Associations of Cardiorespiratory Fitness and Fatness With Cardiovascular Risk Factors Among Adolescents: The NHANES 1999–2002

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Background: This study aimed to examine combined and independent effects of cardiorespiratory fitness and fatness on cardiovascular risk factors among U.S. adolescents. Methods: Data from adolescents age 12 to 19 years participating in the NHANES 1999 to 2002 were used. Fitness level was determined by submaximal treadmill test and was dichotomized as ‘not fit’ or ‘fit’ according to the FITNESSGRAM. Fatness level was categorized as ‘not fat’ or ‘fat’ based on the CDC BMI growth charts. Gender-specific multivariable linear regression analyses were conducted to compare age-, race/ethnicity-, fatness-, and waist circumference-adjusted means of blood pressure, lipids, lipoproteins, C-peptide, insulin, and C-reactive protein (CRP) levels. Results: A total of 3202 adolescents (1629 boys) were included for data analysis. Among boys, total cholesterol, triglycerides, insulin, and CRP mean levels were significantly higher (P < .05) in the ‘not fit’ group than in the ‘fit’ group, after adjustment for fatness level and waist circumference. Among girls, the fatness level- and waist circumference-adjusted means of total cholesterol (P < .01) and LDL-C (P < .09) were higher in the ‘not fit’ than ‘fit’ groups. Conclusion: Cardiorespiratory fitness, independent of fatness, may have beneficial effects on lipid profiles among girls, and on lipid profiles, insulin metabolism, and inflammation levels among boys.

Keywords: VO₂max, BMI, obesity, metabolic syndrome, cardiometabolic

Hypertension, hypercholesterolemia, type 2 diabetes, and a cluster of cardiovascular (CV) risk factors (called the metabolic syndrome) have increasingly been reported in the adolescent population. Because the pediatric metabolic syndrome has been demonstrated to predict not only development of pediatric type 2 diabetes, but also adult metabolic syndrome, type 2 diabetes, and cardiovascular disease, it is important to identify determinants of CV risk in adolescents for interventions to reduce childhood type 2 diabetes and the risk of chronic diseases later in life.

The positive association between obesity and CV risk in children and adolescents is well documented. Because the pediatric metabolic syndrome has been demonstrated to predict not only development of pediatric type 2 diabetes, but also adult metabolic syndrome, type 2 diabetes, and cardiovascular disease, it is important to identify determinants of CV risk in adolescents for interventions to reduce childhood type 2 diabetes and the risk of chronic diseases later in life.

Cardiorespiratory fitness (hereafter ‘fitness’) has also been demonstrated to be inversely associated with CV risk in children and adolescents. Carnethon et al examined associations of fitness with CV risk factors and the metabolic syndrome among adolescents age 12 to 19 years using the U.S. National Health and Nutrition Examination Survey (NHANES) 1999 to 2002 data. In their study, low fitness was associated with high waist circumference and hypercholesterolemia in both boys and girls, and the metabolic syndrome in boys. However, the observed associations did not account for fatness and therefore, they may have been confounded or mediated by fatness. Identifying independent effects of fatness and fitness on CV risk factors would help establish their causal relationships and inform cardiovascular disease prevention strategies. Investigators have examined fatness-independent effects of fitness on CV risk factors in adolescents and the results are inconsistent. Studies of Eisenmann and colleagues and the European Youth Heart Study show combined influence of fat and fitness. In a representative sample of U.S. adolescents from NHANES 1999 to 2002 data, Imperatore et al showed a significant independent association between fitness and insulin sensitivity among boys, but not among girls. However, other studies reported that associations between fitness and CV risk factors were not significant after adjustment for fatness. Expanding on the work of Carnethon et al and Imperatore et al, this study aimed to determine whether fitness, independent of fatness, is associated with CV risk factors among adolescents using NHANES 1999 to 2002 data. We hypothesized that fitness has direct beneficial effects on CV health among adolescents.
Materials and Methods

Participants

The NHANES is an ongoing cross-sectional national survey, which examines a nationally representative sample of the noninstitutionalized civilian U.S. population selected using a stratified multistage probability sample design. The NHANES over-samples adolescents age 12 to 19 years, persons over age 60 years, low-income persons, African Americans, and Mexican Americans. The NHANES is comprised of household interview and mobile examination center (MEC) examinations. Age, gender, and race/ethnicity were asked in household interviews. Physical examinations including anthropometry, dual energy x-ray absorptiometry (DXA), fitness testing, and laboratory measurements were performed in a MEC. A detailed description of the study design and methodology for the NHANES can be found at the NHANES website, http://www.cdc.gov/nchs/nhanes.htm.

This report used 1999–2000 and 2001–2002 NHANES datasets. A total of 4732 adolescents age 12 to 19 years participated in MEC examinations. From this group, 3875 (82%) participated in the fitness component of the examination according to its exclusion criteria such as medical conditions, medication use, physical limitations, limits on heart rate and blood pressure, and irregular heart rates (details of exclusion criteria are available at the NHANES website), and 3,310 adolescents (70%) completed the fitness test. To identify outlier observations or observations that were considered to be biologically implausible values of height, weight, and BMI, a SAS program provided by the Center for Disease control and Prevention (CDC) was used (http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/sas.htm). Participants with extremely-high estimated maximal oxygen uptake (VO2max) values (≥80 mL/kg/min in boys and ≥70 mL/kg/min in girls) were also defined as outliers. Those 35 identified outliers and 10 participants who did not have recorded height and weight values were excluded from our data analysis, resulting 3265 participants (69%). The NHANES protocol was approved by the National Center for Health Statistics institutional review board. Written informed consent and child consent were obtained from all participants. More information on characteristics of participants is available in other published papers.14,20,32

Measurement and Categorization of Fitness and Fatness

Submaximal treadmill testing was used to estimate fitness levels. On the basis of their gender, age, body mass index (BMI), and self-reported physical activity, the participants who met eligibility criteria were assigned to an appropriate test protocol. Details of exercise protocols can be found at the NHANES website. The submaximal treadmill test protocol was designed to elicit a heart rate that was approximately 75% of the age-predicted maximum (220 – age) by the end of the test. Each protocol included a 2-minute warm-up, 2 3-minute exercise stages, and a 2-minute cool-down period. Heart rate was monitored continuously using an automated monitor with 4 electrodes connected to thorax and abdomen of the participant and was recorded at the end of warm-up, each exercise stage, and each minute of recovery. Oxygen uptake data were also collected during exercise testing. Using the submaximal test results, estimated VO2max was predicted based on the equation developed by Jackson and colleagues.33 For the purpose of the current investigation, participants were dichotomized into low-fit (‘not fit’) and moderate/high-fit (‘fit’) groups based on gender- and age-specific cut-points of VO2max suggested in the FITNESSGRAM program.34,35

Fatness levels were determined by gender- and age-specific BMI percentiles. BMI was preferred to DXA-measured fat mass to ensure a larger sample size; only 63% of girls had DXA examination because girls 8 to 17 years of age were excluded from the DXA component in 1999 due to concerns over how to handle the reporting of pregnancy test results for minors.36 However, since BMI is known to be a less accurate indicator of adiposity than DXA-measured fat mass in adolescents, we tested the validity of BMI against DXA-measured fat mass as a criterion measure in a subgroup who had both BMI and DXA data. Height and weight were measured according to standard methods and BMI was calculated as weight in kilograms divided by the square of height in meters. Based on the CDC gender- and age-specific BMI growth charts,37 those with BMI ≥ 85th percentile were categorized as overweight/obese (‘fat’) and those with 5th < BMI < 85th percentile as normal-weight (‘not fat’). Underweight participants, those with BMI ≤ 5th percentile (41 boys and 22 girls), were excluded to ensure that only participants with healthy levels of BMI were included in the normal-weight (‘not fat’) category. Therefore 3202 NHANES participants were included in the final data analysis. Four fitness/fatness groups were constructed separately by gender: ‘not fat and fit,’ ‘not fat and not fit,’ ‘fat and fit,’ and ‘fat and not fit.’

Measurement of Cardiovascular Risk Factors

Waist circumference, SBP, DBP, total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), plasma glucose, C-peptide, insulin, and C-reactive protein (CRP) were investigated as CV risk factors in this study. Waist circumference was measured at the midpoint between the bottom of the rib cage and above the top of the iliac crest during minimal respiration. Blood pressure was measured 3 to 4 times with all participants in the seated position using a mercury sphygmomanometer (the first measurement was excluded). The first and fifth
Korotkoff sounds were recorded to represent systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. The average of 3 BP assessments was used for analysis. DBP values recorded as 0 were set to missing. Blood was sampled at MECs by trained personnel according to standardized procedures. Procedure manuals for measurements of CV risk factors are available at the NHANES website. Blood samples were analyzed for lipid, glucose, c-peptide, insulin, and CRP levels. Because TG, LDL-C, glucose, C-peptide, and insulin values were measured only from those who participated in the morning MEC session after an overnight fast, only 1344 of 3202 participants (42%) were included for data analyses of those variables.

**Statistical Analysis**

Gender-specific analyses were conducted using the Statistical Analysis System (SAS) version 9 (Cary, NC). To test the validity of BMI against DXA-measured fat mass, age- and gender-specific Pearson correlation coefficients were estimated. The sensitivity and specificity of the fatness categorization by BMI were also examined against overfat cut-points (25% in boys and 32% in girls) from the FITNESSGRAM based on DXA-derived percent body fat.

The prevalence of fitness/fatness groups was calculated according to gender and ethnicity. Because of nonnormal distributions of all of the observed CV risk factor variables, they were transformed by taking the natural logarithm. Multivariable linear regression models were fitted using the SURVEYREG procedure to obtain estimated least-squares means and 95% confidence intervals that were adjusted for age and race/ethnicity effects; the complex sampling design of the NHANES was taken into account using cluster, stratum, and weight options to produce national estimates. These models included either the fitness group variable alone, or both the fitness and fatness group variables. If waist circumference was significantly different between the ‘fit’ and ‘not fit’ groups within a fatness level, further adjustment for waist circumference was included to eliminate the abdominal fat effect and allow a more conservative examination of the fitness effect. A fitness-by-fatness interaction effect was considered for inclusion in models that also included both the fitness and fatness group variables; the quadratic effect of age (age²) was also considered. If the p-value associated with an interaction effect was < 0.20, the interaction term was included in the final regression model. Statistical significance for fatness and fitness effects was evaluated by testing the significance of the regression parameter estimates associated with these group and interaction effects (α = 0.05).

**Results**

Figure 1 shows the race/ethnicity and fitness/fatness group proportions among the 1629 boys and 1573 girls. The ‘not fat and fit,’ the ‘not fat and not fit,’ the ‘fat and fit,’ and the ‘fat and not fit’ groups constituted 51.9%, 15.8%, 16.0%, and 16.3% of boys, and 46.7%, 19.0%, 18.3%, and 16.0% of girls. More Mexican American boys were ‘fat and not fit’ (24.3%) than White boys (14.4%, P < .05). More Black girls (23.1%) were ‘fat and not fit’ than White girls (12.5%, P < .05). BMI was highly correlated with DXA-measured fat mass in the subgroup that had both measures (gender- and age-specific Pearson correlation coefficients r = .93 to 0.96 in both boys and girls). The sensitivity and specificity of the fatness categorization by BMI were 83% and 90% in boys and 62% and 95% in girls, respectively. Gender- and age-specific correlations between estimated VO2max and BMI were low to moderate (r = –0.19 to –0.46 in boys and r = –0.08 to –0.29 in girls).

Figure 2 illustrates the comparisons of age- and race/ethnicity-adjusted CV risk factor means between the ‘fit’ and ‘not fit’ groups, and among the 4 fitness/fatness groups in boys. Results for waist circumference are not shown in Figure 2. The ‘not fit’ group had significantly higher waist circumference, TC, TG, C-peptide, insulin, CRP (P < .001), LDL-C, and SBP (P < .01), and significantly lower HDL-C (P < .001) than the ‘fit’ group.
Figure 2 — Age- and race/ethnicity-adjusted means of cardiovascular risk factors among boys. Note. The first 2 bars represent age- and race/ethnicity-adjusted means and 95% confidence intervals of the ‘fit’ and ‘not fit’ groups. The last 4 bars represent age-, race/ethnicity-, and waist circumference-adjusted means and 95% confidence intervals of the ‘fit’ and ‘not fit’ groups within the ‘not fat’ and ‘fat’ groups. * Six cardiovascular risk factors were significantly different between the ‘fit’ and ‘not fit’ groups ($P < .05$). † After adjustment for fatness, only total cholesterol, triglyceride, insulin, and CRP levels were significantly different between the ‘fit’ and ‘not fit’ groups ($P < .05$). CRP = C-reactive protein; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; SBP = systolic blood pressure; total chol = total cholesterol.
DBP and glucose levels were not significantly different between the ‘fit’ and ‘not fit’ groups ($P > .10$, not shown in Figure 2). When adjusted for fatness levels, the mean differences between the ‘fit’ and ‘not fit’ groups for waist circumference, TC, TG, C-peptide, insulin, and CRP remained statistically significant ($P < .05$). Because a significant mean difference in waist circumference between the ‘fit’ and ‘not fit’ groups within the ‘fat’ group was identified ($P < .01$), waist circumference was added to the regression models for boys. Nonetheless, the fitness effect remained significant for TC, TG, insulin, and CRP ($P < .05$), and was suggestive for C-peptide ($P < .06$). An interaction effect for fatness and fitness was identified only in SBP ($P < .05$); but the mean differences between the ‘fit’ and ‘not fit’ groups within each fatness group was minimal (<2 mmHg). Levels of the observed CV risk factors were similar between the ‘not fat and not fit’ and ‘fat and fit’ groups. TG, C-peptide, and insulin levels were higher in the ‘not fat and not fit’ group than the ‘fat and fit’ groups, although the differences were not statistically significant.

Among girls, waist circumference, TC ($P < .001$), insulin, CRP ($P < .01$), SBP, LDL-C ($P < .05$), and C-peptide levels ($P < .01$) were higher in the ‘not fit’ group than in the ‘fit’ group (Figure 3, results for waist circumference are not shown in Figure 3); the means

**Figure 3** — Age- and race/ethnicity-adjusted means of cardiovascular risk factors among girls. **Note.** The first 2 bars represent age- and race/ethnicity-adjusted means and 95% confidence intervals of the ‘fit’ and ‘not fit’ groups. The last 4 bars represent age-, race/ethnicity-, and waist circumference-adjusted means and 95% confidence intervals of the ‘fit’ and ‘not fit’ groups within the ‘not fat’ and ‘fat’ groups. * Five cardiovascular risk factors were significantly different between the ‘fit’ and ‘not fit’ groups ($P < .05$). † After adjustment for fatness, only total cholesterol levels were significantly different between the ‘fit’ and ‘not fit’ groups ($P < .05$). CRP = C-reactive protein, LDL-C = low-density lipoprotein-cholesterol; SBP = systolic blood pressure; total chol = total cholesterol.
of other CV variables (DBP, TG, HDL-C, and glucose) were not significantly different between the ‘fit’ and ‘not fit’ groups (P > .10, not shown in Figure 3). After adjustment for fatness levels and waist circumference, the mean difference remained significant only for TC (P < .01) and was suggestive for LDL-C (P < .09), while the mean differences in SBP, C-peptide, insulin, and CRP were no longer significant (P > .15).

Discussion

Main Findings
This study aimed to determine whether fitness, independent of fatness, was associated with CV risk factors among U.S. adolescents. We found that among boys, high TC, TG, C-peptide, insulin, and CRP levels were associated with low fitness, independent of overall fatness (BMI) and abdominal fatness (waist circumference). Among girls, only high TC and LDL-C were associated with low fitness, independent of overall fatness (BMI) and abdominal fatness (waist circumference).

Consistency With Literature
Seven studies20–26 have demonstrated that fitness is independently associated with CV risk factors. Among them, 5 studies20–24 reported gender-specific fitness effects. In particular, results from the Aerobics Center Longitudinal Study demonstrated an association in boys, but not girls.22 These findings are in contrast with 5 other studies22–31,39 that found CV risk factors were not associated with fitness after adjustment for fatness.

The lack of consistency across studies could be due to limitations of sample size and of population representation, methodologic differences such as quantifications (expression) and categorizations of fitness and fatness levels, and the ability to control for potentially confounding factors. For example, Ekelund et al26 expressed fitness level as watts per kg fat-free mass and demonstrated that fitness was inversely associated with the metabolic syndrome risk. The authors pointed out that because fitness was normalized by fat-free mass, not body mass, some residual confounding from adiposity may distort the true association between fitness and metabolic risk, resulting in overestimation of the magnitude of associations. However, Armstrong and Welsman40 argued that normalization of VO2max by body mass may “overcorrect” for differences in body size between individuals, and that test duration for indirect fitness tests involving weight-bearing activity may underestimate VO2max in heavier children. In the current study, however, observed low correlations (Pearson correlation coefficients r = –0.21 in boys and r = –0.18 in girls) between body mass (kg) and mass-related VO2max (mL/kg body mass/min) suggest that mass-related VO2max was not over-adjusted and it is unlikely that the fitness level of overweight adolescents was underestimated due to normalization of VO2max by body mass. Because the strength of the statistical association between fitness and CV risk factors depends on how the exposures and outcomes are measured and expressed,31 caution should be taken in interpreting associations. Our study used conventional expressions of fitness (mL/kg/min) and fatness (gender- and age-specific BMI percentile) and widely accepted cut-points for categorizations of fitness and fatness levels in a representative sample of U.S. adolescents. Furthermore, we adjusted not only for fatness levels by BMI, but also for waist circumference to eliminate a residual abdominal fatness effect. These methodologic approaches would be expected to improve the internal and external validity of our results.

Modeling Relationships Among Fitness, Fatness, and Cardiovascular Risk in Adolescents
Our results support that the fitness effect on CV risk factors may be mostly mediated (or confounded) by fatness among girls, while a direct pathway from fitness to CV risk factors may exist among boys. The gender discrepancy of the fitness effect cannot be explained by fitness and fatness associations because the correlation coefficients between estimated VO2max and BMI was lower in girls than in boys (r = –0.08 to –0.29 in girls and r = –0.19 to –0.46 in boys). The fact that girls are more likely to have higher percent body fat and lower fitness levels may explain less fitness effect among girls than among boys. Further research is required to ascertain whether the gender difference that we observed is due to biological difference or the difference of fitness/fatness distributions.

In modeling relationships among fitness, fatness and CV risk, it is difficult in observational studies to determine whether fatness is a confounder, mediator, or modifier in a relationship between fitness and CV risk.41 Furthermore, roles of fitness and fatness in CV risk may differ according to specific risk factors, although CV risk factors tend to cluster and their physiology is interrelated. In this study, for example, lipid profiles, insulin-related factors, and CRP, but not BP, were associated with fitness among boys. How fitness and fitness interact with each other to impact CV health is unclear, but fitness may play an important role in blood lipids, insulin and inflammatory mechanisms, independent of fatness among boys.

Public Health Implications
In parallel with the childhood obesity epidemic, type 2 diabetes and clustering of CV risk factors are increasingly reported among children and adolescents. Our findings confirmed that maintaining healthy weight is important for favorable lipid profiles and prevention of type 2 diabetes in adolescents.42,43 In addition, this study suggests that maintaining fitness and a healthy weight will provide additive health benefits among boys. Overweight children may reduce CV risk through improved fitness even without weight loss and high fitness may promise better CV health even among nonoverweight boys. Fitness improvement should be targeted in interventions to improve lipid profiles and prevent progression to impaired glucose tolerance and type 2 diabetes through improved muscle insulin sensitivity and reduced inflammation among overweight boys. Because moderate-to-vigorous physical activity (MVPA) improves maximal respiratory fitness,44 MVPA can be used as a strategy to improve fitness.
Strengths, Limitations, and Future Study

The use of a large representative sample of U.S. adolescents enabled us to evaluate separate effects of fitness and fatness and increase the generalizability of study results. Another advantage of this study is that BMI was cross-checked with fat mass measured by DXA in a subsample and was found to have a very strong association, which helps to increase the confidence that the results are internally valid. However, several limitations should be acknowledged. Because results of the current study are drawn from cross-sectional surveys, temporal relationships between observed variables cannot be established. It is intuitively less likely that CV risk factors influenced fitness levels, as long as participants were not clinically ill enough to decrease physical activity. In fact, clinically unhealthy participants were excluded from the fitness test based on the exclusion criteria (18% of MEC participants). Due to the exclusion criteria, it is likely that a high-risk segment of the population was excluded, which leads results toward the null-hypothesis. Therefore, the current study may have underestimated the relationship between fitness and CV risk factors. However, when means of BMI, age, and CV risk factors between those who completed the fitness test (the completed) and nonparticipants or those who did not complete the fitness test (the noncompleted, 30% of MEC participants) were compared, no significant differences were identified in most observed variables (mean differences between the completed vs. the noncompleted: 0.2 years of age, 0.3 kg/m² of BMI, 1 mmHg of SBP, 7 mg/dL of TC), whereas mean CRP levels were significantly different (1.65 mg/dL vs. 2.52 mg/dL for the completed vs. the noncompleted). In addition, other potentially confounding factors such as genetic predisposition and physical maturity were not considered.

For future research, firstly, longitudinal investigations are required to allow an examination of the associations between change of fitness levels and CV risk factors during adolescence; because data used in previous and current studies have been mostly drawn from cross-sectional studies, it is impossible to determine within-individual effects of fitness on CV risk factors. Secondly, the fitness association with CV risk factors was examined here; however, physical activity may have different effects on CV risk from fitness, given the fact of a weak relationship between physical activity and fitness in adolescents ($r = 0.16$ to 0.17). Future research should investigate the relationship between objectively-measured physical activity and CV risk in adolescents independent of fitness and fatness, which can provide evidence for the hypothesis that physical activity not only indirectly improves CV health though fitness improvement and weight loss, but directly improve CV health even without fitness improvement or weight loss.

References


