Fitness, Fatness, and Survival in Adults With Prediabetes

OBJECTIVE
The purpose of this study was to examine independent and joint associations of cardiorespiratory fitness (CRF) and different adiposity measures with mortality risk in individuals with prediabetes (or impaired fasting glucose).

RESEARCH DESIGN AND METHODS
We examined associations of CRF and fatness with cardiovascular disease (CVD) and all-cause mortality in a cohort of 17,044 participants (89% men) with prediabetes (defined as 100 mg/dL ≤ fasting plasma glucose < 126 mg/dL), who did not have a history of diabetes, CVD, or cancer.

RESULTS
We identified 832 deaths (246 from CVD) during 13.9 ± 7.0 years (mean ± SD) follow-up. Normal-weight individuals who were unfit (lowest one-third) had a higher risk of all-cause (hazard ratio 1.70 [95% CI 1.32–2.18]) and CVD (1.88 [1.13–3.10]) mortality compared with the normal-weight and fit (upper two-thirds) reference group in a model adjusted for age, sex, examination year, and multiple risk factors. The mortality risk for fit individuals who were overweight or obese did not differ significantly from the reference group. Similar patterns were observed for sex-specific thirds of waist circumference and % body fat.

CONCLUSIONS
CRF markedly modifies the relationship between adiposity and mortality in persons with prediabetes. Unfit individuals have a higher and fit individuals have a lower mortality risk irrespective of adiposity level in this high-risk group.

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The prevalence of type 2 diabetes mellitus (DM) in the U.S. has increased to nearly 26 million and could double or triple by 2050, according the latest estimates from the American Diabetes Association (1). It is estimated that another 79 million people have pre-DM or impaired fasting glucose (1), which progresses to DM at an estimated rate of 5% per year (2). In addition, prediabetes increases the risk for all-cause and cardiovascular disease (CVD) mortality (3). Therefore, there is an urgent need to clarify risk factors for mortality that are specific to individuals with pre-DM as part of an overall strategy to reduce the hazards of this condition.
In two recent, large observational studies in adults with type 2 DM who were free of CVD, those who were normal weight had higher mortality risk than those who were overweight or obese (the so-called “obesity paradox”) (4,5). However, there are limited data on whether the obesity paradox observed in DM extends to pre-DM, which was reported only in women (6). Furthermore, cardiorespiratory fitness (CRF) modifies the obesity paradox in patients with coronary heart disease (7) and heart failure (8), but to our knowledge this has not been examined in individuals with pre-DM.

In a previous report from the Aerobics Center Longitudinal Study (ACLS), we examined associations of CRF and adiposity measures with risks of incident impaired fasting glucose (9). In the present investigation, we extend observations on the relative importance of fitness versus fatness as risk factors in adults with pre-DM by examining independent and joint associations of CRF and three standard clinical measures of adiposity (BMI, waist circumference [WC], and body fat percentage [%BF]) with CVD and all-cause mortality. We hypothesized that the obesity paradox would be present in this population overall but that adiposity level would be a weaker predictor than CRF for CVD mortality and all-cause mortality. Additionally, since there is controversy regarding the impact of different levels of impaired fasting glucose (e.g., <110 vs. >110 mg/dL) on CVD risk (10–13), the impact of adiposity and CRF was also assessed at these levels of pre-DM.

**RESEARCH DESIGN AND METHODS**

The ACLS is a prospective epidemiological investigation of participants that began in the 1970s. All patients underwent extensive health examinations at the Cooper Clinic in Dallas, Texas. Participants in the current study were drawn from a cohort of 17,967 men and women with pre-DM or impaired fasting glucose (defined as 100 mg/dL ≤ fasting plasma glucose < 126 mg/dL) and who completed a maximal exercise tolerance test at least once during 1974–2002. Participants were unpaid volunteers, sent by their employers, health care providers, or self-referred, and gave informed consent to join the study. The Cooper Institute Institutional Review Board reviewed and approved the study protocol annually.

Participants were excluded from the final analysis if they were underweight (BMI < 18.5 kg/m²) (n = 125); had a history of DM (n = 57), myocardial infarction (n = 26), stroke (n = 6), or cancer (n = 70); had an abnormal resting or exercise electrocardiogram (ECG) (n = 168); died during the first year of follow-up (n = 34); or had missing data on any one of the three adiposity measures (n = 437). These criteria resulted in 17,044 participating (1,910 women), aged 20–82 years, who were followed until date of death or 31 December 2003. Participants were predominantly white, well educated, and within the middle to upper socioeconomic strata. Additional information on study methods and characteristics of this cohort has previously been published (7,9,14).

**Clinical Evaluation**

A standardized medical examination by a physician, including personal and family histories, was completed for all participants before exercise testing. Blood pressure was measured with standard auscultatory methods after the participant had been seated for five minutes. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mmHg or a physician diagnosis. Abnormal exercise ECG responses included rhythm and conduction disturbances and ischemic ST-T wave abnormalities as previously described in detail (15). Previously, we found 90% agreement between the ECG interpretation recorded in our database and a group of three physicians who read a random sample of 357 patient records (15). Fasting plasma glucose and total cholesterol levels were determined in the Cooper Clinic clinical chemistry laboratory, which participates in and meets the quality-control standards of the Centers for Disease Control and Prevention Lipid Standardization Program. DM was defined as a fasting glucose concentration of ≥ 126 mg/dL, previous physician diagnosis, or use of insulin. Hypercholesterolemia was defined as a total cholesterol concentration of ≥ 240 mg/dL or previous physician diagnosis. Personal history of myocardial infarction, stroke, hypertension, diabetes and cancer, family history of CVD, smoking habits, alcohol intake, and physical activity habits was obtained from a standardized questionnaire.

**Cardiorespiratory Fitness**

Symptom-limited maximal treadmill exercise testing was performed based on a modified Balke protocol (15) as previously described (7,9,14). The test end point was volitional exhaustion or termination by the physician for medical reasons. Total test time correlates highly (r ≥ 0.92) with directly measured maximal oxygen uptake in both men (16) and women (17). For standardized interpretation of exercise test performance, maximal METs (1 MET = 3.5 mL O₂ uptake/kg/min) were estimated based on the final treadmill speed and grade (18). CRF was grouped for our primary analysis using age- and sex-specific tertiles of the maximal exercise duration.

**Adiposity Measures**

Measures of adiposity included BMI, which was calculated from measured weight in kilograms divided by the square of measured height in meters; %BF, which was assessed with hydrostatic weighing, with the sum of seven skinfold measures, or with both assessments, following standardized protocols (19) (a detailed description of our hydrodensiometry procedures has previously been published [20]); and WC, which was measured at the level of the umbilicus. BMI exposure groups were based on standard clinical definitions: normal-weight BMI (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥ 30.0 kg/m²). For groups based on %BF and WC, we used sex-specific tertiles from this population.

**Mortality Surveillance**

All participants were followed for mortality from the baseline date to the date of death or 31 December 2003. We used the National Death Index as the primary data source for mortality surveillance, augmented with official death certificates obtained from the department of vital records within the decedent’s state of residence. The
National Death Index has been shown to be an accurate method of ascertaining deaths in observational studies, having high sensitivity (96%) and specificity (100%) (21). CVD mortality was determined using ICD-9 codes 390–449.9 before 1999 and ICD-10 codes 100–178 from 1999–2003.

**Statistical Methods**

Descriptive analyses summarized baseline characteristics of participants by sex and BMI groups. The mean levels of continuous variables were compared using ANOVA, while χ² tests compared the distribution of categorical variable values. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs, according to exposure categories: CRF, BMI, %BF, or WC. In multivariable analyses, we adjusted for age, sex, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks/week or not), hypercholesterolemia, hypertension, and family history of CVD (present or not for each) (model 1). Then, we additionally adjusted for BMI, %BF, and WC when CRF was the exposure or for CRF (treadmill test duration in minutes) when BMI, %BF, or WC was the exposure (model 2).

To determine whether the association between adiposity and mortality in adults with pre-DM differed by age, we used BMI categories as exposure and examined the association in younger adults (<55 years) and older adults (≥55 years). We also examined whether this association varied by follow-up time, analyzing separately those participants who were followed <10 years and ≥10 years. And finally, we also examined this association separately by fasting glucose levels (100–109 vs. 110–125 mg/dL).

The joint effects of adiposity and CRF were examined by using combined groups as previously reported (7). We created six categories based on categories of BMI (normal-weight BMI, overweight, and obesity), WC (tertiles), or %BF (tertiles) and dichotomized these into fit (middle and upper tertiles) and unfit (lower tertile). Reference groups were fit—normal weight, fit—lower WC, and fit—lower BF%, respectively. To further assess the effects of follow-up time and smoking, we repeated these analyses in subjects with ≥10 years of follow-up and in smokers versus nonsmokers. Cumulative hazard plots grouped by exposures suggested no appreciable violations of the proportional hazards assumption. Data analyses were performed using SPSS, version 20.0 (IBM), and all P values are two-sided with an α level of 0.05.

**RESULTS**

A total of 832 deaths (246 due to CVD) occurred in 17,044 participants (88.8% men) during 13.9 ± 7.0 years of follow-up. Prevalence of normal-weight, overweight, and obesity was 37, 47, and 16%, respectively. Mean age at baseline was 45.9 ± 9.2 and 47.6 ± 10.1 years for men and women, respectively. Significant trends across ascending BMI groups included increasing age (P < 0.001), decreasing maximal METs (P < 0.001), and a higher prevalence of physical inactivity (P < 0.001), current smoking (P < 0.001), hypercholesterolemia (P < 0.001), hypertension (P < 0.001), and family history of CVD (P < 0.001) (Table 1).

Multivariable analysis showed that higher CRF was associated with a

| Table 1—Baseline characteristics of participants with prediabetes* by sex and BMI groups: ACLS, 1974–2002 (n = 17,044) |
|-------------|-------------|-------------|-------------|-------------|
| **Sex**     | **BMI groups** | **P**        | **Sex**     | **BMI groups** | **P**        |
| n           | Men          | Women       | Normal      | Overweight   | Obese       |
| Age (years) | 45.9 ± 9.2   | 47.6 ± 10.1 | <0.001      | 45.6 ± 9.9   | 46.4 ± 9.0  | 46.1 ± 8.7  | <0.001 |
| BMI (kg/m²) | 26.8 ± 3.7   | 24.4 ± 4.4  | <0.001      | 23.0 ± 1.5   | 27.1 ± 1.4  | 33.1 ± 3.3  | <0.001 |
| WC (cm)     | 94.9 ± 10.6  | 76.2 ± 11.2 | <0.001      | 82.9 ± 8.6   | 95.0 ± 7.0  | 109.1 ± 10.4| <0.001 |
| %BF         | 22.1 ± 6.0   | 28.5 ± 6.8  | <0.001      | 19.1 ± 5.8   | 23.4 ± 5.0  | 29.8 ± 4.9  | <0.001 |
| Treadmill time (min) | 18.4 ± 4.8  | 13.1 ± 4.6  | <0.001      | 19.8 ± 5.3   | 17.6 ± 4.4  | 13.8 ± 3.9  | <0.001 |
| Maximal METs | 11.9 ± 2.4  | 9.4 ± 2.1   | <0.001      | 12.6 ± 2.7   | 11.5 ± 2.1  | 9.7 ± 1.8   | <0.001 |
| Total cholesterol (mg/dL) | 212.0 ± 41.9 | 206.4 ± 39.5 | <0.001 | 203.8 ± 37.8 | 215.3 ± 44.0 | 217.1 ± 40.7 | <0.001 |
| Fasting blood glucose (mg/dL) | 106.1 ± 5.5 | 105.3 ± 5.2 | <0.001 | 105.1 ± 4.9 | 106.1 ± 5.5 | 107.5 ± 6.1 | <0.001 |
| Blood pressure (mmHg) |                   |                   |               |               |               |               |               |
| Systolic     | 121.9 ± 13.1 | 116.5 ± 15.2 | <0.001      | 118.2 ± 13.5 | 121.9 ± 12.9 | 127.0 ± 13.1 | <0.001 |
| Diastolic    | 81.8 ± 9.5   | 78.0 ± 10.0  | <0.001      | 78.5 ± 9.2   | 82.1 ± 9.2  | 86.2 ± 9.7  | <0.001 |
| Physically inactive | 3,648 (24.1) | 463 (24.2)  | 0.889       | 1,103 (17.5) | 2,021 (25.2) | 987 (36.5)  | <0.001 |
| Current smokers | 2,448 (16.2) | 159 (8.3)   | <0.001      | 796 (12.6)   | 1,381 (17.2) | 430 (15.9)  | <0.001 |
| Heavy drinkers | 1,407 (9.3)  | 224 (11.7)  | 0.001       | 573 (9.1)    | 790 (9.8)   | 268 (9.9)   | 0.251 |
| Hypercholesterolemia | 4,611 (30.5) | 512 (26.8)  | 0.001       | 1,408 (22.3) | 2,705 (33.7) | 1,010 (37.4) | <0.001 |
| Hypertension  | 4,936 (32.6) | 441 (23.1)  | <0.001      | 1,315 (20.8) | 2,677 (33.3) | 1,385 (51.3) | <0.001 |
| Family history of CVD | 904 (6.0)   | 136 (7.1)   | 0.525       | 295 (4.7)    | 540 (6.7)   | 205 (7.6)   | <0.001 |

Data are means ± SD or n (%) unless otherwise indicated. For data reported as mean ± SD, differences between groups were examined by ANOVA. For data reported as n (%), differences between groups were examined by χ² tests. *Fasting glucose ≥100 mg/dL and >126 mg/dL plus no history of diabetes or insulin use.
lower all-cause and CVD mortality risk (Table 2). Compared with participants in the lower third of CRF, those in the middle and upper thirds of CRF had 29 and 37% lower risks of total mortality, respectively. Additional adjustment for BMI, WC, and percent BF (model 2) did not appreciably alter these results. Similar results were found for CVD mortality in participants in the upper third of CRF, but individuals in the middle third of CRF did not differ significantly from the lower third of CRF after adjustment for the adiposity measures (model 2). Multivariable analysis revealed that associations of adiposity with mortality differed by adiposity measure and mortality outcome and were attenuated after adjustment for CRF (model 2). Compared with their normal reference groups, obese individuals had a 53% higher, and the upper third of WC had a 28% higher, all-cause mortality risk. However, after adjustment for CRF, these groups did not differ significantly from their respective reference groups. All-cause mortality risk in four adiposity groups (overweight, middle and upper thirds of %BF, and middle third of WC) did not differ significantly from their respective reference groups. However, there was between 15 and 22% lower all-cause mortality risk in these groups after adjustment for CRF (model 2).

Associations of adiposity measure with CVD mortality risk were nonsignificant after adjustment for CRF (model 2), except for the obese group, which had a 76% higher CVD mortality risk.

Multivariable analysis showed that risk of all-cause and CVD mortality varied according to BMI group when stratified by age (<55 years and ≥55 years), follow-up time (<10 years and ≥10 years), and fasting glucose levels (100–109 mg/dL and 110–125 mg/dL) (data not shown). Stratification by age did not alter the results for all-cause mortality risk in the overweight and obese groups. However, obese individuals who were <55 years old had a higher risk of CVD mortality (HR 2.25 [95% CI 1.50–3.35]). While stratification by follow-up time did not alter the results for the overweight group, obese participants with follow-up of ≥10 years had a higher all-cause (1.32 [1.00–1.73]) and CVD (2.42 [1.51–3.85]) mortality risk. Stratification by fasting glucose level revealed two notable differences. In the glucose 100–109 mg/dL group, the overweight group had a higher risk of all-cause mortality (0.80 [0.67–0.96]) and the obese group had a higher risk of CVD mortality (2.30 [1.42–3.72]).

Finally, we evaluated the joint effects of CRF and adiposity measures on all-cause mortality (Fig. 1) and CVD mortality (Fig. 2) in multivariable analysis. Among fit participants, all-cause and CVD mortality risks for BMI categories of overweight and obese did not differ significantly from the normal-weight and fit reference group. In contrast, among unfit participants, a higher risk of all-cause mortality was found across BMI categories of normal weight (HR 1.70 [95% CI 1.32–2.18]), overweight (1.27 [1.03–1.57]), and obese (1.91 [1.50–2.44]). A similar pattern was observed among unfit persons for CVD mortality, except that obese participants had a much higher risk (3.20 [2.09–4.88]). Similar patterns among fit and unfit participants for all-cause and CVD mortality were seen for WC and %BF. The results from repeat analyses in subjects with >10 years of follow-up and in smokers versus nonsmokers were nearly identical.

CONCLUSIONS

While our study, which included >17,000 adults with pre-DM who were free of preexisting DM, CVD, or cancer, provided evidence for an obesity paradox across three different measures of adiposity (BMI, WC, and %BF), CRF negated this effect. Repeating the analyses for subjects with >10 years of follow-up and stratifying by smoking status did not appreciably alter our main findings. Two quite recent studies (4,5)
reported an obesity paradox in patients with DM who were free of CVD. Since both of these studies used BMI as the adiposity measure, comparisons with our study are limited to this exposure. In their study of 2,625 participants (50% women) with >10 years of follow-up, Carnethon et al. (4) found that overweight/obese (BMI $\geq 25 \text{ kg/m}^2$) participants had a lower all-cause mortality compared with those who were normal weight (BMI 18.5–24.9 kg/m²), but there was no significant difference between groups for CVD mortality. However, the relationship of obesity measures and mortality are complex, and not all studies confirm an obesity paradox in patients with T2DM. Some studies have reported that obese patients have a higher mortality risk than their normal-weight counterparts (22,23). Furthermore, a phenotype known as “metabolically unhealthy normal weight” has been described (24,25). In this subgroup of individuals, mortality risk is similar to their metabolically unhealthy obese counterparts, as was observed in the low CRF normal-weight and obese subgroups in the current study. However, in the study of Carnethon et al. (4), lower weight in patients with new-onset diabetes might reflect uncontrolled diabetes and are therefore not analogous to normal-weight persons with pre-DM.

In the study of Khalangot et al. (5), which included 81,603 individuals (66% women) with 2.7 years of follow-up, the all-cause and CVD mortality risk for BMI 30.0–34.9 did not differ significantly from the BMI 25.0–29.9 kg/m² reference group. However, the all-cause and CVD mortality risk was higher for BMI $\geq 35.0 \text{ kg/m}^2$ as well as for BMI 18.5–24.9 kg/m². These findings accord with a more recent study of 106,640 Scottish patients whose BMI was measured within a year after diagnosis of DM in which only BMI $\geq 25.0$ and $>35.0 \text{ kg/m}^2$ had increased all-cause mortality risk (26). In each of these studies, the obesity paradox was more pronounced for all-cause than CVD mortality, which is overall consistent with our results. This is in contrast to findings in patients with CVD in whom the obesity paradox was equally strong for all-cause and CVD mortality (7,27,28). Therefore, the protective
effect of higher BMI against CVD mortality observed in CVD may not extend to metabolic diseases. However, further study is required to ascertain the true nature of the obesity paradox by cause-specific mortality in different disease states.

In the few available studies (7,8,29,30) that have examined the impact of CRF on the obesity paradox in CVD populations, obesity was associated with lower mortality among unfit patients. In the current study, however, we did not observe this association. In fact, a more than threefold higher CVD mortality was observed in unfit and obese individuals compared with fit and normal-weight individuals. The failure of higher adiposity to be protective in unfit individuals with pre-DM suggests a different dynamic in metabolic disorders compared with CVD states. But the question still remains as to why CVD mortality risk was not higher for obese individuals who were fit. One possible mechanism may be the effect of regular exercise on hepatic lipid concentration. In one study (31), a 4-week aerobic exercise training program reduced hepatic lipid concentration in obese men and women in the absence of weight loss. In another study (32) of ACLS men, nonalcoholic fatty liver disease was 10 times more likely in unfit (upper two-thirds) men compared with fit (upper two-thirds) men. Together, these results suggest that regulation of hepatic lipid concentration may be an important pathogenic site that is modified by CRF independent of standard measures of adiposity. Therefore, future studies on the relationship between adiposity and mortality in patients with DM and pre-DM should focus on the influence of CRF as an effect modifier.

In addition to our main finding that the paradoxical association of adiposity with mortality is modified by CRF, other confounders, such as age, follow-up time, and fasting glucose level, should also be considered. For example, we found that CVD mortality was higher for obese individuals who were younger than 55 years old or followed for ≥10 years. Previous studies (33,34) found that differences in incidence of events across metabolically healthy BMI
subgroups were evident only after 8–10 years of follow-up. However, in our analysis of individuals with >10 years of follow-up, we found only minor differences across the adiposity subgroups with low or high CRF.

Importantly, CVD mortality was more than twofold higher in obese participants with fasting glucose of 100–109 mg/dL compared with their normal-weight counterparts in contrast to obese individuals with fasting glucose of 110–125 mg/dL, whose CVD mortality risk did not differ significantly from their normal-weight counterparts. Future studies of CRF, fatness, and survival in pre-DM should be stratified by fasting glucose level, since some studies have questioned the cut point of 100 vs. 110 mg/dL for impaired glucose tolerance (10–13). There are several limitations to the current study. First, the ACLS cohort consists primarily of white men and women from middle to upper socioeconomic status. Therefore, the results may not extend to other groups of men and women. Second, since we did not have information on changes in any of the baseline variables during follow-up, we could not assess how any changes might have influenced the results. Third, we evaluated the influence of CRF from a single baseline measure. Many factors that affect CRF, such as genetics, recent and lifelong physical activity patterns, aging, and illness, as well as longitudinal changes in CRF, were not accounted for in our analysis (18). Fourth, we lacked complete information on the duration of pre-DM and therefore could not factor in the likelihood of developing complications associated with longer duration of impaired fasting glucose and whether participants adopted favorable lifestyle changes after learning of their diagnosis. Finally, medication and dietary information are not available to be included in the analysis.

In conclusion, these findings demonstrate that the obesity paradox observed in DM partly extends to patients with pre-DM or impaired fasting glucose but that CRF modifies the relationship between adiposity and survival as previously observed in CVD populations. Therefore, when the significance of the obesity paradox phenomenon is translated to public health policy, CRF should be considered. Our findings support preserving or increasing CRF over weight loss as a primary strategy to reduce mortality risk in persons with pre-DM. The results of our study underscore the importance of CRF in health promotion and disease prevention. Most adults can maintain or improve their CRF by engaging in 30 min of moderate-intensity physical activity such as brisk walking ≥5 days per week (35). Future studies on CRF, fatness, and survival in pre-DM should further examine the impact of fasting glucose levels (<110 vs. >110 mg/dL), age, and follow-up time.

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