Cardiorespiratory Fitness and Body Mass Index as Predictors of Cardiovascular Disease Mortality Among Men With Diabetes

Timothy S. Church, MD, MPH, PhD; Michael J. LaMonte, PhD; Carolyn E. Barlow, MS; Steven N. Blair, PED

Background: Questions remain as to whether higher levels of cardiorespiratory fitness, a measure of regular physical activity, are associated with lower risk of cardiovascular disease (CVD) mortality in overweight and obese individuals with diabetes. Our objective was to quantify the independent and joint relations of cardiorespiratory fitness (hereafter, fitness) and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) with CVD mortality in men with diabetes.

Methods: This study was conducted using prospective observational data from the Aerobics Center Longitudinal Study. Study participants comprised 2316 men with no history of stroke or myocardial infarction and who were diagnosed as having diabetes (mean [SD] age, 50 [10] years); had a medical examination, including a maximal exercise test during 1970 to 1997 with mortality surveillance to December 31, 1998; and had a BMI of 18.5 or greater and less than 35.0. The main outcome measure was CVD mortality across levels of fitness with stratification by BMI.

Results: We identified 179 CVD deaths during a mean (SD) follow-up of 15.9 (7.9) years and 36 710 man-years of exposure. In a model containing age, examination year, fasting glucose level, systolic blood pressure, parental history of premature CVD, total cholesterol level, cigarette smoking, abnormal resting, and exercise electrocardiograms, a significantly higher adjusted risk of mortality was observed in men with a low fitness level who were normal weight (hazard ratio, 2.7 [95% confidence interval, 1.3-5.7]), overweight (hazard ratio, 2.7 [95% confidence interval, 1.4-5.1]), and class 1 obese (hazard ratio, 2.8 [95% confidence interval, 1.4-5.1]) compared with normal weight men with a high fitness level.

Conclusion: In this cohort of men with diabetes, low fitness level was associated with increased risk of CVD mortality within normal weight, overweight, and class 1 obese weight categories.

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Rates of obesity and diabetes are at an all-time high among US adults, with current age-adjusted prevalence estimates of 31% and 8.6%, respectively.1,2 Both conditions are associated with increased risk of premature death from cardiovascular diseases (CVDs).3,4 Diabetes prevalence is 3- to 5-fold higher in obese than in normal weight individuals.5 Because the risk of major CVD events in patients with diabetes approaches that of those without diabetes with established CVD, diabetes has been designated a CVD risk equivalent.6 An expert panel recently indicated that convincing evidence supports physical activity and cardiorespiratory fitness (hereafter, fitness) as important independent determinants of mortality in overweight and obese individuals.7,9 Low levels of activity and fitness are also independently associated with increased mortality in individuals with diabetes.7,8,12 Previous reports from the Aerobics Center Longitudinal Study (ACLS) have consistently shown an inverse gradient of mortality rates across levels of fitness in normal weight, overweight, and class 1 obese weight categories.

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Little is known about the joint association of physical activity or fitness and obesity status with CVD mortality in individuals with diagnosed diabetes. We previously followed up 2196 men with diabetes for a mean of 14.6 years after a clinical examination that included a maximal exercise test.9 There were 275 all-cause deaths during 32 161 man-

Author Affiliations: The Cooper Institute, Dallas, Tex.
years of exposure. Normal weight, overweight, and obese men with diabetes and a low fitness level had a 4- to 5-fold higher risk of death compared with men with diabetes but with a higher fitness level and normal body weight. The number of CVD deaths was insufficient for meaningful analyses during this earlier study. A separate analysis among all men in the ACLS showed that a low fitness level was a strong independent predictor of CVD mortality, irrespective of body weight classification. The clinical relevance of a low fitness level in obese individuals with diabetes may be even more onerous with respect to CVD outcomes. The ACLS population has grown and mortality surveillance has been updated since our earlier study in men with diabetes. The primary aims of this study of men with diabetes were to examine (1) the risk of CVD mortality associated with fitness level and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters); (2) the dose-response relationship between categories of fitness and CVD mortality within levels of BMI; and (3) the shape of the fitness–CVD mortality curve when fitness is quantified by increments of maximal metabolic equivalents (METs).

METHODS

PARTICIPANTS

The ACLS is an ongoing epidemiology study composed of patients from the Cooper Clinic, Dallas, Tex. Participants for the current analysis were men aged 21 to 99 years who completed at least 1 clinical examination during 1970 to 1998, had no history of myocardial infarction or stroke, had a BMI of 18.5 or greater and less than 35.0, and for whom at least 1 year of follow-up was available. The upper BMI limit of 35.0 was used because (1) this marks the transition from class 1 to class 2 obesity, (2) there are a limited number of individuals with a BMI greater than 35.0 in the ACLS data set, and (3) most importantly, we did not want to use an open-ended BMI category that could lead to inaccurate generalizations over a wide BMI range (>35 in the ACLS data set). Personal and family health histories were obtained from a self-administered questionnaire. The dichotomous variables of abnormal resting electrocardiogram (ECG) and abnormal exercise ECG were determined by the patient's physician at the time of examination, and there are no data available related to specific abnormalities. However, anecdotally, as part of a limited in-house ECG review study, it was observed that most exercise ECGs labeled as abnormal were due to ST-segment depression. Parental history of premature CVD was defined as a parent who had a stroke or myocardial infarction before the age of 50 years. Cigarette smoking was defined as never smoked, past smoker, and current smoker based on self-report.

We assessed fitness with a symptom-limited maximal treadmill exercise test using a modified version of the protocol of Balke and Ware. Specific details on the treadmill speed and grade of each exercise stage are described elsewhere. The 12-lead ECG was monitored continuously during exercise testing. Patients were given verbal encouragement to reach maximal exertion, and the test was terminated when the men were exhausted or if the physician stopped the test for medical reasons. Exercise duration on this protocol is highly correlated (r=0.92) with measured maximal oxygen uptake. We quantified exercise capacity as maximal METs (1 MET=3.5 mL of oxygen uptake/kg·min−1) using a previously validated regression formula: [(1.44 × exercise duration in minutes) + 14.99] + 3.5. An antecubital venous blood sample was obtained and plasma concentrations of lipids and glucose were determined with automated bioassays in the Cooper Clinic laboratory that meets quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program. Resting blood pressure was measured with standard auscultatory methods. Personal and family health histories were obtained from the department of vital records in the deceased's state of residence. Cardiovascular disease mortality was defined as International Classification of Diseases, Ninth Revision codes 390.0 to 449.9. The mean (SD) duration of follow-up was 15.9 (7.9) years (range, 1-27.7 years), through which 179 CVD deaths were identified during 36,710 man-years of exposure.

CLINICAL EXAMINATION

The comprehensive health evaluation was completed following an overnight fast and is described in detail elsewhere. Briefly, BMI was computed from measured height and weight. An antecubital venous blood sample was obtained and plasma concentrations of lipids and glucose were determined with automated bioassays in the Cooper Clinic laboratory that meets quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program. Resting blood pressure was measured with standard auscultatory methods. Personal and family health histories were obtained from a self-administered questionnaire. The dichotomous variables of abnormal resting electrocardiogram (ECG) and abnormal exercise ECG were determined by the patient's physician at the time of examination, and there are no data available related to specific abnormalities. However, anecdotally, as part of a limited in-house ECG review study, it was observed that most exercise ECGs labeled as abnormal were due to ST-segment depression. Parental history of premature CVD was defined as a parent who had a stroke or myocardial infarction before the age of 50 years. Cigarette smoking was defined as never smoked, past smoker, and current smoker based on self-report.

STATISTICAL ANALYSES

Descriptive statistics were used to summarize baseline characteristics based on survival status. Continuous variables were compared using the unpaired, 2-tailed t test, and categorical variables were compared using the χ2 test. Cox proportional hazard models were used to assess the association between CVD mortality and fitness in METs, BMI, fasting glucose level, systolic blood pressure, parental history of premature CVD, total cholesterol level, cigarette smoking, abnormal resting, and exercise ECGs.

Fitness was defined categorically as low (lowest 20%), moderate (middle 40%), or high (upper 40%) of the previous published age-specific distribution of maximal exercise duration from the ACLS population. Body mass index was categorically defined as normal weight (18.5-24.9), over-
The cohort of men with diabetes had 179 cardiovascular disease deaths during 36,709 man-years of observation. A, Survival rates by body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) categories of normal weight (BMI, 18.5-24.9), overweight (25.0-29.9), and class 1 obese (BMI, 30.0-34.9). B, Survival rates for the low-, moderate-, and high-fit categories. C, Survival curves for combinations of fitness and BMI. The moderate- and high-fit groups are combined to form the fit group. The overweight group and the obese groups are combined. The resulting 4 fitness-BMI groups are (1) fit-normal weight, (2) fit-overweight/obese, (3) low-fit (least fit 20%)-normal weight, and (4) low-fit-overweight/obese.

The mean age of the study participants was 50 (10) years, and the mean BMI was 26.8 (3.4). The prevalence of normal weight, overweight, and class 1 obesity was 32.3%, 47.7%, and 20.0%, respectively. Decedents were older and had lower exercise capacity and less favorable cardiovascular risk factor profiles at baseline compared with survivors (Table 1). Survival curves for CVD mortality by BMI categories, high fitness categories, and the 4 fitness-BMI groups are shown in the Figure.

In a multivariable model after adjusting for age and examination year, an HR (95% CI) of 1.2 (1.10-1.32) for CVD mortality was associated with each incremental

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**Table 1. Baseline Characteristics of 2316 Men With Diabetes Grouped by Survival Status (Aerobics Center Longitudinal Study, 1970-1997)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors (n = 2137)</th>
<th>CVD Mortality (n = 179)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man-years of observation</td>
<td>34,487</td>
<td>2222</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>49.6 (9.9)</td>
<td>56.0 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.9 (3.4)</td>
<td>27.0 (3.2)</td>
<td>.70</td>
</tr>
<tr>
<td>Maximal METs obtained, METs</td>
<td>10.4 (2.1)</td>
<td>8.9 (2.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cholesterol level, mg/dL</td>
<td>225.1 (43.7)</td>
<td>233.4 (48.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Fasting glucose level, mg/dL</td>
<td>134.4 (48.9)</td>
<td>146.3 (60.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>126.5 (15.6)</td>
<td>133.4 (16.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>83.5 (9.9)</td>
<td>85.6 (11.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>35.8</td>
<td>28.0</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>44.0</td>
<td>48.6</td>
<td>.10</td>
</tr>
<tr>
<td>Current</td>
<td>20.2</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>30.4</td>
<td>49.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parental history of premature CVD, %</td>
<td>14.1</td>
<td>21.0</td>
<td>.003</td>
</tr>
<tr>
<td>Abnormal resting ECG, %</td>
<td>8.0</td>
<td>22.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abnormal exercise ECG, %</td>
<td>11.8</td>
<td>36.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; CVD, cardiovascular disease; ECG, electrocardiogram; MET, metabolic equivalent.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert glucose to millimoles per liter, multiply by 0.0555.

*Unless otherwise indicated, values are presented as mean (SD).
1-MET difference in fitness (Table 2). The only other predictors with CVD mortality risk were fasting glucose level (per 10-mg/dL increment: HR, 1.04 [1.02-1.06]), systolic blood pressure (per 10-mm Hg increment: HR, 1.10 [1.01-1.19]), and abnormal exercise ECG (2.2 [1.55-3.09]). Conversely, the HR of mortality associated with each 1-U increment in BMI was 1.00 (0.95-1.05).

We next examined the joint association of fitness level and BMI of CVD mortality (Table 3). Because of the small number of individuals in the high-fit–obese category, this group was combined with the moderate-fit–obese group, resulting in 8 fitness-fatness groups. The prevalence of a moderate to high fitness level was lower in overweight men (69%) and class 1 obese men (45%) than in the normal weight men (84%), but many overweight or class 1 obese men were at least moderately fit. It is worth noting that the death rates in the overweight or class 1 obese men with a moderate or high fitness level were less than one half of the death rates in the overweight or class 1 obese men with a low fitness level. A significantly higher age and examination year adjusted risk of mortality was observed in men with a low fitness level who were normal weight (HR, 4.2 [95% CI, 2.0-8.6]), overweight (HR, 4.3 [95% CI, 2.30-7.9]), and class 1 obese (HR, 4.5 [95% CI, 2.3-8.7]) compared with normal weight men with a high fitness level. Additional adjustment for fasting glucose level, systolic blood pressure, parental history of premature CVD, total cholesterol level, cigarette smoking, abnormal resting, and exercise ECGs attenuated the CVD mortality risk associated with a low fitness level. For example, the HR (95% CI) of CVD mortality for the low-fit men who were normal weight, overweight, and class 1 obese decreased to 2.7 (1.3-5.7), 2.7 (1.4-5.1), and 2.8 (1.4-5.6), respectively, in the fully adjusted model. Despite being class 1 obese, the individuals in the combined moderate–high-fit group were statistically at no higher risk for CVD mortality compared with the high-fit–normal weight group.

To further examine the dose-response characteristics between fitness levels and CVD mortality in our population of men with diabetes, we computed the HR of mortality for categories of fitness defined by increments of 1 MET across the range of 7 to 13 METs (Table 4). Men with an exercise capacity of 9.0 to 9.9 METs were the reference group. In analysis adjusted for age and examination year, an exercise capacity less than 9 METs was associated with higher CVD mortality risk, whereas MET levels of 9 and greater had similar mortality risk (P value for trend, <.001). Additional adjustment for fasting glucose level, systolic blood pressure, parental history of premature CVD, total cholesterol level, cigarette smoking, and abnormal resting and exercise ECGs attenuated many of the HRs, but the pattern remained similar and the P value for trend remained highly significant (P<.001).

We previously reported that a low fitness level is strongly associated with higher risk of all-cause mortality in men with diabetes and that this relation is evident

### Table 2. Age- and Examination Year–Adjusted Hazard Ratios (HRs) of CVD Death (n = 179) According to Exercise Capacity, BMI, and Other Clinical, Health Status, and Lifestyle Variables for 2316 Men With Diabetes, Aerobics Center Longitudinal Study, 1970-1997

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal METs obtained (per 1-MET increment)</td>
<td>1.20 (1.10-1.32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (per 1-unit increment)</td>
<td>1.00 (0.95-1.05)</td>
<td>.90</td>
</tr>
<tr>
<td>Fasting glucose (per 10-mg/dL increment)</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP (per 10-mm Hg increment)</td>
<td>1.10 (1.01-1.19)</td>
<td>.04</td>
</tr>
<tr>
<td>Parental history of premature CVD</td>
<td>1.72 (1.20-2.50)</td>
<td>.004</td>
</tr>
<tr>
<td>Total cholesterol level (per 10-mg/dL increment)</td>
<td>1.02 (0.98-1.05)</td>
<td>.33</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1.05 (0.73-1.49)</td>
<td>.80</td>
</tr>
<tr>
<td>Current</td>
<td>1.26 (0.82-1.95)</td>
<td>.29</td>
</tr>
<tr>
<td>Abnormal resting ECG</td>
<td>1.32 (0.90-1.92)</td>
<td>.16</td>
</tr>
<tr>
<td>Abnormal exercise ECG</td>
<td>2.2 (1.55-3.09)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; ECG, electrocardiogram; HR, hazard ratio from Cox proportional hazard models; METs, metabolic equivalents (1 MET = 3.5 mL of oxygen uptake/kg−1 per minute−1).

Within normal weight, overweight, and obese subgroups of our population. The present study expands on these findings by using additional follow-up and mortal events to verify that higher levels of fitness are inversely related to CVD mortality in normal weight, overweight, and class 1 obese men with diabetes. Specifically, we found that men who are overweight or class 1 obese but are at least moderately fit have lower CVD mortality risk compared with men who are normal weight but unfit. Equally important, and perhaps contrary to conventional wisdom, we did not observe higher CVD mortality risk in overweight or obese men once their level of fitness was taken into account. Strengthening the public health importance of our findings, we observed that 69% of overweight and 45% of class 1 obese men with diabetes were at least moderately fit, which provides further evidence that avoiding the low-fitness category is a reasonable and obtainable goal for overweight and obese individuals. Previous work from our cohort has shown that men categorized as having moderate fitness reported a mean of 130 minutes of physical activity. The volume of physical activity is in accord with current recommendations for individuals with diabetes and for individuals who are overweight or obese. Thus, avoiding low levels of fitness is an obtainable goal for most people.

Though fitness has a genetic component (25%-40%), it is clear that regular physical activity is the major determinant of fitness. This is supported by numerous randomized and controlled studies showing that exercise training improves fitness and that bed rest reduces fitness. In the present study we found that 77% and 46% of men in the high-fit and moderate-fit groups, respectively, reported participating in regular physical ac-
...and exercise electrocardiograms. The primary aim of the present report is not to diminish the importance of weight control for individuals with diabetes but rather to emphasize the health benefits of regular physical activity and adequate fitness, which appear to be independent of body weight. It is well known that physical activity counseling is underused in the clinical setting, even in high-risk populations such as individuals with diabetes. Our present results extend our previous observations and provide further evidence of an intrinsic value in encouraging patients of any weight to be physically active as a means of reducing mortality risk. However, if weight loss is a goal, there is substantial evidence that regular physical activity is a critical component of long-term weight loss. Thus, whether overall health, weight loss, or both are the clinical goals, regular physical activity should be the foundation of the clinical treatment plan and counseling.

Given the central role that skeletal muscle plays in glucose homeostasis and insulin resistance and the well-established role of regular aerobic exercise in improving glycemic control, the importance of avoiding a sedentary lifestyle and a low fitness level by individuals with diabetes cannot be overstated. Further, compared with sedentary individuals, those who are physically active have been shown to have lower blood pressure, better lipid profiles including particle sizes, reduced visceral fat at a given weight, lower markers of systemic inflammation, better cardiac function, healthier blood vessels, and higher heart rate variability, all of which may be particularly important in the high CVD risk condition of diabetes. Thus, the mechanisms responsible for the reduced CVD mortality risk in individuals...
with diabetes that are associated with maintaining at least moderate levels of fitness are likely to be complex and multifactorial.

As a note of caution, it stands to reason that there is a level of obesity at which the benefits of more physical activity or higher levels of fitness do not overcome risks and conditions associated with excess body fat. We do not yet have sufficient data in individuals with a BMI of 35.0 or greater to evaluate whether a moderate to high fitness level is associated with lower mortality risk in those with class 2 or 3 obesity.

The predominantly white, well-educated, middle to upper class, male subject group limits the ability to generalize the results of our study but should not affect the internal validity. However, there is no compelling reason to assume that the benefits of moderate and high fitness levels would be any less in women or other ethnic groups. The lack of information on medication use prevents the evaluation of medications as a possible effect modifier. For example, the possibility exists that there could be differences in pharmacotherapy across fitness levels. 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. However, the observation was that the lowest-fit individuals may be more likely than high-fit individuals to be receiving more pharmacotherapy, which would shift the data toward the null, further strengthening our findings.

There is an inverse relation between fitness and CVD mortality within this cohort of men with diabetes, and this association is independent of BMI. These results further reinforce that medical care providers should give increased attention to counseling for increasing activity and improving fitness in their patients with diabetes, both for the intrinsic benefits associated with increased fitness and for the critical role regular physical activity plays in long-term weight loss and maintenance.

CONCLUSIONS

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Correspondence: Timothy S. Church, MD, MPH, PhD, The Cooper Institute, 12330 Preston Rd, Dallas, TX 75230 (tchurch@cooperinst.org).
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REFERENCES


Correction

Error in Figure Labels. In the Original Investigation by McClung et al titled “Opposite Bone Remodeling Effects of Teriparatide and Alendronate in Increasing Bone Mass,” published in the August 8, 2005, issue of the ARCHIVES (2005;165:1762-1768), the labels in the figure key for Figure 3 on page 1765 should have been switched. The circle indicates the Alendronate Group; the triangle, the Teriparatide Group. Also on the same page in Figures 2 and 3 the labels “Area/DXA” should have been “Integral DXA.”