

## REVIEW ARTICLE

# Aerobic fitness, fatness and the metabolic syndrome in children and adolescents

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## Abstract

The paediatric obesity epidemic is well documented. Recently, there has also been the emergence of type 2 diabetes and the metabolic syndrome (MetS) among children and adolescents. Although it is well known that obesity is linked to the metabolic syndrome in youth, the role of physical activity and fitness on the metabolic syndrome is unclear. The purpose of this review was to examine the concepts of and associations between fitness, fatness and the MetS in children and adolescents. In general, the association between fatness and the MetS (or components of the MetS) is stronger than those for fitness. Furthermore, the correlation between fatness and the MetS remains significant after controlling for fitness, whereas the correlation between fitness and MetS does not remain significant after controlling for fatness. When subjects are cross-tabulated into categories (fat-fit, etc.), there is good evidence that fitness attenuates the MetS score among fat children and adolescents. The reasons for these observations possibly involve genetics, adipocytokines and mitochondrial function. Further study is needed to understand the role of physical activity and other environmental factors on this phenomena. In addition, longitudinal studies of the fat-fit phenotype are required and should include measurements of the hormonal milieu, adipokines and the oxidative capacity of skeletal muscle during childhood and adolescence.

## INTRODUCTION

The number of key position and review papers on the topic of obesity and cardiovascular and metabolic risk factors (1–8) identifies the magnitude, and significance, of this health problem in contemporary society. In spite of the widely recognized magnitude of these conditions, there is a gap in our understanding of the genetic and environmental factors associated with the metabolic syndrome (MetS) during adolescence. Several recent reviews have provided an overview of the epidemiology and pathogenesis of the MetS in children and adolescents (5,9–13). In this review paper, the focus is on the relationships between fitness, fatness and MetS phenotypes among children and adolescents. First, the constructs of fitness, fatness and the MetS will be operationally defined. Second, the univariate associations between fitness,

fatness and the MetS among children and adolescents will be reviewed. Next, a historical perspective of the 'fat but fit' hypothesis will be presented prior to summarizing four studies from my research group that examine the combined influence of fitness and fatness on the MetS in children and adolescents. The paper concludes with a discussion of some potential mechanisms explaining why we observe the independent and combined associations between fitness, fatness and the MetS.

## OPERATIONAL DEFINITIONS OF FITNESS, FATNESS AND THE METABOLIC SYNDROME

### Fitness

When the term fitness is used in the exercise science community, it is commonly accepted that it is being referred to as health-related physical fitness. However, it is important to understand that health-related physical fitness is not a unitary concept but rather consists of several individual components (muscular, cardiorespiratory, motor,

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metabolic, morphological) which consist of subcomponents (e.g., metabolic fitness includes glucose metabolism, lipid profile, fuel utilization, etc.) (14). Typically, when studies report the association between fitness and cardiovascular disease (CVD) risk factors, the term fitness refers to aerobic fitness and often maximal aerobic power or maximal oxygen consumption (VO<sub>2</sub>max). It is also important to note that aerobic fitness is not synonymous with habitual physical activity. Physical activity is a behaviour defined as any bodily movement produced by skeletal muscles that results in substantial increase in energy expenditure over resting energy expenditure, whereas aerobic fitness is a physiologic trait.

Maximal or peak VO<sub>2</sub> can be measured in the laboratory by indirect calorimetry during a graded treadmill or cycle ergometry test or predicted from submaximal (physical working capacity at heart rate of 170 (PWC<sub>170</sub>)) or field tests (20-m shuttle run or 1.6 km run). VO<sub>2</sub>max can be defined as the maximal ability of an organism to take up, deliver and utilize oxygen to produce energy via aerobic metabolism. This process occurs via the flow of oxygen through a series of conductors and resistors until it reaches its final destination—the oxygen sink—the mitochondrion (15). The link between aerobic fitness and MetS and the mitochondrion will be considered later in this paper.

### Fatness

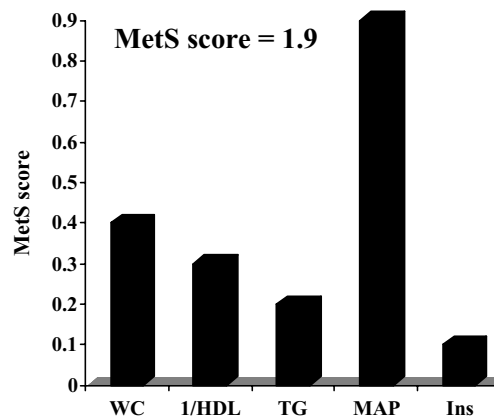
Body fatness is a construct that is more easily agreed upon and is generally regarded as an expression of adipose tissue mass at the whole-body or regional level. This latter expression is important in the context of this paper given the central role of visceral adiposity on the MetS. At the cellular level, the role of the adipocyte on the pathogenesis of the MetS will be discussed later in the paper.

Body fatness can be measured by a wide range of methodologies including sophisticated imaging techniques (dual X-ray absorptiometry, magnetic resonance imaging) to simple anthropometric techniques. The simplest of anthropometric techniques, the measurement of stature and body mass, can be used to calculate the body mass index (BMI), which is often used in clinical practice and epidemiological studies to classify individuals into normal weight, overweight or obese categories. In this paper, the terms overweight and obesity are being used to represent the upper two categories of weight status (as opposed to the Center's for Disease Control terminology of 'at risk of overweight' and 'overweight').

### Metabolic syndrome

Recently, we have seen the emergence of the MetS among children and adolescents (16,17). The MetS is generally considered as the clustering or co-occurrence of biomarkers associated with atherosclerotic and insulin resistance, namely elevated levels of abdominal adiposity, blood pressure, triglycerides and glucose, and a low level of high-density lipoprotein-cholesterol (18).

Since few (4–6%) youth possess the MetS (16,17,19) and there is no universal definition of the MetS, we (20–23) and others (24) have used a continuous (rather than dichoto-



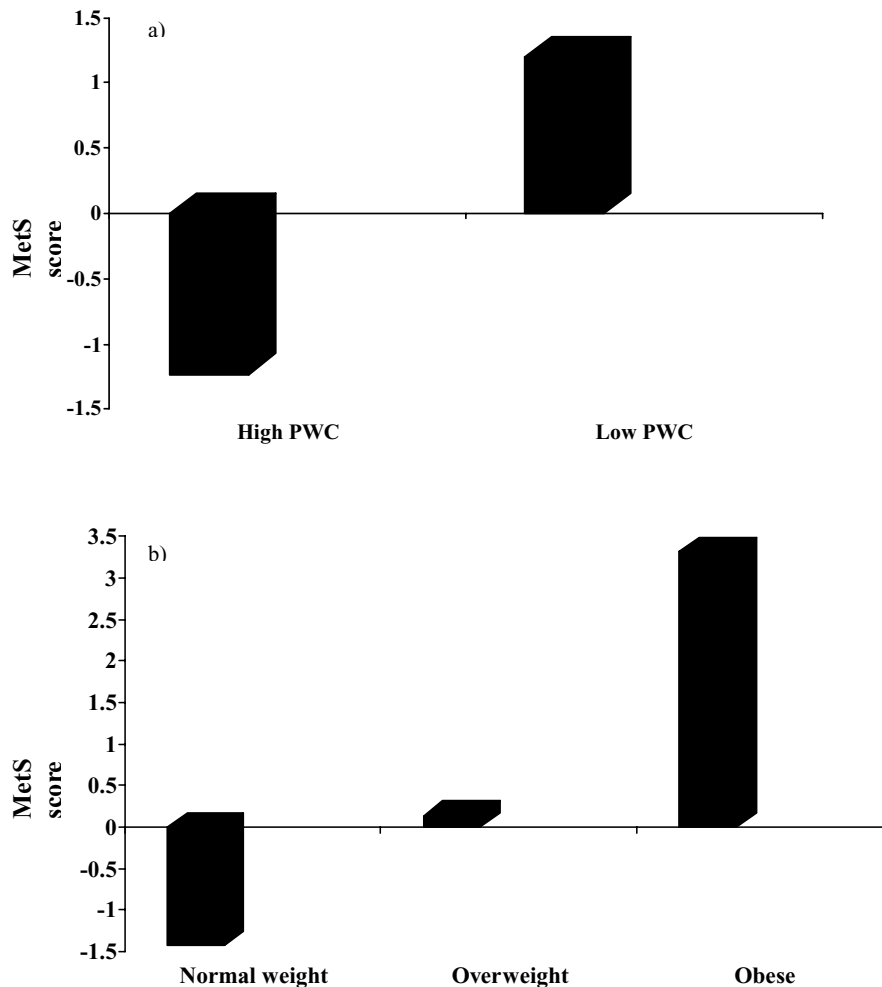
**Figure 1** An example of the calculation of the metabolic syndrome score based on the sum of age- and sex-adjusted standardized residuals for waist circumference (WC), high density lipoprotein-cholesterol (HDL-C), triglycerides (TG), mean arterial pressure (MAP) and insulin (Ins).

mous) MetS score. In general, the score is calculated as the sum of residuals (or z-scores or standard deviation scores) from selected components of the MetS. A lower score is indicative of a better profile and a higher score is worse. Figure 1 shows an example of the individual components of the MetS score which is equal to 1.9. Here, the subject possessed a higher WC, TG, mean arterial pressure and insulin and lower HDL-C compared to others in the sample. A limitation of the MetS score is that it is specific to the sample from which it was derived.

### WHAT ARE THE UNIVARIATE RELATIONSHIPS BETWEEN AEROBIC FITNESS, FATNESS AND CVD RISK FACTORS/METS IN CHILDREN AND ADOLESCENTS?

Several excellent reviews have summarized the associations between fitness, fatness and CVD risk factors (4,5,25). In general, the correlations between aerobic fitness ( $r < 0.30$ ), adiposity ( $r < 0.40$ ) and CVD risk factors are low-to-moderate among samples of children and adolescents that are not restricted to obese subjects. As an example, the correlations between fitness, fatness, and CVD risk factors among 12-year-old boys from the Northern Ireland Young Hearts Study ranged from 0.01 to 0.16 for fitness and 0.12 to 0.26 for fatness (26). To my knowledge, no published study has examined the associations between fitness, fatness and MetS score in children or adolescents. We have found a correlation of 0.44 for fitness and 0.52 for fatness in a sample of 7- to 9-year-old children (Eisenmann, unpublished data). These results indicate that fatness shows stronger associations with components of the MetS and the MetS score than fitness. In addition, it appears that the correlations with the MetS score are stronger than for individual CVD risk factors.

Another approach that has been taken to examine the association between fitness or fatness and CVD risk factors is to categorize subjects into groups (median split, tertiles, quartiles, or by clinically relevant cutpoints—normal weight, overweight, obese). In general, the results show significant



**Figure 2** Differences in the metabolic syndrome score of 7- to 9-year-old subjects group by (a) low and high aerobic fitness and (b) normal weight, overweight and obese status.

differences in CVD risk factors at the extremes (i.e., least vs. most fit or normal vs. overweight/obese). For example, using our data of 7- to 9-year-olds we show significant differences in the MetS by PWC and across BMI categories (Fig. 2). The latter finding is also supported by the prevalence of the MetS phenotype between normal weight (0.1%), overweight (6.8%), obese (28.7%) 12- to 19-year-old adolescents participating in NHANES III (16).

An important statistical consideration for the correlation between fatness and metabolic syndrome is the fact that waist circumference is included in the definition of metabolic syndrome. However, in our studies the relationships hold when waist circumference is removed from the metabolic syndrome score as well. Another very important point related to the above findings is that there is significant collinearity between fatness and fitness. In other words, the obese are the unfit, therefore the above findings represent a common phenomena. This is a good point, but when one examines the association between aerobic fitness and fatness the correlation generally ranges from 0.40 to 0.60 (26–29). Using a correlation of 0.50, this means that the shared

variance is only 25%. Thus, considerable heterogeneity in aerobic fitness exists within fatness categories.

#### THE IDEA OF 'FAT BUT FIT': THE PIONEERING WORK OF DR. STEVE BLAIR

The observation that some obese individuals possess good aerobic fitness was first explored in the context of disease risk in 1995 (30). The authors used the approach of cross-tabulating subjects into distinct fatness and fitness categories and calculated disease risk among the groups. Since the original publication, Blair and colleagues have repeatedly shown that within a fatness category, aerobic fitness attenuates the risk of disease (31–33). In a recent study specific to the MetS, the greatest MetS score was found in the low fitness-obese category and the lowest score was found in the high fitness-normal weight group. Within levels of fatness, risk for significant elevations in the MetS score was lower for the higher fitness groups (34).

**Table 1** Summary of studies examining combined influence of fatness and fitness on metabolic syndrome score in children and adolescents

| Study  | Subjects  | Fatness | Fitness                  | Categorization                           | Metabolic syndrome score          |
|--|---|---------|--------------------------|--|-----------------------------------|
| Quebec Family Study (QFS)                      | 8–18 years<br>378 boys<br>358 girls             | BMI     | PWC 150                  | Median split                             | TC:HDL, HDL, LDL, TG, GLU and MAP |
| Aerobics Center Longitudinal Study (ACLS)      | 8–18 years<br>296 boys<br>188 girls             | BMI     | TM time to exhaustion    | Median split                             | WC, HDL, TG, GLU and MAP          |
| Australian Health and Fitness Survey (AHFS)    | 9, 12, 15 years old<br>860 males<br>755 females | fat (%) | Est. VO2max (1.6 km run) | Modified FITNESSGRAM                     | WC, HDL, TG and MAP               |
| Physical activity across the curriculum (PAAC) | 7–9 years old<br>192 girls<br>183 boys          | BMI     | PWC 170                  | BMI - CDC cutpoints PWC-<br>median split | WC, HDL, TG, HOMA and MAP         |

### EPIDEMIOLOGICAL STUDIES OF 'FAT BUT FIT' AND THE METS IN CHILDREN AND ADOLESCENTS

Based on this historical perspective of the combined influence of fatness and fitness on disease risk, I now want to turn the attention to the focus of this review paper—fatness and fitness and the MetS among children and adolescents. Here, the methodologies (Table 1) and results from four studies (20,23,35,36) from our research group examining this issue are highlighted. To our knowledge, these are the only studies conducted on this topic using the approach of cross-tabulating groups. Each of these studies possess strengths and weaknesses and overall, show that the fitness modifies the fatness influence on the metabolic risk.

#### Quebec Family Study (QFS)

The QFS is perhaps best known for its contributions to the genetics of health-related physical fitness (37). The subjects were recruited from the greater Québec City area. The sample included 416 boys and 345 girls, 9–18 years of age. Fatness was considered as the BMI and aerobic fitness was determined by the PWC 150. The MetS score included the TC: HDL, LDL, TG, GLU and MAP. Four fatness-fitness categories were determined based on the median split of age-adjusted BMI and PWC 150. The results indicated differences within BMI categories with the low fit subjects possessing a higher risk score. Differences also existed at the extremes with the high fit/low BMI subjects having the best risk factor score and the low fit/high BMI subjects possessing the highest risk factor score for both males and females. The main effects for BMI and PWC were statistically significant ( $p < 0.05$ ) in both males and females and the interaction between BMI and PWC was statistically significant ( $p < 0.05$ ) in females.

#### Aerobics Center Longitudinal Study (ACLS)

As indicated in the previous section, the ACLS is well known for its contributions to the association of fitness and fatness-fitness and chronic disease risk among adults. The sample included 296 boys and 188 girls, 8–18 years of age. Fat-

ness was considered as the BMI and aerobic fitness was determined by the treadmill time to exhaustion. The MetS score included WC, HDL, TG, GLU and MAP. The results showed significant differences across groups among males ( $p = 0.001$ ) while a trend for significance was present among females ( $p = 0.15$ ). In both males and females the high BMI/low fit group had the highest MetS scores, which represents a poorer CVD risk factor profile (0.87 and 0.41, respectively). In males, the MetS score for the high fit/low BMI and the low fit/low BMI group were similar ( $-0.87$  and  $-0.86$ , respectively), suggesting body fatness may be associated with the MetS score more than cardiorespiratory fitness. Although the similarity among low BMI groups was not seen in the female group, the MetS scores were noticeably lower compared to those in the high BMI group.

#### Limitations and recommendations

Following the first two analyses using this approach, we realized the following limitations: (1) use of the median split and lack of using clinically relevant cutpoints, and (2) lack of aerobic fitness expressed as VO2max. One approach to combat the problem of the median split/lack of clinically relevant cutpoints was to use FITNESSGRAM cutpoints. FITNESSGRAM is a comprehensive youth fitness assessment and promotion system developed by the Cooper Institute (Dallas, TX, USA) that is used by more than 6000 schools/school districts across the United States (38). The health-related fitness measures are evaluated by criterion-reference standards to classify youth into 'Healthy Fitness Zone' or 'Needs Improvement' categories.

#### Australian Health and Fitness Survey (AHFS)

The AHFS was a cross-sectional population study of approximately 8500 schoolchildren 7–15 years of age that assessed health-related fitness and self-reported health behaviours (39). The design of the survey was a two-stage probability sample. The first stage was the selection of schools and the second stage consisted of a random sample of boys and girls of each year of age from the total school enrollment. The overall response rate was 67.5% for those participating in

the field and technical measures portion of the study. In the present analysis, 1615 (860 males and 755 females) 9, 12, and 15-year olds are included based on complete data for blood chemistries, 1.6 km run time, and anthropometry. The analyses were restricted to these age strata as funding limitations prevented more costly procedures such as blood chemistry from being administered to the entire survey sample. The particular ages were chosen to represent prepubertal, peripubertal and postpubertal stages of maturation. Instead of BMI, skinfold thicknesses was used to estimate percent body fat and aerobic fitness was expressed as estimated VO<sub>2</sub>max from the 1.6 km run time. The MetS score consisted of measures of WC, MAP, TG and HDL-C. Fatness-fitness groups were first attempted by grouping subjects by FITNESSGRAM cutpoints. For fatness, a percent fat of 25% in males and 32% in females was used. Aerobic fitness cutpoints for VO<sub>2</sub>max were 42 mL/kg/min in males and 35–39 mL/kg/min (age-dependent) in females. However, about 90% of males and females fell into the low fat-high fitness category based on these cutpoints. Based on the inadequate sample size per stratum, the cutpoints were adjusted based on quartile splits which resulted in the following cutpoints for VO<sub>2</sub>max (48 mL/kg/min for males and 42 mL/kg/min for females) and %fat (18% for males and 30% for females). Although a majority of subjects were still classified into the low fat/high fit group (approximately 67%), this breakdown was used for the statistical analysis since reducing the cutpoints further would fall outside the intentions of analyzing the data by health-related cutpoints. There was a strong, linear relationship across groups in both sexes ( $F = 60.6$ ,  $p < 0.001$  in males and  $F = 57.3$ ,  $p < 0.001$  in females). In males and females the high fat/low fit group had the highest MetS score (2.22 and 2.23, respectively) and the low fat/high fit group had the lowest score (–0.55 and –0.65, respectively). The difference between the two extreme groups was significant ( $p < 0.05$ ). As shown, these scores were similar in both sexes. There were also significant differences between the low and high fat subgroups within a fitness group in both sexes. Within a fatness group, the higher fitness group showed lower scores except in the low fatness group in males.

#### Physical activity across the curriculum (PAAC)

PAAC is a physical activity intervention in Eastern Kansas. A subsample of 2nd and 3rd grade children (ages 7–9 years old) from each school were recruited for additional baseline testing. This analysis included 375 children (192 girls and 183 boys). The BMI was used to classify subjects into normal weight, overweight and obese categories. Aerobic fitness was assessed as the PWC 170 and subjects were categorized by median split for fitness. The MetS score included WC, HDL-C, TG, MAP and the homeostatic model assessment of insulin resistance (HOMA-IR). It is noteworthy to mention the percentage of children in each category: (36% normal weight-high PWC, 19% normal weight-low PWC, 8% overweight-high PWC, 13% overweight-low PWC, 5% obese-high PWC, and 18% obese-low PWC). Furthermore, 35% of subjects in the normal weight group possessed low

fitness, while 30% of overweight and obese subjects possessed high fitness. In general, the normal weight-high fit group possessed the better MetS score and the obese-unfit group possessed the worst MetS score. Of particular note are the differences within BMI groups by fitness level and the comparison of values between the normal weight-unfit subjects and the overweight and obese subjects with high fitness. For example, the MetS score was significantly lower in high fitness children in the normal and obese groups compared to their low fitness counterparts within the same BMI group. Furthermore, the MetS scores were not significantly different between the normal weight-low fitness group and overweight high fitness group or the overweight-low fitness group and obese-high fitness group.

#### INDEPENDENT ASSOCIATIONS OF FATNESS AND FITNESS?

Another approach that can be taken to examine the independent association between fitness and CVD risk factors and fatness and CVD risk factors is to use partial correlations controlling for the concomitant effects of the third variable. That is, the zero order correlation between fatness and CVD risk factors can first be examined and then the same correlation can be examined by also controlling for fitness. The same can be done for the association for fitness and CVD risk factors. Previous studies using this approach have shown that once fatness was used as covariate the correlation between fitness and CVD risk factors was reduced substantially (26,28). In contrast, when the relationship between fatness and CVD risk factors is observed in this same manner, the correlations are not reduced and remain significant.

#### SOME THOUGHTS ON POTENTIAL MECHANISMS

So, what can explain the epidemiological associations between fitness, fatness and the MetS?

#### Aerobic fitness and the metabolic syndrome: the potential role of mitochondrial function

Recently, data have been published on rodents that have been bred for high aerobic capacity and low aerobic capacity (40,41). Among offspring in the 11th generation, there was a 347% difference in running capacity. As may be expected based on the aforementioned associations between fitness and CVD risk factors, there were significant differences in CVD risk factors between high capacity and low capacity runners (41). Furthermore, there were significant differences in several mitochondrial proteins between the two groups which suggests the link between mitochondrial function and the MetS. The results were also apparent among 5-week-old rodents which roughly corresponds with human adolescence.

#### The adipocyte: beyond a storage depot

The exact mechanisms underlying the associations between fatness and the MetS remain unknown. Recent studies in adipocyte biology indicate that the adipocyte is not merely a storage depot for triglycerides but also a

metabolically active secretory organ (42,43). The proteins secreted by the adipocyte have collectively been referred to as adipocytokines or adipokines. To date, several adipokines (e.g. adiponectin, resistin, tumor necrosis factor- $\alpha$ , etc.) have been identified, which influence various aspects of the pathogenesis of the MetS. In children and adolescents, 'abnormal' adipokine levels have been shown in the obese state (44).

### Are there differences in physical activity levels?

What explains the better MetS score among fit obese (or lean) children and adolescents compared to their unfit counterparts? Habitual physical activity levels certainly seem to be a probable candidate. Unfortunately, only the QFS includes a measure of physical activity. Estimated total daily energy expenditure from the 3-day Bouchard diary does not differ across the four fatness-fitness categories. To my knowledge, no other study has addressed if physical activity levels differ between obese fit and obese unfit children. Therefore, additional studies are needed in this area.

### Genetics

Based on the findings among the high and low capacity running rodents, Dr. Jeffrey Flier stated 'If you happen to have drawn the wrong genes, you may be subject to not only not being a long distance runner but also to diabetes and cardiovascular disease.' (Science, Jan 2005, p. 22). This statement perhaps best describes the fat-unfit-MetS phenotype. Indeed, such a phenotype may be partially due to either the pleiotropic effects of a single gene or a set of 'bad' genetic polymorphisms for fatness and fitness. On the other hand, the fat-fit phenotype may be partially due to 'bad' genetic polymorphisms for fatness genes and 'good' polymorphisms for aerobic fitness. To date, several genes have been identified for aerobic fitness (45) and fatness (obesity) (46).

### SUMMARY AND CONCLUSIONS

This paper has reviewed the concepts of and associations between fitness, fatness and the MetS in children and adolescents. In general, the association between fatness and the MetS (or components of the MetS) is stronger than those for fitness. Furthermore, the correlation between fatness and the MetS remains significant after controlling for fitness, whereas the correlation between fitness and MetS does not remain significant after controlling for fatness. When subjects are cross-tabulated into categories (fat-fit, etc.), there is good evidence that fitness attenuates the MetS score among fat children and adolescents. The reasons for these observations possibly involve genetics, adipocytokines and mitochondrial function among others. Further study is needed to understand the role of physical activity and other environmental factors on this phenomenon. In addition, longitudinal studies of the fat-fit phenotype are required and should include measurements of the hormonal milieu, adipokines and the oxidative capacity of skeletal muscle during childhood and adolescence.

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