Exercise Capacity and Body Composition as Predictors of Mortality Among Men With Diabetes

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OBJECTIVE — To quantify the relation of fitness to mortality among men with diabetes, adjusted for BMI and within levels of BMI.

RESEARCH DESIGN AND METHODS — In this observational cohort study, we calculated all-cause death rates in men with diabetes across quartiles of fitness and BMI categories. Study participants were 2,196 men with diabetes (average age 49.3 years, SD 9.5) who underwent a medical examination, including a maximal exercise test, during 1970 to 1995, with mortality follow-up to 31 December 1996.

RESULTS — We identified 275 deaths during 32,161 person-years of observation. Risk of all-cause mortality was inversely related to fitness. For example, in the fully adjusted model, the risk of mortality was 4.5 (2.6–7.6), 2.8 (1.6–4.7), and 1.6 (0.93–2.76) for the first, second, and third fitness quartiles, respectively, with the fourth quartile (highest fitness level) as the referent (*P* for trend <0.0001). There was no significant trend across BMI categories for mortality after adjustment for fitness. Similar results were found when the fitness-mortality relation was examined within levels of body composition. In normal-weight men with diabetes, the relative risks of mortality were 6.6 (2.8–15.0), 3.2 (1.4–7.0), and 2.2 (1.1–4.6) for the first, second, and third quartiles of fitness, respectively, as compared with the fourth quartile (*P* for trend <0.0001). We found similar results in the overweight and obese weight categories.

CONCLUSIONS — There was a steep inverse gradient between fitness and mortality in this cohort of men with documented diabetes, and this association was independent of BMI.

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While the importance of physical activity and weight loss in the prevention of diabetes is now well established by randomized clinical trials, few studies have examined the relative contribution of weight and physical activity on morbidity and mortality in individuals with diabetes (1,2). A better understanding of the relative contributions of weight control and physical activity to mortality may guide clinical recommendations.

We previously reported that low cardiorespiratory fitness and physical inactivity are independent predictors of all-cause and cardiovascular disease (CVD) mortality in men with type 2 diabetes (3). However, this study examined these exposures in multivariable models and, thus, did not allow for evaluation of the relative values of physical activity, fitness, or weight as mortality predictors. We have performed additional follow-up and can now extend our previous work by examining the relation of fitness and mortality within BMI categories.

The primary aims of this study of men with diabetes were to examine *1*) the risk of mortality associated with fitness and BMI when examined as continuous and categorical variables and *2*) the dose-response relationship between fitness and mortality both with adjustment for BMI and within levels of BMI.

RESEARCH DESIGN AND METHODS

— The Aerobics Center Longitudinal Study (ACLS) is a prospective epidemiologic investigation. Participants for the analyses reported here are 2,196 men with diabetes examined at least once during 1970 to 1995 and who completed at least 1 year of follow-up. Diabetes case subjects were defined as men who reported use of insulin ($n = 47$), a physician-diagnosed history of diabetes, or a fasting plasma glucose level ≥7.0 mmol/l (≥126 mg/dl) at baseline (4). The men were predominantly non-Hispanic whites, well educated, and either currently or previously employed in professional or executive positions. All participants were U.S. residents and ranged in age from 23 to 79 years (average 49.3 ± 9.5). All men gave informed consent for participation in the examination and registration in the follow-up study. The study protocol was approved annually by The Cooper Institute Institutional Review Board.

Mortality surveillance

We followed study participants for mortality from their baseline examination until their death or until 31 December 1996. The primary method of mortality surveillance has been accomplished by use of the National Death Index.

Clinical examination

The evaluation consisted of a physical examination by a clinic physician, obtaining blood by venipuncture from an antecubital vein, measurement of blood pressure, anthropometry, maximal exercise test on a treadmill, and completion of an extensive questionnaire on demographic characteristics, health history, family medical history, and a health habit inventory.

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Abbreviations: CVD, cardiovascular disease; MET, metabolic equivalent.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Blood chemistry analyses were performed in the laboratory of the Cooper Clinic, which participates in and meets quality control standards of the Centers for Disease Control and Prevention (CDC) Lipid Standardization Program. Height and weight were measured on a standard physician's balance beam scale and stadiometer. We calculated BMI and assigned men to categories of normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI ≥30.0 kg/m^2) (5). Body composition was assessed by hydrostatic weighing (n = 1,051), by skinfold thickness (n = 989), or both (n = 402). Because not all participants underwent hydrostatic weighing, we standardized the body fat measurement using methods previously described, resulting in 2,040 men (242 decedents) with body fat percentages available for analysis (6).

Blood pressure measurements were obtained using mercury manometers following the American Heart Association protocol (7). Men who reported a history of physician-diagnosed hypertension were classified as hypertensive. Individuals were classified as never, past, or current smokers based on self-report questionnaire. We defined baseline CVD as history of heart attack, stroke, abnormal resting or exercise electrocardiogram, and parental history of premature CVD as reporting a parent who had a stroke or myocardial infarction before the age of 50. Participation in regular physical activity was defined as reporting regular walking, jogging, cycling, or participation in a racket sport.

We measured fitness by a maximal exercise test following a modified Balke protocol (8). Patients began walking on a treadmill at 88 m/min (3.3 mph) with no elevation. After the first minute, the incline was increased to 2% and was increased 1% each minute thereafter until the 25th minute. For the few men still able to continue the test beyond 25 min, the elevation was maintained at 25% and the speed increased by 5.4 m/min (0.2 mph) each minute until the end of the test. The test was terminated when the men were exhausted or if the physician stopped the test for medical reasons. Time on the treadmill test with this protocol is highly correlated (R = 0.92) with measured maximal oxygen uptake ($V\text{O}_{2max}$) (9). We express fitness as maximal metabolic equivalents (METs = work metabolic rate/resting metabolic rate = 3.5 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}) attained during the treadmill test. We calculated METs from estimated $V\text{O}_{2max}$ for the Balke protocol using the formula $V\text{O}_{2max} = 1.44 \cdot$ (minutes on treadmill) + 14.99 (9).

Statistical analyses

We calculated the mean and SD of each variable with participants categorized as survivors or decedents. To assess the independent association of fitness and BMI as continuous variables as well as to evaluate the contributions of traditional CVD risk factors, we used log-linear proportional hazard models.

We calculated MET quartiles and evaluated risk of mortality by four log-linear proportional hazards models —first adjusting only for age and year of examination, second by adding nonmodifiable risk factors (history of cancer or CVD events or family history of CVD), third by adding modifiable risk factors (smoking, systolic blood pressure, cholesterol, and glucose), and fourth by adding BMI. In a similar fashion, we evaluated the risk of mortality across BMI categories with the fourth model adjusting for fitness. To further assess the body composition–mortality relation, we also evaluated thirds of body fat percent instead of BMI categories.

We examined the association of fitness to mortality within levels of BMI by cross-tabulated MET and BMI categories to create 12 fitness-BMI categories (MET quartile 1, normal weight; MET quartile 2, overweight; MET quartile 4, obese). Due to a small number of deaths in the MET quartile 4 obese cell, we combined this group with the MET quartile 3 obese group, resulting in a final total of 11 categories. Log-linear proportional hazard models were used to estimate adjusted relative risks for mortality for each fitness-BMI category. We used the continuous variables of METs and BMI to test linear trends. We repeated the analyses using body fat percentage quartiles instead of BMI categories.

RESULTS — The study population included 2,196 diabetic men followed for 1–26 years; the average was 14.6 (7.1) years. We identified 275 deaths during 32,161 person-years of observation. The cohort characteristics, grouped by survival status, are shown in Table 1. At baseline, survivors were younger and fitter and had better metabolic profiles, included fewer smokers, and had a lower prevalence of hypertension and previous CVD compared with decedents. To verify our assumption that increased fitness is due primarily to physical activity, we examined the prevalence of self-reported regular physical activity across fitness quartiles. We observed a strong direct association with the prevalence of regular physical activity of 24.2, 33.6, 47.4, and 79.0 across the fitness quartiles (P for trend = 0.005). A total of 94% of participants achieved a maximal heart rate of ≥85%, supporting the premise that the exercise test was a maximal effort for most.

Risks of death according to clinical variables and BMI and/or fitness (METs) are in Table 2. There was a significant increment in risk of death for each unit of BMI (4% per BMI unit). Fasting glucose levels, systolic blood pressure, total cholesterol, parental history of and presence of CVD, and current cigarette smoking all contributed significantly to risk of death. In a second model including fitness and clinical variables other than BMI, we found a 25% lower risk of death per each MET unit. We included both fitness and BMI in another model with clinical variables and found a 26% lower risk of death per MET unit ($P < 0.0001$), but there was no significant association of BMI to mortality in this model.

Next we evaluated associations of fitness and BMI as categorical variables to risk of death (Table 3). We adjusted all models for age and year of examination and added nonmodifiable and modifiable risk factors and either BMI or fitness. When compared with the highest fitness quartile, there were progressively higher risks of death across the three remaining quartiles in all models. Overweight and obese men had a higher risk of death than men of normal weight, although this trend became nonsignificant when fitness was included in the model. Similar results were found when examining mortality risks across fitness and body fat categories (data not presented).

We next calculated the distribution of fitness across BMI categories and found an inverse association between fitness and BMI. For individuals of normal weight, the distribution across fitness quartiles 1–4 was 9.9, 14.9, 29.8, and 45.5%, respectively; for overweight individuals, the distribution was 19.4, 31.3, 30.8, and

Table 1—*Baseline characteristics of 2,196 men with diabetes grouped by survival status, Aerobics Center Longitudinal Study, 1970–1996*

	Participants		
	Survived	Died	*P*
n	1,921	275	
Person-years of observation	29,008	3,153	
Age (years)	48.5 ± 9.3	54.4 ± 8.6	<0.001
BMI (kg/m^2)	27.5 ± 4.5	27.6 ± 4.4	0.54
Exercise tolerance (METs)	10.5 ± 2.1	8.8 ± 1.9	<0.001
Total cholesterol level (mmol/l [mg/dl])	5.8 ± 1.1 [225.9 ± 43.4]	6.1 ± 1.2 [235.0 ± 47.7]	0.001
Fasting glucose (mmol/l [mg/dl])	7.5 ± 2.7 [134.3 ± 49.3]	8.1 ± 3.4 [146.0 ± 60.7]	<0.001
Systolic blood pressure (mmHg)	126.0 ± 15.0	132.8 ± 17.3	<0.001
Diastolic blood pressure (mmHg)	83.5 ± 9.7	85.7 ± 11.4	<0.001
Cigarette smoking (%)			
Never	36.1	26.5	0.007
Past	44.0	49.1	
Current	19.9	24.4	
Physically active (%)*	46.8	38.9	0.01
Hypertension (%)	30.2	44.4	<0.0001
Family history of premature CVD (%)	15.0	17.1	0.38
Prevalent CVD (%)	15.3	34.5	<0.0001

Data are means ± SD, unless otherwise indicated. *Regular physical activity was defined as participating in walking, jogging, cycling, or participation in a racket sport during the previous 3 months.

18.5%, respectively; and for obese individuals, the distribution was 49.1, 33.3, 14.3, and 3.3%, respectively. Within all three BMI categories, we found an incrementally lower risk of death across fitness quartiles (Fig. 1). The greatest difference in risk was seen in the highest BMI category between the lowest fitness quartile (relative risk 5.6 [95% CI 2.3–13.8]) and the next fitness quartile (2.1 [0.8–5.6]). Similar results were found when examining mortality risks across fitness and body fat categories (data not presented).

CONCLUSIONS — Our primary finding is that fitness had a strong and independent inverse association with mortality in men with diabetes, and this result was seen in all BMI and body fatness groups. We previously reported that low fitness is a risk factor for mortality in men with diabetes (3). The current study expands on these findings by showing a stepwise relation between fitness and mortality and that this relation is evident within all BMI strata. Furthermore, a more direct evaluation of body fatness (% body fat) yielded results similar to those for BMI. To our knowledge, this is the largest group of men with diabetes undergoing assessment of body fatness and fitness by objective laboratory testing.

Approximately half of all obese indi-

Table 2—*Age and examination year adjusted for risk of death according to cardiorespiratory fitness (maximal METs attained during the exercise test), BMI, and other clinical, health status, and lifestyle variables for 2,196 men with diabetes, Aerobics Center Longitudinal Study, 1970–1996*

	BMI only			Treadmill METs only			BMI and treadmill METs		
Variable	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Cardiorespiratory fitness (for each 1-MET increase)		—		0.75	(0.70–0.81)	<0.0001	0.74	(0.68–0.80)	<0.0001
BMI (for each 1-kg/m^2 increment)	1.04	(1.02–1.07)	0.003		—		0.98	(0.95–1.01)	0.27
Fasting glucose (for each 10-mg/dl increment)	1.04	(1.02–1.05)	<0.0001	1.04	(1.02–1.05)	<0.0001	1.04	(1.02–1.05)	<0.0001
Systolic blood pressure (for each 10-mmHg increment)	1.12	(1.04–1.20)	0.002	1.10	(1.02–1.17)	0.02	1.10	(1.02–1.18)	0.01
Prevalent CVD	1.80	(1.38–2.34)	<0.0001	1.34	(1.02–1.76)	0.04	1.30	(0.98–1.72)	0.07
Family history of premature CVD	1.45	(1.05–1.99)	0.023	1.39	(1.01–1.91)	0.04	1.37	(1.00–1.89)	0.05
Total cholesterol level (for each 10-mg/dl increment)	1.03	(1.00–1.06)	0.04	1.02	(1.00–1.05)	0.10	1.02	(1.00–1.05)	0.12
Cigarette smoking									0.65
Past	1.23	(0.92–1.64)	0.16	1.08	(0.81–1.44)	0.61	1.07	(0.80–1.43)	
Current	1.75	(1.24–2.46)	0.001	1.27	(0.89–1.80)	0.19	1.25	(0.88–1.77)	0.21

Table 3—*Risk of mortality across fitness categories (quartiles of maximal METs attained during the exercise test) and BMI categories*

	Fitness quartiles (METs)							
	≤8.82		8.83–10.08		10.09–11.71		>11.71	
Adjustments	RR	95% CI	RR	95% CI	RR	95% CI	RR (ref)	*P* for trend
Age, examination year	5.72	(3.54–9.24)	3.01	(1.84–4.93)	1.64	(0.97–2.79)	1.0	<0.0001
Above + nonmodifiable risk factors*	5.23	(3.22–8.49)	2.93	(1.79–4.80)	1.62	(0.95–2.75)	1.0	<0.0001
Above + modifiable risk factors	4.29	(2.61–7.05)	2.68	(1.62–4.44)	1.58	(0.92–2.70)	1.0	<0.0001
Above + BMI	4.49	(2.64–7.64)	2.77	(1.65–4.66)	1.60	(0.93–2.76)	1.0	<0.0001

	BMI categories (kg/m^2)					
	<25.0	25.0–29.9		≥30.0		
Adjustments	RR (ref)	RR	95% CI	RR	95% CI	*P* for trend
Age, examination year	1.0	1.23	(0.93–1.63)	1.86	(1.34–2.59)	0.0003
Above + nonmodifiable risk factors*	1.0	1.23	(0.93–1.63)	1.82	(1.31–2.53)	0.0005
Above + modifiable risk factors†	1.0	1.07	(0.81–1.43)	1.51	(1.08–2.10)	0.02
Above + fitness (treadmill METs)	1.0	0.81	(0.61–1.09)	0.81	(0.56–1.16)	0.22

*Nonmodifiable risk factors include history of cancer or cardiovascular event or parental history of premature cardiovascular event; †modifiable risk factors include smoking, resting systolic blood pressure, cholesterol, and glucose.

viduals in this study were in the lowest fitness quartile and these low-fitness obese men had a 5.6-fold higher risk of death than men in the reference group—the most fit quartile of normal-weight men. Obese men with fitness levels greater than the lowest quartile were at no increased risk for mortality when compared with men in the reference group. However, the obese group had a relatively small sample size; therefore, these results must be confirmed in larger studies.

Previous work in our cohort indicates that men who walked an average of 130 min per week were moderately fit (10). Because the METs cutoff of the low-fit category in the previous publication was identical with the MET cutoff for this analysis, the Surgeon General's Report recommendation of 30 min of moderate intensity physical activity most days of the week will keep most individuals out of the lowest fitness quartile. Therefore, we believe that performing 150 min of moderate intensity physical activity per week should be a strong recommendation to individuals with diabetes.

Although fitness has a genetic component (25–40%), it is clear that regular physical activity is perhaps the major de-

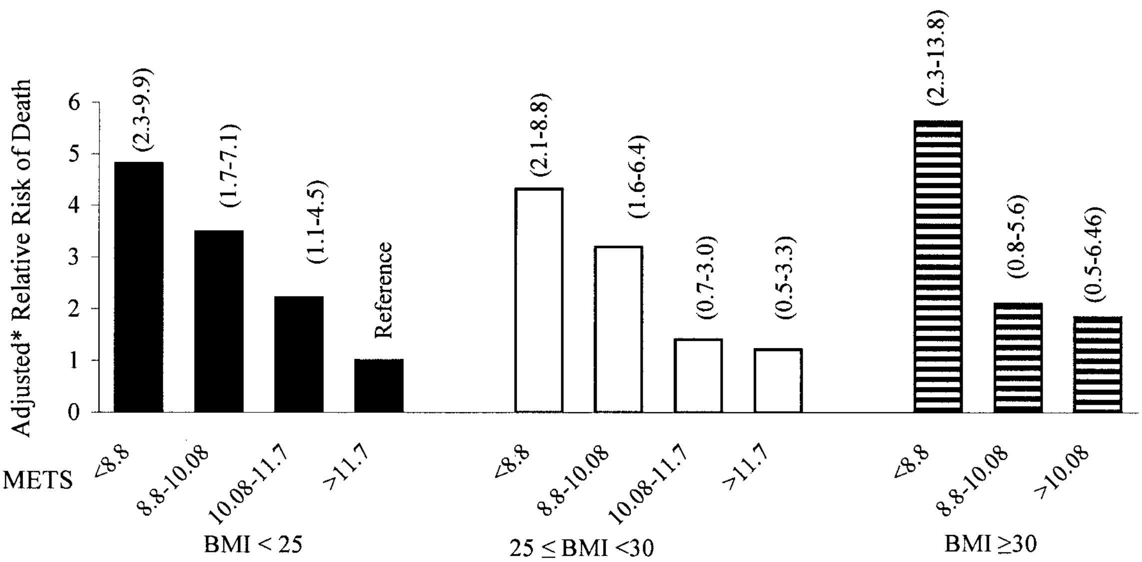

Figure 1—*Data from 2,196 men with diabetes with 275 all-cause deaths during 32,161 person-years of observation. Age and examination year–adjusted risk of mortality is shown by quartiles of fitness within levels of body composition (normal weight, overweight, and obese) as assessed by BMI. The BMI categories are defined as normal weight (BMI 18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Within the highest body composition groups, the two highest quartiles of fitness had to be combined due to the small number of men in those two quartiles.*

terminant of fitness (11,12). This is supported by numerous studies showing that exercise training increases fitness in a predictable way and that bed rest reduces fitness (13–16). In the current study, we found that 79% of men in the highest quartile of fitness reported participating in regular physical activity, a rate that was threefold higher than in men in the lowest fitness quartile. Therefore, we assume that the objective measure of fitness used in our study is an excellent marker of physical activity habits.

Although many clinicians counsel their patients with diabetes to be physically active, this is often done in the context of weight control. Our results suggest that there is intrinsic value in encouraging patients to be active and fit, whether or not it helps them lose weight. These results should not be interpreted to minimize the importance of weight control and other treatments in the management of diabetes, but our data present a strong rationale for establishing physical activity and fitness as major targets of clinical interventions for patients with diabetes.

We insert a note of caution in regard to focusing more emphasis on increasing physical activity and fitness in patients with diabetes. We believe it is reasonable to assume that there is a level of obesity at which the benefits of more physical activity or higher levels of fitness do not overcome the metabolic abnormalities and risks of excess body fat. Our study sample had >6% of men with a BMI >35 kg/m^2; therefore, the results must be extrapolated with caution to men with diabetes and BMI >35 kg/m^2. However, because regular physical activity is a critical element of successful weight control, including the prevention of additional weight gain, the importance of regular physical activity remains important, even for patients with Class II or Class III obesity.

The predominantly white, well-educated, middle- to upper-class, male subject group limits the generalizability of the results of our study but should not affect the internal validity. However, there is no strong reason to assume that the benefits of moderate and high fitness would be any less in women or other ethnic groups. Our previous studies have shown, in analyses in which enough deaths occurred for parallel analyses in women and men, that the inverse gradient of mortality across fitness groups is similar for the two sexes (17–19). We do not have sufficient numbers of members of minority groups to perform stratum-specific analyses, but other studies on the relation of physical activity or cardiorespiratory fitness to morbidity or mortality are consistent with those reported here (20,21). The lack of pharmacotherapy information in our database prevents the evaluation of medication use as a possible effect modifier. However, in this affluent patient population with excellent access to medical care, it is reasonable to assume that the percentage of men receiving pharmacotherapy is relatively high compared with most populations. Furthermore, the possibility exists that there could be differences in pharmacotherapy across fitness levels. However, individuals with the lowest fitness may be more likely than high-fit individuals to be receiving more pharmacotherapy, which would shift the data toward the null. This hypothesis is supported by the recent abstraction of medication data for 400 men in whom we found the prevalence of statin medication in the lowest fit groups to be 25%, compared with 20% in the moderate- and high-fit groups.

There is a steep inverse relation between fitness and mortality within this cohort of men with documented diabetes, and this association is independent of BMI or body fat percentage. These results suggest that clinicians should give increased attention to counseling for increasing activity and improving fitness in their patients with diabetes, not only as a means to improve weight control but also for the intrinsic benefits associated with increased cardiorespiratory fitness that are independent of weight.

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