Cardiorespiratory Fitness, LDL Cholesterol, and CHD Mortality in Men

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ABSTRACT

FARRELL, S. W., C. E. FINLEY, and S. M. GRUNDY. Cardiorespiratory Fitness, LDL Cholesterol, and coronary heart disease (CHD) Mortality in Men. *Med. Sci. Sports Exerc.*, Vol. 44, No. 11, pp. 2132–2137, 2012. **Introduction**: There are no published data regarding the joint association of cardiorespiratory fitness (CRF) and LDL cholesterol concentration with subsequent CHD mortality in men. **Methods**: A total of 40,718 healthy men received a comprehensive baseline clinical examination between 1971 and 2006. CRF was determined from a maximal treadmill exercise test. Participants were divided into categories of low (quintile 1), moderate (quintiles 2–3), and high (quintiles 4–5) CRF by age group, as well as by Adult Treatment Panel III–defined LDL categories. HRs for CHD mortality were computed with Cox regression analysis. **Results**: A total of 557 deaths due to CHD occurred during 16.7 ± 9.0 yr (681,731 man-years) of follow-up. After adjustment for age, examination year, smoking status, family history, and body mass index, a significant positive trend in CHD mortality was shown across decreasing categories of CRF. HRs with 95% confidence interval were 1.0 (referent), 1.18 (0.94–1.47), and 2.10 (1.65–2.67) for high, moderate, and low fit groups, P trend <0.0001. Adjusted HRs were significantly higher across increasing LDL categories: 1.0 (referent), 1.30 (0.87–1.95), 1.54 (1.04–2.28), 2.16 (1.45–3.21), and 2.02 (1.31–3.13), P trend <0.0001. When grouped by CRF category as well as by LDL category, there was a significant positive trend ($P < 0.02$) in adjusted mortality across decreasing categories of CRF within each LDL category. **Conclusions**: CRF is strongly and inversely associated with CHD mortality in men. Compared with men with low CRF, at a moderate to high level of CRF, the risk of mortality within each LDL category is significantly attenuated. This study suggests that measurement of CRF should be considered for routine cardiovascular risk assessment and risk management. **Key Words:** FITNESS, LDL CHOLESTEROL, CARDIOVASCULAR DISEASE, CHD, JOINT ASSOCIATION

EPIDEMIOLOGY

Cardiovascular disease accounts for approximately 400,000 deaths in US men annually. Coronary heart disease (CHD accounts for nearly 225,000 (56%) of these deaths (22). Well-established major risk factors for CHD include elevated LDL cholesterol concentration (6,17) and sedentary lifestyle (7,24). Measurement of LDL is a major focus for determining the risk of CHD and for determining subsequent treatment strategy (15). According to the most recent National Health and Nutrition Examination Survey (NHANES) data, although mean LDL values have decreased from 134 to 119 mg·dL^{-1} since the late 1970s (10), approximately 35 million men have LDL values of ≥130 mg·dL^{-1} (22). However, because CHD mortality sometimes occurs in the absence of hyperlipidemia, data regarding other risk factors and their joint associations with LDL are needed.

Physical inactivity is also highly prevalent in the US-population (19,23). Most studies that have examined the association between physical activity and cardiovascular disease mortality have relied on self-reported assessment of physical activity habits (2,24,30). An important variable that is related to physical activity is cardiorespiratory fitness (CRF), a physiological characteristic that quantifies the ability of the body to transport and use oxygen at the working muscle and is dependent primarily on maximal cardiac output, maximal arterial–venous oxygen difference, and efficient shunting of blood to working skeletal muscle. In a recent study using criterion methods of measuring CRF and physical activity, the correlation between the two was only modest (r = 0.37) (14). Although there are data regarding the association between objective measures of CRF and cardiovascular disease morbidity and mortality (7,8,18,21,29), there are no data regarding the joint association of CRF and LDL cholesterol concentrations with subsequent CHD mortality. Thus, the purpose of this investigation is to examine the relationship among CRF and LDL cholesterol categories with CHD mortality in a cohort of apparently healthy men.

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Submitted for publication April 2012.
Accepted for publication June 2012.

0195-9131/12/4411-2132/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e31826524be

METHODS

Study participants and measurements. Briefly, the aim of the Cooper Center Longitudinal Study is to examine prospectively the association of health behaviors and chronic disease biomarkers to clinical outcomes in men and women.

Participants in the present study were 40,718 men who completed baseline examinations at the Cooper Clinic in Dallas, TX, between 1971 and 2006. All participants were US residents, and the majority (approximately 90%) self-reported that they were white and from middle to upper socioeconomic strata. Participants were either self-referred or referred by their primary care physician. The study was reviewed and approved annually by the institutional review board at The Cooper Institute. After receiving written informed consent, a clinical evaluation was performed and included a physician examination, fasting blood chemistry assessment, personal and family health history, anthropometry, resting blood pressure and ECG, and a maximal graded treadmill exercise test. LDL cholesterol was calculated by using the Friedewald equation. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. All procedures were administered by trained technicians who followed standardized measurement protocols. The Cooper Clinic laboratory meets the quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program.

CRF was quantified as the duration of a maximal treadmill exercise test using a modified Balke protocol as described elsewhere (3). Exercise duration from this protocol has been shown to correlate highly (r = 0.92) with directly measured maximal oxygen uptake in men (25). To prevent misclassification of CRF, patients who did not achieve at least 85% of age-predicted maximal heart rate (n = 3637) were excluded from the analyses. To standardize exercise test performance, we computed maximal MET (1 MET = 3.5 mL O_2 uptake·kg^{-1}·min^{-1}) levels of CRF on the basis of the final treadmill speed and grade (1).

Smoking history was obtained from a standardized questionnaire and grouped categorically for analysis (never, past, and current smoker). Men with previously diagnosed CHD at baseline (n = 664) were excluded from the analyses, as were men with a BMI of <18.5 kg·m^{-2} (n = 68) and men with <2 yr of follow-up (n = 1271).

Vital status was ascertained primarily using the National Death Index. CHD deaths were identified using the *International Classification of Diseases*, *9th revision* (codes 410.0–414.9 and 429.2) for deaths occurring before 1999 and *10th revision* (codes 120–126) for deaths during 1999–2008.

Statistical analyses. We followed the study participants for mortality from the date of their examination to the date of death for decedents or to December 31, 2008, for survivors. Cox proportional hazards regression analysis was used to estimate HRs and 95% confidence intervals (CIs) of CHD mortality according to exposure categories. In our primary analysis, CRF was grouped according to age-standardized quintiles of maximal exercise duration as described elsewhere (7). In accordance with our previous studies, high CRF was defined as the upper 40% (quintiles 4–5), moderate CRF as the next lowest 40% (quintiles 2–3), and low CRF as the lower 20% (quintile 1) of the age-standardized distribution (7). LDL cholesterol level was grouped according to the Adult Treatment Panel III Guidelines (<100, 100–129, 130–159, 160–189, and ≥190 mg·dL^{-1}) (15). Multivariable analyses included age (years), examination year, smoking status (never, past, and current smoker), family history of cardiovascular disease, and BMI. These five factors will henceforth be called covariables. Tests of linear trends in mortality rates and risk estimates across exposure categories were computed using ordinal scoring. We next examined the joint associations of CRF and LDL exposure categories with CHD mortality. We assessed interaction among exposure groups using likelihood ratio tests of nested models. All P values are two-sided, and $P < 0.05$ was regarded as statistically significant. All statistical analyses were performed using SAS (version 9.1, 2002; SAS Institute Inc., Cary, North Carolina).

RESULTS

There were 557 CHD deaths during an average follow-up period of 16.7 ± 9.0 yr. Descriptive baseline characteristics of the cohort are presented in Table 1. Baseline characteristics of the cohort by CRF category are presented in Table 2. All of the variables were significantly associated ($P < 0.001$) with categories of CRF; more favorable values were seen across incremental CRF categories.

We next computed HRs and 95% CIs as measures of the strength of association for CRF and LDL with adjusted CHD mortality (Table 3). HRs of mortality across categories of CRF were 1.0 (referent), 1.18 (0.94–1.47), and 2.10 (1.65–2.67) for high, moderate, and low fit men, P for trend <0.0001. Further adjustment for LDL had little effect on the strength or pattern of the association (data not shown). Adjusted HRs of CHD mortality across incremental categories of LDL were 1.0 (referent), 1.30 (0.87–1.95), 1.54 (1.04–2.28), 2.16 (1.45–3.21), and 2.02 (1.31–3.13), P for trend <0.0001. Further adjustment for CRF had little effect on the strength or pattern of the association (data not shown).

We further regressed CHD mortality rates on CRF and LDL exposures (Fig. 1). As shown, adjusted HRs for mortality were higher across decreasing CRF categories within each LDL category. The lowest risk of mortality was observed in men with moderate and high CRF with LDL values <100 mg·dL^{-1} (referent), whereas the highest risk was present in men with low CRF and LDL 160–189 mg·dL^{-1}, (HR = 4.74, 2.34–9.61). Although the number of deaths in the lowest LDL category (<100 mg·dL^{-1}) was low (n = 29), the HR for the low CRF category was 2.92-fold higher than for the moderate and high CRF categories. This pattern was similar in the three LDL categories within the range of <100 to 159 mg·dL^{-1}. However, at higher LDL levels, although HRs in the low CRF category remained the highest, HRs in the moderate CRF category were higher than that in the high CRF category. In other words, in the high CRF categories, increasing LDL levels had relatively little effect on HRs for CHD mortality. In the moderate CRF categories,

TABLE 1. Baseline characteristics for all men and by vital status in 40,718 men who were followed for an average of 16.7 ± 9.0 yr, Cooper Center Longitudinal Study, 1971–2008.

	All	CHD Decedents	Survivors	*P* Value for Difference
N	40,718	557	40,161	
Total man-years exposure (total)	16.7 ± 9.0 (681,731)	16.7 ± 7.2 (9287)	16.7 ± 9.1 (672,444)	0.86
Age (yr)	44.8 ± 9.6	53.1 ± 10.2	44.6 ± 9.6	<0.0001
BMI ($kg \cdot m^{-2}$)	26.7 ± 3.9	27.2 ± 4.1	26.7 ± 3.9	0.002
Waist circumference (cm)	94.0 (10.6)	97.4 (11.4)	94.0 (10.6)	<0.0001
Percentage body fat	21.5 ± 6.3	23.3 ± 6.5	21.5 ± 6.2	<0.0001
Systolic blood pressure (mm Hg)	121.5 ± 13.4	128.6 ± 15.6	121.4 ± 13.3	<0.0001
Diastolic blood pressure (mm Hg)	81.5 ± 9.6	84.4 ± 10.1	81.4 ± 9.6	<0.0001
Glucose ($mg \cdot dL^{-1}$)	99.6 ± 15.7	105.4 ± 26.0	99.5 ± 15.5	<0.0001
Triglycerides ($mg \cdot dL^{-1}$)	125.9 ± 69.0	146.8 ± 77.5	125.7 ± 68.8	<0.0001
Total cholesterol ($mg \cdot dL^{-1}$)	205.1 ± 39.0	224.0 ± 39.1	204.9 ± 38.9	<0.0001
LDL cholesterol ($mg \cdot dL^{-1}$)	133.4 ± 35.3	151.3 ± 34.1	133.1 ± 35.3	<0.0001
HDL cholesterol ($mg \cdot dL^{-1}$)	46.6 ± 11.9	43.3 ± 11.7	46.6 ± 11.9	<0.0001
Treadmill time (min)	18.2 ± 4.9	14.5 ± 5.3	18.3 ± 4.9	<0.0001
Maximal METs	11.8 ± 2.4	10.0 ± 2.5	11.8 ± 2.4	<0.0001
Smoking (%)				
Never	23,591 (57.9)	159 (28.6)	23,422 (58.3)	
Past	10,586 (26.0)	252 (45.2)	10,344 (25.7)	
Current	6541 (16.1)	146 (26.2)	6395 (15.9)	<0.0001
Family history of MI or stroke (%)	21,237 (52.2)	320 (57.5)	20,917 (52.1)	0.01

Unless otherwise indicated, values are means ± SD. 1 MET = 3.5 mL O_2 uptake$\cdot kg^{-1} \cdot min^{-1}$.
MI, myocardial infarction.

increasing LDL had progressively greater effect on mortality at LDL levels of ≥160 $mg \cdot dL^{-1}$.

DISCUSSION

To our knowledge, this is the first article that has examined the joint associations between measures of CRF and LDL with subsequent CHD mortality in men. There was a strong positive trend in adjusted CHD mortality across decreasing CRF categories. Within each LDL category, men with low CRF had higher mortality than men with moderate to high CRF. Importantly, 60.3% of CHD deaths occurred in men with LDL levels below 160 $mg \cdot dL^{-1}$, and 27.3% of deaths occurred in those with LDL levels below 130 $mg \cdot dL^{-1}$. Within these LDL categories, a disproportionate number of deaths occurred in men with low CRF. Thus, even with moderate, low, or very low LDL levels, low CRF still carries a relatively high risk for CHD mortality.

An important point to consider when interpreting the joint associations of CRF and LDL with mortality is the method in which CRF was grouped for this analysis. Currently, there is not a widely accepted method of defining CRF levels for use in clinical or public health research. Our group has standardized the definition of low fit (unfit) to the bottom 20% of the age-standardized distribution of maximal exercise duration within the overall cohort; individuals in the remaining 80% of the distribution are considered to be fit (8). These definitions are in accord with the observation in the Cooper Center Longitudinal Study that individuals in the lower 20% of the CRF distribution have disproportionately high all-cause mortality.

Clinical trials with LDL-lowering drugs have shown that even when low LDL levels are present, the likelihood of CHD events depends on the severity of concomitant risk factors, for example, hypertension (4), HDL (5), diabetes (31),

TABLE 2. Baseline characteristics by CRF level (fitness) for 40,718 men who were followed for an average of 16.7 ± 9.0 yr, Cooper Center Longitudinal Study, 1971–2008.

	Low Fitness (Quintile 1)	Moderate Fitness (Quintiles 2–3)	High Fitness (Quintiles 4–5)	*P* for Trend
N	8194	16,901	15,623	
Total man-years exposure (total)	16.9 ± 9.3 (138,477)	16.4 ± 9.1 (277,047)	17.0 ± 8.8 (266,207)	0.05
CHD deaths, *n* (%)	229 (2.8)	195 (1.2)	133 (0.9)	<0.0001
Age (yr)	45.3 ± 9.8	44.9 ± 9.5	44.2 ± 9.7	<0.0001
BMI ($kg \cdot m^{-2}$)	29.8 ± 5.0	26.9 ± 3.2	24.9 ± 2.5	<0.0001
Waist girth (cm)	103.2 ± 12.4	95.1 ± 8.8	88.4 ± 7.5	<0.0001
Percentage body fat	26.5 ± 5.8	22.5 ± 5.2	17.9 ± 5.3	<0.0001
Systolic blood pressure (mm Hg)	124.3 ± 14.2	121.4 ± 13.0	120.2 ± 13.1	<0.0001
Diastolic blood pressure (mm Hg)	84.1 ± 10.0	81.9 ± 9.5	79.6 ± 9.1	<0.0001
Glucose ($mg \cdot dL^{-1}$)	104.1 ± 23.6	99.4 ± 13.9	97.4 ± 11.4	<0.0001
Triglycerides ($mg \cdot dL^{-1}$)	161.4 ± 77.7	132.2 ± 68.0	100.5 ± 53.9	<0.0001
Total cholesterol ($mg \cdot dL^{-1}$)	212.4 ± 41.1	207.6 ± 38.6	198.6 ± 37.1	<0.0001
LDL cholesterol ($mg \cdot dL^{-1}$)	138.2 ± 37.7	135.9 ± 34.9	128.0 ± 33.8	<0.0001
HDL cholesterol ($mg \cdot dL^{-1}$)	41.9 ± 10.5	45.3 ± 11.0	50.4 ± 12.5	<0.0001
Treadmill time (min)	12.0 ± 2.6	17.0 ± 2.3	22.8 ± 3.2	<0.0001
Maximal METs	8.9 ± 1.2	11.2 ± 1.1	14.0 ± 1.8	<0.0001
Smoking (%)				
Never	3988 (48.7)	9737 (57.6)	9866 (63.2)	
Past	2078 (25.4)	4241 (25.1)	4267 (27.3)	
Current	2128 (26.0)	2923 (17.3)	1490 (9.5)	<0.0001
Family history of MI or stroke (%)	4436 (54.1)	8824 (52.2)	7977 (51.1)	<0.0001

Unless otherwise indicated, values are means ± SD. 1 MET = 3.5 mL O_2 uptake$\cdot kg^{-1} \cdot min^{-1}$.
MI, myocardial infarction.

TABLE 3. Adjusted[a] HRs (95% CIs) for CHD mortality across CRF and LDL cholesterol categories in 40,718 men who were followed for an average of 16.7 ± 9.0 yr, Cooper Center Longitudinal Study, 1971–2008.

Fitness Category	High (Quintiles 4–5)	Moderate (Quintiles 2–3)	Low (Quintile 1)			*P* Trend
Total *n*	15,623	16,901	8194			
CHD deaths (*n*)	133	195	229			
HR	1.0	1.18	2.10			<0.0001
95% CI	Referent	0.9–1.5	1.6–2.7			
LDL, mg·dL^{-1}	**<100**	**100–129**	**130–159**	**160–189**	**≥190**	
Total *n*	6575	13,136	12,468	5965	2574	
CHD deaths (*n*)	29	123	184	152	69	
HR	1.0	1.30	1.54	2.16	2.02	<0.0001
95% CI	Referent	0.9–2.0	1.0–2.3	1.4–3.2	1.3–3.1	

[a] Adjusted for age, examination year, smoking status, family history of cardiovascular disease, and BMI.

and metabolic syndrome (13). The current findings are in accord with this observation; the CRF categories modify risk for each LDL level. However, the HR patterns within each LDL category were not the same. Within each of the three lowest LDL categories, moderate and high CRF provided very similar protection from CHD mortality. However, within the two highest LDL categories, there was a greater attenuation of risk in the high CRF compared with the moderate CRF categories. CRF appears to be an unusually powerful mortality risk predictor. Although the reasons for this risk potency are not fully understood, previous studies in this cohort have shown that individuals in the lowest CRF category carry the highest burden of standard coronary risk factors. In addition, CRF is influenced by habitual physical activity. Multiple studies have shown that CRF can be improved by exercise training (26,27,33), and other reports show that exercise training associates with a lower risk for CHD (12,33).

To qualify for the moderate CRF category, a 50- to 59-yr-old man would need to achieve a maximal MET level of 8.9 or higher. This is equivalent to covering approximately 1.2 miles in the Cooper 12-min run–walk test (11) or achieving a treadmill time of approximately 8.5 min on a standard Bruce treadmill exercise test. This level of CRF can be achieved by many, perhaps even most, apparently healthy men through moderate amounts and intensities of regular physical activity such as brisk walking. The powerful relationship between CRF and CHD mortality observed in this study is unlikely to be explained entirely by differences in habitual physical activity among the groups. Individuals with high CRF likely do exercise regularly, which could contribute to their lower CHD risk. However, differences in mortality between groups at low and moderate CRF levels almost certainly cannot be explained entirely by differences in exercise habits. Several factors other than lack of exercise training have been reported to predispose to a low CRF level. These include total body obesity, upper body obesity, insulin resistance of muscle, cigarette smoking, asthma, and unrecognized CHD (20). Furthermore, Bouchard et al. (9) estimated that genetic

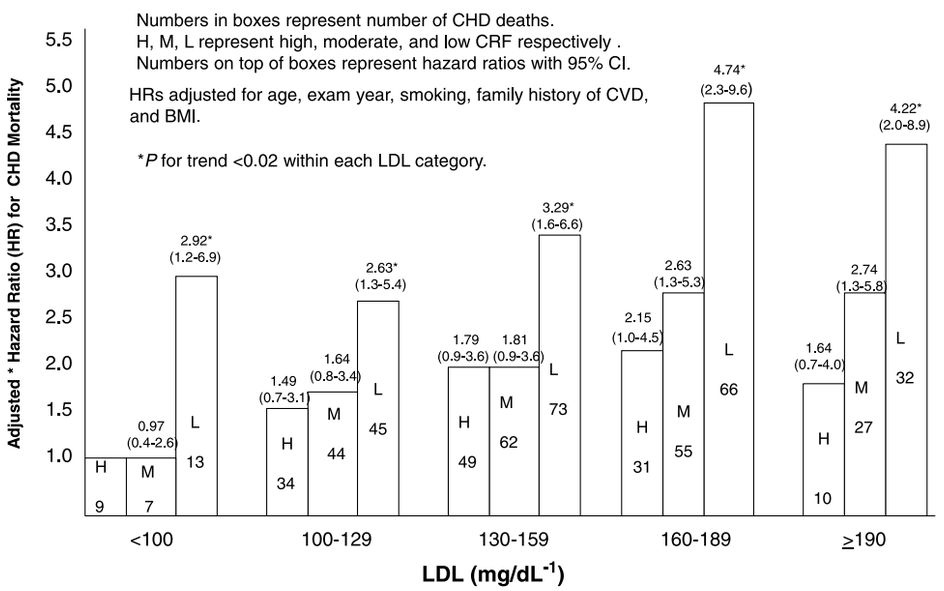

FIGURE 1—Joint exposures of CRF and LDL cholesterol with CHD mortality in 40,718 men followed for (16.7 ± 9.0) yr, Cooper Center Longitudinal Study, 1971–2008.

factors contribute upward of 50% to the variability in CRF. All these factors could contribute in one way or another to increased CHD mortality in individuals with low CRF.

Among the strengths of the current study are a large and well-characterized cohort of men, an extensive follow-up with a relatively large number of CHD deaths for analysis, and the use of objective measures for CRF, BMI, and blood lipid exposures. We adjusted mortality rates for several confounders including age, examination year, smoking, family history of cardiovascular disease, and BMI. To decrease the likelihood that preexisting subclinical disease was present at baseline, we excluded men with a BMI <18.5 $kg \cdot m^{-2}$ as well as those with <2 yr of follow-up.

This study also has limitations. The cohort is primarily white and from middle to upper socioeconomic strata; therefore, our findings must be cautiously interpreted when generalized to other populations. However, the homogeneity of sociodemographic factors in our population sample strengthens the internal validity of our findings by reducing potential confounding by these issues. We also point out that the median-estimated $\dot{V}O_{2max}$ for Cooper Center Longitudinal Study men is actually very similar to the values obtained during NHANES, which uses a stratified random sample of the US population. For example, the median-estimated $\dot{V}O_{2max}$ for Cooper Center Longitudinal Study versus NHANES men in the 40- to 49-yr age group is 40.1 and 40.9 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively, (32). Although we excluded men with <2 yr of follow-up, we cannot completely rule out the possibility that the higher CHD mortality in the lowest CRF category was due in part to subclinical CHD at baseline. We did not have sufficient data for medication use to include in this analysis, which is a potential confounder. A lowering of LDL levels due to drugs could contribute to the lower CHD risk in the lower LDL categories, but LDL-lowering drugs should not have affected the relative risk in each of the three CRF levels in each LDL range. We also did not have more extensive information on smoking habits, such as the number of pack-years. We note that the HR (2.02) for men with LDL ≥190 $mg \cdot dL^{-1}$ is somewhat lower than expected as compared with the HR (2.16) for men with LDL 160–189 $mg \cdot dL^{-1}$. We speculate that this may be due to the relatively small sample size in the former group (n = 2574). As the number of men with LDL ≥190 $mg \cdot dL^{-1}$ increases in our cohort over time, we would obtain a higher level of statistical power.

This study raises the question of whether measurement of CRF should be used in routine cardiovascular risk assessment and risk management. There is a well-accepted principle that for management of risk factors, such as elevated LDL, the intensity of therapy should be adjusted to absolute, not relative, risk (15). Persons with established CHD are known to be at high absolute risk for future coronary events and thus are deserving of intensive LDL-lowering therapy; further risk assessment adds little to form treatment strategies. In individuals without atherosclerotic cardiovascular disease risk, absolute risk is best estimated by multiple risk factor algorithms, such as those of the Framingham Heart Study. However, Gupta et al. (16) recently reported that measuring CRF improved prediction of cardiovascular disease mortality beyond traditional risk factors. Thus, identifying persons with low CRF should allow physicians to raise the absolute risk estimate beyond that predicted by standard risk factor algorithms. Patients who are at low risk by standard risk factors may be good candidates for an LDL-lowering drug if they have both low CRF and LDL cholesterol above 100 $mg \cdot dL^{-1}$. The JUPITER trial showed the benefit of LDL-lowering therapy in middle-age persons with low LDL levels when their risk was raised by elevation of an inflammatory marker (28). Measurement of CRF may be an additional tool for identifying persons at increased risk.

Available evidence indicates that lifestyle factors such as physical inactivity, obesity, and cigarette smoking contribute to low CRF. This evidence justifies intensive lifestyle intervention, and persons found to have a low level of CRF should achieve further risk reduction beyond LDL lowering.

The authors thank Kenneth H Cooper, MD, MPH, for establishing the Cooper Center Longitudinal Study; William L. Haskell, PhD, for helpful comments and suggestions; and Melba Morrow for editorial assistance.

There is no conflict of interest to declare by any of the authors.

There are no funding sources to declare.

The results of the present study do not constitute endorsement by American College of Sports Medicine.

EPIDEMIOLOGY

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