

## Clinical Investigations

# Association Between Cardiorespiratory Fitness and Risk of Heart Failure: A Meta-Analysis

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## ABSTRACT

**Background:** Evidence emerges that cardiorespiratory fitness (CRF) might be implicated in the development of heart failure (HF). This meta-analysis aimed to quantify the association between CRF exposed at baseline and HF risk with dose–response analysis and to assess whether CRF changes over time are correlated with alterations in HF risk.

**Methods and Results:** Cohort studies that assessed the association between CRF and risk of HF in subjects without baseline HF were included. Study-specific multivariate-adjusted relative risks (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model. Ten studies from 8 articles were included, enrolling 8987 incident HF cases from 154,598 participants. The RR of HF per 1-metabolic equivalent (MET) higher CRF at baseline was 0.82 (95% CI 0.80–0.84) in the overall population. The RRs were similar in men (0.82, 95% CI 0.80–0.85) and women (0.81, 95% CI 0.78–0.84), and remained minorly changed in patients with existing diabetes, hypertension, or cardiovascular disease at entry. No evidence of a nonlinear relationship between CRF at baseline and risk of HF was observed ( $P_{\text{nonlinearity}} = .18$ ). The RR of HF per 1-MET increase in CRF over time was 0.79 (95% CI 0.67–0.93), and the measurement of CRF provided incremental value to the prediction of HF beyond conventional models.

**Conclusions:** High or increased CRF resulted in reduced risk of HF in a dose-dependent manner, supporting the necessity to increase CRF to prevent HF in clinical practice. (*J Cardiac Fail* 2019;25:537–544)

**Key Words:** Cardiorespiratory fitness, heart failure, meta-analysis.

Heart failure (HF) has become a global pandemic that affects ~26 million individuals worldwide.<sup>1,2</sup> Recent evidence shows that the total cost for HF management, which is estimated to be 4-fold higher than individuals without HF,<sup>3</sup> accounts for 1%–3% of the global medical expenditure.<sup>1,4</sup> Despite advances achieved in treating HF, HF still remains one

of the leading causes of hospitalization and mortality.<sup>5,6</sup> Therefore, it highlights the importance and necessity of identifying risk factors serving as preventive or therapeutic targets for HF.

In 2015 two independent meta-analyses provide consistent evidence that increased physical activity led to reduced risk of HF by up to 40%,<sup>7,8</sup> suggesting that physical inactivity is a modifiable risk factor of HF. Yet physical activity mainly stands for the behavior of body movement produced by muscle contraction,<sup>9</sup> and its assessment in clinical settings relies largely on self-report questionnaires, which are often subject to recall bias and prone to inaccuracy.<sup>10</sup> Being assessed by an exercise stress test,<sup>9</sup> cardiorespiratory fitness (CRF) is an objective measure that indicates the level of aerobic health and reflects one's capability on exercise performance.<sup>9</sup> Although CRF correlates with physical activity, it appears superior in the prediction of cardiovascular or all-cause mortality.<sup>11–13</sup> As a result, exploring the association between CRF and risk of HF would be of interest, which may also provide additional evidence to the statement that CRF could be used as a vital sign and should be routinely assessed in clinical practice.<sup>14</sup>

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Although the prior meta-analysis by Echouffo-Tcheugui et al<sup>7</sup> was able to show that physical fitness reduced the incidence of HF, the authors obtained their finding by pooling only 3 cohort studies from 2 articles,<sup>15,16</sup> while recently the number of studies with large sample sizes and long follow-up periods has more than doubled,<sup>17–23</sup> enabling the possibility to investigate the potential moderators of heterogeneity (eg, gender difference) and the outcomes in disease-specific populations (eg, patients with diabetes). Moreover, a dose–response analysis that helps to better understand the shape of the quantitative association between CRF and risk of HF was still lacking so far. Besides, compared with a single CRF measure at baseline, the changes in CRF over time may better reflect the pattern of CRF variation and could minimize the risk of recall bias, whereas its relationship with risk reduction of HF has not been systematically evaluated.<sup>24,25</sup>

Therefore, this meta-analysis aimed to investigate the association between CRF exposed at baseline and HF risk with dose–response analysis and to assess whether CRF changes over time are correlated with alterations in HF risk. In addition, we examined whether CRF had any incremental value in HF prediction in order to help facilitating its use in the establishment of a disease prediction model.

## Methods

### Search Strategy and Selection Criteria

This meta-analysis was conducted with reference to the Meta-analysis Of Observational Studies in Epidemiology guideline.<sup>26</sup> A literature search of the PubMed, Cochrane Library, and Web of Science was performed for the period up to March 2019, using a combination of the terms/words associated with “cardiorespiratory fitness” and “heart failure” (Online Resource 1). Reference lists from identified articles or reviews were hand-checked for other eligible studies.

Cohort studies published in English that reported the association of CRF with HF incidence (hospitalization) and/or mortality among populations free from HF at entry were included, where CRF was determined using exercise stress tests. Relative risk (RR) estimates such as hazard ratios (HRs) or odds ratios had to be provided with 95% confidence intervals (CIs) or they could be calculated. Studies were excluded if they were posters, reviews, had significant population overlaps (>50%), or did not have sufficient data to calculate the RRs. Studies were also excluded if they enrolled only young individuals at entry (eg, <20 years).<sup>18</sup> This was mainly done to minimize the potential genetic effect on CRF measured at baseline and to lower the heterogeneity across potentially included studies that enrolled individuals aged over 40 years in general.<sup>19–23</sup> To avoid double counting of a cohort that gets multiple publications, the one with the longest length of follow-up or having the most complete information on CRF was selected.

### Data Collection and Risk of Bias Assessment

The items extracted for each study were as follows: first author, publication year, study location, mean age and body

mass index (BMI) of participants, mean length of follow-up, number of participants and HF events, measurement of CRF, CRF levels at different exposure categories, and covariates adjusted. In case of different adjustment models, the model with the biggest number of covariates (except using death as a competing risk) was chosen. For studies providing sex-specific data, they were treated as 2 separate datasets as suggested by Eikendal et al.<sup>27</sup> Moreover, this also lies in the evidence that the incidence of HF was different between men and women.<sup>28</sup>

The risk of bias was assessed using the 9-star Newcastle–Ottawa scale, and studies with more than 6 stars were judged of high quality. All data collection and study quality assessment were initially performed by one author (S.Q.), which were then checked by another author (X.C.). Disagreements were resolved by discussion if occurred.

### Data Synthesis and Statistical Analysis

The effect size was presented as RR with 95% CIs per 1-metabolic equivalent (MET) higher CRF at baseline or per 1-MET increase in CRF over time by pooling the study-specific RRs using a random-effects model, which accounts better for heterogeneity than a fixed-effects one.<sup>29</sup> To enable the analysis, HR was considered equal to RR, and all study-specific CRF was standardized to MET unit, where 1-MET corresponds to 3.5 mL/min/kg of oxygen consumption. If the study-specific RR per 1-MET higher CRF at baseline was not provided,<sup>30</sup> it was calculated using the approach described by Greenland and Longnecker<sup>31</sup> by assuming a linear association of the natural logarithm of HRs with increased CRF as previously suggested.<sup>31,32</sup> For studies reporting CRF by ranges,<sup>19</sup> its median was assumed to be the average of the upper and lower boundaries.<sup>29</sup> If the upper or lower boundary for a certain CRF category was open-ended, its width was considered equal to the adjacent category.<sup>29,33</sup> To further show the association of CRF with risk of HF, a dose–response analysis using restricted cubic spline was applied to model the CRF level with three knots at fixed percentiles (10%, 50%, and 90%) of the distribution.<sup>34</sup> A *P* value for nonlinearity was calculated using a null hypothesis test, where the coefficient of the second spline was equal to 0.

Heterogeneity was assessed using the  $I^2$  statistic, with its value >50% indicating substantial heterogeneity.<sup>29</sup> Subgroup analyses of sex (male vs female), study design (prospective vs retrospective), geographical location (America vs Europe), equipment for exercise stress test (treadmill vs ergometer), and adjustment for BMI, smoking, or lipid profiles (yes vs no), as well as meta-regression analyses on mean BMI and age at entry and length of follow-up were performed to assess their influence on the outcomes. Additional analyses (sensitivity analyses) were used to explore whether the association existed in disease-specific populations (eg, individuals with diabetes, hypertension, or cardiovascular disease) or would be affected upon the removal of the study using data imputation on HF risk.<sup>30</sup> Publication bias was detected using the Begg’s

and Egger's tests, with either  $P < .10$  as the threshold of significance.<sup>29</sup> All analyses were performed using STATA software (version 14.0, College Station, TX), and all tests were 2-sided with  $P < .05$  being considered statistically significant unless otherwise stated.

## Results

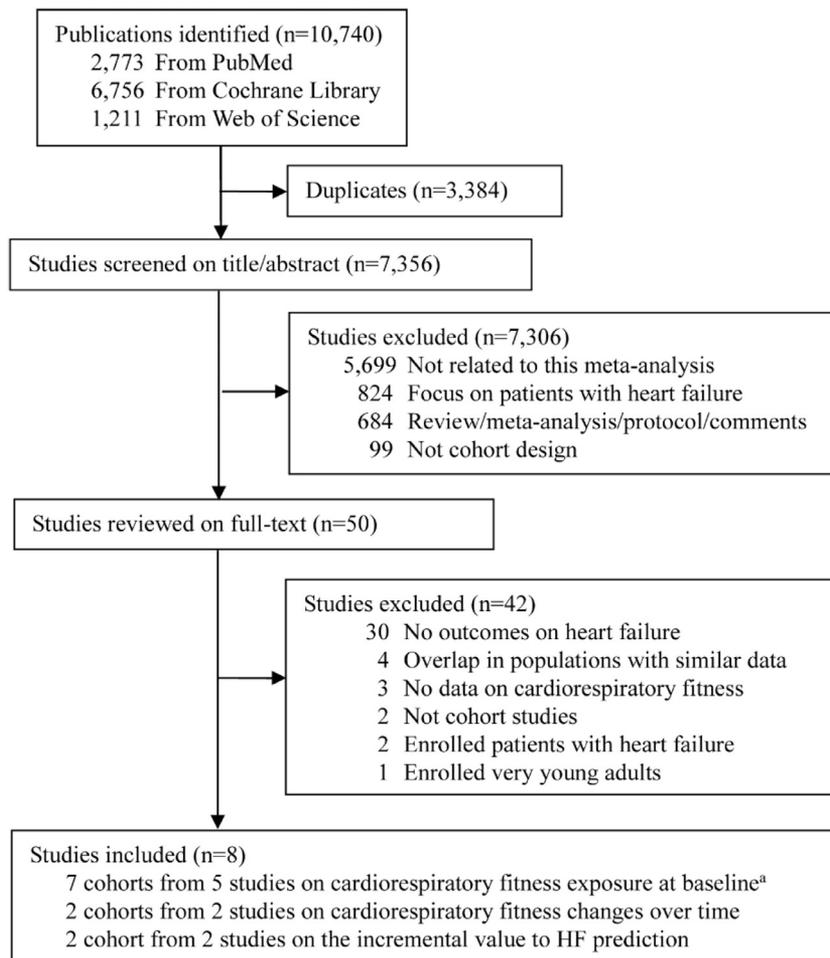
### Characteristics of Included Studies

Of the retrieved 10,740 publications, 8 articles were found to be eligible for this meta-analysis,<sup>15–17,19,20,24,25,30</sup> upon the exclusion of 10,732 publications with the reasons listed in Fig. 1. Because the study by Myers et al<sup>20</sup> showed a significant population overlap along with comparable HF outcomes with the study from Kokkinos et al,<sup>17</sup> it was not included in the analysis of the association of HF risk with CRF exposed at baseline but was considered for the analysis of the incremental value of CRF to HF prediction (Table 1). Moreover, because 2 articles provided sex-specific results,<sup>15,19</sup> a total of 10 studies with 8987 incident HF cases from 154,598 participants during a mean follow-up of 11.6 years (range 6.5–20.4 years) were finally included,<sup>15–17,19,20,24,25,30</sup>

Among studies that reported the association of HF risk with each 1-MET higher CRF at baseline (5 prospective<sup>15–17,30</sup> and 2 retrospective cohorts<sup>19</sup>; Table 1), the average age of included participants was 58.0 years (range 43.4–67.8 years), and their BMI was 26.6 kg/m<sup>2</sup> (range 23.8–28.9 kg/m<sup>2</sup>). The included studies defined an incident HF event as HF hospitalization and/or death according to the International Classification of Diseases codes using patient records in general (Online Resource 2), with the mean incidence rate of HF calculated to be 7.7 per 1000 person-years among individuals aged 5[mt] 0 years (Table 1). All studies utilized maximal or maximal symptom-limited workload to measure CRF, with 8 performed on treadmills and 2 on ergometers (Online Resource 2). Eight studies were conducted in North America<sup>15,17,19,20,24,30</sup> and 2 in Northern Europe.<sup>16,25</sup> All studies were rated with at least 7 stars, indicative of good quality.

### Association of CRF Exposed at Baseline With HF Risk

Seven studies from 5 publications assessed the association of CRF exposed at baseline with HF risk (Table 1).<sup>15–17,19,30</sup> The pooled RR of HF per 1-MET higher CRF was 0.82 (95% CI 0.80–0.84; Fig. 2A),



**Fig. 1.** Study selection process. <sup>a</sup>The study by Myers et al<sup>20</sup> was not included because of the significant population overlap with the study by Kokkinos et al<sup>17</sup> and 2 studies provided sex-specific data.<sup>15,19</sup>

**Table 1.** Characteristics of Included Studies

Author (year)	Country	Study	Follow-up (y)	Age (y)*	Men (%)	BMI (kg/m <sup>2</sup> )	Sample size		HF incidence (1000 person-years)
							Total	Case	
CRF at baseline and HF risk									
Berry <sup>15</sup> (2013) <sup>†</sup>	USA	CCLS	6.5	67.8	100	26.8	16,303	907	8.7
Berry <sup>15</sup> (2013) <sup>‡</sup>	USA	CCLS	6.5	67.7	0	23.8	4339	144	5.2
Khan <sup>16</sup> (2014)	Finland	KIHDS	20.4	52.4	100	26.8	1873	152	4.0
Kokkinos <sup>17</sup> (2019)	USA	ETHOS	13.4	58	100	28.9	20,254	2,979	10.8
Kupsky <sup>19</sup> (2017) <sup>†</sup>	USA	FIT	6.8	58.5	100	NA	35,685	2,814	11.6
Kupsky <sup>19</sup> (2017) <sup>‡</sup>	USA	FIT	6.8	58.5	0	NA	30,644	1,838	8.8
Farrell <sup>30</sup> (2013)	USA	CCLS	19.8	43.4	100	26.7	44,674	153	0.2
CRF changes over time and HF risk									
Pandey <sup>24</sup> (2015)	USA	CCLS	4.2	46.7	84.3	26.9	8683	>138	NA
Khan <sup>25</sup> (2018)	Finland	KIHDS	14.3	50.1	100	26.3	481	46	NA
Incremental value of CRF to HF prediction									
Khan <sup>16</sup> (2014)	Finland	KIHDS	20.4	52.4	100	26.8	1873	152	4.0
Myers <sup>20</sup> (2017)	USA	VETS	USA	58.3	100	28.8	21,080	1902	7.4

CCLS, Cooper Center Longitudinal Study; ETHOS, Exercise Testing and Health Outcomes Study; FIT, Henry Ford Exercise Testing; KIHDS, Kuopio Ischaemic Heart Disease Risk Factor Study; NA, not applicable; VETS, Veterans Exercise Testing Study.

\*Represents the mean or average datum at baseline.

<sup>†</sup>Represents the study enrolling men only.

<sup>‡</sup>Represents the study enrolling women only.

exhibiting minor evidence of substantial heterogeneity ( $I^2 = 47\%$ ). No evidence of publication bias was detected ( $P = .37$  for Begg's test, and 0.10 for Egger's test).

Sex-stratified analysis showed that the pooled RRs were comparable between men (0.82, 95% CI 0.80–0.85) and women (0.81, 95% CI 0.78–0.84;  $P_{\text{interaction}} = .62$ ). Similar findings were also observed across other subgroups as listed in Table 2. Meta-regression analysis suggested that none of the variables including BMI or age at entry, or the length of follow-up could significantly moderate the RR of HF for every 1-MET higher CRF ( $P = .11, 0.64, \text{ and } .69$ , respectively).

Dose–response analysis showed that there was no obvious evidence of a non-linear association between CRF and HF risk in the overall population (6 studies, <sup>15–17,19,30</sup>  $P_{\text{nonlinearity}} = .18$ ; Fig. 2B), or specifically in men (4 studies, <sup>15–17,30</sup>  $P_{\text{nonlinearity}} = .10$ ; Fig. 2C) or in women (1 study, <sup>15</sup>  $P_{\text{nonlinearity}} = .32$ ).

Sensitivity analyses suggested that the RRs of HF per 1-MET higher CRF were 0.84 (95% CI 0.81–0.87), 0.84 (95% CI 0.82–0.86), and 0.85 (95% CI 0.83–0.88) in patients with diabetes, hypertension, and cardiovascular disease, respectively<sup>16,19</sup> (Fig. 3), exhibiting no significant differences from the results observed in the overall or specific disease-free populations (all  $P_{\text{interaction}} > .10$ ). Moreover, when removing the study with data imputation on HF (death) risk per 1-MET higher CRF,<sup>30</sup> the outcome remained minorly changed (RR 0.83, 95% CI 0.82–0.84).

#### Association of CRF Changed Over Time With HF Risk

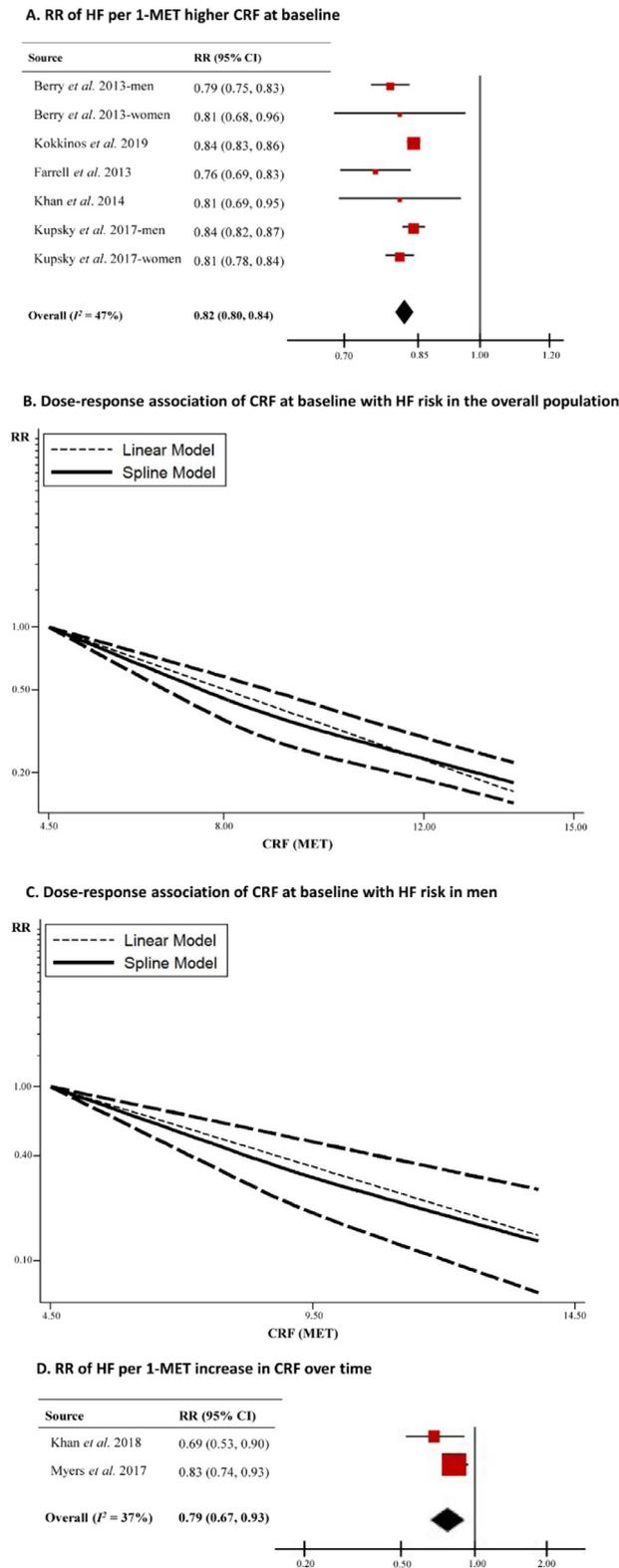
Two studies enrolling more than 184 incident HF cases from 9164 participants reported the association of

CRF changes with HF risk over a mean period of 9.3 years.<sup>24,25</sup> Results showed that the RR of HF per 1-MET increase in CRF changed over time was 0.79 (95% CI 0.67–0.93,  $I^2 = 37\%$ ; Fig. 2D) after adjusting for conventional risk factors. However, the study by Khan et al<sup>25</sup> indicated that this association did not exist in patients with diabetes (RR 0.50, 95% CI 0.21–1.15) or with cardiovascular disease (RR 0.93, 95% CI 0.69–1.27).

**Table 2.** Subgroup Analysis on the Association Between CRF at Baseline and Risk of HF

Variable	CRF (per 1-MET higher)			
	N	RR (95% CI)	$I^2$ (%)	$P_{\text{interaction}}$
Sex				
Men	5	0.82 (0.80, 0.85)	57	
Women	2	0.81 (0.78, 0.84)	<1	.62
Country				
North America	6	0.82 (0.80, 0.83)	35	
North Europe	1	0.81 (0.69, 0.95)	NA	.88
Study design				
Prospective	5	0.81 (0.77, 0.85)	56	
Retrospective	2	0.83 (0.80, 0.86)	56	.43
Equipment for exercise stress test				
Treadmill	6	0.82 (0.80, 0.84)	56	
Ergometer	1	0.81 (0.69, 0.95)	NA	.88
Adjustment for confounders				
BMI Yes	4	0.82 (0.79, 0.85)	43	
No	3	0.82 (0.78, 0.85)	63	>.99
Smoking Yes	6	0.82 (0.80, 0.84)	56	
No	1	0.81 (0.69, 0.95)	NA	.88
Lipids Yes	5	0.83 (0.81, 0.84)	48	
No	2	0.77 (0.71, 0.84)	<1	.11

NA, not applicable.



**Fig. 2.** Association between CRF and HF risk. (A) RR of HF per 1-MET higher CRF at baseline. (B) Dose-response analysis for CRF in the overall population. (C) Dose-response analysis for CRF in men. (D) RR of HF per 1-MET increase in CRF over time. CRF was modeled with restricted cubic splines with 3 knots. Lines with long dashes represent the pointwise 95% CIs for the fitted linear trend (solid line). Lines with short dashes represent the linear trend.

## Incremental Value of CRF to HF Prediction

Two studies explored the incremental value of CRF to HF prediction beyond the models using conventional risk factors.<sup>16,20</sup> Khan *et al.*<sup>16</sup> found that CRF addition increased the net reclassification index by 1.05 (95% CI 1.00–1.09) and the integrated discrimination index by 0.6% (95% CI 0.22%–0.98%), whereas Myers *et al.*<sup>20</sup> observed that the net reclassification index was increased by 0.37 (95% CI 0.31–0.43) and the integrated discrimination index by 3.0% (95% CI 0.01%–6.9%). Because of the large differences on these results between studies, the meta-analytical approach was not performed.

## Discussion

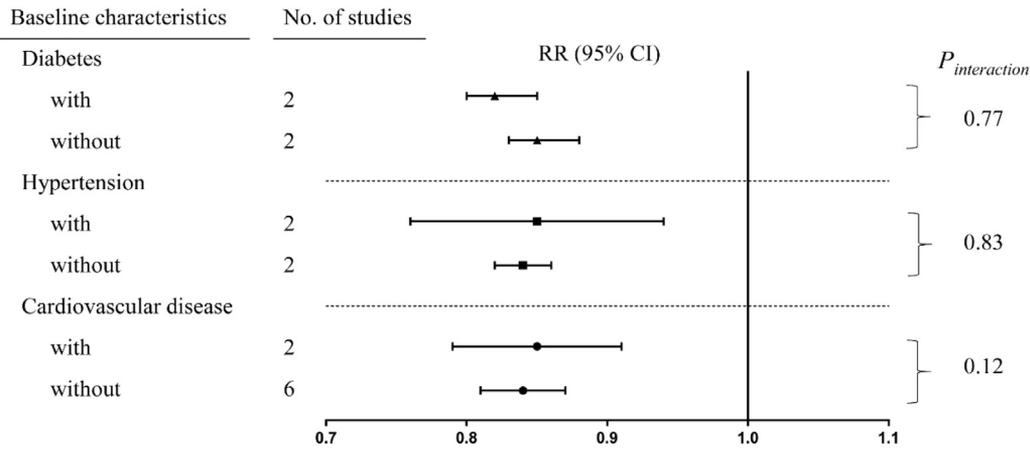
### Summary of the Main Findings

Results from this meta-analysis of currently available cohort studies indicated that the risk of HF was reduced by 18% per 1-MET higher CRF at baseline in a dose-dependent manner. The magnitude of this risk reduction was comparable between men and women, and was similar to those observed in the disease-specific populations. This study also showed that the risk of HF was decreased by 21% per 1-MET increase in CRF over time, and the measurement of CRF in addition to the traditional risk factors may improve the prediction ability for HF as evidenced by the study-specific improvements in both the net reclassification index and the integrated discrimination index, albeit with small magnitudes.

### Interpretations

Our study showed that high CRF was associated with decreased risk of HF, which is in line with the result from a prior meta-analysis that enrolled 3 studies with ~20,000 participants.<sup>7</sup> However, our current meta-analysis included 7 studies with more than 154,000 individuals,<sup>15–17,19,30</sup> and therefore the estimate of the association might be more robust. Of note, our work extends the previous study by showing for the first time that there was a linear inverse dose-response relationship between high CRF and risk of HF, that an increase in CRF over time was also associated with reduced risk of HF regardless of the baseline CRF, and that CRF provided incremental value to HF prediction beyond conventional models. Along with the evidence that elevated CRF predicts risk of type 2 diabetes,<sup>35</sup> cardiovascular events, and all-cause mortality,<sup>36</sup> these results are in support of the recommendation that CRF is worth being adopted as a vital sign in clinical routine.<sup>14</sup>

The observed risk reduction in HF associated with high or increased CRF might be mediated by several biological mechanisms. Increasing evidence shows that high CRF is related to altered body mass, enhanced insulin sensitivity, lowered blood pressure, improved endothelial function, and reduced oxidative stress,<sup>37–39</sup> all of which may delay the progression of atherosclerosis and subsequently retard the development of HF.<sup>40</sup> On the other hand, aerobic exercise, which leads to increased CRF,<sup>41,42</sup> is helpful to alter the remodeling of the heart by



**Fig. 3.** The association between CRF at baseline and HF risk among populations with or without a specific disease.

reducing left ventricular mass, end diastolic volume, and wall thickness,<sup>43,44</sup> and improve the cardiac function by increasing the cardiac output with optimized oxygen utilization,<sup>44</sup> thus contributing to reduced risk of HF.

There is evidence that the age-standardized incidence and prevalence of HF are higher in men than in women,<sup>45</sup> and that women are more prone to developing HF with preserved ejection fraction than men,<sup>27</sup> indicative of a possible sexual disparity. Yet our meta-analysis did not detect such a disparity regarding the protective effect of CRF against HF. This could be also partly supported by the results from the dose–response analysis that a linear relationship between CRF and HF risk existed in both men and women. In addition, Kupsky et al,<sup>19</sup> noted that the risk of progressing to HF was much lower with high CRF in patients aged below 50 years than those above. However, our meta-regression analysis indicated that age had little effect in modifying this association. It seems likely that the difference in the target populations and the statistical approaches might largely contribute to this inconsistency.

Diabetes, hypertension, and cardiovascular disease are well recognized risk factors for HF,<sup>1,46</sup> and their presence at entry might confound the protective effects of CRF. However, our sensitivity analyses, which grouped participants with or without diabetes, hypertension, or cardiovascular disease, showed consistently that high CRF leads to reduced risk of HF, and therefore, the presence of these diseases appeared to have minor influence on the estimates. Moreover, our subgroup analysis also suggested that the association of CRF with HF risk was not significantly affected by lipid profiles. Taken together, these highlight that the inverse association between high CRF and risk of HF could be generalized from the general (overall) population to the diseased patients, and support the necessity of increasing CRF to prevent HF.

**Implications**

The results of this meta-analysis may aid in the understanding of the etiology of HF and help to diversify the

options for HF risk stratification or prediction model establishment. However, given that physical activity and CRF are correlated with but different from each other,<sup>11</sup> and that increased physical activity reduces risk of HF<sup>8</sup> and is associated with favorable metabolic health profiles independent of CRF,<sup>47</sup> it remains interesting to address whether there would be any interaction effect between them with regard to HF risk. This is of clinical importance, since this would highlight whether it is more important to increase physical activity via interventions like pedometers<sup>48</sup> or to improve CRF through aerobic interval exercise training.<sup>41</sup> Moreover, almost all included individual studies in this meta-analysis utilized maximal exercise tests to determine CRF. Yet recent evidence emerges that CRF measured using submaximal exercise tests might carry a comparable or even superior prognostic utility with less time consumption and fewer uncomfortable feeling.<sup>49</sup> In addition, the estimation of CRF with reference to nonexercise algorithms provides also a valid indication of health outcomes.<sup>50</sup> Therefore, it is necessary to explore whether they could serve as new alternatives to predict HF events.

**Strengths and Limitations**

Our meta-analysis is to date the most comprehensive study that explores the association of CRF with HF risk, and exhibits enhanced statistical power by enrolling more than 154,000 participants with long follow-up periods than any individual study in the estimate of this association. Yet this study has several limitations. First, although all studies were cohort designed and well controlled for potential risk factors for HF, there still exists the possibility that our results might be subject to residual confounding. Second, our subgroup and meta-regression analyses showed that the association of CRF with HF risk could not be significantly moderated by BMI, while we did not test the interaction effect between BMI and CRF on HF risk. But there is evidence that CRF may mediate BMI-associated HF risk.<sup>51</sup> Third, the evidence regarding whether an increase in CRF over time would significantly reduce risk of HF, in

particular among patients with diabetes or existing cardiovascular disease remained somehow inadequate, which might be mainly because of the very limited number of studies. Therefore, this issue requires further investigation. Fourth, although the approaches or formulas in obtaining CRF were well recognized, some of the included studies did not use the gas-exchange measures as the gold standard to get the most accurate levels of CRF.<sup>15,30</sup> Finally, all eligible studies were from Western countries (America and Europe), and it remains unclear whether our conclusion could be applied to individuals from Eastern countries like China. Moreover, despite no evidence of publication bias detected using the quantitative approaches, the inclusion of studies published in English only may still incur publication bias.

### Conclusion

In conclusion, this meta-analysis suggested that high or increased CRF was associated with lowered risk of HF, supporting the recommendation of improving CRF to prevent HF. Further studies are needed to assess the interaction effects between physical activity and CRF and between obesity and CRF on HF risk, which may help to better target the interventions.

### Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.cardfail.2019.04.008](https://doi.org/10.1016/j.cardfail.2019.04.008).

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