Association of Cardiorespiratory Fitness With Coronary Heart Disease in Asymptomatic Men

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Abstract

Objective—To examine the association of cardiorespiratory fitness (CRF) with risk of coronary heart disease (CHD) while controlling for an individual's Framingham Risk Score (FRS)–predicted CHD risk.

Patients and Methods—The study included 29,854 men from the Aerobics Center Longitudinal Study, who received a baseline examination from January 1, 1979, to December 31, 2002. Coronary heart disease events included self-reported myocardial infarction or revascularization or CHD death. Multivariable survival analysis investigated the association between CRF, FRS, and CHD. Cardiorespiratory fitness was analyzed as both a continuous and a categorical variable. The population was stratified by "low" and "moderate or high" risk of CHD to test for differences in the FRS stratified by CRF.

Results—Compared with men without incident CHD, men with incident CHD were older (mean age, 51.6 years vs 44.6 years), had lower average maximally achieved fitness (10.9 metabolic equivalent of tasks vs 12.0 metabolic equivalent of tasks [METs]), and were more likely to have moderate or high 10-year CHD risk ($P<.001$). Cardiorespiratory fitness, defined as maximal METs, exhibited a 20% lower risk of CHD (hazard ratio, 0.80; 95% CI, 0.77–0.83) for each 1-unit MET increase. Among men in the low CRF strata, individuals with moderate or high 10-year CHD risk, according to the FRS, had a higher CHD risk (hazard ratio, 6.55; 95% CI, 3.64–11.82) than men with low CHD risk according to the FRS.

Conclusion—Clinicians should promote physical activity to improve CRF so as to reduce CHD risk, even to patients with otherwise low CHD risk.

The American Heart Association[1] stated that one of its 2020 Impact Goals was to reduce deaths from cardiovascular disease (CVD) by 20%. Most CVD deaths in 2006 and 2007

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were caused by coronary heart disease (CHD), which is defined as plaque accumulation in the arteries of the heart, decreasing the supply of oxygen-rich blood.[2] Several risk factors have been shown to predict CHD, including smoking,[3] diabetes,[4] hypertension,[5] and hypercholesterolemia.[6]

Coronary heart disease risk equations, such as the Framingham Risk Score (FRS), have been developed and used to account for these and other risk factors.[7] The FRS provides a sex-specific risk score that accounts for age, systolic and diastolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, diabetes diagnosis, and smoking status.[8] Previous studies[9–11] have modified the FRS with the addition of C-reactive protein,[10] deletion of diabetes diagnosis,[11] and alterations to blood pressure definitions[12]; yet none of these modifications involved assessing the association between cardiorespiratory fitness (CRF), FRS, and CHD.

Previous research reports CRF's significant protective effects on all-cause mortality,[13,14] cancer-related mortality,[15] diabetes incidence,[16] CHD incidence,[17] and CHD mortality.[8,18,19] Barlow et al[20] reported that a 1-unit metabolic equivalent of task (MET) increase in baseline CRF resulted in an 18% decrease in CVD mortality in FRS-classified "low-risk" adults over a 30-year follow-up period. However, this result reflects control for additional factors besides CRF, such as body mass index (calculated as the weight in kilograms divided by the height in meters squared) and family history of early CHD, which are not included in the FRS.

The aim of this study was to examine the association of CRF with 10-year risk of CHD while controlling for an individual's FRS–predicted CHD risk. Our secondary aim was to investigate whether the relationship between CRF and 10-year risk of CHD differs in "moderate- or high-risk" men.

PATIENTS AND METHODS

Aerobics Center Longitudinal Study

The Aerobics Center Longitudinal Study (ACLS) is a prospective cohort study involving a large group of men and women. The participants were patients of the Cooper Clinic, in which they received a preventive medical examination and counseling on health behaviors during periodic visits. The participants were examined at least once from January 1, 1979, to December 31, 2002, at the Cooper Clinic, Dallas, Texas. The protocol for the ACLS was reviewed annually and approved by the institutional review board of the Cooper Institute. Women were excluded from these analyses because of a small number of CHD events (n=45). Men were included on the basis of the following criteria: (1) age at baseline examination between 30 and 74 years; (2) complete data for outcome and predictor variables; and (3) free of CVD or cancer diagnosis at baseline. A flow diagram of the study population is depicted in Figure 1.

Clinical Examination

The baseline clinical examination included an electrocardiogram, a 12-hour fasting blood chemistry analyses including cholesterol and glucose measurements, blood pressure

assessment, and a maximal exercise test.[21–23] A standardized questionnaire was used to assess smoking status and other risk factors.

Outcome Measure—Coronary heart disease was defined through self-report of either revascularization (including bypass, coronary balloon, angioplasty, or stent) or myocardial infarction or CHD- specific mortality. A mail-back questionnaire was administered in 1982, 1986, 1990, 1995, 1999, and 2004, in which participants were asked to report their history of revascularization or myocardial infarction along with the incident date. The National Center for Health Statistic's National Death Index was used to identify CHD deaths in the ACLS cohort; *International Classification of Disease* (Ninth and Tenth revisions) codes 410.0 to 414.0 were used to determine CHD as the primary cause of death. In accordance with FRS's follow-up time definition, the maximal follow-up time for the ACLS study population was 12 years.

Application of the FRS—The FRS was derived from the Framingham Heart Study,[7] which is an ongoing observational study initiated in 1948 and primarily recruits residents of Framingham, Massachusetts. In a study published in 1998,[8] the main outcome was a CHD event defined as a myocardial infarction, coronary insufficiency, or CHD death. This version of the FRS[8] incorporated categorical variables for age, hypertension, total cholesterol level, HDL-C level, smoking status, and diabetes to determine a point value that could be summed and interpreted as an overall 10-year risk of CHD. The definition of the risk factors was kept consistent with the 1998 FRS report,[8] and the risk factors were categorized on the basis of the score sheet. Diabetes was diagnosed if the fasting glucose level was higher than 140 mg/dL (to convert to mmol/L, multiply by 0.0259), and smoking status was self-reported.

The FRS was applied using the categorical risk factors and the specified points[8] to every individual, and men were stratified on the basis of their level of 10-year CHD risk according to the FRS. Men with 10-year CHD risk lower than 10%[20] (ie, point summation, 5 points) were classified as "low" risk of CHD, and men with 10-year CHD risk higher than 10% (ie, point summation, >5 points) were classified as "moderate or high" risk of CHD.

Cardiorespiratory Fitness—The Balke maximal exercise treadmill test[24] was used to determine CRF, which was analyzed as a categorical variable.

The categorical definition of CRF was based on a participant's age-specific treadmill time from the entire ACLS cohort and consisted of 3 levels: low (bottom least fit 20%), moderate (next fit 40%), and high (most fit top 40%). The corresponding treadmill time and MET values have been assigned across 20 to 39, 40 to 49, 50 to 59, and 60 years and above on the basis of our previously published articles[25] to maintain methodology consistency, because there are no established cut points for CRF to classify different levels of fitness. In the present analysis, the mean treadmill time and MET values across low, moderate, and high CRF groups were 11.5 minutes and 8.6 METs, 16.1 minutes and 10.7 METs, and 22.1 minutes and 13.6 METs, respectively. The following regression formula was used to convert maximal treadmill time to METs[26]:

$$\text{METs} = \frac{(1.44 \times \text{minutes of exercise duration}) + 14.99}{3.5}$$

Treadmill time converted to METs is analogous to Vo_2peak.[27]

Statistical Analyses

Descriptive statistics were computed for the total ACLS male population and stratified by incidence of CHD. Men with and without incident CHD were compared for mean age; proportion of men with low, moderate, or high CRF; proportion of men with moderate or high 10-year CHD risk according to the FRS; hypertension classification; total cholesterol and HDL-C levels; diabetes diagnosis; and smoking status. We calculated age-adjusted incidence rates per 10,000 person-years for 10-year CHD risk and CRF. To determine each of the aforementioned covariate's association with CHD events, univariate survival analysis was performed. Cox proportional hazards models adjusted for baseline examination year were fit to determine the association between CRF and CHD events while controlling for 10-year CHD risk. We tested for the interaction between CRF and FRS using survival analysis of a population stratified by low, moderate, and high CRF while adjusting for baseline examination year. Men with low 10-year CHD risk served as the reference group. We constructed a receiver operating characteristic curve for a sensitivity analysis to determine the CRF's added predictive power of the FRS for 10-year CHD risk. SAS version 9.3 (SAS Institute Inc) was used to perform all analyses.

RESULTS

During a 12-year follow-up period (248,890 person-years of exposure), there were 499 incident CHD events. The FRS was applied to approximately 30,000 men in the ACLS cohort (Table 1). The incidence of CHD in men with moderate or high 10-year CHD risk was 37.6 per 10,000 person-years as compared with 19.7 for men with low 10-year CHD risk. Age-adjusted CHD incidence in men with low, moderate, or high CRF was 26.5, 23.6, and 16.5 per 10,000 person-years, respectively. Compared with men without incident CHD, men with incident CHD were older, had higher prevalence of stage I hypertension, had a lower HDL-C level (<35 mg/dL), and were more likely to have moderate or high 10-year CHD risk (P<.0001 for all stated comparisons).

Table 2 presents the univariate associations between the FRS risk factors and the risk of CHD. Men with optimal blood pressure were 33% less likely to experience a CHD event than were men with normal blood pressure (hazard ratio [HR], 0.67; 95% CI, 0.52–0.87), whereas men with stage I hypertension were at a significantly higher risk of CHD (HR, 1.55; 95% CI, 1.23–1.97). Men with an HDL-C level of 60 mg/dL or higher were at a significantly lower risk of CHD than were men with an HDL-C level of 45 to 49 mg/dL. Men diagnosed with diabetes and who reported being smokers were at a significantly higher risk of CHD than were nondiabetic individuals and nonsmokers. Table 3 presents the univariate and multivariable associations between CRF categories, moderate or high 10-year CHD risk, and CHD events. Men with moderate or high 10-year CHD risk had an almost 6-fold (HR, 5.66;

95% CI, 4.25–7.55) higher risk of CHD than did men with low 10-year CHD risk. A univariate analysis revealed an inverse association between CRF and CHD. Cardiorespiratory fitness, categorized into low, moderate, and high, exhibited that men with high CRF had 33% (HR, 0.67; 95% CI, 0.51–0.88) lower risk of CHD than did men who had low CRF (see Table 3). Model 2 evaluates a similar association, but defines CRF as a categorical variable and shows that men with high CRF have 26% lower CHD risk while controlling for moderate or high 10-year CHD risk.

Figure 2 shows the association between CRF, FRS, and 10-year CHD risk through stratification of the population by low, moderate, and high CRF.

Among men with low CRF, individuals with moderate or high 10-year CHD risk were 6.5 times (HR, 6.55; 95% CI, 0.64–11.82) more likely to develop CHD than those with low CHD risk. This association was similar but attenuated in men with moderate and high CRF (HR, 4.76; 95% CI, 3.03–7.47 and HR, 5.52; 95% CI, 3.36–9.05, respectively). Our sensitivity analysis revealed that CRF (area under the curve, 0.80) did not add to the predictive power of the FRS for 10-year CHD risk (area under the curve, 0.80) (P=.97).

DISCUSSION

Both FRS and CRF were strong independent predictors of CHD. Cardiorespiratory fitness had a significant protective effect on CHD in men after controlling for 10-year CHD risk according to the FRS point summation. When men were stratified by low, moderate, and high CRF, CRF's protective effect was still apparent but overshadowed by the strong association between FRS-predicted CHD risk and CHD events. To our knowledge, this is the first study to investigate the association between CRF and CHD in men with low and moderate or high 10-year CHD risks.

The FRS is composed of CHD risk factors such as hypertension, cholesterol levels, diabetes diagnosis, and smoking status.[8] Various versions[8,28–30] that have included these risk factors have repeatedly shown the predictive power of the FRS.[31] Myocardial ischemia is common in patients with hypertension[4,5,32]; although a recent study reported a 1.4-mm Hg decrease in mean systolic blood pressure from 1994 to 2005 that could be associated with a 20% reduction in CHD deaths.[33] Diabetes diagnosis also has been shown to significantly increase a person's risk of CHD.[34,35] Diabetes can cause impairment in the cardiac muscle that may lead to cardiomyopathy, congestive heart failure, or ischemic heart disease and can increase the 5-year mortality rate after myocardial infarction.[4] Doyle et al[36] published one of the first studies examining the association between smoking and CHD. They concluded that although problems with blood pressure and cholesterol were absent, participants who reported being smokers were at a significantly higher risk of CHD mortality than were nonsmokers.[36]

Our univariate analysis revealed that the FRS was a significant predictor of 10-year CHD risk for men in the ACLS cohort. Our previous research reported the categorical FRS risk factors for men in the ACLS cohort, and the HRs[31] were similar to those reported in the original FRS report.[24] The FRS applied to the ACLS cohort reported a Hosmer-Lemeshow c statistic of 0.78 (95% CI, 0.75–0.79).[31]

We also found that CRF has a significant protective effect on CHD, similar to findings previously reported in the literature.[13,16,18,37,38] Ekelund et al[19] investigated the relationship between CRF and CHD in asymptomatic men and found that during a 9-year follow-up the more fit men had the least CHD risk compared with the least fit individuals. Lee et al[18] built on these findings by analyzing CRF's association with CVD while controlling for body composition. They reported that lean unfit men had 3 times higher risk of dying from CVD (relative risk, 3.16; 95% CI, 1.12–8.92) than did lean fit men. Improved CRF may reduce CHD risk through improved muscle mass[39,40] and increase in arterial oxygen content.[39–41] Research has shown that CRF can increase the double product threshold for ischemic ST-segment depression,[42,43] a decrease in the magnitude of ST-segment depression, and diminished maximal ST-segment depression.[42] Cardiorespiratory fitness may also have a positive effect on coagulation[44,45] and may protect against thrombosis.[19]

Our findings regarding the association between CRF, FRS, and risk of CHD are consistent with recent findings.[46,47] Barlow et al[20] investigated the association between CRF and CVD mortality in men and women who were at low risk of CHD events. They concluded that a 1-unit MET increase in CRF resulted in an 18% decrease in CVD mortality during a 30-year follow-up period.[20] Gupta et al[48] used the ACLS cohort with data ranging from 1970 through 2006 and used a traditional CHD risk factor model that adjusts for age, systolic blood pressure, diabetes diagnosis, total cholesterol level, and smoking status and reported that CRF-augmented CHD risk factor model correctly reclassified participants with CHD death on the basis of their 10-year risk[48] as compared with the traditional FRS model.

The present study builds on the aforementioned research by applying the FRS to a large, single-center, longitudinal cohort with the same level of precision as that of the Framingham Heart Study that generated the FRS. The American College of Cardiology and the American Heart Association recently developed the Pooled Cohort Equation for estimating artherosclerotic CVD[49] that encompasses risk factors similar to those of the FRS but offers risk estimates for myocardial infarction, CHD death, stroke, and stroke death and does not include fitness.[50] This project focused on previously defined CHD that includes angioplasty and revascularization while excluding stroke and stroke death. Future research should investigate the potential effect the Pooled Cohort Equation may have on artherosclerotic CVD with the addition of CRF.

To our knowledge, this is the first prospective cohort to investigate CRF's association with 10-year risk of CHD while controlling for the FRS[8] in its entirety. A possible limitation to the present study is the homogeneity of the ACLS population. At the time of enrollment, the ACLS consisted of mostly men (mean age, 42 years) and was predominantly non-Hispanic whites (>95%). However, a comparison study between the ACLS and 2 large population-based cohorts found that the results of the ACLS were similar to those obtained from those 2 cohorts.[51] In addition, ACLS' homogeneity improves internal validity by controlling potential confounders such as socioeconomic status and education, although generalizations from this study should be made cautiously.

CONCLUSION

Our study found that CRF and FRS are both significant predictors of CHD events. Men with moderate and high CRF have a lower risk of CHD than do men with low CRF; this association remains in men with moderate or high 10-year CHD risk when stratified into low, moderate, and high CRF. Cardiorespiratory fitness is a modifiable predictor of CHD, and improved CRF may lead to an improvement in the FRS and 10-year CHD risk, as well as an improvement in the ability to predict long-term CHD risk. Clinicians should vigorously promote exercise therapy and increase in physical activity to their patients in an effort to increase CRF in the long-term prevention of CHD. Researchers should consider developing a randomized clinical trial to determine the overall effect that CRF changes may have on an individual's FRS–predicted CHD risk, the individual components of the risk score, and ultimately the effect on 10-year risk of CHD.

Acknowledgments

Abbreviations and Acronyms

ACLS	Aerobics Center Longitudinal Study
CHD	coronary heart disease
CRF	cardiorespiratory fitness
CVD	cardiovascular disease
FRS	Framingham Risk Score
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
MET	metabolic equivalent of task

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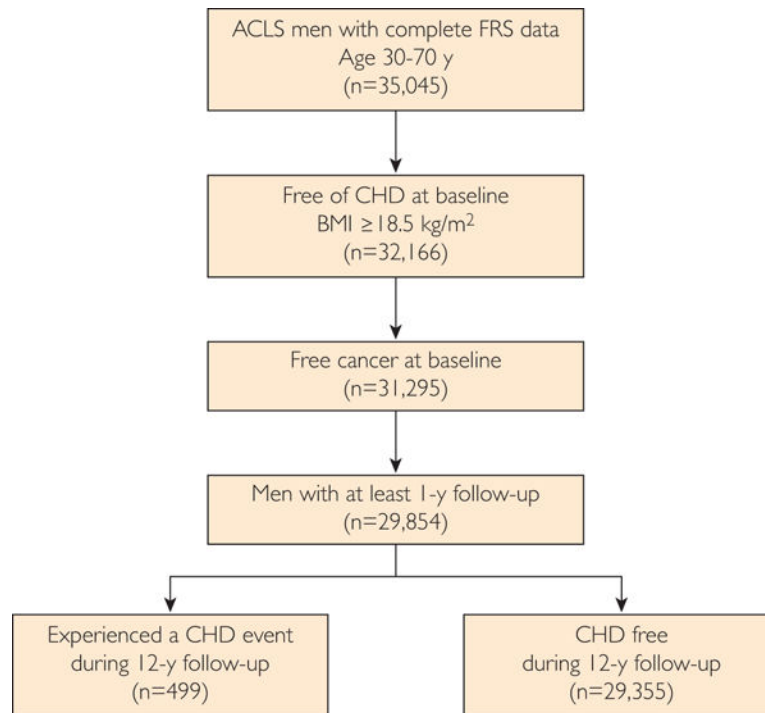**FIGURE 1.**
Study flow and Aerobic Center Longitudinal Study (ACLS) inclusion criteria depicting final sample size and coronary heart disease (CHD) event frequency. BMI = body mass index; FRS = Framingham Risk Score.
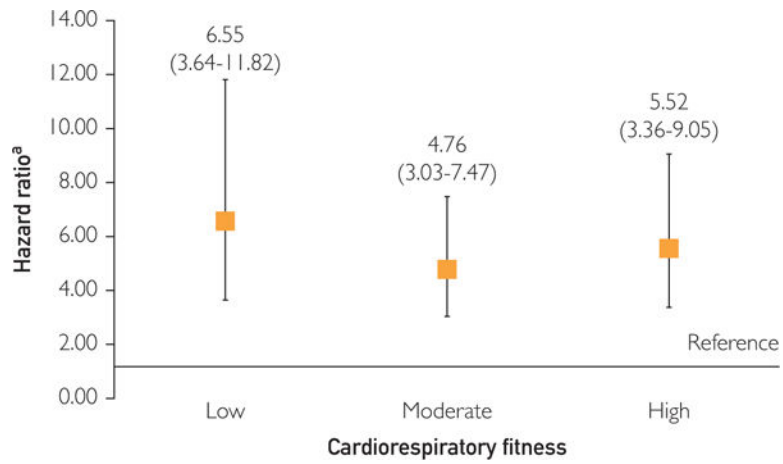
FIGURE 2.
Adjusted hazard ratios (95% CIs) for the relationship between moderate or high 10-year coronary heart disease risk (as classified by the Framingham Risk Score) and coronary heart disease, stratified by low, moderate, and high cardiorespiratory fitness. Low 10-year coronary heart disease risk served as the reference group.
[a]Adjusted for baseline examination year

TABLE 1

Comparison of Demographic Characteristics Between Men (n=29,854) With Incident CHD and Those Without Incident CHD in the Aerobics Center Longitudinal Study Prospective Cohort[a,b]

Risk factor	Total population (N=29,854)	Men with incident CHD (n=499)	Men without incident CHD (n=29,355)	P[c]
Age range (y)	30–74	31–73	30–74	
Mean age (y)	44.7	51.6	44.6	<.001
Mean fitness, maximally achieved MET	12.0	10.9	12.0	<.001
Cardiorespiratory fitness				
Low	11.6	13.4	11.5	.19
Moderate	38.5	43.3	38.4	.03
High	50.0	43.3	50.1	.0029
Mean FRS (points)	3.5	6.2	3.5	<.001
Moderate or high 10-y CHD risk	2.1	10.4	1.9	<.0001
Blood pressure (mm Hg)				
Optimal (SBP<120, DBP<80)	28.8	19.4	29.0	<.0001
Normal (SBP<130, DBP<85)	31.8	30.3	31.9	.45
High normal (SBP<140, DBP<90)	16.0	19.6	15.9	.02
Stage I HTN (SBP<160, DBP<100)	18.7	25.5	18.6	<.001
Stage II–IV HTN (SBP 160, DBP 100)	4.7	5.2	4.7	.56
Total cholesterol level (mg/dL)				
<160	9.2	3.8	9.3	<.001
160–199	34.1	19.2	34.4	<.001
200–239	36.9	40.5	36.8	.09
240–279	15.3	27.3	15.1	<.001
280	4.5	9.2	4.5	<.001
HDL-C level (mg/dL)				
<35	15.6	25.3	15.4	<.001
35–44	34.1	38.7	34.1	.03
45–49	15.6	13.0	15.6	.11
50–59	21.4	15.8	21.5	.021
60	13.3	7.2	13.4	<.001
Diabetes	1.4	4.4	1.3	<.001
Current smoking	16.6	21.8	16.5	.001

[a] CHD = coronary heart disease; DBP = diastolic blood pressure; FRS = Framingham Risk Score; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; HTN = hypertension; MET = metabolic equivalent of task; SBP = systolic blood pressure.

[b] SI conversion factor: To convert mg/dL values to mmol/L, multiply by 0.0259.

[c]The Student t test was used to calculate the difference between incident CHD and no incident CHD groups for age, mean fitness level, and mean FRS points. The χ^2 test was used to determine the statistically significant difference for remaining categorical variables.

TABLE 2

Univariate Survival Associations Between the Framingham Risk Score Risk Factors and 10-Y Coronary Heart Disease Risk[a,b]

Risk factor	Model 1: Univariate model	
	HR	95% CI
Age	1.09	1.08–1.10
Blood pressure (mm Hg)		
Optimal (SBP<120, DBP<80)	0.67	0.51–0.88
Normal (SBP<130, D<85)	1.00	–
High normal (SBP<140, DBP<90)	1.36	1.06–1.76
Stage I HTN (SBP<160, DBP<100)	1.55	1.23–1.97
Stage II–IV HTN (SBP 160, DBP 100)	1.34	0.89–2.04
Total cholesterol level (mg/dL)		
<160	0.77	0.47–1.26
160–199	1.00	–
200–239	1.87	1.47–2.38
240–279	2.89	2.22–3.75
280	3.03	2.14–4.31
HDL-C level (mg/dL)		
<35	1.82	1.35–2.46
35–44	1.33	1.01–1.76
45–49	1.00	–
50–59	0.89	0.64–1.23
60	0.64	0.43–0.96
Diabetes	3.54	2.31–5.42
Current smoking	1.51	1.22–1.87

[a]DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; HR ¼ hazard ratio; HTN = hypertension; SBP = systolic blood pressure.

[b]SI conversion factor: To convert mg/dL values to mmol/L, multiply by 0.0259.

TABLE 3

Crude and Adjusted Associations Between CRF, FRS, and CHD[a]

Risk factor	Model 1: Univariate model		Model 2[b]: Multivariable model	
	HR	95% CI	HR	95% CI
10-y CHD risk[c]				
Low	1.00	–	1.00	–
Moderate or high	5.66	4.25–7.55	5.38	4.03–7.19
CRF				
Low 1.00		–	1.00	–
Moderate	0.93	0.71–1.22	0.98	0.75–1.30
High	0.67	0.51–0.88	0.74	0.56–0.98

[a]CHD = coronary heart disease; CRF = cardiorespiratory fitness; FRS = Framingham Risk Score; HR = hazard ratio.

[b]Model 2 investigates the association between CRF (categorized into low, moderate, and high) and CHD events while controlling for moderate or high 10-y CHD risk and baseline examination year.

[c]Low or moderate or high 10-y CHD risk is a comparative risk calculated from the summation of FRS points. Moderate or high risk is defined as a sum of >5 points.