Relationship of Leisure-Time Physical Activity and Mortality

The Finnish Twin Cohort

Urho M. Kujala, MD; Jaakko Kaprio, MD; Seppo Sarna, PhD; Markku Koskenvuo, MD

Context.—Physical activity and fitness are believed to reduce premature mortality, but whether genetic factors modify this effect is not known.

Objective.—To investigate leisure physical activity and mortality with respect to familial aggregation of health habits during childhood and factors that may enable some individuals to achieve higher levels of fitness.

Design.—Prospective twin cohort study.

Setting.—Finland.

Subjects.—In 1975, at baseline, 7925 healthy men and 7977 healthy women of the Finnish Twin Cohort aged 25 to 64 years who responded to a questionnaire on physical activity habits and known predictors of mortality. Those who reported exercising at least 6 times per month with an intensity corresponding to at least vigorous walking for a mean duration of 30 minutes were classified as conditioning exercisers, those who reported no leisure physical activity were classified as sedentary, and other subjects were classified as occasional exercisers.

Main Outcome Measures.—All-cause mortality and discordant deaths among same-sex twin pairs from 1977 through 1994.

Results.—Among the entire cohort, 1253 subjects died. The hazard ratio for death adjusted for age and sex was 0.71 (95% confidence interval [CI], 0.62-0.81) in occasional exercisers and 0.57 (95% CI, 0.45-0.74) in conditioning exercisers, compared with those who were sedentary (*P* for trend $<$.001). Among the twin pairs who were healthy at baseline and discordant for death (n=434), the odds ratio for death was 0.66 (95% CI, 0.46-0.94) in occasional exercisers and 0.44 (95% CI, 0.23-0.83) in conditioning exercisers compared with those who were sedentary (*P* for trend, .005). The beneficial effect of physical activity remained after controlling for other predictors of mortality.

Conclusion.—Leisure-time physical activity is associated with reduced mortality, even after genetic and other familial factors are taken into account.

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OBSERVATIONAL STUDIES have suggested that high physical activity or fitness reduces premature mortality.[1-13] However, genetic selection or early childhood experiences may make it easier for some individuals to achieve high levels of physical activity or fitness and favor them with longevity.[13] In the past few years, the importance of familial factors in longevity and mortality has been increasingly recognized. The identification of specific genes that increase susceptibility to major causes of death, such as coronary heart disease and cancer, has stimulated much research. The relative importance of factors over which the individual has little or no control, such as sex, intrauterine and childhood environment, or family history, compared with factors that can be modified, such as diet, smoking, and physical activity, needs further clarification. One method to distinguish between physical activity and genetic and other familial factors is to study family members, in particular, twins who share some or all of the same genes and nearly always the same childhood environment. In this study, we investigated leisure physical activity as a predisposing or preventive factor for premature mortality in the Finnish Twin Cohort.

METHODS

Selection of Subjects

The Finnish Twin Cohort was compiled from the Central Population Registry of Finland in Helsinki via procedures described elsewhere.[14] In brief, the baseline sample comprised all same-sex twin pairs born in Finland before 1958 and with both cotwins alive in 1967. The original cohort also included other subjects who were not twins but who had the same family name and home parish and were born on the same day. The target group for the present study consisted of cohort subjects aged 25 to 64 years on January 1, 1976.

Subjects were mailed a questionnaire in autumn 1975 that included items on physical activity, occupation, body weight, height, alcohol use, smoking, and physician-diagnosed diseases. Among those whose addresses could be identified (93.5% of subjects), the response rate for twins was 87.6% and, for other subjects, 62.8% (as those found to be singletons were no longer sent a reminder). Zygosity (monozygotic, dizygotic, or unclassified) was defined on the basis of questions about strangers confusing the twins in childhood and similarity in childhood appearance, which have been used in other large twin samples.[15] The 2-fold ratio of dizygotic-monozygotic twins reflects the high frequency of fraternal twinning in Finland until the 1960s.[16]

From the Unit for Sports and Exercise Medicine, Institute of Biomedicine (Dr Kujala), and the Department of Public Health, University of Helsinki (Drs Kaprio and Sarna), Helsinki, Finland; and the Department of Public Health, University of Turku, Turku, Finland (Dr Koskenvuo).

Reprints: Urho M. Kujala, MD, Unit for Sports and Exercise Medicine, Mannerheimintie 17 (Töölö Sports Hall), FIN-00250 Helsinki, Finland (e-mail: Urho.Kujala@helsinki.fi).

We included subjects who supplied complete questionnaire data and were alive on January 1, 1977. Because chronic disease may restrict the ability to exercise, we excluded at baseline subjects with certain chronic diseases. Based on the questionnaire, we excluded subjects who reported physician-diagnosed angina pectoris, myocardial infarction, stroke, or diabetes or who had angina pectoris according to standard chest pain history items included in the questionnaire.[17,18] Using the reliable nationwide hospital discharge register maintained by the National Board of Health,[19] we also excluded subjects with inpatient admissions for diabetes (*International Classification of Diseases, Revision 8*[20] [*ICD-8*] code 250), cardiovascular disease except for hypertension or venous diseases (*ICD-8* codes 390-399 or 410-449), or chronic obstructive pulmonary diseases (*ICD-8* codes 490-493) between 1972 and December 31, 1976. In addition, we eliminated all subjects who had been granted reimbursable medication for selected chronic diseases other than hypertension before December 31, 1976, based on data obtained from the Social Insurance Institution of Finland.[21] We also excluded those who had had incident malignant cancer before 1977 according to the Finnish Cancer Registry.[22]

Assessment of Physical Activity

At baseline we asked subjects about their leisure physical activity, including monthly frequency, mean duration, and mean intensity of physical activity sessions; their opinion of their overall physical activity level; and physical activity during the journey to and from work, using a series of structured questions (questionnaire available from authors).[23] In the categorical classification of leisure physical activity, those who reported exercising at least 6 times per month for a mean duration of at least 30 minutes and with a mean intensity corresponding to at least vigorous walking to jogging were classified as conditioning exercisers. Those who reported not partaking in leisure physical activity were considered sedentary. As a check, sedentary subjects also had to report in other questions that the intensity of any activities did not exceed walking and that they participated in physical activities less than 6 times a month. Other subjects were classified as occasional exercisers.

We also classified subjects according to the intensity and total volume of leisure physical activity. For intensity, we classified the subjects according to their participation in vigorous leisure physical activities (yes/no) in which the intensity was greater than walking (ie, at least the equivalent of jogging or running), without any qualifications on frequency or duration. For volume of activity, we calculated an activity metabolic equivalent (MET) index by assigning a multiple of resting metabolic rate (MET score) to each activity and by calculating the product of intensity × duration × frequency of activity.[24] In this calculation, we used the following MET values (work metabolic rate divided by resting metabolic rate): 4 (for exercise intensity corresponding to walking), 6 (vigorous walking to jogging), 10 (jogging), and 13 (running). We also used a MET value of 4 for physical activity during the work journey (usually walking). The activity MET index was expressed as the score of leisure MET hours per day. Only baseline physical activity data were used in the mortality analyses. To assess changes in physical activity patterns over time, a questionnaire with identical physical activity items was readministered in 1981 to the twins, with a response rate of 91%.

Risk Factor Assessment

Using the subjects' self-reports at baseline, we obtained information on other predictors of mortality: occupational group, body mass index (reported weight in kilograms divided by the square of reported height in meters), cigarette smoking, and alcohol consumption. Classification by occupational group was based on job title according to the Central Statistical Office of Finland in Helsinki.[25] Smoking status was classified from responses to a detailed smoking history,[26] and the lifelong dose of smoking was calculated as pack-years (equivalent to smoking 1 pack [20 cigarettes] per day for a year). Alcohol use was recorded in beverage-type specific items on frequency and quantity, converted into grams of absolute alcohol per day.[27]

Mortality Follow-up and Statistical Analyses

To further minimize the effect of occult antecedent disease, we allowed a lag period of at least 1 year after physical activity assessment; the all-cause mortality follow-up began on January 1, 1977, and continued to December 31, 1994. During follow-up, causes of death were available from the Cause of Death Bureau files at the Central Statistical Office of Finland. Cause of death was recorded using *ICD-8* codes. In 52% of cases, cause of death was clear based on forensic or medical autopsy; in other cases, the cause of death was clear based on clinical history. When studying natural-causes mortality (nonviolent causes: *ICD-8* codes 000-799), mortality from external causes (including injuries, suicides, and homicides) was excluded.

We first studied all-cause mortality in the entire study cohort by calculating hazard ratios (HRs) during follow-up by physical activity category and adjusting for age, smoking, occupational group, and use of alcohol at baseline using the Cox proportional hazards model.[28] Our analyses of individuals were based on the statistical assumption of independent observations, which was not strictly true, as 36.8% of subjects were age-matched siblings of other study subjects. However, the correlations between twins for physical activity patterns were only very modest overall. The twin-cotwin intraclass correlation of activity MET index was 0.25 for male twin pairs (0.41 for monozygotic pairs and 0.20 for dizygotic pairs) and 0.20 for female twin pairs (0.38 for monozygotic pairs and 0.13 for dizygotic pairs).

Twin pairs discordant for death were examined to determine whether the mortality of physically active subjects differed from that of their sex- and age-matched sedentary siblings (either monozygotic or dizygotic). This study design does include adjustment for sex and age. These cotwins represent persons who have nearly always shared the same childhood environment and have part or all of their genes in common by descent. We calculated odds ratios (ORs) of death in discordant twin pairs using conditional logistic regression analysis.[29] The twins were classified as discordant for death if one had died during the follow-up period and the cotwin was alive at the end of it. Zygosity by physical activity interaction was fitted after the main effects to test whether the risk of death by physical activity level differed by degree of genetic relatedness. Under the null hypothesis of no genetic selection, the ORs were not expected to differ. We first studied all-cause mortality, but we also studied twin pairs discordant for deaths from natural causes during follow-up.

All significance tests were 2-tailed. The analyses were performed with the SAS statistical package version 6.11 and the EPICURE program package.[29]

RESULTS

Complete questionnaire data on leisure physical activity and all risk factors were obtained for 19 126 subjects (9400 men and 9726 women), 3224 of whom had chronic diseases (criteria above). Our final study cohort included 15 902 subjects (7925 men and 7977 women) who were presumably healthy at baseline (Table 1).

Among the study subjects, the majority were occasional exercisers, approximately 15% were sedentary, and 55% of men and 38% of women participated in vigorous activity. The Spearman correlation between the activity MET indexes

Table 1.—Characteristics of the Finnish Twin Cohort,*

Characteristic	Men (N=7925)	Women (N=7977)
Age at baseline, mean (SD), y	37.1 (9.6)	38.1 (10.4)
Body mass index, mean (SD), kg/m²	24.31 (3.49)	22.87 (4.05)
Cigarette smoking, % of subjects		
Nonsmokers	58.8	80.1
Current smokers	41.2	19.9
Lifetime smoking, mean (SD), pack-years		
All subjects	9.3 (11.5)	2.1 (4.8)
Current smokers	16.3 (11.8)	8.3 (7.1)
Use of alcohol, geometric mean (SD), g/d	5.93 (6.0)	1.1 (8.2)
Occupational group, %		
White-collar workers	12.8	6.7
Clerical workers	23.4	35.6
Skilled workers	44.5	30.6
Unskilled workers	8.2	12.5
Farmers	8.9	9.7
Other	2.1	5.0
Categorical leisure physical activity, %		
Sedentary	15.2	16.5
Occasional exercisers	68.8	78.2
Conditioning exercisers	16.0	5.3
Participation in vigorous activity, % yes	54.8	38.0
MET index quintile, % of subjects		
Quintile I (<0.58 MET h/d)	17.5	23.1
Quintile II (0.59-1.29)	20.1	19.2
Quintile III (1.30-2.49)	20.3	22.4
Quintile IV (2.50-4.49)	21.6	20.6
Quintile V (>4.50)	20.5	14.7

*Metabolic equivalent (MET) index was calculated by assigning a multiple of resting metabolic rate to each activity and calculating the product of intensity × duration × frequency.

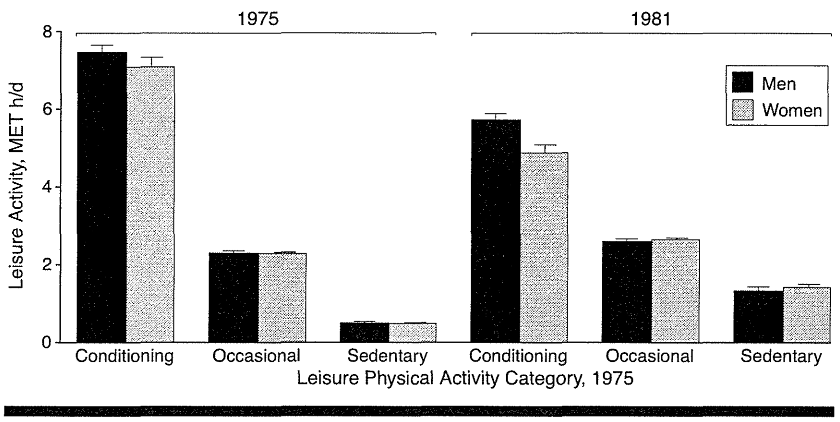

Figure 1.—Leisure activity metabolic equivalent (MET) index as cumulative MET hours per day (mean and SEM) in 1975 and 1985 by leisure physical activity category in 1975. See Table 1 footnote for description of calculation of MET index.

in 1975 and 1981 was 0.48 for men and 0.41 for women. The means of activity MET index in 1975 and 1981 by categorical physical activity in 1975 are shown in Figure 1.

Of the entire study cohort, 1253 subjects (829 men and 424 women) who were healthy at baseline died during the follow-up period. Natural causes (ie, nonviolent causes) explained the death in 1035 subjects (82.6%, 659 men and 376 women). The most common specific causes of death were coronary heart disease in 319 subjects (237 men and 82 women) and cancer in 362 subjects (202 men and 160 women). No differences in all-cause mortality of individuals were observed by zygosity or twinship. The age-adjusted HR of death in women compared with men was 0.41 (95% confidence interval [CI], 0.36-0.46). After adjustment for age and sex, both occasional and conditioning exercisers had reduced risks of death compared with those who were sedentary (*P* for trend <.001). This finding persisted after further adjustment for smoking, occupational group, and use of alcohol (*P* for trend, .002) (Table 2) and was found when analyzed for men and women separately. After adjustment for all covariates, the all-cause mortality HR in those who participated in vigorous activity compared with the others was 0.74 (95% CI, 0.64-0.85; *P*<.001). After adjustment for all covariates, the decrease of HR of death by increasing MET index quintile was 5% (95% CI, 1%-9%; *P* for trend, .02).

Among the twin pairs, 434 same-sex twin pairs were discordant for death during follow-up, of which 173 also were discordant for categorical physical activity (Table 3). Occasional and conditioning exercisers had reduced risks of death compared with those who were sedentary among these twin pairs (*P* for trend, .005) (Table 4). Smoking habits explained some of the risk, but subsequent adjustment for other risk factors (including occupation, alcohol use, hypertension, and body mass index) changed the ORs only minimally (Table 4). The interactions between sex and physical activity category and zygosity and physical activity category were both nonsignificant in the pairwise analyses, thereby revealing that the risk of death declined with increasing physical activity category in both men and women (Figure 2). However, the statistical power to study differences by zygosity was low because, as expected, monozygotic twins had less extreme differences in their physical activity habits. Of the 120 death-discordant monozygotic twin pairs, only 1 time did it happen that 1 twin was sedentary and the cotwin was a conditioning exerciser at baseline; in this case, the conditioning exerciser survived.

In an analysis of the role of leisure physical activity in terms of intensity and total volume among twin pairs, the adjusted OR for mortality among those who participated in vigorous activity compared with the others was 0.79 (95% CI, 0.56-1.10). After adjustment for all covariates among twin pairs discordant for death and activity MET index, the OR of death compared with the lowest MET quintile decreased with increasing MET quintile (*P* for trend, .04) (Figure 3).

There were 340 twin pairs who were healthy at baseline and discordant for death from natural causes during follow-up, among whom occasional exercisers (OR, 0.70; 95% CI, 0.47-1.04) and conditioning exercisers (OR, 0.38; 95% CI, 0.18-0.77) had reduced risks of death compared with sedentary cotwins (*P* for trend, .01). After adjustment for smoking, occupational group, and alcohol use, the OR was 0.79 (95% CI, 0.51-1.21) for occasional exercisers and 0.52 (95% CI, 0.24-1.13) for conditioning exercisers (*P* for trend, .04).

Table 2.—Risks of All-Cause Mortality, 1977-1994, Among Subjects of the Finnish Twin Cohort Healthy and Aged 25 to 64 Years in 1975 (N=15 902), According to Leisure Physical Activity Category*

Activity Category	N	No. of Deaths	Hazard Ratio† (95% CI)	Hazard Ratio‡ (95% CI)	Hazard Ratio§ (95% CI)
Sedentary	2516	302	1.0	1.0	1.0
Occasional exercisers	11 694	869	0.71 (0.62-0.81)	0.76 (0.67-0.87)	0.80 (0.69-0.91)
Conditioning exercisers	1692	82	0.57 (0.45-0.74)	0.68 (0.53-0.88)	0.76 (0.59-0.98)
P for trend			<.001	<.001	.002

*The sedentary group is the reference group. CI denotes confidence interval. Adjustment for baseline body mass index and hypertension changed the hazard ratios only minimally.
†Adjusted for age and sex.
‡Adjusted for age, sex, and smoking (pack-years and smoking status).
§Adjusted for age, sex, smoking, occupational group, and use of alcohol (log-transformed).

Table 3.—Leisure Physical Activity Category in 1975 Among 434 Same-Sex Twin Pairs of the Finnish Twin Cohort Discordant for Death, 1977-1994

	Activity Category of Deceased Twin		
Activity Category of Surviving Twin	Sedentary	Occasional Exerciser	Conditioning Exerciser
Sedentary	29	49	0
Occasional exerciser	70	219	21
Conditioning exerciser	6	27	13

Table 4.—Risks of Death Among 434 Same-Sex Twin Pairs of the Finnish Twin Cohort Discordant for Death, 1977-1994, According to Leisure Physical Activity Category Compared With Sedentary Category in 1975*

Activity Category	Nonadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)	Adjusted Odds Ratio‡ (95% CI)
Sedentary	1.0	1.0	1.0
Occasional exercisers	0.66 (0.46-0.94)	0.70 (0.48-1.01)	0.73 (0.50-1.07)
Conditioning exercisers	0.44 (0.23-0.83)	0.56 (0.29-1.09)	0.56 (0.29-1.11)
P for trend	.005	.04	.06

*The sedentary group is the reference group. CI denotes confidence interval. Adjustment for baseline body mass index and hypertension changed the odds ratios only minimally.
†Adjusted for smoking (pack-years and current smoking habit).
‡Adjusted for smoking, occupational group, and use of alcohol (log-transformed).

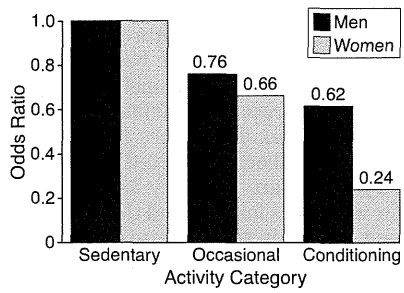

Figure 2.—Risks of death, 1977 to 1994, among 286 male and 148 female twin pairs discordant for death during the follow-up of the Finnish Twin Cohort, aged 25 to 64 years and healthy in 1975, according to leisure physical activity category compared with those who were sedentary in 1975 and adjusted for baseline smoking, occupational group, and use of alcohol.

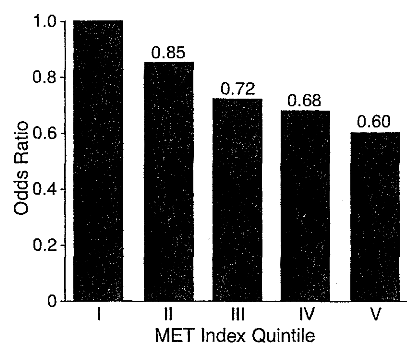

Figure 3.—Risks of death, 1977 to 1994, among 434 same-sex twin pairs discordant for death during the follow-up of the Finnish Twin Cohort, aged 25 to 64 years and healthy in 1975, according to activity metabolic equivalent (MET) index quintiles compared with the lowest MET quintile in 1975 and adjusted for baseline smoking, occupational group, and use of alcohol. See Table 1 footnote for description of calculation of MET index.

COMMENT

The results from the entire study cohort are consistent with earlier study findings[1-13] that there is an inverse association between baseline physical activity and future premature mortality. In an earlier study of Danish twins born between 1870 and 1900, Herskind et al[30] reported that longevity was moderately heritable. In our study, to evaluate the hypothesis that genetic or other familial selection explains the association between leisure physical activity and mortality, we studied baseline physical activity in twin pairs discordant for death during follow-up. Comparison of the physically active cotwins with their less active siblings produced further evidence that familial factors do not explain the mortality differences by physical activity found in individual-based analyses. In recent studies of the effects of longitudinal changes in physical activity and fitness, Paffenbarger et al[8] found that increased physical activity and Blair et al[10] that increased physical fitness were associated with reduced mortality. These findings support our conclusion.

We were unable to identify significant differences in mortality between monozygotic and dizygotic pairs by physical activity, but the relatively small number of discordant monozygotic pairs in the analysis reduced the power to detect possible differences by zygosity. The finding that leisure physical activity habits differ less among monozygotic than dizygotic twin pairs is in accordance with earlier findings.[31] Because monozygotic twins usually have both similar genetic background and rather similar lifestyle habits, end points more sensitive than mortality should be studied to explore the effects of physical activity among monozygotic twin pairs. In choosing discordance in deaths as the main outcome of this study, our primary aim was not to study the differences by zygosity but rather to compare mortality in the population with mortality differences in siblings.

The categorization of baseline physical activity was based on our questionnaire items concerning frequency, intensity, and duration of exercise. All these factors are to some extent related to improved maximal oxygen uptake and prevention of diseases.[32,33] Our analyses also revealed that both participation in vigorous activity and activity volume (MET index) contributed to the reduction in mortality. Despite similar relative risks, the statistical significance was reduced because of the lower number of observations in pairwise analyses compared with individual-based analyses. The dyspnea score (a hierarchal 5-category assessment of the degree of breathlessness associated with different levels of daily physical activity),[17] which we found to be significantly associated ($P<.001$) with the leisure physical activity MET index among both sexes, was further evidence of the validity of the physical activity questions in our baseline questionnaire.

Although individuals who exercise also may differ in other lifestyle habits, the beneficial effect of physical activity remained after controlling for other predictors of mortality. Some of these covariates (eg, hypertension, smoking) have a role in the causal pathway between physical activity and premature mortality. Further adjustment for baseline body mass index and hypertension changed the relative risks only minimally.

Despite sex differences in mortality rates, it has been suspected that sedentary habits are probably as hazardous for women as for men and that inconsistent results in the literature regarding physical inactivity and morbidity in women probably are the result of misclassification because of inadequate assessment measures.[34,35] In our study, the assessment method was similar for men and women, but the statistical power for analyzing the associations among women was lower because of their smaller number of deaths. Even though the mean leisure physical activity MET index for those classified as conditioning exercisers was similar for both sexes, vigorous physical activity in 1975 was less common in women, which further weakened the possibility of studying the effects of physical activity in our female subjects. However, our findings from the pairwise analyses of the beneficial effect of high physical activity on mortality were similar for men and women.

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PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/9466636						
対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	25-64歳			( )		前向き研究
	対象数	10000以上	空白		( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	な し	な し	な し	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )
図 表							
図表掲載箇所							
概 要 (800字まで)	背景：身体活動は、尚早な死亡を減少させると考えられているが、遺伝がこの効果を変化させるか否かは知られていない。目的：より高いレベルの体力を実現することを可能にする個人の要因と幼少期における家族という集合体を考慮し、余暇時間における身体活動と死亡率との関係を調査すること。デザイン：プロスペクティブな双生児のコホート研究。設定：フィンランドにて。対象者：1975年のベースライン時において、質問紙によって運動習慣に回答した25～64歳のフィンランド人双生児である7925人の健康な男性および7977人の健康な女性であった。少なくとも歩行に対応する強度で平均30分の時間、月に6回の運動をおこなっていると報告した人を運動実践群として、余暇時間において身体活動をおこなっていない人は座業群として、その他の対象者は仕事による活動群としてそれぞれ分類された。主な測定結果：1977～1994年の同性双生児の組の全死亡と不一致の死亡状況。結果：全体の中では、1253の対象者が死亡した。年齢と性による補正後の危険率は、座業群と比較して、仕事による活動群で0.71（95%信頼区間 0.62-0.81）、運動実践群で0.57（95%信頼区間 0.45-0.74）であった（$P < 0.001$）。ベースライン時における健康な双生児と不一致の死亡（$n = 434$）の間で、死に対するオッズ比は、座業群のそれらに比べて、仕事による活動群で0.66(95% 信頼区間, 0.46-0.94)、運動実践群で0.44 (95% 信頼区間, 0.23-0.83)であった（$P < 0.005$）。身体活動の有益な効果は、他の死亡予測因子で調整した後も残存した。結論：余暇時間における身体活動は、遺伝や家族の要因を考慮しても死亡を減少させることに関係した。						
結 論 (200字まで)	遺伝的要因が考慮された場合において、身体活動量が多いことは全死亡リスクを低下させる。						
エキスパートによるコメント (200字まで)	双生児の大規模前向き研究という極めて困難な研究デザインで行われた価値のある研究。						

担当者 宮地 劉

Physical Activity and Mortality in Postmenopausal Women

Lawrence H. Kushi, ScD; Rebecca M. Fee, MPH; Aaron R. Folsom, MD; Pamela J. Mink, MPH; Kristin E. Anderson, PhD; Thomas A. Sellers, PhD

Objective.—To evaluate the association between physical activity and all-cause mortality in postmenopausal women.

Design.—Prospective cohort study with 7 years of follow-up through December 31, 1992.

Setting and Participants.—Subjects were 40 417 postmenopausal Iowa women, aged 55 to 69 years at baseline in 1986. Physical activity was assessed by mailed questionnaire.

Main Outcome Measure.—All-cause mortality (n=2260).

Results.—After adjustment for potential confounders and excluding women who reported having cancer or heart disease and those who died in the first 3 years of follow-up, women who reported regular physical activity were at significantly reduced risk of death during follow-up compared with women who did not (relative risk [RR], 0.77; 95% confidence interval [CI], 0.66-0.90). Increasing frequency of moderate physical activity was associated with reduced risk of death during follow-up (from rarely or never engaging in activity to activity at least 4 times per week, RRs, 1.0 [referent], 0.76, 0.70, and 0.62; *P* value for trend<.001). A similar pattern was seen for vigorous physical activity (corresponding RRs, 1.0, 0.89, 0.74, and 0.57; *P* value for trend=.06). Reduced risks of death with increased physical activity were evident for cardiovascular diseases (n=729) and respiratory illnesses (n=147). Women who engaged only in moderate but not vigorous physical activity also benefited, with moderate activity as infrequently as once per week demonstrating a reduced mortality risk of 0.78 (95% CI, 0.64-0.96).

Conclusions.—These results demonstrate a graded, inverse association between physical activity and all-cause mortality in postmenopausal women. These findings strengthen the confidence that population recommendations to engage in regular physical activity are applicable to postmenopausal women.

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IT IS widely accepted that physical activity has beneficial health effects. Studies have demonstrated healthful effects on prevention or management of hypertension,[1] coronary disease,[2] diabetes mellitus,[3] and osteoporosis,[4] among other conditions. These effects and the growing number of studies that have examined the association between physical activity and mortality, primarily from coronary heart disease[5-9] and all causes,[10-25] have led several organizations to recommend regular activity as a health measure.[26,27]

From the Division of Epidemiology, University of Minnesota School of Public Health, Minneapolis.

Reprints: Lawrence H. Kushi, ScD, Division of Epidemiology, University of Minnesota School of Public Health, 1300 S 2nd St, Suite 300, Minneapolis, MN 55454-1015.

A substantial majority of studies investigating the association of physical activity with mortality have been conducted in men. This is evidenced in part by the 1989 US Preventive Services Task Force recommendations on exercise, in which it is stated that the benefits of exercise on coronary artery death have been observed in men but that "efficacy in women is presumed on the basis of extrapolation."[28] In the surgeon general's 1996 report, *Physical Activity and Health*,[29] just 3 studies with women[10-12] were cited in its section on overall mortality.

There have been several other studies of physical activity and all-cause mortality in women,[15-21] most of which indicate a beneficial effect of activity. However, the majority of these were conducted in relatively small populations, and only some included older women. The Iowa Women's Health Study, a large prospective study of postmenopausal women, provided the opportunity to examine the association between physical activity, measured at baseline in 1986, with subsequent mortality over 7 years of follow-up.

METHODS

Subjects

Subjects were recruited from women aged 55 to 69 years who had a valid Iowa driver's license in 1985 (N=195 294). In January 1986, 99 826 of these women were randomly selected and sent a 16-page questionnaire; 41 836 women returned the questionnaire and form the cohort under study. Although women were not excluded from potential recruitment based on race, 40 901 (99.2%) of the cohort members are white or of European descent. Cohort members have mortality rates similar to nonresponders, except for smoking-related causes such as heart disease and lung cancer, which were higher among nonresponders.[30]

Physical Activity Assessment

The baseline questionnaire included questions related to health habits such as smoking and dietary habits, alcohol use, personal medical history including reproductive history, family medical history, and anthropometry, including weight and body circumferences. Leisure physical activity was assessed in 2 ways. First, participants were asked a general question about regular physical activity that has been used for over 3 decades by the Gallup poll[31]: "Aside from any work you do at home or at a job, do you do anything regularly—that is, on a daily basis—that helps keep you physically fit?" Second, participants completed 2 questions asking how often they participate in moderate physical activity (eg, bowling, golf, light sports or physical exercise, garden-

Table 1.—Selected Demographic and Other Characteristics According to Level of Physical Activity Among Postmenopausal Iowa Women, 1986

	Physical Activity Level		
Characteristics	Low (n=18 940)	Medium (n=10 987)	High (n=9919)
Age, mean±SD, y	61.6±4.2	61.8±4.2	61.9±4.2
Body mass index, mean±SD, kg/m²	27.7±5.6	26.7±4.7	26.1±4.4
Body mass index at age 18 y, mean±SD, kg/m²	21.7±3.3	21.6±3.0	21.5±2.9
Total daily energy intake, mean±SD, kJ	7444±2617	7532±2495	7536±2545
Alcohol intake, % none	59	53	54
Education, % beyond high school	34	42	45
Current smoker, %	19	13	10
History of high blood pressure, %	40	37	35

ing, or taking long walks) or vigorous activity (eg, jogging, racket sports, swimming, aerobics, or strenuous sports). Activities listed for moderate activity generally require 6.0 METs (work metabolic rate/resting metabolic rate) or less, while those listed for vigorous activity generally require greater than 6.0 METs.[27] Response options to these questions ranged from "rarely or never" to "more than 4 times a week."

Responses to the questions assessing moderate and vigorous activity were considered individually and were also combined to form a 3-level (low, medium, and high) physical activity index based on frequency and intensity of activity. Women who reported participating in vigorous activity 2 or more times per week or those who reported participating in moderate physical activity more than 4 times per week comprised the high category. Women reporting vigorous activity once a week or moderate activity 1 to 4 times per week were categorized as having medium activity. The remaining women, who reported participating in vigorous or moderate activity a few times a month or less, comprised the low physical activity category.

These measures of physical activity are validated indirectly by the observation that across the physical activity index categories, study subjects' average body mass index (BMI) (weight in kilograms divided by the square of height in meters) were 27.7 kg/m² for low, 26.7 kg/m² for medium, and 26.1 kg/m² for high activity levels. Although less striking, mean energy intakes, estimated by a semiquantitative food frequency questionnaire, also differed as expected, averaging 7444 kJ per day among women with low physical activity and 7536 kJ per day among those with high physical activity. These and other characteristics of the study population according to physical activity level are shown in Table 1.

Exclusions

Women were excluded from analysis if they were not postmenopausal at baseline (n=569), if they did not respond to questionnaire items regarding cigarette smoking (n=653), or if none of the questions pertaining to physical activity had been answered (n=197). These exclusions left a total of 40 417 women eligible for follow-up.

Ascertainment of End Points

Deaths were identified annually through linkage of cohort members with the State Health Registry of Iowa and the National Death Index. The underlying cause of death was coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*). As of December 31, 1992, after approximately 7 years of follow-up, 2284 deaths had been documented in the study cohort. Of these deaths, 1101 were due to cancer (*ICD-9* codes 140-239.9), 739 were due to cardiovascular disease, including ischemic heart disease, cerebrovascular disease, or peripheral vascular disease (*ICD-9* codes 390-459.9), 150 were due to respiratory disease, including acute respiratory infections, pneumonia or influenza, or chronic obstructive pulmonary disease (*ICD-9* codes 460-519.9), 57 were due to injury (*ICD-9* codes 800-959.9), and 237 were due to other causes.

Data Analysis

Proportional hazards regression was used to compute relative risks (RRs), their 95% confidence intervals (CIs), and *P* values for trend in RRs. There was no evidence that proportional hazards assumptions were violated. Multivariate-adjusted models included the following covariates: age at baseline, age at menarche (<13 years or ≥13 years), age at menopause (<45 years, 45-49 years, or ≥50 years), age at first live birth (<30 years or ≥30 years), parity, alcohol intake (none, <4 g/d, and ≥4 g/d), total energy intake, cigarette smoking (current, past, or never), use of estrogen replacement therapy (ever or never), BMI at baseline, BMI at age 18 years, waist-to-hip ratio, educational level (did not graduate from high school, high school graduate, some college or technical school, or college graduate), marital status (currently married or other), first-degree female relative with cancer (used only in total mortality and cancer mortality analyses), and history of high blood pressure or diabetes (used only in total mortality, cardiovascular disease mortality, and other mortality analyses).

Analyses were first conducted in the total eligible cohort to examine overall associations of leisure physical activity and mortality. Second, since women who were ill at baseline may be less likely to be active and more likely to die, analyses were conducted after excluding women who responded affirmatively at baseline to the questions, "Have you ever been told by a doctor that you have ... heart disease or angina or [had a] heart attack?" or "Have you ever been diagnosed by a physician as having any form of cancer, other than skin cancer?" Analyses were also conducted after excluding women who died in the first 3 years of follow-up as another approach to diminish the influence of this bias. Finally, analyses excluding women who reported baseline heart disease or cancer or who died in the first 3 years of follow-up were conducted.

RESULTS

Table 2 shows the RRs and 95% CIs of death from all causes according to different measures of physical activity, adjusted for age only and for multiple covariates. Higher levels of physical activity were associated with a decreased risk of death. For example, among women reporting regular physical activity compared with those reporting no regular physical activity, the multivariate-adjusted RR was 0.78 (95% CI, 0.71-0.86). For moderate activity, increasing frequency was associated with decreasing risk. Multivariate-adjusted RRs from low to high frequency of moderate activity were 1.0, 0.71, 0.63, and 0.59 (*P* for trend<.001). A similarly strong, monotonic trend was seen for vigorous activity and the physical activity index.

Since women who are ill tend to be less active and may be at increased risk of death, analyses were conducted in subgroups of participants according to reported personal history of cancer or heart disease at baseline and by excluding deaths that occurred during the first 3 years of follow-up. As shown in Table 3, the multivariate-adjusted inverse associations of physical activity with death were slightly less striking among women with no baseline disease and women who survived at least 3 years of follow-up than in the total cohort. Nonetheless, there were still strong and consistent inverse associations of physical activity with death. Among women with no baseline disease, after excluding those who died in the first 3 years of follow-up, the RR of death for those who had any regular physical activity compared with those who had none was 0.77 (95% CI, 0.66-0.90). Increasing frequency of moderate and vigorous physical activity were also associated with decreased risk of mortality.

These inverse associations were also apparent if the most active category was the reference category. For example, for the physical activity index, the RR of death during the follow-up period was 1.15 (95% CI, 0.93-1.43) for medium activity and 1.40 (95% CI, 1.16-1.70) for low activity in comparison to women with high activity.

To examine whether the effect of physical activity was stronger for younger or older postmenopausal women, we conducted analyses stratified by 5-year categories of age at baseline. In all age categories, mortality was inversely associated with physical activity when early deaths were omitted and when subjects with and without baseline disease were considered separately (Table 4). There was no statistical evidence of an age and physical activity interaction.

Analyses were also conducted with subjects stratified by waist-to-hip ratio (in quartiles) and by smoking status (current, past, or never). There was little suggestion that the effect of physical activity was modified by waist-to-hip ratio. In smoking-stratified analyses, inverse associations were seen for all smoking status categories between risk of mortality and physical activity. As measured by the physical activity index variable, physical activity was associated with decreased mortality risk most strongly for past smokers, with an RR of 0.49 (95% CI, 0.38-0.63) for the highest level of the index compared with the lowest. For current smokers, the cor-

Table 2.—Relative Risks (RR) of Total Mortality According to Level of Physical Activity Among 40 417 Postmenopausal Women in Iowa, 1986-1992

			RR (95% Confidence Interval)	
Physical Activity Variables	**Deaths**	**Person-Years**	**Age-Adjusted**	**Multivariate-Adjusted***
Regular physical activity				
No	1518	157 379	1.00	1.00
Yes	742	111 811	0.67 (0.61-0.73)	0.78 (0.71-0.86)
Frequency of moderate physical activity				
Rarely/never	722	55 404	1.00	1.00
1/wk to a few a month	621	76 318	0.63 (0.57-0.70)	0.71 (0.63-0.79)
2-4 times/wk	560	82 633	0.51 (0.46-0.57)	0.63 (0.56-0.71)
>4 times/wk	365	55 973	0.48 (0.42-0.54)	0.59 (0.51-0.67)
P value for trend			<.001	<.001
Frequency of vigorous physical activity				
Rarely/never	2000	222 967	1.00	1.00
1/wk to a few a month	139	23 138	0.70 (0.59-0.83)	0.83 (0.69-0.99)
2-4 times/wk	85	16 423	0.61 (0.49-0.76)	0.74 (0.59-0.93)
>4 times/wk	30	6242	0.55 (0.38-0.79)	0.62 (0.42-0.90)
P value for trend			<.001	.009
Physical Activity Index†				
Low	1309	126 545	1.00	1.00
Medium	519	74 170	0.66 (0.60-0.73)	0.77 (0.69-0.86)
High	415	67 138	0.58 (0.52-0.65)	0.68 (0.60-0.77)
P value for trend			<.001	<.001

*Adjusted for age at baseline, age at menarche, age at menopause, age at first live birth, parity, alcohol intake, total energy intake, cigarette smoking, estrogen use, body mass index at baseline, body mass index at age 18 years, waist-to-hip ratio, first-degree female relative with cancer, high blood pressure, diabetes, education level, and marital status.

†See "Methods" section for definition.

Table 3.—Multivariate-Adjusted Relative Risks* (RR) of Total Mortality According to Level of Physical Activity, Stratified for Baseline Disease Status and Excluding the First 3 Years of Deaths, Among Postmenopausal Women in Iowa, 1986-1992

	Cohort (Size of Cohort; No. of Deaths)							
	Women With Baseline Disease† (7263; 1007)		Women Without Baseline Disease† (33 154; 1277)		Women Who Survived at Least 3 y (39 581; 1448)		Women Without Disease† Who Survived 3 y (32 763; 886)	
Physical Activity Variables	**Deaths‡**	**RR (95% CI)**	**Deaths‡**	**RR (95% CI)**	**Deaths‡**	**RR (95% CI)**	**Deaths‡**	**RR (95% CI)**
Regular physical activity								
No	672	1.00	846	1.00	955	1.00	580	1.00
Yes	324	0.56 (0.67-0.80)	418	0.80 (0.70-0.90)	482	0.80 (0.72-0.91)	289	0.77 (0.66-0.90)
Frequency of moderate physical activity								
Rarely/never	345	1.00	377	1.00	429	1.00	251	1.00
1/wk to a few a month	271	0.75 (0.63-0.89)	350	0.73 (0.62-0.84)	415	0.78 (0.67-0.90)	256	0.76 (0.63-0.91)
2-4 times/wk	236	0.61 (0.51-0.73)	324	0.68 (0.58-0.80)	362	0.69 (0.59-0.80)	231	0.70 (0.58-0.85)
>4 times/wk	148	0.51 (0.41-0.63)	217	0.67 (0.56-0.80)	233	0.63 (0.53-0.75)	141	0.62 (0.50-0.78)
P value for trend		<.001		<.001		<.001		<.001
Frequency of vigorous physical activity								
Rarely/never	893	1.00	1107	1.00	1267	1.00	766	1.00
1/wk to a few a month	52	0.82 (0.61-1.10)	87	0.89 (0.71-1.13)	90	0.57 (0.68-1.06)	62	0.89 (0.67-1.12)
2-4 times/wk	37	0.83 (0.59-1.18)	48	0.74 (0.55-1.00)	56	0.76 (0.57-1.01)	35	0.74 (0.52-1.05)
>4 times/wk	10	0.49 (0.26-0.95)	20	0.73 (0.46-1.17)	17	0.50 (0.30-0.85)	12	0.57 (0.31-1.07)
P value for trend		.04		.13		.008		.06
Physical Activity Index§								
Low	598	1.00	711	1.00	820	1.00	493	1.00
Medium	220	0.71 (0.61-0.84)	299	0.82 (0.71-0.95)	335	0.81 (0.71-0.92)	211	0.82 (0.69-0.98)
High	169	0.60 (0.50-0.72)	246	0.75 (0.64-0.87)	270	0.71 (0.60-0.82)	167	0.71 (0.59-0.86)
P value for trend		<.001		<.001		<.001		<.001

*Adjusted for age at baseline, age at menarche, age at menopause, age at first live birth, parity, alcohol intake, total energy intake, smoking status, estrogen use, body mass index at baseline, body mass index at age 18 years, waist-to-hip ratio, first-degree female relative with cancer, high blood pressure, diabetes, education level, and marital status.

†Baseline disease refers to self-report of any cancer other than skin cancer, heart disease, angina, or heart attack. CI indicates confidence interval.

‡Totals may differ from column headings or among activity variables due to missing data.

§See "Methods" section for definition.

Table 4.—Multivariate-Adjusted Relative Risks* (RR) of Total Mortality According to Physical Activity Index, Stratified for Age, Among Postmenopausal Women in Iowa and Excluding Baseline Disease† and the First 3 Years of Follow-up, 1986-1992

	Age Group					
	<60 y (n=13 148‡)		60-64 y (n=13 044‡)		≥65 y (n=10 850‡)	
Cohorts	Deaths	RR (95% CI)	Deaths	RR (95% CI)	Deaths	RR (95% CI)
			All Women			
Low activity	298	1.00	471	1.00	540	1.00
Medium activity	133	0.88 (0.71-1.09)	175	0.74 (0.61-0.89)	211	0.74 (0.63-0.88)
High activity	89	0.74 (0.58-0.96)	147	0.67 (0.55-0.82)	179	0.66 (0.55-0.79)
P value for trend		.02		<.001		<.001
			Women Without Disease at Baseline			
Low activity	161	1.00	246	1.00	304	1.00
Medium activity	79	0.97 (0.73-1.29)	91	0.72 (0.56-0.93)	129	0.82 (0.66-1.02)
High activity	47	0.80 (0.57-1.13)	87	0.73 (0.56-0.95)	112	0.74 (0.59-0.94)
P value for trend		.20		.02		.01
			Women Who Survived at Least 3 y			
Low activity	186	1.00	304	1.00	330	1.00
Medium activity	86	0.95 (0.73-1.25)	111	0.71 (0.56-0.89)	138	0.82 (0.66-1.00)
High activity	54	0.74 (0.54-1.02)	93	0.65 (0.51-0.83)	123	0.74 (0.59-0.92)
P value for trend		.07		<.001		.008
			Women Without Disease at Baseline Who Survived at Least 3 y			
Low activity	115	1.00	176	1.00	202	1.00
Medium activity	59	1.00 (0.72-1.40)	69	0.72 (0.53-0.97)	83	0.80 (0.61-1.05)
High activity	36	0.82 (0.55-1.22)	52	0.58 (0.42-0.81)	79	0.78 (0.59-1.03)
P value for trend		.32		.002		.09

*Adjusted for age at baseline, age at menarche, age at menopause, age at first live birth, parity, alcohol intake, total energy intake, cigarette smoking, estrogen use, body mass index at baseline, body mass index at age 18 years, waist-to-hip ratio, first-degree female relative with cancer, high blood pressure, diabetes, education level, and marital status.

†Baseline disease refers to self-report of any cancer other than skin cancer, heart disease, angina, or heart attack. CI indicates confidence interval.

‡These numbers indicate the number of women in each age stratum for the total cohort, with no missing data for Physical Activity Index or covariates. Numbers of women in subcohorts differ due to exclusion for baseline disease or survival of at least 3 years.

responding RR was 0.76 (95% CI, 0.59-0.97), and for those who never smoked, it was 0.77 (95% CI, 0.66-0.90).

Table 5 presents the multivariate-adjusted RRs of mortality from specific causes by level of physical activity; these are presented for women without baseline disease and excluding deaths in the first 3 years of follow-up. Mortality risk for each cause of death category was lower among women reporting regular physical activity as opposed to no regular physical activity. An inverse association between physical activity and risk of mortality was also seen using the physical activity index in each cause of death category. These associations were most striking for respiratory illnesses and cardiovascular diseases but were modest and not statistically significant for cancer; the categories injury and other causes were based on small numbers and also were not statistically significant. Risk of death from cardiovascular disease decreased with increasing frequency with both moderate (RRs from low to high frequency, 1.0, 0.86, 0.74, and 0.53; *P* for trend=.003) and vigorous physical activity (RRs from low to high frequency, 1.0, 0.85, 0.59, and 0.20; *P* for trend=.09). The risk of respiratory death decreased strikingly as physical activity level increased among the cohort (eg, for most frequent moderate physical activity compared with least frequent, RR, 0.18; 95% CI, 0.06-0.52).

Because of suggestions that physical activity is inversely associated with all-cause mortality only at vigorous and not at moderate levels,[32] analyses were performed among subjects who reported moderate activity but "rare or no" vigorous activity. Very few subjects (n=32) reported vigorous activity in the absence of any moderate activity, and so it was therefore not possible to examine the effects of engaging only in vigorous activity.

Among all cohort members who reported moderate activity in the absence of any vigorous activity, a clear inverse association was seen (Table 6). From low to high frequency of moderate physical activity, the RRs were 1.0, 0.73, 0.69, and 0.61 (*P* for trend<.001). This inverse association remained after exclusion of women with reported disease at baseline and after excluding deaths in the first 3 years of follow-up. In this group of women, RRs of dying, from low to high frequency of moderate activity, were 1.0, 0.78, 0.77, and 0.67 (*P* for trend=.004). Thus, moderate activity as infrequently as once per week was associated with decreased mortality risk (RR, 0.78; 95% CI, 0.64-0.96).

COMMENT

The principal finding from this prospective study in postmenopausal women is a consistent, graded, inverse association between frequency of leisure physical activity and total mortality. Based on a 3-level index combining frequency and intensity of physical activity, women in the highest level of the index had approximately a 30% lower risk of death from all causes compared with those in the lowest level, while women in the middle level had an intermediate level of risk. The inverse association of physical activity with mortality was noted for measures of both moderate and vigorous activity and was apparent for those with and without reported cancer and cardiovascular disease at baseline. Exclusion of deaths in the first 3 years of follow-up did not alter these findings.

To our knowledge, this prospective study of physical activity and mortality from all causes, with 2284 deaths over a 7-year follow-up period, is one of the largest to date to be conducted in women. Although most previous studies of activity and all-cause mortality in women have been supportive of an inverse association, most have been conducted in relatively small cohorts with substantially fewer deaths than occurred in this study. One of the largest of these, the Longitudinal Study on Aging, followed up 3679 women and 2222 men aged 70 years and older over a 5-year period.[16] In that study, there were 1098 deaths, about half of which occurred among the women; several different questions related to activity indicated an inverse association between activity and mortality. In another relatively large study, the Framingham Study, 1404 women aged 50 to 74 years were followed up for a period of 16 years; at the end of follow-up, 319 of the women had died.[14] The authors reported that women in the third or fourth quartile of activity had an RR of all-cause mortality of about 0.65 compared with the lowest quartile of activity. An analysis from the Framingham Study that focused on men and women aged 75 years or older also showed an inverse association of activity with all-cause mortality.[15] It was also reported in the NHANES I Epidemiologic Follow-up Study, where 673 deaths occurred after 10 years among 2197 women, that inactivity increased risk of total mortality.[17]

In our study, the inverse associations of physical activity with mortality were most striking for deaths due to respiratory or cardiovascular causes. These findings are in agreement with the great majority of studies, mostly conducted in men,

Table 5.—Multivariate-Adjusted Relative Risks* (RR) of Mortality From Specific Causes According to Level of Physical Activity Among 32 763 Postmenopausal Women in Iowa Free of Baseline Disease† Who Survived at Least 3 Years Since Baseline, 1986-1992

Physical Activity Variables	Cancer§ Deaths¶	Cancer§ RR (95% CI)	Cardiovascular Disease‖ Deaths¶	Cardiovascular Disease‖ RR (95% CI)	Respiratory Illnesses Deaths¶	Respiratory Illnesses RR (95% CI)	Injury Deaths¶	Injury RR (95% CI)	Other Causes‖ Deaths¶	Other Causes‖ RR (95% CI)
Regular Physical Activity										
No	272	1.00	496	1.00	46	1.00	20	1.00	74	1.00
Yes	163	0.93 (0.76-1.14)	178	0.72 (0.54-0.95)	10	0.33 (0.16-0.67)	5	0.45 (0.16-1.24)	28	0.69 (0.44-1.09)
Frequency of moderate physical activity										
Rarely/never	114	1.00	72	1.00	24	1.00	7	1.00	34	1.00
1/wk to a few a month	116	0.79 (0.60-1.03)	83	0.86 (0.61-1.21)	19	0.63 (0.34-1.17)	8	0.94 (0.31-2.82)	30	0.66 (0.39-1.11)
2-4 times/wk	117	0.80 (0.61-1.05)	69	0.74 (0.52-1.05)	10	0.30 (0.14-0.67)	9	0.99 (0.33-2.97)	26	0.54 (0.31-0.94)
>4 times/wk	86	0.85 (0.63-1.15)	36	0.53 (0.34-0.82)	4	0.18 (0.06-0.52)	2	0.37 (0.07-1.91)	13	0.45 (0.23-0.88)
P value for trend		.33		.003		<.001		.26		.02
Frequency of vigorous physical activity										
Rarely/never	366	1.00	233	1.00	55	1.00	25	1.00	87	1.00
1/wk to a few a month	37	1.09 (0.77-1.53)	16	0.85 (0.50-1.44)	0	0.00 . . .#	0	0.00 . . .	8	1.06 (0.48-2.30)
2-4 times/wk	20	0.83 (0.52-1.33)	8	0.59 (0.28-1.25)	1	0.30 (0.04-2.17)	1	0.59 (0.08-4.44)	5	1.11 (0.44-2.76)
>4 times/wk	7	0.69 (0.31-1.54)	2	0.20 (0.03-1.41)	0	0.00 . . .	0	0.00 . . .	3	1.45 (0.46-4.63)
P value for trend		.28		.09		.99		.99		.53
Physical Activity Index**										
Low	221	1.00	151	1.00	42	1.00	15	1.00	64	1.00
Medium	107	0.92 (0.72-1.16)	65	0.86 (0.63-1.17)	10	0.42 (0.20-0.87)	8	0.97 (0.38-2.48)	21	0.55 (0.32-0.96)
High	99	0.94 (0.73-1.21)	42	0.55 (0.38-0.81)	5	0.24 (0.09-0.61)	3	0.45 (0.13-1.63)	18	0.64 (0.37-1.10)
P value for trend		.64		.002		.003		.22		.11

Cause of Death‡

*Adjusted for age at baseline, age at menarche, age at menopause, age at first live birth, parity, alcohol intake, total energy intake, cigarette smoking, estrogen use, body mass index at baseline, body mass index at age 18 years, waist-to-hip ratio, education level, and marital status.
†Baseline disease refers to self-report of any cancer other than skin cancer, heart disease, angina, or heart attack.
‡Causes of death were classified according to *International Classification of Diseases, Ninth Revision* code as follows: cancer, 140-209; cardiovascular diseases, 390-459; respiratory illnesses, 460-519; injury, 800-959; other causes, all other codes.
§Analyses also adjusted for first-degree female relative with cancer. CI indicates confidence interval.
‖Totals may differ among activity variables due to missing data.
¶Analyses also adjusted for history of high blood pressure and history of diabetes.
#Ellipses indicate that confidence intervals were not able to be calculated because there were no deaths.
**See "Methods" section for definition.

Table 6.—Multivariate-Adjusted Relative Risks* (RR) of Total Mortality According to Frequency of Moderate Physical Activity Among Postmenopausal Women in Iowa Who Reported No Vigorous Physical Activity, Excluding Baseline Disease† or the First 3 Years of Deaths, 1986-1992

Frequency of Moderate Physical Activity	All Women (27 974; 1787) Deaths	All Women (27 974; 1787) RR (95% CI)	Women Without Baseline Disease† (22 589; 968) Deaths	Women Without Baseline Disease† (22 589; 968) RR (95% CI)	Women Who Survived at Least 3 y (27 313; 1126) Deaths	Women Who Survived at Least 3 y (27 313; 1126) RR (95% CI)	Women Without Disease† Who Survived 3 y (20 718; 665) Deaths	Women Without Disease† Who Survived 3 y (20 718; 665) RR (95% CI)
Rarely/never	680	1.00	352	1.00	402	1.00	231	1.00
1/wk to a few a month	498	0.73 (0.65-0.83)	274	0.75 (0.63-0.88)	331	0.81 (0.69-0.94)	198	0.78 (0.64-0.96)
2-4 times/wk	381	0.69 (0.60-0.78)	210	0.74 (0.62-0.89)	244	0.76 (0.64-0.90)	147	0.77 (0.62-0.95)
>4 times/wk	228	0.61 (0.52-0.71)	132	0.68 (0.55-0.84)	149	0.67 (0.55-0.82)	89	0.67 (0.52-0.88)
P value for trend		<.001		<.001		<.001		.004

Cohort (Size of Cohort; No. of Deaths)

*Adjusted for age at baseline, age at menarche, age at menopause, age at first live birth, parity, alcohol intake, total energy intake, cigarette smoking, estrogen use, body mass index at baseline, body mass index at age 18 years, waist-to-hip ratio, first-degree female relative with cancer, history of high blood pressure, history of diabetes, education level, and marital status.
†Baseline disease refers to self-report of any cancer other than skin cancer, heart disease, angina, or heart attack. CI indicates confidence interval.

that have examined the association of activity, exercise, or fitness with cardiovascular disease.[2,6-9,22-25] There are relatively few studies of activity and cardiovascular mortality in women. In a recent report from the Framingham Heart Study, no association was observed between physical activity and 16-year mortality from cardiovascular diseases among women.[14] However, other studies in women have generally been supportive of an inverse association between activity levels and cardiovascular mortality.[5,10,13,19]

We observed only a small inverse association of physical activity with deaths due to cancer that was not statistically significant. Of the studies examining activity and all-cause mortality in women, only 2 reported associations with deaths due to cancer.[10,14] An inverse association with cancer mortality was observed in one of these studies[14] and was suggested in the other[10]; in the former, the inverse association was also seen among men. In contrast, no association between physical activity and cancer deaths was observed in a 10-year follow-up of participants in the Multiple Risk Factor Intervention Trial, a study of men.[23] One other study found an inverse association of activity with cancer mortality among men between 50 and 70 years of age but not among men who were older.[25]

The inverse associations of physical activity with death from respiratory causes was striking; this has not been reported in other studies. However, unlike with cancer or heart disease, we did not have baseline information on history of respiratory illnesses. Thus, we cannot determine whether respiratory deaths among the more sedentary were due to more severe underlying disease rather than to lack of physical activity. While the risk of respiratory deaths was inversely associated with activity even among those who never smoked cigarettes in this cohort (RRs for low, medium, and high activity, 1.0, 0.5, and 0.4; *P* for trend=.22), there were only 13 such deaths, and this does not control adequately for other causes of respiratory illnesses. Further studies are required to clarify these associations.

Recently, it was reported in the Harvard Alumni Study that all-cause mortality was decreased among men who participated in vigorous activities but not among men who participated in nonvigorous activities.[32] Although our measures of physical activity intensity are less precise than in that study, even relatively infrequent levels of moderate activity—engaging in such activities no more than 1 time per week—were associated with decreased risk of all-cause mortality in these Iowa women (Table 6). More frequent and intense levels resulted in greater reductions in risk. While we are unable to derive an estimate of energy expenditure from our questions, it is clear that the activities categorized as "moderate" in our questionnaire require less than 6.0 METs,[27] the cutpoint used for this classification in the Harvard Alumni Study.[32]

While the reasons for the discrepancy in findings between these 2 studies are not clear, they may relate to differences in assessment of physical activity, greater variation in moderate activity levels in our study, or more precise categorization of moderate activities on the part of the women in our study than the men in the Harvard Alumni Study. Perhaps most important are differences in activity level related to the age and sex of our cohort. For example, it is known that men are more likely than women to engage in vigorous activity, and the total amount of time engaging in physical activity declines with age.[27] The activities categorized as moderate by our questionnaire may encompass a range of activities that would be considered vigorous for this population of postmenopausal women. Thus, although in absolute terms the categories of moderate and vigorous activity may be comparable between our study and the Harvard Alumni Study, in relative terms, these may differ considerably.

In our study, no information was collected on changes in activity levels; thus, it is not possible to examine whether adopting more physically active lifestyles in the postmenopausal years is associated with decreased mortality risk. In a recent Swedish study, there was an increase in mortality risk among those who decreased their activity.[33] In our study, there was also no specific assessment of lifetime or occupational physical activity levels. Thus, our observations pertain to the effects of current leisure physical activity.

In summary, the findings from this study add to the evidence that regular physical activity is associated with decreased risk of all-cause mortality, in particular mortality from cardiovascular diseases. These observations, in a large cohort of postmenopausal women, strengthen the confidence that population recommendations to maintain physically active lifestyles can apply not just to women but also to older women. Even infrequent moderate activity—as little as once per week—is associated with decreased risk of death compared with a sedentary lifestyle.

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エキスパートレビューのフォーマット

論文名	Physical activity and mortality in postmenopausal women.						
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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		(　　)		コホート研究
	性別	女性	(　　)		(　　)		(　　)
	年齢	55-69歳	[redacted]		(　　)		前向き研究
	対象数	10000以上	空白		(　　)		(　　)
調査の方法	質問紙	(　　)					
アウトカム	予 防	心疾患予防	な し	ガン予防	な し	(　　)	(　　)
	維持・改善	な し	な し	な し	な し	(　　)	(　　)
図 表							
図表掲載箇所							
概 要 (800字まで)	目的:閉経女性における身体活動とすべての死亡ケース(例)との関係を評価する。デザイン: 1992年12月31日までの7年間の追跡調査によるプロスペクティブコホートスタディ。設定と参加者:対象者は、1986年時点で55～69歳のアイオワ州に在住する閉経女性40417名。身体活動は、郵送された質問紙により評価。主な測定結果:すべての死亡者数(n=2260)。結果:ガンもしくは心臓病を持ち、追跡調査の最初の3年以内に死亡が報告された女性を除き、さらに潜在的交絡因子による補正を施した後、定期的な身体活動をおこなっていると報告した女性とそうでない女性を比べた結果、追跡調査期間中、死亡リスクが有意に減少した(相対リスク0.77; 95%信頼区間, 0.66-0.90)。中程度身体活動の頻度の増加は、追跡期間中における死亡リスクの減少との間に関連がみられた(身体活動をほとんどあるいは全く従事しない者から1週間に少なくとも4回活動している者まで、相対リスクはそれぞれ、1.0、0.76、0.70、0.62; P <.001)。同様のパターンが活発な身体活動者においてもみられた(対応する相対リスクはそれぞれ、1.0、0.89、0.74、0.57; P=.06)。増加した身体活動による死亡リスクの減少は、心血管疾患(n=729)や呼吸器疾患(n=147)において明白であった。また、活発でない身体活動だけに従事していた女性も、週に1回程度の中程度身体意活動で死亡リスクの減少0.78 (95%信頼区間, 0.64-0.96)を示す論拠が得られた。結論:これらの結果は、格付けされた閉経女性において身体活動とすべての死亡原因との間に負の相関を示している。これらの知見は、定期的な身体活動に従事するよう閉経女性に対してポピュレーションアプローチすることは適切であることを示唆している。						
結 論 (200字まで)	強いスポーツは行わなくても、日常的な活動、もしくは週1回程度の適度な運動で、相対的全死亡リスクは減らせる。						
エキスパートによるコメント (200字まで)	閉経は女性の生活習慣病リスクを急激に増加させる。閉経後の女性でも身体活動の重要性を証明した点にこの研究の意義がある。						

担当者　宮地 劉

Original Contributions

Exercise Intensity and Longevity in Men

The Harvard Alumni Health Study

I-Min Lee, MBBS, ScD; Chung-cheng Hsieh, ScD; Ralph S. Paffenbarger, Jr, MD, DrPH

Objective.—To examine the independent associations of vigorous (≥6 resting metabolic rate [MET] score) and nonvigorous (<6 MET score) physical activity with longevity.

Design.—Prospective cohort study, following up men from 1962 or 1966 through 1988.

Setting/Participants.—Subjects were Harvard University alumni, without self-reported, physician-diagnosed cardiovascular disease, cancer, or chronic obstructive pulmonary disease (n=17 321). Men with a mean age of 46 years reported their physical activities on questionnaires at baseline.

Main Outcome Measure.—All-cause mortality (3728 deaths).

Results.—Total energy expenditure and energy expenditure from vigorous activities, but not energy expenditure from nonvigorous activities, related inversely to mortality. After adjustment for potential confounders, the relative risks of dying associated with increasing quintiles of total energy expenditure were 1.00 (referent), 0.94, 0.95, 0.91 and 0.91, respectively (*P* [trend]<.05). The relative risks of dying associated with less than 630, 630 to less than 1680, 1680 to less than 3150, 3150 to less than 6300, and 6300 or more kJ/wk expended on vigorous activities were 1.00 (referent), 0.88, 0.92, 0.87, and 0.87, respectively (*P* [trend]=.007). Corresponding relative risks for energy expended on nonvigorous activities were 1.00 (referent), 0.89, 1.00, 0.98, and 0.92, respectively (*P* [trend]=.36). Analyses of vigorous and nonvigorous activities were mutually adjusted. Among men who reported only vigorous activities (259 deaths), we observed decreasing age-standardized mortality rates with increasing activity (*P*=.05); among men who reported only nonvigorous activities (380 deaths), no trend was apparent (*P*=.99).

Conclusions.—These data demonstrate a graded inverse relationship between total physical activity and mortality. Furthermore, vigorous activities but not nonvigorous activities were associated with longevity. These findings pertain only to all-cause mortality; nonvigorous exercise has been shown to benefit other aspects of health.

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FEW PHYSICIANS, if any, would dispute that physical activity enhances health. Among other benefits, increased activity is associated with decreased incidence of coronary heart disease,[1] hypertension,[2] non–insulin-dependent diabetes mellitus,[3] and colon cancer,[4] and increased longevity.[5] What is uncertain, however, are the kinds and intensity of physical activity that should be prescribed for health. In England, Morris et al[6,7] found that to reduce coronary heart disease risk, moderately vigorous exercise is necessary. Similarly, in a recent study from Finland, Lakka et al[8] reported that only more intense, conditioning physical activity reduces the risk of myocardial infarction; less intense, nonconditioning activities have no effect. Yet others maintain that as long as total energy output—even if amassed from light or moderate exercise—is increased, risks of coronary heart disease[1,9-13] and premature mortality from any cause[5,9-11,13,14] are decreased. For example, in the Multiple Risk Factor Intervention Trial,[9] an inverse relationship between leisure time physical activity and risk of coronary heart disease and total mortality was observed among men engaged predominantly in light to moderate activities. Dutch men and women who habitually carried out light exercise (leisure-time walking, cycling, and gardening) also enjoyed decreased coronary heart disease risk.[15]

Despite this lack of consensus and the fact that few studies have compared directly the relative merits of vigorous and nonvigorous exercise, a commonly prescribed exercise regimen borrows from recommendations for developing and maintaining cardiorespiratory fitness. These regimens prescribe exercise intense enough to produce sweating or hard breathing (60% to 90% of maximum heart rate), for at least 20 minutes, three times per week.[16,17] Recently, the Centers for Disease Control and Prevention and the American College of Sports Medicine issued a new, less stringent recommendation[18]: "Every US adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week." This recommendation was meant to encourage more exercise among the almost 60% of US adults who engage in little or no leisure-time activity.[19]

Which is the more valid stance? To provide further information—at least, for total mortality—we investigated the relative merits of vigorous and nonvigorous exercise and their associations with premature mortality. Is, for example, 2100 kJ (500 kcal) expended in vigorous exercise associated with the same decrease in mortality risk as an equal amount expended in nonvigorous activity?

From the Department of Epidemiology, Harvard School of Public Health, Boston, Mass (Drs Lee, Hsieh, and Paffenbarger); Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (Dr Lee); and Division of Epidemiology, Stanford (Calif) University School of Medicine (Dr Paffenbarger).

Reprint requests to Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115 (Dr Lee).

SUBJECTS AND METHODS

Study Subjects

The Harvard Alumni Health Study is an ongoing cohort study that searches for predictors of chronic disease in men who matriculated as undergraduates at Harvard University, Boston, Mass, between 1916 and 1950. The cohort was established when 21 582 alumni (68% response) returned a mailed questionnaire on medical history and health practices in either 1962 or 1966. Eligible subjects for our study were men who reported no physician-diagnosed cardiovascular disease, cancer, or chronic obstructive pulmonary disease. Additionally, subjects had to provide data on physical activity, body weight, height, cigarette habit, physician diagnosis of hypertension and diabetes mellitus, vital status of both parents, and, if parents were deceased, age at parental death. Alumni who satisfied these criteria numbered 17 321.

Assessment of Physical Activity and Other Predictors of Mortality

We assessed physical activity by asking alumni about flights of stairs climbed, city blocks walked, types of sports or recreational activities engaged in, and the time (hours per week) spent on each of these sports and recreational activities.[20] Although we did not ask specifically about occupational activity, alumni were unlikely to have expended much energy on the job apart from walking and climbing stairs. Physical activity assessment was validated by comparison of estimates of energy expenditure obtained from the questionnaire against the following: (1) other widely accepted and used physical activity questionnaires, (2) physiologic variables known to be influenced by physical activity, (3) total energy intake, (4) physical activity diaries, and (5) mechanical devices that measure bodily movement. On the basis of these criteria, this physical activity questionnaire has been shown to be reliable and valid.[21-27]

Climbing up and down one flight of stairs daily rated 118 kJ/wk, and walking 1 block daily, 235 kJ/wk. We assigned a multiple of resting metabolic rate (MET score) to every activity.[28] Since resting metabolic rate is approximately 4.2 kJ/kg of body weight per hour, we estimated the energy expended on each activity by multiplying its MET score by 4.2, body weight in kilograms and hours per week of participation. We then summed kilojoules per week from flights climbed, blocks walked, and activities performed, to provide an index of total energy expenditure per week.

We were interested in two components of total energy expenditure: that derived from vigorous activities (requiring ≥6 METs)[29] and that from nonvigorous (ie, light and moderate) activities (requiring <6 METs).[29] (Examples of vigorous activities reported by alumni include walking briskly, running or jogging, swimming laps, playing tennis, and shoveling snow.) Thus, for each alumnus, we further estimated energy expenditure from vigorous and nonvigorous activities separately.

Using alumni self-reports, we obtained information on other predictors of mortality: Quetelet's index (weight in kilograms divided by the square of height in meters), cigarette habit, physician diagnosis of hypertension or diabetes mellitus, and early parental death (defined as death occurring before age 65 years).

Ascertainment of Mortality

The Harvard Alumni Office maintains weekly rosters of deceased alumni. Their records indicate mortality follow-up data are unavailable for fewer than 1% of alumni.[30] Using information from the Alumni Office, we obtained copies of death certificates. The end point of interest for the present study was all-cause mortality occurring after return of the 1962 or 1966 questionnaire through 1988.

Statistical Analysis

We first compared age-standardized mortality rates, by means of the indirect method,[31] for increments of total, vigorous, and nonvigorous energy expenditure. To make statistical adjustment for several potential confounders simultaneously, we proceeded to use proportional hazards regression to analyze time to mortality or censoring.[32] Cumulative hazard plots disclosed no gross violation of proportional hazard assumptions. Mortality rate ratios (relative risks) were modeled as a function of physical activity. For total energy expenditure, we categorized alumni into quintiles (0 to <2524, 2524 to <4738, 4738 to <8001, 8001 to <13 142, and ≥13 142 kJ/wk). When investigating the independent associations of vigorous and nonvigorous energy expenditure with longevity, instead of using terms for total energy expenditure, we included terms for its two components. We categorized alumni according to five groups each of vigorous (<630, 630 to <1680, 1680 to <3150, 3150 to <6300, and ≥6300 kJ/wk) and nonvigorous (same cutoff points) energy expenditure. Potential confounders included in regression models were age (single years), Quetelet's index (<22.5, 22.5 to <23.5, 23.5 to <24.5, 24.5 to <26.0, or ≥26.0 kg/m^2), cigarette habit (never, former, or current smoker), and physician-diagnosed hypertension or diabetes mellitus (no vs yes). Although early parental death (neither, one, or both parents dying early) was unlikely to be related to physical activity and thus was not a confounder, it also was included since we were interested in its influence on mortality.

We tried to avoid observing an artifactual association between physical inactivity and increased mortality by excluding alumni with cardiovascular disease, cancer, and chronic obstructive pulmonary disease from the starting population. To minimize further the potential impact of this bias, we conducted additional analyses that omitted the first 5 years (arbitrarily chosen) of follow-up, because mortality among individuals with other illnesses that could limit physical activity, and also increase mortality risk, would likely occur early in follow-up.

Table 1.—Characteristics of Harvard Alumni in 1962 or 1966, According to Quintiles of Total Energy Expenditure*

Characteristic	Quintile of Total Energy Expenditure 1	2	3	4	5
Mean age, y	46.8	46.1	45.8	45.5	46.4
Mean Quetelet's index, kg/m^2	24.65	24.31	24.14	24.19	24.47
Cigarette habit, %					
Never smokers	20.1	21.9	20.9	21.1	20.2
Former smokers	32.1	30.4	32.0	31.9	33.5
Current smokers	47.8	47.7	47.1	47.0	46.3
Mean No./d of cigarettes smoked by current smokers	27	27	26	26	26
% reporting physician-diagnosed hypertension or diabetes mellitus	12.0	10.2	9.2	10.1	9.6
Early parental death (<65 y), %					
Neither parent dying early	66.9	65.4	64.6	66.3	67.6
1 parent dying early	29.0	30.7	30.6	29.6	28.0
Both parents dying early	4.1	3.9	4.8	4.1	4.4
% of total energy expenditure expended in vigorous activities†	41.7	32.1	32.2	38.9	43.5

*All characteristics (except mean age) were age standardized. Energy expenditure was estimated in kilojoules per week from climbing stairs, walking, and participating in sports or recreational activities. Quintile 1 represents the lowest energy expenditure.

†Among alumni who did expend energy in climbing stairs, walking, or participating in sports or recreational activities (17 090 of 17 321 alumni). Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (METs).

Ninety-five percent confidence intervals were calculated for estimated relative risks, and all P values were from two-tailed tests. To assess whether vigorous and nonvigorous energy expenditure differed significantly in their independent associations with longevity, we used the covariance matrix to estimate variance for the difference between the two parameter estimates.[33]

RESULTS

Table 1 describes alumni characteristics at study entry by quintiles of total energy expenditure. The mean age of alumni was 46 years, with little variation across quintiles. The mean Quetelet's index decreased as energy expenditure increased from the lowest to the third category, then increased beyond that. Almost half of the alumni smoked cigarettes in 1962 or 1966; the proportion who smoked declined steadily with increasing energy expenditure. Approximately 10% of alumni declared a physician diagnosis of hypertension or diabetes mellitus, while approximately 30% reported that one or both parents had died early. Table 1 also presents, for alumni who declared some form of physical activity (n=17 090), the proportion of total energy expenditure derived from vigorous activities.

We then examined age-standardized mortality rates by level of energy expenditure (Table 2). Between 1962 or 1966 and 1988, a total of 3728 deaths occurred in 384 681 person-years of observation. Mortality generally declined with increasing total energy expenditure (P=.001). At about 14 700 kJ/wk of total energy expenditure, mortality appeared to stabilize. Mortality also declined with higher levels of vigorous energy expenditure, regardless of the level of nonvigorous activity, up to 12 600 kJ/wk. Beyond this level of vigorous energy expenditure, mortality increased slightly. However, the overall inverse association was significant (P<.001). On the other hand, nonvigorous energy expenditure, regardless of the level of vigorous activity, was not associated with mortality (P=.87).

To consider other potential confounders, we proceeded to multivariate analyses, adjusting additionally for Quetelet's index, smoking, hypertension, diabetes mellitus, and early parental death. Total energy expenditure, in quintiles, continued to relate significantly and inversely to mortality. The adjusted relative risks were 1.00 (referent), 0.94 (95% confidence interval, 0.86 to 1.04), 0.95 (0.86 to 1.05), 0.91 (0.83 to 1.01), and 0.91 (0.82 to 1.00), respectively (P for trend<.046).

With the findings in Table 2, we could not determine whether vigorous physical activity, nonvigorous physical activity, or both was responsible for the inverse relationship with mortality. We thus conducted multivariate analyses to adjust mutually for vigorous and nonvigorous energy expenditure, while simultaneously adjusting for potential confounders (Table 3). Vigorous energy expenditure again was significantly and inversely related to mortality (P=.007), whereas the trend for nonvigorous energy expenditure again was not significant (P=.36). However, relative risk estimates for vigorous energy expenditure did not differ significantly from corresponding estimates for nonvigorous energy expenditure.

To minimize potential bias from ill health in the starting population, we conducted additional analyses that omitted the first 5 years after physical activity assessment (see "Statistical Analysis" section). We analyzed 3297 deaths (Table 4). Vigorous energy expenditure remained significantly and inversely related to mortality (P=.007), but we again observed no significant trend with nonvigorous energy expenditure (P=.32). Relative risk estimates for the two kinds of energy expenditure differed significantly at 1680 kJ/wk and higher. Trends for the two types of energy expenditure also differed significantly (P=.02).

We next tried to account for changes in physical activity over time. In 1977, we had sent another questionnaire to surviving alumni that requested updated information on medical history and health habits, including physical activity. Seventy-six percent of surviving alumni responded. We conducted further analyses that updated physical activity in 1977 for alumni who returned a questionnaire that year and who continued to be free of self-reported, physician-diagnosed cardiovascular disease, cancer, or chronic obstructive pulmonary disease. We also built in a 5-year lag after either physical activity assessment. Relative risks of mortality for the same five categories of vigorous energy expenditure were 1.00 (referent), 0.89 (95% confidence interval, 0.79 to 1.00), 0.83 (0.71 to 0.97), 0.76 (0.63 to 0.91), and 0.75 (0.64 to 0.89), respectively (P for trend=.001). Corresponding relative

Table 2.—Age-Standardized Mortality Rates Among Harvard Alumni, 1962 or 1966 Through 1988, According to Energy Expended on All, Vigorous, and Nonvigorous Activities in 1962 or 1966*

Physical Activity in 1962 or 1966, kJ/wk	No. of Deaths	Person-Years	Age-Standardized Mortality Rate/10 000
Energy expended on all activities			
<2100	700	65 241	103.78
2100-<4200	850	82 859	102.55
4200-<6300	553	55 670	99.79
6300-<8400	360	41 005	92.30
8400-<10 500	292	32 665	92.88
10 500-<12 600	222	26 347	88.35
12 600-<14 700	182	20 421	88.05
≥14 700	569	60 473	90.76
P for trend	...	...	<.001
Energy expended on vigorous activities			
<2100	2730	250 181	102.25
2100-<4200	401	44 373	95.90
4200-<6300	158	24 590	74.26
6300-<8400	107	17 098	76.94
8400-<10 500	104	14 222	89.97
10 500-<12 600	50	9389	62.00
12 600-<14 700	43	6564	79.29
≥14 700	135	18 264	86.23
P for trend	...	...	<.001
Energy expended on nonvigorous activities			
<2100	1276	135 930	97.81
2100-<4200	855	94 574	94.92
4200-<6300	590	59 321	101.63
6300-<8400	245	27 100	90.40
8400-<10 500	203	19 620	96.98
10 500-<12 600	152	14 779	90.33
12 600-<14 700	101	9842	89.43
≥14 700	306	23 515	102.22
P for trend	...	...	.87

*Energy expenditure was estimated from climbing stairs, walking, and participating in sports or recreational activities. Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (METs); nonvigorous activities, those that required less than 6 METs.

Table 3.—Relative Risks of All-Cause Mortality Among Harvard Alumni, 1962 or 1966 Through 1988, According to Vigorous and Nonvigorous Physical Activity in 1962 or 1966*

	Energy Expenditure, kJ/wk				
Kind of Activity	<630	630-<1680	1680-<3150	3150-<6300	≥6300
Vigorous activity					
No. of deaths	1459	1123	428	279	439
Relative risk (B1)	1.00	0.88	0.92	0.87	0.87
95% confidence interval	Referent	0.82-0.96	0.82-1.02	0.77-0.99	0.78-0.97
Nonvigorous activity					
No. of deaths	481	652	784	804	1007
Relative risk (B2)	1.00	0.89	1.00	0.98	0.92
95% confidence interval	Referent	0.79-1.01	0.89-1.12	0.88-1.12	0.82-1.02
P (B1−B2)	...	.88	.29	.18	.53

*Relative risks are adjusted for age, Quetelet's index, cigarette habit, physician-diagnosed hypertension or diabetes mellitus, and early (<65 years) parental death. Relative risks for vigorous and nonvigorous energy expenditure are mutually adjusted. Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (MET); nonvigorous activities, those that required less than 6 METs. P of trend across categories of vigorous energy expenditure is .007. P of trend across categories of nonvigorous energy expenditure is .36.

Table 4.—Relative Risks of All-Cause Mortality Among Harvard Alumni, 1967 or 1971 Through 1988, According to Vigorous and Nonvigorous Physical Activity in 1962 or 1966*

	Energy Expenditure, kJ/wk				
Kind of Activity	<630	630-<1680	1680-<3150	3150-<6300	6300+
Vigorous activity					
No. of deaths	1282	998	379	250	388
Relative risk (B1)	1.00	0.88	0.91	0.87	0.86
95% confidence interval	Referent	0.81-0.96	0.81-1.02	0.76-1.00	0.76-0.96
Nonvigorous activity					
No. of deaths	386	579	691	713	928
Relative risk (B2)	1.00	0.98	1.09	1.08	1.05
95% confidence interval	Referent	0.86-1.11	0.96-1.23	0.96-1.23	0.93-1.18
P (B1−B2)	...	.19	<.044	.02	.02

*Relative risks are adjusted for age, Quetelet's index, cigarette habit, physician-diagnosed hypertension or diabetes mellitus, and early (<65 years) parental death. Relative risks for vigorous and nonvigorous energy expenditure are mutually adjusted. Vigorous activities were defined as those that required 6 or more units of resting metabolic rate (METs); nonvigorous activities, those that required less than 6 METs. P of trend across categories of vigorous energy expenditure is .001. P of trend across categories of nonvigorous energy expenditure is .32. Analyses exclude first five years after physical activity assessment.

risks for nonvigorous energy expenditure were 1.00 (referent), 0.94 (0.79 to 1.12), 0.97 (0.82 to 1.15), 0.96 (0.81 to 1.14), and 0.89 (0.75 to 1.04), respectively (P for trend=.18). The trend across categories of vigorous energy expenditure differed significantly from that across categories of nonvigorous energy expenditure (P=.001).

We observed similar findings among men younger than 55 years and among older men. There also was no interaction by Quetelet's index; findings did not differ between leaner (<24.5 kg/m^2) and heavier (≥24.5) men.

In a final effort to disentangle the independent associations of the two kinds of energy expenditure with mortality, we examined alumni who reported only one kind of activity in 1962 or 1966. Alumni who performed only vigorous activities (and no nonvigorous exercise) numbered 919; of these, 259 died during follow-up. On the basis of this small number, we observed a marginally significant trend (P=.05) of decreasing age-standardized mortality with increasing vigorous energy expenditure (data not shown, but available from the authors on request). Among 1195 alumni who reported only nonvigorous activity (and no vigorous exercise) in 1962 or 1966, 380 died during follow-up. In age-standardized analysis, we found nonvigorous energy expenditure and mortality to be unrelated (P=.99) (data not shown, but available from the authors on request).

COMMENT

These prospective data demonstrate a graded, inverse relationship between an index of total physical activity and mortality in middle-aged men, concurring with most other investigations.[9-11,13,14] Of the components of total physical activity, we found vigorous (activities at ≥6 METs) but not nonvigorous (<6 METs) exercise to be associated with decreased mortality. Men who expended 6300 kJ/wk or more in vigorous exercise had 0.75 to 0.87 times the risk of dying during follow-up, compared with those who expended less than 630 kJ/wk. This difference in mortality risk is of approximately the same magnitude as that between alumni 20% or more overweight[34] and those of ideal weight,[5] or that between alumni who smoked one pack of cigarettes or less daily and nonsmokers.[5]

These data also suggest that the decrease in mortality associated with higher levels of energy expenditure may taper off after approximately 14 700 kJ/wk of total energy expenditure or 12 600 kJ/wk of vigorous energy expenditure (Table 2). In a British study, investigators noted a similar finding among younger men, ie, declining rates of coronary heart disease with increasing physical activity levels until the most active category ("very frequent sporting exercise or frequent sporting exercise plus other recreational activities"), in which rates began to increase. Some investigators have postulated that this phenomenon may be explained by the increased oxidative stress associated with prolonged physical exertion.[35] However, when we classified alumni according to their total energy expenditure in 1977 (instead of 1962 or 1966, as in the present analyses), we observed that mortality continued to decline at 14 700 kJ/wk.[5]

It is unclear to us why vigorous, but not nonvigorous, physical activity is associated with greater longevity. A recent report suggested that for favorable changes in high-density lipoprotein cholesterol and triglyceride levels, a threshold intensity of 5 to 6 METs of conditioning exercise is needed.[36] However, exercise intensity appears unrelated to the magnitude of decrease in blood pressure levels.[2] Perhaps the inverse association between physical activity and mortality is related not so much to exercise itself, but to the improved cardiorespiratory fitness that is induced.[37,38] Vigorous exercise is more effective than nonvigorous activity for cardiorespiratory conditioning. The kind of vigorous activity also may be relevant; for example, jogging, which is sustained and dynamic, is effective for such conditioning, whereas heavy yardwork is unlikely to be as sustained and thus would be less effective in conditioning.

Several previous studies also have examined the association of vigorous and nonvigorous exercise with health. Morris et al[6,7] found an inverse relationship between physical activity and coronary heart disease incidence only among British men who reported vigorous sports. A similar observation was made among Finnish men by Lakka et al.[8] However, Shaper et al[12] reported that even among British men with little vigorous ("sporting") exercise, myocardial infarction rates apparently decreased (not formally tested) with increasing physical activity. Slattery et al[11] also observed apparent decreases in age-adjusted death rates (not formally tested) with increasing light to moderate activity among US railroad workers who reported no vigorous activity. Among men who reported some vigorous activity, the trend with increasing light to moderate activity was unclear. In multivariate analyses adjusting for age, smoking, blood pressure, and serum cholesterol level, the estimated coefficient for vigorous activity was significant, and that for light to moderate activity, nonsignificant. However, investigators did not examine whether the coefficients for the two kinds of activity differed significantly.

In investigating the independent, relative merits of vigorous and nonvigorous activity, the issues involved are analogous to those in epidemiologic studies of diet. We wished to investigate the independent associations of vigorous and nonvigorous physical activity with mortality, apart from their contributions to total energy expenditure, and their relative merits. In studies of dietary fat and coronary heart disease, investigators are interested in the effect of fat that is independent of other nutrients, and of total energy intake.[39] To separate this effect, various analytic strategies have been proposed.[39-42] We have adapted one of these strategies[40] to achieve our end. As noted by Willett[39] and restated recently by Wacholder et al,[43] it is not adequate merely to note that the coefficient of one kind of energy expenditure (nutrient) is significant, and the coefficient of the other, nonsignificant. The appropriate focus should be the *difference* in coefficients (ie, [B1−B2] in Tables 3 and 4).

The most plausible alternate explanation for our findings is that alumni reported light and moderate activities with greater imprecision than vigorous activities, resulting in greater misclassification of the former. We had no data to test this hypothesis. In a separate validation study of our physical activity questionnaire, Ainsworth et al[27] reported that in men aged 21 to 59 years, the correlation between energy expenditure estimated from the questionnaire and that estimated from physical activity diaries was .69 for activities of 6 METs or more. For lower-intensity activities, the correlations were less than .35. However, among healthy alumni in the present study, the correlation between nonvigorous energy expenditure in 1962 or 1966 and 1977 was comparable with that for vigorous energy expenditure (r=.35 and .40, respectively). These low correlations imply that during the long follow-up, patterns of physical activity had changed. In further analyses that did account for changes in physical activity in 1977, we arrived at similar conclusions.

We could not determine whether our findings resulted from differences in diet, blood pressure levels, glucose tolerance, or serum lipid levels. We were unable to make statistical adjustment for dietary differences because we did not have detailed dietary information for alumni before 1988. According to the dietary data of 1988, estimated total energy consumed increased with increasing total, vigorous, and nonvigorous energy expenditure. However, the proportion of total energy consumed as fat or saturated fat did not vary across activity categories. Thus, confounding by fat intake was unlikely, with the caveat that diet in 1988 may not reflect earlier diet adequately. Some investigators argue that differences in blood pressure levels, glucose tolerance, and serum lipid levels should not be controlled for. Physical training lowers blood pressure levels,[2] increases insulin sensitivity,[44] and favorably influences lipid profiles.[45] Therefore, these variables may represent some of the mechanisms through which physical activity modifies mortality risk. Rather than being true confounders, then, they may represent events in the causal pathway and thus should not be controlled for.[31] We did not have data on serum lipid levels, but we took into account physician-diagnosed hypertension and diabetes mellitus. Self-reported physician-diagnosed disease among these alumni is believed to be valid.[4,20,30] Not adjusting for these diseases did not materially alter findings.

Although these observational data preclude a conclusion of causality,[46] several highly plausible mechanisms exist that link increased physical activity to decreased mortality. In addition to those described previously, physical training also improves cardiac mechanical and metabolic function,[47] reduces platelet aggregation, and increases fibrinolytic activity.[48] Our findings indicate that sedentary individuals should increase their activity level to enhance longevity. Specifically, vigorous activities were associated with greater longevity. However, we strongly believe that even nonvigorous exercise is preferable to sedentariness. Our findings pertain only to all-cause mortality; meanwhile, even modest exercise has been shown to improve, for example, lipid and glucose profiles.[49,50]

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エキスパートレビューのフォーマット

論文名	Exercise intensity and longevity in men. The Harvard Alumni Health Study.						
著 者	Lee IM, Hsieh CC, Paffenbarger RS Jr						
雑誌名	JAMA						
巻・号・頁	273巻 1179-1184ページ						
発行年	1995						
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/7707624						
対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	46歳	[redacted]		( )		前向き研究
	対象数	10000以上	空白		( )		( )
調査の方法	質問紙	( )					
アウトカム	予 防	な し	な し	な し	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )
図 表							
図表掲載箇所							
概 要 (800字まで)	目的:活発な運動(6 METsもしくはそれ以上)と低中強度(6 METs以下)運動が死亡リスクに及ぼす効果とその独立した関連性を長期間にわたり調査すること。デザイン:1962もしくは1966年から1988年までの調査によるコホート研究。対象者および設定:対象者は、医師によって心血管疾患、ガン、または慢性閉塞性肺疾患と診断されていない、自己記入式質問紙調査に回答したハーバード大学同窓生(n=17321)であった。対象者(平均年齢46歳)においては、ベースラインにおける質問紙調査に基づいて身体活動が報告された。主な測定結果:すべての原因による死亡(3728名)。結果:低中強度活動のエネルギー消費量ではなく、活発な活動のエネルギー消費量および総エネルギー消費量と死亡率との間に負の相関関係がみられた。潜在的交絡因子補正後、死亡の相対リスクは総エネルギー消費量が増加する5段階において、それぞれ1.00(referent)、0.94、0.95、0.91. 0.91(P <.005)の関係性を示した。相対リスクを630、630～1679、1680～3149、3150～6299、6300 kJ/week以上の活発な活動の各消費量からみてみると、それぞれ1.00(referent) 0.88、0.92、0.87、0.87(P <.007)の関係性を示した。これを低中強度活動での消費量で一致させると、相対リスクは、1.00(referent)、0.89、1.00、0.98、0.92 (P =0.36)の関係性を示した。活発な活動および低中強度活動を相互に調整した場合、活発な活動(259名が死亡)のみの間では、活動量の増加に伴う年齢標準化による死亡率の低下が観察された(P=0.05)が、低中強度の活動(380名が死亡)のみでは、同様の傾向はみられなかった(P=0.99)。結論:これらのデータは、総身体活動量と死亡率との間で、等級ごとに負の相関関係を示すことを立証するものである。さらに、活発な活動の量は寿命との関連性がみられた。これらの知見は、すべての死亡原因に対してのみ適用される。						
結 論 (200字まで)	高い強度の運動(6メッツ以上)であれば週当たり1680KJ以上行えば総死亡リスクを減らせる。						
エキスパートによるコメント (200字まで)	単に身体活動量のみでなく、活動の強度にフォーカスを当てて検討した貴重なデータである。比較的高い強度の運動を行えば、身体活動が多いことに加えてさらに利益があるかもしれない。						

担当者 宮地 劉