

Prevention Conference VII

Obesity, a Worldwide Epidemic Related to Heart Disease and Stroke Group II: Age-Dependent Risk Factors for Obesity and Comorbidities

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Dynamic processes that occur over the life span determine the development of obesity and associated chronic diseases. Perturbations, or “insults,” that determine excessive weight gain leading to obesity may occur anytime from before conception to embryonic, fetal, infant, childhood, adolescent, and adult life. These insults can affect both somatic growth and the maturation of metabolic systems and may include a range of determinants, including societal, lifestyle, biological, and genetic factors that often act in concert with one another.

A life-course approach to chronic disease (Figure 1) classifies determinants in several different ways.¹ A critical period refers to a specific period of development when an insult has lasting effects on the structure or function of organs, tissues, and body systems. When the insult is not completely deterministic, these periods may be referred to as sensitive rather than critical. Effects during critical periods may act alone or be modified by later insults. Alternatively, some insults may act at any period of development; they may accumulate over time independently or be correlated through clustering. These models are useful in helping determine which early life factors are important in the assessment of later disease. Although age-dependent risk factors may vary worldwide, identification of common critical or sensitive periods and plausible determinants will help improve overall treatment and prevention of obesity over the life span.

Intrauterine Influences

Small birth weight is associated with higher mortality from cardiovascular disease and higher levels of risk factors for cardiovascular disease, including type 2 diabetes mellitus and hypertension. These relationships suggest that part of the risk for cardiovascular disease may be “programmed” in utero.

Programming occurs when an event in a crucial, early period of life permanently alters structure or function.²

Higher birth weight is associated with higher body mass index (BMI) and increased prevalence of obesity in adult life, although the effect size is relatively small. Lower birth weight is associated with increased truncal fat or a higher waist-to-hip ratio once body mass has been taken into account. These general patterns have been found in developed and developing countries.³ The relationship between birth weight and subsequent obesity/fat mass distribution may depend on metabolic programming established in utero but manifested later in life. Such programming may also occur without altering birth size and may reflect various maternal influences, such as hyperglycemia, undernutrition, or smoking.²

The main importance of intrauterine life in relation to later obesity may be in determining the vulnerability of individuals to increased body mass in childhood or adult life. Those who become obese as adults tend to have been heavier at birth and to have an accelerated gain in body mass through childhood and adolescence. Those who develop coronary heart disease also have accelerated gain in body mass during childhood but tend to be lighter at birth. The discordance in these patterns of intrauterine and childhood growth may shed light on apparently paradoxical time and geographic trends in obesity and cardiovascular disease. They suggest sensitive or critical periods in early life for the prevention of obesity-related disease.⁴

It seems paradoxical that although adult BMI is a strong predictor of hypertension, type 2 diabetes mellitus, and coronary heart disease, birth weight is both *directly* related to later BMI and *inversely* related to coronary disease and its risk factors. Birth weight is a proxy for many intrauterine processes. The prenatal processes that underlie development

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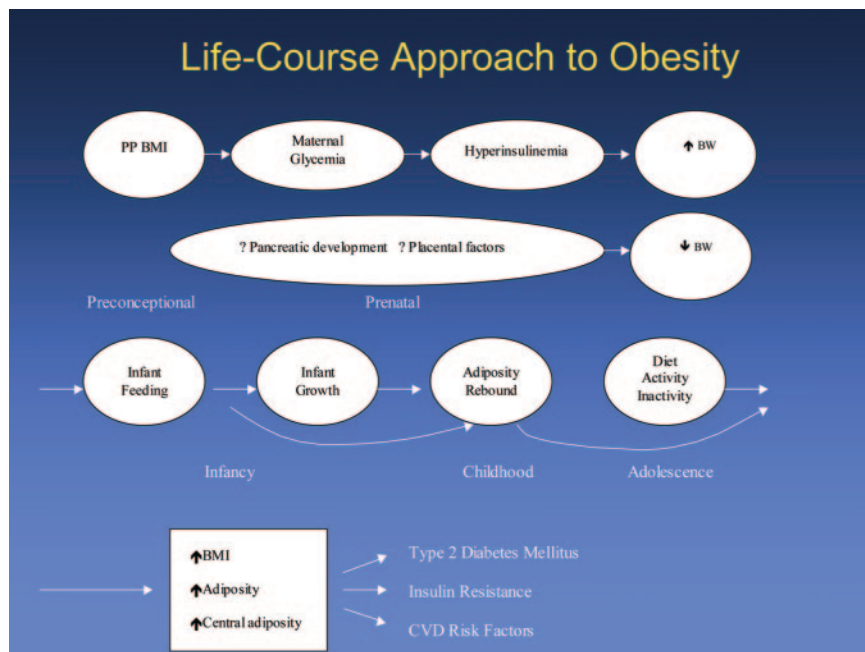


Figure 1. Life-course approach to obesity. BW indicates birth weight and PP BMI, prepregnancy body mass index.

of obesity may differ from those that determine cardiovascular risk.⁵

Early Childhood

Factors in early childhood may lead to obesity through one or more of several pathways, including metabolic programming (discussed above), establishment and tracking of lifestyle behaviors, and early pathological changes. During infancy, breastfeeding may protect against the development of excess weight during childhood. Most but not all epidemiological studies demonstrate this protective effect, which could be mediated by behavioral and/or physiological mechanisms. Residual confounding by cultural factors associated with both the decision to breastfeed and later obesity also is possible, however. Recent data also suggest that rapid weight gain during infancy is associated with obesity later in childhood, perhaps reflecting a combination of genetically determined catch-up growth and postnatal environmental factors.⁶⁻⁹

Adiposity rebound is most commonly measured as the age at which BMI is at its nadir and generally occurs between ages 4 and 8 years. Several studies show that earlier age at adiposity rebound is associated with the development of obesity. Several factors, however, limit its clinical utility. BMI is not a direct measure of adiposity, and other fatness measures do not show the same associations. In addition, early age at adiposity rebound is often a byproduct of excess weight gain in the first years of life, itself probably a more important etiologic factor. Moreover, BMI at age 7 or 8 years is as good a predictor of obesity as age at adiposity rebound and is easier to measure.^{10,11}

Future epidemiological studies will benefit from detailed information on infant feeding and frequent longitudinal measures throughout childhood of direct measures of fatness as well as height and weight. In the meantime, clinicians can confidently recommend breastfeeding for its myriad benefits, including possible prevention of obesity.

Adolescence

Adolescence is recognized universally as a time of transition from childhood to adulthood. From the standpoint of obesity, it is important both for the timing of obesity development and because it is the period during which obesity-related comorbidities begin to appear. Obesity during adolescence is directly associated with obesity in adulthood.^{12,13} This phenomenon of tracking has important implications for early efforts to prevent the development of obesity and to treat it once it has developed. Furthermore, obesity in adolescence is associated with the dysmetabolic syndrome and clustering of risk factors for development of cardiovascular disease,^{14,15} including blood pressure elevation and dyslipidemias. Obesity in adolescence also may be associated with other risk factors for cardiovascular disease such as inflammation, as reflected in C-reactive protein levels.¹⁶

Recent data emphasize that adolescence is a critical period for the development and expression of obesity-related comorbidities. These comorbidities include type 2 diabetes,^{17,18} obstructive sleep apnea,^{19,20} renal dysfunction,²¹ early atherosclerosis,^{22,23} and cardiac structural and functional abnormalities, including left ventricular hypertrophy.²⁴ In the past 10 years there has been a dramatic increase in the prevalence of type 2 diabetes mellitus in adolescents. Thus, diseases that previously were considered adult problems have now become adolescent problems.

Adults

In addition to genetic factors that provide a large at-risk population, the modern environment promotes behaviors that cause obesity, specifically behaviors related to overeating and physical inactivity. Few data, however, bear directly on behavioral and lifestyle factors related to weight gain in the population. Some researchers have advanced the idea that decreased physical activity is the most salient factor,^{26,27} whereas other data hint that dietary intake may also play a

role.^{28,29} One potentially important aspect of determining risk for weight gain in adulthood is again identifying “vulnerable” or sensitive periods for weight gain; however, recent analyses of 2 such potentially important periods, pregnancy and menopause, indicate they are probably of less consequence than once thought.^{30,31}

Although it is important to improve the ability to determine the individuals who are most at risk for developing obesity during the adult years, determining the risk factors for obesity associated with comorbidities is even more important. Observations of differences in the expression of obesity-related comorbidities indicate that some characteristics may be important in determining such risk. These include such phenotypic characteristics as ethnicity, distribution of body fat,^{32,33} fat deposition in muscle and organs,³⁴ behavioral characteristics such as physical activity,³⁵ as well as genetic factors and the interactions of genetic characteristics with the environment in which they are expressed.³⁶ Additional progress in prospectively determining risk factors for weight gain and obesity that result in complications is critical for the most effective targeting of prevention and treatment efforts.

Elderly

Obesity and overweight syndromes and their relation to cardiovascular risk factors remain enigmatic in older persons. Given that some older persons who are overweight or obese survive to an older age, it could be suggested that overweight or obesity also may be protective from a metabolic or cardiovascular standpoint. It is unclear whether obesity and overweight carry the same health risks in older persons. Dysregulation of energy balance is commonly found in older persons.³⁷ The extremes of both fatness and leanness present unique health challenges for older individuals. Obesity and its impact on cardiovascular disease may be a different phenomenon in elderly persons, but this has not been systematically examined.

Clinicians have been reluctant to prescribe significant weight loss in older persons. This is partially due to the loss of some fat-free mass (and probably muscle mass) with weight loss programs. Given the age-related decline in muscle mass³⁸ and its negative consequences on function, strength, glucose disposal, etc, it is unclear whether the benefits of weight loss outweigh the risks associated with loss of muscle mass, stress of losing weight, etc. It should be noted, however, that weight loss has been shown to provide favorable changes in cardiovascular risk factors.³⁹ For example, substantial weight loss reduces the acute phase C-reactive protein in older women who achieve a weight loss of 15 kg. Although older men and women can succeed in losing weight, maintaining a reduced body weight is a significant challenge. This is important because if reduced body weight in older persons is not maintained, the cardioprotective effects of the weight loss will be lost. Attempts to identify metabolic predictors of weight regain have been problematic but do represent an emerging area of public health interest in obesity research.⁴⁰ Clearly, an understanding of metabolic and behavioral factors that contribute to successful weight loss and weight loss retention in older persons represents an important public health concern.

Birth Cohort Changes in BMI

In the United States, the prevalence of obesity has been rapidly increasing among adults for decades. Concerns have arisen that the rate of increase has accelerated recently. Risk of morbidity and mortality associated with obesity increases across the entire range of BMI, however, and is not restricted to changes that affect only the proportion of persons who are obese (ie, BMI ≥ 30.0 kg/m²).

By using approaches similar to those previously used to examine birth cohort trends in cholesterol⁴¹ and blood pressure,⁴² Howard and colleagues examined changes in the distribution of BMI across US birth cohorts as sampled in the National Health Examination Survey and the National Health and Nutrition Examination Surveys I, II, and III.⁴³ Data were analyzed for 50 091 participants born between 1887 and 1975 and examined between 1959 and 1994 at ages 18 through 74 years. Each percentile of BMI demonstrated steady and significant increases, suggesting that the increase in BMI has been occurring over many decades and is greater at the higher percentiles of BMI. Specifically, at age 50 the 10th, 25th, 50th, 75th, and 90th percentiles of BMI (adjusted for age, race, and sex) were estimated to be greater by 0.31, 0.51, 0.69, 1.00, and 1.37 kg/m², respectively, for successive 10-year increments in date of birth ($P < 0.001$ for each estimate). Levels of predicted (ie, “smoothed”) BMI from these models are shown in Figures 2A (10th percentile), 2B (50th percentile), and 2C (90th percentile). Because the adverse health effects of obesity increase across the entire range of BMI, these data suggest that the dual effects of a general upward shift of BMI distribution, coupled with an accelerated shift at the highest BMI levels (note the expansion of the vertical scale from Figure 2A to Figure 2C), may be associated with larger public health implications than previously predicted. As the distribution of BMI shifts upward, the portion of the BMI distribution passing through the thresholds of overweight (25 kg/m²) and obesity (30 kg/m²) includes a larger segment of the population. As such, even for a constant shift in the distribution of BMI, there should be a more rapidly increasing prevalence of those categorized as overweight and obese by the thresholds.

Summary

It is evident that persons are susceptible to periods of excess weight gain over the entire life span. This weight gain tends to be gradual, additive, and small. Over shorter periods of time this weight gain may go unnoticed, but over several years it becomes significant. Critical periods of life can be identified when excess weight gain leads to increased susceptibility to obesity or its comorbidities and exacerbation of the obese state later in life. If common determinants of obesity can be identified at various sensitive and critical life stages, improved treatment and prevention strategies can be more effectively developed and implemented worldwide. To this end, data on the determinants of weight gain and risk factors that lead to obesity and related comorbidities are particularly important.

Research Priorities/Directions

Future research priorities/directions should include studies of the following:

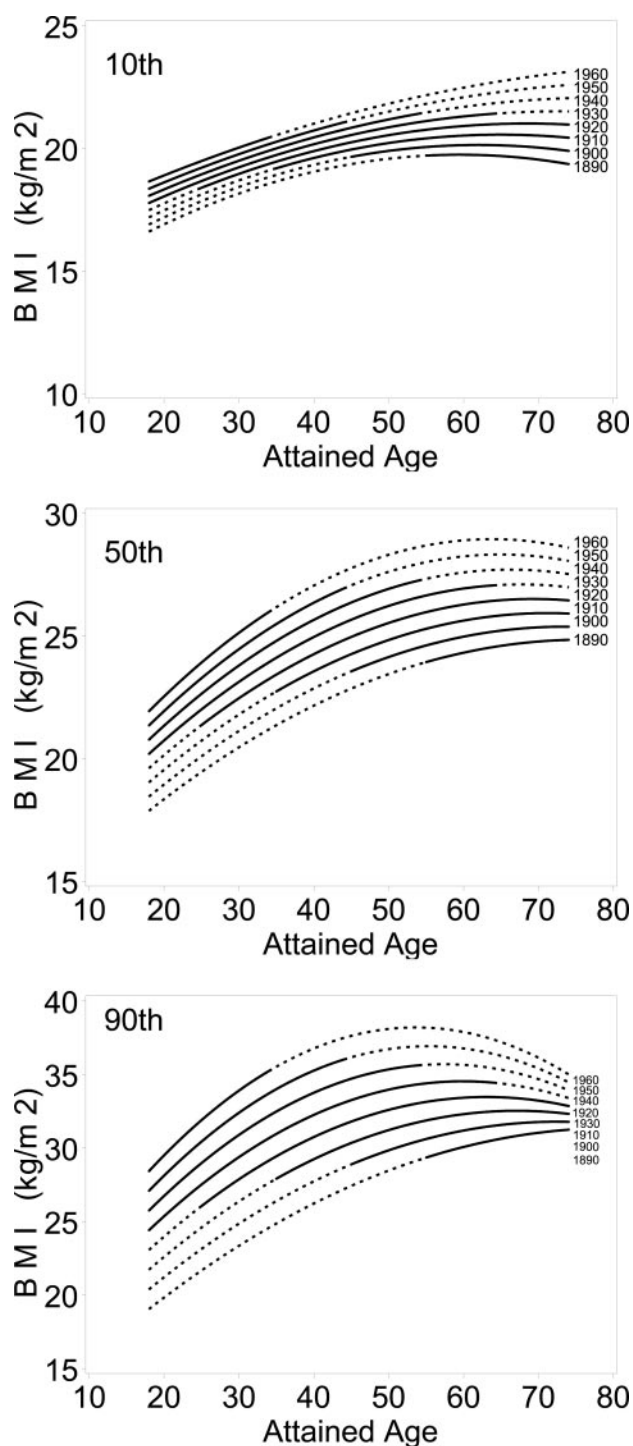


Figure 2. The 10th (A), 50th (B), and 90th (C) predicted or “smoothed” percentiles of BMI are presented as a function of age (horizontal axis) and birth cohort (individual lines, with birth year shown to the right of each line). The solid portion of each line indicates the ages for which data were available from the NHANES Surveys. The dashed portion represents extrapolated values beyond the range of observed data.

- Secular trends in birth weight/gestation distribution and their relationship to secular trends in obesity and its comorbidities
- Mechanisms underlying the relationships between fetal growth and later obesity and associated comorbidities

(including relationships with both higher and lower birth weights)

- Relationships between maternal glycemia (and its determinants) and diabetes/obesity/comorbidities in offspring
- Interrelationships between fetal and childhood growth in the genesis of obesity and related comorbidities
- Association between infant feeding and later obesity in both developed and developing countries and studies to minimize confounding by socioeconomic (SES) determinants
- Mechanisms by which infant feeding affects later obesity
- Determinants of adiposity rebound
- Cardiovascular, structural, and functional changes related to obesity, metabolic syndrome and type 2 diabetes mellitus, and obstructive sleep apnea
- Mechanisms of development of insulin resistance and type 2 diabetes mellitus and their role in the development of further obesity
- Process of fat distribution in obesity development during adolescence and young adulthood and its role in the development of comorbidities
- Determinants of patterns of dietary intake and physical activity across the life span and in diverse populations
- Sensitive periods for weight gain, to provide targeted periods for prevention efforts
- Strategies for identifying persons at risk for obesity-related comorbidities
- Determination of whether obesity is a risk factor for cardiovascular disease and other major complications in older persons
- Advantages of the treatment of obesity in older persons
- Factors that predict weight loss and successful weight loss maintenance across the life span
- Effects of obesity on the development of comorbidities across the life span
- Effects of obesity on comorbidities with changes in BMI, especially at higher levels

These research findings will add to the existing knowledge base on the determinants of obesity and associated comorbidities across the life span. Advocating a life-course approach toward prevention and treatment of obesity will more fully address the larger, complex, and additive issues of when and why people are more susceptible to excessive weight gain during critical or sensitive periods. The identification of age-dependent risk factors for obesity and comorbidities is key to addressing the worsening worldwide epidemic of obesity.

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