

**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 ($\text{VO}_{2\text{max}}$) 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.

Keywords: exercise, cardiovascular disease, aerobic capacity, $\text{VO}_{2\text{max}}$, physical activity

List of Abbreviations

ACLS - Aerobics Center Longitudinal Study

AHA – American Heart Association

BMI- Body mass index

CPX – Cardiopulmonary exercise testing

CHD – Coronary heart disease

CR – Cardiac rehabilitation

CRF – Cardiorespiratory fitness

CV – Cardiovascular

CVD – Cardiovascular disease

HFH - Henry Ford Hospital

MET - Metabolic equivalent

MI - Myocardial infarction

NHANES - National Health and Nutrition Examination Survey

O₂ – Oxygen

PA – Physical Activity

PAD - Peripheral arterial disease

T2D – Type 2 diabetes

UK – United Kingdom

VA - Veterans Affairs Medical Centers

VO_{2max} – maximal oxygen consumption; aerobic capacity

Cardiorespiratory fitness (CRF), also known as aerobic capacity (i.e., $\text{VO}_{2\text{max}}$), was initially described by Hill and Lupton 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.¹ 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 all-cause mortality, which was independent of sex and persisted after adjustment for traditional cardiovascular (CV) disease (CVD) risk factors (e.g., age, blood cholesterol, blood pressure, obesity, smoking status, family history, blood glucose and type 2 diabetes/T2D). Another notable finding was that the largest reduction in all-cause mortality occurred between the lowest and next lowest CRF quintiles, suggesting that the least fit cohort could receive the greatest survival benefit by increasing CRF. After more than two decades of additional research, this association was confirmed and extended by Kodama et al. in a meta-analysis of 33 investigations which included 102,980 healthy men and women,⁷ indicating that higher CRF was 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. Since this meta-analysis, there have been numerous additional studies that have further clarified

the relationship between CRF and mortality and morbidity. A recent scientific statement by the American Heart Association (AHA) put forth a compelling case for CRF as a vital sign.⁸

Although we are not yet to the point where there is global recognition that PA and exercise are medicine and CRF is a primary means to assess baseline status, future health trajectory, and therapeutic efficacy of a PA prescription, the evidence continues to grow. Therefore, 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.

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**.

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 referred for diagnostic exercise testing.¹⁹⁻²⁴ 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.²⁴⁻²⁷

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.⁷ 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.^{10,19,22} 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,¹⁴⁻¹⁷ the study population from Canada (Calgary) was presumed to be 80% White,²⁷ 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.²⁸ Mortality follow-up periods began at 1-year for the majority of studies and ranged between 10 to 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.²⁹⁻³¹ The gold standard method is cardiopulmonary exercise testing (CPX) with directly measured $\text{VO}_{2\text{max}}$, which has a known biological variability of 3-4%.³⁰ 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.²⁵ Although this demonstrates the need for future studies using directly measured $\text{VO}_{2\text{max}}$, it underscores how consistent and powerful CRF is as a forecaster of mortality given 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.³¹ 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.^{10-13,19,21-24,32-37} 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.³⁸ 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 $\text{VO}_{2\text{max}}$ from test duration.^{20,27,28} Submaximal exercise testing has also been used, typically

during cycle ergometry, to predict $\text{VO}_{2\text{max}}$.^{15,16,39} Additionally, estimating CRF from non-exercise prediction equations^{17,18,40} or self-reported CRF¹⁴ 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 $7.0 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Table 2).

Recent Advances

Numerous studies since the Kodama et al.⁷ 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.^{15,16,28,33,41} Jensen and colleagues¹⁵ 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).¹⁶ 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^{9,14,18,26,28,33,34} 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 VO_2 ($\text{L}\cdot\text{min}^{-1}$) rather than the more commonly used and preferred expression of VO_2 relative to body weight ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). 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 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 women;⁷ 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 independently^{13,14,18,19} 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. 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.¹⁹ 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 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.⁴³ Additionally, CRF is apparently higher in White compared to Black men and women^{32,44} 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 a 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 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.⁴² 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 T2D^{47,48} 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,⁴⁹ including those undergoing CR, even after adjusting for traditional risk factors, comorbidities, and disease severity.^{27,50,51} 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.²⁶ 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 colleagues⁵² 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.⁵² 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.³⁷ 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.³⁷ These data suggest that changes in CRF later in life can have a profound influence on mortality risk.

Shah et al.²⁸ 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.²⁸ 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.²⁵ 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 $\text{VO}_{2\text{max}}$, was on average $5.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (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 colleagues²⁷ 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.⁵³ 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.⁸ 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.⁵⁴ Considerable evidence suggests these estimated CRF values can identify those at increased risk of both all-cause and disease-specific, especially CVD-, mortality.^{9,17,18,40} However, strong consideration should be given to periodically obtaining a directly measured $\text{VO}_{2\text{max}}$ from CPX as was recently recommended.⁸ The classic work of Wasserman⁵⁵ 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 of patient populations are considered.^{56,57}

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.

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Table 1. Characteristics of the populations followed to assess the relationship of CRF and mortality.

Study	Cohort	Participants	Baseline Health / Age (y)	Sex (n, %F)	Country	Racial/Ethnic	Follow-up Time Average & [range] (y)	Mortality Type
*Al-Mallah ¹⁹	Henry Ford Exercise Testing Project	Referred for exercise testing	CVD risk factors/ 52.8±12.7 M, 54.0±12.4 F	57,284 (49%)	US	M: 68% W, 24% B, 8.1% O, F: 60% W, 34% B, 6% O	median: 10 [0.1 – 22]	all-cause
Dhoble ²⁰	Mayo Clinic	Referred for exercise testing	No CVD or cancer / 49.3 (range 25-85)	6,514 (42%)	US	81% W, 19% O	8.1± 3.7 [1-15]	all-cause & CVD
Edwards ⁴²	NHANES	Health study participants	39.9 / (range 20-85)	9251 (49.7%)	US	70% W	median: 8.9 [5-12]	all-cause
**Farell ¹⁰	CCLS	Self-referred	No CVD / 44.8± 9.6	66,371 (25.7%)	US	90% W, 10% O	16.7± 9 [2-37]	CVD
Holtermann ¹⁴	Copenhagen City Heart Study	Random sample of adult population living in Copenhagen	No CVD / 3 groups: 46.8, 41.5, 41.5	8,936 (57%)	Denmark	100% W	median: 19.1 all-cause [1-20], 17.9 CVD mortality [1-22]	all-cause & CVD
Jensen ¹⁵	Copenhagen Male Study	Recruited men from 14 worksites	No Cancer / 48.8 y± 5.4y	5131 (0%)	Denmark	100% W	28.3 ± 11.4 all-cause [0-40], 28.0± 11 cancer [0-44]	all-cause & cancer
**Jimenez-Pavon ¹¹	ACLS	Self-referred	No CVD / 44.2 ± 10 (range: 20-	55,456 (24.4%)	US	90% W, 10% O	14.7 [1-29]	Sudden cardiac death

			100)					
*Kokkinos ²²	Veterans Affairs Medical Centers	Referred for exercise testing	No CVD / 58.2± 11	20,590 (37%)	US	63% B, 37% W	11.9±7.5 [.3-33]	Major adverse cardiac events, including fatal
Ladenvall ¹⁶	Gothenburg	Men from Gothenburg that were born in 1913	No previous MI or locomotor disturbances / 54	792 (0%)	Sweden	100% W	Group I: 25 ± 9.6; II: 25.6± 9.7; III: 27.5± 10.0 [0-45]	all-cause & CVD
Laukkanen ²⁵	Kuopio IHD risk factor study	Randomly selected men from this study group	17.9% IHD, 2.6% diabetes / 50.7±6.7 (range 42 to 60)	579 (0)	Finland	100% W	median: 13.3 [0-15]	all-cause
Martin ²⁷	APPROACH CANADA	Referred to Cardiac Rehab, Cardiac Wellness Institute of Calgary	CAD / 60± 10.3	5,641 (24%)	Canada	80% W, 20% O	n/a [1-14]	all-cause
Nes ¹⁷	HUNT	Residents of Nord-Trondelag county > 20y of age who participated in the HUNT survey.	No CVD or physical disability / 43.5±15.9 M, 44.1±16.3 F	37,112 (51%) / 43.5±15.9 M, 44.1±16.3 W	Norway	97% W	24± 5.9 [n/a]	all-cause & CVD

Park ³⁹	Health promotion center at Seoul National University Hospital	Men completed a medical check-up and graded exercise test	No MI, stroke, or Cancer / 55.7 \pm 11.1	18,775 (0%)	Korea	100% A	6.4 [0-10]	all-cause, CVD, & cancer
Robsaahm ⁴⁶	Oslo Ischemic Study	Invited from 5 companies practicing annual or biannual health exams	No CVD, cancer, other chronic disease or conditions / 49.3 (37-62)	2341 (0%)	Norway	100% W	26.2 [n/a]	cancer
Shah ²⁸	CARDIA	Balanced enrollment across 4 sites by sex, age, race, and education.	No CVD / 24.8 \pm 3.6 (18-30)	4,872 (54%)	US	51% B, 49% W	median: 26.9 [n/a]	all-cause
Sawada ⁴¹	Tokyo Gas Co.	Male employees-completing annual health exams	No CVD, cancer, other chronic disease or conditions / 35y (19-59)	8760 (0%)	Japan	100% A	20.2 [n/a]	all-cause & cancer
Stamatakis ¹⁸	Participants of England or Scottish Health Survey	Health survey participants	No CVD / ~50 M, ~51 F (35-70)	32,319 (55%)	England and Scotland	90% W, 10% O	9 \pm 3.5 [n/a]	all-cause & CVD

Abbreviations: A-asian, B-black, CVD-cardiovascular disease, F-female, IHD-ischemic heart disease, M-male, MI-myocardial infarction, O-other, W-white

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

** The largest of these 2 studies was used for the racial/ethnic summary calculations

Data are expressed as mean \pm SD unless otherwise noted

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

Study	CRF measure	Exercise Mode	Exercise Test Protocol	Measurement Method	Measurement Error (ml O₂•kg⁻¹•min⁻¹)
Edwards et al. ⁴²	Non-Ex Prediction Equation	n/a	n/a	Est. VO _{2max} : (age, sex, BMI, WC, RHR, smoke, PA)	SEE= 5.3 (F), 5.8 (M)
Holtermann et al. ¹⁴	Non-Ex Prediction Equation	n/a	n/a	SRCF: 3 categories	n/a
Nes et al. ¹⁷	Non-Ex Prediction Equation	n/a	n/a	Est. VO _{2max} : (sex specific: age, BMI or WC, PA index, RHR)	SEE= 5.70
Stamatakis et al. ¹⁸	Non-Ex Prediction Equation	n/a	n/a	Est. VO _{2max} : (age, sex, BMI, RHR, PA)	SEE= 6.9
Jensen et al. ¹⁵	Submaximal Ex test	Cycle ergometer	Astrand - Submaximal	Est. VO _{2max} : nomogram W and HR	SEE=5.7
Ladenvall et al. ¹⁶	Submaximal Ex test	Cycle ergometer	Astrand - Submaximal	Est. VO _{2max} : extrapolation measured VO ₂ vs. HR	n/a
Park et al. ³⁹	Submaximal Ex test	Cycle ergometer	not described	Est. VO _{2max} : 'skilled observer'	n/a
Sawada et al. ⁴¹	Submaximal Ex test	Cycle ergometer	Graded to 85% APMHR	Est. VO _{2max} : nomogram W and HR	SEE=5.7
ACLS/CCLS Cohort ^{9,11,13,33,34}	Maximal Ex test	Treadmill	Balke	Est. VO _{2max} : speed/grade or Est. CRF cohort-quintiles	SEE= 4.2 to 4.35
Dhoble et al. ²⁰	Maximal Ex test	Treadmill	Bruce, Naughton, modified Naughton	FAC: actual/predicted TM Time	n/a
H Ford Cohort ^{19,21,32,35}	Maximal Ex test	Treadmill	Bruce	Est. VO _{2max} : speed/grade	SEE= 4.2 to 4.35
Martin et al. ²⁷	Maximal Ex test	Treadmill	Bruce	Est. VO _{2max} : protocol specific equation using	SEE= 4.92

				speed/grade	
Robsaahm et al. ⁴⁶	Maximal Ex test	Cycle ergometer	Begin at 100 W, 50W/6 min stage	Est. CRF as total work performed	n/a
Shah et al. ²⁸	Maximal Ex test	Treadmill	Balke	Est. CRF as maximal test time	n/a
VA Cohort ^{22,23,26,36,37}	Maximal Ex test	Treadmill	Individualized ramp, Bruce	Est. VO _{2max} : speed/grade	SEE= 4.2 to 4.35
Laukkanen et al. ²⁵	Maximal Ex test	Cycle ergometer	50W warm-up, 20W/min	VO _{2max} : CPX	n/a - CPX Gold Standard

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