Cardiorespiratory Fitness and Long-Term Mortality

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EDITORIAL COMMENT

Cardiorespiratory Fitness and Long-Term Mortality

Targeting the Least Fit With Incidental Physical Activity*

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Cardiorespiratory fitness (CRF), which is commonly expressed as relative maximal oxygen uptake in milliliters per minute per kilogram or metabolic equivalents (METs) (1 MET = approximately 3.5 ml/kg/min), is a vital physiological indicator that corresponds to the integrated ability of the cardiac, pulmonary, muscular, and cellular systems to transport oxygen to the mitochondria to perform physical activity (PA). CRF has a genetic component that is similar in magnitude to other major physiological risk factors for cardiovascular disease (CVD) (1), but it is also highly modifiable through PA. Paradoxically, CRF is perhaps the only major physiological risk factor that is not routinely assessed in clinical practice, and despite consistent evidence that shows that even algorithm-estimated CRF improves CVD risk prediction (2), it is not part of any major CVD risk calculation (1). The only known prescription for poor CRF is regular engagement in PA of a certain intensity.

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In this issue of the *Journal,* Clausen et al. (3) examined the association between CRF and mortality in the Copenhagen Male Study (CMS) over an impressive follow-up period of 46 years. CMS participants were employees from a range of diverse industries, including construction, railway, military, and health care (4). Among the 5,107 middle-aged (ages 40 to 59 years) men who completed the baseline examination in 1970 to 1971, 4,700 (92%) died during follow-up; of those deaths, 2,149 (45.7% of total events) were attributed to CVD mortality. Such an unusually high mortality rate is not surprising considering the long follow-up, the baseline age range of the cohort, and the life expectancy at age 50 years among men in Denmark in 1970 (25 years) (5).

CRF grouping was based on age-standardized z-scores distribution: below lower limit of normal (bottom 5% of z-distribution, mean CRF: 20.7 ± 2.0 ml/kg/min); low normal (between mean and bottom 5%, mean CRF: 28.3 ± 3.1 ml/kg/min); high normal (between mean and top 5%, mean CRF: 37.1 ± 4.1 ml/kg/min); and above the upper limit of normal (top 5% of z-distribution, mean CRF: 49.6 ± 4.8 ml/kg/min). By this classification, the categories of CRF were dependent on the distribution of CRF in this specific study sample rather than existing cutoffs. Compared with the bottom 5% of the CRF z-distribution, the multivariable-adjusted life expectancy gains were 2.1 and 2.9 years for the low and high normal ranges, respectively, and 4.9 years for the top 5% of the CRF distribution. However, when competing mortality risks were taken into account, there were no statistically significant gains specifically for CVD mortality.

Like most epidemiological evidence, this study was based on a single baseline examination of CRF. Reverse causation, which is defined as undiagnosed and/or prodromal and/or subclinical disease that both compromised the exposure (CRF) and predisposed subjects to an earlier death, is a serious issue in epidemiological studies and can lead to deceptive

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conclusions. The long follow-up and the large number of events permitted the investigators to examine possible reverse causation by repeating the all-cause mortality analyses without the 361 participants who died during the first 10 years of follow-up. However, life expectancy gains were only slightly attenuated (1.8, 2.6, and 4.3 years) compared with the analyses in the full sample described above. Although the reassurance offered by this additional analysis was a notable strength of the study, the long follow-up also added some uncertainty to the interpretation of the data, which merits discussion. Drawing potentially causal inferences between states and events that are far apart by nearly 5 decades is difficult, because of the likely plethora of changes that are bound to occur (e.g., changes in participant behavior, life circumstances, and also broader societal changes). One of the most dramatic ecological changes that occurred in Copenhagen during the study period was a major shift toward physically active transportation. Between 1970 and 2016, there was an approximately 2.5-fold surge in cycling for transportation among Copenhagen residents (6). By 2016, 41% of all commuting trips in Copenhagen were done by bicycle, and nearly 20% of all trips were done on foot (6). Considering that uncompromised physical capacity, including adequate CRF, enables PA participation, it is plausible that those participants with a normal or high CRF at baseline in 1970 to 1971 were also more likely to increase incidental PA as the active transportation city infrastructure improved over time. Such a likely reciprocal association between CRF and PA is important to acknowledge in interpreting the current results, and it is unfortunate that no repeated measures of CRF were included in the analysis. The reported life years gained might reflect increased PA that would not only lead to a slower age-related decline in CRF but could also act through a number of cardiometabolic and psychological health pathways. Under such a scenario, the results found by Clausen et al. (3) might over-estimate the independent associations of CRF with future mortality risk. It was also unclear what the role of occupational PA was because only leisure-time PA was considered a confounder, despite previous CMS data that showed interactions between physical demands at work and CRF in terms of all-cause mortality risk (4).

The preceding life expectancy estimates (3) showed that there was relatively little variation (2.1 to 2.9 years) in the middle 90% of the age-adjusted CRF distribution, which corresponded to a wide range of average CRF levels (e.g., approximately 23 to 47 ml/kg/min for men aged 50 years). Essentially, the results of the current study imply that the substantial longevity gains might be realized simply by moving away from the least-fit end of the CRF distribution. This is in line with previous observations in a predominately male U.S. sample in which more than half the reduction in all-cause mortality occurred between the low and moderate CRF groups (7). Also, the present data (3) corroborated the well-established substantial gains attained at the lower spectrum of PA, whereby the largest reduction in mortality risk was seen when the groups who did little and/or no PA were compared with those who did some but did not meet the PA guidelines (8).

How does all this translate into a public health and clinical practice message? It is worth noting that the intensity of PA has a strong impact on CRF improvements (1). Higher intensities lead to more rapid and larger CRF gains even when the volume of PA is modest (e.g., high-intensity interval training programs) (9). This does not necessarily mean that those with the lowest CRF should be prescribed high-intensity exercise. In general, when the baseline CRF is lower, less vigorous intensity is needed to produce beneficial improvements in CRF. For example, in adults with a CRF <10 METs (35 ml/kg/min), an intensity of approximately 50% heart rate or theoretical maximum CRF reserve is adequate (1). For most middle-aged people, such an intensity could be walking at a pace that makes the person slightly out of breath when sustained for more than a few minutes. Even slower than brisk walking pace has been associated with substantial all-cause and CVD mortality gains (10): compared with a habitually slow walking pace in upper middle and older age, a medium pace has been shown to be associated with 44% lower CVD mortality risk, with little further gains for a brisk and/or fast pace (10). The 2018 U.S. Physical Activity Guidelines Advisory report (11) acknowledged the importance of light intensity PA for health, but little is currently known about its CRF-promoting potential. Although longitudinal epidemiological and experimental evidence is lacking, it is encouraging that beneficial associations of objectively measured incidental light intensity activity and CRF were reported in a cross-sectional study (12).

In summary, the study by Clausen et al. (3) made excellent use of a historical data resource and contributed important information on the question of whether CRF is associated with long-term mortality risk. However, a few inherent data limitations precluded conclusive assertions as to what extent low CRF is an independent risk factor for long-term

mortality, or if it acts through other pathways involving PA and other known or unknown changes that occurred during the long follow-up period. Regardless of whether the identified associations were causal or predictive, the current study supported the use of CRF as a clinical vital sign (1). Promoting incidental PA such as active transportation in the least fit and least physically active segments of the middle-aged adult population is a safe investment that will likely lead to improvements in CRF and will certainly save lives.

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