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

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Abstract: ***Background:*** **This paper is the first 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: **In Part I, the evidence suggesting a causal link between physical activity and CHD protection independent of other CHD risk factors is reviewed, accounting for bias, confounding, and different study designs.**

Results: **A strong, consistent inverse relation is found. Using meta-analytic techniques, the relative risk of the independent relation of physical inactivity to CHD is 1.37, with a 95 percent confidence interval (1.27–1.48).**

Conclusions: **A graded biologic response of CHD protection to physical activity is shown, but the intensity, duration, and frequency of activity necessary for CHD benefit remain unclear. Plausible biologic mechanisms for the inverse relation of physical activity to CHD are the risk factor modifications that accrue with physical activity. (J Am Board Fam Pract 1992; 5:31-42.)**

The US Preventive Services Task Force recently recommended physical activity counseling for all sedentary persons as part of a national primary prevention strategy.[1] This recommendation was based largely upon the strength of the epidemiologic evidence linking coronary heart disease (CHD) protection and physical activity. Additional less-consistent literature showing an inverse relation between physical activity and hypertension, obesity, and osteoporosis was cited as the scientific basis for this recommendation. The purpose of this report is to review critically the scientific evidence that led to the task force recommendation. Part I focuses on the questions: Is there an inverse cause-and-effect relation between physical activity and CHD? Is this relation independent of other cardiovascular risk factors? Part II will focus on the questions: Is there an inverse cause-and-effect relation between cardiovascular fitness and CHD? What is the relation between cardiovascular fitness and physical activity? Is prescribed physical activity safe and is counseling effective? Answers to these questions will allow clinicians to make an informed decision about the scientific credibility of the US Preventive Task Force recommendation on physical activity counseling.

The criteria used to establish this causal link are those proposed by Sackett, et al.[2] and include (1) establishing an association between exposure and outcome, while accounting for bias and confounding, using well-designed epidemiologic studies; (2) demonstrating an appropriate temporal sequencing between exposure and outcome; (3) establishing an appropriate gradient of biologic response to increasing exposure of the causative agent; (4) evaluating the consistency among studies using different study designs and methods of measurement; and (5) identifying plausible biologic mechanisms to explain the causal link between exposure and outcome.

Establishing this causal link, however, is not enough to recommend therapy in asymptomatic

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adults. Clinical trials that show a therapeutic intervention can be both effective and safe and are usually considered necessary before an intervention is recommended. For example, clinical trials establishing the efficacy of treating hypercholesterolemia in asymptomatic subjects were believed necessary before establishing the National Cholesterol Education Program (NCEP) guidelines, despite considerable epidemiologic evidence showing a causal relation between hypercholesterolemia and CHD.[3-12] Accordingly, issues of safety and efficacy of the physical activity and physical activity counseling are discussed.

Physical activity, exercise, cardiovascular fitness, and physical fitness represent distinct behaviors or attributes. The inappropriate use of these terms by investigators has led to confusion about their respective roles in CHD protection. The definitions of physical activity, exercise, physical fitness, and cardiovascular fitness used in this review are those proposed by Caspersen, et al.[13] and are presented in Table 1. Most of the epidemiologic studies have examined the relation of physical activity (leisure time and job related) to CHD.[14-29] All randomized clinical trials have evaluated exercise in secondary prevention (preventing recurrent CHD).[30-35] Because only a few epidemiologic studies actually studied exercise with regard to primary prevention, this review focuses on physical activity. Additionally, as all of the epidemiologic studies regarding physical fitness and CHD evaluated cardiovascular fitness and not other aspects of physical fitness, the second part of this review focuses on cardiovascular fitness.[36-42]

Thus by limiting the discussion to primary prevention and using the definitions of physical activity and cardiovascular fitness in Table 1, a cohesive understanding of the scientific literature can be attained.

Table 1. Definitions of Physical Activity, Exercise, Physical Fitness, and Cardiovascular Fitness.

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Physical activity can be related to leisure-time activities (gardening, household chores, sports, or exercise) or job-related activities. The degree of physical activity is usually quantitated in degrees of exertion related to rest, metabolic equivalents (METs), or in thermal equivalent of energy expended such as kilojoules. One MET of activity (3.5 mL of oxygen consumption per kilogram per minute) for 24 hours is equal to 24 kcal/kg or 100.8 kJ/kg.

Exercise is defined as planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness. This activity can include aerobic exercise or anaerobic exercise.

Physical fitness is a set of attributes that people have or achieve that relates to the ability to perform physical activity. The health-related components of physical fitness include (1) cardiorespiratory endurance or cardiovascular fitness, (2) muscular endurance, (3) muscular strength, (4) body composition, and (5) flexibility. The skill-related components of physical fitness that lead to enhanced athletic ability include (1) agility, (2) balance, (3) coordination, (4) speed, (5) power, and (6) reaction time.

Cardiovascular fitness is the attribute related to cardiorespiratory endurance. It is reliably measured by maximal exercise testing as maximum oxygen consumption measured in milliliters of oxygen per kilogram per minute. It can be estimated reliably by submaximal exercise tests. It is determined by the combination of constitutional factors (genes, sex, body mass, age), as well as environmental factors (regular aerobic physical activity, previous experience with the exercise test equipment, motivational state), and confounding factors (degree of overall disability and cardiac or respiratory dysfunction).

Methods

All articles written in English relating to the relation of physical activity, physical fitness, exercise, 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, and angina, were recorded. More than 75 articles were reviewed. For the purpose of the summary analysis, only the most recent study was included if several publications came from the same study population. Because women were included in only a few studies, they are not included in the summary analysis.

For the purpose of the meta-analysis of the independent relation of physical inactivity and CHD, a two-step process was used. Only epidemiologic studies using well-defined measures of exposure (standardized interviews, self-reported questionnaires, or meticulous job classification) were included. Studies that used cardiovascular fitness (the attribute) and not physical activity as the measure of exposure were analyzed separately to avoid misclassification bias. Additionally, only easily standardized hard endpoints (CHD mortality, myocardial infarction, or sudden death)

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were evaluated to decrease measurement error of the outcome. Second, only studies in which the multivariate independent relation of physical inactivity and CHD was available were analyzed. This selection of studies controls for confounding bias by adjusting for physical activity affecting body mass index, smoking, lipid status, and blood pressure, all of which can affect CHD outcomes.[43-52] As a result of these selection criteria, the majority of the studies used in previous meta-analyses, which only adjusted for age, are not included in the meta-analytic summary.[53,54]

To compare these results with previous unadjusted summary estimates of the relative risk (RR) of physical activity and CHD, physical inactivity was studied. Methodological details of this meta-analytic summary are given in the Appendix. The appropriateness of the weighted mean as a meta-analytic summary of the effect of physical inactivity and CHD relies upon a relatively stringent homogeneity of variance assumption. This homogeneity of variance assumption implies that the difference in studies reflects background variation of an overall effect. To make this assumption, no systematic bias related to population differences, differences in outcomes measured (CHD mortality versus myocardial infarction incidence), or different exposures measured (total activity, vigorous exercise, and job-related activity) should be present.

To test for systematic bias, the studies' relative risk and 95 percent confidence intervals (95 percent CI) were analyzed by study design and endpoint utilized.

Testing for Causality between Physical Activity and CHD

Are There True Experiments in Humans Showing an Association?

Randomized Clinical Trials

Despite the clear inferential advantages of randomized clinical trials, no primary prevention trials of physical activity have progressed beyond a pilot stage. This lack of clinical trials has been due to the perceived problems with finding adequate numbers of subjects to insure sufficient statistical power, the cost of such a study, the problems of dropout, and crossover of intervention and control groups. Additionally, ethical and logistical issues about management of other risk factors, such as diet, lipids, smoking, and blood pressure, make a randomized primary prevention trial of physical activity unlikely to be attempted.

Epidemiologic Studies

In a review of the published scientific literature, using only one comparison per study, 35 of 52 studies have reported an inverse relation between physical activity and CHD.[14,16-26,28,29,53]

It is well known from epidemiologic and training studies that in small groups, regular physical activity leads to changes in blood pressure,[43-45] diabetes mellitus control[46,47] and insulin sensitivity,[47] lean body mass,[48] lipid profiles,[49-51] and smoking behavior.[52] Each of these factors also independently contributes to CHD incidence and mortality. This relation of cardiac risk factor to physical activity and CHD is by definition confounding bias. Consequently, in evaluating the true independent association of physical activity and cardiovascular fitness to CHD, these confounding factors need to be measured and adjusted for in the analysis before any causal inference can be made reliably.

Fourteen studies listed in Table 2 have been performed that allow for the evaluation of physical activity and CHD independent of other cardiac risk factors (smoking, blood pressure, and cholesterol).[14,16-26,28,29] Of these 14 studies, 12 reported a statistically significant inverse relation of physical activity and CHD,[14,16-26] and all the studies showed a trend in that direction. Case-control studies showed a greater risk of physical inactivity when compared with cohort studies but were less precise as revealed by the width of the 95 percent confidence intervals. Eleven different measures of assessing physical activity were used, including measures of leisure-time physical activity, total activity, and job-related activity. The health insurance plan study[14] and the San Francisco longshoreman study[21] showed an inverse relation between job-related physical activity and CHD, whereas the British civil servants,[16] King's County primary cardiac arrest,[24] Eastern Finland,[25] and San Francisco federal studies[28] did not show occupation-related activity as a risk factor. These results are consistent with comparisons to 14 additional studies for which the unadjusted relation of physical inactivity and CHD have been analyzed.[54] In these studies only 50 percent of the cohort studies that evaluated occupationally re-

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Table 2. Epidemiologic Studies with Adjusted Relative Risks of Physical Inactivity and Coronary Heart Disease.

Study	Design	Exposed Cases	Exposure Type	Number of Participants	RR (95% CI)	Adjustment
US Railroad[19]	Prospective cohort	434 (CHD death)	Leisure	2,562	1.28 (0.99–1.63)	A, Cig, SBP, C
MRFIT[20]	Prospective cohort	225 (CHD death)	Leisure	12,138	1.49 (1.09–2.04)	C, DBP, Cig, A, HDL
Harvard alumni[26]	Historical cohort	441 (CHD death)	Total	16,936	1.57 (1.18–2.09)	A, Cig, hypertension
Framingham[23]	Prospective cohort	371 (CHD death)	Total	1,166	1.21 (1.04–1.40)	A, BP, Cig, O, GI, ECG
San Francisco federal employees[28]	Prospective cohort	65 (CHD death)	Total,* job	2,065	1.19 (0.90–1.57)	A, C, SBP, Cig
Honolulu heart[22]	Prospective cohort	406 (definite CHD)	Total	8,006	1.45 (1.14–1.89)	C, SBP, BMI, A, pulse, LVH, Cig, ETOH
Lipid research clinics follow-up[29]	Prospective cohort	– (definite CHD)	Total, leisure,* job	1,533	1.02 (0.71–1.47)	A, Cig, LDL, FHx, CHD
Puerto Rico heart[17]	Prospective cohort	81 (definite CHD)	Total	2,389 (Rural)	1.32 (1.01–1.7)	A, SBP, Rel Wt, Cig, HR, C
Eastern Finland[25]	Prospective cohort	90 (CHD death)	Total,* leisure, job	15,088	1.40 (1.1–1.7)	A, FHx, health status, BMI, Ed, SN, Cig,C
Netherlands[18]	Case–control	473 (acute coronary events)	Leisure	1,348	2.22 (1.67–3.03)	A, sex, angina, social, Cig, O, BP, FHx, DM
King's County[24]	Case–control	163 (1° cardiac arrest)	Leisure,* job	326	2.63 (1.22–5.55)	Cig, HTN, DM, R, Ed, Oc
San Francisco longshoreman[21]	Historical cohort	291 (CHD death)	Job	3,263	2.2 (1.01–4.82)	A, BP, Cig, O, GI, ECG, R
Health insurance plan[14]	Case- control	613 (first MI)	Leisure,* job	110,000	1.5 (1.1–2.0)	Wt, BP, R, Ed, Cig
British civil servants[16]	Prospective cohort	1138 (clinical CHD)	Leisure,* job	17,944	2.2 (1.86–3.08)	BP, C, Cig, Wt

RR = relative risk, CI = confidence interval, A = age, C = cholesterol, SBP = systolic blood pressure, DBP = diastolic blood pressure, BP = blood pressure, Cig = cigarettes, HDL = high-density cholesterol, LDL = low-density cholesterol, LVH = left ventricular hypertrophy, ETOH = alcohol, O = obesity, GI = glucose intolerance, Ed = education, FHx = family history of CHD, ECG = electrocardiogram, HR = heart rate, SN = social network, BMI = body mass index, R = race, Wt = weight, Rel Wt = relative weight, DM = diabetes mellitus, Oc = occupation.

*Exposure utilized in determining relative risk.

lated physical activity reported an inverse relation with CHD.

When leisure-time physical activity was assessed exclusively, seven out of eight studies showed an independent inverse relation.[14,16,18-20,24,25,29] Only the Eastern Finland study,[25] which had an independent inverse relation for total activity but not leisure-time physical activity, differed from this pattern. Of the seven studies that looked at total daily activity, five showed an independent inverse relation[17,22,23,25,26] and two did not.[28,29] These discrepant results are most compatible with differing degrees of misclassification bias of the degree of physical activity. Thus, occupational classification discriminates poorly between sedentary and active persons in most study populations, whereas leisure-time physical activity is less prone to this misclassification bias.

Many of the studies evaluated multiple outcomes, such as total mortality, CHD death, or definite CHD. To allow comparison between studies and to reduce measurement error, CHD death or definite CHD was used in my analysis. Total mortality analyzed in 3 of the 14 studies showed the same inverse independent relation as CHD death or incidence.[20,23,27] This finding suggests that selective mortality was not a substantial bias in these studies. All 14 studies showed an association in the unadjusted analysis. In 12 of the studies in which the independent association was

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analyzed by multivariate techniques,[17-26,28,29] the relation was diminished in each circumstance but was statistically significant in 10 of the 12 studies.[17,26] Smoking, blood pressure, and age were analyzed as confounders in each study, but only the Multiple Risk Factor Intervention Trial (MRFIT) study analyzed high-density lipoprotein cholesterol as a potential confounder.[20] In this study of leisure-time physical activity, the lowest tertile of physical activity was compared with the most active tertile, which showed an independent inverse relation with total and CHD mortality (RR = 1.49, 95 percent CI = 1.09–2.04).

In summary, it appears that there are valid experiments in humans that establish an independent inverse relation between leisure-time physical activity and CHD incidence and total mortality.

Is the Association Strong?

Figure 1 is a graph of the relative risk and 95 percent confidence intervals derived from all the studies in which a multivariate estimate of the relative risk of sedentary lifestyle was performed.[17-26,28,29] Pooling the 12 studies in which the relative risks were adjusted for known confounders results in a median relative risk of physical inactivity of RR = 1.42. Using a meta-analytic technique to account for the different precision of the various studies, a weighted mean relative risk of RR = 1.37 was derived. The 95 percent confidence interval for such a pooled estimate was 1.27–1.48 with a chi-square test for homogeneity $\chi^2_h = 22.26$, $P = 0.02$. This relative risk and 95 percent confidence interval suggest that a statistically significant relation between physical inactivity and CHD exists independent of traditional risk factors. The chi-square test for homogeneity result suggests that the homogeneity of variance assumption has been violated.

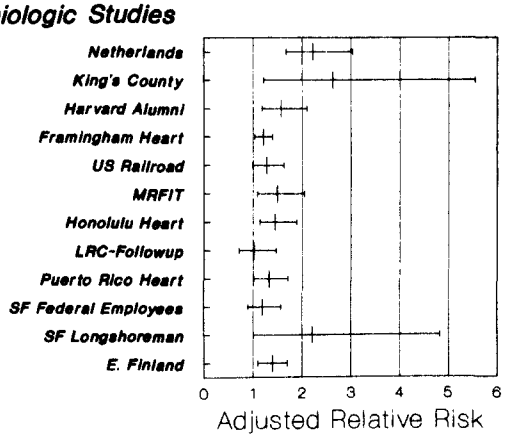

Figure 1. Relative risk and 95% confidence intervals for physical inactivity and coronary heart disease.

Stratifying the results by similar study design and clinical outcomes, the chi-square tests of homogeneity show no violation of homogeneity assumptions and reveal relative risks of similar magnitudes. For cohort studies using CHD death as the endpoint, the RR = 1.30, 95 percent CI (1.17–1.45), $\chi^2_h = 3.31$, $df = 3$, $P = 0.65$. For cohort studies using clinical CHD as the endpoint, the RR = 1.27, 95 percent CI (1.11–1.47), $\chi^2_h = 2.74$, $df = 3$, $P = 0.56$. For case-control studies, the RR = 2.27, 95 percent CI (1.72–2.99), $\chi^2_h = 0.167$, $df = 1$, $P = 0.32$.

In summary, looking at the individual studies graphically or by pooling the results in a meta-analytic summary either by their median or weighted mean average relative risk, the relation of physical inactivity to CHD is consistently present. This relation is present in both the unadjusted and adjusted analyses with little difference in the strength of association in cohort studies measuring leisure-time physical activity. The strength of the association and therefore the risk of physical inactivity (RR ~ 1.3) appear considerably less, however, than other traditional risk factors, such as hypercholesterolemia, cigarette smoking, and hypertension (RR ~ 2.1–2.5), after adjusting for study design and accounting for confounding bias.

Is the Association Consistent from Study to Study?

Examining the 52 published reports of physical activity and CHD by study design allows for a clear inference to be made about the consistency of this relation.[14,16-26,28,29] Fifty percent of the cross-sectional studies showed an inverse relation of physical activity to CHD, whereas 60 percent of the case-control studies showed the same relation. Forty-two percent of cohort studies in which occupational categories defined physical activity showed an inverse relation to CHD, whereas 79 percent of the cohort studies in which physical activity was measured by leisure-time activity showed such an inverse relation.

Analyzing the 12 studies in which the adjusted relation between physical activity and CHD was

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established shows that 83.3 percent reported a statistically significant inverse relation of physical activity to coronary heart disease, and all the studies showed a trend in that direction.[17-26,28,29] Caution should be taken when simply counting the number of positive studies in coming to a conclusion. If the 17 percent of studies that did not show the above relation used more precise measures of the true relation, then an incorrect conclusion could be drawn.

Pooling the above 12 studies by means of a weighted average, the studies that are most precise are weighted the most. Using this technique, the relative risk is 1.37 and its 95 percent confidence interval is 1.27–1.48 for the overall average risk. This estimate of the pooled risk is consistent with the range of the individual studies, suggesting that the association is consistent.

In summary, as the measurement of physical activity becomes more precise either by study design or by measurement techniques, a consistent inverse relation to CHD is found. Thus, the criterion that the association be consistent study to study appears to have been met.

Is the Temporal Relation Correct?

Early studies using cross-sectional or case-control methods could not show temporality. Since those early studies, a large body of prospective cohort studies have reported this inverse relation. Two of the most influential prospective studies, the British civil servant study[15,16] and the Harvard alumni study,[26,27] both relied upon self-reports of physical activity without examining subjects prior to the onset of the determination of their outcomes. Thus, a cohort, free of CHD, was not part of the study design of these important epidemiologic studies. Consequently, the inverse relation of physical activity and CHD in these two studies could represent differential misclassification bias. For example, subjects with premorbid CHD might decrease their activity, leading to a spurious inverse association between physical activity and CHD, and not reflect a true cause-and-effect relation.

Additional studies in which the subjects initially were found to be free of CHD have been performed. The investigators have conclusively established the appropriate exposure first, disease later temporal relation necessary for causal inference.[17,19,20,22,23]

Is There a Dose-Response Relation?

This requirement of causality suggests that increasing levels of physical activity be associated with a decreasing frequency of coronary heart disease. Because more than 30 different methods have been used to measure physical activity in epidemiologic studies, it is not surprising that the above question is difficult to answer conclusively.

Threshold Effect

There is some evidence that a threshold of vigorous physical activity is required for CHD benefit. The British civil servant examination demonstrated a threshold effect.[15,16] Only those participants who performed 31.5 kJ (7.5 kcal) of vigorous activity showed an inverse relation between physical activity and CHD. Lesser degrees of activity did not show this inverse relation.

Additional support for a threshold effect is found in the King's County primary cardiac arrest study.[24] In this study, only greater than 6 metabolic equivalents of physical activity was protective against CHD. In neither study was the duration of physical activity evaluated as a separate factor. Contrary to this apparent threshold effect, the Netherlands study, MRFIT study, Harvard alumni study, Framingham heart study, and Puerto Rico heart study have shown benefit from more moderate degrees of activity.[17-20,23,26]

Intensity of Activity

In the Netherlands study in which habitual walking, cycling, and gardening (WCG), as well as vigorous exercise, were compared with sedentary lifestyle, a benefit was shown for both moderate levels of activity (WCG) and vigorous exercise.[18] Previous interpretation of this study suggested that moderate activity (WCG) was as beneficial as vigorous exercise. This interpretation, however, does not seem warranted when the study is reviewed more carefully. The odds ratio (OR) of physical inactivity is 4.76 for vigorous activity compared with OR = 2.22 for WCG when the same referent group (sedentary) is used. Thus, it appears that vigorous activity exerts greater protective benefits than more moderate degrees of activity.

Contrary to this statement is the evidence from the MRFIT study.[20] This study found no difference between the second and third tertiles of physical activity in establishing the inverse rela-

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tion between physical activity and CHD. Comparing physical inactivity with heavy activity, the relative rate was 1.49, and for moderate activity (the middle tertile), the relative rate was not significantly different (RR = 1.56).

Measuring kilojoules or total kilocalories of energy expended per day in vigorous activity and using this as an estimate of the combined effect of intensity and duration of activity does not account for the possibility that short bursts of vigorous activity may have benefits different from those derived from longer durations of moderate activity. This issue was addressed in the US Railroad study, which found that 4200 kJ (1000 kcal) of moderate activity was equivalent to 420 kJ (100 kcal) of vigorous activity per day in CHD benefits.[19]

Dose-Response Relation

The Harvard alumni study, Framingham heart study, Puerto Rico heart study, and the San Francisco longshoreman study all show a linear dose-response relation of physical activity to CHD.[17,21,23,27] The US Railroad study found both a threshold of 823 kJ/d (196 kcal/d) and a dose-response relation for CHD benefit.[19] Reviewing the literature, Haskell[55] contended that there appears to be a threshold of 630 kJ/d (150 kcal/d) above baseline levels of activity necessary for CHD protection. Also there appears an increasing, though not necessarily linear, benefit up to 1680 kJ/d (400 kcal/d) or 12,600 kJ/wk (3000 kcal/wk). Additionally, there appears to be a plateau of benefits after 14,700 kJ/wk (3500 kcal/wk) as reported by the Harvard alumni and Puerto Rico heart studies.[17,27]

The lack of consistency in establishing a linear dose-response relation may be explained by the effect of measurement error in determining the amounts of physical activity that are actually performed by the subjects. This nondifferential misclassification bias of moderate levels of activity has been shown by LaPorte, et al.[56] using large-scale–integrated activity monitors. LaPorte, et al. reported a greater correlation between self-reported activity and a "gold standard" measure of physical activity (large-scale–integrated activity monitors) in more active college students and school children than in sedentary MRFIT participants and postmenopausal women.

Another explanation of these discrepant results is that vigorous activity that changes cardiovascular fitness exerts greater CHD benefits than do low levels of physical activity. This nonlinear enhancement of CHD benefits would be plausible if enhanced cardiovascular fitness leads to CHD benefits by a mechanism different from low levels of physical activity.

In summary, there does appear to be a graded biologic response of CHD to physical activity, but whether it is linear or has a threshold or both is not clear. Further study of the intensity, duration, and frequency of physical activity necessary for CHD benefit needs to be performed before this question can be answered reliably.

Does the Association Make Biologic Sense?

Table 3 adapted from Fox and Metcalf[57] lists the proposed mechanisms by which physical activity could lead to CHD protection. Physical activity produces significant risk factor modifications suggesting a plausible mechanism by which physical activity could reduce the incidence of CHD and

Table 3. Proposed Mechanism by Which Physical Activity May Reduce Incidence of Coronary Heart Disease.*

System Effect	Mechanism of Action
Modifies risk factors	Lowers triglycerides, raises high-density lipoproteins, improves glucose intolerance, decreases obesity, lowers arterial blood pressure, less catecholamine excess during stress, reduces cigarette smoking
Retards atherosclerosis	Direct effect on endothelium, smooth muscle proliferation
Prevents coronary thrombosis	Decreases platelet adhesiveness, increases fibrinolysis, increases in plasma volume
Remodels coronary arteries	Increases coronary artery diameter, increases coronary collateral vascularization
Improves myocardial function	Increases efficiency of heart for a given workload, decreases heart rate, reduces vulnerability to arrhythmias
Improves physiologic capacity	Enhanced peripheral blood distribution, enhanced oxygen use by peripheral tissues, improved lung function
Increases psychological well-being	Less depression, better relaxation and sleep, enhanced self-image, improved stamina
Improves nutrition	Expanded diet permits greater intake of vitamins, minerals, and other desirable dietary elements (antioxidants, fiber, etc.)

*Adapted from Fox and Metcalf.[57]

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CHD mortality.[43-52] Animal studies have suggested several different mechanisms for the beneficial effect of regular physical activity. In a study of monkeys on atherogenic diets, "exercise was associated with substantially reduced overall atherosclerotic involvement, lesion size, and collagen accumulation; it also produced much larger hearts and wider coronary arteries, further reducing the degree of luminal narrowing."[58 p 1483]

This suggestion that physical activity might have direct effects on atherosclerosis and the coronary artery anatomy has been studied in humans. Rose, et al.[59] found that on autopsy, the cross-sectional area of coronary arteries in men with highly active occupations was greater than sedentary men. Using angiographic data, Fried and Pearson[60] found increased coronary artery diameters with increased physical activity. Additional evidence of the direct effect of exercise on atherosclerosis comes from the work of Selvester, et al.[61] Examining serial angiograms they found a reduction in the progression of coronary atherosclerosis in the most active group. I have found that regular exercise, but not work-related physical activity, is inversely related to angiographically defined premature coronary atherosclerosis in white men (work in progress).

Evidence that physical activity affects clotting factors,[62,63] fibrinogen,[64] and platelet aggregability[65] and therefore leads to decreased thrombosis also has been shown.

Other potential mechanisms by which physical activity may reduce the risk of CHD include decreasing vulnerability to arrhythmias and improving the efficiency of myocardial mechanics through decreasing myocardial oxygen consumption for a given workload. Experimental evidence supporting these mechanisms in humans is limited.[66,67] Although evidence of coronary dilation and the direct effects on atherosclerosis for exercise in humans appears promising, there has been no evidence for development of collateral circulation with regular exercise.[68]

Thus, it appears that there are plausible biologic mechanisms to explain the proposed exposure-to-outcome relation. The most conclusive data exist for the role of physical activity in changing traditional cardiovascular risk factors (smoking, blood pressure, lipids). Evidence for other mechanisms is growing.

Discussion

Findings from this meta-analysis of the independent relation of physical activity and CHD are consistent with the previous reviews by Powell, et al.[53] and Berlin and Colditz.[54] Powell, et al. in 1984 reviewed 47 studies and found a strong, consistent relation between physical inactivity and CHD.[53] Berlin and Colditz, using the same studies as Powell, et al. in addition to the more recent studies included in the present review, came to the same conclusions.[54] Both of these analyses mixed measures of cardiovascular fitness (attribute) and physical inactivity (behavior) in their summary analysis. This mixed analysis of cardiovascular fitness and physical activity leads to concerns about misclassification bias. Because cardiovascular fitness is less prone to measurement error and shows a greater relative risk, when added to studies of physical activity, the true effect of physical activity would tend to be overestimated (bias the results away from the null hypothesis). Because cardiovascular fitness is to a large extent determined by constitutional factors, differences found in such a mixed analysis can reflect these genetic differences and not be referable to differences in physical activity in cardiovascularly fit and unfit groups. In addition, whereas sex and age were evaluated as potential confounders in the above summary analysis, the roles of lean body mass, lipids, smoking, and blood pressure were not analyzed.

In estimating the strength of the association, Powell, et al.[53] calculated the median relative risk of all studies, pooling leisure-time and job-related activity. They included many case-control studies that had greater odds ratios but were less precise. Because their summary statistic did not take into account the varying precision of the studies pooled, their relative risk of 1.9 is probably an overestimate of the true relative risk.[69]

Berlin and Colditz,[54] using an overall weighted average for the unadjusted relation of leisure-time physical activity and CHD, estimated a pooled relative risk of 1.3 with a 95 percent confidence interval of 1.1 to 1.5. They included studies that measured cardiovascular fitness and did not evaluate the independent association of physical inactivity to CHD. The misclassification and confounding bias in their analysis appear to make little difference in the estimate of the relative risk compared with my multivariate analysis. These

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similar estimates of the relative risk may be because misclassification bias from mixing cardiovascular fitness and physical activity tends to bias the results away from the null hypothesis and confounding bias tends to bias toward the null hypothesis. Thus, the net effect is an estimate of the relative risk of physical inactivity to CHD similar to that of the present study.

Selection bias is of particular concern in assessing the validity of observational studies of physical activity and CHD.[70] Subjects who are physically active are self-selected and therefore other characteristics, such as underlying health, disability status, or a constitutional predisposition to CHD protection, associated with this self-selection process may lead to spurious associations between the exposure (physical activity) and CHD.

Summary

All the diagnostic criteria necessary to assert that the scientific evidence showing a cause-and-effect relation between physical activity and CHD have been met. This relation appears independent of the effects of physical activity on other cardiovascular risk factors (smoking, cholesterol, hypertension, weight) but is attenuated in the adjusted analysis. Few studies have evaluated the role of high-density lipoprotein cholesterol as a potential confounder. Questions persist about the role of self-selection in the performance of physical activity and about the problem of misclassification bias in early epidemiologic studies. Additionally, the intensity, duration, and frequency necessary to gain health benefits are unclear. Lastly, the degree to which physical activity exerts its effect through enhancement of cardiovascular fitness is not known.

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. Trout KS. How to read clinical journals: IV. To determine etiology or causation. Can Med Assoc J 1981; 124:985-90.
3. 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.
4. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight, and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project Research Group. J Chronic Dis 1978; 31:201-306.
5. Keys A. Seven countries. A multivariate analysis of death and coronary heart disease. Cambridge, MA: Harvard University Press, 1980.
6. 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.
7. Goldbourt U, Medalie JH, Neufeld HN. Clinical myocardial infarction over a five-year period: III. A multivariate analysis of incidence, the Israel ischemic heart disease study. J Chronic Dis 1975; 28:217-37.
8. 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.
9. 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.
10. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 1986; 8:1245-55.
11. 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.
12. 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.
13. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985; 100:126-31.
14. 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(6)(Suppl):1-106.
15. Morris JN, Chave SP, Adam C, Sirey C, Epstein L, Sheehan DJ. Vigorous exercise in leisure-time and the incidence of coronary heart disease. Lancet 1973; 1:333-9.
16. Morris JN, Everitt MG, Pollard R Jr, Chave SP. Vigorous exercise in leisure-time: protection against coronary heart disease. Lancet 1980; 2:1207-10.
17. Garcia-Palmieri MR, Costas R Jr, Cruz-Vidal M, Sorlie PD, Havlik RJ. Increased physical activity: a

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protective factor against heart attacks in Puerto Rico. Am J Cardiol 1982; 50:749-55.
18. Magnus K, Matroos A, Strackee J. Walking, cycling, and gardening, with and without seasonal interruption, in relation to acute coronary events. Am J Epidemiol 1979; 110:724-33.
19. Slattery ML, Jacobs DR Jr, Nichaman MZ. Leisure time physical activity and coronary heart disease death. The US Railroad Study. Circulation 1989; 79:304-11.
20. Leon AS, Connett J, Jacobs DR Jr, Rauramaa R. Leisure-time physical activity levels and risk of coronary heart disease and death. The Multiple Risk Factor Intervention Trial. JAMA 1987; 258:2388-95.
21. Paffenbarger RS Jr, Laughlin ME, Gima AS, Black RA. Work activity of longshoremen as related to death from coronary heart disease and stroke. N Engl J Med 1970; 282:1109-14.
22. Donahue RP, Abbott RD, Reed DM, Yano K. Physical activity and coronary heart disease in middle-aged and elderly men: the Honolulu Heart Program. Am J Public Health 1988; 78:683-5.
23. Kannel WB, Belanger A, D'Angostino R, Israel I. Physical activity and physical demand on the job and risk of cardiovascular disease and death: the Framingham Study. Am Heart J 1986; 112:820-5.
24. Siscovick DS, Weiss NS, Hallstrom AP, Inui TS, Peterson DR. Physical activity and primary cardiac arrest. JAMA 1982; 248:3113-7.
25. Salonen JT, Slater JS, Tuomilehto J, Rauramaa R. Leisure time and occupational physical activity: risk of death from ischemic heart disease. Am J Epidemiol 1988; 127:87-94.
26. Paffenbarger RS Jr, Wing AI, Hyde RT. Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1978; 108:161-75.
27. Paffenbarger RS Jr, Hyde RT, Wing AI, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. N Engl J Med 1986; 314:605-13.
28. Rosenman RH, Bawol RD, Oscherwitz M. A 4-year prospective study of the relationship of different habitual vocational physical activity to risk and incidence of coronary heart disease in volunteer male federal employees. Ann NY Acad Sci 1977; 301: 627-41.
29. Sisconick DS, Ekelund LG, Hyde JS, Johnson JL, Gordon DJ, LaRosa JC. Physical activity and coronary heart disease among symptomatic hypercholesterolemic men: the Lipid Research Clinics Coronary Primary Prevention Trial. Am J Public Health 1988; 78:1428-31.
30. 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.
31. Palatsi I. Feasibility of physical training after myocardial infarction and its effect on return to work, morbidity and mortality. Acta Med Scand Suppl 1976; 599:7-84.
32. 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.
33. 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.
34. 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.
35. Rechnitzer PA, Sangal S, Cunningham DA, Andrew G, Buck C, Jones NL, et al. A controlled prospective study on the effect of endurance training the recurrence rate of myocardial infarction. A description of the experimental design. Am J Epidemiol 1975; 102:358-65.
36. 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.
37. 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.
38. Sobolski J, Kornitzer M, DeBacker G, Dramaix M, Abramowicz M, Degre S, Denolin H, 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.
39. 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.
40. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men: The Lipid Research Clinics Mortality Follow-up Study. N Engl J Med 1988; 319: 1379-84.
41. Slattery ML, Jacobs DR Jr. Physical fitness and cardiovascular disease mortality. The US Railroad Study. Am J Epidemiol 1988; 127:571-80.
42. Blair SN, Kohl HW 3d, Paffenbarger RS, 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.
43. Amery A, Fagard R, Lijnen P, Reybrouck T. Role of the renin-angiotensin and of the adrenergic system in the blood pressure regulation at exercise in normotensive subjects and in hypertensive patients. Cardiology 1981; 68:103-17.
44. Duncan JJ, Farr JE, Upton J, Hagan RD, Oglesby ME, Blair SN. The effects of aerobic exercise on plasma catecholamines and blood pressure in patients with mild essential hypertension. JAMA 1985; 254:2609-13.

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45. Paffenbarger RS Jr, Wing AL, Hyde RT, Jung DL. Physical activity and incidence of hypertension in college alumni. Am J Epidemiol 1983; 117:245-57.
46. Vranic M, Berger M. Exercise and diabetes mellitus. Diabetes 1979; 28:147-63.
47. Richter EA, Ruderman NB, Schneider SH. Diabetes and exercise. Am J Med 1981; 70:201-9.
48. Epstein LH, Wing RR. Aerobic exercise and weight. Addict Behav 1980; 5:371-88.
49. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. N Engl J Med 1988; 319:1173-9.
50. Hartung GH, Foreyt JP, Mitchell RE, Vlasek I, Gotto AM Jr. Relation of diet to high-density lipoprotein cholesterol in middle-aged marathon runners, joggers, and inactive men. N Engl J Med 1980; 302:357-61.
51. Thompson PD, Cullinane EM, Sady SP, Flynn MM, Bernier DN, Kantor MA, et al. Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. Circulation 1988; 78:25-34.
52. Dannenberg AL, Keller JB, Wilson PW, Castelli WP. Leisure time physical activity in the Framingham Offspring Study. Description, seasonal variation, and risk factor correlates. Am J Epidemiol 1989; 129:76-88.
53. Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. Ann Rev Public Health 1987; 8:253-7.
54. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. Am J Epidemiol 1990; 132:612-28.
55. Haskell WL. Physical activity and health: need to define the required stimulus. Am J Cardiol 1985; 55:4D-9D.
56. La Porte RE, Cauley JA, Kinsey CM, Corbett W, Robertson R, Black-Sandler R, Kuller LH, Falkel JO. The epidemiology of physical activity in children, college students, middle-aged men, menopausal females and monkeys. J Chronic Dis 1982; 35:787-95.
57. Fox SF, 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, 1982:127-42.
58. 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.
59. Rose G, Prineas RJ, Mitchell RA. Myocardial infarction in the intrinsic calibre of coronary arteries. Br Heart J 1967; 29:548-52.
60. Fried LP, Pearson TA. Physical activity and coronary artery diameter: a protective mechanism independent atherosclerosis and thrombosis. Clin Res 1984; 32:221A.
61. 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.
62. Meade TW, Mellow S, Brozovic M, Miller GJ, Chakrabarti RR, North WR, Haines AP, et al. Haemostatic function and ischemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986; 533-7.
63. Kopitsky RG, Switzer ME, Williams RS, McKee PA. The basis for the increase in factor VIII procoagulant activity during exercise. Thromb Haemost 1983; 49:53-7.
64. 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.
65. Rauramaa R, Salonen JT, Seppänen K, Salonen 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.
66. Noakes TD, Higginson L, Opie L. Physical training increases ventricular fibrillation thresholds of isolated red hearts during normoxia, hypoxia and regional ischemia. Circulation 1983; 67:24-30.
67. 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.
68. Nolewajka AJ, Kostuk WJ, Rechnitzer PA, Cunningham DA. Exercise and human collateralization: an angiographic and scintigraphic assessment. Circulation 1979; 60:114-21.
69. Powell KE, Caspersen CJ, Koplan JP, Ford ES. Physical activity and chronic diseases. Am J Clin Nutr 1989; 49:999-1006.
70. LaPorte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: problems and prospects. Public Health Rep 1985; 100:131-46.
71. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9:1-30.

Appendix

The measures of effect (relative rate, relative risk, or odds ratios) greater than unity represent an inverse relation of physical activity and CHD. Using either the relative risk and 95 percent confidence intervals in the individual published papers for physical inactivity or the inverse of the estimate for physical activity, the individual point

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estimates and their 95 percent confidence intervals were derived by the method described by Greenland.[71] In studies where these estimates were not given directly, the log RR was estimated from the betas or hazard functions of the logistic or hazard models given in the individual study. The standard error for each estimate was obtained either directly from the paper or from the assumption of symmetric 95 percent confidence intervals about the log RR given by the formula: standard error (SE) = [log RR (upper 95% CI) – log RR (lower 95% CI)]/3.92 or from the *P* value or *Z* score given by SE = log RR/Zp.

The overall weighted average is given by $RR(av) = Exp[\Sigma(\log RR)(1/SE^2)/\Sigma(1/SE^2)]$, where $(1/SE^2)$ is the weighting factor. The 95 percent confidence interval for the $RR(av) = Exp\{\log RR(av) \pm 1.96(1/[\Sigma(1/SE^2)]^{1/2}\}$. A chi-squared statistic for homogeneity of variance was computed for each meta-analytic summary using the formula: $\chi^2_h = \Sigma[(1/SE^2)]^*[\log RR - \log RR(av)^2]$. Where the homogeneity of variance assumption was violated, stratification of the results was performed to account for differences in study design and outcomes, so that the robustness of the meta-analytic summary could be assessed.

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