# BMI–Mortality Paradox and Fitness in African American and Caucasian Men With Type 2 Diabetes

Peter Kokkinos, phd<sup>1,2,3</sup> Jonathan Myers, phd<sup>4,5</sup> Charles Faselis, md<sup>1,3</sup>

Michael Doumas, md<sup>1</sup> Raya Kheirbek, md<sup>1</sup> Eric Nylen, md<sup>1,3</sup>

**OBJECTIVE**—To assess the association between BMI, fitness, and mortality in African American and Caucasian men with type 2 diabetes and to explore racial differences in this association.

**RESEARCH DESIGN AND METHODS**—We used prospective observational data from Veterans Affairs Medical Centers in Washington, DC, and Palo Alto, California. Our cohort (N = 4,156; mean age 60 ± 10.3 years) consisted of 2,013 African Americans (mean age, 59.5 ± 9.9 years), 2,000 Caucasians (mean age, 60.8 ± 10.5 years), and 143 of unknown race/ethnicity. BMI, cardiac risk factors, medications, and peak exercise capacity in metabolic equivalents (METs) were assessed during 1986 and 2010. All-cause mortality was assessed across BMI and fitness categories.

**RESULTS**—There were 1,074 deaths during a median follow-up period of 7.5 years. A paradoxic BMI–mortality association was observed, with significantly higher risk among those with a BMI between 18.5 and 24.9 kg/m<sup>2</sup> (hazard ratio [HR] 1.70 [95% CI 1.36–2.1]) compared with the obese category (BMI  $\geq$ 35 kg/m<sup>2</sup>). This association was accentuated in African Americans (HR 1.95 [95% CI 1.44–2.63]) versus Caucasians (HR 1.53 [1.0–2.1]). The fitness–mortality risk association for the entire cohort and within BMI categories was inverse, independent, and graded. Mortality risks were 12% lower for each 1-MET increase in exercise capacity, and ~35–55% lower for those with an exercise capacity >5 METs compared with the least fit ( $\leq$ 5 METs).

**CONCLUSIONS**—A paradoxic BMI–mortality risk association was observed in African American and Caucasian patients with diabetes. The exercise capacity–mortality risk association was inverse, independent, and graded in all BMI categories but was more potent in those with a BMI  $\geq 25 \text{ kg/m}^2$ .

#### Diabetes Care 35:1021–1027, 2012

**O** besity is now a major health issue in the U.S., adversely affecting nearly all the major coronary heart disease risk factors, including type 2 diabetes mellitus (DM) (1,2). Recent evidence from large epidemiologic studies support a significantly higher mortality risk only in individuals with a relatively low BMI, with no excess risk associated with obesity observed in some populations (3). Others have reported reductions in mortality risk among overweight or obese subjects, a puzzling observation that has

been termed the *obesity paradox* (4–6). This paradoxic relationship appears to occur in only particular clinical populations, such as heart failure, the elderly, or patients referred for exercise testing for clinical reasons (1,2,4–6). Recent evidence from a large cohort of Asian subjects also suggests that the obesity paradox may be related to socioeconomics, ethnicity, or both. Higher BMI was associated with greater risk among East Asian subjects (3).

From the <sup>1</sup>Cardiology Department, Veterans Affairs Medical Center, Washington, DC; the <sup>2</sup>Georgetown University School of Medicine, Washington, DC; <sup>3</sup>The George Washington University School of Medicine and Health Sciences, Washington, DC; the <sup>4</sup>Cardiology Division, Veterans Affairs Palo Alto Health Care System, Palo Alto, California; and <sup>5</sup>Stanford University, Stanford, California.

Obesity often coexists in individuals with type 2 DM; however, the association between BMI and mortality risk is less clear in this population. For example, no such association was found in the large United Kingdom Prospective Diabetes Study (UKPDS) (7). In contrast, in the Translating Research Into Action for Diabetes (TRIAD) study (8), higher mortality rates were only reported in those with a BMI  $<26 \text{ kg/m}^2$  compared with overweight individuals (BMI 26-29.9 kg/m<sup>2</sup>). A V-shaped association was observed in a Chinese cohort (9) and a U-shaped association in a large Ukrainian cohort (10).

Increased physical activity patterns and higher exercise capacity are associated with lower mortality in nondiabetic (11–14) and diabetic individuals (15–18). This reduction in mortality occurs in proportion to the level of fitness and is independent of BMI (15–18). We recently reported an inverse and graded association between exercise capacity and mortality risk in men with type 2 DM. The association was stronger and more graded in Caucasians compared with African Americans (18).

Collectively, the aforementioned studies suggest that the BMI–mortality association in individuals with type 2 DM is not well defined. Moreover, the role of fitness in this association and possible racial differences has not been adequately addressed. Therefore, in the current study, we sought to assess the relationship between adiposity, exercise capacity, and all-cause mortality in African American and Caucasian male veterans with type 2 DM.

### RESEARCH DESIGN AND METHODS

#### **Participants**

Between 1986 and 2010, symptom-limited exercise tolerance tests (ETT) were performed on more than 20,000 veterans at the Veterans Affairs Medical Centers (VAMCs) in Washington, DC, and Palo Alto, California, as part of routine evaluations or to assess exercise-induced ischemia. This information, along with the

Corresponding author: Peter Kokkinos, peter.kokkinos@med.va.gov.

Received 11 December 2011 and accepted 27 January 2012.

DOI: 10.2337/dc11-2407

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individual's medical history, was electronically stored. From this cohort, we identified those with type 2 DM, defined by ICD coding. We excluded women and those with any of the following: 1) history of an implanted pacemaker, 2) left bundle branch block, 3) unable to complete the test, 4) BMI  $< 18.5 \text{ kg/m}^2$ , 5) impaired chronotropic response; and 6) those with AIDS or HIV. After these exclusions, the participant group (n = 4,156) consisted of 2,013 African Americans, mean age (years  $\pm$  SD) 59.6  $\pm$  10; 2,000 Caucasians,  $60.8 \pm 10$ ; and 143 unknown races,  $58.4 \pm 11$ . The institutional review board at each institution approved the study, and all subjects gave written informed consent before undergoing ETT.

All demographic, clinical, and medication information was obtained from the subject's computerized medical records just before their ETT and verified by each individual. A standardized scale was used to assess body weight (kg) and height (m), and BMI was calculated as kg/m<sup>2</sup>. Demographic data are included in Table 1.

Dates of death were verified from the VA Beneficiary Identification and Record Locator System File. This system is used to determine benefits to survivors of veterans and has been shown to be 95% complete and accurate (19). Vital status was determined as of 28 December 2010.

#### **Exercise assessments**

Exercise capacity was assessed by a standard treadmill test using the Bruce protocol at the VAMC, Washington, DC, and by an individualized ramp protocol, as described elsewhere (20), for men assessed at the VAMC, Palo Alto, California. Peak exercise capacity in metabolic equivalents (METs) was estimated using standardized equations based on peak speed and grade for the ramp protocol (20) and on peak exercise time for the Bruce protocol (21). Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping (22). Medications were not altered before testing.

### Determination of BMI and fitness categories

Individuals were classified according to four predetermined BMI categories adopted by the American Heart Association as indicators of adiposity (23): BMI 18.5–24.9 (normal weight; n = 668); 25–29.9 (overweight; n = 1,610); 30–34.9 (obese I; n = 1,160) and  $\geq 35 \text{ kg/m}^2$  (obese II and III; n = 718).

We also formed four fitness categories based on the MET level achieved. Those who achieved a peak MET level  $\leq$ 5METs (lowest 25th percentile of the cohort) comprised the lowest fitness category (Least-Fit; *n* = 1,162); those with a peak MET level of 5.1–7.0 (26th to 50th percentile) comprised the moderate fit category (Moderate-Fit; *n* = 1,163); those with a peak MET level of 7.1–8.7 (51st to 75th percentile) comprised the fit category (Fit; *n* = 995), and those with a peak MET level >8.7 (>75th percentile), comprised the highest fit category (High-Fit; *n* = 836).

To further explore the effect of fitness on mortality risk, we formed two groups within each fitness category (a total of eight) based on the presence (fitness category/risk factors) or absence of additional risk factors (fitness category/no additional risk factors).

#### Statistical analysis

Follow-up time is presented as mean  $\pm$  SD and median years. Mortality rate was

#### Table 1—Demographic and clinical characteristics according to BMI categories

	BMI categories						
	Entire cohort	18.5–24.9	25.0-29.9	30-34.9	>35	Р	
Participants (n)	4,156	668	1,610	1,160	718	—	
Age (years)	$60.0 \pm 10.3$	$61.2 \pm 11.0$	$61.4 \pm 10$	$59.6 \pm 9.9$	$57.0 \pm 9.4$	< 0.001	
Weight (kg)	$93.1 \pm 18.3$	$71.6 \pm 7.9$	$85.5 \pm 8.1$	$99.7 \pm 9.5$	$119.5 \pm 16.2$	< 0.001	
$BMI(kg/m^2)$	$30.0 \pm 5.5$	$22.9 \pm 1.5$	$27.4 \pm 1.4$	$32.2 \pm 1.3$	$39.1 \pm 4.1$	< 0.001	
Resting heart rate (bpm)	$75 \pm 14$	$74 \pm 14$	$75 \pm 14$	$76 \pm 14$	$77 \pm 13$	0.001	
Resting blood pressure							
Systolic (mmHg)	$134 \pm 21$	$135 \pm 23$	$134 \pm 22$	$134 \pm 21$	$132 \pm 19$	0.14	
Diastolic (mmHg)	$79 \pm 12$	$77 \pm 12$	$78 \pm 12$	$79 \pm 12$	$80 \pm 12$	0.08	
Peak MET*	$6.8 \pm 2.6$	$7.2 \pm 3.1$	$7.1 \pm 2.7$	$6.7 \pm 2.4$	$6.3 \pm 1.9$	0.001	
African American	48.5	40.7	47.6	51.3	53.1	0.001	
Caucasian	48.1	54.2	48.4	46.1	45.0	0.001	
CVD	34.9	34.1	35.5	35.6	33.1	0.65	
Family history of CVD	15.9	18.6	15.4	16.4	13.5	0.068	
Smoking	31.7	31.1	32.2	30.5	33.1	0.62	
Dyslipidemia	39.5	30.7	37.1	44.4	45.4	< 0.001	
Hypertension	70	57	66.6	76.6	79.2	< 0.001	
<b>β</b> -Blocker	19.4	14.2	17.6	22.7	22.9	0.001	
Calcium channel blocker	21.2	19	21.6	21.5	21.9	0.50	
ACE-I/ARBs	34	20.1	33.2	37.2	43.6	< 0.001	
Diuretics	16	9.4	12.7	18.9	24.5	< 0.001	
Vasodilators	9.4	13.2	10.4	7.7	6.4	< 0.001	
Statins	18.4	8.8	15.9	22.9	25.8	< 0.001	
Insulin	27.6	23.3	26.4	29.9	26.0	0.38	
Oral hypoglycemic agents	39.1	35.9	40	37.7	42.8	0.175	

Continuous data are presented as mean  $\pm$  SD and categoric data as percentage. *P* values are for trend. \*1 MET = 3.5 mL O<sub>2</sub>/kg/min.

calculated as the ratio of events by the person-years of observation. Continuous variables are presented as mean (SD) values and categoric variables as relative frequencies (%). Baseline associations between categoric variables were tested using  $\chi^2$ analysis. One-way ANOVA was applied to evaluate mean differences between age and BMI among fitness categories. Post hoc procedures (Bonferroni) were performed for multiple comparisons. Equality of variances between groups was tested by Levene's test.

The hazard ratio (HR) for all-cause mortality was calculated for each BMI and fitness category using Cox proportional hazard models. For BMI categories, individuals with a BMI  $\geq$  35 kg/m<sup>2</sup> (lowest mortality group) comprised the reference group. For fitness categories, individuals with an exercise capacity  $\leq 5$  MET were considered the Least-Fit and comprised the reference group. The analyses were adjusted for age, history of cardiovascular disease (CVD), cardiovascular medications (ACE-I, angiotensin receptor blockers [ARBs],  $\beta$ -blockers, calcium channel blockers, diuretics, vasodilators, statins), race, and risk factors (hypertension, dyslipidemia, smoking) and (when appropriate) METs and BMI. Cox proportional hazard models were also used to assess risk among the eight fitness and risk-factor categories. These analyses were adjusted for age, CVD, and cardiovascular medications, as above, and the Least-Fit and no additional risk factors category comprised the reference group. The assumption of proportionality for all Cox proportional hazard analyses was graphically tested and fulfilled the criteria. Values of P <0.05 using two-sided tests were considered statistically significant. All statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL).

**RESULTS**—The median follow-up period was 7.5 years (3.3, 7.5, and 11.8 for 25th, 50th and 75th percentiles), comprising 33,112 person-years. There were 1,074 deaths (25.8%), with an average annual mortality of 32.4 events per 1000 person-years of observation. There was no interaction between site-by-METs (P = 0.51), race-by-fitness categories (P = 0.14), or race-by-BMI categories (P = 0.16), and therefore, the data were not stratified by site or race.

Demographic and clinical characteristics for the entire cohort and BMI categories are presented in Table 1. Within BMI categories, body weight, resting heart

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rate, prevalence of dyslipidemia and hypertension, the use of  $\beta$ -blockers, ACE/ ARB-I, diuretics, and statins were progressively greater when moving from the normal BMI category (18.5–24.9 kg/m<sup>2</sup>) to the highest BMI category ( $\geq$ 35 kg/m<sup>2</sup>). Conversely, age and the use of vasodilators were progressively lower.

## Predictors of all-cause mortality across fitness and BMI categories

Multivariate Cox proportional hazards analysis revealed that age (HR 1.04 [95% CI 1.03–1.05]); hypertension (1.42 [1.2– 1.6]), smoking (1.34 [1.1–1.5]), BMI (0.96 [0.95–0.97]), and exercise capacity were strong predictors of mortality. The adjusted mortality was reduced by 12% for every 1-MET increase (0.88 [0.85–0.90]) for the entire cohort. Within each BMI category, the mortality risks per 1-MET increases were 11% lower (0.89 [0.85-0.94]) for those with BMI of 18.5 to 24.9 kg/m<sup>2</sup>, and 14% lower (0.86 [0.83-0.90]) for individuals with a BMI of 25 to 29.9 kg/m<sup>2</sup>. The mortality risks were 18% lower per MET for the two highest BMI groups (BMI 30-34.9 [0.82 (0.76-0.88)] and BMI  $\geq$  35 kg/m<sup>2</sup> [0.82 (0.74–0.91)]).

Mortality risk for the entire cohort was significantly higher (39.7%) among those in the lowest BMI group (BMI < 25kg/m<sup>2</sup>) and declined progressively to 27.3%, 21.6%, and 16.6% for the next three BMI groups, respectively (P <0.001 for all comparisons). Similar patterns were observed in African Americans and Caucasians. However, mortality in African Americans in the lowest BMI category (BMI  $<25 \text{ kg/m}^2$ ) was substantially higher than in Caucasians (45.6% vs. 35.6%, respectively; P = 0.01). The risk for individuals of unknown race was not considered because of the small number of participants (n = 141).

## Mortality risk according to BMI categories

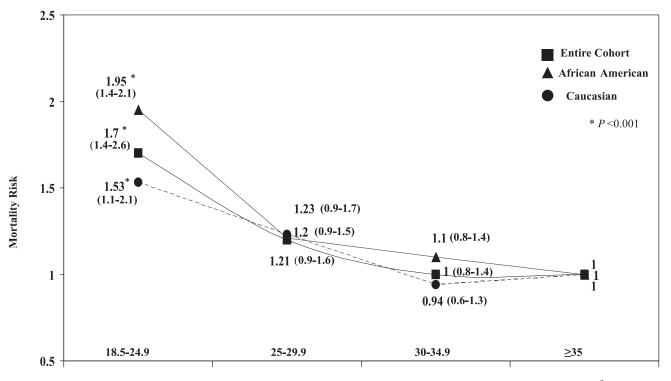
The fully adjusted Cox proportional hazards model for the entire cohort revealed a paradoxic association between BMI categories and mortality, with significantly higher risk among those with a BMI between 18.5 and 24.9 (HR 1.70 [95% CI 1.36–2.1]) compared with those with BMI  $\geq$ 35 kg/m<sup>2</sup>. No significant increase in risk was noted for the remaining BMI categories (Fig. 1). When mortality risk was assessed for African Americans and Caucasians separately, the HR was 1.95 (1.44–2.63) for African Americans in the BMI group 18.5–24.9 kg/m<sup>2</sup> and 1.53 (1.0–2.1) for Caucasians, with no significant change in mortality risk for the remaining BMI categories (Fig. 1). To partially account for reverse-causation, we excluded those with an exercise capacity  $\leq$ 5 METs who died within the initial 2 years of follow-up and repeated the analysis. The trend was similar, with a mortality risk of 1.67 (95% CI 1.32–2.1) for the entire cohort, 1.83 (1.34–2.51) for African Americans, and 1.49 (1.0–2.1) for Caucasians in the BMI group 18.5–24.9 kg/m<sup>2</sup> (data not shown).

## Mortality risk according to fitness categories

HRs across fitness categories for the entire cohort and each BMI category are presented in Table 2. The adjusted mortality risks for the four fitness categories are shown, with those in the Least-Fit category ( $\leq 5$  MET) as the reference group. For the entire cohort in the fully adjusted model, the mortality risk was progressively lower as exercise capacity increased, such that the moderately fit and most fit categories had ~50% reductions in risk (P < 0.001 for trend). Similarly, the adjusted risks in each BMI category were progressively lower with increased exercise capacity, ranging between 23 and 67% (Table 2). We observed similar trends when we repeated the analyses for African Americans and Caucasians separately, for those with and without CVD, and when we excluded those with low exercise capacity ( $\leq 5$ METs) who died within the initial 2 years of follow-up (Table 2).

We then assessed possible differences in mortality risk between individuals with additional risk factors compared with those without, for each fitness category. We used the Least-Fit category and no risk factors (Least-Fit/no additional risk factors) as the reference group, adjusting for age, BMI, race, CVD, and cardiac medications. The findings, illustrated in Fig. 2, revealed the following: 1) the mortality risk was significantly higher for those in the Least-Fit category with one or more risk factors (HR 1.50 [95% CI 1.17-1.93]; P = 0.001; 2) there was no difference in risk for individuals in the next fitness category (Moderate-Fit) with risk factors  $(0.98 \ [0.75-1.28]; P = 0.88)$ , but was 34% lower in those in this category with no risk factors (0.66 [0.47-0.87]; P = 0.04); and 3) in the two highest fit categories, the risk was similar for those with additional risk factors but substantially lower for individuals in the highest fit

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**Figure 1**—Adjusted mortality risk (95% CI) according to BMI categories. \*Different from the highest BMI category ( $\geq$ 35 kg/m<sup>2</sup>).

category (>8.8 METs) and no additional risk factors (0.37 [0.23–0.60]).

**CONCLUSIONS**—In the current study, we assessed the interrelationships between BMI, exercise capacity, and all-cause mortality in African American and Caucasian male veterans with type 2 DM. We observed a significantly higher mortality risk (70%) in those with BMI within the normal range (18.5–24.9 kg/m<sup>2</sup>) versus heavier subjects, a phenomenon that has

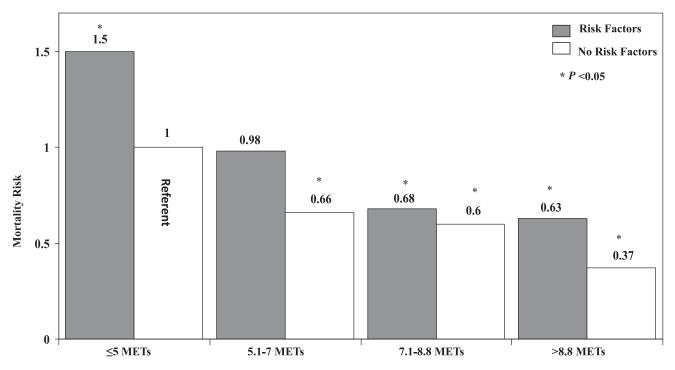
been termed the *obesity paradox* (1,3–6). This paradoxic association was evident in both races, with a substantially higher mortality rate in African Americans (95%) than Caucasians (53%).

Although the reasons for this paradoxic association are not clear, incomplete control for confounding or reverse causation bias could be partly involved. In an effort to control for reverse-causation, we excluded individuals with an exercise capacity  $\leq 5$  METs who died within the initial 2 years of follow-up and repeated the analysis. The trend remained similar, with a mortality risk of 67% (P < 0.001) in the normal BMI category versus the obese group for the entire cohort, 83% for African Americans (P < 0.001), and 49% (P < 0.03) for Caucasians. A plausible explanation for the relatively higher mortality rates observed in African Americans may be racial differences in the pathophysiology of insulin resistance. African Americans exhibit higher

Table 2—Adjusted HRs	for	• mortality	risk	according	to	exercise	capacity*

Groups	n	≤5 METs (25%)	5.1–7.0 METs (21–50%)	7.1–8.7 METs (51–75%)	>8.7 METs (>75%)	Р
Entire cohort	4,156	Referent	0.65 (0.56–0.76)	0.49 (0.40–0.59)	0.44 (0.35–0.55)	< 0.001
African Americans	2,013	Referent	0.68 (0.51-0.76)	0.52 (0.40-0.66)	0.41 (0.28-0.59)	< 0.001
Caucasians	2,000	Referent	0.63 (0.50-0.80)	0.41 (0.31-0.55)	0.48 (0.36-0.64)	< 0.001
BMI: 18.5–24.9	668	Referent	0.59 (0.42-0.82)	0.60 (0.42-0.85)	0.51 (0.35-0.74)	< 0.001
BMI: 25.0–29.9	1,610	Referent	0.77 (0.61-0.97)	0.44 (0.32-0.59)	0.41 (0.29-0.58)	< 0.001
BMI 30–34.9	1,160	Referent	0.62 (0.46-0.83)	0.40 (0.27-0.59)	0.33 (0.19-0.59)	< 0.001
BMI ≥35	718	Referent	0.45 (0.29-0.70)	0.61 (0.36-1.0)	0.38 (0.16-0.90)	0.001
CVD	1,450	Referent	0.73 (0.60-0.89)	0.45 (0.34-0.59)	0.49 (0.33-0.73)	< 0.001
No CVD	2,706	Referent	0.56 (0.44-0.70)	0.50 (0.39-0.64)	0.40 (0.30-0.52)	< 0.001
Excluding those with an exercise capacity ≤5 METs who died within the initial 2 years of follow-up		Referent	0.75 (0.64–0.87)	0.58 (0.48–0.70)	0.56 (0.45–0.70)	<0.001

Data are HR (95% CI). P values are for trend. \*Adjusted for age, β-blockers, calcium channel blockers, ACE-I, ARBs, diuretics, statins, hypertension, history of smoking, history of CVD, race, and dyslipidemia.



**Figure 2**—Adjusted mortality risk within each fitness category for diabetic individuals with and without additional risk factors. \*Different from lowest fit category ( $\leq 5$  METs) with no additional risk factors.

rates of insulin resistance and diabetes (24,25) that cannot be explained by differences in body weight or body composition (26), are more prone to the deleterious effects of stress hormones (27), and have higher perceived stress levels compared with Caucasians (27). Finally, weight loss as a result of occult diseases associated with muscle wasting cannot be excluded (28).

Our findings of increased mortality only in those with BMI  $< 25 \text{ kg/m}^2$  are in accord with those reported by the TRIAD study (8), but do not support a V-shaped or U-shaped BMI-mortality associations reported recently (9,10). Nevertheless, the higher mortality rate in the lower BMI category is a common finding in diabetic (8-10) and nondiabetic populations (3–6) and deserves further consideration. Our finding of substantially higher mortality rates in African American patients with diabetes compared with Caucasians in those with BMI  $<25 \text{ kg/m}^2$  also adds another factor to the already perplexing BMI-mortality association and may partly explain the inconsistencies in this association reported by previous studies (7-10). Further exploration of the interaction between fitness and ethnicity and the obesity paradox is warranted.

Regarding the fitness–BMI–mortality interaction, we found that exercise capacity was an independent and powerful

predictor of risk for all-cause mortality among diabetic individuals regardless of BMI levels. After adjusting for cardiac medications and traditional CVD risk factors, the overall mortality risk was 12% lower for every 1-MET increase in exercise capacity. This varied within each BMI category, with substantially greater reductions in risk (18%) observed for individuals in the two highest BMI categories. When mortality risk was considered within fitness categories, we observed a graded association between mortality risk and exercise capacity. Specifically, for the entire cohort, when compared with the Least-Fit category, the risk was 35% lower for those in the Moderate-Fit category and 50% lower for individuals in the two fittest categories. The trend was similar within each BMI category (Table 2).

In general, these findings are in accord with previous reports that show associations between fitness and mortality risk in apparently healthy individuals (11) and in those with CVD (14,29), hypertension (30), and DM (15–18) and extend previous reports of an inverse exercise capacity–mortality association in individuals with type 2 DM. In addition, the current study adds to the existing body of literature in that we assessed the effect of exercise capacity on mortality risk in patients with diabetes burdened by additional risk factors. In this regard, the Least-Fit individuals with no risk factors (reference group) were compared with those with and without risk factors within each fitness category. The findings (Fig. 2) support the following conclusions: First, the mortality risk for individuals in the Least-Fit category with one or more risk factors was 50% higher compared with the Least-Fit individuals with no additional risk factors. Second, the increased risk observed in individuals with additional risk factors was virtually eliminated (HR 0.98; P = 0.76) when moving from the Least-Fit to the next fitness category (5.1-7 METs). Third, the risk was further reduced (by 32%) for those who achieved 7.1-8.7 METs and by 37% for those who achieved > 8.7 METs. Finally, for individuals with no additional risk factors, the risk was reduced by 34%, 40%, and 63% for the respective moderate, fit, and high-fitness categories.

These findings support the concept that the inherent health risk imposed by additional cardiac risk factors in patients with diabetes is at least partially neutralized by relatively small increases in exercise capacity. Moreover, higher levels of fitness (>7 METs) provide an added protection similar to that observed in those without risk factors. This finding, in particular, makes a unique contribution to

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existing knowledge by providing information on the association between exercise capacity and mortality in diabetic individuals with additional CVD risk factors. As has been recently reported in other conditions (30,31), the public health message of this observation is that low fitness should be considered by health professionals to be as important a risk factor as other traditional risk factors.

Several other aspects of the current study are noteworthy. First, the fitnessmortality association was assessed in the largest clinically referred cohort of diabetic individuals (n = 4,156) roughly half of whom were African American, including 33,112 person-years and 1,074 deaths (25.8%). Second, the probability of reverse causality was likely reduced for the following reasons: First, the long follow-up period reduces the potential for confounding due to underlying illness, low BMI, and low fitness. Second, the equal access to care independent of a patient's financial status provided by the Veterans Health Administration (32) permits epidemiologic evaluations while minimizing the influence of disparities in medical care (33). Finally, the existence of electronic health records within the VA Healthcare System enables detailed observation of history and alterations in health status, coupled with the exclusion of individuals with low exercise capacity ( $\leq 5$  METs) who died during the first 2 years of follow-up, minimizes the potential impact of pre-existing disease on our findings.

### Limitations

The current study was retrospective and, therefore has several limitations. First, only male veterans were included, which limits the ability to generalize the findings to women. There is also the possibility of a beneficial "veteran effect" (6,34). Briefly, veterans must fulfill weight criteria at the time of enlistment and maintain weight during their service, resulting in the exclusion of obese individuals. Therefore, late onset of obesity in our sample may be lessening the duration of exposure to obesity-related risk (35,36). Second, adiposity was determined only by BMI, which does not provide information on body fat distribution. Third, information regarding BMI and fitness levels was available only at baseline, negating evaluation of the effects of changes during the followup period in either or both of these factors. Fourth, we did not have enough patients who were extremely lean (BMI

<18.5 kg/m<sup>2</sup>) to draw conclusions on mortality rates in these subjects. Finally, the potential effects of reverse causality cannot be excluded.

#### Conclusion

Similar to previous studies in Veterans, we observed a paradoxic BMI-mortality risk association in African American and Caucasian patients with diabetes, with heavier subjects exhibiting better survival. This association was more pronounced in African American than in Caucasian individuals. The current study also confirms the strong relationship between exercise capacity and mortality. The exercise capacity-mortality risk association was inverse, independent, and graded for the entire cohort and in all BMI categories regardless of race. The presence of additional cardiac risk factors combined with low exercise capacity increased mortality risk significantly. Conversely, mortality risk declined progressively with increased fitness, regardless of the presence or absence of additional cardiac risk factors. Our findings support the concept that even small improvements in exercise capacity, regardless of BMI level, can counteract the increased mortality risk associated with diabetes.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

P.K. contributed to data collection, statistical analyses, and writing of the manuscript. J.M. contributed to data collection and to the writing and editing of the manuscript. C.F. contributed to the discussion and to the editing of the manuscript. M.D. researched data, assisted in writing the RESULTS section, and edited the manuscript. R.K. researched data and reviewed and edited the manuscript. E.N. contributed to the interpretation of the data and to the editing of the manuscript. P.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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