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Cardiorespiratory Fitness, Waist Circumference and Alanine Aminotransferase in Youth

Jennifer L. Trilk[1], **Andrew Ortaglia**[2], **Steven N. Blair**[2], **Matteo Bottai**[3], **Timothy S. Church**[4], and **Russell R. Pate**[2]

[1]Department of Biomedical Sciences, University of South Carolina School of Medicine Greenville, Greenville, South Carolina

[2]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina

[3]Institute of Environmental Medicine, Unit of Biostatistics, Karolinska Institutet, Stockholm, Sweden

[4]Preventive Medicine Laboratory, Pennington Biomedical Research Center, Baton Rouge, Louisiana

Abstract

Non-alcoholic fatty liver disease (NAFLD) is considered the liver component of the metabolic syndrome and is strongly associated with cardiometabolic diseases. In adults, cardiorespiratory fitness (CRF) is inversely associated with alanine aminotransferase (ALT), a blood biomarker for NAFLD. However, information regarding these associations is scarce for youth.

Purpose—To examine associations between CRF, waist circumference (WC) and ALT in youth.

Methods—Data were obtained from youth (n=2844, 12-19 years) in the National Health and Nutrition Examination Survey (NHANES) 2001-2004. CRF was dichotomized into youth FITNESSGRAM® categories of "low" and "adequate" CRF. Logistic and quantile regression were used for a comprehensive analysis of associations, and variables with previously-reported associations with ALT were *a priori* included in the models.

Results—Results from logistic regression suggested that youth with low CRF had 1.5 times the odds of having an ALT>30 than youth with adequate CRF, although the association was not statistically significant (P=0.09). However, quantile regression demonstrated that youth with low CRF had statistically significantly higher ALT (+1.04, +1.05, and +2.57 U/L) at the upper end of the ALT distribution (80^{th,} 85th, and 90th percentiles, respectively) than youth with adequate CRF. For every 1-cm increase in WC, the odds of having an ALT>30 increased by 1.06 (P<0.001), and the strength of this association increased across the ALT distribution.

Conclusions—Future studies should examine whether interventions to improve CRF can decrease hepatic fat and liver enzyme concentrations in youth with ALT ≥80th percentile or in youth diagnosed with NAFLD.

Contact Information: Jennifer L. Trilk, Department of Exercise Science, Arnold School of Public Health, 921 Assembly St., Suite 212, University of South Carolina, Columbia, SC 29208, Phone: 803-777-0280, Fax: 803-777-2504, trilk@mailbox.sc.edu.

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Keywords

Adolescents; Exercise; Metabolic Syndrome X; Non-alcoholic Fatty Liver Disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a significant public health issue in youth, as NAFLD can lead to cirrhosis and hepatocellular carcinoma, both of which increase mortality risk in adults (29). In addition, NAFLD is considered the liver component of the metabolic syndrome (24;31) and is strongly associated with type 2 diabetes and multiple cardiovascular risk factors in overweight and obese youth and adults (39). Therefore, prevention and treatment of pediatric NAFLD are significant public health aims.

The European Youth Heart Study demonstrated that cardiorespiratory fitness (CRF) is inversely correlated to the metabolic syndrome (33). In a smaller study in youth, Wittmeier et al. (39) demonstrated that CRF also is inversely associated with magnetic resonance spectroscopy (MRS)-assessed hepatic triglyceride content, independent of total body and visceral fat mass (39). However, other studies in youth and adults have found that body fat mediates these associations (9;32). Since CRF also is inversely associated with lower body weight and central adiposity (15), changes in CRF may directly and/or indirectly affect NAFLD with or without changes in body fat.

The gold standard for diagnosis of NAFLD is via liver biopsy, but because this diagnostic sometimes is not feasible, ultrasound and MRS also have been used. However, all of these diagnostic methods are impractical in large-scale studies due to cost and subject burden. Alanine aminotransferase (ALT), the enzyme most closely-related to liver fat accumulation (38) and a blood biomarker for NAFLD (3;19), is easily available and low cost, making it the most widely-used surrogate marker for NALFD in epidemiologic studies (13). Associations between CRF and ALT have been examined in adults (9); however, only two smaller studies have examined these associations in 12 year-old youth who were obese (N=241) (3) or in 12-18 year-old youth (N=95) who were categorized into normal weight/ obese subgroups with/without the metabolic syndrome (19). To our knowledge, no study has examined the association of CRF, waist circumference (WC) and ALT in a large sample of youth of different cardiorespiratory fitness, age, race, gender and waist circumference.

The purpose of this study was to comprehensively examine associations between CRF, WC and ALT in a nationally-representative sample of U.S. youth.

Materials and Methods

The present study utilized data obtained from the 2001-2002 and 2003-2004 US National Health and Nutrition Survey (NHANES). NHANES is a complex, multistage probability design that is weighted to represent the U.S. Census civilian non-institutionalized population (e.g. a method to measure of the number of people in the population represented by that sample person); it combines household interviews with standardized physical examinations and blood testing, and is designed to assess the health and nutritional status of the United States population (13).

NHANES obtains written informed consent from all participants that undergo in the in-home interviews and the health exams. Ambulatory children ages 12-19 years at the time of the exam who had complete data for demographic and anthropometric characteristics, CRF, and comprehensive blood biomarkers related to NAFLD were assessed. Adolescents who

tested positive for Hepatitis B, C, and autoimmune hepatitis, and girls who were pregnant or may be pregnant were excluded. A total of 4272 male and female adolescents completed examination procedures. Of those, n=4233 were negative for Hepatitis B surface antigen, Hepatitis B core antibody and Hepatitis C antibody; n=4020 had complete data for ALT values, n=3572 had waist circumference measures, and n= 2844 had complete data for estimated VO_{2max}. Therefore, analyses were performed on n=2844 youth. The University of South Carolina's Institutional Review Board approved of the data analysis from NHANES.

Medical examination and questionnaires

The medical examination/questionnaire protocol in NHANES is explained in Survey Operations Manuals, Brochures, Consent Documents for 2003-2004 (6), **(pp3-20 to 3-29).** Briefly, standing height, weight, and waist circumference (WC) were measured by a physician during the medical examination, and children 12 years and older were asked to provide a blood sample for blood chemistry analysis. Alanine aminotransferase (ALT) was analyzed using an enzymatic rate method. Tests for Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody were performed in duplicate using a standard procedure described in NHANES *Laboratory Protocols* (7;8).

Cardiorespiratory fitness

The protocol to assess cardiorespiratory fitness in NHANES is explained in the *Cardiovascular Fitness Procedures Manual* (27), **(pp3-1 to 3-42)**. Briefly, a trained health or medical technician administered one of eight submaximal treadmill tests dependent upon age, body mass index, and self-reported level of physical activity. Each protocol included a 2-minute warm-up, two 3-minute exercise stages, and a 2-minute cool down period. The protocol goal was to elicit a heart rate that was approximately 75% of the age-predicted maximum (220-age) by the end of the test. Heart rate was monitored throughout the test, and blood pressure was measured at the end of each stage. Rate of perceived exertion was obtained from the participants using the Borg scale. Maximal oxygen uptake ($\dot{V}O_{2max}$) was estimated using a calculation that extrapolated the measured heart rate responses to known levels of exercise workloads, assuming the relation between heart rate and oxygen consumption is linear during exercise (27). Estimated $\dot{V}O_{2max}$ (ml·kg ·min^{-1}) was then categorized based on the gender-specific FITNESSGRAM® CRF categories for youth and young adults 12-19 years (10). FITNESSGRAM® is a criterion-referenced standard for youth that is used to link CRF to health outcomes. "Low" level of CV fitness is defined as an estimated VO_{2max} below the 20th percentile of the Aerobics Center Longitudinal Study (ACLS) data of the same gender and age group; "moderate" fitness is defined as a value between the 20th and 59th percentile, and "high" fitness is defined as at or above the 60th percentile (28).

Statistical analyses

Logistic regression was used to examine youth's level of CRF and WC with the odds of having an elevated ALT, whereas quantile regression was used to examine the youth's level of CRF and WC across ALT percentiles to obtain a more complete description of the associations (particularly at the tails of the ALT distribution). Since $\dot{V}O_{2max}$ was estimated and because the assumption of linearity cannot be made between $\dot{V}O_{2max}$ and ALT, categorical CRF was used based on the criteria used in the youth FITNESSGRAM® program. Categories of "Low, Moderate, High" CRF were dichotomized into "low" and "adequate" CRF, with adequate CRF used as the reference (27). This categorization was performed because youth aged 12-19 years in the "low" category fail to meet the levels of cardiorespiratory fitness deemed appropriate by experts for health.

For logistic regression, each observation for ALT was dichotomized and the odds of observing ALT > 30 U/L were modeled using SURVEYLOGISTIC in SAS® 9.2 (Statistical Analysis Software, Cary, NC). Although some investigators have used a cut-off point of 40 U/L for adult men, others have used a cutoff of 30 U/L (11;30;34;35);(37). A cutoff of ALT > 30 U/L was used in this study of adolescent boys and girls because Fraser et al. (14) found that a cutoff of 30 U/L was significantly associated with waist circumference and insulin resistance in a nationally-representative sample of youth (NHANES 199-2004). In addition, Strauss et al. (36) used the cutoff of 30 U/L that was consistent of the 97^{th} percentile for youth in NHANES III. Finally, new cutpoints to define healthy ranges for serum ALT are suggested to be lower for men and women (12;23). A preliminary analysis was conducted to assess possible interactions between activity level and gender. No statistical significance was found; therefore, logistic regression for ALT > 30 U/L was performed on the pooled genders. In addition, since some have argued for a lower cutpoint of 19 U/L for women (22;30), a separate logistic regression was performed on girls only, with an ALT > 19 U/L used as the threshold for elevated ALT. Variables with previously-reported associations with ALT (age, race, gender, WC) were *a priori* included in the models. The statistical significance was set at 0.05.

Quantile regression was used to assess the associations of CRF and WC across adjusted ALT percentiles. The survey package in the statistical software "R", version 2.12.2, was extended to accommodate quantile regression and used to account for the complex NHANES survey design (25), as the QUANTREG procedure in SAS is not appropriate for survey data. Variables with previously-reported associations with ALT (age, race, gender, WC) were *a priori* included in the models. For the independent categorical variable, the regression coefficients represent the difference between the adjusted percentiles of the outcome variable between groups. For percentiles from 0.1 to 0.9, a 95% confidence interval was calculated and interpreted. To assess the need for stratifying by gender, a separate analysis was performed to examine the interaction between activity level and gender. No significant interaction was detected. As a result, the main effects model adjusted for gender described above was used.

Results

Demographic and anthropometric characteristics of the 2844 youth were weighted to account for the complex survey design and are displayed in Table 1. The majority of youth (93%) had a normal ALT (≤ 30 U/L). Mean (SE) of ALT was 18.8 (0.2) U/L with a median (SE) of 16.0 (0.1) U/L. Of the total weighted sample, 7% had an ALT > 30 U/L. Of the girls studied, 17% had ALT > 19 U/L. Sixty-two percent of youth met the FITNESSGRAM® standards for CRF, while 38% failed to meet the levels of cardiorespiratory fitness deemed appropriate by experts for health (Table 1). Significant differences were observed between boys and girls for age, ALT, other liver enzymes (aspartate aminotransferase, AST; and γ-glutamyltransferase, GGT), estimated $\dot{V}O_{2max}$, and WC ($P < 0.05$).

Table 2 displays the results of the regression coefficients for the logistic and quantile regression models that examined the associations between the independent variables (CRF and WC) and the dependent adjusted ALT variable. The results from the logistic regression suggest that youth with low CRF had 1.5 times the odds of having ALT>30 as compared to youth with adequate CRF, however it was not statistically significant (P=0.09). Similarly, the results of the quantile regression suggest that youth with low CRF tend to have higher ALT values, as compared to those with adequate CRF, with the magnitude of the effect increasing as the percentiles increase (Figure 1) and becoming significant at the 80^{th}, 85^{th}, and 90^{th} percentiles of ALT (+1.04, +1.05, and +2.57 U/L, respectively). Finally, for girls

only, the odds of having an ALT >19 U/L are significantly increased (adjusted OR=1.6, *P*=0.03) for girls with low CRF as compared to girls with adequate CRF.

A positive association was found between WC and the adjusted ALT for both models. The logistic regression model suggests that youth are 1.06 times as likely to have ALT > 30 for each 1 cm increase in WC (*P*<0.001 from Table 2). Similarly, girls are 1.05 times as likely to have ALT > 19 for each 1 cm increase in WC (P<0.001 from Table 2). The quantile regression model also indicated a strong, positive significant association for WC in youth across the entire distribution of adjusted ALT percentiles, with the strength of the association increasing as percentiles increased (Figure 2).

Discussion

This is the first study to examine associations between cardiorespiratory fitness, waist circumference and ALT in a large, nationally-representative sample of U.S. youth. Positive associations between youth with low CRF, WC and an ALT were observed in both models. These results suggest that low CRF may be a risk factor for pediatric NAFLD independent of age, race, and central adiposity, particularly at the upper tail of the ALT distribution. Waist circumference seems to be a stronger risk factor for pediatric NAFLD, as indicated by the increasing magnitude of association with increasing ALT percentiles.

Very little information comparing CRF and ALT is available in youth. Of the existing studies, the associations seem consistent with the current findings. In 12 year olds, Bougle et al. (3) found a significant inverse association between laboratory-measured $\dot{V}O_{2max}$ and ALT in overweight girls (n = 135, *P* = 0.012) and a non-significant trend in overweight boys (n = 106, *P* = 0.065). Kelishadi et al. (19) observed that CRF had the highest inverse correlation with ALT in 12-18 year olds (N=95) regardless if they were of normal weight or overweight, were metabolically normal or had metabolic disorder. In adults, Church et al. (9) found significant inverse associations between CRF and ALT, however, the association was attenuated after adjusting for WC. In adults with differing severity of the disease, Krasnoff et al. (21) found that all patients demonstrated below average age-predicted CRF as assessed by $\dot{V}O_{2peak}$ The current study adds to the literature that CRF plays an important role in NAFLD in addition to other chronic diseases.

Beginning at the 50th percentile of ALT, a positive (non-significant) association was observed between youth who had low CRF and ALT, with the association becoming significant at the 80th percentile of ALT. Since ALT levels are relatively healthy in stable individuals, it is reasonable to conclude that CRF may not affect ALT levels within normal limits. However, youth above the 50th percentile may particularly benefit from higher intensity physical activity and/or exercise training to improve CRF and subsequently prevent incidence of NAFLD. Johnson et al. (18) observed that 4 weeks of aerobic exercise training increased $\dot{V}O_{2max}$ by 13% and decreased hepatic triglyceride concentration by 21% independent of changes in body weight. Improvements in muscle quality and CRF include improved muscle mitochondrial quality, number and function, increased muscle capillarization and blood flow, increased muscle postreceptor insulin signaling, glucose uptake and subsequently enhanced insulin sensitivity (4). These cardiometabolic improvements can increase muscle fatty acid metabolism, decrease circulating triglycerides and subsequent liver triglyceride accumulation. Given that NAFLD is now identified as the liver component of the metabolic syndrome, these mechanistic adaptations demonstrate the importance of higher-intensity physical activity or exercise training and subsequent improvement of CRF for the prevention or management of the metabolic syndrome and NAFLD.

A strong positive association between waist circumference and ALT was found in both models. A number of studies demonstrate a strong correlation between obesity/waist circumference and NAFLD (2;13;28), and interventions that prioritized weight loss have found decreases in liver fat and ALT (16;17). However, rapid weight loss (e.g., from severe caloric restriction or gastric surgery) is contraindicated, as it has been shown to increase inflammation and promote steatohepatitis (1;26). In addition, lifestyle weight loss interventions usually observe modest and often not sustained body weight change, with many individuals returning to baseline weight after 1-3 years (12). However, improving cardiorespiratory fitness through increasing physical activity may decrease NAFLD and improve other cardiometabolic factors independent of weight loss (18). Indeed, regardless of body fatness, individuals who have high cardiorespiratory fitness have been shown to have lower cardiovascular and metabolic risk than individuals of the same body fatness who are less fit (23). In addition to the mechanisms mentioned above, exercise training-improvements in NAFLD can be independent of a weight loss intervention by increasing muscle fatty acid metabolism, which cannot be achieved through energy restriction (14).

Assessing associations in health sciences is commonly performed using logistic regression (for categorical outcome variables) or linear regression (for continuous outcome variables); however, performing analyses on the mean of the outcome variable may overlook associations at the tails of the distribution, such as with elevated ALT levels. In addition, in cases in which the distribution of ALT is skewed (13), the median is a better measure of central tendency as compared to the mean. Traditionally used in econometrics, quantile regression (20) was used in this study because by modeling many ALT percentiles, it allowed the investigators to differentiate associations across the entire adjusted ALT distribution, which provided a comprehensive description of the association between CRF, WC and ALT. These properties, along with the freedom from any distributional assumptions, made quantile regression an attractive method for assessing cardiorespiratory fitness and waist circumference in youth across percentiles of ALT.

Strengths of the study include using a nationally-representative sample of adolescents to assess associations, using an objectively-measured laboratory measurement of CRF, and assessing waist circumference instead of BMI to estimate body fatness and in particular central obesity. Also, use of quantile regression provided a more detailed description of the associations between cardiorespiratory fitness, waist circumference and ALT. One limitation to this study was using a proxy measure (ALT) to assess NAFLD. ALT is the most closely-related enzyme to liver fat accumulation (38). However, Burgert et al. (5) questioned the sensitivity and specificity of ALT as a diagnostic tool for pediatric NAFLD, as they found that one-half of their patients with normal ALT had a MRI-assessed hepatic fat fraction > 5.5%, the cutoff for NAFLD diagnosis. In addition, neither ALT, nor another biomarker, can predict degree of the disease or progression to cirrhosis. Therefore, a direct link between elevated ALT and NAFLD diagnosis should be made with caution. Another limitation was not excluding for possible alcohol consumption. However, when examining prevalence of elevated ALT in the same cohort of adolescents (NHANES 2003-2006), Fraser et al.(13) found no statistical difference in results when analyses were limited to 12-15 year olds. Finally, this study was cross-sectional, and therefore causality cannot be assumed.

In conclusion, clinically-meaningful inverse associations between CRF and ALT were found in NHANES youth, particularly in youth above the 80th percentile for ALT. A strong positive association was found between waist circumference and ALT. Future studies should examine whether interventions to improve CRF in NAFLD youth can decrease hepatic fat and liver enzyme concentrations. In addition, using quantile regression allows for a comprehensive analysis of associations regarding cardiorespiratory fitness and health epidemiology and therefore is warranted.

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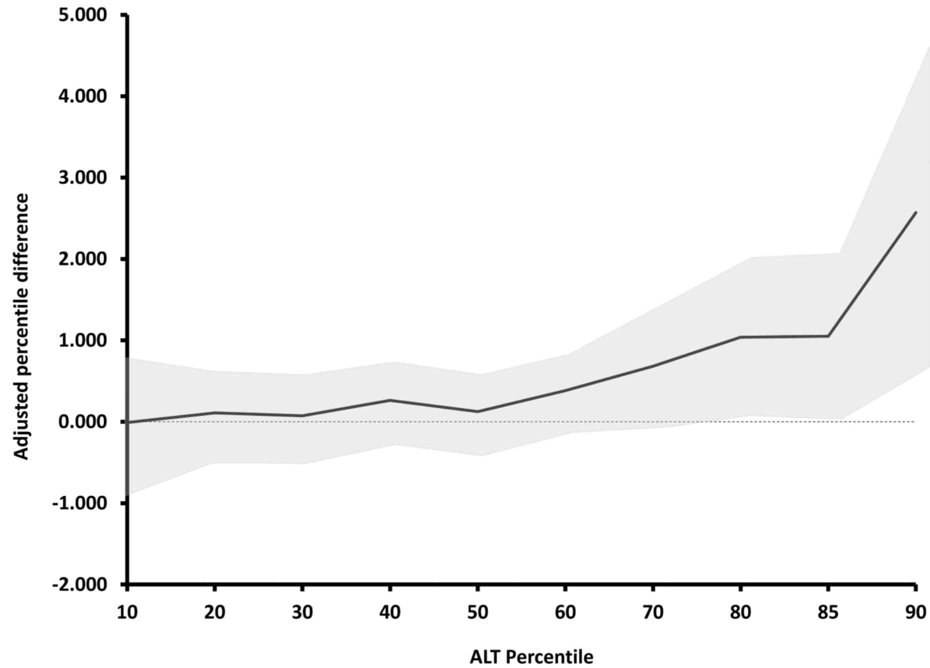

Figure 1.

Quantile regression coefficients (with 95% confidence interval) for the association of cardiorespiratory fitness across adjusted ALT percentiles.

Note (Caption below figure): Percentile difference adjusted for age, race, and waist circumference. The gray area corresponds to the 95% confidence interval. CRF: dichotomous variable, reference category was youth with adequate CRF.

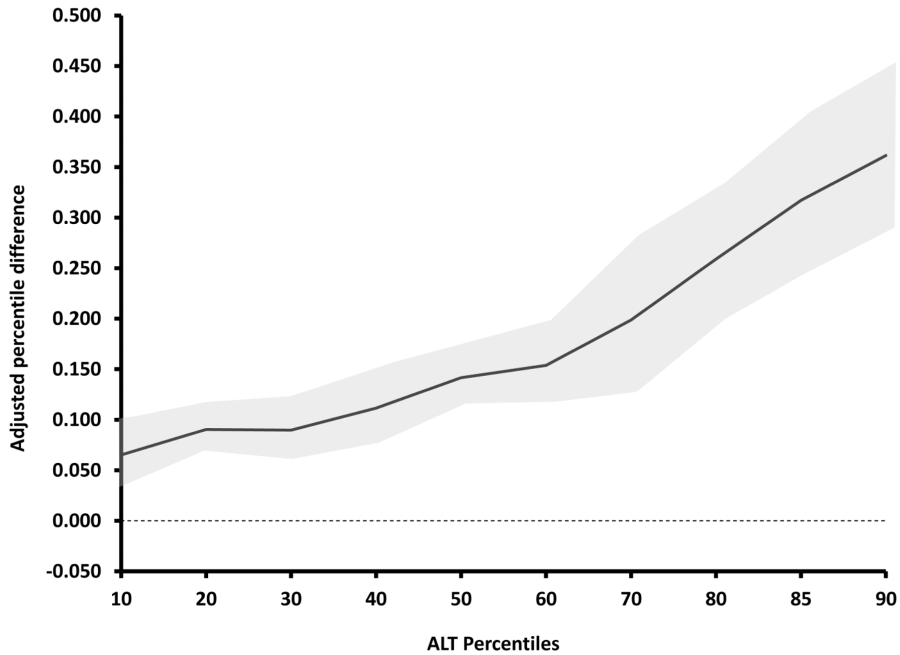

Figure 2.

Quantile regression coefficients (with 95% confidence interval) for the association of waist circumference across adjusted ALT percentiles.

Note (Caption below figure): Percentile difference adjusted for age, race, and CRF. The gray area corresponds to the 95% confidence interval.

Table 1

Participant characteristics, demographics, and cardiorespiratory fitness (N = 2844, weighted total sample N= 20,054,593). Continuous variables are weighted mean (SE), median (SE); categorical variables are weighted percent.

Variable	Total (N=2844)	Males (n=1462)	Females (n=1382)
Age (y)	15.5 (0.1), 15.5 (0.1)	15.7 (0.1), 15.7 (0.1)	15.4(0.1) *, 15.2(0.2)
Race/ethnicity (%)			
Non-Hispanic White	62.5 (2.8)	62.8 (3.0)	62.1 (3.0)
African American	14.0 (1.6)	13.5 (1.7)	14.6 (1.6)
Mexican American	11.5 (1.7)	11.8 (1.8)	11.3 (1.8)
Other	12.0 (1.6)	11.9 (1.8)	12.1 (1.8)
ALT (U/L)	18.8 (0.2), 16.0(0.1)	21.1 (0.4), 17.5 (0.2)	16.4(0.2) *, 14.6(0.1)
AST (U/L)	23.9(0.3), 21.7(0.2)	26.1 (0.4), 23.7(0.2)	21.6(0.4) *, 19.9(0.2)
GGT (U/L)	14.8 (0.2), 12.5 (0.1)	16.6 (0.3), 14.1 (0.3)	12.7(0.2) *, 11.0(0.2)
BMI (k/m^2)$^{\Phi}$	23.0 (0.2), 21.8 (0.1)	23.0 (0.2), 21.9 (0.2)	22.9 (0.2), 21.6 (0.1)
Waist circumference (cm)	80.1 (0.5), 77.0 (0.4)	81.1 (0.6), 77.7 (0.5)	79.0 (0.7) *, 76.2 (0.6)
Estimated VO_{2max} ($ml\text{-}kg^{-1}\text{-}min^{-1}$)	42.0 (0.4), 40.8 (0.5)	45.6 (0.5), 44.6 (0.5)	38.1 (0.3) *, 37.3 (0.4)
Adolescents with low CRF (%)	37.9 (2.2)	36.6 (2.8)	39.4 (2.0)
Adolescents with adequate CRF (%)	62.1 (2.2)	63.4 (2.7)	60.6 (2.1)

*P<0.05

$^{\Phi}$N=2843

Table 2

Odds Ratios (with f-values) in the multivariable models of logistic regression (ALT30 and ALT19; N = 2844, weighted total sample N= 20,054,593).

CRF (low vs. adequate)			WC	
	Odds Ratio	***P-value***	***Odds Ratio***	***P-value***
ALT30	1.5	0.095	1.06	<0.001 [*]
ALT19 [Φ]	1.6	0.03 [*]	1.05	<0.001 [*]

Models are *a priori* adjusted for age, gender, race, and WC. WC also examined as an independent variable after adjusting for age, gender,race, and CRF.

[Φ]Girls only (n=1382); cutpoint of ALT >19 U/L.

[*]P<0.05