Table 2. Baseline Characteristics According to Depressive Symptoms at Baseline

Characteristic	Prevalent Depressive Symptoms No (n = 2,858)	Prevalent Depressive Symptoms Yes (n = 338)	P-Value
Age, mean	77.3	77.6	.17
Education, years, mean	10.7	10.8	.70
Married, %	83.8	76.9	.001
Body mass index, kg/m^2, mean	23.6	23.1	.003
Hypertension, %	75.2	70.1	.04
Diabetes mellitus, %	29.9	29.0	.75
Alcohol, oz/day	18.2	19.2	.66
Ever smoker, %	37.5	38.3	.86
Prevalent coronary heart disease, %	21.7	24.9	.18
Prevalent cerebrovascular attack, %	3.9	7.4	.003
Prevalent cancer, %	13.1	16.0	.14
Prevalent Parkinson's disease, %	0.7	2.1	.009
Dementia, %			
Prevalent	2.7	4.4	.06
Incident	9.4	15.6	.02
Cognitive impairment, %			
Prevalent	9.5	15.4	<.001
Incident	25.7	34.0	.03
Prevalent functional impairment (%)	13.4	21.8	<.001
Distance walked, miles (Examination 4) (%)			.005
<0.25	33.5	39.4	
0.25–1.5	36.0	38.5	
>1.5	30.5	22.2	

Table 3. Logistic Regression Models Showing Relationships Between 8-Year Incident Depressive Symptoms and Distance Walked per Day with Adjustments for Confounding Variables

Walking Distance (Low is Reference)	Odds Ratio (95% Confidence Interval)	P-Value
Model 1		
Intermediate	0.53 (0.33–0.83)	.006
High	0.59 (0.38–0.92)	.02
Model 2		
Intermediate	0.52 (0.32–0.83)	.006
High	0.61 (0.39–0.97)	.04
Model 3		
Intermediate	0.52 (0.32–0.84)	.007
High	0.61 (0.38–0.97)	.04

Model 1 unadjusted.

Model 2 adjusted for age, education, marital status, body mass index, hypertension, diabetes mellitus, alcohol use, smoking status, prevalent coronary heart disease, stroke, cancer, Parkinson's disease, dementia, cognitive impairment, and functional impairment.

Model 3 adjusted for factors in Model @ and 8-year incident dementia or cognitive impairment.

expected, it was found that those who walked more had significantly lower rates of prevalent depressive symptoms in cross-sectional analyses. It was also found that elderly men who walked longer distances per day were less likely to develop new depressive symptoms over 8 years of follow-up. There appeared to be a threshold effect in the protective effect of walking on the development of incident depressive symptoms, with not much difference between those in the intermediate- and high-walking-distance groups. Subjects in the highest-walking-distance group at baseline were 41% less likely to develop depressive symptoms 8 years later. Even after adjusting for potential confounding variables, they were still 39% less likely to develop depressive symptoms. When stratified according to chronic disease status at baseline, this association remained significant only in the healthy group of men with no chronic diseases at baseline.

Previous large longitudinal studies have examined the relationship between physical activity and depressive symptoms.[24,25] In the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study,[24] self-reported physical activity was measured using a questionnaire and depressive symptoms according to the CES-D in 3,016 men and women. The findings suggested that recreational physical activity was an independent predictor of depression levels 8 years later for white women who were not depressed at baseline. There was no significant difference for white men who were not depressed at baseline, although a lower level of physical activity was a strong predictor of continued depression at follow-up.

The Alameda County Study was another large longitudinal study of 4,828 men and women using a self-reported physical activity index and a depression questionnaire to evaluate the relationship between level of physical activity and risk of subsequent depression.[25] It concluded that, in a population sample without depression, men and women who reported low activity level at baseline were at a significantly greater risk of depression at follow-up (<9 years) than those who reported high activity levels at baseline.

Table 4. Logistic Regression Models Showing Relationships Between 8-Year Incident Depressive Symptoms and Distance Walked per Day, Stratified According to Presence or Absence of Chronic Diseases

Walking Distance (Low is Reference)	Odds Ratio (95% Confidence Interval)	P-Value
Healthy*		
Intermediate	0.39 (0.21–0.71)	.002
High	0.61 (0.35–1.06)	.08
Sick†		
Intermediate	0.99 (0.45–2.21)	.99
High	0.64 (0.28–1.48)	.30

Adjusted for age, education, marital status, cardiovascular risk factors, and functional impairment.

*Healthy (n = 1,880/3,196, 58.8%): absence of coronary heart disease, stroke, cancer, Parkinson's disease, or dementia or cognitive impairment at baseline.

†Sick (n = 1,316/3,196, 41.2%): coronary heart disease, stroke, cancer, Parkinson's disease, or dementia or cognitive impairment at baseline.

More recently, the Rancho Bernardo Study examined the effects of physical activity on depressive symptoms in 2,375 older men and women.[14] Subjects were interviewed about physical activity, and according to the Beck Depression Inventory, individuals who were more physically active had lower depression scores at baseline and at follow-up 8 years later, although a long-term protective effect of exercise was not found. Depression scores of participants who reported exercise at the earlier visit but not at the second evaluation were similar to those of participants who did not report exercise at either visit. A subsequent study on the same cohort attributed these results to the exclusion of disabled participants and found that physical activity is protective against development of incident major depression using DSM-IV criteria.[13]

The results of the current study are in agreement with the findings of a previous study[13] and confirm the protective effect that physical activity has on incident depressive symptoms. However, despite these results and exclusion of those with depressive symptoms at baseline, this is an observational study, and therefore it cannot be inferred that walking prevents depressive symptoms. Undoubtedly, depressive symptoms can lead to less physical activity and vice versa. The objective of the current study was to add to the body of knowledge information about the potential benefits of walking in elderly men and to provide further information regarding which subjects seem to benefit the most from this level of physical activity.

A few mechanisms have been suggested that attempt to explain the association between physical activity and depressive symptoms. Physiologically, the prominent hypothesis is that exercise increases the availability of brain neurotransmitters such as serotonin, dopamine, and norepinephrine. Levels of these neurotransmitters are lower in patients with depression and higher in plasma after exercise, although it is unclear whether this leads to a higher level in the brain in humans.[26,27]

This analysis of subjects with and without chronic disease at baseline has not been examined previously and is unique to this study. It suggests that walking can contribute to fewer depressive symptoms in a healthy group of older adults but that this potential benefit might not be enough to compensate for the effects of chronic disease.

LIMITATIONS AND STRENGTHS

The study population included only elderly Japanese-American men in Hawaii. Therefore, these findings may not be generalizable to women or other ethnic groups or settings. There may be some concern that participants were excluded because of incomplete or invalid answers on the CES-D 11. It is possible that some of these invalid depression scales may have been due to more-severe cognitive impairment or medical burden. These subjects may have had higher depressive symptoms because of this. The elimination of these participants could have skewed the evaluation of depressive symptoms mainly in the group who walked less than 0.25 miles/day.

Strengths of the study are that it is a large, population-based cohort that has had excellent follow-up since 1965. Out-migration rates are low, and follow-up examinations have had excellent response rates. Hospital surveillance for chronic diseases is essentially complete, because this is an island population. Longitudinal analyses were possible, and the follow-up period for incident depressive symptoms was relatively long. The study sample of retired elderly men living in the mild climate of Hawaii had the advantage of more reliably assessing self-reported physical activity. As opposed to other climates, Hawaii allows for year-round walking and thus more-accurate and -consistent recollection of distance walked by the subjects. It is also likely that the activity level of these elderly, retired men was of low intensity, considering that most reasons for walking would be for domestic or leisure activities.

CONCLUSIONS

In summary, this study confirmed the hypothesis that daily physical activity, specifically walking, is strongly independently protective against the development of depressive symptoms over 8 years of follow-up in elderly Japanese-American men without chronic disease. Even a low level of daily physical activity in elderly individuals has protective effects against the development of depressive symptoms. These effects are likely to occur in a healthier subset of the elderly population. Activities that promote physical activity, particularly activities that are well tolerated and easily instituted, are beneficial to this population. Future research should aim to further define other forms of physical activity and the effect they have on the development of depressive symptoms. A randomized clinical trial of walking in elderly subjects would provide more-definitive data on the cause-and-effect relationship between physical activity and depression.

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Author Contributions: Study concept and design: TLS, KHM. Acquisition of subjects and data: KHM, KF, GWR, HP, LRW. Analysis and interpretation of the data: TLS, KHM, KF, RDA, GWR, HP, PLB, LRW. Preparation of manuscript: TLS, KHM. Critical review of manuscript: KF, RDA, GWR, HP, PLB, LRW.

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Appendix 1. Center for Epidemiologic Studies Depression Scale Questionnaire (11-Item Version)

Below is a list of the ways you might have felt or behaved. Please indicate how often you have felt this way during the **past week**.

Would you say in the last week . . .	Rarely or none of the time (less than 1 day)	Some or a little of the time (1–2 days)	Occasionally or a moderate amount of the time (3–4 days)	Most of the time
1. You were bothered by things that usually don't bother you.	0	1	2	3
2. You did not feel like eating, your appetite was poor.	0	1	2	3
3. You had trouble keeping your mind on what you were doing.	0	1	2	3
4. You felt that everything you did was an effort.	0	1	2	3
5. You felt depressed.	0	1	2	3
6. You felt hopeful about the future.	3	2	1	0
7. You felt fearful.	0	1	2	3
8. Your sleep was restless.	0	1	2	3
9. You were happy.	3	2	1	0
10. You felt lonely.	0	1	2	3
11. You could not get going.	0	1	2	3

論文名	Effect of walking distance on 8-year incident depressive symptoms in elderly men with and without chronic disease: the Honolulu-Asia Aging Study
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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	男性	( )		( )		( )
	年齢	71-93(82歳)	[redacted]		( )		前向きコホート
	対象数	1000～5000			( )		( )
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	心理的指標改善	( )	( )

図 表

Table 3. Logistic Regression Models Showing Relationships Between 8-Year Incident Depressive Symptoms and Distance Walked per Day with Adjustments for Confounding Variables

Walking Distance (Low is Reference)	Odds Ratio (95% Confidence Interval)	P-Value
Model 1		
Intermediate	0.53 (0.33–0.83)	.006
High	0.59 (0.38–0.92)	.02
Model 2		
Intermediate	0.52 (0.32–0.83)	.006
High	0.61 (0.39–0.97)	.04
Model 3		
Intermediate	0.52 (0.32–0.84)	.007
High	0.61 (0.38–0.97)	.04

Model 1 unadjusted.
Model 2 adjusted for age, education, marital status, body mass index, hypertension, diabetes mellitus, alcohol use, smoking status, prevalent coronary heart disease, stroke, cancer, Parkinson's disease, dementia, cognitive impairment, and functional impairment.
Model 3 adjusted for factors in Model @ and 8-year incident dementia or cognitive impairment.

図表掲載箇所

概 要（800字まで）

<目的>ホノルル在住の日系アメリカ人高齢男性において、歩行がうつの発症に及ぼす影響について検討すること。<方法>コホート名：The Honolulu-Asia Aging Study.、対象者数：1417人、人種：アジア系アメリカ人、追跡期間：8年、因子評価方法詳細：歩行距離を質問票で評価、一日に何ブロック歩きますか？と聞き、1マイル12ブロックとして歩行距離に換算。ハーバード卒業生研究の質問の一部。うつ発症評価はCES-Dの1の質問表で評価した。<結果>因子の単位：マイル／日、歩行距離の範囲：第一分位：0-0.24マイル／日、第2分位：0.25-1.49マイル／日、第3分位：1.5マイル／日以上。各分位のうつ発症相対危険度は、第1分位を基準とし、第2分位：0.52(0.32-0.83)、第3分位：0.61(0.39-0.97)であった。有意差ありの最低分位は第2分位であった。また全ての参加者の中で、慢性疾患のない者では、歩行距離とうつ発症に関係が見られたが、慢性疾患者ではこのような関係は見られなかった。

結 論（200字まで）

研究開始時に健康なハワイ在住日系アメリカ人で1日あたり0．25マイル（400m）以上歩く男性は、うつの発症リスクが有意に低い。

エキスパートによるコメント（200字まで）

高齢者のうつは将来の認知の発症とも関連する。高齢者では、移動、余暇時間、家事など目的を問わず1日当たりわずか400m、5-10分程度歩くだけで、高齢者のうつが抑制できることを明らかにした点に意義がある。

担当者　宮地元彦

4. 最大酸素摂取量の
基準値策定に用いた文献

JAMA
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Original Contributions

Physical Fitness and Incidence of Hypertension in Healthy Normotensive Men and Women

Steven N. Blair, PED; Nancy N. Goodyear, MSPH; Larry W. Gibbons, MD, MPH; Kenneth H. Cooper, MD, MPH

• We measured physical fitness, assessed by maximal treadmill testing in 4,820 men and 1,219 women aged 20 to 65 years. Participants had no history of cardiovascular disease and were normotensive at baseline. We followed up these persons for one to 12 years (median, four years) for the development of hypertension. Multiple logistic risk analysis was used to estimate the independent contribution of physical fitness to risk of becoming hypertensive. After adjustment for sex, age, follow-up interval, baseline blood pressure, and baseline body-mass index, persons with low levels of physical fitness (72% of the group) had a relative risk of 1.52 for the development of hypertension when compared with highly fit persons. Risk of hypertension developing also increased substantially with increased baseline blood pressure.

(*JAMA* 1984;252:487-490)

SELF-REPORTS of exercise participation are associated with reduced total mortality[1] and mortality from coronary heart disease.[2,3] Low levels of physical fitness are associated with increased incidence of myocardial infarction.[4] Regular aerobic exercise increases physical fitness,[5] improves lipid metabolism,[6] and reduces body fat.[7] Physical fitness is associated with improved high-risk profiles for coronary heart disease in cross-sectional and longitudinal studies in men and women.[8-10]

See also pp 528.

Aerobic exercise may reduce blood pressure in moderate hypertensives,[11] although the evidence is weak and previous studies have numerous design flaws. Incidence of hypertension is associated with low levels of vigorous exercise in a large epidemiologic study of Harvard alumni.[12]

The purpose of this study was to examine the association between baseline physical fitness and the development of hypertension in a group of normotensive men and women followed up for one to 12 years.

SUBJECTS AND METHODS

Study participants were men and women who received a preventive medical examination at the Cooper Clinic in Dallas during 1970 to 1981 and participated in a follow-up mail survey in 1982. The follow-up interval ranged from one to 12 years, with a median of four years. Persons were included in the study if they had no history of hypertension or other cardiovascular disease, had normal resting and exercise ECGs, had resting BPs under 141 mm Hg systolic and 91 mm Hg diastolic, and had achieved at least 85% of their age-predicted maximum heart rate on an exercise test at the initial clinic visit. There were 4,820 men and 1,219 women aged 20 to 65 years at baseline who met all entry criteria for the study.

Clinical Examination

The baseline examination was given after an overnight fast and after participants gave their informed consent. The examination included a medical history, a physical examination, a questionnaire on demographic characteristics and health habits, height and weight measurements, blood pressures, resting ECG, blood chemistries, and a maximal treadmill exercise test.[13] Resting blood pressure was obtained by trained technicians with mercury sphygmomanometers according to a standard protocol. Six readings were taken after a five-minute rest, and the lowest reading was recorded for analysis. Diastolic pressure was recorded at the disappearance of sound. Examination procedures have been described in more detail in previous reports.[8-10]

Physical fitness, defined here as physical work capacity, was assessed by a maximal treadmill test. Data used for analysis were the maximum treadmill times achieved by patients during the exercise test. Specifically, treadmill speed was set at 3.3 mph. The grade of the treadmill was 0% for the first minute, raised 2% for the second minute, and raised 1% each minute up to the 25th minute. After 25 minutes, the grade remained constant and the speed was increased 0.2 mph each minute until the test was terminated. Participants were encouraged to give a maximal effort. Total test time from the treadmill test is highly correlated with maximal oxygen uptake in men (r=.92)[14] and women (r=.94).[15]

Follow-up Study

Incidence of hypertension was ascertained in 1982 as part of a follow-up study. Twelve thousand two hundred twenty-five

From the Department of Health Education, School of Public Health, University of South Carolina, Columbia (Dr Blair and Ms Goodyear); the Institute for Aerobics Research (Drs Blair and Cooper), and the Cooper Clinic (Drs Gibbons and Cooper), Dallas.

Reprint requests to the Institute for Aerobics Research, 12200 Preston Rd, Dallas, TX 75230 (Dr Blair).

patients (77% response rate) responded to a mail survey on current health habits and health status. After exclusions for history of hypertension (907 patients), elevated blood pressure (1,267 patients), failure to achieve 85% of maximal heart rate on the treadmill test (498 patients), abnormal ECG (1,681 patients), out of the age range (451 patients), or missing values (1,382 patients); 6,039 patients remained for analysis. It is important to consider whether or not selection bias might have significantly influenced the results. Respondents to the mail survey were similar to nonrespondents. At their first clinic visit the two groups differed less than one year on age, 1 mm Hg on systolic BP, 1.5 minutes on treadmill time, 4 mg/dL on cholesterol, and one unit on the body mass index (weight/height^2 for men and weight/height$^{1.5}$ for women).[16] Persons who died were not included in the analysis since mortality follow-up and coding for cause of death are still incomplete.

The survey questionnaire included questions on current health habits and health status. A case-finding question, designed to identify physician-diagnosed ailments, was patterned after a similar question used by Paffenbarger et al[2,12] in studies on college alumni. In the present study, participants were asked if a physician had ever told them that they had hypertension or high blood pressure. If yes, the year of diagnosis was obtained. Normotensive participants who had no history of hypertension at the baseline clinic visit, but who reported hypertension during follow-up, were classified as incident cases of hypertension. Persons who reported taking antihypertensive medication during follow-up were also classified as hypertensive.

Paffenbarger et al[12] report good sensitivity (82%) and specificity (98%) for the hypertension question in their mail survey. In the present study, accuracy of responses was checked by a careful study of possible coding and keypunch errors.[17] The validity of self-reported hypertension was then checked in a group of 207 respondents to the mail survey. Random samples of participants who had recent follow-up clinic visits were selected for validation. Of 48 persons who were classified as hypertensive from the mail survey, 47 cases were confirmed at the clinic visit, for a sensitivity of 98%. There were 159 persons randomly selected who did not report hypertension on the mail questionnaire. Of these, 158 were found to be nonhypertensive at the clinic visit (specificity, 99%). Age, blood pressure, and body mass index were examined to determine if patients returning for examinations were similar to nonreturnees. The two groups differed less than two years on age, 2 mm Hg on systolic BP, one unit on body mass index, and 1.5 minutes on treadmill time at their first clinic visit. These findings support the validity of the follow-up questionnaire hypertension classifications.

Data Analysis

Data analysis was done with the Statistical Analysis System software package.[18] To aid in understanding the effects of baseline systolic and diastolic blood pressures and physical fitness in predicting subsequent hypertension, relative risks were calculated using multiple logistic regression[19] after adjusting for sex, age, body mass index, and follow-up interval. Logistic regression was used for the primary analysis since almost one third of the subjects had missing values for the year of hypertension diagnosis. The logistic analysis categorizes a person as either having the disease or not and does not rely on the time between the start of the study and diagnosis as do other methods of survival analysis. To further clarify the importance of the missing data on year of diagnosis, two Cox proportional hazards models were examined.[20] One Cox model was run defining time between baseline and time of diagnosis, when year of diagnosis was unknown, as the longest possible time (calculated as 1982 minus the year of baseline examination) and one defining this time period as the shortest possible time (one year). In the logistic and hazard models, resting systolic blood pressure was divided into three categories: high, at least 130 mm Hg or greater; medium, 121 to 129 mm Hg; and low, 120 mm Hg or less. Diastolic blood pressure was also categorized: high, 85 mm Hg or greater; medium, 81 to 84 mm Hg; and low, 80 mm Hg or less. Age was entered as a continuous variable in both the logistic and hazard models and follow-up interval was entered as continuous in the logistic model. Six age- and sex-specific categories for physical fitness (very poor to superior) have been established at the Cooper Clinic.[8,9] The top two categories (excellent and superior) were combined and comprised the reference physical fitness category in logistic analyses. These two categories represent a maximal treadmill time at or above the 85th percentile on all persons who have been tested at the Cooper Clinic. Participants in the present study were somewhat more physically fit than typical patients at the Cooper Clinic as indicated by a higher percentage being in the top two categories (29% of the men, 27% of the women). The remaining four physical fitness categories (very poor to good) comprised the comparison group. This breakpoint was determined by previous logistic analyses where the maximum likelihood estimates were almost identical for each of the bottom four categories when compared with the top two categories, indicating that the association between physical fitness and hypertension may not be entirely linear, but that the threshold for an effect may be limited to the higher levels of fitness. Selection of the breakpoint is supported by earlier cross-sectional studies on patients at the Cooper Clinic indicating that clinically important and statistically significant associations between coronary heart disease risk factors (including blood pressures) tend to be concentrated in the top two physical fitness categories (especially for men).[8,9]

RESULTS

Baseline characteristics for the 6,039 study subjects are presented in Table 1. These data are from the first clinic visit for each patient. These patients were comparable on body mass index to adults measured in the National Health and Nutrition Examination Survey.[16] Because they were deliberately selected to be normoten-

Table 1.—Characteristics of 6,039 Men and Women Patients*

Characteristics	Men	Women
Age, yr	41.5±8.5†	40.1±8.9
Weight, kg	80.3±10.8	59.2±9.3
Height, m	1.79±.06	1.65±.06
Resting blood pressure		
Systolic, mm Hg	117.0±10.0	109.3±11.0
Diastolic, mm Hg	77.5±7.1	73.0±7.7
Body mass index‡	25.11±2.94	27.97±4.12
Treadmill time	1,067±274	750±241

*Patients were from the Cooper Clinic, Dallas, and were healthy and normotensive at baseline.

†Values are means ±SDs.

‡Body mass index=weight (kg)/height (m)^2 for men and weight (kg)/height (m)$^{1.5}$ for women.

Table 2.—Maximum Likelihood Estimates of Logistic Parameters*

Variable	Logistic Estimate	SE	P
Intercept	−8.07	.70	. . .
Sex	.15	.21	.498
Age, yr	.03	.01	<.001
Follow-up interval	.20	.02	<.001
Systolic BP,†‡ 120-129 mm Hg	.50	.18	.005
Systolic BP,†‡ ≥130 mm Hg	1.05	.20	<.001
Diastolic BP,‡§ 80-84 mm Hg	.48	.18	.008
Diastolic BP,‡§ ≥85 mm Hg	.91	.21	<.001
Body mass index	.05	.02	.007
Low physical fitness	.42	.18	.018

*Relating potential risk factors at the time of initial examination to hypertension risk in 6,039 normotensive patients at the Cooper Clinic, Dallas.

†Reference category equals less than 120 mm Hg.

‡Systolic and diastolic blood pressure were measured at rest.

§Reference category equals less than 80 mm Hg.

sive, mean blood pressures were slightly below national norms.[21] Slightly more than a quarter of the patients were in the high fitness category.

There were 240 cases of new hypertension reported during the follow-up period. Bivariate analyses indicated a strong association between incident cases of hypertension and physical fitness in both men and women. Since several factors such as age, obesity, and length of follow-up could contribute to a spurious association between physical fitness and hypertension, multivariate analyses were performed.

The result of the logistic analysis is given in Table 2. The maximum-likelihood estimates are expressed in logits where a unit of change in each independent variable changes the logit of risk for that particular variable by the parameter estimate. After adjustment for sex, age, baseline blood pressures, and body mass index, the relative risk of hypertension in the low fitness group was 1.52 times the risk of a person in the high fitness group (95% confidence interval=1.08 to 2.15, P=.02). Risks calculated from the Cox models were similar to those from the logistic analysis: relative risk (RR)=1.46 (P=.02) when the missing follow-up periods were defined as the longest possible time and RR=1.51 (P=.02) when the missing follow-up time was defined as the shortest possible time.

Additional logistic models were calculated to further explore the association between physical fitness and hypertension. Consistency of the fitness and hypertension relationship was examined in age and follow-up interval categories. Since blood pressure response during the treadmill test could be associated with risk of hypertension and with fitness, maximal systolic blood pressure was also added to the model. Relative risks from these analyses are given in Table 3.

Table 3.—Relative Risk of Hypertension Developing*

Category	Relative Risk: Low Fitness	Relative Risk: High Fitness
Follow-up interval†		
1-5 yr	1.48	1.0
6-12 yr	4.62	3.16
Age†		
<50 yr	1.51	1.0
≥50 yr	1.93	1.28
Physical fitness†	1.52	1.0
Physical fitness‡	1.62	1.0

*By follow-up interval, age category, and physical fitness.
†Logistic model with age, follow-up interval, resting blood pressures, and physical fitness.
‡Logistic model with blood pressure response to the treadmill test added to the model.

Both baseline blood pressure and low levels of physical fitness were independent contributors to the risk of developing hypertension in this study. The relative risks for various combinations of these variables are given in Table 4. The risk increases tenfold for the person who is in the highest blood pressure categories at the time of entry into the study and has a low level of physical fitness compared with the person who has none of these risk characteristics. The risk ratios presented here indicate a multiplicative rather than an additive effect as multiple risk factors are added.

A subsample of study participants had a second clinic examination during the follow-up period. After determining their fitness category at the second examination, participants were classified into two groups. Group 1 consisted of 1,032 persons who were in the low fitness category at both examinations. Group 2 contained 271 persons who moved from the low fitness category at the first examination to the high category at the second examination. There were 38 persons in the two groups who became hypertensive during follow-up. The incidence of hypertension was 18 per 1,000 in the high fitness group and 32 per 1,000 in the low fitness group. A multiple logistic analysis was performed controlling for sex, age, body mass index, and follow-up interval. The adjusted RR of 1.5 was in the predicted direction, but was not statistically significant.

COMMENT

In the present study physical fitness was significantly associated with hypertension risk after simultaneous adjustment for the possible confounding factors of body mass index, age, sex, follow-up interval, and baseline

Table 4.—Relative Risks of Hypertension Among Normotensive Patients at Cooper Clinic, Dallas, in a One- to 12-Year Follow-up*

Systolic BP,† 120-129 mm Hg	Systolic BP,† 130-139 mm Hg	Diastolic BP,† 81-84 mm Hg	Diastolic BP,† 85-89 mm Hg	Low Physical Fitness†	Relative Risk	95% Confidence Interval
−	+	−	+	+	10.80	(6.28-18.58)
−	+	−	+	−	7.10	(4.27-11.81)
−	+	+	−	+	7.02	(3.90-12.68)
−	+	+	−	−	4.62	(2.95-7.24)
+	−	−	+	+	6.23	(3.54-10.97)
−	+	−	−	+	4.35	(2.56-7.39)
+	−	−	+	−	4.10	(2.75-6.10)
+	−	+	−	+	4.06	(2.33-7.05)
−	+	−	−	−	2.85	(1.95-4.19)
−	−	−	+	+	3.78	(2.24-6.37)
+	−	+	−	−	2.66	(1.74-4.08)
−	−	−	+	−	2.48	(1.66-3.71)
−	−	+	−	+	2.46	(1.50-4.02)
+	−	−	−	+	2.51	(1.52-4.13)
−	−	+	−	−	1.62	(1.14-2.30)
+	−	−	−	−	1.65	(1.16-2.34)
−	−	−	−	+	1.52	(1.08-2.15)
−	−	−	−	−	1.00	... ...

*By specific combinations of blood pressures and physical fitness categories adjusted for sex, age, body mass index, and length of follow-up.
†A plus indicates presence of characteristic; minus, absence of characteristic.

blood pressure levels. After adjustment, the overall excess risk for persons with low levels of physical fitness in this study was 52%. This is somewhat higher than the excess risk of 35% reported by Paffenbarger et al[12] for Harvard alumni who did not participate in vigorous sports play in middle age. Although our study participants included both men and women, both study groups represent well-educated persons with a relatively high socioeconomic status and are preponderantly white.

We have not found other studies in which baseline physical fitness was studied as a predictor for hypertension. Gillum et al[22] reported that exercise heart rate (which is a marker for physical fitness) at baseline was associated with blood pressure readings 32 years later in 112 men.[22] Men below the median exercise heart rate had follow-up BPs 10 (systolic) and 5 (diastolic) mm Hg lower than men in the upper half of the distribution.

Other possible confounding variables for the observed association between physical fitness and hypertension could be dietary factors such as caffeine, salt, or alcohol intake. We doubt that this is the case as preliminary analyses on patients at the Cooper Clinic indicate no association between dietary patterns and physical fitness, and in a previous study we found that highly active and sedentary people have qualitatively similar diets.[23]

Although subjects in the present study were normotensive at baseline (≤140 mm Hg systolic BP and ≤90 mm Hg diastolic BP), baseline blood pressures were powerful predictors of hypertension risk. This is not surprising in view of previous reports,[24] but it is of clinical interest that even patients in the normal range (120 to 129 mm Hg systolic BP and 81 to 84 mm Hg diastolic BP) had almost a threefold increase in risk over subjects with lower baseline levels. When these normal levels of blood pressure were found in physically unfit persons, the risk of hypertension increased to four times the risk of highly fit subjects in the lowest blood pressure category.

Assumption of causality in any biomedical study requires elucidation of a plausible biologic mechanism. Although we do not have additional data in the present study to address this issue directly, a possible mechanism has been suggested by Bjorntorp.[25] Higher resting heart rates and cardiac outputs are associated with elevated systolic blood pressures. Because all three variables are mediated by sympathetic nervous system activity, excess sympathetic nervous system stimulation may be an underlying cause. Exercise may reduce sympathetic nervous system activity. A preliminary report by Duncan et al[26] from our laboratory supports this hypothesis. In a randomized clinical trial on the effects of exercise on mild hypertension, patients in the exercise group significantly ($P<.01$) reduced their blood pressure compared with the control group. Patients in the exercise group who had elevated plasma catecholamine levels reduced their blood pressures more than patients with normal catecholamine levels. Change in plasma catecholamine was correlated ($r=.52$, $P=.02$) with change in systolic blood pressure.

The implications of the present study are of clinical importance. Normotensive persons can be categorized with regard to risk of the development of future hypertension. Persons at the upper end of the "normal" range might be candidates for advice on lifestyle habits that could favorably affect their risk of experiencing high blood pressure. In any case, these patients would warrant increased attention in monitoring their blood pressure levels over time. This is especially true if the patient is physically unfit.

The Cooper Clinic physicians and technicians collected the baseline data. Mike Smith, MS, provided data processing support, Diann Dunkley helped prepare the manuscript, and Kirby Jackson provided statistical advice.

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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	男女混合	( )		( )		( )
	年齢	20-65歳			( )		前向き研究
	対象数	5000～10000	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予 防	高血圧症予防	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)	本研究では、20～65歳の4,820人の男性と1,219人の女性を対象とし、トレッドミルを用いた最大酸素摂取量を測定した。対象者は研究参加時には正常血圧であって、心臓血管疾患歴が全くなかった。その後、1～12年間(中央値4年)高血圧の発症の有無を追跡調査した。 体力が低い群(全体の72%)の性、年令、追跡期間、ベースラインの血圧と、BMIで調節した高血圧発症の相対危険度は、体力が高い群に対して1.52であった。また、ベースラインの血圧が高くなることによって高血圧発症のリスクが高くなった。
結 論 (200字まで)	体力が低いことは、他の要因を調査しても高血圧の発症リスクを高くする。
エキスパートによるコメント (200字まで)	体力が高血圧発症に関連することを最初に明確にした代表的な文献である。

担当者 呉泰雄・髙田和子

The Association of Cardiorespiratory Fitness and Physical Activity With Incidence of Hypertension in Men

Nancy L. Chase[1], Xuemei Sui[1], Duck-chul Lee[1] and Steven N. Blair[1,2]

BACKGROUND
Few prospective studies have simultaneously investigated the relationship between physical activity, cardiorespiratory fitness (CRF), and the development of hypertension in initially normotensive individuals. In the Aerobics Center Longitudinal Study (ACLS), we examined this association among initially healthy normotensive men.

METHODS
Participants were 16,601 men aged 20–82 years who completed a baseline examination during 1970–2002 and were followed for hypertension incidence. Physical activity was self-reported and CRF was quantified from the duration of a maximal treadmill test.

RESULTS
A total of 2,346 men reported hypertension during a mean 18 years of follow-up. Event rates per 10,000 man-years adjusted for age and examination year were 86.2, 76.6, and 66.7 across physical activity groups of sedentary, walker/jogger/runner (WJR), and sport/fitness, respectively, and 89.8, 78.4, and 64.6 for low, middle, and high CRF, respectively (trend $P < 0.0001$). These associations persisted after further adjustment for body mass index (BMI), smoking, alcohol intake, resting systolic blood pressure, baseline health status, family history of diseases, and survey response patterns.

CONCLUSION
Both physical activity and CRF are associated with lower risk of developing hypertension in a graded fashion. These findings provide a basis for health professionals to emphasize the importance of participating in regular physical activity to improve fitness for the primary prevention of hypertension in men.

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Elevated systolic and diastolic blood pressure are associated with increased risk for stroke, coronary heart disease, congestive heart failure, peripheral vascular disease, and renal disease.[1] In patients with cardiovascular disease (CVD), elevated systolic blood pressure is one of the strongest predictors of secondary CVD events.[2] Lifestyle modifications such as increasing physical activity, losing weight, and reducing sodium are recommended for treating hypertension.[3,4]

Most previous studies have reported that higher levels of physical activity are related to a reduced risk of incident hypertension.[5–11] The physical activity measures employed in these studies have been based on self-reported questionnaire measures. Self-reported measures of physical activity are only modestly correlated with objective measures obtained using criterion methods.[12–15] One approach to objectively assess recent physical activity level is to assess cardiorespiratory fitness (CRF).[15,16] However, few prospective studies have investigated the relationship between baseline CRF levels and the development of hypertension in initially normotensive individuals.[17–20] Therefore, it is important to understand how or if different types of physical activity and CRF, an objective reproducible measure that reflects the functional consequences of recent physical activity habits, disease, and genetics,[21] have different effects on the incidence of hypertension.

To the best of our knowledge, only one study has simultaneously examined CRF, vigorous exercise, and incident hypertension.[19] However, this report was limited by only studying runners. Therefore, the goal of the current study was to evaluate the independent and joint associations among fitness, various types of physical activity, and incident hypertension in a cohort of men enrolled in the Aerobics Center Longitudinal Study (ACLS).

METHODS

Participants. The ACLS is a prospective study of the health effects of physical activity and fitness. Data were obtained from patients of the Cooper Clinic, a preventive medicine clinic in Dallas, Texas. Participants were self- or employer referred to the clinic for various services such as preventive medical examinations and health, nutrition, and exercise counseling. Participants for the current analysis were 16,601 men aged

[1]Department of Exercise Science, University of South Carolina, Columbia, South Carolina, USA; [2]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, South Carolina, USA. Correspondence: Xuemei Sui (msui@gwm.sc.edu)

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20–82 years who completed a health examination during 1970–2002. At baseline, all participants were free of known CVD and cancer. They also reported no physician diagnosis of hypertension and had resting blood pressure of <140/90 mm Hg at baseline. A large majority of participants were Caucasian (97%) and from middle and upper socioeconomic strata. Very few participants were from other ethnic groups (0.6% African American and 2.4% Asians and others). All participants provided written consent to participate in the examination and in the follow-up research. The study protocol was reviewed and approved annually by the Cooper Institute Institutional Review Board.

Clinical examination. Clinical examinations were completed after a 12-h fast and have been described in detail elsewhere.[22,23] Briefly, information pertaining to personal and family health histories, personal health habits, and demographic information was obtained from standardized medical history questionnaires. Height and weight were measured in light clothing and without shoes using a standard clinical scale and stadiometer. Body mass index (BMI) was calculated as kg/m^2. Seated blood pressure was recorded as the first and fifth Korotkoff sounds using auscultation methods.[24] Fasting serum samples were analyzed for lipids and glucose using standardized automated bioassays at the Cooper Clinic Laboratory, which participated in and met quality control criteria of the Centers for Disease Control and Prevention Lipid Standardization Program. Diabetes mellitus was defined as fasting plasma glucose concentration of 126 mg/dl or greater, a history of physician diagnosis, or insulin use. Hypercholesterolemia was defined as total cholesterol of 240 mg/dl or greater. Personal history of CVD (myocardial infarction or stroke), information on smoking habits (current smoker or not), alcohol intake (drinks per week), family history of CVD or hypertension, and physical activity habits (sedentary, walker/jogger/runner (WJR), and sport/fitness participants) were obtained from a standardized questionnaire.

Physical activity. Physical activity status was categorized into three mutually exclusive groups according to the usual type of physical activity reported during the preceding 3 months.[25,26] Sedentary individuals were those participants who answered "no" to all activity questions (running, walking, jogging, bicycling, swimming, racquet sports, and other strenuous sports). Sport/fitness activity (hereafter referred to as "sport") participants were those who answered "no" to the run/walk/jog question but "yes" to a wide range of questions about participation in racquet sports, other strenuous sports (football, basketball, softball, etc.), cycling, stair climbing, cross-country skiing, aerobic dancing, or swimming. Due to the small number of participants and hypertension events in different sport groups, it was not possible to evaluate separate sport categories. We classified participants as WJR if they answered "yes" to the question, "Have you participated in a run/walk/jog program in the last three months?"

CRF. CRF was quantified as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol.[22,27] The treadmill test began with the patient walking 88 m/min at 0% grade. At the end of the first minute, elevation was increased to 2% and thereafter increased 1% per minute until the 25th min. For those who were able to continue past 25 min, the treadmill speed was increased by 5.4 m per minute, for each minute after the 25th. Exercise duration on this protocol is highly correlated with measured maximal oxygen uptake in men ($r = 0.92$).[28] The test endpoint was volitional exhaustion or termination by the supervising physician. Maximal metabolic equivalents (METs, 1 MET = 3.5 ml O_2 uptake/kg/min) were estimated from the final treadmill speed and grade.[29] We categorized men into thirds depending on age-specific (20–29, 30–39, 40–49, 50–59, and ≥60 years) distributions of treadmill time.

Morbidity surveillance. The incidence of hypertension was ascertained from responses to mail-back health surveys in 1982, 1986, 1990, 1995, 1999, and 2004. The aggregate survey response rate across all survey periods in the ACLS is ~65%. Nonresponse bias is a concern in epidemiological surveillance. This issue has been investigated in the ACLS,[30] and found not to present a major source of bias. Baseline health histories and clinical measures were similar between responders and nonresponders and between early and late responders.[30] The endpoint was defined as a participant report of a physician diagnosis of hypertension and has been described in detail elsewhere.[17,18,31] We previously verified the accuracy of self-reported, physician-diagnosed hypertension in this cohort and observed 98% sensitivity and 99% specificity.[17] Our methods of case ascertainment are similar to those used in other established epidemiologic studies on hypertension.[9,32,33]

Statistical analysis. Baseline characteristics of the population were calculated for physical activity and CRF categories. Differences in covariates were tested using analysis of variance tests for continuous variables and chi-square tests for categorical variables. We performed an overall F-test for one-way analysis of variance and then compared two pairs of groups (sedentary vs. WJR or sport, low vs. middle or high fitness), which had been planned in advance, with the least-squares means procedure if the overall F-test was statistically significant. We used Fisher's Z transformation to examine the correlations among physical activity categories and exercise duration by assessing Pearson coefficients (Table 3). Treadmill test duration was compared across the three physical activity groups using general linear models with Bonferonni *post hoc* comparison tests (Figure 1). Follow-up time among noncases was computed as the difference between the date of the baseline examination and the date of the last returned survey in which the participant reported being free of hypertension. Follow-up time among cases was computed as the difference between the baseline examination date and the reported date of the hypertension event. If a diagnosis date was not provided, we used the midpoint between the date of the case-finding survey and either the baseline examination date or the date of the last returned survey in which the participant reported being free of hypertension. Cox proportional hazards regression analysis was used to estimate hazard ratios, 95% confidence intervals, and hypertension incidence rates (per 10,000 man-years) according to exposure categories. Multivariable analyses included controls for baseline measures: age (in years), BMI (kg/m^2), smoking status (current smoker or not), alcohol intake (≥5 drinks/wk or not), resting systolic and diastolic blood pressure (mm Hg), medical conditions (the presence or absence, separately measured, of diabetes or hypercholesterolemia), and family history of CVD or hypertension (present or not for each). We also constructed indicator variables (yes/no) for each survey period to account for differences in survey response patterns in order to reduce the influence of ascertainment bias.[18,31] To standardize for surveillance period and length of follow-up, we entered these variables, as well as the year of the baseline examination, into our analyses as covariables. Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption. Finally, we examined the joint effects of physical activity (sedentary, WJR, and sport) and CRF (low, middle, and high) on incident hypertension. For this analysis, we created nine activity-fitness combination categories. We compared the effect of each combination of activity and fitness status (sedentary-low, sedentary-middle, sedentary-high, WJR-low, WJR-middle, WJR-high, sport-low, sport-middle, and sport-high) with the referent group (sedentary-low). We also performed additional analyses using logistic regression

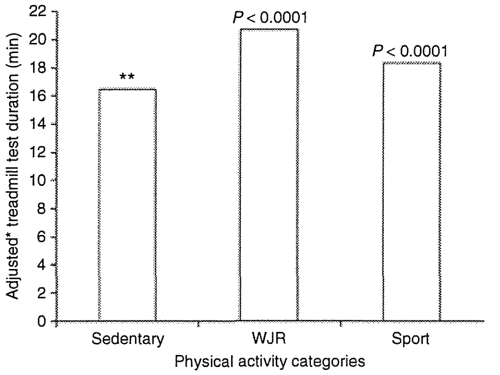

Figure 1 | Associations between cardiorespiratory fitness (expressed by treadmill test duration in minutes) and physical activity categories. *Adjusted for age, examination year, survey response patterns, body mass index (kg/m^2), current smoking (yes or no), alcohol intake (≥5 drinks/wk, yes or no), resting systolic and diastolic blood pressure (mm Hg), hypercholesterolemia (yes or no), diabetes (yes or no), family history of hypertension (present or not), and family history of cardiovascular disease (present or not). **Reference. WJR, walker/jogger/runner.

Table 1 | Baseline characteristics of study participants by physical activity categories, Aerobics Center Longitudinal Study, 1970–2002

	Physical activity categories			
	Sedentary	WJR	Sport	*P* value
N	5,030	8,400	3,171	
Age (mean ± s.d., years)	43.5 ± 9.1	43.8 ± 9.4	44.1 ± 9.7[a]	0.04
Waist circumference (mean ± s.d., cm)	93.9 ± 14.3	88.4 ± 15.9[a]	90.2 ± 16.1[a]	<0.0001
Body mass index (mean ± s.d., kg/m^2)	26.0 ± 3.4	25.2 ± 2.9[a]	25.8 ± 3.2[a]	<0.0001
Exercise tolerance (mean ± s.d., METs)	10.7 ± 1.9	13.1 ± 2.4[a]	11.8 ± 2.0[a]	<0.0001
Treadmill test duration (mean ± s.d., min)	16.0 ± 4.0	20.9 ± 4.6[a]	18.3 ± 4.2[a]	<0.0001
Lipids (mean ± s.d., mg/dl)				
Total cholesterol	213.5 ± 38.8	203.0 ± 37.6[a]	205.8 ± 38.5[a]	<0.0001
HDL-C	43.8 ± 11.6	47.8 ± 12.1[a]	46.0 ± 11.6[a]	<0.0001
Triglycerides	140.0 ± 101.7	112.9 ± 80.4[a]	124.2 ± 78.6[a]	<0.0001
Fasting blood glucose (mean ± s.d., mg/dl)	100.2 ± 17.2	98.2 ± 12.6[a]	98.5 ± 13.5[a]	<0.0001
Blood pressure (mean ± s.d., mm Hg)				
Systolic	117 ± 9	117 ± 10	116 ± 9[a]	0.004
Diastolic	77 ± 7	76 ± 7[a]	77 ± 7	<0.0001
Current smoker (%)	22.1	10.8[a]	16.5[a]	<0.0001
Alcohol consumption (≥5 drinks/week) (%)	33.4	38.1[a]	35.9	<0.0001
Hypercholesterolemia (%)	22.8	14.4[a]	16.9[a]	<0.0001
Diabetes (%)	4.6	2.6[a]	2.9[a]	<0.0001
Family history of hypertension (%)	8.6	11.4[a]	12.0[a]	<0.0001
Family history of CVD (%)	3.4	4.4[a]	4.4[a]	0.02

SI conversion factors: To convert total cholesterol and HDL-C values to mmol/l, multiply by 0.0259; triglycerides values to mmol/l, by 0.0113; glucose values to mmol/l, by 0.0555. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; METs, maximal metabolic equivalents achieved during the treadmill test; WJR, walker/jogger/runner.
[a]Significantly different from sedentary individuals ($P < 0.05$).

Table 2 | Baseline characteristics of study participants by cardiorespiratory fitness categories, Aerobics Center Longitudinal Study, 1970–2002

	Cardiorespiratory fitness thirds			
	Low	Middle	High	*P* for trend
N	5,518	5,533	5,550	
Age (mean ± s.d., years)	44.3 ± 8.5	43.3 ± 9.4[a]	43.6 ± 9.4[a]	<0.0001
Waist circumference (mean ± s.d., cm)	96.1 ± 15.5	90.4 ± 15.1[a]	85.1 ± 14.9[a]	<0.0001
Body mass index (mean ± s.d., kg/m²)	26.9 ± 3.7	25.5 ± 2.7[a]	24.3 ± 2.2[a]	<0.0001
Exercise tolerance (mean ± s.d., METs)	9.7 ± 1.2	12.0 ± 0.9[a]	14.7 ± 1.8[a]	<0.0001
Treadmill test duration (mean ± s.d., min)	13.9 ± 2.6	18.8 ± 2.0[a]	24.1 ± 3.0[a]	<0.0001
Lipids (mean ± s.d., mg/dl)				
Total cholesterol	214.0 ± 38.9	206.9 ± 38.3[a]	199.1 ± 36.5[a]	<0.0001
HDL-C	42.4 ± 10.8	45.5 ± 11.1[a]	50.6 ± 12.4[a]	<0.0001
Triglycerides	152.7 ± 106.1	122.6 ± 85.0[a]	94.0 ± 53.7[a]	<0.0001
Fasting blood glucose (mean ± s.d., mg/dl)	100.7 ± 17.0	98.4 ± 13.1[a]	97.4 ± 12.1[a]	<0.0001
Blood pressure (mean ± s.d., mm Hg)				
Systolic	117 ± 9	116 ± 10[a]	117 ± 10	0.02
Diastolic	78 ± 6	77 ± 7[a]	77 ± 7[a]	<0.0001
Physical activity (%)				
Sedentary	55.4	26.6[a]	9.0[a]	<0.0001
WJR	24.5	50.9[a]	76.3[a]	<0.0001
Sport	20.1	22.5[a]	14.7[a]	<0.0001
Current smoker (%)	24.3	14.1[a]	7.6[a]	<0.0001
Alcohol consumption (≥5 drinks/week) (%)	37.4	35.8	35.6	0.09
Hypercholesterolemia (%)	23.0	17.2[a]	12.1[a]	<0.0001
Diabetes (%)	5.4	2.6[a]	1.9[a]	<0.0001
Family history of hypertension (%)	8.7	11.1[a]	12.1[a]	<0.0001
Family history of CVD (%)	3.3	4.3[a]	4.7[a]	0.0004

SI conversion factors: To convert total cholesterol and HDL-C values to mmol/l, multiply by 0.0259; triglycerides values to mmol/l, by 0.0113; glucose values to mmol/l, by 0.0555. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; METs, maximal metabolic equivalents achieved during the treadmill test; WJR, walker/jogger/runner.
[a]Significantly different from low cardiorespiratory fitness ($P < 0.05$).

to verify the results to account for the possible inaccuracy of the diagnostic date of incident hypertension. All *P* values were calculated assuming 2-sided alternative hypotheses; *P* values <0.05 were taken to indicate statistically significant comparisons. All analyses were performed using SAS statistical software, version 9.1 (SAS, Cary, NC).

RESULTS

The baseline characteristics of the study sample by their physical activity and CRF measures are presented in Table 1 and Table 2, respectively. The proportion of men who participated in the sport category was 19.1%. There were significant differences in the three physical activity groups on all of the baseline variables (Table 1). The average duration of WJR per week was 11 miles (data not shown). Participants with lower CRF values tended to be older, were less active, had higher BMI values, and were more likely to have major CVD risk factors, such as hypercholesterolemia, diabetes, and less likely to have family history of hypertension or CVD (Table 2). Table 3 shows that all three activity groups and treadmill exercise duration were significantly correlated. Each of the activity groups was modestly correlated with CRF levels. After adjusting for the potential confounders, treadmill test duration within WJR and sport groups was significantly higher compared with sedentary men, respectively (Figure 1).

Table 3 | Univariate associations between physical activity categories and treadmill exercise duration

	Pearson correlation coefficients*			
	Sedentary	WJR	Sport	Treadmill test duration
Sedentary	1.00	−0.67	−0.32	−0.40
WJR		1.00	−0.49	0.42
Sports			1.00	0.33
Treadmill test duration (min)				1.00

WJR, walker/jogger/runner.
*$P < 0.0001$.

Table 4 | Rates and hazard ratios for developing hypertension, according to baseline physical activity and cardiorespiratory fitness (CRF) category

	Cases	Man-years	Rate[a]	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
Physical activity					
Sedentary	863	101,355	86.2	1.0 (Referent)	1.0 (Referent)
WJR	1131	147,000	76.6	0.82 (0.75–0.90)	0.87 (0.79–0.95)
Sport	352	51,878	66.7	0.74 (0.65–0.84)	0.76 (0.66–0.86)
P for linear trend			<0.0001	<0.0001	<0.0001
CRF thirds					
Low	969	106,884	89.8	1.0 (Referent)	1.0 (Referent)
Middle	765	99,151	78.4	0.82 (0.75–0.90)	0.89 (0.80–0.98)
High	612	94,239	64.6	0.64 (0.57–0.71)	0.71 (0.64–0.80)
P for linear trend			<0.0001	<0.0001	<0.0001

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; WJR, walker/jogger/runner.
[a]Rate per 10,000 man-years adjusted for age and examination year. [b]Model 1: adjusted for baseline age, examination year, and survey response pattern. [c]Model 2: adjusted for all variables in Model 1 plus body mass index (kg/m^2), current smoking (yes or no), alcohol intake (≥5 drinks/wk, yes or no), resting systolic and diastolic blood pressure (mm Hg), hypercholesterolemia (yes or no), diabetes (yes or no), family history of hypertension (present or not), and family history of CVD (present or not).

Over a mean (s.d., range) 18.1 (8.1, 1–34) years of follow-up (300,312 man-years), we documented 2,346 incident cases of hypertension. Age and examination year-adjusted hazard ratios and event rates (per 10,000 man-years) for the categories of physical activity and thirds of CRF are presented in Table 4. Across physical activity groups, the event rates were 86.2, 76.6, and 66.7 in men who were sedentary, who participated in WJR activity, and who participated in sport activity, respectively. After further adjusting for survey response pattern, the men in the WJR group had 13% lower, and men in the sport category had 24% lower hypertension risks than sedentary men. Additional adjustment for BMI, smoking, alcohol intake, systolic and diastolic blood pressure, hypercholesterolemia, diabetes, and family history of hypertension or CVD did not significantly change the results. For CRF, an inverse gradient (P trend < 0.0001) of incident hypertension event rates was observed across incremental thirds of CRF groups. After adjustment for the same covariables, men with middle and high CRF had an 11% and 29% lower hypertension risk than did men with low CRF (P trend < 0.0001).

Finally, we analyzed the joint associations of physical activity and CRF with incident hypertension. Figure 2 shows the age- and examination year-adjusted event rates across physical activity (sedentary, WJR, and sport/fitness activity) and CRF (low, middle, and high) categories, which resulted in nine activity-CRF groups. The event rate in the high CRF men who participated in the sport/fitness activities was the lowest among the nine combination groups. The adjusted incidence rate was inversely related to CRF within each of the physical activity categories (all $P < 0.05$ for trends). However, there was no association between WJR or sport/fitness activity groups and outcome within the low and middle CRF groups, compared with the sedentary men ($P > 0.05$ for each). There was an inverse association between sport group and outcome within the high CRF group, compared with the sedentary men ($P = 0.003$). The results were similar when we performed logistic regression models instead of Cox regression models. Therefore, only the proportional hazard analysis results are shown.

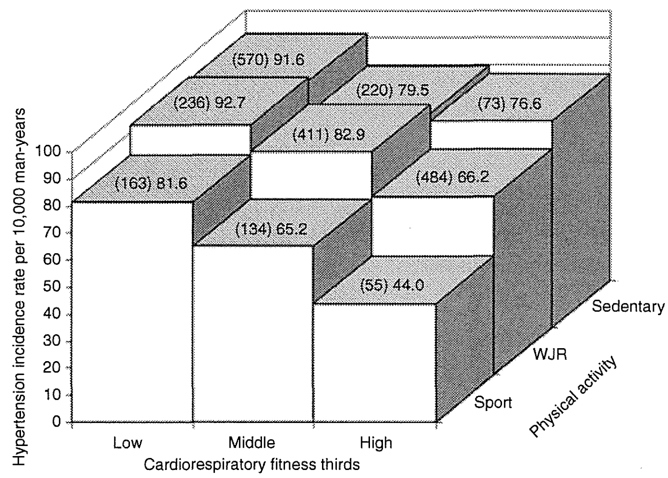

Figure 2 | Total number of cases (N) and age- and examination year-adjusted hypertension incidence rates per 10,000 man-years according to cardiorespiratory fitness and physical activity categories. The adjusted incidence rates were inversely related to cardiorespiratory fitness within each of the physical activity categories (all $P < 0.05$ for trend); however, there was no association between WJR or sport/fitness activity groups and outcomes within the low and middle fitness groups, compared with the sedentary men (all $P > 0.05$). There was an inverse association between sport/fitness activity group and outcome within the high fitness group, compared with the sedentary men ($P = 0.003$). WJR, walker/jogger/runner.

DISCUSSION

The principal finding of this report is that both higher CRF and participating in sport or walking/jogging/running decrease the risk of developing hypertension in comparison with low fitness or sedentary lifestyle, respectively. We believe that this is the first study that has evaluated both fitness and different types of activity in relation to risk of incident hypertension. Sedentary men had the highest incidence rate of hypertension, while men who participated in sport activity had the lowest rates of incident hypertension. After adjustment for several potential confounders, the inverse association between the sport or WJR group and the risk of hypertension was attenuated, but remained significant. These results suggest that regular activity like walking/jogging/running or participating in sports, appears to reduce the risk of developing hypertension.

The data reported here also show an inverse dose-response association between CRF and risk of incident hypertension in initially normotensive and healthy middle-aged men. The association persisted after extensive adjustment for potential confounding factors. The inverse association also persisted when stratified on the physical activity groups. This further strengthens the evidence that there is an inverse relationship between higher CRF levels and lower risk of hypertension.

Our results are consistent with several large, epidemiological studies examining the association between physical activity and the incidence of hypertension.

The Harvard Alumni Study showed that men who regularly participated in sports activity had a 19–29% lower risk of developing hypertension.[8,9] Lack of strenuous exercise independently predicted a higher risk of hypertension.[9] Alumni who did not participate in vigorous physical activity had a 35% greater risk of hypertension than those who did.[9] In a later analysis, Paffenbarger and Lee[8] concluded that lack of moderately vigorous physical activity, being overweight, and family history of hypertension increased the risk of developing hypertension. In the Atherosclerosis Risk in Communities Study, Pereira *et al.*[10] showed an inverse association between leisure-time physical activity and incidence of hypertension in 7,459 African American and Caucasian adults aged 45–65 years between 1987 and 1995. Caucasian men in the highest quartiles of sports and leisure activity had 23% and 34% lower risk of developing hypertension in comparison with Caucasian men in the lowest quartiles.[10] Caucasians who maintained or increased their amount of sports or exercise had a 14% and 22% reduction in the odds of developing hypertension in men and 15% and 17% in women.[10] Folsom *et al.*[34] examined the 2-year incidence of hypertension in a cohort of 41,837 women aged 55–69 years and found that high levels of leisure physical activity were associated with a 30% reduction in risk of hypertension. However, physical activity no longer contributed to hypertension risk after adjustment for age, BMI, waist-to-hip ratio, and smoking status.[34]

Higher CRF levels are associated with lower risk of developing hypertension.[17,18] Our previous studies found that participants with higher fitness levels had lower incidence rates of hypertension in men[17] and in women[18]. Barlow *et al.*[18] examined 4,884 middle-aged normotensive women in the ACLS and found that women in the middle and high fitness categories had a 61% and 81% lower risk of developing hypertension in comparison with low-fit participants. Carnethon *et al.*[35] showed that each 1-min decrease in maximal treadmill performance was associated with a 19% higher 15-year risk of developing hypertension among men and women. This study also suggests that 21% of the hypertension cases could be avoided by increasing fitness levels.[35] In the current study, we found a 11% and 29% lower risk of incident hypertension in men who were middle and high fit compared with men who were low fit, respectively.

Previous literature shows that self-reported measures of physical activity are only modestly correlated with objective measures obtained using criterion methods.[12–15] We found similar associations in the current study (Table 3 and Figure 1). Further joint analysis (Figure 2) showed that in each physical activity group, the hypertension risk was significantly lower across incremental fitness levels. These results support the hypothesis that middle and high fitness levels favorably influence hypertension risk across different types of physical activity. These findings are in agreement with a recent study that found that higher CRF reduces the odds for hypertension, independent of physical activity, and is an important risk factor separate from physical activity.[19]

Several mechanisms are speculated regarding the inverse relationship between physical activity and hypertension, though these possible mechanisms were beyond the scope of this investigation. Regular physical activity can reduce norepinephrine. The reduction in norepinephrine was associated with decreased spillover, which suggests that sympathetic nervous system activity was decreased.[36] This in turn may cause reductions in vasoconstriction and total peripheral resistance.[37] Other studies[38,39] have found that nitric oxide production, which influences endothelial cell-dependent vasodilation, is increased through exercise training. Increased insulin sensitivity was also a possible pathway by which physical activity influences blood pressure.[40,41]

Strengths of the current study include the extensive baseline examination to detect subclinical disease, the large size of the cohort, the relatively long follow-up period, the assessment of different types of physical activity, and the objective measures of CRF levels, which were quantified from the use of maximal exercise testing. Participation in certain sports may be confounded by education level, health knowledge, and other sociodemographic factors. However, a majority of the participants in this study were Caucasian, well educated, middle to upper class, which limits the generalizability of the study's findings, although this limitation should not affect the study's internal validity. There was insufficient information about hypertension medication use or dietary habits to include these factors in the analysis. Due to the widespread geographic distribution of patients evaluated at the Cooper Clinic, we were unable to verify all reported hypertension events. However, based on a random sample of verified events, it appears that an acceptable level of agreement exists between the participant's self-reported history and his medical records. In terms of exposure assessment, we classified men at study enrollment, but in the present analysis we were unable to evaluate the effect of changes in physical activity and fitness over time on our outcomes. It is possible that sedentary or low fit men increased their activity or fitness levels at some point in the follow-up interval. In addition, others may have experienced decreases in these characteristics. Such misclassification of exposure would likely lead to underestimating the magnitude of the association observed in the present study. We did not have sufficient information on frequency and intensity reported in the WJR or sports group. Therefore, we could not account for exercise volume in each of the activity groups. Future studies should include such information whenever possible.

In conclusion, our prospective findings in a large cohort of initially normotensive and healthy middle-aged men show that both physical activity and CRF are independent predictors of incident hypertension in men. Lifestyle modification has long been encouraged particularly for those with hypertension as well as for the entire population.[42] We believe health professionals should counsel their sedentary patients to become physically active through participating in regular physical activity, such as walking, jogging, bicycling, swimming, and playing sports,[43] and to improve their fitness for the primary prevention of hypertension.

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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	男性	(　　)		(　　)		(　　)
年齢	20-82歳			(　　)		前向き研究
対象数	10000以上			(　　)		(　　)

調査の方法	実測	(質問紙)

アウトカム

予　防	高血圧症予防	な し	な し	な し	( )	(　　)
維持・改善	な し	な し	な し	な し	( )	(　　)

図　表

Table 4 | Rates and hazard ratios for developing hypertension, according to baseline physical activity and cardiorespiratory fitness (CRF) category

	Cases	Man-years	Rate[a]	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
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P for linear trend			<0.0001	<0.0001	<0.0001

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; WJR, walker/jogger/runner.
[a]Rate per 10,000 man-years adjusted for age and examination year. [b]Model 1: adjusted for baseline age, examination year, and survey response pattern. [c]Model 2: adjusted for all variables in Model 1 plus body mass index (kg/m^2), current smoking (yes or no), alcohol intake (≥5 drinks/wk, yes or no), resting systolic and diastolic blood pressure (mm Hg), hypercholesterolemia (yes or no), diabetes (yes or no), family history of hypertension (present or not), and family history of CVD (present or not).

図表掲載箇所　P637，表3

概　要（800字まで）

本研究は，身体活動および全身持久力と高血圧発症との関連について検討したエアロビクスセンターの縦断研究（ACLS）である．16601名の健康で正常血圧の男性を対象とし，平均18.1年間追跡された．身体活動は，過去3か月間の活動について質問され，不活動群，ウォーキング・ジョギング・ランニング活動群，スポーツ活動群の3つに分類された．全身持久力は，修正版Balkeトレッドミルプロトコルによって評価された．年齢特異的な分布を考慮し，低体力，中体力，高体力の3つにカテゴリー化された．高血圧発症リスクとの関連について検討した結果，身体活動において不活動群であった者と比較した場合の調整ハザード比は，ウォーキング・ジョギング・ランニング活動群で0.87(95%CI:0.79–0.95)，スポーツ活動群で0.76(0.66–0.96)となり，量反応関係が認められた(P trend <0.0001)．同様に，全身持久力において低体力であった者と比較して，中体力の者の調整ハザード比は0.89(0.80–0.98)，高体力の者では0.71(0.64–0.80)と，量反応関係が認められた(P trend <0.0001)．スポーツ活動群，かつ高体力の者では，調整発症率が最も低かった．

結　論（200字まで）

身体活動量が多い者，全身持久力が高い者は，高血圧発症リスクが低いことが示され，身体活動と全身持久力は独立した予測因子であることが示された．

エキスパートによるコメント（200字まで）

アメリカのエアロビクスセンターで行われた大規模なコホート研究により，全身持久力および身体活動と高血圧発症リスクとの関連について明らかにしたものである．日常の活発な身体活動や全身持久力を高めるような有酸素運動を推奨する上で重要なエビデンスのひとつである．

担当者　　川上諒子

PHYSICAL FITNESS AS A PREDICTOR OF CARDIOVASCULAR MORTALITY IN ASYMPTOMATIC NORTH AMERICAN MEN

The Lipid Research Clinics Mortality Follow-up Study

Lars-Göran Ekelund, M.D., Ph.D., William L. Haskell, Ph.D., Jeffrey L. Johnson, M.S., Fredrick S. Whaley, Ph.D., Michael H. Criqui, M.D., M.P.H., and David S. Sheps, M.D., M.S.P.H.

Abstract Limited data are available on the relation between physical fitness and mortality from cardiovascular disease. We examined this question in a study of 4276 men, 30 to 69 years of age, whom we followed for an average of 8.5 years. Examinations at base line included assessment of conventional coronary risk factors and treadmill exercise testing. The heart rate during submaximal exercise (stage 2 of the exercise test) and the duration of exercise were used as measures of physical fitness. Men with incomplete data (n = 308) or who were using cardiovascular drugs (n = 213) were excluded from the analysis. Men who had clinical evidence of cardiovascular disease at base line (n = 649) were analyzed separately. Forty-five deaths from cardiovascular causes occurred among the remaining 3106 men.

A lower level of physical fitness was associated with a higher risk of death from cardiovascular and coronary heart disease, after adjustment for age and cardiovascular risk factors. The relative risk of death from cardiovascular causes was 2.7 (95 percent confidence interval, 1.4 to 5.1; P = 0.003) for healthy men with an increment of 35 beats per minute in the heart rate during stage 2, and 3.0 (95 percent confidence interval, 1.6 to 5.5; P = 0.0004) for those with a decrement of 4.4 minutes in the exercise time spent on the treadmill. The corresponding values for death from coronary heart disease were 3.2 (95 percent confidence interval, 1.5 to 6.7; P = 0.003) and 2.8 (95 percent confidence interval, 1.3 to 6.1; P = 0.007), respectively.

We conclude that a lower level of physical fitness is associated with a higher risk of death from coronary heart disease and cardiovascular disease in clinically healthy men, independent of conventional coronary risk factors. (N Engl J Med 1988; 319:1379-84.)

SUBSTANTIAL evidence suggests that regular physical activity is associated with a reduced risk of coronary heart disease.[1-4] It is also known that regular physical activity is associated with higher levels of physical fitness, as measured by maximal oxygen uptake and heart-rate response to submaximal exercise,[5,6] and with a more favorable risk profile for coronary heart disease.[7-10] However, limited data are available on the relation between physical fitness as measured by exercise testing and subsequent cardiovascular morbidity or mortality.[11-13]

The purpose of the present study was to test the hypotheses that physical fitness, as assessed by measurements easily obtained from a standard treadmill exercise test, is associated with subsequent mortality from coronary heart disease and cardiovascular disease in a heterogeneous population of asymptomatic middle-aged men and that this relation is independent of other major cardiovascular risk factors.

Methods

Study Participants

The Lipid Research Clinics Prevalence survey, conducted between 1972 and 1976, consisted of a preliminary screening of men and women sampled from predefined populations at 10 participating centers in the United States and Canada. Fasting plasma cholesterol and triglyceride levels were determined in 17,400 men and 16,400 women between 30 and 69 years of age during this initial visit (Visit 1). The following groups were invited to return for a second visit (Visit 2): (1) a random sample made up of 15 percent of all eligible participants; (2) those whose plasma cholesterol levels at Visit 1 met or exceeded 6.20 mmol per liter (240 mg per deciliter) for participants 30 to 39 years of age, 6.70 mmol per liter (260 mg per deciliter) for those 40 to 49 years of age, and 7.25 mmol per liter (280 mg per deciliter) for those 50 years of age or older; (3) those whose plasma triglyceride levels at Visit 1 exceeded 2.82 mmol per

From the Department of Medicine (L.-G.E., D.S.S.) and the Collaborative Studies Coordinating Center, Department of Biostatistics (J.L.J., F.S.W.), University of North Carolina, Chapel Hill; the Stanford Center for Research in Disease Prevention, Stanford University, Stanford, Calif. (W.L.H.); and the Division of Epidemiology, Department of Community and Family Medicine, University of California, La Jolla (M.H.C.). Address reprint requests to Basil M. Rifkind, M.D., at the Lipid Metabolism–Atherogenesis Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Rm. 401, Federal Bldg., Bethesda, MD 20892.

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