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Revisiting age-predicted maximal heart rate: Can it be used as a valid measure of effort?

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Abstract

Introduction—Despite high error ranges, age-predicted maximal heart rate (APMHR) is frequently used to gauge the achievement of adequate effort during an exercise test. The current analysis revisits this issue using the Fitness Registry and the Importance of Exercise: National Database (FRIEND Registry).

Methods—A total of 4,796 (63% male) apparently healthy subjects underwent a maximal cardiopulmonary exercise test on a treadmill. The mean age, maximal heart rate (HR), and maximal aerobic capacity of the cohort were 43 ± 12 years, 178 ± 15 beats per minute, and 36.1 ± 10.6 mlO₂ · kg⁻¹ · min⁻¹, respectively. All subjects reached or surpassed a peak respiratory exchange ratio of 1.10. A linear regression equation using age to predict maximal HR was validated in 3,796 subjects and cross-validated in the remaining 1,000 (randomly assigned).

Results—The APMHR equation in the validation cohort was as follows: $209.3 - 0.72(\text{age})$. The *r* value and standard error of estimate for this regression was 0.61 ($P < .001$) and 11.35 beats/min, respectively. A 1-sample *t* test revealed that the mean difference between actual maximal HR and APMHR was not significantly different from 0 (mean difference = 0.32, $P = .43$). However, Bland-Altman revealed high limits of agreement (upper 25.31 and lower -24.67) and a significant proportional bias.

Discussion—The APMHR equation derived from this analysis included a large cohort of apparently healthy individuals with maximal exercise effort validated by the criterion standard (ie, peak respiratory exchange ratio). Using APMHR in this capacity should be discouraged, and new approaches to gauging an individual's exercise effort should be explored.

Determining one's maximal aerobic capacity and the physiologic response to a maximal exertional stimulus affords a wealth of clinically valuable information.¹ A key to the value of information obtained from aerobic exercise testing is the assurance of maximal effort. The noninvasive criterion standard for determining maximal aerobic effort is the peak respiratory

exchange ratio (RER). A peak RER ≥ 1.10 , which is the ratio of carbon dioxide production to oxygen consumption (VO_2), is widely accepted as an indicator of maximal aerobic exercise effort.² Unfortunately, ventilatory expired gas analysis is not available in all settings that conduct exercise tests. For example, ventilatory expired gas analysis is rarely performed in cardiology stress testing laboratories that perform exercise assessments in individual with suspected myocardial ischemia. In the absence of ventilatory expired gas analysis, there is a need for other approaches to ensure maximal effort has occurred.

Age-predicted maximal heart rate (APMHR) is a well-established method by which health care professionals have gauged exercise effort; the only factor considered in this regression is one's age.³ Although numerous age-based regressions have been proposed, the most commonly used prediction equation for APMHR is $220 - \text{age}$.⁴ Moreover, achieving $\geq 85\%$ of APMHR is commonly used to define an "acceptable exercise effort" in clinical exercise testing laboratories, despite the fact that such an approach is not recommended given the considerable prediction error (ie, an SD of ± 12 beats per minute [bpm]).³

Previous analyses used to develop APMHR regression equations have not always required a peak RER ≥ 1.10 as an inclusion criterion for validation cohorts.⁴⁻⁶ Such a study, in a sample of sufficient size to perform both a robust validation and cross-validation analysis, may be used to more definitively determine if APMHR is a valid approach to quantifying exercise effort. The primary aim of the current investigation was to undertake such an analysis.

Methods

In 2014, a multi-institutional initiative, the "Fitness Registry and the Importance of Exercise: A National Data Base" (FRIEND) Registry was established by the cardiorespiratory fitness (CRF) advisory board with the primary charge of establishing normative CRF values in the United States across the adult life span.⁷ Briefly, laboratories from within the United States that were experienced in cardiopulmonary exercise testing (CPX) administration and had access to data collected with rigorous methodology were invited to be considered for inclusion in the FRIEND Registry. The CPX laboratories contributing data to the FRIEND Registry were all determined to be, by the CRF advisory board, well-established, demonstrating valid and reliable calibration and testing procedures as well as using experienced personnel qualified to conduct exercise tests. The characteristics of all participating CPX laboratories are consistent with recommendations provided in recently published guidelines.^{8,9} These CPX laboratories were provided a core guidance document, as well as a standardized Excel spreadsheet to be used for data submission to contribute their data to FRIEND. The guidance document contained an established glossary of terms and a data dictionary. This document enabled participating sites to prepare data in a manner consistent with the established goals of the national registry project.¹⁰ Through this process, data entry errors were also minimized. Contact information for the FRIEND core CPX laboratory (ie, e-mail and phone) was also provided to participating sites in the event questions arose while preparing their data set for submission. Participating CPX laboratories were responsible for obtaining local institutional review board approval for inclusion in the FRIEND Registry, providing documentation that they were authorized to submit de-identified, coded data to the core CPX laboratory housed at the University of Illinois at

Chicago. Institutional review board approval for the core CPX laboratory was also obtained at the University of Illinois at Chicago. The FRIEND advisory board reviewed the data from each CPX laboratory for uniformity prior to inclusion in the registry. Databases from each participating site included key baseline characteristics and CPX measures. The University of Illinois Chicago core CPX laboratory performed an analysis of all submitted data to ensure data points were within expected normal ranges and subsequently created a single merged database. In the event errors were identified or data points were outside the normal expected range, the CPX laboratory submitting the data in question was contacted for clarification, data validation and, if needed, correction.

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Cohort and study data points

The current analysis included 4,796 tests from the following participating CPX laboratories: (1) Ball State University; (2) Brooke Army Medical Center, (3) John Hopkins University, (4) Southern Connecticut State University, and (5) University of Tennessee. Tests were conducted between September 1998 and January 2015. Ninety-three percent of the tests were conducted to assess the functional capacity of individuals within a given community. Five percent of the tests were conducted to assess ventilatory mechanics during exercise (ie, exertional dyspnea), and the remaining 2 percent were conducted as part of a research protocol. Inclusion criteria for the current analysis included CPX data on men and women: (1) aged ≥ 20 years, (2) with maximal exercise tests performed on a treadmill, and (3) achieving a peak RER value ≥ 1.10 . Any subject identified as having a preexisting medical condition (eg, cardiovascular disease, hypertension, diabetes, pulmonary disease, etc) and/or taking a β -blocking or calcium-channel blocking agent was excluded. Thus, the cohort included apparently healthy subjects who achieved maximal exertion by established peak RER criteria.² Peak $\dot{V}O_2$, peak RER, resting and maximal heart rate (HR), peak systolic blood pressure, peak rate pressure product (RPP), and peak rating of perceived exertion on the 6-20 Borg scale³ were the CPX variables reported in the current study. The treadmill protocol used for the exercise test varied (eg, ramp, Balke, Bruce, other) according to subject characteristics (eg, age, exercise habits, etc) and CPX laboratory preference. Subjects were encouraged to minimize handrail use during the exercise test. Given ventilatory expired gas analysis was used to define maximal effort (ie, peak RER), the potential influence of treadmill protocol and handrail use on gauging exercise effort is minimized.

Statistical analysis

Continuous data are reported as mean and SD, whereas categorical data are reported as frequencies and percentages. A linear regression equation was initially used to derive an

APMHR prediction equation in the entire cohort. Using all 4796 subjects, bootstrapping was used for validation, with 1,000 bootstrap samples drawn. Next, random sampling was used to create a validation (n = 3,796) or cross-validation (n = 1,000) cohort. The independent-sample *t* test and χ^2 tests were used to compare differences in key continuous and categorical variables, respectively, in the validation and cross-validation cohorts. Linear regression analysis was used to derive an APMHR prediction equation using age in the validation cohort. To further assess performance of the regression developed in the validation cohort as well as the established 220 – age prediction, linear regression analysis was used to assess the ability of both equations to predict maximal HR in the cross-validation cohort. A linear regression analysis was then run in the cross-validation cohort to assess stability of the regression developed in the validation cohort. Actual maximal HR and APMHR values, using the regression developed in the validation cohort, were compared in the cross-validation cohort using a 1-sample *t* test. A Bland-Altman plot, which is a method that graphically compares 2 approaches to measurement, was used to further assess the agreement between actual maximal HR and APMHR values in the cross-validation cohort. Linear regression analysis, using the difference between (*y* axis) and mean of (*x* axis) maximal HR and APMHR in the cross-validation cohort, was also used to assess the presence of proportional bias. To determine any potential impact of sex on APMHR, a stepwise linear regression was performed using both age and sex as potential independent variables in the entire study cohort. In addition, to determine if higher peak RER thresholds for maximal effort (1.20-1.29 and 1.30) reduced prediction error, additional linear regression analyses were performed in these subgroups selected from the entire study cohort. The SPSS 22.0 (IBM, Armonk, NY) statistical software package was used for all analyses. All tests with a *P* value < .05 were considered statistically significant.

Results

Linear regression analysis results using the entire cohort produced the following statistically significant (*P* < .001) APMHR equation: 209.2 – 0.72(age). The *r* value and standard error of the estimate (SEE) for this equation was 0.60 and 11.7, respectively. Table I lists the bootstrap analysis for this regression, demonstrating a small standard error and narrow 95% CIs for both coefficients.

Key comparisons between the validation and cross-validation cohorts are listed in Table II; no significant differences were detected. Mean peak VO₂ values indicated a well-preserved, normal aerobic capacity. As expected based on the exclusion criteria, effort was excellent as indicated by a mean peak RER value of ≈1.20. Mean peak RPP and RPE values further support a high level of exercise effort by the cohort assessed. Both cohorts were predominantly male but, given the large sample size, there were a significant number of females included in the analysis. Leg fatigue was the primary test termination criteria in 82% of the exercise tests. Dyspnea was the primary termination criterion in 17% of the tests, whereas chest discomfort/arrhythmias were the primary termination criterion in only 1%. This distribution of termination criteria can be expected for an apparently healthy sample.

The linear regression analysis for the validation and cross-validation cohorts are listed in Table III and Figures 1 and 2. Both regression equations were statistically significant (*P* < .

001). Moreover, the r values, SEEs, and the β coefficients between the 2 regression equations were strikingly similar.

The ability of the equation derived from the validation cohort [$209.3 - (0.72 * \text{age})$] as well as the established $220 - \text{age}$ equation to predict maximal HR values in the cross-validation cohort were both assessed via linear regression. Both linear regressions were statistically significant ($P < .001$); the r value (0.57) and SEE (12.76) derived for each regression (ie, maximal HR-dependent variable and APMHR derived from the regression equations as the independent variable) were identical.

The 1-sample t test indicated that the mean difference between maximal HR and APMHR (derived from [$209.3 - (0.72 * \text{age})$]) in the cross-validation cohort was not significantly different from 0 (mean 0.318, $P = .43$). Bland-Altman analysis is illustrated in Figure 3, which revealed high limits of agreement (upper 25.31 and lower -24.67 , range 49.98 bpm) and a negative trend as the maximal HR-APMHR mean (x axis) increased. Linear regression analysis as part of the Bland-Altman analysis, using the difference between (y axis) and mean of (x axis) maximal HR and APMHR, revealed a significant relationship ($r = 0.58$, $P < .001$; equation = $120.48 - 0.68(\text{HR} - \text{APMHR mean})$, SEE = 10.40), indicating a proportional bias.

In the entire cohort, stepwise linear regression using age and sex as independent variables revealed that the latter did not add significant value in predicting maximal HR ($r = 0.604$ with age alone and $r = 0.605$ with age and sex). Results from the linear regression analyses for peak RER 1.20-1.29 and 1.30 subgroups are listed in Table IV. Using this higher objective threshold to define maximal exercise effort did not appreciably change the prediction equation, the r value, or SEE.

Discussion

The results of the current study further explore the validity of APMHR in quantifying subject effort during maximal aerobic exercise testing on a treadmill. Key strengths of the current analysis include the following: (1) a large total sample as well as validation and cross-validation cohorts, one of the largest examining this issue in the literature to date; (2) use of a peak RER 1.10 as an inclusion criterion, providing an objective determination of subject effort; and (3) a good representation of data points across the adult life span. The main finding of the current analysis is that, even with a criterion standard indicator of effort (ie, peak RER 1.10), there is no significant alteration in accuracy from previously proposed APMHR regression equations.^{6,11,12} In fact, prediction using the regression developed in the current study performed identically to $220 - \text{age}$ in the cross-validation cohort. More importantly, the SD of the prediction equation in the current study is strikingly similar to previous investigations (ie, $\approx \pm 12$ bpm).^{3,6,11,13} The substantial prediction error is further supported by the large standard limits of agreement illustrated in the Bland-Altman analysis (Figure 3). In addition, Bland-Altman analysis revealed a significant proportional bias, indicating agreement between APMHR and maximal HR is not consistent across the range of possible measurements. Thus, use of the Bland-Altman analysis in the current study more clearly highlights the substantial limitations associated with using APMHR: (1) from a

clinical perspective, there is poor agreement between APMHR and maximal HR, and (2) agreement is influenced by values derived from the APMHR equation. Factoring an individual's sex does not appear to improve prediction or measurement error, an observation that has also been reported in previous investigations.¹¹ Subgroup analyses using higher peak RER thresholds were also performed and did not improve the prediction error or alter the regression equation; to our knowledge, the current analysis is the first to analyze the accuracy of APMHR using peak RER thresholds at or above 1.20 and 1.30. These findings lend further convincing evidence that the prediction error associated with APMHR cannot be meaningfully improved upon. From the current study in conjunction with the overall body of related literature, there appears to be clear consensus that one can expect the prediction error associated with APMHR using any of the currently available prediction equations, with 95% CIs, to be $\approx\pm 24$ bpm. These findings, both current and previous, all point toward significant limitations in the validity of APMHR in predicting the actual maximal HR response to exercise.

The ramifications of inaccurate assessment of exercise effort using APMHR vary depending on the setting. The use of APMHR in the cardiac stress testing laboratory certainly has clinically important ramifications, particularly when 85% of APMHR is used as an exercise termination criterion. It has been estimated that approximately 40% of exercise testing laboratories use 85% of APMHR as a primary end point for exercise testing.¹⁴ Jain et al¹⁴ assessed 300 individuals with a positive ECG result for signs of ischemia during exercise testing. Using the conventional 220 – age equation, 232 of these individuals exercised to >85% of APMHR. In these 232 individuals, only 62% has a positive ECG result at 85% of APMHR. Pinkstaff et al¹⁵ collected peak RER data in 238 subjects undergoing nuclear stress testing for signs suggestive of myocardial ischemia. The health professionals conducting the stress test and determining termination criteria were blinded to peak RER level. Only 52% of the cohort attained a peak RER ≥ 1.10 . The number and percentage of patients in <1.00, 1.00-1.09, and ≥ 1.10 peak RER subgroups who achieved an APMHR of at least 85%, using the 220 – age equation, were 21 (68%), 58 (69%), and 92 (75%), respectively (percent difference not significantly different between subgroups). Moreover, several APMHR equations were assessed for their ability to predict attainment of a peak RER ≥ 1.10 using receiver operating characteristic curve analysis; the area under the curve was not significant for any equation. The number and percentage of patients with either an equivocal or abnormal myocardial perfusion scan in the <1.00, 1.00-1.09, and ≥ 1.10 peak RER subgroups were 10 (32%), 22 (26%), and 41 (33%), respectively. Of note, the percentage of equivocal scans in the peak RER <1.00 subgroup was significantly higher (90%) compared with the 1.00-1.09 (73%) and ≥ 1.10 (68%) subgroups ($P < .007$). From these findings, the authors concluded that use of achieving 85% APMHR as a sole-test termination criteria results in a large proportion of exercise tests in this setting being submaximal. The authors further posited that this practice may result in a proportion of individual's undergoing nuclear stress testing being misdiagnosing as having no indication of clinically significant myocardial perfusion defects. Such an incorrect conclusion likely changes the subsequent course of medical assessment and management, potentially increasing the risk of adverse events. As such, given the results of the present study as well as the collective body of literature, APMHR, in particular the 85% threshold, is not a clinically valid termination criterion for

maximal exercise testing. This view is echoed by a recently published American Heart Association scientific statement on exercise testing and training.³ Exercise testing laboratories should therefore implement policies clearly stating tests will not be terminated using an APMHR threshold.

Although APMHR is not able to accurately predict an individual's maximal exercise HR, there may still be utility in its clinical use. There is a robust body of literature indicating chronotropic incompetence, commonly defined as an inability to achieve at least 85% of APMHR,³ is a prognostically ominous marker.^{16–21} As such, the assessment of the chronotropic response to exercise by comparing the HR response to maximal exercise in relation to APMHR may still provide clinically valuable information. Most previous studies have used the 220 – age APMHR equation to define the occurrence of chronotropic incompetence. The regression equation validated and cross-validated in the present study is strikingly similar to that proposed by Tanaka et al.⁶ Future research should perform a comprehensive evaluation of which currently available regression equation elicits a chronotropic index with optimal clinical utility. In addition, use of HR prediction equations during exercise may hold yet to be defined utility in newly emerging areas, particularly ones that are focused on leveraging technology (eg, Apple Health Kit).²²

Maximal exercise testing clearly provides a wealth of valuable information related to an individual's health, diagnosing a host of pathophysiologic processes and prognosis; this is the case for apparently healthy individuals as well as virtually all patient populations.^{1–3,10,23–25} To obtain optimally valuable information, ensuring maximal effort during the exercise test, capturing the full physiologic response to exercise throughout an individual's capacity to exert himself/herself aerobically, is of paramount importance. As such, a different approach is needed to gauging exercise effort. Ventilatory expired gas analysis provides for the measurement of peak RER, which is the criterion standard measure of effort during aerobic exercise testing.² When possible, clinical exercise testing laboratories should consider the feasibility of integrating ventilatory expired gas analysis into their exercise assessments.²⁴ Exercise testing with ventilatory expired gas analysis is already commonplace in certain patient populations, including those diagnosed as having heart failure or those presenting with unexplained exertional dyspnea.^{2,24} Given the potential for misdiagnosis with submaximal exercise effort,^{14,15} inclusion of ventilatory expired gas analysis in tests for suspected myocardial ischemia may be advantageous. The authors do recognize that the inclusion of this technology may not always be feasible or supported. When ventilatory expired gas analysis is not available, every effort should be made to ensure individuals put forth a maximal effort and a predicted HR threshold should not be used as a termination criteria.

In conclusion, the current study in accordance with the broader body of literature in this area indicate that the prediction error associated with using APMHR achieved during exercise testing to assess effort is unacceptably high. As such, using APMHR in this capacity should be discouraged and new approaches to gauging an individual's exercise effort should be explored.

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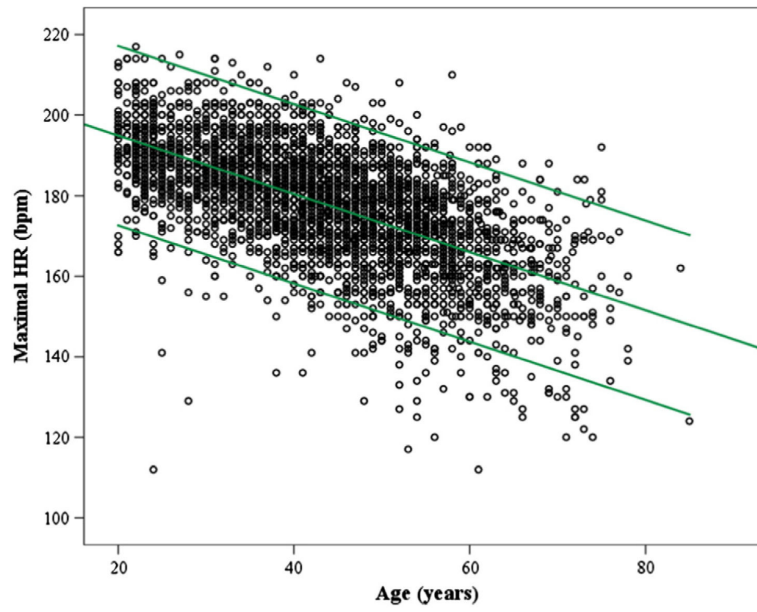


Figure 1.
Scatterplot line of best fit and 95% CIs for validation cohort.

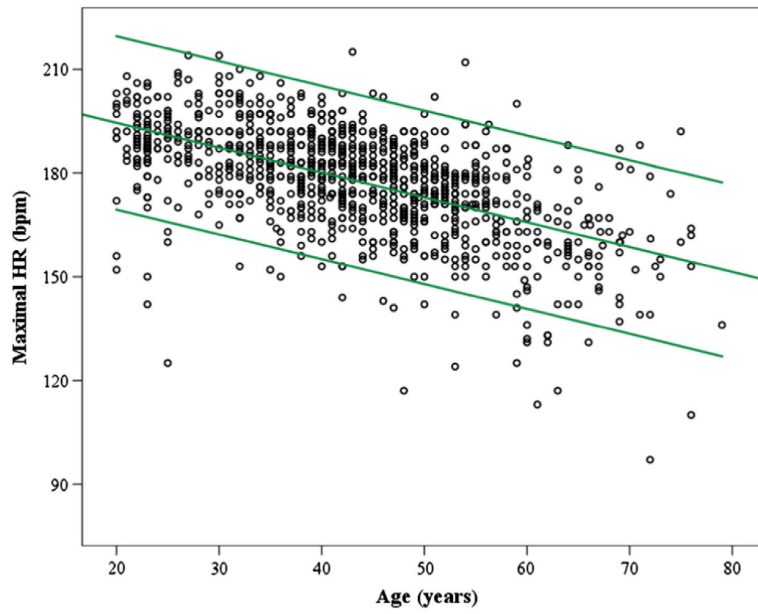


Figure 2. Scatterplot line of best fit and 95% CIs for cross-validation cohort.

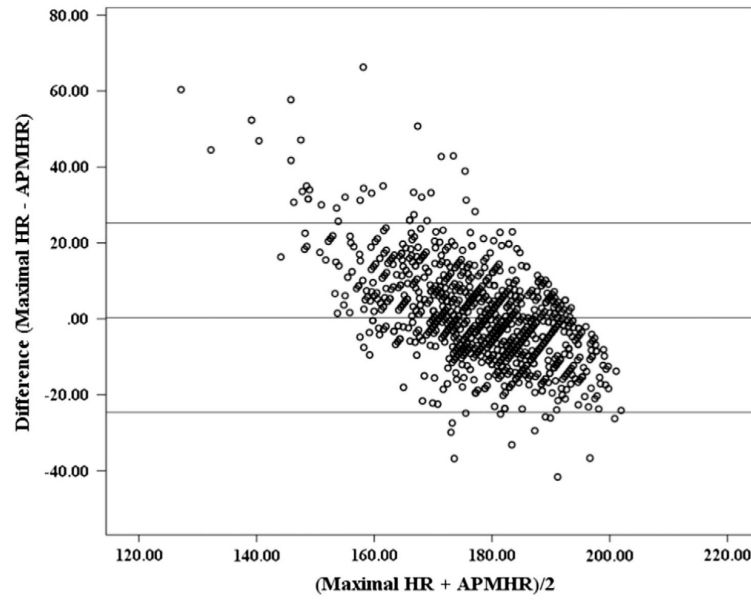


Figure 3. Bland-Altman plot in the cross-validation cohort. Regression for calculation of APMHR used in Bland-Altman analysis: $209.3 - 0.72(\text{age})$.

Table I

Bootstrap of coefficients for linear regression analysis derived from the entire cohort

	<i>B</i>	<i>SE</i>	<i>P</i>	<u>95% CI</u>	
				Lower	Upper
Constant	209.2	0.69	.001	207.9	210.6
Age	-0.72	0.02	.001	-0.75	-0.69

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Table II

Comparison of key variable in the validation and cross-validation cohorts

	Validation (n = 3796)	Cross-validation (n = 1000)
Age (y)	43 ± 12	43 ± 12
Sex (% male)	63	64
BMI (kg/m ²)	26.0 ± 5.4	26.1 ± 5.4
Resting HR (bpm)	66 ± 11	66 ± 10
Maximal HR (bpm)	178 ± 14	178 ± 16
Peak systolic BP (mm Hg)	178 ± 25	179 ± 25
Peak RPP (bpm * mm Hg)	31,259 ± 4683	31,386 ± 4874
Peak RPE	18 ± 2	18 ± 2
Peak VO ₂ (mlO ₂ · kg ⁻¹ · min ⁻¹)	36.1 ± 10.6	36.0 ± 10.5
Peak RER	1.21 ± 0.08	1.21 ± 0.09

Abbreviation: *BMI*, Body mass index.

No statistically significant differences.

Table III

Linear regression analysis results

	Validation (n = 3796)	Cross-Validation (n = 1000)
Equation	209.3 – 0.72(age)	208.8 – 0.72(age)
r Value	0.61	0.57
SEE	11.4	12.8

r Values for both regressions are statistically significant ($P < .001$).

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Table IV

Linear regression analysis results for peak RER 1.20-1.29 and 1.30 subgroups

	Peak RER 1.20-1.29 (n = 1589)	Peak RER 1.30 (n = 690)
Equation	208.3 – 0.68(age)	208.8 – 0.66(age)
r Value	0.57	0.56
SEE	11.6	11.6

r Values for both regressions are statistically significant ($P < .001$).

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