DOI:10.1158/1055-9965.EPI-08-0846

Longitudinal Study (ACLS). We tested the hypothesis that CRF is associated with cancers of the colorectum, pancreas, esophagus, stomach, or gallbladder, for which there is prior evidence of an association (7-10, 14, 15), and generated hypotheses on the association between cancers of the liver or small intestine and either CRF or other measures of physical activity, for which there are no prior data.

Materials and Methods

Study Population. The ACLS is an ongoing cohort study of patients who were examined during a preventive medical examination in Dallas, TX, between 1974 and 2003. This study was reviewed and approved by the Cooper Institute Institutional Review Board on an annual basis. The sample for the current analysis was 38,801 primarily White, well-educated, middle-to-upper socioeconomic status men ages 20 to 88 years. The inclusion criteria required that men had no prior history of cancer, ulcer disease, gallbladder trouble, jaundice, hepatitis, cirrhosis, or colon polyps. At baseline, all participants completed a symptom limited treadmill test. The men in the analyses reported here are very similar to the overall ACLS cohort, with only minor differences in some clinical variables. The death rate for the subgroup of men in this analysis is not significantly different from the age, risk factor, health status, and family history-adjusted rates for the overall cohort.

Baseline Examination. Participants arrived for the clinical examination after an overnight fast of at least 12 h and gave their written informed consent to participate in the examination and the follow-up study. Information was collected pertaining to personal and family health histories, fasting blood chemistry analyses, anthropometry, resting blood pressure and electrocardiogram, and a maximal graded exercise test. Examination methods and procedures followed a standard manual of operations as described previously (18). Briefly, body mass index (BMI) was computed from measured height and weight (kg/m^2). Resting blood pressure was recorded as the first and fifth Korotkoff sounds by ausculatatory methods. Serum samples were analyzed for lipids and glucose using standardized automated bioassays by a laboratory that participates in the Centers for Disease Control and Prevention Lipid Standardization Program and meets its quality-control standards. Information on smoking habits (never, past, and current smoker), alcohol intake (number of drinks per week), personal history of diabetes, and family (from parents and siblings; first-degree relatives) history of cancer from all-cause was obtained from a standardized questionnaire. One unit of alcohol is defined as 12 ounces (3.41 dL) of beer, 5 ounces (1.421 dL) of wine, or 1.5 ounces (0.4262 dL) of hard liquor.

We determined CRF at the baseline examination using a maximal exercise test on a treadmill. CRF was assessed as the duration of the exercise test using a modified Balke protocol (18, 19). The treadmill speed was 88 m/min for the first 25 min. During this time, the grade was 0% for the first minute and 2% the second minute and increased 1% for each minute. After 25 min, the grade remained constant while the speed increased 5.4 m/min each minute until test termination. Patients were encouraged to give a maximal effort during the test. Men included in the present analyses reached at least 85% of their age-predicted maximal heart rate [220-age (years) beats per minute] on the test. The duration of the maximal exercise treadmill test on this protocol is highly (and positively) correlated with directly measured maximal oxygen uptake in men (ref. 20; $r = 0.92$), an accepted measure of CRF. Maximal metabolic equivalents (MET; 1 MET = 3.5 mL O_2 uptake/kg/min) were estimated from the final treadmill speed and grade (21). We used our previously published age-specific distribution of treadmill duration from the overall ACLS population to define fitness groups as low (lowest 20%), moderate (middle 40%), and high (upper 40%) to maintain consistency in the study methods and because we have found that a low level of fitness, defined in this way, is an independent predictor of mortality (18, 22) and morbidity (23). The respective cut points for total treadmill time and METs in the low, moderate, and high fitness groups were described in detail in a recent report (23).

Ascertainment of Digestive Cancer Death. All participants were followed from the date of their baseline examination until their date of death or December 31, 2003. The National Death Index was the primary data source for mortality surveillance. The National Death Index has been shown to be an accurate method of ascertaining deaths in observational studies, with high sensitivity (96%) and specificity (100%; ref. 24). The underlying cause of death was determined from the National Death Index report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of residence. Causes of cancer death were identified using *International Classification of Diseases, Ninth Revision* codes for deaths occurring before 1999 and *International Classification of Diseases, Tenth Revision* codes (in parentheses) for deaths during 1999 to 2003. Our primary outcome for this analysis was death from digestive cancers, 150-159 (C15-C26), and our secondary mortality outcomes were esophagus, 150 (C15); stomach, 151 (C16); small intestine, 152 (C17); colon, 153 (C18); rectum, 154 (C19-C21); liver, 155 (C22); gallbladder and intrahepatic bile ducts, 156 (C23-C24); pancreas, 157 (C25); and other and ill-defined digestive organs, 158-159 (C26).

Statistical Analysis. Baseline characteristics of the population were calculated for the entire study group and by CRF categories. Differences in covariates were assessed using *F* tests. Kaplan-Meier plots were used to compare survival curves. The crude and multivariate-adjusted log-rank tests were used to determine significance. Cox proportional hazards models were used to estimate adjusted hazard ratios (HR), associated 95% confidence intervals (95% CI), mortality rates (deaths/10,000 person-years of follow-up), and linear trends of mortality for levels of each fitness category. When calculating HR, the low fitness group was used as the reference category. Multivariable-adjusted models controlled for the potential confounding effects of baseline age (years), examination year, smoking (never, past, or current smoker), alcohol intake (drinks per week), and family history of cancer (whether present). Examination year was included as a covariate to control for variation in the length of follow-up in this ongoing study. We

DOI:10.1158/1055-9965.EPI-08-0846

Table 1. Baseline characteristics according to CRF, ACLS, Dallas, TX, 1974-2003

Characteristics	All (n = 38,801)	CRF			P_{trend}
		Low (n = 6,665)	Moderate (n = 15,315)	High (n = 16,821)	
Mean (SD) age (y)	43.8 (9.7)	43.6 (9.4)	44.0 (9.6)	43.6 (9.9)	<0.001
Mean (SD) height (cm)	178.9 (6.9)	178.0 (8.6)	179.0 (6.6)	179.3 (6.5)	<0.001
Mean (SD) BMI (kg/m^2)	26.3 (3.4)	28.6 (4.2)	26.7 (3.2)	24.9 (2.5)	<0.001
Mean (SD) METs achieved during the treadmill test	11.6 (2.5)	8.5 (1.3)	10.7 (1.2)	13.7 (1.9)	<0.001
Mean (SD) treadmill time duration (min)	17.9 (5.2)	11.1 (2.7)	16.0 (2.5)	22.3 (3.5)	<0.001
Mean (SD) lipids (mmol/L)					
Total cholesterol	5.5 (1.1)	5.7 (1.1)	5.5 (1.0)	5.3 (1.2)	<0.001
High-density lipoprotein-cholesterol	1.2 (0.3)	1.0 (0.3)	1.1 (0.3)	1.3 (0.3)	<0.001
Triglycerides	1.6 (1.4)	2.2 (2.1)	1.7 (1.2)	1.2 (1.0)	<0.001
Mean (SD) fasting blood glucose (mmol/L)	5.6 (2.8)	5.8 (1.5)	5.6 (1.0)	5.5 (4.1)	<0.001
Mean (SD) blood pressure (mm Hg)					
Systolic	122 (14)	124 (14)	122 (13)	120 (13)	<0.001
Diastolic	81 (10)	84 (10)	82 (10)	79 (9)	<0.001
Cigarette smoking (%)					
Never	70.8	59.0	68.9	77.2	
Past	10.8	7.4	10.2	12.7	<0.001
Current	18.4	33.6	20.9	10.1	
Mean (SD) alcohol drinking (drinks/wk)	7.9 (11.4)	8.3 (11.5)	8.1 (11.6)	7.5 (11.2)	<0.001
Diabetes* (%)	5.4	10.1	5.7	3.3	<0.001
Family history of cancer (%)	1.0	0.8	1.2	1.1	0.04

*Diabetes was defined as glucose ≥126 mg/dL or history of physician-diagnosed diabetes.

conducted additional analyses that further adjusted for baseline differences in two factors that could plausibly mediate the association between CRF and digestive cancer mortality: BMI (<25 versus ≥25 kg/m^2) and diabetes (whether diagnosed before or at the examination). Unfortunately, we have no information on nonsteroidal anti-inflammatory drug usage to include in the model. Cumulative hazards plots grouped by exposure had no appreciable violations of the proportional hazards assumption.

Next, we conducted Cox regression analyses of CRF stratified by categories of BMI (<25 versus ≥25 kg/m^2). We also examined the risk of total digestive system cancer across increments of METs to assess the shape of the fitness-mortality curve. Finally, we explored the site-specific cancer deaths across fitness levels. Statistical analyses were done using SAS (version 9.1; SAS Institute) software. All P values were calculated based on two-sided hypothesis tests, and 95% CIs were calculated at the 95% level.

Results

At baseline, the mean (SD) age of the study participants was 43.8 (9.7) years, the mean treadmill test duration was 17.9 (5.2) min, and the mean CRF measure was 11.6 (2.5) METs. The distribution of participant characteristics for several digestive cancer risk factors is given in Table 1 across categories of CRF. Men in the high fitness group were more likely to have a lower BMI, to have more favorable lipid and blood pressure profiles, to be nonsmokers, and to have less diabetes compared with men with low CRF. The Kaplan-Meier plot depicts the total digestive cancer death rates by fitness group (Fig. 1). After adjusting for all the risk factors, the resulting log-rank test did not change materially (χ^2 = 14.9; P < 0.001).

In a mean length of 17 years of follow-up and 661,169 person-years of observation, 283 total digestive cancer deaths were identified. A steep inverse gradient (P_{trend} < 0.001) of total digestive cancer mortality rates was observed across CRF groups (Table 2). After adjusting for potential confounders (age, examination year, smoking status, alcohol intake, and family history of cancer), men with moderate and high CRF had 37% and 49% lower risk of death from digestive cancers, respectively, than did men with low CRF (P_{trend} < 0.001). Additional adjustment for BMI and personal history of diabetes did not materially change the magnitude or the pattern of the association.

To explore possible effect modification of the association between CRF and total digestive cancer by BMI, we stratified the analysis according to BMI category (<25 and ≥25 kg/m^2; Table 2). The age-adjusted death rate was inversely related to CRF within the normal weight (18.5 < BMI < 25 kg/m^2; P_{trend} = 0.009) and overweight/obese [BMI ≥ 25 kg/m^2; P_{trend} = 0.003; because of the small number of deaths (only 1 death) in

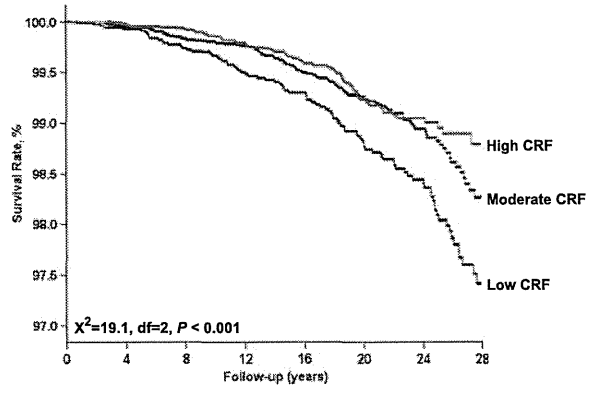

Figure 1. Kaplan-Meier plots for mortality due to total digestive system cancer, ACLS, Dallas, TX, 1974-2003.

DOI:10.1158/1055-9965.EPI-08-0846

Table 2. Rates and HR for digestive system cancer mortality by CRF groups, ACLS, Dallas, TX, 1974-2003

	Deaths from digestive system cancer	Mortality rate*	HR† (95% CI†)	HR‡ (95% CI‡)
All men (n = 38,801)				
Low CRF	90	6.8	1.00 (reference)	1.00 (reference)
Moderate CRF	110	4.0	0.63 (0.47-0.85)	0.66 (0.49-0.88)
High CRF	83	3.3	0.51 (0.37-0.70)	0.56 (0.40-0.80)
P_{trend}		<0.001	<0.001	0.001
Men with BMI < 25 kg/m^2 (n = 15,422)				
Low CRF	18	5.7	1.00 (reference)	
Moderate CRF	37	3.8	0.75 (0.42-1.37)	
High CRF	40	2.7	0.51 (0.28-0.94)	
P_{trend}		0.009	0.02	
Men with BMI ≥ 25 kg/m^2 (n = 23,379)				
Low CRF	72	7.2	1.00 (reference)	
Moderate CRF	73	4.1	0.60 (0.42-0.85)	
High CRF	43	4.2	0.62 (0.418-0.94)	
P_{trend}		0.003	0.01	

*Rate is expressed as per 10,000 person-years and adjusted for age.
†Model 1: adjusted for age, examination year, smoking status (never, past, or current), alcohol intake (drinks per week), and family history of cancer (present or not).
‡Model 2: adjusted for all variables in model 1 plus BMI (<25 versus ≥ 25 kg/m^2) and personal history of diabetes (present or not).

obese (BMI ≥ 30 kg/m^2) men with high CRF, we combined the overweight and obese groups]. Similar patterns of association were noted after adjusting for confounders.

To examine the dose-response characteristics between CRF levels and total digestive cancer mortality in our population of men, we computed the age-adjusted death rates (per 10,000 person-years) for categories of CRF defined by increments of 1 MET across the range of 7 to 14 METs (Fig. 2). An exercise capacity of <8 METs was associated with >3-fold higher risk of total digestive cancer mortality compared with men having a capacity of ≥11 METs (P_{trend} < 0.001). Across incremental MET levels (from <7.0 to ≥14.0 METs), the covariates (including BMI and diabetes)-adjusted HR (95% CI) of mortality were 1.0, 0.75 (0.43-1.30), 0.48 (0.30-0.76), 0.39 (0.23-0.66), 0.43 (0.26-0.71), 0.36 (0.21-0.63), 0.38 (0.21-0.69), 0.28 (0.15-0.53), and 0.38 (0.19-0.76; P_{trend} < 0.001). Excluding the first 5-year of follow-up did not materially change the magnitude and the pattern of the association (P_{trend} < 0.001).

Because of the small number of site-specific cancer deaths and the similar trends in total digestive cancer mortality across fitness levels, the moderate- and high-fit groups were combined into one group (fit) and the low-fit group (unfit) was used as the reference (Fig. 3). For all digestive system cancers combined, the adjusted mortality risk associated with being fit was 0.62 (95% CI, 0.47-0.82). Being fit was associated with a lower risk of mortality from colon cancer [0.61 (0.37-1.00)], colorectal cancer [0.58 (0.37-0.92)], and liver cancer [0.28 (0.11-0.72)]. The associations between fitness and small intestine, gallbladder, and pancreatic cancer were suggestive of a reduced risk, but the HR (95% CI) did not reach statistical significance [0.36 (0.02-6.61), 0.83 (0.09-7.74), and 0.75 (0.45-1.24), respectively].

Because baseline age may influence results, we conducted additional sensitivity analyses by repeating the above analysis in men with baseline age 35 to 74 years (n = 32,137). The patterns of the association between fitness and digestive cancer mortality across different baseline age ranges were similar (data not shown).

Discussion

In this study, we observed an inverse association between CRF and risk of total digestive cancer mortality, with men in the moderate and high CRF groups showing 34% and 44% lower risk, respectively, of dying of digestive cancers after adjustment of confounding by age, smoking, drinking, and family history of cancer. Excluding men with pre-diabetes and diabetes did not materially change the results. Men with an exercise capacity <8 METs had >3-fold higher risk of dying of digestive cancer compared with those with higher MET level (≥11). These data suggest that an exercise capacity of at least 8 METs may be needed to provide substantially protective benefits.

To the best of our knowledge, only one previous study has assessed the association of CRF with risk of dying of

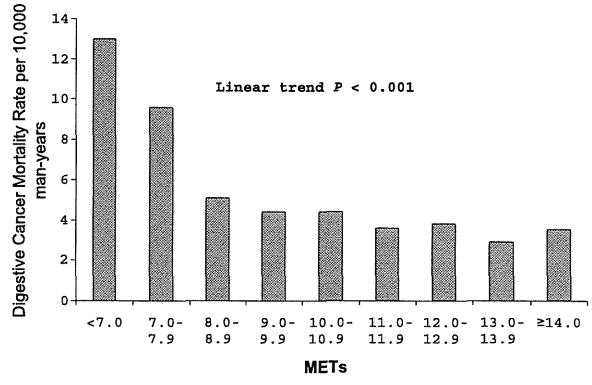

Figure 2. Age-adjusted mortality rates (per 10,000 man-years) of total digestive system cancer by CRF levels quantified in 1-MET increments obtained during a maximal treadmill test in men, ACLS, Dallas, TX, 1974-2003. Number at risk (number of cases) in <7.0, 7.0 to 7.9, 8.0 to 8.9, 9.0 to 9.9, 10.0 to 10.9, 11.0 to 11.9, 12.0 to 12.9, 13.0 to 13.9, and ≥14.0 was 859 (33), 1,096 (27), 4,465 (53), 4,135 (33), 6,014 (44), 5,827 (30), 5,180 (25), 5,872 (20), and 5,353 (18).

DOI:10.1158/1055-9965.EPI-08-0846

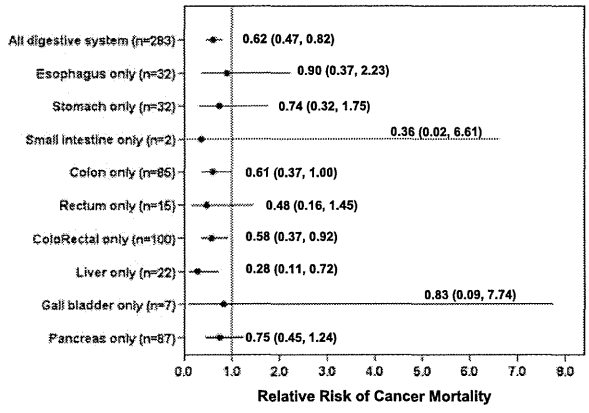

Figure 3. Risk of site-specific digestive cancer mortality associated with being fit (the upper 80% of the distribution of CRF) as defined by achieving at least a moderate level of fitness during maximal exercise testing, ACLS, Dallas, TX, 1974-2003. The reference group was the unfit group (the lowest 20% of the distribution of CRF). We used Cox proportional hazards models to estimate the HR, which include age, examination year, smoking, alcohol intake, personal history of diabetes, family history of cancer, and BMI as covariates. *Bars,* 95% CI.

digestive cancer (16). However, that article examined the role of CRF and risk of fatal digestive cancer events in men with pre-diabetes or diabetes, whereas our article examined a much broader male population. Our results were similar to the previous article's findings and show that higher levels of CRF are associated with substantially lower risk of dying from digestive cancers (including colorectal and liver cancers). In that study, Thompson et al. (16) found men who were fit, as defined by achieving at least a moderate level of fitness during a maximal exercise test, had a 45% lower risk of digestive cancer mortality. In our study, we found that men with at least a moderate fitness level had a 34% lower digestive cancer risk than did men with low CRF. In our study, it appeared that, beyond a CRF level of 8 METs (Fig. 2), there were no substantial decreases in risk of digestive cancer death. This finding of an apparent CRF threshold adds insight into the association between CRF and digestive cancer death. Although CRF has a genetic component (25-40%; refs. 25, 26), it is clear that usual physical activity habits are the primary determinant of fitness. CRF can be enhanced in most individuals through participation in moderate and vigorous physical activities, such as brisk walking, bicycling, and jogging, for ≥30 min on most days of the week (~8 kcal/kg/wk; ref. 27). This consensus public health recommendation will produce a maximal capacity of at least 8 METs in most individuals.

Our finding of an inverse association between physical activity and colorectal cancer risk is consistent with evidence from previous studies (28-30). A previous meta-analysis estimated ~20% to 40% lower risk of colon cancer for high versus low leisure-time physical activity (29). In our study, we found men with at least a moderate fitness level had a 42% lower risk of death from colorectal cancer than did men with low CRF.

We did not observe a significant inverse association between CRF and mortality from pancreatic cancer, a finding that is consistent with many studies (12, 13, 16, 31-35) but discrepant from others (9, 10, 36). However, we did observe a 25% reduction in mortality at this site among more fit men, but the small number of deaths limited the precision of our estimates. Given that the strength of the CRF-pancreatic cancer association was somewhat weaker than the risk estimates we observed for colorectal and liver cancer mortality (HR, 0.28-0.58), it may be that the association between pancreatic cancer and activity-related exposure is weaker. Because physical activity is a complex behavior and often imprecisely measured in epidemiologic studies, the combination of exposure measurement error and a weaker association may account for the heterogeneity in previous reports using self-reported physical activity as the exposure. We speculate that these two factors may be contributing to the inconsistency in previous findings. Future studies will be warranted to further explore this issue and confirm the present findings.

Little information is available on the association between physical activity or CRF and other types of digestive cancer. In this study, higher fitness was shown to be associated with significantly lower risk of liver cancer. This is consistent with the findings among men with pre-diabetes and diabetes (16). The findings with regard to stomach cancer have not been consistent. We found an inverse trend on stomach cancer as well as in men with diabetes (16), although the trend was not statistically significant possibly due to the small number of deaths. The British Regional Heart Study found the same nonsignificant inverse trend between physical activity and stomach cancer (15). In contrast, the Japanese Hawaiian Cancer Study found increased activity to be associated with higher risk of stomach cancer, but the results were preliminary (14). Only one previous study reported a lower risk of oral/esophagus cancer with moderate vigorous activity (15). We observed a similar trend. Regarding bladder cancer, neither the Japanese Hawaiian Cancer Study (14) nor the current study found any association between activity and urinary bladder cancer; however, the British Regional Heart Study (15) showed significant increase in risk of bladder cancer among men who were vigorously active. Finally, we observed a nonstatistically significant lower risk of small intestine cancer among men with high fitness. Despite the absence of a prior hypothesis for the sites shown in Fig. 3, fitness appeared to be protective overall. These findings may provide clues for future research, in studies having larger sample sizes and employing rigorous methods of measuring fitness (such as were available to us).

Several biological mechanisms have been proposed to explain how higher levels of physical activity may protect against cancer in general and cancers of the digestive tract in particular. Physical activity is known to affect cancer development through immune system function, insulin sensitivity, and growth factor levels (37-39). It is unclear which mechanisms are important for different sites of digestive cancer. Any or all of these mechanisms may influence general susceptibility to cancer (38). There are links between colorectal cancer and central obesity (40, 41) and insulin and the insulin-like growth factor-I axis (42). Biologically, it appears that insulin resistance and abnormal glucose metabolism may

DOI:10.1158/1055-9965.EPI-08-0846

be related to increased risk of pancreatic cancer. We specifically examined two potential obesity-related mediators of the association (BMI and diabetes) in our sequential models and found that adjustment for these factors had relatively little influence on the strength of associations observed. This finding suggests adiposity and diabetes, as measured in our study, are not strong mediators of the associations of interest. Evidence suggests that higher plasma glucose level after an oral glucose load is predictive of pancreatic cancer mortality (5) as is a diagnosis of diabetes (4). However, little is known about the specific mechanisms between physical activity and stomach, small intestine, liver, bladder, and other digestive tract cancers. Potential mechanisms, specific to gastrointestinal health, include decreased fecal transit time, reduced bile secretion, altered prostaglandin synthesis, and gut flora (43). Additional research is needed to clarify the complicated association between activity and digestive tract cancers.

This large prospective study with a long follow-up interval has several strengths that should be considered. First, it is rare to have a measure of fitness in a prospective study of digestive cancer mortality. Second, our extensive baseline examination to evaluate health status (such as cancer and diabetes), careful measurement of body size, and other lifestyle factors addresses the potential for confounding by these factors to influence our results. Our study also has limitations that should be considered. First, we are unable to adjust for dietary factors such as fiber and saturated fat intake in the current study. Second, although we had a hard endpoint of digestive cancer mortality, it is not possible to determine completely whether higher levels of CRF protected men against developing cancer or whether it aided their survival after their diagnosis. However, the low 5-year survival rates for many of these cancers (especially pancreatic and liver cancer) make incidence and mortality essentially interchangeable (as virtually everyone diagnosed with the cancer dies of the cancer; ref. 44). Fitness also appeared to be protective against esophagus, stomach, small intestine, and gallbladder cancer mortality, although statistical significance was not achieved because of the small number of deaths associated with these sites. Third, few studies have examined the relationship between physical activity and cancer risk in anatomic segments of the colon with conflicting results (45). Unfortunately, we do not have data regarding specific subsite colon cancer risk. Another limitation to the current findings is that the study population consists mainly of White men in the middle and upper socioeconomic strata; thus, results may not be generalizable to other adult populations but should not affect the internal validity of our findings. 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 fitness over time on our outcomes. It is possible, but not very likely, that many low-fit men increased their fitness levels at some point in the follow-up interval. Additionally, others may have experienced decreases in this component. Therefore, we cannot examine whether changes in fitness and other exposures occurred during follow-up. However, such misclassification of exposure would likely underestimate the magnitude of the association observed in the present study. We had insufficient information to assess the effect of aspirin and other nonsteroidal anti-inflammatory drugs on outcome. Future studies should include such information whenever possible.

In summary, the findings from this study provide evidence supporting a protective role of CRF on risk of digestive cancer mortality and that a relatively low threshold of CRF may be needed. The consensus public health guideline to obtain 150 min/wk of moderate-intensity physical activity will improve fitness levels and produce this threshold in most individuals. Given the public health burden of digestive cancer, future research needs to determine the specific biological characteristics of exercise related to digestive cancer risk and if a dose-response relationship exists.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank Dr. Kenneth H. Cooper for establishing the ACLS, the Cooper Clinic physicians and technicians for collecting the baseline data, and the staff at the Cooper Institute for data management.

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論文名	Cardiorespiratory fitness and digestive cancer mortality: findings from the aerobics center longitudinal study
著 者	Peel JB, Sui X, Matthews CE, Adams SA, Hébert JR, Hardin JW, Church TS, Blair SN.
雑誌名	Cancer Epidemiol Biomarkers Prev.
巻・号・頁	18(4) 1111-1117
発行年	2009
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/19293313

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	20-88歳(43.8歳)	[redacted]		( )		前向きコホート
対象数	10000以上			( )		( )
調査の方法	実測	( )				
アウトカム 予 防	なし	なし	ガン予防	なし	(死亡)	( )
アウトカム 維持・改善	な し	な し	な し	なし	(	( )

図 表

Table 2. Rates and HR for digestive system cancer mortality by CRF groups, ACLS, Dallas, TX, 1974-2003

	Deaths from digestive system cancer	Mortality rate*	HR† (95% CI‡)	HR‡ (95% CI‡)
All men (n = 38,801)				
Low CRF	90	6.8	1.00 (reference)	1.00 (reference)
Moderate CRF	110	4.0	0.63 (0.47-0.85)	0.66 (0.49-0.88)
High CRF	83	3.3	0.51 (0.37-0.70)	0.56 (0.40-0.80)
P_{trend}		<0.001	<0.001	0.001
Men with BMI < 25 kg/m^2 (n = 15,422)				
Low CRF	18	5.7	1.00 (reference)	
Moderate CRF	37	3.8	0.75 (0.42-1.37)	
High CRF	40	2.7	0.51 (0.28-0.94)	
P_{trend}		0.009	0.02	
Men with BMI ≥ 25 kg/m^2 (n = 23,379)				
Low CRF	72	7.2	1.00 (reference)	
Moderate CRF	73	4.1	0.60 (0.42-0.85)	
High CRF	43	4.2	0.62 (0.418-0.94)	
P_{trend}		0.003	0.01	

*Rate is expressed as per 10,000 person-years and adjusted for age.
†Model 1: adjusted for age, examination year, smoking status (never, past, or current), alcohol intake (drinks per week), and family history of cancer (present or not).
‡Model 2: adjusted for all variables in model 1 plus BMI (<25 versus ≥ 25 kg/m^2) and personal history of diabetes (present or not).

図表掲載箇所	P.1114, Table 2
概 要 (800字まで)	Aerobics Center Longitudinal Studyに参加している38801名の男性(20-88歳、平均年齢43.8±9.7歳)を対象に、追跡期間平均17年間における消化器系ガンによる死亡と、体力との関連について検討を行った。体力は、改変されたBalke protocol Tredmilテストにより評価され、最大酸素摂取量が推定された。この年齢別の最大酸素摂取量を元に体力の下位20%集団(Low CRF)、中位40%集団(Moderate CRF)、上位40%集団(High CRF)に分類した。それぞれのMETsは、8.5±1.3、10.7±1.2、13.7±1.9であった。消化器系ガンによる死亡のハザード比は、それぞれ1.0、0.66(0.49-0.88)、0.56(0.4-0.8)であり、中程度の体力を有することで、最も体力が低い集団と比較して消化器系ガンによる死亡のリスクが低下することが示された。また部位別に検討を行ったところ、結腸直腸がん(0.58(0.37-0.92))、肝がん(0.28(0.11-0.72))における死亡のリスクと関連していた。
結 論 (200字まで)	男性において、体力が高いことで消化器系ガン、特に結腸直腸がん、肝がんによる死亡のリスクが低下することが示された。
エキスパートによるコメント (200字まで)	消化器系のガンによる死亡を包括的に検討しており、同じ集団を用いた中で結腸直腸ガンおよび肝がんの死亡リスクに体力が保護的影響を及ぼしていることが示された点において重要な見解であると言える。今回関連が認められなかったその他の消化器系ガンについてはそれらのガンによる死亡の少なさの影響もあると考えられるため慎重な解釈が必要であろう。

担当者 村上晴香

PHYSICAL FITNESS AS A PREDICTOR OF MORTALITY AMONG HEALTHY, MIDDLE-AGED NORWEGIAN MEN

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Abstract *Background.* Despite many studies suggesting that poor physical fitness is an independent risk factor for death from cardiovascular causes, the matter has remained controversial. We studied this question in a 16-year follow-up investigation of Norwegian men that began in 1972.

Methods. Our study included 1960 healthy men 40 to 59 years of age (84 percent of those invited to participate). Conventional coronary risk factors and physical fitness were assessed at base line, with physical fitness measured as the total work performed on a bicycle ergometer during a symptom-limited exercise-tolerance test.

Results. After an average follow-up time of 16 years, 271 men had died, 53 percent of them from cardiovascular disease. The relative risk of death from any cause in fitness quartile 4 (highest) as compared with quartile 1 (lowest) was 0.54 (95 percent confidence interval, 0.32 to 0.89; P = 0.015) after adjustment for age, smoking status, serum lipids, blood pressure, resting heart rate, vital capacity, body-mass index, level of physical activity, and glucose tolerance. Total mortality was similar among the subjects in fitness quartiles 1, 2, and 3 when the data were adjusted for these same variables.

The adjusted relative risk of death from cardiovascular causes in fitness quartile 4 as compared with quartile 1 was 0.41 (95 percent confidence interval, 0.20 to 0.84; P = 0.013). The corresponding relative risks for quartiles 3 and 2 (as compared with quartile 1) were 0.45 (95 percent confidence interval, 0.22 to 0.92; P = 0.026) and 0.59 (95 percent confidence interval, 0.28 to 1.22; P = 0.15), respectively.

Conclusions. Physical fitness appears to be a graded, independent, long-term predictor of mortality from cardiovascular causes in healthy, middle-aged men. A high level of fitness was also associated with lower mortality from any cause. (N Engl J Med 1993;328:533-7.)

PHYSICAL activity beyond a certain level and duration is necessary to improve physical fitness[1] and may be an important factor in the prevention of death from ischemic heart disease.[2] Since physical activity is more difficult to quantify than the level of physical fitness, however, the latter has gained popularity in the assessment of both cardiovascular function and long-term cardiovascular health. Recent reports[3-11] conclude that a low level of physical fitness is associated with increased mortality from cardiovascular causes during the subsequent five to eight years, a finding that corroborates our observations over a seven-year period in 2014 apparently healthy men 40 to 59 years of age.[12]

The aims of the present study were to search for a possible graded association between physical fitness and overall mortality or mortality from cardiovascular causes and to determine whether our results after 7 years[12] would persist after the substantially longer observation period of 16 years.

METHODS

Subjects

The subjects participating in this study were recruited from five companies in Oslo, Norway, from 1972 through 1975. The male employees of these companies included both white-collar and blue-collar workers considered to be typical of the healthy working male population of Norway. All 2341 healthy men 40 to 59 years of age working for the companies were invited to participate in the study, and 2014 of them (86 percent) accepted. None were using cardioactive drugs or drugs that might affect exercise performance or heart-rate response.

A subject was considered healthy if none of the following disorders were present, as determined by a thorough screening of the health file or by medical examination: coronary heart disease, other heart diseases, hypertension treated with drugs, diabetes mellitus, cancer, advanced pulmonary disease, advanced renal disease, liver disease, and miscellaneous diseases, including disorders of the musculoskeletal system preventing the subject from taking a symptom-limited bicycle exercise test. The details of the selection procedures have been presented elsewhere.[13]

From the Medical Department, Central Hospital of Akershus, Nordbyhagen, Norway (L.S., J.E., G.E.), and the National University Hospital (E.T.), the Ullevaal Hospital (R.M.), and the Department of Work Physiology, University of Oslo (K.R.) — all in Oslo, Norway. Address reprint requests to Dr. Jan Erikssen at the Medical Department, Central Hospital of Akershus, N-1474 Nordbyhagen, Norway.

Base-Line Measurements

The study was carried out at the National University Hospital of Oslo (the Rikshospitalet). The examination included a comprehensive medical history, physical examination, a panel of blood tests (including a lipid profile and an intravenous glucose-tolerance test), phonocardiography, chest radiography, a spirographic study, resting electrocardiography, and a symptom-limited bicycle exercise-tolerance test.[12] Physically active men were defined as those who exercised at least twice a week to the level of sweating and becoming short of breath, participated in sports competitions, or both.[14] With respect to smoking habits, the participants were described as having never smoked, as having formerly smoked, or as currently smoking either 1 to 9 or 10 or more cigarettes daily. Resting blood pressure and heart rate were measured after the patient had been in the supine position for five minutes. Cholesterol and triglyceride concentrations were determined by standardized methods, as reported elsewhere,[15] as were details of the intravenous glucose-tolerance test.[16] To measure glucose tolerance, the rate of disappearance of glucose, expressed as the percentage disappearing per minute (the K value), was used.[16] In the spirographic study, vital capacity and forced vital capacity in one second were measured with a Bernstein spirometer, and peak expiratory flow with a Wright peak flowmeter, as described elsewhere.[17] All the participants were examined between 7:30 a.m. and 10:30 a.m. after abstaining from eating and smoking for at least 12 hours.

The exercise tests were conducted on an electrically braked Elema bicycle that was repeatedly calibrated during the study. When set at a particular workload, the cycle ergometer demands a constant output of energy from the test subject, regardless of the rate at which the subject pedals. The initial workload was set at 1.405 kcal per minute in all but 2 percent of the subjects, who started at 0.703 kcal per minute because their state of physical fitness appeared to be very poor. Increments of 0.703 kcal per minute were added every six minutes. The subjects were encouraged to continue exercising until they were exhausted. If a subject stated that he felt unable to continue the test, without giving specific reasons, the test was always terminated, regardless of other findings. The exercise protocol specified the following reasons for terminating a test: major cardiac arrhythmias, a drop in the systolic blood pressure of at least 10 percent on two successive measurements one minute apart to-

ward the end of the test, heart block, ST-segment depression greater than 3 mm, severe dyspnea, or increasing chest pain.

Work capacity was calculated as the sum of the work performed (in kilocalories) at each workload until the termination of the test. Physical fitness was measured as the difference between the observed and expected work capacities according to the subject's body weight (as defined below under Statistical Analysis).

Exercise testing was repeated within two weeks in 130 participants. The two measurements of work capacity were within 5 percent of each other for 90 percent of the men and within 10 percent of each other for the entire group.

Identification of Deaths

Information about the times and causes of death was 100 percent complete by December 31, 1989. These data were obtained from the Norwegian Central Bureau of Statistics, as described elsewhere.[12] The specific causes of death are given according to the *International Classification of Diseases, 9th Revision*. On the basis of this information, each death was classified as having either a cardiovascular or a noncardiovascular cause.

Statistical Analysis

A graph of work capacity and body weight suggested linear associations in the group with a body weight of ≤75 kg and in the group with a body weight of >75 kg, with a shallower slope in the latter group. Linear regression analysis was performed separately in the two groups, with work capacity used as the dependent variable and body weight as the independent variable. The resulting regression function was calculated for each subject, and this value was labeled "expected working capacity according to body weight."

The association between the subject's fitness level and mortality (from cardiovascular, noncardiovascular, and all causes) was first assessed by presenting annual mortality according to the fitness quartiles. The relation between the fitness level and the variables studied was assessed by determining the mean values for the variables in each fitness quartile.

The association between the time to death (from cardiovascular causes or all causes) and the measurement of fitness, as well as selected variables, was investigated by means of the proportional-hazards model.[18] Three models were investigated. The first referred to mortality from cardiovascular causes and included physical fitness, age, and smoking status. The second model included, in addition, resting systolic blood pressure, resting heart rate, cholesterol and triglyceride levels, body-mass index (the weight in kilograms divided by the square of the height in meters), vital capacity, physical-activity level, and glucose tolerance as assessed by the intravenous glucose-tolerance test (the K value).[16] The third model referred to overall mortality and included the same variables as the second model.

The results obtained with the models are presented as relative risks. For a continuous variable, the relative risk of death from cardiovascular causes associated with a given change in the variable is presented after adjustment for all other variables in the model. The change studied was 2 SD (in the direction of increased risk) above the mean values for systolic blood pressure, cholesterol level, triglyceride level, vital capacity, and body-mass index; for age, the change studied was an increase of 10 years. For the graded variables (e.g., fitness level and smoking status) and the binary variables (e.g., K value and physical-activity level), the relative risks of death from cardiovascular causes between groups are presented. All the P values presented are two-tailed.

The assumptions of the proportional-hazards model were checked for all three models and found to be adequately met. The models were computed with the use of the proportional-hazards general procedure for a linear model in the SAS computer package.[19]

Results

All 2014 men included in the study completed the exercise test according to the protocol, and 97.4 percent started the second stage of the test. Twenty-two exercise tests were terminated because the subjects had increasing chest pain during the test. None had reported chest pain during their usual activities. Three exercise tests were interrupted because the subject's blood pressure reached 300 mm Hg; 1 had a decrease in blood pressure of at least 10 percent; 21 had arrhythmias; none had heart block; and 9 had ST-segment depressions of more than 3 mm. Of the 54 men who had at least one of these complications 32, 11, 5, and 6 belonged to fitness quartiles 1, 2, 3, and 4, respectively, when all 2014 men were categorized in fitness quartiles. Because of the possibility that these 54 men had cardiovascular disease at base line, they were excluded from further analysis. The remaining 1960 men, who stopped exercising because of obvious exhaustion, because they said they were unable to exercise further, or both, make up the present series. Their mean age was 49.9 years (range, 40.0 to 59.9). The average follow-up period was 15.9 years (range, 14 to 17), during which 271 of the men died, 143 (52.8 percent) of them from cardiovascular diseases (89 percent of these men died from myocardial infarction or had sudden and unexpected deaths). Of the 143 men who died of cardiovascular causes, 61 were in fitness quartile 1, 45 in quartile 2, 26 in quartile 3, and 11 in quartile 4. There were 45, 32, 38, and 13 deaths from other causes in the respective quartiles, for an overall mortality of 106, 77, 64, and 24, respectively.

Table 1 shows the values in each fitness quartile for a number of selected base-line variables. The higher the level of fitness, the higher the vital capacity and the lower the resting heart rate, blood pressure, cholesterol level, and prevalence of smoking. A high level of fitness was also strongly associated with a high level of physical activity in leisure time. All these associations were statistically significant ($P<0.001$). Virtually identical results were found when the data were corrected for differences in mean age among the quartiles (data not shown).

The relation between the fitness measure and annual mortality (from cardiovascular, noncardiovascular, and all causes) is shown in Table 2. Age-adjusted mortality from cardiovascular causes decreased with increasing fitness among both smokers and nonsmokers, and in all but the highest fitness quartile, smokers had a higher mortality due to cardiovascular causes than nonsmokers. In the highest fitness quartile, smokers and nonsmokers had similar mortality from cardiovascular causes.

The relation between fitness level and age-adjusted cumulative mortality from cardiovascular causes over the 16-year period is shown in Figure 1. Mortality from cardiovascular causes was very low in all the fitness subgroups during the first four years of observation, whereas the difference in mortality between quartile 1, the lowest fitness quartile, and the other three began to appear only after five years. The difference between quartile 4, the highest fitness quartile, and quartiles 2 and 3 was first observed after seven years and increased consistently thereafter. Mortality from cardiovascular causes was similar in quartiles 2 and 3 during the first 13 years,

whereas a tendency toward a difference in favor of quartile 3 was seen at 16 years.

Relative Risks among Fitness Quartiles

Mortality from Cardiovascular Causes

The relative risk of death from cardiovascular causes in quartile 4 as compared with quartile 1 was 0.30 (95 percent confidence interval, 0.15 to 0.61; P<0.001) after adjustment for age and smoking status. This relative risk was 0.41 (95 percent confidence interval, 0.20 to 0.84; P = 0.013) after further adjustment for systolic blood pressure, cholesterol level, triglyceride level, vital capacity, K value, resting heart rate, body-mass index, and physical-activity level (Table 3). The relative risk of death from cardiovascular causes in quartile 4 as compared with quartile 3 was 0.50 (95 percent confidence interval, 0.23 to 1.05; P = 0.068) after adjustment for age and smoking status.

A high level of physical activity as defined in the present study had no independent prognostic value, nor did body-mass index, resting heart rate, or fasting triglyceride level. All the other variables were significantly and independently associated with mortality from cardiovascular causes (Table 3).

Overall Mortality

After adjustment for the same variables that were used in the model for mortality from cardiovascular causes, the relative risk of mortality from any cause was as follows when the three other quartiles were compared with quartile 1: for quartile 4, 0.54 (95 percent confidence interval, 0.32 to 0.89; P = 0.015); for quartile 3, 1.00 (95 percent confidence interval, 0.71 to 1.41; P = 0.92); and for quartile 2, 0.92 (95 percent confidence interval, 0.66 to 1.28; P = 0.58). It is noteworthy that a comparison between quartiles 4 and 3 revealed a relative risk in quartile 4 of 0.53 (95 percent confidence interval, 0.32 to 0.87; P = 0.010), whereas the comparison of quartile 4 with quartile 2 revealed a relative risk of 0.59 (95 percent confidence interval, 0.36 to 0.96; P = 0.031). Thus, overall mortality was significantly lower in quartile 4 than in all three other quartiles.

Table 1. Base-Line Clinical and Laboratory Values in 1960 Healthy Men 40 to 59.9 Years of Age, According to Fitness Level.*

VARIABLE	FITNESS QUARTILE			
	1 (LOWEST) (N = 490)	2 (N = 491)	3 (N = 492)	4 (HIGHEST) (N = 487)
	mean±SD			
Total work performed (kcal)	16.3±4.3	22.2±4.3	27.5±4.1	40.2±10.0
Duration of exercise test (min)	9.6±2.1	12.2±1.8	14.3±1.5	18.5±3.0
Age (yr)	52.6±5.2	51.0±5.2	48.8±5.1	46.6±4.6
Resting heart rate (beats/min)	64±10	62±10	61±9	59±9
Blood pressure (mm Hg)				
Systolic	137±20	131±18	127±16	125±15
Diastolic	91±11	88±10	86±10	85±10
Cholesterol (mg/dl)	263±46	263±46	255±46	247±46
Triglycerides (mg/dl)	126±68	121±68	113±58	101±48
Body-mass index	25.5±2.8	24.6±2.9	24.0±2.5	24.0±2.5
Vital capacity (ml)	4029±860	4304±800	4539±857	4827±867
	percent			
K value ≤0.9	9.2	7.1	6.5	4.3
Current smokers	53	49	43	28
Physically active†	5	6	12	29

*To convert values for cholesterol to millimoles per liter, multiply by 0.02586, and to convert values for triglycerides to millimoles per liter, multiply by 0.01129.

†As defined in the Methods section.

Discussion

Our study has demonstrated a graded, inverse association between physical fitness and mortality from cardiovascular causes over a period of 16 years that is independent of age and conventional coronary risk factors. These findings corroborate and amplify our previous reports after a follow-up of seven years[3,12] and are in close accord with the findings of other recent studies.[4-11]

After adjustment for age and smoking status, overall mortality and mortality from cardiovascular causes were both observed to be lower among men in the quartile with the highest level of fitness than among the men in the remaining quartiles. Thus, although physical fitness appears to be more closely associated with mortality from cardiovascular causes than with overall mortality, the men in the quartile with the highest level of fitness appeared to be protected from death from all causes. In a previous study, Blair et al. reported an inverse relation between fitness and

Table 2. Annual Age-Adjusted Mortality from Cardiovascular, Noncardiovascular, and All Causes in 1960 Men during 16 Years of Follow-up, According to Fitness Level and Smoking Status.

SMOKING STATUS AND CAUSE OF DEATH*	FITNESS QUARTILE†			
	1 (LOWEST)	2	3	4 (HIGHEST)
	annual mortality per 100			
Never smoked				
CVD	0.62	0.29	0.24	0.23
Other	0.25	0.34	0.24	0.17
All	0.87	0.63	0.48	0.40
Former smokers				
CVD	0.53	0.35	0.22	0.14
Other	0.28	0.31	0.40	0.23
All	0.81	0.66	0.62	0.37
1–9 cigarettes daily				
CVD	0.55	0.88	0.41	0.26
Other	0.55	0.26	0.69	0.26
All	1.10	1.14	1.10	0.52
≥10 cigarettes daily				
CVD	0.70	0.66	0.68	0.26
Other	0.67	0.53	0.93	0.39
All	1.37	1.19	1.61	0.65

*CVD denotes cardiovascular disease.

†Among the men included in this analysis who never smoked, 113 were in quartile 1, 113 in quartile 2, 110 in quartile 3, and 159 in quartile 4. Among former smokers, there were 119, 135, 172, and 190 in the respective quartiles; among men smoking 1 to 9 cigarettes daily, 77, 91, 86, and 65; and among men smoking 10 or more cigarettes daily, 181, 152, 124, and 73.

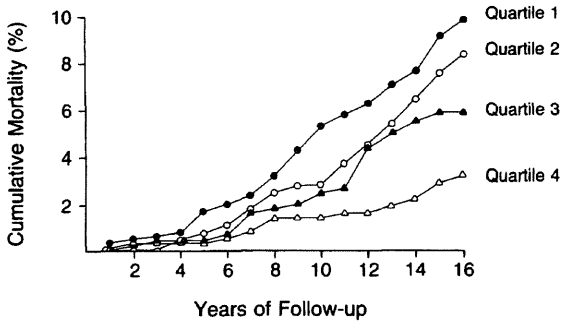

Figure 1. Cumulative Age-Adjusted Mortality from Cardiovascular Causes over 16 Years of Follow-up, According to Fitness Quartile.

death from cancer.[6] However, their data were not adjusted for smoking status.

Maximal work capacity, as defined in the present study, has been shown to be highly correlated with maximal oxygen uptake,[20] indicating that our measure of fitness is closely related to this most accepted measure of physical fitness.[1] To our knowledge, no study has suggested reduced survival in the presence of a high level of physical fitness. Instead, all major published studies, both North American[4,6-8,10] and European,[3,5,9] suggest a favorable long-term outcome in subjects with high as compared with low levels of physical fitness, regardless of how fitness is measured and defined.[4-10] The unadjusted risk ratio of 4.8 for mortality from cardiovascular causes over seven years in our study when subjects from the lowest fitness quartile were compared with those from the highest[3] is close to the risk ratios reported by others during follow-up periods of seven to nine years.[4,6,10,11]

We also observed a marked difference in mortality from cardiovascular causes between the subjects with intermediate levels of physical fitness (quartiles 2 and 3) and those with high levels (quartile 4). This finding would have remained undetected if our cohort had been followed for only 10 years (Fig. 1), as was the case in previous studies.[4-7]

These associations between fitness and mortality from cardiovascular causes can be used to assess the risk of cardiovascular disease among healthy subjects only if the subjects tested in the cited studies were truly healthy.[3-10] This prerequisite seems to have been met despite variation in the methods of selecting subjects.[3-10] Our selection procedure ought to have been reasonably successful in excluding subjects with preexisting cardiovascular disease, as the very low initial mortality suggests (Fig. 1).

Although the genetic component of physical fitness, as defined by a subject's maximal oxygen uptake, has been suggested to be approximately 40 percent,[21] this leaves about 60 percent of the variation between people attributable to other causes. Among these, physical activity, the key determinant,[1,2] is known to influence favorably a number of risk factors for coronary heart disease, such as the levels of cholesterol and triglycerides, and blood pressure.[3,22-25] Moreover, physical activity improves glucose tolerance and insulin sensitivity,[26] increases fibrinolysis,[27,28] increases levels of high-density lipoprotein cholesterol,[25] improves oxygen uptake in the heart as well as in peripheral tissues,[1] and increases the dimensions of coronary arteries and the formation of collateral vessels in animals.[29-31] Physical training also reduced the tendency to coronary vasospasm in one animal model[29] and increased the threshold for ventricular fibrillation in exercising rats.[32,33] Regular exercise also lowers the resting heart rate by increasing vagal tone.[34] A low heart rate is associated with a low mortality rate in humans[35,36] and appears to protect against the development of coronary atherosclerosis in monkeys.[37] Platelet aggregation has also been shown to decrease in exercising subjects.[38,39] Furthermore, a high level of physical activity appears to protect against death from cardiovascular disease.[2]

Although physical activity is not an independent predictor of mortality from cardiovascular causes, a close, direct correlation between reported physical activity and level of physical fitness was found in our study, as in previous studies.[4,40] Our estimates of physical activity during leisure hours are too crude, however, to allow speculation about its role in the prevention of death from cardiovascular disease.[14]

The associations in the present report, as in most others, have been corrected for differences in well-recognized coronary risk factors.[3-12] Thus, although our findings may conceivably be explained by important, currently unrecognized risk factors, a low level of physical fitness appears to be an important coronary risk factor.

Table 3. Relative Risk of Death from Cardiovascular Causes in 1960 Healthy Men during 16 Years of Follow-up, Associated with Specific Changes or Comparisons of Base-Line Variables.

VARIABLE*	RELATIVE RISK	95 PERCENT CONFIDENCE INTERVAL	P VALUE
Age (increase of 10 yr)	2.9	2.0–4.3	<0.001
Smoking status (vs. those who never smoked)			
≥10 cigarettes/day	1.8	1.1–2.8	0.032
1–9 cigarettes/day	2.0	1.2–3.2	0.003
Former smokers	1.0	0.6–1.6	0.95
Fitness level (vs. quartile 1)			
Quartile 4	0.41	0.20–0.84	0.013
Quartile 3	0.45	0.22–0.92	0.026
Quartile 2	0.59	0.28–1.22	0.15
K value (≤0.9 vs. >0.9)	2.0	1.3–3.4	0.005
Systolic blood pressure (increase of 36 mm Hg)	1.5	1.1–2.1	0.010
Cholesterol (increase of 93 mg/dl [2.4 mmol/liter])	1.5	1.1–2.1	0.004
Vital capacity (decrease of 1702 ml)	1.4	1.05–2.1	0.029
Triglycerides (increase of 120 mg/dl [1.36 mmol/liter])	1.1	0.7–1.7	0.62
Body-mass index (increase of 5.4)	1.1	0.7–1.7	0.56
Physical activity (active vs. not active)	1.1	0.7–1.7	0.53
Resting heart rate (increase of 18 beats/min)	1.2	0.8–1.8	0.20

*For categorical variables, the risks for categories are compared, whereas for continuous variables, risks are given for an increase in the variable of 2 SD in the direction of increased risk, as described in the Methods section.

Although studies showing a favorable association between fitness and mortality might be more likely to be published than negative studies, the uniformity of the published literature and the observed graded relation argue against a publication bias of any consequence. Many previous studies may be criticized for possible selection biases or inadequate descriptions of selection procedures,[3-12] but these shortcomings notwithstanding, the results from all these studies are remarkably similar.[3-12] Accordingly, the aggregate data in the literature represent a body of evidence that, according to epidemiologic principles,[41] suggests a causal relation between physical fitness and mortality from cardiovascular causes. The associations observed worldwide are consistent, strong, graded, plausible, coherent, appropriately sequenced, and reasonably unbiased.[41] Only experimental evidence, difficult to obtain in humans, is still lacking in the final chain of proof.[41]

Whether genetic superiority among fit subjects explains these findings is unknown, but the close association between fitness level and mortality from cardiovascular causes tends to argue against it as the only explanation. Instead, one may speculate whether low fitness in the absence of disease often signifies a lifestyle with inherent unfavorable consequences for cardiovascular health.

This apparently simple pattern, also observed by others,[3-10] is complicated in our study by the finding of strikingly low overall mortality in the men from the highest fitness quartile as compared with those in the other three quartiles. The reason for this finding remains obscure, although several explanations may be conjectured. We have no data to allow further speculations, however, and this finding should be considered an observation that warrants further study.

We are indebted to Mrs. Solveig Eggen for her assistance in the preparation of the manuscript.

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論文名	Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men.						
著　者	Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K.						
雑誌名	N Engl J Med						
巻・号・頁	328(8)巻　　533-537ページ						
発行年	1993						
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/8426620						
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	40-59歳			( )		前向き研究
	対象数	1000～5000	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予　防	心疾患予防	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)	背景：低体力が心血管病変による死亡の独立した危険因子であることを示す多くの研究があるにもかかわらず、その問題は争点として残っている。我々は、1972年からノルウェー人男性を16年間にわたり追跡調査し、この疑問について研究した。方法：我々の研究には40～59歳までの健康な男性1960人(研究参加を求めた84%の人)を含んだ。通常の冠動脈危険因子と心肺体力についてはベースラインで評価し、体力については自転車エルゴメータによる運動負荷テストを症候限界までおこなわせ、得られた総負荷量を用いた。結果：平均16年間の追跡調査の結果、全体の53%に当たる271人の男性が心血管疾患で死亡した。年齢、喫煙状況、血清脂質、血圧、安静時心拍数、肺活量、BMI、身体活動水準、および耐糖能などの補正後において、体力水準1(最も弱い)と4(最も強い)で比較した際のあらゆる死亡原因の相対リスクは、0.54 (95%信頼区間、0.32～0.89; P=0.015)であった。データをこれらと同様の変数に適応させた時の全死亡率は、体力水準1、2(弱い)、3(やや強い)の群の間で同様であった。心血管原因により補正された死亡の相対的リスクは、体力水準1と4を比較すると0.41(95%信頼区間、0.20～0.84; P=0.013)であった。体力水準2および3における相対リスク(1との比較)は、それぞれ0.45 (95%信頼区間、0.22～0.92; P=0.026)、0.59(95%信頼区間、0.28～1.22; P=0.15)であった。結論：体力は、中高年者における心血管原因による死亡に対して格付けられた、独立した、長期間の予測因子になるとみられる。高体力水準もまた、いかなる原因からみても低						
結　論 (200字まで)	体力は中年男性の循環器病死亡リスクの予測因子である。また、高い体力レベルのみが全死亡リスクを減らすことができる。						
エキスパートによるコメント (200字まで)	体力と循環器疾患ならびに総死亡との関連について最もよくデザインされ、最も頻繁に引用される研究の一つ。						

担当者　宮地 劉

Clinical and Experimental Pharmacology and Physiology (1993) **20**, 483–487

FIVE YEAR PROSPECTIVE STUDY ON BLOOD PRESSURE AND MAXIMAL OXYGEN UPTAKE

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(Received 6 April 1992; revision received 3 March 1993)

SUMMARY

1. The relationship between physical fitness (maximal oxygen uptake $\dot{V}_{O_2max}$) and incidence of hypertension was investigated through a prospective study for a total of 16525 human-years of observation.

2. This study involved 3305 Japanese males whose blood pressure (BP) was normal when they received their first physical examination before the age of 50. They were monitored from 1983 to 1988. The BP of 425 subjects was diagnosed as hypertension in the fifth year.

3. Fitness levels were divided into quintiles according to $\dot{V}_{O_2max}$ levels, and were compared with the changes of BP and relative risk of hypertension after adjustment for age, initial percentage of body fat (PFAT), initial BP, alcohol consumption, cigarette smoking status and familial history of hypertension. The increase in BP of subjects in the least fit group was higher than in any other group. Relative risk was calculated using a multiple logistic regression and was 1.9× higher in the least fit group compared with the fittest group.

4. The subjects were classified into three groups: the improved $\dot{V}_{O_2max}$ group, the deteriorated $\dot{V}_{O_2max}$ group and the unchanged $\dot{V}_{O_2max}$ group. The increase in BP of the improved $\dot{V}_{O_2max}$ group was significantly lower than the other two groups after adjustment for changes in PFAT, age, initial PFAT, initial BP, fitness level, alcohol consumption, cigarette smoking status and familial history of hypertension.

5. It is concluded that low $\dot{V}_{O_2max}$ level is related to higher incidence of hypertension. An improved $\dot{V}_{O_2max}$ would therefore be able to prevent hypertension.

Key words: hypertension, maximal oxygen uptake, physical fitness, prospective study.

INTRODUCTION

Physical fitness is inversely associated with the incidence of hypertension. Kiyonaga *et al.* (1985) suggest that moderate regular exercise lowers blood pressure in patients with essential hypertension because it reduces plasma catecholamine levels, and increases levels of plasma prostaglandin E and the urinary excretion of sodium (Kiyonaga *et al.* 1985). There is evidence from case-control studies that moderate

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regular exercise has a significant depressor effect on hypertensive patients independent of bodyweight loss (Duncan *et al.* 1985; Nelson *et al.* 1986). There are also some cross-sectional studies which indicate that the incidence of hypertension is related to the degree of physical fitness (Gyntelberg & Meyer 1974; Cooper *et al.* 1976; Fraser *et al.* 1983; Gibbons *et al.* 1983; Siconolfi *et al.* 1985; Tanaka *et al.* 1990).

However, there is limited prospective evidence for a relationship between physical fitness and blood pressure (Paffenbarger *et al.* 1983; Blair *et al.* 1984; Hofman *et al.* 1987; Paffenbarger *et al.* 1991). The studies that have been done have involved mainly western subjects.

Thus, a prospective study was performed to determine the relationship between maximal oxygen uptake and incidence of hypertension after adjustment for confounding factors in Japanese whose diet generally contains about twice as much salt, but less animal fat than a western diet.

METHODS

A total of 3305 Japanese male employees aged between 20 and 55 years (mean age 32 years) was used for the present analysis. The subjects were followed for 5 years, 1983–1988, so that the development of hypertension could be examined. All subjects received medical examinations. In 1983 subjects were free from hypertension and had no prior history of cardiovascular disease, hepatic disease, renal disease, diabetes or stroke.

Systolic and diastolic blood pressures (SBP, DBP) were measured using a mercury sphygmomanometer after the subjects had rested for >3 min in a sitting position. The SBP was operationally defined as the pressure in the cuff at the time of appearance of the first Korotkoff sound. The fifth phase of the sound was used as an approximation of the DBP. Height and weight were measured, and the percentage of body fat (PFAT) was estimated from the sum of the triceps and subscapula skinfolds measured with a skinfold caliper (Nagamine & Suzuki 1964) using Brozek's formula (Brozek *et al.* 1963). To determine physical fitness, maximal oxygen uptake ($\dot{V}_{O_2max}$), a widely accepted measure of physical fitness, was estimated using the Astrand-Ryhming Nomogram (Astrand & Ryhming 1954). This estimate was shown to be highly correlated ($r = 0.94$) with directly measured $\dot{V}_{O_2max}$ (Siconolfi *et al.* 1982). This exercise test was performed twice — before and after the 5 year period.

Alcohol consumption, cigarette smoking status and familial history of hypertension

The physical fitness levels were divided into quintiles according to $\dot{V}_{O_2max}$/wt after adjustment for age, initial PFAT, initial blood pressure, alcohol consumption, cigarette smoking status and familial history of hypertension. Alcohol consumption, cigarette smoking status and familial history of hypertension were determined from a medical inquiry. Individuals with the lowest $\dot{V}_{O_2max}$ were classified into the first quintile. Conversely, subjects who had the highest $\dot{V}_{O_2max}$ were classified into the fifth quintile. In addition, after 5 years, the subjects were classified into three groups: (i) the improved physical fitness group consisting of those whose $\dot{V}_{O_2max}$ had improved by >15%; (ii) the deteriorated physical fitness group comprising those whose $\dot{V}_{O_2max}$ had decreased by >15%; (iii) the group with unchanged physical fitness.

Data were analysed using the Statistical Analysis System software package (SAS Users Guide 1982). A multiple logistic regression and analysis of covariance were used to evaluate the relationship between blood pressure and maximal oxygen uptake after adjustment for confounding factors.

RESULTS

The variables of weight, PFAT, resting SBP and DBP and $\dot{V}_{O_2max}$ in 1983 and 1988 are shown in Table 1. Mean values of $\dot{V}_{O_2max}$ indicate that the subjects of this study were representative of a wide study previously done in Japan (Kobayashi 1982). There were significant differences between 1983 and 1988 for all the above variables.

The blood pressure values of 72 subjects were SBP≥160 mmHg or DBP≥95 mmHg and 353 subjects were 160 mmHg>SBP≥140 mmHg or 95 mmHg>DBP≥90 mmHg after 5 years. The above persons (72+353) were diagnosed as having hypertension.

The relationship of the physical fitness levels to the increase in blood pressure during the 5 year period was characterized by the following inverse relationship: the lower the physical fitness level, the higher the increase in both SBP and DBP (Fig. 1).

The increase in blood pressure of subjects in quintile I was higher than that in the other four quintiles. Relative risk of incidence of hypertension was calculated using a multiple logistic regression after adjustment for age, initial PFAT, initial blood pressure, alcohol consumption, cigarette smoking status and familial history of hypertension. The relative risk was

Table 1. Characteristics of 3305 males in 1983 and 1988

	1983				1988			
	Mean	s.d.	Min.	Max.	Mean	s.d.	Min.	Max.
Height (cm)	168.7	5.6	147	190	168.8	5.6	147	190
Weight (kg)	63.8	7.8	40	96	65.7	8.3	42	104
BMI (kg/m$_2$)	22.4	2.4	16.5	32.9	23.0	2.6	16.1	35.8
PFAT (%)	14.0	3.8	4	34	15.3	3.5	8	30
SBP (mmHg)	122.7	10.0	86	138	125.7	11.5	84	179
DBP (mmHg)	69.3	10.2	30	88	72.6	7.7	50	105
$\dot{V}_{O_2max}$ (mL/kg per min)	40.4	7.4	22.7	79.1	38.2	7.5	18.2	76.4

For SBP, DBP and $\dot{V}_{O_2max}$ in 1988, there were 3304 subjects.

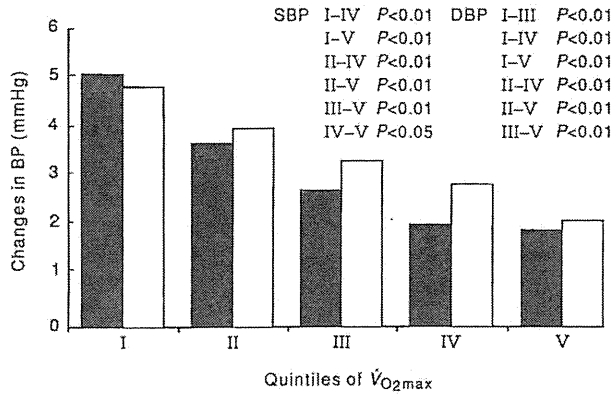

Fig. 1. Initial fitness quintiles and changes in blood pressure of subjects after adjustment for age, initial PFAT, initial blood pressure, alcohol consumption, cigarette smoking status and familial history of hypertension. Quintiles: I, <33.6; II, 33.6–37.2; III, 37.3–40.9; IV, 41.0–45.4; V, <45.4 mL/kg per min. (■) SBP; (□) DBP.

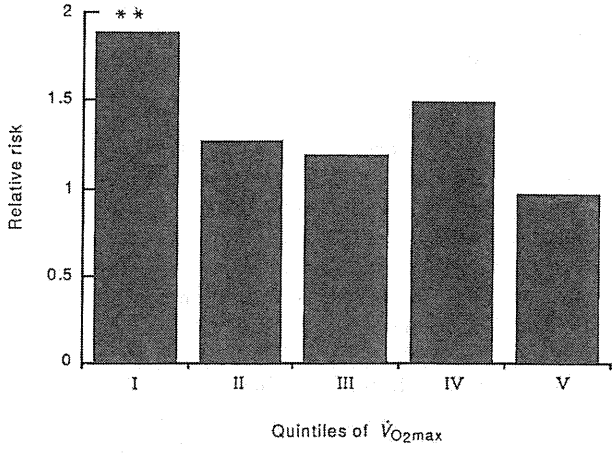

Fig. 2. Initial fitness quintiles and relative risk of hypertension incidence after adjustment for age, initial PFAT, initial blood pressure, alcohol consumption, cigarette smoking status and familial history of hypertension. $^{**}P<0.01$.

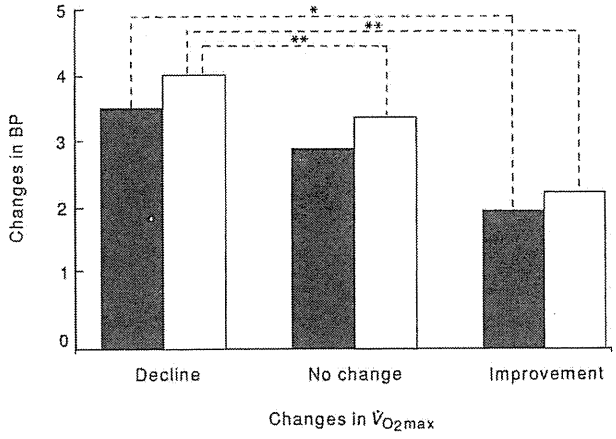

Fig. 3. Changes in maximal oxygen uptake and changes in blood pressure after adjustment for changes in PFAT, age, initial PFAT, initial blood pressure, initial fitness level, alcohol consumption, cigarette smoking status and familial history of hypertension. Decline, ≤15%; improvement, ≥15%. (■) SPB; (□) DBP. $^{*}P<0.05$, $^{**}P<0.01$.

1.9× higher in quintile I compared with quintile V (Fig. 2).

The increase of SBP and DBP in the $\dot{V}_{O_2max}$ improved group was significantly lower than in the other two groups (Fig. 3).

DISCUSSION

The major finding of this study is that blood pressure changes and incidence of hypertension for 5 years are related to physical fitness. To our knowledge, this is the first prospective report to show that the change in blood pressure with age is associated with the level of physical fitness.

In cross-sectional studies, physically active groups were found to have lower blood pressure than inactive groups (Gyntelberg & Meyer 1974; Cooper *et al.* 1976; Fraser *et al.* 1983; Gibbons *et al.* 1983; Siconolfi

et al. 1985; Tanaka *et al.* 1990). For example, Cooper *et al.* (1976) showed that subjects with very poor physical fitness levels had significantly higher SBP compared with those who had excellent physical fitness levels. However, in order to verify these findings, evidence from a prospective study was needed.

Recently, the influence of physical fitness on the incidence of hypertension was examined by prospective study. Paffenbarger *et al.* (1983, 1991) reported that a high incidence of hypertension was associated with low physical activity in a large epidemiologic study on Harvard alumni (1983) and Pennsylvania alumni (1991). In their studies, age-adjusted relative risk of hypertension was 1.35 and 1.06, respectively, when the group which did vigorous sports was compared with the inactive group. In the present study, the relative risk in quintile I was 1.9 when compared with quintile V. This value is somewhat higher than the results of Paffenbarger and co-workers. They obtained information on the physical activity of subjects from mailed questionnaires. However, in the present study, physical fitness levels were assessed from maximal oxygen uptake, which is an objective measure of physical fitness and is influenced by physical activity. It should therefore show the relative risk of hypertension more accurately.

Blair *et al.* (1984) reported that after adjustment for sex, age, follow-up interval, baseline blood pressure and baseline body-mass index, persons with low physical fitness levels measured from maximal running performance on a treadmill had a relative risk of hypertension of 1.52 compared with the high fitness group. The lowest four fitness categories (very poor to good) were compared with the top two categories (excellent and superior). On the other hand, our study showed that quintile I had a significantly higher relative risk of hypertension compared with quintiles II–V. This result suggested that the break point existed between quintile I and II (Fig. 2). This finding indicates that the least fit group (quintile I) is most susceptible to hypertension.

Recent case-control studies have provided evidence that moderate and regular aerobic training has a significant depressor effect on hypertensive patients independent of bodyweight loss (Duncan *et al.* 1985; Kiyonaga *et al.* 1985; Nelson *et al.* 1986). These studies suggested that higher physical fitness was related to a lower incidence of hypertension, and thus moderate regular exercise, which lowers blood pressure, is an important non-pharmacological treatment for hypertension. The present study provides some evidence to support these findings.

It is concluded that low maximal oxygen uptake level is related to a higher incidence of hypertension, and improved maximal oxygen uptake would help to prevent hypertension.

ACKNOWLEDGEMENTS

We thank Chiaki Nakamura for his valuable comments on the manuscript. We also express our thanks and appreciation to all those who have helped in this study.

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論文名	Five year prospective study on blood pressure and maximal oxygen uptake.
著 者	Sawada S, Tanaka H, Funakoshi M, Shindo M, Kono S, Ishiko T.
雑誌名	Clin Exp Pharmacol Physiol.
巻・号・頁	20 483-487
発行年	1993
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/8403528

対象の内訳		ヒト	動物	地 域	国内	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	20-55歳			( )		前向き研究
	対象数	1000～5000	空白		( )		( )
調査の方法	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	
図表掲載箇所	
概 要 (800字まで)	体力(最大酸素摂取量VO2max)と高血圧発症の関係を合計1万6525人年について検討した。この調査は1983年から1988年までに身体検査を受けた50歳以下の正常血圧の男性3305人を対象にした。5年間で、425人が高血圧症と診断された。体力は、VO2maxで分けた4群で、BPの変化と年齢、初期の体脂肪率、初期のBP、アルコール摂取、喫煙、家族歴と調節した高血圧発症と血圧の変化の相対危険度を比較した。最も体力の低い群での血圧の増加は、体力の最も高い群に比べて、1.9倍多かった。体力の変化により3群に分けて比較すると、VO2maxが増加した群では、体脂肪率の変化、年齢、初期の体脂肪率、初期のBP、体力、アルコール摂取、喫煙、高血圧家族歴で調節した血圧の増加は、体力が低下した群、変わらなかった群に比べて、有意に低かった。
結 論 (200字まで)	VO2maxが低いことは高血圧症の発症とかなりの関連がある。 したがって、VO2maxをあげることは高血圧症を予防できるだろう。
エキスパートによるコメント (200字まで)	日本人を対象として体力と高血圧発症を検討した研究として重要である。

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Cardiorespiratory Fitness and the Incidence of Type 2 Diabetes

Prospective study of Japanese men

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OBJECTIVE — To investigate the association between cardiorespiratory fitness and the incidence of type 2 diabetes among Japanese men.

RESEARCH DESIGN AND METHODS — This prospective cohort study was conducted in 4,747 nondiabetic Japanese men, aged 20–40 years at baseline, enrolled in 1985 with follow-up to June 1999. Cardiorespiratory fitness was measured using a cycle ergometer test, and Vo_{2max} was estimated. During a 14-year follow-up, 280 men developed type 2 diabetes.

RESULTS — The age-adjusted relative risks of developing type 2 diabetes across quartiles of cardiorespiratory fitness (lowest to highest) were 1.0 (referent), 0.56 (95% CI 0.42–0.75), 0.35 (0.25–0.50), and 0.25 (0.17–0.37) (for trend, $P < 0.001$). After further adjustment for BMI, systolic blood pressure, family history of diabetes, smoking status, and alcohol intake, the association between type 2 diabetes risk and cardiorespiratory fitness was attenuated but remained significant (1.0, 0.78, 0.63, and 0.56, respectively; for trend, $P = 0.001$).

CONCLUSIONS — These results indicate that a low cardiorespiratory fitness level is an important risk factor for incidence of type 2 diabetes among Japanese men.

Diabetes Care 26:2918–2922, 2003

A 1997 survey conducted by the Japanese government's Ministry of Health, Labor and Welfare reported the estimated number of patients with type 2 diabetes to be 6.9 million in Japan, and it is currently projected that the number of diabetic patients is dramatically increasing (1). In view of the fact that insulin secretion capacity is reported to be genetically lower among the Japanese than among Caucasians (2,3), Japanese appear to be more prone to the development of type 2 diabetes (4,5). With the overall Japanese lifestyle becoming more like the western lifestyle, a high-fat diet and low physical activity (which are known to be risk factors for the development of type 2 diabetes) are becoming more prevalent in Japan. Therefore, preventing type 2 diabetes is an important issue to be resolved. Because people who have low cardiorespiratory fitness are more likely to be insulin resistant (6), it is reasonable to surmise that a lower cardiorespiratory fitness level is a risk factor for the development of type 2 diabetes.

To our knowledge, only two prospective cohort studies have examined the association between cardiorespiratory fitness and the risk of type 2 diabetes. Both studies show an inverse relationship between cardiorespiratory fitness and the development of type 2 diabetes among the western populations (7,8). However, no such studies have been conducted in the Japanese population. Thus, this study was designed to prospectively determine whether low cardiorespiratory fitness in Japanese men is a risk factor for the development of type 2 diabetes.

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Received for publication 8 May 2003 and accepted in revised form 10 July 2003.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Subjects

The subjects for this study were 5,984 male employees between 20 and 40 years of age who had participated in an annual health examination conducted at the Tokyo Gas Company in 1985. Among these men, 335 were excluded because they were found at the health examination to have at least one of the following: diabetes ($n = 102$), cardiovascular disease including hypertension ($n = 228$), tuberculosis ($n = 3$), and gastrointestinal disease ($n = 9$). Also excluded were 904 other men who did not perform and/or complete a submaximal exercise test. These exclusions left 4,745 men who were followed until June 1999 to determine whether they subsequently developed type 2 diabetes.

Clinical examination

The Industrial Safety and Health Law in Japan requires the employer to conduct annual health examinations of all employees, and employees are required by law to participate. Height and weight were measured on a standard physician's scale and stadiometer, and BMI was calculated. Blood pressure was measured by the auscultatory method with a mercury sphygmomanometer; diastolic pressure was recorded as the disappearance of sound. Fasting blood glucose tests have been adopted since 1988 in subjects 35 years of age and those ≥40 years of age. A questionnaire was administered before the