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# An Estimation Model for Cardiorespiratory Fitness in Adults with Rheumatoid Arthritis

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**ABSTRACT**

LIFF, M. H., M. HOFF, T. FREMO, U. WISLØFF, and V. VIDEM. An Estimation Model for Cardiorespiratory Fitness in Adults with Rheumatoid Arthritis. *Med. Sci. Sports Exerc.*, Vol. 52, No. 6, pp. 1248–1255, 2020. **Purpose:** Cardiopulmonary exercise testing of peak oxygen uptake ($\dot{V}O_{2peak}$) is the gold standard to measure cardiorespiratory fitness (CRF). For resource-intensive evaluation, equations estimating CRF (eCRF) may be used. The purpose was to investigate if an eCRF equation from a healthy population is useful in persons with rheumatoid arthritis (RA), and if necessary, develop new equations for eCRF in this group. **Methods:** $\dot{V}O_{2peak}$ results from 93 persons with RA were compared with eCRF calculated by an established equation for healthy individuals including age, sex, physical activity (PA index), resting HR (RHR), and waist circumference. Because of deviation from the observed $\dot{V}O_{2peak}$, new equations for eCRF in persons with RA were developed from regression analysis of variables associated with observed $\dot{V}O_{2peak}$. **Results:** The established equation overestimated CRF ($R^2 = 0.48$, root mean square error [RMSE] = 7.07). The new RA equation more accurately estimated CRF ($R^2 = 0.81$, RMSE = 4.44) (female = 0, male = 1; never smoked = 0, ever smoked = 1): eCRF = 77.961 + (sex × 28.791) − (age × 0.358) − (age–sex interaction × 0.326) − (body mass index [BMI] × 0.700) − (RHR × 0.125) − (smoking × 1.854) + (PA index × 0.211) − (patient global RA assessment × 0.071). Alternative new RA equation ($R^2$ = 0.79, RMSE = 4.63): eCRF = 77.851 + (sex × 25.460) − (age × 0.381) − (age–sex interaction × 0.254) − (BMI × 0.743) − (RHR × 0.115) − (smoking × 2.154) + (PA index × 0.209). **Conclusions:** The new RA equations better predicted CRF in individuals with RA, preventing overestimation in low-fit persons. The new equation should be preferred when estimating CRF in individuals with RA. The alternative equation, without patient global assessment, is useful for individuals with RA in population-based studies. **Key Words:** $\dot{V}O_{2PEAK}$, PREDICTED FITNESS, PERSON-SPECIFIC MEDICINE, INFLAMMATORY ARTHRITIS

The gold standard method for measuring cardiorespiratory fitness (CRF) is by cardiopulmonary exercise testing (CPET) of maximal or peak oxygen uptake ($\dot{V}O_{2peak}$), where peak uptake denotes the situation where the criteria for a maximal test were not met (1,2). Cardiorespiratory fitness is inversely associated with cardiovascular disease (CVD) in the general population (2–7). Thus, there is an increasing focus on exercise that increases CRF in prevention and treatment of lifestyle-related diseases (2). Higher demands on the cardiorespiratory and musculoskeletal system, particularly with exercise of high intensity, have the effect of improving CRF (2,7), which in turn is associated with reduced cardiovascular risk factors (7,8).

Despite the importance of CRF for health, measurements of $\dot{V}O_{2peak}$ in health care settings is rare for different reasons, including the cost and time consumption of the methods, as well as the potential risks related to maximal physical efforts. Therefore, various equations for estimated CRF (eCRF) have been developed (2,9–11). In a previous study in a general healthy population, low eCRF was independently associated with CVD and all-cause mortality (12). Compared with CPET, eCRF equations are easily accessible, save time, and reduce cost (2,13). An example is the The Norwegian population-based

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Nord-Trøndelag Health Study (HUNT) equation (11), which was developed from the $\dot{V}O_{2peak}$ results of 4631 healthy participants of the fitness study of the third survey of the Nord-Trøndelag Health Study (HUNT3 Fitness study) (14,15). The HUNT equation has been implemented in other studies regarding fitness and is one of the equations of choice for nonexercise estimation of CRF during routine clinical visits for healthy people in a scientific statement from the American Heart Association (AHA) (2,16). The variables included in the HUNT equation are age, sex, resting HR (RHR), waist circumference and a physical activity summary index (PA index) score (Table 1) (11). Equations for eCRF also make investigation of fitness easier in population-based studies, where simple measurements and questions can be included (2,16).

Equations for eCRF are often developed from measurements of $\dot{V}O_{2peak}$ in relatively healthy populations without specific diseases. It is not obvious that such equations are valid for people suffering from rheumatoid arthritis (RA) and to our knowledge, no eCRF equation has previously been developed particularly for persons with RA. Rheumatoid arthritis is the most common autoimmune rheumatic disease with a prevalence of approximately 1% (17,18) and a life time risk close to 4% in women and 2% in men (19). Persons with RA have an increased burden of CVD, cardiovascular risk factors, and higher mortality rates from CVD compared with age-matched controls (18), and those with higher CRF have lower blood pressure, reduced insulin resistance and significantly better lipid profiles compared with persons with reduced CRF (20). Improvement of CRF in persons with RA is associated with reduction of risk factors for CVD (21).

Rheumatoid arthritis affects joints (arthritis) and internal organs, including the vasculature. Furthermore, body composition may be altered in persons with RA (18). Such pathophysiological changes may alter the associations of CRF to RHR and/or waist circumference, which are used in the HUNT eCRF equation. We have previously found that CRF in persons with RA was associated not only with some of the same variables as in the general healthy population but also with other variables including smoking habits and the patient global assessment of RA disease activity (patient global RA assessment [PGA]) (22).

TABLE 1. The PA summary index.[a]

| | |
|---|---|
| How Frequently Do You Exercise? | |
| Never | 0 |
| Less than once a week | 0 |
| Once a week | 1 |
| Two to three times a week | 2 |
| Almost everyday | 3 |
| How hard do you push yourself? | |
| Take it easy | 0 |
| Heavy breath and sweat | 5 |
| Push near exhaustion | 10 |
| How long does each session last? | |
| <15 min | 1 |
| 16–30 min | 1 |
| 30–60 min | 1.5 |
| >60 min | 1.5 |

[a]Developed for the original HUNT equation. The index is calculated as the product of the points given for each question (11).

The American College of Sports Medicine (ACSM) and AHA 2007 recommendations for PA to promote and maintain health in healthy adults (23) are central to the 2018 European League Against Rheumatism (EULAR) recommendations for PA in people with arthritis (24). With the increasing focus on PA as an important contributor to health in people with RA and the association of low CRF to CVD in the healthy population, estimating CRF levels in persons with RA is of practical importance.

On this background, we hypothesized that an equation for eCRF suitable for persons with RA (new RA equation) would need to be adjusted compared with equations developed for the general population. Thus, the purpose of this study was to develop a new RA equation that best represents the actual $\dot{V}O_{2peak}$ in persons with RA by: 1) comparing $\dot{V}O_{2\ peak}$ test results with the eCRF calculated by the HUNT equation in persons with RA; 2) if there were deviations between the observed and estimated results of CRF, developing a specific equation for persons with RA; 3) developing a new alternative RA equation for eCRF in persons with RA in population-based studies without access to RA-specific variables. The HUNT equation was selected because it was developed using data from the same region of Norway as the persons with RA that would be included in our study. Furthermore, it takes three important aspects of PA into account when calculating the eCRF, that is, frequency, duration, and intensity, which we found would be relevant in persons who may have physical limitations to movement.

## METHODS

As previously described (22), a convenience sample of adults with RA ($n$ = 93) fulfilling the 1987 American College of Rheumatology (ACR) (25) and/or the 2010 ACR/EULAR classification criteria for RA (26), were recruited from February 17, 2017, to January 4, 2018, from the outpatient clinic at the Rheumatology Department at St. Olavs University Hospital and from the group of persons with RA attending patient-centered follow-up.

Power calculations were based on the following assumptions (22): from the literature, we assumed that the most relevant variables associated with fitness in the general population would explain 60% of the variance in measured $\dot{V}O_{2peak}$ (i.e., $R^2 = 0.60$). Given $\alpha = 0.05$, with inclusion of 100 persons with RA, the power to identify one or more RA-related variables that would increase $R^2$ to 0.65 would be 0.96. Useful data were available from 93 participants, which resulted in a power of 0.95 to detect this increase in $R^2$, considered as satisfactory.

Testing of $\dot{V}O_{2max}$ was performed on a treadmill identical to that used in previous studies in our group and followed the American College of Cardiology/AHA (ACC/AHA) guidelines for exercise testing (27). The relevant exclusion criteria in our study were unstable heart conditions, chronic obstructive/restrictive pulmonary disease necessitating use of oxygen therapy, or physical disability making a treadmill test impossible.

Because RA patients sometimes exhibit physical limitations, experienced personnel at the *NeXt Move* core facility at NTNU - Norwegian University of Science and Technology determined the best individual CPET regimen during a 6-min

warm-up on a treadmill (Woodway PPS55; USA Inc., Waukesha, WI). They detected inclination and functional running or walking speed, in addition to subjective moderate aerobic intensity based on rated perceived exertion (RPE Borg scale 6–20) (22,28). Participants were fitted with an HR monitor (H7, Polar Electro, Kempele, Finland) and facemask (7450 Series V2 CPET mask, Hans Rudolph Inc., Shawnee, KS). An individualized ramp protocol with gradual increase in workload was used, until either exhaustion or fulfillment of the criteria for $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$). Gas was measured every tenth second using a mixing chamber ergospirometry system (Metalyzer II; Cortex Biophysik Gmbh, Leipzig, Germany). Maximal oxygen uptake ($\dot{V}O_{2max}$) was defined using the following criteria: 1) $\dot{V}O_2$ leveling off (<2 $mL \cdot min^{-1} \cdot kg^{-1}$) despite increase in workload and 2) respiratory exchange ratio ≥1.05. If the criteria for $\dot{V}O_{2max}$ were not met, the term $\dot{V}O_{2peak}$ was used instead. $\dot{V}O_{2peak}$ was defined as the mean of the participant's three successive highest $\dot{V}O_2$ registrations achieved during the CPET. There were 17.2% of the 93 patients that qualified for $\dot{V}O_{2peak}$. For simplicity, the term $\dot{V}O_{2peak}$ is used for all patients.

The ergospirometry system was calibrated according to a standardized protocol every day before use and subsequently before every fourth test if performing multiple tests on the same day. The operating protocol also details the methods for turbine change, check of ambient pressure, gas, and flow. Turbine change and sensor adjustment to ambient conditions were performed before every test to ensure accurate flow and gas measurements, and the system is regularly validated biologically against the gold standard (Douglas bag) and mechanically using a metabolic simulator.

Information collected at the same visit or extracted from medical records covered smoking habits, medications, comorbidities (cancer, CVD (hypertension/angina/myocardial infarction), diabetes, chronic obstructive pulmonary disease/chronic restrictive pulmonary disease [COPD/CRPD]), as well as the RA-specific variables year of RA diagnosis, anticitrullinated protein antibody, rheumatoid factor, the modified Health Assessment Questionnaire (mHAQ) (29), the physician global RA assessment (0–100 mm scale) (30), Disease Activity Score 28 (31), EULAR remission criteria (32), and the PGA (30). The question asked in the PGA was: "Considering all the symptoms from your rheumatic disease during the last week, how do you think your state is?" They then responded on a 0- to 100-mm visual analog scale; "0" meaning, "Good, no symptoms; and "100" meaning, "very bad." High-sensitivity C-reactive protein ($mg \cdot L^{-1}$), blood pressure (mm Hg), RHR (bpm), waist circumference (cm), height (m), and weight (kg) were measured (22). Body mass index (BMI) was calculated as the body weight (kg) divided by the squared value of height (m).

The RHR and blood pressure were measured after 10 min of rest in a comfortable chair. Smoking status was defined as smoker (previous and present) versus never smoker. The PA index used was developed for the HUNT equation, based on answers to separate questions on PA (frequency, duration, and intensity) (Table 1) (11). Participants were also categorized in two categories, depending on whether they fulfilled the ACSM/AHA 2007 recommendations for PA (23).

All participants provided written informed consent. The Regional Committee for Medical and Health Research Ethics approved the study (2016/275), which was performed in compliance with the Helsinki Declaration.

**Statistical analysis.** Data are given as counts and percentages, mean with standard deviation (SD) or median with interquartile range in parenthesis. All Statistical analyses were performed using STATA (Version 15.0; StataCorp, College Station, TX).

The eCRF was calculated with the HUNT equation in all 93 participants, and the agreement of the observed and the calculated $\dot{V}O_{2peak}$ from the HUNT equation was analyzed using scatterplots of observed versus predicted $\dot{V}O_{2peak}$ and by equivalence testing (33). With this method, the difference between the observed and predicted $\dot{V}O_{2peak}$ is calculated for all participants. The mean and 90% confidence interval (CI) of this difference is evaluated against a predefined equivalence region, which indicates how big the difference may be for the two measurements still to be considered equivalent. Because there is no generally accepted equivalence region for eCRF versus measured $\dot{V}O_{2peak}$, we evaluated against an equivalence region of 1 metabolic equivalent of task (MET) (3.5 $mL \cdot min^{-1} \cdot kg^{-1}$), 1.5 MET (5.3 $mL \cdot min^{-1} \cdot kg^{-1}$) or 2 MET (7.0 $mL \cdot min^{-1} \cdot kg^{-1}$). Evaluation was performed for all participants as well as for participants with measured $\dot{V}O_{2peak} < 30\ mL \cdot min^{-1} \cdot kg^{-1}$ ($n = 45$) because these participants were considered more vulnerable if their eCRF was inaccurate.

Variables associated with $\dot{V}O_{2peak}$ in persons with RA were assessed using multivariable linear regression analyses with $\dot{V}O_{2peak}$ as the dependent variable. Explanatory variables were selected based on previous literature: age, sex, and the age–sex interaction, BMI, smoking (present or previous vs never smoker), RHR and the PA index. Body mass index was considered easier to measure accurately than alternative variables, including waist circumference. Other potential explanatory variables that might be important in RA patients included comorbidity (cancer, CVD, diabetes, COPD/CRPD), coded as a single yes/no variable, and systolic blood pressure (SBP). We also considered a selection of common RA-specific variables: PGA and the physician global RA assessment, mHAQ, various disease activity scores, including the Disease Activity Score 28 (DAS28), remission criteria (DAS28 or ACR/EULAR), time since diagnosis, seropositivity, and disease-modifying antirheumatic medication.

Subselection of these variables was performed first using Lasso (least absolute shrinkage and selection operator) regression (34) with 1000 repetitions. This procedure reduces the risk of overfitting. By setting the coefficients of irrelevant variables to 0, Lasso regression identifies the smallest useful set of variables among variables that may be highly correlated. We therefore only selected the variables with a coefficient different from 0 in the Lasso regression for inclusion in the multivariable linear regression models. All selected variables were forced into the models resulting in full models, which were then reduced to the final models by removal of nonsignificant variables. The final variables in the new RA equation were age,

TABLE 2. Participant characteristics.

| | Total, $N = 93$ |
|---|---|
| Age (yr), median (IQR) | 60 (52–66) |
| Women, *n* (%) | 68 (73) |
| Height (m), mean (SD) | 1.69 (0.09) |
| Weight (kg), mean (SD) | 76.4 (12.3) |
| BMI (kg·m$^{-2}$), mean (SD) | 26.7 (3.9) |
| Comorbidity, *n* (%) | 38 (41) |
| Cardiovascular (HT, angina, MI) | 21 (23) |
| Respiratory (COPD and/or CRPD) | 18 (19) |
| Diabetes | 4 (4) |
| Cancer (previous or present) | 5 (5) |
| Smoking, *n* (%)[a] | |
| Never smoked | 35 (38) |
| Previous smoker | 51 (55) |
| Present smoker | 7 (8) |
| SBP (mm Hg), median (IQR) | 122 (114–131) |
| RHR (bpm), mean (SD) | 66 (10) |
| ACSM/AHA 2007 recommendations for PA, *n* (%) | |
| Does not fulfill ACSM/AHA 2007 recommendations | 64 (69) |
| Fulfills ACSM/AHA 2007 recommendations | 29 (31) |
| Seropositivity (ACPA and/or RF), *n* (%) | 75 (81) |
| Disease duration (yr), median (IQR) | 10 (5-19) |
| Patient global RA assessment (0–100 mm), median (IQR) | 24 (10-36) |
| Physician global RA assessment (0–100 mm), median (IQR) | 10 (0-12) |
| mHAQ, median (IQR) | 0.13 (0-0.38) |
| mHAQ, mean (SD) | 0.26 (0.31) |
| hsCRP, median (IQR) | 1.75 (0.75-3.13) |
| DAS28 (hsCRP), *n* (%) | |
| Remission | 39 (42) |
| Low disease activity | 23 (25) |
| Moderate disease activity | 28 (30) |
| High disease activity | 3 (3) |
| Mean (SD) | 2.56 (1.04) |
| ACR/EULAR remission, *n* (%) | 25 (27) |
| Medication, *n* (%) | |
| bDMARD (present) | 54 (58) |
| cDMARD (present) | 74 (80) |
| Corticosteroids (any form during last year) | 39 (42) |
| $\dot{V}O_{2peak}$ (mL·min$^{-1}$·kg$^{-1}$), median (IQR) | 30.6 (25.2–37.7) |
| 20–39 yr | 45.4 (43.8–51.1) |
| 40–49 yr | 39.3 (32.2–42.7) |
| 50–59 yr | 31.2 (26.2–37.8) |
| 60–69 yr | 27.2 (25.0–32.4) |
| ≥70 yr | 26.4 (19.7–31.9) |

ACPA, anticitrullinated protein antibody; bDMARD, biological disease modifying anti rheumatic drugs; cDMARD, conventional disease modifying anti rheumatic drugs; hsCRP, high sensitivity C-reactive protein; HT, hypertension; IQR, interquartile range; MI, myocardial infarction; RF, rheumatoid factor.
[a]Total sum is 101% due to rounding.

sex, BMI, RHR, smoking, PA index, patient global RA assessment. A new alternative RA equation was made by removing the only RA-specific variable that remained in the new RA equation, that is, the patient global RA assessment. To identify the best variable to represent body composition, we performed a sensitivity analysis substituting BMI with the waist-to-height ratio in the new RA equation.

Model assumptions were evaluated using residual plots including residual versus predicted value plots to assess homoscedasticity. Multivariate outliers were assessed using Cook's distance. The models were compared using the $R^2$, root mean square error (RMSE) (i.e., the standard deviation of the unexplained variance), Akaike information criterion, and Bayesian information criterion. *P* values <0.05 were considered significant. The agreement of the observed and the calculated $\dot{V}O_{2peak}$ from eCRF calculated by the new RA equation and the alternative new RA equation were analyzed using scatterplots of observed versus predicted $\dot{V}O_{2peak}$ and by equivalence testing with equivalence regions as described above (33). Internal validation of the new RA equation was performed by bootstrapping ($n = 1000$) to compare original and bootstrapped CI of the coefficients, and by k-fold cross validation ($n = 25$ folds). Bivariate Pearson's correlation coefficients were also calculated.

In addition, two RA equations including SBP and one RA equation where the PA index was substituted with fulfillment or not of the ACSM/AHA 2007 PA recommendations (23) were developed through a similar process as described above.

## RESULTS

Participant characteristics and $\dot{V}O_{2peak}$ results are shown in Table 2. Using the HUNT equation, RMSE was 7.07 and $R^2$ was 0.48. The corresponding RMSE and $R^2$ values using the best-fitting RA equations are shown in Table 3. There were no outliers or overly influential cases in the new RA models.

When comparing the observed $\dot{V}O_{2peak}$ results to those estimated by the HUNT equation and the new RA equation (Fig. 1), there were some discrepancies between observed and estimated CRF for both models. However, the smallest differences between measured and estimated CRF was found with the new RA equation. These findings are illustrated in the scatterplots for observed versus calculated eCRF for the HUNT and new RA equation (Fig. 1).

Figure 2 shows the results from equivalence testing of the HUNT equation and new RA equation versus observed $\dot{V}O_{2peak}$, respectively. The mean and 90% CI for the difference from measured $\dot{V}O_{2peak}$ using the HUNT equation were 1.0 (−6.3 to 8.3) mL·min$^{-1}$·kg$^{-1}$ for all participants ($n = 93$), and 3.7 (−5.0 to 12.4) mL·min$^{-1}$·kg$^{-1}$ for participants with measured $\dot{V}O_{2peak} < 30$ ($n = 43$). For the new RA equation, the mean and CI were 0 (−5.3 to 5.3) mL·min$^{-1}$·kg$^{-1}$ for all participants

TABLE 3. The best-fitting new RA equations.

| **RA Equation** | | | | |
|---|---|---|---|---|
| **$R^2 = 0.81$, RMSE = 4.44** | **Coefficient** | **SE** | ***P*** | **CI** |
| Sex (female = 0, male = 1) | 28.791 | 6.431 | <0.001 | 15.990 to 41.592 |
| Age (yr) | −0.358 | 0.050 | <0.001 | −0.456 to −0.260 |
| Age and sex interaction | −0.326 | 0.109 | 0.004 | −0.542 to −0.110 |
| BMI (kg·m$^{-2}$) | −0.700 | 0.125 | <0.001 | −0.949 to −0.451 |
| RHR (bpm) | −0.125 | 0.050 | 0.013 | −0.224 to −0.027 |
| Smoking (never = 0, ever = 1) | −1.854 | 1.019 | 0.073[a] | −3.881 to 0.173 |
| PA summary index | 0.211 | 0.058 | <0.001 | 0.096 to 0.325 |
| Patient global RA assessment (mm) | −0.071 | 0.025 | 0.005 | −0.120 to −0.022 |
| Constant | 77.961 | 5.439 | <0.001 | 67.144 to 88.779 |
| **Alternative RA Equation** | | | | |
| **$R^2 = 0.79$, RMSE = 4.63** | **Coefficient** | **SE** | ***P*** | **CI** |
| Sex (female = 0, male = 1) | 25.460 | 6.602 | <0.001 | 12.333 to 38.589 |
| Age (yr) | −0.381 | 0.051 | <0.001 | −0.483 to −0.280 |
| Age and sex interaction | −0.254 | 0.110 | 0.024 | −0.473 to −0.034 |
| BMI (kg·m$^{-2}$) | −0.743 | 0.130 | <0.001 | −1.000 to −0.485 |
| RHR (bpm) | −0.115 | 0.052 | 0.029 | −0.217 to −0.012 |
| Smoking (never = 0, ever = 1) | −2.154 | 1.057 | 0.045 | −4.256 to −0.052 |
| PA summary index | 0.209 | 0.060 | 0.001 | 0.089 to 0.328 |
| Constant | 77.851 | 5.670 | <0.001 | 66.577 to 89.125 |

[a]Smoking in the RA equation had $P = 0.073$ but was kept in the equation to avoid deterioration of overall model fit.

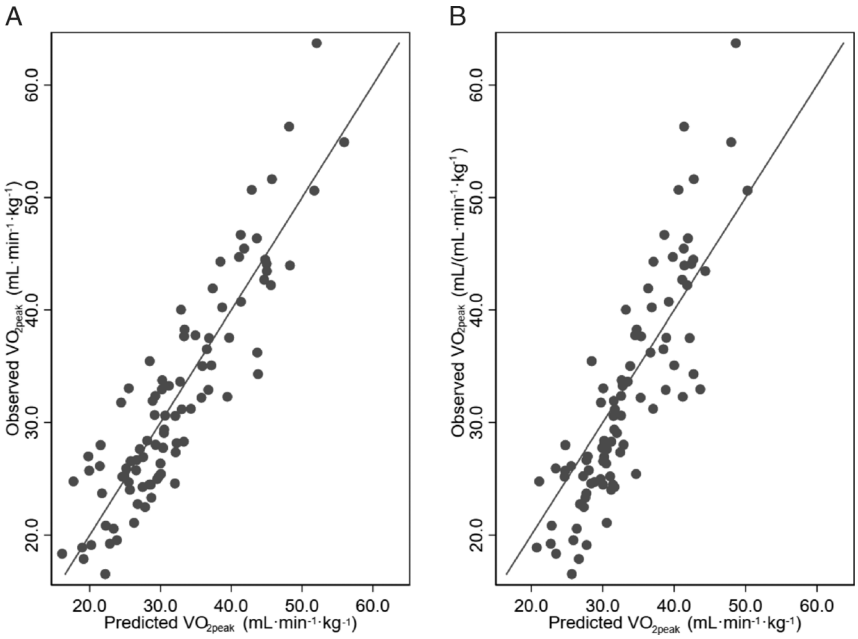


**FIGURE 1—Observed vs predicted $\dot{V}O_{2peak}$ in persons with RA. Observed vs predicted $\dot{V}O_{2peak}$ (mL·min$^{-1}$·kg$^{-1}$) using Panel A: The RA equation. Panel B: The HUNT equation (11). The diagonal lines indicate identity between observed and predicted $\dot{V}O_{2peak}$. With the HUNT equation, there was a systematic tendency to overestimation of low observed $\dot{V}O_{2peak}$ and underestimation of high observed $\dot{V}O_{2peak}$.**

($n$ = 93), and 1.4 (−4.4 to 7.2) mL·min$^{-1}$·kg$^{-1}$ for participants with measured $\dot{V}O_{2peak}$ < 30 mL·min$^{-1}$·kg$^{-1}$.

Bootstrapped ($n$ = 1000) CI for the new RA equation were very close to original CI, indicating that the results were unbiased. Furthermore, the 25-fold cross-validation gave a mean (SD) RMSE of 4.32 (1.68), which is close to that of the new RA equation. The bivariate correlations for the variables in the new RA equation are given in a correlation matrix (see Table, Supplemental Digital Content 1, describing the correlation matrix for variables in the new RA equation, http://links.lww.com/MSS/B872).

In the new alternative RA equation, where the only RA-specific variable (PGA) was omitted, the graphs were very similar to those of the complete new RA equation (see Figure, Supplemental Digital Content 2, describing observed vs predicted $\dot{V}O_{2peak}$ in persons with RA, http://links.lww.com/MSS/B873 and Figure, Supplemental Digital Content 3, describing the results from equivalence testing of the HUNT equation and the new alternative RA equation vs measured $\dot{V}O_{2peak}$, http://links.lww.com/MSS/B874). The eCRF model from sensitivity analysis where BMI in the new RA equation was substituted with the waist-to-height ratio showed a somewhat reduced fit ($R^2$ = 0.80, RMSE 4.51).

Two additional new RA equations including SBP (see Table, Supplemental Digital Content 4, describing a new RA equation and new alternative RA equation when the SBP is known, http://links.lww.com/MSS/B875), and one new RA equation where the PA index was substituted with fulfillment or not of the ACSM/AHA 2007 recommendations for PA (23) (see Table, Supplemental Digital Content 5, describing a new RA equation based on fulfillment or not of ACSM/AHA 2007 recommendations for PA, http://links.lww.com/MSS/B876) were developed to allow for the use of the equation in settings lacking more detailed PA information.

## DISCUSSION

In this study, we developed an equation for the estimation of CRF for persons with RA, with better fit than a previously published equation from a healthy population. The new RA equation included these self-reported variables: age, sex, smoking status, PA index, and patient global RA assessment, as well as measurements of BMI and RHR. The accessibility of the variables of the new RA equation makes it resource saving in a clinical setting, especially if a web-based calculator becomes available which may also be used by the person with RA. A new alternative RA equation without the patient global RA assessment permits investigation of CRF in persons with RA based on general information in population-based studies.

**New RA equation instead of HUNT equation for persons with RA.** The new RA equation explained 81% of the variability of the $\dot{V}O_{2peak}$ in persons with RA in the present study, whereas the HUNT equation (11) explained 48% of the variability of $\dot{V}O_{2peak}$. The scatterplot of eCRF clearly showed better fit with the new RA equation than the HUNT equation, with less deviation from the measured $\dot{V}O_{2peak}$ for the lowest and highest values. This substantiates that eCRF for persons with RA should be calculated using the new RA equation, even if equivalence testing showed that it did not perfectly predict the measured $\dot{V}O_{2peak}$.

The discrepancy between the actual $\dot{V}O_{2peak}$ test results (observed CRF) and the estimated CRF (eCRF) using the HUNT

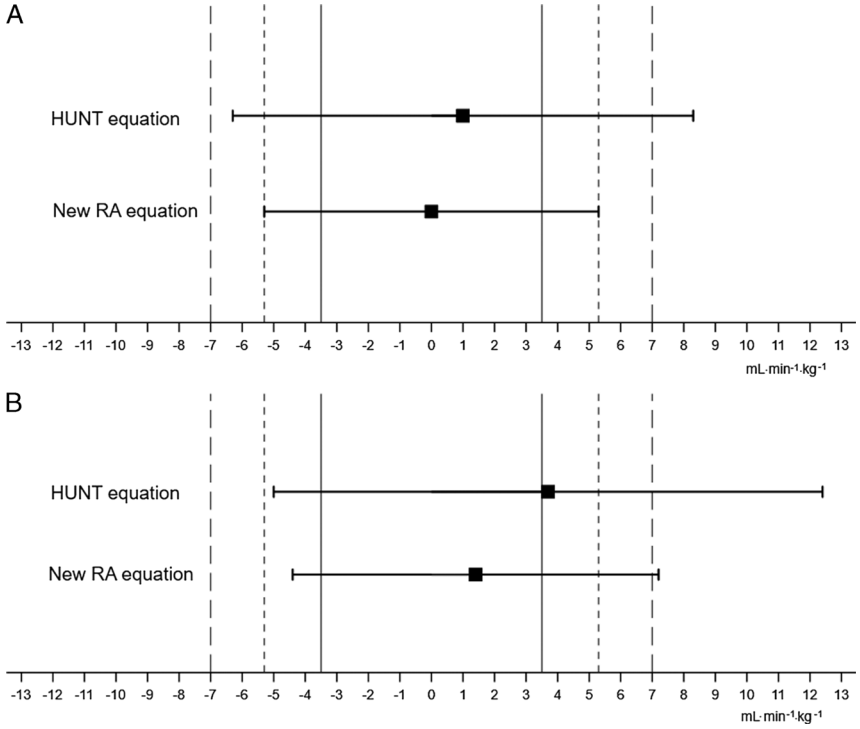


**FIGURE 2—Equivalence testing of the new RA equation and the HUNT equation vs measured $\dot{V}O_{2peak}$. Panel A: Equivalence testing including all participants ($n$ = 93). The HUNT equation was nonequivalent to $\dot{V}O_{2peak}$ measurement with respect to all equivalence regions, as seen by the CI falling above all region limits and below the 1 MET and 1.5 MET region limits. The new RA equation was equivalent to $\dot{V}O_{2peak}$ measurement when using the 2 MET and 1.5 MET equivalence regions. Panel B: Equivalence testing including participants with measured $\dot{V}O_{2peak}$ < 30 mL·min$^{-1}$·kg$^{-1}$ ($n$ = 45). Both the HUNT equation and the new RA equation were nonequivalent to $\dot{V}O_{2peak}$ measurement with respect to all equivalence regions, as seen by the CI falling above all region limits and below the 1 MET region limit. The HUNT equation more strongly tended to over-estimate $\dot{V}O_{2peak}$ in this group of participants. The horizontal bars represent the 90% CI of the mean (square). In both figures, the following equivalence regions are marked vertically: Solid line ± 1 MET (±3.5 mL·min$^{-1}$·kg$^{-1}$), short dashed line ± 1.5 MET (±5.3 mL·min$^{-1}$·kg$^{-1}$), long dashed line ± 2 MET (±7 mL·min$^{-1}$·kg$^{-1}$).**

equation is of particular importance for persons with RA with the lowest observed CRF. This was the main reason to develop a new RA equation. As previously reported for healthy individuals (11), the HUNT equation tended to overestimate CRF for persons with RA with the lowest observed $\dot{V}O_{2peak}$ test results. In a previous study, CVD mortality was reduced by 20% to 22% per $\dot{V}O_{2peak}$ increase of 3.5 mL·min$^{-1}$·kg$^{-1}$ in both men and women (1). This substantiates the possible negative consequence of overestimating CRF to the extent that was seen using the HUNT equation for those in the subgroup with measured CRF below 30 mL·min$^{-1}$·kg$^{-1}$. Because of this overestimation, the HUNT equation might give the impression that improving CRF is not very important in persons with RA belonging to the group where improvement is most important. The new RA equation showed less overestimation in these most vulnerable persons. Underestimation of high fitness with the HUNT equation, where the new RA equation was also more accurate, is of less clinical importance.

**Considerations regarding variable selection.** BMI is implemented in the new RA equation, whereas the HUNT equation uses waist circumference instead. Both BMI and waist circumference were significant predictors ($P$ < 0.001), but accurate measurement of waist circumference may be difficult because it depends on body shape. The sensitivity analysis substituting BMI with waist-to-height ratio indicated that using this variable did not lead to improved prediction. We, therefore, chose BMI, which is a familiar measurement for both physicians and people with RA. Electronic apps for BMI are available, where you key in height and weight, and the app does the calculation.

The patient global RA assessment (30) was the only significant RA-specific variable. Persons with RA were asked to evaluate the disease activity of their RA during the last week. Adults with RA are used to this score when evaluated at the Rheumatology department, as part of the commonly used Disease Activity Score of 28 (31), or as an independent scale. The phrasing of the question might vary slightly, and there are some concerns that various phrasings might give different responses (35). Therefore, it is of importance to use a phrasing similar to that given in the present study.

**When to use the new RA equation.** Because previous findings suggest that improvement of CRF reduces cardiovascular risk factors in persons with RA (21), the possibility to estimate CRF in this group may improve care by guiding and stimulating PA. For instance, repeated measurement and recalculation can give important information when evaluating the effect of changes in PA. The eCRF improvement might inspire continuation of workout, whereas equal or decreased eCRF indicates lack of effective training and could lead to change of exercise training regimens. The new RA equation may, therefore,

contribute to planning and inspire to PA, both in pretraining and posttraining periods, and at clinical visits. Health professionals like the patient's general practitioner, rheumatologist, physical therapist, or nurse, in addition to the patient herself or himself, may calculate the eCRF. In addition to being a less resource-intensive method than $\dot{V}O_{2peak}$ testing by CPET, a potential web-based calculator for eCRF for persons with RA would make the calculation even easier.

**Generalizability of the new RA equation.** The eCRF equations developed for healthy people are used in various countries, regardless of different socioeconomic status and different cultures (16). The ACR and EULAR have developed common classification criteria for RA (26), and these criteria are also accepted in other regions of the world. As long as RA is diagnosed using the same criteria, the new RA equation is probably generalizable to other countries. As expected, persons with RA had reduced $\dot{V}O_{2peak}$ test results compared with the healthy HUNT population (22), and this is a finding similar to what other studies on RA and cardiorespiratory fitness have found (36), which further strengthens the impression that the participants were representative of other persons with RA. The fact that only one third of the persons with RA fulfilled the ACSM/AHA 2007 recommendations for PA (23) indicates that the included participants were not especially physically active. The new RA equation should be externally validated; however, internal validation showed that the equation is not strongly biased. The finding that the eCRF equation developed from a healthy population did not have an adequate fit in the most vulnerable persons with RA raises the question if similar discrepancies are relevant in other chronic conditions.

## CONCLUSIONS

The new RA equation gives more precise estimates of eCRF than the previously published equation developed for a healthy population. This prevents overestimation of the eCRF in persons with RA having the lowest $\dot{V}O_{2peak}$ test results. The new RA equation may, therefore, become an important tool in the care for individual persons with RA to reduce cardiovascular risk. For use in population-based studies, the new alternative RA equation without RA-specific variables is a useful alternative.

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