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BRIEF REPORT

Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality: A Population-Based Follow-up Study

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Abstract

Few studies have investigated long-term changes in cardiorespiratory fitness (CRF), defined by indirect measures of CRF, and all-cause mortality. We aimed to investigate whether long-term change in CRF, as assessed by the gold standard method of respiratory gas exchange during exercise, is associated with all-cause mortality. A population-based sample of 579 men aged 42 to 60 years with no missing data at baseline examination (V1) and at reexamination at 11 years (V2) were included. Maximal oxygen uptake (VO_{2max}) was measured at both visits using respiratory gas exchange during maximal exercise testing, and the difference (ΔVO_{2max}) was calculated as VO_{2max} (V2) − VO_{2max} (V1). Deaths were ascertained annually using national death certificates during 15 years of follow-up after V2. The mean ΔVO_{2max} was −5.2 mL/min*kg. During median follow-up of 13.3 years (interquartile range, 12.5-14.0 years), 123 deaths (21.2%) were recorded. In a multivariate analysis adjusted for baseline age, VO_{2max}, systolic blood pressure, smoking status, low- and high-density lipoprotein cholesterol and triglyceride levels, C-reactive protein level, body mass index, alcohol consumption, physical activity, socioeconomic status, and history of type 2 diabetes mellitus and ischemic heart disease, a 1 mL/min*kg higher ΔVO_{2max} was associated with a 9% relative risk reduction of all-cause mortality (hazard ratio, 0.91; 95% CI, 0.87-0.95). This study suggested that in this population, long-term CRF reduction was associated with an increased risk of mortality, emphasizing the importance of maintaining good CRF over the decades.

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Physical fitness is strongly associated with lower cardiovascular disease (CVD) mortality. Multiple studies have reported a consistent inverse association between cardiorespiratory fitness (CRF) and mortality even after adjustment for traditional risk factors.[1,2] Cardiorespiratory fitness is a measure of cardiac and respiratory functioning. Directly measured maximal oxygen uptake (VO_{2max}), an objective and quantitative measure of CRF, is the gold standard for assessing the amount of oxygen consumption during exercise.[3-5] Individual CRF levels have been found to be a stronger predictor of mortality than traditional risk factors, including smoking, hypertension, high cholesterol level, and type 2 diabetes mellitus,[6,7] as well as other exercise test variables, such as ST-segment depression and hemodynamic responses.[1]

The association between CRF and mortality has been proposed to persist across the lifespan, with a single measurement of CRF in midlife strongly associated with the lifetime risk decades later. On the other hand, few studies have assessed the relationship between changes over time in CRF and risk of mortality.[8-10] These studies, however, relied on an indirect estimation of CRF (ie, treadmill time)[8,9] or exercise scores.[10] To help clarify the existing evidence, we assessed whether long-term changes in CRF, as assessed by the gold standard method of oxygen consumption during exercise testing, predict all-cause mortality in the general population.

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PATIENTS AND METHODS

Study Population

The study population is a representative sample of men living in Kuopio and its surrounding rural communities in Eastern Finland. The study group comprised participants in the Kuopio

Ischaemic Heart Disease Risk Factor Study, a longitudinal population-based study designed to investigate risk factors for CVD and related outcomes.[11] These individuals were 42 to 61 years of age during baseline examinations performed between March 20, 1984, and December 5, 1989. Of 3235 potentially randomly selected eligible men, 2682 (82.9%) volunteered to participate in this study.The present analysis is based on 579 men participating in the follow-up study with no missing data on exercise testing and covariates and who had assessment of CRF at baseline (visit 1 [V1]) and at 11-year examination (visit 2 [V2]; mean ± SD interval, 11.1±0.37 years); the repeated assessment was performed without a prespecified clinical indication for exercise testing. The study was approved by the Research Ethics Committee of the University of Eastern Finland, and each participant gave written informed consent.

Assessment of CRF

Maximal oxygen uptake was used as a measure of CRF, which was assessed using a respiratory gas exchange analyzer during maximal symptom-limited cycle ergometer exercise tolerance testing. The standardized testing protocol comprised a 3-minute warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min, with direct analyses of respiratory gases by the breath-by-breath method using an MGC analyzer (Medical Graphics Corp). The MCG analyzer expresses VO_{2max} as mean values recorded over 8 seconds, and the VO_{2max} was defined as the highest value for or the plateau of oxygen uptake.[11,12] All men with the assessed highest VO_{2max} during the repeated exercise tests were included in the study.[11,12] Although the plateau in oxygen uptake could not have been reached despite an increase in the workload of exercise, the highest (ie, peak) value of oxygen uptake was always defined. The assessment of CRF was performed at V1 and repeated at the 11-year examination (V2). We also tested nonexercise test–based CRF derived from age, body mass index (BMI), heart rate at rest, and physical activity as previously reported.[13]

Assessment of Baseline and 11-Year Risk Factors

A participant was defined as a smoker if he had ever smoked cigarettes, cigars, or a pipe on a regular basis within the past 30 days. Resting blood pressure was measured between 8 and 10 AM using a random-zero sphygmomanometer. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory.[12] The BMI was calculated as the weight in kilograms divided by the height in meters squared. Diabetes was defined as a fasting blood glucose level of at least 126 mg/dL (to convert to mmol/L, multiply by 0.0555) or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment. The collection of blood specimens and the measurement of serum lipid, lipoprotein, creatinine, and glucose levels have been described elsewhere.[14] Serum C-reactive protein levels were measured using an immunometric assay (Immulite high-sensitivity C-reactive protein assay, Siemens Medical Solutions Diagnostics). Medication use, baseline diseases, physical activity level, and socioeconomic status were assessed by self-administered questionnaires. Prevalent ischemic heart disease was defined as a previous myocardial infarction, angina pectoris, or the use of nitroglycerin for chest pain at least once a week. The detailed assessment of physical activity and socioeconomic status has been described in previous studies.[15,16] The assessments of risk factors were repeated similarly at V1 and V2.

Ascertainment of Outcomes

All-cause deaths that occurred from V2 (March 1, 2000, through December 31, 2001) through December 31, 2012, were included as an outcome. There were no losses to follow-up. All the study participants were under continuous surveillance for the development of new outcome events. The sources of information were the national death certificates, followed for up to 15 years after V2.[11,15]

Statistical Analyses

For all the analyses, natural logarithm ($\log_e$)–transformed values of nonnormal distributed variables (C-reactive protein levels, BMI, serum triglyceride levels, alcohol consumption, and physical activity) were used. Descriptive data are presented as mean ± SD or median (interquartile range) for continuous variables and as numbers (percentages) for categorical variables. Differences between V1 and V2 values were estimated using the paired

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t test for continuous variables and the Cochran Q test for categorical ones. Analyses of the associations between CRF change and all-cause mortality involved Cox regression modeling; V2 marked the beginning of follow-up. Hazard ratios (HRs) were estimated per 1-unit change in VO_{2max} (ΔVO_{2max}; difference between V2 and V1), with adjustment for values of VO_{2max} and other potential confounders at V1; confounders were selected on the basis of their previously established role as risk factors.[11] We also adjusted HRs using VO_{2max} at V1 and all other confounders at V2. The proportional hazards assumption was verified for all variables by inspection of the plots of the Schoenfeld residual for covariates. We performed 2 supplementary analyses. First, we reported HRs in metabolic equivalents (METs; 1 MET = 3.5 mL/min*kg) and ΔVO_{2max} (absolute VO_{2max} value). Second, we used V1 data on age, BMI, resting heart rate, and physical activity to estimate with a linear regression the value of CRF (estimated CRF [eCRF])[13]; the coefficients derived from the regression were applied to age, BMI, resting heart rate, and physical activity values at V2 to calculate 11-year eCRF. Then, the change between V2 and V1 eCRF (ie, ΔeCRF) was included in a model adjusted for eCRF and other potential confounders at V1 to assess the relationship between the nonexercise method for assessing CRF (ie, formula-based estimation) and mortality. Two-sided analyses were performed using Stata software version 13 (StataCorp LP), and CIs are presented at the 95% level.

RESULTS

At baseline, 152 participants (26.3%) were smokers and mean ± SD age and VO_{2max} were 50.7±6.7 years and 32.8±7.9 mL/min*kg, respectively; excluding triglycerides levels, all other variables statistically significantly changed after 11 years, with a mean ± SD ΔVO_{2max} of −5.2±5.6 mL/min*kg (Table). During median follow-up of 13.3 years (interquartile range, 12.5-14.0 years), 123 deaths (21.2%) were recorded, with a crude incidence rate of

TABLE. Characteristics of 579 Study Participants at Baseline and 11 Years[a,b]

Variable	Baseline values	11-year values	*P* value[c]
Age (y), mean ± SD	50.7±6.7	61.8±6.4	<.001
Systolic blood pressure (mm Hg), mean ± SD	131±15	134±17	<.001
LDL cholesterol (mg/dL), mean ± SD	146±34	135±35	<.001
HDL cholesterol (mg/dL), mean ± SD	51±11	45±11	<.001
C-reactive protein (mg/L), median (IQR)	1.06 (0.60-1.96)	1.32 (0.70-2.80)	<.001
BMI (kg/m^2), median (IQR)	26.2 (24.3-28.6)	26.8 (25.0-29.5)	<.001
Triglycerides (mg/dL), median (IQR)	99 (73-141)	102 (73-139)	.81
Alcohol consumption (g/wk), median (IQR)	36 (8-97)	40 (9-109)	.006
Energy expenditure of physical activity (kcal/d), median (IQR)	308 (175-489)	385 (224-600)	<.001
Socioeconomic status, mean ± SD[d]	6.99±3.92	10.51±4.83	<.001
Smoking (yes) (No. [%])	152 (26.3)	103 (17.9)	<.001
History of ischemic heart disease (yes) (No. [%])	104 (17.9)	148 (25.6)	<.001
History of type 2 diabetes mellitus (yes) (No. [%])	15 (2.6)	70 (12.1)	<.001
VO_{2max} (mL/min*kg), mean ± SD	32.8±7.9	27.6±6.9	<.001
VO_{2max} (mL/min), mean ± SD	2624±665	2245±580	<.001
RER at maximal exercise, mean ± SD[e]	1.17±0.10	1.12±0.12	<.001

[a]BMI = body mass index (calculated as the weight in kilograms divided by the height in meters squared); HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; RER = respiratory exchange ratio; VO_{2max} = maximal oxygen uptake; ΔVO_{2max} = VO_{2max} at 11 years − VO_{2max} at baseline.

[b]SI conversion factors: To convert cholesterol values to mmol/L, multiply by 0.0259; to convert C-reactive protein values to nmol/L, multiply by 9.524; to convert triglyceride values to mmol/L, multiply by 0.0113.

[c]*P* values indicate differences between 11-year and baseline values; for non-normally distributed data, paired *P* values are calculated using the log-transformed variables.

[d]Socioeconomic status is a summary index combining measures of income, occupation, occupational prestige, material standard of living, and housing conditions (all assessed using self-reported questionnaires).

[e]The RER is the ratio of carbon dioxide production to oxygen consumption at maximal exercise (the highest RER value during the exercise test).

16.9 (95% CI, 14.2-20.2) per 1000 person-years. The relationship between CRF change and all-cause mortality is described in the Figure.

In an analysis adjusted for only VO_{2max} at V1, a 1 mL/min*kg higher ΔVO_{2max} was associated with a mortality HR of 0.90 (95% CI, 0.87-0.94; $P<.001$), corresponding to 0.70 (95% CI, 0.61-0.80) per 1 MET and 0.998 (95% CI, 0.998-0.999) per 1 mL/min higher ΔVO_{2max}. In a multivariate analysis adjusted for VO_{2max}, age, systolic blood pressure, smoking status, low- and high-density lipoprotein cholesterol and triglyceride levels, C-reactive protein level, BMI, alcohol consumption, physical activity, socioeconomic status, and history of type 2 diabetes mellitus and ischemic heart disease at V1, a 1 mL/min*kg higher ΔVO_{2max} was associated with a 9% relative reduction of all-cause death, ie, HR 0.91 (95% CI, 0.87-0.95; $P<.001$; Figure), corresponding to 0.71 (95% CI, 0.61-0.83) per 1 MET and 0.998 (95% CI, 0.998-0.999) per 1 mL/min higher ΔVO_{2max}. When the multivariate analysis was adjusted for VO_{2max} at V1 and all other covariates assessed at V2 (477 participants and 98 deaths without missing data), the result was similar (HR, 0.88; 95% CI, 0.84-0.93; $P<.001$) per 1 mL/min*kg higher ΔVO_{2max}, corresponding to an HR of 0.65 (95% CI, 0.55-0.76) per 1 MET and 0.998 (95% CI, 0.998-0.999) per 1 mL/min higher ΔVO_{2max}.

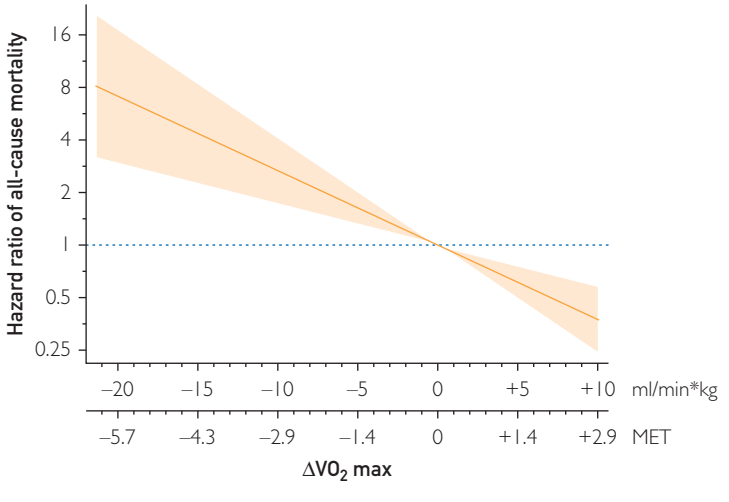

FIGURE. Cardiorespiratory fitness change and risk of all-cause mortality.

Using a nonexercise testing method for assessing CRF, in a model adjusted for eCRF, systolic blood pressure, smoking status, serum low- and high-density lipoprotein cholesterol levels, triglyceride levels, history of type 2 diabetes and ischemic heart disease, C-reactive protein levels, alcohol consumption, and socioeconomic status at V1, the HR per 1 mL/min higher ΔeCRF resulted in an HR of 0.998 (95% CI, 0.996-0.999; $P=.001$; 431 participants and 90 deaths without missing data).

DISCUSSION

In this study, we found a strong inverse association between long-term change in directly measured CRF and all-cause mortality. A smaller decrease in CRF over 11 years was associated with a lower risk of all-cause death in a graded manner in this population-based sample of men. The observed association was independent of risk factors assessed at baseline and at 11 years.

Blair et al[8] reported that participants who maintained or improved to sufficient CRF levels were less likely to die of any causes during follow-up than persistently unfit participants within 2 CRF examinations. More recently, Kokkinos et al[9] found that survival improved significantly when unfit individuals became fit at least 6 months after the initial CRF test. The results of this study suggested that individuals enhancing their fitness from a low-fit to a fit level using different categories for indirectly estimated CRF status yields significant health benefits even at an advanced age. Last, a similar association was found in a study using a score to estimate physical fitness.[10] The present study is based on a population-based sample of men with repeated and direct assessment of CRF using a similar interval for all participants, whereas previous studies were constructed based on participants referred to exercise testing at varying intervals between 2 repeated tests[8,9] and on indirect CRF assessment or exercise scores.[10]

Cardiorespiratory fitness is a simple, practical component that can be measured easily in clinical practice, and directly assessed CRF is one of the strongest risk factors for mortality.[11,17] We also previously found that CRF is one of the strongest risk factors when

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combined with common cardiovascular risk scores.[18] Because exercise testing with assessment of CRF is a widely available measure, it should be used to help assess the risk of premature death in particular populations, including patients with previous CVD, those with common cardiovascular risk factors or symptoms, and those who are inactive but plan to become much more active. On the basis of these results, we recommend counseling on a physically active lifestyle to improve and maintain good CRF levels. We also found that higher nonexercise test–based CRF changes were related to lower all-cause mortality. This finding indicates that nonexercise test–based estimation of CRF could also be a useful tool when exercise testing is not available; only the assessment of age, resting heart rate, BMI, and physical activity level is needed for nonexercise test estimation of CRF.[13]

It is possible that the higher mortality rates in men with low levels of CRF were at least partly due to underlying chronic diseases (diagnosed or undiagnosed) associated with an increased risk of mortality (reverse causality). However, we adjusted for baseline and 11-year covariates (including diseases) to avoid this bias, which is a typical feature of follow-up studies. We also acknowledge that the generalizability of these findings is limited by the study population, consisting of middle-aged Finnish men only; these results need to be replicated in other ethnic groups, including different age groups. On the other hand, strengths of this study include the rigorous measurement of baseline and follow-up risk factors, the direct and repeated measurement of CRF at similar intervals, the large and homogeneous community-based sample, and the long-term follow-up without missing data on outcomes.

CONCLUSION

The results of this study underline the importance of sustained CRF to reduce the risk of long-term mortality. Maintaining a good CRF level is one of the most attainable beneficial lifestyle changes that a person can achieve primarily by physical exercise.

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Abbreviations and Acronyms: **BMI** = body mass index; **CRF** = cardiorespiratory fitness; **CVD** = cardiovascular disease; **eCRF** = estimated cardiorespiratory fitness; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **IQR** = interquartile range; **LDL** = low-density lipoprotein; **MET** = metabolic equivalent; **RER** = respiratory exchange ratio; **VO_{2max}** = maximal oxygen uptake; **ΔVO_{2max}** = VO_{2max} at 11 years − VO_{2max} at baseline

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REFERENCES

1. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301(19):2024-2035.
2. Kaminsky LA, Arena R, Beckie TM, et al; American Heart Association Advocacy Coordinating Committee; Council on Clinical Cardiology; and Council on Nutrition, Physical Activity, and Metabolism. The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association. *Circulation*. 2013;127(5):652-662.
3. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001; 104(14):1694-1740.
4. Kaminsky LA, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the Fitness Registry and the Importance of Exercise National Database. *Mayo Clin Proc*. 2015;90(11): 1515-1523.
5. Balady GJ, Arena R, Sietsema K, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(2): 191-225.
6. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793-801.
7. Blair SN, Kampert JB, Kohl HW III, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996;276(3): 205-210.
8. Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. *JAMA*. 1995;273(14):1093-1098.
9. Kokkinos P, Myers J, Faselis C, et al. Exercise capacity and mortality in older men: a 20-year follow-up study. *Circulation*. 2010; 122(8):790-797.

10. Erikssen G, Liestøl K, Bjørnholt J, Thaulow E, Sandvik L, Erikssen J. Changes in physical fitness and changes in mortality. *Lancet*. 1998;352(9130):759-762.
11. Laukkanen JA, Lakka TA, Rauramaa R, et al. Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med*. 2001;161(6):825-831.
12. Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med*. 1994;330(22):1549-1554.
13. Stamatakis E, Hamer M, O'Donovan G, Batty GD, Kivimaki M. A non-exercise testing method for estimating cardiorespiratory fitness: associations with all-cause and cardiovascular mortality in a pooled analysis of eight population-based cohorts. *Eur Heart J*. 2013;34(10):750-758.
14. Salonen JT, Salonen R, Seppänen K, Rauramaa R, Tuomilehto J. HDL, HDL2, HDL3 subfractions, and the risk of acute myocardial infarction: a prospective population study in eastern Finnish men. *Circulation*. 1991;84(1):129-139.
15. Laukkanen T, Khan H, Zaccardi F, Laukkanen JA. Association between sauna bathing and fatal cardiovascular and all-cause mortality events. *JAMA Intern Med*. 2015;175(4):542-548.
16. Laukkanen JA, Rauramaa R, Mäkikallio TH, Toriola AT, Kurl S. Intensity of leisure-time physical activity and cancer mortality in men. *Br J Sports Med*. 2011;45(2):125-129.
17. Laukkanen JA, Kurl S, Salonen R, Rauramaa R, Salonen JT. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study. *Eur Heart J*. 2004;25(16):1428-1437.
18. Laukkanen JA, Rauramaa R, Salonen JT, Kurl S. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. *J Intern Med*. 2007;262(2):263-272.