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Cross-validation of Non-exercise Estimated Cardiorespiratory Fitness: The NHANES Study

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Abstract

Background: Cardiorespiratory Fitness (CRF) is an independent health predictor of circulatory and respiratory systems and can be estimated using non-exercise equations. However, the accuracy of such equations in a national representative population is unknown. The objective of this study was to cross-validate 11 CRF equations developed by three different researchers using a United States representative population.

Methods and Findings: The study included 2470 adult males and females from the National Health and Nutrition Examination Survey (1999 to 2004) with measured CRF (mCRF) available in terms of maximum oxygen consumption (VO2max). The relationships between non-exercise estimated CRFs and measured VO2max were analyzed by examining the Constant Error (CE), Standard Error of Estimate (SEE), correlation coefficient (r) and Root Of Mean Square Error (RMSE). The estimated CRFs from four equations for males and six equations for females were different from mCRF, with CE values ranging from -0.712 (Jurca2) to 0.457 mL/kg/min (Jackson/fat/2level) for males and from -3.722 (Rexhepi2014) to 1.166 mL/kg/min (Jackson/fat/2level) for females ($P<0.05$ for all). Moreover, SEE, r and RMSE values ranged from 0.036 to 0.079 mL/kg/min, 0.21 to 0.344 mL/kg/min and 2.172 to 2.657

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mL/kg/min, respectively. Furthermore, the lowest RMSE values for males (Jackson/fat/5level) and females (Jurca2) represented 20.33% and 21.09% of the mean mCRFs, respectively.

Conclusion: Among the 11 equations, Jackson/fat/5level for males and Jurca2 for females provided the most valid non-exercise equations to estimate CRF in a representative US population. Future studies are warranted to develop more accurate equations based on age, gender, race and health status.

Keywords

Validation; NHANES; Cardiorespiratory Fitness; Non-Exercise

Abbreviations

BMI: Body Mass Index; CE: Constant Error; CRF: Cardiorespiratory Fitness; CS: Current Smoker; Ecrf: Estimated CRF; FFM: Fat Free Mass; mCRF: Measured CRF; Mets: Metabolic Equivalents of Task; NHANES: National Health and Nutrition Examination Survey; PA: Physical Activity; r: Correlation Coefficient; RHR: Resting Heart Rate; RMSE: Root of Mean Square Error; SEE: Standard Error of Estimate; WC: Waist Circumference

Introduction

Cardiorespiratory Fitness (CRF) is an independent health predictor of circulatory and respiratory systems and is associated with a lower risk of mortality and morbidity, particularly cardiovascular disease [1-3]. Normally presented as maximum Metabolic Equivalents of Task (METs) or maximum oxygen consumption (VO2max), CRF is used to objectively estimate or quantify an individual habitual physical activity status [3]. A maximal treadmill test is commonly considered to be the most valid method of measuring cardiovascular fitness [4,5]. Due to numerous contraindications to maximal exercise testing, sometimes submaximal exercise testing, such as 1-km walking test, is used instead of maximal testing. There is still no consensus on the optimal distance and time of the walk/run test to predict CRF. Through a meta-analysis of 123 studies, researchers concluded that 1.5 km and 12 min walk/run test was an effective alternative method to estimate CRF [6]. However, the existing maximal and submaximal exercise testing methods to measure CRF are usually costly and not feasible for large populations [7-9].

Several research groups have developed non-exercise equations to estimate CRF. In 2005, Jurca, et al., developed and validated two equations that used variables of age, gender, Body Mass Index (BMI), Resting Heart Rate (RHR) and self-reported Physical Activity (PA) [10].

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In 2012, Jackson, et al., developed four equations for men and women that included variables of age, percent of body fat (% fat), Waist Circumference (WC), RHR, Current Smoker (CS) and PA [11]. Also in 2012, Chiaranda, et al., developed and cross-validated two equations for males with cardiovascular disease using or not using β-blockers (BB), using 1-km walking test on a treadmill, which includes variables of age, BMI, mean walking speed for BB users and age, BMI and mean walking speed and peak Heart Rate (HR max) for non-BB users [5]. More recently, Rexhepi and colleagues developed an equation to estimate VO2max, which included variables of age, weight and RHR [12]. These equations are created from different populations, which makes it challenging to compare their accuracy.

Some of the above equations have been validated in other populations. Sloan, et al., cross-validated the Jurca equation among a small sample of 100 Singaporeans [13]. Mailey, et al., validated the same algorithm among 172 people aged 60-80 years [14]. Williford et al cross-validated the 1990 Jackson equation among 165 women [15,16]. Malek, et al., validated 18 equations among aerobically trained subjects (93 male and 49 female) [17]. Grazzi, et al., validated the outdoor reproducibility of the Chiaranda equation among 50 male outpatients with cardiac disease, using 1-km walking test on a flat track [5,18]. Previously, however, no study has been conducted to concurrently cross-validate non-exercise equations derived from different studies in a United States representative population. Therefore, the objective of this study was to cross-validate the selected non-exercise CRF equations in the National Health and Nutrition Examination Survey (NHANES) by comparing the measured CRF (mCRF) with the non-exercise equation estimated CRF (eCRF).

Materials and Methods

Study Population

NHANES (1999-2004) was designed to assess the health and nutritional status of adults and children in the United States [19]. Combining interviews and physical examinations, data from the survey are composed of demographic, socioeconomic, dietary, PA and health-related questions, medical, dental and physiological measurements, as well as laboratory tests. According to the manual of NHANES, data about CRF was available among those apparently healthy individuals. After excluding participants whose values on measured CRFs were missing (n=25 527), who were younger than 18 years (n=1992) and whose BMI was beyond the range of 18.5 to 40 (n=137), 2470 participants were included in the final analysis (1356 men and 1114 women). These participants have complete information about race/ethnicity, education, smoking status, physical examination (including height, weight, WC and RHR) and self-reported PA during the last month. In addition, according to the NHANES procedures, participants who were greater than 12 weeks pregnancy and taking medications such as calcium

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channel blockers, anti-arrhythmics, beta blockers, nitrates, nitroglycerin and digitalis were excluded.

Measured CRF

Each participant was assigned an exercise protocol from a total of eight different submaximal treadmill protocols based on their maximum oxygen consumption calculated by their gender, interview age, BMI and PA readiness code. Each protocol involved a two-minute warm-up, two three-minute exercise stages and two minutes of recovery (if necessary). Blood pressure and heart rate were monitored throughout. Participants performed a submaximal treadmill test until they felt pain in their chest, shoulders, or thighs or other unexpected situations occurred, such as elevated exercise blood pressure (> 260 mmHg systolic and/or >115 mmHg diastolic), significant drop (>20 mmHg) in systolic blood pressure during exercise, or rating of perceived exertion > 17. The goal of the predetermined exercise protocol was to elicit a heart rate that is approximately 75% of the predicted maximum heart rate by the end of the treadmill test.

Lightly touching handrails for balance purposes is allowed, but only if absolutely necessary. The participant's resting blood pressure and heart rate were measured and recorded in the physician's office prior to the treadmill test. Blood pressure and heart rate were monitored throughout the treadmill test with an automated electronic heart rate and blood pressure monitor Colin STBP-780. Calibration of the system was performed before each test by using a mercury manometer to calibrate the Colin STBP-780 after and treadmill calibration was checked weekly to ensure accuracy of testing results [19]. VO2max was calculated from the heart rate response to the submaximal work according to the linear relationship between heart rate (beats/min) and oxygen consumption (mL/kg/min), which was considered reliable and valid [7,8,20]. Measured CRF in METs in the current study was obtained from VO2max by dividing 3.5.

Non-exercise estimated CRF

Table 1 lists the 11 selected non-exercise equations to estimate CRF in METs (1 MET=3.5 mL O^2/kg/min).

Age was calculated by computing number of months between the date of birth and the interview date and then divided by 12. Sex was defined as 0 for women and 1 for men. BMI was calculated as weight in kilograms divided by the square of height in meters, WC was collected in centimetres, % fat was defined as percent body fat (Fat Free Mass (FFM) and was predicted by bio-impedance in the NHANES study$\%fat = \frac{weight-FFM}{weight}$), which was considered as a reference method to estimate percent body fat and RHR was measured by pulse rate in beats

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per min [21]. Current smoker was defined as smoked cigarettes, used chew tobacco/snuff, or smoked, cigars or pipes now or during last 5 days.

The PA questionnaire included 47 kinds of sports activities and other activities. Intensity values of activities (METs) were distributed according to a standardized coding scheme developed by Ainsworth [22-24]. A list of the intensity values can be found in the PAQIAF file at CDC's website [25]. PA was grouped into two and five categories based on the existing algorithms. For two categories, the active group refers to those who engaged in at least 150 minutes a week of moderate-intensity (expend 3.0 to 5.9 times the amount of energy expended at rest), 75 minutes a week of vigorous-intensity aerobic physical activity (expend 6.0 or more times the energy expended at rest), or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Conversely, the inactive group included those who do not meet this criterion [26]. For five categories, PA was divided into five groups [10]. Level 1 group was defined as those who had 0 to 4 occasions of at least moderate activity in the past 4 weeks. Level 2 group was defined as those who had 5 to 11 occasions of at least moderate activity in the past 4 weeks. Level 3 group was defined as those who had more than 12 occasions of moderate activity in the past 4 weeks. Level 4 group was defined as those who had at least 12 occasions of a mix of moderate and vigorous activities in the past 4 weeks. Level 5 group was defined as those who had more than 12 occasions of vigorous activity in the past 4 weeks.

Statistical Analysis

Continuous variables and categorical variables were presented as mean ± standard error and percentage across gender. Linear regression and Pearson's Chi-square tests were used to test the differences between mCRF and eCRF. Sampling weight, strata and cluster were considered due to the complex design of NHANES study.

The cross-validation analyses of the 11 equations in this study were based on the evaluations of the differences and correlations between mCRF and eCRF by calculating the constant error (CE = mean difference for mCRF - eCRF), correlation coefficient (r), standard error of estimates (SEE, $SEE = SD_y\sqrt{(1-r^2)}$) and root of mean square error (RMSE, $\sqrt{MSE} = \sqrt{nSS_{error}/(n-p)w}$, n is the number of the participants, p is the degree of freedom, w is the sum of the sampling weights over all observations). The Z value and p-value were analyzed using the median two-sample test since both of the two CRF values did not follow a normal distribution. We then examined the mean prediction bias between mCRF and eCRF values by Bland-Altman plot [27].

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All analyses were performed using SAS software, version 9.4 (SAS Inst., Cary, NC, USA). All the tests of significance were conducted with α=0.05. The validation is applied to the whole sample and the sub-sample stratified by BMI (normal vs. overweight/obese).

Author	Definition	Formula
Jurca, et al., (2005)	Jurca1	18.81+2.49×Sex-0.08×age-0.17×BMI-0.05×RHR+0.81×PA1+1.17×PA2+2.16×PA3+3.05×PA4
	Jurca2	21.41+2.78×Sex-0.11×age-0.17×BMI-0.05×RHR+0.35×PA1+0.29×PA2+0.64×PA3+1.21×PA4
Jackson, et al., (2012)	Jackson_fat_5 level PA	13.4967+(Age×0.1200)-(Age2×0.0017)-(%fat×0.0817)-(WC×0.0140)-(RHR×0.0342)+(PA1×0.2402)+(PA2×0.2735)+(PA3×0.7432)+(PA4×1.0346)-(CS×0.3207) (Women)
		17.7357+(Age×0.1620)-(Age2×0.0021)-(%fat×0.1057)-(WC×0.0422)-(RHR×0.0363)+(PA1×0.2153)+(PA2×0.3655)+(PA3×0.8092)+(PA4×1.1989)-(CS×0.4378) (Men)
	Jackson_fat_2 level PA	13.7415+(Age×0.1223)-(Age2×0.0018)-(%fat×0.0819)-(WC×0.0141)-(RHR×0.0349)+(Active×0.6061)-(CS×0.3188) (Women)
		18.1395+(Age×0.1662)-(Age2×0.0022)-(%fat×0.1077)-(WC×0.0431)-(RHR×0.0380)+(Active×0.6429)-(CS×0.4339) (Men)
	Jackson_bmi_5level PA	14.5493+(Age×0.1136)-(Age2×0.0016)-(BMI×0.1500)-(WC×0.0088)-(RHR×0.0359)+(PA1×0.2091)+(PA2×0.2275)+(PA3×0.7021)+(PA4×1.0070)-(CS×0.3005) (Women)
		20.8013+(Age×0.1610)-(Age2×0.0022)-(BMI×0.2240)-(WC×0.0334)-(RHR×0.0375)+(PA1×0.2163)+(PA2×0.3447)+(PA3×0.7877)+(PA4×1.1961)-(CS×0.4306) (Men)
	Jackson_bmi_2level PA	14.7873+(Agex0.1159)-(Age2x0.0017)-(BMIx0.1534)-(WCx0.0088)-(RHRx0.0364)+(Activex0.5987)-(CSx0.2994) (Women)
		21.2870+(Age×0.1654)-(Age2×0.0023)-(BMI×0.2318)-(WC×0.0337)-(RHR×0.0390)+(Active×0.6351)-(CS×0.4263) (Men)
Rexhepi (2014)	Rexhepi 2014	VO2max×1000/weight/3.5
		Where VO2max= 3.542 + (–0.014 × age) + (0.015 × weight) + (–0.011 × RHR)
BMI: Body Mass Index; CS: Current Smoking; PA: Physical Activity; RHR: Resting Heart Rate; WC: Waist Circumference; %fat, percent body fat. CS: o=smoking, 1=non-smoking; Sex: 0=female, 1=male; Active: 0=not active, 1=active		

Table 1: List of the 11 non-exercise Cardiorespiratory Fitness (CRF) equations.

Results

Table 2 shows the descriptive characteristics of the participants by gender. The baseline characteristics were completely different between males and females (P<0.05 for all) except in race/ethnicity and education.

The results of cross-validation analyses are presented in Table 3. The z values ranged from -3.823 (P < 0.0001) to 2.458 (P =0.014) for males and from -29.06 (P < 0.0001) to 14.488 (P < 0.0001) for females. Measured VO2max is close to the estimated CRFs in Jackson/bmi/5level (P=0.357), Jackson/bmi/2level (P=0.357) and Rexhepi2014 (P=0.124) for males and Jurca1 (P=0.8654) for females. The CE values ranged from -0.712 (Jurca2) to 0.457 (Jackson/fat/2level) for males and -3.722 (Rexhepi2014) to 1.166 (Jackson/fat/2level) for females. The validity coefficients (Rs) ranged from 0.258 (Rexhepi2014) to 0.344 (Jackson/fat/5level) for males and from 0.21 (Jackson/bmi/2level) to 0.266 (Jurca2) for females. The SEE values ranged from 0.051 (Jackson/bmi/2level) to 0.06(Jurca1) for males and from 0.036 (Jackson/fat/2level) to 0.079 (Jurca1) for females. Accounting for the errors related to both the CE and SEE, the RMSE values ranged from 2.582 (Jackson/fat/5level) to 2.657 (Rexhepi2014) for males and from 2.172 (Jurca/2) to 2.204 (Jackson/bmi/2level) for females.

The Bland-Altman plots present the agreement between measured and estimated CRF values (Fig. 1). The variance of difference between eCRF and mCRF is unstable as the average of eCRF and mCRF increases. Moreover, the difference between eCRF (Rexhepi2014) and mCRF is the largest among these seven comparisons.

After dividing the population into three groups according to BMI (BMI<25 as normal weight, 25≤BMI<30 as overweight and 30≤BMI≤40 as obese), subgroup analyses were conducted (Tables 4 and 5). In the normal weight group (598 males and 551 females), the eCRF from Jackson/fat/5level (P=0.817) and Jackson/fat/2level (P=0.5632) for men or Jackson/bmi/5level (P=0.081) and Jackson/bmi/2level (P=0.081) for women were close to the corresponding mCRFs. %RMSE values are lower than those from the overall sample, which indicates these equations fit the normal weight group.

In the overweight group (507 males and 309 females), the eCRF from Jurca1 (P=0.028) and Jurca2 (P<0.0001) for men were different from the corresponding mCRFs and the eCRF values from Jurca1 for women were similar to the actual VO2max values. %RMSE values are obviously higher than those from the overall sample in men, which indicates these equations may not fit the overweight men. However, the results of the overweight women are opposite.

In the obese group (251 males and 254 females), only the eCRFs from Jurca1 for men and from Jurca2 for women were close to the corresponding mCRFs. %RMSE values were lower than those among the overall sample, which indicates these equations were valid for obese subgroup.

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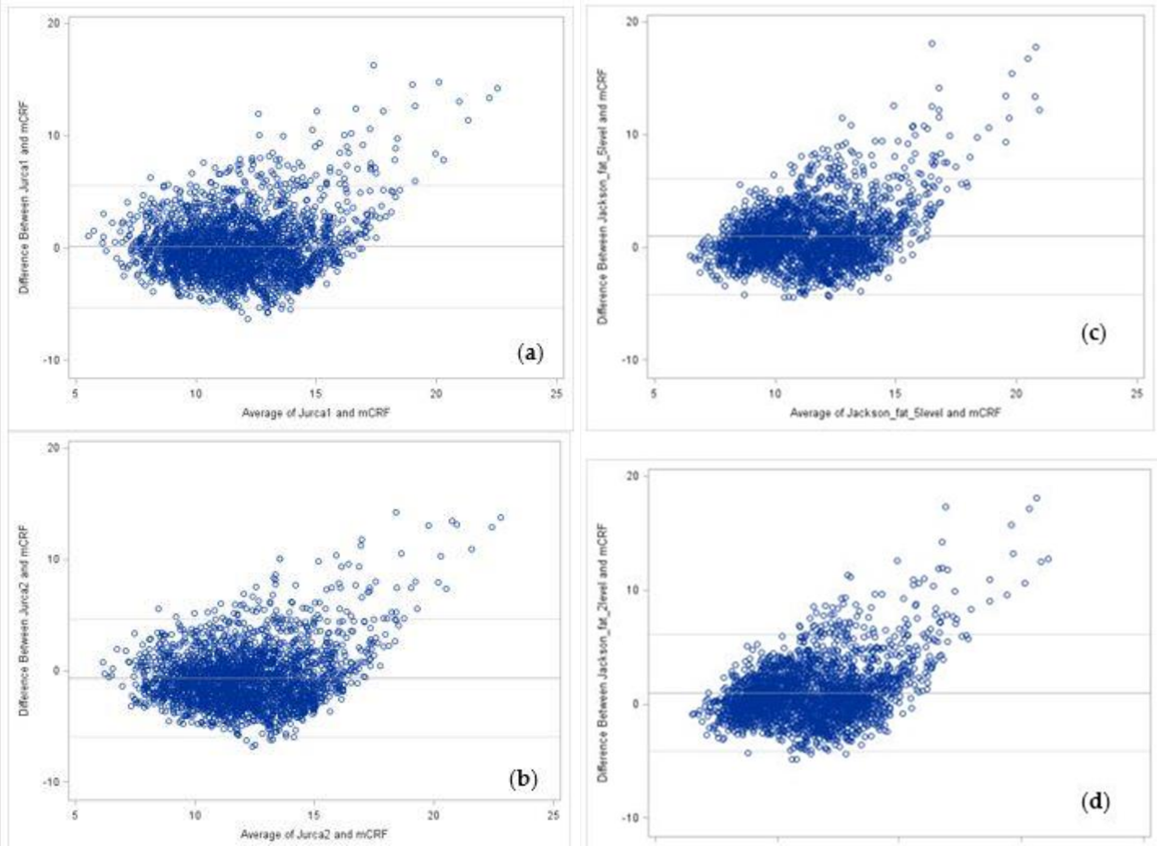

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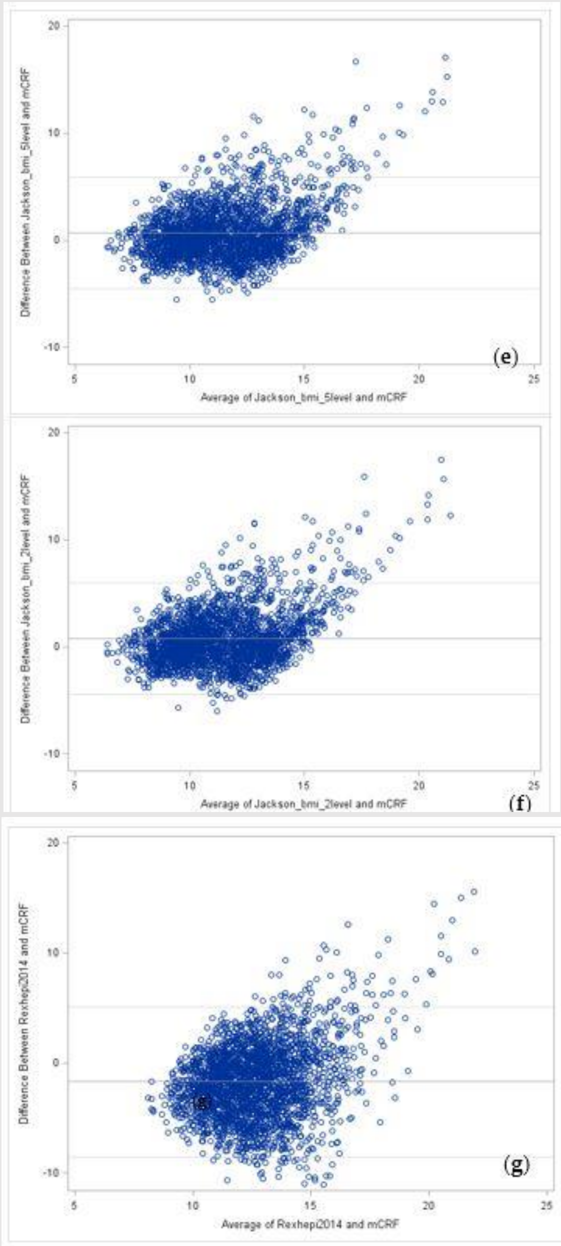

Figure 1: Bland-Altman plots representing both males and females show the differences between estimated Cardiorespiratory Fitness (CRF) from (a) Jurca1; (b) Jurca2; (c) Jackson_fat_5level; (d) Jackson_fat_2level; (e) Jackson_bmi_5level; (f) Jackson_bmi_2level); (g) Rexhepi2014 and measured CRF. The dark line in each plot indicates the mean difference and light lines indicate the 95% limits of agreement.

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Variables	All	Men	Women	P-value
	(N=2470)	(N=1356)	(N=1114)	
Age (years)	32.1（0.3）	31.7(0.3)	32.6(0.4)	0.0215
Height (cm)	171.4（0.3）	177.8(0.3)	164.0(0.2)	<.0001
Weight (kg)	77.5(0.4)	84.2(0.5)	69.6(0.5)	<.0001
BMI (kg/m²)	26.2(0.1)	26.6(0.1)	25.9(0.2)	0.0051
WC (cm)	90.0(0.3)	93.6(0.4)	85.8(0.5)	<.0001
RHR (bpm.)	70.7(0.4)	68.3(0.4)	73.4(0.4)	<.0001
PA（%）				
2-level				0.0004
0	26	21.9	30.8	
1	74	78.1	69.2	
5-level				<.0001
0	15	15.3	14.6	
1	17.3	18.6	15.9	
2	14.8	10.8	19.4	
3	12.7	14.1	11	
4	40.2	41.2	39.1	
Current smoker（%）	30.8	36.9	23.7	<.0001
Race/ethnicity（%）				0.4566
Non-hispanic White（%）	73.4	72.6	74.3	
Non-hispanic Black（%）	9.1	9	9.2	
Hispanic and other（%）	17.5	18.4	16.5	
Education(≥12years)（%）	82.4	81.3	83.6	0.1287
BMI: Body Mass Index; PA: Physical Activity; RHR: Resting Heart Rate; WC: Waist Circumference; %fat: percent body fat.				

Table 2: Baseline characteristics of participants by gender.

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Equation	Men (N=1356)								
	Difference Analysis				Correlation Analysis				
	X	CE	Z	P	R	SEE	%SEE	RMSE	%RMSE
Measured CRF	12.7±0.1								
Jurca1	12.7±0.1	0.076±0.095	-4.531	<0.0001	0.321	0.060	0.476	2.605	20.51
Jurca2	13.5±0.1	-0.712±0.103	-13.823	<0.0001	0.311	0.051	0.405	2.614	20.58
Jackson_fat_5level	12.3±0.1	0.456±0.095	2.458	0.014	0.344	0.055	0.435	2.582	20.33
Jackson_fat_2level	12.3±0.1	0.457±0.099	2.227	0.026	0.333	0.053	0.414	2.593	20.42
Jackson_bmi_5level	12.4±0.1	0.360±0.100	-0.922	0.357	0.312	0.053	0.416	2.613	20.57
Jackson_bmi_2level	12.4±0.1	0.365±0.105	-0.922	0.357	0.293	0.051	0.401	2.629	20.7
Rexhepi2014	12.5±0.1	0.217±0.108	-1.537	0.124	0.258	0.051	0.403	2.657	20.92
	Women (N=1114)								
	Difference Analysis				Correlation Analysis				
	X	CE	Z	P	R	SEE	%SEE	RMSE	%RMSE
Measured CRF	10.3±0.1								
Jurca1	9.9±0.1	0.392±0.078	-0.169	0.8654	0.251	0.079	0.771	2.182	21.18
Jurca2	10.4±0.1	-0.101±0.078	-7.286	<0.0001	0.266	0.062	0.604	2.172	21.09
Jackson_fat_5level	9.2±0.0	1.146±0.072	13.556	<0.0001	0.257	0.038	0.366	2.178	21.15
Jackson_fat_2level	9.1±0.0	1.166±0.076	14.488	<0.0001	0.259	0.036	0.346	2.179	21.16
Jackson_bmi_5level	9.6±0.0	0.698±0.073	5.596	<0.0001	0.218	0.046	0.446	2.199	21.35
Jackson_bmi_2level	9.6±0.0	0.758±0.076	5.596	<0.0001	0.21	0.044	0.429	2.204	21.4
Rexhepi2014	14.0±0.1	-3.722±0.078	-29.06	<0.0001	0.213	0.076	0.736	2.202	21.38
CE: Constant Error; R: Correlation Coefficient; RMSE: Root of Mean Square Error; SEE: Standard Error of Estimates. X, CE, SEE and RMSE between measured versus predicted peak·VO2 mean values in ml/kg/min.									

Table 3: Comparison of the various Cardiorespiratory Fitness (CRF) equations by gender.

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Equation	Difference Analysis				Correlation Analysis				
	X	CE	Z	P	R	SEE	%SEE	RMSE	%RMSE
				18.5≤BMI<25 (N=598)					
Measured CRF	13.4±0.1								
Jurca1	13.8±0.1	-0.348±0.124	-7.053	<0.0001	0.309	0.089	0.666	2.546	19
Jurca2	14.5±0.1	-1.109±0.130	-13.18	<0.0001	0.308	0.085	0.632	2.547	19.01
Jackson_fat_5level	13.1±0.1	0.284±0.126	0.231	0.817	0.328	0.082	0.611	2.529	18.87
Jackson_fat_2level	13.1±0.1	0.316±0.126	0.5781	0.5632	0.315	0.075	0.562	2.541	18.96
Jackson_bmi_5level	13.7±0.0	-0.289±0.125	-5.087	<0.0001	0.318	0.046	0.347	2.539	18.95
Jackson_bmi_2level	13.7±0.0	-0.270±0.129	-5.087	<0.0001	0.294	0.04	0.3	2.559	19.1
Rexhepi2014	14.0±0.1	-0.580±0.143	-8.209	<0.0001	0.201	0.083	0.62	2.623	19.57
				25≤BMI<30 (N=507)					
Measured CRF	12.5±0.2								
Jurca1	12.3±0.1	0.207±0.185	-2.197	0.028	0.272	0.078	0.625	2.751	22.01
Jurca2	13.1±0.1	-0.610±0.190	-8.852	<0.0001	0.226	0.058	0.465	2.785	22.28
Jackson_fat_5level	12.1±0.1	0.392±0.176	0.188	0.851	0.272	0.07	0.559	2.751	22.01
Jackson_fat_2level	12.1±0.1	0.368±0.183	0.439	0.6603	0.243	0.065	0.519	2.773	22.18
Jackson_bmi_5level	12.1±0.0	0.401±0.178	0.439	0.66	0.248	0.044	0.351	2.769	22.15
Jackson_bmi_2level	12.1±0.0	0.385±0.186	0.188	0.851	0.205	0.039	0.313	2.798	22.38
Rexhepi2014	12.1±0.0	0.457±0.181	-0.565	0.572	0.13	0.047	0.374	2.835	22.68
				30≤BMI≤40 (N=251)					
Measured CRF	11.9±0.1								
Jurca1	11.2±0.1	0.645±0.164	-0.803	0.422	0.086	0.114	0.961	2.306	19.38
Jurca2	12.0±0.1	-0.131±0.146	-4.013	<0.0001	0.097	0.094	0.789	2.304	19.36
Jackson_fat_5level	11.0±0.1	0.933±0.151	3.3	0.001	0.201	0.089	0.748	2.268	19.06
Jackson_fat_2level	11.0±0.1	0.927±0.147	2.943	0.0033	0.226	0.083	0.698	2.255	18.95
Jackson_bmi_5level	10.3±0.1	1.569±0.167	7.045	<0.0001	0.117	0.093	0.778	2.299	19.32
Jackson_bmi_2level	10.3±0.1	1.594±0.163	7.937	<0.0001	0.137	0.086	0.72	2.293	19.27
Rexhepi2014	10.6±0.1	1.306±0.144	4.905	<0.0001	0.047	0.065	0.543	2.312	19.43

CE: Constant Error; R: Correlation Coefficient; RMSE: Root of Mean Square Error; SEE: Standard Error of Estimates.
X, CE, SEE and RMSE between measured versus predicted peak·VO2 mean values in ml/kg/min

Table 4: Subgroup analyses across categories of Body Mass Index (BMI) in men.

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Equation	Difference Analysis				Correlation Analysis				
	X	CE	Z	P	R	SEE	%SEE	RMSE	%RMSE
				18.5≤BMI<25 (N=551)					
Measured CRF	10.7±0.1								
Jurca1	10.8±0.1	-0.044±0.115	-3.553	0.0004	0.288	0.074	0.691	2.252	21.05
Jurca2	11.2±0.1	-0.504±0.127	-9.093	<0.0001	0.267	0.059	0.553	2.266	21.18
Jackson_fat_5level	9.6±0.0	1.121±0.106	8.612	<0.0001	0.303	0.045	0.423	2.241	20.94
Jackson_fat_2level	9.6±0.0	1.153±0.109	8.973	<0.0001	0.282	0.042	0.39	2.256	21.1
Jackson_bmi_5level	10.3±0.0	0.408±0.116	1.746	0.081	0.267	0.037	0.341	2.266	21.18
Jackson_bmi_2level	10.2±0.0	0.469±0.119	1.746	0.081	0.23	0.034	0.318	2.288	21.38
Rexhepi2014	15.4±0.1	-4.731±0.127	-25.714	<0.0001	0.169	0.064	0.6	2.318	21.66
				25≤BMI<30 (N=309)					
Measured CRF	9.9±0.1								
Jurca1	9.6±0.1	0.286±0.169	-0.08	0.936	0.073	0.12	1.209	2.029	20.49
Jurca2	10.1±0.1	-0.192±0.141	-4.421	<0.0001	0.138	0.093	0.942	2.014	20.34
Jackson_fat_5level	9.0±0.1	0.906±0.113	6.833	<0.0001	0.104	0.053	0.536	2.023	20.43
Jackson_fat_2level	8.9±0.0	0.941±0.111	6.994	<0.0001	0.126	0.044	0.444	2.018	20.38
Jackson_bmi_5level	9.4±0.1	0.503±0.116	3.939	<0.0001	0.022	0.051	0.518	2.034	20.55
Jackson_bmi_2level	9.3±0.0	0.581±0.114	4.743	<0.0001	0.038	0.043	0.432	2.034	20.55
Rexhepi2014	13.2±0.1	-3.284±0.129	-18.248	<0.0001	0.058	0.08	0.809	2.031	20.52
				30≤BMI≤40 (N=254)					
Measured CRF	9.8±0.2								
Jurca1	8.1±0.2	1.743±0.186	5.496	<0.0001	0.062	0.156	1.594	2.069	21.11
Jurca2	8.7±0.1	1.137±0.164	1.773	0.076	0.137	0.129	1.315	2.053	20.95
Jackson_fat_5level	8.3±0.1	1.560±0.158	9.042	<0.0001	0.021	0.072	0.737	2.072	21.14
Jackson_fat_2level	8.3±0.1	1.525±0.161	8.333	<0.0001	0	0.066	0.676	2.073	21.15
Jackson_bmi_5level	8.1±0.1	1.776±0.158	9.574	<0.0001	0.029	0.079	0.808	2.072	21.14
Jackson_bmi_2level	8.0±0.1	1.807±0.163	9.574	<0.0001	0.011	0.078	0.798	2.073	21.15
Rexhepi2014	11.4±0.1	-1.574±0.168	-10.283	<0.0001	0.01	0.093	0.948	2.073	21.15

Table 5: Subgroup analyses across categories of Body Mass Index (BMI) in women.

Discussion

The purpose of the present study was to cross-validate 11 existing non-exercise CRF equations using data from the NHANES, which includes age, gender, BMI, RHR and self-reported PA. To the best of our knowledge, this is the first study to concurrently cross-validate the non-exercise equations developed by Jurca, Jackson and Rexhepi in a U.S. representative population. Our results showed that most of the prediction equations are valid, but not as good as the results in their original studies [12,28,29]. Three equations (Jackson/bmi/5level, Jackson/bmi/2level and Rexhepi2014) for males and Jurca1 for females in the present study slightly underestimated CRF (P>0.05 for each, Table 3). Most algorithms also underestimated CRF in both males and females. The eCRF from Jurca1 equation for females and Rexhepi2014

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equation for males were similar to mCRF, especially the latter which only slightly underestimated CRF by 0.217 METs.

As presented in Table 3, the correlation coefficients in the current study were lower than the values from the original studies [12,28,29]. The SEE values for the algorithms in the current study were generally lower than the common studies for both males and females, indicating that the eCRF from the selected equations was not comparable to those associated with other indirect methods for estimating CRF [30-34]. Commonly, SEE values for estimating CRF from various field methods such as step count tests, walk/run tests, or submaximal cycle ergometer tests represent approximately 10%-20% of the mCRF [17]. The variation of mCRF in the sample population in this study was commonly smaller than that in other studies, resulting in a smaller SEE value in this study [14,35,36]. Larger sample size and relatively young and middle-aged people with a small age span might explain the smaller variation of mCRF in the current study.

Although the SEE value provides considerable information in regard to the error related to the regression for mCRF versus eCRF, to determine the accuracy of an equation, the RMSE value is the best single criterion due to its combining errors related to both SEE and CE [17]. In the present study, Jackson/fat/5level (2.582 METs; 20.3% of mCRF) and Jurca2 (2.172 METs; 21.1% of mCRF) displayed the lowest RMSE values for males and females, respectively. The SEE and TE will be equal only when the means for actual and predicted VO2max values are identical (CE =0). Valid equations exhibit close agreement between the SEE and TE values [37]. In the present investigation, there were large differences (≥2.527 ml/kg/min for the males and ≥ 2.103 ml/kg/min for the females) between the SEE and TE for all equations. Based on the low RMSE and SEE values, no relationships between the CE values and mCRF, high correlation coefficients and small differences between the SEE and TE values, Jackson/fat/5level was the best recommendation for estimating CRF in males and Jurca2 in females. However, all of these equations need to be improved due to their low R values, which were apparently lower than previous studies [38-40].

As shown in Tables 4 and 5, results from the subgroup analyses are consistent with those of the overall sample. In the normal weight group, Jackson/fat/5level was the best equation for both males and females. In the overweight group, Jurca1 and Jurca2 were the best equations for males and females, respectively. In the obese group, Jackson/fat/2level and Jurca2 were the best equations for men and women, respectively. Obviously, there is a descending trend for accuracy when the average BMI of the population is ascending, which indicates that these equations' application range is not wide and that BMI could be considered as a factor affecting the accuracy of these equations. Cureton, et al., suggested that BMI may have a negative effect on the prediction of CRF, which is reasonable due to BMI's crude reflection of body fatness [41]. On the other hand, excessive amount of body fat has a negative effect on cardiorespiratory functions and oxygen uptake [42-44]. Therefore, as BMI increases, CRF value will decrease. Our results are consistent with Rexhepi, et al., showing that the selected equations are more applicable to people with higher maximum oxygen consumption [12]. Therefore, the increasing BMI indirectly reduces the accuracy of these estimations.

PA distribution was different between the current study and the previous studies. The distribution of PA in the present study (the proportion of Level 4 was 40.2%) was apparently different from that in Jurca et al study (the proportion of Level 4 was 6.0% for Jurca1 and 15.1% for Jurca2) which could contribute to the differences between the present and the previous study. There is evidence that PA is the primary determination of individual CRF level [10,45,46]. We could also see that PA was heavily weighted in Jurca's and Jackson's models. Jackson et al pointed out that non-exercise models had a tendency to underestimate highly fit individuals due to the design of the PA scale [15]. Furthermore, the sample population in our study was apparently fitter compared with original populations [10-12]. Therefore, it is plausible that equations used in the study underestimated highly fit people [16]. They also assumed that less misclassification contributed to stronger association for CRF, which indicated that the division of PA in the present study, which is not in accordance with that in the study of Jurca, et al., may be the reason for the weaker correlation.

Jackson et al reported that the percentage fat algorithms were more accurate than the BMI models, with which the present results were consistent [11]. They also reported that equations with two-level physical activity were nearly as accurate as five-level, which were different from the current study. From the present results, the percentage fat/bmi algorithm with five-level was more accurate than the percentage fat/bmi algorithm with two-level, except for women in the overweight group (Table 5) and men in fat group (Table 4).

Rexhepi, et al., suggested that the equation might accurately predict the VO2max values of athletes, which indicated that this equation was more applicable among populations whose average VO2max was high [12]. The present results supported this, for men (VO2max values were higher) had lower CE, SEE% and RMSE% values and higher correlation coefficients than women. The correlation coefficients among the normal group who had the largest average mCRF were apparently higher than in the other group (Table 4). Prediction of the Rexhepi equation was not as accurate as others, which was supposed to be weak at estimating CRF among normal population not athletes. Moreover, Rexhepi2014 was not related with gender, which might be the reason of lower correlation with mCRF than other equations which were gender-specific or deriving gender as a variable. Overall, the gender-specific equations were more accurate [47,48].

The major strength of the study is that the application of these eleven equations is relatively unified, resulting in the validation of CRF being comparable and meaningful. One of the limitations of this study is that the grouping of PA is not consistent with all of the original studies due to the available data in the NHANES, which may contribute to the differences among them. And participants ranged in age from 18-49 year (mean=32.1 years), younger than the population from the studies conducted by Jurca and Jackson (mean=41.6-48.2 years)

[10,11]. Second, the age range of the current study was relatively narrow, leading to the result being not broadly representative of the population. Further validation of the equation in a wider age group is needed to improve its clinical value. Third, some variables available in the NHANES were inaccurate due to measurement concerns such as the definition of %fat and mCRF, which were estimated by algorithms. Fourth, it is not accurate to divide the VO2 max by 3.5 to get the measured CRF value. Wilms et al. demonstrated that as BMI increased, a 1-MET value would gradually decrease rather than simply using the constant 3.5 ml O2/kg/min, especially among overweight to severely obese subjects [49]. However, the influence of individual differences on the estimated value can be appropriately reduced by using measured or predicted Resting Metabolic Rate (RMR) (ml O2/kg/min or kcal/kg/h) as the correction factor [50]. Fifth, a maximal treadmill test is commonly considered to be the most valid method of measuring cardiovascular fitness; nevertheless, the eight NHANES protocols were all submaximal exercise tests, which may lead to relatively larger SEE, typically in the range of ±10% to 15% [4]. Finally, the number of subjects in each group was relatively small in the sub-study, which might result in reduced statistical power.

Conclusion

The current study findings support that non-exercise estimated CRF from Jackson/fat/5level for males or Jurca2 for females and treadmill-based estimates of CRF are moderately correlated in a representative US population. Therefore, these methods could provide an alternative method for estimating CRF when the objective measurement of CRF is not feasible. In addition, equations are more applicable for normal BMI group. This observation indicates we might be able to choose the equations that are more accurate for certain BMI status. Future studies are warranted to develop and validate more accurate non-exercise equations according to age, gender, race and health status.

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Availability of Data and Materials

The NHANES data are publicly available from the National Center for Health Statistics:

https://wwwn.cdc.gov/nchs/nhanes/Default.aspx

Competing and Conflicting Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

The concept and design for paper was by XS and JZ; QS, SC and YW analyzed the data; QS drafted the first draft; SC, YW, JZ, CJL and XS all provided critical input to the manuscript draft for intellectual content and approved final document.

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