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# Feasibility, Methodology, and Interpretation of Broad-Scale Assessment of Cardiorespiratory Fitness in a Large Community-Based Sample

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## Abstract

Cardiorespiratory fitness (CRF) is intricately related to health status. The optimal approach for CRF quantification is through assessment of peak oxygen uptake ($VO_2$), but such measurements have been largely confined to small referral populations. Here we describe protocols and methodological considerations for peak $VO_2$ assessment and determination of volitional effort in a large community-based sample. Maximum incremental ramp cycle ergometry cardiopulmonary exercise testing (CPET) was performed by Framingham Heart Study participants at a routine study visit (2016–2019). Of 3486 individuals presenting for a multi-component study visit, 3116 (89%)

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Disclosures

None

Declaration of interests

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completed CPET. The sample was middle-aged (54±9 years), with 53% women, body mass index 28.3±5.6 kg/m$^2$, 48% with hypertension, 6% smokers, and 8% with diabetes. Exercise duration was 12.0±2.1 minutes (limits 3.7–20.5). No major cardiovascular events occurred. A total of 98%, 96%, 90%, 76%, and 57% of the sample reached peak respiratory exchange ratio (RER) values of ≥1.0, ≥1.05, ≥1.10, ≥1.15, and ≥1.20, respectively (mean peak RER=1.22±0.10). With rising peak RER values up to ≈1.10, steep changes were observed for percent predicted peak $VO_2$, $VO_2$ at the ventilatory threshold/peak $VO_2$, heart rate response, and Borg (subjective dyspnea) scores. More shallow changes for effort dependent CPET variables were observed with higher achieved RER values. In conclusion, measurement of peak $VO_2$ is feasible and safe in a large sample of middle-aged, community-dwelling individuals with heterogeneous cardiovascular risk profiles. Peak RER ≥1.10 was achievable by the majority of middle-aged adults and RER values beyond this threshold did not necessarily correspond to higher peak $VO_2$ values.

### Keywords

Cardiopulmonary exercise testing; epidemiology; fitness; exercise

## INTRODUCTION

Cardiopulmonary exercise testing (CPET) is a powerful clinical tool for objective evaluation of physiologic exercise responses, including peak oxygen uptake ($VO_2$), the “gold standard” measure of cardiorespiratory fitness. Peak $VO_2$ is associated with important health outcomes in a wide variety of populations[1,2] leading multiple societies to advocate for including its assessment as “the 5th vital sign”[3]. Despite growing acknowledgment of the relevance of cardiorespiratory fitness, CPET assessment is often confined to individuals at the extremes of the fitness spectrum, such as athletes and patients with advanced cardiopulmonary diseases. One explanation for the limited of penetration of CPET for widespread clinical use is that data on large-scale CPET assessment of community-dwelling individuals are not available, and standardized protocols and methodologies are, therefore, not well defined. There also remains a lack of consensus regarding the precise respiratory exchange ratio (ratio of carbon dioxide output to $VO_2$; RER) value that should be considered “sufficient” volitional effort to report peak $VO_2$ as a valid measurement[4–7]. Here, we describe the rationale, development, and implementation of the study protocols that were used to complete CPET evaluations in >3000 community-dwelling participants from the Framingham Heart Study (FHS). We also evaluated the relationships of peak RER with effort-dependent exercise variables to inform appropriate RER cut points.

## METHODS

The FHS is a prospective community-based cohort study. It began with enrollment of the Original Cohort in 1948 (n=5209)[8] and now includes their children and the children’s spouses (Second Generation [Gen 2], recruited starting in 1971, n=5124)[9], and their grandchildren and grandchildren’s spouses (Third Generation [Gen 3], enrolled in 2002–2005, n=4095)[10]. The OMNI-2 sample represents a separate multi-ethnic sample enrolled alongside the Gen 3 cohort[11]. At the 3$^{rd}$ study visit of the Gen 3 and OMNI-2 cohorts

(2016–2019), all participants were offered CPET on a voluntary basis, regardless of their participation in other components of the FHS visit[12–14]. Participants were not eligible for CPET if they had a medical contraindication to exercise such as a recent myocardial infarction or heart surgery, unexplained chest pain, requirement for supplemental $O_2$ therapy, or recent orthopedic surgery, among other conditions (Supplemental Table 1). Participants were encouraged to try the exercise cycle even if they anticipated that musculoskeletal issues would preclude maximum cycle exercise. The Boston University Medical Center and Massachusetts General Hospital Institutional Review Boards approved all study protocols. All participants provided informed written consent.

The exercise protocol was designed to optimize feasibility, data fidelity, blood sampling at peak exercise, and comparison of individuals across sex, age, and underlying health status. Cycle ergometry was selected as the exercise modality due to its safety across age groups and underlying health conditions[15] and the ability to assess precise workloads to derive $VO_2$/work relationships during a gradual continuous ramp protocol. Participants were asked to fast overnight as part of a comprehensive examination on the day of the CPET, though prolonged fasting is not a required for performing CPET. Participants were also instructed to not perform exercise prior to arrival on the day of their study visit. CPET assessments were performed starting at 8am and scheduled at 30-minute intervals, conducted primarily in the mornings. CPET assessments were interspersed with other testing during the ≈4-hour FHS study visit.

The CPET proceeded through the following steps. First, participants changed into exercise shorts and sneakers. Second, participants were oriented to the cycle ergometer and were provided instructions on what to expect during testing and proper hand signals to alert study staff to any symptoms or questions. Third, ECG leads were placed on the chest and limbs. Fourth, the cycle seat height was adjusted and “practice” pedaling was performed for a few rotations to ensure the participant was comfortably seated. Following these introduction steps, the formal exercise protocol was begun (Figure 1). This included 4 minutes of resting gas exchange data, 3 minutes of unloaded (“freewheel”) exercise, incremental ramp exercise, 3 minutes of unloaded pedaling (“active recovery”), and 1 minute of resting post-exercise gas exchange. The active recovery period was included to mitigate post-exercise vasodilation and vagal responses. Blood was drawn via peripheral venipuncture immediately following conclusion of maximum incremental exercise. All examinations were performed on the same cycle ergometer (Lode, Netherlands). Heart rate and ECGs were monitored continuously with wireless ECG equipment (Mortara, Milwaukee, WI). Blood pressure was measured every 2 minutes manually via sphygmomanometry (Welch Allyn, Skaneateles, NY). Subjective dyspnea assessment was performed using the modified 10 point Borg scale[16] every 2 minutes and at peak exercise.

CPET guidelines recommend an optimal exercise time of 8–12 minutes, citing overly steep ramp protocols that limit peak $VO_2$ attainment when exercise duration is <6 minutes and boredom/fatigue and inefficiency with exercise durations exceeding 16 minutes[7,17]. However, the data supporting this recommendation are limited[18]. Indeed, recent studies have suggested that exercise times of 7–26 minutes elicit valid peak $VO_2$ assessments[19]. For this study, we sought to balance the goal of achieving similar exercise durations across

individuals and performing tests efficiently with the competing priority of using the minimal number of necessary ramp protocols to simplify testing protocols and facilitate comparisons among individuals. We, therefore, used 2 ramp protocols (15 and 25 watts/minute) with a target exercise duration of 12±6 minutes to accommodate the expected variation in peak watts achievable in our heterogeneous sample. Study staff assigned participants to 1 of the 2 ramp protocols based on a gross estimate of the predicted peak watts after considering age, sex, height, weight, and exercise habits.

The CPET assessment was performed in a separate room with an adjustable air conditioner unit to avoid high room temperatures. At least 1 (and typically 2) exercise physiologists and a supervising physician were present for all CPET examinations. Participants were free to stop the assessment at any time. Blood pressure, heart rate, and ECG were continuously monitored by the supervising physician. Standardized criteria were established for stopping the CPET assessment early (Supplemental Table 1).

Breath-by-breath gas exchange data were measured by the same metabolic cart (MedGraphics, St. Paul, MN) in all participants. CPET instruments were calibrated according to manufacturer instructions. Prior to each day's testing, flow calibration was performed with a 3L syringe (<1–15 sec duration) to achieve ±3% agreement with calculated volumes. Before each individual test, 1) the barometric pressure, temperature, and relative humidity were recorded; 2) gas analyzer calibration was performed with 2 precision-analyzed gas mixtures; and 3) transport delays between the gas sampling point and each gas analyzer were determined[17]. A calibration logbook was maintained to assess long-term trends in addition to daily calibration procedures. Tabular data was acquired and configured with Medgraphics BREEZESUITE software with real-time tabular and graphical display of exercise variables and mid 5-of-7 breath moving average integration of gas exchange variables. To remove erroneous breaths (such as from a cough), the metabolic cart was programmed to eliminate breaths below an RER value of 0.5 and to include only breaths with expired carbon dioxide and $VO_2$ values of at least 50 ml/minute.

Breath-by-breath gas exchange data were configured uniformly following each CPET assessment in the core laboratory. The highest 30-second median value during the final minute of loaded exercise was used to calculate peak $VO_2$. The predicted peak $VO_2$ was estimated using the Wasserman and Hansen formula[20]. The ventilatory anaerobic threshold (VAT) was calculated using the V-slope method on primary breath-by-breath data[21]. A standardized VAT adjudication process was implemented. The VAT for each participant was interpreted by 2 independent reviewers and compared. If the values determined by the 2 reviewers differed by >10%, a 3$^{rd}$ party performed an independent review and the closer 2 of 3 values were averaged. Maximum predicted heart rate (MPHR) was estimated as 220-age. The $VO_2$/work relationship was determined as the change in $VO_2$ (in ml/min) divided by the change in work (watts) measured from 1 minute into the incremental ramp portion of exercise up until peak exercise.

Clinical characteristics of the study sample were displayed as mean ± SD or n (%) as appropriate; data for those that exercised and those that did not were compared using two-sample t-tests or chi-squared tests. We evaluated the association of peak RER with

clinical variables including age, sex, body mass index (BMI), hypertension, diabetes, and current smoking with multivariable linear regression models. To evaluate the associations of peak RER with effort dependent exercise variables (% predicted peak $VO_2$ [n=3105]; $VO_2$ at the VAT as a % of peak $VO_2$ [$VO_{2VAT}/VO_{2peak}$; n=3069], and % MPHR; n=2878]), we used generalized additive models with splines for peak RER. For analyses of % MPHR, we excluded (n=228) individuals on atrioventricular nodal blocking medications. For visualization purposes, we plotted the marginal means and 95% confidence intervals across RER values of 0.95 to 1.40, noting that these regressions are done across individuals (and not in the same individual with repeated measures).

## RESULTS

Of 3521 Gen 3/OMNI-2 examination 3 participants, 3486 presented to the FHS research center (n=35 were home visits) and 3117 initiated exercise. One participant was noted to be tachycardic at rest prior to starting exercise and therefore did not perform exercise. Of the 3116 individuals (89% of the whole sample) who completed exercise (Table 1), 10 were unable to tolerate the mouthpiece used to measure gas exchange resulting in a sample size of 3106 individuals with comprehensive gas exchange variables. The exercise sample was middle aged (54±9 years), 53% women, and mean BMI was in the overweight range (28.3±5.6 $kg/m^2$). Our sample represented a relatively healthy community-based population with 48% with hypertension, 6% smokers, 8% with diabetes, and ≈1% with coronary artery disease. Compared with individuals who completed CPET, those who did not perform exercise were older, with a higher prevalence of coronary artery disease, atrial fibrillation, and cardiovascular risk factors (Table 1).

Among the 370 individuals who did not exercise, 124 individuals declined participation, 61 were unable to exercise due to limitations regarding the length of time of the voluntary study visit, technical issues, or staffing limitations, and 185 participants had medical conditions that precluded maximal effort exercise. These conditions included symptomatic cardiac or pulmonary disease (n=97), musculoskeletal or orthopedic limitations (n=43), pulmonary conditions precluding exercise (n=12), neurologic disease limiting exercise (n=15), or other medical conditions (n=18), (Supplemental Table 2).

There were no major cardiovascular events, such as acute coronary syndrome, sustained ventricular arrhythmias, or death (Table 2). One patient required hospital referral after developing atrial fibrillation with rapid ventricular response during exercise (with a history of paroxysmal atrial fibrillation). Due to the possibility that actionable clinical findings might be observed during this exercise study of asymptomatic volunteers, we developed a protocol to notify participants' primary care providers of any potentially relevant clinical findings. This occurred in 80 participants (2.6%) and most frequently was prompted by ST segment depression, T-wave changes, or ventricular ectopy (Table 2). Post-exercise vasovagal symptoms (e.g., bradycardia, hypotension) occurred in 30 individuals; 8 participants experienced syncope or hypotension considered clinically relevant and warranting primary care physician notification.

Participants were assigned to 1 of 2 ramp protocols (15 watts/minute: n=1941; or 25 watts/minute: n=1175); 386 men (26.5%) and 1,555 women (93.6%) completed the 15 watts/minute protocol. Mean exercise duration was 12.0±2.1 minutes (limits 3.7–20.5), Figure 2. Overall, 3101 (99.5%) of participants exercised within a desirable time period of 12±6 minutes.

Consistency of gas exchange measures in exercising participants was monitored throughout the study period to ensure proper calibration of equipment. Resting $VO_2$ (in ml/kg/min, for example one metabolic equivalent or 3.5 ml/kg/min) and $VO_2$/work are recognized to have similar values among individuals who do not have cardiorespiratory disorders[22,23] and can be used, therefore, to monitor for instrument drift in gas exchange measures. Accordingly, we evaluated for consistency among resting $VO_2$, and $VO_2$/work according to the sequence number of the participant's test during the day and observed similar values among each of the 6 testing sequences (across different individuals; Supplemental Figure 1). Of 3106 participants who completed the gas exchange measures, a value for the VAT was able to be determined in 3067 (99%).

The mean peak RER was 1.22±0.10 with a wide distribution (Figure 3A). In Figure 3B, we demonstrate the proportion of participants reaching each successive RER cut point. Only 52 participants in our study failed to reach an RER of ≥1.0 and the reasons for stopping early are shown in Table 3. These participants had higher rates of clinical findings leading to study staff stopping the test early or removal of the mouthpiece by the participant early (versus the whole sample). A total of 96%, 90%, 76%, and 57% of the sample reached RER values of ≥1.05, ≥1.10, ≥1.15, and ≥1.20, respectively. These findings were consistent in the older participants in our sample: of 109 individuals ≥70 years, 86 (79%) reached a peak RER ≥1.10. By contrast, 72% of the whole sample (and 77% of those not on atrioventricular nodal blocking drugs) achieved greater than 85% of the MPHR. In multivariable-adjusted regression models, higher age, female sex, BMI, diabetes, and smoking were all associated with a lower peak RER ($P < 0.05$ for all), but together these clinical variables explained a small percentage of the variance in observed peak RER (model adjusted $R^2=0.078$), Table 4.

Next, we compared the peak RER values achieved across different participants with effort-dependent physiological variables (Figure 4). We observed a steep rise in the % predicted peak $VO_2$ with a higher peak RER up to a RER value of 1.10, and a continued slight rise to a RER of ≈1.20 (Figure 4). In addition, the $VO_{2VAT}/VO_{2peak}$ averaged >60% in individuals with RER <1.10, whereas individuals in higher RER strata had $VO_{2VAT}/VO_{2peak}$ ratios of ≈50%, lending more evidence of submaximum peak effort in individuals only reaching peak RER <1.10. Individuals achieving >85% MPHR (considered diagnostic for clinical stress tests without gas exchange data) exhibited peak RER values of ≈1.10. The observed relations of % predicted peak $VO_2$, % MPHR, and $VO_{2VAT}/VO_{2peak}$ were consistent across categories of age, sex, and obesity (Supplemental Figure 2). Subjective dyspnea at peak exercise (assessed by the Borg score) was higher in individuals up to a peak RER value of 1.10 but was essentially unchanged (on average) in other individuals thereafter (Figure 4).

## DISCUSSION

We describe our experience developing and applying a carefully designed standardized CPET protocol to a large sample of middle-aged community-dwelling adults. We observed this CPET protocol to be highly feasible with ≈90% completion rate within the 30-minute allotted time periods. Maximum effort CPET was safe with no serious adverse events observed. Gas exchange data were highly consistent across a large number of tests, and 97% of participants achieved exercise durations of 12±6 minutes[18]. We observed a wide variation in the peak RER achieved, but 90% of participants were able to achieve a peak RER of ≥1.10, a threshold above which measures requiring peak volitional effort became more consistent across individuals. Together, this report provides a blueprint for applying CPET to a wide array of community-dwelling adults in future studies and, potentially, for clinical care.

While the safety of maximum effort CPET has been previously reported in hospital-based referral samples[24–26], our study extends these observations to a large heterogeneous sample of community-dwelling individuals. The safety profile observed in our study must be interpreted in the context of the careful protocols that were used. Prior to exercise, participants were screened for symptomatic cardiovascular disease (CVD) and the exercise tests were supervised by cardiologists, who were instructed to halt the test if any concerning clinical symptoms or CPET features were observed. We conclude therefore, that maximum effort CPET is safe in the community when performed with pre-exercise screening questions and dedicated supervision.

In community-dwelling adults without an indication for stress testing, 2.6% of individuals demonstrated potentially clinically relevant exercise-induced abnormalities. Of these, 1.2% had ECG findings consistent with myocardial ischemia. While this is expectedly lower than the 3% with ischemic ECG features observed in a hospital-based referral sample of individuals with known cardiovascular disease[24], our findings highlight the potential value of provocative exercise testing to unmask subclinical ischemic heart disease in the community. Moreover, CPET provides information about peak $VO_2$ (and other gas exchange patterns that may complement peak $VO_2$), which is prognostic of health outcomes across broad populations and may provide incremental value in predicting future CVD[1,2]. The feasibility, reliability, and safety of CPET in our heterogeneous sample indicates that CPET may have broader utility in clinical care than its current use primarily in advanced cardiopulmonary disease. Future rigorous study of the cost effectiveness of performing CPET in broad patient populations is warranted to complement studies suggesting cost-effectiveness of pre-operative CPET[27].

Reproducible and accurate interpretation of maximum effort CPET data relies on dependable noninvasive assessments of volitional effort expended. A higher peak RER reflects increased carbon dioxide ventilation to counteract rising lactate production and a value of ≥1.10 is generally considered as a threshold above which peak-effort dependent variables can be reliably interpreted[7]. However, there is substantial heterogeneity in the target peak RER across studies[4–7] and the relations of achieved peak RER and effort-dependent variables is incompletely understood. Importantly, 90% of participants in our

sample were able to achieve a RER ≥1.10, which differs substantially from the <50% of participants achieving RER ≥1.10 in a large study of patients with systolic heart failure[28]. Our findings are more consistent with a recent study by Wagner et al. involving 526 healthy individuals in whom a peak RER ≥1.10 was achieved in 92% of individuals <70 years of age[29]. However, while Wagner et al. reported that only 51% of individuals ≥70 years old were able to reach peak RER ≥1.10[29], we did not observe a sharp decline in the achieved peak RER in older participants.

Our findings provide a consistent picture that peak RER ≥1.10 is an appropriate threshold to conclude that maximum effort was expended. Furthermore, the limited variance in RER explained by clinical factors supports broad application of a single RER threshold across sex, age group, and clinical risk factor profile. Analyzing the associations of peak RER and peak Borg scores permitted assessment of how closely perceived dyspnea was related to objective metabolic responses to exercise. We observed uncoupling of RER values ≥1.10 with perceived exertion, reinforcing the use of RER ≥1.1 as an appropriate threshold of volitional effort.

Our study does have several limitations. Our sample was mostly middle-aged and of European descent; further studies are warranted to extend our findings to other racial/ethnic and age groups. The peak RER analyses were conducted across individuals (not within the same individual at different settings). Future studies with repeated tests in individuals are necessary to discern the direct effects of volitional effort (peak RER) on the achieved peak $VO_2$. Lastly, participants performed cycle exercise for this study which is recognized to result in lower peak $VO_2$ values compared to treadmill exercise[30].

In conclusion, we report our experience conducting maximum effort CPET in a large sample of middle-aged, community-dwelling individuals with heterogeneous cardiovascular risk profiles. CPET is safe and feasible with careful planning, supervision, and quality control monitoring. A peak RER of ≥1.10 was achieved by >90% of participants and RER values beyond this threshold were not necessarily associated with higher values for peak effort dependent variables.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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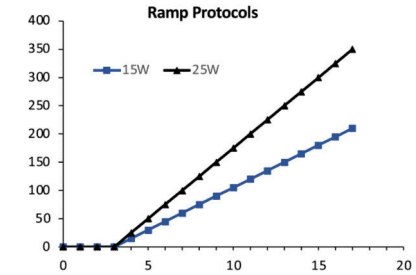
**CPET assessment (total time 30 minutes)**

| Step | ~Time (mins) | Protocol action |
|---|---|---|
| 1 | 2 min | Change into exercise clothes |
| 2 | 2 min | Orientation to test |
| 3 | 1 min | ECG lead placement |
| 4 | 1 min | Seat adjustment and practice cycling |
| 5 | 4 min | Resting gas exchange data collected |
| 6 | 3 min | Unloaded "freewheel" exercise |
| 7 | 8-12 min | Incremental ramp exercise |
| 8 | 3 min | Unloaded pedaling "active recovery" |
| 9 | 1 min | Post-exercise gas exchange |
| 10 | 1 min | Mouthpiece and ECG lead removal |



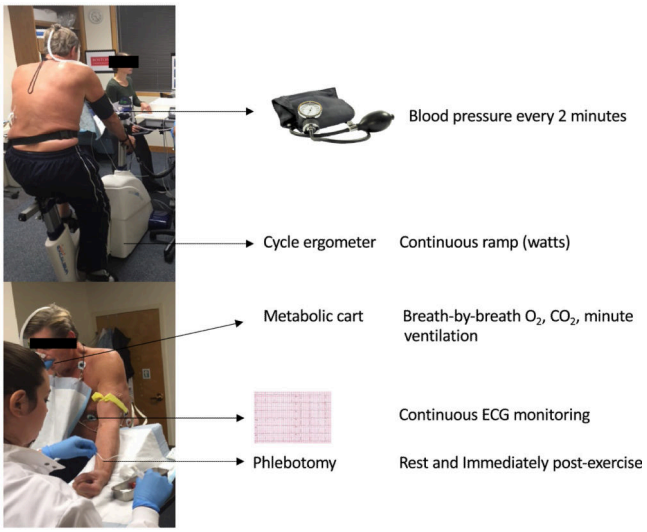
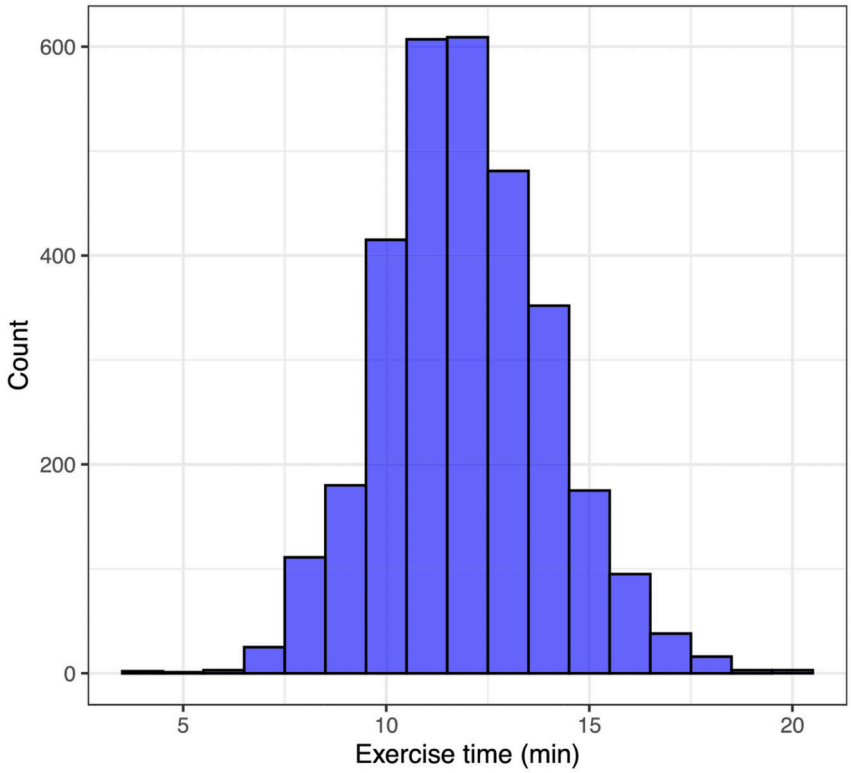




**Figure 1. CPET assessment protocol.**

The time breakdown of the 30-minute assessment, the two different ramp protocols, and the primary measured variables are depicted.




| Ramp protocol | Mean ± SD | Min, Max | 6-18 min of exercise, N (%) |
|---|---|---|---|
| Combined (N=3116) | 12.0±2.1 | 3.7, 20.5 | 3101 (99.5%) |
| 15 watt/min (N=1941) | 11.8±2.2 | 3.7, 20.5 | 1929 (99.4%) |
| 25 watt/min (N=1175) | 12.2±1.7 | 6.6, 18.8 | 1172 (99.7%) |

**Figure 2. Distribution of exercise time in the study sample.**

Total exercise time includes t3 minutes of unloaded (“freewheel”) and incremental ramp exercise and is plotted for the whole sample (i.e., inclusive of both ramp protocols).

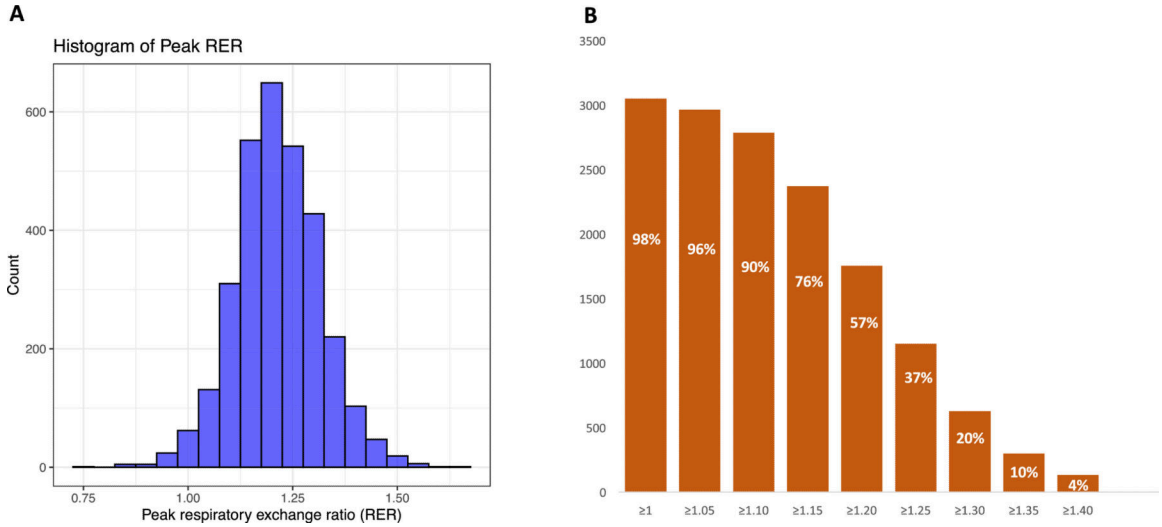



**Figure 3. Peak respiratory exchange ratio (RER) values.**

A. Histogram of peak RER.

B. Number of individuals meeting each RER threshold. Percentage of the whole sample exceeding each threshold are shown in white.

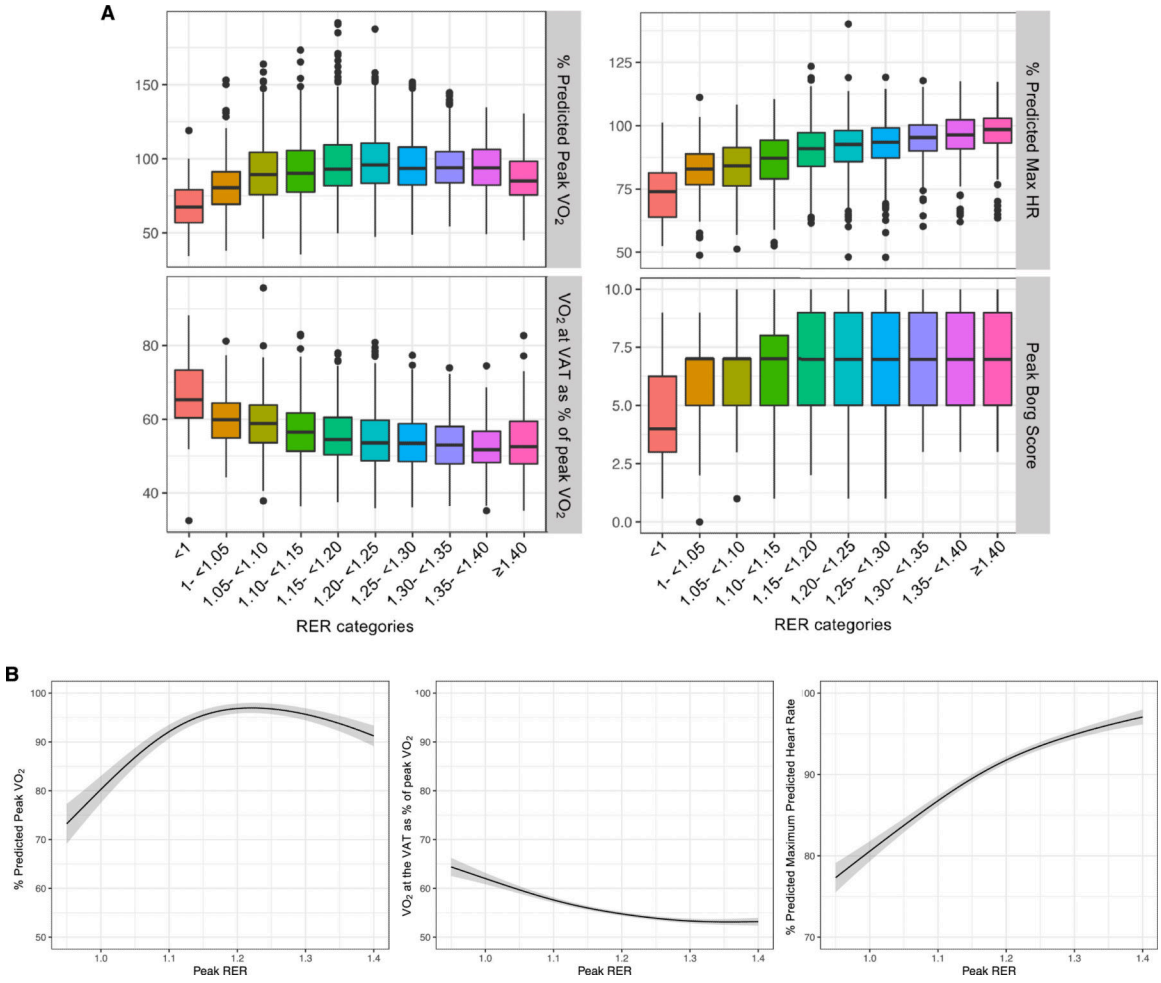



**Figure 4. Relations of peak RER with effort-dependent variables.**

Sample sizes are: n=3106 for % predicted peak $VO_2$, n=3067 for $VO_2$ at VAT as % of peak $VO_2$, n=2878 (after excluding n=228 using nodal blocking agents), n=3115 for peak Borg score.

A. Box plots of values for effort-dependent exercise variables by peak RER categories.

B. Estimated marginal means (and 95% confidence interval) of each effort-dependent exercise variable as a function of peak RER (by GAM). The RER domain was arbitrarily selected as 0.95–1.40 to capture a breadth of physiologic RER values.

**Table 1.**

Clinical characteristics of the study sample

| Characteristic | Exercise sample (N=3116) | Individuals who did not exercise (N=370) | P-value |
|---|---|---|---|
| Age (years) | 54±9 | 60±10 | <0.001 |
| Women | 1662 (53%) | 215 (58%) | 0.092 |
| Nonwhite | 289 (9%) | 43 (12%) | 0.174 |
| Hypertension | 1501 (48%) | 248 (67%) | <0.001 |
| Current smoker | 199 (6%) | 42 (11%) | 0.001 |
| Lipid treatment | 674 (22%) | 152 (41%) | <0.001 |
| Body mass index (kg/m$^2$) | 28.3±5.6 | 31.3±7.6 | <0.001 |
| Total cholesterol (mg/dL) | 191±36 | 179±39 | <0.001 |
| HDL cholesterol (mg/dL) | 60±19 | 56±19 | 0.002 |
| Diabetes mellitus | 238 (8%) | 70 (19%) | <0.001 |
| Coronary artery disease | 27 (0.9%) | 19 (5.1%) | <0.001 |
| Atrial fibrillation | 44 (1.4%) | 53 (14%) | <0.001 |
| Peak RER | 1.21±0.10 | -- | -- |
| Resting $VO_2$ (ml/kg/min) | 3.51±0.59 | -- | -- |
| Peak $VO_2$ (ml/kg/min) | 22.7±7.0 | -- | -- |
| Peak $VO_2$ (% predicted) | 94.3±20.5 | -- | -- |

Data for those that exercised and those that did not were compared using two-sample t-tests (for continuous variables) or chi-squared tests (for categorical variables).

**Table 2.**

Adverse events and clinically relevant findings

| Event type | N (% of sample) |
|---|---|
| **Serious cardiovascular event (N=1)** | |
| Acute coronary syndrome | |
| Persistent ventricular arrythmia | 0 |
| Death | 0 |
| Required immediate medical care (atrial fibrillation in participant with known paroxysmal atrial fibrillation) | 1 (0.03%) |
| **Exercise finding warranting notification of primary care physician (N=80)** | |
| Chest discomfort | 5 (0.16%) |
| Severe hypertensive exercise response | 2 (0.06%) |
| Exercise induced headache | 1 (0.03%) |
| ST depressions or T-wave inversions | 38 (1.22%) |
| Ventricular ectopy | 23 (0.74%) |
| Atrial arrhythmias | 3 (0.10%) |
| Post-exercise vagal response including hypotension or syncope | 8 (0.26%) |

All exercise findings prompting notification of primary care physicians are included

**Table 3.**

Reasons for stopping exercise (peak RER <1.0 vs. others)

| Reason | Peak RER <1.0 (N=52) | Peak RER ≥1.0 (N=3064) | P-value |
|---|---|---|---|
| Test stopped early for ECG or BP criteria | 10 (19%) | 50 (2%) | <0.001 |
| Participant removed mouthpiece early | 8 (15%) | 130 (4%) | <0.001 |
| Mouthpiece discomfort/ dry mouth | 10 (19%) | 346 (11%) | 0.07 |
| Leg fatigue | 8 (15%) | 1567 (51%) | <0.001 |
| Shortness of breath | 5 (10%) | 412 (13%) | 0.42 |
| Chest discomfort | 0 (0%) | 5 (0.2%) | 0.77 |

Groups are compared using chi-squared test

Abbreviations: ECG, electrocardiogram; BP, blood pressure

**Table 4.**

Multivariable associations of clinical variables and peak RER

| Clinical variable | Est. beta | P-value |
|---|---|---|
| Age | −0.0004±0.0002 | 0.042 |
| Women | −0.040±0.004 | $<2\times10^{-16}$ |
| Log(body mass index) | −0.100±0.010 | $<2\times10^{-16}$ |
| Hypertension | −0.006±0.004 | 0.11 |
| Diabetes | −0.020±0.007 | 0.003 |
| Smoking | −0.048±0.007 | $4\times10^{-11}$ |

The estimated (“est.”) beta coefficient represents the change in peak RER associated with a 1-unit change for continuous variables or presence vs. absence of categorical variables.

The adjusted $R^2$ of the model is 0.078.