Cardiorespiratory Fitness and Metabolic Risk

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The present study sought to evaluate the relation between cardiovascular risk factors and cardiorespiratory fitness (CRF) in a large population. Low CRF has been associated with increased total mortality and cardiovascular mortality. The mechanisms underlying greater cardiovascular mortality have not yet been determined. A series of cardiovascular risk factors were measured in 59,820 men and 22,192 women who had undergone determinations of CRF with maximal exercise testing. The risk factor profiles were segregated into 5 quintiles of CRF. With decreasing CRF, increases occurred in obesity, triglycerides, non–high-density lipoprotein cholesterol, triglyceride/high-density lipoprotein ratios, blood pressure, metabolic syndrome, diabetes, and cigarette smoking. Self-reported physical activity declined with decreasing levels of CRF. In conclusion, it appears likely that the enrichment of cardiovascular risk factors, especially metabolic risk factors, account for a portion of the increased cardiovascular mortality in low-fitness subjects. The mechanisms responsible for this enrichment in subjects with a low CRF represent a challenge for future research. Published by Elsevier Inc. (Am J Cardiol 2012;109:988–993)

Previously, research from the Aerobics Center Longitudinal Study (ACLS) showed that the lowest quintile of cardiorespiratory fitness (CRF) has an unusually high mortality.[1,2] This excess mortality was attributed mainly to cardiovascular disease (CVD) and cancer. Although the greater mortality associated with low CRF likely results in part from sedentary life habits, the ACLS reports have observed that a low CRF is accompanied by a clustering of CVD risk factors. The present study examined the pattern of cardiovascular risk factors across CRF quintiles in an expanded cohort of ACLS, the Cooper Center Longitudinal Study (CCLS). We addressed the question of the potential mechanisms that might explain why the CVD risk factors increase as CRF decreases.

Methods

CCLS was a prospective cohort study of participants aged 20 to 90 years who visited the Cooper Clinic (Dallas, Texas) for the first time from 1970 to 2009 and completed a maximal graded exercise treadmill test. These criteria resulted in 59,820 men and 22,192 women for the present analysis.

The details of the medical examination, including anthropometric and laboratory measures and metabolic syndrome diagnosis have been previously reported.[3–5] The risk factor measures included in the present report included triglycerides, high-density lipoprotein (HDL) cholesterol, non–HDL cholesterol, systolic and diastolic blood pressure, and the presence or absence of diabetes and cigarette smoking at the first study. During their medical examination, the participants completed a symptom-limited maximal treadmill exercise test using a modified Balke protocol 3. The treadmill test duration is strongly correlated to the measured maximum oxygen uptake in men ($r = 0.92$) and women ($r = 0.94$). Age- and gender-specific distributions of treadmill duration were computed for the following age groups: 20 to 39, 40 to 49, 50 to 59, 60 to 79, and >79 years. Each gender- and age-specific distribution was divided into fifths of CRF to provide the quintiles of CRF.

Physical activity was assessed by self-reported participation in recreational or leisure time activities during the previous month. For each activity, the number of sessions per week and the average duration per session were reported. From these data, we converted the frequency and duration to minutes of activity weekly. Each activity was classified as either moderate or vigorous intensity according to the average intensity of each activity using the compendium of physical activities developed by Ainsworth et al.[6] If employed, most of the participants had sedentary jobs.

Vital status was ascertained primarily using the National Death Index. Coronary heart disease (CHD) and CVD deaths were identified using the "International Classification of Diseases: 9th revision (codes 410.0 to 414.9 and 429.2) for deaths occurring before 1999, and 10th revision (codes I20 to I25 for deaths occurring from 1999 to 2006). The mean ± SD follow-up time for the mortality assessment for the men and women was 17.8 ± 9.1 and 16.0 ± 9.2 years, respectively.

We calculated the baseline characteristics for the participants stratified by gender. Analysis of variance was used to examine differences in the continuous data. The Mantel-Hanzel chi-square test and Fisher exact test were used to examine the differences in categorical variables. All analyses were performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

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Table 1
Baseline descriptive characteristics, Cooper Center Longitudinal Study (CCLS), 1970–2009

Variable	Women (n = 22,192)	Men (n = 59,820)
Age (years)	44.5 ± 9.8	44.3 ± 10.5
Body mass index (kg/m^2)	26.9 ± 4.0	23.6 ± 4.5
Weight (lb)	191	145
Treadmill duration (s)	1,049.3 ± 306.4	796.9 ± 274.6
Total cholesterol (mg/dl)	207.1 ± 40.5	198.7 ± 37.9
Triglycerides (mg/dl)	140.0 ± 119.3	94.9 ± 64.0
High-density lipoprotein cholesterol (mg/dl)	46.2 ± 12.1	63.4 ± 15.8
Non–high-density low cholesterol (mg/dl)	160.9 ± 31.5	135.3 ± 5.8
Triglyceride/high-density low cholesterol ratio	3.6 ± 9.4	1.7 ± 1.6
Systolic blood pressure at rest (mm Hg)	122.5 ± 13.7	113.3 ± 14.7
Diastolic blood pressure at rest (mm Hg)	81.8 ± 9.7	76.1 ± 9.6
Personal history of diabetes	2.20%	1.50%
Metabolic syndrome	17.90%	5.50%
Current smoker	17.10%	9

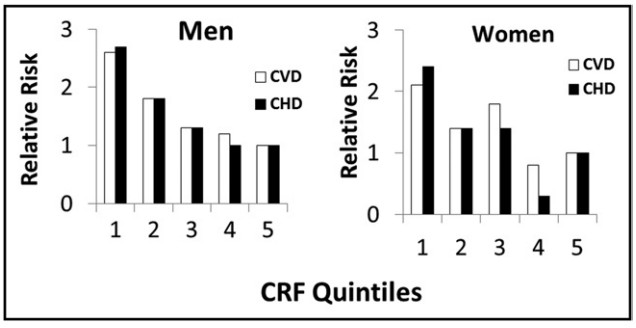

Figure 1. CVD and CHD mortality in men and women plotted against quintiles of CRF.

Results

The baseline characteristics of the participants are listed in Table 1. The total CVD and CHD deaths for CCLS from 1970 through 2006 across the quintiles of CRF are shown in Figure 1. The total number of men was 53,772 and of women was 18,852. Mortality relative risk was set at 1.0 for CRF at quintile 5, the most fit group. In men, the relative risk for both CVD and CHD mortality increased progressively with decreasing CRF. The shape of the inverse relation appeared to be curvilinear. A similar, but less consistent, pattern was observed for women; this inconsistency was likely related to the lower sample size, fewer deaths, and lower absolute risk.

The body fat parameters for men and women were plotted against the quintiles of CRF (Figure 2). In quintile 1, the average weight of the men and women was 86.8 and 65.9 kg, respectively. The body mass index and waist girth were similarly elevated. The body fat parameters were not disproportionately high in CRF quintile 1 compared to the successive quintiles; instead, the body fat measures declined linearly, with increasing quintiles from lowest to highest.

The self-reported history of physical activity intensity was recorded for the subjects in each CRF quintile (Figure 3). The number of hours per week of moderate-intensity and high-intensity physical activity are shown in Figure 3. Many of the subjects reported both moderate-intensity and high-intensity activities. For both types of activity, the highest levels were observed for those in the fifth CRF quintile. The levels declined in the lower quintiles, although striking differences were not found among the lower 2 or 3 quintiles.

Figure 4 shows the plasma lipid parameters for the quintiles of CRF. In both men and women, the triglyceride and non-HDL cholesterol concentrations increased with decreasing CRF, and the HDL cholesterol levels decreased. Adjustment for body weight had little effect on the relation with CRF (Figure 4). The patterns of lipid concentrations showed similar trends to those for mortality (Figure 1). The triglyceride/HDL cholesterol ratios increased with decreasing CRF in men. However, in women, the ratios were less elevated in quintile 1 but also increased progressively throughout from the higher to lower quintiles.

With declining CRF, the systolic blood pressure levels increased 5 mm Hg in men and 7 mm Hg in women. The increases were progressive and smooth (Figure 5). Figure 5 also shows that the incidence of self-reported diabetes increased with lowering CRF in both men and women; however, the prevalence, even in the unfit categories, was relatively low. In men, 28% of the quintile 1 cohort were smokers, and this decreased progressively to 7% in quintile 5. Fewer women than men were smokers; however, the same pattern of change over quintiles was noted. The 10-year risk of CHD using the Framingham risk score was 10.8% in quintile 1 in men and 5% in women. The risk declined linearly in both genders with increasing fitness. The prevalence of the metabolic syndrome in CRF quintile 1 was 31% in men and decreased sharply to 4% in quintile 5 (Figure 6). Women had a much lower prevalence than men; however, even in women, the metabolic syndrome was much more frequent in the lowest quintile of CRF. In contrast, the metabolic syndrome was virtually nonexistent in the highest CRF quintiles of women.

Discussion

The present analysis has confirmed previous reports that lower CRF is associated with increases in CVD risk factors. However, previous reports focused primarily on the relation between CRF and mortality—and less on the overall pattern of risk factors in consecutive CRF categories.[1,2] The results from the present study have shown in detail the patterns of the association of CVD risk factors in each CRF category. The risk factor levels, on average, were tightly linked to CRF category. The triglyceride and non–HDL cholesterol levels increased with decreasing CRF. The HDL cholesterol concentrations decreased, and the triglyceride/HDL cholesterol ratios increased sharply with decreasing fitness. Those in the lowest CRF quintile had the greatest systolic blood pressure. Moreover, a greater frequency of diabetes was found in the subjects with the lowest CRF. Of particular interest, the inverse relation between the prevalence of the metabolic syndrome and CRF was striking.

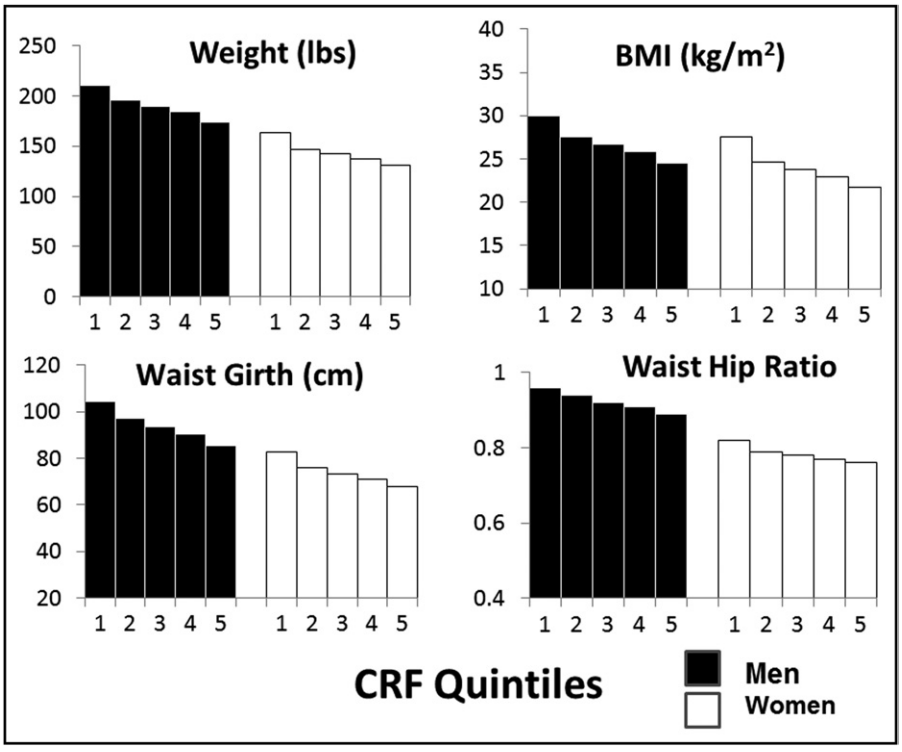

Figure 2. Body fat parameters for men and women plotted against quintiles of CRF.

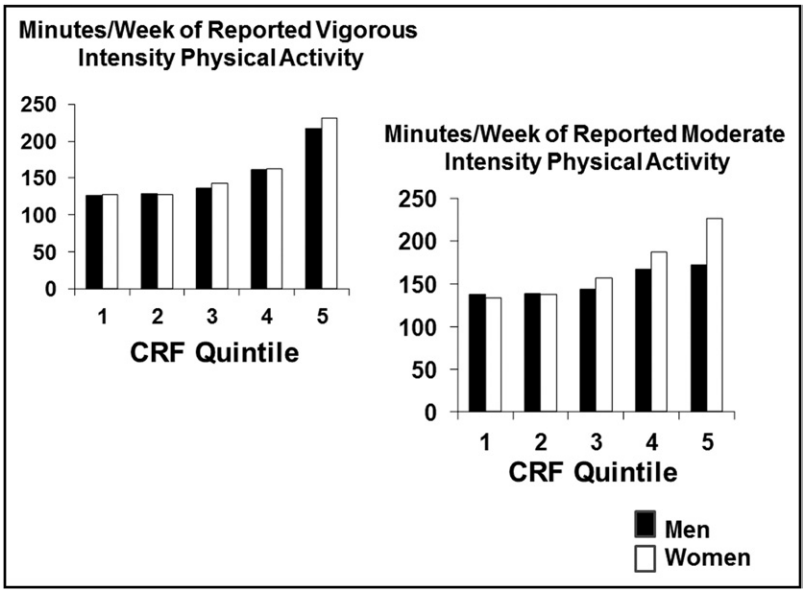

Figure 3. Minutes per week of reported moderate and vigorous intensity physical activity for men and women plotted against quintiles of CRF.

CRF reflects the capacity of the circulatory and respiratory systems to supply oxygen to the skeletal muscles during sustained exercise. It also reflects the ability of muscles to sustain forceful contractility during treadmill testing. In contrast, the risk factors discussed are largely metabolic in origin. The mechanistic link between CFR and metabolic status is by no means clear. Still, an obvious possible connection is through regular aerobic exercise. A greater level of habitual physical activity should increase CRF and enhance energy expenditure, thereby reducing the metabolic risk factors. In the present analysis, self-reported physical activity was lower in the lower quintiles of CRF. In a previous report on a smaller sample of this population, the age adjusted R^2 reported for moderate, vigorous intensity of physical activity and CRF was 0.22 for men and 0.20 for women.[7] These findings are in accordance with evidence from randomized controlled trials that aerobic exercise of moderate or vigorous intensity performed frequently over weeks or months will significantly increase CRF in men or women by 10% to 20%.[8,9] With little doubt, regular exer-

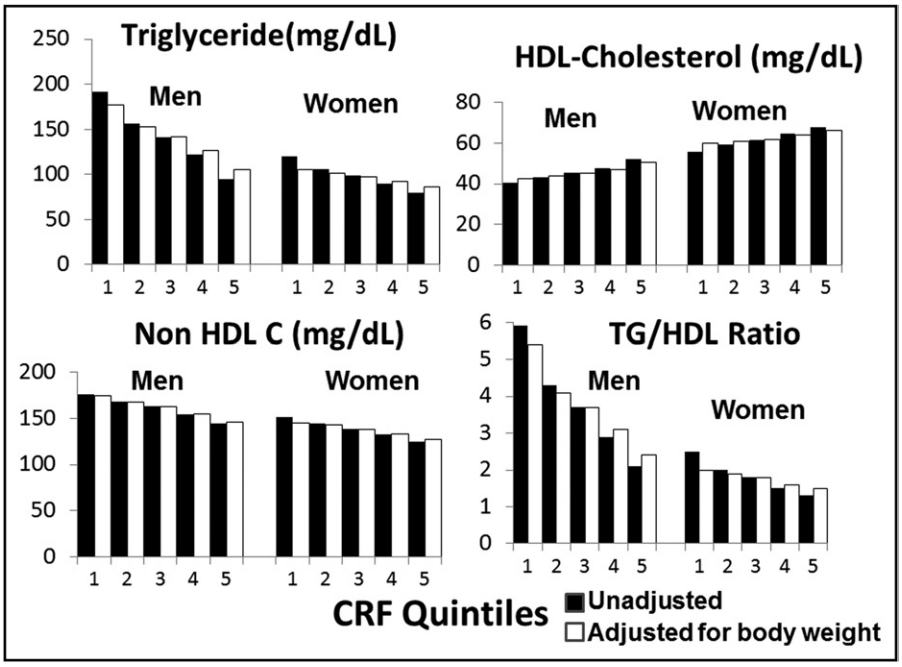

Figure 4. Plasma lipid measures for men and women plotted against quintiles of CRF. Values are shown unadjusted and after adjustment for body weight.

Figure 5. Systolic blood pressure (SBP), diabetes prevalence, smoking prevalence, and 10-year risk of CHD for men and women plotted against quintiles of CRF.

cise will improve both CRF and metabolic risk factors; however, the reported activities from the present and previous studies appear insufficient to account for the strong relation between CRF and the metabolic risk factors observed in our study. Whether exercise training can reverse the risk factors observed in low-CRF subjects can only be determined by intervention trials.

Previous studies have shown that a lower CRF is associated with increased body weight.[10] In the present analysis, body weight, body mass index, waist girth, and the waist/hip ratio all increased progressively and linearly with decreasing CRF. The reason low CRF connects with overweight or obesity is unclear. The possible mechanisms include increased energy intake in low CRF subjects, decreased total

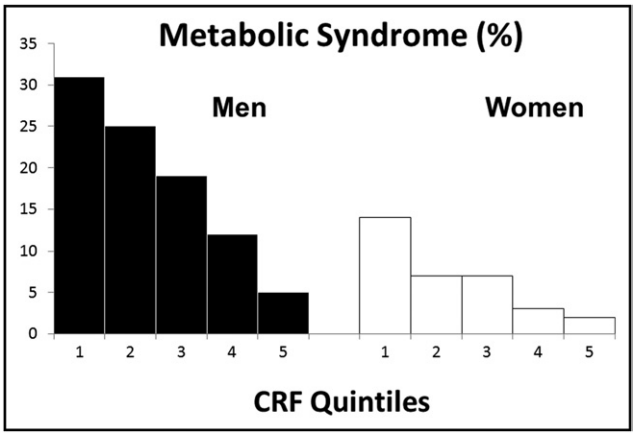

Figure 6. Metabolic syndrome prevalence for men and women plotted against quintiles of CRF.

energy expenditure, and a genetically determined, higher body weight set point. Whether low CRF predisposes to obesity or vice versa is unknown. There has been no solid research to differentiate among these 3 mechanisms (or others) to account for obesity in subjects with low CRF. Of interest, a recent report indicated that severely obese persons have a reduced metabolic rate at rest, as well as impaired CRF.[11] The investigators speculated that a reduced metabolic rate at rest would result in an energy imbalance and weight gain. However, most subjects in the present study were not severely obese. Also, whether those with moderate obesity have a reduction in the metabolic rate at rest, and if so, whether any moderate weight gain could reduce CRF has not been documented.

Regardless of the mechanisms underlying obesity in low CRF subjects, it seems almost certain that obesity, and in particular, upper body obesity (as reflected by a greater waist/hip ratio), contribute importantly to the increase in metabolic risk factors. Obesity is a known factor for all metabolic risk factors, including insulin resistance and diabetes, dyslipidemia, and hypertension.[5] Nonetheless, adjusting for obesity did not fully account for the inverse association between risk factor severity and CRF level.

Pérusse et al[12] indicated that ≥50% of the variability in CRF can be attributed to heritable factors. Genetic variation can result from factors such as muscular strength, maximum exertional oxygen uptake, heart size, lean mass, skeletal muscle growth, and bone mineral density.[13] Some of these factors could be independent of the usual CVD risk factors, but others could be related. To date, no specific genetic variants have been identified that can explain both CRF levels and metabolic risk factors.

One attractive possibility whereby risk factors could be linked to CRF is insulin resistance. It has been postulated that insulin resistance in the skeletal muscle leads to all the risk factors of the metabolic syndrome.[14] Theoretically, insulin resistance could impair muscle function in a way to reduce CRF. The latter possibility has not been tested adequately. However, because both obesity and physical inactivity contribute to insulin resistance,[15,16] the possibility that insulin resistance impairs muscular function or even cardiorespiratory capacity should not be overlooked. Another consideration is whether some subjects have primary insulin resistance in the muscle,[17,18] which could impair exercise capacity.

Finally, as might be expected, cigarette smoking has consistently been shown to be 1 risk factor contributing to total mortality in the ACLS.[19] Moreover, an inverse relation exists between smoking and CRF. The increase in smoking frequency was stepwise and progressive with decreasing CRF. We might speculate that smoking is a direct cause of low CRF, possibly acting through smoking-induced insulin resistance.[20]

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