Cardiorespiratory fitness and mortality from all causes, cardiovascular disease and cancer: dose–response meta-analysis of cohort studies

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ABSTRACT

Objective Current evidence of the associations between cardiorespiratory fitness (CRF) and mortality is limited. We performed a meta-analysis to assess the dose–response association of CRF with mortality from all causes, cardiovascular disease (CVD) and cancer in healthy population.

Methods PubMed, EMBASE and Web of Science were searched up to 26 December 2019 for reports of cohort studies giving risk estimates for all-cause, CVD and cancer mortality by level of CRF. Cohort studies were included if CRF was assessed by an exercise stress test and reported as at least three levels or per incremental increase, and the association of CRF with all-cause, CVD and cancer mortality was evaluated. Generalised least-squares regression models were used to assess the quantitative relation of CRF with all-cause, CVD and cancer mortality.

Results 34 cohort studies were eligible for the meta-analysis. The pooled relative risks (RRs) for all-cause, CVD and cancer mortality per one-metabolic equivalent increase in CRF were 0.88 (95% CI 0.83 to 0.93), 0.87 (95% CI0.83 to 0.91) and 0.93 (95% CI 0.91 to 0.96), respectively. As compared with lowest CRF, with intermediate CRF, the summary RRs for all-cause, CVD and cancer mortality were 0.67 (95% CI 0.61 to 0.74), 0.60 (95% CI 0.51 to 0.69) and 0.76 (95% CI 0.69 to 0.84), respectively, and with highest CRF were 0.47 (95% CI 0.39 to 0.56), 0.49 (95% CI 0.42 to 0.56) and 0.57 (95% CI 0.46 to 0.70), respectively.

Conclusion Our analysis showed inverse dose–response associations of CRF with all-cause, CVD and cancer mortality, which provides evidence for public health recommendations for preventing all-cause, CVD and cancer mortality.

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INTRODUCTION

Cardiovascular disease (CVD) and cancer were the two most common causes of death in 2017, accounting for 27.3 million (ie, 48.9%) deaths worldwide.[1] More than 25% of the CVD and cancer mortality must be reduced by 25% to lower death due to non-communicable diseases according to the 25×25 Global Action Plan launched by WHO by 2025.[2 3] Therefore, preventive approaches focused on modifying risk factors for mortality could contribute to important improvements in health and longevity.

Cardiorespiratory fitness (CRF) reflects the integrated ability to transport oxygen from the atmosphere to the mitochondria during exercise and is directly related to the integrated function of numerous systems, which is considered to reflect total body health. Mounting evidence shows that CRF is associated with several health outcomes, such as CVD,[4] type 2 diabetes mellitus[5] and cancer.[6] Previous meta-analysis assessing the association of CRF and all-cause mortality included only cohort studies published up to 2008,[4] and many relevant studies with longer follow-up have been updated recently. As well, a recent meta-analysis including six prospective studies only involved categorical analyses of the association between CRF and cancer mortality in 2014.[7] Besides, the association of CRF and CVD mortality was analysed by only dichotomous analysis with body mass index.[8] How much the risk reduction of cancer and CVD mortality could be predicted by a per incremental increase in CRF is unknown. Quantifying the associations between CRF and mortality from all causes, CVD and cancer mortality based on current epidemiological studies would provide further evidence for future research and public health recommendations.

Therefore, we performed the present meta-analysis to assess the qualitative and quantitative associations between CRF and all-cause, CVD and cancer mortality in healthy population based on cohort studies.

METHODS

Search strategy

We followed the protocol for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for this meta-analysis.[9] PubMed, EMBASE and Web of Science were searched up to 26 December 2019 for English reports of studies examining the associations between CRF and mortality from all causes, CVD and cancer. Details of the search terms are in online supplemental table 1. Reference lists of identified articles were also manually searched for relevant articles.

Study selection

Three researchers (YZ, MH and RQ) screened the studies independently. Cohort studies were included if (1) study participants were adults (≥18 years old); (2) the association of CRF with all-cause, CVD and cancer mortality was evaluated; (3) CRF was assessed by an exercise stress test and reported as at least three levels or per incremental increase and (4) relative risks (RRs) or HRs with 95% CIs relating to each category of CRF were

reported. We excluded studies if (1) study participants had a specific disease (eg, coronary heart disease, diabetes or hypertension) and (2) papers were conference summaries, clinical trial reports or reviews. If multiple articles based on the same cohort were published, we chose the one with the longest follow-up or the largest sample size.

Data extraction and quality assessment

Two researchers (MH and RQ) independently extracted data on the first author, publication year, country, sample size, number of cases, follow-up years, sex, mean or median age of study participants at baseline, measurement of CRF, levels of CRF, number of cases and person-years/number of participants for each CRF category, RRs/HRs of mortality with 95% CIs (adjusted by the most confounders) and variables adjusted for in the analysis. Any disagreement was resolved by the third researcher (YZ).

The quality of each study was assessed by the Newcastle-Ottawa Scale (NOS).[10] Scores ranged from 0 to 9 points, with higher scores indicating higher study quality. Scores of 0–3, 4–6 and 7–9 were considered poor, fair and good quality, respectively. Two researchers (MH and RQ) independently did the NOS assessment and any disagreement was resolved by the third researcher (YZ).

Data synthesis and analysis

Due to the low incidence of outcomes (all-cause, CVD and cancer mortality), we used RRs (95% CIs) as the unified effect size for all studies, and assumed that HRs reported for outcomes in the original study were approximately RRs.[11] A random-effects model was used to pool adjusted RRs and 95% CIs for the categorical and dose–response analyses.

We first performed dose–response analyses to quantify the risk reduction of all-cause, CVD and cancer mortality per one-metabolic equivalent (MET) (equal to 3.5 mL/min/kg oxygen consumption) increase in CRF. For studies not reporting the specific RRs of mortality per one-MET increase, we used the generalised least squares regression[12] (estimates the linear dose–response coefficient taking into account the covariance for each exposure category within each study because they are estimated relative to a common referent CRF exposure category) to estimate study-specific dose–response associations and the random-effects model to pool the study-specific dose–response RRs (95% CIs) of all-cause, CVD and cancer mortality for per one-MET increase in CRF. For each study, the median or mean CRF in each category was assigned to the corresponding RR. When the median or mean CRF per category was not provided, the midpoint of the upper and lower boundaries in each category was used as the mean CRF exposure. The width of the interval was assumed to be the same as the closest category if the highest or lowest category for CRF was open-ended.

We then performed categorical analyses to assess the associations of risk of all-cause, CVD and cancer mortality with different CRF levels. The highest, medium and lowest categories of CRF reported in included studies were assigned as the highest, intermediate and lowest categories. For studies with more than three CRF groups, all medium groups were combined to calculate the RRs for the assigned intermediate category by using a random-effects or fixed-effects model.

Heterogeneity was tested by Cochran Q and I^2 statistics.[13] A $p<0.10$ was considered statistically significant for the Q statistic, and $I^2 \approx 25\%$, 50%, 75% were considered low, moderate and high heterogeneity, respectively. Subgroup analyses were conducted by sex, region, equipment, sample size and follow-up period. In addition, meta-regression analyses were applied to try to find out the source of heterogeneity. We also performed sensitivity analyses by omitting one study at a time to examine the influence of each study on the pooled results. Publication bias was graphically assessed by funnel plot and further evaluated by Egger's test, with $p<0.05$ indicating potential publication bias. The trim and fill methods were used to correct any publication bias detected. All analyses involved using Stata V.12.1 (StataCorp). A two-tailed $p<0.05$ was considered statistically significant if not specified.

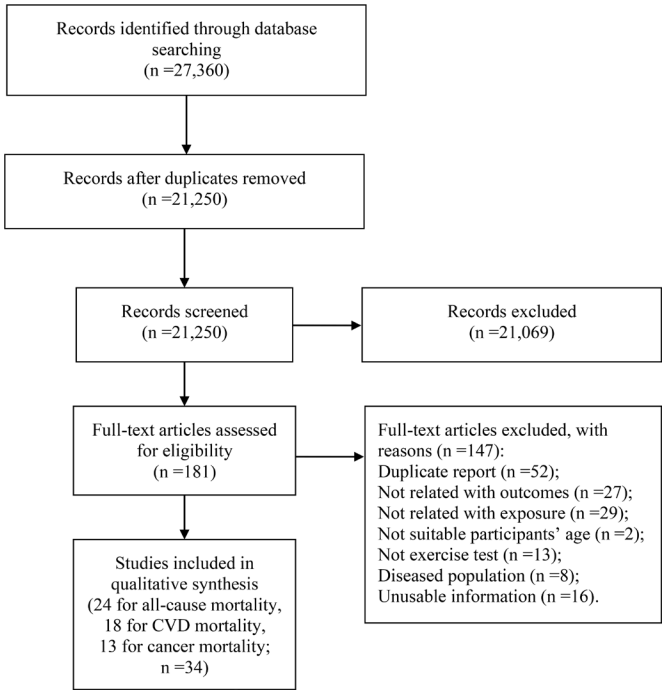

Figure 1 Flow chart of study selection. CVD, cardiovascular disease.

RESULTS

As shown in figure 1, of the 27 360 records identified by the literature search, 34 were finally included in the meta-analysis (online supplemental table 2), 24 records provided information on the association between CRF and all-cause mortality 18 on CVD mortality and 13 on cancer mortality. There were 24 studies meeting the inclusion criteria for dose–response analyses and 28 studies for categorical analyses.

The characteristics of the included records are in table 1. Among the records, 22 were from North America, 10 from Europe and 2 from Asia. Sample sizes ranged from 184 to 1 547 478 and follow-up period from 5.0 to 44.1 years. A total of 21 records assessed CRF with treadmill exercise tests, 11 with ergometer exercise tests and 2 with the Canadian home fitness test. Details of the specific CRF measurements are in online supplemental table 3. In total, there were 29 studies using Cox model, 3 studies using proportional hazards model (not referring to Cox model directly), 1 study using Poisson model and 1 study using Logistic model (online supplemental table 4). All studies were graded good quality (online supplemental table 5) and most studies adjusted adequately for several potential confounders (online supplemental table 4).

Dose–response analyses

Figure 2 shows the dose–response analysis of CRF and all-cause mortality, with 625 400 participants and 34 734 cases.

Table 1 Characteristics of studies included in the meta-analysis

First author (publication year)	Country	Sample size (% men)	Age (years), mean (range or SD)	Follow-up (years)	Cardiorespiratory fitness assessment	Specific outcomes (No of deaths)
Vainshelboim et al (2019)	USA	184 (100%)	59.3 (15.2)	12.0	Treadmill	Cancer mortality (6)
Vainshelboim et al (2019)	USA	4694 (100%)	58.1 (17.3)	12.7	Treadmill	Cancer mortality (500)
Steell et al (2019)	UK	73 259 (54.2%)	56.8 (8.1)	5.0	Ergometer	All-cause mortality (1374); CVD mortality (353); Cancer mortality (551)
Letnes et al (2019)	Norway	4527 (48.8%)	48.2 (13.5)	8.8	Treadmill	All-cause mortality (91); CVD mortality (18)
Harb et al (2019)	USA	126 356 (59.1%)	53.5 (12.6)	8.7	Treadmill	All-cause mortality (9929)
Farrell et al (2019)	USA	19 838 (0%)	44.9 (10.5)	19.2	Treadmill	CVD mortality (391)
Ekblom-Bak et al (2019)	Sweden	266 109 (53.0%)	18–74	7.6	Ergometer	All-cause mortality (2750); CVD mortality (455); Cancer mortality (1623)
Mandsager et al (2018)	USA	122 007 (59.2%)	53.4 (12.6)	8.4	Treadmill	All-cause mortality (13 637)
Kim et al (2018)	UK	70 913 (47.0%)	57.2 (8.2)	5.7	Ergometer	All-cause mortality (832); CVD mortality (117); Cancer mortality (503)
Imboden et al (2018)	USA	4137 (56.2%)	42.8 (12.2)	24.2	Treadmill	All-cause mortality (727); CVD mortality (212); Cancer mortality (201)
Hussain et al (2018)	USA	12 043 (63.0%)	52.1 (13.0)	14	Treadmill	All-cause mortality (1,590)
Engeseth et al (2018)	Norway	2014 (100%)	50 (40–59)	35	Ergometer	All-cause mortality (1178); CVD mortality (528)
Kunutsor et al (2017)	Finland	1663 (100%)	52.2 (5.4)	25.6	Ergometer	All-cause mortality (719); CVD mortality (33)
Jensen et al (2017)	Denmark	5131 (100%)	48.8 (5.4)	44.1	Ergometer	All-cause mortality (4486); Cancer mortality (1527)
Crump et al (2017)	Sweden	1 547 478 (100%)	≥18	28.2	Ergometer	All-cause mortality (64 343); CVD mortality (10381)
Al-Mallah et al (2016)	USA	57 284 (51.5%)	53.4 (≥18)	10	Treadmill	All-cause mortality (6402)
Lakoski et al (2015)	USA	12 258 (100%)	49 (9)	7.5	Treadmill	CVD mortality (495); Cancer mortality (281)
Wickramasinghe et al (2014)	USA	2906 (0%)	41.5 (10.2)	28	Treadmill	CVD mortality (96)
Sawada et al (2014)	Japan	8523 (100%)	35 (19–59)	20.2	Ergometer	Cancer mortality (143)
Kokkinos et al (2014)	USA	18 102 (100%)	58.4 (11.4)	11.5	Treadmill	All-cause mortality (5106)
Shuval et al (2012)	USA	29 402 (100%)	42.8 (9.1)	17.4	Treadmill	All-cause mortality (1830)
Farrell et al (2011)	USA	14 256 (0%)	43.8 (10.2)	15.2	Treadmill	Cancer mortality (250)
Laukkanen et al (2010)	Finland	2268 (100%)	52.8 (5.1)	16.7	Ergometer	All-cause mortality (593); Cancer mortality (159)
Farrell et al (2010)	USA	11 335 (0%)	45.0 (20–90)	12.3	Treadmill	All-cause mortality (292)
Park et al (2009)	Korea	18 775 (100%)	55.7 (11.1)	6.4	Ergometer	All-cause mortality (547); CVD mortality (101); Cancer mortality (262)
Laukkanen et al (2007)	Finland	1639 (100%)	52.2 (42–60)	16.6	Ergometer	CVD mortality (116)
Stevens et al (2004)	Russia	1359 (100%)	40–59	20.5	Treadmill	All-cause mortality (221); CVD mortality (98)
Evenson et al (2004)	USA	3995 (49.8%)	40–59	25	Treadmill	All-cause mortality (639); CVD mortality (206)
Mora et al (2003)	USA	2994 (0%)	46.5 (30–80)	20.3	Treadmill	All-cause mortality (427); CVD mortality (147)
Gulati et al (2003)	USA	5721 (0%)	52.4 (10.8)	8.4	Treadmill	All-cause mortality (180)
Gulati et al (2003)	USA	5636 (0%)	52.4 (10.7)	9	Treadmill	CVD mortality (52)
Slattery et al (1998)	USA	2431 (100%)	50 (22–79)	18.5	Treadmill	All-cause mortality (630)
Villeneuve et al (1998)	Canada	7651 (NA)	45 (20–69)	7	Canadian Home Fitness Test	All-cause mortality (129)
Arraiz et al (1992)	Canada	2174 (NA)	30–69	7	Canadian Home Fitness Test	CVD mortality (37); Cancer mortality (32)

CVD, cardiovascular disease; NA, not available.

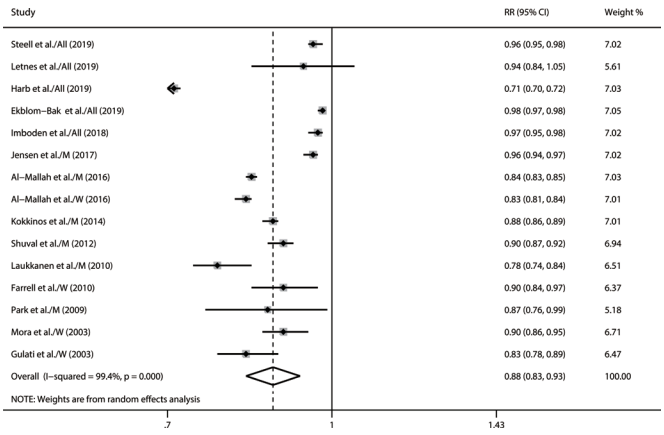

Figure 2 Meta-Analysis of all-cause mortality per one-metabolic equivalent increased level of cardiorespiratory fitness. RR, relative risk.

The pooled RR for all-cause mortality per one-MET increase in CRF was 0.88 (95% CI 0.83 to 0.93), with high heterogeneity (I^2=99.4%; $P_{heterogeneity}$ <0.001). We found no publication bias by the funnel plot (online supplemental figure 1) and Egger's test (p=0.171).

Figure 3 shows the pooled estimates for the reduction in risk of CVD mortality per one-MET increase in CRF with 392 240 participants and 2045 cases. With each one-MET increase in CRF, the risk of CVD mortality was decreased by 13% (RR 0.87, 95% CI 0.83 to 0.91; I^2=80.3%; $P_{heterogeneity}$ <0.001). Publication bias was observed by the asymmetrical funnel plot (online supplemental figure 2) and Egger's test, but the result was not altered after using the trim-and-fill method to adjust for publication bias.

Eleven records were included in the dose–response analysis of CRF and cancer mortality with 409 594 participants and 5503 cases (figure 4). The summary RR per one-MET increase in CRF was 0.93 (95% CI 0.91 to 0.96; I^2=76.6%; $P_{heterogeneity}$ <0.001). No publication bias was detected by the funnel plot (online supplemental figure 3) and Egger's test (p=0.154).

For the dose–response analyses of CRF with all-cause, CVD and cancer mortality, we conducted subgroup analyses across sex, region (USA vs non-USA), equipment (treadmill vs ergometer), sample size (<10 000 vs≥10 000) and follow-up period (<10 vs≥10 years). The dose–response associations were consistent in most subgroups for all-cause and cancer mortality and all subgroups for CVD mortality (table 2). Our sensitivity analyses

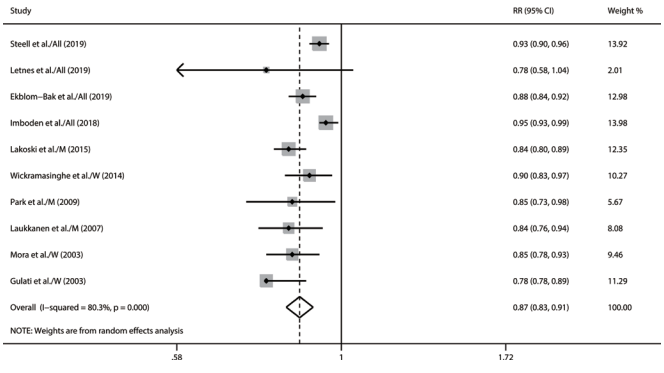

Figure 3 Meta-analysis of cardiovascular disease mortality per one-metabolic equivalent increased level of cardiorespiratory fitness. RR, relative risk.

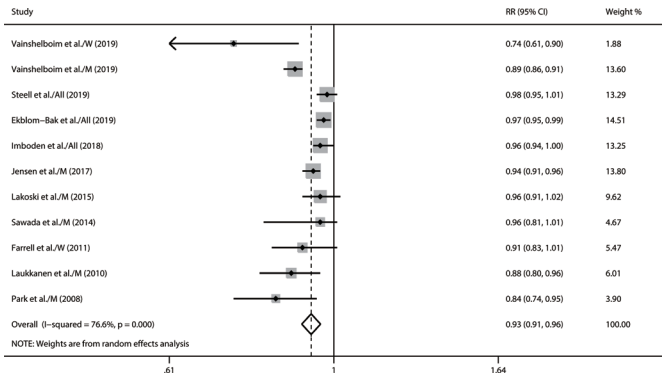

Figure 4 Meta-analysis of cancer mortality per one-metabolic equivalent increased level of cardiorespiratory fitness. RR, relative risk.

suggested that the summary risk was substantially unchanged when we removed one study each time.

Categorical analyses

We performed categorical analyses to summarise the risk of all-cause mortality for two subgroups (intermediate vs lowest CRF (online supplemental figure 4) and highest vs lowest CRF (online supplemental figure 5)), with 2 187 550 participants and 106 238 cases. As compared with lowest CRF, with intermediate and highest CRF, the risk of all-cause mortality was 0.67 (95% CI 0.61 to 0.74; I^2=82.0%; $P_{heterogeneity}$ <0.001) and 0.47 (95% CI 0.39 to 0.56; I^2=96.7%; $P_{heterogeneity}$ <0.001). Publication bias was detected by the funnel plot (online supplemental figure 6) and Egger's test (p=0.008) for intermediate CRF. When the trim and fill method was used to adjust for publication bias, the result was not altered.

We included 13 publications in the categorical analyses of risk of CVD mortality with intermediate (online supplemental figure 8) and highest CRF (online supplemental figure 9), with 1 952 352 participants and 13 530 cases. When comparing intermediate and highest versus lowest CRF, the pooled RRs were 0.60 (95% CI 0.51 to 0.69; I^2=57.1%; $P_{heterogeneity}$=0.006) and 0.49 (95% CI 0.42 to 0.56; I^2=40.5%; $P_{heterogeneity}$=0.064), respectively. No publication bias was observed by the funnel plot (online supplemental figures 10 and 11) and Egger's test (p=0.142 for intermediate CRF; p=0.116 for highest CRF).

We included 12 publications to summarise the risk of cancer mortality with intermediate (online supplemental figure 12) and highest CRF (online supplemental figure 13), with 409 422 participants and 5482 cases. As compared with lowest CRF, with intermediate and highest CRF, the pooled RRs for cancer mortality were 0.76 (95% CI 0.69 to 0.84; I^2=40.6%; $P_{heterogeneity}$=0.071) and 0.57 (95% CI 0.46 to 0.70; I^2=75.0%; $P_{heterogeneity}$ <0.001). No evidence of publication bias was found by funnel plot (online supplemental figures 14 and 15) and Egger's test (p=0.360 for intermediate CRF; p=0.169 for highest CRF).

Subgroup analyses were conducted across sex, region (USA vs non-USA), equipment (treadmill, ergometer and Canada home fitness test), sample size (<10 000 vs≥10 000) and follow-up period (<10 vs≥10 years). Results showed that the size or direction of the pooled estimates was robust in most subgroups (online supplemental tables 6 and 7). The results of meta-regression showed these factors were not the source of heterogeneity for the dose–response analyses, while few factors appeared to the heterogeneity in the categorical analyses (online supplemental tables 6 and 7). Sensitivity analyses revealed that the pooled estimates were substantially unchanged.

Table 2 Dose–response subgroup analyses of cardiorespiratory fitness and all-cause, cardiovascular disease and cancer mortality

Subgroups	All-cause mortality					CVD mortality					Cancer mortality				
	N	RR (95% CI)	I^2	P^1	P^2	N	RR (95% CI)	I^2	P	P^2	N	RR (95% CI)	I^2	P	P^2
All	15	0.88 (0.83 to 0.93)	99.4%	<0.001	–	10	0.87 (0.83 to 0.91)	80.3%	<0.001	–	11	0.93 (0.91 to 0.96)	76.6%	<0.001	–
Sex					0.756					0.087					0.067
Men and women	5	0.90 (0.80 to 1.03)	99.8%	<0.001		4	0.92 (0.88 to 0.96)	65.8%	0.033		3	0.97 (0.96 to 0.98)	0.0%	0.650	
Men	6	0.87 (0.82 to 0.92)	97.4%	<0.001		3	0.84 (0.80 to 0.88)	0.0%	0.989		6	0.92 (0.88 to 0.95)	62.7%	0.020	
Women	4	0.86 (0.82 to 0.90)	76.4%	0.005		3	0.84 (0.77 to 0.92)	74.4%	0.020		2	0.84 (0.68 to 1.02)	71.1%	0.063	
Region					0.196					0.755					0.483
USA	9	0.86 (0.80 to 0.92)	99.1%	<0.001		5	0.86 (0.80 to 0.93)	89.3%	<0.001		5	0.92 (0.87 to 0.97)	79.4%	0.001	
Non-USA	6	0.93 (0.90 to 0.96)	92.0%	<0.001		5	0.89 (0.85 to 0.93)	48.5%	0.100		6	0.95 (0.92 to 0.98)	61.5%	0.024	
Equipment					0.301					0.610					0.483
Treadmill	10	0.87 (0.81 to 0.93)	99.0%	<0.001		6	0.86 (0.80 to 0.93)	86.9%	<0.001		5	0.92 (0.87 to 0.97)	79.4%	0.001	
Ergometer	5	0.93 (0.90 to 0.96)	93.5%	<0.001		4	0.89 (0.85 to 0.94)	55.6%	0.080		6	0.95 (0.92 to 0.98)	61.5%	0.024	
Sample size					0.594					0.705					0.272
<10 000	6	0.90 (0.86 to 0.94)	92.4%	<0.001		6	0.86 (0.79 to 0.93)	85.1%	<0.001		6	0.92 (0.88 to 0.96)	75.9%	0.001	
≥10 000	9	0.87 (0.80 to 0.95)	99.7%	<0.001		4	0.88 (0.84 to 0.93)	74.7%	0.008		5	0.96 (0.93 to 0.99)	44.6%	0.125	
Follow-up period					0.853					0.383					0.178
<10 years	6	0.88 (0.76 to 1.01)	99.7%	<0.001		6	0.86 (0.80 to 0.91)	82.0%	<0.001		4	0.97 (0.94 to 0.99)	46.9%	0.130	
≥10 years	9	0.88 (0.83 to 0.93)	97.9%	<0.001		4	0.89 (0.84 to 0.95)	69.9%	0.019		7	0.92 (0.88 to 0.95)	71.2%	0.002	

P^1 was the test by Cochran Q; P^2 was the test by meta-regression.
CVD, cardiovascular disease; RR, relative risk.

DISCUSSION

Our study is the first meta-analysis, to our knowledge, to quantify the association of CRF with CVD and cancer mortality. The dose–response analyses showed that a per one-MET increase in CRF was associated with 12%, 13% and 7% reduced risk of all-cause, CVD and cancer mortality. In the categorical analyses, the reduction was 33%, 40% and 24%, respectively, for the intermediate versus lowest category of CRF and 53%, 51% and 43%, respectively, for the highest vs lowest category. Subgroup and sensitivity analyses revealed consistent associations in most results.

The result is consistent with another meta-analysis also finding an inverse dose–response association between CRF and all-cause mortality.[4] Also, the previous meta-analysis estimated CRF according the two publications[14 15] when data on CRF were not available for dose–response analysis, whereas we included only studies directly reporting CRF as MET or maximal oxygen consumption for the dose–response analysis. In addition, studies included in our analysis had a longer follow-up period. Finally, a meta-analysis exploring the joint association of CRF and fatness on all-cause mortality also showed a strong inverse association between CRF and mortality.[16]

We first quantified the dose–response association between CRF and mortality from CVD or cancer and found 13% and 7% reduced risk of CVD and cancer mortality per one-MET increase in CRF. A previous meta-analysis including six prospective studies found intermediate and highest CRF associated with reduced risk of cancer mortality as compared with lowest CRF,[7] which is consistent with our results. As compared with this meta-analysis, we included more studies with longer follow-up period and many more participants (409 422 vs 71 654), which may suggest more convincing evidence of the association between CRF and cancer mortality. A meta-analysis exploring the joint association of CRF and fatness on CVD mortality showed twice the risk of CVD mortality for unfit individuals regardless of body mass index.[8] Our analysis assessed CRF as three categories and found an inverse association of intermediate and highest CRF with CVD mortality as compared with lowest CRF.

Our results indicate reduced risk of mortality from all causes, CVD and cancer for individuals with higher CRF. As described in recent American Heart Association scientific statements, the overall predictive ability of CRF is comparable to that obtained with the Framingham Risk Score and European Systematic Coronary Risk Evaluation algorithm.[17–19] Measurement of CRF in clinical practice may be helpful to identify individuals with increased risk of mortality. Considering that the costs and modest risk associated with exercise testing, estimating CRF using non-exercise algorithms based on readily available clinical variables may be also a convenient way in public health and clinical settings. Results from the Aerobic Centre Longitudinal Study showed that estimated CRF based on age, body mass index, waist circumference, resting heart rate, physical activity and smoking was inversely associated with risk of all-cause mortality.[20] It should be noted that the sample populations in the algorithms are mostly derived from North America and Europe and needed to expand to other populations.

Our findings showed reduced risk of all-cause, CVD and cancer mortality by 12%, 13% and 7%, respectively with per one-MET increase in CRF. Gaining one-MET in CRF may be achieved by performed various endurance-type physical activity regimens frequently over weeks or months in most adults.[18 21] CRF appears more responsive to intensity than session duration or frequency, and high-intensity, moderate-intensity continuous and sprint interval training were suggested based on individuals' physical quality. With physical inactivity and sedentary behaviour becoming more prevalent and pervasive worldwide, increasing CRF would modulate the negative effect of physical inactivity and sedentary behaviour and has great implications for public health.[22 23] Given the associations of CRF and risk of mortality from all causes, CVD and cancer observed in this study and previous studies,[4 6] public health campaigns focusing on increasing CRF should be launched to improve people's health and longevity.

Several potential mechanisms may account for the inverse associations between CRF and risk of mortality from all causes, CVD and cancer. CRF is associated with inflammation level,[24] circulating steroid hormone levels,[25] growth factor production,[26] antioxidant capacity[27] and immune function.[28] As well, increased CRF is associated with low abdominal obesity,[29] low incidence of dyslipidaemia,[30] low blood pressure[31] and improved insulin sensitivity,[32] which may reduce the incidence of all-cause, CVD and cancer mortality.

The main strength of this study is that we first quantified the dose–response association of CRF with CVD and cancer mortality and provide comprehensive epidemiological evidence about the relation between CRF and all-cause mortality. However, our meta-analysis has several limitations. First, we assigned reported CRF as lowest, intermediate and highest CRF for categorical analyses, but the assigned CRF categories contain different levels of CRF in different studies, which may affect the magnitude of associations. Second, we failed to identify the thresholds of low, moderate and high CRF across age, sex and race. Third, although extracted risk estimates were adjusted for various known risk factors, we cannot rule out residual or unmeasured confounding. Fourth, this study showed high heterogeneity in most analyses of the relation between CRF and mortality from all causes, CVD and cancer. Fifth, restriction of language to English may result in selection bias. Sixth, using mean, median or midpoint may distort the dose–response curve and lead to loss of power or precision. Finally, although the study was based on cohort studies, the summarised associations of CRF with all-cause, CVD and cancer might not be causal, because this research question

What are the findings?

⇒ Our study is the first meta-analysis to quantify the association of cardiorespiratory fitness (CRF) with cardiovascular disease (CVD) and cancer mortality. Per one-metabolic equivalent increase in CRF was associated with 12%, 13% and 7% decreased risk of all-cause, CVD and cancer mortality, respectively. As compared with lowest CRF, subjects with intermediate CRF had 33%, 40% and 24% decreased risk of all-cause, CVD and cancer mortality, respectively, and with highest CRF had 53%, 51% and 43%, respectively.

How might it impact on clinical practice in the future?

⇒ Our findings provide further evidence for offering public health recommendations to increase CRF for preventing all-cause, CVD and cancer mortality. Estimating CRF using non-exercise algorithms based on readily available clinical variables may be also a convenient way in public health and clinical settings.

can only be answered by well-designed randomised controlled trials.

CONCLUSION

In conclusion, results from the meta-analysis show high CRF associated with reduced risk of mortality from all causes, CVD and cancer in healthy population, which supports the recommendation to increase CRF to improve people's health. Further research is needed to identify the threshold of low, moderate and high CRF across age, sex and ethnicity.

Contributors YZ, DH and MH conceived, designed and performed the work; YZ, MH and RQ drafted the initial search strategy, screened the studies and analysed the data; XS, YY, JL, FH, MZ, ZZ and DH revised the manuscript. YZ and MH had full access to the cohort-specific data and take full responsibility for the integrity of the data and the accuracy of the meta-analyses. YZ is the study guarantor.

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