How Accurate Is the Prediction of Maximal Oxygen Uptake with Treadmill Testing?

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Abstract

Background
Cardiorespiratory fitness measured by treadmill testing has prognostic significance in determining mortality with cardiovascular and other chronic disease states. The accuracy of a recently developed method for estimating maximal oxygen uptake (VO2peak), the heart rate index (HRI), is dependent only on heart rate (HR) and was tested against oxygen uptake (VO2), either measured or predicted from conventional treadmill parameters (speed, incline, protocol time).

Methods
The HRI equation, METs = 6 x HRI – 5, where HRI = maximal HR/resting HR, provides a surrogate measure of VO2peak. Forty large scale treadmill studies were identified through a systematic search using MEDLINE, Google Scholar and Web of Science in which VO2peak was either measured (TM-VO2meas; n = 20) or predicted (TM-VO2pred; n = 20) based on treadmill parameters. All studies were required to have reported group mean data of both resting and maximal HRs for determination of HR index-derived oxygen uptake (HRI-VO2).

Results
The 20 studies with measured VO2 (TM-VO2meas), involved 11,477 participants (median 337) with a total of 105,044 participants (median 3,736) in the 20 studies with predicted VO2 (TM-VO2pred). A difference of only 0.4% was seen between mean (±SD) VO2peak for TM-VO2meas and HRI-VO2 (6.51±2.25 METs and 6.54±2.28, respectively; p = 0.84). In contrast, there was a highly significant 21.1% difference between mean (±SD) TM-VO2pred and HRI-VO2 (8.12±1.85 METs and 6.71±1.92, respectively; p<0.001).

Conclusion
Although mean TM-VO2meas and HRI-VO2 were almost identical, mean TM-VO2pred was more than 20% greater than mean HRI-VO2.
Introduction

When assessed as oxygen consumption (VO\textsubscript{2}), cardiorespiratory fitness (CRF) may be measured either using a treadmill with conventional gas analysis equipment (TM-VO\textsubscript{2meas}) or predicted from equations based on treadmill speed, incline or treadmill time (TM-VO\textsubscript{2pred})\cite{1}.

The prognostic importance of CRF has been extensively investigated in recent meta-analyses confirming the strong inverse relationships between CRF and all-cause mortality in healthy individuals \cite{2} and in patients with either coronary artery disease (CAD) or congestive heart failure (CHF) \cite{3–6}. The prospective studies included in these reviews involve large numbers of subjects and have shown that a 1 MET (equal to 3.5 mL O\textsubscript{2}·kg\textsuperscript{-1}·min\textsuperscript{-1}) increment increase in CRF is associated with an approximate 10–20% reduction in all cause and cardiovascular mortality \cite{2,7} with a similar effect being observed with CHF \cite{6,8}.

Logistics of large studies necessitate prediction of peak VO\textsubscript{2} (VO\textsubscript{2peak}) as measurement of VO\textsubscript{2} is costly and time consuming. Equations have been determined for the various treadmill protocols based on the variables of treadmill speed, incline or the test time for a particular protocol, a common reference being ACSM publications \cite{1}. However, many factors may contribute to the error of TM-VO\textsubscript{2pred}. They include 1) treadmill handrail support \cite{9–13}, 2) failure to use population specific equations \cite{14–18}, 3) inappropriate testing protocol \cite{19–21}, 4) delayed oxygen kinetics \cite{22–24}, 5) reproducibility of cardiopulmonary parameters \cite{25,26}, 6) altered mechanical efficiency with treadmill walking \cite{27} and 7) lack of treadmill calibration \cite{28}.

Cardiovascular pathology frequently screened for with treadmill testing includes both CAD and CHF. In using CRF as an outcome measure from a treadmill test, VO\textsubscript{2peak} is commonly expressed as METs with 1 MET being the VO\textsubscript{2} at rest with current convention stating that it is equal to 3.5 mL O\textsubscript{2}·kg\textsuperscript{-1}·min\textsuperscript{-1} \cite{29}. Kaplan-Meier curves have been used extensively to document the link between CRF and long-term morbidity/mortality \cite{30,31}. Although VO\textsubscript{2} can be predicted from treadmill speed, incline or the test time for a particular protocol, currently the only way to ensure an accurate measurement of VO\textsubscript{2} is direct measurement with gas analysis.

Using only two simple measurements, rest HR and an activity HR (either sub-maximal or maximal), the recently published HR index (HRI = activity HR/rest HR), equation for predicting VO\textsubscript{2} expressed as METs is associated with a high correlation between HRI and VO\textsubscript{2}, the equation being METs = 6 x HRI - 5 \cite{32}. The HRI equation was derived from group mean data from 60 studies in which an exercise test contained a resting HR (HR\textsubscript{rest}), and a VO\textsubscript{2} measured at the activity HR (either submaximal or peak) and expressed in the form of mLO\textsubscript{2}·kg\textsuperscript{-1}·min\textsuperscript{-1} or METs. The original data are shown as a regression plot in Fig 1. The utility of this equation is that it provides a simple independent surrogate method of estimating VO\textsubscript{2} using only the rest and either the sub-maximal or maximal activity HR measurements. Though the HRI equation was developed from aggregate data, there has been no analysis to date that has established its predictive accuracy for assessment of VO\textsubscript{2}.

The objective of this study was to compare aggregate HRI-derived VO\textsubscript{2} (HRI-VO\textsubscript{2}) data against VO\textsubscript{2peak} from two different treadmill tests, either: 1) VO\textsubscript{2} measured with conventional gas analysis equipment (TM-VO\textsubscript{2meas}) or 2) VO\textsubscript{2} predicted from equations based on treadmill speed, incline or treadmill time (TM-VO\textsubscript{2pred}).

Methods

Study selection

Treadmill studies involving assessment of VO\textsubscript{2peak}, reporting either TM-VO\textsubscript{2meas} or TM-VO\textsubscript{2pred}, were identified through a systematic search conducted on at least a monthly basis.
from October 2011 till March 2013 using MEDLINE, Google Scholar and Web of Science. Search terms included (in various combinations) exercise testing, oxygen uptake, VO\textsubscript{2}, CRF, cardiovascular disease (CVD), CAD, CHF and physical activity. With publications having the prerequisite HR data extensive cross-referencing was undertaken to source other publications with eligible criteria [33].

Eligibility criteria for study inclusion are 1) >100 patients enrolled, 2) documented VO\textsubscript{2peak} (either measured or predicted) expressed as either mL O\textsubscript{2} kg\textsuperscript{-1} min\textsuperscript{-1} or as METs, 3) measured maximal HR (HR\textsubscript{max}) associated with VO\textsubscript{2peak}, and 4) measured HR\textsubscript{rest}. Where large scale studies included cycle ergometry in conjunction with treadmill testing, the study was excluded. In publications likely to have used a similar subject cohort based on 1. participating authors, 2. study location, 3. time period when the study was performed and 4. characteristics of the study population e.g. healthy, suspected or known CAD the most recent publication was chosen. From the HR data, a predicted MET value (VO\textsubscript{2peak}) was derived using the HRI equation (METs = 6 x HR index– 5, where HR index is HR\textsubscript{max}/HR\textsubscript{rest}).

At the time of closure of data acquisition in March 2013 a total of 40 studies (TM-VO\textsubscript{2meas}; n = 20 studies, TM-VO\textsubscript{2pred}; n = 20 studies) had been identified with all but one being published since 1991. MEDLINE searching identified 19 of the 40 studies (TM-VO\textsubscript{2meas}; n = 11 studies, TM-VO\textsubscript{2pred}; n = 8 studies) used in this analysis with the remaining 21 studies being sourced through Web of Science, Google Scholar and cross referencing. The TM-VO\textsubscript{2meas} studies had a bias towards clinical outcomes related to CHF whereas the TM-VO\textsubscript{2pred} studies were frequently associated with long-term outcome (survival) in screening for CVD. Though multiple search strategies were used to obtain studies meeting selection criteria it is acknowledged that even with rigorous attention to search detail, suitable studies may have been missed.

Fig 2 details the study selection process at the completion of data acquisition in March 2013.

**Statistical analysis**

Categorical variables were expressed as numbers and percentages with continuous variables expressed as mean ± standard deviation. Student’s paired t-test was used to compare HRI-VO\textsubscript{2}
against both TM-VO\textsubscript{meas} and TM-VO\textsubscript{pred}. Results are expressed in two formats, namely 1) pooled data for each of TM-VO\textsubscript{meas} and TM-VO\textsubscript{pred} against HRI-VO\textsubscript{2} expressed as group means and shown in the form of line of identity and Bland Altman plots [34] and 2) CRF data shown in tertiles for both TM-VO\textsubscript{meas} and TM-VO\textsubscript{pred} groups against HRI-VO\textsubscript{2}.

**Results**

**Studies used in the analyses**

There were 11,477 subjects in the 20 TM-VO\textsubscript{meas} studies (range 110 to 4631, median 337) and, with each study mean VO\textsubscript{2meas} value representing a data point, there was a total of 45 data points. There was a considerably larger number of subjects at 105,044 (range 772 to 22,275, median 3,736) in the 20 TM-VO\textsubscript{pred} studies and, with each study mean VO\textsubscript{2pred} value...
representing a data point, there were 57 data points. Age and gender distribution was similar for the TM-VO$_{2\text{meas}}$ (51.0 years and 64.9% males) and TM-VO$_{2\text{pred}}$ groups (52.9 years and 71.0% males).

The principal details of the 40 treadmill studies used in the analysis are outlined in Table 1. These include the test protocol, use of handrail support and the health status of participants. Of the 20 TM-VO$_{2\text{meas}}$ studies, 14 (70%) involved subjects with CHF and all 14 used protocols other than the standard Bruce protocol [35]. The design of these alternate protocols reduced the stage increment of VO$_2$ usually to 2 METs or less with certain ramp protocols having increments of less than 1 MET per minute. In only two of the TM-VO$_{2\text{meas}}$ studies was hand rail support mentioned, being ‘not permitted’ in one study (Dressendorfer [36]) and ‘discouraged’ in the other (Oliveira [37]).

Typically, subjects with known or suspected CVD or with significant cardiovascular risk factors were involved in the TM-VO$_{2\text{pred}}$ studies (Table 1). A Bruce protocol, either as the standard or a modified protocol, was used in 13 (65%) of the 20 TM-VO$_{2\text{pred}}$ studies. With TM-VO$_{2\text{pred}}$ studies, the use of handrail support was defined in seven studies (35%) and not stated in the remaining 13 studies. Descriptors of handrail support used for these seven studies were ‘discouraged’ in 3 studies, ‘not permitted’ in 3 studies and ‘light hand rail support’ in 1 study. Predictive treadmill equations in TM-VO$_{2\text{pred}}$ studies were either given or referenced in only 12 (60%) of the 20 studies.

Characterization of study groups

**A. Group means: oxygen consumption and heart rate.** The mean TM-VO$_{2\text{pred}}$ reported in the 20 studies was 8.12 METS; the mean TM-VO$_{2\text{meas}}$ reported in the 20 studies was 6.51 METS, a difference of 1.61 METS or 24.7% (Table 2). The mean HR$_{\text{rest}}$ with TM-VO$_{2\text{pred}}$ was 75.6 beats-min$^{-1}$ and with TM-VO$_{2\text{meas}}$ was 77.6 beats-min$^{-1}$; the mean HR$_{\text{max}}$ for TM-VO$_{2\text{pred}}$ 146.3 beats-min$^{-1}$ and TM-VO$_{2\text{meas}}$ 147.1 beats-min$^{-1}$ (Table 2). However, the absolute differences in group means for HR$_{\text{rest}}$ and HR$_{\text{max}}$ between TM-VO$_{2\text{pred}}$ and TM-VO$_{2\text{meas}}$ were small at 2.0 beats-min$^{-1}$ for HR$_{\text{rest}}$ and only 0.8 beat-min$^{-1}$ for HR$_{\text{max}}$ (Table 2).

Alternatively if VO$_2$peak is determined by HRI-VO$_2$ the difference between TM-VO$_{2\text{pred}}$ and TM-VO$_{2\text{meas}}$ is reduced to only 0.17 MET or 2.6% (TM-VO$_{2\text{pred}}$ 6.71 METs, TM-VO$_{2\text{meas}}$ 6.54 METs), a not unexpected result in view of the small differences in HR$_{\text{rest}}$ and HR$_{\text{max}}$ between these two groups (Table 2).

**B. Comparison of measured VO$_2$ and predicted VO$_2$ versus VO$_2$ predicted by HRI.** When using the HRI to calculate VO$_2$peak, there was no significant difference (0.4%, p = 0.84) in the pooled VO$_2$ data with mean (± SD) MET values of 6.51(±2.25) for TM-VO$_{2\text{meas}}$ and 6.54 (±2.28) for HRI-VO$_2$ (Fig 3A). However, a highly significant difference (21.1%, p <0.001) was seen between TM-VO$_{2\text{pred}}$ and HRI-VO$_2$ with respective values of 8.12 (±1.85) METs and 6.71 (±1.92) METs (Fig 3A).

Even when expressed in tertiles based on HRI-VO$_2$, there were no significant differences between TM-VO$_{2\text{meas}}$ and HRI-VO$_2$ by VO$_2$ tertile; tertile 1, 2.4% (p = 0.42), tertile 2, -4.1% (p = 0.18) and tertile 3, 0.7% (p = 0.83) (Fig 3B). By comparison, each tertile for the TM-VO$_{2\text{pred}}$ groups showed a significant difference from HRI-VO$_2$; tertile 1, 31.2% (p<0.001), tertile 2, 29.6% (p<0.001) and tertile 3, 9.1% (p = 0.03) (Fig 3C).

The plot of TM-VO$_{2\text{meas}}$ against HRI-VO$_2$ shows a uniform distribution around the line of identity with the Bland Altman plot suggesting that there is no bias between these two separate methods of determining VO$_2$peak (Fig 4A and 4B). However, a similar line of identity plot for TM-VO$_{2\text{pred}}$ against HRI-VO$_2$ indicates a strong bias with the Bland Altman plot indicating a systematic error in support of over-prediction of TM-VO$_{2\text{pred}}$ (Fig 5A and 5B).
Table 1. Description of studies, patient diagnosis, and test protocol in which oxygen uptake was either measured or predicted using a prediction equation (Pred EQ).

| First Author | Year | n   | Age (years) | Male% | Category  | Test   | Rail support | Pred EQ |
|--------------|------|-----|-------------|-------|-----------|--------|--------------|---------|
| **Measured VO<sub>2</sub>** |      |     |             |       |           |        |              |         |
| Bard         | 2006 | 355 | 51          | 72    | CHF       | ramp   | ns           |         |
| Diller       | 2006 | 727 | 33          | 52    | ACHD      | MB     | ns           |         |
| Dressendorfer| 1993 | 182 | 57          | 100   | CAD       | MB     | NP           |         |
| Elmariah     | 2006 | 594 | 52          | 72    | CHF       | ramp   | ns           |         |
| Harrington   | 1997 | 131 | 59          | 100   | CHF, H    | MB     | ns           |         |
| Ingle        | 2007 | 394 | 65          | 74    | CHF       | MB     | ns           |         |
| Jorde        | 2008 | 278 | 52          | 77    | CHF       | Na     | ns           |         |
| Kohrt        | 1991 | 110 | 64          | 50    | H         | B,O    | ns           |         |
| Kubrychtova  | 2009 | 712 | 56          | 72    | CHF       | O      | ns           |         |
| Lanier       | 2012 | 302 | 52          | 75    | CHF       | Na     | ns           |         |
| McDonough    | 1970 | 144 | 51          | 100   | H         | B      | ns           |         |
| Nes          | 2012 | 463 | 48          | 49    | H         | ramp   | ns           |         |
| Oliveira     | 2009 | 948 | 57          | 100   | CPD, H    | ramp   | DIS          |         |
| Osada        | 1998 | 154 | 52          | 75    | CHF       | MB, MNa | ns           |         |
| Peterson     | 2003 | 369 | 51          | 72    | CHF       | O      | ns           |         |
| Robbins      | 1999 | 487 | 52          | 71    | CHF, H    | Na     | ns           |         |
| Schalcher    | 2003 | 146 | 52          | 88    | CHF       | ramp   | ns           |         |
| Stolker      | 2006 | 221 | 49          | 68    | CHF       | O      | ns           |         |
| Williams     | 2001 | 219 | 56          | 76    | CHF       | B, MB  | ns           |         |
| Witte        | 2006 | 355 | 66          | 68    | CHF, H    | MB     | ns           |         |
| **Predicted VO<sub>2</sub>** |      |     |             |       |           |        |              |         |
| Adabag       | 2008 | 12555 | 46        | 100   | CAD<sup>+</sup> | B | ns | EQ-S |
| Aijaz        | 2008 | 10987 | 54        | 75    | CVD, CVD<sup>+</sup> | B | ns | ns |
| Arruda-Olson | 2002 | 5798  | 62        | 57    | CAD, CAD<sup>7</sup> | B, MB, Na | ns | ns |
| Carnethon    | 2003 | 4487 | 25        | 45    | H         | MBa    | ns           |         |
| Cheng        | 2003 | 2333 | 49        | 100   | DM        | MBa    | ns           |         |
| Elhendy      | 2001 | 1618 | 55        | 35    | CAD<sup>7</sup> | B, MB, Na | ns | ns |
| Gulati       | 2010 | 5437 | 52        | 50    | CAD<sup>+</sup> | B | LS | EQ-R |
| Kim          | 2007 | 22275 | 51       | 59    | CVD<sup>+</sup> | B, MB, O | NP | EQ-R |
| Kokkinos     | 2009 | 4631 | 61        | 100   | HT        | B, ramp | DIS | EQ-R |
| Lai          | 2004 | 5625 | 59        | 100   | CVD<sup>7</sup> | ramp, O | ns | EQ-R |
| Lauer        | 1999 | 2953 | 58        | 64    | CVD<sup>+</sup>, CVD<sup>7</sup> | B, MB | NP | EQ-R |
| Lipinski     | 2005 | 1914 | 52        | 100   | CAD, CHF, CAD<sup>+</sup> | ramp, O | ns | ns |
| Mahenthiran  | 2005 | 1268 | 60        | 52    | CAD, CAD<sup>+</sup> | B | ns | ns |
| McAuley      | 2007 | 6876 | 58        | 97    | CAD, CAD<sup>+</sup> | ramp | DIS | EQ-R |
| Mora         | 2003 | 2985 | 47        | 0     | CAD<sup>+</sup> | B | ns | EQ-R |
| Morrow       | 1993 | 2546 | 59        | 100   | CAD<sup>+</sup>, CAD, CHF | ramp, O | ns | EQ-R |
| Myers        | 2002 | 6213 | 59        | 100   | CAD, CAD<sup>+</sup> | ramp | DIS | EQ-R |
| Negishi      | 2013 | 914  | 56        | 56    | DM        | B, MB  | NP | EQ-R |
| Peteiro      | 2010 | 2947 | 62        | 61    | CAD, CAD<sup>7</sup> | B, MB, Na | ns | ns |
| Shaw         | 2011 | 772  | 63        | 0     | CAD<sup>7</sup> | B, MB  | ns | ns |

References are available in the supplementary digital content. **Category:** ACHD, adult congenital heart disease; CAD, coronary artery disease (CAD<sup>+</sup>, absent; CAD<sup>7</sup>, suspected); CHF, congestive heart failure; CPD, cardiopulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; H, healthy; HT, hypertension. **Treadmill test:** B, Bruce protocol; Ba, Balke protocol; Na, Naughton protocol; ramp, ramp protocol; M, modified protocol; O, other protocol; **Rail support:** ns, not stated; NP, not permitted; DIS, discouraged; LS, light support; **Equation:** EQ-S, stated equation; EQ-R, referenced equation; ns, not stated.

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It is crucial to have high quality CRF data for use in epidemiological studies as management strategies involving both pharmacological and lifestyle intervention rely on this accuracy. The utility of the HRI equation [32] as a surrogate measure of VO\textsubscript{2} expressed in METs is confirmed in this study when assessed against VO\textsubscript{2peak} for both TM-VO\textsubscript{2meas} measured with conventional gas analysis equipment and for TM-VO\textsubscript{2pred} predicted from equations based on treadmill speed, incline or treadmill time. A close agreement between HRI-VO\textsubscript{2} and TM-VO\textsubscript{2meas} was observed in the 20 TM-VO\textsubscript{2meas} studies with only a 0.4% difference (p = 0.84) between group means. By comparison, a highly significant 21.1% (p < 0.001) over-prediction of VO\textsubscript{2peak} was observed when comparing HRI-VO\textsubscript{2} against TM-VO\textsubscript{2pred} in the 20 TM-VO\textsubscript{2pred} studies.

### Discussion

Table 2. Heart rate and oxygen consumption data for TM-VO\textsubscript{2meas} and TM-VO\textsubscript{2pred}

| Studies     | Data points | HR\textsubscript{rest} beats min\textsuperscript{-1} | HR\textsubscript{peak} beats min\textsuperscript{-1} | VO\textsubscript{2peak} METs | HRI-VO\textsubscript{2} METs |
|-------------|-------------|---------------------------------|---------------------------------|----------------------------|-----------------------------|
| TM-VO\textsubscript{2pred} | 20          | 57                              | 146.3 ± 16.6                    | 8.12 ± 1.85                | 6.71 ± 1.92                 |
| TM-VO\textsubscript{2meas} | 20          | 45                              | 147.1 ± 18.8                    | 6.51 ± 2.25                | 6.54 ± 2.28                 |

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![Fig 3. Comparison of pooled data from 20 studies for TM-VO\textsubscript{2meas} and TM-VO\textsubscript{2pred} against HRI-VO\textsubscript{2}](image-url)

A. Comparison of group mean data for 20 TM-VO\textsubscript{2meas} and TM-VO\textsubscript{2pred} Studies against HRI-VO\textsubscript{2} (mean ± SE), B. Comparison of cardiorespiratory fitness tertiles from 20 studies for TM-VO\textsubscript{2meas} against HRI-VO\textsubscript{2} (mean ± SE). Percentage difference between TM-VO\textsubscript{2meas} and HRI-VO\textsubscript{2} shown within figure and C. Comparison of cardiorespiratory fitness tertiles from 20 studies for TM-VO\textsubscript{2pred} against HRI-VO\textsubscript{2} (mean ± SE). Percentage difference between TM-VO\textsubscript{2pred} and HRI-VO\textsubscript{2} shown within figure.

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magnitude of the potential error using TM-VO$_{2pred}$ challenges the current methods of treadmill prediction of CRF which appear to lead to overestimation of CRF and potentially to false prognostic classification.

If the magnitude of the disparity between HRI-VO$_2$ and TM-VO$_{2pred}$ as shown in this study is, for example, applied to the outcome data of CRF as expressed in METs in the meta-analysis by Kodama [2], there is a strong likelihood of a false classification based on the over-prediction of CRF. For example, in treadmill studies investigating the effect of handrail support, a practice that lengthens treadmill time, VO$_{2peak}$ is over-predicted by 20% to 30% [9–13,17] which would lead to a potentially false prognostic classification of CRF. To correct for the consistently observed over-prediction of VO$_{2peak}$ of around 20% resulting from the use of
Foster has developed simple modifications of the ACSM equations for use when handrail support is observed during treadmill testing [17]. None of the 20 TM-VO$_2$pred studies used in this analysis referenced use of the Foster or similar equations to correct for observed handrail support. This prediction error could potentially apply to other published studies that express results in the form of survival tables and Kaplan-Meier curves. The measurement of CRF is not only limited to CVD. CRF also defines long-term risk in both healthy subjects and other common medical conditions, such as stroke [38], dementia [39] and diabetes mellitus [40]. In the TM-VO$_2$pred group of studies, the smallest difference (9.1%) between HRI-VO$_2$ and TM-VO$_2$pred was observed in the highest CRF tertile. Presumably, the fittest subjects find less difficulty with treadmill walking and so have less need for handrail support. Conversely, the least fit, i.e., the lowest tertile, are most likely to utilize handrail support, even when instructed otherwise, and, in the present study, they demonstrated a 31.2% difference.

![Graph showing line of identity and Bland Altman plot for TM-VO$_2$pred](image)

**Fig 5. Line of Identity and Bland Altman plot for TM-VO$_2$pred.** A. Line of identity for TM-VO$_2$pred and B. against Bland Altman plot for TM-VO$_2$pred against HRI-VO$_2$.

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between HRI-VO$_2$ and TM-VO$_{2\text{pred}}$. Results from the HUNT 3 Fitness Study also noted the greatest overestimation of VO$_{2\text{peak}}$ in the least fit subjects [18].

Collectively the 20 TM-VO$_{2\text{pred}}$ studies used in this analysis involve a tenfold greater number of subjects when compared with the 20 TM-VO$_{2\text{meas}}$ studies, whether considering the total number of subjects (105,044 TM-VO$_{2\text{pred}}$ versus 11,477 TM-VO$_{2\text{meas}}$) or the median number (3,736 TM-VO$_{2\text{pred}}$ versus 337 TM-VO$_{2\text{meas}}$). This observation indicates an inherent bias in using predicted VO$_2$ studies for epidemiological purposes. In recognizing the need for high quality population CRF data, the Fitness Registry and the Importance of Exercise: A National Database (FRIEND) was established in 2014 [41]. A recent publication from this group has provided age-related reference standards of CRF from 7783 tests in which VO$_{2\text{max}}$ was determined by gas analysis, the authors highlighting the shortcomings of using TM-VO$_{2\text{pred}}$ largely because of over-prediction of VO$_{2\text{max}}$ associated with hand rail support [42]. Their statement together with the observations in the present review suggest that, for the continued use of TM-VO$_{2\text{pred}}$ data, a reappraisal of current methods used for prediction of VO$_{2\text{peak}}$ warrants consideration.

One important question arising from this analysis is the value of using maximal HRI to predict VO$_{2\text{peak}}$ from HR derived values (rest and peak) as opposed to treadmill parameters (speed, incline or treadmill time). When calculating maximal HRI, two independent predictors of future CVD risk, namely an estimated VO$_{2\text{peak}}$ [2,43] and HR$_{\text{rest}}$ [44] are incorporated within the HRI. The maximal HRI is based on two measured values of HR and, when used as an index, there is minimal predictive error especially when compared to VO$_{2\text{pred}}$ using equations based on speed, incline or treadmill time. As a 1.0 MET increment corresponds to a HRI increment of 0.167, Kaplan-Meier curves ranging from <5 to >10 METs have a corresponding HRI range from 1.67 to 2.50 (e.g., 5 METs = Rest [HRI = 1] + 4 METs [HRI = 4 x 0.167] = 1.67). In considering a range of activity from rest (1.0 MET) to the maximum aerobic performance of an elite athlete (e.g. 19 METs), the corresponding range of HRI would be from 1 to 4. The simplicity of calculating HRI together with the range of index used for clinical evaluation suggests that it could provide a useful addition to the assessment of CRF. To illustrate this, a range of 5, 10 and 15 MET levels have corresponding HRIs of 1.67, 2.5 and 3.33.

**Study Limitations**

This review has used the simple concept of HRI as a surrogate measure of VO$_2$. The equation was established from aggregate data acquired from 60 studies. In applying the HR index to this analysis, we have compared aggregate data from TM-VO$_{2\text{pred}}$ and TM-VO$_{2\text{meas}}$ against HRI-VO$_2$ with no intention of indicating the individual predictive accuracy of the equation. Ideally the use of individual, as opposed to aggregate data would have been preferable but it was beyond the capability of this analysis.

**Conclusions**

The usefulness of CRF is well established for assessing CV risk with treadmill testing providing a simple and convenient method of assessing CRF. The aggregate analysis used in this study shows a close relationship, i.e., a non-significant 0.4% difference, between HRI-VO$_2$ and TM-VO$_{2\text{meas}}$ but a large and highly significant 21.1% difference between HRI-VO$_2$ and TM-VO$_{2\text{pred}}$. This overestimation of TM-VO$_{2\text{pred}}$ and so CRF, challenges the validity of predicting VO$_{2\text{peak}}$ from equations based on treadmill speed, incline or protocol time when attempting to document a link between CRF and long-term morbidity/mortality.
Supporting Information

S1 File. Supplementary Reference List– 40 treadmill studies. File listing the 40 treadmill studies used for analysis.

(RTF)

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Investigation: JRW.
Methodology: JRW NBO.
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References

1. ACSM (2000) ACSM’s Guidelines for Exercise Testing and Prescription. 6th edition. Philadelphia, PA: Lippincott Williams & Wilkins.
2. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. (2009) Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women. JAMA 301: 2024–2035. doi: 10.1001/jama.2009.681 PMID: 19454641
3. Echouffo-Tcheugui JB, Butler J, Yancy CW, Fonarow GC (2015) Association of physical activity or fitness with incident heart failure: A systematic review and meta-analysis. Circ Heart Fail 8: 853–861. doi: 10.1161/CIRCHEARTFAILURE.115.002070 PMID: 26175539
4. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. (2008) Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 156: 292–300. doi: 10.1016/j.ahj.2008.03.017 PMID: 18657659
5. McNeer JF, Margolis JR, Lee KL, Kisslo JA, Peter RH, Kong Y, et al. (1978) The role of the exercise test in the evaluation of patients for ischemic heart disease. Circulation. 57: 64–70. PMID: 6183999
6. Berry JD, Pandey A, Gao A, Leonard D, Farzaneh-Far R, Ayers C, et al. (2013) Physical fitness and risk for heart failure and coronary artery disease. Circ Heart Fail 6: 627–634. PMID: 23677924
7. Gander JC, Sui X, Hébert JR, Hazlett LJ, Cai B, Lavie CJ, et al. (2015) Association of cardiorespiratory fitness with coronary heart disease in asymptomatic men. Mayo Clin Proc 90: 1372–1379. doi: 10.1016/j.mayocp.2015.07.017 PMID: 26434963
8. Khan H, Kunutsor S, Rauramaa R, Savonen K, Kalogeropoulos AP, Georgiopoulou VV, et al. (2014) Cardiorespiratory fitness and risk of heart failure: a population-based follow-up study. Eur J Heart Fail 16: 180–188. doi: 10.1002/ejhf.37 PMID: 24464981
9. Pinkstaff S, Peberdy MA, Kontos MC, Fabiato A, Finucane S, Arena R (2011) Overestimation of aerobic capacity with the bruce treadmill protocol in patients being assessed for suspected myocardial ischemia. J Cardiopulm Rehabil Prev 31: 254–260. doi: 10.1097/HCR.0b013e58211e3ed PMID: 21427601
10. Berling JM, Foster C, Gibson M, Doberstein S, Porcari JP (2006) The effect of handrail support on oxygen uptake during steady state treadmill exercise. J Cardiopulm Rehabil Prev 26: 250.

11. Zeimetz G, McNeil J, Hall J, Moss R (1985) Quantifiable changes in oxygen uptake, heart rate, and time to target heart rate when hand support is allowed during treadmill exercise. J Cardiopulm Rehabil 5: 525–530.

12. Haskell WL, Savin W, Oldridge N, DeBusk R (1982) Factors influencing estimated oxygen uptake during exercise testing soon after myocardial infarction. Am J Cardiol 50: 299–304. PMID: 7102560

13. Manfrez MJ, Yu GH, Varmá AA, Mallis GI, Kearney K, Karageorgis MA (1994) The effect of limited handrail support on total treadmill time and the prediction of VO2 max. Clin Cardiol 17: 445–450. PMID: 795592

14. Foster C, Hare J, Taylor M, Goldstein T, Anholm J, Pollock M (1984) Prediction of oxygen uptake during exercise testing in cardiac patients and healthy volunteers. J Cardiopulm Rehabil 4: 537–542.

15. Foster C, Jackson AS, Pollock ML, Taylor MM, Hare J, Sennett SM, et al. (1984) Generalized equations for predicting functional capacity from treadmill performance. Am Heart J 107: 1229–1234. PMID: 6720550

16. McConnell TR, Foster C, Conlin NC, Thompson NN (1991) Prediction of functional capacity during treadmill testing: effect of handrail support. J Cardiopulm Rehabil Prev 11: 255–260.

17. Foster C, Crowe A, Daines E, Dumit M, Green MA, Lettau S, et al. (1996) Predicting functional capacity during treadmill testing independent of exercise protocol. Med Sci Sports Exerc 28: 752–756. PMID: 8784763

18. Loe H, Nes BM, Wisløff U (2016) Predicting VO2peak from Submaximal-and Peak Exercise Models: The HUNT 3 Fitness Study, Norway. PLoS ONE 11: e0144873. doi: 10.1371/journal.pone.0144873 PMID: 26794677

19. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ (1983) Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol 55: 1558–1564. PMID: 6643191

20. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, et al. (1991) Comparison of the ramp versus standard exercise protocols. J Am Coll Cardiol 17: 1334–1342. PMID: 2016451

21. Oparisch C, Myers J (2001) Working Group Report. Recommendations for exercise testing in chronic heart failure patients. Eur Heart J 22: 37–45. PMID: 11133208

22. Roberts JM, Sullivan M, Froelicher VF, Genter F, Myers J (1984) Predicting oxygen uptake from treadmill testing in normal subjects and coronary artery disease patients. Am Heart J 108: 1454–1460. PMID: 6507241

23. Alexander NB, Dengel DR, Olson RJ, Krajewski KM (2003) Oxygen-uptake (VO2) kinetics and functional mobility performance in impaired older adults. J Gerontol A Biol Sci Med Sci 58: M734–M739.

24. Mezzani A, Agostoni P, Cohen-Solal A, Corra U, Jegier A, Kouidi E, et al. (2009) Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 16: 249–287. doi: 10.1097/HJR.0b013e2823914f8 PMID: 19440156

25. Sullivan M, Genter F, Savvides M, Roberts M, Myers J, Froelicher V (1984) The reproducibility of hemodynamic, electrocardiographic, and gas exchange data during treadmill exercise in patients with stable angina pectoris. Chest 86: 375–382. PMID: 6467998

26. Elborn J, Stanford C, Nicholls D (1990) Reproducibility of cardiopulmonary parameters during exercise in patients with chronic cardiac failure. The need for a preliminary test. Eur Heart J 11: 79–81. PMID: 2106439

27. Levy WC, Maichel BA, Steele NP, Leclerc KM, Stratton JR (2004) Biomechanical efficiency is decreased in heart failure during low-level steady state and maximal ramp exercise. Eur J Heart Fail 6: 917–926. PMID: 15556054

28. Hiatt WR, Cox L, Greenwald M, Griffin A, Schechter C (2005) Quality of the assessment of primary and secondary endpoints in claudication and critical leg ischemia trials. Vasc Med 10: 207–213. PMID: 16235774

29. Gagge AP, Burton AC, Bazett HC (1941) A practical system of units for the description of the heat exchange of man with his environment. Science 94: 428–430. PMID: 17758307

30. Myers J, Prakash M, Froelicher V, Do D, Parthington S, Atwood JE (2002) Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 346: 793–801. PMID: 11893790

31. Kubrzychtova V, Olson TP, Bailey KR, Thapa P, Allison TG, Johnson BD (2009) Heart rate recovery and prognosis in heart failure patients. Eur J Appl Physiol 105: 37–45. doi: 10.1007/s00421-008-0870-2 PMID: 18797918
32. Wicks JR, Oldridge NB, Nielsen LK, Vickers CE (2011) HR index—a simple method for the prediction of oxygen uptake. Med Sci Sports Exerc 43: 2005–2012. doi: 10.1249/MSS.0b013e318217276e PMID: 21364476

33. Robinson KA, Dunn AG, Tsafnat G, Glasziou P (2014) Citation networks of related trials are often disconnected: implications for bidirectional citation searches. J Clin Epidemiol 67: 793–799. doi: 10.1016/j.jclinepi.2013.11.015 PMID: 24725642

34. Bland JM, Altman D (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 327: 307–310.

35. Bruce RA, Kusumi F, Hosmer D (1973) Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 85: 546–562. PMID: 4632004

36. Dressendorfer R, Franklin B, Gordon S, Timmis G (1993) Resting oxygen uptake in coronary artery disease. Influence of chronic beta-blockade. Chest 104: 1269–1272. PMID: 8104769

37. Oliveira RB, Myers J, Araujo CGS, Abella J, Mandic S, Froelicher V (2009) Maximal exercise oxygen pulse as a predictor of mortality among male veterans referred for exercise testing. Eur J Cardiovasc Prev Rehabil 16: 358–364. doi: 10.1097/HJR.0b013e3283292fe8 PMID: 19357518

38. Do Lee C, Folsom AR, Blair SN (2003) Physical activity and stroke risk a meta-analysis. Stroke 34: 2475–2481. doi: 10.1161/01.STR.0000091843.02517.9D PMID: 14500932

39. DeFina LF, Willis BL, Radford NB, Gao A, Leonard D, Haskell WL, et al. (2013) The association between midlife cardiopulmonary fitness levels and later-life dementia: a cohort study. Ann Intern Med 158: 162–168. doi: 10.7326/0003-4819-158-3-201302050-00005 PMID: 23381040

40. Helmarich SP, Ragland DR, Leung RW, Paffenbarger RS Jr (1991) Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 325: 147–152. doi: 10.1056/NEJM199101023250302 PMID: 2052059

41. Kaminsky LA, Arena R, Beckie TM, Brubaker PH, Church TS, Forman DE, et al. (2013) The importance of cardiorespiratory fitness in the United States: the need for a national registry a policy statement from the American Heart Association. Circulation 127: 652–662. doi: 10.1161/CIR.0b013e31827ee100 PMID: 23295916

42. Kaminsky LA, Arena R, Myers J (2015) Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: Data from the Fitness Registry and the Importance of Exercise National Database. Mayo Clin Proc 90: 1515–1523. doi: 10.1016/j.mayocp.2015.07.026 PMID: 26455884

43. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr., Clark DG, Cooper KH, Gibbons LW (1989) Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 262: 2395–2401. PMID: 2795824

44. Fox K, Borger JS, Camm AJ, Danchin N, Ferrari R, Sendon JLL, et al. (2007) Resting heart rate in cardiovascular disease. J Am Coll Cardiol 50: 823–830. doi: 10.1016/j.jacc.2007.04.079 PMID: 17719466