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Determining Cardiorespiratory Fitness With Precision: Compendium of Findings From the FRIEND Registry☆

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ABSTRACT

Healthy living (HL) behaviors and characteristics are central to both preventing and treating a myriad of chronic diseases; a key HL characteristic is cardiorespiratory fitness (CRF). Knowing an individual's CRF provides vital information when assessing health status and formulating a plan of care. Normative reference values as well as thresholds that denote varying degrees of health and future risk exist for measures of CRF. However, improving upon the precision of CRF reference standards according to key factors as well as precision in how CRF assessments can be used to assess health status and prognosis is needed. The current review will: 1) provide an overview of current approaches to CRF assessment and interpretations; 2) describe more recent efforts to improve upon the precision of CRF values; and 3) describe the Fitness Registry and the Importance of Exercise: A National Data Base (FRIEND) for the precision of CRF as a clinical measure.

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Healthy living (HL) behaviors and characteristics are central to both preventing and treating a myriad of chronic disease[1,2]; a key HL characteristic is cardiorespiratory fitness (CRF).[3] While maximal or peak aerobic capacity is a central component of CRF, other diagnostic measures, including heart rate, blood pressure and pulmonary ventilation (V_E), provide additional resolution related to physiologic function and

Abbreviations and acronyms: ACSM, American College of Sports Medicine; AHA, American Heart Association; BMI, Body mass index; CASS, Coronary Artery Surgery Studies; COPD, Chronic obstructive pulmonary disease; CPX, Cardiopulmonary exercise testing; CRF, Cardiorespiratory fitness; CRFe, Estimate of cardiorespiratory fitness; CVD, Cardiovascular disease; ET, Exercise training; FRIEND, Fitness Registry and the Importance of Exercise: A National Data Base; HL, Healthy living; MET, Metabolic equivalent; MVV, Maximal voluntary ventilation; PA, Physical activity; VO_{2max}, Maximal oxygen consumption; VO_{2peak}, Peak oxygen consumption; VA, Veterans Affairs Medical Centers; V_E, ventilation; WC, Waist circumference.

☆ Statement of Conflict of Interest: see page 81.

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health.[4] Irrespective of an individual's current health status, from apparently healthy to a confirmed diagnosis of one or more chronic diseases, CRF portends important information regarding health trajectory and future risk for untoward events. Simply stated, individuals with a higher CRF are at a significantly lower risk for the development of chronic diseases and associated risk factors as well as adverse events (e.g., myocardial infraction) and premature mortality and is associated with lower healthcare costs.[5,6] In this context, knowing an individual's CRF provides integral information to health professionals when assessing health status and formulating a plan of care.[7] In recognition of the importance of CRF to one's current and future health, the American Heart Association (AHA) recently published a scientific statement affording vital sign status to this important health measure.[8]

Normative reference values as well as thresholds that denote varying degrees of health and risk for future adverse events exist for measures of CRF, primarily peak/maximal aerobic capacity. However, improving upon the precision of CRF reference standards according to key factors (e.g., age, sex, mode of exercise, etc.) as well as precision in how CRF assessments can be used to assess health status and prognosis is needed. Ideally, measured CRF is assessed in the context of an individual, accounting for their age and unique health phenotype and compared to reference standards that provide for the most accurate comparison possible. The current review will: 1) provide an overview of current approaches to CRF assessment and interpretations; 2) describe more recent efforts to improve upon the precision of CRF values with the use of cardiopulmonary exercise testing (CPX); and 3) describe the Fitness Registry and the Importance of Exercise: A National Data Base (FRIEND) for the precision of CRF as a clinical measure.

Current methods for CRF assessment and interpretation

Understanding the factors that influence differences in CRF is important. Data from the HERITAGE study suggested that heritable factors, after adjusting for age and sex, were associated with ~50% of the variation in CRF in adults.[9] Physical activity (PA), especially in the form of exercise training (ET), is the key HL behavior that can modify an individual's CRF.[10–12] Accordingly, international public health statements strongly recommend regular PA worldwide.[13] However, it is important to recognize that individuals' CRF responsiveness to changes in PA or ET behaviors is variable.[14] Additionally, when comparing which is a better indicator of health outcomes, CRF has been shown to be a stronger predictor than measures of PA.[15,16] Thus, knowledge of an individual's PA habits, although important, has limitations in terms of clinical value. CRF is a more precise measure and thus its regular assessment is important.

Given the importance of CRF, a recent AHA Scientific Statement recommended that CRF should be routinely assessed in the clinical setting.[3] As such, clinicians should be familiar with the range and hierarchy for assessment options available to obtain a CRF value.

The accepted gold-standard method for CRF is from the measure of maximal or peak oxygen consumption (VO_{2max} or VO_{2peak}) through cardiopulmonary exercise testing (CPX). This method requires performing a maximal bout of exercise, typically on either a treadmill or cycle ergometer, with measurements of V_E and expiratory gas (oxygen and carbon dioxide) analysis. Recommendations for laboratory equipment and guidelines for standardized procedures have been established by the AHA.[17,18] Previously, the ability to obtain CRF via CPX was considered to be limited due to the need for expensive equipment and specifically trained personnel. However, much has changed in recent years. Most clinical facilities already have blood pressure and electrocardiographic equipment and many also have dedicated space with a treadmill or cycle and perform diagnostic exercise testing for referred populations. Recognizing the increasing demand for CPX instrumentation more vendors have entered the market, which has both lowered equipment cost and provided a range of price options that allow tailoring packages that fit institutional circumstances. Additionally, responding to the need and interest related to health benefits associated with PA, many universities have developed and now offer degree programs in exercise science. Other allied health professionals also have opportunities to obtain training and certificates in exercise test administration. Thus, the availability of trained personnel is currently much less of an issue. Another significant change was introduced in 2014 with an AHA statement that concluded "*in most cases, clinical exercise tests can be safely supervised by properly trained non-physician health professionals*," which eases both scheduling and cost.[19] Given these favorable changes, CPX is has become a more feasible choice for CRF assessment.

Presently there is not a consensus opinion for when CRF should be assessed for the first time, nor for how frequently is should be assessed. The 2016 AHA statement[3] recommended CRF be measured in routine clinical practice similar to other preventative health related tests. For the general population, if feasible, CPX is the preferred method, however for chronic disease populations it is recommended as the best choice.

When CPX is not feasible, other procedures can be used to obtain an estimate of CRF (CRFe). These will briefly be described here, with a more complete review available in the 2016 AHA statement.[3] CRFe can also be derived by performing an exercise test with a maximal effort, typically as indicated by achieving a combination of high ratings of perceived exertion and high percentage of an age-estimated maximal heart rate. This method shares some key similarities as CPX in that specialized equipment and personnel are required, although as mentioned above many clinical facilities already provide this for patients referred for suspected cardiac disease. Maximal exercise test time or the maximal workload (speed and grade for treadmill tests or watts for cycle ergometer tests) from the tests can be used in regression equations that have been developed to estimate VO_{2max}. The prediction error with these equations is generally 1–1.5 metabolic equivalents (METs).

When maximal exercise testing is not available, other options that still involve exercise can be considered. One approach is to perform a submaximal exercise test, usually on a cycle ergometer but protocols are also available using treadmills or steps.[20] CRFe is derived from measuring heart rate at one or more exercise workloads. This method may be of particular value for situations where individualizing an exercise prescription is a goal, as the individual's heart rate response to an exercise stimulus can be observed performing multiple levels. Prediction equations or nomograms can be used to derive CRFe, with standards errors ~±10–15% of VO_{2max}. Another option to consider is what is referred to as field tests.[20] These most commonly involve walking or running a fixed distance (e.g. 1 or 1.5 miles) or for a fixed amount of time (e.g. 12 min). These methods are more commonly used in fitness or school settings as they allow groups of people to complete the test at the same time. A common clinical variation of this type of test is the 6-minute walk test.[21] As the standard errors of prediction of VO_{2max} for these field tests are lower than those for submaximal or maximal exercise tests, it is typical that only categories (ex. Poor, Fair, Average, Good, Excellent) are used as an indicator of functional capacity.

One other widely available option for obtaining CRFe is performed without exercise, using 'nonexercise' prediction equations.[3] The most basic versions of these use only an individual's age and sex. However, accuracy of the predictions improves if additional information is known about the individual, such as body weight and PA status. Recently, this approach was offered in a web-based version, with data reported for 730,432 people from around the world.[22] Interestingly, the prediction error with these equations is generally 1–2 METs, which is similar to the other methods. As the information needed for this option should be available in all electronic medical records, the 2016 AHA statement recommended "*at a minimum, all adults should have CRF estimated each year using a nonexercised algorithm during their annual healthcare examination*."[3] CRFe has gained consideration as a clinical vital sign.[23]

Regardless of the method used for CRF assessment, the ultimate goal is providing clinical meaning to the test result value. It is widely accepted that low-CRF is associated with increased rates of both morbidity and mortality. These findings have been demonstrated in multiple cohorts with data from men and women, in different races, and from multiple countries.[3] Typically, these studies used cohort-specific classifications of CRF which can vary considerably between the cohorts. For example, in the VA-cohort studied by Kokkinos et al.[24], low-CRFe was defined as <5 METs, whereas in a cohort from Gothenburg, Sweden studied by Lavendall et al.[25] low-CRFe was defined as <6.9 METs, and in a Copenhagen Male Study cohort studied by Jensen et al.[26] low-CRFe was defined as <8.3 METs. Beyond the differences in the cohorts, some of the variability may be due to the different methods used for CRFe, which in the 3 studies cited were estimated from either maximal exercise test time or submaximal heart rate and workload.

Another approach that has been used to demonstrate how CRF predicts morbidity or mortality is to report the relationship per 1 MET difference in CRF. Kodama et al.[27] published a meta-analysis of 33 studies reporting associations between CRF and morbidity or mortality outcomes. In their analyses they used values <7.9 METs for the low-CRF classification. They reported that a 1 MET higher CRF was associated with a 13% reduction in all-cause mortality and a 15% reduction in coronary heart disease of cardiovascular disease (CVD) mortality. A recent review of studies published since 2009 reported some studies showing reduced morbidity or mortality of ~10% per 1 MET higher CRF and others with the reduction as much as 30% per 1 MET higher CRF.[28] Again, some of this variation may be due to differences in cohorts, outcomes assessed, and the CRF methods. However, it seems clear that standardizing CRF interpretations would be helpful to reduce some of this variability and provide a clearer understanding of CRF data.

Value of CPX-derived CRF as the standard

Until the 1980s, exercise capacity was generally expressed as an estimated value based on maximal work rate achieved on a treadmill or cycle ergometer. The CPX method was generally limited to the domain of research physiologists and pulmonary medicine. The concept that estimated exercise capacity was an important marker of risk was demonstrated in the seminal Coronary Artery Surgery Studies (CASS) conducted in the late 1970s and early 1980s.[29] The CASS investigators observed that among patients with preserved left ventricular function and triple vessel disease, 7-year survival was 100% for those achieving stage V of the modified Bruce protocol (~13 METs) and only 53% among those who could only complete the beginning stage of the protocol (~3.5 METs). A number of relatively small follow-up studies were performed during the 1980s confirming the role of estimated METs in predicting outcomes in patients with CVD.[30,31] Studies performed at this time also established several important limitations associated with estimating exercise capacity from work rate. These studies documented that measuring exercise capacity directly using CPX technology provided superior precision and reproducibility when compared to estimating exercise capacity from exercise time or work rate.[32–38] In the last two decades, an abundance of studies documenting the value of directly-measured VO_{2max} as the standard metric for CRF have been published. It is now widely appreciated that CRF, when determined directly by CPX methods, is not only more precise compared to CRFe from work rate but CPX provides a wealth of additional information that is useful for assessing the presence and extent of CVD as well as stratifying risk.[39–41]

In addition to being the gold standard expression of CRF, VO_{2max} and other ventilatory gas exchange responses during exercise are also useful in terms of understanding the physiology and mechanisms underlying exercise intolerance for many different clinical conditions. Moreover, CRF expressed as VO_{2max} has numerous other clinical applications, including estimation of risk, evaluation of the efficacy of therapy, making PA recommendations, quantifying the response to exercise training, and the assessment of disability.[3,17,39–43] In recent years, a growing body of data has demonstrated that CRF powerfully predicts risk for adverse events across the spectrum of health and disease; in many studies, CRF has been shown to outperform the traditional risk factors in terms of health outcomes. The strength of CRF in risk stratification has reinvigorated the clinical value of CPX, which has been employed less frequently in recent years in favor of more advanced diagnostic imaging procedures (e.g., exercise stress echocardiography, exercise myocardial perfusion imaging, pharmacologic testing).[42,43] This issue was addressed in a recent AHA Scientific Statement which supported the application of CRF as a risk factor to be measured and treated just as a clinician would assess and treat hypertension, lipid abnormalities, smoking, diabetes or other established risk markers.[3]

Establishment and the importance of FRIEND

Along with the recognition of the value of CRF in recent years has come a need to develop ways to incorporate CRF into clinical, public health, and research settings. This need was recognized in a 2013 policy statement by the AHA entitled, "The Importance of Cardiorespiratory Fitness in the United States: The Need for a National Registry".[3] This scientific statement was part of an initiative to develop a national registry termed "Fitness Registry and the Importance of Exercise: A National Data Base" (FRIEND).[4] The FRIEND registry began with preliminary funding to establish a CRF registry office at Ball State University and the core CPX laboratory at the University of Illinois at Chicago, and by forming an independent advisory board. The FRIEND registry was designed to enhance the value of CRF across environments, including the clinical setting and workplace as well as the public, to better inform national policy efforts on physical fitness, physical activity and health. A key goal of the FRIEND registry was to address the need to educate healthcare providers regarding the importance of CRF. This is particularly imperative given that numerous studies have shown that most health care providers do not routinely counsel their patients on PA.[19,44] Moreover, despite the importance of CRF in the overall risk paradigm as mentioned above, CRF is rarely given much attention by clinicians, who usually focus on conventional risk factors or diagnostic tests which generate income.[3,4,19,44]

A second goal of the FRIEND initiative involves appropriately classifying CRF; in other words, what should be considered a normal reference standard for age- and gender-related CRF. A person's VO_{2max} is only meaningful if it is considered in terms of what is normal for a given individual if he or she were healthy. This is important because VO_{2max} declines with age and on average higher values are observed in men compared with women. For example, a given CRF value has a much different meaning in an elderly female compared to a middle-aged male. Knowing an individual's CRF expressed as a percentage of what is normal for gender and age, with as much precision as possible, not only appropriately classifies a person in the context of their expected CRF but provides a reference for activity counseling, risk stratification, and evaluation of therapy.[45] Therefore, it is critical to have a reference framework for comparison when assessing VO_{2max}. However, determining what constitutes a normal reference standard for gender and age is complicated by several factors, including definition of normalcy, genetics, body mass, and population heterogeneity.[19,46–51] While there have been a number of studies in this area, the available reference standards have limited generalizability, particularly in certain populations. For example, few reference samples have been large enough to firmly establish "normal standards".[4,52] In addition, virtually all previous normal standards are specific to the population from which they were drawn, and there have been comparatively few women included in these studies. Paap and Takken[46] for example, performed a systematic review of this issue and reported that only 4 studies met their criteria for high quality, and there were only 2 quality studies using treadmill testing. Although the equations developed by Hansen, Sue and Wasserman (commonly termed the Wasserman equations)[53,54] are widely used, they were derived from a relatively limited sample and often do not function well in populations other than middle-aged, normal weight males (e.g., overweight, the elderly, or females).[46–52]

Reference standards from the FRIEND registry

The FRIEND registry provided an ideal opportunity to improve upon existing reference standards for CRF.[55] The FRIEND data has advantages over previous efforts addressing this issue, including the fact that it overcomes many of the shortcomings cited in the Paap and Takken review,[46] the American Thoracic Society Guidelines,[21] and the AHA Scientific Statement on CPX.[17] The FRIEND registry includes a large and diverse sample of healthy men and women in the US whose exercise tests met objectively verified criteria for maximal effort. One of the initial analyses from the FRIEND investigators involved the establishment of categorical reference values for CRF in men and women tested on the treadmill.[55] This analysis included 4611 men and 3172 women. Gender-specific percentiles for CRF from treadmill exercise across age deciles compared to earlier values (using estimated VO_{2max} from treadmill work rate) published by the Cooper Clinic are shown in Table 1. Notably, there is a slightly steeper decline in VO_{2max} per age decade among both men and women in the FRIEND registry relative to the Cooper Clinic data. However, this underscores the importance of differences between measured VO_{2max} from CPX and VO_{2max} estimated from work rate, which is less precise.[32–38] Table 2 shows a comparison of mean reference values for VO_{2max} from the FRIEND registry compared with 2 recent studies from Norway, including the HUNT CRF study.[56,57] Similar to the Cooper data, both Norwegian men and women had higher CRF values for each age group than those in the US. All of these studies are consistent in that the annual decrease in VO_{2max} is greater for men than women, and that there are ~7–10% reductions in VO_{2max} per age decade. This initial FRIEND report provided the first reference data for VO_{2max} using treadmill data from a large sample of subjects in the United States and a second report provided the first reference data for VO_{2max} using cycle data.[58]

There remained a need for a widely applicable regression equation for CRF standards appropriate for men and women across the spectrum of age. As mentioned above, previous equations did not meet standards for quality, some were unwieldy, and they tended to function poorly among particular populations (e.g. women, obese, or elderly).[46–51] The FRIEND registry was therefore applied in an effort to improve upon previous regression formulas for age- and gender-expected standards for VO_{2max}, initially using treadmill testing.[59] Data were derived from maximal treadmill tests among 7783 healthy men and women (20–79 years). A separate, independent cohort of 1287 healthy subjects was employed to validate the performance of the FRIEND equation. The regression equation for VO_{2max} derived from the FRIEND registry was compared to the validation cohort as well as two older but commonly used equations (Wasserman and European). Age, gender, and body weight were the only significant predictors of VO_{2max}, and these factors accounted for a large proportion of variance in VO_{2max} (multiple $R = 0.79$, $R^2 = 0.62$, $p < 0.001$; $SEE = 7.2\ ml \cdot kg^{-1} \cdot min^{-1}$). The resultant equation for VO_{2max} was:

$$VO_{2max}\ ml \cdot kg^{-1} \cdot\ min^{-1} = 79:9 - (0.39 \times age) - (13.7 \times gender)\ (0 = male, 1 = female) - (0.127 \times weight\ [lbs]).$$

The percentages of VO_{2max} achieved from the Wasserman, FRIEND and European equations stratified by the entire cohort and by gender, age decile and body mass index (BMI) are shown in Table 3. Among the key findings were the considerable differences between age-predicted values achieved comparing the Wasserman and European equations; the Wasserman equation tended to be systematically higher than measured VO_{2max} while the European equation tended to be lower. For example, the average VO_{2max} expressed as a percentage of normal differed by 42% between the Wasserman and European reference standards. Among severely obese subjects (BMI >35 kg/m^2), the percentage of normal in the overall sample reflected unusually high CRF using the Wasserman equation (125.5%) and highly impaired CRF using the European equation (68.6%). Bland-Altman plots demonstrated a lower average error between the FRIEND equation and the two traditional equations; a bias of only 0.4 $ml \cdot kg^{-1} \cdot min^{-1}$ was observed between the measured and predicted VO_{2max} values for the FRIEND equation, whereas the bias ranged between −3.4 $ml \cdot kg^{-1} \cdot min^{-1}$ and 5.9 $ml \cdot kg^{-1} \cdot min^{-1}$ for the Wasserman and European equations. The clinical implications of this variation are obvious, including misclassification of risk in which a high-risk patient who may benefit from an intervention could be inappropriately excluded or vice-versa.

The equation derived from the FRIEND registry, in contrast, was comparatively stable across gender, age, and BMI (Table 3). It is of course not surprising that the FRIEND equation yielded predicted values of roughly 100% across the age spectrum given that the FRIEND registry was used to develop the equation. Importantly however, using a broad independent population, the percentage predicted values from the FRIEND equation remained roughly 100% across gender, age decades, and BMI. Bland-Altman plots also indicated that the average error between measured and predicted VO_{2max} was lower using the FRIEND equation in the independent sample. While these observations require further validation with other independent populations, they suggest that the FRIEND equation provides a more suitable standard for classifying CRF relative to age.

Table 1
Sex-specific percentiles for CRF from treadmill exercise tests with measured VO_{2max} obtained from FRIEND and predicted VO_{2max} ($mLO_2 \cdot kg^{-1} \cdot min^{-1}$) reported by the Cooper Clinic[a,b].

Age group (y)	Percentile						
	5th	10th	25th	50th	75th	90th	95th
Men from FRIEND[c]							
20–29	29.0	32.1	40.1	48.0	55.2	61.8	66.3
30–39	27.2	30.2	35.9	42.4	49.2	56.5	59.8
40–49	24.2	26.8	31.9	37.8	45.0	52.1	55.6
50–59	20.9	22.8	27.1	32.6	39.7	45.6	50.7
60–69	17.4	19.8	23.7	28.2	34.5	40.3	43.0
70–79	16.3	17.1	20.4	24.4	30.4	36.6	39.7
Men from Cooper Clinic[d]							
20–29	31.8	34.7	39.0	43.9	48.5	54.0	55.5
30–39	31.2	33.8	37.8	42.4	47.0	51.7	54.1
40–49	29.4	32.3	35.9	40.1	44.9	49.6	52.5
50–59	26.9	29.4	32.8	37.1	41.8	46.8	49.0
60–69	23.6	25.6	29.5	33.8	38.3	42.7	45.7
70–79	20.8	23.0	26.9	30.9	35.2	39.5	43.9
Women from FRIEND[c]							
20–29	21.7	23.9	30.5	37.6	44.7	51.3	56.0
30–39	19.0	20.9	25.3	30.2	36.1	41.4	45.8
40–49	17.0	18.8	22.1	26.7	32.4	38.4	41.7
50–59	16.0	17.3	19.9	23.4	27.6	32.0	35.9
60–69	13.4	14.6	17.2	20.0	23.8	27.0	29.4
70–79	13.1	13.6	15.6	18.3	20.8	23.1	24.1
Women from Cooper Clinic[d]							
20–29	27.6	29.5	33.0	37.8	42.4	46.8	49.6
30–39	25.9	28.0	32.0	36.7	41.0	45.3	47.4
40–49	25.1	26.6	30.2	34.5	38.6	43.1	45.3
50–59	23.0	24.6	28.0	31.4	35.2	38.8	41.0
60–69	21.8	23.0	25.1	28.8	32.3	35.9	37.8
70–79	19.6	21.5	24.2	27.6	29.8	32.5	37.2

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[a] CRF = cardiorespiratory fitness; CPX = cardiopulmonary exercise testing; FRIEND = Fitness Registry and the Importance of Exercise National Database; Vo_{2max} = maximal oxygen uptake.

[b] All patients are considered free of known cardiovascular disease.

[c] The FRIEND CRF data were measured with CPX.

[d] The Cooper Clinic data reported were predicted from Balke test time or work rate.

Table 2
Mean reference values for CRF with measured Vo_{2max} obtained on the treadmill from FRIEND compared to previously published values[a,b].

Sex	Age group (y)					
	20–29	30–39	40–49	50–59	60–69	70–79
Male						
FRIEND[39]	47.6 ± 11.3 (n = 513)	43.0 ± 9.9 (n = 963)	38.8 ± 9.6 (n = 1327)	33.8 ± 9.1 (n = 1078)	29.4 ± 7.9 (n = 593)	25.8 ± 7.1 (n = 137)
Loe et al.[57]	54.4 ± 8.4 (n = 199)	49.1 ± 7.5(n = 324)	47.2 ± 7.7 (n = 536)	42.6 ± 7.4 (n = 466)	39.2 ± 6.7 (n = 300)	35.3 ± 6.5 (n = 76)
Evardsen et al.[56]	48.9 ± 9.6 (n = 38)	46.2 ± 8.5 (n = 73)	42.7 ± 9.3 (n = 91)	36.8 ± 6.6 (n = 88)	32.4 ± 6.4 (n = 81)	30.1 ± 4.8 (n = 23)
Female						
FRIEND	37.6 ± 10.2 (n = 410)	30.9 ± 8.0 (n = 608)	27.9 ± 7.7 (n = 843)	24.2 ± 6.1 (n = 805)	20.7 ± 5.0 (n = 408)	18.3 ± 3.6 (n = 98)
Loe et al	43.0 ± 7.7 (n = 215)	40.0 ± 6.8 (n = 359)	38.4 ± 6.9 (n = 493)	34.4 ± 5.7 (n = 428)	31.1 ± 5.1 (n = 240)	28.3 ± 5.2 (n = 53)
Evardsen et al	40.3 ± 7.1 (n = 37)	37.6 ± 7.5 (n = 63)	33.0 ± 6.4 (n = 86)	30.4 ± 5.1 (n = 79)	28.7 ± 6.6 (n = 59)	23.5 ± 4.1 (n = 41)

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[a] CRF = cardiorespiratory fitness; CPX = cardiopulmonary exercise testing; FRIEND = Fitness Registry and the Importance of Exercise National Database; Vo_{2max} = maximal oxygen uptake.

[b] Data are expressed as a means ± SD with sample sizes for each age range. All patients were considered free of known cardiovascular disease.

The above equation was derived from treadmill testing, but it would be advantageous to similarly have a simple, validated equation that could be used for either the treadmill or the cycle ergometer. This was addressed by the FRIEND investigators among 10,881 healthy men and women.[60] Of these, 7617 and 3264 individuals were randomly selected for development and validation of the equation, respectively. In addition, a Brazilian sample of 1619 healthy subjects constituted a second, independent validation cohort. The prediction equation was similarly determined using multiple regression analysis, and again comparisons were made with the widely-used Wasserman and European equations. The resulting regression equation was:

VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$) = 45.2–0.35 × age − 10.9 × gender (male = 1; female = 2) − 0.15 × weight (pounds) + 0.68 × height (inches) − 0.46 × exercise mode (treadmill = 1; bike = 2) (R = 0.79, $R^2 = 0.62$, standard error of the estimate = 6.6 $ml \cdot kg^{-1} \cdot min^{-1}$). Percent-predicted VO_{2max} for the US and Brazilian validation cohorts were 102.8% and 95.8%, respectively, suggesting that the FRIEND equation performed well in a separate, independent population. The new equation performed better than the traditional equations, particularly among women and individuals ≥60 years old, groups that have been problematic in the past in terms of identifying normal standards. The FRIEND equation is simpler to apply than commonly-used equations, employing a simple coding of 1 or 2 for gender and exercise mode, and resulted in a lower average error between measured and predicted VO_{2max} than traditional equations even when applied to an independent cohort. However, unlike conventional equations, the FRIEND equations are new and lack extensive application over many years in diverse populations. This will be required to appropriately determine their utility and portability in both clinical and healthy populations.

Effect of body habitus

Notably, the regression equations for normal standards for VO_{2max} based on the FRIEND cohort included body mass (height, weight, BMI, and/or waist circumference [WC]) in addition to age and gender as the only significant determinants of VO_{2max}. Other clinical and demographic factors undoubtedly have a small influence on VO_{2max}, but for practical purposes they do not have a major impact, at least in healthy individuals. While not all previous equations have included body habitus, it appears to be an important factor influencing normal standards for exercise capacity. In an analysis of 5030 healthy subjects from the FRIEND registry (split into validation [4030] and cross validation [1000] groups), the effect of BMI and WC on predicting VO_{2max} was investigated.[61] In both the validation and cross-validation models, WC added significant predictive value to age and gender in predicting VO_{2max}. The influence of BMI was similar to that for WC, suggesting that either of these indices of body habitus may be included in regression models for VO_{2max}.

Normal standards for maximal exercise ventilation

Because VO_{2max} is the product of maximal exercise V_E and the amount of oxygen extracted by the tissues, maximal V_E is a critical

Table 3
Percentage of peak VO_2 achieved from the Wasserman, FRIEND and European equations stratified by the entire cohort and by gender, age group and BMI.[60]

	WASSERMAN equation	FRIEND equation	EUROPEAN equation	p values
Total (n = 7759)	118.0 ± 26.5[a,b]	100.6 ± 23.0	101.2 ± 28.2	p < 0.001
Gender				
Men (n = 4601)	109.9 ± 22.1[a,b]	99.6 ± 20.2	110.0 ± 28.2[a]	p < 0.001
Women (n = 3158)	130.0 ± 27.9[a,b]	102.1 ± 23.5	88.5 ± 23.2[a]	p < 0.001
Age groups (years)				
20–29 (n = 901)	113.9 ± 22.9[a,b]	100.5 ± 20.2	100.8 ± 24.0	p < 0.001
30–39 (n = 1571)	113.3 ± 21.8[a,b]	99.0 ± 20.4	98.6 ± 25.4	p < 0.001
40–49 (n = 2169)	117.2 ± 24.8[a,b]	100.5 ± 21.4	101.0 ± 27.8	p < 0.001
50–59 (n = 1882)	121.0 ± 27.7[a,b]	101.9 ± 24.2	101.0 ± 29.1	p < 0.001
60–69 (n = 1001)	122.8 ± 31.7[a,b]	101.0 ± 28.4	104.3 ± 32.2[a]	p < 0.001
70–79 (n = 235)	128.4 ± 36.9[a,b]	101.4 ± 28.4	112.0 ± 28.2[a]	p < 0.001
BMI groups (kg/m^2)				
<25 (n = 3195)	121.0 ± 25.7[a,b]	102.9 ± 21.0	115.0 ± 27.7[a]	p < 0.001
25–29.9 (n = 2586)	112.6 ± 24.5[a,b]	97.3 ± 19.0	101.4 ± 23.2[a]	p < 0.001
30–34.9 (n = 1180)	116.7 ± 27.3[a,b]	95.6 ± 19.2	84.9 ± 18.6[a]	p < 0.001
>35 (n = 798)	125.5 ± 30.7[a,b]	109.7 ± 38.9	68.6 ± 15.3[a]	p < 0.001

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[a] Significantly different in relation to FRIEND equation (p < 0.001).

[b] Significantly different in relation to European equation (p < 0.001).

Table 4
Peak ventilation (L/min) during cardiopulmonary exercise testing data from the FRIEND Registry (n = 5232).[62]

Age (years)*	20–29	30–39	40–49	50–59	60–69	70–79
Men** (n = 3043)	130 ± 30 (434)	121 ± 25 (524)	113 ± 25 (756)	103 ± 25 (748)	93 ± 24 (458)	80 ± 24 (123)
Women (n = 2189)	89 ± 21 (324)	78 ± 19 (360)	74 ± 16 (536)	67 ± 15 (557)	59 ± 14 (325)	53 ± 12 (87)

Data are mean ± SD.
Reprinted from: Kaminsky LA, Harber MP, Imboden MT, Arena R, Myers J. Peak Ventilation Reference Standards from Exercise Testing: From the FRIEND Registry. Med Sci Sports Exerc. Published Ahead of Print (August 7, 2018): https://journals.lww.com/acsm-msse/Abstract/publishahead/Peak_Ventilation_Reference_Standards_from_Exercise.96841.aspx with permission from Wolters Kluwer Health, Inc.
* $p < 0.05$ each age-group different from all other age-groups by ANOVA.
** $p < 0.05$ men different from women in each age group by ANOVA.

determinant of VO_{2max}. By definition, CRF is paralleled by the extent to which an individual can move air into and out of the lungs. Thus, maximal exercise V_E is an important limiting factor during exercise in many conditions, including patients with heart failure and moderate to severe chronic obstructive pulmonary disease (COPD). Maximal exercise V_E is often compared to maximal voluntary ventilation (MVV) and is typically considered normal if the ratio between V_E and MVV ranges between 50 and 80%.[28] Alternatively, maximal V_E is subtracted from MVV to calculate breathing reserve, with values <15 L/min considered abnormal.[53] Few efforts have been made to develop reference standards for maximal exercise V_E. Such standards would provide enhanced opportunities to include maximal V_E in the interpretation of CPX results. A normal standard for maximal VE would also allow future investigations to evaluate the extent to which maximal V_E contributes to the diagnosis and/or prognosis of patients with chronic diseases.

Among 3043 men and 2189 women from the FRIEND registry, normal standards for maximal exercise V_E were determined.[62] Table 4 provides maximal V_E values measured during CPX for both men and women across 6 decades of age groups. As expected, maximal V_E was significantly higher for men and for each younger age group. On average, men's maximal V_E was 41% higher than women and maximal V_E declined ~7% and 9% among men and women, respectively, per age decade from the twentieth to the seventieth decades. The regression equation for maximal V_E was:

$$\text{Maximal } V_E\ (\text{L/ min}) = 17.32-(28.33 * \text{sex}\ [\text{men} = 0, \text{women} = 1])-0.79\ (\text{age}\ [\text{years}]) +1.85 * (\text{height}\ [\text{inches}]); \text{SEE} = 21.7$$

Although maximal V_E has generally received relatively little attention compared to other CPX responses over the years, it has important applications for CRF and many disease states. Reference standards for maximal exercise V_E are lacking in the literature. The standards derived from the FRIEND registry can be applied for the interpretation of maximal V_E along with other measures obtained during CPX. Future studies should explore the potential contribution of the maximal V_E response to exercise and its relation to health and disease outcomes. Additionally, factors that may influence maximal V_E and its change with age, such as ET, should be explored.

Predicting VO_{2max} from work rate

While VO_{2max} measured directly using ventilatory gas exchange techniques is the recognized standard for determining CRF, CPX is not always available for routine clinical exercise testing. Because the external work rate achieved (treadmill speed and grade or watts achieved on a cycle ergometer) parallels measured VO_2, VO_{2max} is often estimated from external work rate. Since the 1970s, the American College of Sports Medicine (ACSM) equation has been the standard used to estimate VO_2 when gas exchange techniques are not available. However, this equation is highly flawed; its shortcomings have been widely recognized in the literature over the years.[3,32–38,63] One of the important limitations of the ACSM equation is that a steady state is assumed, which is unrealistic at maximal exercise. In addition, the accuracy of predicting VO_{2max} from the external work rate is influenced by age, the presence of disease, CRF, walking efficiency, handrail use, and other factors. Moreover, the ACSM equations were developed >4 decades ago, and were based on a relatively small number of college-aged subjects. Thus, a need exists to develop better regression equations to predict VO_2 from the external work rate.

Among 7983 apparently healthy subjects from the FRIEND registry, an effort was made to improve upon the traditional ACSM equation using treadmill exercise.[64] Seventy percent of the sample was used to develop the equations, and the remaining 30% was used to validate the equations. Using a multiple regression procedure and considering clinical and demographic factors in addition to work rate, the following equation was generated:

$$VO_{2max}\ (\text{ml } O_2 \text{ kg/ min}) = \text{Speed (m/ min)} \times (0.17 + \text{fractional grade} \times 0.79) + 3.5$$

The FRIEND equation predicted VO_{2max} with an overall error ~4 times lower than that associated with the traditional ACSM equation (5.1% vs. 21.4% respectively). The prediction error was particularly high for the ACSM equation when using particular protocols. Although the ACSM equation for treadmill testing has a lengthy history and tradition and has been widely applied in many different settings (clinical evaluations, epidemiologic studies, certification exams, energy expenditure during physical activity, etc.), the greater precision exhibited by the FRIEND equation suggests that exercise laboratories should consider adapting the FRIEND equation for the estimation of VO_{2max} during exercise testing.

Conclusions

CRF is now considered a vital sign. As described in the current review, there is a need to improve the precision by which CRF is assessed and used to evaluate current health status and future risk. Moreover, efforts by FRIEND have helped to advance the precision of CRF prediction and normative values. As these efforts continue, the information obtained from a CRF assessment will become even more valuable to health professionals who are charged with optimizing outcomes for individuals under their care.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

Disclosures

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