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HIGHLIGHTED TOPIC | *Biology of Physical Activity in Youth*

Genes, exercise, growth, and the sedentary, obese child

Margarita Teran-Garcia, Tuomo Rankinen, and Claude Bouchard

Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, Louisiana

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Teran-Garcia M, Rankinen T, Bouchard C. Genes, exercise, growth, and the sedentary, obese child. *J Appl Physiol* 105: 988–1001, 2008. First published June 5, 2008; doi:10.1152/japplphysiol.00070.2008.—It is still not possible to provide an evidence-based answer to the question of whether regular exercise is essential for normal growth. It is also unclear whether very low levels of exercise result in growth deficits. Regular exposure to exercise is characterized by heterogeneity in responsiveness, with most individuals experiencing improvements in fitness traits but a significant proportion showing only very minor gains. Whether a sedentary mode of life during the growing years results in a permanent deficit in cardiorespiratory fitness or a diminished ability to respond favorably to regular exercise later in life remains to be investigated. Although several genes have been associated with fitness levels or response to regular exercise, the quality of the evidence is weak mainly because studies are statistically underpowered. The special case of the obese, sedentary child is discussed, and the importance of the "energy gap" in the excess weight gain during growth is highlighted. Obese, sedentary children have high blood pressure, dyslipidemia, elevated glycemia and type 2 diabetes, hepatic steatosis, respiratory problems, orthopedic complications, and other health disorders more frequently than normal weight, physically active children. The role of genetic differences in the inclination to be sedentary or physically active is reviewed. An understanding of the true role of genetic differences and regular exercise on the growth of children will require more elaborate paradigms incorporating not only DNA sequence variants and exercise exposure but also information on nutrition, programming, and epigenetic events during fetal life and early postnatal years.

cardiorespiratory fitness; children; obesity; growth genetics

DRAMATIC CHANGES HAVE OCCURRED in developed countries over the past 50 years in the lifestyle and physical growth of children and adolescents. Their dietary habits have changed substantially, and they now consume more sweetened carbonated beverages, fruit juices with added sugars, and fast food and other convenience foods rich in fat, sugar, and salt. North American children are also generally more sedentary at any grade level as they are less likely to walk or cycle to school, and they spend several hours every day watching television, playing video games, or simply working or spending leisure time at their computers. Their participation in sports and other activities decreases as they get closer to maturity. They attain sexual maturity at an earlier age. They are also taller and heavier than before. In developed countries, children have a better chance of surviving to adulthood and are bigger than ever before.

Unfortunately, there are major drawbacks, and the overall health status of contemporary children and adolescents is not as good as it should be. Only a small minority of children have dietary habits that meet current food and nutrition guidelines. Most youth do not meet the minimal physical activity recommendation on a regular basis. The prevalence of overweight has increased about threefold in boys and girls over the past few decades in the United States. Most other developed countries have also experienced recent increases in the prevalence of childhood overweight and obesity. The sedentary, obese child used to be the exception but is rapidly becoming the norm. Along with these traits, one now sees a worsening of the risk factor profile for cardiovascular disease and Type 2 diabetes mellitus among children and adolescents. An ominous sign that the health status of today's youth is in decline is the observation that the prevalence of Type 2 diabetes is on the rise during adolescence. Nevertheless, a significant body of small-scale experimental studies has indicated that the course of this progressively worsening situation can be essentially stopped and even reversed if children consumed a healthy diet, reduced the time spent in sedentary pursuits, exercised regularly, and maintained a normal body weight. However, attempts to replicate these findings in large-scale intervention studies have generally failed.

In this review, we will focus on the role of genetic variation and exercise on the growing child. Particular attention will be devoted to the case of the sedentary, obese child. The interplay between caloric intake and energy expenditure in the etiology of the so-called "energy gap" in children will be discussed. The

Address for reprint requests and other correspondence: C. Bouchard, Pennington Biomedical Research Center, 6400 Perkins Road. Baton Rouge, LA 70808 (e-mail: bouchac@pbrc.edu).

role of genetic differences in the propensity to be sedentary or physically active will also be reviewed.

GENETICS OF FITNESS AND TRAINABILITY

Genetics and Fitness

Studies on animal models strongly support the hypothesis that there is a significant genetic component to variation in endurance performance in the untrained state. For instance, rats from 11 different inbred strains were tested for maximal running capacity on a treadmill (7). The COP rats were the lowest performers, whereas the DA rats were the best runners based on duration of the run, distance run, and vertical work performed. The heritability of aerobic endurance performance was estimated at 50% in these untrained rodents (7).

The heritability of human cardiorespiratory fitness, measured as oxygen consumption during maximal exercise ($\dot{V}O_{2max}$), has been estimated from a few family and twin studies. The intraclass correlations for monozygotic twins ranged from ~0.6 to 0.9, whereas those for dizygotic twins ranged from 0.3 to 0.5, and the heritability estimates varied between 25 and 65%. $\dot{V}O_{2max}$ in the sedentary state is characterized by a significant familial resemblance, as demonstrated by four studies (14, 56, 61, 72). The most comprehensive of these is the HERITAGE Family Study in which two cycle ergometer tests were performed on separate days on members of sedentary families of Caucasian descent (14). In the latter, an *F* ratio of 2.72 was found when comparing the between-family variance to the within-family variance for $\dot{V}O_{2max}$ in the sedentary state. Maximum likelihood estimation of familial correlations (spouse, 4 parent-offspring, and 3 sibling correlations) revealed a maximal heritability of 51% for $\dot{V}O_{2max}$ adjusted for age, sex, body mass, fat-free mass, and fat mass. However, the significant spouse correlation indicated that the genetic heritability was likely <50% (14).

Data on the heritability of physical performance phenotypes in children and adolescents have been reviewed elsewhere (16). Of particular interest here are the results of the Canada Fitness Survey (49) and the Leuven Longitudinal Twin Study (80, 81). In the Canada Fitness Survey, data on trunk flexibility, push-ups, sit-ups, and grip strength were available in 1,264 individuals from 502 nuclear families (49). Mean ages of the parents and children were 37 (SD 10) and 12 (SD 5) yr, respectively. ANOVA showed that between-family variance was 1.4–2.1 times greater than within-family variance. Maximal heritability estimates for trunk flexibility, push-ups, sit-ups, and grip strength were 64, 37, 59, and 48%, respectively. A subgroup of 834 individuals from the original Canada Fitness Survey was remeasured 7 years later for the same musculoskeletal phenotypes. The heritability estimates for the 7-yr changes in these traits were 48, 52, 41, and 32%, respectively (49).

In the Leuven Longitudinal Twin Study, vertical jump, a measure of explosive strength, and arm pull, a measure of static strength, were measured in 105 pairs of mono- and dizygotic twins (80, 81). The measurements were done annually for 8 years, starting at 10 yr of age. Autocorrelation (to quantify the degree of stability from age to age in a trait) analyses showed that both the explosive and static strength tracked well from early to late adolescence, especially when the strength phenotypes were individually aligned on age at peak height velocity (80, 81). Structural equation modeling revealed that the proportion of total variance explained by additive genetic effects ranged from 60 to 87% in boys and from 7% (apparently an outlier) to 88% in girls for vertical jump and arm pull scores.

Overall, research indicates that measures of fitness aggregate in families are affected by additive genetic effects. Genetic effects seen in children seem to remain stable throughout adolescence. However, it is also evident that nongenetic factors (including lifestyle factors shared among family members such as diet, television viewing time, and so forth) contribute in a major way to the familial resemblance observed in fitness.

Contribution of specific genes. Fitness traits are complex and multifactorial in nature. In the most recent version of the human gene map for physical performance and health-related fitness, 18 autosomal and 3 mitochondrial genes were associated with endurance phenotypes, and 14 genes (all autosomal) were associated with speed and muscle strength-related traits (85).

The majority of the genes listed in the human fitness gene map are based on only one study with positive findings. However, two genes have received more attention: angiotensin converting enzyme (*ACE*) and α-actinin 3 (*ACTN3*). Since the first report in 1997, 42 publications have reported results from association studies on exercise-related phenotypes with an insertion/deletion variant in the *ACE* locus. The I allele, which is associated with lower circulating *ACE* activity, has been reported to be more frequent in endurance athletes than in sedentary controls and to be associated with higher aerobic capacity or muscular efficiency in some but not all studies. On the other hand, some studies have reported that the D allele (associated with high circulating *ACE* levels) is associated with better performance in short-duration sprints and in strength-related tasks. Again, the results are inconclusive due to numerous negative studies (both published and unpublished) and by the almost universal lack of statistical power in the published studies.

A C/T transition in codon 577 of the *ACTN3* gene replaces an arginine residue (R577) with a premature stop codon (X577), resulting in a nonfunctional gene product. The stop codon variant is quite common in humans, with allele frequencies ranging from 10% in African populations to 50% in Caucasians and Asians. Some studies have reported that the frequency of the stop codon allele or homozygosity for the stop codon variant (X577X) is lower in sprint and strength athletes than in the general population (91, 118). In a cohort of 507 Greek school boys, those with the X577X homozygote were significantly slower in a 40-m sprint than those with homozygotes for the functional allele. However, the *ACTN3* R577X genotype was not associated with sprint time in 439 girls of the same study (74).

There is a dearth of data on the roles of *ACE* and *ACTN3* in fitness phenotypes during the growing years. What is available is equivocal and does not permit a firm conclusion regarding their contributions. This conclusion should not be surprising in light of recent recommendations for the conduct of high-quality genotype-phenotype association studies for complex human traits (24). Among the recommendations made, those on sample size, quality of the phenotype measurement, study design, adjustment for population stratification, adjustment for multiple testing, and genotyping errors are particularly relevant. Most studies dealing with fitness traits have been under-

powered to establish a definitive genotype-phenotype relationship. Since the effect of size of a given gene on fitness is generally small, the sample size necessary to achieve significance with a credible, very small *P* value is quite high. Even when a study generates a very small *P* value, the results should be interpreted with caution until replication studies can confirm the initial findings.

Genetics and Response to Exercise

Regular exercise induces several beneficial changes in organs and biological pathways that lead to better physical performance and improved health outcomes. However, it is evident that there are marked interindividual differences in physiological changes brought about by regular physical activity. The concept of heterogeneity in responsiveness to standardized exercise programs was first introduced ~25 yr ago (18). In a series of exercise training studies that we undertook with young and healthy adult volunteers, we were able to show that individual differences in training-induced changes in several physical performance and health-related fitness phenotypes are quite large, with the range between low and high responders reaching severalfold (15, 18, 19, 62, 98).

The most extensive data on the individual differences in trainability come from the HERITAGE Family Study, where healthy but sedentary subjects followed a highly standardized, well-controlled, laboratory-based endurance-training program for 20 wk. The average increase in $\dot{V}O_{2max}$ was 384 ml O_2 (SD 202). The training responses varied from no change to increases of more than 1,000 ml O_2/min (13, 17). The response distribution for $\dot{V}O_{2max}$ is depicted in Fig. 1. A similar picture emerged for training-induced changes in several other phenotypes, such as blood pressure, heart rate, stroke volume, cardiac output, plasma insulin and lipid levels, and skeletal muscle traits (20, 54, 55, 115, 116). For example, systolic and diastolic blood pressures measured during steady-state submaximal (50 W) exercise decreased, on average, by 7 and 3.5 mmHg, respectively, in response to exercise training (116). However, the responses varied from marked decreases (systolic blood pressure > 25 mmHg and diastolic blood pressure > 12 mmHg) to no changes or, in some cases, even to slight increases (17, 116). Similar heterogeneity in responsiveness to exercise training has been reported in other populations (25, 43, 51, 108). The proportion of people who do not show clinically meaningful improvements for a given trait in response to regular exercise ranges from ~10 to 40%.

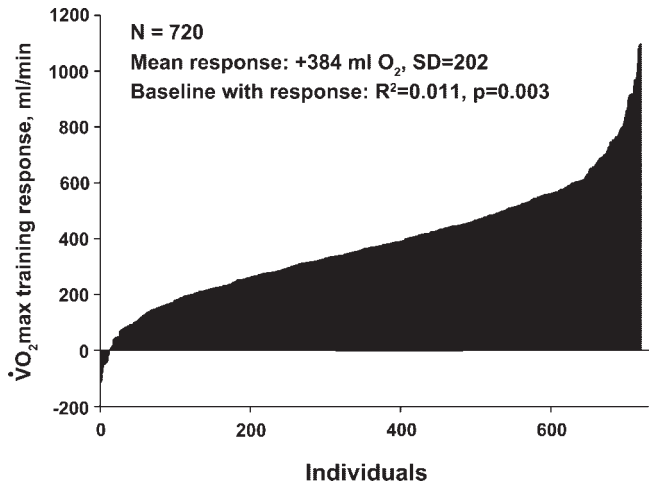

Fig. 1. Distribution of oxygen consumption during maximal exercise ($\dot{V}O_{2max}$) changes. Shown is heterogeneity in responsiveness of $\dot{V}O_{2max}$ expressed in ml O_2 gained after being trained for 20 wk with a highly standardized program. The average increase reached 384 ml O_2 (SD 202). The range of response was from about zero gain to an increase of 1,000 ml O_2 (17). Used with permission from Ref. 17.

An important issue is whether the changes observed in response to an exercise regimen correlate with one another. If they do, it would imply that some people would be high responders and others would be nonresponders for a number of physiological and metabolic pathways (84). We are able to address this question using the data of the HERITAGE Family Study, and the correlations are summarized in Table 1. The total sample of HERITAGE was divided in the two ethnic groups (Blacks and Whites), and subjects <19 yr of age were considered separately from those 20 yr and older. The training-induced changes in $\dot{V}O_{2max}$, fat mass, and plasma insulin, total cholesterol, and triglyceride levels were used for these analyses. Most correlations are small and nonsignificant. No clear differences were shown between Blacks and Whites or between younger and older subjects. One important conclusion can be reached on the basis of these correlation patterns: there is no evidence for subgroups of individuals being universal high responders or low responders to regular exercise.

The high degree of heterogeneity in responsiveness to the fully standardized exercise program of the HERITAGE Family Study was only marginally associated to baseline level, age, sex, total amount of work actually performed during the training program, and ethnic differences. However, the high and low responses to regular exercise were characterized by significant familial aggregation; i.e., there were families with mainly low responders and others in which all family members showed significant improvements. In earlier studies conducted with pairs of young adult monozygotic twins, the $\dot{V}O_{2max}$ response to standardized training programs showed six to nine times more variance between genotypes (between pairs of twins) than within genotypes (within pairs of twins) based on the findings of three independent studies (15). Thus gains in absolute $\dot{V}O_{2max}$ were much more heterogeneous between pairs of twins than within pairs of twins (Fig. 2*A*). In the HERITAGE Family Study, the increase in $\dot{V}O_{2max}$ showed 2.6 times more variance between families than within families, with the maximal heritability estimate being 47% (Fig. 2*B*) (13). Similar evidence of familial aggregation was also evident for other training response phenotypes, with heritability estimates ranging from 20 to 60% (3, 4, 86). These observations support the notion that individual variability is a normal biological phenomenon, which may in part reflect genetic diversity (17, 19).

Data on the responsiveness to exercise training in children are quite abundant, but several issues remain poorly understood. For instance, we still do not know for sure whether children of all ages are as responsive as adults to exercise programs designed to increase cardiorespiratory fitness or muscular strength or power. Although there are exceptions, most studies dealing with the training response of prepubertal children have observed that the mean increase in $\dot{V}O_{2max}$ was generally in the range of 5–10% of the baseline level (67). However, there are data suggesting that a higher training response may be elicited if children exercised at higher inten-

Table 1. *Correlation coefficients between cardiorespiratory fitness and risk factor training responses in the HERITAGE Family Study cohorts*

	Delta/Delta									
	Blacks					Whites				
	Fat mass	Insulin	Cholesterol	Triglycerides	SBP	Fat mass	Insulin	Cholesterol	Triglycerides	SBP
					Age ≤ 19 yr					
$\dot{V}O_{2max}$	0.21	−0.16	0.05	0.12	0.20	−0.02	−0.07	−0.21	−0.12	−0.00
Fat mass		0.14	0.48	0.36	0.44		−0.04	0.38*	0.12	0.05
Insulin			0.08	0.22	0.00			−0.03	−0.19	−0.02
Cholesterol				0.22	0.07				0.57‡	0.06
Triglycerides					−0.15					−0.01
					Age >19 yr					
$\dot{V}O_{2max}$	−0.02	0.12	0.04	0.04	0.10	−0.20‡	−0.02	0.01	0.01	−0.09
Fat mass		0.18	0.22*	0.16	0.05		0.10	0.12	0.09	0.06
Insulin			0.21*	0.12	0.01			0.06	0.06	0.03
Cholesterol				0.27†	0.03				0.30‡	0.04
Triglycerides					0.09					0.16†

Number of subjects: Blacks ≤ 19 yr = 24; Blacks > 19 yr = 223; Whites ≤ 19 yr = 46; Whites > 19 yr = 427. $\dot{V}O_{2max}$, O_2 consumption during maximal exercise; SBP, systolic blood pressure. Statistical significance: *$P \leq 0.01$; †$P < 0.001$; ‡$P < 0.0001$.

sity levels than would be expected based on adult studies. An early report by Massicotte and Macnab (66) provided the proof of concept evidence for the latter notion. This is a relatively understudied area that deserves more attention with an emphasis on the mechanisms that account for differences in trainability. For these studies to be properly interpreted, it will be important to take into account the scaling issue: reporting the changes as $\dot{V}O_{2max}$ per kilogram of body mass is clearly inappropriate as the trainability phenotype is confounded by the growth-associated changes in body mass. One useful design could be that proposed earlier by Weber et al. (113) in adults but used more recently by Danis et al. (29) in prepubertal boys. The design relies on pairs of monozygotic twins in which one member of each pair is exercised while the cotwin serves as a control. Although the method does not allow for a true test of the genotype-training interaction effect, it makes it possible to test for the effect of an exercise intervention against an optimal sedentary control group (perfectly matched for age, sex, and genotype). Incidentally, Danis et al. observed that 6 mo of training did not increase absolute $\dot{V}O_{2max}$ compared with the growth taking place in the control group but that it improved exercise lactate threshold.

The situation is much clearer in the postpubertal years, with the response to training being comparable to that seen in adults (67). In the HERITAGE Family Study, the age of the offspring ranged from 17 to 41 yr. We constructed two groups using the opposite ends of the age distribution: adolescents (age <20 yr) and early middle-aged (age 30–41 yr). Only one member was selected from each family for the analyses. As shown in Table 2, the well-known age-related differences in cardiorespiratory fitness, body mass, low-density lipoprotein cholesterol, and resting blood pressure were observed in the sedentary state (baseline). However, changes brought about by 20 wk of endurance training in these risk factors did not differ between the young and the older group. The only possible exception was for high-density lipoprotein cholesterol in Blacks: the older group showed a slightly greater increase than their younger counterparts (Table 2). These results suggest that there are few, if any, differences in responsiveness to exercise training between previously sedentary adolescent and early middle-aged individuals. These results are compatible with other data indicating that regular physical activity induces beneficial changes in fitness and cardiovascular and Type 2 diabetes risk factors in adolescents that are comparable to those observed in adults.

However, it is important to recognize that being physically active is not necessarily the same as being engaged in exercise training. Regular physical activity translates in a favorable fitness and risk factor profile, but exercise training leads to an even better profile. For instance, a 15 yr activity score (from 13 to 27 yr) in 83 men and 98 women of the Amsterdam Growth and Health Longitudinal Study was positively related to $\dot{V}O_{2max}$ at 27 yr (50), but the effect was relatively small. If the activity score was 30% above the group average, the magnitude of the improvement in the $\dot{V}O_{2max}$ at 27 yr was only 2%. Moreover, as in adults, training-induced health benefits are lost quite rapidly after cessation of training (23). Unfortunately, there are very few studies in which the response of children and adults to regular exercise was compared as part of the same design.

Contributions of specific genes. Two studies have observed a greater increase in left ventricular mass after exercise training in *ACE* D/D homozygotes compared with I/I homozygotes (71, 75). These results suggest that DNA sequence variation at the *ACE* locus may modify cardiovascular responsiveness to regular exercise. As for the *ACTN3* gene, X577X homozygotes showed lower baseline values but greater increases in dynamic muscle strength after 12 wk of strength training in 352 young adult Caucasian and Asian women, whereas no differences were found in training responses between the genotypes among 247 men (27). However, a strength training study in elderly men and women found exactly the opposite. In women (n = 86), the X577X homozygotes showed significantly higher baseline knee extensor concentric peak power than shown by heterozygotes and R577R homozygotes, whereas the improvements brought about by resistance training tended to be greater in the R577R homozygotes than in stop codon homozygotes (31). Thus data on the associations between the *ACTN3* R577X genotype and the changes brought about by resistance training

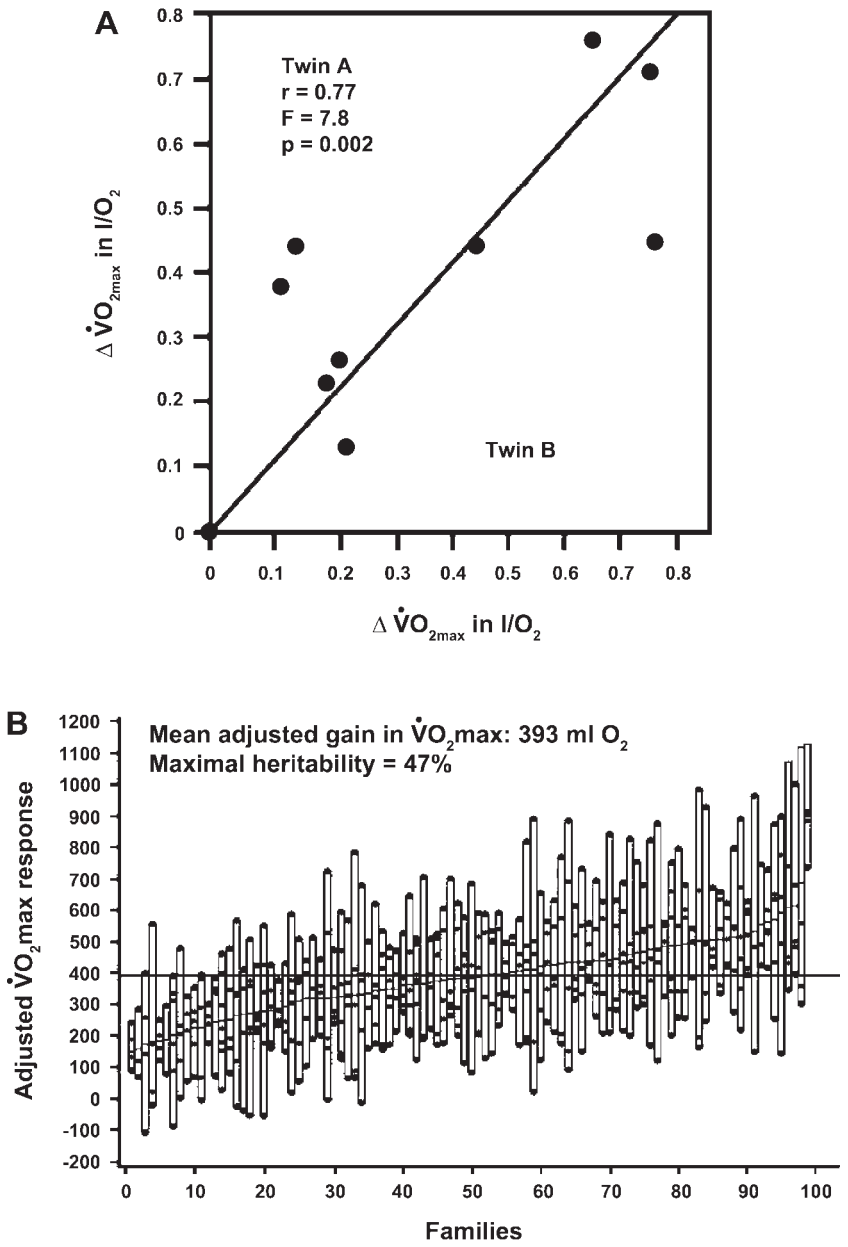

Fig. 2. *A*: training response in 10 pairs of monozygotic twins. Intrapair resemblance (intraclass coefficient) in 10 pairs of monozygotic twins for training changes is shown in liters of O_2 per min after 20 wk of standardized endurance training (15). Used with permission from Ref 15. *B*: age- and sex-adjusted response in $\dot{V}O_{2max}$ phenotype plotted against family rank (i.e., families ranked by family mean). Adjusted $\dot{V}O_{2max}$ response value for each individual was calculated as the residual from regression model plus group mean. Each family is enclosed within a bar. Dot, individual data points; solid horizontal dash, family mean. Horizontal reference line is group mean. From Ref. 13.

on muscle strength remain ambiguous. Moreover, there is a lack of information on the role of other specific genes and sequence variants on the response to regular exercise in children and adolescents.

Gene expression studies have been used to identify novel candidate genes that could subsequently become the target of more focused genetic or mechanistic studies. In such experiments, large numbers of genes covering many pathways are simultaneously assayed in a single experiment, with confirmation of differences in specific gene expression being undertaken with real-time quantitative PCR. The number of experiments published to date that are relevant to the issue of exercise is increasing, but thus far we know of no such studies dealing with growth of children. Nonetheless, useful information can be gathered from these early studies, particularly for our understanding of the genes associated with the differential ability to respond to exercise training. The first applications in humans were by Roth et al. (90), who investigated the effects of a 9-wk strength training program on the vastus lateralis gene expression profile in 20 sedentary subjects (5 young men, 5 young women, 5 older men, 5 older women). The strength training program consisted of unilateral knee extension exercises of the dominant leg. The subjects exercised three times per week, and each training session consisted of four sets of high-volume, heavy resistance knee extensions. A total of 69 genes showed >1.7-fold difference in expression levels after the training period in the pooled data. Fourteen of these genes were identified in all age-by-sex subgroups, with 12 of them showing decreased and 2 showing increased expression levels after the training program.

Subsequently, a study dealt with differences in skeletal muscle expression of more than 18,000 genes between a group of eight subjects who showed no change in insulin sensitivity and eight others who increased their insulin sensitivity by

Table 2. *Selected metabolic and cardiovascular phenotypes in the sedentary state (baseline) and their responses to a 20-week endurance training program in young and older offspring from the HERITAGE Family Study*

	Blacks			Whites		
	Young	Old	*P* Value	Young	Old	*P* Value
n	23	47	NA	44	34	NA
Age	18.2 (0.9)	36.0 (4.1)	NA	18.1 (0.8)	35.3 (3.2)	NA
Sex (male/female)	30%/70%	30%/70%	0.956	50%/50%	47%/53%	0.797
BMI	25.0 (7.3)	30.0 (5.8)	0.0027	22.0 (3.0)	26.2 (4.2)	<0.0001
$\dot{V}O_{2max}$, ml/min						
Baseline	2,143 (532)	2,085 (698)	0.022	2,731 (755)	2,491 (629)	<0.0001
Response	+319 (178)	+358 (171)	0.975	+358 (226)	+428 (184)	0.888
W_{max}, W						
Baseline	151 (40)	145 (47)	0.102	213 (59)	184 (55)	0.0003
Response	+43 (19)	+46 (25)	0.596	+48 (27)	+51 (28)	0.724
LDL cholesterol, mmol/l						
Baseline	2.46 (0.61)	2.97 (0.68)	0.0458	2.29 (0.64)	3.03 (0.85)	0.0079
Response	−0.03 (0.32)	+0.09 (0.44)	0.088	+0.08 (0.42)	−0.10 (0.36)	0.581
HDL cholesterol, mmol/l						
Baseline	1.10 (0.32)	1.02 (0.21)	0.888	1.02 (0.20)	1.02 (0.31)	0.412
Response	−0.00 (0.16)	+0.06 (0.13)	0.039	+0.04 (0.10)	+0.04 (0.15)	0.593
Triglycerides, mmol/l						
Baseline	0.94 (0.85)	1.02 (0.50)	0.768	1.02 (0.49)	1.32 (0.66)	0.522
Response	+0.04 (0.27)	−0.06 (0.38)	0.406	−0.01 (0.35)	+0.05 (0.36)	0.827
Resting SBP, mmHg						
Baseline	120 (7)	125 (15)	0.383	116 (9)	116 (9)	0.95
Response	−0.6 (4.6)	−0.9 (9)	0.638	−0.5 (6.8)	+0.7 (5.2)	0.756
Resting DBP, mmHg						
Baseline	67 (7)	76 (8)	0.0064	61 (7)	67 (7)	0.0005
Response	+0.6 (5.0)	−0.2 (5.6)	0.693	+2.3 (6.6)	+0.2 (4.4)	0.636
Insulin, pmol/l						
Baseline	75 (32)	87 (83)	0.139	70.3 (32)	56 (25)	0.015
Response	−0.4 (39)	−8.3 (22)	0.088	−3.4 (23)	−3.1 (23)	0.979
S_I						
Baseline	3.2 (2.4)	2.3 (1.9)	0.6802	4.6 (2.4)	4.4 (2.1)	0.052
Response	+0.6 (2.6)	+0.6 (2.1)	0.921	+0.1 (2.5)	+0.4 (2.6)	0.074

The younger subjects are 17–19 yr old, and older subjects are 30–40 yr old. BMI, body mass index; W_{max}, maximal work rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; DBP, diastolic blood pressure; S_I, insulin sensitivity index derived from the minimal model analysis (MINMOD units: 10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$).

~100% in response to 20 wk of endurance training (105). In this study, 703 transcripts were differentially expressed between the high and low responders before the exercise program and more than 1,100 after the program. Using a cut-off value of 40%, we found that there were 42 transcripts that were overexpressed at baseline and 240 posttraining in the high responders compared with the low responders. In contrast, 5 transcripts were downregulated at baseline and 121 posttraining in the high responders vs. the low responders. Interestingly, no differences in gene expression were observed between low and high responders for genes involved in insulin-signaling pathways, glucose transport, glycogen metabolism, glycolysis, mitochondrial biogenesis, or fatty acid oxidation. Differentially expressed genes associated with responder status included *SKI*, *FHL1*, and *TTN*. In a subsequent study, single nucleotide polymorphisms in *FHL1* were associated with changes in fasting insulin, insulin sensitivity, and disposition index (from minimal model analysis) in response to the exercise program (106).

A similar approach with a focus on genes that are differentially expressed between eight subjects who improved their $\dot{V}O_{2max}$ with 6 wk of endurance training and eight others who showed no improvement reported that over 500 genes were activated in response to the program (108). The expression of two genes (*angiopoietin 1* and *TIE2*) was particularly enhanced in skeletal muscle in response to aerobic training but only when subjects experienced an increase in aerobic capacity. In a separate experiment, the same group reported that there were 470 differentially upregulated genes when comparing muscle biopsy samples obtained from 8 sedentary subjects before and after 6 wk of aerobic training (109). This approach clearly has the potential to generate strong candidates for future genetic and perhaps epigenetic studies relevant to our understanding of the role of exercise on growth.

EXERCISE AND GROWTH

There are still many issues that have not been addressed when it comes to the relations between exercise and growth of children as reviewed in the 2004 edition of a textbook on growth, maturation, and physical activity (65). Despite recent advances, whether regular exercise is necessary for normal growth to occur cannot be addressed on the basis of solid experimental evidence.

As was reviewed elsewhere, four types of studies have been published on the issue of the role of exercise on growth of children (65). Some studies are purely correlational in nature, i.e., an indicator of exercise participation is correlated with a growth indicator. A second approach consists of comparing groups of active vs. inactive youth for growth or maturation phenotypes. As one can expect, the strength of the evidence

from these types of studies is rather weak and little can be concluded from these lines of research. A third category of studies includes longitudinal data on groups of active and less active children. This approach yields better quality data, but the findings are weakened by the fact that subjects were not randomly assigned to a group; i.e., they self-selected to be more or less active. The last approach is experimental. It requires that children be randomly assigned to an exercise or a control group. Ideally, the intervention should last for years. Needless to say, few studies meet these standards, although a growing number of them focus on body weight and adiposity.

Regular exercise has no effect on rate of growth in height and on adult stature as revealed by longitudinal observations on Dutch girls and boys and Belgian and Canadian boys (11, 69, 94). Exercise has been shown to increase bone mineral density before, during, and after puberty in a skeletal site-specific manner, as illustrated by several studies that used a variety of designs (21). Regular physical activity that incorporates bone-loading activities can also enhance bone mineral density (28). The response of long bones to exercise during growth appears to be variable according to maturity status and between boys and girls. Despite a large body of data, it is still not clear whether there is a specific critical period during the growing years when bones may be most responsive to exercise, including resistance exercise (28). As a matter of fact, several studies suggest that exercise may be beneficial for bone mineral accrual throughout the growth period (21). However, there is also some evidence for a role of DNA sequence variation in the estrogen receptor α (*ESR1*) gene on the response of bone mineral density to regular exercise in growing girls (104). Other markers in the *vitamin D receptor* and *IL-6* genes have also been associated with bone area changes in response to exercise regimen (12).

Regular exercise increases muscle mass and volume. In a randomized study of 20 normal-weight girls who exercised 5 days a week for 5 wk and 20 controls (overall: 9.1 yr old, SD 0.1), total energy expenditure was 17% higher in the exercising girls and thigh muscle volume measured by MRI was increased by 4.3% (33). From a number of studies reviewed elsewhere (65), it appears that strength or resistance exercise training leads to muscle strength and muscle mass increases at all ages during growth. However, the net gains caused by the training program over the changes expected due to growth alone tend to be small during the years preceding puberty. Of importance here is the fact that all of the studies are of short duration. Whether years of exposure to strength or resistance exercise training have larger effects on muscle performance and muscle mass or muscle physiology before, during, or after puberty is unknown. It is also not clear whether the present level of inactivity of large segments of children and adolescent populations will result in diminished skeletal muscle development and muscle functions.

Regular exercise is also associated with higher $\dot{V}O_{2max}$ during childhood and adolescence (33, 50, 70) but particularly after puberty, as reviewed above. In contrast, sedentary children and adolescents have been shown to have lower cardiorespiratory fitness. Whether a sustained sedentary mode of life during the growing years will result in a permanent deficit in cardiorespiratory fitness or a diminished ability to respond favorably to regular exercise later in life remains to be investigated.

One important question that has not yet been satisfactorily answered is that of the role of regular exercise on biological maturation. It is an extremely complex one that cannot be fully addressed by observational studies. On the basis of comparisons of groups of active and less active boys followed from 13 to 18 yr of age, exercise does not affect skeletal maturity (10). In boys, age at peak height velocity is not influenced by levels of habitual physical activity, but there are no comparable data for girls (65). The evidence is more complex and heterogeneous for sexual maturation. Most of the evidence is on girls and focuses on age at menarche, a late pubertal event. Regular exercise defined as sport participation does not appear to affect the timing and sequence of pubertal events in either sex. However, in girls, there is suggestive evidence of a delayed sexual maturation in a significant fraction of those who engage in highly competitive gymnastics and to a lesser degree in dancers and runners (88). This trend is not seen in girls competing in other sports such as swimming, tennis, speed skating, and others. For instance, competitive gymnasts experience in large numbers a later age at menarche, menstrual irregularity, and a depressed peak height velocity. Although the causes of these effects on sexual maturation are still a matter of debate, intensity and volume of training and caloric restriction are commonly incriminated. However, one cannot rule out that a strong selection bias may contribute to these observations. For instance, it may be advantageous to have early morphological traits that favor performance in these competitive activities or a genotype that drives a slower rate of sexual maturation. In contrast, boys who excel in competitive sports tend to exhibit advanced skeletal and sexual maturity (64).

Overall, it is still not possible to provide an evidence-based answer to the question of whether regular exercise is essential for normal growth to occur. It is obviously a very complex issue that cannot be solely addressed with studies conducted on growing boys and girls. We are of the view that animal experimentation is an absolute necessity in this case if we are ever going to be in a position to investigate not only standard indicators of growth but also metabolic markers, biochemical pathways, and molecular composition in growth and exercise-sensitive tissues. The lessons from such studies could then be taken for further testing in the more constrained setting of short-term experimental trials conducted in growing boys and girls. The topic is of critical importance when one considers the potential impact of low rates of energy expenditure and associated sedentary time on metabolism and risk for common chronic diseases such as Type 2 diabetes and cardiovascular diseases (42).

THE SEDENTARY, OBESE CHILD

Presently, ~17% of children and adolescents in the United States are overweight or obese, and the prevalence of excess weight during the growing years continues to rise (76). The prevalence of excess weight in pediatric populations is actually much higher if other methods of assessment are used (58). Likewise, children and adolescents appear to spend an increasing amount of their discretionary time in sedentary activities such as watching television, surfing the Web, playing video games, and engaging in other computer-based pursuits (79). This is clearly not compensated by more participation in sports

and fitness activities. The general trend is therefore for a growing proportion of children to become sedentary and obese.

It should be obvious from a large body of data that the combination of sedentariness with obesity is particularly deleterious from a metabolic point of view. On the basis of our present understanding, it seems as if the cardiovascular and endocrine systems are the most affected by the dyad of inactivity and obesity, although all organs and systems are likely to be affected. In this regard, the increasing frequency of insulin resistance, metabolic syndrome, and Type 2 diabetes among sedentary, obese children and adolescents plus the growing incidence of nonalcoholic hepatic steatosis and steatohepatitis in these populations represent ominous signs (87, 96).

Obese, sedentary children and adolescents exhibit more frequently than others hypertension, dyslipidemia, and markers of atherosclerosis (2, 9). High blood pressure is present in 20–30% of 5- to 11-yr-old overweight children (34), and overweight children and adolescents are more likely to be hypertensive as young adults (77). Hypertension in childhood may cause end-organ damage (e.g., left ventricular hypertrophy) and predispose children to early atherosclerosis development and higher occurrence of cardiovascular complications during adulthood (40). Intima media thickness, measured by ultrasound of the carotid arteries or aorta, has been used as a surrogate marker of atherosclerosis because it correlates with the severity of coronary artery disease. Increased intima media thickness has been demonstrated in obese children (38, 95).

Type 2 diabetes accounts for a growing percentage of new childhood diabetic cases. Besides an increased risk for diabetes among sedentary, obese children, other endocrine/metabolic diseases include gout, very early sexual maturation, hyperandrogenism, and polycystic ovary syndrome (2).

Orthopedic complications related to being overweight or obese during childhood are manifested as increased incidences of Blount disease, acute fractures, spinal complications (back pain and scoliosis), and slipped capital femoral epiphysis (82, 114). Blount disease is a skeletal disorder that takes place as a mechanical response to unequal or early weight bearing when genu varum is at its peak, causing undue stress on the medial tibial condyle. Obesity can overload the proximal tibial epiphysis, potentially resulting in abnormal and slowed growth of this physeal segment and producing a progressive varus deformity of the tibia (bowed legs and tibial torsion). This may result in a poor walking pattern, abnormal joint loading, pain, and instability. In the long term, it may predispose the knee to premature degeneration (82). A higher fracture incidence is observed in children at the time of the pubertal growth spurt, and obesity can increase this risk. An imbalance between body weight and bone mass increases stress on growing bones and joints, which may result in joint damage and may contribute to higher risk of developing osteoarthritis in adulthood (114).

Gastroenterological problems related to obesity include nonalcoholic steatohepatitis or NASH (96), constipation (78), gastroesophageal reflux, diverticulitis, and gallbladder disease (47). Ten percent to 30% of obese children have elevated liver aminotransferases, suggesting obesity-related steatosis (96). A recent report confirmed the suspected higher prevalence of gallbladder disease in obese children and adolescents (47).

Obesity-related respiratory problems include asthma, hypoventilation syndrome, obstructive sleep apnea (OSA), which are potentially life threatening, and sleep-disordered breathing (SDB). A link between childhood asthma and obesity has been proposed, but the data are still inconclusive (30). The risk of having OSA increases by 12% per unit of increment (1 kg/m^2) of body mass index (30). OSA in children is associated with an increased left ventricular mass index, which in adults is a strong predictor of coronary heart disease, stroke, and sudden death (39, 119). However, the long-term relationship between childhood obesity, OSA, and future coronary heart disease events has not yet been established. SDB represents a spectrum of sleep disturbances in children ranging from primary snoring to OSA. Children with SDB also display hyperactivity, increased aggression, irritability, emotional instability, and somatic complaints (30, 89).

Finally, one needs to recognize that psychological and behavioral problems associated with childhood obesity include poor self-esteem, withdrawal from interaction with peers, depression, anxiety, and feelings of chronic rejection (5).

THE ENERGY GAP IN CHILDHOOD OBESITY

Using NHANES and CARDIA study data, it has been estimated that the average weight gain over time in adults can be accounted for by an energy imbalance of ~100 kcal/day (44). The latter value has generated confusion because it has been erroneously interpreted by many to mean that the difference in daily energy intake between normal-weight people and obese individuals was of the order of 100 kcal/day. The difference is obviously much larger. The energy imbalance is also known as the "energy gap" and is defined here as the difference in the amount of calories consumed or expended between normal weight individuals and overweight or obese persons at various levels of excess weight but when weight stability is present. Estimating the energy gap under weight-stability conditions requires that a few key principles be considered. First, not all of the excess calories consumed are recovered as energy stored in the body, and a conversion fraction of 65% is often used. Second, there is a continuous increase in total energy expenditure associated with the gain in body mass, which translates into higher resting metabolic rates that need to be incorporated in the computation of the energy gap. Third, as people become bigger, they expend more calories to move around, even for fidgeting or spontaneous activities. Fourth, when dealing with the energy gap in growing children or adolescents, the energy cost of growth needs to be taken into account.

In one report that incorporated all of the above, it was observed that the energy gap was of the order of 120 kcal when the excess weight was 2 kg after 10 yr of growth and ~230 kcal for an excess weight of 4 kg (112). However, the energy gap went up very dramatically in those who became overweight or obese, attaining values of 700–1,000 kcal/day. As predicted, the energy imbalance was estimated to be quite low in the early phase of weight gain but became much larger in the latter years of the weight gain among those who became overweight children.

When dealing with the sedentary, obese child, we need to appreciate that we are not dealing with a daily energy imbalance of the order of 100 kcal compared with normal-weight children. Rather, the magnitude of the energy gap is likely to be almost 10 times larger, and we should therefore not be surprised by the very modest success achieved by the short-term

treatment modalities based on voluntary changes in dietary and physical activity behavior.

GENETICS OF PHYSICAL ACTIVITY LEVEL

Research on the level of physical activity as a behavior has mainly focused on psychological, social, and environmental factors. The biological basis of physical activity has only recently become a topic of interest (92, 107).

Studies on the genetics of physical activity level are not extensive, but evidence from both twin and family studies suggests that genetic factors could be involved in the determination of physical activity level. Several twin studies have addressed this issue, and the findings are summarized in Table 3. The largest twin study targeting physical activity as a main outcome measure included 13,676 monozygotic and 23,375 dizygotic pairs of 19- to 40-yr-old twins from six European countries and from Australia. The individuals were classified as physically active if they reported at least 60 min of exercise or activities per week with a minimum intensity of four metabolic equivalents. Maximal heritabilities ranged from 48 to 70% with no significant differences between men and women, except in Norwegian twins (men 28%, women 56%) (102). These estimates are in line with the results of other studies based on much smaller numbers of twin pairs (Table 3).

Observations from family studies agree with findings of the twin studies. In the Framingham Children's Study (73), physically active fathers or physically active mothers were more likely to have active offspring than inactive fathers or mothers. When both parents were active, the children were 5.8 times more likely to be active than children of two inactive parents. These results are thus compatible with the notion that genetic or other factors transmitted across generations predispose a child to be active or inactive. In the Québec Family Study, maximal heritabilities derived from the maximum likelihood estimates of familial correlations reached 25%, 16%, and 19% for the degree of inactivity, time spent in moderate to strenuous physical activities, and total level of physical activity, respectively (99). In 1,030 Hispanic children (average age 11.0 yr) from 319 families, the maximal heritabilities for total physical activity, sedentary activity, and light and moderate activities varied from 46% to 57%. Furthermore, a genome-wide linkage analysis revealed a quantitative trait locus (QTL) on chromosome 18q with logarithm of odds scores of 4.07, 2.79, 2.28, and 2.2 for sedentary, light, total, and moderate activities, respectively (22). Interestingly, a recent study conducted on inbred strains of mice differing in spontaneous levels of activity identified four significant QTLs and 14 suggestive QTLs for spontaneous activity (57). Three of these QTLs accounted each

Table 3. *Summary of the intraclass correlations from twin studies for physical activity-level phenotypes*

Source	Physical Activity Trait	Age, yr	Sex	Number of Pairs		Correlation Coefficients	
				MZ	DZ	MZ	DZ
Kaprio et al. (48)	Total physical activity	>18	Male	1,537	3,507	0.57	0.26
Koopmans et al. (52)	Sports participation	18–22	Male	249	241	0.89	0.60
			Female	329	303	0.85	0.72
Aarnio et al. (1)	Leisure-time physical activity outside the school	16	Male	147	191	0.72	0.45
		16	Female	231	179	0.64	0.41
Lauderdale et al. (53)	Intermittent moderate activities	33–51	Male	1,006	530	0.38	0.12
	Jogging/running (>10 miles/wk)					0.53	0.07
	Strenuous racquet sports (>5 h/wk)					0.52	0.28
	Bicycling (>50 miles/wk)					0.58	0.14
	Swimming (>2 miles/wk)					0.39	0.35
Beunen and Thomis (10)	Sports participation	15	Male	17	19	0.66	0.62
			Female	17	19	0.98	0.71
Maia et al. (63)	Sports participation index	12–25	Male	85	68	0.82	0.46
			Female	118	85	0.90	0.53
	Leisure-time physical activity		Male	85	68	0.69	0.22
			Female	118	85	0.72	0.56
Stubbe et al. (102)	Sports participation	13–14	Male	115	87	0.88	0.82
		15–16	Male	136	112	0.80	0.68
		17–18	Male	100	96	0.88	0.65
		19–20	Male	92	82	0.86	0.35
		13–14	Female	161	109	0.87	0.84
		15–16	Female	185	115	0.83	0.81
		17–18	Female	148	113	0.80	0.68
		19–20	Female	158	97	0.83	0.53
Franks et al. (36)	Physical activity index	4–10	Mixed[a]	62	38	0.78	0.80
	Physical activity energy expenditure	4–10	Mixed[a]	62	38	0.87	0.76
Joosen et al. (46)	Physical activity (accelerometer)	18–39	Mixed	12	8	0.88	0.42
	Activity-induced energy expenditure	18–39	Mixed	12	8	0.82	0.64
Stubbe et al. (103)	Physical activity	19–40	Males	5,668	7,945	0.59	0.32
		19–40	Females	8,008	9,395	0.58	0.29
McGue et al. (68)	Self-rated ability on athletic competition	27–80	Male	226	202	0.50[b]	0.26[b]
		27–86	Female	452	345		
McGuire et al. (69)	Perceived athletic self-competence	10–18	Male	45	49	0.58[b]	0.23[b]
		10–18	Female	47	48		

[a]55% and 50% males in monozygotic (MZ) and dizygotic (DZ) twins, respectively; [b]coefficients adjusted for sex.

for ~6% of the variance in activity level, whereas the fourth QTL explained at least 11%.

Data on molecular markers of physical activity phenotypes in humans are still scarce. In brief, the candidate genes with positive findings reported so far include *dopamine D_2 receptor*, *ACE*, *leptin receptor*, *melanocortin 4 receptor*, *calcium-sensing receptor*, and *aromatase* (*CYP19A1*). The first four genes were investigated with an a priori hypothesis on the association between physical activity and DNA sequence variation (59, 100, 101, 117). In the other studies, activity was treated as a covariate in association analyses whose true focus was on other traits such as bone mineral density (60, 93). None of the studies reported to date meet the requirements for a convincing demonstration of an association between a genotype and a phenotype as defined in a previous section of this paper.

This is an area that clearly deserves further research. The question is of considerable significance. Why are there so many children and adolescents opting spontaneously for a sedentary mode of life? Why are there so few of them engaging regularly in strenuous exercise? Why do we find so often a small subset of adolescents who seem to enjoy participating in a whole array of demanding sports and exercise?

EXERCISE, PROGRAMMING, AND EPIGENETICS

Events occurring during gametogenesis, fertilization, and fetal life have begun to receive serious attention for their potential contributions to postnatal biological and behavioral determinants of health and disease. For instance, a low birth weight, a surrogate marker of insufficient maternal nutrition, has been associated with childhood and adulthood obesity as well as type 2 diabetes (8, 41). In a recent study, it was shown that maternal hyperglycemia during pregnancy was associated with an increased risk of obesity in 5- to 7-yr-old offspring (45). The relationship was also observed in Caucasians and in other ethnic groups.

The role of exercise of the pregnant mother on fetal and postnatal outcomes has received some attention. Exercise in the pregnant mother has been reported to modify the delivery of oxygen and substrate to the maternal-fetal interphase, thereby affecting both placental and fetal growth (26). In physically active mothers, oxygen and substrate delivery to the maternal-fetal interphase may decrease up to 50% during acute exercise but may increase significantly at rest and during average everyday activities. Regular exercise in early and midpregnancy seems to stimulate placental growth (26). On the other hand, regular moderate-intensity weight-bearing exercise has been reported to be associated with greater birth weights, whereas babies of mothers who are engaged in vigorous activities during the second half of pregnancy seem to have lower birth weights due to lower fat mass, although they have fat-free mass and crown-to-heel length similar to that shown in babies of moderately active mothers (26).

Little is known about the role of maternal nutritional deficiencies on the physiological fitness of the fetus and the newborn child. Interestingly, a recent study showed that Wistar rat offspring of mothers who were undernourished during pregnancy but adequately nourished after birth had a diminished locomotor activity level shortly after birth that persisted later in postnatal life (14 mo) compared with rats born from mothers who were fed ad libitum during pregnancy (111).

Some of the preceding observations may be explained by biological programming of the fetus with lasting biological and behavioral consequences throughout postnatal life. However, a growing body of data suggests that epigenetic events could also be implicated by altering gene expression modulating a phenotype or creating a predisposition over and above that inscribed in the DNA sequence of genes. Methylation of DNA and chemical alterations of nucleoproteins may potentially have relevance for obesity, fitness, or trainability, but the data are almost nonexistent at this time. Epigenetic modifications may provide a new path toward the understanding of some of the variance unaccounted for in classical genetic studies. Indeed, epigenetic differences arising during the lifetime of an individual could be of particular interest when it comes to accounting for differences to standardized protocols or for discordance in phenotypes between brothers or sisters identical by descent. A proof of concept for this notion was provided in an experiment performed on 40 pairs of monozygotic twins. It was observed that the patterns of epigenetic modifications were more divergent in older twins than in infant twin pairs (35). With the use of a combination of whole genome and locus-specific methods, it was found that about one-third of monozygotic pairs harbored epigenetic differences between siblings in DNA methylation and histone modification, which had an impact on gene expression. The full implications of these observations for fitness and the risk of diseases remain to be understood.

CONCLUSIONS

There is a clear consensus that youth of developed countries, particularly the United States, are experiencing unprecedented levels of excess weight. It also appears that the same may be true for physical inactivity, as recently reported from the accelerometer data of the National Health and Nutritional Examination Survey 2003–2004 cross-sectional sample (110). In the latter case, it was shown that 42% of children, 6–11 yr of age, but only 6% of adolescents met the recommended level of 60 min/day of physical activity. Of interest also was the observation that only 5% of adults achieved 30 min of daily physical activity as recommended. This pattern of behavior combined with the present food environment is setting the stage for a dual epidemic of obesity and sedentariness among children and adolescents. The more time that children spend in sedentary activities, the less fit they are (79).

The obese, sedentary child may one day be the norm at various stages of the growth period. One can already make predictions based on accumulated evidence on children presently affected by this unhealthy profile. Children will be less fit and will show early signs of metabolic dysregulation, ectopic fat deposition, and worsening of the risk profile for type 2 diabetes and cardiovascular disease. Genetic studies have taught us that some children who are particularly susceptible may present with overt manifestations of these diseases even during their growing years. A number of those with inherited resistance to metabolic imbalance even when obese and sedentary may be able to delay these adverse outcomes for many years. However, if obesity and physical inactivity persist, diabetes and cardiovascular disease will eventually strike a large fraction of these individuals later in adulthood.

Changing the situation will be a major challenge for two reasons. First, both excess adiposity and the propensity to be physically inactive are influenced by a number of genes that are still poorly understood but whose global influence appears to be rather strong. For instance, the recently identified sequence variants in the *FTO* gene increase the risk of excess weight in children and adults (37, 97). Thus the risk of obesity increases by 30% for each risk allele. Although the homozygotes for the risk allele weigh only 3–4 kg more on average, it is only the mean effect, and the population-attributable risk of the *FTO* sequence variants for obesity is estimated to be ~20% (32, 37). Interestingly, two studies revealed that the genetic susceptibility engendered by two *FTO* risk alleles was suppressed if the homozygotes were physically active (6, 83). Second, our present social and built environment is strongly obesogenic and favors a sedentary lifestyle. Thus there are powerful biological and environmental forces opposing attempts to regulate body weight at a lower level and to adopt and maintain a physically active lifestyle. Although we are all convinced that regular physical activity, a healthy and nutrient-rich diet, and a normal body weight should be the cardinal features of all growing children, population data reveal that we are presently moving in the opposite direction on all three fronts. Thus it is quite possible that the obese, sedentary child will become the norm in a not too distant future. The consequences for the health of future generations and the health care budgets of nations are likely to be disastrous.

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