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# Impact of fitness and changes in fitness on lipids and survival

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ABSTRACT

In the past five decades, cardiorespiratory fitness (CRF) has become fairly established as an important risk factor or marker for cardiovascular disease (CVD), as well as CVD - and all-cause mortality. Substantial evidence supports a strong inverse association between baseline levels of CRF and the risk of developing CVD risk factors, including dyslipidemia. Additionally, accumulating evidence also supports that maintaining or improving a certain level of CRF over time leads to a lower rate of developing CVD risk factors, such as dyslipidemia, and also improves survival. Recent evidence also supports the role of resistance exercise and muscular strength to reduce the development of metabolic syndrome and hypercholesterolemia and potentially reduce development of diabetes as well, in addition to improving survival. Therefore, great efforts are needed to increase both CRF and muscle strength with aerobic exercise and resistance exercise in the primary and secondary prevention of CVD.



**Contents**



Cardiovascular disease (CVD) remains the leading cause of death in the United States (US) and across much of the Westernized World. In efforts to reduce CVD, many organizations, including the American Heart Association (AHA), American College of Cardiology, and the American College of Sports Medicine, and many other leading organizations, have emphasized that sedentary behavior and physical inactivity are major modifiable risk factors for CVD.[1–3] Nevertheless, a substantial percentage of the US and world's population have either low or very low levels of physical activity (PA) and exercise training. [1–5] Cardiorespiratory fitness (CRF) is perhaps one of the strongest risk factors for CVD, CVD mortality, and all-cause mortality. Although there may be some genetic or non-exercise factors that contribute to the level of CRF, most effects have been attributed to PA and exercise training.[1,2] Therefore, promoting levels of PA and exercise to increase levels of CRF are needed in the US and worldwide to reduce chronic diseases, especially CVD.[1–5]

Recently, the impact of resistance exercise and muscular strength on CVD risk factors and survival has also been assessed.[6–8] In addition to aerobic exercise training, there may be independent effects of resistance exercise and muscular strength and fitness on CVD risk factors and survival.[6–8]

In this Issue of Progress in Cardiovascular Diseases, emphasis is directed on the importance of dyslipidemia, especially levels of low-density lipoprotein cholesterol (LDL-C), on CVD risk in primary and secondary prevention of CVD. Although pharmacotherapy is emphasized, we also focus on the effects of lifestyle modifications (such as increasing aerobic and anaerobic PA via exercise training, resistance exercise, and

*Abbreviations:* ACLS, Aerobics Center Longitudinal Study; AHA, American Heart Association; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent; PA, physical activity; TC, total cholesterol; TG, triglyceride; US, United States.

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increases in muscular strength) in improving CRF as a means to modify the degree of baseline dyslipidemia.[1,6–8] Therefore, the purpose of this review is to describe the therapeutic role of PA and exercise training and CRF on plasma lipids and long-term survival.[9,10]

## Baseline CRF and dyslipidemia

The impact of CRF on lipid profiles have been reviewed in detail elsewhere, with numerous studies, including brief randomized exercise training controlled trials and cross-sectional studies, that link CRF to the individual components of a lipid profile.[9,10] Nevertheless, longitudinal epidemiologic studies on the relationship between CRF and the risk of developing dyslipidemia have been limited. Sarzynski and colleagues[11] from the CARDIA cohort showed that high levels of CRF in young adulthood were independently related with the risk of high triglycerides (TGs) during the transition to middle age in both genders. In fact, the incident rate of TGs >200 mg/dL over 25 years was 42% lower in the higher quartile of baseline CRF compared with the lower quartile. The CARDIA study also noted a 40% higher risk of having LDL-C > 160 mg/dL associated with low CRF, although this was largely impacted by obesity status.[12] A new recent study from the well-known Aerobics Center Longitudinal Study (ACLS) assessed the level of the CRF and the development of atherogenic dyslipidemia, the triad of lipid abnormalities, including high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, TGs > 200 mg/dL and LDL-C > 160 mg/dL, observing a 43% lower risk of the atherogenic dyslipidemic phenotype associated with high CRF, although the inverse relationship became nonsignificant when adjusted for baseline lipid levels.[13] Therefore, baseline lipid values may strongly impact the observed association of CRF with subsequent dyslipidemia, which may be strongly dependent on baseline levels of LDL-C, TGs, and HDL-C.

## Baseline CRF and survival

During the past 4 decades, numerous studies have indicated a powerful inverse association between CRF and all-cause mortality.(1–3 14, 15). Blair et al[16] from the landmark ACLS reported that men in the least fit CRF quintile had an 82% higher risk of mortality compared to the most fit quintile, which was similar to the effects of CRF on survival in women. In a meta-analysis of 33 cohort studies in 103,000 men and women, each one metabolic equivalent (MET) increase in exercise capacity was associated with a 13% reduction in mortality.[17] Many more recent studies have provided additional support for the importance of METs or peak oxygen consumption on exercise testing for predicting survival, reporting 10% to 25% improvements in survival for each one MET increase in CRF,[1–5,10,14,15,18] leading the AHA to call for CRF as a vital sign.[18]

## Association between changes in CRF and dyslipidemia

The findings on the overall impact of CRF increases following an exercise training intervention and the changes in lipid profiles are mixed.[10] The findings regarding the effects of exercise training on most lipid components, including total cholesterol (TC), LDL-C, and TGs have been variable, with both positive and null results.[10] However, our data from formal cardiac rehabilitation and exercise training programs have typically produced 15% reductions in TGs, 6% increases in HDL-C (higher in those with baseline low levels) and significant improvements in the overall lipid profiles and prevention of the metabolic syndrome (Table).[19] However, typically the most consistent finding from exercise intervention studies have been improvements in HDL-C, ranging from 3% to 22% increases for moderate intensity aerobic exercise training.[20] This is also supported by a meta-analysis showing quite significant increases (average 2.5 mg/dL) following exercise training.[21]

However, two reports from the ACLS reported beneficial effects of improvements in CRF on other plasma lipids.[22,23] Lee et al[22] followed 3148 healthy adults for developing hypercholesterolemia (arbitrarily defined as TC ≥240 mg/dL or physician-diagnosis) and found a 25% lower risk in those who maintained or improved CRF during a 6-year follow-up. A more recent ACLS report showed that those who maintained their CRF over a mean follow-up of 8.9 years had a 44% lower risk of developing atherogenic dyslipidemia, as defined previously, compared with those whose CRF had decreased during follow-up, even after correcting for changes in weight and baseline individual components of the lipid triad.[23]

## Human aging, lipid profiles, and CRF

As with arterial blood pressure, human aging has generally been associated with a worsening lipid profile, as well as increased risk of both CVD- and all-cause mortality.[12] We have recently evaluated the trajectory of lipids and lipoproteins with varying CRF levels in the ACLS cohort.[24] Park and colleagues[24] studied 11,418 men without known dyslipidemia or CVD between 1970 and 2006 and reported a parabola-shaped trajectory of TC, LDL-C, TGs, and non-HDL-C with aging, showing gradual increases into the mid40s to early 50s with subsequent declines. However, in this large cohort, increasing levels of CRF were associated with favorable effects on blood lipids and lipoproteins. We can see that favorable TC levels in those with high CRF persisted until the advanced ages of 60s and mid-70s, well beyond those with low CRF levels, who reached TC values >200 mg/dL before the age of 40 (Fig. 1). The interaction of CRF on LDL-C, TGs, HDL-C and non-HDL-C are shown in Fig. 2. Additionally, and probably more importantly and as we reviewed in detail elsewhere, (1,9,10,19), our fit patients with CVD risk factors, such as hypertension, diabetes mellitus (DM), obesity, as well as dyslipidemia, usually have a better overall and CVD prognosis than do unfit patients without these CVD risk factors, demonstrating the impact of CRF on chronic diseases, especially CVD.

## Impact of CRF and statins on risk of DM and survival

Although substantial evidence supports the widespread use of statins for all patients with established CVD and many with moderate-

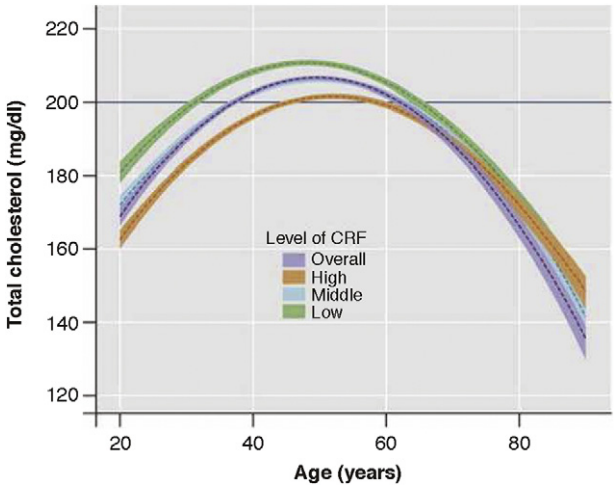


**Fig. 1.** Trajectories of total cholesterol with aging. The purple dashed line represents the crude overall trajectory; the other dashed lines represent each category of CRF (orange for high CRF, light blue for middle CRF and green for low CRF), assuming constant waist circumference residual (−0.179, mean of the residual). Shaded areas represent 95% confidence intervals for each CRF category. The solid blue horizontal line indicates the established abnormal cutoff of ‡200 mg/dl for total cholesterol. CRF: Cardiorespiratory fitness. Reproduced with permission from Elsevier from Park YM et al., *J Am Coll Cardiol* 2015;65:2091–2100.[24]

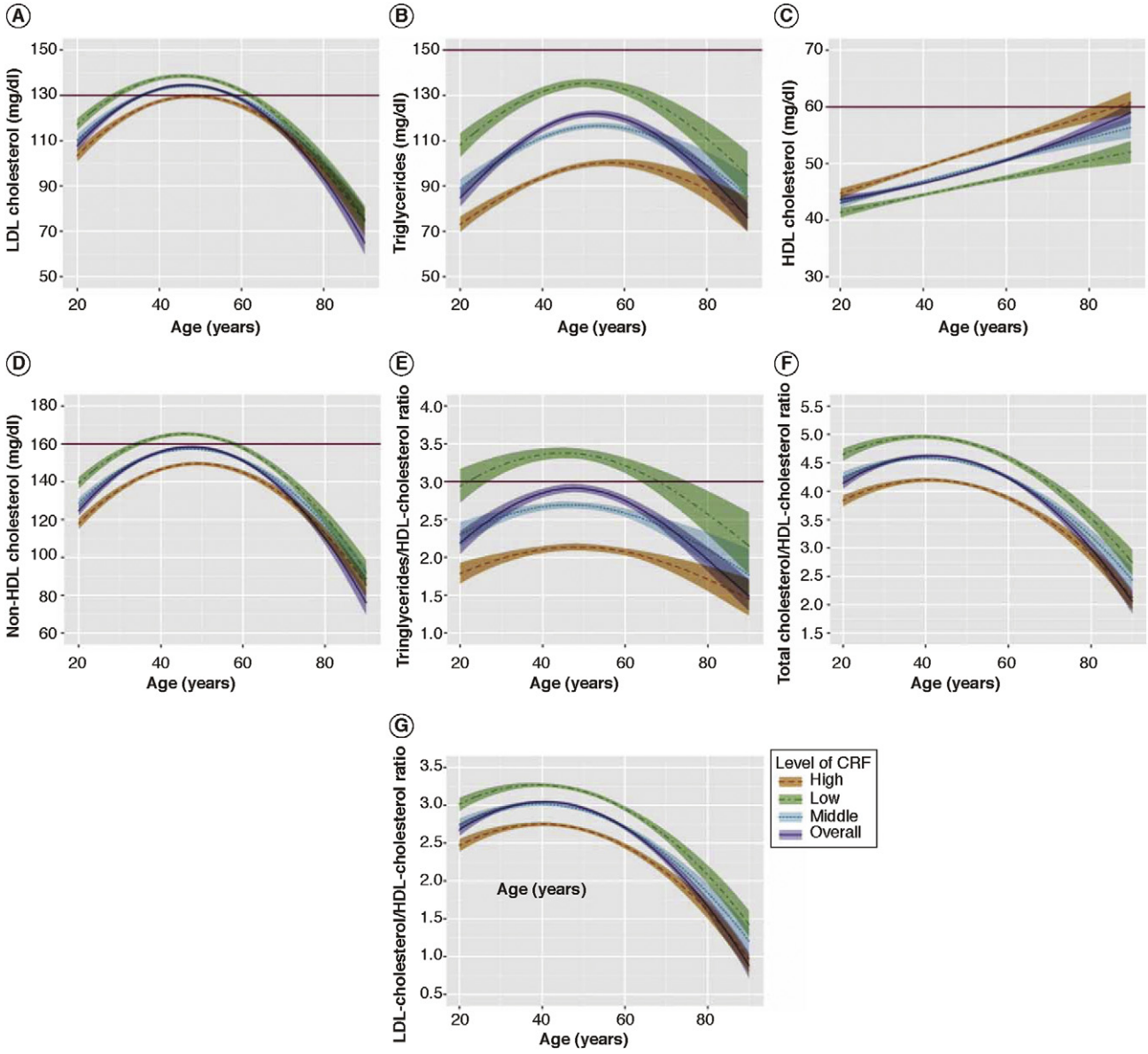


**Fig. 2.** The estimated trajectories of lipids and lipoproteins with aging by levels of CRF. The purple solid line represents the crude overall trajectory; the other lines represent each category of CRF (orange dashed line for high CRF, blue dotted line for middle CRF and green dotted-dashed line for low CRF), assuming constant waist circumference residual (−0.179, mean of the residual). The shaded areas represent 95% confidence intervals for each CRF category. The red horizontal solid line in each panel indicates the established abnormal cutoff for lipid and lipoproteins: (A) LDL-C ‡130 mg/dl; (B) triglycerides ‡150 mg/dl; (C) ‡60 mg/dl for HDL-C; (D) ‡160 mg/dl for non-HDL-C; (E) triglycerides/HDL-C ‡3.0. No abnormal cutoff was established for (F) total cholesterol/HDL-C ratio and (G) LDL-C/HDL-C ratio. CRF was categorized into low (lower than 33.3th percentile), middle (those within 33.3th to 66.7th percentile) and high (higher than 66.7th percentile) groups, according to the distribution of age-standardized CRF at baseline. CRF: Cardiorespiratory fitness; HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol. Reproduced with permission from Elsevier from Park YM et al., *J Am Coll Cardiol* 2015;65:2091–2100.[24]

and high-risk primary prevention,[25] some attention has been directed at the impact of statins, especially at higher doses, to increasing the risk of DM.[26] We have recently compared 4092 statin-treated patients with 3019 non-statin controls who were assessed for CRF and development of DM. [26] The incidence of new DM was 24% higher in the statin-treated patients, but the risk of DM progressively declined with increasing CRF, being 34% lower in the high-fit patients compared with the low-fit. Compared with non-statin treated patients, increasing risk of DM was only evident in the least fit and low fit patients (+50% and + 22%, respectively). Therefore, higher CRF, which is known to be a potent predictor of survival in patients with DM,[27,28] also markedly reduces the risk of developing DM with statins.

Since statins are known to reduce CVD risk in patients with DM, the combination of statins and higher CRF may be particularly good for CVD prevention. In fact, a prior Veterans Administration Study assessed 10,043 dyslipidemic subjects during a mean follow-up of 10 years.[29] Statin treatment was associated with an almost 50% reduction in mortality. Additionally, in all patients higher CRF was associated with progressive reductions in mortality regardless of statin use. This study demonstrated that both statins and higher CRF were independent predictors of better survival in dyslipidemic subjects, reinforcing the importance of PA to increase CRF in patients with dyslipidemia.[29]

## Recent studies on resistance exercise, muscular strength, and lipids on prognosis

Although most of the evidence has focused on aerobic exercise training to improve CRF, we have been involved in several recent studies on the impact of resistance exercise on plasma lipids[30,31] and on survival,[8] as well as the impact of muscular strength on development of DM[7] and

on the risk of sudden cardiac death.[32] In a study of 7418 participants from the ACLS population, 15% developed metabolic syndrome during a mean follow-up of 4 years.[30] Meeting the resistance exercise guidelines was associated with a 17% lower risk of developing the metabolic syndrome after adjusting for confounders and aerobic PA/exercise training. Importantly, <1 h per week of resistance exercise was associated with a 29% reduction in the risk of developing metabolic syndrome. In fact, higher amounts of resistance exercise did not provide additional benefits. In the subgroup who met both resistance exercise and the aerobic exercise guidelines, there was a 25% lower risk of developing metabolic syndrome during follow-up compared with those who met neither the resistance exercise nor aerobic exercise training guidelines (Table 1).

More recently, we assessed the impact of resistance exercise on the development of hypercholesterolemia (defined as TC ≥240 mg/dL or physician-diagnosis) in 7317 men from the ACLS followed on average for 4 years.[31] During follow-up, 20% developed hypercholesterolemia; individuals meeting the resistance exercise guidelines of at least 2 days per week had a 13% lower risk of developing hypercholesterolemia after adjusting for confounders, baseline factors, and aerobic exercise.

In fact, <1 h per week of resistance exercise and <2 sessions per week were both associated with over 30% reductions in development of hypercholesterolemia, and as in the study for metabolic syndrome, higher amounts did not provide additional benefits. Meeting both the guidelines for resistance exercise and aerobic exercise reduced the risk of hypercholesterolemia by 21%.

Interestingly, we recently reported the impact of resistance exercise on CVD- and all-cause mortality in 12,591 participants from the ACLS during a 5–10 year follow-up, showing somewhat similar results as with the metabolic syndrome and hypercholesterolemia studies.[8] This study showed that resistance exercise frequency of 1, 2, or 3 times weekly or total amounts 1–59 min per week was associated with 40%–70% decreased risk of total CVD events independent of aerobic exercise training. However, there was no risk reduction for higher amounts of weekly resistance exercise with similar results for CVD- and all-cause mortality. Therefore, even resistance exercise as little as once per week and <1 h per week was associated with reductions in CVD events and CVD- and all-cause mortality.[8]

Likewise, recent studies have also focused on muscular strength and its relationship with CVD-morbidity and mortality.[6,8] Certainly, for many years, muscle strength and fitness have been associated with reduced CVD risk factors and better prognosis.[6] We have recently assessed the impact of muscular strength on subsequent development of DM in 4681 adults followed for over 8 years, and those in the middle level of muscle strength, DM was 32% lower than in those in the lower levels of muscle strength, even after adjusting CRF. Again, however, no association was found between the upper level of muscle strength and incident type 2 DM.

Certainly, substantial data indicates that higher CRF markedly reduces CVD- and all-cause mortality.[1–5,14–19] Additionally, the effects of CRF on sudden cardiac death has also been summarized, suggesting 14% to 22% reductions in sudden cardiac death per one MET increase in CRF.[33,34] We recently assessed the effects of muscular strength on the risk of sudden cardiac death in 8116 men, demonstrating that muscle strength was associated with fairly markedly reduced risk of sudden cardiac death, independently of several risk factors, including aerobic PA.[32] However, these results were attenuated and no longer statistically significant when CRF was assessed in the model. However, we noted that in those in the middle third of muscular strength, the risk of sudden cardiac death was reduced by 58% even after adjusting for CRF. Moreover, the joint analysis demonstrated that being both fit and strong was associated with a significant 72% reduction in the risk of sudden cardiac death. Although this study did not assess the impact of muscle strength on plasma lipids, a prior cross-sectional analysis in the ACLS cohort found no beneficial effects of muscular strength on TC, TGs, LDL-C or HDL-C in a cohort of 5460 men and 1193 women that also took into account confounders from CRF and body composition (sum of the skin fold, body mass indices, or weight).[35]

**Table 1**
Impact of cardiac rehabilitation and exercise training programs on lipids and cardiometabolic parameters.

| | |
|---|---|
| **Improvements in lipid profiles** | |
| Total cholesterol | −5% |
| Triglycerides | −15% |
| HDL-C | +6% (higher with low baseline) |
| LDL-C | −2% |
| LDL-C/HDL-C | −5% (higher in certain groups) |
| **Reductions in inflammation** | |
| hs-CRP | −40% |
| **Reductions in obesity indices** | |
| BMI | −1.5% |
| % Fat | −5% |
| Metabolic syndrome | −37% |
| **Improvements in exercise capacity** | |
| Estimated METs | +35% |
| Peak $VO_2$ | +15% |
| Peak AT | +11% |

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; BMI – body mass index; METs = metabolic equivalents; $VO_2$ = oxygen consumption; AT = anaerobic threshold.

## Conclusions

Certainly, the wealth of data indicates the potential for higher CRF and muscle strength to protect against CVD risk factors and CVD. Although the impact of CRF on plasma lipids has been variable, the constellation of data suggests modest impacts on dyslipidemia, particularly atherogenic dyslipidemia (combinations of hypercholesterolemia, hypertriglyceridemia and low levels of HDL-C). Also, increases in CRF over time may lead to attenuation of the adverse lipid effects that occur with aging. Resistance exercise training seems to have beneficial effects to prevent hypercholesterolemia as well as the metabolic syndrome, and low-to-moderate doses of resistance exercise appeared to be associated with better survival, even independent of CRF. On the other hand, although muscular strength may be associated with reduction in DM and overall CVD, including risk of sudden cardiac death, there are no obvious interactions with plasma lipids. Certainly, few of the studies have evaluated the impact of CRF and muscular strength with modern day lipid treatments, including combinations of statins and non-statin medications, and none on the impact of other therapies discussed in this Lipid Issue.

## Declaration of competing interest

None.

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