Special Article

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Metabolic precursors and effects of obesity in children: a decade of progress, 1990–1999[1–4]

Michael I Goran

ABSTRACT Current data suggest that 20% of US children are overweight. An analysis of secular trends suggested a clear upward trend in body weight in children of 0.2 kg/y between 1973 and 1994. In addition, childhood obesity is more prevalent among minority subgroups, such as African Americans. Obesity that begins early in life persists into adulthood and increases the risk of obesity-related conditions later in life. Obesity is now considered a disease of epidemic proportions, not just in the United States but also worldwide. In the past 10 y there has been a tremendous increase in the number of studies examining the etiology and health effects of obesity in children. The major objectives of this article are to *1*) review highlights in pediatric obesity research from 1990 to 1999; *2*) summarize our research on the roles of energy expenditure, physical activity, and aerobic capacity in the etiology of pediatric obesity, and on ethnic differences in the relation between obesity and type 2 diabetes risk factors in children; and *3*) discuss areas of future study that will require greater emphasis as the field of childhood obesity research evolves over future years. *Am J Clin Nutr* 2001; 73:158-71.

KEY WORDS Energy metabolism, physical activity, insulin secretion, acute insulin response, insulin sensitivity, African American children, white children, obesity, body composition, fat distribution

MAJOR HIGHLIGHTS IN PEDIATRIC OBESITY RESEARCH, 1990–1999

As shown in **Figure 1**, there has been a tremendous increase in the number of studies of obesity in children since 1970. To identify the studies that had the greatest effect on the field over the period 1990–1999, a citation analysis was performed using the search terms "obesity" and "children" or "adolescents." For each year, the top 10 articles cited were identified, and the list was reviewed for thematic issues, originality, and significance. The most frequently cited articles are summarized below and in **Table 1**.

Epidemiology

In the mid 1990s, reports from national studies showed a clear upward trend in the prevalence of obesity (1). This finding was echoed in several large cohort studies in children, including analysis of 5 National Health and Nutrition Examination Surveys (NHANES; 1963–1965, 1966–1970, 1971–1974, 1976–1980, and 1988–1991) of trends in overweight in children (aged 6–11 y) and adolescents (aged 12–17 y). Although there is no clear definition of obesity in children, the most widely accepted definition is that a body mass index (BMI; in kg/m^2) between the 85th and 95th percentiles indicates a risk of overweight and that a BMI greater than the 95th percentile indicates overweight. Throughout this article, I will use that definition when appropriate; otherwise, I will use the definitions specified in each of the relevant articles. In the most recent NHANES, the prevalence of overweight was 22% and the prevalence of obesity was 10.9% for all racial and ethnic groups combined. The highest prevalence of overweight in girls was found among non-Hispanic blacks (15–30% for girls aged 12–17 y and 17–31% for girls aged 6–11 y). For boys, the highest prevalence rates were found in Mexican Americans (13–27% for the older group and 18–33% for the younger group). The prevalence of overweight was 5–7% higher than in the earlier surveys.

Other studies examined and established the value of childhood BMI for predicting overweight later in life. One frequently cited study incorporated data from 4 longitudinal studies of 277 male and 278 female white subjects (born between 1929 and 1960) (3). The NHANES II percentiles for childhood values (for white subjects, by age and sex) of BMI were used as a reference. The probability of overweight at age 35 y for children with BMIs in the 95th and 75th percentiles increased with age. The analyses of sensitivity and specificity indicated that the prediction of adult weight was the most accurate for BMI at age 18 y and only moderately accurate for BMI at ages <13 y. The 60th percentile was accordingly chosen as the cutoff at 18 y for prediction of overweight at age 35 y. The odds ratio for overweight in adulthood of children with BMIs in the 75th percentile was significantly greater than for those with BMIs in the

[1] From the Institute for Prevention Research, the Department of Preventive Medicine, University of Southern California, Los Angeles.

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[4] Address reprint requests to MI Goran, 1540 Alcazar Street, Room 208-D, University of Southern California, Los Angeles, CA 90033. E-mail: goran@usc.edu.

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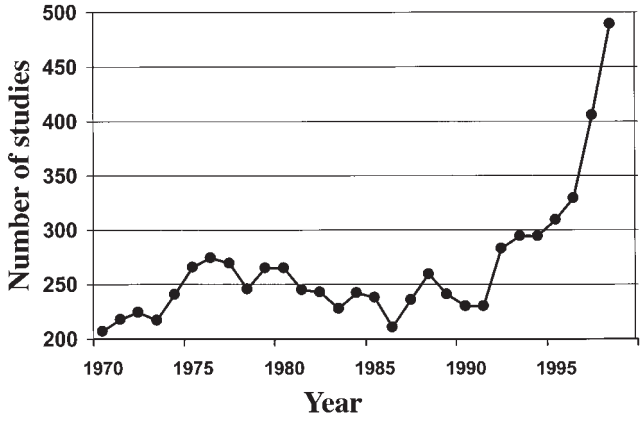

FIGURE 1. Number of published studies per year since 1970 in the area of obesity in children.

50th percentile (1–10 times for males and 1.5–8 times for females), whereas the corresponding odds ratios for the 95th compared with the 75th percentile were slightly lower (1.3–6.1 for males and 1.4–4.9 for females). These data show that the persistence of pediatric obesity into adulthood increases according to the age at which obesity is initially present. In addition, this study provided data for the identification of children at a high risk (>95th percentile) of adult overweight.

Another frequently cited study examined the relation between childhood and adult obesity and between child and parent obesity (4). A retrospective cohort study was conducted with use of data obtained from members of the Group Health Cooperative of Puget Sound. An average BMI was calculated for measurements between the ages of 21 and 29 y for the 854 subjects who were born between 1965 and 1970, had at least one outpatient visit after the age of 21 y, and had weight measured during various periods. The risk of adult obesity was greater at any age in both obese and nonobese children if at least one parent was obese. This effect was most pronounced in children aged <10 y. As each child aged, the effect of parental obesity was outweighed by the child's own obesity status. This study indicated that obese children aged ≤9 y with obese parents may benefit the most from preventive attention because patterns may not be completely established at that age, provided that due consideration is given to physical and psychological factors. Treatment after age 10 y should be considered on the basis of the child's obesity status.

Toward the end of the 1990s, new data were analyzed that renewed concern relating to sedentary behavior by showing an increased in the prevalence of obesity and disturbing patterns in television viewing in children (5). In a sample of 4063 children aged 8–16 y from NHANES III, physical activity decreased notably in girls, with 20.1% of 14–16-y-old girls reporting one or fewer bouts of vigorous activity per week; 26% of the children reported watching ≥4 h of television/d, and 43% of non-Hispanic blacks watching television to this extent. Boys and girls who watched ≥4 h of television/d had the highest skinfold thicknesses and the highest BMIs. Interestingly, the relation between physical activity and BMI was not significant but there was a significant relation between sedentary activity (as measured by television viewing) and BMI, highlighting the importance of inactivity in the etiology of obesity.

By 1997, the upward trend in the prevalence of obesity in children was reemphasized on the basis of an epidemiologic study that showed a clear upward secular trend in body weight in children that was equivalent to a 0.2-kg increase in body weight/y at any given age (2). Collectively, these studies provided major evidence to suggest that the trend of increasing obesity in children may be the result of environmental and cultural changes related to physical inactivity in our society.

Health risk

During the period 1990–1992, several studies from the Bogalusa Heart Study were cited frequently. The Bogalusa study is a longitudinal study of cardiovascular disease risk factors in a large cohort of white and African American children in Louisiana. This study generated numerous articles that were reviewed elsewhere in more detail (20). One of the most cited studies examined the tracking of serum lipids and lipoproteins in 1586 black and white children at 3-y intervals over a period of 12 y (1973–1974 to 1984–1986). Total cholesterol among boys was relatively constant until ≈13–14 y of age and then decreased until ≈18 y of age, followed by an increase beginning at ≈19–20 (slightly earlier for black boys) until 25–26 y of age. The pattern for LDL cholesterol was similar, with a greater increase in white than in black boys. White children showed a progressive rise in triacylglycerol concentrations until age 26 y, which was noted only in the oldest cohort of black males. HDL-cholesterol

TABLE 1
Most frequently cited studies of pediatric obesity, 1990–1999

Topic and reference	Major findings
Epidemiology	
1	Most recent national prevalence estimates of overweight (22%) and obesity (11%) in children
2	Secular trend showing 0.2-kg/y trend for increasing body weight in children
3, 4	Persistence of adolescent obesity into adulthood
5	Decrease in physical activity in children
Health	
6, 7	Tracking of cardiovascular risk factors from childhood to adulthood
8	Autopsy study showing atherosclerotic lesions and fatty streaks in youth and young adults
9	Long-term social consequences of adolescent obesity
10	55-y follow-up of obese adolescents showing long-term mortality outcome
11	Increased incidence of type 2 diabetes in adolescents
12, 13	Observation of visceral fat in children and association with health risk
Etiology	
14	Observation of rare leptin mutation causing obesity in children
15	Studies on leptin and body fat showing that, in general, leptin concentrations are normal relative to body fat
16, 17	Lower energy expenditure in children
Methodology	
18	Application of dual-energy X-ray absorptiometry for body composition in children
Treatment	
19	Establishment of clinical guidelines

concentrations decreased somewhat for black children and white girls but decreased dramatically for white boys, beginning at ≈13–14 y of age. These results, combined with those for LDL concentrations, show notably increased ratios of LDL to HDL cholesterol over time. Correlation coefficients for total cholesterol and LDL-cholesterol concentrations measured 12 y apart were highly significant across all age, race, and sex groups. An age trend for triacylglycerol appeared only for white boys. Significant correlation coefficients were also obtained for HDL-cholesterol concentrations; as with other measures, tracking was best for older cohorts. Significant tracking was also observed with respect to elevated total cholesterol concentrations at baseline and follow-up. About 50% of children above the 75th percentile (age-, race-, and sex-specific) at baseline remained in this category at follow-up. Overall tracking was better in the older (9–14 y) than in the younger children (2–8 y). Triacylglycerol and VLDL-cholesterol concentrations remained in the high-risk range in 35% and 38% of the population, respectively. Tracking of HDL cholesterol was significant for the older cohorts, particularly that of white boys. Baseline total cholesterol concentrations were the best predictors of follow-up results, followed by change in obesity status (in kg/m^3). Similar results were obtained for the various lipoproteins (HDL-cholesterol concentrations were inversely related to an increase in obesity). When the guidelines of the National Cholesterol Education Program were used to evaluate risk status, 91% of the subjects with very elevated cholesterol at follow-up could have been identified during childhood through cholesterol or obesity measurements.

In addition, an autopsy study of young adults who were killed accidentally was among the first to show that the progression of atherosclerotic plaques and cardiovascular risk had already begun in young adulthood (8). Autopsies were performed in 204 people (86 white males, 52 black males, 36 white females, and 30 black females) who died between the ages of 2 and 39 y; 93 of these were surveyed previously in the Bogalusa Heart Study for cardiovascular risk factors, including BMI, blood pressure, cigarette smoking status, and serum lipids. The aorta and coronary arteries were opened and stained at autopsy to determine the percentage of intimal surface with atherosclerotic lesions, fatty streaks, fibrous plaques, complicated lesions, and calcified lesions. There were various strong associations of the given risk factors with different types of lesions in different areas. The risk-factor variables as a group were most strongly associated with the prevalence of fatty streaks in the coronary arteries. Strong trends of increasing prevalence of lesions were evident as the number of risk factors increased. For example, the extent of fibrous-plaque lesions in the coronary arteries was 12 times as great in persons with 3 or 4 risk factors as in those with none.

Although the Bogalusa study established clear cross-sectional patterns between body fat and risk (and shorter-term tracking), longer-term health aspects were not determined. The relation between obesity during adolescence and the socioeconomic status of the subjects 7 y later was examined in 10 039 individuals (9). Overweight at baseline (defined as a BMI above the 95th percentile for age and sex) was associated with lower household income, lower intelligence, and lower parental education levels for women only. After 7 y, lower levels of socioeconomic attainment were evident in subjects who were overweight at baseline, more significantly so in women. This relation was preserved after control for a series of baseline characteristics (including income, parental education, and self esteem). Women who were overweight adolescents were less likely to marry, had lower household incomes, and had completed fewer years of school. Overweight men were also less likely to marry. This study therefore highlighted the long-term negative social effect of obesity in adolescents.

In an effort to further elucidate the relation between adolescent overweight and subsequent morbidity and mortality, a 55-y follow-up was conducted of participants in the 1922–1935 Harvard Growth Study (10). Attempts were made to contact participants who had either been overweight (BMI above the 75th percentile for 2 y between the ages of 13 and 18 y) or lean (BMI between the 25th and 50th percentiles). Whereas women had no increased risk of mortality related to adolescent overweight, men who were overweight during adolescence were about twice as likely to die (from all causes or from coronary heart disease) compared with those in the lean group, although this factor decreased slightly when adjusted for the influence of adult BMI. Smoking status and exercise status did not significantly change the positive correlations between adolescent overweight and coronary heart disease, atherosclerosis, colorectal cancer (in men), gout (in men), and arthritis (in women). No significant differences in functional capacity were noted between subgroups of men, whereas women who had been overweight adolescents were 8 times as likely to report difficulty with activities of daily living as were women who had been lean.

Perhaps one of the most dramatic and disturbing findings in the past decade was that of Pinhas-Hamiel et al (11) in 1996, ie, the tremendous increase in the incidence of type 2 diabetes in children and adolescents. Before the publication of this study it was generally thought that type 2 diabetes was restricted to older age groups and did not affect children. However, the increased incidence of type 2 diabetes in the pediatric population was shown clearly by an examination of clinical cases that diagnosed diabetes. In an analysis of 1027 patients aged 0–19 y who were diagnosed with diabetes in Cincinnati, only 4% of diabetes cases were classified as type 2 before 1982. By 1994, 16% of diabetes cases were classified as type 2 diabetes; in 10–19-y-olds, 33% of all cases of diabetes were identified as type 2. This translated to a 10-fold increase in the incidence of type 2 diabetes between 1982 and 1994. Moreover, in addition to family history and ethnicity (greater risk in African Americans), obesity was identified as a major risk factor for type 2 diabetes. This study was important because it reshaped our thinking in several ways. First, type 2 diabetes was not necessarily a slowly progressing disease that affected adults but, in susceptible individuals, could be manifested as early in life as adolescence. Second, the study clearly emphasized obesity as substantially more than a body weight issue in children.

Around that time, parallel studies in adults examined the relation between body fat and risk of diabetes, focusing on visceral fat as the compartment of body fat that seemed to be more highly related to disease risk. The concept of syndrome X was established and summarized as a constellation of risk factors consisting of visceral fat, hypertension, dyslipidemia, and insulin resistance (21). In the mid 1990s, several studies began to appear that showed the existence of visceral fat in children and adolescents (12, 13) and showing significant correlation between visceral fat and risk factors such as fasting insulin and lipid concentrations (12). These relations were not limited to obese adolescents but were apparent across the spectrum of lean and obese individuals and were evident as early in life as age 6–7 y (13). Some studies in this area are reviewed in more detail below.

Etiology

A major revolution in the field of obesity research in the 1990s was the discovery of leptin, an adipose tissue–derived hormone (22). Several studies that showed strong positive correlations between body fat and circulating leptin were conducted in children (15, 23). Mutations in the gene encoding leptin, a secreted protein that is thought to act at the hypothalamus and affects appetite, energy expenditure (EE), and neuroendocrine axes, were shown to result in extreme obesity in mice (24). One study showed that a similar, albeit rare, mutation accounts for extreme obesity in humans (14). Two extremely obese children, related within a consanguineous family, were examined for mutations of the gene for leptin and were found to be homozygous for a mutation involving the deletion of a guanine nucleotide that is normally present in codon 133, resulting in a frame-shift mutation (causing not only an incorrect sequence of amino acids after the mutation but also premature truncation of the protein). Serum leptin concentrations were found to be extremely low in both subjects. Both subjects had normal birth weights and subsequent rapid increases in weight, with a history of marked hyperphagia. In addition, fasting insulin was elevated in the older of the 2 subjects, suggesting a possible age-related trend for insulin resistance. None of these phenotypic landmarks were observed in the heterozygous parents or siblings (heterozygous or wild-type homozygous), implying either the compensation of the wild-type allele for the mutated version or simply unnecessary fine-tuning for the optimal function of leptin. These results were consistent with those found in mice (eg, normal birth weights, severe obesity associated with hyperphagia and impaired satiety, and hyperinsulinemia and insulin resistance). However, in the general population, leptin is highly correlated with body fat (15).

Methodology

The field of pediatric obesity was further propelled by several technologic advances that made it more feasible to apply new research techniques to the pediatric population. Before the 1990s, few detailed studies characterized basic energy metabolism and body composition in children. In the late 1980s, several methodologic advances were made in the field, including the validation of the doubly labeled water method for assessing free-living EE in humans (25), which was later applied to infants (26) and children (16). Application of this method to children in laboratories led to the discovery that total free-living EE and thus energy requirement was ≈25% lower in children than had previously been expected (16). This finding was consistent in studies performed in children living in Vermont, Arizona, and Northern Ireland (16, 17, 27).

Another important technical development related to new techniques for assessing body composition. Before the 1990s, few studies had described body composition in children, and available techniques included skinfold-thickness measurement, which has a limited accuracy; underwater weighing, which is difficult to perform in children; and other highly specialized research techniques, such as total body potassium, that are only available in a few laboratories. These limitations changed rapidly with the development of dual-energy X-ray absorptiometry (DXA) for accurate, relatively simple, and noninvasive measurement of whole-body lean, bone, and fat tissue. Several studies validated this technique in the pediatric body weight range (18, 28), and the technique quickly became a widely used research tool.

Treatment

Guidelines for diagnosing and treating overweight adolescents were established by an expert committee (19). BMI was identified as the most accurate clinical tool for assessing obesity. In evaluating the validity of BMI cutoff points for identifying adolescents with very high body fat, specificity values were emphasized in an attempt to minimize the number of adolescents who were incorrectly identified as being overweight. Subjects with a BMI above the 95th percentile or >30, whichever is smaller, should be considered as overweight and undergo in-depth medical assessment. (The limit of 30 is supported by significant evidence that a BMI higher than this indicates severe health risks.) Subjects with a BMI above the 85th percentile should be considered at risk of overweight and referred to a second level of screening that incorporates additional risk factors, such as family history, blood pressure, total cholesterol, a large increment in BMI over the previous year, and the adolescent's concern about weight.

Summary

The major advances in the field in the past decade are summarized briefly in Table 1. Note that many of these findings originated from investment in long-term, carefully designed longitudinal cohort studies. In addition, major developments in technology have allowed for more detailed examinations of the influence of obesity on health risk than were previously possible. Other than a publication on clinical guidelines, there was a notable lack of studies related to the treatment and prevention of obesity in children.

SUMMARY OF WORK BY OUR GROUP DURING THE PERIOD 1990–1999

In the following sections I will summarize the findings from our own studies in the area of EE, body composition, fat distribution, and diabetes risk in children. Our studies on EE incorporated measures of resting metabolic rate by indirect calorimetry and the doubly labeled water technique for assessment of free-living total EE (TEE) over 2 wk. In combination, these 2 techniques provide an estimate of physical activity–related EE (AEE) by difference [TEE minus resting EE (REE) after adjustment for the thermic effect of a meal]. In addition, we measured aerobic fitness by using a treadmill test to exhaustion. We used DXA, which we validated in the pediatric body weight range in pigs (18), to measure whole-body lean, bone, and fat mass (FM) and used computed tomography to measure visceral and subcutaneous abdominal fat by direct imaging. We used the frequently sampled intravenous-glucose-tolerance test to assess insulin sensitivity and the acute insulin response by using the Bergman minimal model. In addition, we conducted cross-sectional and longitudinal studies as summarized below. Our longitudinal cohorts include annual repeated measurements in 75 young white children studied in Burlington, VT, between 1990 and 1997 and annual measurements in an ongoing cohort study of 220 white and African American children studied in Birmingham, AL. Our major findings from articles published in the period 1990–1999 are summarized briefly in **Table 2**, and selected studies are discussed in more detail below.

Role of energy expenditure in the etiology of obesity

The average child consumes >2 million kJ (close to half a million kilocalories) per year. Despite this huge energy intake,

TABLE 2
Summary of major findings relating to childhood obesity, 1990–1999[1]

Topic	Reference	Major findings	Unanswered questions
Energy expenditure			
TEE, AEE, and energy requirements	16	TEE 25% lower than recommended intake in 4–6-y-old children Low AEE (≈1130 kJ/d) TEE most significantly related to FFM, body weight, and REE (r = 0.80–0.86)	Need to develop prediction equations that are accurate at the individual level
Determinants of REE	29	Major determinants were FFM (partial r = 0.77), sex (partial r = 0.12; 222 kJ/d higher in boys), and FM (partial r = 0.16) Effects of FFM, sex, and FM on REE are similar to that seen in adults	Explanation of the influence of sex and FM on REE
Measurement of REE	30	11% higher with use of an outpatient postprandial protocol than with an inpatient fasting protocol The CV for repeat measures of the postprandial protocol was 5% for REE and 3% for respiratory quotient The outpatient protocol is a reliable and practical alternative	Unclear whether it is more appropriate to measure REE by using outpatient protocol or more controlled conditions of an inpatient protocol
Prediction equations for REE	31	Most published prediction equations for REE in children are inaccurate except for the FAO/WHO/UNU equations	Need for more accurate equations for both research and clinical settings
Mohawk children	32	Mohawk children have a higher TEE independent of FFM because of a 628-kJ/d higher AEE (REE was similar) Subcutaneous fat more central in Mohawk children	The source of the higher AEE was unknown Do differences in TEE and AEE influence subsequent weight change? Do Mohawk children have more VFAT?
Guatemalan children	33	No differences in EE between short and normal stature Lower body water and FM in short children is proportional to their lower FFM	Further studies on the mechanism and nutritional implications of short stature
African American children	34	TEE, REE, and AEE were similar in white and African American children	Need to examine ethnic difference in EE components at other stages of maturation Need to examine ethnic differences in qualitative aspects of physical activity
Hormonal indexes of maturation	35	Sex-steroid hormones significantly correlated with REE and TEE (r = 0.3–0.8) but all correlations were nonsignificant after adjustment for body composition Hormonal indexes of maturation did not influence EE in African American and white children	Lack of effect may be due to low hormone concentrations in prepubertal children Ethnic differences in hormones and EE may become more apparent as children mature
Sex, seasonality, ethnicity, and geographic location	36	Analysis of 232 measurements of TEE TEE higher in spring than in fall, higher in boys than in girls, and higher in Vermont than in Alabama (all effects ≈628 kJ/d) Seasonal and geographic effect explained by AEE Sex differences explained by REE White, Mohawk, and African American children have similar EE but Guatemalan children have a lower TEE because of a lower AEE Weight was the best predictor of TEE (r = 0.81) $\dot{V}O_2$max was the best predictor of AEE (r = 0.54)	Best equations predicted 73% of variance in TEE; additional markers of activity needed Further studies needed to examine seasonal effect and the effect of location Reason for lower TEE and AEE in Guatemalan children is unclear (eg, effects of altitude?)
Children of lean and obese parents	37	Children of obese parents do not have major defects in TEE, AEE, or REE 6% lower REE only in children with either an obese mother or an obese father than in children with 2 lean or 2 obese parents	Need to reevaluate the hypothesis that children of obese parents have a lower EE, which leads to obesity Need to identify other risk factors Inverse relations between EE and obesity may be due to spurious correlations
Obese and nonobese girls	38	Obese and nonobese girls had similar levels of all components of EE and fitness after differences in body composition were controlled for	Need to examine whether there are qualitative differences in physical activity that may influence energy regulation
Longitudinal study of EE and fatness	39	4-y rate of change in fat relative to lean tissue was not affected by any component of EE Change in fat was influenced by initial fatness, parental fatness, and sex (higher gain in girls)	Other aspects of activity and eating behavior may be related to fat gain Need to examine role of EE in fat gain during other periods of development and other subgroups at greater risk of obesity
Changes in EE during growth	40	4-y increases in FM, FFM, and REE similar in boys and girls In boys, TEE increased gradually from age 5.5 to 9.5 y In girls, reduction in TEE and 50% reduction in AEE between age 6.5 and 9.5 y	Suggests energy conservation in girls or behavioral and cultural changes before puberty, which require further investigation Need to examine similar aspects in boys at later ages as they approach puberty

(Continued)

TABLE 2 *(Continued)*

Topic	Reference	Major findings	Unanswered questions
Body composition			
Examination of BIA	41	Relations between total body water and ht^2/R is robust across independent laboratories The Kushner equation relating ht^2/R to total body water is accurate in young children	Accuracy of equations during puberty is unknown Equations are useful only for estimating total body water, so other equations for FFM and FM are needed
Validation of DXA	18	Validation of DXA in the pediatric weight range with use of carcass analysis in pigs Derived instrument- and software-specific correction factors Precision estimates were 1% for lean and 4% for fat	Reason for nonexact one-to-one relation remains to be clarified
Comparison of techniques	42	FM by skinfold-thicknesses and BIA overestimated compared with DXA FM by DXA best predicted by subscapular and triceps skinfold thickness, weight, sex, and ht^2/r ($R^2 = 0.91$; SEE = 0.94 kg)	Need to extend findings to older age groups, different stages of maturation, and other ethnic groups
Development of prediction equations	43	Previously developed equations did not accurately predict FM measured by DXA in the larger sample New equations were successfully cross-validated by using weight, triceps circumference, sex, ethnicity and abdominal skinfold thickness ($R^2 = 0.95$)	Equations were limited to white and African American children aged 4–11 y and at Tanner stages <3
Energy intake			
Food-frequency method	44	Food-frequency questionnaire overestimated energy intake by 40% relative to TEE Overestimation was not explained by sex or body composition	Need to adapt questionnaires for children, particularly with regard to portion sizes and recall ability
24-h recall	45	3 d of 24-h recall with use of the multiple-pass interview technique provides accurate group estimates of energy intake based on TEE	Need technique for accurate individual estimates Need better methods to eliminate potential for misreporting
Dietary fat and body fat	46	Maternal obesity influenced dietary fat intake in children Relation between dietary fat and obesity was significant in boys ($r = 0.48$) but not girls	Need to determine behavioral basis for influence of mother's obesity status on child's intake Need to examine individual susceptibility to dietary fat in long-term longitudinal studies Need to examine potential sex dimorphism in relations
Dietary fat, body fat, and serum lipids	47	No evidence of a link between dietary fat and lipids Data suggest that FM may be more important than dietary fat in the course of cardiovascular disease	FM, fat distribution, and diet explained only 20% of the variance in lipids; therefore, other factors may have been involved Findings may have been limited by suboptimal measures of dietary intake
Visceral fat			
Observation in young children	13	VFAT established in children aged 4–9 y Trunk skinfold thickness is a better predictor of VFAT than is the waist-to-hip ratio	Need to identify stronger anthropometric and laboratory indexes of VFAT Is lower level of VFAT in children proportional to their smaller body size? Changes in VFAT during growth
Variation in white and African American children	48	Wide variation in VFAT, not related to percentage body fat Lower VFAT in African American children	Need to confirm lower VFAT volume, beyond single slice measures Reasons for lower VFAT in African American children is not known
Prediction equations	49	Developed and cross-validated prediction equations for VFAT and SAFAT with use of anthropometry with or without DXA Typical indexes are not useful for predicting VFAT (eg, waist-to-hip ratio, saggital diameter)	Need to verify equations in children at later stages of maturation and in other ethnic groups More detailed DXA scan analysis may improve the accuracy and specifity of equations
Physical activity			
Caltrac accelerometry	50	Caltrac activity counts over 3 d were unrelated to AEE over 14 d by doubly labeled water	Need to develop better methods for assessing individual levels of physical activity May need separate methods to assess overall energy cost and frequency, duration, and intensity

(Continued)

TABLE 2 *(Continued)*

Topic	Reference	Major findings	Unanswered questions
Physical activity and FM	51	Time devoted to activity explained a small portion of variance in FM (10%), whereas AEE was unrelated Time devoted to activity and AEE should be considered as separate variables	Need to examine whether longer bouts of activity (which can be sustained at low intensity) are more effective for reducing body fat than are shorter bouts
Strength training, fitness, and EE	52	5 mo of a school-based strength-training program increased strength in obese girls but had no effect on any component of EE or aerobic fitness	Need to identify optimal exercise programs that have beneficial effects on EE
Strength training and VFAT	53	After 5 mo of a school-based strength-training program, VFAT was unchanged, whereas all other fat compartments increased Strength training had no significant effect on plasma glucose and insulin response to an oral glucose load	Unknown mechanism of effect of strength training on VFAT Need to identify optimal exercise programs that also benefit insulin action and secretion
$\dot{V}O_2$max in African American children	54	African American and white children had similar $\dot{V}O_2$ at rest and during submaximal exercise but $\dot{V}O_2$max was 15% lower in African American children independent of FFM, FM, and EE	Role of muscle-fiber type and hemoglobin in explaining lower $\dot{V}O_2$max Does lower $\dot{V}O_2$max affect habitual physical activity pattern? Long-term implications and clinical significance of lower $\dot{V}O_2$max
Sociocultural determinants	55	No ethnic difference in physical activity after adjustment for social class and compared with 2 parents Higher television viewing and vigorous exercise in children with 1 compared with 2 parents Physical activity measures poorly intercorrelated, ie, multidimensional nature of physical activity	Accounted for only 10–15% of variance in activity; other studies in more diverse populations that examine physiologic, sociocultural, behavioral, and environmental factors are needed
Leptin			
Sex, ethnicity, and body composition	23	Leptin highly related to body fat ($r \approx 0.9$) No significant sex difference in leptin after adjustment for body composition and fat distribution No significant difference in leptin between white and African American children	Need to examine sex differences in leptin, body composition, and fat distribution during later stages of maturation
Leptin and EE	56	Leptin was significantly related to TEE, REE, and AEE ($r = 0.3$–0.5) but this effect disappeared after control for FFM, FM, sex, and ethnicity	Need further studies (eg, manipulation of leptin) to determine whether leptin is related to EE
Insulin action			
Fat distribution and insulin response	57	Higher fasting insulin and insulin response to oral glucose in African American children Body fat and visceral fat highly related to insulin response in white and African American children ($r = 0.4$–0.8) Higher insulin response in African American children not explained by body fat or fat distribution	Cause of higher fasting insulin and insulin response Examine whether higher insulin response was due to insulin sensitivity or to pancreatic response
Visceral fat and insulin sensitivity	58	Visceral fat related to triacylglycerol and insulin but not insulin sensitivity Obese and African American children had lower insulin sensitivity and higher AIR but this was not explained by VFAT African American children had significantly higher fasting insulin, lower insulin sensitivity, and higher AIR that were not explained by fat or fat distribution	Reason for ethnic differences in insulin, insulin sensitivity, and apparent overcompensation of AIR Do ethnic differences relate to long-term disease risk? Does VFAT affect insulin via hepatic insulin extraction? Interventions that lead to beneficial changes in insulin, insulin sensitivity, and AIR

[1] EE, energy expenditure; TEE, total energy expenditure; REE, resting energy expenditure; AEE, activity energy expenditure; FFM, fat-free mass; FM, fat mass; VFAT, visceral fat; SAFAT, subcutaneous abdominal fat; DXA, dual-energy X-ray absorptiometry; BIA, bioimpedance analysis; *R*, resistance; AIR, acute insulin response; $\dot{V}O_2$max, maximal oxygen uptake.

most healthy children can strike a remarkable balance between energy intake and EE, which, other than the energy deposition of growth [which accounts for ≈84 kJ (20 kcal)/d in growing children], results in a state of energy balance (**Figure 2**). This accurate balance between energy intake and EE is an example of homoeostatic regulation and results in the maintenance of body weight and body energy stores. Regulation of energy balance is achieved over the long term despite large fluctuations in both energy intake and EE within and between days. Obesity is the end result of a mismatch between energy intake and EE, such that intake exceeds expenditure, resulting in net accumulation of energy stores in the body. However, it remains unclear whether obesity is due to excess energy intake or a reduction in EE. In this section, previous studies from our laboratory that examined the influence of EE on the cause of obesity will be reviewed.

Although it is a popular belief that reduced EE or physical activity is a risk factor for excess fat gain during growth in chil-

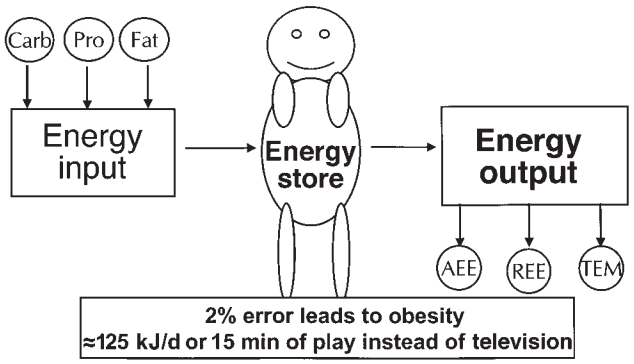

FIGURE 2. The components of energy balance. Carb, pro, and fat represent energy input from carbohydrate, protein, and fat, respectively. AEE, activity energy expenditure; REE, resting energy expenditure; TEM, thermic effect of feeding.

dren (59, 60), this hypothesis remains controversial and has been difficult to prove (61, 62). We examined TEE by using the doubly labeled water method, 24-h sedentary metabolic rate in a metabolic chamber, and resting metabolic rate in obese and nonobese girls (38). All components of EE were similar in lean and obese children after adjustment for body composition. Thus, cross-sectional differences in FM were not related to variation in EE components. We also examined EE in children of obese parents as a model of the preobese state (37). Seventy-four prepubertal children ($\bar{x}$ ± SD age: 5.0 ± 0.9 y) were divided into 4 groups according to the obesity status of their parents: both parents nonobese, obese father and nonobese mother, obese mother and nonobese father, or 2 obese parents. TEE and AEE were not significantly different among the 4 groups after adjustment for fat-free mass (FFM), and there were no significant correlations between components of EE in children and body fat in their mothers or fathers (37). However, REE was ≈6% lower in the children with either an obese mother or an obese father than in children who had either 2 lean or 2 obese parents.

We also examined EE in groups of children with higher risks of obesity (eg, Mohawk Indians and African Americans). In Mohawk children in upstate New York, the prevalence of obesity was estimated to be 44% (63). However, TEE was actually 8.5% higher in Mohawk than in white children living in Vermont because of a 37% higher AEE in the Mohawk children (32). We did not detect any ethnic difference in any component of EE in prepubertal African American compared with white children (34), although most other studies detected lower EEs in African Americans (64–67). This issue of ethnic differences in EE in African Americans is reviewed in more detail below.

A major limitation of most studies that examined the role of EE in the etiology of obesity is their cross-sectional design. Because growth of individual components of body composition is likely to be a continuous process, longitudinal studies are needed to evaluate the rate of body fat change during the growing process. The influence of EE components on the rate of change in body fat relative to FFM over a 4-y period was examined in a longitudinal study of prepubertal children of lean and obese parents in Burlington, VT (39). The average rate of change in absolute FM was 0.89 ± 1.08 kg/y (range: –0.44 to 5.6). The rate of change in FM adjusted for FFM was 0.08 ± 0.64 kg/y (range: –1.45 to 2.22) and was similar among children of 2 nonobese parents and children with 1 nonobese and 1 obese parent but significantly higher in children with 2 obese parents (0.61 ± 0.87 kg/y). The major determinants of change in fat adjusted for FFM were sex (greater relative fat gain in girls), initial fatness, and parental fatness; none of the components of EE were inversely related to change in fat adjusted for FFM (39).

In another longitudinal study, we examined 72 white children (55 girls and 17 boys) and 43 African American children (24 girls and 19 boys) from Birmingham, AL (33). Aerobic fitness; REE, TEE, and AEE; and body composition were measured at baseline and then annually for 3–5 y. Initial FM was the main predictor of increasing adiposity but there was also a significant negative relation between aerobic fitness and the rate of increasing adiposity ($F_{1,82} = 3.92$, $P = 0.05$). With every increase of 0.1 L/min of fitness, there was a decrease of 0.081 kg fat/kg lean mass gained. None of the measures of EE significantly predicted increasing adiposity in either the white or the African American children. These results suggest that aerobic fitness may be more important than absolute EE in the development of obesity in white or African American children (68). Alternatively, these results could be a reflection of the fact that a measure of aerobic fitness is a more accurate and sensitive indicator of physical activity than is AEE derived from doubly labeled water.

Although we have yet to detect a significant role of EE components in predicting fat gain during growth, there are critical periods of development during which large changes in EE may occur. For example, we examined individual changes in EE and physical activity during prepubertal growth in boys and girls (40). TEE, REE, AEE, reported physical activity by questionnaire, and FM and FFM were measured 3 times over 5 y in 11 boys (5.3 ± 0.9 y at baseline) and 11 girls (5.5 ± 0.9 y at baseline). Four-year increases in fat (≈6 kg) and FFM (≈10 kg) and REE [≈840 kJ (200 kcal)/d] were similar in boys and girls. In boys, TEE increased at each measurement year, whereas in girls, there was an initial increase from age 5.5 y [5711 ± 1382 kJ (1365 ± 330 kcal)/d] to age 6.5 y [7594 ± 1640 kJ (1815 ± 392 kcal)/d], but by age 9.5 y, there was a significant reduction [6728 ± 1188 kJ (1608 ± 284 kcal)/d], with no change in energy intake. The sex difference in change in TEE over time was explained by a 50% reduction in physical activity (kJ/d and h/wk) in girls between the ages of 6.5 and 9.5 y (40). These data suggest a sex dimorphism in the developmental changes in EE before adolescence, with a conservation of energy utilization in girls achieved through a marked reduction in physical activity.

Collectively, the findings presented above do not provide strong evidence to support a role of EE in the development of obesity, in contrast with the results of some previous studies (59, 60). This discrepancy could be explained by several additional factors. For example, differences or changes in EE, energy intake, or both could occur at distinct critical periods of development (eg, in early infancy or adolescence) and may thus result in energy imbalance. In addition, there could be individual differences and susceptibility to the effect of altered EE on the regulation of energy balance. Thus, the effect of EE on the etiology of obesity could vary in different subgroups of the population and could also have a differential effect within individuals at different stages of development. It is conceivable that susceptible individuals fail to compensate for periodic fluctuations in EE. Also, although a 14-d measurement of EE by doubly labeled water is considered a long-term measurement, this period is actually short compared with the time scale for

the development of obesity, which can be slow. For example, in our previously cited longitudinal study (39) that compared children of 2 obese parents with children of 2 nonobese parents, the difference in the rate of change in FM relative to FFM was <1 kg fat/y, or <3 g excess fat gain/d. This is equivalent to a continual daily energy imbalance of 105 kJ (25 kcal)/d (≈2% of total daily energy flux). From a methodologic standpoint, even the most sophisticated of current techniques would be unable to identify this energy imbalance as a "defect" in EE components (or as an excess in energy intake, relative to needs).

In summary, our work in the field of energy metabolism in children has led to the following major developments, and others summarized in Table 2:

1) EE, and thus energy requirements, are lower than expected.
2) EE is not necessarily related to obesity in children or to parental obesity.
3) EE does not appear to be a major risk factor for the development of obesity during prepubertal growth.
4) The major predictors of increased fat gain during growth are initial fat, parental fat, and sex.
5) The average energy imbalance responsible for fat gain is generally very small, even in children who are developing obesity.
6) Physical activity declines in girls immediately before puberty.
7) Environmental and behavioral factors relating to physical activity may be more significant than inherent metabolic characteristics in the development of obesity.

Studies in African American compared with white children

In the past decade there has been a surge of interest in examining the etiology of obesity and the increased susceptibility to health risk in African Americans. This has occurred because of the greater prevalence of obesity among African Americans, including children (69), and the higher risk of type 2 diabetes. Our laboratory has been highly active in this area, and a review of our findings to date is presented below.

As discussed above, some studies in children (65, 64), adolescents (70), and adults (71, 72) showed that EE is lower in African American than in white persons. Our work in African American prepubertal children showed that all components of EE (TEE, REE, and AEE) are similar in white and African American children after adjustment for body composition as measured by DXA (34). One possible explanation for inconsistent findings among studies relates to differences in maturation state, which could influence EE through its relation to changes in the quality of FFM or effects of hormones on EE. Even within a physically defined stage of maturation, there may be more subtle differences in maturation, which could be reflected by differences in hormones such as dehydroepiandrosterone-sulfate and androstenedione. However, we showed that in prepubertal children, even after adjustment for differences in these hormone concentrations and control for variations in body composition, EE components were not significantly different between white and African American children (35). In a longitudinal study of 92 white children (mean age at baseline: 8.3 y) and 64 African American children (mean age at baseline: 7.9 y), we examined how increasing Tanner stage influences the relations between REE and body composition (73). After adjustment for ethnicity, sex, FFM, and FM, REE decreased with Tanner stage. The reduction in REE was significant from Tanner stage 1 to Tanner stages 3, 4, and 5 but not to Tanner stage 2. After adjustment for age, Tanner stage, and body composition, REE was significantly higher in the white than in the African American children [≈250 kJ (60 kcal)/d]. Collectively, these data suggest that the ethnic difference in REE may emerge during puberty, possibly because of changes in the metabolic quality of FFM.

If there is a lower resting metabolic rate in African Americans, the more important questions may be *1*) Does a low metabolic rate influence the subsequent development of obesity? and *2*) What is the mechanism underlying the low metabolic rate? In a longitudinal study of 72 white children (55 girls and 17 boys) and 43 African American children (24 girls and 19 boys), initial FM was the main predictor of increasing adiposity and none of the measures of EE significantly predicted increasing adiposity in either white or African American children (74).

A more significant factor in the etiology of obesity may be the lower aerobic fitness of African American children, which, as discussed earlier, is predictive of changes in body fat during growth (74). We examined resting oxygen consumption, submaximal oxygen consumption, and maximal oxygen consumption ($\dot{V}O_2$max) in 44 African American and 31 white prepubertal children aged 5–10 y. We observed that $\dot{V}O_2$max was 15% lower in the African American children and that there were no significant differences in resting or submaximal oxygen consumption. Moreover, the lower $\dot{V}O_2$max persisted in African American children after adjustment for soft lean tissue mass and leg lean tissue mass, as measured by DXA, and after adjustment for TEE and AEE as assessed by doubly labeled water.

Although a lower level of cardiovascular fitness was observed consistently among African Americans in many other studies, the physiologic mechanism behind this observation has yet to be established. Several as yet unexamined factors could explain the lower $\dot{V}O_2$max in African American children. Although the lower aerobic capacity in African American children does not appear to be explained by leg soft lean tissue mass, it may be explained by differences in muscle fiber type. African American men were found to have a greater percentage of type 2 anaerobic fibers and a lower percentage of type 1 aerobic fibers than white men (75). Because fiber type and $\dot{V}O_2$max were shown to be significantly correlated in adults, it is possible that the lower proportion of type 1 fibers in African Americans may limit the ability of African Americans to perform continuous endurance-type activities that require a steady rate of aerobic energy transfer. Another factor involves ethnic differences in hemoglobin concentrations. When hemoglobin is low, there is a decrease in the blood's oxygen-carrying capacity and a corresponding decrease in the ability to perform even mild aerobic exercise. Pivarnik et al (68) found that, in a group of African American and white adolescent females with a mean age of 13.5 y, the African American girls had hemoglobin concentrations that were significantly lower than those of the white girls.

The implications and clinical significance of the difference in $\dot{V}O_2$max between African American and white children remain to be fully defined. Current epidemiologic data indicate that a low fitness level is a powerful precursor of mortality in adults. Moderate levels of physical fitness appear to have a protective influence against the effect of such mortality predictors as smoking, hypertension, and hypercholesterolemia (76). It is unknown whether aerobic capacity or physical activity patterns in children affect long-term health outcomes. However, it has been postulated that physical activity or fitness during childhood serves as the foundation for a lifetime of regular physical activity (77). Low $\dot{V}O_2$max is one of the few modifiable factors that we observed to predict an increase in body fat during childhood

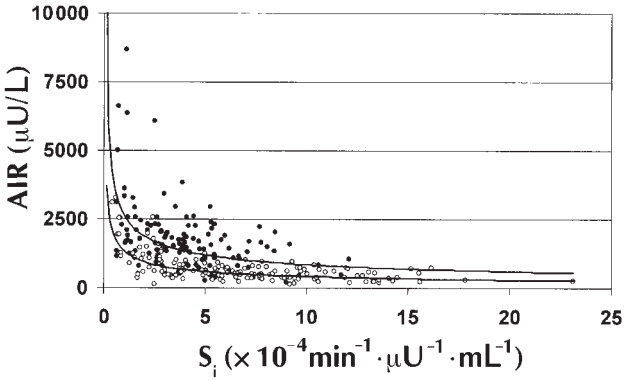

FIGURE 3. Hyperbolic relation between acute insulin response (AIR) and insulin sensitivity (S_i) in white (○; dashed line) and African American (●; solid line) children. AIR and S_i were measured in the fasted state with use of a frequently sampled intravenous-glucose-tolerance test using the Bergman minimal model technique.

growth (73). Further research is warranted both to evaluate current physical activity patterns of children of different ethnic and cultural groups and to find appropriate ways to educate and motivate children to adopt regular physical activity patterns. The long-term relation between aerobic fitness and the risk of obesity and other chronic diseases has yet to be determined, especially across different ethnic groups.

Another consistently reported finding relates to a different distribution of body fat in African American children compared with white children. Previous studies using anthropometry suggested that fat distribution differs among some ethnic groups (32, 78). Earlier studies showed that African American and Mexican American children and adults have greater skinfold thicknesses in the central region than those seen in white subjects (78). However, because most studies of ethnic differences in fat distribution were limited to skinfold data, it is unknown whether the findings represent differences in subcutaneous abdominal, intraabdominal, or visceral fat. In 101 white and African American obese and nonobese boys and girls, we found that the regression slope between visceral and subcutaneous abdominal fat was significantly lower in the African American than in the white children (0.17 ± 0.02 and 0.23 ± 0.02 cm^2 visceral fat/cm^2 subcutaneous fat, respectively) (48). Although the study was limited to a cross-sectional analysis, this finding suggests that the rate of accumulation of visceral relative to subcutaneous abdominal fat is 26% lower in African American than in white children.

Thus, the suggestion of higher levels of central fat in the ethnic groups mentioned, as indicated by skinfold-thickness measurements, is not validated by direct measurements of visceral fat, of which there is actually less accumulation in African Americans early in life. The lower measurements of visceral fat in African American children occur across the spectrum of fatness and are similar between boys and girls (48). In addition, the ethnic difference in visceral fat may be due to a differential partitioning of adipose tissue within the abdominal region, with African Americans depositing more fat subcutaneously. However, the important issue (in terms of health risk) is whether ethnicity influences the magnitude of the relations between visceral fat and the subsequent development of disease risk factors.

We studied the relation between visceral fat and risk factors for type 2 diabetes in white and African American children. In adults, the basic pathophysiology of type 2 diabetes was detailed from several longitudinal studies that showed that insulin resistance leads eventually to a failure in insulin secretion that results in full-blown type 2 diabetes (79). Thus, type 2 diabetes occurs in individuals who are unable to sustain an increased insulin secretion to compensate for the increasing insulin resistance (ie, a reduced disposition index) (80, 81). In Kahn's Banting Lecture in 1994 (79), type 2 diabetes (in adults) was summarized as a disease with a "very slow and progressive pathogenesis." This description contrasts sharply with the much more rapid progression from the prediabetic to the diabetic state in adolescent diabetes (82). In this area of research, we examined 3 questions: *1*) Are the relations between risk factors as identified in adults for type 2 diabetes and body fat evident in children? *2*) If so, are these relations explained by amounts of visceral fat? *3*) Is the higher prevalence of risk factors for type 2 diabetes (eg, higher fasting insulin and greater insulin sensitivity) in African American children explained by differences in body fat or visceral fat?

We examined differences in insulin action and secretion relative to body composition, fat distribution, physical activity, and diet in healthy lean and obese African American and white children. Insulin sensitivity, the acute insulin response, the disposition index, and glucose intolerance were assessed with use of a frequently sampled intravenous-glucose-tolerance test and minimal modeling. Body fat and lean mass were determined by using DXA, and abdominal fat distribution (visceral compared with subcutaneous) was assessed by using computed tomography. The key findings were significantly higher acute insulin responses, fasting insulin concentrations, and disposition indexes and significantly lower insulin sensitivities in African Americans (58). These differences were highly significant even after adjustment for total body fat and visceral fat and emphasized that African American children have a greater risk of type 2 diabetes at an early age, independent of level of adiposity and fat distribution. Using multiple regression analysis, we showed that obesity, visceral fat, and ethnicity conferred separate and independent health risks. Total fat tended to be related to fasting insulin, whereas visceral fat tended to be related to insulin sensitivity. However, multiple colinearity between these fat compartments made it difficult to identify whether visceral fat had any unique effects. One of the most consistent findings in our studies so far is the elevation in the acute insulin response, which was significant even when expressed relative to insulin sensitivity. These data from 146 observations in white children and 130 observations in African American children are shown in **Figure 3**, showing the hyperbolic relation described by Bergman (81), such that the acute insulin response rises sharply in response to a lower insulin sensitivity. These data in African American children show the up-regulation, or overcompensation, of the β cell to release insulin when insulin sensitivity is low.

Both cardiovascular fitness and physical activity, especially vigorous physical activity (in terms of hours per week reported by recall), were associated with insulin secretion and sensitivity in children in general (83). However, neither cardiovascular fitness nor vigorous physical activity explained the ethnic differences in insulin variables. Finally, we examined whether dietary factors explained these ethnic differences in insulin profile by examining macronutrient intakes and intakes of specific food groups from triplicate dietary recalls. None of the dietary factors we evaluated explained the significantly different variables of insulin action or secretion (84).

TABLE 3
Summary of risk factor differences in African American compared with white adults and children

Risk factor	Children	Adults	Comments
Visceral fat	Lower	Lower	Less accumulation relative to subcutaneous abdominal fat In contrast with higher central skinfolds Not necessarily related to differences in health risk
Aerobic fitness	Lower	Lower	Not explained by differences in body composition Related to insulin sensitivity but does not explain lower levels Predicts fat gain in children
Physical activity	Variable	Variable	May depend on specific population being examined and component (eg, frequency and intensity)
Energy expenditure	Similar or lower	Similar or lower	Ethnic difference may diverge during maturation Quality of fat-free mass may be important Does not necessarily explain obesity risk
Lipids	Lower triacylglycerol	Lower triacylglycerol	Partially explained by lower visceral fat Not explained by lower insulin sensitivity
Insulin sensitivity	Lower	Lower	Not explained by body fat, visceral fat, fat distribution, diet, or physical activity
Acute insulin response	Higher	Higher	Not explained by body fat, visceral fat, fat distribution, diet, or physical activity Not explained by lower insulin sensitivity Indicates overcompensation of insulin release in response to insulin sensitivity May result in long-term strain on the β-cell

The major findings in African Americans are summarized in **Table 3**, which shows that most of the differences in metabolic profile between African American and white persons are similar between children and adults. The key findings in children are that:

1) EE is not significantly different between prepubertal African American and white children.
2) Lower resting energy may evolve during puberty and may be a function of body composition, especially the metabolic quality of FFM.
3) EE does not predict increased fat gain in white and African American children.
4) Aerobic capacity is lower in African American than in white children and may be more significant than EE in the development of obesity.
5) Visceral fat is lower in African American than in white children but may not necessarily be related to the altered insulin kinetics.
6) Fasting insulin and the acute insulin response are significantly higher and insulin sensitivity is significantly lower in African American than in white prepubertal children; these differences are not explained by differences in body fat, body fat distribution, diet, or physical activity.

FUTURE CHALLENGES

In the past decade there have been tremendous advances in the field of pediatric obesity research. However, the challenges that lie ahead are probably even greater than those already overcome. As summarized in Table 2, the studies that we performed in this area generated more questions than answers. In the coming decade, the major challenges in pediatric obesity research will lie in several areas.

Treatment

What is the optimal long-term treatment regime (pharmacology versus behavioral intervention versus prevention) for overweight children and adolescents? How can treatment be tailored to meet individual needs? Should all obese children be treated, or just those at the highest risk? How do we treat children for obesity-related diseases, such as type 2 diabetes, that are normally associated with adults? Will the age of onset of heart disease be lower in the future? If so, how should this development be addressed?

Physiology

What is the underlying pathophysiology of obesity, and why does obesity affect health? What are the genetic factors that influence obesity, and how do these interact with environmental risk factors? Is the relevant physiology different at critical stages of development? What is the role of the in utero environment in the pathophysiology of obesity and long-term health risk?

Prevention

What are the most effective preventive interventions for reducing the risk of obesity and its associated health risk? Who should be targeted? What are the optimal behavior models around which to shape prevention strategies? What modifiable environmental factors should be targeted for obesity prevention? How can government, schools, industry, academia, and foundations be stimulated to work cooperatively to solve important public health issues related to pediatric obesity?

Epidemiology

What are the trends for population prevalence estimates in the United States and around the world? What will be the effect of our rapidly evolving, fast-paced society on secular trends related to physical activity, diet, and metabolic risk in children? Should obesity in children be defined on the basis of body weight indexes or on health risk factors? How should we screen children?

Cultural and ethnic disparities

Why are some subgroups of the population at greater risk of obesity and its associated health risks? What are the underlying

physiologic or environmental explanations for ethnic disparities in the epidemiology of obesity and related diseases? What is the role of acculturation in the development of obesity?

Methodology

How can we obtain more accurate and precise measures of habitual physical activity and diet? How can we obtain simple and accurate measures of body composition, fat distribution, and EE?

Modeling

How can we devise more sophisticated and comprehensive analytic models for deciphering longitudinal growth data to infer more about causation?

Other areas

In addition, more attention needs to be devoted to studying the metabolic, physical, and behavioral changes during adolescence because this period of development seems crucial in terms of obesity and health. Traditionally, puberty has been characterized simply as a period of accelerated growth and dynamic hormonal changes, but this period of transition has not been studied in great detail. Additional changes associated with puberty are likely to include rapid changes in metabolic control related to insulin action and secretion that would be expected to interact with other physiologic events and susceptibility factors to increase the risk of type 2 diabetes and coronary heart disease. It is known that there are dramatic increases in lean tissue and body fat during puberty, but the nature of changes in visceral fat and their subsequent effect on metabolic disease risk are unclear. Because physical activity and fitness have also been suggested to decrease during adolescence, the long-term effect of this decrease on muscle mass development during this period of growth should be examined carefully. It is conceivable that such developmental changes may result in an adolescent sarcopenia because of inadequate muscle development due to inactivity during growth and development. Because these rapid metabolic changes result in increased health risk during puberty and are specific to the adolescent growth period, we should not assume that the pathophysiology is similar to that observed in adults. Specific studies of adolescents are crucial; to distinguish the metabolic risks of puberty from those of adulthood, a syndrome termed the metabolic syndrome of puberty warrants further in-depth investigation. We hope to revisit progress in these research areas in more detail in another 10 y.

I thank the family of Dr Kretchmer for endowing the Kretchmer Award in memory of his outstanding contributions and leadership in the area of childhood nutrition. I am sincerely grateful to the hundreds of children and their families for generously volunteering to participate in our studies over the years. In addition, numerous mentors, colleagues, fellows, and students have contributed to this work over the past 10 y; without them, none of it would have been possible. I would also like to thank Katrina Hervey, who assisted with the preparation of the manuscript.

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