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.

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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-

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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

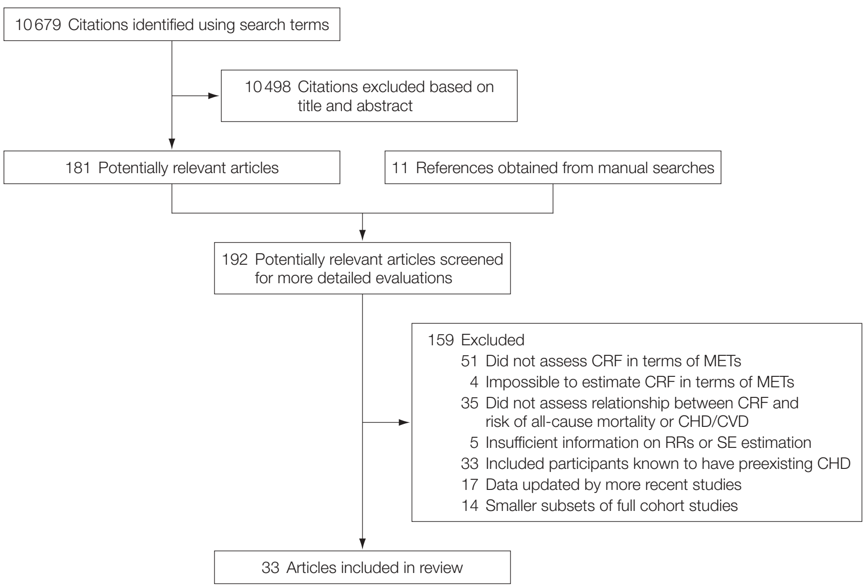
Data abstracted were the first author's name, year of publication, country of origin, specific outcomes, duration of follow-up, methods for outcome assessment, instrument or methods for measurement of CRF, whether maximal exercise testing (defined as instructing participants to continue exercise until 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]:

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

these surely don't affect mortality

meta-regression on confounders

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 $P \leq .05$ was considered statistically significant, except for the test of publication bias for which the recommended levels are $P \leq .10$.[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.

(*) existing confounding control

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).

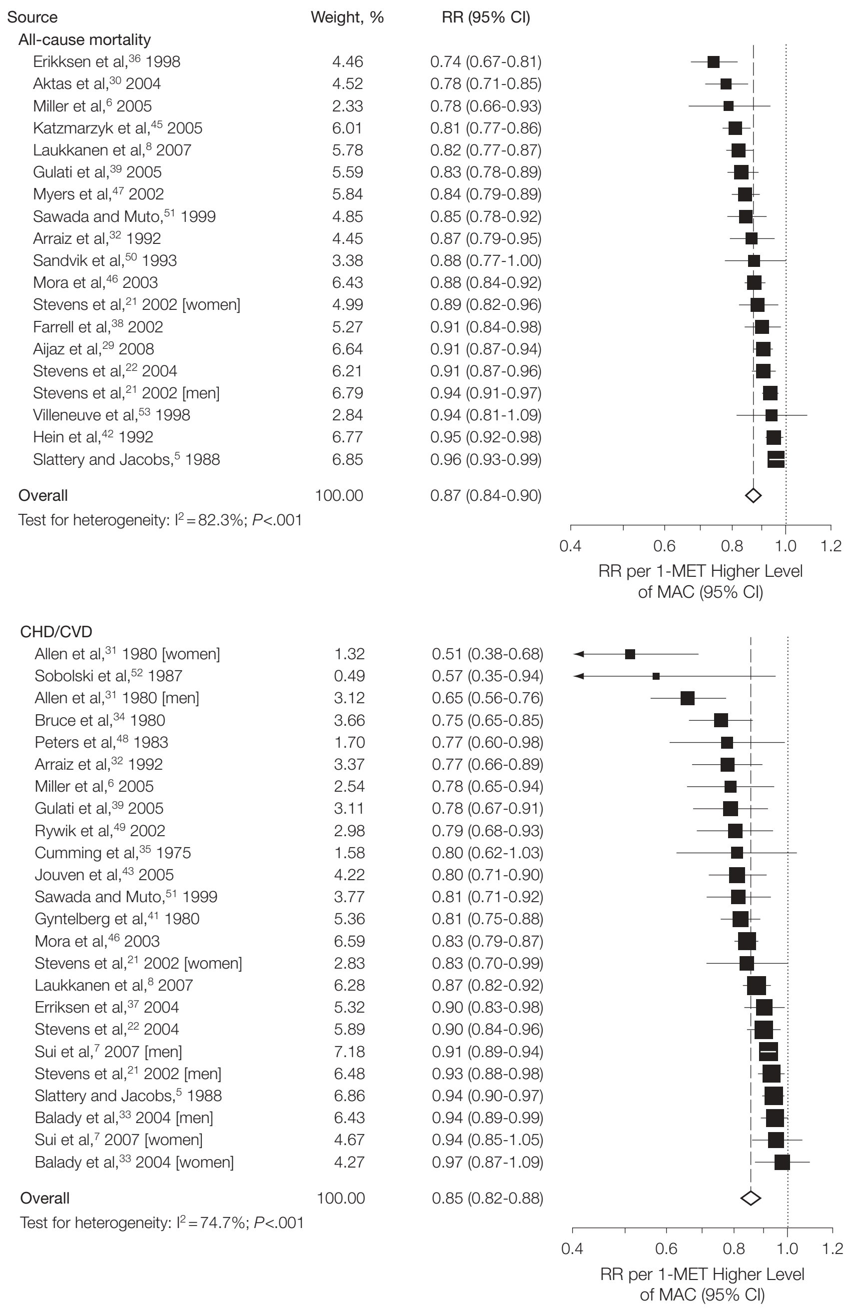
TABLE 2 shows the results of analyses investigating the associations of study characteristics on each outcome. The finding of risk reduction per higher MET for all-cause mortality and CHD/CVD was consistently significant in all of the stratified analyses. However, studies with a follow-up of at least 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



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

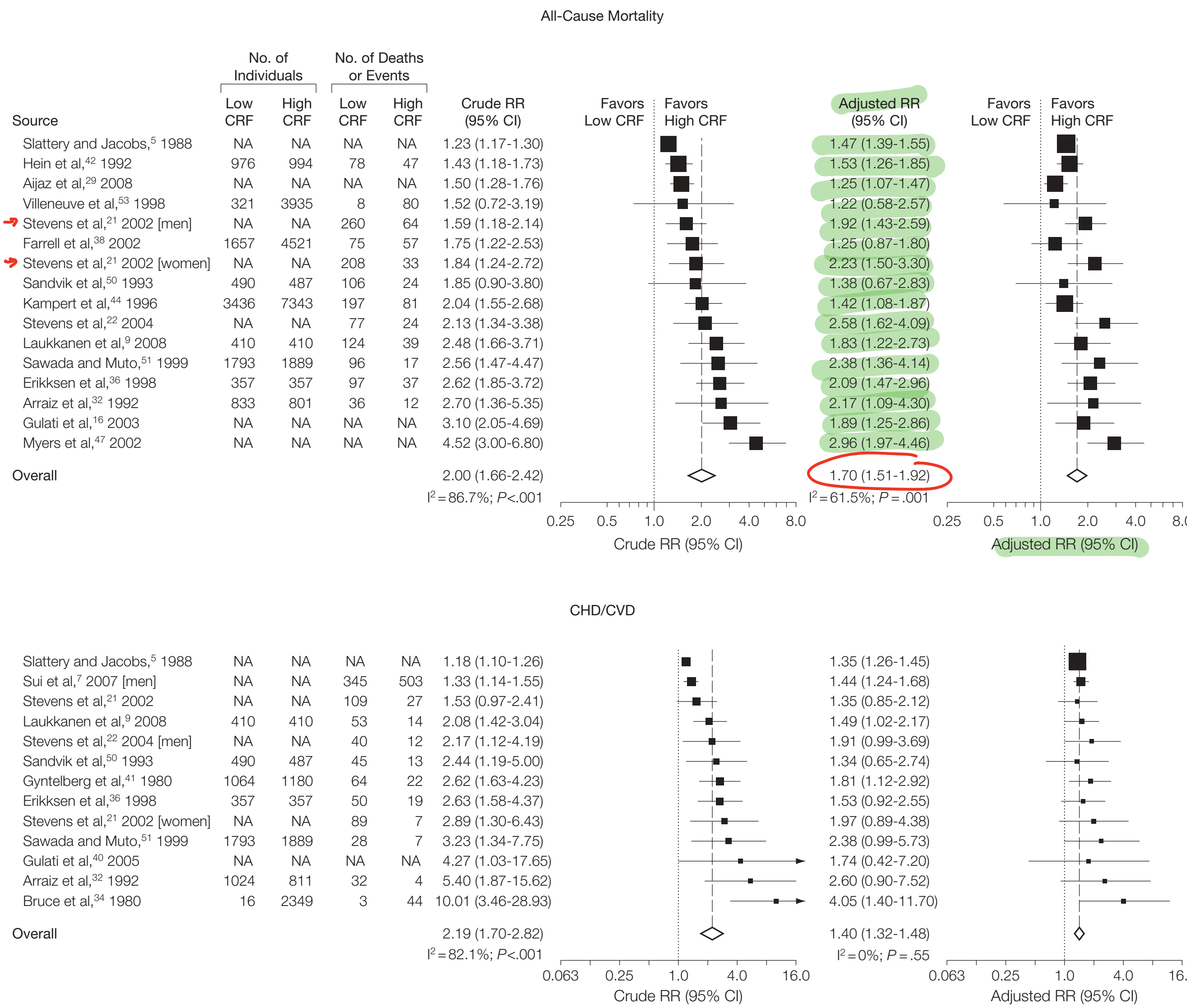
	All-Cause Mortality			CHD/CVD		
Characteristics	No. of Cohorts	RR (95% CI)	*P* Value[a]	No. of Cohorts	RR (95% CI)	*P* Value[a]
Mean age, ≥50 y						
No	10	0.90 (0.86-0.93)	.10	16	0.89 (0.88-0.91)	.80
Yes	9	0.84 (0.80-0.89)		8	0.84 (0.79-0.90)	
Only men						
No	8	0.87 (0.84-0.91)	.88	8	0.84 (0.81-0.87)	.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

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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.

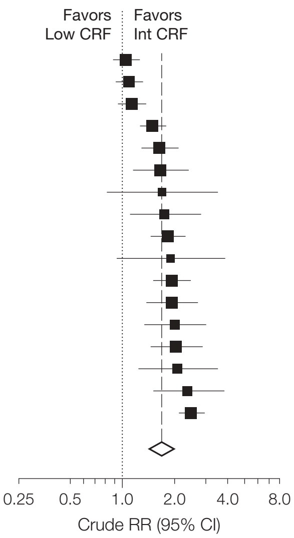
cant risk reduction of all-cause mortality.[60] However, using CRF may be preferable to using physical activity as risk predictors because 1 prior study[61] suggested that physical fitness was more strongly correlated with CHD than physical activity.

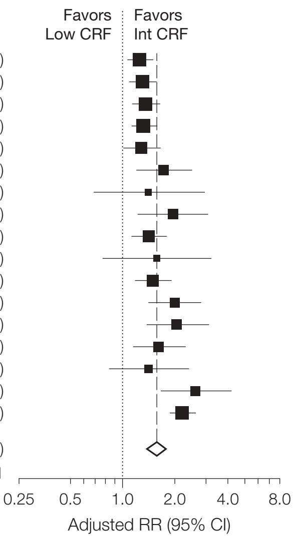
According to the results reported herein, the minimum CRF level that is associated with significantly lower event rates for men and women is approximately 9 and 7 METs (at 40 years old), 8 and 6 METs (at 50 years), and 7 and 5 METs (at 60 years), respectively. This means that women and men younger than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

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

All-Cause Mortality

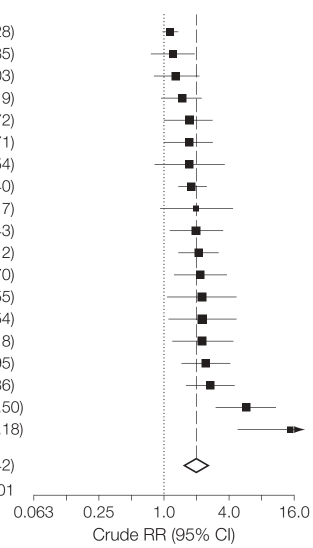
Source	No. of Individuals, Low CRF	No. of Individuals, Int CRF	No. of Deaths or Events, Low CRF	No. of Deaths or Events, Int CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Hein et al,[42] 1992 [second]	976	1012	78	62	1.05 (0.89-1.25)	1.26 (1.06-1.49)
Hein et al,[42] 1992 [fourth]	976	1010	78	61	1.09 (0.91-1.30)	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

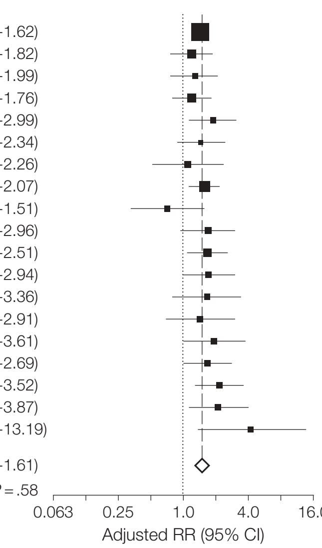




CHD/CVD

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





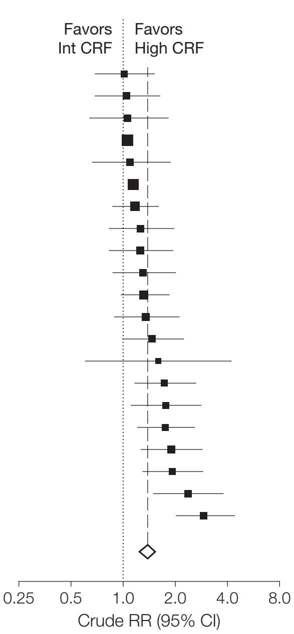
CHD indicates coronary heart disease; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; Int, intermediate; MET, metabolic equivalent; NA, not available; RR, risk ratio. Low and intermediate CRF categories were defined as less than 7.9 METs and 7.9 to 10.8 METs of maximal 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.

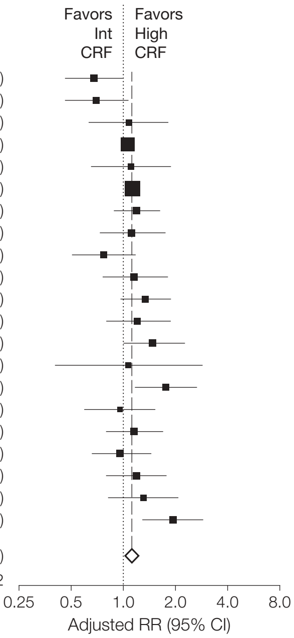
would need to complete stage I (1.7 mph at gradient 10°) and stage II (2.5 mph at gradient 12°), respectively, of the standard Bruce protocol, which is one of the most commonly used treadmill tests in clinical settings.[14] If the CRF level is expressed in terms of walking speed, men around 50 years 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

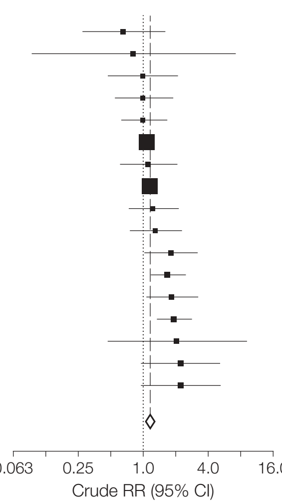
Source	No. of Individuals: Int CRF	No. of Individuals: High CRF	No. of Deaths or Events: Int CRF	No. of Deaths or Events: High CRF	Crude RR (95% CI)	Adjusted RR (95% CI)
Villeneuve et al,[53] 1998	3395	321	41	8	1.02 (0.69-1.51)	0.68 (0.46-1.01)
Erikksen et al,[36] 1998 [second]	357	357	39	37	1.05 (0.69-1.61)	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

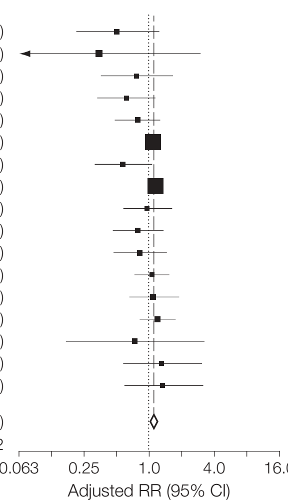




CHD/CVD

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 equivalent; 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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