Impact of Cardiorespiratory Fitness on All-Cause and Disease-Specific Mortality: Advances Since 2009

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Abstract
Cardiorespiratory fitness (CRF) has been one of the most widely examined physiological variables, particularly as it relates to functional capacity and human performance. Over the past three decades, CRF has emerged as a strong, independent predictor of all-cause and disease-specific mortality. The evidence supporting the prognostic use of CRF is so powerful that the American Heart Association recently advocated for the routine assessment of CRF as a clinical vital sign. Interestingly, the continuity of evidence of the inverse relationship between CRF and mortality over the past decade exists despite a wide variation of methods used to assess CRF in these studies, ranging from the gold-standard method of directly measured maximal oxygen uptake (VO2max) during cardiopulmonary exercise testing to estimation from exercise tests and non-exercise prediction equations. This review highlights new knowledge and the primary advances since 2009, with specific reference to the impact variations in CRF have on all-cause and disease-specific mortality.

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VO2max
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Cardiorespiratory fitness (CRF), also known as aerobic capacity (i.e., \( VO_{2\text{max}} \)), was initially described by Hill and Lupton\(^1 \) as the maximum amount of oxygen (\( O_2 \)) that can be taken in, transported to, and utilized by the working tissue during dynamically strenuous exercise involving large muscle mass. Since its characterization, CRF has perhaps been one of the most widely examined physiological variables, particularly as it relates to functional capacity and human performance. Historically, physical activity (PA), in the form of exercise of moderate-to-vigorous intensity, to improve CRF was associated with athletic training, whereas chronic moderate-intensity PA has been primarily related to health.\(^2\)\(^-\)\(^4\) Although the health benefits of regular PA have been advocated since antiquity,\(^5\) the connection between CRF and mortality was established in a prospective study of 10,224 men and 3120 women followed for over 8 years as part of the Aerobics Center Longitudinal Study (ACLS).\(^6\) The primary findings were an inverse relation between CRF and mortality follow-ups based on a single baseline assessment of characteristics. The majority of epidemiologic studies since 2009 were mortality follow-ups based on a single baseline assessment of CRF. Their participant characteristics, follow-up duration and mortality type are summarized in Table 1.

### Participant referral and health status

Participants in these studies were generally individuals who voluntarily underwent health and medical screening services (Cooper Clinic; ACLS)\(^9\)-\(^13\) or enrolled in Asian, European and Scandinavian country-specific population-based health studies, which likely represent a wide sampling of health characteristics.\(^9\),\(^14\)-\(^18\) The most common inclusion criterion was that individuals were free from known CVD at baseline, with a few studies also including the absence of malignant neoplasms, when cancer mortality was an outcome measure. However, three large medical systems, the Veterans Affairs Medical Centers (VA), Henry Ford Hospital (HFH), and the Mayo Clinic, studied cohorts derived from populations primarily associated with lower all-cause and coronary heart disease (CHD/CVD mortality. The authors noted that each 1-metabolic equivalent (MET) increment in CRF was associated with a 13% and 15% lower risk of all-cause and CHD/CVD mortality, respectively.

## Methodological characteristics

One of the most remarkable features of the studies showing an association between lower levels of CRF and increased all-cause and CVD mortality is the robustness of the findings. This section provides a brief overview of the range of methodological characteristics in studies that have demonstrated this association. The majority of epidemiologic studies since 2009 were mortality follow-ups based on a single baseline assessment of CRF. Their participant characteristics, follow-up duration and mortality type are summarized in Table 1.
referred for diagnostic exercise testing. Although there are numerous indications for exercise testing, patients commonly present with symptoms or other clinical findings suggestive of CVD. Additionally, some have included patients with known CVD or peripheral arterial disease (PAD) at baseline.

Another notable consideration is the global distribution of participants undergoing a CRF assessment. Although most studies were from U.S. based populations, other investigations have evaluated participants from Canada, Denmark, Finland, Japan, Korea, Norway, Sweden, and the UK (England and Scotland), producing results similar across the various countries. This is consistent with the Kodama et al. meta-analysis which also included subjects from Belgium and France.

**Participant sex and racial/ethnic characteristics**

The majority of participants in the investigations reviewed here were men. Since multiple reports have been published from each of the three largest cohorts (ACLS, VA, and HFH), the citation with the largest study population was used to determine the sex and racial/ethnic proportions as representative of the cohort. In the reports summarized in Table 1, there were a total of 285,268 participants included, of which ~65% were men. Because reporting of racial/ethnic background was inconsistent for these studies, we made the following assumptions when calculating racial/ethnic proportions for four classifications: Asian, Black, White, and other. Studies from the Scandinavian countries were assumed to be 100% White, the study population from Canada (Calgary) was presumed to be 80% White, and reports that stated predominantly White were calculated as 90% White and 10% other. With those assumptions, 73% of the participants included in Table 1 were White, 11% Black, 13% Asian, and 8% other (which could include Asian or Black).

**Participant age and follow-up**

Most studies reported a mean baseline participant age of 43–62 years; however, one study reported an average age of 25 years. Mortality follow-up periods began at 1-year for the majority of studies and ranged between 10 and 45 years. The shortest mean or median follow-up time was 6 years and the longest was 28 years with most in the 10–15 year time frame.

**Assessment of CRF**

The AHA has played a key role in setting standards for the assessment of CRF in numerous scientific statements. The gold standard method is cardiopulmonary exercise testing (CPX) with directly measured VO₂max, which has a known biological variability of 3%–4%. As shown in Table 2, this methodology was only used in one study that examined the association between CRF and all-cause and CVD mortality. Although this demonstrates the need for future studies using directly measured VO₂max it underscores how consistent and powerful CRF is as a forecastor of mortality given that its prognostic power has been demonstrated using a variety of measurement methods. In many clinical settings, exercise tests without ventilatory expired gas analysis (CPX), most often using a treadmill, are generally performed to levels perceived as indicating peak or maximal effort. However, without an objective marker of effort, the attainment of true maximum is uncertain. In the ACLS, VA, and HFH cohorts, CRF was estimated from the attained speed, grade and duration at the highest stage of a treadmill exercise test. The prediction equations (separate equations for walking speeds, running speeds, and cycle workrates) used for this estimate were developed using steady-state, submaximal exercise levels. Thus, applying these to workrates associated with maximal level effort may result in estimation error. Other studies that employed exercise tests to perceived maximum effort utilized protocol specific regression equations to predict VO₂max from test duration. Submaximal exercise testing has also been used, typically during cycle ergometry, to predict VO₂max. Additionally, estimating CRF from non-exercise prediction equations or self-reported CRF is becoming more prevalent. It is important to recognize that with any prediction equation, there is an associated estimation error. The standard errors associated with the indirect CRF assessment methods used in these studies ranged from ±4.2 to 7.0 ml kg⁻¹ min⁻¹ (Table 2).

**Recent advances**

Numerous studies since the Kodama et al. meta-analysis in 2009 have further clarified the impact of CRF on mortality by incorporating longer follow-up periods, examining individuals throughout the lifespan, diversifying subject populations by age, sex, ethnicity, and specific medical histories, and by incorporating changes in CRF in the overall risk assessment. Several studies have recently evaluated the predictive value of a baseline measure of CRF on mortality with follow-up durations >20 years. Jensen and colleagues followed 5131 men, as part of the Copenhagen Male Study, for cancer and all-cause mortality for more than four decades. The graded inverse relationship between CRF, estimated from submaximal cycle ergometer testing, and both cancer and all-cause mortality was consistent across tertiles of CRF and independent of traditional risk factors, PA and social class. Further, the relationship persisted even after excluding individuals who died within the first 20 years of follow-up, demonstrating the predictive power of CRF on long-term survival. The graded relationship between CRF and all-cause, but not CVD mortality, was reinforced in a smaller cohort study of Swedish men (n = 792) that conducted an exercise test at 54 years of age and were followed for up to 45 years (mean follow-up duration was 26 years). As compared with traditional risk factors, the predictive power of CRF on mortality was second only to cigarette smoking. The lack of a significant inverse association between CRF and CVD mortality is inconsistent with several recent reports and is likely due to a relatively small sample size. This inconsistency may also be related to the classification of CRF based on estimated absolute VO₂ (l·min⁻¹) rather than the more commonly used and preferred expression of VO₂ relative to body weight (ml·kg⁻¹·min⁻¹). These two investigations with the longest reported follow-up periods only evaluated Scandinavian men. The longest duration follow-up in a cohort with a predominant
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Participants</th>
<th>Baseline Health/Age (y)</th>
<th>Sex (n, %F)</th>
<th>Country</th>
<th>Racial/Ethnic</th>
<th>Follow-Up Time Average and [Range] (y)</th>
<th>Mortality Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Mallah et al.a,19</td>
<td>Henry Ford Exercise Testing Project</td>
<td>Referred for exercise testing</td>
<td>CVD risk factors/52.8 ± 12.7 M, 54.0 ± 12.4 F</td>
<td>57,284 (49%)</td>
<td>US</td>
<td>M: 68% W, 24% B, 8.1% O; F: 60% W, 34% B, 6% O</td>
<td>Median: 10 [0.1-22]</td>
<td>All-cause</td>
</tr>
<tr>
<td>Dhoble et al.20</td>
<td>Mayo Clinic</td>
<td>Referred for exercise testing</td>
<td>No CVD or cancer/49.3 (range 25-85) 39.9/(range 20-85)</td>
<td>6514 (42%)</td>
<td>US</td>
<td>81% W, 19% O</td>
<td>8.1 ± 3.7 [1-15]</td>
<td>Median: 8.9 [5-12]</td>
</tr>
<tr>
<td>Edwards and Loprinzi42</td>
<td>NHANES</td>
<td>Health study participants</td>
<td>No CVD/44.8 ± 9.6 No CVD/3 groups: 46.8, 41.5</td>
<td>9251 (49.7%)</td>
<td>US</td>
<td>70% W</td>
<td>All-cause</td>
<td>Median: 19.1 all-cause, [1-20], 17.9 CVD mortality</td>
</tr>
<tr>
<td>Farrell et al.b,10</td>
<td>CCLS Copenhagen City Heart Study</td>
<td>Self-referred Random sample of adult population living in Copenhagen</td>
<td>No cancer/48.8 y ± 5.4</td>
<td>5131 (0%)</td>
<td>Denmark</td>
<td>100% W</td>
<td>All-cause and cancer</td>
<td>28.3 ± 11.4 all-cause [0-40], 28.0 ± 11 cancer [0-44]</td>
</tr>
<tr>
<td>Holtermann et al.14</td>
<td>Kawasaki Coronary Artery Study</td>
<td>Recruited men from 14 workplaces Self-referred</td>
<td>No CVD/44.2 ± 10 (range: 20-100)</td>
<td>55,456 (24.4%)</td>
<td>US</td>
<td>90% W, 10% O</td>
<td>11.9 ± 7.5 [3-33]</td>
<td>Major adverse cardiac events, including fatal dissection</td>
</tr>
<tr>
<td>Ladenvall et al.16</td>
<td>Veterans Affairs Medical Centers Gothenburg</td>
<td>Referred for exercise testing</td>
<td>No previous MI or locomotor disturbances/54</td>
<td>20,590 (37%)</td>
<td>US</td>
<td>63% B, 37% W</td>
<td>17.9% IHD, 2.6% diabetes/50.7 ± 6.7 (range 42 to 60)</td>
<td>Group I: 25 ± 9.6; II: 25.6 ± 9.7; III: 27.5 ± 10.0 [0-45]</td>
</tr>
<tr>
<td>Laukkanen et al.25</td>
<td>Kuopio IHD risk factor study</td>
<td>Randomly selected men from this study group</td>
<td>CAD/60 ± 10.3</td>
<td>579 (0)</td>
<td>Finland</td>
<td>100% W</td>
<td>All-cause</td>
<td>Median: 13.3 [0-15]</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort</td>
<td>Participants</td>
<td>Baseline Health/Age (y)</td>
<td>Sex (n, %F)</td>
<td>Country</td>
<td>Racial/Ethnic</td>
<td>Follow-Up Time Average and [Range] (y)</td>
<td>Mortality Type</td>
</tr>
<tr>
<td>---------------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>Nes et al.17</td>
<td>HUNT</td>
<td>Residents of Nord-Trondelag county &gt;20 y of age who participated in the HUNT survey</td>
<td>No CVD or physical disability/43.5 ± 15.9 M, 44.1 ± 16.3 F</td>
<td>37,112 (51%)</td>
<td>Norway</td>
<td>97% W</td>
<td>24 ± 5.9 [n/a]</td>
<td>All-cause and CVD</td>
</tr>
<tr>
<td>Park et al.39</td>
<td>Health promotion center at Seoul National University Hospital</td>
<td>Men completed a medical check-up and graded exercise test</td>
<td>No MI, stroke, or cancer/55.7 ± 11.1</td>
<td>18,775 (0%)</td>
<td>Korea</td>
<td>100% A</td>
<td>6.4 [0-10]</td>
<td>All-cause, CVD, and cancer</td>
</tr>
<tr>
<td>Robsahm et al.46</td>
<td>Oslo Ischemic Study</td>
<td>Invited from 5 companies practicing annual or biannual health exams</td>
<td>No CVD, cancer, other chronic disease or conditions/49.3 (37–62)</td>
<td>2341 (0%)</td>
<td>Norway</td>
<td>100% W</td>
<td>26.2 [n/a]</td>
<td>Cancer</td>
</tr>
<tr>
<td>Shah et al.28</td>
<td>CARDIA</td>
<td>Balanced enrollment across 4 sites by sex, age, race, and education</td>
<td>No CVD/24.8 ± 3.6 (18-30)</td>
<td>4872 (54%)</td>
<td>US</td>
<td>51% B, 49% W</td>
<td>Median: 26.9 [n/a]</td>
<td>All-cause</td>
</tr>
<tr>
<td>Sawada et al.41</td>
<td>Tokyo Gas Co.</td>
<td>Male employees-completing annual health exams</td>
<td>No CVD, cancer, other chronic disease or conditions/35 (19–59)</td>
<td>8760 (0%)</td>
<td>Japan</td>
<td>100% A</td>
<td>20.2 [n/a]</td>
<td>All-cause and cancer</td>
</tr>
<tr>
<td>Stamataxis et al.18</td>
<td>Participants of England or Scottish Health Survey</td>
<td>Health survey participants</td>
<td>No CVD/~50 M, ~51 F (35–70)</td>
<td>32,319 (55%)</td>
<td>England and Scotland</td>
<td>90% W, 10% O</td>
<td>9 ± 3.5 [n/a]</td>
<td>All-cause and CVD</td>
</tr>
</tbody>
</table>

Abbreviations: A, Asian; B, Black; CVD, cardiovascular disease; F, female; IHD, ischemic heart disease; M, male; MI, myocardial infarction; O, other; W, White. Data are expressed as mean ± SD unless otherwise noted.

a For cohorts with multiple reports (ACLS/CCLS, HFH, and VA), the largest sample from each cohort was used.

b The largest of these 2 studies was used for the racial/ethnic summary calculations.
portion of women (n = 2650, 54%) was 26 years, in which a significant relationship between high CRF and reduced risk of all-cause mortality was observed, though sex-specific analyses were not performed.28 While recent studies have substantiated that CRF is a strong indicator of mortality over a long follow-up duration, there is a need for additional analyses in female cohorts.

**Relationships for men and women**

The inverse relationship between CRF and mortality is similar in both men and women7; however, surprisingly few studies have performed sex-specific analyses. Although sex is typically adjusted for in statistical models, among studies published since 2009 with a substantial cohort of women (>40%)13,14,18–20,28,32,35,42 only four have reported results for sexes independently13,14,18,19 and only one has compared men and women using CRF estimated from exercise testing.19 These studies have consistently shown that the CRF related benefit for mortality is independent of sex, though it remains important to consider sex in the risk classification as women typically have lower CRF than men. This was highlighted by Al-Mallah et al.19 comparing men and women referred for exercise testing as part of the HFH Exercise Testing Project.19 Although men had on average a CRF that was 1.7 METs higher than women, the survival benefit for men at a specific CRF level was similar to that of women with a 2.6 MET lower CRF. Thus, sex should be considered when establishing cut-points or thresholds for CRF as it relates to mortality.

### CRF through the lifespan

The relationship between CRF and mortality has most commonly been assessed in investigations that utilized a single measure of CRF, typically obtained during midlife (45–55 years) with subsequent follow-up for outcomes. Recent studies have

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**Table 2 – Methods used to assess CRF in the studies of the relationship of CRF and mortality.**

<table>
<thead>
<tr>
<th>Study</th>
<th>CRF Measure</th>
<th>Exercise Mode</th>
<th>Exercise Test Protocol</th>
<th>Measurement Method</th>
<th>Measurement Error (ml O₂ kg⁻¹ min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards et al.⁴²</td>
<td>Non-Ex Prediction Equation</td>
<td>n/a</td>
<td>n/a</td>
<td>Est. VO₂max: (age, sex, BMI, WC, RHR, PA)</td>
<td>SEE = 5.3 (F), 5.8 (M)</td>
</tr>
<tr>
<td>Holtermann et al.¹⁴</td>
<td>Non-Ex Prediction Equation</td>
<td>n/a</td>
<td>n/a</td>
<td>SRCF: 3 categories</td>
<td>n/a</td>
</tr>
<tr>
<td>Nes et al.¹⁷</td>
<td>Non-Ex Prediction Equation</td>
<td>n/a</td>
<td>n/a</td>
<td>Est. VO₂max: (sex specific: age, BMI or WC, PA index, RHR)</td>
<td>SEE = 5.70</td>
</tr>
<tr>
<td>Stamatakis et al.¹⁸</td>
<td>Non-Ex Prediction Equation</td>
<td>n/a</td>
<td>n/a</td>
<td>Est. VO₂max: (age, sex, BMI, RHR, PA)</td>
<td>SEE = 6.9</td>
</tr>
<tr>
<td>Jensen et al.¹⁵</td>
<td>Submaximal Ex test</td>
<td>Cycle ergometer</td>
<td>Astrand—submaximal</td>
<td>Est. VO₂max: Homogram W and HR</td>
<td>SEE = 5.7</td>
</tr>
<tr>
<td>Ladenvall et al.¹⁶</td>
<td>Submaximal Ex test</td>
<td>Cycle ergometer</td>
<td>Astrand—submaximal</td>
<td>Est. VO₂max: extrapolation measured VO₂ vs. HR</td>
<td>n/a</td>
</tr>
<tr>
<td>Park et al.³⁹</td>
<td>Submaximal Ex test</td>
<td>Cycle ergometer</td>
<td>Not described</td>
<td>Est. VO₂max: ‘skilled observer’</td>
<td>n/a</td>
</tr>
<tr>
<td>Sawada et al.⁴¹</td>
<td>Submaximal Ex test</td>
<td>Cycle ergometer</td>
<td>Graded to 85% APMHR</td>
<td>Est. VO₂max: Homogram W and HR</td>
<td>SEE = 5.7</td>
</tr>
<tr>
<td>ACLS/CCLS cohort⁹,¹¹,¹³,³³,³⁴</td>
<td>Maximal Ex test</td>
<td>Treadmill</td>
<td>Balke</td>
<td>Est. VO₂max: speed/grade or Est. CRF cohort-quintiles</td>
<td>SEE = 4.2 to 4.35</td>
</tr>
<tr>
<td>Dhoble et al.²⁰</td>
<td>Maximal Ex test</td>
<td>Treadmill</td>
<td>Bruce, Naughton, modified Naughton Bruce</td>
<td>FAC: actual/predicted TM time</td>
<td>n/a</td>
</tr>
<tr>
<td>HFH cohort¹⁹,²¹,³²,³⁵</td>
<td>Maximal Ex test</td>
<td>Treadmill</td>
<td>Bruce</td>
<td>Est. VO₂max: speed/grade</td>
<td>SEE = 4.2 to 4.35</td>
</tr>
<tr>
<td>Martin et al.²⁷</td>
<td>Maximal Ex test</td>
<td>Treadmill</td>
<td>Bruce</td>
<td>Est. VO₂max: Protocol specific equation using speed/grade</td>
<td>SEE = 4.92</td>
</tr>
<tr>
<td>Robsahm et al.³⁶</td>
<td>Maximal Ex test</td>
<td>Cycle ergometer</td>
<td>Begin at 100 W, 50 W/6 min stage Balke</td>
<td>Est. CRF as total work performed</td>
<td>n/a</td>
</tr>
<tr>
<td>Shah et al.²⁸</td>
<td>Maximal Ex test</td>
<td>Treadmill</td>
<td>n/a</td>
<td>Est. CRF as maximal test</td>
<td>n/a</td>
</tr>
<tr>
<td>VA cohort²²,²³,²⁶,³⁶,³⁷</td>
<td>Maximal Ex test</td>
<td>Treadmill</td>
<td>Individualized ramp, Bruce</td>
<td>50 W warm-up, 20 W/min VO₂max: CPX</td>
<td>n/a—CPX gold standard</td>
</tr>
<tr>
<td>Laukkanen et al.²⁶</td>
<td>Maximal Ex test</td>
<td>Cycle ergometer</td>
<td>50 W warm-up, 20 W/min</td>
<td>VO₂max: CPX</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Abbreviations: APMHR, age-predicted maximal heart rate; BMI, body mass index; CPX, cardiopulmonary exercise test; Ex, exercise; F, female; FAC, functional aerobic capacity; HR, heart rate; M, male; PA, physical activity; RHR, resting heart rate; SEE, standard error of estimate; VO₂, oxygen consumption; W, watts; WC, waist circumference.
extended the literature by examining CRF at various baseline ages and by attempting to establish age-specific cut points indicative of increased mortality risk. The CARDIA study estimated CRF in young adults (18–30 years) who were followed for over >25 years and reported that each additional minute attained during maximal treadmill testing (~1MET) was associated with a 15% reduction in all-cause mortality after adjusting for traditional risk factors and left ventricular mass.28 These findings further support the prognostic value of CRF even in young adulthood and highlight the importance of targeting structured exercise and/or lifestyle PA interventions to improve CRF earlier in life. Interestingly, improving CRF earlier in life may confer added mortality benefit as each 1-MET higher CRF is associated with a 15% reduction in mortality risk in men <60 years as compared with an 11% reduction per 1-MET in men ≥60 years.36 CRF has also emerged as a strong independent predictor of mortality in older men (65–92 years) as part of the Veterans Exercise Testing Study, in which each 1-MET higher CRF was associated with a 12% reduction in all-cause mortality.37 The greatest reduction in mortality risk was observed at a low absolute CRF level (5 METs), suggesting that those with the lowest CRF level will experience the greatest survival benefit by improving CRF. A larger cohort of the VA study established age-specific CRF thresholds for mortality risk in order to more appropriately account for the robust influence of age on CRF and improve its prognostic utility. Not surprisingly, the threshold CRF for mortality benefit decreased with age.36 Though the graded relationship between CRF and mortality was present across all age categories, the impact of low CRF may be greater at a younger age. Specifically, the least fit men in the <50 years and 50–59 years age groups had an ~80% higher mortality risk compared to the reference group while the least fit men in the 60–69 years and ≥70 years age groups had 48% and 30% higher mortality risks, respectively.36 The importance of CRF assessed at different ages (45 years, 55 years, 65 years) on lifetime risk of CVD mortality was examined in men as part of the Cooper Center Longitudinal Study.33 A graded inverse relationship existed between CRF and CVD mortality for each age group; however, the impact of high CRF on CVD mortality was greater at younger ages given that the risk of CVD mortality was 4-fold higher (13.7 vs 3.4%) in low versus high CRF groups when assessed at age 45 years. Further, this difference was 2-fold higher when CRF was measured at 55 years (34.2 vs 15.3% for low and high CRF, respectively) and 65 years (35.6 vs 17.1% for low and high CRF, respectively).33 Collectively, these studies support the prognostic value of a single CRF measurement at any point across the lifespan for all-cause and CVD mortality. However, the evidence presented in this update suggests a higher CRF at younger ages confers the greatest survival benefit.

Impact of CRF in diverse populations

The scope of investigation between CRF and mortality has been recently expanded to encompass more diverse subject populations varying in race, ethnicity, comorbidities, and specific causes of mortality. Race may account for up to 20% of the variance in CRF.35 Additionally, CRF is apparently higher in White compared to Black men and women35,44 though the inverse relationship between CRF and mortality is not influenced by race.32,45 Collectively, these data suggest that the potential beneficial effect of CRF on mortality is independent of sex and race.

CRF and disease-specific mortality

Historically, there has been an emphasis on CRF as a strong predictor of all-cause and CVD mortality, though recent work has examined the relationship between CRF and disease-specific mortality. Low CRF has been associated with an increased risk of incident cancer while the relationship with cancer mortality appears less studied. Nevertheless, high CRF has reportedly been linked with a lower cancer mortality in male Japanese,41 Korean39 and Norwegian46 cohorts. Similarly, Jensen et al.15 reported an inverse graded relationship between CRF and cancer mortality in Danish men followed for 42 years. Importantly, the relationship persisted after excluding men who died in the first 20 years of follow-up, minimizing the influence of reverse causation. Higher CRF measured in midlife has also been associated with a lower risk of death from cancer and CVD in men receiving a cancer diagnosis after age 65 years.34 Further, males with high CRF who developed cancer later in life demonstrated a 68% risk reduction in CVD mortality compared to those with low CRF.

CRF has also been linked with specific forms of CVD mortality such as sudden cardiac death and length of survival following a myocardial infarction (MI).11,24 Analysis of a large cohort of men and women from the ACLS showed that individuals with moderate and high CRF had 44% and 48% lower risk of sudden cardiac death, respectively, compared to those with low CRF.11 Further, each 1-MET improvement in CRF was associated with a 20% risk reduction in sudden cardiac death.11 CRF also appears to be beneficial for short-term survival after an MI as higher CRF was associated with reduced mortality at 28, 90, and 365 days post-event.24 Each 1-MET increase was associated with a ~10% reduction in mortality at each time point. Accordingly, these studies have expanded the cardioprotective impact of CRF on all-cause and CVD mortality by including specific causes of death.

Although CRF has been shown to be an independent predictor of several chronic diseases, recent work has examined the relationship between CRF and mortality outcomes in individuals with specific medical conditions, which represents an exciting area of growth in this field. Using data from the National Health and Nutrition Examination Survey (NHANES) cohort, each 1-MET increase in CRF estimated from non-exercise equations9 was associated with a 24% reduction in risk of all-cause mortality in individuals with an elevated gamma gap (≥3.1 g/dl) which may be indicative of infection, malignancy, or inflammatory disease.52 These findings suggest that CRF may be protective in the presence of novel biomarkers that are associated with a heightened risk of CVD and mortality. CRF has previously been associated with mortality in men with diagnosed T2D47,48 and this relationship has been expanded to show that CRF is a predictor of all-cause mortality in women with impaired fasting glucose or undiagnosed T2D.13 These findings suggest that CRF is a good prognostic tool for long-term outcomes among individuals early in the development of metabolic disease, supporting expansion of CRF assessment to other clinical settings (e.g., endocrinology). Similarly, moderate-to-high CRF is associated
with reduced mortality in patients with CHD, including those undergoing CR, even after adjusting for traditional risk factors, comorbidities, and disease severity. CRF, an integral component of Veterans Exercise Testing Study, has also been shown to be a strong independent predictor of all-cause and CVD mortality in patients with PAD. Collectively, these studies have expanded the prognostic value of CRF in healthy and unhealthy individuals, as well as populations with specific medical conditions and chronic diseases.

Changes in CRF and mortality

The relationship between CRF and mortality is most commonly evaluated using a single CRF assessment, usually during mid-life, which has shown strong prognostic potential. However, CRF likely changes across the lifespan as it is influenced by age, PA level and many lifestyle and health parameters, suggesting that a single measure is suboptimal for predicting long-term health outcomes. The impact of changes in CRF on mortality was initially reported by Blair and colleagues and recent investigations have used serial measures of CRF to examine its relationship with long-term outcomes. In a cohort of almost 10,000 men who performed two exercise tests on average 5 years apart at the Cooper Clinic, mortality rates were highest in men who were unfit (least fit quintile) at both time points and lowest in men who were fit (quintiles 2 through 5) at both examinations. Importantly, men who improved from unfit at the first assessment to fit at the second demonstrated a 44% lower all-cause mortality risk compared to those that remained unfit. Moreover, each additional minute of exercise time (Balke protocol) was associated with a 7.9% decrease in risk of mortality. These seminal findings support a cause-and-effect relation between improved CRF and reduced mortality, rather than merely an association between these variables, highlighting the potential survival impact of exercise/physical activity interventions. A similar design was used in a smaller cohort of older (mean age, 70 years) men from the Veterans Exercise Testing Study that had serial exercise tests performed every 4 years on average. After adjustment for traditional risk factors and compared to men who were unfit (≤5 METs) at both assessments, risk of all-cause mortality was 61% lower in men who remained fit (>5 METs), 41% lower in men that changed from fit to unfit, and 35% lower in men that were unfit and became fit. These data suggest that changes in CRF later in life can have a profound influence on mortality risk.

Shah et al. examined changes in CRF across a 7-year span in young adults (mean age, 25 years) who were followed for ~20 years after the second assessment. Each 1-minute reduction in exercise test duration (modified Balke treadmill test) between serial measures was associated with a 21% increase in all-cause mortality, with larger decreases in CRF being associated with further reductions in survival. The relationship between changes in CRF over time and mortality was most recently examined in a cohort (n = 579; age 51 years) of Finnish men that underwent maximal cycle ergometer testing on two occasions separated by 11 years and were then followed for 15 years for mortality outcomes. A novel methodological aspect of this study was that CRF was measured with the gold-standard method of CPX which provides a direct, quantitative measure of CRF. CRF, measured as VO_{2max} was on average 5.2 ml•kg\(^{-1}•\)min\(^{-1}\) (1.5 METs) lower at the second test and a graded relationship existed between the change in CRF and risk of all-cause mortality, whereby a smaller decrease in CRF was associated with a reduced risk. These data highlight the importance of promoting lifestyle factors to enhance or maintain CRF at any stage during the lifespan but particularly in early adulthood in order to reduce the risk of all-cause mortality.

There is ample evidence that changes in CRF over time, either increases or decreases, are associated with reciprocal changes in risk of mortality. These studies have examined CRF over relatively long durations (>4 years). Less is known about short-term (<1 years) changes, such as would occur in response to changes in PA patterns upon adoption of a structured exercise program or more physically active lifestyle. Martin and colleagues examined the impact of changes in CRF after a 12-week exercise-based cardiac rehabilitation program in a cohort of >5600 patients with known CVD. Overall, each 1-MET improvement in CRF following the CR program was associated with a 13% reduced risk of all-cause mortality. However, the salutary effect was most notable in the least fit (<5 METs) patient cohort, among whom each 1-MET improvement was associated with a 30% reduction in mortality risk. These data further support the beneficial impact of implementing exercise interventions in low-fit clinical populations. Additional studies are needed to clarify the influence of short-term changes in CRF on mortality in apparently healthy populations.

Importance of assessing CRF

The recently published AHA Scientific Statement made a compelling case for routinely assessing CRF and making it a clinical vital sign. Certainly, the update of research presented in this statement strongly supports the importance of assessing CRF. An approach that can be implemented immediately in clinical settings with information already available in electronic medical records is utilizing non-exercise prediction equations to obtain an estimate of CRF. Recently, results from a Web-based version of a non-exercise CRF estimator provided global estimates for >730,000 adults. Considerable evidence suggests that these estimated CRF values can identify those at increased risk of both all-cause and disease-specific, especially CVD-, mortality. However, strong consideration should be given to periodically obtaining a directly measured VO_{2max} from CPX as was recently recommended. The classic work of Wasserman et al. demonstrates how this single measure involves the integrative coordination of multiple physiological systems to consume and extract O\(_2\) from the environment, and transport it and nutrients to metabolically active tissues to perform work. Therefore, limitations in the pulmonary, CV, or neuromuscular systems resulting from disease and/or deconditioning will likely reduce CRF, which supports the value of CRF as the best single measure of overall health status. The commonly cited barriers suggesting that CPX requires expensive equipment and trained personnel are much less relevant than in the past. This is especially true when additional value-added features of CPX for both diagnostic and prognostic applications in varied patient populations are considered.
Conclusion

Numerous studies since 2009 overwhelmingly support the use and/or importance of CRF as an independent predictor of all-cause and disease-specific mortality in varied populations. However, additional research with CPX derived CRF in women and specific ethnic/racial groups worldwide is needed to aid in the identification of age, sex and race-specific normative data and threshold values to more accurately guide clinical decisions. Collectively, contemporary research further supports the widespread implementation of structured exercise and/or PA interventions\(^{58,59}\) to improve CRF across the lifespan, but particularly in early adulthood to enhance long-term survival.

Statement of conflict of interest

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

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