Criterion-Referenced Cut-Points In Cardiorespiratory Fitness Associated With Metabolic Syndrome In Adult Americans

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CRITERION-REFERENCED CUT-POINTS IN CARDIORESPIRATORY FITNESS ASSOCIATED WITH METABOLIC SYNDROME IN ADULT AMERICANS

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Table of Contents

List of Figures

List of Tables

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To my Grandma and Grandpa,

although you were not here to see me succeed

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And to my family and friends,

for you are the ones that inspire me.

Abstract

Purpose: To identify criterion-referenced cut-points in cardiorespiratory fitness (CRF) associated with metabolic syndrome (MetS) in a nationally-representative sample of young- and middle-aged American adults.

Methods: The analytic sample comprised 3302 Americans aged 20–49 years who participated in the 1999–2000, 2001–2002, and 2003–2004 cycles of the National Health and Nutrition Examination Survey. CRF was assessed by a submaximal run/walk test on a treadmill. MetS was determined using American Heart Association criteria, measured as the presence of three or more risk factors (high waist circumference, high blood pressure, high fasting triglycerides, high fasting glucose, and low high-density lipoprotein cholesterol). Receiver operating characteristic (ROC) curves were used to identify gender- and age group-specific cut-points for CRF associated with increased MetS. Effect sizes of 0.56, 0.64, and 0.71 were used as thresholds for low, moderate and high, respectively.

Results: ROC analysis demonstrated high discriminatory ability of CRF to detect MetS for men aged 20–29 years (AUC = 0.77, 95% confidence interval [CI] = 0.65, 0.89), with low discriminatory ability for women aged 20–29 years (AUC = 0.59, 95%CI = 0.46, 0.72) and 40–49 years (AUC = 0.59, 95%CI = 0.49, 0.70). There was negligible discriminatory ability for all other gender and age groups (i.e., AUC <0.56).

Conclusion: This study identified the first criterion-referenced cut-points in CRF associated with MetS in a nationally-representative sample of young- and middle-aged American adults. It shows that CRF was inconsistently associated with MetS, with high discriminatory ability for men aged 20–29 years and negligible to low discriminatory ability for all other gender and age groups. CRF, therefore, shows poor utility as a screening tool for MetS except for young men.

Criterion-Referenced Cut-Points in Cardiorespiratory Fitness Associated with Metabolic Syndrome in Adults

Metabolic syndrome (MetS) is a clustering of cardiometabolic risk factors (i.e., elevated waist circumference, blood pressure, fasting blood glucose, hypertriglyceridemia, and decreased low-density lipoprotein cholesterol [LDL-c]) used in clinical, epidemiological, and research settings, as well as for population health surveillance, to identify individuals at increased risk of cardiovascular disease, type 2 diabetes, and stroke (1–5). The prevalence of MetS among American adults has remained stable from 2011–2016 at approximately 34%, though significant temporal increases have been found among young adults (aged 20–39 years), women, and some races (e.g., Asian, Hispanic) (6). The high prevalence of MetS is consistent with the high disease burden associated with cardiovascular disease (~US$200 billion annually) and type 2 diabetes (~US$245 billion annually), the first and eighth leading causes of death in the United States (2,3,7).

Typically, cardiometabolic risk factors are evaluated periodically in clinical settings using laboratory and questionnaire data to determine if lifestyle or pharmacological intervention is indicated (2). The primary risk algorithm used in the United States may misclassify risk in certain racial/ethnic groups, underestimate risk in those with low socioeconomic status, relies on self-reporting of some risk factors with known reporting bias (e.g., physical activity), and since age is a main component of disease risk, most adults under 40 years will not possess great enough risk to justify intervention (2). Thus, many adults who would benefit from lifestyle intervention, especially during early adulthood may not receive adequate information to initiate it. In addition, collecting and analyzing blood samples is time consuming, invasive, and expensive. These barriers impact the frequency of routine monitoring in clinical settings and pose significant challenges for research and population surveillance efforts needed to monitor the efficacy of population-based interventions.

Adult cardiorespiratory fitness (CRF) is significantly associated with cardiovascular and all-cause mortality (8). The American Heart Association (9) recommends CRF as a clinical vital sign because it substantially improves the net reclassification of patients in clinical settings when added to traditional risk factors. Indirect calorimetry using expired gas analysis is considered the criterion measure of CRF (i.e., maximal oxygen uptake [$\dot{V}O_{2max}$]) [9]. Unfortunately, such testing is time consuming, expensive, ecologically invalid, and requires participants to exercise at maximal capacity, which increases the risk of adverse events for some individuals. Non-gas submaximal exercise testing on the other hand is simple, relatively inexpensive, ecologically valid, and because exercise is performed at a lower intensity, the risk of adverse events is lower compared to maximal testing (9). Submaximal CRF tests (e.g., walking/running, bench stepping) are also excellent measures of functional endurance (i.e., the ability to perform submaximal ambulatory aerobic exercise using a familiar activity of daily living), which are viable tools for clinical screening and population health surveillance.

Establishing minimum levels of CRF associated with poor health outcomes (e.g., MetS) are known as cut-points. Such cut-points allow end users (e.g., clinicians, exercise professionals, teachers) to identify those who are at potential risk of poor health based on CRF test results (i.e., those in need of CRF improvement through a physical activity intervention). Cut-points have typically been established using either a normative-referenced or criterion-referenced approach. In the norm-referenced approach, an individual's CRF is compared to reference population data (normally nationally representative data) (10), although such norms may require frequent updating (especially for adult CRF given evidence of recent global declines) and the degree to which they are related to health outcomes of interest (e.g., MetS) is often poorly established. (11) The criterion-referenced approach on the other hand, compares an individual's CRF level with an absolute criterion-referenced cut-point, below which a risk to health may exist. Few studies have reported criterion-referenced health-related cut-points for CRF among adults. For example, a meta-analysis by Kodama and colleagues (2009) reported cut-points in $\dot{V}O_{2max}$ associated with increased risk of death and cardiovascular events of greater than 25–32 ml/kg/min and 18–25 ml/kg/min for 40-to 60-year-old men and women, respectively (8). In another study, Wolfe Phillips and colleagues (2020) used population-representative Canadian data and reported cut-points in $\dot{V}O_{2max}$ (estimated from modified Canadian Aerobic Fitness Test [mCAFT] results) associated with poor metabolic health of greater than 28–43 ml/kg/min and 23–37 ml/kg/min for 18-to 69-year-old men and women, respectively (12,13). Unfortunately, no criterion-referenced health-related cut-points for CRF are available for American adults. The aim of this study, therefore, was to identify criterion-referenced cut-points in CRF associated with MetS in a nationally-representative sample of young- and middle-aged Americans adults.

Methods

Survey Design and Study Population

Secondary analyses of data from the 1999–2000, 2001–2002, and 2003– 2004 cycles of the National Health and Nutrition Examination Survey (NHANES) were used for this study. These cycles of the NHANES were selected because they included CRF measurements. The NHANES program is conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). NHANES recruits a representative sample of the non-institutionalized civilian United States population using stratified, multistage, probability-based sampling. Oversampling of certain groups (e.g., persons aged 12–19 years and 60 years and older, Hispanics, non-Hispanic Blacks, pregnant women) was performed in the 1999–2004 cycles to generate reliable data that represented all ages and races/ethnicities in the United States. Data were first collected by trained technicians using household interviews, and second, at a mobile examination center where participants had additional physical and laboratory measures taken.

In the 1999–2004 cycles, 9964 individuals aged 20–49 years were screened, with 7437 examined at the mobile examination center. Of them, 2577 individuals were ineligible for CRF testing because they (a) were more than 12 weeks pregnant (n=595), (b) were physical limited preventing them from treadmill use (n=792), (c) had known cardiovascular disease, or signs/symptoms thereof (n=723), (d) lung or breathing conditions (n=515), (e) asthma symptoms (n=250), (f) were using medications (e.g., antiarrhythmics, β-blockers, nitrates, calcium channel blockers, digitalis) (n=231); or (g) other reasons (n=594).

Of those eligible to participate in CRF testing, 1558 did not meet the criteria for CRF estimation due to either early test termination (n=691) or insufficient/missing data (n=867).

Reasons for early test termination included: excessively high heart rate (*n*=425), repeated sudden heart rate variability (±30 beats/minute) (*n*=17), abnormal blood pressure response (*n*=55), participant request (*n*=82), unable to walk on the treadmill without gripping the handrails for support (*n*=55), overexertion (e.g., lightheadedness, shortness of breath, nausea) (*n*=33), technician discretion (n=32), or other specified reasons (*n*=71). Reasons for insufficient/missing data included: participant refusal (*n*=107), insufficient time to complete the test (*n*=540), equipment issues (*n*=71), insufficient/missing data (*n*=28), and otherwise unclassifiable reasons (*n*=121). This exclusion resulted in a final sample of 3302 adults aged 20 years and older.

Cardiorespiratory Fitness Test

CRF was assessed by a submaximal run/walk test on a treadmill (Quinton MedTrack ST65 Treadmill). Participants were assigned to 1 of 8 submaximal testing protocols based on their $\dot{V}O_{2max}$ predicted from age, gender, body mass index (BMI), and self-reported physical activity levels (14). The CRF protocol is described in detail elsewhere (14). Each protocol included a 2-minute warm-up, two 3-minute exercise stages, and a 2-minute cool-down, with the goal to achieve elicit a heart rate response of approximately 80% of the age predicted heart rate maximum (220 – age) by the end of the second exercise stage. Heart rate and blood pressure were measured using an automated sphygmomanometer (Colin Medical Instruments Corporation, San Antonio, Texas) at the end of the warm-up, end of each exercise stage, and each minute of recovery. Participants' rating of perceived exertion was also recorded using Borg's 6 to 20-point scale at the end of the warm-up and each exercise stage (15).

Using the equation developed by Jackson et al. (16), $\dot{V}O_{2max}$ (mL/kg/min) was estimated by extrapolating the predetermined age-specific heart rate maximum to the recorded heart rate at the end of the two exercise stages. This approach assumes a linear relationship between oxygen consumption and heart rate during treadmill exercise. In this analysis, estimated $\dot{V}O_{2max}$ values greater than 75 ml/kg/min were coded as 75 ml/kg/min (*n*=24).

Metabolic Syndrome

The NHANES anthropometry, physical examination, and laboratory procedures are described in detail elsewhere (17–21). Briefly, waist circumference was measured at end-tidal expiration using a steel measuring tape placed directly on the skin at the level of the superior lateral border of the iliac crests. Blood pressure was measured using a mercury sphygmomanometer and an appropriately sized cuff, with the average of three recordings used. Fasting triglycerides, blood glucose, and high-density lipoprotein cholesterol (HDL-c) were measured through blood plasma assays. The American Heart Association (AHA) cut-points (22) were used to determine MetS, measured as the presence of three or more of the following five risk factors: waist circumference ≥102 cm (men) or ≥88 cm (women); systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; fasting triglycerides ≥1.7 mmol/L (150 mg/dL); fasting glucose ≥5.6 mmol/L (≥100 mg/dL); and HDL-c <1.0 mmol/L (40 mg/dL) (men) or <1.3 mmol/L (50 mg/dL) (women). To account for accuracy of risk factor assessment, individuals taking prescription medication (e.g., antiarrhythmics, β-blockers, calcium channel blockers) to control any of the above risk factors were identified as at risk. Only 1561 individuals with an estimated $\dot{V}O_{2max}$ had all five risk factors for analysis.

Statistical Analyses

Statistical analyses were performed using the Statistical Analysis System Enterprise Guide (v9.4, SAS Institute, Cary, NC). All analyses were stratified by gender (male and female) and age group (20–29 years, 30–39 years, 40–49 years). Gender- and age group-specific cut-points for CRF associated with increased MetS were identified using receiver operating characteristic

(ROC) curve analysis. ROC curve values were plotted as sensitivity and 1–specificity for each potential cut-point value. The cut-point for the detection of MetS that optimized both sensitivity and specificity was obtained from Youden's index, with greater accuracy reflected by a higher score. The area under the curve (AUC) was calculated as a summary statistic that summarizes the discriminatory ability of CRF. To interpret the magnitude of AUC values, effect sizes of 0.56, 0.64 and 0.71 were used as thresholds for low, moderate and high, respectively, with effect sizes <0.56 considered to be negligible (23). Sample weights (survey, strata, and cluster weights), which account for the NHANES complex survey design (including oversampling), survey non-response, and post-stratification, were used to generate unbiased nationally-representative estimates (17).

Results

Descriptive statistics for the 1999–2004 NHANES cycles are shown in Table 1. Data were stratified by those who completed CRF testing and had $\dot{V}O_{2max}$ estimated and those who did not (i.e., participants who were ineligible for CRF testing or who were eligible but excluded [see Section titled "Survey design and study population" for more details]). On average, the CRF for men (43.7 ml/kg/min) was 22% higher compared to women (35.9 ml/kg/min).

Metabolic Syndrome Prevalence

While the prevalence of MetS increased with age, compared to adults who had $\dot{V}O_{2max}$ estimated, the prevalence of MetS among adults who did not have $\dot{V}O_{2max}$ estimated was, on average, 1.4-fold higher (range: 1.0–1.7). Similarly, mean values for the individual risk factors were 5%, 2%, 4%, and 21% higher for waist circumference, systolic blood pressure, total cholestrol, and triglycerides among adults who did not have $\dot{V}O_{2max}$ estimated. Among men and women respectively, approximately 33% and 38% had low HDL-c, 8% and 5% had elevated glucose, 32% and 19% had elevated triglycerides, 42% and 63% had high waist circumference, and 22% and 14% had high blood pressure.

Table 1. Descriptive statistics for American adults aged 20–49 years who completed CRF testing and had $\dot{V}O_{2max}$ estimated compared to those who did not.

	Estimated $\dot{V}O_{2max}$	**95% CI**	**Not Estimated/Eligible**	**95% CI**
Sample size, *n*	3302		4537	
Female %	47.8 (0.02)	(47.8, 47.8)	59.2 (0.02)	(59.2, 59.2)
Age, years	33.6 (8.7)	(33.3, 33.9)	34.9 (8.6)	(34.7, 35.2)
Ethnicity, %				
Non-Hispanic white	47.4 (0.04)	(47.3, 47.5)	42.7 (0.04)	(42.6, 42.8)
Non-Hispanic black	19.9 (0.07)	(19.8, 20.0)	22.9 (0.05)	(22.8, 23.0)
Mex American/Other	32.8 (0.05)	(32.7, 32.9)	34.5 (0.04)	(34.4, 34.6)
Education level less than high school %	25.5 (0.06)	(25.4, 25.6)	30.4 (0.05)	(30.3, 30.5)
Prevalence of MetS Classification[a], %				
Males				
20–29 years	5.2 (0.01)	(5.2, 5.2)	9.0 (0.01)	(8.95, 9.0)
30–39 years	10.7 (0.01)	(10.7, 10.8)	14.4 (0.02)	(14.4, 14.5)
40–49 years	13.4 (0.02)	(13.4, 13.4)	17.5 (0.01)	(17.5, 17.6)
Females				
20–29 years	6.2 (0.01)	(6.1, 6.2)	6.0 (0.01)	(6.0, 6.0)
30–39 years	6.7 (0.01)	(6.7, 6.7)	11.0 (0.01)	(11.0, 11.0)
40–49 years	11.9 (0.02)	(11.8, 11.9)	19.2 (0.02)	(19.2, 19.3)
Average Male $\dot{V}O_{2max}$	43.7 (8.9)	(43.3, 44.1)		
Average Female $\dot{V}O_{2max}$	35.9 (8.7)	(35.5, 36.4)		
Body Mass Index, kg/m^2	27.4 (5.9)*	(27.2, 28.6)	28.9 (6.8)	(28.7, 29.1)
Waist Circumference, cm	92.3 (14.3)*	(91.8, 92.8)	96.9 (16.1)	(96.4, 97.4)
Resting Systolic blood pressure, mmHg	115.2 (12.3)*	(114.8, 115.6)	117.3 (16.0)	(116.8, 117.8)
Resting Diastolic blood pressure, mmHg	70.8 (10.8)	(70.4, 71.1)	70.7 (14.4)	(70.2, 71.2)
HDL-c, mmol/L	1.3 (0.4)*	(1.3, 1.4)	1.4 (0.4)	(1.4, 1.4)
Triglycerides, mmol/L	1.4 (1.4)*	(1.4, 1.5)	1.7 (1.5)	(1.7, 1.8)

Abbreviations: n = sample size; SD = standard deviation; SE = standard error; $\dot{V}O_{2max}$ = maximal oxygen uptake (ml/kg/min); MetS = metabolic syndrome.
[a]Metabolic syndrome defined using the American Heart Association (17) cut-points.
[b] Values are expressed as percentage (SE) or mean (SD).
* Statistical significance from those without an estimated $\dot{V}O_{2max}$ or not eligible at $P < 0.05$.

Cut-points and AUC

Table 2 shows the ROC curve determined cut-points (and corresponding AUCs) in CRF associated with MetS for Americans aged 20–49 years. CRF demonstrated high and significant discriminatory to detect MetS for men aged 20–29 years (AUC = 0.77, 95%CI = 0.65, 0.89), with low and non-significant discriminatory ability for women aged 20–29 years (AUC = 0.59, 95%CI = 0.46, 0.72) and 40–49 years (AUC = 0.59, 95%CI = 0.49, 0.70). Negligible and non-significant discriminatory ability for CRF was demonstrated for the remaining gender and age groups (i.e., AUC <0.56) (Figure 1). The CRF cut-points associated with MetS were 35.8, 40.7, and 33.8 ml/kg/min for men aged 20–29, 30–39, and 40–49 years, respectively. The corresponding values were 30.0, 44.6, and 29.4 ml/kg/min for women aged 20–29, 30–39, and 40–49 years, respectively.

Table 2. Receiver operating characteristic curve determined cut-points in CRF associated with MetS for American adults aged 20–49 years.

		$\dot{V}O_{2max}$ Values		Association with Metabolic risk		
	n	**Mean (SD)**	**95% CI**	**ROC Cut-Point**	**AUC(SE)**	**95% CI**
Males						
20–29 years	677	45.0 (8.7)	(44.3, 45.7)	35.8	0.77 (0.06)	(0.65, 0.89)
30–39 years	578	43.0 (8.8)	(42.3, 43.7)	40.7	0.54 (0.05)	(0.43, 0.65)
40–49 years	469	42.7 (8.9)	(41.8, 43.4)	33.8	0.54 (0.06)	(0.42, 0.66)
Females						
20–29 years	584	36.9 (8.7)	(36.2, 37.6)	30.0	0.59 (0.07)	(0.46, 0.72)
30–39 years	555	35.8 (8.2)	(35.1, 36.5)	44.6	0.49 (0.06)	(0.36, 0.62)
40–49 years	439	34.8 (9.1)	(34.0, 35.7)	29.4	0.59 (0.06)	(0.49, 0.70)

Abbreviations: n = sample size; SD = standard deviation; SE = standard error; $\dot{V}O_{2max}$ = maximal oxygen consumption (ml/kg/min); CI = confidence interval; ROC = receiver operating characteristic; AUC = area under the curve.

[a] Includes all race/ethnicity groups.

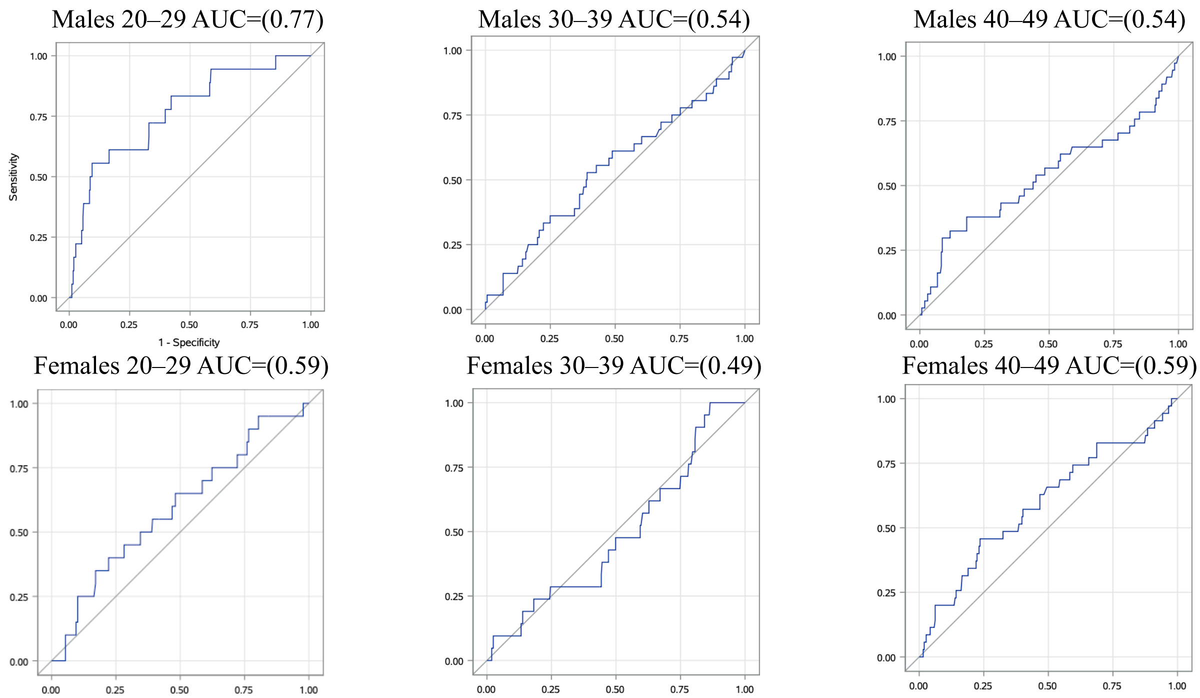

Figure 1. Receiver operating characteristic curves for CRF associated with MetS which show 1–specificity (*x*-axis) and sensitivity (*y*-axis) for American men (top three panels) and women (bottom three panels) aged 20–29 years (left two panels), 30–39 years (middle two panels), and 40–49 years (right two panels). Data source NHANES cycles 1999–2000, 2001–2002, 2003–2004.

Abbreviation: AUC = area under the curve.

Discussion

Findings

This study is the first to identify criterion-referenced cut-points for CRF associated with MetS in a nationally-representative sample of young- and middle-aged American adults. Using ROC curve analyses, a high and significant discriminatory ability for CRF among men aged 20–29 years was found, with negligible to low and non-significant discriminatory ability among all other gender and age groups. These results indicate that CRF has poor utility as a screening tool for MetS in young- and middle-aged American adults, except for young men aged 20–29 years.

Comparisons to Literature

Our findings do not line up with previous literature between CRF and metabolic risk. The challenge with identifying cut-points in CRF to metabolic risk and other health outcomes is diversity in definitions and criteria to define those at risk. In our case, the criteria is set by the AHA to identify those at metabolic risk. (5) While our study didn't find significant cut-points in CRF associated with MetS aside from in young men age 20–29 years, others did. A meta-analysis by Kodama et al. (8) showed that low CRF was significantly associated with early all-cause mortality and an increased risk of cardiovascular disease. (8) Differences in health outcomes may be a possible reason for the creation of cut-points by Kodama et al. opposed to our results. While our study included estimates of $\dot{V}O_{2max}$ collected through the use of a submaximal treadmill protocol, Kodama et al. included various modalities of CRF assessment (e.g., cycle ergometer). (8) Other differences between our study and Kodama et al.(8) include analyzed populations. The use of a meta-analysis by Kodama et al. (8) allowed for representation of various populations while ours was limited to a non-institutionalized American sample.

A study conducted by Wolfe-Phillips et al. (12) came to similar conclusions for differences in their determined cut-points and that of Kodama et al. (8). While both our study and Wolfe-Phillips et al. used ROC curve analysis to determine cut-points in CRF cut-associated with cardiometabolic risk. (12) Our cut-points did not reflect that of Wolfe-Phillips et al. (8). Differences in protocols used to estimate CRF values (mCAFT step-test) may be the reason for the creation of Canadian cut-points in CRF associated to metabolic risk. (12) Aside from different samples and CRF operationalization, criterion to determine metabolic risk was also different. Criterion used by Wolfe-Phillips et al. established those with elevated levels of waist circumference, blood pressure, and HDL-c to be at metabolic risk.

Unfortunately, the study by Wolfe-Phillips et al. is the only other research that has established cut-points in CRF associated with cardiometabolic health for young- and middle-aged adults. (12) After a validity analysis of both the submaximal treadmill test and the Canadian step test literature indicated a modest correlation ($r = 0.43$) between estimated values and measured values of CRF collected by NHANES. (27) While the mCAFT step test reported a strong correlation of ($r = .88$). (28) The nature of correlation between estimated and actual CRF values points towards using the mCAFT step test regarding that it better represents correctly estimated VO_{2max} than the NHANES submaximal treadmill test.

Strengths and limitations

Strengths of this study include the use of objectively measured CRF and MetS risk factors, the use of the AHA criteria for classification of MetS, and the large nationally-representative sample. (17) However, a limitation of the NHANES dataset is the strict inclusion criteria for the CRF treadmill test, potentially resulting in a sample healthier than the U.S.

population and representative of only young- and middle-aged American adults who were 'fit' to complete submaximal CRF testing. (24, 26)

Conclusion

This study identified the first criterion-referenced cut-points in CRF associated with MetS in a nationally-representative sample of young- and middle-aged American adults. ROC analysis showed that CRF had high discriminatory to detect MetS for men aged 20–29, with negligible to low discriminatory ability for all other gender and age groups. CRF, therefore, shows poor utility as a screening tool for MetS except for young men.

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