

Changes in Physical Fitness and All-Cause Mortality

A Prospective Study of Healthy and Unhealthy Men

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Objective.—To evaluate the relationship between changes in physical fitness and risk of mortality in men.

Design.—Prospective study, with two clinical examinations (mean interval between examinations, 4.9 years) to assess change or lack of change in physical fitness as associated with risk of mortality during follow-up after the subsequent examination (mean follow-up from subsequent examination, 5.1 years).

Setting.—Preventive medicine clinic.

Study Participants.—Participants were 9777 men given two preventive medical examinations, each of which included assessment of physical fitness by maximal exercise tests and evaluation of health status.

Main Outcome Measures.—All-cause (n=223) and cardiovascular disease (n=87) mortality.

Results.—The highest age-adjusted all-cause death rate was observed in men who were unfit at both examinations (122.0/10 000 man-years); the lowest death rate was in men who were physically fit at both examinations (39.6/10 000 man-years). Men who improved from unfit to fit between the first and subsequent examinations had an age-adjusted death rate of 67.7/10 000 man-years. This is a reduction in mortality risk of 44% (95% confidence interval, 25% to 59%) relative to men who remained unfit at both examinations. Improvement in fitness was associated with lower death rates after adjusting for age, health status, and other risk factors of premature mortality. For each minute increase in maximal treadmill time between examinations, there was a corresponding 7.9% ($P=.001$) decrease in risk of mortality. Similar results were seen when the group was stratified by health status, and for cardiovascular disease mortality.

Conclusions.—Men who maintained or improved adequate physical fitness were less likely to die from all causes and from cardiovascular disease during follow-up than persistently unfit men. Physicians should encourage unfit men to improve their fitness by starting a physical activity program.

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LOW LEVELS of physical fitness are associated with an increased risk of all-cause and cardiovascular disease (CVD) mortality, with age-adjusted relative risks (RRs) of CVD up to eightfold greater for unfit groups than their fit counterparts.¹⁻¹⁰ The increased risk among unfit individu-

als is substantially greater than the risk reported for inactive participants in studies of physical activity and mortality, in which an approximate doubling of risk is seen when inactive groups are compared with active groups.¹¹ Physical fitness (a condition) is measured more objectively and with greater reliability than physical activity (a behavior), which may account for the differences in the strength of the relationship between these two exposures and mortality.

Studies on fitness and mortality have relied on a single baseline assessment of fitness, with subsequent follow-up for mortality.^{1-5,7,8,10} With single exposure assessments, it is difficult to discount the hypothesis that genetic factors or other confounding variables are an important cause of the relationship between fitness and mortality. Moreover, changes in the variable of interest during follow-up may affect the subsequent risk of mortality. One way to examine this issue more completely is to evaluate the effect of changes in physical fitness on risk of mortality. Extended follow-up in the Aerobics Center Longitudinal Study provides an opportunity to evaluate the relationship of changes in physical fitness with mortality in a cohort of men with two clinical examinations and subsequent follow-up for mortality. We tested the hypothesis that changes in physical fitness, especially in men with an initial low level of fitness, produced changes in risk of mortality.

SUBJECTS AND METHODS

Subjects and Design

Study participants were 9777 men, ranging in age from 20 to 82 years at

baseline, who completed at least two preventive medical examinations at the Cooper Clinic in Dallas, Tex, from December 1970 through December 1989. Although women are included in the cohort there are too few women in the study with two examinations to perform the analyses reported herein.¹² All study subjects were residents of the United States, had complete examinations at both visits, and achieved at least 85% of their age-predicted maximal heart rate (220 - age [years]) during both treadmill tests. A total of 268 men were excluded because of failure to achieve the maximal heart rate criterion; 140 were excluded at baseline, and an additional 128 were excluded for failing to reach 85% or more of age-predicted maximal heart rate at the subsequent examination.

Analyses were performed in the entire population and within health status subgroups. The 6819 men who had normal resting and exercising electrocardiograms, and no history or evidence of myocardial infarction, stroke, diabetes, or hypertension at both examinations, were defined as the apparently healthy subgroup. Men with one or more of these conditions at either or both of the examinations were classified as unhealthy. The 2958 unhealthy men had a total of 3836 chronic conditions because some men had more than one condition. The distribution of conditions in this group was as follows: myocardial infarction, 178; hypertension, 1733; diabetes mellitus, 374; cancer, 192; abnormal resting electrocardiogram, 861; and abnormal exercise electrocardiogram, 498.

The average (\pm SD) interval between the two examinations was 4.9 ± 4.1 years (range, 1 to 18 years). Follow-up for mortality after the subsequent examination was an average of 5.1 ± 4.2 years (range, 1 to 18 years) (total follow-up, 47 560 man-years). These intervals were comparable for the health status groups. The interval between examinations was 4.8 ± 4.0 years in healthy men and 5.2 ± 4.3 years in unhealthy men. Follow-up was 4.7 ± 4.0 and 5.2 ± 4.4 years, respectively, in the healthy and unhealthy groups.

Clinical Examination

The study protocol was reviewed and approved annually by the Institutional Review Board. After patients gave their written informed consent and subsequent registration in a follow-up study, examinations followed an overnight fast of at least 12 hours. Components of the examination included a self-administered personal and family medical history, including demographic factors and health behavior, a physical examination by a physician, anthropometry, blood pressure measurement, and blood chemis-

try analyses. All patients completed a maximal treadmill exercise test, which included measurement of resting and exercising electrocardiograms and blood pressures. Trained laboratory technicians, with physician supervision, administered the assessments in accord with a standard manual of operations. Details of examination procedures have been published elsewhere.¹²

The primary exposure variable for the analyses presented herein is the level of physical fitness. As used in this report, *physical fitness* refers to exercise test tolerance to a standard treadmill protocol,¹³ and treadmill test duration was the variable used in the present analyses. Test time with this protocol is highly correlated with measured maximal oxygen uptake ($r = .92$ in men¹⁴); thus, physical fitness in this report is analogous to aerobic power.

Blood pressures were measured by auscultatory techniques with a mercury sphygmomanometer. Diastolic pressure was recorded as the disappearance of sound. Serum samples were analyzed by automated methods for lipids and glucose. Weight and height were measured on a standard physicians' balance beam scale and stadiometer. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Cigarette smoking habits, alcohol intake, health behaviors, and family medical histories were self-assessed by questionnaire at the time of the examinations. Data on medication use in the cohort are incomplete and are not included in the analyses presented herein.

To evaluate the hypothesis that changes in fitness are caused by changes in self-reported activity, we computed change in treadmill time for self-reported physical activity habits during the month before the clinical examination in the subgroup of men who were examined after January 1, 1987. There were 1512 men available for analysis who had two complete examinations. A three-category physical activity index was computed for each man. Men who reported no leisure-time physical activity received an activity score of 0, those who played sports or walked or ran up to 16.1 km (10 miles) a week a score of 1, and those who walked or ran more than 16.1 km (>10 miles) a week a score of 2. The index was computed for each of the two examinations, and a change in activity score was obtained for each subject. Average change (adjusted for age and follow-up interval) in treadmill test time from the first to the subsequent examination was 8 seconds for men who had no increase in activity, 41 seconds for men who increased their activity by one category on the physical activity index, and 93

seconds for men who had a two-category change in the physical activity index. Each of these adjusted means was significantly different from the others ($P < .001$), thereby supporting our assumption that change in fitness is an overall marker for change in activity.

Mortality Surveillance

We followed up participants for mortality from the second examination to the date of death or to December 31, 1989.

Mortality follow-up was accomplished by means of the National Death Index. Possible decedents were identified by the National Death Index, and this list was reviewed by three of us (S.N.B., H.W.K., and C.E.B.). This process identified individuals from 44 states for retrieval of death certificates. We then contacted the department of vital statistics in each of these states and requested copies of the official death certificates. We compared information on the death certificates with clinical records to confirm that the death certificate pertained to that individual. The underlying cause of death was coded by a nosologist according to the *International Classification of Diseases, Ninth Edition, Revised*, with CVD defined for the analyses presented herein as codes 390 to 449.9.

Data Analysis

Previous follow-up studies of this cohort show that age-adjusted all-cause mortality is substantially higher in the first (least fit) quintile than in the second.¹² Therefore, for categoric analyses, unfit is defined as the least fit quintile and fit refers to all others (quintiles 2 through 5). Quintile cutoff points for each age group were established by means of measurements from the first examination (data not shown). Treadmill time cutoff points and associated units of work metabolic rate divided by resting metabolic rate (METs) for the unfit category were less than 14.0 minutes (10.0 METs) for men aged 20 to 39 years, less than 12.0 minutes (9.2 METs) for men aged 40 to 49 years, less than 10.0 minutes (8.4 METs) for men aged 50 to 59 years, and less than 6.7 minutes (7.0 METs) for men aged 60 years and older. We also analyzed change in fitness as a continuous variable in proportional hazards regression models, where change was calculated for each participant by subtracting the treadmill time in minutes of the first test from that of the final test.

Kaplan-Meier¹⁵ survival curves were generated to evaluate the survival experience of initially unfit men who either remained unfit or became fit. Mortality rates were calculated for men who

Table 1.—Baseline Characteristics From First Examination of 9777 Men, Aerobics Center Longitudinal Study, 1970 Through 1989*

Characteristic	All Men		Healthy Men (n=6819)	Unhealthy Men (n=2958)
	Survivors (n=9554)	Decedents (n=223)		
Age, y	43.0±9.2	51.4±10.4	41.7±8.8	46.8±9.6
Weight, kg	82.4±11.5	81.9±12.2	81.7±11.1	83.7±12.3
Body mass index, kg/m ²	25.7±3.1	25.8±3.1	25.4±3.0	26.3±3.4
Total cholesterol, mmol/L (mg/dL)	5.5±1.3 (213±50)	5.9±1.1 (228±43)	5.4±1.4 (209±54)	5.7±1.1 (220±43)
Resting blood pressure, mm Hg				
Systolic	120.9±13.3	127.5±16.6	118.4±11.9	127.1±14.8
Diastolic	80.3±9.3	83.6±11.6	78.7±8.5	84.3±10.0
Peak treadmill duration, min	18.0±4.8	14.1±5.0	18.7±4.7	16.3±4.8
METs†	11.7±2.0	10.1±2.1	12.0±1.9	11.0±2.0
Cigarette smoking, %	16.5	20.2	16.4	17.1

*Data are mean±SD.

†Work metabolic rate/resting metabolic rate; peak value achieved during the maximal exercise treadmill test.

either changed or remained unchanged in physical fitness status as deaths per 10 000 man-years of observation. Rates were age adjusted by the direct method with the entire population used as the standard. Age groups used in the adjustment were 20 to 39 years, 40 to 49 years, 50 to 59 years, and 60 or more years. The RR of death for fitness and fitness change was calculated by means of the age-adjusted rates, with the men unfit at both examinations as the reference category. Multivariate statistical models using proportional hazards regression were constructed to calculate adjusted RR¹⁶ for both all-cause and CVD mortality. These models included age to the nearest year; interval between examinations in years; baseline physical fitness level; change in fitness level; baseline values for weight, resting systolic blood pressure, serum cholesterol, fasting blood glucose, cigarette smoking habit; and family history of coronary heart disease. Furthermore, a binary variable indicating health status (healthy or unhealthy) was added in analyses of the total population. Data on change in risk factors were examined in additional models. The 95% confidence intervals (CIs) around all point estimates also were calculated.¹⁷

RESULTS

Results reported herein are from 9777 men with at least two complete examinations during the study period. There were 223 deaths (103 in healthy men and 120 in unhealthy men) during 47 561 man-years of observation, and 87 deaths were caused by CVD. Baseline characteristics of survivors and decedents and for the healthy and unhealthy subgroups at the first examination are shown in Table 1. Because of the 8.4-year average age difference between survivors and decedents, age-adjusted data (not shown) also

were calculated. This had little effect on the means and SDs, although the differences between survivors and decedents narrowed slightly for all variables. Decedents were older and less physically fit and generally had less favorable risk profiles than survivors. There were differences between the healthy and unhealthy cohorts for several clinical characteristics, including weight, total cholesterol, and blood pressure.

Figure 1 shows survival curves for men who were unfit at both examinations and men who were unfit at the first examination but improved to be classified as fit at the subsequent examination. The persistently unfit men had lower probability of survival. The survival curves diverge continuously throughout the 18 years of follow-up.

Age-adjusted all-cause and CVD death rates for fitness categories are shown in Table 2. Men who were unfit at both visits had the highest death rate, men who were fit at both visits had the lowest death rate, and men who changed fitness status had intermediate rates. Overall, men who were initially unfit and became fit had a 44% lower age-adjusted risk of all-cause mortality (RR, 0.56; 95% CI, 0.41 to 0.75) and a 52% lower age-adjusted risk of CVD mortality (RR, 0.48; 95% CI, 0.31 to 0.74) than their peers who remained unfit. Because 75% to 82% of the man-years of observation and a large proportion of deaths were in the group of men who were fit at both examinations, we performed additional analyses to evaluate the possibility that there might be a gradient of change in risk with the amount of fitness change in the initially fit group. Table 2 also shows the death rates for fit men who improved from fitness quintile 2 or 3 to quintile 4 or 5, and for men who were in quintile 4 or 5 at both examinations. Men in quintile 2 or 3 at both examinations constitute the ref-

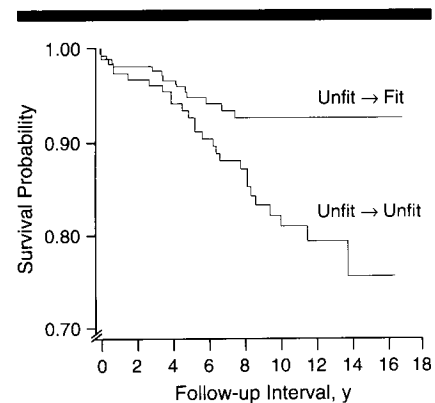


Figure 1.—Survival curves for change or lack of change in physical fitness in all men. The lower line represents survival experience in men in the least fit quintile at both examinations; upper line, men who were unfit at baseline but became fit (quintiles 2 through 5) by the final examination.

erence category. The men who were initially fit and further improved their fitness level had a 15% lower risk of death from all causes than men in the reference category, whereas the men in quintiles 4 or 5 at both examinations were at the lowest risk (RR, 0.71; 95% CI, 0.46 to 1.09). Corresponding figures for CVD mortality were 28% lower risk for men who improved their fitness, whereas persistently highly fit men had the lowest risk (RR, 0.48; 95% CI, 0.23 to 1.01).

We examined the relationship between fitness change groups and all-cause mortality within specific age groups (Figure 2). Men who were initially unfit and became fit by the subsequent examination had lower death rates than men who were unfit at both examinations. Death rates for those who increased their fitness ranged from 33% lower than for those who remained unfit in the 40- to 49-year age group to more than 70% lower than for those who remained unfit in the 20- to 39-year and 50- to 59-year age groups. Men aged 60 years and older who improved their fitness had death rates 50% lower than those of the persistently unfit men. For each age group, men who were fit at both examinations experienced the lowest death rates.

Proportional hazards regression analyses showed that improved physical fitness was associated significantly with lower adjusted risks of all-cause and CVD mortality (Figure 3). Results are consistent for all-cause and CVD mortality, and in healthy and unhealthy men. Changes in other risk factors did not add significantly to the prediction of mortality and thus were excluded from the final models presented herein. After adjustment for potential confounders, each minute increase in treadmill time from the first to the subsequent visit was

Table 2.—Continuities and Changes in Physical Fitness and Age-Adjusted, All-Cause, and Cardiovascular Disease Mortality in 9777 Men, Aerobics Center Longitudinal Study, 1970 Through 1989

Physical Fitness		Man-Years (MY) of Follow-up	No. of Men	No. of Deaths	Age-Adjusted Death Rate/10 000 MY	Relative Risk	95% Confidence Interval
1st Examination	2nd Examination						
All Cause							
Unfit*	Unfit	2937	373	32	122.0	1.00	...
Unfit	Fit†	4054	650	25	67.7	0.56	0.41-0.75
Fit	Unfit	1624	221	9	63.3	0.52	0.38-0.70
Fit	Fit	38 946	8533	157	39.6	0.33	0.23-0.47
Cardiovascular Disease							
Unfit	Unfit	2826	356	15	65.0	1.00	...
Unfit	Fit	4017	638	13	31.4	0.48	0.31-0.74
Fit	Unfit	1594	215	3	27.9	0.43	0.28-0.67
Fit	Fit	38 572	8432	56	14.2	0.22	0.12-0.39
Quintiles							
2-3	2-3	9759	1506	46	48.6	1.00	...
2-3	4-5	6748	1517	25	41.3	0.85	0.56-1.29
4-5	4-5	19 713	5025	69	34.4	0.71	0.46-1.09

*Quintile 1 of age-specific fitness distribution.

†Quintiles 2 through 5 of age-specific fitness distribution.

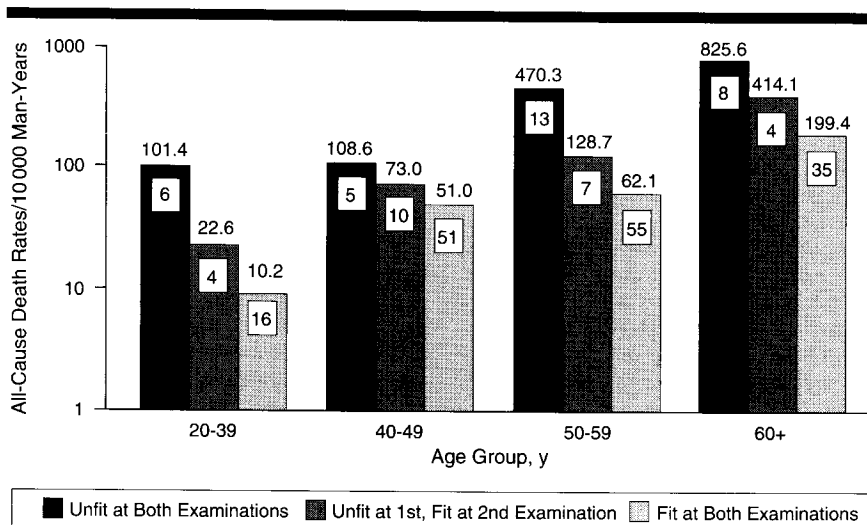


Figure 2.—All-cause death rates per 10 000 man-years (log scale) in 9777 men by age groups and change or lack of change in physical fitness. Death rates are shown atop the bars and the numbers of deaths within the bars.

associated with a reduction in risk of mortality of 7.9% ($P=.001$) for all-cause mortality and 8.6% ($P=.027$) for CVD mortality in the analyses for all men combined. A 4-minute increase in treadmill time with this protocol is equivalent to an increase of approximately 2 METs or 7.0 mL/kg per minute in maximum oxygen consumption, a degree of improvement typically seen in exercise training programs. An increase in treadmill time of 4 minutes in the current study was associated with an estimated reduction of approximately 30% in mortality risk after other variables in the model were taken into account.

Although the proportional hazards analyses statistically adjusted for health

status, subclinical disease at baseline potentially might confound these results by adversely affecting fitness and also increasing risk of mortality. To evaluate this possibility further, we performed analyses on subgroups of the cohort who died within 3 years of follow-up and compared them with men who died more than 3 years after the subsequent examination. When compared with men who were unfit at both examinations, the men who improved from unfit to fit had an age-adjusted RR for all-cause mortality of 0.67 (95% CI, 0.61 to 0.74) in the first 3 years of follow-up and 0.38 (95% CI, 0.26 to 0.56) in the later follow-up interval. Additional analyses were done by constructing multivariable re-

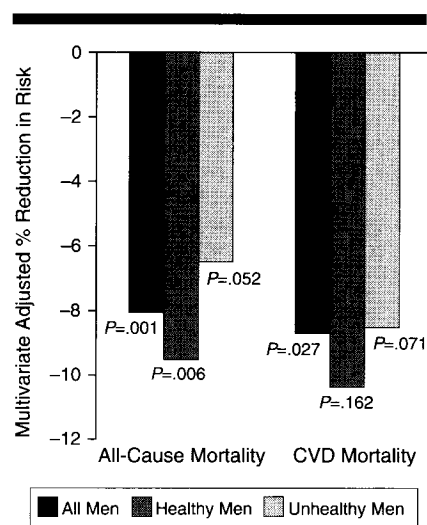


Figure 3.—Adjusted percentage reduction in risk for all-cause and cardiovascular disease (CVD) mortality from proportional hazards regression analyses. The bars show reduction in risk for each minute improvement in treadmill time from the first to the subsequent examination. Zero indicates the reference category of no change in treadmill time. Risks were adjusted for baseline age, fitness, family history of coronary heart disease, systolic blood pressure, total cholesterol level, fasting glucose level, weight, smoking status, and interval between examinations. Analyses for all men combined were also adjusted for health status. The numbers of deaths per category for all men, healthy men, and unhealthy men, respectively, were as follows: all-cause mortality, 220, 100, and 120; and CVD mortality, 85, 26, and 59.

gression models (controlling for potential confounders described above) for each of the two follow-up intervals. The results of these models were consistent with a reduced risk for all-cause mortality associated with improved fitness in both follow-up periods.

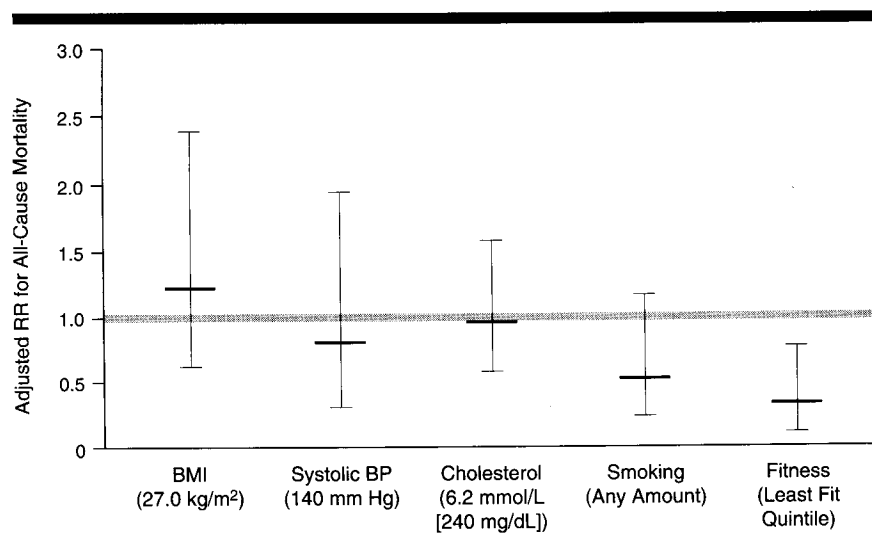


Figure 4.—Relative risks (adjusted for age, family history of coronary heart disease, health status, baseline values, and changes for all variables in the figure, and interval in years between examinations) of all-cause mortality by favorable changes in risk factors between first and subsequent examinations. The analyses were for men at risk on each particular variable at the first examination. Cutoff points designating high risk are given parenthetically at the bottom of the figure. The number of men at high risk (and the number of deaths) for each characteristic were as follows: body mass index (BMI), 2691 (66); systolic blood pressure (BP), 1013 (55); cholesterol, 2212 (79); cigarette smoking, 1609 (45); and physical fitness, 1015 (56).

The proportional hazards regression analyses also demonstrated risk reduction for other favorable lifestyle or clinical status changes. Figure 4 presents results of proportional hazards analyses by showing adjusted RR estimates for losing weight, lowering blood pressure, reducing cholesterol, stopping smoking, and improving fitness in men at risk for each of these factors at the first examination. These RRs were adjusted for age in years, family history of coronary heart disease, interval between examinations, and baseline and change values of all variables in the figure. Standard definitions for identifying high-risk status at the baseline examination were used for overweight (body mass index, ≥ 27.0 kg/m²), high blood pressure (resting systolic blood pressure, ≥ 140 mm Hg), and hypercholesterolemia (≥ 6.2 mmol/L [≥ 240 mg/dL]). With the exception of weight loss, all other presumed favorable changes were associated with reduced risk of mortality, although the 95% CI included 1.0 for all variables except physical fitness.

COMMENT

We observed a reduction in mortality risk in the total population of men who maintained or improved physical fitness. This reduction was present in both healthy and unhealthy men, and the results were consistent across age groups. Changes in fitness, either an increase or decrease, were associated with hypothesized and biologically plausible changes in risk, irrespective of the baseline fitness level.

Multivariable statistical modeling showed that the findings were independent of confounding by other known risk factors. Both baseline status and changes in risk factors were considered in the analyses. Maximal exercise testing provides an objective assessment of physical fitness, and increases in exercise test tolerance are caused by physiologic changes in the oxygen supply system. It is well established that physical fitness increases with exercise training,¹⁸ and although there are important individual differences in the response to training, only a minority of individuals are completely unresponsive. We therefore assume that the changes in fitness reported herein are the result of a more physically active way of life, and analyses in this cohort show significant increases in treadmill test time in men who increase their activity.

Hereditry is a possible explanation for the higher death rates in unfit individuals. There is a genetic contribution to aerobic power, estimated to be in the range of 25% to 40%.¹⁹ Data presented in the current study do not support the hypothesis that hereditary factors are solely responsible for the relationship between fitness and mortality. Men who were unfit at their initial examination but who became fit by the time of their subsequent examination had a 44% reduction in risk of mortality during follow-up compared with similar unfit men who did not improve; this association is unlikely to result from heredity. In a previous report, we showed an inverse gradient of death rates across fitness cat-

egories in men and women who had a family history of coronary heart disease, as well as those who did not have this characteristic, which suggests that the relationship between fitness and mortality is independent of parental history of coronary heart disease.¹²

Few studies on physical activity, fitness, and health have been able to evaluate the effect of change in the exposure variables to risk. A report from the Harvard Alumni Study showed that an increase in physical activity is associated with a reduction in mortality risk during follow-up.²⁰ Healthy, middle-aged, inactive men at baseline who began to participate in moderately vigorous sports had a 23% lower risk of dying than men who remained sedentary. Furthermore, there was a graded association of mortality risk across categories of increases and decreases in total energy expended per week in physical activity.²¹ Data from the Alameda County Study²² on change in physical activity and mortality are consistent with the Harvard Alumni Study, and results in each of these studies remained after adjustment for several potential confounding variables.

When coronary heart disease mortality was considered in the Harvard Alumni Study, the size of the risk reduction associated with increased physical activity was equivalent to that associated with other favorable changes, such as stopping smoking and avoiding obesity and hypertension.²⁰ For example, men who stopped smoking reduced their risk by 44% relative to men who continued to smoke, and men who started a moderately vigorous exercise program reduced their risk by 41% compared with the men who remained sedentary. Men in the Aerobics Center Longitudinal Study who improved their fitness had a 64% reduction in risk of death (Figure 4) compared with men who stayed unfit. This reduction in mortality risk was greater than for any of the other risk characteristics and was the only statistically significant reduction in multivariate analyses.

The results of this investigation are consistent with biological plausibility. Increased levels of physical activity and fitness are hypothesized to act through beneficial fibrinolytic, hemodynamic, blood chemistry, blood pressure, and electrical changes to the cardiovascular system.²³ Presumably, such changes were enhanced among those participants who improved their physical fitness.

This study has limitations in that the population was predominantly white men from middle to upper socioeconomic strata, and these factors limit the generalizability of the findings. However,

the internal validity of the study is not affected by the nature of the population. Strengths of the study include an objective assessment of physical fitness, and the thorough evaluations at the two clinical examinations provide extensive data on health status, health behaviors, and other risk factors, thus allowing for control of many potentially confounding variables.

Results presented herein show the effect of changes in physical fitness on mortality and provide additional support for the hypothesis that an active and fit way

of life improves health and delays death. The most important new information from this study is the relationship between *changes* in fitness and risk of mortality. Prospective studies with a one-time assessment of the exposure variable can be questioned because of concerns about the influences of hereditary factors, undetected preexisting disease, and uncertainty about the influences of making changes in activity and fitness. This study and recent reports on physical activity change²⁰⁻²² alleviate some of these concerns. Physicians can have con-

fidence that their patients will reduce risk of mortality by increasing physical activity and improving fitness.

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