**New Generalized Equation for Predicting Maximal Oxygen Uptake (From the Fitness Registry and the Importance of Exercise National Database)**

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**Abstract**

Impaired cardiorespiratory fitness (CRF) is closely linked to chronic illness and associated with adverse events. The American College of Sports Medicine (ACSM) regression equations (ACSM equations) developed to estimate oxygen uptake have known limitations leading to well-documented overestimation of CRF, especially at higher work rates. Thus, there is a need to explore alternative equations to more accurately predict CRF. We assessed maximal oxygen uptake (VO2 max) obtained directly by open-circuit spirometry in 7,983 apparently healthy individuals who participated in the Fitness Registry and the Importance of Exercise National Database (FRIEND). We randomly sampled 70% of the participants from each of the following age categories: <40, 40- 50, 50-70 and >=70) and used the remaining 30% for validation. Multivariable linear regression analysis was applied to identify the most relevant variables and construct the best prediction model for VO2 max. Treadmill speed and treadmill speed \* grade were considered in the final model as predictors of measured VO2 max and the following equation was generated: VO2 max in ml O2●kg-1●min-1= Speed (m/min) \* (0.17 + Fractional Grade \* 0.79) +3.5. The FRIEND equation predicted VO2 max with an overall error >4 times lower than the error associated with the traditional ACSM equations (5.1±18.3% vs 21.4±24.9%, respectively). Overestimation associated with the ACSM equation was accentuated when different protocols were considered separately. In conclusion, The FRIEND equation predicts VO2 max more precisely than the traditional ACSM equations with an overall error >4 times lower than that associated with the ACSM equations.

**Key Words:** VO2 max prediction, New Equation, FRIEND Database

**Introduction**

 Cardiorespiratory fitness (CRF) is defined as the capacity of the cardiovascular and pulmonary systems to meet the oxygen demands of skeletal muscle during physical work. Accordingly, an individual’s highest oxygen uptake (VO2 max) during physical work represents maximal aerobic capacity. CRF is closely linked to risk for chronic disease and associated adverse events.1-4 Direct assessment of VO2 max is performed in a laboratory or clinical setting by open-circuit spirometry, requiring specialized equipment and trained personnel, limiting a widespread application. Thus, regression equations for walking and running speeds were developed and have been adapted over the years by the ACSM to estimate energy requirements at submaximal, steady states (defined as a constant VO2) and subsequently used to estimate VO2 at maximal, non-steady state work rates during a progressive exercise test.5 This estimated metabolic demand for a given work rate 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, 7 However, the steady-state assumed by these equations is influenced significantly by several factors including the individual’s age, health and fitness status, walking efficiency and handrail use.7,8 In addition, the most commonly used equations for walking and running speeds were developed nearly four decades ago, using a specific protocol and were based on relatively few (<100), young (19-26 years old) participants in most studies. These factors contribute to the well-documented overestimation of VO2 max (MET levels) that occur during a progressive exercise test.7,9 Since the primary indication for exercise testing is for clinical reasons10 the objective of this study was to develop clinically-applicable equations, derived from direct assessment of VO2 max to more accurately define peak MET levels for different exercise testing protocols.

**Methods**

 Our cohort included 7,983 apparently healthy individuals (4,798 men and 3,183 women) who participated in The Fitness Registry and the Importance of Exercise National Database (FRIEND), established in 2014. FRIEND is a multi-institutional initiative with the primary objective of establishing normative CRF values for the United States across the adult lifespan.11 Participants completed a graded exercise treadmill test in one of the eight participating CPX laboratories (see Acknowledgments) with geographic representation from Connecticut, Indiana, Illinois, Louisiana, Maryland, North Carolina, Tennessee, and Texas. VO2 maxwas measured directly in all participants by open-circuit spirometry. The procedures used for acquiring and managing the FRIEND registry data have been previously reported. 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 recently guidelines.12, 13

 The indication for the exercise tests was 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. Inclusion criteria included age ≥20 years (mean age 47±13 years), and free from overt cardiovascular disease (CVD; coronary artery disease, peripheral artery disease, or heart failure) or chronic obstructive pulmonary disease at the time of the test and peak respiratory exchange ratio ≥1.0. Any tests terminated for abnormal clinical findings or before achieving voluntary maximal effort were excluded.14 Maximal effort was determined by a peak respiratory exchange ratio ≥1.0.

 We applied multivariable linear regression analysis to identify the most relevant variables associated with VO2 max, in order to construct the best prediction model for VO2 max estimation. We randomly sampled 70% of the participants form the following age categories: <40, 40- 50, 50-70 and >=70). The remaining 30% of participants were used for validation. The variables considered in variable selection were: 1) treadmill speed (meters●minute-1); 2) treadmill grade (%); 3) interaction between treadmill speed and grade; 4) resting heart rate (HR), 5) resting blood pressure (BP); 5) history of CVD ; 6) exercise time (minutes); 7) body mass index (BMI); 8) height; 9) age (years); and 10) gender. 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 are constructed using 70% of the cohort. Then, the prediction errors for the models were found using the validation data (30% of the cohort), which were used to decide when to terminate the selection procedure. The order of variables that entered into the final model was: 1) treadmill speed; 2) treadmill speed \* grade; 3) gender; 4) exercise time; 5) age; 6) resting systolic BP; and (7) BMI. The contribution of the variables selected to predict VO2 max was further investigated by the 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 square error over the validation data (Validation ASE).

**Results**

 For each of the evaluation criteria, the precision of the model improved significantly when treadmill speed and the interaction of treadmill speed and grade were introduced in the model. The addition of the remaining variables did not change the model appreciably. This was confirmed by the average squared error that included 70% of the entire cohort and validation sample (the remaining 30%) for each variable entering the model (**Figure 1**). Consequently, treadmill speed and treadmill speed \* grade were the variables considered in the final model as predictors of measured VO2 max. Subsequently, the following equation was generated.

**VO2 max in ml O2●kg-1●min-1= Speed \* (0.17 + Fractional Grade \* 0.79) +3.5**

**Where Speed is in meters●minute-1**

**Model G: F + BMI**

Comparisons between the predicted values based on the ACSM equations and the FRIEND equation for the entire group and for each protocol are presented in **Table 1**. The ACSM equations overestimate VO2 max, as previously reported since the first edition of the ACSM guidelines 5 with a percent error for the entire cohort of 21.4 ± 24.9 versus 5.1±18.3 for the FRIEND equation. For different protocols using the ACSM equations, the percent error ranged from -32.0%±5.1 for the Modified Balke to 39.8% ± 26.4 for the BSU/Bruce-Ramp protocol. In contrast, the percent error using the FRIEND equation ranged from 1.7±15.4 for the Bruce protocol to 12.8±21.0 for the Bruce-Ramp. Thus, overall the FRIEND equation consistently outperformed the existing ACSM equations for predicting VO2 max for each protocol.

 **Tables 2-6** present the MET levels per stage for different protocols estimated by the ACSM and FRIEND equations. Compared to the FRIEND protocol, the MET levels achieved are consistently overestimated by the ACSM equations when using the Bruce protocol, and underestimated when using the Modified Bruce (**Table 2**). In general, for the remaining protocols (Balke-Ware, Modified Naughton, Modified Balke, and Ramp), workloads defined by MET levels ≤5.0 were underestimated by the ACSM equations whereas those >7.0 METs are overestimated by the ACSM equations (**Tables 3-6**).

**Discussion**

**Model G: F + BMI**

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 In the current study, we derived a new equation (FRIEND equation) that estimates directly measured VO2 max more accurately than the currently used ACSM equations. The overall error of the FRIEND equation is >4 times lower than the error associated with the values obtained from the ACSM equations (5.1±18.3% vs 21.4±24.9%, respectively). The overestimation of the ACSM equations is accentuated when protocols are considered separately. In general, a common theme that was apparent for all protocols studied was that workloads associated with MET levels ≤5.0 were underestimated by the ACSM equations and those >7.0 METs were overestimated.

The main factor that distinguishes the FRIEND equation and renders it superior to the ACSM equations in predicting VO2 max is that the FRIEND equation was constructed to predict a known value of directly measured VO2 max. In contrast, the ACSM equations predict VO2 max using an extrapolation of VO2 measured at a submaximal workload, assuming that a steady-state was achieved. However, steady-state is influenced by a number of factors, including age. Since the majority of the subjects in these studies were relatively young (19-26 years old), VO2 max will be overestimated by the ACSM equations when applied to older populations. Moreover, steady-state is rarely achievable during a progressive exercise test.

Additional attributes of the FRIEND equation include the relatively large database of 7,983 participants, both men (n=4,798) and women (n=3,183); Black (n=395) and White (n=7,588), with a wide age range (20-91 years), derived from different regions across the USA. This allowed us to examine whether gender and race had a significant impact on the predictive power of the model. Finally, since the FRIEND equation is based on a measured VO2 max value the need for two equations to account for different treadmill speeds is eliminated. Collectively, these attributes make the FRIEND equation more applicable to different populations. On the other hand, a potential limitation of the FRIEND equation is the exclusion of diseased populations in the FRIEND registry.

In conclusion, the accuracy of the FRIEND equation for predicting VO2 max is superior to that associated with the ACSM equations (overall error >4 times lower). Since the majority of treadmill tests are performed for clinical reasons and the importance of CRF in the clinical setting, this overwhelming superiority warrants that manufacturers of exercise assessment apparatus (treadmills) and exercise laboratories consider adapting the FRIEND equation for the estimation of VO2 max during exercise testing.

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**Figure 1** Average Squared Error change with variables considered in the multiple regression models (Model A-G). The graph represents 70% of the entire cohort data set (open circles), and the remaining 30% (x), used for validation. 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.Note that the interaction between treadmill speed and grade (Model B) are the strongest predictors of measure VO2 max.