Influences of Cardiorespiratory Fitness and Other Precursors on Cardiovascular Disease and All-Cause Mortality in Men and Women

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Objective.—To quantify the relation of cardiorespiratory fitness to cardiovascular disease (CVD) mortality and to all-cause mortality within strata of other personal characteristics that predispose to early mortality.

Design.—Observational cohort study. We calculated CVD and all-cause death rates for low (least fit 20%), moderate (next 40%), and high (most fit 40%) fitness categories by strata of smoking habit, cholesterol level, blood pressure, and health status.

Setting.—Preventive medicine clinic.

Study Participants.—Participants were 25,341 men and 7,080 women who completed preventive medical examinations, including a maximal exercise test.

Main Outcome Measures.—Cardiovascular disease and all-cause mortality.

Results.—There were 681 deaths during 211,996 man-years of follow-up, and 89 deaths during 52,982 woman-years of follow-up. Independent predictors of mortality among men, with adjusted relative risks (RRs) and 95% confidence intervals (CIs), were low fitness (RR, 1.52; 95% CI, 1.28-1.82), smoking (RR, 1.65; 95% CI, 1.39-1.97), abnormal electrocardiogram (RR, 1.64; 95% CI, 1.34-2.01), chronic illness (RR, 1.63; 95% CI, 1.37-1.95), increased cholesterol level (RR, 1.34; 95% CI, 1.13-1.59), and elevated systolic blood pressure (RR, 1.34; 95% CI, 1.13-1.59). The only statistically significant independent predictors of mortality in women were low fitness (RR, 2.10; 95% CI, 1.36-3.21) and smoking (RR, 1.99; 95% CI, 1.25-3.17). Inverse gradients were seen for mortality across fitness categories within strata of other mortality predictors for both sexes. Fit persons with any combination of smoking, elevated blood pressure, or elevated cholesterol level had lower adjusted death rates than low-fit persons with none of these characteristics.

Conclusions.—Low fitness is an important precursor of mortality. The protective effect of fitness held for smokers and nonsmokers, those with and without elevated cholesterol levels or elevated blood pressure, and unhealthy and healthy persons. Moderates fitness seems to protect against the influence of these other predictors on mortality. Physicians should encourage sedentary patients to become physically active and thereby reduce the risk of premature mortality.

THE RELATION of physical inactivity to various health problems is well established. Biological mechanisms that contribute to the lower risk associated with activity include improved lipoprotein profile and carbohydrate metabolism, lower blood pressure, and weight loss. The inverse association between physical activity or cardiological fitness and disease remains after statistical adjustment for these and other potentially confounding variables.

Lower death rates associated with regular physical activity are consistent in different populations. However, these studies were not specifically designed to investigate thoroughly the relation of activity or fitness to mortality within various risk groups, nor to compare systematically the strength of association of low activity or fitness with the strength of other mortality predictors. Examination of such relations will allow assessment of possible effect modification of fitness and other mortality predictors. We extended observations in the Aerobics Center Longitudinal Study by quantifying the relation of fitness to risk of cardiovascular disease (CVD) and all-cause mortality within strata of other predictors of early mortality and compared the strengths of associations between fitness and other predictors of mortality.

SUBJECTS AND METHODS

Study Participants

Study participants were 25,341 men and 7,080 women who ranged in age from 20 to 88 years at baseline and completed a preventive medical examination between December 6, 1970, and December 31, 1980.
All study participants were residents of the United States, had complete data from the medical examination, and achieved at least 85% of their age-predicted maximal heart rate (220 minus age in years) during the treadmill test. Most study participants were apparently healthy at baseline, although 1986 men and 350 women had an abnormal resting or exercise electrocardiogram (ECG), and 4892 men and 958 women reported a history of 1 or more of the following chronic illnesses at baseline: myocardial infarction, stroke, hypertension, diabetes mellitus, or cancer.

Clinical Examination

The baseline evaluation was performed after participants gave their informed written consent for the medical examination and subsequent registration in the follow-up study. Examinations followed an overnight fast of at least 12 hours and included a personal and family health history, a physical examination, a questionnaire on demographic characteristics and health habits, anthropometry, resting ECG, blood chemistry analyses, blood pressure measurement, and a standardized maximal exercise test on a motor-driven treadmill. All procedures were administered by technicians who followed a standard manual of operations.

Height and weight were measured on a standard physician’s scale and stadiometer, and body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressures were measured by auscultatory methods with a mercury sphygmomanometer. Serum samples were analyzed by automated techniques in a laboratory participating in the Centers for Disease Control and Prevention Lipid Standardization Program. Current smokers or those who quit smoking within 2 years of the examination were classified as smokers, and those who had never smoked or had quit smoking more than 2 years before the examination were classified as nonsmokers. We adopted this conservative definition of smoking status because some smokers may have quit temporarily in preparation for the examination, and mortality risk for recent quitters is similar to that of continuing smokers.

We measured participants’ cardiorespiratory fitness with a maximal exercise test following a standard protocol. Specific details of treadmill speed and elevation have been described. Exercise test performance with this protocol correlates highly (r>0.92) with measured maximal oxygen uptake. The advantage in using fitness in this study is that, although there is a genetic component, fitness is determined primarily by exercise habits and is measured more objectively than self-report of physical activity, thus reducing misclassification bias.

Mortality Surveillance

We followed up study participants for mortality from the date of their baseline examination to the date of death for decedents, or to December 31, 1989, for survivors. We used the National Death Index to identify possible decedents and then retrieved official death certificates from 44 states for those study participants. The underlying cause and up to 4 contributing causes of death were coded by a nosologist according to the International Classification of Diseases, Ninth Edition, Revised, with CVD mortality defined as codes 390 to 449.9.

Data Analysis

Treadmill time at the baseline examination was used to group study participants into fitness categories based on age-and sex-specific cutoffs. The least fit 20% of participants in each age-sex group were classified as low fit, the next 40% as moderately fit, and the remaining 40% as high fit. Participants were classified as healthy unless they reported chronic illnesses or had an abnormal ECG at baseline. Indicators of high- and low-risk categories of other variables were based on standard cutoffs. Log-linear proportional hazards models were used to estimate relative risks (RRs) of CVD and all-cause mortality separately for men and women. Cox partial likelihood methods were used to fit all models, providing point estimates, 95% confidence intervals (CIs), and hypothesis tests. Survival time in days was counted from the day of examination until death or end of observation on December 31, 1989. Mortality rates per 10,000 person-years of observation are reported as adjusted by Cox regression. All reported P values are 2-sided.

RESULTS

The average follow-up interval from baseline examination to date of death or to December 31, 1989, was 8.4 years (range, 0.1-19.1 years) in men and 7.5 years (range, 0.1-18.9 years) in women. In men, 601 deaths occurred during 211,996 manyears of observation, with 225 deaths from CVD. In women, 89 deaths occurred during 52,982 woman-years of follow-up, with 21 deaths from CVD. Baseline descriptive characteristics of the study group are shown in Table 1.

Adjusted death rates and RRs for CVD mortality and all-cause mortality among men and women are shown in Table 2 and Table 3, respectively. Data are given for low cardiorespiratory fitness and 8 other predictors of early death. Low fitness, cigarette smoking, elevated systolic blood pressure, elevated serum cholesterol level, and poor health status (abnormal ECG or chronic illness) were associated significantly with CVD mortality and all-cause mortality in men. Low fitness and smoking were related significantly to all-cause mortality in women. Only elevated fasting glucose level and abnormal ECG were associated with CVD mortality in women, although low fitness was borderline.
Table 2.—Cardiovascular Disease Mortality and All-Cause Mortality Risk Analyses for Selected Mortality Predictors, Men, Aerobics Center Longitudinal Study, 1970 Through 1989*  

<table>
<thead>
<tr>
<th>Mortality Predictor</th>
<th>Cardiovascular Disease</th>
<th>All Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Subjects</td>
<td>Person-Years of Follow-up (% of Person-Years)</td>
</tr>
<tr>
<td>Low fitness (20% least fit)</td>
<td>5223</td>
<td>54,729 (26)</td>
</tr>
<tr>
<td>Current or recent smoker</td>
<td>6730</td>
<td>60,829 (29)</td>
</tr>
<tr>
<td>Systolic blood pressure ≥140 mm Hg</td>
<td>2759</td>
<td>26,399 (12)</td>
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<tr>
<td>Cholesterol ≥6.2 mmol/L (≥240 mg/dL)</td>
<td>6025</td>
<td>51,262 (24)</td>
</tr>
<tr>
<td>Either parent dead of coronary heart disease</td>
<td>6499</td>
<td>53,440 (25)</td>
</tr>
<tr>
<td>Body mass index ≥27 kg/m²</td>
<td>8198</td>
<td>65,534 (31)</td>
</tr>
<tr>
<td>Fasting glucose ≥8.7 mmol/L (≥120 mg/dL)</td>
<td>1356</td>
<td>13,229 (6)</td>
</tr>
<tr>
<td>Abnormal electrocardiogram</td>
<td>1866</td>
<td>15,660 (7)</td>
</tr>
<tr>
<td>Chronic ill health</td>
<td>4802</td>
<td>41,016 (19)</td>
</tr>
<tr>
<td>Total</td>
<td>25,341</td>
<td>211,999 (100)</td>
</tr>
</tbody>
</table>

*All comparisons are dichotomies, with the referent category being the low-risk group (relative risk = 1), and the high-risk group data shown in the table. Data for the reference categories are not included, but can be estimated for each predictor by subtracting the values in the table for the high-risk group from the totals (25,341 men, 211,996 men-years, 601 deaths from all causes, 226 deaths from cardiovascular disease, 7,000 women, 52,982 woman-years, 69 deaths from all causes, 21 from cardiovascular disease). Ellipses indicate not applicable.  
†Adjusted for age and examination year.  
‡Adjusted for age, examination year, and each of the other variables in the table.  
§Crude rate.

Table 3.—Cardiovascular Disease Mortality and All-Cause Mortality Risk Analyses for Selected Mortality Predictors, Women, Aerobics Center Longitudinal Study, 1970 Through 1989*  

<table>
<thead>
<tr>
<th>Mortality Predictor</th>
<th>Cardiovascular Disease</th>
<th>All Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Subjects</td>
<td>Person-Years of Follow-up (% of Person-Years)</td>
</tr>
<tr>
<td>Low fitness (20% least fit)</td>
<td>1352</td>
<td>13,066 (25)</td>
</tr>
<tr>
<td>Current or recent smoker</td>
<td>1321</td>
<td>10,811 (20)</td>
</tr>
<tr>
<td>Systolic blood pressure ≥140 mm Hg</td>
<td>416</td>
<td>3959 (7)</td>
</tr>
<tr>
<td>Cholesterol ≥6.2 mmol/L (≥240 mg/dL)</td>
<td>1223</td>
<td>9034 (7)</td>
</tr>
<tr>
<td>Either parent dead of coronary heart disease</td>
<td>1768</td>
<td>13,474 (25)</td>
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<tr>
<td>Body mass index ≥27 kg/m²</td>
<td>777</td>
<td>5486 (10)</td>
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<tr>
<td>Fasting glucose ≥8.7 mmol/L (≥120 mg/dL)</td>
<td>148</td>
<td>1202 (2)</td>
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<tr>
<td>Abnormal electrocardiogram</td>
<td>350</td>
<td>2816 (5)</td>
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<tr>
<td>Chronic ill health</td>
<td>958</td>
<td>7085 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>7080</td>
<td>52,982 (100)</td>
</tr>
</tbody>
</table>

*All comparisons are dichotomies, with the referent category being the low-risk group (relative risk = 1), and the high-risk group data shown in the table. Data for the reference categories are not included, but can be estimated for each predictor by subtracting the values in the table for the high-risk group from the totals (25,341 men, 211,996 men-years, 601 deaths from all causes, 226 deaths from cardiovascular disease, 7,000 women, 52,982 woman-years, 69 deaths from all causes, 21 from cardiovascular disease). Ellipses indicate not applicable.  
†Adjusted for age and examination year.  
‡Adjusted for age, examination year, and each of the other variables in the table.  
§Crude rate.

statistical significance (P=.05). Among women, smoking and elevated blood pressure have RRs for CVD mortality that are similar in magnitude to those for men. Failure to observe significant RRs for these variables may be due to low statistical power resulting from the small number of CVD deaths in women. The increased mortality risk in low-fit men and women is one of the strongest antecedents of mortality seen in these analyses.  

We next calculated death rates for all-cause mortality in cross-tabulation analyses, using 3 levels of cardiorespiratory fitness and 2 categories of the other mortality predictors. Results for men are shown in Figure 1 for fitness categories by smoking, systolic blood pressure, serum cholesterol level, and health status. An inverse gradient of risk was seen across fitness groups...
within each stratum of the other predictors, a lower death rate in both strata of each of the other predictors for moderately fit men when compared with low-fit men, and an even lower rate for high-fit men. The reduced risk for all-cause mortality in the high-fit men compared with the low-fit men ranged from 32% for elevated systolic blood pressure to 50% for elevated cholesterol level and poor health status. We performed similar analyses for fitness stratified by fasting glucose level, family history, and body mass index. Results were similar to those shown in Figure 1, i.e., inverse gradients of risk were seen across fitness categories in both strata of each of these other predictors (data not shown). The association of fitness to mortality was similar and was statistically significant in both strata of each of these variables.

We conducted similar cross-tabulation analyses in men for fitness and other mortality predictors with CVD as the outcome. Results (data not shown) were similar to those for the all-cause mortality analyses, except that fitness was not associated with CVD mortality in men with systolic blood pressure 140 mm Hg or higher. The trends across fitness categories were significantly different (P = .005) in men who had normal blood pressure compared with men who had elevated systolic blood pressure.

Figure 2 shows cross-tabulations of fitness to other risk characteristics in relation to all-cause mortality in women, with results that are consistent with those observed in men. For each of the predictors considered, the moderate- and high-fit women in each stratum had lower death rates than the low-fit women, although the rates were more unstable due to the smaller number of deaths. High-fit women with elevated cholesterol levels had a 25% lower risk of death than low-fit women, which was the smallest difference in risk between high- and low-fit women. The largest difference in risk for the high-fit women was in those with systolic blood pressure of 140 mm Hg or greater, who had an 81% lower risk of all-cause mortality when compared with low-fit women. Differences in risk for other subgroups were between these extremes. Too few CVD deaths occurred in women to reliably perform these analyses for the end point of CVD death.

We calculated death rates for cross-tabulations of fitness by presence or absence of nonspecific combinations of the 3 other major CVD mortality predictors: cigarette smoking, high blood pressure, and high cholesterol level. Standard categories were used to identify high risk status for the other predictors (current or recent smoking, systolic blood pressure of ≥140 mm Hg, and cholesterol level of ≥6.2 mmol/L [240 mg/dL]). Participants were grouped in 5 risk categories based on the total number of the other predictors that were present (0, any 1, or any 2 out of 3), which then were cross-tabulated with the 3 fitness categories.

Figure 3 shows the results for all-cause mortality, which were consistent for men and women. The analyses for women are shown for 2 cardiopulmonary fitness categories (moderate- and high-fitness categories combined) because of the small number of deaths. A higher cumulative total of other predictors was associated with increased risk in each fitness category. A graded inverse trend of death rates was seen from low to high fitness within strata of the number of other risk factors. We observed a large difference in risk between the highest and lowest
risk groups. For example, in men, multivariable adjusted death rates were 57.3 per 10,000 man-years of observation in low-fit men with 2 or 3 risk factors, and 17.6 per 10,000 man-years in high-fit men with none of the other risk factors. The RR for these 2 contrasting groups was 3.25 (95% CI, 2.28-4.69), and the RR for the same groups of women was 4.18 (95% CI, 1.78-9.78). High-fit men with 2 or 3 of the other predictors had a 15% lower death rate than low-fit men with none of the other predictors. Similar data for women were even more striking; the adjusted all-cause death rate was 31.6 per 10,000 woman-years of observation in the low-fit women with no other predictors, whereas fit women with 2 or 3 predictors had a death rate of 16.1 per 10,000, ie, almost 50% lower.

COMMENT

Three principal observations from the analyses presented herein from this group of well-educated men and women deserve notice, although the extent to which the results can be extended to other populations is unknown. First, the inverse gradient of mortality rates across fitness categories was consistent in various strata of the other mortality predictors. The general pattern was that of a considerably lower death rate in moderately fit men and women compared with those in the low-fit group. Adjusted all-cause death rates were from 17% to 39% lower in moderately fit mean compared with low-fit men who smoked cigarettes, had elevated blood pressure, elevated cholesterol levels, or were unhealthy. The lower mortality rates for similar analyses for women ranged from 48% to 67%. For most analyses, we found an even lower risk for high-fit participants compared with moderately fit participants.

Men and women with normal levels of the other mortality predictors also benefited from being in the moderate fitness category compared with the low-fit category. Moderately fit men who were nonsmokers had a 41% lower all-cause death rate than those who were in the corresponding low-fit category. Similar data for the other predictors showed lower death rates of 39% in those with normal blood pressure, 27% in those with normal cholesterol level, and 33% in the healthy group. Compared with low-fit women, moderately fit women had lower all-cause death rates of 55% in nonsmokers, 54% in normotensives, 56% in those with normal cholesterol levels, and 46% in the healthy group.

The second major finding of our analyses was the substantial strength and independence of low cardiorespiratory fitness as a precursor for CVD and all-cause mortality. The RRs for low fitness were among the highest seen in our analyses. The adjusted RRs of all-cause mortality due to low fitness (1.52) and cigarette smoking (1.65) were similar in men. The RR for these 2 characteristics was approximately 2 in women. These results are consistent with our earlier finding that becoming fit has a similar effect on reduction in mortality to stopping smoking. In comparison, other significant precursors of all-cause mortality in men, elevated blood pressure and cholesterol levels, had RRs of about 1.3. In men, low fitness had a strong association with CVD mortality (RR, 1.70), and was similar to elevated cholesterol level (RR, 1.65).

The third major finding was that moderate and high levels of cardiorespiratory fitness seem to provide protection against the force of combinations of other mortality predictors on deaths (Figure 3). Death rates were higher in persons
Cardiorespiratory fitness and all-cause mortality by the number of multiple risk factors in 25,341 men (top) and 7,080 women (bottom) in the Aerobics Center Longitudinal Study. Height of the bars shows all-cause death rates adjusted for age, year of baseline examination, chronic illness (myocardial infarction, stroke, diabetes, hypertension, or cancer), abnormal electrocardiogram, parental history of death of coronary heart disease, fastigio blood glucose level, and body mass index. Numbers in the bars represent the number of deaths. Cardiorespiratory fitness categories for men are low fitness, least fit 20%; moderate fitness, next 40%; and high fitness, most fit 40% for women, the moderate and high fitness categories are combined. The 3 categories of multiple risk factors are none, 1, and 2 or 3 all among current or recent smoking, total cholesterol level of 6.2 mmol/L (240 mg/dL) or higher, and systolic blood pressure of 140 mm Hg or higher.

with multiple risk factors, but fitness was inversely associated with death rates in persons who had no other predictors or had any 1, and in those with any 2 or all 3 predictors. High-fit persons with multiple predictors had lower death rates than low-fit persons who had no other predictors.

Previous studies show that regular exercise improves cardiorespiratory fitness, and has a beneficial effect on blood pressure, lipoprotein profile, and glucose tolerance, and thus should be considered therapeutic in persons with abnormalities of these risk factors. Physicians and patients sometimes become discouraged when a patient begins an exercise program in an attempt to reduce weight, lower blood pressure, or reduce cholesterol levels and, despite good adherence to exercise, the clinical variable fails to improve. Our study underscores the strong, graded, and independent association of fitness with CVD and all-cause mortality. Whether our subjects were unhealthy or healthy, smokers or nonsmokers, had elevated blood pressure or increased cholesterol levels or normal values for these variables, were obese or had normal weights, did or did not have a family history of coronary heart disease, or had combinations of other mortality predictors or were at low risk by standard criteria, all seemed to benefit from being moderately or highly fit compared with low-fit men and women of like risk profile. We believe that physicians should counsel all of their sedentary patients to become more physically active and improve their cardiorespiratory fitness.

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References