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Midlife Cardiorespiratory Fitness and the Long-Term Risk of Mortality

46 Years of Follow-Up

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ABSTRACT

BACKGROUND A high cardiorespiratory fitness (CRF) level is recommended to promote healthy aging. However, the association between CRF and very-long-term prognosis is unclear, and reverse causation may bias results in studies with shorter follow-up.

OBJECTIVES This study investigated the association between CRF and mortality in middle-aged, employed men free of cardiovascular disease (CVD).

METHODS Participants from the Copenhagen Male Study, established in 1970 to 1971, were included and stratified into 4 age-adjusted maximal oxygen consumption (V_{O_2}max) categories: below the lower limit of normal (lowest 5%); low normal (45%); high normal (45%); and above the upper limit of normal (top 5%). V_{O_2}max was estimated by using a bicycle ergometer. Multivariable restricted mean survival time models were performed for all-cause and cardiovascular mortality using Danish national registers.

RESULTS A total of 5,107 men with a mean age of 48.8 ± 5.4 years were included in the study. During the 46 years of follow-up, 4,700 (92%) men died; 2,149 (42.1%) of the men died of CVD. Compared with below the lower limit of normal CRF, low normal CRF was associated with 2.1 years (95% confidence interval [CI]: 0.7 to 3.4; $p = 0.002$), high normal with 2.9 years (95% CI: 1.5 to 4.2; $p < 0.001$), and above upper limit of normal with 4.9 years (95% CI: 3.1 to 6.7; $p < 0.001$) longer mean life expectancy. Each unit increase in V_{O_2}max was associated with a 45-day (95% CI: 30 to 61; $p < 0.001$) increase in longevity. Estimates for cardiovascular mortality were similar to all-cause mortality. Results were essentially unchanged when excluding individuals who died within the first 10 years of follow-up, suggesting a minimal role of reverse causation.

CONCLUSIONS CRF was significantly related to longevity over the course of 4 decades in middle-aged, employed men free of CVD. The benefits of higher midlife CRF extend well into the later part of life. (J Am Coll Cardiol 2018;72:987–95)

According to the World Health Organization, cardiovascular diseases (CVDs) are the leading cause of death worldwide, and almost 1 in every 3 deaths in the United States in 2013 was caused by a CVD (1,2). Since the mid-20th century, studies have shown that physical activity and cardiorespiratory fitness (CRF) are inversely associated with CVD and mortality, and even a small increase in CRF is related to a significantly lower risk of death (3-6). CRF is a measure of the maximum oxygen uptake

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ABBREVIATIONS AND ACRONYMS

AULN = above upper limit of normal

BLLN = below lower limit of normal

CRF = cardiorespiratory fitness

CVD = cardiovascular disease

HN = high normal

LN = low normal

Vo_2max = maximal oxygen consumption

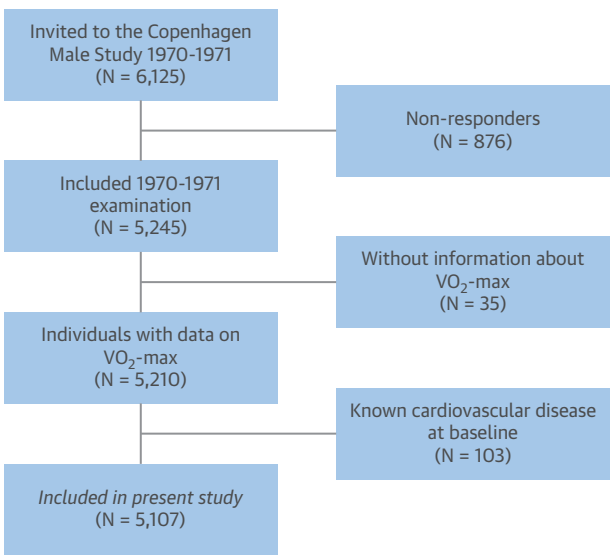
per minute per kilogram body weight, and it can be estimated with nonexercise algorithms, as well as with exercise-based tests (e.g., treadmill or bicycle tests) (6,7).

SEE PAGE 996

Current knowledge on the association between CRF and cardiovascular and all-cause mortality has been established with epidemiological studies of prospective cohorts (6). Hence, to the best of our knowledge, sparse evidence of this association after more than 25 years exists (6,8). In studies with short follow-up, the possibility of reverse causation cannot be excluded (i.e., the fact that underlying nondiagnosed, unmeasured disease may cause a lower CRF at inclusion).

The present study investigated the relation between CRF, assessed objectively by using the Åstrand bicycle ergometer test, and mortality, with >4 decades of follow-up. The very long follow-up in the present study allows the role of reverse causation to be addressed. With 46 years of follow-up, we hypothesized that the long-term risks of cardiovascular mortality and all-cause mortality were inversely associated with objectively measured CRF in middle-aged, employed men free of CVD at inclusion.

FIGURE 1 Flowchart: the Copenhagen Male Study



In 1970 to 1971, middle-aged, employed men from private and public workplaces in Copenhagen were invited to participate in the Copenhagen Male Study. Participants underwent clinical examination, including assessment of cardiovascular risk factors, socioeconomic status, and estimation of cardiorespiratory fitness level (maximal oxygen consumption [Vo_2max]) by using the Åstrand bicycle ergometer test.

METHODS

STUDY POPULATION. The present study is based on the study population in a prospective cohort, the Copenhagen Male Study. This study was originally established in autumn 1970 to spring 1971 with the recruitment of 5,245 men between 40 and 59 years of age from workplaces in Copenhagen. Initial examination included measurement of blood pressure, height, and weight. CRF was estimated with Åstrand's nomogram by using a standard bicycle ergometer test (9). Heart rate was measured by using a stethoscope and stopwatch in a working steady state, and 100, 150, and 200 W were used as workloads. The workloads were chosen from the subject's weight and height or the heart rate in the first minute of the examination and, in a few cases, different workloads were used.

All subjects were interviewed by a physician (F.G.) at inclusion, and a questionnaire on cardiovascular risk factors was completed. The anamneses included general health status and previous CVDs, such as coronary heart disease. The questionnaire included information on self-reported physical activity, smoking and alcohol consumption, and the occurrence of familial coronary heart disease, hypertension, or diabetes. Because no standard questionnaire on physical activity was available in 1970 to 1971, Gyntelberg et al. (10–12) created their own questionnaire, classifying self-reported physical activity as high, moderate, or low. The included questions have previously been described in detail. Alcohol consumption was also classified as high, moderate, or low. Subjects reported history of smoking as never smoked, former smoker, or present smoker. As described in previous studies (11), the subjects were subdivided into 3 social classes based on level of education and current occupation.

In the present analysis, we excluded all subjects who answered "yes" to previous CVD at inclusion. Of the 5,245 men originally included in the Copenhagen Male Study, 35 did not perform the bicycle ergometer test and 103 had pre-existing CVD at inclusion, resulting in a total of 5,107 men in the present study (**Figure 1**).

ENDPOINTS. All-cause mortality and cardiovascular mortality were used as endpoints. Vital status as of March 22, 2017, was extracted from the Danish national Central Person Register and used as the end of follow-up in the all-cause mortality analysis. In the cardiovascular mortality analysis, information about death from CVDs (International Classification of

TABLE 1 Demographic Characteristics

	All	Below Lower Limit of Normal CRF	Low Normal CRF	High Normal CRF	Above Upper Limit of Normal CRF	p Value
Subjects	5,107 (100.0)	258 (5.0)	2,289 (45.0)	2,304 (45.0)	256 (5.0)	
All-cause mortality	4,700 (92.0)	247 (95.7)	2,107 (92.0)	2,112 (91.7)	234 (91.4)	0.15
Cardiovascular mortality	2,149 (42.1)	129 (50.0)	968 (42.3)	960 (41.7)	92 (35.9)	0.013
Age at inclusion, yrs	48.8 ± 5.4	49.0 ± 5.3	48.7 ± 5.3	48.8 ± 5.4	48.7 ± 5.1	0.73
CRF, ml/(kg · min)	32.9 ± 7.2	20.7 ± 2.0	28.3 ± 3.1	37.1 ± 4.1	49.6 ± 4.8	<0.001
Body mass index, kg/m^2						<0.001
<20	2,444 (47.9)	63 (24.5)	897 (39.3)	1,294 (56.2)	190 (74.2)	
20–25	2,319 (45.5)	137 (53.3)	1,183 (51.8)	936 (40.7)	63 (24.6)	
>25	335 (6.6)	57 (22.2)	204 (8.9)	71 (3.1)	3 (1.2)	
Hypertension (SBP >140 mm Hg)	2,115 (41.4)	175 (67.8)	1119 (48.9)	768 (33.3)	53 (20.7)	<0.001
Diabetes	41 (0.8)	5 (1.9)	18 (0.8)	15 (0.7)	3 (1.2)	0.15
Smoking						<0.001
Never	449 (8.8)	24 (9.3)	201 (8.8)	201 (8.7)	23 (9.0)	
Former	977 (19.1)	59 (22.9)	496 (21.7)	389 (16.9)	33 (12.9)	
Present	3,681 (72.1)	175 (67.8)	1,592 (69.6)	1,714 (74.4)	200 (78.1)	
Alcohol intake						<0.001
Low	4,120 (80.7)	180 (69.8)	1,801 (78.7)	1,913 (83.0)	226 (88.3)	
Moderate	809 (15.8)	56 (21.7)	396 (17.3)	330 (14.3)	27 (10.5)	
High	178 (3.5)	22 (8.5)	92 (4.0)	61 (2.6)	3 (1.2)	
Leisure-time physical activity						<0.001
Light	874 (17.1)	74 (28.7)	469 (20.5)	306 (13.3)	25 (9.8)	
Moderate	3,670 (71.8)	168 (65.1)	1,611 (70.5)	1,723 (74.8)	168 (65.6)	
High	559 (11.0)	16 (6.2)	206 (9.0)	274 (11.9)	63 (24.6)	
Socioeconomic status						0.030
High	847 (16.6)	33 (12.8)	362 (15.8)	402 (17.5)	50 (19.5)	
Moderate	1,434 (28.1)	88 (34.1)	654 (28.6)	637 (27.7)	55 (21.5)	
Low	2,820 (55.3)	137 (53.1)	1,268 (55.5)	1,264 (54.9)	151 (59.0)	

Values are n (%) or mean ± SD.
CRF = cardiorespiratory fitness; SBP = systolic blood pressure.

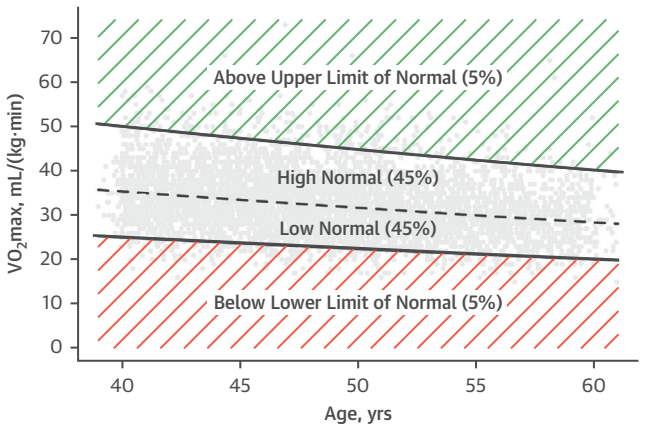
Diseases-8th Revision: 390 to 458; International Classification of Diseases-10th Revision: I00 to I99) were extracted from death certificates in the Danish Register of Causes of Death until December 31, 2015, which was used as the end of follow-up.

CATEGORIES OF CRF LEVELS. Initial analyses revealed that estimated Vo_2max decreased with age; thus, a younger individual would be more likely to have a higher Vo_2max than an older individual. We therefore developed age-standardized Vo_2max by determining the residuals from the age versus Vo_2max regression and dividing these residuals by the SD to obtain *z* scores. The distribution of Vo_2max was right-skewed and was therefore log-transformed before standardization. The 4 categories of age-adjusted CRF levels were defined as follows: below lower limit of normal, including individuals with age-adjusted Vo_2max below -1.64 SDs from the mean (*z* score <-1.64) equal to the lowest 5% of the population; low normal (LN), including individuals with age-adjusted Vo_2max between -1.64 and zero SDs from the mean (45%); high normal (HN), including individuals with age-adjusted Vo_2max between zero and 1.64 SDs from the mean (45%); and above upper limit of normal (AULN), including individuals with age-adjusted Vo_2max above 1.64 SDs from the mean (highest 5%) (13).

STATISTICAL ANALYSIS. Stata version 12.1 (StataCorp, College Station, Texas) and R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) (14) were used for all statistical analyses. For baseline characteristics, the study population was divided into categories of CRF and analyzed with the chi-square test (categorical variables) and the analysis of variance test (continuous variables).

The associations between CRF and the endpoints were analyzed by using restricted mean survival time based on pseudo-observations (15) in models adjusting for age alone and in multivariable models. The relationship between CRF and the endpoints was also analyzed by using natural numbers per 1 ml/(kg · min) in a continuous model. In the multivariate model, we adjusted for age at inclusion, body mass index (<20, 20 to 25, or >25 kg/m^2), self-reported physical

FIGURE 2 Distribution of CRF (Vo_2max) According to Age in 5,107 Middle-Aged, Employed Men Without CVD



The population is categorized into clinically relevant groups by *z* scores of age-adjusted maximal oxygen consumption (Vo_2max). Below lower limit of normal represents the lowest 5% of the population, with *z* scores <-1.64. Low normal represents 45% of the population, with *z* scores between -1.64 and 0. High normal represents 45% of the population, with *z* scores between 0 and 1.64. Above upper limit of normal represents the highest 5% of the population, with *z* scores >1.64. CRF = cardiorespiratory fitness; CVD = cardiovascular disease.

activity (light, moderate, or high), baseline diabetes (yes/no), smoking status (present, prior, or never), alcohol consumption (0 to 2 U/day, 3 to 5 U/day, or >5 U/day), systolic blood pressure >140 mm Hg, and socioeconomic status (high, middle, or low). The figures display cumulative incidence. Test for trend was performed by using the contrast post-estimation command in Stata.

Furthermore, in a competing risk analyses, the association between CRF and cardiovascular mortality with noncardiovascular mortality as a competing risk was performed by using pseudo-observations according to the method of Parner and Andersen (16). Finally, to analyze the influence of reverse causation, we additionally performed analyses on all-cause mortality with the exclusion of subjects dying within the first 10 years of follow-up. A p value <0.05 was considered significant.

ETHICS. The Copenhagen Male Study was not approved by an ethical committee, as this committee did not exist at the initiation of the study.

RESULTS

BASELINE CHARACTERISTICS. Baseline characteristics are shown in Table 1. During the study's 46 years of follow-up, 4,700 (92.0%) men died, with 2,149 (42.1%) deaths of cardiovascular causes. Higher CRF was associated with lower prevalence of hypertension, lower body mass index, and lower alcohol consumption. Also, men with higher CRF reported higher physical activity. Individuals in the higher CRF categories were more likely to smoke compared with men in the lower CRF categories. The relationship between age and Vo_2max according to categories of CRF is shown in Figure 2.

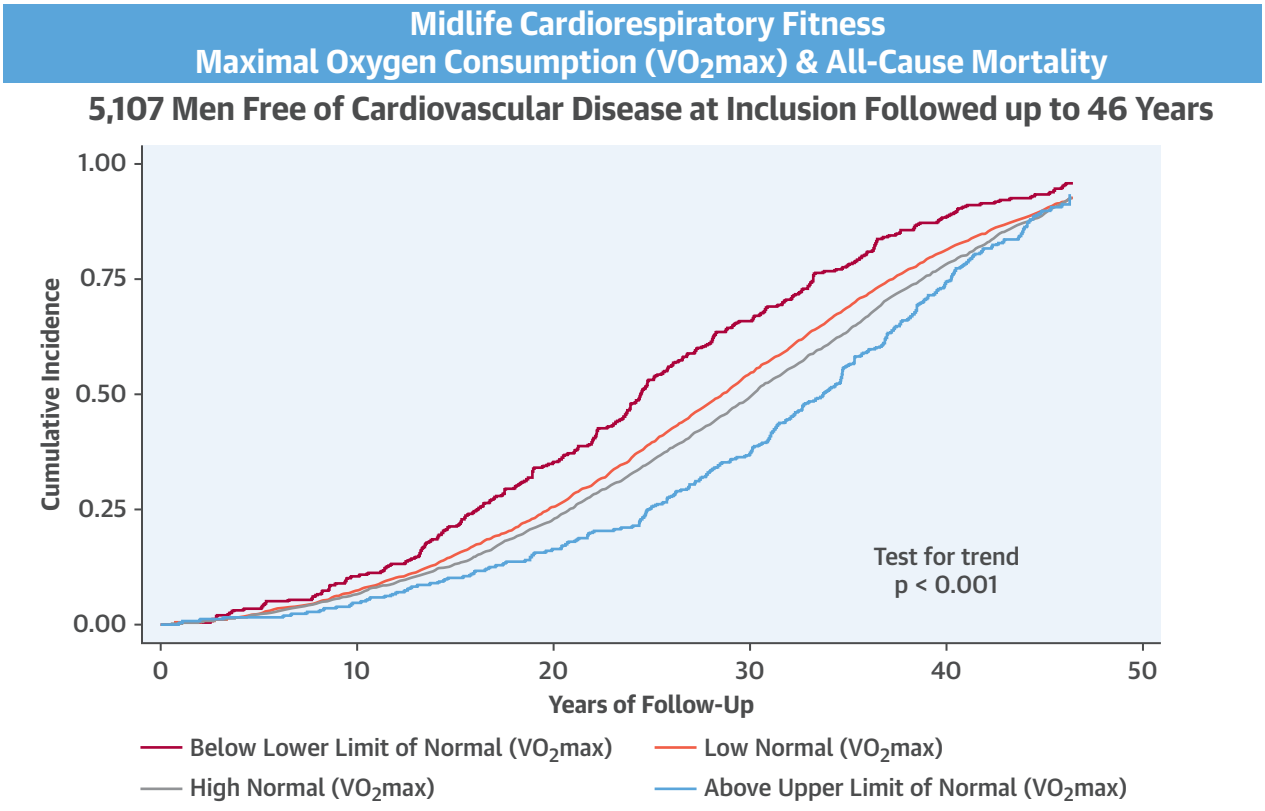
CRF AND ALL-CAUSE MORTALITY. The Central Illustration shows the cumulative incidence of all-cause mortality according to category of CRF. As shown, higher levels of CRF were associated with increased longevity (test for trend: $p < 0.001$). In the age-only adjusted model, compared with individuals in the below lower limit of normal CRF category, an LN CRF was associated with 3.0 years (95% CI: 1.6 to 4.3; $p < 0.001$) longer life expectancy, HN with 4.2 (95% CI: 2.8 to 5.6; $p < 0.001$) years longer life expectancy, and the AULN CRF category with 6.4 years (95% CI: 4.6 to 8.3; $p < 0.001$) longer life expectancy. After multivariable adjustments, the corresponding increases in life expectancy were 2.1 years (95% CI: 0.7 to 4.4; $p = 0.002$), 2.9 years (95% CI: 1.5 to 4.2; $p < 0.001$), and 4.9 years (95% CI: 3.1 to 6.7; $p < 0.001$), respectively. All between-category estimates were highly significantly different from each other (all $p \leq 0.002$).

In the full multivariable model, using natural units of Vo_2max as a continuous variable, each 1-ml/(kg · min) increase in Vo_2max was associated with a 45-day (95% CI: 30 to 61; $p < 0.001$) increase in longevity.

CRF AND CARDIOVASCULAR MORTALITY WITH A COMPETING RISK. The cumulative incidence of cardiovascular mortality according to categories of CRF is shown in Figure 3. Higher levels of CRF were associated with an increased cumulative incidence of cardiovascular mortality. In the age-only adjusted model, LN CRF was associated with a 3.3-year (95% CI: 1.8 to 4.9; $p < 0.001$) increase in longevity, HN with a 4.4-year (95% CI: 2.9 to 5.9; $p < 0.001$) increase, and AULN CRF with a 6.7-year (95% CI: 4.6 to 8.9; $p < 0.001$) increase (Figure 4). In the full multivariable models, the respective estimates were 2.2 years (95% CI: 0.7 to 3.9; $p < 0.001$), 2.6 years (95% CI: 1.0 to 4.1; $p < 0.001$), and 4.5 years (95% CI: 2.4 to 6.6; $p < 0.001$). In the multivariable model with Vo_2max as a continuous variable, a 1-ml/(kg · min) increase in Vo_2max was associated with an estimated 30-day (95% CI: 14 to 49; $p < 0.001$) increase in life expectancy.

In a competing risk model with noncardiovascular mortality as the competing risk, all estimates were nonsignificant (all $p > 0.15$). In the competing risk model with Vo_2max as a continuous model, the estimate was coeff. 0.000 (95% CI: -0.002 to 0.002;

CENTRAL ILLUSTRATION **Physical Fitness and Longevity: All-cause Mortality**



Clausen, J.S.R. et al. J Am Coll Cardiol. 2018;72(9):987–95.

Cumulative incidence of all-cause mortality according to categories of age-adjusted cardiorespiratory fitness level in 5,107 middle-aged, employed men without cardiovascular disease (CVD) followed up for up to 46 years. Cardiorespiratory fitness was related to longevity in a dose-response-dependent manner. Vo_2max = maximal oxygen consumption.

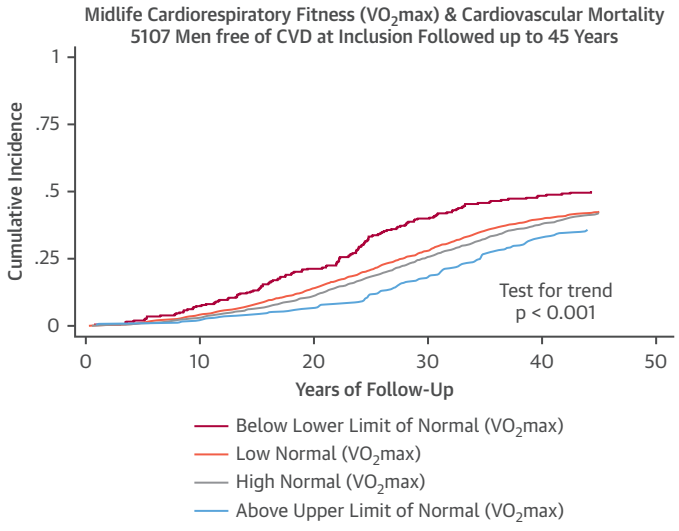
p = 0.97), suggesting that the relation between CRF and mortality is not specific to cardiovascular mortality.

SENSITIVITY ANALYSIS: EXCLUDING SUBJECTS DYING IN THE FIRST 10 YEARS OF FOLLOW-UP. To examine the role of reverse causation, we excluded all men who died within the first 10 years of follow-up (n = 361) (Figure 4), leaving 4,728 men remaining in the analysis. In the full multivariable model, LN CRF was associated with a 1.8-year (95% CI: 0.6 to 3.1; p = 0.003) increase in longevity, HN CRF with a 2.6-year increase (95% CI: 1.4 to 3.9; p < 0.001), and an AULN CRF with a 4.3-year (95% CI: 2.6 to 5.9; p < 0.001) increase.

DISCUSSION

MAIN FINDINGS. The present study investigated the relationship between midlife CRF (Vo_2max) estimated with a bicycle ergometer and long-term risk of all-cause and cardiovascular mortality in 5,107 healthy, employed, middle-aged men with a follow-up of 46 years. We had several main findings. First, based on age-standardized estimates of Vo_2max, clinically relevant categories of CRF revealed significant differences in mean survival time across groups. Second, we showed that higher CRF was associated with longevity in a dose-response-dependent manner, independent of potential confounding factors. After multivariable adjustment, overall mean survival time was ~5 years longer in the highest 5% versus the lowest 5% CRF category. Third, the association between CRF and longevity was robust to the exclusion of men dying within the first 10 years of follow-up. It is therefore not likely that underlying unmeasured illness could explain the observed association between CRF and longevity, suggesting a minimal role

FIGURE 3 Cumulative Incidence of Cardiovascular Mortality According to Categories of Age-Adjusted CRF Level in 5,107 Middle-Aged, Employed Men Without CVD



Cardiorespiratory fitness is inversely associated with cardiovascular mortality. Abbreviations as in Figure 2.

of reverse causation. Overall, these results indicate that higher midlife CRF is a strong protecting factor for all-cause mortality, even after 4 decades.

COMPARISON WITH PUBLISHED REPORTS. Today, there is substantial evidence supporting an inverse association of CRF with cardiovascular and all-cause mortality, and the findings of the present study are generally in line with previous studies. Artero et al. (17) followed up >43,000 adults free of CVD and cancer for a median of 15 years, showing that both measured and estimated CRF were inversely associated with cardiovascular and all-cause mortality, as well as with nonfatal cardiovascular events in men. These findings are supported in prior papers on the Copenhagen Male Study (18,19) and by several other prospective cohorts with estimated or measured CRF, including the Aerobics Center Longitudinal Study and the Henry Ford Exercise Testing Project (8,20–25). A large meta-analysis by Kodama et al. (6) reported that an increase of 1 metabolic equivalent unit in maximal aerobic capacity resulted in a 13% risk reduction of all-cause mortality.

Although CRF is not yet used routinely in clinical practice, studies suggest that it is an even stronger predictor of long-term cardiovascular and all-cause mortality than conventional risk factors such as hyperlipidemia, obesity, hypertension, and insulin resistance (26). Previous studies have confirmed that the addition of CRF to conventional risk factors improved prediction of long-term cardiovascular events and mortality (8,27–29). Using a bicycle ergometer, for instance, to assess CRF is a practical, quick, and cheap test with minimal adverse effects (8). An estimated CRF through a nonexercise algorithm has been suggested as a practical and effective method of CVD and mortality risk classification, which might increase its clinical feasibility even further (7,30). Previous studies have found associations between CRF and cardiovascular mortality (8,17–25), which is in line with the present study.

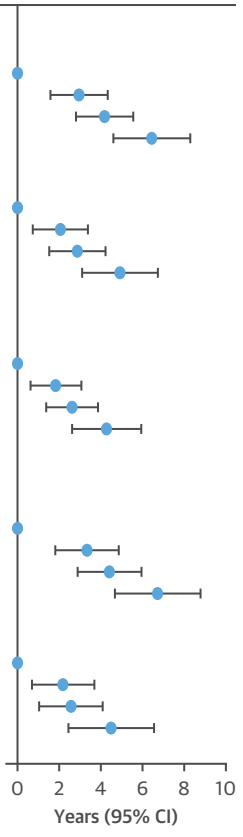
In our study, estimates for cardiovascular mortality were similar to estimates from the all-cause mortality analyses. The competing risk model with noncardiovascular mortality as the competing event provided insignificant estimates, which suggests that the relationship between CRF and mortality is not specific to death from cardiovascular causes in the present population of middle-aged men without CVD at baseline. Results from the Cooper Center Longitudinal Study also showed an attenuated relationship between CRF and cardiovascular mortality when considering competing risks (31) and are therefore in line with the present study.

REVERSE CAUSATION. In observational studies, reverse causation is always a possibility, especially if the follow-up time is short. However, this study has a follow-up time of 46 years, which, to our knowledge, is the longest prospective cohort with objectively measured CRF to date. The inverse association between midlife CRF and all-cause mortality was robust to the exclusion of subjects dying within the first 10 years. The role of reverse causation in the present study is therefore likely to be minimal, and the present study thus strengthens the body of published reports with similar findings in studies with shorter follow-ups.

PATHOPHYSIOLOGICAL CONSIDERATIONS. The pathophysiological relationship between low CRF and mortality is complex and not yet fully understood. Studies in mice suggest that physical activity significantly suppresses tumor growth (32). Also, inflammation plays a well-documented role in the development of atherosclerosis and CVDs (33,34), and high CRF has been associated with lower levels of inflammatory markers such as C-reactive protein and interleukin-6 (35,36). Other theories include improvement of endothelial function, formation of cardiac collaterals, and development of new vessels mediated by a high level of physical activity (37). High endothelial function, measured by the ability of the endothelium to vasodilate through the release of nitric oxide, is anticipated to have

FIGURE 4 Relation Between CRF and All-Cause and Cardiovascular Mortality

CRF Category	No. of Participants	Events No. (%)	Survival Increase Years (95% CI)	P-Value
All-Cause Mortality				
Adjusted for age				
Below Lower Limit of Normal	258	247 (96%)	0.0 (reference)	
Low Normal	2,289	2,107 (92%)	3.0 (1.6-4.3)	<0.001
High Normal	2,304	2,112 (92%)	4.2 (2.8-5.6)	<0.001
Above Upper Limit of Normal	256	234 (91%)	6.4 (4.6-8.3)	<0.001
Multivariable adjusted				
Below Lower Limit of Normal	257	246 (96%)	0.0 (reference)	
Low Normal	2,276	2,095 (92%)	2.1 (0.7-3.4)	0.002
High Normal	2,299	2,107 (92%)	2.9 (1.5-4.2)	<0.001
Above Upper Limit of Normal	256	234 (91%)	4.9 (3.1-6.7)	<0.001
Sensitivity analysis, multivariable: Excluding deaths within 10 years				
Below Lower Limit of Normal	230	219 (95%)	0.0 (reference)	
Low Normal	2,107	1,928 (92%)	1.8 (0.6-3.1)	0.003
High Normal	2,147	1,956 (91%)	2.6 (1.4-3.9)	<0.001
Above Upper Limit of Normal	244	222 (91%)	4.3 (2.6-5.9)	<0.001
Cardiovascular Mortality				
Adjusted for age				
Below Lower Limit of Normal	258	129 (50%)	0.0 (reference)	
Low Normal	2,289	968 (42%)	3.3 (1.8-4.9)	<0.001
High Normal	2,304	960 (42%)	4.4 (2.9-5.9)	<0.001
Above Upper Limit of Normal	256	92 (36%)	6.7 (4.7-8.8)	<0.001
Multivariable adjusted				
Below Lower Limit of Normal	257	129 (50%)	0.0 (reference)	
Low Normal	2,276	962 (42%)	2.2 (0.7-3.7)	0.004
High Normal	2,299	956 (42%)	2.6 (1.0-4.1)	<0.001
Above Upper Limit of Normal	256	92 (36%)	4.5 (2.4-6.6)	<0.001



Differences in mean survival time in years according to categories of cardiorespiratory fitness (CRF) are shown. Both age-adjusted and multiadjusted models are displayed. In addition, the multiadjusted model with the exclusion of all individuals dying during the first 10 years of follow-up is presented. As shown, these estimates are essentially similar to estimates in the full cohort, suggesting minimal influence of reverse causation. The multivariable models include age at inclusion, body mass index, self-reported leisure-time physical activity, diabetes, smoking, alcohol, hypertension, and socioeconomic status.

anti-inflammatory and antithrombotic properties that ultimately reduce the risk of cardiovascular events (38). Importantly, CRF reflects both physical activity and genetics, as suggested by twin studies (39), and congenital factors may play a considerable role in the association between CRF and long-term mortality.

STUDY LIMITATIONS. First, maximal aerobic power (Vo_2max) was estimated with Åstrand's nomogram by using a bicycle ergometer with submaximal exercise. This method is reported to have a correlation coefficient of 0.83 compared with the more precise test with maximal exercise and analysis of expired gas, ultimately resulting in an underestimation of CRF (40). Misclassification of Vo_2max would, however, possibly bias the findings toward the null hypothesis and therefore cannot explain the results. Second, we have no information on changes in CRF in the follow-up period, which might influence the results. Third, residual confounding cannot be excluded but may have been reduced by the inclusion of socioeconomic status as a possible confounder.

CONCLUSIONS

The present study showed that higher levels of midlife CRF in healthy, middle-aged, employed men are highly associated with longevity. With a follow-up of 46 years, the present study is, to our knowledge, the longest follow-up to date of objectively measured CRF. The association between midlife CRF and longevity is robust to the exclusion of subjects dying within the first 10 years of follow-up,

indicating a minimal influence of reverse causation. The findings of the study show that the benefits of higher midlife CRF extend well into the later part of life. Fitness-enhancing physical activity should be recommended by health care professionals to improve public health and promote healthy aging.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Men with higher CRF in the fourth to sixth decades of life gain a dose-dependent increase in longevity and health benefits that extend well into their later years.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the exercise regimens associated with greatest long-term health advantages and assess whether these differ for men and women.

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