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**A New Generalized Cycle Ergometry Equation for Predicting Maximal Oxygen Uptake: The Fitness Registry and the Importance of Exercise National Database (FRIEND)**

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**Abstract**

**Background:** To develop a clinically applicable equation derived from direct assessment of maximal oxygen uptake (VO2 max) to predict VO2 max assessed indirectly during cycle ergometry.

**Design:** VO2 max was assessed by open-circuit spirometry during a graded maximal exercise test using cycle ergometry. Multivariable linear regression analysis was applied to identify the most relevant variables and construct the best prediction model for VO2 max using a random sample of 70% from each of the following age categories: <40, 40 to 50, 50 to 70 and >70 years; the remaining 30% was used for validation. Work rate (Watts\*6.12/kg of body weight) and gender were considered in the final regression model as predictors of measured VO2 max and the resulting equation was compared to the traditional American College of Sports Medicine (ACSM) equation.

**Methods:** Participants were part of the Fitness Registry and the Importance of Exercise National Database (FRIEND), a multi-institutional initiative with the primary objective of establishing normative VO2 max values across the adult lifespan. The final cohort consisted of 5,100 (3.378 males; mean age 35.9±12.1) and 1722 females; mean age=47.5±14.0 years).

**Results:** The following equation was generated: VO2 max in ml O2●kg-1●min-1= 1.74\* (Watts\*6.12/kg of body weight) + 3.5. The derived FRIEND-ergometry equation predicted VO2 max with an overall relative bias of 0.51% ± 0.11) compared to a 15.46% ± 0.13 associated with the traditional ACSM equations (p<0.001). This predictive value was independent of gender, race, cardiac risk factors and cardiac; antihypertensive; metabolic; and/or lipid-lowering medication.

**Conclusion:** The FRIEND-ergometry equation is considerably more precise than the traditional ACSM equation with an overall error >30 times lower than that associated with the ACSM equation.

***Key Words:*** *VO2 max prediction, Ergometry Equation, FRIEND database*

**Introduction**

 Direct assessment of maximal oxygen uptake (VO2 max) is usually performed by the open-circuit spirometry method, reflecting the peak capacity of the cardiovascular and pulmonary systems to meet the oxygen demands of the skeletal muscle during physical work. The mode of exercise testing is predominantly a treadmill in the United States and a cycle ergometer in Europe and other countries. VO2 max, often referred to as cardiorespiratory fitness (CRF) and recently proposed as a vital sign1 is convincingly associated with many clinical outcomes,2-5 and provides valuable information related to both functional capacity and exercise prescription.6 The important clinical relevace of directly measured CRF is impacted by the direct assessment of VO2 max, at times, being cost prohibitive, prompting the development of indirect, relatively low-cost methods and regression equations to estimate the metabolic demand for a given work rate. This estimated metabolic demand has conventionally been expressed in metabolic equivalents (METs). One MET is considered to be equivalent to the amount of oxygen (O2) consumed at rest (approximately 3.5 ml O2●kg-1●min-1).6-8 These regression equations are based on direct assessment of VO2 at submaximal, steady state work rates (defined as a constant VO2) on relatively few college-age participants, but are traditionally used to estimate VO2 at maximal, non-steady state work rates during a progressive exercise test for all ages.6-10 However, the steady-state assumed by these equations is influenced significantly by several factors including exercise intensity, the exercise protocol and an individual’s health status and age.6,11 Thus, the accuracy of the equation diminishes when applied to non-steady state workloads or to middle-aged and older populations (7). Not surprisingly, the overestimation of VO2 max (MET levels) that occurs during a progressive exercise test is well-documented.6,12 This was clearly demonstrated in our previous work, where the equation derived from the FRIEND database was applied to estimate VO2 max based on directly measured VO2 using established treadmill protocols.13 Since the primary indication for exercise testing is usually clinical [i.e., individuals with suspected or confirmed medical conditions such as cardiovascular disease (CVD)],1 the objective of this study was to develop a clinically-applicable equation derived from direct assessment of VO2 max to more accurately define peak MET levels during cycle ergometry.

**Methods**

 Individuals that participated in the Fitness Registry and the Importance of Exercise National Database (FRIEND), and completed a maximal exercise test were considered for the study. FRIEND is a multi-institutional initiative established in 2014 with the primary objective of establishing normative CRF values for the United States and other countries across the adult lifespan.14 The indication for the exercise tests varied, but was most often the determination of CRF prior to entry into an exercise program or research study. Participant screening was specific to each laboratory’s procedures to rule out contraindications for exercise testing and for risk stratification.15

 For this study, subjects were excluded if they were diagnosed with: 1) history of cancer (any kind); 2) cardiovascular disease; 3) chronic obstructive pulmonary disease; 4) chronic kidney disease; and 5) peripheral artery disease. Excluded were also those whose exercise tests were terminated for abnormal clinical findings and/or before achieving voluntary maximal effort (peak respiratory exchange ratio <1.0) and those <18 years old.15

 The final cohort consisted of 5,100 subjects (3,378 males; mean age (±SD) 35.9±12.1 years) and females (n=1,722; mean age=47.5±14.0 years) subjects. All participants completed a graded exercise test using cycle ergometry in one of the eight participating CPX laboratories (see Acknowledgments) with geographic representation from California, Connecticut, Indiana, Illinois, Louisiana, Massachusetts, Maryland, North Carolina, Oregon, Tennessee, and Texas in the United States and from the Netherlands and Spain in Europe. VO2 max was measured directly in all participants by open-circuit spirometry. Maximal effort was determined by a peak respiratory exchange ratio ≥1.0. The procedures used for acquiring and managing the FRIEND registry data have been previously reported.14,15 In brief, the CPX laboratories contributing data to FRIEND all used valid and reliable calibration and testing procedures and using experienced personnel qualified to conduct exercise tests. Although some variations in laboratory equipment, protocols, and procedures existed, the characteristics of all participating CPX laboratories are consistent with recommendations provided in recent guidelines.16,17

**Statistics**

 We applied multivariable linear regression analysis to identify the most relevant variables associated with VO2 max, in order to construct the best prediction model. We randomly sampled 70% of the participants from the following age categories: <40, 40- 50, 51-70 and >=70). The remaining 30% of participants were used for validation. The variables considered in the regression model were: age, gender, race, work rate, smoking status, diabetes type 2, hypertension, and medications (cardiac, antihypertensive or lipid-lowering agents). The stepwise selection was adopted and selection stopped when the candidate for entry had a p-value greater than 0.15 and the candidate for removal had a p-value less than 0.15. During the selection process, models were constructed using 70% of the cohort. The prediction errors for the models were then determined using the validation data (30% of the cohort), which were used to decide when to terminate the selection procedure. The contribution of the variables selected to predict VO2 max was further investigated by variable selection criteria including Akaike information criterion (AIC), corrected Akaike information criterion (AICC), the Sawa Bayesian Information Criterion (SBC), Adjusted R-square statistic, the Predicted Residual Sum of Squares Statistic (PRESS) and the average squared error over the validation data (Validation ASE). The two variables entered into the final model were work rate (Watts \* 6.12/kg of body weight) and gender. To determine whether the accuracy of predicting measured VO2 max differed by gender, these analyses were repeated using a gender-specific equation. All statistical tests with a p-value <0.05 were considered statistically significant.

**Results**

Baseline characteristics of the entire group are presented in Table 1. Over 11% of the participants have hypertension and very few smoke, have diabetic, or dyslipidemia. However, over 57% are overweight (40.2%) or obese (17.2)

Table 1 Baseline Characteristics of Participants

|  |  |
| --- | --- |
| Age (yr)  | 39.8±13.9 |
| Weight (kg) | 81.5±13.1 |
| Height (m) | 1.76± 0.11 |
| BMI | 26.6±4.8 |
|  *Normal Weight (<25.0 kg/m2)* *Overweight (25.0-29.9 kg/m2)* *Obese (≥30 kg/m2)* | 2,173 (42.7%)2046 (40.2%)875 (17.2%) |
| Hypertension n (%) | 583 (11.4%) |
| Diabetes (%) | 40 (0.8%) |
| Dyslipidemia (%) | 72 (1.1%) |
| Smoking Status (%) | 107 (2.1%) |
| Antihypertensive Medications (%) | 525 (10.3%) |
| Lipid Lowering Medications (%) | 52 (1%) |

 Multiple linear regression analysis revealed that for each of the evaluation criteria, the precision of the model improved significantly when work rate and gender were introduced in the model. The addition of the remaining variables did not change the model appreciably, as indicated by the mean squared error for the entire cohort and validation sample (30% of the entire cohort) for each variable entering the model (**Figure 1**).



 Model A: Model B: Model C: Model D: Model E: Model F:

 Work rate A + Age B + CRF\* C + Gender D + Smoking E+ Medications

 Status

**\* CRF=**Cardiac Risk Factors (hypertension, diabetes type 2, and/or dyslipidemia

**Figure 1** Average squared error change with variables considered in the multiple regression models (Model A-G). The stepwise selection was used and variables with high contribution to VO2 max in ml O2● kg-1●min-1 entered to the model first. Lower average squared error values indicate greater predictive value of the model.

It is apparent that the variables with the highest contribution in minimizing the average square error is work rate and age (Table 2). Considering the the minimal contribution of age in the model (Coefficient Estimate=0.102), work rate only was used in the final model as the predictor of measured VO2 max. In addition, when gender was considered, gender-specific models provided a slightly more accurate prediction of VO2 max for each gender (Table 2). Thus, we present both an overall and gender-specific formulas.

Table 2 Parameters used in the model and their contribution

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **Estimate** | **Standard Error** | **t Value** | **Pr>[t]** |
| Work Rate/Kg | 1.736 | 0.005 | 306.31 | <0.001 |
| Age | 0.010 | 0.003 | 2.87 | 0.004 |
| Cardiac Risk Factors | 0.936 | 0.317 | 2.95 | 0.003 |
| Gender | -1.149 | 0.145 | -10.28 | <0.001 |
| Smoker | -1.560 | 0.427 | -3.65 | <0.001 |
| Cardiac/AntihypertensiveMedications | 0.684 | 0.335 | 2.04 | 0.041 |

 **Male: 1.76 \* [Watts\*6.12/body weight (kg)] +3.5**

 **Female: 1.65 \* [Watts\*6.12/body weight (kg)] +3.5**

The non-gender-specific equation:

**VO2 max in ml O2●kg-1●min-1= 1.74\* [Watts\*6.12/body weight (kg)] +3.5**

Comparisons between the predicted values based on the ACSM equations, the FRIEND equation, and the gender-specific equation for males and females are presented in Table 3. The relative bias is calculated by the predicted value - true value/true value. The ACSM equation overestimated VO2 max by over 15% for the entire cohort (average relative bias: 15.46 % ± 0.13). When applied separately to males and females, the overestimation was twice as much for females compared to males (23.77% vs 11.23%, respectively). The non-gender specific FRIEND equation, overestimated VO2 max by only 0.51% (average relative bias: 0.51% ± 0.11). When applied to males and females separately, VO2 max was underestimated by -0.78% for males and overestimated by 3.04% for females. When the gender-specific FRIEND equation was applied VO2 max was overestimated by merely 0.26% for males, and underestimated (-1.37%) for females. Similar findings were observed when the equations were applied to the validation sample representing 30% of the cohort.

Finally, the overestimation of METs by the ACSM equation can be corrected by the following formula:

**ACSM-derived METs - 0.06\* (Watts\*6.12/kg) - 3.5**

**Discussion**

 In the current study, we derived a new equation for cycle ergometry (FRIEND- Ergometry equation) that estimates directly measured VO2 max more accurately than the widely-used ACSM equation. The overall relative bias of the non-gender specific FRIEND-Ergometry equation was 0.51% ± 0.11%, with minimal differences noted when the gender-specific equations were applied. Thus, the non-gender specific FRIEND-Ergometry equation can be effectively applied to both males and females.

In contrast, the ACSM equation overestimated VO2 max by 15.46% ± 0.13%. The overestimation of VO2 max was even more pronounced when applied to females and males separately (11.23% for males and 23.77% for females). Given the significant role CRF plays in clinical decision making,1 and its association with health outcomes, substantially high overestimation of VO2 max by the ACSM equation (especially in females) make the FRIEND equation more clinically relevant than the ACSM equation.

The current FRIEND equation for cycle ergometry extends the recently published FRIEND equation we developed for predicting METs using standardized treadmill exercise protocols.13 The FRIEND equation for VO2 max using treadmill protocols is:

**VO2 max in ml O2/kg/min = Speed (m) \* (0.17 + Fractional Grade \* 0.79) + 3.5**

This formula predicts VO2 max more precisely than the traditional ACSM equations with an overall error >4 times lower than that associated with the ACSM equations. In addition, it is simple to use as it does not require a different formula for walking and running. The superiority of both FRIEND equations in predicting VO2 max over the existing ACSM equations is indisputable. Thus, broad adaptation of the two equations can considerably increase the accuracy of estimated VO2 max. In clinical and research settings where ventilatory gas exchange equipment is unavailable, these equations provide a reasonably accurate reflection of functional capacity and an improvement over traditional methods of estimating VO2 max. While these findings require validation from other populations, they appear to resolve a widely-recognized shortcoming of the traditional equations used to estimate VO2 max. 6-10

**Strengths and weaknesses of the study**

The main factor that distinguishes the FRIEND-Ergometry equation and suggests it is superior to the ACSM equation in predicting VO2 max is that the FRIEND-Ergometry equation was constructed to predict a known value of directly measured VO2 max. In contrast, the ACSM equations were developed decades ago from steady-state exercise, and an extrapolation is required that assumes subjects maintain steady-state at maximal exercise. However, steady-state is influenced by a number of factors, including age, fitness, pedaling efficiency, and others, and a steady-state is rarely achieved at high levels of exercise. In addition, since the majority of the subjects in the studies in which the ACSM equations were developed were relatively young (19-39 years),6, 10,11 VO2 max will likely be overestimated by the ACSM equations when applied to older populations. These are primary reasons to explain why the ACSM equations, although widely-used, are known to have limited accuracy, particularly in clinical settings.6,8,11,12

Additional attributes of the FRIEND-Ergometry equation include the relatively large database of 5,100 participants, including both men (n=3,378) and women (n=1,722); White (n=4,617); Black (n=268), Hispanic (n=59) and other ethnicities (156), with a wide age range (18-87 years), derived from different regions across the USA and Europe. This allowed us to examine whether gender, race, and other factors had a significant impact on the predictive power of the model. To determine the potential effects of gender and race, gender-specific equations were developed, and race was used as an independent predictor. It is noteworthy that neither race nor gender had an appreciable effect on the predictive value of the FRIEND-Ergometry equation (Tables 1-3). Finally, the accuracy of the FRIEND-Ergometry equation is similar to the recently reported FRIEND equation derived developed for treadmill testing.13 Collectively, these qualities make the FRIEND- ergometry equation more portable to different populations.

Several limitations of the study should be noted. Although all tests were performed for functional capacity assessment, reasons for test referral varied (clinical assessment, fitness screening, research evaluation) and the choice of treadmill protocols, equipment, and data collection procedures, although consistent with current guidelines7,12,17 were specific to each laboratory. In addition, we included subjects with particular conditions (e.g., diabetes and obesity), musculoskeletal concerns (e.g., back pain and osteoarthritis), and CVD risk factors, which may have limited exercise capacity in these individuals.

In conclusion, the FRIEND-Ergometry equation predicted measured VO2 max with an overall relative bias of 0.51%. The bias of the gender-specific equations was

-0.78% for males and 3.04% for females. In contrast, the relative bias associated with the ACSM equations was 15.46% for the entire group; 23.77% for female and 11.23% for males. Since the majority of exercise tests are performed for clinical reasons and the determination of CRF in the clinical setting, these findings make the FRIEND equation more clinically relevant than the ACSM equation. Therefore, we suggest that manufacturers of exercise assessment apparatus (cycle ergometers) and exercise laboratories consider adapting the FRIEND-Ergometry equation for the estimation of VO2 max during exercise testing using cycle ergometry. Additional studies are needed in different populations to further explore the portability of the FRIEND equation.

Table 3 Measured and Estimated Oxygen Consumption Based on the American College of Sports Medicine (ACSM)\* and the Fitness Registry and the Importance of Exercise National Database (FRIEND) Equations (Mean ± Standard Deviation)

1. Entire Cohort (n=5,100)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MeasuredMaximal Oxygen Uptake | FRIENDMaximal Oxygen Uptake | Gender-Specific FRIEND Maximal Oxygen Uptake | ACSM FormulaMaximal Oxygen Uptake |
|  | Mean (SD) | Mean (SD) | Relative Bias % (SD) | Mean (SD) | Relative Bias % (SD) | Mean (SD) |  Relative Bias % (SD) |
| Male (n=3378) | 42.43 (9.57) | 41.94 (9.33) | -0.78 (0.09) | 42.39 (9.44) | 0.26 (0.09) | 46.77 (9.65) | 11.23 (0.10) |
| Female (n=1722) | 23.25 (10.01) | 24.01 (10.81) | 3.04 (0.13) | 22.95 (10.25) | -1.37 (0.12) | 28.22 (11.18) | 23.77 (0.15) |
| All (n=5100) | 35.95 (13.30) | 35.89 (13.00) | 0.51 (0.11) | 35.82 (13.38) | -0.29 (0.10) | 40.51 (13.45) | 15.46 (0.13) |

1. Validation Using 30% of the Cohort (n=1,530)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | MeasuredMaximal Oxygen Uptake | FRIENDMaximal Oxygen Uptake | Gender-Specific FRIEND Maximal Oxygen Uptake | ACSM FormulaMaximal Oxygen Uptake |
|  | Mean (SD) | Mean (SD) | Relative Bias % (SD) | Mean (SD) | Relative Bias % (SD) | Mean (SD) | Relative Bias % (SD) |
| Male (n=1133) | 42.30 (9.81) | 41.84 (9.58) | -0.77 (0.09) | 42.28 (9.69) | 0.27 (0.09) | 46.66 (9.91) | 11.34 (0.10) |
| Female (n=625) | 23.06 (9.91) | 23.81 (10.7) | 3.04 (0.13) | 22.76 (10.15) | -1.37 (0.13) | 28.01 (11.07) | 23.83 (0.15) |
| All (n=1758) | 35.46 (13.48) | 35.43 (13.2) | 0.59 (0.11) | 35.34 (13.58) | -0.31 (0.1) | 40.03 (13.66) | 15.78 (0.13) |

**FRIEND Consortium Contributors:**

Ball State University (Leonard Kaminsky), Brooke Army Medical Center (Kenneth Leclerc), Cone Health (Paul Chase), Johns Hopkins University (Kerry Stewart), Pennington Biomedical Research Center (Timothy Church), Southern Connecticut State University (Robert Axtell), Taylor University (Erik Hayes), University of Illinois-Chicago (Jacob Haus), University of Tennessee, Knoxville (David Bassett)

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**Data sharing:** No additional data available.

**Transparency:** The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

**Authorship:**

PK and JM: Contributed to the conception or design of the work and the writing of the manuscript.

LAK and RA: Contributed to the acquisition, management of the database and assisted in the revisions of the manuscript.

JZ: Contributed to all the statistical analyses and interpretation of the data.

All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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