Early retiring is a significant social problem in western countries. Methods to prevent early retiring and to maintain working ability are needed. More prospective studies are needed to investigate the effect of physical activity, cardiorespiratory fitness, and exercise intervention programmes in the prevention of early retiring. In the present study even moderate levels of physical fitness were associated with a decreased risk of disability pension, especially due to cardiovascular diseases. Consequently, more attention should be paid to improvement of cardiorespiratory fitness by physically active lifestyle in the working age population.

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REFERENCES

1 **Hytti H.** *Early retirement—the Finnish model,* Helsinki Social Insurance Institution, Finland, Studies in social security and health. 1998;**32**:164–71.
2 **Kaprio J,** Sarna S, Fogelholm M, *et al.* Total and occupationally active life expectancies in relation to social class and marital status in men classified as health at 20 in Finland. *J Epidemiol Community Health* 1996;**50**:653–60.
3 **Månsson N,** Eriksson K, Israelsson B, *et al.* Body mass index and disability pension in middle-aged men—non-linear relations. *Int J Epidemiol* 1996;**25**:80–5.
4 **Upmark M,** Lundberg I, Sadigh J, *et al.* Psychosocial characteristics in young men as predictors of early disability pension with a psychiatric diagnosis. *Soc Psychiatr Epidemiol* 1999;**34**:533–40.
5 **Yelin E,** Henke C, Epstein W. Work disability among persons with musculoskeletal conditions. *Arthritis Rheum* 1986;**29**:1322–33.
6 **Milhous R,** Haugh L, Frymoyer J, *et al.* Determinants of vocational disability in patients with low back pain. *Arch Phys Med Rehabil* 1989;**70**:589–93.
7 **Bonzani P,** Millender L, Keelan B, *et al.* Factors prolonging disability in work-related cumulative trauma disorders. *J Hand Surg* 1997;**22**:30–4.
8 **Aronoff G,** Feldman J, Campion T. Management of chronic pain and control of long-term disability. *Occup Med* 2000;**15**:755–70.
9 **Mittag O,** Kolenda K, Nordman K, *et al.* Return to work after myocardial infarction/coronary artery bypass grafting: patients' and physicians' initial viewpoints and outcome 12 months later. *Soc Sci Med* 2001;**52**:1441–50.
10 **Appelberg K,** Romanov K, Heikkila K, *et al.* Interpersonal conflict as a predictor of work disability: a follow-up study of 15,348 Finnish employees. *J Psychosom Res* 1996;**40**:157–67.
11 **Manninen P,** Riihimäki H, Heliövaara M, *et al.* Overweight, gender and knee osteoarthritis. *Int J Obes Relat Metab Disord* 1996;**20**:595–7.
12 **Månsson N,** Råstam L, Eriksson K, *et al.* Socioeconomic inequalities and disability pension in middle-aged men. *Int J Epidemiol* 1998;**27**:1019–26.
13 **Biering-Sørensen F,** Lund J, Høydalsmo O, *et al.* Risk indicators of disability pension. *Danish Medical Bulletin* 1999;**46**:258–62.
14 **Berg M,** Helakorpi S, Puska P. Finnish adults health behaviour. Spring 1993. *Publications of the Social Insurance Institution* 1993:**B10**.
15 **Lakka T,** Venäläinen J, Rauramaa R, *et al.* Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. *N Engl J Med* 1994;**330**:1549–54.
16 **Vuori I.** Exercise and physical health: musculoskeletal health and functional capabilities. *Res Q Exerc Sport* 1995;**66**:276–85.
17 **Fletcher G,** Balady G, Blair S, *et al.* Statement on exercise: benefits and recommendations for physical activity programs for all Americans. *Circulation* 1996;**94**:857–62.
18 **Laukkanen J,** Lakka T, Rauramaa R, *et al.* Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med* 2001;**161**:825–31.
19 **Linton S,** van Tulder M. Preventive interventions for back and neck pain problems: what is the evidence? *Spine* 2001;**26**:778–87.
20 **Blair S,** Kampert J, Kohl HI, *et al.* Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996;**276**:205–10.
21 **Sesso H,** Paffenbarger RJ, Lee I. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation* 2000;**102**:981–6.
22 **Lee I.** *Physical activity, fitness, and cancer,* Champaign, IL, Human Kinetics Publishers, 1994.
23 **Kujala U,** Kaprio J, Kannus P, *et al.* Physical activity and osteoporotic hip fracture risk in men. *Arch Intern Med* 2000;**160**:705–8.
24 **Vuori I.** Dose-response of physical activity and low back pain, osteoarthritis and osteoporosis. *Med Sci Sports* 2001;**33**:551–86.
25 **Hildebrandt V,** Bongers P, Dul J, *et al.* Review: The relationship between leisure time, physical activities and musculoskeletal symptoms and disability in worker populations. *Int Arch Occup Environ Health* 2000;**73**:507–18.
26 **Buckwalter J,** Lane NE. Athletics and osteoarthritis. *Am J Sports Med* 1997;**25**:873–81.
27 **Lequesne M,** Dang N, Lane N. Sport practice and osteoarthritis of the limbs. Review. *Osteoarthritis Cartil* 1997;**5**:75–86.
28 **Arokoski J,** Jurvelin J, Väätäinen U, *et al.* Normal and pathological adaptations of articular cartilage to joint loading. Review. *Scand J Med Sci Sports* 2000;**10**:186–98.
29 **Manninen P,** Riihimäki H, Heliövaara M, *et al.* Physical exercise and risk of severe knee osteoarthritis requiring arthroplasty. *Rheumatology* 2001;**40**:432–7.
30 **Dunn AL,** Trivedi MH, O'Neal H. Physical activity dose-response effects on outcomes of depression and anxiety. *Med Sci Sports Exerc* 2001;**33**:587–97.
31 **Salonen J.** Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Clin Res* 1988;**20**:46–50.
32 **Lynch J,** Kaplan G, Cohen R, *et al.* Childhood and adult socioeconomic status as predictors of mortality in Finland. *Lancet* 1994;**26**:524–7.
33 **Tiihonen J,** Pesonen U, Kauhanen J, *et al.* CYP2A6 genotype and smoking. *Mol Psychiatry* 2000;**5**:347–48.
34 **Lakka H,** Lakka T, Tuomilehto J, *et al.* Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men. *Arch Intern Med* 2000;**160**:1160–8.
35 **Kauhanen J,** Julkunen J, Salonen J. Coping with inner feelings and stress: heavy alcohol use in the context of alexithymia. *Behav Med* 1992;**18**:121–6.
36 **Rothman K,** Greenland S. *Modern epidemiology,* 2nd ed. USA: Lippincott-Raven, 1998.
37 **Pate R,** Heath G, Dowda M, *et al.* Associations between physical activity and other health behaviors in a representative sample of US adolescents. *Am J Public Health* 1996;**86**:1577–81.
38 **Morris C,** Froelicher V. Cardiovascular benefits of physical activity. *Herz* 1991;**16**:222–36.
39 **Smith SJ,** Blair S, Criqui M, *et al.* Preventing heart attack and death in patients with coronary disease. *Circulation* 1995;**92**:2–4.
40 **Lakka T,** Laukkanen J, Rauramaa R, *et al.* Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann Intern Med* 2001;**134**:12–20.
41 **van Tulder M,** Malmivaara A, Esmail RBK. Exercise therapy for low back pain: a systematic review within the framework of the Cochrane collaboration back review group. *Spine* 2000;**25**:2784–96.
42 **Puntila E,** Kröger H, Lakka T, *et al.* Physical activity in adolescence and bone density in peri- and postmenopausal women: a population-based study. *Bone* 1997;**21**:363–7.
43 **Lobstein D,** Mosbacher B, Ismail A. Depression as a powerful discriminator between physically active and sedentary middle-aged men. *J Psychosom Res* 1983;**27**:69–76.
44 **Tuomi K,** Eskelinen L, Toikkanen J, *et al.* Work load and individual factors affecting work ability among aging municipal employees. *Scand J Work Environ Health* 1991;**17**(suppl 1):128–34.
45 **Nygård C,** Eskelinen L, Suvanto S, *et al.* Associations between functional capacity and work ability among elderly municipal employees. *Scand J Work Environ Health* 1991;**17**(suppl 1):122–7.
46 **Kriska A,** Bayles C, Cauley J, *et al.* A randomized exercise trial in older women: increased activity over two years and the factors associated with compliance. *Med Sci Sports Exerc* 1986;**18**:557–62.
47 **King A,** Haskell W, Youg D, *et al.* Long-term effects of varying intensities and formats of physical activity on participation rates, fitness, and lipoproteins in men and women aged 50 to 65 years. *Circulation* 1995;**91**:2596–604.
48 **Donchin M,** Woolf O, Kaplan L, *et al.* Secondary prevention of low-back pain. A clinical trial. *Spine* 1990;**15**:1317–20.
49 **Gundewall B,** Liljeqvist M, Hansson T. Primary prevention of back symptoms and absence from work. *Spine* 1993;**18**:587–94.
50 **Ostwald S.** Changing employees' dietary and exercise practices: an experimental study in a small company. *J Occup Med* 1989;**31**:90–6.
51 **Cardinal B,** Sachs M. Prospective analysis of stage-of-exercise movement following mail-delivered, self-instructional exercise packets. *Am J Health Promotion* 1995;**9**:430–2.
52 **Salomaa V,** Arstila M, Kaarsalo E, *et al.* Trends in the incidence of and mortality from coronary heart disease in Finland, 1983–1988. *Am J Epidemiol* 1992;**136**:303–15.
53 **Uemura K,** Pisa Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. *World Health Stat Q* 1988;**41**:155–78.
54 **Månsson N,** Merlo J. The relation between self-rated health, socioeconomic status, body mass index and disability pension among middle-aged men. *Eur J Epidemiol* 2001;**17**:65–9.

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対象の内訳							
	ヒト	動物		欧米		縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男性	( )	地 域	( )	研究の種類	( )
年齢	42-60(51.3)			( )		前向き研究
対象数	1000～5000			( )		( )

調査の方法	実測	( )				
アウトカム	予 防	な し	な し	な し	介護予防	( ) ( )
	維持・改善	な し	な し	な し	な し	( ) ( )

図 表

Table 3 Adjusted relative risk (OR) of disability pension by disease category in fifths of maximal oxygen uptake and the duration of exercise test

	Any reason (n=790) OR (95% CI)	Cardiovascular diseases* (n=219) OR (95% CI)	Musculoskeletal disorders† (n=312) OR (95% CI)	Mental disorders‡ (n=108) OR (95% CI)	Other reasons§ (n=151) OR (95% CI)
Maximal oxygen uptake (ml/kg/min)					
7.38–25.67	2.08 (1.36–3.19)	3.58 (1.91–6.70)	2.20 (1.26–3.83)	1.44 (0.73–2.83)	2.04 (0.96–4.34)
25.68–29.47	1.72 (1.15–2.56)	2.10 (1.11–3.93)	2.03 (1.20–3.44)	1.10 (0.57–2.13)	2.23 (1.11–4.47)
29.48–33.10	1.73 (1.18–2.54)	1.93 (1.03–3.60)	2.18 (1.31–3.64)	1.41 (0.77–2.59)	1.58 (0.78–3.21)
33.11–37.61	1.54 (1.05–2.25)	1.85 (1.00–4.57)	1.71 (1.02–2.89)	0.96 (0.51–1.81)	1.89 (0.95–3.74)
37.62–65.40 (reference)	1.0	1.0	1.0	1.0	1.0
Duration of exercise test (min)					
1.50–9.54	2.33 (1.50–3.61)	4.56 (2.40–8.65)	1.98 (1.12–3.48)	2.29 (1.12–4.70)	2.07 (1.01–4.24)
9.55–10.82	1.54 (1.04–2.30)	2.14 (1.13–4.06)	1.71 (1.01–2.89)	1.29 (0.65–2.58)	1.40 (0.71–2.75)
10.83–12.06	1.73 (1.18–2.51)	2.43 (1.31–4.48)	1.96 (1.19–3.24)	1.93 (1.05–3.56)	0.95 (0.47–1.93)
12.07–13.49	1.46 (1.01–2.11)	2.00 (1.07–3.74)	1.44 (0.86–2.41)	1.33 (0.71–2.51)	1.38 (0.73–2.61)
13.50–21.85 (reference)	1.0	1.0	1.0	1.0	1.0

Adjusted for age, education, occupation, body mass index, alcohol consumption, smoking, and respective reason for retirement (cardiovascular diseases, musculoskeletal disorders, mental disorders, or other chronic diseases).
*Cardiovascular diseases include coronary heart disease, cardiac insufficiency, hypertension, claudication, and stroke.
†Musculoskeletal disorders include back problems and osteoarthritis.
‡Mental disorders include those diagnosed by doctor or severe psychic illnesses that required hospitalisation.
§Other reasons include respiratory, metabolic, dermatological, digestive tract, eye and ear diseases, injuries, cancers, malformations, and non-classifiable diseases.

図表掲載箇所	P768, Table3
概 要 (800字まで)	42－60歳の男性1307名を対象に、体力が、その後の障害年金受給に及ぼす影響を検討した論文である。本研究が行われた国はフィンランドであり、疾患や疾患がもたらす身体障害がある場合、障害年金が受給できることから、障害年金受給をそれらの指標としている。また、自転車エルゴメーターを用いて症候限界による最大下の運動負荷試験を実施し、最大酸素摂取量を求めた。最大酸素摂取量を5分位に分割し(37.62－65.40、33.11－37.61、29.48-33.10、25.68-29.47、7.38-25.67ml/min/kg)、障害年金受給のリスク(RR)を検討した。最も高い群と比較して、それよりも低い群は、筋骨格系の障害による年金受給のリスクが、それぞれ、1.71(1.02-2.89)、2.18(1.31-3.64)、2.03(1.20-3.44)、2.20(1.26-3.83)と増加していった。また、心血管疾患による年金受給のリスクとも強く関連していた。
結 論 (200字まで)	体力は、将来、筋骨格系の障害や心血管疾患による年金受給のリスクを下げることが示された。
エキスパートによるコメント (200字まで)	疾患の発症は、個人のQOLに大きくかかわるとともに、国における医療費にも大きな影響を及ぼす。本研究では、障害年金受給といった医療費の観点から、体力を高めることがそれらの抑制に有効であることも示している。日本においても、このような観点からの研究は非常に重要であり、今後、多くの研究者により遂行されることが望まれる。

担当者　村上晴香

ORIGINAL INVESTIGATION

Cardiorespiratory Fitness Attenuates the Effects of the Metabolic Syndrome on All-Cause and Cardiovascular Disease Mortality in Men

Peter T. Katzmarzyk, PhD; Timothy S. Church, MD, PhD; Steven N. Blair, PED

Background: The metabolic syndrome is a prevalent condition that carries with it an increased risk of type 2 diabetes mellitus, cardiovascular disease (CVD), and mortality.

Objective: To determine the relationship between cardiorespiratory fitness (CRF) and mortality in healthy men and in those with the metabolic syndrome.

Methods: The sample included 19 223 men, aged 20 to 83 years, who received a clinical evaluation between 1979 and 1995 with mortality follow-up through December 31, 1996. There were 15 466 healthy men (80.5%) and 3757 men with the metabolic syndrome (19.5%).

Results: A total of 480 deaths (161 due to CVD) occurred during 196 298 man-years of follow-up. After adjustment for age, year of examination, smoking status, alcohol consumption, and parental CVD, the relative risks (RRs) (95% confidence interval) of all-cause and CVD mortality were 1.29 (1.05-1.57) and 1.89 (1.36-2.60), respectively, for men with the metabolic syndrome compared with healthy men. After the inclusion of CRF, the associations were not significant. The RRs comparing unfit with fit men for all-cause mortality were 2.18 (1.66-2.87) in healthy men and 2.01 (1.38-2.93) in men with the metabolic syndrome, whereas the RRs for CVD mortality for unfit vs fit men were 3.21 (2.03-5.07) in healthy men and 2.25 (1.27-3.97) in men with the metabolic syndrome. A significant dose-response relationship between CRF and mortality was also observed in men with the metabolic syndrome.

Conclusion: In this sample, CRF provided a strong protective effect against all-cause and CVD mortality in healthy men and men with the metabolic syndrome.

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RISK FACTORS FOR CHRONIC diseases tend to cluster within individuals,[1,2] and the metabolic syndrome is such a constellation of risk factors that predispose toward the development of type 2 diabetes mellitus and cardiovascular disease (CVD). Ford et al[3] estimate that the prevalence of the metabolic syndrome is approximately 22% among adults in the United States, which translates into 47 million people having the condition in 2000. The metabolic syndrome is hypothesized to result from insulin resistance in several organ systems and pathways, and abdominal obesity is a central feature.[4] Given that the prevalence of obesity among adults in the United States has increased from 15% in the 1976-1980 period to 30.5% in 1999-2000,[5] studies of the medical sequelae of obesity such as the metabolic syndrome are important and timely.

An operational definition of the metabolic syndrome was proposed by the National Cholesterol Education Program Adult Treatment Panel III (ATP III)[6] and recently validated.[7] A 2002 study[8] has reported that middle-aged Finnish men diagnosed with the metabolic syndrome under the ATP III criteria have a significantly elevated risk of all-cause and CVD mortality. There is a need to replicate these results in other populations. A major new feature in the updated ATP III guidelines is the focus on the primary prevention of coronary heart disease in people with multiple risk factors. The guidelines highlight the importance of therapeutic lifestyle changes, including increased physical activity and reduction of body weight, in the treatment and prevention of metabolic disorders and coronary heart disease. However, little is known about the effects of cardiorespiratory fitness (CRF) on attenuating the mortality risk associated with the metabolic syndrome.

METHODS

PARTICIPANTS

The sample included 19 223 men, aged 20 to 83 years (mean [SD] age, 43.1 [9.7] years), from the Aerobics Center Longitudinal Study (ACLS)[9] who had complete data for CRF and the metabolic syndrome. The sample was restricted to men with no personal history of coronary heart disease, stroke, or cancer at the time of the baseline examination. The participants were well educated (approximately 75% were college graduates) and were predominantly non-Hispanic whites. All participants attended the Cooper Clinic in Dallas, Tex, for clinical evaluations between 1979 and 1995. Although baseline data collection for the ACLS began in 1970, the required clinical measurements for diagnosing the metabolic syndrome were only available for participants beginning in 1979. All men gave their informed consent to participate in the clinical examination and subsequent follow-up study. All study protocols were approved annually by The Cooper Institute institutional review board.

CLINICAL EXAMINATION

Metabolic Syndrome

All clinical measurements were made in the morning following at least a 12-hour fast. Waist circumference (WC) was measured at the level of the umbilicus with a plastic anthropometric tape, and blood pressure measurements were obtained with a mercury sphygmomanometer using auscultory methods. A fasting blood sample was obtained by venipuncture, and serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and plasma glucose levels were assayed with automated techniques at the Cooper Clinic Laboratory, which participates in and meets the quality control standards of the US Centers for Disease Control and Prevention Lipid Standardization Program. Metabolic syndrome was defined according to the criteria established by ATP III.[6]

Participants were diagnosed as having the metabolic syndrome if they had 3 or more of the following 5 risk factors: (1) high blood pressure (≥130 mm Hg systolic or ≥85 mm Hg diastolic); (2) central obesity (WC >102 cm [>40 in]); high TG level (≥1.69 mmol/L [≥150 mg/dL]); low HDL-C level (<1.04 mmol/L [<40 mg/dL]); and high fasting plasma glucose level (≥6.1 mmol/L [≥110 mg/dL]). Men with normal blood pressure or fasting plasma glucose who indicated a history of physician-diagnosed hypertension (n=861) or type 2 diabetes mellitus (n=32), respectively, were also coded as positive for high blood pressure or high fasting plasma glucose, which added an additional 208 men to the metabolic syndrome category. It should be noted that the results obtained were virtually identical to those reported in this study when these men were excluded.

Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed by a maximal treadmill exercise test using a modified Balke protocol.[10] Time until exhaustion on the treadmill was used to estimate the maximum oxygen uptake ($\dot{V}O_{2max}$) in metabolic equivalents (MET=3.5 mL of oxygen/kg per minute) from the Balke protocol using the following formula: $\dot{V}O_{2max}=(1.44\times[\text{No. of minutes on treadmill}]+14.99)/3.5$.[11] Participants were assigned to either unfit or fit categories using age-adjusted maximum METs. Men in the lower quintile (20%) were classified as unfit, whereas men in the upper 4 quintiles (80%) were classified as fit. These fitness criteria are from previous reports on the cohort.[12]

Covariates

Information on cigarette smoking, alcohol consumption, and parental history of CVD were collected using a medical history questionnaire. Parental history of CVD was coded as a dichotomous variable (0, no history; 1, either parent had a stroke or coronary event before age 50 years). Cigarette smoking status was coded as never smoked, former smoker, or current smoker. Alcohol consumption was coded as none, light (<15 units/wk), moderate (15-30 units/wk), and heavy (>30 units/wk). One unit of alcohol was defined as one bottle or can of beer (355 mL [12 oz]), a glass of wine (148 mL [5 oz]), or one shot of hard liquor (44 mL [1.5 oz]).

MORTALITY SURVEILLANCE

Follow-up continued until participants died or until December 31, 1996, for survivors. Deaths were identified from the National Center for Health Statistics National Death Index, and the cause of death was determined from official death certificates obtained from departments of vital records in the states of deceased participants. The National Death Index has established validity for use in cohort studies, with a sensitivity of 96% and specificity of 100%.[13] A nosologist coded the death certificates for the underlying and up to 4 contributing causes of death, and CVD mortality was defined as codes 390 to 449.9 of the *International Classification of Diseases, Ninth Revision*.

STATISTICAL ANALYSES

Cox proportional hazards regression was used to estimate the adjusted relative risk (RR) of mortality associated with the metabolic syndrome, including age, year of examination, smoking status, alcohol consumption, and parental history of CVD as covariates. Cardiorespiratory fitness (in METs) was then added to the model as a continuous variable to examine its effect on the relation between the metabolic syndrome and mortality. Given that abdominal obesity is a key component of the metabolic syndrome, the body mass index (BMI) was not included as a covariate in these models owing to the high degree of covariation between BMI and WC.

Mortality rates (per 10 000 man-years of follow-up), adjusted for age and year of examination, were calculated for unfit and fit healthy men and men with the metabolic syndrome. Cox proportional hazards regression was also used to evaluate the relationship between fitness category (unfit vs fit) and mortality after stratifying the sample into healthy men and men with the metabolic syndrome. The BMI was included as a covariate in these models to examine the influence of body weight status on the observed relationships. The dose-response relationship between CRF and mortality was examined in men with the metabolic syndrome by dividing this group into lower, middle, and upper tertiles of age-adjusted CRF (METs). For this analysis, the residuals from a regression of CRF on age were used as age-adjusted values. All analyses were conducted using SAS statistical software and procedures (SAS Institute, Cary, NC), and mortality data were restricted to those dying at least 1 year after their clinical evaluation.

RESULTS

The characteristics of the participants at baseline are summarized in **Table 1**. The prevalence of the metabolic syndrome in the sample was 19.5%. Fit men within each

Table 1. Baseline Characteristics in 19 223 Men Across Cardiorespiratory Fitness Categories in Healthy Men and Men With the Metabolic Syndrome*

Characteristic	Healthy Men		Men With Metabolic Syndrome	
	Fit (n = 14 028)	Unfit (n = 1438)	Fit (n = 2494)	Unfit (n = 1263)
Age, y	42.4 ± 9.7	42.3 ± 9.5	46.8 ± 9.5	44.4 ± 9.1†
Height, cm	178.8 ± 6.5	177.1 ± 6.6†	179.6 ± 6.7	179.0 ± 6.8†
Weight, kg	81.0 ± 10.3	86.9 ± 14.4†	92.7 ± 12.6	102.2 ± 16.3
Body mass index‡	25.3 ± 2.7	27.6 ± 4.1†	28.7 ± 3.2	31.8 ± 4.5†
Waist circumference, cm	90.5 ± 8.2	97.5 ± 10.9†	101.3 ± 9.2	109.5 ± 11.8†
Triglycerides, mmol/L	1.2 ± 0.7	1.6 ± 0.8†	2.5 ± 1.1	2.6 ± 1.1†
HDL cholesterol, mmol/L	1.2 ± 0.3	1.1 ± 0.3†	0.9 ± 0.2	0.9 ± 0.2†
Fasting glucose, mmol/L	5.4 ± 0.6	5.5 ± 0.9†	6.0 ± 1.3	6.2 ± 1.7†
Diastolic blood pressure, mm Hg	78.9 ± 8.8	80.2 ± 8.7†	86.5 ± 8.8	86.7 ± 9.2
Systolic blood pressure, mm Hg	118.4 ± 12.1	118.4 ± 11.9	127.7 ± 12.9	126.9 ± 12.7
Maximal METs	12.6 ± 1.8	9.1 ± 1.1†	11.1 ± 1.4	8.7 ± 1.1†
Alcohol consumption, %§				
None	24.3	29.8	27.9	34.2
Light	31.3	26.3	27.2	26.4
Moderate	22.1	18.2	19.5	15.1
Heavy	22.3	25.8	25.3	24.2
Smoking, %§				
Never	48.6	34.8	42.9	33.5
Former	36.5	30.4	40.7	36.7
Current	14.9	34.8	16.4	29.8

Abbreviations: HDL, high-density lipoprotein; MET, metabolic equivalent (3.5 mL of oxygen/kg per minute).
SI conversion factors: To convert reported triglyceride levels to conventional units (mg/dL), divide by 0.0113; HDL cholesterol (mg/dL), divide by 0.0259; and fasting glucose (mg/dL), divide by 0.0555.
*Unless otherwise indicated, data are mean ± SD.
†$P<.05$, t test between fit and unfit men, within metabolic syndrome categories.
‡Calculated as the weight in kilograms divided by the square of height in meters.
§$P<.05$, χ^2 test between fit and unfit men, within metabolic syndrome categories.

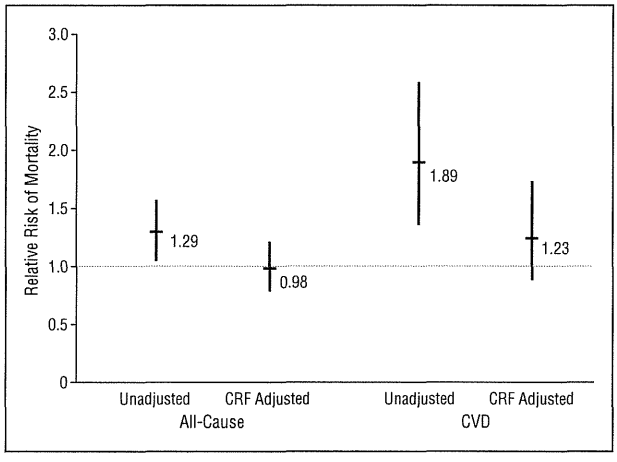

Figure 1. Relative risks of all-cause and cardiovascular disease (CVD) mortality associated with the metabolic syndrome before and after the inclusion of cardiorespiratory fitness (CRF) as a covariate in 19 223 men aged 20 to 83 years from the Aerobics Center Longitudinal Study. All models include age, year of examination, smoking status, alcohol consumption, and family history of CVD as covariates. Error bars represent 95% confidence intervals.

metabolic syndrome category had a better metabolic fitness profile than unfit men (ie, significantly smaller WCs, lower TG and plasma glucose levels, and higher HDL-C levels). During 196 298 person-years of follow-up, there were 480 deaths (161 due to CVD). After adjustment for age, smoking status, alcohol consumption, and parental history of CVD, the RRs (95% confidence interval [CI]) of all-cause and CVD mortality were 1.29 (1.05-1.57) and 1.89 (1.36-2.60), respectively, in men with the metabolic syndrome compared with healthy men. After the further inclusion of CRF (METs) as a covariate, the RRs (95% CI) of all-cause and CVD mortality were reduced to 0.98 (0.79-1.21) and 1.23 (0.88-1.73), respectively, and were no longer statistically significant (**Figure 1**).

The all-cause and CVD death rates (per 10 000 man-years of follow-up), adjusted for age and year of examination, for unfit and fit healthy men and men with the metabolic syndrome are presented in **Figure 2**. The overall death rates were higher in men with the metabolic syndrome, but they were greatly attenuated by CRF.

The adjusted RRs (95% CI) comparing unfit with fit men for all-cause mortality were 2.18 (1.66-2.87) in healthy men and 2.01 (1.38-2.93) in men with the metabolic syndrome, after including age, smoking status, alcohol consumption, parental history of CVD, and BMI as covariates. The corresponding RRs (95% CI) for CVD mortality were 3.21 (2.03-5.07) in healthy men and 2.25 (1.27-3.97) in men with the metabolic syndrome (**Table 2**). A dose-response relationship between CRF and mortality is clearly evident in men with the metabolic syndrome (**Figure 3**). Men in the middle and lower tertiles of CRF had 1.42 (95% CI, 0.84-2.39) and 2.70 (95% CI, 1.63-4.47) times the risk of all-cause mortality, respectively, of men in the upper tertile. Similarly, men in the middle and lower tertiles of CRF had 2.08 (95% CI, 0.90-4.80) and 3.48 (95% CI, 1.52-8.01) times the risk of CVD mortality of men in the upper tertile, re-

spectively. It should be noted that the analyses were rerun after taking BMI out of the adjusted models, and the results were unchanged.

COMMENT

As the prevalence of obesity increases in this and other countries, the ability to identify high-risk individuals for obesity-related disorders becomes increasingly important. The present study provides further evidence of the validity of the ATP III[6] definition of the metabolic syndrome; men diagnosed with the metabolic syndrome were 1.29 times more likely to die of any cause and 1.89 times more likely to die of CVD than healthy men (Figure 1). These results support those of Lakka and colleagues,[8] who recently reported that middle-aged Finnish men diagnosed as having the metabolic syndrome under the ATP III criteria were 4.26 (95% CI, 1.62-11.2) times more likely to die over 11 years of follow-up than healthy men. Our results also are consistent with those of 2 studies that examined the association between the metabolic syndrome (using different diagnostic criteria) and mortality rates.[14,15] The metabolic syndrome, defined under the criteria of the World Health Organization,[16] was associated with 2.96 times the risk of CVD mortality over 6.9 years of follow-up in a sample from Finland and Sweden.[14] Additionally, a cluster of low HDL-C level and high blood pressure, blood glucose level, and TG level was associated with 2.49 times the risk of CVD death over an average of 7 years of follow-up in an Italian study.[15] The somewhat lower relative risk of mortality observed in the present sample of well-educated, middle- to upper-class business executives and professionals might be owing to better medical care than that received by the participants in the 3 earlier studies. For example, the baseline data for the present study were collected during a preventive medicine examination. Nevertheless, our results show that even in this sample of men, most of whom had access to excellent medical care, the metabolic syndrome was still associated with mortality.

To our knowledge, the present study is the first to explicitly test the hypothesis that CRF attenuates the mortality risk associated with the metabolic syndrome. In healthy men and those with the metabolic syndrome, there was a substantially lower risk in fit men than in unfit men. The finding of a dose-response relationship between CRF and mortality in men with the metabolic syndrome, similar to what has been observed in the entire ACLS cohort,[9] indicates that physical activity may be a valuable tool in the treatment of the metabolic syndrome and the prevention of further health problems.

Although central obesity (large WC) is a component of the metabolic syndrome, the finding in the present study that CRF remained a significant predictor of mortality in men with the metabolic syndrome after the inclusion of BMI as a covariate suggests that CRF was associated with mortality risk independent of body weight status. The fact that the results were virtually identical when BMI was not included as a covariate indicates that body weight status was not an important modifier of mortality risk in this sample of men who were already diagnosed as having the metabolic syndrome once the effects of CRF were accounted for. This finding further supports the notion that CRF is an independent determinant of health status, regardless of body weight. The mechanisms by which CRF provides a protective effect against the mortality risk associated with the metabolic syndrome still need to be determined.

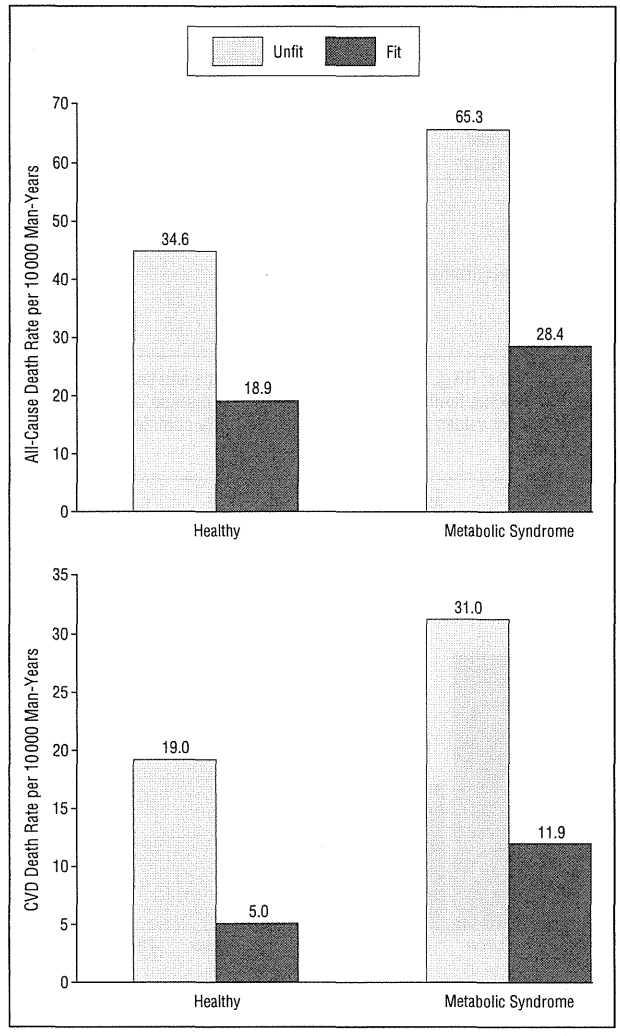

Figure 2. All-cause and cardiovascular disease (CVD) death rates per 10000 man-years of follow-up in fit and unfit healthy men and men diagnosed as having the metabolic syndrome, adjusted for age and year of examination. Results are from 19223 men aged 20 to 83 years from the Aerobics Center Longitudinal Study.

The prevalence of the metabolic syndrome in this sample of predominantly well-educated professional men was 19.5%. This is slightly lower than the prevalence of the metabolic syndrome in the United States, which has been recently estimated at 24.0% in men, based on data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994).[3] The lower prevalence of the metabolic syndrome in the present sample is mainly owing to a lower prevalence of abdominal obesity (large WC) (19.5% vs 30.5%) and high TG level (20.5% vs 35.1%) rather than differences in low HDL-C level (35.2% vs 36.8%), high blood pressure (41.7% vs 37.2%), or high blood glucose level (13.5% vs 15.6%). Given that the ACLS sample consists of men measured at baseline between 1979 and 1995 and the NHANES III

Table 2. Adjusted Relative Risks for All-Cause and Cardiovascular Disease Mortality by Fitness Group in Healthy Men and Men With the Metabolic Syndrome

Health and Fitness Group	Man-Years	No. of Deaths	All-Cause Mortality*		Cardiovascular Disease Mortality*	
			RR_{age}	RR_{all}	RR_{age}	RR_{all}
Healthy						
Fit	144 688	274	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Unfit	15 774	74	2.36 (1.82-3.05)	2.18 (1.66-2.87)	3.81 (2.48-5.86)	3.21 (2.03-5.07)
Metabolic syndrome						
Fit	23 556	67	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Unfit	12 280	65	2.30 (1.63-3.26)	2.01 (1.38-2.93)	2.61 (1.55-4.40)	2.25 (1.27-3.97)

Abbreviations: RR_{age}, relative risks adjusted for age and year of examination; RR_{all}, relative risks adjusted for age, year of examination, alcohol consumption, cigarette smoking, family history of cardiovascular disease, and body mass index.
*Nonreferent values reported as relative risk (95% confidence interval).

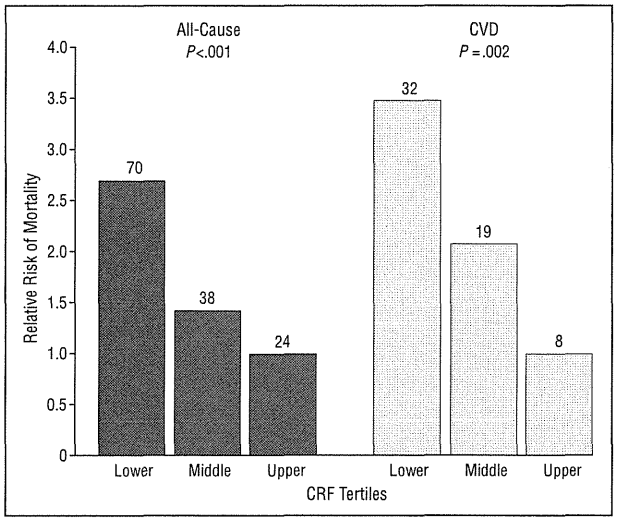

Figure 3. Relative risks of all-cause and cardiovascular disease (CVD) mortality in men diagnosed as having the metabolic syndrome across baseline tertiles (lower, middle, and upper) of cardiorespiratory fitness (CRF) in 3757 men aged 20 to 83 years from the Aerobics Center Longitudinal Study. Relative risks are adjusted for age, year of examination, smoking status, alcohol consumption, family history of CVD, and body mass index. Numbers atop bars indicate the number of deaths; *P* values are for tests of linear trend across the cardiorespiratory fitness categories.

occurred between 1988 and 1994, the recent increases in the prevalence of obesity in the United States are likely more represented in the NHANES III sample than in the ACLS cohort; 62% of the men in the present study (n=11 846) were evaluated for baseline measures between 1979 and 1987. Nevertheless, men diagnosed as having the metabolic syndrome were 1.29 times more likely to die from any cause and 1.89 times more likely to die from CVD than healthy men.

Based on the results of this study, the estimated population attributable risk (P[(RR−1)/RR], where P indicates population prevalence)[17] of the metabolic syndrome in male residents of the United States is 5.4% for all-cause mortality and 11.3% for CVD mortality, assuming that 24% of men in the United States currently have the metabolic syndrome.[3] This suggests that approximately 1 in 20 deaths and 1 in 10 CVD deaths in men are directly attributable to the metabolic syndrome. Thus, the results reinforce the stance of the ATP III guidelines[6] that emphasize the treatment of patients with multiple risk factors, including those with the metabolic syndrome. Furthermore, the public health burden associated with the metabolic syndrome is substantial, and the finding that physical fitness may greatly attenuate the relative risk of both all-cause and CVD mortality strengthens the argument for aggressive public health campaigns aimed at increasing physical activity levels in the population.

The present study has several strengths. First, the large sample size allowed for the examination of interactions between the metabolic syndrome and CRF through the cross-tabulation of these indices, which enhances the clinical utility of the findings. Second, the CRF data were obtained using a maximal treadmill test to exhaustion, and maximum treadmill time is highly correlated with directly measured maximum oxygen uptake (r=0.92).[11] This allowed for the objective quantification of mortality risk associated with CRF level while minimizing the introduction of technical errors and errors of measurement that can occur with fitness measurements obtained from submaximal exercise data or self-reported physical activity data from a questionnaire. Third, the use of measured clinical data on CVD risk factors allowed for the diagnosis of the metabolic syndrome using the recent ATP III guidelines, which also increases the clinical utility of the findings.

The main weakness of this study is that the sample was predominantly white, middle to upper class, and all male, which limits the generalizability of the results. Further, the lack of dietary information for the participants is a limitation in that dietary factors are known to influence the component risk factors in the metabolic syndrome.

In conclusion, the metabolic syndrome was significantly associated with mortality in this sample. Low CRF was an important risk factor for premature mortality in healthy men and men with the metabolic syndrome. In fact, CRF attenuated much of the risk associated with the metabolic syndrome, which indicates that the promotion of the measurement of CRF in clinical medicine may aid in risk stratification and that the promotion of physically active lifestyles should be a public health priority.

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REFERENCES

1. Criqui MH, Barrett-Connor E, Holdbrook MJ, Austin M, Turner JD. Clustering of cardiovascular disease risk factors. *Prev Med.* 1980;9:525-533.
2. Genest J, Cohn JS. Clustering of cardiovascular risk factors: targeting high-risk individuals. *Am J Cardiol.* 1995;76:8a-20a.
3. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA.* 2002;287:356-359.
4. Bjorntorp P. Etiology of the metabolic syndrome. In: Bray GA, Bouchard C, James WPT, eds. *Handbook of Obesity.* New York, NY: Marcel Dekker; 1998:573-600.
5. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA.* 2002;288:1723-1727.
6. The EP. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
7. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol.* 2002;156:1070-1077.
8. Lakka H-M, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA.* 2002;288:2709-2716.
9. Blair SN, Kohl HW, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA.* 1989;262:2395-2401.
10. Balke B, Ware RW. An experimental study of physical fitness in Air Force personnel. *U S Armed Forces Med J.* 1959;10:675-688.
11. Pollock ML, Bohannon RL, Cooper KH, et al. A comparative analysis of four protocols for maximal treadmill stress testing. *Am Heart J.* 1976;92:39-46.
12. Blair SN, Kampert JB, Kohl HW, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA.* 1996;276:205-210.
13. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol.* 1984;119:837-839.
14. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24:683-689.
15. Trevisan M, Liu J, Bahsas FB, Menotti A. Syndrome X and mortality: a population-based study. *Am J Epidemiol.* 1998;148:958-966.
16. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, I: diagnosis and classification of diabetes mellitus. *Diabet Med.* 1998;15:539-553.
17. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health.* 1998;88:15-19.

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PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/15159266

対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	空白	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	20-83(43.1±9.7)歳			( )		前向き研究
	対象数	10000以上	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予 防	な し	肥満予防	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:メタボリックシンドロームは、II型糖尿病、心血管疾患(CVD)、および死亡の強力なリスクファクターである。目的:メタボリックシンドロームを保有する者および健常者における全身持久性体力(CRF)と死亡率との関係を決定すること。方法:サンプルは、1979-1995年の間に臨床評価を受け、1996年12月31日まで追跡調査をおこなった20-83歳の19223名の男性が含まれた。彼らは、15466 の健常者(80.5%)とメタボリックシンドロームを保有する3757名の男性(19.5%)である。結果:196298(人/年)の追跡調査により、合計480名の死亡(CVDで161名)が確認された。年齢、調査年、喫煙状態、アルコール消費、および親のCVD補正後において、全死亡原因およびCVD死亡率の相対リスク(RRs)(95%信頼区間)は、メタボリックシンドロームと健常者を比べると、それぞれ1.29(1.05-1.57)と1.89(1.36-2.60)であった。CRFを包含すると、その関係は有意ではなかった。全死亡原因における低体力者と高体力者の比較によるRRsは、健常者で2.18(1.66-2.87)、メタボリックシンドローム保有者で2.01(1.38-2.93)であったが、CVD死亡率におけるRRsは、健常者で3.21(2.03-5.07)、メタボリックシンドローム保有者で2.25(1.27-3.97)であった。また、CRFと死亡率との有意な容量依存関係もメタボリックシンドローム保有者において観測された。結論:この標本では、CRFはメタボリックシンドロームと共に健常者における全死亡原因とCVD死亡率に対しても強い防護効果を提供したといえる。
結 論 (200字まで)	メタボリックシンドロームがあってもなくても、低心肺体力は総死亡、循環器病死亡の死亡率を2倍程度に引き上げる。
エキスパートによるコメント (200字まで)	体力の効果に目を奪われがちであるが、メタボ者は循環器病死亡のリスクが健常者より1. 8倍も高いことを忘れてはならない。

担当者　宮地 劉

Cardiorespiratory Fitness, Glycemic Status, and Mortality Risk in Men

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JESÚS A. VILLEGAS, MD
STEVEN N. BLAIR, PED

OBJECTIVE— To determine the association of baseline cardiorespiratory fitness to all-cause mortality across the range of blood glucose levels.

RESEARCH DESIGN AND METHODS— Data from a prospective study of 8715 men (average age 42 yr), followed for an average of 8.2 yr (range 1–15 yr), were analyzed. Cardiorespiratory fitness was assessed by maximal-exercise treadmill testing. Men with evidence of clinical vascular disease or who did not achieve 85% of their age-predicted maximum heart rate during exercise testing were excluded from analyses.

RESULTS— Age-adjusted death rates increased with higher levels of fasting blood glucose. Regardless of glycemic status, fit men had lower age-adjusted all-cause death rates than their less fit counterparts. For men with fasting blood glucose ≥7.8 mM or physician-diagnosed non-insulin-dependent diabetes mellitus (NIDDM), the age-adjusted death rates per 10,000 person-yr of follow-up in unfit and fit subjects were 82.5 and 45.9, respectively. The age-adjusted relative risk of death due to all causes was significantly elevated in the lower-fitness group within each of three glycemic status levels: fasting blood glucose <6.4 mM; relative risk (RR) = 1.93 (95% confidence interval [95% CI] 1.15–3.26); fasting blood glucose 6.4–7.8 mM; RR = 3.42 (95% CI 2.27–5.15); and fasting blood glucose ≥7.8 mM or with NIDDM, RR = 1.80 (95% CI 1.25–2.58). Multivariate analyses, controlling for risk factors of mortality (age, resting systolic blood pressure, serum cholesterol, body mass index, family history of heart disease, follow-up interval, and smoking habit) showed a higher risk of death due to all causes for unfit compared with fit men. Multivariate risks of death associated with low fitness, compared with higher fitness (RR), in the three glycemic status groups were: fasting blood glucose <6.4 mM, RR = 1.38 (95% CI 1.09–1.74); fasting blood glucose 6.4–7.8 mM, RR = 1.61 (95% CI 0.91–2.86); and fasting blood glucose ≥7.8 mM or with NIDDM, RR = 1.92 (95% CI 0.75–4.90).

CONCLUSIONS— These data suggest that risk of death increases with less-favorable glycemic status, and that cardiorespiratory fitness may attenuate the forces of impaired carbohydrate metabolism on mortality from any cause.

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Diabetes mellitus is a disease that increases the risk of human mortality, particularly that due to coronary heart disease (1). Less-severe forms of impaired carbohydrate metabolism (ICM) are not only the best predictors of future incidence of diabetes (2–5) but also have been postulated as conditions that may increase the risk for death due to all causes and to cardiovascular disease in particular. However, studies on this issue have provided conflicting evidence (6–10).

Higher levels of physical activity and cardiorespiratory fitness, on the other hand, are believed to reduce the risk of death due to all causes, cardiovascular disease, and perhaps some cancers (11–14). Furthermore, data from both animals (15,16) and humans (17–20) show that higher levels of exercise and fitness may favorably affect glucose homeostasis. Thus, high levels of physical activity and fitness might be beneficial in improving the mortality experience of people with ICM. Although this rationale provides the basis for exercise and increased physical fitness as a widely accepted clinical treatment for hyperglycemia and diabetes mellitus, long-term effects of exercise and fitness in these patients are virtually unknown. It is partly for this reason that, after critically evaluating the results of available studies, a recent National Institutes of Health Consensus Development Conference (21) expressed skepticism as to the overall benefits of exercise training for people with non-insulin-dependent diabetes mellitus (NIDDM).

It is possible that regular physical activity might benefit patients with ICM even if glycemic control is not improved, but no data are available on this issue. The purpose of this study is to report the results of an investigation into the association of baseline cardiorespiratory fitness to subsequent all-cause mortality in men across the range of glycemic control.

RESEARCH DESIGN AND METHODS— Subjects in this study were 8715 male patients (age 20–84 yr) of a preventive medicine clinic in Dallas, Texas, who were examined at baseline between 1971 and 1982; 190 (age 21–79 yr) subsequently died. All subjects were free of exercise and resting electrocardiographically determined coronary heart disease, self-reported history of myocardial infarction, stroke, or hypertension at baseline. Furthermore, patients who reported being treated with insulin were also excluded.

A complete preventive medical examination was given to all subjects after an overnight fast. Medical history and demographic information, health habits, anthropometry, blood chemistry analysis, blood pressures, electrocardiography, and a cardiorespiratory fitness determination by maximal-exercise treadmill testing were included as part of the examination. Serum glucose in these subjects was measured after a 12-h overnight fast. Specifically, serum glucose was measured with the hexokinase–glucose-6-phosphate dehydrogenase enzymatic method. Other specific procedures and protocols have been reported previously (13,22–23).

There are several distinct dimensions to physical fitness (24), but we refer to cardiorespiratory fitness (measured by time on maximal-exercise treadmill test) as the fitness variable throughout this study. Maximal O_2 uptake, the most widely accepted measure of cardiorespiratory fitness, was estimated by the total duration of time in which a subject was able to complete a maximal-exercise treadmill test (25). Treadmill speed was begun at 88 m/min. A 0% grade was maintained for the 1st min of the test. The grade was increased to 2% the 2nd min of the test and was subsequently raised 1% each minute of the test up to the 25th min. After this time, the speed of the treadmill was increased 5.4 m/min until test termination. Patients were encouraged to give maximal effort on the test and those who did not reach at least 85% of their age-predicted maximal heart rate (220-age) were excluded from further study. Total duration of this test is highly correlated with measured O_2 uptake in healthy men (26).

Quintile cutoff points were defined from the population age-group–specific distribution of treadmill times. Physically unfit men (n = 1365) were defined as those in the bottom 20% of the treadmill time distribution; all others were categorized as fit (n = 7350). Previous work from our group has identified individuals in the 1st quintile as being at significantly increased risk of death, relative to more-fit people (13).

Glycemic status was defined from values measured from fasting blood glucose and self-report of physician-diagnosed diabetes mellitus. Glucose tolerance tests were not available for these patients. Three levels of blood glucose profile were created concordant with the recommendations of the National Diabetes Data Group (27): group 1, fasting blood glucose <6.4 mM; group 2, fasting blood glucose 6.4–7.8 mM; and group 3, fasting blood glucose ≥7.8 mM or a reported personal history of NIDDM. All cases of insulin-dependent diabetes mellitus were excluded from these analyses. The number of men in each of the three groups were 8108, 509, and 98, respectively.

Study subjects were followed for mortality events from their baseline visit through 1985. The average length of follow-up was slightly >8 yr, and the total follow-up experience in this cohort was 64,784 person-yr. Mortality follow-up used various sources to achieve a 94% vital status ascertainment rate. Official death certificates were obtained for most (88%) decedents, and causes of death were coded by a nosologist with the *International Classification of Diseases*, 9th revision (ICD-9).

Mortality rates were computed for each of the two fitness categories within the three glycemic groups and were age-adjusted by the direct method with the total follow-up in each category as the standard. Multivariate estimation of relative risks (RR) with logistic regression was used to examine the independent effects of cardiorespiratory fitness as a risk factor for all-cause mortality in each glycemic control group after adjustment for potential confounding variables of mortality.

RESULTS— The data in Table 1 are baseline descriptive information and risk-factor status of each of the three glycemic groups. Means and 95% confidence intervals (CI) for continuous data and percentage distributions of smoking status are presented. Variables in Table 1 generally show an unfavorable trend across the three groupings. Specifically, mean age, weight, body mass index (BMI), blood pressure, and cholesterol are higher in men with higher levels of fasting blood glucose. Mean time on treadmill (cardiorespiratory fitness) is incrementally lower with higher levels of fasting blood glucose.

All-cause mortality rates by glycemic status within each of the two fitness groupings are shown in Fig. 1. Fit men with fasting blood glucose <6.4 mM had the lowest age-adjusted death rate (21.4/10,000 person-yr), although the highest death rate was in those men who were unfit and had a fasting blood glucose of 6.4–7.8 mM (101.6/10,000 person-yr). A significant linear trend of increasing death rates across glycemic status groups was seen in the fit men (slope = 18.2, 95% CI = 3.3–33.1). The unfit men also demonstrated an increasing slope (2.8), but CIs around this estimate included unity (−15.2–20.7). Moreover, within each class of glycemic status, those who were fit had lower mortality rates than those who were unfit. Note that those men who were fit and were in the most unfavorable glycemic control category

Table 1—*Descriptive information and risk-factor status by glycemic status (Cooper Clinic healthy men, 1971–1985)*

	<6.4 mM (N = 8108)		6.4–7.8 mM (N = 509)		≥7.8 mM or NIDDM (N = 98)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age (yr)	41.7	41.5–41.9	46.0	45.1–46.8	47.3	45.6–49.0
Weight (kg)	80.7	80.5–81.0	85.7	84.5–87.1	87.3	84.0–90.6
Body mass index (kg/m^2)*	25.5	25.4–25.6	27.2	26.8–27.6	28.0	27.0–29.0
Systolic blood pressure (mmHg)	119.5	119.2–119.8	126.6	125.3–127.9	128.3	125.0–131.6
Diastolic blood pressure (mmHg)	79.3	79.1–79.5	83.6	82.8–84.4	83.7	81.9–85.5
Treadmill time (s)	1022.1	1016.1–1028.1	876.5	853.2–899.8	794.2	741.2–847.2
Total cholesterol (mM)	5.42	5.40–5.45	5.87	5.77–5.97	5.94	5.72–6.17
Glucose (mM)	5.39	5.38–5.40	6.80	6.78–6.83	9.40	8.68–10.11
Follow-up (yr)	8.2	8.1–8.3	9.6	9.3–9.9	9.1	8.5–9.8
Current smoker (%)	22.8		20.4		27.5	

CI, confidence interval.
*Missing heights for 47 men and were unable to calculate body mass index for 37 in group 1, 6 in group 2, and 4 in group 3.

(≥7.8 mM or NIDDM) had an age-adjusted all-cause mortality rate (45.9/10,000 person-yr) that approximated that of those who were classified as unfit and had fasting blood glucose <6.4 mM (41.5/10,000 person-yr). The age-adjusted RR of death due to all causes was significantly elevated in the low-fitness group within each of the three glycemic status categories: group 1, RR = 1.93 (95% CI 1.15–3.26); group 2, RR = 3.42 (95% CI 2.27–5.15); and group 3, RR = 1.80 (95% CI 1.25–2.58).

There were 105 deaths due to ischemic cardiovascular disease (ICD-9 390–448) in these men. Eighty-two deaths occurred in group 1, 13 in group 2, and 10 in group 3. Death rates per 10,000 person-yr of observation in those men who were unfit at baseline in each of the three ascending fasting blood glucose groups are shown in Fig. 2. A pattern similar to that of the all-cause mortality rates is seen in both fit and unfit men. However, the cardiovascular disease death rate in men who were unfit and in group 3 is lower than in similar men who were fit. Two deaths occurred in this category. The age-adjusted RR of death due to cardiovascular disease was significantly elevated in the low-fitness group within two of the three glycemic groups: group 1, RR = 2.54 (95% CI 1.26–5.13); group 2, RR = 2.98 (95% CI 1.77–5.02); and group 3, RR = 0.67 (95% CI 0.40–1.11).

The data in Table 2 are mortality information by separate exposures of other risk factors stratified by each of the three glycemic status groups. In general, similar associations are observed across the three levels of glycemic control. Higher blood pressure and cholesterol, cigarette smoking, and lower cardiorespiratory fitness were associated with higher risk of death in each of the three groups. Little association was seen for BMI in the two lower glycemic status groups. A significant protective association was noted for higher BMI in the highest glycemic status group, although there was a lower RR in each of the three groups. This estimate (highest glycemic control category) is based on a total of two deaths in the higher BMI group.

Multiple logistic regression was used to estimate the risk of all-cause mortality in the low-fitness group relative to the high-fitness group for each of the three glycemic control categories (Table 3). The RR estimates for the three groups within each glycemic control category are adjusted for simultaneous associations with age, BMI, glucose, systolic blood pressure, serum total cholesterol, smoking habit, family history of heart disease, and follow-up interval. In those men whose fasting blood glucose value was <6.4 mM, the risk of all-cause mortality in the lower 20% of the fitness distribution, relative to the other 80%, was 1.38. Men with elevated blood glucose (6.4–7.8 mM) and who were in the low-fitness group had an RR of death of 1.61. Finally, men with blood glucose values ≥7.8 mM or a history of NIDDM were at a 92% increased risk of all-cause mortality if they were unfit. The 95% CIs around risk estimates for the two higher blood glucose categories included unity.

Multivariate estimates of the RR of cardiovascular disease death in the

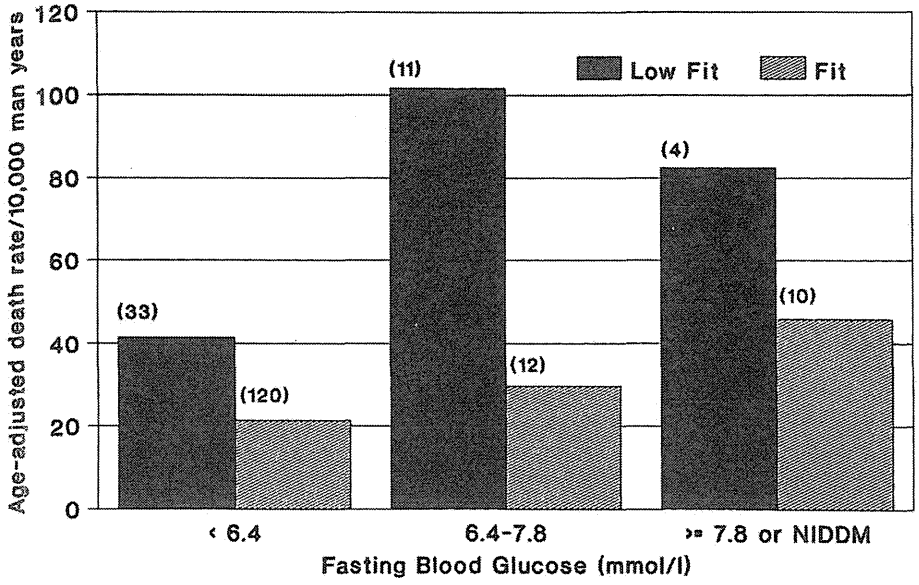

Figure 1—*Age-adjusted all-cause death rates/10,000 person-yr of observation by fitness grouping within glycemic status (Cooper Clinic men, 1971–1985). Numbers of deaths on which each rate is based are in parentheses above bars.*

low-fitness men at baseline was elevated in each of the three glycemic control groups. Estimates were: group 1, 1.62 (95% CI 1.21–2.18); group 2, 1.43 (95% CI 0.69–3.00), and group 3, 1.80 (95% CI 0.67–4.82).

Multivariate analyses were also conducted with cardiorespiratory fitness values treated as a continuous variable rather than as two categorical variables. After adjustment for the potential confounding variables, results similar to those above were observed. Per minute of lower treadmill time, RR estimates for all-cause mortality in each of the three glycemic control categories were: group 1, 1.09 (95% CI 1.04–1.14); group 2, 1.20 (95% CI 1.04–1.38); and group 3, 1.28 (95% CI 0.98–1.67). Comparable values for risk of cardiovascular disease death per minute of lower treadmill time in the three glycemic control categories were: group 1, 1.09 (95% CI 1.02–1.16); group 2, 1.14 (95% CI 0.94–1.38); and group 3, 1.25 (95% CI 0.96–1.64).

CONCLUSIONS— The data presented suggest a direct association between glycemic status and all-cause mortality. Men with lower levels of fasting blood glucose died at lower rates than their less glucose-tolerant counterparts. Furthermore, at each level of glycemic control, fit men had a lower risk of dying during the follow-up than unfit men. The increased risk appears to hold after multivariate adjustment for age and other confounding factors, although in some cases, these increased risks are not statistically different from unity, perhaps due to fewer deaths in some categories. This apparent relationship of cardiorespiratory fitness to mortality in ICM men is quite similar to that seen in men with a normal glucose profile. Thus, cardiorespiratory fitness is a substantial effect modifier of the observed relationship between blood glucose level and all-cause mortality in this group of men.

This study, the first to our knowledge to investigate the association between cardiorespiratory fitness and mortality across the spectrum of glycemic control and on a population basis, suggests that higher levels of cardiorespiratory fitness may attenuate the adverse impact of hyperglycemia and clinical diabetes mellitus on subsequent all-cause mortality. Indeed, the data suggest that fit men with blood glucose levels ≥7.8 mM or with NIDDM are at similar risk of death to those men who are unfit and who have a normal blood glucose profile. Because cardiorespiratory fitness can be improved by regular physical activity, these findings (although not conclusive) seem to support the use of physical activities that increase cardiorespiratory fitness as a cornerstone to the effective management of patients with abnormal blood glucose profiles or NIDDM.

The biological mechanisms through which this association may be operating are of interest. One explanation may be that increased cardiorespiratory fitness is working through its effects on other risk factors for death. Indeed, after controlling for the potential confounding factors, differences in death rates between unfit and fit men were attenuated from the differences seen with age adjustment only. Nonetheless, low-fitness men in group 2 (fasting blood glucose 6.4–7.8 mM) were still 61% more likely to die than their high-fitness counterparts, and the low-fitness men in group 3 (fasting blood glucose ≥7.8 mM or NIDDM) were 92% more likely to die than similarly classified fit men.

Higher levels of physical activity and cardiorespiratory fitness favorably alter or associate with more favorable levels of many of the variables that were controlled for in these analyses (23), and these factors are more prevalent in people with higher levels of blood glucose and those individuals who develop diabetes (28). Therefore, it is plausible that some of the beneficial effects of higher levels of cardiorespiratory fitness observed in the age-ad-

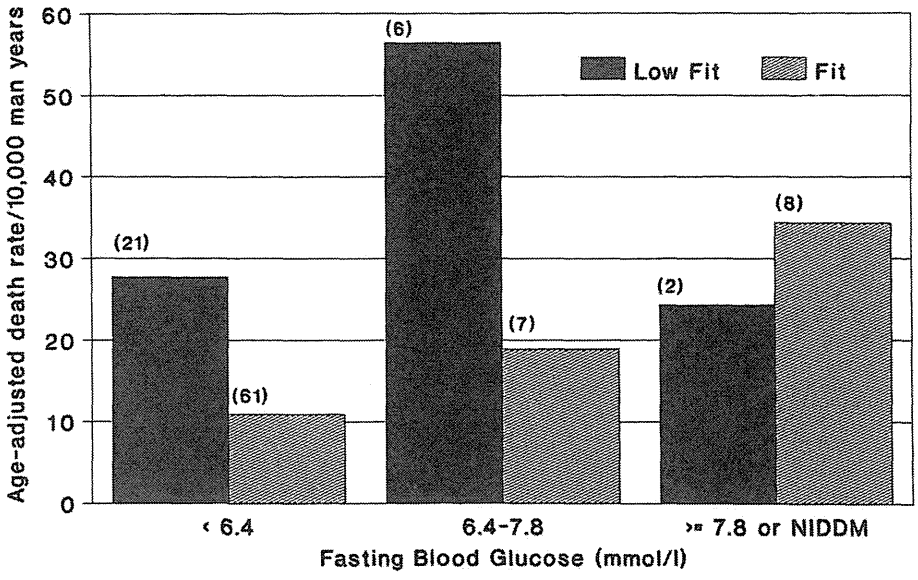

Figure 2—*Age-adjusted cardiovascular disease death rates/10,000 person-yr of observation by fitness grouping within glycemic status (Cooper Clinic men, 1971–1985). Numbers of deaths on which each rate is based are in parentheses above bars.*

justed rates is through beneficial effects on these or other factors that may not have been completely controlled for or were not available for analysis in this study (i.e., insulin sensitivity, adiposity or fat distribution, platelet aggregability, coronary perfusion, and propensity toward ventricular arrhythmias). Physically fit people may also have larger, more muscular hearts and could, therefore, be more likely to survive acute myocardial infarctions.

There are several possible limitations to our study, one of which is the method of classifying these men into exposure groups. The National Diabetes Data Group recommends two fasting plasma glucose determinations and sometimes an oral glucose tolerance test to correctly diagnose individuals as having diabetes mellitus or impaired glucose tolerance (27). Our measure of glycemic status was a single fasting plasma glucose value. Thus, the presence of false-positives and false-negatives cannot be ruled out. Although such misclassification is possible, our investigation of the mortality experience across the range of fasting plasma glucose levels would seem to minimize the problem, especially given the trends of increasing death rates across glycemic categories.

Instability in some death rates in these analyses is an issue. There was a total of four deaths (2 due to cardiovascular disease) in the unfit men whose fasting glucose values were ≥7.8 mM or who had NIDDM. This may help explain why the death rates (all cause and cardiovascular disease) were greater in low-fitness men with fasting glucose values 6.4–7.8 mM compared with the ≥7.8 mM or NIDDM category. The instability is further evidenced by the wide CIs around the risk estimates in this group (Table 3). The choice to maintain the clinically relevant categories for analyses was more important than having equivalent representation among groupings.

The maximal heart rate and disease history exclusions were made to help ensure that the group under study was apparently healthy (other than possible NIDDM). This means that associations similar to those reported here in people who happen to be afflicted with one or more of the exclusion criteria are unknown. Despite the exclusions, there is still a possibility that people with subclinical disease were not excluded and that disease may be in the causal pathway affecting (lowering) fitness levels. Other analyses have shown no difference in the association between fitness level and the risk of mortality between people with a short-term follow-up (<3 yr) and a longer-term follow-up (≥3 yr) (13). Although this does not definitively rule out the presence of subclinical disease, it would indicate that such an effect is not biasing the mortality results.

Our study population was largely from middle to upper socioeconomic classes and was generally well-educated, who chose to come to a preventive medicine clinic for an elective medical evaluation. However, the study group was similar on key physiological variables when compared with other representative samples of North-American men (29). Blood pressures, estimates of maximal O_2 uptake, and body weight were similar to those of men in the Lipid Research Clinics Prevalence Study and the Canada Fitness Survey. Moreover, total cholesterol was actually slightly higher, on the average, in our subjects than in the Lipid Research Clinics data, and the prevalence of ICM was similar to that estimated for all U.S. men (30).

Although physical activity was not directly analyzed in these analyses, it is possible to estimate the amount of exercise necessary to move from the low-fitness group (lower 20%) to the higher-fitness group. For example, the estimated maximal O_2 uptake for a 40- to 49-yr-old man in this study who was in the lower 20% of the fitness distribution would be <32 ml · kg^{-1}.

Table 2—*Age-adjusted all-cause mortality rates and relative risks of death by glycemic status and other risk-factor levels (Cooper Clinic healthy men, 1971–1985)*

	Deaths	Follow-up (person-yr)	Age-adjusted death rates*/ 10,000 person-yr	Relative risk	95% confidence interval
Glycemic status <6.4 mM					
Fitness					
High	120	54,670	21.4	1.0	
Low	33	10,114	41.5	1.9	1.2–3.3
Systolic blood pressure (mmHg)					
<140	127	58,977	22.3	1.0	
≥140	26	5806	27.7	1.2	0.7–2.2
Age (yr)					
<50	88	52,098	13.4	1.0	
≥50	65	12,688	10.0	0.7	0.3–1.7
Cholesterol (mM)					
<6.24	88	50,341	18.3	1.0	
≥6.24	65	14,441	41.4	2.3	1.3–3.9
Smoking					
No	102	51,136	19.3	1.0	
Yes	51	13,648	42.9	2.2	1.3–3.7
Body mass index (kg/m^2)					
<27.4	126	51,004	24.3	1.0	
≥27.4	27	13,779	19.8	0.8	0.4–1.4
Family history coronary heart disease					
No	122	51,237	24.9	1.0	
Yes	31	13,546	19.4	0.8	0.4–1.4
Glycemic status 6.4–7.8 mM					
Fitness					
High	12	3621	29.7	1.0	
Low	11	1268	101.6	3.4	2.3–5.1
Systolic blood pressure (mmHg)					
<140	14	3828	38.4	1.0	
≥140	9	1059	76.4	2.0	1.3–2.9
Age (yr)					
<50	9	3350	18.4	1.0	
≥50	14	1537	28.6	1.5	0.9–2.8
Cholesterol (mM)					
<6.24	11	2998	39.0	1.0	
≥6.24	12	1889	58.2	1.5	1.0–2.2
Smoking					
No	14	3959	35.5	1.0	
Yes	9	925	96.3	2.7	1.8–4.0
Body mass index (kg/m^2)					
<27.4	15	2954	50.8	1.0	
≥27.4	8	1933	48.0	0.9	0.6–1.4
Family history coronary heart disease					
No	17	3324	83.9	1.0	
Yes	6	1563	31.4	0.4	0.2–0.6

Table 2—*Continued.*

	Deaths	Follow-up (person-yr)	Age-adjusted death rates*/10,000 person-yr	Relative risk	95% confidence interval
Glycemic status ≥7.8 mM or non-insulin-dependent diabetes mellitus					
Fitness					
High	10	2016	45.9	1.0	
Low	4	669	82.5	1.8	1.2–2.6
Systolic blood pressure (mmHg)					
<140	10	2278	43.9	1.0	
≥140	4	407	98.4	1.8	1.2–2.5
Age (yr)					
<50	5	1839	18.6	1.0	
≥50	9	846	33.5	1.8	1.0–3.2
Cholesterol (mM)					
<6.24	5	1568	31.2	1.0	
≥6.24	9	1116	81.3	2.6	1.7–3.9
Smoking					
No	7	1948	34.2	1.0	
Yes	7	737	103.5	3.0	2.1–4.5
Body mass index (kg/m^2)					
<27.4	12	1905	63.0	1.0	
≥27.4	2	780	25.6	0.4	0.2–0.6
Family history coronary heart disease					
No	9	1751	53.0	1.0	
Yes	5	934	48.5	0.9	0.6–1.3

* Adjusted to population distribution of age.

min^{-1} (<12.016 min on the treadmill). Based on available data from studies performed at this and other research centers, it is likely that 30 or 40 min of moderate-intensity exercise (e.g., a brisk walk) 3–5 days/wk would be sufficient to improve to, or maintain, the moderate fitness level in this study.

Although the exact exercise prescription necessary for good health is unknown, this and other studies suggest that the amount of cardiorespiratory fitness necessary to obtain health benefits appears not to be that attainable only by elite athletes but rather is attainable by most men without a substantial investment in either time or intensity. Clinicians are urged to relay this message to their patients when appropriate.

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Table 3—*Age- and multivariate-adjusted risks of death by glycemic status in low-fitness men relative to high-fitness men (Cooper Clinic healthy men, 1971–1985)*

	Age		Multivariate*	
Glycemic status	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval
<6.4 mM	1.9	1.2–3.3	1.38	1.09–1.74
6.4–7.8 mM	3.4	2.3–5.1	1.61	0.91–2.86
≥7.8 mM	1.8	1.2–2.6	1.92	0.75–4.90

*Adjusted for associations with age, serum cholesterol, resting systolic blood pressure, age, body mass index, smoking habit, family history of heart disease, and follow-up interval.

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References

1. West KM: Epidemiology of Diabetes and Its Vascular Lesions. New York, Elsevier, 1978
2. Kadowaki T, Miyake Y, Hagura R, Ahanuma Y, Kajinuma H, Kuzuya N, Takaku F, Kosaka K: Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 26:44–49, 1984
3. Keen H, Jarrett RJ, McCartney P: The ten-year follow-up of the Bedford Survey (1962–1972): glucose tolerance and diabetes. *Diabetologia* 22:73–78, 1982
4. King H, Zimmet P, Raper LR, Balkau B: The natural history of impaired glucose tolerance in the Micronesian population of Nauru: a six-year follow-up study. *Diabetologia* 26:39–43, 1984
5. Jarrett RJ, Keen H, Fuller JH, McCartney M: Worsening to diabetes in men with impaired glucose tolerance ("borderline diabetes"). *Diabetologia* 16:25–30, 1979
6. Stenhouse NS, Murphy BP, Welborn TA: Busselton population study: risk associated with asymptomatic hyperglycemia. *J Chronic Dis* 32:693–98, 1979
7. Stamler R, Stamler J, Lindberg HA, Marquardt J, Berkson DM, Paul O, Lepper M, Dyer A, Stevens E: Asymptomatic hyperglycemia and coronary heart disease in middle-aged men in two employed populations in Chicago. *J Chronic Dis* 32:805–15, 1979
8. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Coronary-heart disease risk and impaired glucose tolerance: the Whitehall Study. *Lancet* 1:1373–76, 1980
9. Pan W-H, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P, Stamler J: Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol* 123:504–16, 1986
10. Jarrett RJ, McCartney P, Keen H: The Bedford Survey: ten-year mortality rates in newly diagnosed diabetics, borderline diabetics, and normoglycemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 22:79–84, 1982
11. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh C: Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 314:605–13, 1986
12. Morris JN, Everitt MG, Pollard R, Chave SPW, Semmence AM: Vigorous exercise in leisure time: protection against coronary heart disease. *Lancet* 2:1207–10, 1980
13. Blair SN, Kohl HW III, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW: Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 262:2395–401, 1989
14. Ekelund L-G, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS: Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men: the Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med* 319:1379–84, 1988
15. Galbo H, Hedeskov K, Capito K, Vinten J: The effects of physical training on insulin secretion of rat pancreatic islets. *Acta Physiol Scand* 111:75–79, 1981
16. Richard D, LeBlanc J: Effects of physical training and food restriction on insulin secretion and glucose tolerance in male and female rats. *Am J Clin Nutr* 33: 2588–94, 1980
17. Seals DR, Hagberg JM, Allen WK, Hurley BF, Dalsky GP, Ehsani AA, Holloszy JO: Glucose tolerance in young and older athletes and sedentary men. *J Appl Physiol Respir Environ Exercise Physiol* 56:1521–25, 1984
18. Miller WJ, Sherman WM, Ivy JL: Effect of strength training on glucose tolerance and post-glucose insulin response. *Med Sci Sports Exercise* 16:539–43, 1984
19. Rogers MA, Yamamoto C, King DS, Hagberg JM, Ehsani AA, Holloszy JO: Improvement in glucose tolerance after 1 wk of exercise in patients with mild NIDDM. *Diabetes Care* 11:613–18, 1988
20. Trovati M, Carta Q, Cavalot F, Vitali S, Banaudi C, Lucchina PG, Fiocchi F, Emanuelli G, Lenti G: Influence of physical training on blood glucose control, glucose tolerance, insulin secretion, and insulin action in non-insulin-dependent diabetic patients. *Diabetes Care* 7:416–20, 1984
21. National Institutes of Health: Consensus development conference on diet and exercise in non-insulin-dependent diabetes mellitus. *Diabetes Care* 10:639–44, 1987
22. Blair SN, Goodyear NN, Gibbons LW, Cooper KH: Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA* 252:487–90, 1984
23. Blair SN, Cooper KH, Gibbons LW, Gettman LR, Lewis S, Goodyear N: Changes in coronary heart disease risk factors associated with increased treadmill time in 753 men. *Am J Epidemiol* 118:352–59, 1983
24. Caspersen CJ, Powell KE, Christenson GM: Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 100:126–31, 1985
25. Balke B, Ware RW: An experimental study of physical fitness in Air Force personnel. *U S Armed Forces Med J* 10: 676–88, 1959
26. Pollock ML, Bohannon RL, Cooper KH, Ayers JJ, Ward A, White SR, Linnerud AC: A comparative analysis of four protocols for maximal stress testing. *Am Heart J* 92:39–46, 1976
27. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–57, 1979
28. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals. *JAMA* 263:2893–98, 1990

29. Blair SN, Kannel WB, Kohl HW, Goodyear NN, Wilson PWF: Surrogate measures of physical activity and physical fitness: evidence for sedentary traits of resting tachycardia, obesity, and low vital capacity. *Am J Epidemiol* 129:1145–56, 1989
30. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20–74 yr. *Diabetes* 36:523–34, 1987

論文名	Cardiorespiratory fitness, glycemic status, and mortality risk in men.						
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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	開始時に21-79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	なし	なし	なし	なし	(死亡)	( )
	維持・改善	なし	なし	なし	なし	( )	( )
図　表							
図表掲載箇所							
概　要 (800字まで)	目的：血糖値レベルの範囲を考慮した際のすべての死亡原因に対する全身持久性体力の基準を決定すること。研究デザインと方法：8715人の男性（平均年齢42歳）を用いたプロスペクティブスタディ、平均8.2年(1-15年間の範囲)の追跡調査から得られたデータを分析した。全身持久性体力はトレッドミルによる最大運動負荷テストにより評価された。臨床診断により心血管系の疾患を持つ男性、もしくは運動負荷テスト中において、年齢による予測最大心拍数の85%を達成しなかった者は分析から除かれた。結果：年齢補正による死亡率は、空腹時血糖が高い水準で増加した。血糖状態が不安定でありながら、体力の高い人では年齢補正された時のすべての死亡率が、そうでない人に比べてより低かった。空腹時血糖が7.8mMかそれ以上、もしくはNIDDM（非インスリン依存性糖尿病）と診断された男性において、体力の高い人と低い人の追跡調査から得られた10000人当たりの年齢補正による死亡率は、それぞれ82.5と45.9であった。年齢補正されたすべての原因による死亡の相対リスクは、低体力者うちの3つの血糖状態の群で有意に高まった：それらは、空腹時血糖6.4mM以下；相対リスク(RR)=1.93、(95%信頼区間 1.15-3.26)、6.4-7.8mM；相対リスク=3.42(95%信頼区間 I 2.27-5.15)、7.8以上mMもしくはNIDDMを持つ人の血糖値、相対リスク=1.80(95%信頼区間 1.25-2.58)。死亡のリスクファクター（年齢、安静時収縮期血圧、血清コレステロール、BMI、心疾患の家族暦、追跡調査の間隔および喫煙習慣）を制御した多変量解析では、体力の高い人と低い人を比較するため、すべての原因で補正した死亡リスクを示した。死亡の多変量リスクは、3つの血糖状態の群において低体力と高体力とを相対リスクで比較した結果は以下のとおりである：6.4 mM以下；相対リスク=1.38(95%信頼区間 1.09-1.74)、6.4-7.8 mM；相対リスク=1.61(95%信頼区間 0.91-2.86)、7.8 mM以上もしくはNIDDMを持つ人；相対リスク=1.92(95%信頼区間 0.75-4.00)						
結　論 (200字まで)	40-50歳で32ml/min/kg以上の体力があれば、血糖値の異常がなければ総死亡リスクを減らせる。その水準を維持するために30-40分の運動を週に3-5日実施すると良い（エビデンスなし）。						
エキスパートによるコメント (200字まで)	高い体力を保持することは死亡リスクを減少させる強力な要因であるが、糖尿病患者では、体力と死亡リスクの関係がなくなることを明らかにし、糖尿病患者に対しては血糖値の改善が必要がある。						

担当者　宮地 劉

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ORIGINAL ARTICLE

A graded association of exercise capacity and all-cause mortality in males with high-normal blood pressure

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Abstract

Introduction. Information regarding the effect of exercise capacity on mortality risk in individuals with high-normal blood pressure is severely limited. Thus, we evaluated the association of exercise capacity and all-cause mortality in individuals with high-normal blood pressure. *Methods.* Exercise test was performed in 1727 males with high-normal blood pressure at two Veteran sites (Washington, DC, and Palo Alto, CA). Fitness status was assessed in metabolic equivalents (METs) at exercise peak. All-cause mortality was recorded for a mean follow-up period of 9.8±6.0 years. *Results.* Exercise capacity was inversely associated with all-cause mortality, and the association was independent of traditional cardiovascular risk factors. For each 1 MET increase in exercise capacity, the adjusted mortality risk was reduced by 13%, underscoring the strong predictive value of exercise capacity that was confirmed by ROC analysis. Data analysis according to fitness levels revealed a threshold level of 4 METs, over which the mortality risk was progressively reduced by 30% (hazard ratio = 0.70; CI 0.51–0.95) for those who achieved 4.1–6.0 METs and 61% (hazard ratio = 0.39; CI 0.26–0.57) for those who achieved 8.1–10 METs. No additional reductions in risk were noted until the MET level achieved exceeded 12 METs. *Conclusions.* We observed a strong, inverse, graded and independent association between exercise capacity and all-cause mortality in individuals with high-normal blood pressure. Our findings indicate that a shift of the fitness curve to the right is associated with significant survival benefits, and even slight differences in fitness levels are associated with substantial reductions in mortality risk.

Key Words: *All-cause mortality, exercise capacity, fitness, high-normal blood pressure*

Introduction

Primary hypertension may be defined as the level of blood pressure at which the benefits of intervention are greater than the risks of not intervening. Although a blood pressure of 140/90 mmHg represents a uniformly accepted level by all guidelines (1–3), some differences exist regarding the definitions of normal blood pressure levels. The American guidelines adopted the term "prehypertension" for individuals with levels of 120–139 mmHg for systolic and/or 80–89 mmHg for diastolic blood pressure (2). In contrast, the European guidelines divide this group in two subgroups: normal (120–129/80–84 mmHg) and high-normal (130–139/85–89 mmHg) (1). The 2003 European guidelines (4) have earned a wide recognition in the hypertension field, being among the most cited articles in the medical literature (5).

Several lines of evidence from large, prospective, observational studies revealed that individuals with high-normal blood pressure are at a greater risk of

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