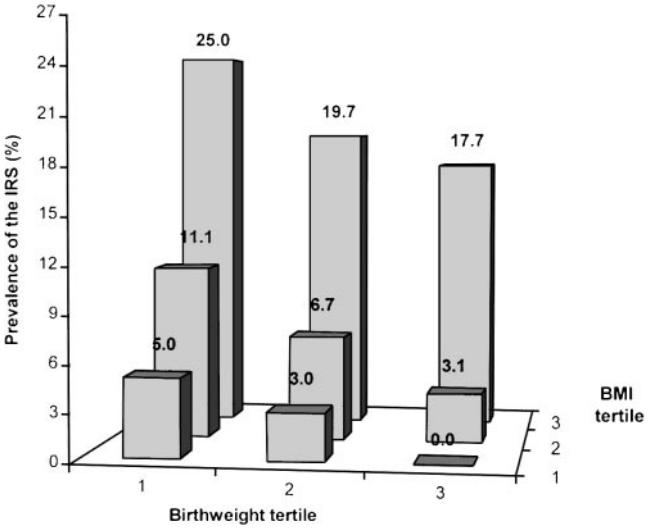

Figure 6: Prevalence of insulin resistance syndrome (IRS) by birth weight tertile and BMI tertile. The highest risk is among those born small but who attained the highest BMI in adulthood. IRS was defined as having two or more of the following conditions: hypertension, diabetes or impaired glucose tolerance, triglycerides >2.8 mM, or high-density lipoprotein cholesterol <0.99 mM in men and <1.2 mM in women (121). Reproduced in modified form with permission from *Diabetologia*. © Springer-Verlag.

In addition, knowledge of the interplay of genetic and environmental influences on growth will offer deeper understanding and, one hopes, more effective prevention measures. Improved animal models and molecular genetic techniques will contribute to this understanding.

Implications for Clinical and Public Health Interventions

The etiologic factors underlying the links between birth weight and later obesity (or central obesity) are not known and, thus, cannot be quantified. Except for general measures to prevent gestational diabetes, which also has known short-term adverse consequences for mother and infant, it is premature to suggest any specific pregnancy interventions to prevent offspring obesity. It is unclear whether proposed programs to reduce rates of low birth weight in order to decrease cardiovascular disease risk would be feasible or effective (113,118). Indiscriminate efforts to increase birth weight may be particularly harmful, because they could increase rates of birth trauma, later obesity and its sequelae, and perhaps some cancers as well.

In contrast, the data have clear implications for childhood interventions. Several studies now indicate that the highest risk for cardiovascular outcomes is associated with the phenotype of lower birth weight and higher BMI in childhood or adulthood. Examples of outcomes that follow this pattern include systolic blood pressure and diabetes among Swedish men at age 50 (111,119); glucose intolerance among 64-year-old men from Hertfordshire (120); insulin resistance among 8-year-old Indian children (82); central obesity among adolescent girls in England (78); risk for coronary disease among Finnish men (Figure 5)(108); and prevalence of the insulin resistance syndrome among Americans of white and Mexican descent (Figure 6) (121).

The combination of lower birth weight and higher attained BMI is characteristic of developing world populations undergoing the transition to urban lifestyles. This "small baby" phenotype is particularly prevalent in certain populations, such as South Asians (122,123). Moreover, in South Asians compared with white Europeans, the prevalence of the insulin resistance syndrome is higher at any level of waist-to-hip ratio (124). These findings, perhaps similar in other developing countries, call attention to the incipient world epidemic of cardiovascular disease, which will shortly be the leading cause of death and disability worldwide (125). Obesity interventions may prevent complications most effectively if they are aimed at individuals and populations with lower birth weights. However, it would be complex and expensive to identify those who are at higher risk, and, therefore, such targeted programs may be less efficient than more widespread campaigns.

The implication for current public health practice, then, is that prevention of obesity starting in childhood is critical and can have lifelong, perhaps multigenerational, impact.

Interventions directed toward improvement in physical activity, television viewing, and diet are needed to stem the rise of obesity throughout the world. Failure to address this epidemic could lead to a vicious cycle of obesity and its consequences, because adolescent obesity among girls is likely to lead to diabetic pregnancies and, thus, increased obesity among their offspring. Prevention of obesity in childhood is an immediate public health challenge in both developed and developing nations, while researchers continue to investigate its fetal origins.

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