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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).

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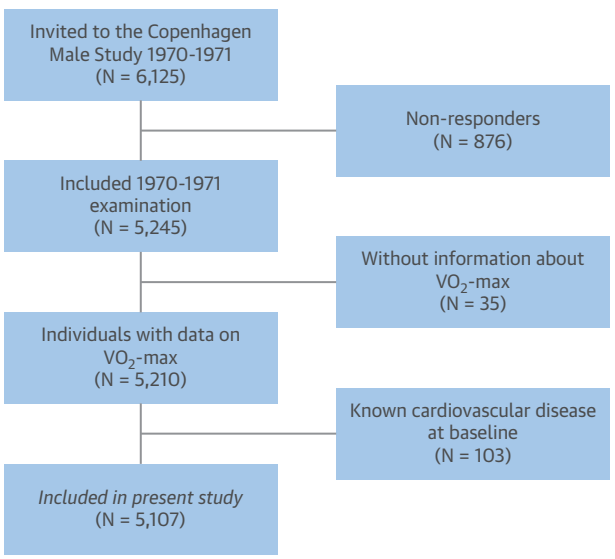
Current knowledge on the association between CRF and cardiovascular and all-cause mortality has been established with epidemiological studies of prospective cohorts (6). Hence, to the best of our knowledge, sparse evidence of this association after more than 25 years exists (6,8). In studies with short 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