The relationship between cardiorespiratory fitness, cardiovascular risk factors and atherosclerosis

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Recommended Citation
Review article

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HIGHLIGHTS

- This review summarized the data on the favorable effects of cardiorespiratory fitness on cardiovascular risk factor burden (hypertension and diabetes).
- High cardiorespiratory fitness is associated with reduced atherosclerosis burden and decreased, and adverse cardiovascular outcomes.
- Cardiorespiratory fitness should be a useful aid to estimate and potentially reclassify risk of atherosclerotic cardiovascular events.

ARTICLE INFO

Keywords:
Cardiorespiratory fitness
Cardiovascular risk factors
Atherosclerosis
Stress testing
METS

ABSTRACT

Cardiorespiratory fitness (CRF) refers to the ability of the cardiopulmonary system to supply oxygen to skeletal muscles during exercise. Regular physical activity optimizes these systems by physiologic means that not only decrease cardiovascular risk factors but also independently affect mortality. Importantly, CRF is an integrative measure of the effects of its upstream risk factors including physical activity and genetics.

In this review, we summarize the main methods that are frequently used to estimate CRF. We cite findings from the major studies on CRF, which demonstrate a beneficial effect on prevalent cardiovascular risk factor burden, subclinical atherosclerosis, and incident adverse outcomes including death, myocardial infarction, stroke, and cancer. We conclude by suggesting the incorporation of CRF into clinical decision-making given the prognostic information it provides.

1. Introduction

Cardiorespiratory fitness (CRF) is a physiologic measure that reflects the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during exercise [1]. As opposed to "physical activity" which is usually a self-reported means of determining energy expenditure and therefore is subject to bias, CRF is an objective measurement. Importantly, it integrates the effects of its determinants which include age, sex, physical activity, and genetics. Genetics are thought to contribute to 25–40% of CRF and it is assumed physical activity makes up for the remaining [2]. CRF is also a reflection of risk factor and disease burden across an individual's lifespan and thus the level of physical activity required to improve CRF is dependent on the initial health of the individual. Numerous studies have shown higher CRF to have a significant protective effect on overall mortality. Its benefit is related to both an attenuation in traditional risk factors and positive influences on an individual's vascular, hematologic, immunologic and nervous systems [3–5]. As such, CRF can be used as a risk biomarker with the potential to inform clinical decision making.

In this review, we summarize methods that are commonly used to measure CRF. We discuss studies evaluating the association of CRF with both prevalent and incident cardiovascular risk factors. We then cite major studies demonstrating a relationship between CRF and prevalent and incident subclinical atherosclerosis, as well as incident adverse outcomes including death, myocardial infarction, stroke, and cancer (Fig. 1).
2. Cardiorespiratory fitness

2.1. Definition

CRF reflects the ability of the heart and lungs to efficiently deliver oxygenated blood to meet the metabolic demands of working muscles during exercise. The gold standard for evaluating CRF is measured maximal oxygen uptake (VO2 max) which is the maximum amount of oxygen a person can consume during exercise [1]. Patients are typically tested on a treadmill or bicycle ergometer using an incremental protocol that progresses from submaximal to maximal effort. VO2 max is often expressed as milliliters of oxygen per kg of body mass per minute [6]. Thus, if an individual loses weight, the VO2 may increase solely due to the weight loss, but the absolute VO2 expressed as L/min might not change. Therefore, VO2 can also be expressed as L of oxygen per minute. When a maximum effort is not possible VO2 max may be estimated based on peak workload achieved (e.g., speed and incline achieved on treadmill), called ‘VO2 peak.’ When estimated, CRF is typically expressed in metabolic equivalents of task (MET) where 1 MET is an estimate of resting oxygen consumption defined as 3.5 mL/kg/min [6,7].

2.2. Measures of fitness and physical activity

There are numerous types of fitness (e.g., cardiorespiratory, strength, balance) and methods to assess each. Interestingly, despite which might be the “best” measure of fitness, even the simplest has been shown to categorize risk. For example, the ability to transition from a cross-legged, seated position on the floor to standing was associated with improved survival in older adults [8]. In a separate study, the ability to perform pushups was inversely associated with incidence of CVD among male firefighters [9]. Each of these tasks is associated with musculoskeletal strength and balance. Individuals with better strength and balance likely have better cardiorespiratory fitness. These types of assessments are not common in medicine. In this section, we briefly contrast measures of fitness in clinical settings.

Maximal oxygen uptake (VO2max) determined from indirect calorimetry (e.g., respiratory gas analysis) measured during a sign and symptom-limited maximal exercise test is the gold standard method to assess cardiorespiratory fitness [10]. It requires a metabolic cart and staff trained in test conduct and data interpretation. This equipment is not common outside of tertiary care heart failure centers, pulmonary function testing laboratories, and human performance laboratories. In the absence of measured VO2max, exercise duration on a given exercise testing protocol or peak workload achieved are frequently used to estimate VO2max. When estimating VO2max this way, it is best practice to describe fitness in metabolic equivalents of task (METs), where 1 MET is an estimate of oxygen consumption at rest (i.e., 3.5 mL O2 per min per kg body mass) [11]. Estimates tend to over predict measured VO2 [10]. This is especially true for treadmill-based protocols where handrail support reduces the external workload [10]. Much of the research related to exercise capacity and prognosis in heart failure is based on measured VO2. However, larger cohort studies like the ones discussed earlier, often use estimated METs. For instance, data from the Aerobics Center Longitudinal Study (ACLS) is based on exercise duration and data from the Henry Ford Exercise Testing Project (the FIT project) is based on peak workload. In spite of the different methods, study results are complimentary.

There are several measures of the physiologic response to acute exercise that are available from a maximal exercise test beyond exercise capacity, such as post-exercise heart rate or oxygen uptake recovery. It is important to note that these additional measures are not surrogates for exercise capacity. While there are several within-person adaptations that are observed in response to an exercise training program, such as lower heart rate at rest and faster recovery heart rate, these responses are not associated with difference in fitness between individuals [12]. In addition to maximal exercise capacity, tests of submaximal exercise capacity are often used. One example that is frequently used is the 6-min walk test (6MWT), which was based on field tests (e.g., Cooper 12-min run test) that were popular through the 1980s [13]. Distance achieved during the 6MWT is a frequently used measure in patients with pulmonary disease, heart failure, and peripheral vascular disease [12]. Advocates state it is a better assessment of an individual’s ability to perform activities of daily living than a test that requires maximal effort. Distance walked during the 6MWT is only modestly correlated with VO2max [12].

Finally, several surveys have been developed to estimate fitness or physical activity. In contrast to fitness (a physiologic construct), physical activity is a behavior. Increasing physical activity, especially through structured exercise training, is associated with improved fitness [12]. However, physical activity is just one determinant of fitness; others include age, sex, body mass, and genetics [15]. Self-reported physical activity has been shown to be related to outcomes separate from measures of fitness [10]. Consumer wearable devices (e.g., Apple Watch, FitBit) use proprietary methods to measure physical activity and estimate fitness. The clinical utility of these measures from these devices is unclear.

3. CRF and atherosclerotic CV risk factors

3.1. Hypertension (prevalence and incidence)

Hypertension affects 46% of all Americans [17]. It is a major risk factor for cardiovascular disease and thus has been a primary focus of prevention [18]. Several studies have demonstrated a relationship between fitness and baseline or incident hypertension [19–21].

In 1976, Cooper et al. examined the relationship between CRF and cardiovascular disease risk factors [22]. The study examined 3000
individuals (100% men, average age 45 years, predominantly white, middle-to-upper socioeconomic class) from Cooper Clinic, a preventive medicine practice located in Dallas, Texas. CRF was evaluated by maximal treadmill stress test (Balke protocol). Participants were divided into categories of fitness (very poor, poor, fair, good, and excellent) based on age-adjusted treadmill times established by percentile norms developed previously at the Institute for Aerobics Research in 1974 [23,24]. Overall, there was an inverse relationship between CRF and cardiovascular risk factors, including prevalent hypertension.

In another study using the Henry Ford Exercise Testing (FIT) Project, Juraschek et al. studied the relationship between fitness and prevalent and incident hypertension [25]. The FIT cohort included a large cohort who underwent physician-referred treadmill stress testing between 1991 and 2009 within the Henry Ford Health System in the Greater Detroit area in Michigan [26]. The study cohort included 35,175 patients with a history of hypertension and 22,109 patients without hypertension. CRF was evaluated using Bruce protocol stress testing [27]. In the multivariate analysis, there was a strong inverse association between peak METs achieved and risk of incident hypertension (p < 0.001) over a median follow up 4.4 years (Fig. 2). Those who achieved ≥12 METs had a 20% lower risk of incident hypertension compared to those with <6 METs (HR 0.80; 95% CI: 0.72, 0.89; ARR 28%). The study also demonstrated a reduction in prevalent hypertension with higher levels of fitness [28].

Of note, prior studies that have examined the association between CRF and hypertension may have had residual confounding given that not all factors may have been accounted for. In comparison, the study by Juraschek et al. adjusted for several variables including demographic variables, cardiovascular risk factor burden, medication use, indication for stress testing, as well as stress test parameters. However, while these are important factors to account for, they are certainly not comprehensive. Adherence to antihypertensive medication was not adjusted for, thereby raising the possibility of residual confounding in this analysis.

### 3.2. Diabetes mellitus

There have been several studies aimed at establishing the link between CRF and metabolic syndrome and diabetes [29–31]. Orakzai et al. investigated the relationship of fitness levels and metabolic syndrome components [32]. The study took place at a single center in Brazil and included a sample of 559 patients all of whom were men with mean age 47 years. Compared to high CRF, patients with low CRF had a relative risk 11.8 (p < 0.0001; ARR 16%) of ≥3 metabolic syndrome risk factors.

Another analysis by Juraschek et al. using the FIT cohort investigated the association between CRF and the development of diabetes [33]. In this study, 46,979 participants without diabetes (mean age 53 years, 52% men, 27% black) were included. The unadjusted cumulative incidence rates were 19.5%, 15.6%, 10.4%, and 5.2% for METs <6, 6–9, 10–11, and ≥12 respectively. The ARR for <6 and ≥12 METs was therefore 14.3%. In adjusted analyses, those who achieved ≥12 METs had a 54% lower risk of developing diabetes (median follow-up 5.2 years) when compared to individuals who achieved <6 METs (HR 0.46, 95% CI 0.41, 0.51) (Fig. 3). Patients who achieved 1 additional MET demonstrated an 8% lower risk of incident diabetes after adjustment for covariates (HR 0.92; p < 0.001). In a study utilizing machine learning, a self-learning data analysis technique with proven applications in medicine, Sakr et al. specifically analyzed the FIT dataset. Using this technique, similar findings were confirmed with higher overall prediction [34].

Given prior studies which had demonstrated a modest rise in diabetes incidence among statin users, a study using data from the FIT project aimed to describe this relationship in conjunction with CRF. Shaya et al. examined the association between CRF and incident diabetes in patients on statin therapy [35]. The analysis was adjusted for demographic characteristics, co-morbid conditions, medications, and indication for stress test. Overall, the study found higher exercise capacity to be associated with a significantly reduced risk of incident diabetes mellitus (ARR 23% over 10 year follow up when comparing <6 METs to ≥12 METs). Results were significant among statin users and non-users with a risk reduction of 6% and 8%, respectively, per 1 additional MET achieved; p < 0.001. Thus, the study concluded that higher CRF is associated with reduced risk for incident diabetes regardless of statin use.

Of note, the study did not fully consider individuals that may...
in the current era, one in two Americans have a lipid abnormality, with roughly 6 in 100 suffering from the lipid triad (low HDL-cholesterol, elevated triglycerides, and elevated small and dense LDL-cholesterol particles) [39]. Numerous epidemiologic studies have described an association between lipid abnormalities and cardiovascular disease [40,41]. In addition, there have since been studies geared toward establishing the link between CRF and dyslipidemia as well.

In one study using the ACSL patient registry, Breneman et al. examined the association of fitness and importantly, change in fitness over time, with dyslipidemia [42]. The study included 9651 patients who were healthy at baseline and underwent two separate maximal treadmill stress tests over a mean duration of two years. A high baseline fitness was associated with lower risk of dyslipidemia (HR 0.57, 95% CI 0.37, 0.89) but this was no longer significant after adjusting for baseline lipid levels (HR 1.03, 95% CI 0.65, 1.64). Participants who maintained their fitness level over time had a 43% lower risk of developing atherogenic dyslipidemia compared to those whose fitness level decreased (OR 0.56; 95% CI 0.34, 0.91; ARR 0.74%). Similar findings were shown in the FIT project too [43].

In addition, there has been a concern whether the use of statins with associated myalgias may be associated with decreased fitness levels. Some previously published studies have suggested that statin use was associated with a decrease in physical activity [44]. Given the link between physical activity and CRF, Quereshi et al. used data from the FIT project to assess whether statin use was associated with CRF [45]. The authors found that statin use was associated with higher METs in both men (METs as a continuous variable; β coefficient = 0.27, 95% CI = 0.15, 0.38) and women (β coefficient = 0.13, 95% CI = 0.03, 0.23). Men and women on statins were more likely to achieve ≥10 METs. Though this suggests that patients on statin therapy may not experience a decrease in physical fitness due to statin therapy, this was only an observational study.

3.3. Dyslipidemia

Coronary artery atherosclerosis, measured using coronary artery calcium (CAC), is an independent risk factor for overt cardiovascular diseases and is used clinically to stratify patients’ atherosclerotic cardiovascular disease (ASCVD) risk [46,47]. Numerous studies have demonstrated that objectively measured CRF is associated with a reduced CAC burden and with cardiovascular disease risk reduction [48]. However, prior studies have not examined the interaction between CAC and CRF and whether high CRF can mitigate the effect of high CAC score.

Choi et al. utilized the Korea Initiatives on Coronary Artery Calcification (KOICA) registry to assess the association of exercise capacity and CAC score with all-cause mortality [49]. This was a retrospective study that included 25,972 Korean individuals (mean age 54 years, 81% men). Each participant in the study was self-referred and asymptomatic at the time of referral. CRF was assessed using maximal treadmill stress test by Bruce protocol. In multivariate analysis, METs ≥10 was inversely associated (HR 0.68, 95% CI 0.48–0.97) with risk of all-cause mortality and CAC ≥400 was directly associated (HR 3.33, 95% CI 1.85–5.99) with mortality risk. Among patients with high CAC score (≥400), effect estimates were approximately 3 times higher among those with poor CRF; HR 3.33 (95% CI 1.85–5.99) in <10 METs vs. 1.11 (95% CI 0.51–2.40) in ≥10 METs, p for interaction = 0.024). The results imply that CRF may attenuate the effect of high CAC scores on mortality in an asymptomatic population.

Interestingly, though regular physical exercise improves overall cardiometabolic health, prior studies have demonstrated an association between vigorous exercise and coronary heart disease events due to advanced coronary arteriosclerosis. Thus, it is speculated that higher physical activity and CRF are associated with a lower risk of developing atherogenic dyslipidemia among women or individuals with a BMI 30 kg/m². The authors’ hypothesis is supported by several studies, but some studies have not revealed significant results. However, a meta-analysis by Tian et al. [31] concluded that a combination of higher CRF and higher BMI is associated with increased coronary artery calcium burden compared to lower CRF and lower BMI. This suggests that the association between CRF and CAC may be confounded by BMI, which is a risk factor for both CRF and CAC.

Lipid metabolism and thus lipid lowering therapy in high BMI in-vivo studies. However, in-vivo studies have shown that statins metabolize statins more efficiently, rather than having an effect on CRF. Moreover, statins may not be as effective in obese patients as they are in non-obese individuals. The authors’ hypothesis is supported by several studies, but some studies have not revealed significant results. However, a meta-analysis by Tian et al. [31] concluded that a combination of higher CRF and higher BMI is associated with increased coronary artery calcium burden compared to lower CRF and lower BMI. This suggests that the association between CRF and CAC may be confounded by BMI, which is a risk factor for both CRF and CAC.

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Fig. 3. Interactive effect of exercise capacity and revascularization status on outcomes. (A–C) Adjusted hazard ratios (HR) for all-cause mortality, myocardial infarction (MI), and downstream revascularizations, respectively, relative to the < 6 metabolic equivalents (METS) non-revascularized group. PCI, percutaneous coronary intervention; CAGB, coronary artery bypass graft surgery. Adapted with permission from [61].
than expected CAC burden in endurance athletes confers a higher risk of cardiovascular disease [50]. The Marathon study took place in Germany and examined the relationship between marathon running and burden of cardiovascular risk factors, prevalent subclinical atherosclerosis, and risk of ASCVD events among high level athletes [51]. Using this cohort, Möhlenkamp et al. studied 108 healthy marathoners (mean age 57 years, all men) who completed > 5 marathons in the prior three years [52]. Cardiovascular disease events were the primary outcome of interest, ascertained by follow-up questionnaires and in-person communication and confirmed with hospital records. Control groups were matched by FRS and age from a separate study (Heinz Nixdorf Recall Study) [53]. CAC distribution was similar in marathon runners and age-matched controls (median CAC 36 vs. 38, p = 0.36), whereas CAC levels in marathon runners were higher than among Framingham risk score-matched controls (p = 0.02). CAC score and number of marathons completed each were independently associated with myocardial late gadolinium enhancement (p = 0.02 for both). Event-free survival was inversely related to CAC level (ARR 14.3% for CAC < 100 compared to CAC ≥ 400; p = 0.018). In adjusted analyses, there was an incremental higher risk of myocardial scarring with higher CAC scores. When compared to a CAC score of 0, risk of myocardial scarring was 1.85 (95% CI 1.23, 2.78) for CAC score of 1–99, 2.87 (95% CI 1.9, 4.33) for CAC 100–399, and 6.06 (95% CI 4.09, 8.96) for CAC ≥ 400. The study demonstrated a correlation between frequent marathon running, CAC burden, and subclinical myocardial damage which may potentially confer a higher than expected risk of coronary events. It also suggested that standard cardiovascular risk stratification models underestimate CAC burden, and clinicians should take this into consideration when providing care for vigorous runners.

In another study, Rudolf et al. evaluated the association of CRF and CVD events stratifying by CAC [54]. The study cohort consisted of participants from the ACLS registry. Total CVD incidence rate was 1.3 per 1000 person-years in patients without CAC as compared to 18.9 per 1000 person-years among those with CAC > 400 (p < 0.001). In adjusted analyses, HR (95% CI) of CVD were 1.85 (95% CI 1.23, 2.78) for CAC 1–99, 2.87 (95% CI 1.9, 4.33) for CAC 100–399, and 6.06 (95% CI 4.09, 8.96) for CAC > 400. Each additional MET achieved was associated with an 11% lower risk of CVD events (95% CI 0.84–0.94). Importantly, there was no significant interaction between CRF and CAC implying that the benefits of CRF are similar across all CAC levels.

3.5. Increased fitness and risk of death

There is mounting evidence that low CRF is associated with all-cause mortality and cardiovascular death. The beneficial effects of CRF begin at > 10 METs [6,55]. One meta-analysis of observational studies from 1966 to 2008 demonstrated that every additional MET achieved on exercise stress testing was associated with a 13% (95% CI 10,16) lower risk of all-cause mortality and 15% (95% CI 12,18) lower risk of cardiovascular death [56].

As CRF is modifiable, there have been studies designed to specifically assess the impact of longitudinal change in CRF over time. Prestgaard et al. evaluated the effects of change in fitness over time with stroke risk and mortality [57]. The authors used data from the Oslo Ischemia study, which recruited 2314 men with a mean age of 49 years old in Oslo, Norway during 1972–1975. Participants were classified into (1) became fit, (2) remained fit, (3) became unfit, and (4) remained unfit categories depending on their results. In regards to mortality, the study found that among individuals with high baseline CRF, those who became unfit had significantly higher risk of death when compared with those who remained fit (HR 1.74; 95% CI 1.35–2.23; ARR 16.4%). In individuals with low baseline CRF, those who became fit had significantly lower risk of death than those who remained unfit (HR 0.66; 95% CI 0.50–0.85; ARR 16.8%). The results stress the importance of fitness attainment and fitness maintenance in reducing overall mortality. Similar findings were replicated from the FIT project [58,59].

3.6. Fitness and coronary artery disease

Of additional interest is the impact of CRF on the development of coronary heart disease (CHD), and similarly whether CRF improves current risk stratification models for CHD. With this in mind, Gander et al. examined the association between CRF and coronary heart disease (CHD) events in the ACLS patient database [60]. Individuals included in the analysis were free of baseline CHD and were followed for 12 years. CHD events included self-reported myocardial infarction, revascularization or CHD death. The authors showed that both CRF and Framingham risk score were independent predictors of coronary heart disease. Men with high CRF had 33% lower risk of CHD events compared to men with low CRF (HR 0.67; 95% CI 0.64, 0.88; ARR 10%). Among men with moderate-to-high risk of CHD, high CRF was associated with a 26% lower risk of CHD events (HR 0.74; 95% CI 0.56, 0.98; ARR 17.9%). Despite these results, sensitivity analyses demonstrated that CRF did not improve the discrimination of incident CHD when added to the Framingham risk score (area under the curve, 0.80, p = 0.97). Thus, it did not add to the predictive power of the Framingham risk score for 10-year CHD risk.

Even among patients with known coronary atherosclerosis and overt coronary artery disease, multiple studies have demonstrated that high CRF protects against additional cardiovascular disease events [61].

In one such study, using data from the Cardiovascular and Cardiorespiratory Adaptations to Routine Exercise-based Cardiac Rehabilitation study (CARE CR), Nichols et al. aimed to study the association of CRF and cardiometabolic risk and 5-year mortality in patients with preexisting coronary artery disease [62]. The study cohort included 70 patients with coronary artery disease categorized as having high, moderate, or low CRF based on VO2 measurement during cardiopulmonary exercise testing. Estimated 5-year mortality was highest in the low CRF group (14.9; 95% CI 11.4, 18.5%). These results suggest that patients with CHD and low CRF have a high mortality risk. As such, in patients with low CRF and CHD, improvements in CRF using cardiac rehabilitation may help to lower mortality risk.

A similar analysis from the FIT project included 9852 adults with known CAD who underwent physician-referred treadmill stress testing [43]. There were 3824 all-cause deaths during a mean follow-up of 11.6 ± 5 years. Each 1-MET increment was inversely associated with mortality risk with a HR of 0.87 [95%CI 0.85–0.89] for non-revascularized patients, 0.87 [0.85–0.90] for revascularized patients using percutaneous coronary intervention, and 0.86 [0.84–0.89] for patients who underwent coronary artery bypass surgery. Within each MET category, there were no significant differences in mortality risk between revascularization groups (Fig. 4).

In another study from the FIT project, Shaya et al. examined the impact of CRF on early mortality after a first myocardial infarction [63]. In this sub analysis, 2061 participants without prior history of MI (mean age 62 years, 38% women, 58% white) were included. As compared to individuals who achieved < 6 METs, those with ≥ 12 METs had lower risk of early mortality at 28, 90, and 365 days (ARR 7.9%, 15.2%, 20.8%, respectively). Each additional 1 MET achieved was associated with a 8–10% lower risk of mortality. The greatest difference in early mortality was observed among those with low CRF, suggesting that the least fit patients may benefit the most from improving CRF through physical activity. Similar data suggest improved CRF is associated with lower heart failure incidence and prevalence [64,65].

3.7. CRF and stroke

Given the healthcare and economic burden in stroke patients, prevention of stroke is of great importance [66]. Multiple studies have investigated the relationship between CRF and stroke reduction [67].
a fully adjusted analysis, Lee et al. examined the association between CRF and stroke mortality in men using the ACLS patient registry [68]. During an average 10-year follow up, it was observed that both high fit and moderate fit men had significantly lower risk of stroke mortality compared with low fit men. Another study by Hooker et al. evaluated the effects of CRF on stroke in a cohort of 61,687 patients without known myocardial infarction or stroke who completed a maximal treadmill exercise test at baseline [69]. After adjusting for several CVD risk factors, higher CRF was significantly associated with lower risk of nonfatal and total stroke in women (HR 0.51, 95% CI 0.27–0.98; HR 0.53, 95% CI 0.29–0.95; ARR 1.8%, 2.3%) and in men (HR 0.5, 95% CI 0.25–0.97, HR 0.62, 95% CI 0.43–0.90; ARR 3.1%, 2.8%). Higher CRF was also associated with lower rates of fatal stroke in men (HR 0.60, 95% CI, 0.43, 0.82; ARR 1.3%).

In another study by Al Rifai et al. using the FIT Project, the authors showed that patients with high CRF defined as METs ≥12 had approximately 60% lower risk of overall, ischemic, and hemorrhagic stroke compared to those with low CRF (METs < 6) (in press). Kurl et al. also assessed the association of CRF and stroke using data from the Kuopio Ischemic Heart Disease Risk Factor Study, which included 2011 men (no women, all white) without prior stroke [70,71]. The relative risk for stroke and ischemic stroke were significantly greater in men with low CRF (VO2 max < 25.2 mL/kg/minute) compared to fit men (VO2 max > 35.3 mL/kg/minute) (RR 3.20 [95% CI, 1.71–6.12] and 3.50 [95% CI 1.66–7.4], respectively; ARR 7.2%, 6.3%, respectively). The associations remained significant after adjustment for numerous risk factors. This relationship was comparable to effect estimates of established stroke risk factors such as blood pressure, obesity, and smoking, which demonstrates that CRF may have a significant impact on mitigating stroke risk.

Using data from previously discussed Oslo Ischemia study, Prestgaard et al. examined effects of a change in CRF over time on development of stroke [57]. The study found that among individuals with high baseline CRF, those who became unfit later on had significantly higher risk of stroke compared with those who remained fit (HR 2.35, 95% CI, 1.49–3.63; ARR 6.8%). In individuals with low

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<td>Choi et al. (2016)</td>
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<td>Mohlenkamp et al. (2008)</td>
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<td>Radford et al. (2018)</td>
<td>Longitudinal</td>
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Fig. 4. *CCLS = Cooper Center Longitudinal Study, formerly the Aerobics Center Longitudinal Study. **FIT = Henry Ford Exercise Testing Project. ***KOICA = Korea Initiatives on Coronary Artery Calcification calcification multicenter registry. ****CARE-CR = Cardiovascular and cardiorespiratory Adaptations to Routine Exercise-based Cardiac Rehabilitation.
baseline CRF, those who became fit had significantly lower risk of stroke than those who remained unfit (HR 0.4; 95% CI 0.21–0.72; ARR 7.3%). Pandey et al. used data from the ACLS cohort to examine the relationship between midlife CRF and risk of stroke after the age of 65 [72]. Higher midlife CRF was inversely associated with stroke hospitalization (HR 0.61, quintiles 4–5 vs. 1; ARR 10.4%). This association remained significant even after adjusting for stroke risk factors as time-dependent covariates (HR 0.63, 95% CI 0.51, 0.79).

### 3.8. CRF and cancer

The benefits of fitness are not limited to cardiovascular system and atherosclerosis but have also been extended to lower cancer incidence. The World Cancer Research Fund and the American Cancer Research Institute have approximated that roughly two-thirds of cancer in individuals is related to lifestyle and is therefore preventable [73].

Vainshelboim et al. aimed to expand on the relationship between CRF and cancer development in an analysis on male veterans enrolled in the Veteran Exercise Testing Study at the Veteran Affairs Medical Center in Palo Alto, CA [74]. Physical activity was determined by basic questionnaire and individuals were categorized as active or inactive. Over a mean follow up of 10 years, the study found that physical activity was inversely associated with cancer mortality in a continuous fashion such that for every 1 MET increase there was a 5% decrease in cancer mortality. There was also a 20% lower risk in cancer death in active compared to inactive individuals (p = 0.02, 95% CI 0.67–0.97). Similar findings were also described in the FIT project [75]. Though not entirely known, possible protective mechanisms involve reduced chronic inflammation, improved insulin sensitivity, optimized immune function, and improved DNA repair among fit individuals [75,76].

### 3.9. Utility of CRF in clinical practice

Given the wealth of studies showing favorable effects of CRF on cardiovascular risk factor burden, subclinical atherosclerosis, and adverse cardiovascular outcomes, we posit that CRF may also aid decision making in clinical practice. While we do not propose that CRF be objectively assessed routinely for the purpose of cardiovascular risk stratification, we argue that this information is a useful adjunct to help estimate and potentially reclassify absolute risk of ASCVD events. For example, individuals with low calculated 10-year ASCVD risk and low CRF may potentially be reclassified to a higher risk stratum where the addition of preventive therapy is warranted. Prospective data is needed to test this approach.

### Table of CRF Studies

<table>
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<th>Increased fitness and risk of death</th>
<th>Prestgaard et al. (2018)</th>
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<td><strong>CRF and Cancer</strong></td>
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<td>Vainshelboim et al. (2017)</td>
<td>Longitudinal</td>
<td>Veteran Exercise Testing Study</td>
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Fig. 4. (continued)
Individuals who perform poorly on exercise stress testing and therefore have low CRF should be encouraged to improve fitness levels through physical activity as prior studies have shown that improving fitness levels over time is beneficial. They also need to be screened for cardiovascular risk factors and treated according to established guidelines. On the other hand, individuals with high CRF should be encouraged to continue engaging in healthy lifestyle option in order to maintain their fitness levels given that decline in fitness in such individuals portends higher risk of events.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References


[4] S.J. Keteyian, J. Myers, B.A. Allen, J.W. Carlson, J.A. Cooper, M.C. Jones, J.P. Probstfield, J.B. Brawner, S.P. Whelton, C.A. Brawner, M.A. Williams, M.H. Al-Mallah, Cardiorespiratory fitness and cardiovascular risk factors and treated according to established guidelines. On the other hand, individuals with high CRF should be encouraged to continue engaging in healthy lifestyle option in order to maintain their fitness levels given that decline in fitness in such individuals portends higher risk of events.

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