Relation Of Physical Activity And Cardiovascular Fitness To Coronary Heart Disease, Part II: Cardiovascular Fitness And The Safety And Efficacy Of Physical Activity Prescription

Charles B. Eaton, M.D., M.S.

Abstract: ***Background:*** **This paper is the second of two reports that together review the scientific evidence regarding the inverse relation between physical activity and cardiovascular fitness and coronary heart disease (CHD).**

Methods: **Using a MEDLINE search with the key words exercise, physical fitness, coronary heart disease, and cardiovascular disease, more than 75 articles were reviewed, evaluating study design, measurement error, bias and confounding, the strength of associations, consistency of results, temporal and dose-response relation, and biologic plausibility.**

Results: **The relative risk in epidemiologic studies comparing the least to the most fit categories ranges from 1.2 to 4.8, which is greater than that for physical inactivity. The differences between cardiovascular fitness (an attribute) and physical activity (a behavior) are highlighted. The range of correlation (r = 0.02 to 0.44) between cardiovascular fitness and physical activity is discussed relative to measurement error and genetic and environmental factors. Studies reporting the safety of regular physical activity suggest an injury rate as high as 35 injuries per 100 persons per year. Efficacy studies limited to secondary prevention trials report a 66 percent compliance rate and 15 percent reduction in total mortality.**

Conclusions: **The scientific evidence implying a causal relation between cardiovascular fitness and CHD is strongly positive, but the clinical and public health implications are unclear. Further research and clinical guidelines are suggested. (J Am Board Fam Pract 1992;5:157-66.)**

The US Preventive Services Task Force recommended physical activity counseling for all sedentary individuals as part of a national primary prevention strategy.[1] This recommendation was based upon the strength of epidemiologic evidence linking increased physical activity and increased cardiovascular fitness with increased longevity and decreased coronary heart disease (CHD) mortality. In a recent review,[2] epidemiologic evidence linking physical activity and CHD protection was critically appraised using the diagnostic tests of causality suggested by Sackett, et al.[3]

Submitted, revised, 28 October, 1991.

From the Department of Family Medicine, Memorial Hospital of Rhode Island, Pawtucket. Address reprint requests to Charles B. Eaton, M.D., M.S., Department of Family Medicine, Brown University/Memorial Hospital of Rhode Island, 111 Brewster Street, Pawtucket, RI 02860.

Partial support for this manuscript was supplied by a Public Health Service National Research Service Award, 5T32 HL07642-04.

This review uses the same criteria to judge the relation of cardiovascular fitness and CHD and discusses the interrelation of physical activity to cardiovascular fitness. Additionally, in this report, the safety and efficacy of physical activity and its prescription are reviewed. A commentary on the research and clinical implications of this critical appraisal is provided.

Cardiovascular fitness is the most studied aspect of physical fitness relating to CHD when compared with other determinants of physical fitness, such as muscular endurance and strength, body composition, flexibility, agility, balance, coordination, speed, power, and reaction time. For this reason, this review focuses on cardiovascular fitness and avoids the term *physical fitness* in the discussion below.

Methods

All articles written in English relating to the relation of physical activity, cardiovascular fitness, and coronary heart disease were identified by a

MEDLINE search using the key words exercise, coronary heart disease, cardiovascular disease, physical fitness, physical activity. A manual review of the literature was undertaken as well. The study design, population characteristics, and method of assessing physical activity, cardiovascular fitness, or exercise were recorded. The year of the study and the endpoints, such as total mortality, CHD mortality, sudden death, nonfatal myocardial infarction (MI), and angina were recorded. More than 75 articles were reviewed.

Testing For Causality between Cardiovascular Fitness and CHD

Are There True Experiments in Humans Showing an Association?

Randomized Clinical Trials

Because cardiovascular fitness is an attribute related to cardiorespiratory endurance, it cannot be randomly allocated but can only be measured in individuals. Thus clinical trials cannot evaluate this potential association.

Epidemiologic Studies

Table 1 lists the seven studies in which the relation of cardiovascular fitness and CHD have been evaluated.[4-10] All seven studies reported a consistent inverse relation between cardiovascular fitness and CHD. Five of the seven studies evaluated age, smoking, cholesterol levels, and blood pressure as confounders,[4,6,8-10] and all showed an independent inverse relation between cardiovascular fitness and CHD. Two studies, the Belgian Factory Workers[6] and the Lipid Research Clinics (LRC) mortality follow-up study,[8] evaluated high-density lipoprotein (HDL) cholesterol as a confounder and again demonstrated an inverse independent relation between cardiovascular fitness and CHD. Of interest, the Los Angeles County Study[4] reported an interaction between traditional risk factors and cardiovascular fitness in which the benefit of enhanced cardiovascular fitness was found only in the group with above-median risk for smoking, increased blood pressure, and elevated cholesterol. This stratification of benefit was not seen in subsequent larger studies, such as the Lipid Research Clinics mortality follow-up study,[8] the US Railroad study,[9] and the Cooper Clinic study.[10]

All the studies had a disease-free cohort that was monitored for a variable period (4.8 to 20 years), thus decreasing misclassification bias of the exposure. All investigators evaluated relatively hard endpoints, including CHD mortality, except in the Los Angeles County study, in which symptomatic myocardial infarction was evaluated. Using such hard endpoints should reduce measurement error of the outcome. In two studies, the US Railroad study[9] and the Cooper Clinic,[10] total mortality was evaluated, as well as CHD mortality, and an independent inverse relation was shown. This suggests that selective mortality did not lead to a spurious association.

In summary, in well-designed epidemiologic studies that account for bias and confounding, an inverse relation of cardiovascular fitness to CHD incidence, mortality, and total mortality has been demonstrated.

Is the Association Strong?

Because different testing procedures for measuring cardiovascular fitness (submaximal cycle ergometer, submaximal and maximal treadmill tests), different cutoff values (stage 2 heart rates, total treadmill duration, work capacity at a fixed heart rate or stage of testing), and different comparisons (above and below median, quartiles, quintiles) were used, it is not surprising that different strengths of association between cardiovascular fitness and CHD incidence were found.

In reviewing the seven studies, however, some generalities about the strength of association can be made. All studies in which the least fit group was compared with the most fit group, a strong consistent relation between increasing benefits and increasing cardiovascular fitness was found. The risk of poor cardiovascular fitness ranges from 1.2 in the US Railroad study to 4.8 in the Oslo study (Table 1). In summary, there appears to be a strong inverse association between cardiovascular fitness and CHD.

Is the Association Consistent?

In all seven studies comparing cardiovascular fitness with CHD, despite different measures of cardiovascular fitness, cutoff values, and populations, an inverse relation has been found. This finding suggests a high degree of consistency. The degree to which poor test performance or classification to the lowest fit categories reflects undiagnosed premorbid CHD or unrecognized disability remains unclear in many of these studies.

Table 1. Cardiovascular Fitness and Coronary Heart Disease.*

Study	Population	Follow-Up (Yr)	Cases	Outcome	Measure of Fitness	RR	Adjustments
Los Angeles County[4]	2779	4.8	36	Symptomatic myocardial infarction	Below median PWC (bicycle)	2.2	Age, Smoking, Chol, Sys BP
Oslo, Norway[7]	2014	7	58	CHD death	Quartiles CW/kg (bicycle)	4.84	—
Norway, Nordbyhagen[5]	1832	7	—	CHD death	Quartiles TW/kg (bicycle)	Graded	—
Belgian Factory Workers[6]	1476	5	19	CHD death	PWC 150/kg (bicycle)	4.0	Age, Smoking, HDL, Sys BP
Lipid Research Clinics mortality follow-up[8]	3106	8.5	45	CHD death	Stage 2 heart rate (treadmill)	3.2	Age, Smoking, HDL, LDL, Sys BP
US Railroad[9]	2431	20	260	CHD death	Exercise heart rate at 3 min (treadmill)	1.2	Age, Sys BP, Chol, Smoking
Cooper Clinic[10]	13,344	8	283	All-cause mortality	Maximal treadmill time	1.58 (men) 1.94 (women)	Age, Smoking, Sys BP, Chol, FHx, Glucose

*RR = relative risk; PWC = physical work capacity (watts); CW = cumulative work (kpm); TW = total work; PWC 150 = physical work capacity at a heart rate of 150 beats/minute; Chol = Cholesterol; Sys BP = systolic blood pressure; FHx = family history of CHD; HDL = HDL cholesterol.

Is the Temporal Relation Correct?

All seven studies were prospective in design and each had an initial disease-free cohort as determined by the history and physical examination of the participants. Thus the appropriate temporal relation for causality is present.

Is There a Dose-Response Relation?

In six of the seven studies, several levels of cardiovascular fitness were evaluated. All investigators were able to show a biological gradient of response of CHD to increasing levels of cardiovascular fitness.[4-10] In the Cooper Clinic study, using the most reliable measurement of cardiovascular fitness (maximal exercise testing), a linear dose-response relation was reported in both men and women. Careful inspection of the results, however, shows that only the most unfit group differed significantly more than by chance from those in the other four quintiles. This lack of statistical significance for each level of cardiovascular fitness suggests that caution should be taken in stating that a definite dose-response relation has been established.

Does the Association Make Biologic Sense?

Evidence that increasing cardiovascular fitness is associated with decreased cardiovascular risk factors (less smoking, lower blood pressure, lower serum cholesterol, elevated high-density lipoprotein cholesterol) is abundant.[6-11] The independent association of cardiovascular fitness and CHD, however, suggests that other biologic mechanisms are operative. Evidence of increased myocardial efficiency by cardiac or peripheral mechanisms, as well as changes in coronary anatomy or thrombotic-related events, could explain the proposed independent relation.[12-23] Most studies evaluating these biologic mechanisms have relied upon physical training and not measured cardiovascular fitness as such. Therefore, while the above mechanisms appear plausible, there is little experimental evidence in humans to validate these assumptions.

Discussion

Cardiovascular fitness as measured by exercise testing is an attribute that is related to a person's genetic makeup, age, weight, regular exercise, and habituation to the test equipment. Although all seven studies reported an inverse relation of cardiovascular fitness to CHD incidence in populations, which of the above factors is responsible for this difference? Clearly, age and weight are accounted for in the statistical analysis. Habituation to the test would appear to be similar be-

tween high- and low-fitness groups and therefore not a factor.

Work by Klissouras[24] measuring maximal aerobic power in 25 pairs of male twins (aged 7 to 30 years) and using a simple additive model of hereditary and environment without interaction showed that approximately 80 percent of the intraindividual variance could be explained by genetics alone. This finding would suggest that when we measure cardiovascular fitness, we might be measuring a constitutional factor that has no ability to be changed. Thus the relation of CHD to cardiovascular fitness would be of little public health importance. More recent studies by Bouchard[25] suggest that only 30 percent of the intraindividual variance is genetic in origin and that 70 percent is susceptible to environmental change.

Understanding the relation between physical activity and cardiovascular fitness is critical in pursuing a primary prevention policy with regard to sedentary lifestyle. The correlation between measures of physical activity and cardiovascular fitness in the epidemiologic studies where both were measured were the following: $r = 0.02$ in the Health Insurance Plan of Greater New York (HIP) job classification study,[26] $r = 0.10$ in the Belgian fitness study,[6] $r = 0.32$ in the Los Angeles County employee study,[4] $r = 0.41$ in the sweat frequency study by Siconolfi, et al.,[27] $r = 0.41$ for total leisure time activity, and $r = 0.44$ for heavy leisure time activity using the Minnesota leisure time activity questionnaire.[28] Thus the correlation between physical activity and cardiovascular fitness is modest to weak in large populations. In the four studies in which physical activity and cardiovascular fitness were measured in the same population, only cardiovascular fitness was predictive of CHD benefit in three (Belgian Factory workers, Los Angeles County employees, and LRC follow-up mortality participants),[4,6,8] whereas both were predictive of CHD benefit in one (US Railroad study).[9] Therefore, it appears that cardiovascular fitness is a better predictor of CHD benefit.

To understand better the interrelation of physical activity and cardiovascular fitness to CHD, the difference between the determinants of a population's cardiovascular fitness and an individual's cardiovascular fitness needs to be explored. On an individual basis, physical activity can in 4 to 6 weeks produce significant gains in cardiovascular fitness. Saltin, et al.[29] showed an approximate 25 percent improvement in maximal oxygen uptake after training individuals after bed rest. This increase in cardiovascular fitness related to physical activity, however, may not be true in epidemiologic studies when the effect of cardiovascular fitness on CHD is studied in aggregate. Here the differences in cardiovascular fitness may not represent changes in conditioning levels of physical activity but may be related to the degree of disability or genetic factors of the study participants.

Some of this lack of correlation between cardiovascular fitness and physical activity could be related to greater misclassification bias associated with physical activity in epidemiologic studies. Additionally, the lack of variability of physical activity in a largely sedentary population and the large genetic component of cardiovascular fitness could explain the modest correlations.

Summary for Cardiovascular Fitness and CHD

Although all the diagnostic tests for a cause-and-effect relation between cardiovascular fitness and CHD are strongly positive, the implication of this causal link to a national primary prevention recommendation is unclear. The association of cardiovascular fitness to CHD has public health and clinical relevance to the degree that changes in behaviors (physical activity) can change cardiovascular fitness.

Safety and Efficacy

Assuming a causal relation between physical inactivity and CHD has been adequately established,[2] recommending a "treatment of physical activity" to asymptomatic individuals requires evidence of safety and efficacy of this intervention. Limited studies have addressed this issue from the perspective of primary prevention.

Safety

Even though the risk of sudden death from jogging and participation in cardiac rehabilitation programs is small,[30-33] there is little evidence about the risk of injury and exacerbation of chronic disease with other common forms of physical activity. No published data exist for the risks of injury in the general population for moderate physical activity, such as walking, aerobic

exercise, swimming, and recreational bicycling. Indirect estimates of the potential risk for injury can be found in the Canadian Fitness study.[34] When asked why participants stopped regular exercise, 19 percent answered injury. For each category, the frequency with which participants stopped exercise because of injury was: jog or run, 22 percent; swimming, 10 percent; aerobics, 21 percent; bicycling, 13 percent; walking, 37 percent; and exercise class, 10 percent. Caution should be taken in interpreting these data, as they reflect only the percentage of those who reported stopping regular exercise, not the injury rate in the total survey population.

A cross-sectional study of runners of the Peachtree road race showed that 35 percent were injured within 1 year.[35] Thirteen percent of the men and 17 percent of the women were injured severely enough that they sought medical attention. Overuse injuries, particularly to knees, were the most common. Additional problems with hazards occurred with strikingly high frequency. Four percent of the participants had dog bites, 7 percent had objects thrown at them, and about 1 percent of the men were involved in vehicular trauma.

In summary, while the life-threatening risk of regular physical activity appears small compared with its perceived benefits, there are few data on the long-term associated morbidity and injury rate of regular physical activity.

Efficacy

Whereas it appears that physical activity prescription is as efficacious as other office-based health promotion strategies[36-39] in obtaining short-term compliance, there are no data on long-term compliance. The only efficacy studies that have been performed have been secondary prevention trials in postmyocardial infarction patients. Table 2 enumerates the six studies in which efficacy has been tested.[40-45] In these highly selected, motivated individuals, 23 to 33 percent were noncompliant with the prescribed exercise regimen. Of the six studies, four showed a trend for CHD benefit,[40-43] but only one showed a statistically significant result (Finnish Multiple Risk Factor Post-Infarction study).[44] Pooling these data, May, et al.[46] reported a clinically relevant but not statistically significant 15 percent reduction in total mortality.

In summary, it is uncertain whether this secondary prevention data can be generalized to answer questions about the efficacy of primary prevention. There are no data on the efficacy of physical activity counseling in asymptomatic populations in reducing CHD incidence and relative sparse data on the effectiveness of physician counseling in promoting changes in physical activity.

Clinical and Research Recommendations

Comparing the scientific evidence available to the US Preventive Services Task Force in developing its recommendations for the prescription of physical activity in sedentary populations with the evidence for the National Cholesterol Education Panel guidelines for cholesterol screening and treatment underscores the limited amount of conclusive evidence available for recommending physical activity.[1,47-55] The purpose of this review is not to make a different set of primary prevention recommendations but rather to prevent premature closure on this issue.

Table 2. Differences in Outcomes (Percentages) in Randomized Clinical Trials of Exercise and Recurrent Coronary Heart Disease Comparing Treatment with Control Groups.

Study	Total Mortality	Coronary Heart Disease	Myocardial Infarction	Sudden Death
Helsinki (1972)[40]	0	0	—	↑59
Göteborg (1975)[42]	↓18	—	↓11	—
Oulu (1976)[41]	↓47	↓28	↓19	—
Finnish Multiple Risk Factor Post-Infarction (1979)[44]	↓27	↓37	—	↓60†
National Exercise and Heart Disease Project (1981)[43]	↓37	↓29.5	↓87*	—
Ontario Heart (1975)[45]	—	—	↑9.2	—

*$P < 0.05$.

†$P < 0.01$.

Further research to establish the necessary scientific basis for physical activity counseling as a primary prevention strategy falls under three major categories. The first area is to establish firmly the cause-and-effect relation between physical activity and CHD benefit. A primary prevention trial of physical activity and CHD mortality is highly unlikely because of problems with the size and duration of such a study, its cost, the problems with compliance (crossovers and dropouts), and the ethics of not concomitantly treating other cardiac risk factors. A primary prevention trial using progression of angiographically defined coronary artery disease as an endpoint might be feasible in high-risk patients who have had either angiography for atypical chest pain or positive exercise stress tests. Statistically significant results could be attained in a trial of modest size with only 1 to 2 years of follow-up. Concerns of cost and compliance therefore could be overcome. Perhaps a more useful approach would be the simultaneous evaluation of repeated measures of cardiovascular fitness and physical activity in a prospective cohort study. This approach would allow for assessment of the effect of changes in physical activity on CHD incidence and mortality. Additionally, it would allow for investigation of the dynamic interrelation of cardiovascular fitness and physical activity with CHD mortality in target populations that are more similar to the US population than are those in clinical trials. Because only one study of physical activity and CHD has evaluated the role of HDL cholesterol as a potential confounder, more prospective studies evaluating this relation need to be performed.

A second area of need is epidemiologic data from well-designed studies quantifying the risk of injury for both moderate and vigorous activity in sedentary populations. Differences in injury rates of exercise participation comparing self-initiated programs with physician-recommended exercise programs would be useful to explore.

The third area needing additional research is the issue of effectiveness of exercise recommendation. Can physicians effectively recommend exercise in such a way as to change patients' behavior? What factors predict adherence to behavioral change and are they modifiable? Are the changes of sufficient duration and strength to change CHD outcomes?

Answers to these research questions would establish a more credible scientific basis for the US Preventive Services Task Force recommendations for physical activity counseling.

Despite the Limitations of the Present Scientific Evidence, Are There Any Useful Clinical Recommendations to Be Made?

The strongest epidemiologic evidence suggests that regular vigorous (6 metabolic equivalents) leisure-time physical activity performed at a frequency and duration recommended by the American College of Sports Medicine (15 to 60 minutes, 3 to 5 times per week) should provide 1680 kJ per day (400 kcal/d) or 12,600 kJ/wk (3000 kcal/wk) of energy expenditure.[56] This level of activity should enhance cardiovascular fitness in most sedentary individuals.[57] In almost all the studies reviewed, such an exercise regimen should lead to increased CHD protection. Whether less vigorous physical activity (of both intensity and duration) that does not enhance cardiovascular fitness is beneficial is speculative. Additionally, whether job-related physical activity is of benefit is also unclear.[2]

Concern that injuries rates associated with vigorous physical activity of 6 metabolic equivalents (METs) or greater (team sports, running or jogging, singles tennis, aerobics, cycling, and lap swimming) are greater than less vigorous activities has not been borne out in the few studies that have looked at this issue.[58,59] Walking has become by far the most common leisure-time physical activity in the United States.[60] Walking briskly at 4.5 to 5 mph with the arms swinging should allow most individuals to meet the 6-MET threshold.[61] For the more cardiovascularly fit individuals, addition of hand weights will provide the necessary metabolic work to meet this 6-MET threshold. Many individuals find pulse-monitoring difficult and a barrier to regular exercise. Dyspnea, which is associated with the production and buffering of lactic acid and which occurs at approximately 65 percent maximum oxygen consumption (VO_2 max), can be a more efficacious guideline to judge the adequacy of exercise during the initial phase of exercise prescription.[62]

I gratefully acknowledge the assistance of the following persons: Thomas A. Pearson, M.D., M.P.H., Ph.D., and David Strogatz, Ph.D., for their help with the epidemiologic methods;

Richard A. Carleton, M.D., Vincent Hunt, M.D., and Larry Culpepper, M.D., M.P.H., who provided invaluable advice and support; and Tasha Ramos, who provided assistance in the preparation of the manuscript.

References

1. Harris SS, Caspersen CJ, Defriese GH, Estes EH Jr. Physical activity counseling for healthy adults as a primary preventive intervention in the clinical setting. Report for the US Preventive Services Task Force. JAMA 1989; 261:3588-98.
2. Eaton CB. Relation of physical activity and cardiovascular fitness to coronary heart disease, Part I: a meta-analysis of the independent relation of physical activity and coronary heart disease. J Am Board Fam Pract 1992; 5:31-42.
3. Department of Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Center. How to read clinical journals: IV. To determine etiology or causation. Can Med Assoc J 1981; 124: 985-90.
4. Peters RK, Cady LD Jr, Bischoff DP, Bernstein L, Pike MC. Physical fitness and subsequent myocardial infarction in healthy workers. JAMA 1983; 249:3052-6.
5. Erikssen J. Physical fitness and coronary heart disease morbidity and mortality. A prospective study in apparently healthy middle age men. Acta Med Scand Suppl 1986; 711:189-92.
6. Sobolski J, Kornitzer M, DeBacker G, Dramaix M, Abramowicz M, Degre S, et al. Protection against ischemic heart disease in the Belgian Physical Fitness Study: physical fitness rather than physical activity? Am J Epidemiol 1987; 125:601-10.
7. Lie H, Mundal R, Erikssen J. Coronary risk factors and the incidence of coronary death in relation to physical fitness. Seven-year follow-up study of middle-aged and elderly men. Eur Heart J 1985; 6: 147-57.
8. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in symptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. N Engl J Med 1988; 319: 1379-84.
9. Slattery ML, Jacobs DR Jr. Physical fitness and cardiovascular disease mortality. The US Railroad Study. Am J Epidemiol 1988; 127:571-80.
10. Blair SN, Kohl HW 3d, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989; 262:2395-401.
11. Abbott RD, Levy D, Kannel WB, Castelli WP, Wilson PW, Garrison RJ, et al. Cardiovascular risk factors and graded treadmill exercise endurance in healthy adults: the Framingham Offspring Study. Am J Cardiol 1989; 63:342-6.
12. Fox SM, Metcalf JA. Physical activity and diet in the treatment of coronary heart disease. In: White PL, Mondeika T, editors. Diet and exercise: synergism in health maintenance. Chicago: American Medical Association, 1982.
13. Kramsch DM, Aspen AJ, Abramowitz BM, Kreimendahl T, Hood WB. Reduction of coronary atherosclerosis by moderate conditioning exercise in monkeys on an atherogenic diet. N Engl J Med 1981; 305:1483-9.
14. Rose G, Prineas RJ, Mitchell RA. Myocardial infarction in the intrinsic calibre of coronary arteries. Br Heart J 1967; 29:548-52.
15. Fried LP, Pearson TA. Physical activity and coronary artery diameter: a protective mechanism independent atherosclerosis and thrombosis. Clin Res 1984; 32:221.
16. Selvester R, Camp J, Sanmarco M. Effects of exercise training on progression of documented coronary arteriosclerosis in men. Ann NY Acad Sci 1977; 301:495-508.
17. Nolewajka AJ, Kostuk WJ, Rechnitzer PA, Cunningham DA. Exercise and human collateralization: an angiographic and scintigraphic assessment. Circulation 1979; 60:114-21.
18. Meade TW, Mellow S, Brozovic M, Miller GJ, Chakrabarti RR, North WR, et al. Haemostatic function and ischemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986; 2:533-7.
19. Kopitsky RG, Switzer ME, Williams RS, McKee PA. The basis for the increase in factor VIII procoagulant activity during exercise. Thromb Haemost 1983; 490:53-7.
20. Williams RS, Logue EE, Louis JL, Barton T, Stead NW, Wallace AG, et al. Physical conditioning augments fibrinolytic response to venous occlusion in healthy adults. N Engl J Med 1980; 302:987-91.
21. Rauramaa R, Salonen JT, Seppänen K, Salonnen R, Venalainen JM, Ihanainen M, et al. Inhibition of platelet aggregability by moderate-intensity physical exercise: a randomized clinical trial in overweight men. Circulation 1986; 74:939-44.
22. Noakes TD, Higginson L, Opie LH. Physical training increases ventricular fibrillation thresholds of isolated red hearts during normoxia, hypoxia and regional ischemia. Circulation 1983; 67:24-30.
23. Ehsani AA, Biello D, Seals Dr, Austin MB, Schultz J. The effect of left ventricular systolic function on maximal aerobic exercise capacity in asymptomatic patients with coronary artery disease. Circulation 1984; 70:552-60.
24. Klissouras V. Heritability of adaptive variation. J Appl Physiol 1971; 31:338-44.
25. Bouchard C. Genetics of aerobic power and capacity. In: Malina RM, Bouchard C, editors. Sport and human genetics. Champaign, IL: Human Kinetics, Vol 4:1986:59-88.
26. Shapiro S, Weinblaff E, Frank CW, Sager RV. Incidence of coronary heart disease in a population insured for medical care: HIP: myocardial infarction, angina pectoris, and possible myocardial infarction. Am J Public Health 1969; 59(Suppl)1-101.

27. Siconolfi SF, Lasater TM, Snow RC, Carleton RA. Self reported physical activity compared with maximal oxygen uptake. Am J Epidemiol 1985; 122:101-5.
28. Leon AS, Jacobs DR Jr, De Backer G, Taylor HL. Relationship of physical characteristics and life habits to treadmill exercise capacity. Am J Epidemiol 1981; 113:653-60.
29. Saltin B, Blomqvist G, Mitchell JH, Johnson RL Jr, Wildenthal K, Chapman CB. Response to exercise after bed rest and training. Circulation 1968; 38(Suppl 7):1-78.
30. Thompson PD, Fun EJ, Carleton RA, Sturner SQ. Incidence of death during jogging in Rhode Island from 1975 through 1980. JAMA 1982; 247: 2535-8.
31. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. N Engl J Med 1984; 311:874-7.
32. Gibbons LW, Cooper KH, Meyer B, Ellison RC. The acute cardiac risk of strenuous exercise. JAMA 1980; 244:1799-801.
33. Vander L, Franklin B, Rubenfire M. Cardiovascular complications of recreational physical activity. Physician and Sports Med 1982; 10:89-93,96,98.
34. Canadian Fitness Survey. Fitness and lifestyle in Canada. Ottawa: Canada Fitness Survey, May 1983.
35. Koplan JP, Powell KE, Sikes RK, Shirley RW, Campbell CC. An epidemiologic study of the benefits and risks of running. JAMA 1982; 248:3118-21.
36. Kelly RB. Controlled trial of a time-efficient method of health promotion. Am J Prev Med 1988; 4:200-7.
37. Logsdon DN, Rosen MA, Demak MM. The INSURE project on lifecycle preventive health services. Public Health Rep 1982; 97:308-17.
38. Russell MA, Wilson C, Tayler C, Baker CD. Effect of general practitioners' advice against smoking. Br Med J 1979; 2:231-5.
39. Inui TS, Yourtee EL, Williamson JW. Improved outcomes in hypertension after physician tutorials. Ann Intern Med 1976; 84:646-51.
40. Kentala E. Physical fitness and feasibility of physical rehabilitation after myocardial infarction in men of working age. Ann Clin Res 1972; 4(Suppl 9):1-84.
41. Palatsi I. Feasibility of physical training after myocardial infarction and its effect on return to work, mortality. Acta Med Scand Suppl 1976; 599:7-84.
42. Wilhelmsen L, Sanne H, Elmfeldt D, Elmfeldt D, Grimby G, Tibblin G. A controlled trial of physical training after myocardial infarction. Effects on risk factors, nonfatal reinfarction, and death. Prev Med 1975; 4:491-508.
43. Shaw LW. The national exercise and heart disease project: effects of prescribed, supervised exercise program on mortality and cardiovascular morbidity in patients after myocardial infarction. Am J Cardiol 1981; 48:39-46.
44. Kallio V, Hamalainen H, Hakkila J, Luurila OJ. Reduction in sudden deaths by multifactorial intervention programme after acute myocardial infarction. Lancet 1979; 2:1091-4.
45. Rechnitzer PA, Sangal S, Cunningham DA, Andrew J, Buck C, Jones NL, et al. A controlled prospective study of the effect of endurance training on the recurrence rate of myocardial infarction. A description of the experimental design. Am J Epidemiol 1975; 102:358-65.
46. May AG, Eberlien KA, Furberg CD, Passamani ER, DeMets DL. Secondary presentation after myocardial infarction: a review of long-term trials. Prog Cardiovasc Dis 1982; 24:331-52.
47. Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and risk of coronary heart disease: the Framingham Study. Ann Intern Med 1971; 74:1-12.
48. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight, ECG abnormalities to incidence of major coronary events: final report of the Pooling Project Research Group. J Chronic Dis 1978; 31:201-306.
49. Keys A. Seven countries. A multivariate analysis of death and coronary heart disease. Cambridge, MA: Harvard University Press, 1980.
50. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of death from coronary heart disease continuous and graded? Findings in 365,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986; 256:2823-8.
51. WHO cooperative trial on primary prevention of ischemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. Report of the Committee of Principal Investigators. Lancet 1984; 2:600-4.
52. The Lipid Research Clinics Coronary Primary Prevention Trial Results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251: 365-74.
53. Canner PL, Berge KG, Wenger NK, Stanler J, Friedman L, Prineas RJ, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 1986; 8:1245-55.
54. Frick MH, Elo O, Happa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317:1237-45.
55. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. Arch Intern Med 1988; 148:36-69.

56. American College of Sports Medicine. Guidelines for exercise testing and prescription. 3rd ed. Philadelphia: Lea & Febiger, 1986.
57. Haskell WL. Physical activity and health: need to define the required stimulus. Am J Cardiol 1985; 55:4D-9D.
58. Lane NE, Bloch DA, Wood PD, Fries JF. Aging, long-distance running, and the development of musculoskeletal disability. A controlled study. Am J Med 1987; 82:772-80.
59. Koplan JP, Siscovick DS, Goldbaum GM. The risks of exercise: a public health view of injuries and hazards. Public Health Rep 1985; 100: 189-95.
60. White CC, Powell KE, Hogelin GC, Gentry EM, Forman MR. The Behavioral Risk Factor Surveys: IV. The descriptive epidemiology of exercise. Am J Prev Med 1987; 3:304-10.
61. Rippe J, Ward A, Porcan J, Freedson P, O'Hanley S, Wilkie S. The cardiovascular benefits of walking. Practical Cardiology 1989; 15:66-71.
62. Thompson PD. The benefits and risks of exercise training in patients with chronic coronary artery disease. JAMA 1988; 259:1537-40.