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TECHNICAL REPORT

THE CAF FITNESS PROFILE

A CASE FOR ASSESSING AEROBIC FITNESS AND BODY COMPOSITION WITHIN THE FORCE EVALUATION

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Suggested format for citation of this document:

Reilly T, Spivock M, Prayal-Brown AL. (2014). The Fitness Profile: A case for assessing aerobic fitness and body composition within the FORCE Evaluation. Technical Report: Department of National Defence, Assistant Deputy Minister (Science and Technology). Ottawa.

THE FITNESS PROFILE:

A CASE FOR ASSESSING AEROBIC FITNESS AND BODY COMPOSITION WITHIN THE FORCE EVALUATION

1.0 Executive Summary

Background: This document represents the results of a broad review of the literature, examining the scientific and logistic feasibility of adding an assessment of cardiorespiratory fitness (CRF) and body composition to the FORCE Evaluation. Given that the FORCE Evaluation is designed to assess operational fitness (the only construct on which career action can be taken under Canadian Human Rights Legislation), it does not provide a global indicator of all aspects of physical fitness. Physical fitness has important implications, both for the individual and the organisation and it is for this reason that this avenue is being explored.

Objective: The content of this document was primarily guided by questions we received from Clinical Council, and our working group which was subsequently developed including members of Clinical Council, as well as representatives from the office of the Judge Advocate General (JAG), DND/CF Legal Advisors (DND/CF LA), Director Health Services Delivery (DHSD), and Director Access to Information Privacy (DAIP). **The document is intended as a compendium of questions and answers, which are based on the systematic literature review to provide objective information regarding the usefulness of assessing aerobic fitness and body composition.**

Methods: An extensive review of the literature was performed in order to assert the scientific rationale for considering health related fitness in the annual FORCE Evaluation. Over 30 longitudinal studies and meta-analyses were reviewed in order to determine the viability of including additional measures within the FORCE Evaluation.

Results: The documentation shows that CRF and body composition represent significant and independent predictors of mortality/morbidity as part of a fitness profile. These results can also be made available to health professionals to be interpreted in conjunction with other clinical measures to better evaluate a patient's health risk.

Conclusions: Body composition can be easily determined by adding a waist circumference measure to the FORCE Evaluation. CRF can be derived by combining completion times on the various elements of the FORCE Evaluation. Both would serve to establish a more complete fitness profile of CAF personnel, which could be used to counsel the individual as well as to provide meaningful metrics to the chain of command.

2.0 List of Acromyms

AC	Abdominal circumference
ACM	All-cause mortality
BMI	Body mass index
BP	Blood pressure
CAF	Canadian Armed Forces
CDS	Chief of the Defence Staff
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
FORCE	Fitness for Operational Requirements of CAF Employment (the new CAF-wide assessment of operational fitness)
JAG	Judge Advocate General
MET	Metabolic Equivalent of Task (or simply metabolic equivalent, is a physiological measure expressing the energy cost of physical activities and is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference metabolic rate, set by convention to 3.5 ml O_2/kg/min)
MeSH	Medical Subject Headings
PHA	Periodic Health Assessment
VO_{2max}	Maximum Aerobic Capacity measured in ml O_2/kg/min
WHR	Waist to hip ratio

3.0 Aim

The objective of this report is to present a scientific and organisational rationale for including measures of aerobic fitness and body composition as part of the annual FORCE Evaluation, in order to obtain a more complete assessment of physical and operational fitness.

4.0 BLUF: Bottom line up front

The current review of literature supports the position that CRF and body composition are both independent and significant predictors of mortality and morbidity. Both could be quite easily and accurately assessed in the context of the FORCE Evaluation and would serve to establish a more complete fitness profile of CAF personnel. Though no career action could or should be taken on these broader measures of physical fitness, the information could serve to counsel the individual as well as to provide metrics to the chain of command to guide and prioritise program delivery.

Moreover, the results of this fitness profile could provide valuable information to health professionals in concert with the Framingham Risk Score which is already calculated in the context of the CAF's periodic health assessment (PHA).

Potential logistic, legal and information privacy concerns have been addressed with relevant stakeholders and mechanisms are currently being put in place to ensure the feasibility of this proposal.

5.0 Background

5.1 Defining fitness

In contrast with physical activity, which is related to the movements that people perform, physical fitness is a set of attributes that people have or achieve. Being physically fit has been defined as "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies" (President's Council on Physical Fitness and Sports, 1971). The most frequently cited components fall into two groups: one related to general physical fitness and the other related to skills and operational performance in specific situations (including elements such agility, balance, power, speed, coordination and reaction time). The general components of physical fitness are (a) cardiorespiratory endurance, (b) muscular endurance, (c) muscular strength, (d) body composition, and (e) flexibility (Casperson et al 1985). The components of skill- and health-related fitness are defined in Table 1:

5.2 The FORCE Evaluation – what it does and does not measure

Throughout the development of the FORCE Program, several questions were raised regarding elements of fitness not covered in this test. Though assessed to be an accurate representation of operational fitness – based on the physical fitness requirements of Universality of Service – the FORCE Evaluation was never intended to be a test of general health-related fitness. Though the FORCE Evaluation does encompass many of the fitness components found in Table 1, it does not specifically assess cardiorespiratory fitness or body composition.

Table 1: - Elements of Health and Skill Related Fitness (adapted from Corbin et al 1980).

Category of fitness	Component	Definition
General Physical Fitness	Cardiorespiratory endurance	relates to the ability of the circulatory and respiratory systems to supply fuel during sustained physical activity and to eliminate fatigue products after supplying fuel
	Muscular endurance	relates to the ability of muscle groups to exert external force for many repetitions or sustained exertions
	Muscular strength	relates to the amount of external force that a muscle can exert
	Body composition	relates to the relative amounts of muscle, fat, bone and other vital parts of the body
	Flexibility	relates to the range of motion available at a joint
Skill Related Fitness	Agility	related to the ability to rapidly change the position of the body in space with speed and accuracy
	Balance	relates to the maintenance of equilibrium while stationary or moving
	Coordination	relates to the ability to use the senses, such as sight and hearing, together with body parts in performing motor tasks smoothly and accurately
	Power	relates to the rate at which one can perform work
	Reaction time	relates to the time elapsed between stimulation and the beginning of the reaction to it
	Speed	relates to the ability to perform a movement within a short period of time

6.0 Research Question

Given CDS' concern over obesity in the CAF as well as the operational focus of the FORCE Evaluation, the Human Performance Research and Development Cell within the Directorate of Fitness, was directed to examine potential avenues for tracking and acting on a broader range of physical fitness components in CAF personnel. To be sure, the only basis for taking career action on personnel fitness would remain the Common Military Task Fitness Evaluation, as predicted by the FORCE Evaluation. A general physical fitness profile would be used as a basis for counselling the individual and directing them toward appropriate resources (e.g., Health Promotion programs, DFIT.ca or PSP-led fitness classes) as well as guiding the chain of command in addressing fitness levels in the CAF.

The research question which guided the current literature review was whether cardiorespiratory fitness (CRF) and body composition could be assessed as part of the FORCE Evaluation in order to better inform personnel and the chain of command regarding fitness levels in the CAF. More specific questions included:

1. How does cardiorespiratory fitness (CRF) relate to risk of mortality and morbidity?
2. What, if anything, does body composition add to this fitness profile?
3. How do these two measurements relate to what is already assessed in the Periodic Health Assessment in the CAF (i.e., the Framingham Risk Score)?
4. How might this additional information benefit
    a. The overall CAF (in terms of tracking and reporting of general fitness levels)
    b. The individual CAF member (in terms of better understanding one's own fitness status)
    c. Medical officers (providing additional information on which to develop a health risk profile)
5. What are the legal/logistic considerations of assessing CRF and body composition in the CAF?

7.0 Methods

7.1 A little help from our friends: Inspiration from other models

In the past decade many other employers have adopted a "Health-Based" fitness approach and applied a cardiovascular fitness standard to reflect the decrease in risk of morbidity, mortality and injury associated with increased fitness. The US National Guard employs a 2 mile run and categorizes personnel on the basis of a 10 year Coronary heart disease risk. This was a result of identifying that their deployed members were experiencing CVD symptoms despite being screened as low or moderate risk on the Framingham profile (469 cardiac referrals of deployed soldiers with a mean age of 39 years) (Talbot et al., 2009).

The US Air Force developed a scoring system on their Fitness test creating a health profile which is determined based on cardiovascular risk, and risk of injury, assessed through a 1.5 mile run, push-ups, sit- ups and abdominal circumference.

Similar emergency services such as The Royal National Lifeboat Institution in the United Kingdom (Reilly and Tipton, 2005), and Firefighters in the USA and Canada (Poplin et al., 2014) all have a cardiovascular fitness standard with the intention of improving health, while not always directly linked to the metabolic demands of the job, but more the categorisation of "fit" and "unfit".

7.2 MeSH keyword search

A broad literature review was conducted in order to better understand the empirical evidence for examining CRF and body composition in the CAF. Searches were conducted in PubMed by combining the following Medical Science Headings (MeSH) from the US National Centre for Biotechnology Information's thesaurus of accepted terms:

- Cardiovascular fitness
- All-cause mortality
- Cardiovascular disease
- Physical fitness
- Military
- Health status indicators
- Body composition
- Body mass index
- Epidemiology
- Waist girth / waist circumference
- Mortality
- Predictor
- Predictive value of tests
- Risk

The studies sought had to involve healthy adults and report some form of risk ratio associated with either CRF or body composition.

8.0 Results

A total of 49 studies (including original papers and meta-analyses) were accepted into the literature review. The majority of the data reported was based on large scale longitudinal epidemiological studies which tested components of fitness and then followed individuals for as many as 35 years. As well, an existing meta-analysis of studies relating CRF to mortality and morbidity (Kodama, et al., 2009; reproduced at Appendix A) was also used as a starting point to locate additional studies. What follows are simply bullet point findings from the various studies, organised in a Frequently Asked Questions and Answers format.

8.1 Cardio-respiratory fitness is a powerful independent predictor of mortality and morbidity

What influence over health / morbidity / mortality does "fitness" offer?

- The Aerobics Center Longitudinal Study (aka Cooper Institute) indicated that men who improved their aerobic fitness (CRF) had a 44% decrease in risk of death compared to men who stay unfit.
- This was a greater influencing factor with regard to risk of mortality when compared to BMI, BP, Cholesterol and Smoking. An active and fit way of life improves health and delays death *despite* other risk factors such as Body Mass Index (BMI), Blood Pressure (BP), Cholesterol and Smoking. This study had a population of males with an average age of 51.4yrs (+/- 10.4) (N=223 deaths out of 9777 men in total) (Blair et al., 1995).
- A consistency is seen across many studies, all showing a strong inverse gradient of mortality and various diseases across fitness groups (Blair et al., 2001; Kampert et al., 1996; Lakka et al., 1994; Oliveria et al., 1996; Villeneuve et al., 1998).
- It was found that increasing one's fitness level has a similar effect as quitting smoking on reducing your mortality risk ratio (Blair et al., 1996).
- The protective effect of CRF on mortality is independent of age, ethnicity, adiposity, smoking status, alcohol intake, and health conditions (Lee et al., 2010)

Was this research performed with "unhealthy" participants? How does fitness influence the Health Risk of mortality for an Asymptomatic Population?

The epidemiological studies cited below began with a population that was of a healthy weight, asymptomatic, had no CVD history and no diabetes or signs/symptoms of any health problems. The following are the findings that apply to an asymptomatic population:

- In men ages 30 to 60 years old, unfit lean men (2^{nd} quintile of fitness) had a 1.37 higher risk of all cause mortality compared to fit lean men in the 5^{th} quintile of fitness (Blair et al., 1989). When comparing the 1^{st} quintile of fitness in the men to the 5^{th} quintile of fitness level, the relative risk of all cause mortality increased to 3.44.
- In the same study, they found that women in the 2^{nd} quintile of fitness (low fitness) have an increase risk of all cause mortality of 2.42. This risk increases to 4.65 when looking at the 1^{st} quintile of fitness in women (Blair et al., 1989).

- Wei et al., (1999) found that in an initial population of non-diabetic men aged 30 to 60+, after taking into consideration age, cigarette smoking, alcohol consumption and parental diabetes, men with low-fitness (least 20% of the cohort study) had a 3.7 fold risk to developing diabetes compared to the 40% most fit individuals (Wei et al., 1999).
- In terms of developing metabolic syndromes, a study looked at the effects of a 1 MET increase in VO_2max on developing metabolic syndromes. On average it was found that a 1 MET increase is associated with a 16% and 17% lower multivariable-adjusted risk of metabolic syndrome in men and women respectively (Lamonte et al., 2005). These values were adjusted for age, current smoking status, alcohol intake, family history of disease, year of baseline examination, and number of baseline metabolic risk factors.
- The same study stated that a transition from a moderate to high fitness category could produce a range of 21%-44% effect decrease in risk of developing metabolic syndrome (Lamonte et al., 2005). Furthermore Blair et al. (1995) found similar results where a change from unfit to fit reduced their mortality risk by 44%.
- In a population of healthy men aged 40-60, it was found that improvements of CRF, regardless of the participants' CRF at baseline, resulted in significantly lower all cause mortality risk (Erikssen et al., 1988)

How do these risk profiles apply to those with a previous history of family cardiovascular disease (CVD)?

- Blair et al., (1989) observed that the reduction in mortality risk in the total population of men who maintained or improved physical fitness was present in both the healthy and unhealthy men and furthermore across the age groups. This study used 9777 men with ages ranging from 20-80 years. Later, Blair et al. (1995) confirmed that their study did not support the hypothesis that hereditary factors are solely responsible for the relationship between fitness and mortality. These ratios are independent of other known risk factors.

How much can an increase in fitness really decrease risk?

- Men who were "unfit" (VO_{2max} < 10.0 METs for 20-39 yrs; VO_{2max}<9.2 METs for 40-49 yrs; VO_{2max}<8.4 METs for 50-59; VO_{2max}<7.0 METs for 60+yrs) at initial exam but then became "fit" had a 44% decrease in risk of mortality compared with similar unfit men who did not improve (Blair et al., 1995).

What is FIT and UNFIT in terms of CRF?

There have been several attempts to define what constitutes a fit or unfit level of CRF. Though different authors have classified this differently, there are also significant similarities in the results. For example:

- Blair et al., (1995) had a clear definition of fit and unfit. It was measured by a treadmill test correlated with VO_2 max with an r=0.92. This study looked at fit and unfit as follows:
    - UNFIT= lowest 20% for age category on the treadmill test
    - MEN (20-40yrs) <10 METs = 35 ml O_2/kg/min
    - MEN (40-50yrs) <9.2 METs = 32.2 ml O_2/kg/min
    - MEN (50-60yrs) <7 METs = 24.5 ml O_2/kg/min
    - MEN – meta analysis (Kodama et al, 2009) 50yrs = VO2 = 27.6 ml O_2/kg/min

Furthermore, this same study concluded that a 1-MET increase in CRF was associated with a reduction in approximately 16% and 17% in mortality risk for men and women respectively (Blair, et al 1995).

- McAuley et al. (2010) looked at the effect of physical fitness on 12417 middle aged (40 to 70 yrs) male veterans. They defined fitness categories as follows:
    - LOW <5 METs,
    - MOD 5-10 METs,
    - HIGH >10 METs)

There were a total of 2800 deaths throughout the duration of the study. They found that elevated BMI generally reduced mortality risk within each fitness category. BMI ranged from <18.5 to >30.

- Kodama et al. (2009) reviewed a series of epidemiological studies together. When classifying the participants, low CRF was defined as <7.9 METs, intermediate as 7.9 to 10.8 METs and high as ≥10.9 METs. Additionally, they were able to extract the minimum CRF level that is associated with significantly lower event rates for men and women stratified by age. In other words, in order to benefit from the additional "shield" CRF may provide for ACM, cardiovascular disease, or other metabolic syndromes, people would have to complete the minimum METs of a VO_{2max} test below:
    - MEN (40yrs) <9 METs
    - MEN (50yrs) <8 METs
    - MEN (60yrs) <7 METs
    - WOMEN (40yrs) <7 METs
    - WOMEN (50yrs) <6 METs
    - WOMEN (60yrs) <5 METs

- Kodama et al.'s Review (2009) included 33 studies. There was a total of 6910 cases of all cause mortality in 102 908 participants and 4484 CVD deaths in 84 323 participants. They concluded that better CRF was associated with lower risk of all cause mortality, Coronary heart disease (CHD) and CVD. A 1-MET increase in a person's VO_{2max} was approximately associated with a 13% and a 15% risk reduction in all cause mortality and Coronary heart disease/CVD, respectively. The relative risk ratio for low fitness versus high fitness was of 1.7 and when comparing low vs moderate fitness it was 1.4 for all cause mortality. In terms of Coronary heart disease/CVD risk ratios, low vs high was at 1.56 and low vs moderate was at 1.47 indicating that even a moderate level of fitness lowers your risk of all cause mortality or CHD/CVD.

- Wei et al. (2000) investigated the effects of physical fitness and mortality using 1263 men aged 50 +/- 10 yrs with type 2 diabetes. The fit and unfit men had a mean exercise tolerance of 10.9 +/- 1.7 METs and 8.0 +/- 1.3 METs, respectively. The unfit men had a 2.1 fold higher risk for death than men who were fit at baseline, irrespective of triglycerides, blood pressure, cholesterol, blood glucose, alcohol, smoking and self reported activity. Each 1 MET increase in CRF was associated with a 25% decrease in all cause mortality.
- Lee et al. (1999) from the Cooper Institute, evaluated the fitness level of 21 925 men aged 30-83 yrs. There were a total of 428 deaths throughout the length of this study. The fit lean men of this study were classified as having an average VO_{2max} of 13.4 METs. At the other end of the spectrum, obese unfit men had the lowest average VO_{2max} of 8.7 METs. Their results supported the hypothesis that moderate to high cardiorespiratory fitness reduces mortality risks across categories of body composition.

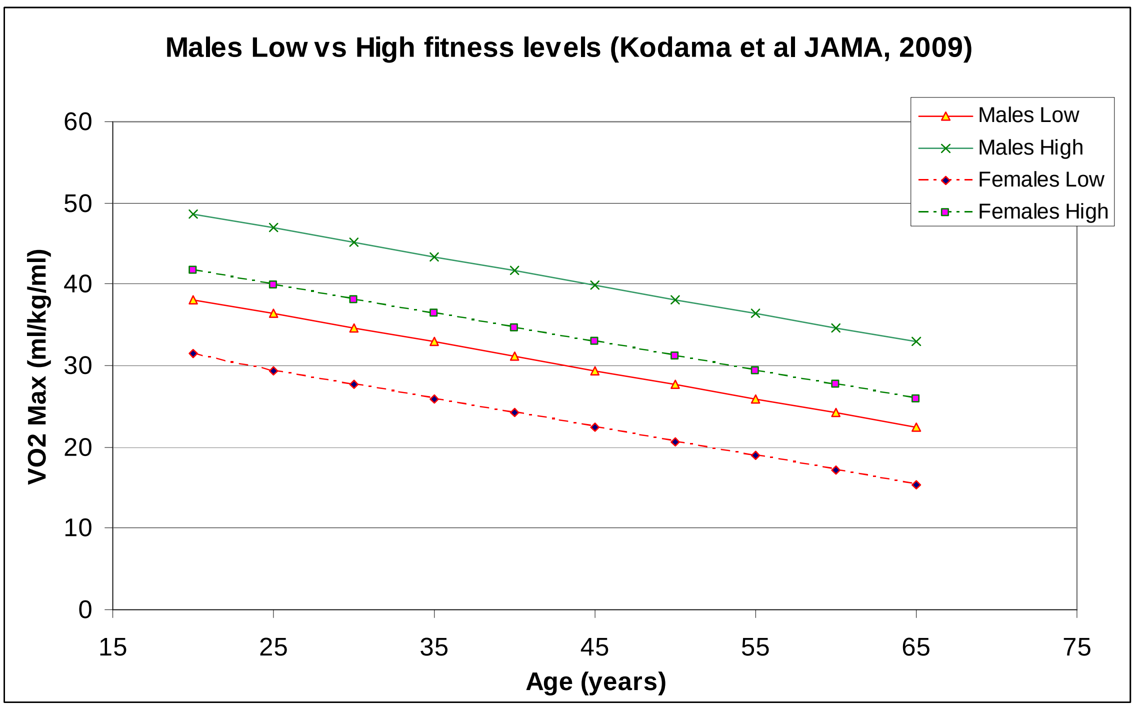

Figure 1 -Cutoffs for low and high fitness levels (VO_{2max}) **based on CRF (Kodama et al, 2009).**

Table 2: Cutoffs for low and high fitness levels based on CRF -VO_{2max} (Kodama et al., 2009)

Age (Yrs)	Males Low $VO_{2\,max}$ (ml O_2/kg/min)	Males High $VO_{2\,max}$ (ml O_2/kg/min)	Females Low $VO_{2\,max}$ (ml O_2/kg/min)	Females High $VO_{2\,max}$ (ml O_2/kg/min)
20	38.15	48.65	31.5	41.65
25	36.4	46.9	29.4	39.9
30	34.65	45.15	27.65	38.15
35	32.9	43.4	25.9	36.4
40	31.15	41.65	24.15	34.65
45	29.4	39.9	22.4	32.9
50	27.65	38.15	20.65	31.15
55	25.9	36.4	18.9	29.4
60	24.15	34.65	17.15	27.65
65	22.4	32.9	15.4	25.9

What is the justification for recommending women have 2 METs lower thresholds?

- Women have approximately 2 METs lower CRF capacity then men, attributed to their smaller muscle mass, lower haemoglobin and blood volume (Fletcher et al., 2001).

Is a self-reported Measure of Physical Activity as useful a measure of CRF?

- When physical activity, physical fitness and possible confounding variables are included in a multivariate model, fitness remains strongly associated with mortality. The association between activity and health however is no longer significant (Blair et al., 2001; Sobolski et al., 1987).
- Findings with physical activity as the exposure variable and all-cause mortality as the outcome are continuously inconsistent and inconclusive (Folgelholm, 2010).
- Studies appear to have a *similar association* between fitness and mortality in women and in men which is often times not picked up by "physical activity" questionnaires (Blair et al., 2001; Kampert et al., 1996; Winett & Carpinelli, 2000).
    - Kampert et al. (1996) noted that there was no association between physical activity and risk of cancer in women and that physical activity was not related to mortality risk for women.
- In comparison to physical fitness models, physical activity models had much more variation and were less accurate in quantifying the association between dose-response and functional limitations (Huang et al., 1998).

- Suggestions to why no trends are seen in women and physical activity may lie in the questionnaires. Most questionnaires may miss activities in which women frequently engage that do not include running or vigorous sports.
    - Questionnaires: problems with specificity, reliability and validity of self-reported data (Winet & Carpinelli, 2000).
    - Physical activity is assessed in most studies by self-report, often times leading to substantial misclassification (Blair et al., 2001).
    - Many questionnaires ask participants to "recall" their activities in the past 3 months or year (Huang et al., 1998; Kampert et al., 1996; Myers et al., 2004; Oliveria et al., 1996; Villeneuve et al., 1998).
- Words that are often associated with physical activity questionnaires are: subjective, attentive, recollection, misclassification, systematic variance (Blair et al., 2001) and self-reported.
- Correlations between reported physical activity and physical fitness measurements ranged from 0.09 to 0.66 (Blair et al., 2001; Lakka et al., 1994; Myers et al., 2004; Oliveria et al., 1996; Sobolski et al., 1987).
- Low levels of both conditioning leisure time physical activity AND cardiorespiratory fitness are important *Independent* coronary risk factors (Lakka et al., 1994).
- Taking both fitness and activity into consideration could provide an extra classification. Among individuals that have similar fitness levels, health is better in those with higher physical activity (Blair et al., 2001; Fogelhom, 2010).

How does CRF relate to risk of injury?

- Poplin et al., (2014) linked annual medical evaluations and injury surveillance to compare levels of aerobic fitness in injured employees with those of non injured employees. The individual outcomes evaluated included all injuries such as exercise-related injuries, sprains and strains. Time-to-event analyses were conducted to determine the association between levels of fitness and injury likelihood. Fitness, defined by relative aerobic capacity ($VO_{2\ max}$), was found to be associated with injury risk. Participants in the lowest fitness level category ($VO_{2\ max}$ <43 ml O_2/kg/min) were 2.2 times more likely (95% CI: 1.72 - 2.88) to sustain injury than were those in the highest fitness level category ($VO_{2\ max}$ >48 ml O_2/kg/min). Those with a $VO_{2\ max}$ between 43 and 48 ml O_2/kg/min were 1.38 times (95% CI: 1.06 -1.78) more likely to incur injury. Hazard ratios were found to be greater for sprains and strains. Our results suggest that improving relative aerobic capacity by 1 metabolic equivalent of task (approximately 3.5 ml O_2/kg/min in VO_{2max}) reduces the risk of any injury by 14%. These findings illustrate the importance of fitness in reducing the risk of injury in physically demanding occupations, such as the fire service, and support the need to provide dedicated resources for structured fitness programming and the promotion of injury prevention strategies to people in those fields.

8.2 Body composition contributes significantly to the prediction as well

Why add abdominal circumference (AC)?

- The US National Guard has identified a significant relationship between AC and CVD risk (19 years longitudinal study). An AC > 35" and an AC >40" for females and males respectively, increases risk of Coronary heart disease (NHLB, 1998)

- The 2006 Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children indicates AC can be used to help determine a patient's risk profile for CVD and overall health risk and provide a reference point for monitoring AC over time to prevent obesity related diseases. They recommend the creation of a national surveillance system that incorporates at minimum the measurements of height, weight and AC (CMA, 2007).

- A significant positive relationship was observed between AC and 10 year CHD risk (men). When controlling for age, AC was predictive variable for a 10 year CHD risk score (6.4% variance) (Ricciardi et al., 2009). The results of this study indicated that AC is the best anthropometric measure to identify unfit males at risk for CHD as assessed by the Framingham Heart Study, compared to % Body fat, BMI and Waist to hip ratio (WHR).

Various guidelines currently exist for an acceptable AC:

- Canadian guidelines for clinical practice (2006) recommend measuring BMI and AC.
    - BMI - International Obesity Task Force
    - Require to measure AC if BMI is ≥25 and ≤ 35 kg/m^2
    - AC ≥94 cm male and AC ≥ 80 cm females are at risk.

- The Canadian Society for Exercise Physiology guidelines (2013) state that acceptable AC should be less than 100 and 90 cm for men and women respectively.

The World Health Organization guidelines state that the acceptable AC should be less than 102 and 88 cm for men and women respectively.

- Lee et al (2005) found that CRF attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in men.

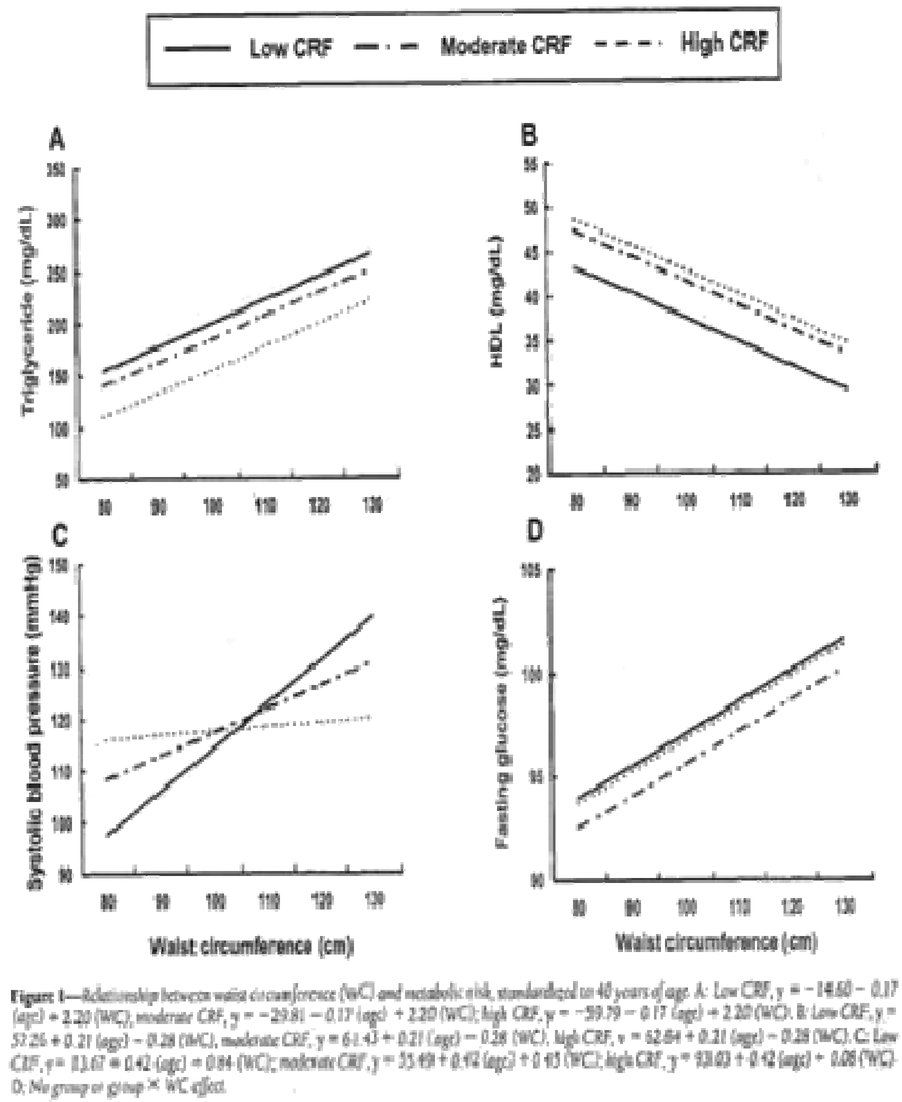

Figure 2 – Relationship between AC and metabolic risk.

Why does AC account for only 25 points in the proposed model?

- For given levels of abdominal subcutaneous fat, visceral fat or AC, men with higher levels of CRF had substantially lower metabolic risk compared with men with low CRF (Lee et al., 2005).
- Adiposity and physical fitness are both important predictors of diabetes *Independent* of several other risk factors (age, smoking, alcohol and parental history) (Katzmarzyk, 2007; Lee et al., 2005; Lee et al., 2009).
- Stevenson et al. (2002 & 2004) report that both CRF and obesity are independent predictors of mortality and that high fitness substantially ameliorated the risk of obesity but did not eliminate it. However, fitness does attenuate the detrimental effects of obesity on mortality. The highest risk of mortality is observed in those who are both obese and unfit (Lee et al., 2010).

8.3 Cardio-respiratory fitness would enhance the overall risk assessment within the PHA

The Framingham risk score (currently used as part of the PHA) is a gender specific predictive algorithm that was developed using categorical variables to allow physicians to predict multivariate Coronary heart disease risk in patients without overt Coronary heart disease (Wilson et al., 1998) for up to a 10 year span. Many versions of this assessment currently exist. In general, age, sex, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure as well as whether or not blood pressure is being treated by medicine are taken into consideration. Some other versions also include Body Mass Index.

How does fitness (CRF) relate to morbidity and mortality compared to Measuring Cholesterol?

- CRF is the same or better predictor than cholesterol for mortality (Wei et al., 2000)
- Elevated Cholesterol has a similar relative risk (1.65) as low fitness (1.7) which were both independently and significantly associated with CVD mortality (Farell et al., 1998).
- A 1-MET increase in CRF is associated with a 0.2 mmol/L (8mg/dL) of high-density lipoprotein cholesterol (Lee et al., 2010; Kodama et al., 2009).
- Low fit men had a higher CVD death rate than mod/high fit men whether they had normal or elevated blood cholesterol levels (Farell et al., 1998).

How does fitness (CRF) relate to morbidity and mortality compared to Measuring Triglycerides?

- A 1-MET higher level is comparable to a 1 mmol/L (88mg/dL) (in men) decrement in triglyceride levels (Lee et al., 2010; Kodama et al., 2009).

How does fitness (CRF) relate to morbidity and mortality compared to Measuring Blood Pressure?

- In hypertensive women, those with high CRF had 81% decrease risk of mortality when compared to those with low CRF (Blair et al., 1996).
- In hypertensive men, those with high CRF had 45-70% decrease risk of mortality when compared to those with low CRF (Church et al., 2001).
- CRF is greater or equal predictor of all-cause mortality when compared to high blood pressure (Blair et al., 1996).
- A 1-MET increase in CRF is associated with a 5.5mmHg decrease in systolic BP (Lee et al., 2010; Kodama et al., 2009)
- There is a strong inverse relationship between CRF and CVD mortality among men with normal BP(Farell et al., 1998).
- Hypertensive men (uncontrolled) have a mortality risk 5.8x greater than moderately fit controlled hypertensive men (Church et al., 2001).

How does fitness (CRF) relate to morbidity and mortality compared to Smoking?

- Low CRF is a strong predictor of mortality with risk comparable if not greater than smoking (Wei et al., 1999).
- After adjustments for all other risks, low fitness and smoking demonstrated the same risk of all cause mortality (Blair et al., 1996).
- Smoking had a similar relative risk (1.57) as low physical fitness (1.7) which were both independently and significantly associated with CVD mortality (Farell et al., 1998).

How does fitness (CRF) relate to morbidity and mortality compared to Glucose Regulation?

- A 1-MET higher level in CRF is comparable to a 1-mmol/L (18mg/dL) decrement in fasting plasma glucose (Lee et al., 2010; Kodama et al., 2009).
- Subjects who were inactive, obese, and had a normal glucose level were associated with an increased risk of type 2 diabetes compared with subjects who were physically active, non obese and had *impaired glucose* regulation (Hu et al., 2004).
- Low CRF is a strong predictor of mortality with risk ratios comparable if not greater than type II diabetes (Wei et al., 1999).
- Men with type 2 diabetes who are unfit have a 2.1 fold high risk for death than men who were fit at baseline (Wei et al., 2000).
- The risk for diabetes is 3.7 folds higher in low-fitness men (Wei et al., 1999).

How can CAF Medical Officers use a VO_{2max} result in a PHA?

The outcome of a fitness profile is not meant to replace or “compete” with the Framingham health risk score – these estimates are assessing distinct constructs. Though useful on its own as a measure, the fitness profile can also serve to enhance the health risk determined at the PHA.

- Many reports have recommended that CRF assessment should be included in the clinical setting based on the importance of CRF to morbidity and mortality prevention (Gibbons et al., 2003; Gulati et al., 2005; Kodama e al., 2009; Myers et al., 2000).

- As previously discussed, the protective effect of CRF on mortality is independent of age, ethnicity, adiposity, smoking status, alcohol consumption as well as health conditions (Blair et al., 2001). CRF is also a useful health indicator for both symptomatic and asymptomatic patients in clinical practice (Gibbons et al., 2002; Gulati, et al., 2005; Myers et al., 2002).

- Many studies suggest that the assessment of an overweight patient’s fitness status is just as important as the measurement of glucose level, cholesterol, blood pressure, smoking and family history (Fogelholm, 2010). While one measure does not replace the other, fitness assessments can complement the health evaluation of an individual especially where one may be categorized as obese but have the shielding effect of a high level of cardiorespiratory fitness (Blair et al., 2001; Blair et al., 1995; Blair et al., 1996).

- Blair et al. (1995) observed a decrease in mortality risk in the population (n=10 000 males) who maintained or improved physical fitness present in both healthy and unhealthy men. Results are consistent across age groups, independent of other confounding risk factors. Clinicians should act on this info (CRF) to promote regular physical activity in order to reduce premature deaths from CVD and all causes (Lee et al., 2010).

- A recent Journal of American Medical Association meta-analysis recommends including CRF into the Framingham scores to allow participants to use CRF as a major risk factor in clinical settings (Kodama et al., 2009).

- Although compelling evidence has shown that CRF is a strong and independent predictor of ACM and CV disease mortality in men and women, the importance of CRF is often overlooked from a clinical perspective compared with other risk factors such as hypertension, diabetes, smoking and obesity. CRF is AT LEAST as important as these traditional risk factors and is often more strongly associated with mortality (Lee et al., 2010).

8.4 Times on the FORCE Evaluation allow for a derivation of oxygen capacity

A measure of oxygen capacity can be derived from FORCE Evaluation results in one of two ways. One of these approaches is by combining the times on select components of the FORCE Evaluation with age into a regression model, which for the moment is yielding a coefficient of determination of 0.63-0.92 (see Fig 3). These coefficients are based on a small convenience sample of existing data on research participants who completed the FORCE Evaluation as well as a maximal graded exercise test. Figure 3a contains data from Phase 3 of Project FORCE with participants where the elements of the current FORCE Evaluation were administered among 13 other tests over 3 days. Figure 3b contains a smaller, more homogenous sample of participants who did perform the FORCE Evaluation as a standalone test, using the current CAF testing protocol. Given that the fitness levels of participants represented in Figure 3b do not reflect those of the overall CAF, it is likely that r^2 value of 0.92 overestimates what would be seen with a larger sample. Given this uncertainty, a study is currently underway which will significantly increase the sample size and narrow the coefficient of determination estimate. It is anticipated that this final coefficient of determination will fall somewhere between 0.63 and 0.92, with early results suggesting that it may fall much closer to the upper end of this range.

Another approach to determining CRF from the FORCE Evaluation is to directly measure the oxygen cost of performing the different elements of the test at various paces. This study is also in the planning stages. Results from both data collections are expected in the spring/summer of 2014.

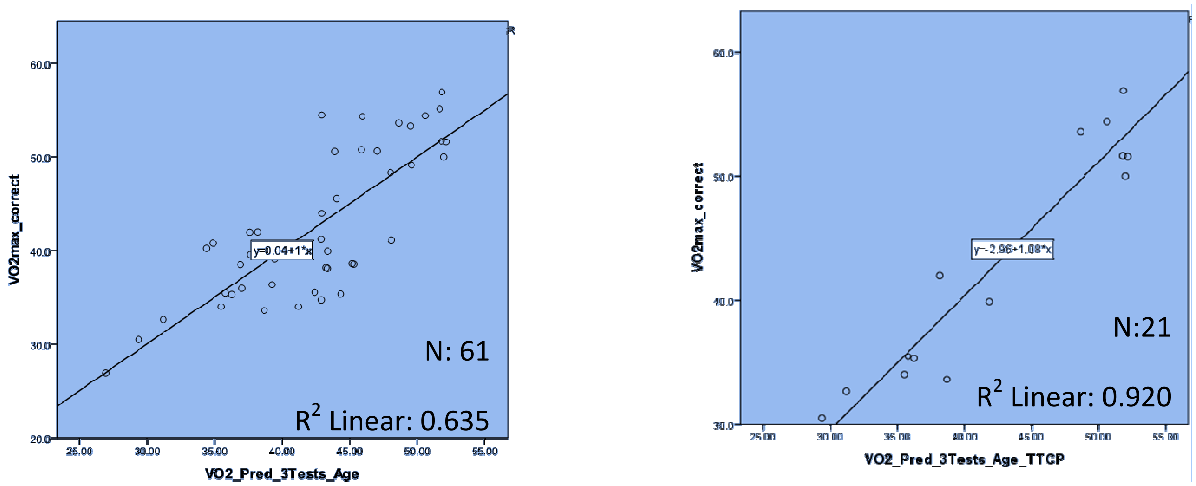

Fig 3a. Plotting all avail sources of data which contain GXT and FORCE, mainly in the context of large research projects

Fig 3b. More homogenous sub-sample where FORCE was administered as a standalone test with current protocols

Figure 3 - Prediction of VO2 using results from the FORCE Evaluation and age.

8.5 Knowledge of one's fitness status can influence behaviour

Godin and Kok (1996) showed that the combined effect of attitude, social norms and perceived behavioural control are very strong predictors of intention to adopt health behaviours, which is in turn a strong predictor of action. Overall, these psychological variables can account for roughly 1/3 of behaviour. In practical terms, this states that at the point of transmission of results to the individual, if staff can ensure that:

- the member has a positive attitude towards fitness,
- he/she understands that fitness is important in the CAF (social norms), and
- believes he/she has the ability to make a positive change with respect to fitness (perceived behavioural control),

there can absolutely be a positive change in the person's behaviour. Furthermore, given that the effect of social norms may be more prominent in an organisation such as the CAF, and that there may be fewer obstacles to overcome (considering the presence of staffed fitness facilities, health promotion information) a behavioural intervention based on these factors has the potential to be even more successful than what has been shown in the general population.

9.0 Discussion

9.1 Organisational implications of the fitness profile: Tracking and reporting

Information yielded from the fitness profile can prove useful to the CAF in several ways:

- The individual would obtain a better understanding of their own fitness level, and be empowered to take actions to address issues where they may exist.
- The CAF chain of command would be in a better position to track trends in overall CAF fitness over time as fitness data could be aggregated to various levels of command. This is particularly relevant given that a recent CRS audit of the CF Health and Physical Fitness Strategy (2008) highlighted the requirement for more robust performance measures and reporting mechanisms relating to health and fitness in the CAF.
- PSP fitness staff (or those administering the fitness test) would have a better basis from which to direct the individual to resources to assist in increasing their fitness (e.g., Health Promotion, fitness classes, DFIT.ca, etc.).
- The CO of a unit would have a better understanding of the fitness of his/her unit and can tailor training activities to particular needs (e.g., agility training to improve time on 20-m Rushes, or requesting a Weight Wellness program to address obesity). Though the Health and Physical Fitness Strategy (2008) did place a certain responsibility on COs for the fitness of their personnel, many have indicated a lack of data on which to act.
- Medical officers would be able to build a more complete health risk profile of patients, and use the opportunity to provide healthy lifestyle counselling to reinforce messages received from fitness personnel.

9.2 How can this information be collected and stored?

The collection and storage of any personal data by the federal government is a tightly regulated process. A Privacy Impact Assessment is currently being conducted in collaboration with the Director of Access to Information Privacy (DAIP) in order to ensure that all regulations are adhered to. A Personal Information Bank will subsequently be developed to house the results of the FORCE Evaluation proper, as well as the abdominal circumference data in accordance with all regulations.

9.3 What are the legal implications of asking CAF personnel to submit to an assessment of abdominal circumference?

Legal counsel from DND/CF LA sees no *à priori* issues with the collection of this data, as tracking general physical fitness can easily be justified in terms of overall operational effectiveness of the CAF.

10.0 References

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11.0 Appendices

11.1 Key Article: *Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women: A Meta-analysis*

Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., Sugawara, A., Totsucka, K., Shimano, H., Ohashi, Y., Yamanda, N., Sone, H.(2009) ***Journal of the American Medical Association***. 301(19):2024-35

Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women

A Meta-analysis

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Context Epidemiological studies have indicated an inverse association between cardiorespiratory fitness (CRF) and coronary heart disease (CHD) or all-cause mortality in healthy participants.

Objective To define quantitative relationships between CRF and CHD events, cardiovascular disease (CVD) events, or all-cause mortality in healthy men and women.

Data Sources and Study Selection A systematic literature search was conducted for observational cohort studies using MEDLINE (1966 to December 31, 2008) and EMBASE (1980 to December 31, 2008). The Medical Subject Headings search terms used included *exercise tolerance, exercise test, exercise/physiology, physical fitness, oxygen consumption*, *cardiovascular diseases, myocardial ischemia*, *mortality, mortalities, death, fatality, fatal, incidence,* or *morbidity*. Studies reporting associations of baseline CRF with CHD events, CVD events, or all-cause mortality in healthy participants were included.

Data Extraction Two authors independently extracted relevant data. CRF was estimated as maximal aerobic capacity (MAC) expressed in metabolic equivalent (MET) units. Participants were categorized as low CRF (<7.9 METs), intermediate CRF (7.9-10.8 METs), or high CRF (>10.9 METs). CHD and CVD were combined into 1 outcome (CHD/CVD). Risk ratios (RRs) for a 1-MET higher level of MAC and for participants with lower vs higher CRF were calculated with a random-effects model.

Data Synthesis Data were obtained from 33 eligible studies (all-cause mortality, 102 980 participants and 6910 cases; CHD/CVD, 84 323 participants and 4485 cases). Pooled RRs of all-cause mortality and CHD/CVD events per 1-MET higher level of MAC (corresponding to 1-km/h higher running/jogging speed) were 0.87 (95% confidence interval [CI], 0.84-0.90) and 0.85 (95% CI, 0.82-0.88), respectively. Compared with participants with high CRF, those with low CRF had an RR for all-cause mortality of 1.70 (95% CI, 1.51-1.92; $P < .001$) and for CHD/CVD events of 1.56 (95% CI, 1.39-1.75; $P < .001$), adjusting for heterogeneity of study design. Compared with participants with intermediate CRF, those with low CRF had an RR for all-cause mortality of 1.40 (95% CI, 1.32-1.48; $P < .001$) and for CHD/CVD events of 1.47 (95% CI, 1.35-1.61; $P < .001$), adjusting for heterogeneity of study design.

Conclusions Better CRF was associated with lower risk of all-cause mortality and CHD/CVD. Participants with a MAC of 7.9 METs or more had substantially lower rates of all-cause mortality and CHD/CVD events compared with those with a MAC of less 7.9 METs.

JAMA. 2009;301(19):2024-2035 www.jama.com

Coronary heart disease (CHD) is a major cause of disability and premature death throughout the world.[1] Epidemiological studies have demonstrated an inverse association between physical fitness and the incidence of CHD or all-cause mortality in healthy or asymptomatic participants. Physical fitness is typically expressed as cardiorespiratory fitness (CRF) and is assessed by exercise tolerance testing[2]; however, it is rare for clinicians to consider CRF when evaluating future risk of CHD.[3]

A major reason for lack of consideration of CRF as a marker of CHD risk may be that the quantitative association of CRF for cardiovascular risk is not well established. The degree of risk reduc-

CME available online at www.jamaarchivescme.com and questions on p 2053.

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tion associated with each incremental higher level of CRF, the criteria for low CRF, and the magnitude of risk associated with low CRF have been inconsistent among studies. Our goal of this meta-analysis was to systematically review the quantitative relationship between CRF and all-cause mortality and CHD or cardiovascular disease (CVD) events in healthy individuals.

METHODS

Search Strategy

The meta-analysis was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology.[4] We performed a systematic literature search of MEDLINE (1966 to December 31, 2008) and EMBASE (1980 to December 31, 2008) for observational cohort studies. Three search themes were combined using the Boolean operator *and*. The first keywords were related to CRF (combined exploded versions of the Medical Subject Headings [MeSH] as follows: *exercise tolerance* OR *exercise test* OR *exercise/physiology* OR *physical fitness* OR *oxygen consumption*); the second keywords were related to the outcome of this meta-analysis (combined unexploded version of MeSH [*cardiovascular diseases*] or the exploded version of MeSH [*myocardial ischemia*]) or the following text words (*mortality* OR *mortalities* OR *death* OR *fatality* OR *fatal* OR *incidence** OR *event** OR *morbidity*); and the third keywords were related to risk estimates (combined text words as follows: *regression analysis* OR *regression model** OR *statistical regression** OR *logistic regression** OR *logit regression** OR *logistic model** OR *logit model** OR *Cox model* OR *hazard model* OR *odds ratio** OR *ORs* OR *relative odds* OR *risk ratio** OR *relative risk** OR *RRs*). We also included studies published in non-English language. In addition, we searched the reference lists of all identified relevant publications.

Inclusion and Exclusion Criteria

We included papers if (1) CRF was assessed by an exercise stress test; (2) the association of CRF with all-cause mortality and with CHD or CVD was evaluated; (3) CRF could be assessed as maximal aerobic capacity (MAC), expressed in units of metabolic equivalents (METs), which is defined as the ratio of intensity of physical activity to that of sitting at rest; and (4) risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) relating to each category of MAC were reported or could be calculated. We excluded studies that were intended only for patients having a specific disease that presented a major risk factor, such as diabetes, hypertension, and familial hypercholesteremia, as well as studies that included patients with CHD or chronic heart failure.

To avoid double counting of a cohort, study selection was limited to a single set of results when multiple publications were available for a single observational study. The first priority for selection was the study with the longest follow-up and the second was the study with full cohort analysis covering the largest number of participants among articles from a single cohort. We conducted 2 separate meta-analyses for risk of all-cause mortality and CHD or CVD in relation to CRF. When an individual study provided data on both CHD or myocardial infarction (MI) and CVD,[5-7] priority for data abstraction was given to CVD because CVD is more comprehensive than CHD and MI. Similarly, if data on both events and deaths were provided,[6,8,9] priority was given to events.

We combined CHD and CVD into 1 outcome (CHD/CVD), which included studies whose outcome was a CVD event, CVD death, CHD event, or CHD death, because the number of eligible studies included was limited. Although criteria for the end point in CHD varied from study to study, the end points that we specified as CHD outcome in our meta-analysis were (1) death from MI; (2) death from CHD including MI; and (3) a CHD event, a term which meant either death from CHD, sudden cardiac death, occurrence of nonfatal CHD, or nonfatal MI. Additionally, we included studies whose outcome was either CVD death (ie, encompassing death from cardiovascular causes other than CHD) or CVD events (ie, lumping together fatal and nonfatal CVD).

Data Abstraction

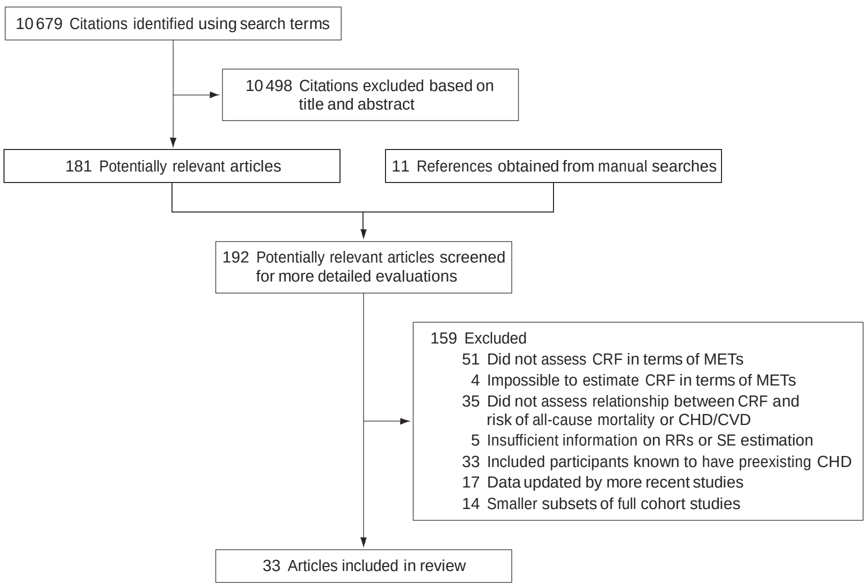
Data abstracted were the first author's name, year of publication, country of origin, specific outcomes, duration of follow-up, methods for outcome assessment, instrument or methods for measurement of CRF, whether maximal exercise testing (defined as instructing participants to continue exercise until their maximal workload) was conducted, mean of participants' age, proportion of men, number of participants and number of new cases (ie, deaths or events) during the observational periods, adjusted variables, and whether participants with abnormal electrocardiogram findings (ie, ST elevation/depression) during exercise testing were included. Two of our investigators (S. Kodama and H. Sone) independently reviewed each published paper and extracted relevant information. Any disagreement was resolved by consensus.

In studies using CRF as a categorical variable, we standardized all reported RRs into comparison of the risk of the lower CRF group with that in the higher CRF group. Therefore, when the lowest CRF group was referent, we converted the reported RR into its reciprocal. When a study provided several RRs, such as unadjusted and adjusted RRs, the most completely adjusted RR was used. The standard error (SE) of each RR was derived from 95% CIs or *P* values. If data related to RR and its corresponding SE were not provided, their value was directly calculated using data on the number of participants (P) and new cases (C) of risk and the reference (ref) groups in each comparison, using the equation:

$$RR=[(C_{risk}/P_{risk})/(C_{ref}/P_{ref})],\ SE^2=[(1/C_{risk})-(1/P_{risk})]+[(1/C_{ref})-(1/P_{ref})].$$

The MAC was calculated from the exercise workload at the termination of exercise testing and relative exercise intensity (ie, proportion of the workload to MAC). The exercise workload was converted into MET units (1 MET corresponds to 3.5 mL/min/kg of oxygen consumption [$\dot{V}O_2$]), according to the Metabolic Calculation Handbook by

Figure 1. Selection of Articles for Meta-analysis



CHD indicates coronary heart disease; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; METs, metabolic equivalents; and RRs, risk ratios.

the American College of Sports Medicine.[10] Relative exercise intensity was estimated using a linear equation according to Swain et al[11]:

$$\text{heart rate at exercise/maximal heart rate} = 0.64 \times (\dot{V}O_2 \text{ at exercise/maximal } \dot{V}O_2).$$

For some specific exercise stress tests, the MAC was directly estimated using the prediction equation determined by a previous validation study for each protocol of the exercise test (the Balke treadmill test,[12,13] the modified Bruce test,[14] and the Canadian Home Fitness test[15]).

When exposure was expressed as a range, we converted it into point estimates expressed as average exposure using the midpoint of the range except for the lowest and highest fit group. If data on the average value were not available, it was estimated by the assumption that the MAC levels of the study population had a normal distribution using the mean value and its SD of each study sample. This assumption is consistent with a prior study.[16] However, if the SD was not available, we assumed that its value equaled 2 METs, according to the statement of the American Heart Association.[17]

After converting all exposures into MET units, we additionally adjusted MET units for age and sex. According to a Statement for Healthcare Professionals From the American Heart Association,[17] we assumed that the MAC is 2 METs lower in women than in men and that for each year of aging, it decreased by 0.1 MET based on a prior study.[18] Finally, we represented CRF as the adjusted MAC under the assumption that all participants were 50-year-old men in the analyses described below.

Dose-Response and Categorical Analyses

We first performed dose-response analyses by summarizing how much risk reduction could be predicted per incremental increase in CRF. The study-specific RR for each higher MET (corresponding to 1-km/h higher running/jogging speed) in MAC, if not reported, was estimated by regressing the natural logarithm of the RR (lnRR) according to each CRF category against its corresponding mean MAC value, using the method described by Greenland and Longnecker.[19]

We then performed categorical analyses to summarize the risk of all-cause mortality and CHD/CVD for low CRF. We assigned every RR reported in each study to 1 of the following 3 comparisons based on the CRF level of risk and reference group: (1) low vs high CRF, (2) low vs intermediate CRF, and (3) intermediate vs high CRF. This method is based on a previous meta-analysis of the relationship between activity level and stroke risk.[20] For studies that presented risk estimates for more than 2 CRF categories, the ranges of the adjusted MAC of the lowest, highest, and in-between categories defined by each study were 5.5 to 7.8, 11.0 to 15.2, and 7.9 to 10.7 METs, respectively; except that in 2 studies,[21,22] the second highest category of CRF was more than 11.0 METs and, in 1 study,[7] the highest category of CRF was 10.6 METs.

To avoid overlap of the CRF range of the 3 categories, we defined low, intermediate, and high CRF as less than 7.9 METs, 7.9 to 10.8 METs, and 10.9 METs or more, respectively. Consequently, we could assign every RR in each study to 1 of the 3 predefined subgroups with 2 exceptions. In 2 studies,[21,22] the mean MAC values for both the highest and the second highest category were the same as the high CRF category (defined by >10.9 METs). Therefore, RR data for comparison between 2 CRF categories could not be included in our categorical analysis for these 2 studies.

Statistical Analysis

The pooled RRs for a 1-MET higher level of MAC and the lower CRF in comparison with the higher CRF within each of the 3 comparisons were estimated by using a fixed-effects or random-effects model.[23] If significant heterogeneity of RRs that was tested by calculating the I^2 statistic[24] was present, we chose the pooled estimates from the random-effects model because it is better than the fixed-effects model and it explains between-study heterogeneity.

To examine the effect of study characteristics on risk reduction per 1-MET higher level of MAC, sensitivity analyses were conducted for the possible confounders (mean age [>50 years or not], sex [only men or not], adjustment for smoking [yes or no], adjustment for multiple confounders, defined as adjustment

Table 1. Characteristics of Studies Included in the Meta-analysis

Source (Location)	No. of Partici-pants	Men, %	Mean (or Midpoint) Age, y	Mean Follow-up, y	Methods for Outcome Measures	Specific Outcomes (CHD/CVD Criteria)	No. of Events for Each Outcome	Instrument for Assessing CRF	Whether Max or Sub Reached[a]
Aijaz et al,[29] 2008 (US)	8620	73	52	16	Registry	All-cause mortality	535	Treadmill	Max
Aktas et al,[30] 2004 (US)	3554	81	57	8	Registry	All-cause mortality	114	Treadmill	Sub
Allen et al,[31] 1980 (US)									
Men	350	100	NA	1.1	Questionnaire	CHD event (MI, sudden cardiac death)	34	Ergometer	Max
Women	302	0	NA				10		
Arraiz et al,[32] 2004 (Canada)	NA	NA	47	7	Registry	All-cause mortality; CVD death (NA)	55; 37	Canadian Home Fitness Test	Sub
Balady et al,[33] 2004 (US)									
Men	1431	100	45	18.2	Hospital record	CHD event (onset of AP, coronary insufficiency, MI)	224	Treadmill	Sub
Women	1612	0	45				81		
Bruce et al,[34] 1980 (US)	2365	100	45	5.6	Questionnaire	CHD event (NA)	47	Treadmill	Max
Cumming et al,[35] 1975 (Canada)	486[b]	100	53	3	Questionnaire	CHD event (NA)	26	Ergometer	Max
Erikssen et al,[36] 1998 (Norway)	1428	100	57	13	Registry	All-cause mortality; CVD death (CHD, stroke, the other CVD)	238; 120	Ergometer	Max
Erikssen et al,[37] 2004 (Norway)	2014	100	49	26	Questionnaire and registry	CHD death (CHD, sudden cardiac death)	300	Ergometer	Max
Farrell et al,[38] 2004 (US)	6925	0	43	11.4	Registry	All-cause mortality	195	Treadmill	Sub
Gulati et al,[16] 2003 (US)	5721	0	52	8.4	Registry	All-cause mortality	180	Treadmill	Max
Gulati et al,[39] 2005 (US)	5636	0	52	9	Registry	All-cause mortality; CVD death (*ICD-9, ICD-10*)	171; 52	Treadmill	Max
Gulati et al,[40] 2005 (US)	5721	0	52	8.4	Registry	CVD death (NA)	180	Treadmill	Max
Gyntelberg et al,[41] 1980 (Denmark)	5249	100	50	5	Registry	CHD event (MI, sudden cardiac death)	170	Ergometer	Sub
Hein et al,[42] 1992 (Denmark)	4999	100	48	17	Registry	All-cause mortality	941	Ergometer	Sub
Jouven et al,[43] 2005 (France)	5713[b]	100	48	23	Hospital record	CHD death (MI death)	210	Ergometer	Sub
Kampert et al,[44] 1996 (US)	25 341	100	43	8.4	Registry	All-cause mortality	601	Treadmill	Sub
Katzmarzyk et al,[45] 2005 (US)	19 173	100	43	10.2	Registry	All-cause mortality	477	Treadmill	Sub
Laukkanen et al,[8] 2007 (Finland)	1639	100	52	16.6	Registry	All-cause mortality; CVD event (*ICD-9, ICD-10*)	304; 340	Ergometer	Max
Laukkanen et al,[9] 2008 (Finland)	1639	100	52	16.6	Registry	All-cause mortality; CVD event (*ICD-9, ICD-10*)	304; 340	Ergometer	Max
Miller et al,[6] 2005 (UK)	578	100	52	7.3	Questionnaire, registry, and hospital record	All-cause mortality; CVD event (*ICD-9*)	68; 62	Ergometer	Sub
Mora et al,[46] 2003 (US)	2994	0	55	20.3	Questionnaire and registry	All-cause mortality; CVD death (NA)	427; 147	Treadmill	Sub
Myers et al,[47] 2002 (US)	2534[b]	100	56	6.2	Registry	All-cause mortality	288	Treadmill and ergometer	Sub
Peters et al,[48] 1983 (US)	2779	100	45	4.8	Hospital record	CHD event (MI, sudden cardiac death)	36	Ergometer	Sub
Rywik et al,[49] 2002 (US)	1083	57	52	8.8	Registry	CHD event (AP, MI, sudden cardiac death)	76	Treadmill	Max

(continued)

Table 1. Characteristics of Studies Included in the Meta-analysis (continued)

Source (Location)	No. of Partici-pants	Men, %	Mean (or Midpoint) Age, y	Mean Follow-up, y	Methods for Outcome Measures	Specific Outcomes (CHD/CVD Criteria)	No. of Events for Each Outcome	Instrument for Assessing CRF	Whether Max or Sub Reached[a]
Sandvik et al,[50] 1988 (Norway)	1960[b]	100	50	15.9	Registry	All-cause mortality; CVD death (NA)	271; 143	Ergometer	Max
Sawada and Muto,[51] 1999 (Japan)	9986[b]	100	37	14	Questionnaire	All-cause mortality; CHD death (*ICD-10*)	247; 72	Ergometer	Sub
Slattery and Jacobs,[5] 1988 (US)	2431	100	50	18.5	Registry	All-cause mortality; CHD death (*ICD-8*)	631; 258	Treadmill	Sub
Sobolski et al,[52] 1987 (Belgium)	1476	100	48	5	Registry	CHD event (MI, sudden cardiac death)	19	Ergometer	Sub
Stevens et al,[21] 2002 (US)									
Men	2860	100	45	26	Questionnaire and registry	All-cause mortality; CVD death (*ICD-9*)	682; 270	Treadmill	Sub
Women	2506	0	47				484; 179		
Stevens et al,[22] 2004 (US)	1359	100	49	19	Questionnaire and registry	All-cause mortality; CVD death (*ICD-9*)	211; 98	Treadmill	Sub
Sui et al,[7] 2007 (US)									
Men	20 278	100	44	10.4	Questionnaire	CVD event (MI, stroke, coronary revascularization)	1512	Treadmill	Sub
Women	5909	0	45				159		
Villeneuve et al,[53] 1998 (Canada)	7561	48	45	7	Registry	All-cause mortality	129	Canadian Home Fitness Test	Sub

Abbreviations: AP, angina pectoris; CHD, coronary heart disease; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; *ICD-8*, *International Classification of Diseases, Eighth Revision*; *ICD-9, International Classification of Diseases, Ninth Revision*; *ICD-10, International Statistical Classification of Diseases, 10th Revision*; MI, myocardial infarction; NA, not available.
[a] Max, workload testing was continued until maximal workload; Sub, maximal workload was predicted from findings of submaximal exercise workload.
[b] Including participants with abnormal exercise electrocardiogram (ie, ST elevation/depression).

for >3 factors among obesity, hypertension, total cholesterol or low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and diabetes [yes or no], mean follow-up [>12 years or <12 years], instrument for assessing CRF [ergometer or others], and maximal exercise testing [yes or no]). To examine the extent to which between-study heterogeneity was explained by these study characteristics, we additionally conducted linear multiple regression analyses by simultaneously entering these confounders as explanatory variables.

Categorical analyses were repeated with multiadjustment for the prespecified confounders to consider the potential heterogeneity of study characteristics among the subgroups (ie, low vs high CRF, low vs intermediate CRF, and intermediate vs high CRF). Tests of interaction were performed to assess whether the association between CRF and the study outcomes varied across these 3 subgroups.

The Begg and Egger tests[25,26] were used for assessment of publication bias (ie, the tendency for positive associations to be published and negative or null associations to be unpublished). We also followed the Duval and Tweedie "trim and fill" procedure[27] as a method of adjustment for suspected publication bias. This method considers the possibility of hypothetical "missing" studies that might exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical missing studies as though they actually existed.

Two-sided $P < .05$ was considered statistically significant, except for the test of publication bias for which the recommended levels are $P < .10$.[28] Data were analyzed using STATA version 10 (STATA Corp, College Station, Texas).

RESULTS

Literature Search and Study Characteristics

FIGURE 1 shows the number of studies that were identified and excluded at different stages of the selection process. A total of 33 studies[5-9,16,21,22,29-53] were included in our meta-analysis. Characteristics of the 33 selected studies comprising 102 980 participants (range, 486-25 341) and 6910 cases (range, 26-941) for all-cause mortality and 84 323 participants (range, 302-20 278) and 4485 cases (range, 10-1512) for CHD/CVD are shown in **TABLE 1**. Twenty-one studies* reported all-cause mortality and 24 studies† reported CVD/CHD. Mean age and follow-up duration ranged from 37 to 57 years and 1.1 to 26 years, respectively. Eight studies[8,33,37,39,45,46,49,52] were used for the dose-response analyses only and 4 studies[9,16,40,44] were used for the categorical analyses only. In 20 studies,‡ RRs were adjusted for smoking and in 9 stud-

*References 5, 6, 8, 9, 16, 21, 22, 29, 30, 32, 36, 38, 39, 42, 44-47, 50, 51, 53.
†References 5-9, 21, 22, 31-37, 39-41, 43, 46, 48-52.
‡References 5, 7-9, 16, 21, 22, 30, 32, 33, 37-39, 44-46, 48, 50, 52, 53.

ies,[7-9,16,33,39,46,50,52] there were multiple study confounders (available in an eTable [http://www.jama.com]).

Dose-response Analyses

FIGURE 2 shows the pooled estimates for the reduction in risk of all-cause mortality and CHD/CVD per higher MET of exercise capacity. Pooled RRs of all-cause mortality and CHD/CVD per 1-MET higher level of MAC were 0.87 (95% CI, 0.84-0.90) and 0.85 (95% CI, 0.82-0.88), respectively. There was evidence of statistical heterogeneity of RRs across studies ($I^2=82.3\%$; $P<.001$ for all-cause mortality; $I^2=74.7\%$; $P<.001$ for CHD/CVD).

TABLE 2 shows the results of analyses investigating the associations of study characteristics on each outcome. The finding of risk reduction per higher MET for all-cause mortality and CHD/CVD was consistently significant in all of the stratified analyses. However, studies with a follow-up of at least 12 years had weaker associations with study outcomes compared with those that had follow-up of less than 12 years for all-cause mortality ($P=.08$) and CHD/CVD events ($P=.004$). The associations between CRF and risk of CHD/CVD events were stronger in studies that used an ergometer for assessing CRF ($P=.009$) or conducted maximal exercise testing ($P=.02$) and were weaker in studies that were adjusted for smoking ($P=.006$) or multiple metabolic factors ($P=.06$). However, these study characteristics did not influence the associations between MAC and risk of all-cause mortality.

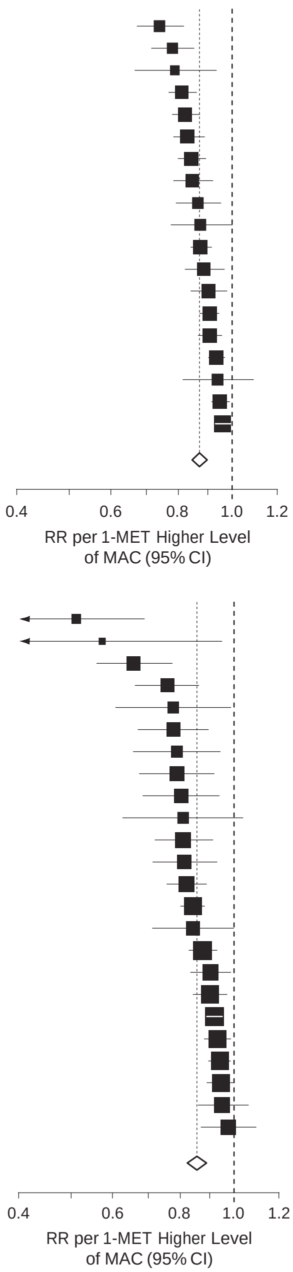
Multiple regression analyses in which all the study characteristics listed in Table 2 were entered as independent variables indicated that study characteristics significantly explained the heterogeneity of the RRs per 1-MET higher level of MAC (all-cause mortality, 79% of total variance; $P=.01$; and CHD/CVD, 67% of total variance; $P=.01$). After adjustment for these study characteristics, there were neither significant differences in risk estimates of CHD/CVD between CHD and CVD (0.89; 95% CI, 0.86-0.92 and 0.89; 95% CI, 0.87-0.90, respectively; $P=.99$) nor between CHD or CVD death and CHD or CVD events (0.88; 95% CI, 0.86-0.90 and 0.90; 95% CI, 0.88-0.91, respectively; $P=.27$).

Categorical Analyses

We performed categorical analyses to summarize the risk of all-cause mortality and CHD/CVD for 3 subgroups (low vs high CRF [**FIGURE 3**], low vs inter-

Figure 2. Meta-analysis of All-Cause Mortality and CHD/CVD per 1-MET Higher Level of MAC

Source	Weight, %	RR (95% CI)
All-cause mortality		
Erikksen et al,[36] 1998	4.46	0.74 (0.67-0.81)
Aktas et al,[30] 2004	4.52	0.78 (0.71-0.85)
Miller et al,[6] 2005	2.33	0.78 (0.66-0.93)
Katzmarzyk et al,[45] 2005	6.01	0.81 (0.77-0.86)
Laukkanen et al,[8] 2007	5.78	0.82 (0.77-0.87)
Gulati et al,[39] 2005	5.59	0.83 (0.78-0.89)
Myers et al,[47] 2002	5.84	0.84 (0.79-0.89)
Sawada and Muto,[51] 1999	4.85	0.85 (0.78-0.92)
Arraiz et al,[32] 1992	4.45	0.87 (0.79-0.95)
Sandvik et al,[50] 1993	3.38	0.88 (0.77-1.00)
Mora et al,[46] 2003	6.43	0.88 (0.84-0.92)
Stevens et al,[21] 2002 [women]	4.99	0.89 (0.82-0.96)
Farrell et al,[38] 2002	5.27	0.91 (0.84-0.98)
Aijaz et al,[29] 2008	6.64	0.91 (0.87-0.94)
Stevens et al,[22] 2004	6.21	0.91 (0.87-0.96)
Stevens et al,[21] 2002 [men]	6.79	0.94 (0.91-0.97)
Villeneuve et al,[53] 1998	2.84	0.94 (0.81-1.09)
Hein et al,[42] 1992	6.77	0.95 (0.92-0.98)
Slattery and Jacobs,[5] 1988	6.85	0.96 (0.93-0.99)
Overall	100.00	0.87 (0.84-0.90)
Test for heterogeneity: $I^2=82.3\%$; $P<.001$		
CHD/CVD		
Allen et al,[31] 1980 [women]	1.32	0.51 (0.38-0.68)
Sobolski et al,[52] 1987	0.49	0.57 (0.35-0.94)
Allen et al,[31] 1980 [men]	3.12	0.65 (0.56-0.76)
Bruce et al,[34] 1980	3.66	0.75 (0.65-0.85)
Peters et al,[48] 1983	1.70	0.77 (0.60-0.98)
Arraiz et al,[32] 1992	3.37	0.77 (0.66-0.89)
Miller et al,[6] 2005	2.54	0.78 (0.65-0.94)
Gulati et al,[39] 2005	3.11	0.78 (0.67-0.91)
Rywik et al,[49] 2002	2.98	0.79 (0.68-0.93)
Cumming et al,[35] 1975	1.58	0.80 (0.62-1.03)
Jouven et al,[43] 2005	4.22	0.80 (0.71-0.90)
Sawada and Muto,[51] 1999	3.77	0.81 (0.71-0.92)
Gyntelberg et al,[41] 1980	5.36	0.81 (0.75-0.88)
Mora et al,[46] 2003	6.59	0.83 (0.79-0.87)
Stevens et al,[21] 2002 [women]	2.83	0.83 (0.70-0.99)
Laukkanen et al,[8] 2007	6.28	0.87 (0.82-0.92)
Erriksen et al,[37] 2004	5.32	0.90 (0.83-0.98)
Stevens et al,[22] 2004	5.89	0.90 (0.84-0.96)
Sui et al,[7] 2007 [men]	7.18	0.91 (0.89-0.94)
Stevens et al,[21] 2002 [men]	6.48	0.93 (0.88-0.98)
Slattery and Jacobs,[5] 1988	6.86	0.94 (0.90-0.97)
Balady et al,[33] 2004 [men]	6.43	0.94 (0.89-0.99)
Sui et al,[7] 2007 [women]	4.67	0.94 (0.85-1.05)
Balady et al,[33] 2004 [women]	4.27	0.97 (0.87-1.09)
Overall	100.00	0.85 (0.82-0.88)
Test for heterogeneity: $I^2=74.7\%$; $P<.001$		



CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MAC, maximal aerobic capacity; MET, metabolic equivalent; RR, risk ratio. Area of each square is proportional to study weight.

mediate CRF [**FIGURE 4**], and intermediate vs high CRF [**FIGURE 5**]). After adjustment for heterogeneity of study characteristics and compared with high and intermediate CRF, respectively, the pooled RRs for the association of low CRF with all-cause mortality were 1.70 (95% CI, 1.51-1.92) and 1.56 (95% CI, 1.39-1.75), respectively. After adjustment for heterogeneity and compared with high and intermediate CRF, respectively, the pooled RRs for the association of low CRF with CHD/CVD events were 1.40 (95% CI, 1.32-1.48) and 1.47 (95% CI, 1.35-1.61), respectively. The pooled RRs for the associations of intermediate CRF with all-cause mortality and CHD/CVD events compared with high CRF were 1.13 (95% CI, 1.04-1.22) and 1.07 (95% CI, 1.01-1.13), respectively. However, tests of the interaction indicated that these estimates for comparisons between intermediate and high risk were significantly lower than for those between low vs high CRF and low vs intermediate CRF ($P<.001$ for any comparisons). Tests of interaction also indicated that there were no significant differences in risk estimates for low vs high CRF compared with low vs intermediate CRF (all-cause mortality, $P=.28$; CHD/CVD, $P=.33$).

Publication Bias

In risk estimates per 1-MET higher level of MAC, there was a statistically significant publication bias according to Egger test (all-cause mortality, $P=.002$; CHD/CVD, $P=.02$). However, adjustment for publication bias by the trim and fill procedure could not detect hypothetical negative unpublished studies that could influence the study. In some of the categorical analyses, statistically significant publication bias was also observed in risk estimates after adjustment for heterogeneity of study characteristics (pooled RR of all-cause mortality for low vs high CRF and low vs intermediate CRF, $P=.03$ by Egger test and $P=.03$ by Begg test, respectively; pooled RR of CHD/CVD for low vs intermediate CRF, $P<.001$ by Egger test). After incorporating the hypothetical studies using trim and fill methods, the risk estimates were attenuated in risk of all-cause mortality for low vs high CRF (RR, 1.48; 95% CI, 1.31-1.68) and low vs intermediate CRF (RR, 1.35; 95% CI, 1.18-1.54), and CHD/CVD for low vs high CRF (RR, 1.38; 95% CI, 1.30-1.45), which suggested the existence of potentially negative studies. Nevertheless, these biases did not change the general conclusions.

COMMENT

Our meta-analysis is the first to our knowledge to quantify CRF as measured by METs, which is a standard scale for expressing exercise workload, and its relationship to all-cause mortality and CHD or CVD events in healthy men and women. According to the dose-response analyses, a 1-MET higher level of MAC was as-

Table 2. Stratified Analyses of Pooled RR of All-Cause Mortality and CVD/CHD for Each MET Higher Level of Maximal Aerobic Capacity

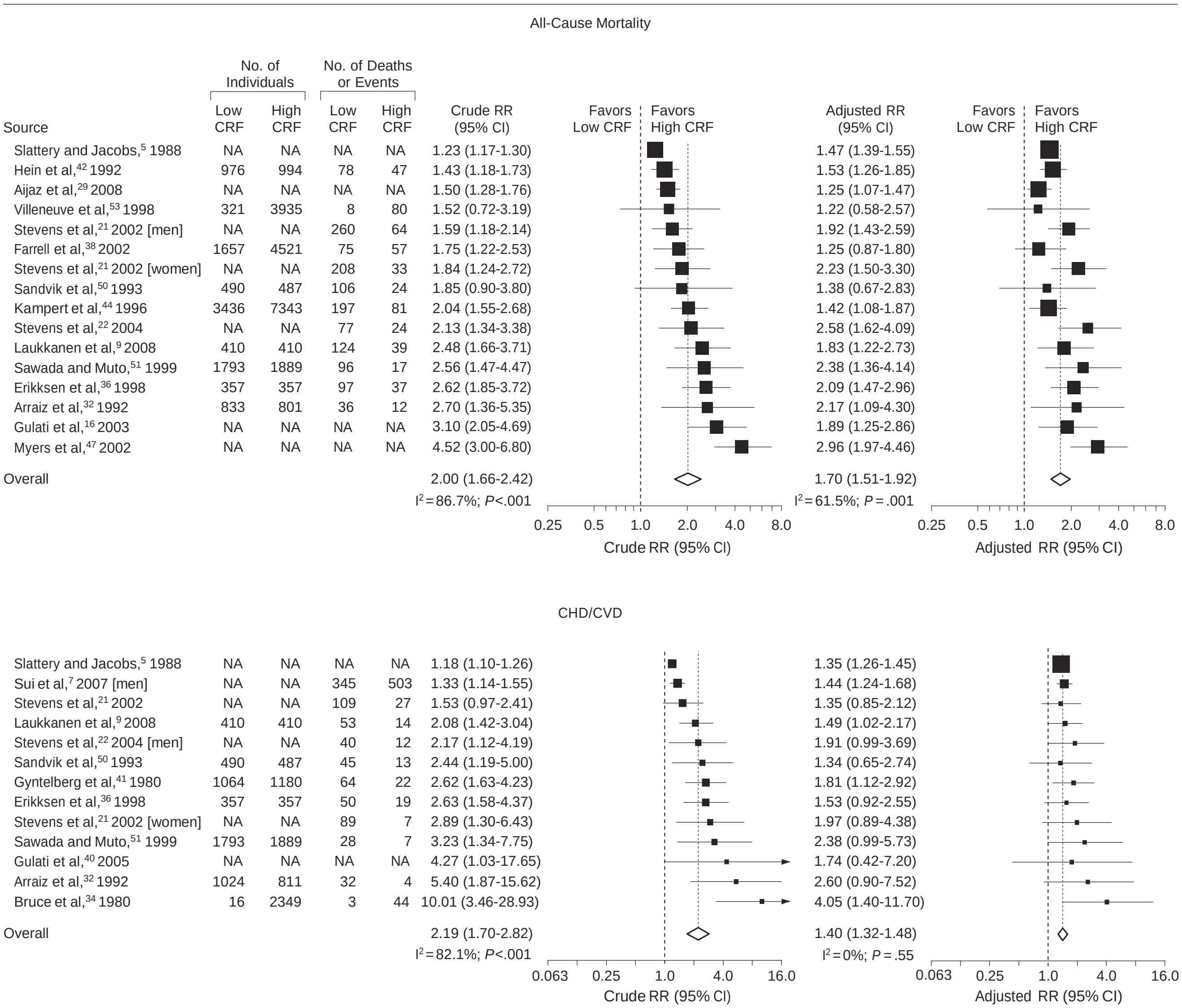
Characteristics	All-Cause Mortality: No. of Cohorts	RR (95% CI)	*P* Value[a]	CHD/CVD: No. of Cohorts	RR (95% CI)	*P* Value[a]
Mean age, >50 y						
No	10	0.90 (0.86-0.93)	.10	16	0.89 (0.88-0.91)	.80
Yes	9	0.84 (0.80-0.89)		8	0.84 (0.79-0.90)	
Only men						
No	8	0.87 (0.84-0.91)	.88	8	0.84 (0.81-0.87)	.60
Yes	11	0.87 (0.83-0.91)		16	0.86 (0.83-0.89)	
Adjustment for confounders, smoking						
No	7	0.87 (0.83-0.93)	.82	10	0.77 (0.70-0.85)	.006
Yes	12	0.87 (0.84-0.90)		14	0.89 (0.86-0.92)	
>3 Metabolic factors[b]						
No	14	0.86 (0.84-0.89)	.67	16	0.81 (0.77-0.86)	.06
Yes	5	0.86 (0.83-0.89)		8	0.89 (0.85-0.93)	
Patients with abnormal exercise electrocardiogram						
No	10	0.85 (0.81-0.90)	.20	16	0.83 (0.79-0.88)	.40
Yes	9	0.90 (0.86-0.93)		8	0.90 (0.88-0.92)	
Mean follow-up, 12 y						
No	8	0.84 (0.82-0.86)	.08	13	0.78 (0.72-0.84)	.004
Yes	11	0.91 (0.9-0.93)		11	0.89 (0.86-0.92)	
Ergometer used to assess CRF						
No	13	0.90 (0.89-0.92)	.82	13	0.89 (0.86-0.92)	.009
Yes	6	0.88 (0.84-0.91)		11	0.78 (0.73-0.84)	
Whether workload testing was continued until maximal workload						
No	15	0.88 (0.85-0.91)	.24	16	0.88 (0.85-0.91)	.02
Yes	4	0.84 (0.76-0.92)		8	0.77 (0.70-0.85)	

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; RR, risk ratio.
[a] Represents meta-regression for differences across strata.
[b] Means of adjustment for more than 3 coronary risk factors among obesity (or body mass index or waist-to-hip ratio), systolic blood pressure (or hypertension), total cholesterol (or low-density lipoprotein cholesterol or hyperlipidemia), high-density lipoprotein cholesterol, and diabetes.

sociated with 13% and 15% decrements in risk of all-cause mortality and CHD/CVD, respectively. From the clinical viewpoint, these values may be considerable. For example, based on risk estimates of the components of metabolic syndrome according to the National Cholesterol Education Program,[54] these findings suggest that a 1-MET higher level of MAC is comparable to a 7-cm, 5-mm Hg, 1-mmol/L, and 1-mmol/L decrement in waist circumference,[55] systolic blood pressure,[56] triglyceride level (in men),[57] and fasting plasma glucose,[58] respectively, and a 0.2-mmol/L increment in high-density lipoprotein cholesterol.[59] It is possible that prediction of CHD risk could be improved by including CRF with already established risk factors for CHD.

In categorical analyses, individuals with low CRF (<7.9 METs in MAC) had a substantially higher risk of all-cause mortality and CHD/CVD compared with those with intermediate and high CRF (7.9-10.8 and >10.9 METs in MAC, respectively). These risk estimates were higher than those for individuals with intermediate CRF compared with those with high CRF, according to the test of interaction. These analyses suggest that a minimal CRF of 7.9 METs may be important for significant prevention of all-cause mortality and CHD/CVD. A previous review suggested that physical activity yielding 1000 kcal energy expenditure per week is needed for signifi-

Figure 3. Meta-analysis of All-Cause Mortality and CHD/CVD for Individuals With Low vs High CRF



All-Cause Mortality

Source	No. of Individuals, Low CRF	No. of Individuals, High CRF	No. of Deaths or Events, Low CRF	No. of Deaths or Events, High CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Slattery and Jacobs,[5] 1988	NA	NA	NA	NA	1.23 (1.17-1.30)	1.47 (1.39-1.55)
Hein et al,[42] 1992	976	994	78	47	1.43 (1.18-1.73)	1.53 (1.26-1.85)
Aijaz et al,[29] 2008	NA	NA	NA	NA	1.50 (1.28-1.76)	1.25 (1.07-1.47)
Villeneuve et al,[53] 1998	321	3935	8	80	1.52 (0.72-3.19)	1.22 (0.58-2.57)
Stevens et al,[21] 2002 [men]	NA	NA	260	64	1.59 (1.18-2.14)	1.92 (1.43-2.59)
Farrell et al,[38] 2002	1657	4521	75	57	1.75 (1.22-2.53)	1.25 (0.87-1.80)
Stevens et al,[21] 2002 [women]	NA	NA	208	33	1.84 (1.24-2.72)	2.23 (1.50-3.30)
Sandvik et al,[50] 1993	490	487	106	24	1.85 (0.90-3.80)	1.38 (0.67-2.83)
Kampert et al,[44] 1996	3436	7343	197	81	2.04 (1.55-2.68)	1.42 (1.08-1.87)
Stevens et al,[22] 2004	NA	NA	77	24	2.13 (1.34-3.38)	2.58 (1.62-4.09)
Laukkanen et al,[9] 2008	410	410	124	39	2.48 (1.66-3.71)	1.83 (1.22-2.73)
Sawada and Muto,[51] 1999	1793	1889	96	17	2.56 (1.47-4.47)	2.38 (1.36-4.14)
Erikksen et al,[36] 1998	357	357	97	37	2.62 (1.85-3.72)	2.09 (1.47-2.96)
Arraiz et al,[32] 1992	833	801	36	12	2.70 (1.36-5.35)	2.17 (1.09-4.30)
Gulati et al,[16] 2003	NA	NA	NA	NA	3.10 (2.05-4.69)	1.89 (1.25-2.86)
Myers et al,[47] 2002	NA	NA	NA	NA	4.52 (3.00-6.80)	2.96 (1.97-4.46)
Overall					2.00 (1.66-2.42) $I^2 = 86.7\%$; $P<.001$	1.70 (1.51-1.92) $I^2 = 61.5\%$; $P = .001$

CHD/CVD

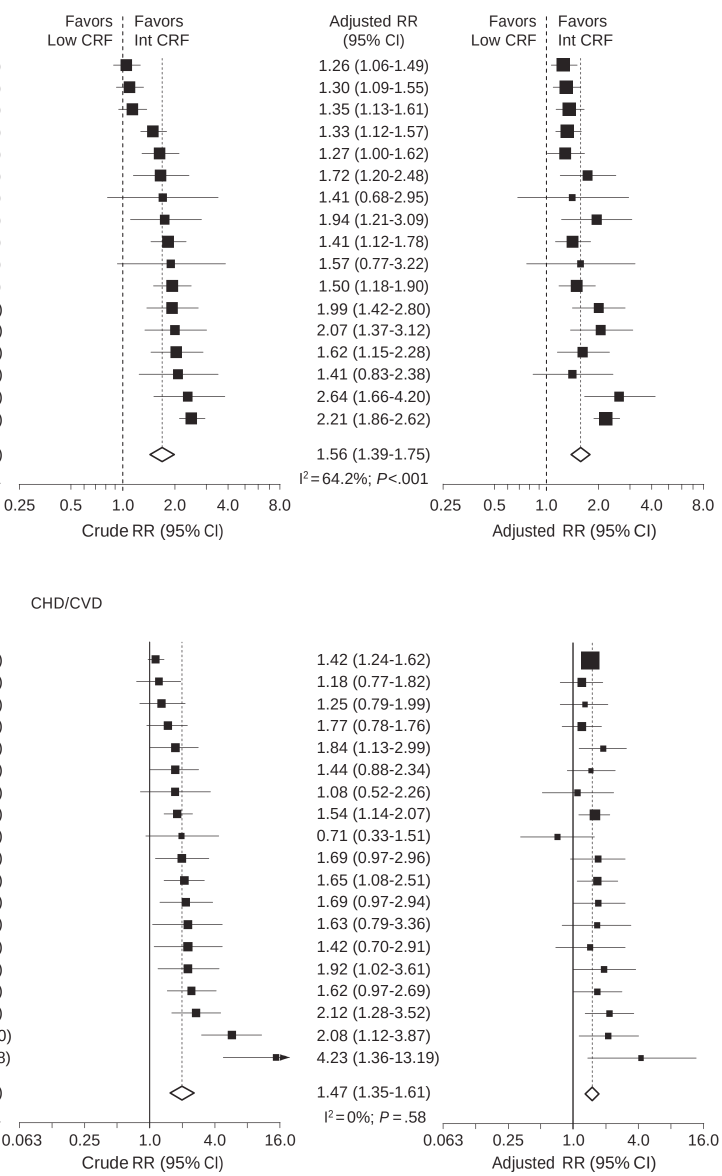
Source	No. of Individuals, Low CRF	No. of Individuals, High CRF	No. of Deaths or Events, Low CRF	No. of Deaths or Events, High CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Slattery and Jacobs,[5] 1988	NA	NA	NA	NA	1.18 (1.10-1.26)	1.35 (1.26-1.45)
Sui et al,[7] 2007 [men]	NA	NA	345	503	1.33 (1.14-1.55)	1.44 (1.24-1.68)
Stevens et al,[21] 2002	NA	NA	109	27	1.53 (0.97-2.41)	1.35 (0.85-2.12)
Laukkanen et al,[9] 2008	410	410	53	14	2.08 (1.42-3.04)	1.49 (1.02-2.17)
Stevens et al,[22] 2004 [men]	NA	NA	40	12	2.17 (1.12-4.19)	1.91 (0.99-3.69)
Sandvik et al,[50] 1993	490	487	45	13	2.44 (1.19-5.00)	1.34 (0.65-2.74)
Gyntelberg et al,[41] 1980	1064	1180	64	22	2.62 (1.63-4.23)	1.81 (1.12-2.92)
Erikksen et al,[36] 1998	357	357	50	19	2.63 (1.58-4.37)	1.53 (0.92-2.55)
Stevens et al,[21] 2002 [women]	NA	NA	89	7	2.89 (1.30-6.43)	1.97 (0.89-4.38)
Sawada and Muto,[51] 1999	1793	1889	28	7	3.23 (1.34-7.75)	2.38 (0.99-5.73)
Gulati et al,[40] 2005	NA	NA	NA	NA	4.27 (1.03-17.65)	1.74 (0.42-7.20)
Arraiz et al,[32] 1992	1024	811	32	4	5.40 (1.87-15.62)	2.60 (0.90-7.52)
Bruce et al,[34] 1980	16	2349	3	44	10.01 (3.46-28.93)	4.05 (1.40-11.70)
Overall					2.19 (1.70-2.82) $I^2 = 82.1\%$; $P<.001$	1.40 (1.32-1.48) $I^2 = 0\%$; $P = .55$

CHD indicates coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; MET, metabolic equivalent; NA, not available; RR, risk ratio. Low and high CRF categories were defined as less than 7.9 METs and 10.9 METs or more of maximal aerobic capacity, respectively, under the assumption that all participants were 50-year-old men. Crude and adjusted RR indicate RRs before and after adjustment for study heterogeneity among the subgroups, respectively.

cant risk reduction of all-cause mortality.[60] However, using CRF may be preferable to using physical activity as risk predictors because 1 prior study[61] suggested that physical fitness was more strongly correlated with CHD than physical activity.

According to the results reported herein, the minimum CRF level that is associated with significantly lower event rates for men and women is approximately 9 and 7 METs (at 40 years old), 8 and 6 METs (at 50 years), and 7 and 5 METs (at 60 years), respectively. This means that women and men younger than 60 years

Figure 4. Meta-analysis of All-Cause Mortality and CHD/CVD for Individuals With Low vs Intermediate CRF



All-Cause Mortality

Source	No. of Individuals: Low CRF	No. of Individuals: Int CRF	No. of Deaths or Events: Low CRF	No. of Deaths or Events: Int CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Hein et al,[42] 1992 [second]	976	1012	78	62	1.05 (0.89-1.25)	1.26 (1.06-1.49)
Hein et al,[42] 1992 [fourth]	976	1010	78	61	1.09 (0.91-1.30)	1.30 (1.09-1.55)
Hein et al,[42] 1992 [third]	976	1007	78	56	1.13 (0.95-1.35)	1.35 (1.13-1.61)
Erikksen et al,[36] 1998 [third]	357	157	97	65	1.49 (1.26-1.77)	1.33 (1.12-1.57)
Kampert et al,[44] 1996 [third]	3436	4560	197	110	1.64 (1.29-2.09)	1.27 (1.00-1.62)
Sawada and Muto,[51] 1999 [fourth]	1793	2123	96	49	1.67 (1.16-2.40)	1.72 (1.20-2.48)
Sandvik et al,[50] 1993 [third]	490	491	106	77	1.69 (0.81-3.54)	1.41 (0.68-2.95)
Myers et al,[47] 2002 [fourth]	NA	NA	NA	NA	1.75 (1.10-2.80)	1.94 (1.21-3.09)
Kampert et al,[44] 1996 [fourth]	3436	4237	197	111	1.82 (1.44-2.29)	1.41 (1.12-1.78)
Sandvik et al,[50] 1993 [second]	490	492	106	64	1.89 (0.92-3.86)	1.57 (0.77-3.22)
Kampert et al,[44] 1996 [second]	3436	5765	197	102	1.92 (1.52-2.44)	1.50 (1.18-1.90)
Sawada and Muto,[51] 1999 [second]	1793	2143	96	35	1.92 (1.37-2.70)	1.99 (1.42-2.80)
Sawada and Muto,[51] 1999 [third]	1793	2038	96	50	2.00 (1.33-3.02)	2.07 (1.37-3.12)
Farrell et al,[38] 2002	1657	747	75	63	2.04 (1.45-2.87)	1.62 (1.15-2.28)
Miller et al,[6] 2005	286	292	45	23	2.08 (1.23-3.52)	1.41 (0.83-2.38)
Myers et al,[47] 2002 [third]	NA	NA	NA	NA	2.39 (1.50-3.80)	2.64 (1.66-4.20)
Erikksen et al,[36] 1998 [second]	357	357	97	39	2.49 (2.10-2.95)	2.21 (1.86-2.62)
Overall					1.68 (1.43-1.97)	1.56 (1.39-1.75)
					$I^2 = 82.9\%$; $P < .001$	$I^2 = 64.2\%$; $P < .001$

CHD/CVD

Source	No. of Individuals: Low CRF	No. of Individuals: Int CRF	No. of Deaths or Events: Low CRF	No. of Deaths or Events: Int CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Sui et al,[7] 2007 [men]	NA	NA	345	664	1.12 (0.98-1.28)	1.42 (1.24-1.62)
Sui et al,[7] 2007 [women, second]	NA	NA	35	63	1.20 (0.78-1.85)	1.18 (0.77-1.82)
Sui et al,[7] 2007 [women, first]	NA	NA	35	61	1.28 (0.81-2.03)	1.25 (0.79-1.99)
Gyntelberg et al,[41] 1980 [fourth]	1064	923	64	34	1.45 (0.97-2.19)	1.77 (0.78-1.76)
Erikksen et al,[36] 1998 [third]	357	357	50	30	1.67 (1.02-2.72)	1.84 (1.13-2.99)
Sawada and Muto,[51] 1999 [fourth]	1793	2038	28	14	1.67 (1.02-2.71)	1.44 (0.88-2.34)
Sandvik et al,[50] 1993 [third]	490	491	45	38	1.69 (0.81-3.54)	1.08 (0.52-2.26)
Jouven et al,[43] 2005	3305	2408	152	58	1.78 (1.32-2.40)	1.54 (1.14-2.07)
Cumming et al,[35] 1980	204	282	15	11	1.96 (0.92-4.17)	0.71 (0.33-1.51)
Sawada and Muto,[51] 1999 [third]	1793	2123	28	14	1.96 (1.12-3.43)	1.69 (0.97-2.96)
Gyntelberg et al,[41] 1980 [third]	1064	1170	64	31	2.05 (1.34-3.12)	1.65 (1.08-2.51)
Miller et al,[6] 2005	286	292	43	19	2.13 (1.22-3.70)	1.69 (0.97-2.94)
Peters et al,[48] 1983	NA	NA	26	10	2.20 (1.06-4.55)	1.63 (0.79-3.36)
Sandvik et al,[50] 1993 [second]	490	492	45	32	2.22 (1.09-4.54)	1.42 (0.70-2.91)
Sawada and Muto,[51] 1999 [second]	1793	2143	28	9	2.22 (1.18-4.18)	1.92 (1.02-3.61)
Erikksen et al,[36] 1998 [second]	357	357	50	31	2.38 (1.43-3.95)	1.62 (0.97-2.69)
Gyntelberg et al,[41] 1980 [second]	1064	912	64	19	2.63 (1.59-4.36)	2.12 (1.28-3.52)
Allen et al,[31] 1980 [men]	21	329	9	25	5.64 (3.03-10.50)	2.08 (1.12-3.87)
Allen et al,[31] 1980 [women]	13	289	4	6	14.82 (4.76-46.18)	4.23 (1.36-13.19)
Overall					1.96 (1.59-2.42)	1.47 (1.35-1.61)
					$I^2 = 74.6\%$; $P < .001$	$I^2 = 0\%$; $P = .58$

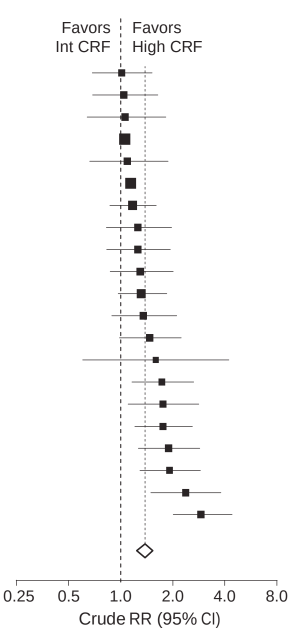
CHD indicates coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; Int, intermediate; MET, metabolic equivalent; NA, not available; RR, risk ratio. Low and intermediate CRF categories were defined as less than 7.9 METs and 7.9 to 10.8 METs of maximal aerobic capacity, respectively, under the assumption that all participants were 50-year-old men. Crude and adjusted RR indicate RRs before and after adjustment for study heterogeneity among the subgroups, respectively. The words first, second, third, and fourth in brackets represent comparisons between the lowest CRF category and the highest, second, third, or fourth CRF category in the relevant study.

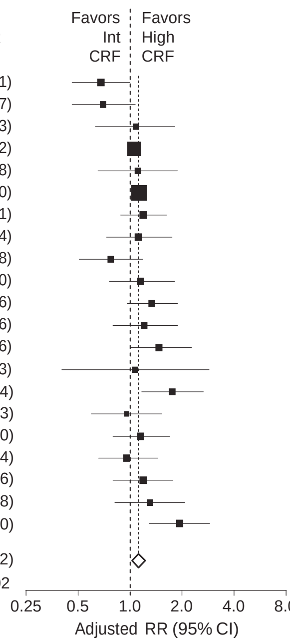
would need to complete stage I (1.7 mph at gradient 10°) and stage II (2.5 mph at gradient 12°), respectively, of the standard Bruce protocol, which is one of the most commonly used treadmill tests in clinical settings.[14] If the CRF level is expressed in terms of walking speed, men around 50 years of age must be capable of continuous walking at a speed of 4 mph and women must continuously walk at 3 mph for prevention of CHD,[17] with the assumption that the anaerobic threshold is 50%

Figure 5. Meta-analysis of All-Cause Mortality and CHD/CVD for Individuals With Intermediate vs High CRF

All-Cause Mortality

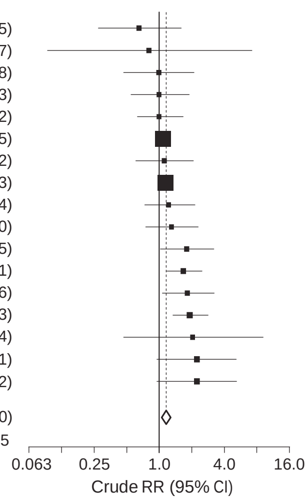
Source	No. of Individuals: Int CRF	No. of Individuals: High CRF	No. of Deaths or Events: Int CRF	No. of Deaths or Events: High CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Villeneuve et al,[53] 1998	3395	321	41	8	1.02 (0.69-1.51)	0.68 (0.46-1.01)
Erikksen et al,[36] 1998 [second]	357	357	39	37	1.05 (0.69-1.61)	0.70 (0.46-1.07)
Stevens et al,[22] 2004 [fourth]	NA	NA	36	27	1.07 (0.63-1.81)	1.08 (0.64-1.83)
Slattery and Jacobs,[5] 1988 [second]	NA	NA	NA	NA	1.07 (1.02-1.13)	1.06 (1.01-1.12)
Stevens et al,[22] 2004 [third]	NA	NA	32	27	1.10 (0.65-1.87)	1.11 (0.65-1.88)
Slattery and Jacobs,[5] 1988 [third]	NA	NA	NA	NA	1.15 (1.10-1.21)	1.14 (1.09-1.20)
Stevens et al,[21] 2002 [men, third]	NA	NA	127	64	1.18 (0.87-1.60)	1.19 (0.88-1.61)
Hein et al,[42] 1992 [third]	1007	994	56	47	1.26 (0.82-1.95)	1.12 (0.73-1.74)
Laukkanen et al,[9] 2008 [second]	410	410	52	39	1.26 (0.83-1.92)	0.77 (0.51-1.18)
Hein et al,[42] 1992 [fourth]	1010	994	61	47	1.31 (0.85-2.02)	1.17 (0.76-1.80)
Stevens et al,[21] 2002 [fourth]	NA	NA	88	64	1.33 (0.96-1.85)	1.34 (0.97-1.86)
Hein et al,[42] 1992 [second]	1012	994	62	47	1.36 (0.88-2.09)	1.21 (0.78-1.86)
Stevens et al,[21] 2002 [women, third]	NA	NA	80	33	1.48 (0.98-2.24)	1.49 (0.99-2.26)
Arraiz et al,[29] 1992	370	801	7	12	1.60 (0.60-4.23)	1.07 (0.40-2.83)
Stevens et al,[21] 2002 [women, fourth]	NA	NA	104	33	1.75 (1.17-2.62)	1.76 (1.18-2.64)
Myers et al,[47] 2002 [third]	NA	NA	NA	NA	1.75 (1.10-2.80)	0.96 (0.60-1.53)
Erikksen et al,[36] 1998 [third]	357	357	65	37	1.76 (1.21-2.56)	1.16 (0.80-1.70)
Gulati et al,[16] 2003	NA	NA	NA	NA	1.90 (1.27-2.84)	0.97 (0.65-1.44)
Laukkanen et al,[9] 2008 [third]	409	410	89	39	1.94 (1.31-2.88)	1.19 (0.80-1.76)
Myers et al,[47] 2002 [fourth]	NA	NA	NA	NA	2.39 (1.50-3.80)	1.31 (0.82-2.08)
Aktas et al,[30] 2004	904	2650	64	50	2.95 (1.98-4.39)	1.95 (1.31-2.90)
Overall					1.38 (1.25-1.53) $I^2=70.7\%$; $P<.001$	1.13 (1.04-1.22) $I^2=43.3\%$; $P=.02$

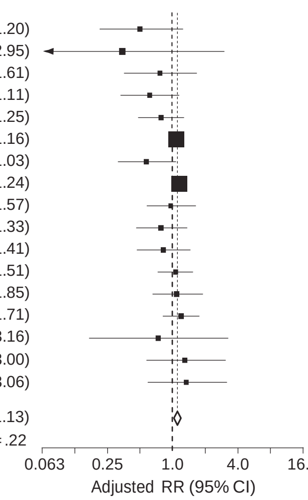




CHD/CVD

Source	No. of Individuals: Int CRF	No. of Individuals: High CRF	No. of Deaths or Events: Int CRF	No. of Deaths or Events: High CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Stevens et al,[22] 2004 [third]	NA	NA	10	12	0.65 (0.27-1.55)	0.50 (0.21-1.20)
Arraiz et al,[32] 1992	376	811	1	4	0.80 (0.09-6.97)	0.34 (0.04-2.95)
Stevens et al,[21] 2004 [fourth]	NA	NA	18	12	0.98 (0.46-2.08)	0.76 (0.36-1.61)
Gyntelberg et al,[41] 1980 [second]	912	1180	19	22	1.00 (0.54-1.83)	0.60 (0.33-1.11)
Stevens et al,[21] 2002 [men, third]	NA	NA	47	109	1.00 (0.62-1.62)	0.77 (0.48-1.25)
Slattery and Jacobs,[5] 1988 [second]	NA	NA	NA	NA	1.06 (0.97-1.15)	1.07 (0.98-1.16)
Erikksen et al,[36] 1998 [second]	357	357	21	19	1.11 (0.60-2.02)	0.56 (0.31-1.03)
Slattery and Jacobs,[5] 1988 [third]	NA	NA	NA	NA	1.13 (1.04-1.23)	1.14 (1.05-1.24)
Stevens et al,[21] 2002 [men, fourth]	NA	NA	35	109	1.22 (0.73-2.04)	0.94 (0.56-1.57)
Gyntelberg et al,[41] 1980 [third]	1170	1180	31	22	1.28 (0.75-2.20)	0.78 (0.45-1.33)
Erikksen et al,[36] 1998 [second]	357	357	30	19	1.58 (0.91-2.75)	0.81 (0.46-1.41)
Laukkanen et al,[9] 2008 [second]	410	410	18	14	1.66 (1.14-2.41)	1.04 (0.72-1.51)
Gyntelberg et al,[41] 1980 [fourth]	923	1180	34	22	1.80 (1.06-3.06)	1.09 (0.64-1.85)
Laukkanen et al,[9] 2008 [third]	409	410	31	14	1.89 (1.31-2.73)	1.18 (0.82-1.71)
Gulati et al,[40] 2005	NA	NA	NA	NA	2.02 (0.46-8.84)	0.72 (0.17-3.16)
Stevens et al,[21] 2002 [women, third]	NA	NA	30	7	2.18 (0.95-5.01)	1.30 (0.57-3.00)
Stevens et al,[21] 2002 [women, fourth]	NA	NA	34	7	2.23 (0.97-5.12)	1.33 (0.58-3.06)
Overall					1.13 (1.07-1.20) $I^2=38.9\%$; $P=.05$	1.07 (1.01-1.13) $I^2=19.8\%$; $P=.22$





CHD indicates coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; Int, intermediate; MET, metabolic equiva- lent; NA, not available; RR, risk ratio. Intermediate and high CRF categories were defined as 7.9 to 10.8 METs and 10.9 METs or more of maximal aerobic capacity, respectively, under the assumption that all participants were 50-year-old men. Crude and adjusted RR indicate RRs before and after adjustment for study heterogeneity among the subgroups, respectively. The words second, third, and fourth in brackets represent comparisons between the second, third, or fourth highest CRF category and the highest CRF category in the relevant study.

to 60% of MAC.[62] It is possible that consideration of low CRF as a major coronary risk factor could be put into practical use in the clinical setting through identification of low exercise tolerance by exercise stress testing or in daily life by the speed at which a person can walk before experiencing exhaustion.

Some cross-sectional population studies have suggested that higher aerobic fitness is associated with more favorable coronary or cardiovascular risk factor profiles[63,64]; therefore, the association between CRF and the risk of all-cause mortality and CHD/CVD could potentially be explained by residual confounding by established risk factors. Our sensitivity analyses indicated that a weaker association was observed between a 1-MET higher level of MAC and risk reduction of CHD/CVD, but not all-cause mortality, in studies with adjustment for smoking or more comprehensive risk factors. This finding suggests that better CRF is independently associated with longevity, while the inverse association between CRF and risk of CHD/CVD is explained partly by established coronary risk factors.

Limitations of this meta-analysis must be considered. First, a possible misclassification bias might affect our results. Misclassification bias could occur in transforming the reported CRF data into MET units. However, all of the prediction equations used in our analyses for estimating MAC have already been validated and are commonly used. Another possible misclassification bias is due to the fact that the definitions of low, intermediate, and high CRF were fundamentally based on study-specific CRF classifications, which varied from study to study but were not based on a standard cutoff. Fortunately, we could assign every exposure in each study to 1 of the 3 categories, which did not overlap with few exceptions, although MAC values in each category are approximately 1 MET smaller than those based on a general standard (eg, data from the National Health and Nutrition Examination Survey[65]). Therefore, the possibility of misclassification bias due to those 2 reasons should be limited. Second, Begg or Egger tests suggested publication bias. However, trim and fill analyses to incorporate potentially existing negative studies did not change the general result, although the risk estimates were moderately attenuated. Nevertheless, this possibility was not fully excluded by this analysis.

Based on the findings of our meta-analysis, we suggest for future research (1) further development of a CHD prediction algorithm (eg, Framingham Scores[66]) that would consider both CRF and the classical coronary risk factors to allow physicians to use CRF as a major risk factor in clinical settings; (2) cost-effectiveness of exercise testing for assessing CRF from the viewpoint of primary prevention of all-cause mortality and CHD; and (3) a clinical trial to determine whether an intervention that improves CRF by exercise reduces the risk of all-cause mortality and CHD.

In conclusion, better CRF was associated with lower risk of all-cause mortality and CHD/CVD. A 1-MET higher level of MAC was associated with a 13% and 15% risk reduction of all-cause mortality and CHD/CVD, respectively. The minimal MAC value for substantial risk reduction in persons aged 50 (SD, 10) years was estimated to be 8 (SD, 1) METs for men and 6 (SD, 1) METs for women. We suggest that CRF, which can be readily assessed by an exercise stress test, could be useful for prediction of CHD/CVD and all-cause mortality risk in a primary care medical practice.

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Acquisition of data: Kodama, Yachi, Sugawara, Totsuka.
Analysis and interpretation of data: Kodama, Tanaka, Asumi, Shimano, Ohashi, Yamada, Sone.
Drafting of the manuscript: Kodama, Maki, Sone.
Critical revision of the manuscript for important intellectual content: Kodama, Saito, Tanaka, Yachi, Asumi, Sugawara, Totsuka, Shimano, Ohashi, Yamada, Sone.
Statistical analysis: Kodama, Saito, Tanaka, Ohashi, Sone.
Obtained funding: Sone.
Administrative, technical, or material support: Kodama, Saito, Tanaka, Maki, Yachi, Asumi, Sugawara, Totsuka, Shimano, Ohashi, Sone.
Study supervision: Yamada, Sone. **Financial Disclosures:** None reported. **Funding/Support:** Drs Kodama and Sone are recipients of a Grant-in-Aid for Scientific Research and Post-doctoral Research Fellowship, respectively, both from the Japan Society for the Promotion of Science (JSPS). This study was also supported by Ministry of Health, Labor and Welfare, Japan.
Role of the Sponsors: The research organizations providing funding support did not have any role in the design and conduct of the study, in the correction, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
Additional Information: The eTable is available at http://www.jama.com.

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