A Prospective Study of Cardiorespiratory Fitness and Risk of Type 2 Diabetes in Women

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OBJECTIVE — The purpose of this study was to determine the independent and joint associations of cardiorespiratory fitness (CRF) and BMI with the incidence of type 2 diabetes in women.

RESEARCH DESIGN AND METHODS — An observational cohort of 6,249 women aged 20–79 years was free of baseline cardiovascular disease, cancer, and diabetes. CRF was measured using a maximal treadmill exercise test. BMI was computed from measured height and weight. The incidence of type 2 diabetes was identified primarily by 1997 American Diabetes Association criteria.

RESULTS — During a 17-year follow-up, 143 cases of type 2 diabetes occurred. Compared with the least fit third, the multivariate (including BMI)-adjusted hazard ratio (HR) (95% CI) was 0.86 (0.59–1.25) for the middle third and 0.61 (0.38–0.96) for the upper third of CRF. For BMI, the multivariate (including CRF)-adjusted HR (95% CI) was 2.34 (1.55–3.54) for overweight individuals and 3.70 (2.12–6.44) for obese individuals, compared with normal-weight patients. In the combined analyses, overweight/obese unfit (the lowest one-third of CRF) women had significantly higher risks compared with normal-weight fit (the upper two-thirds of CRF) women.

CONCLUSIONS — Low CRF and higher BMI were independently associated with incident type 2 diabetes. The protective effect of CRF was observed in individuals who were overweight or obese, but CRF did not eliminate the increased risk in these groups. These findings underscore the critical importance of promoting regular physical activity and maintaining normal weight for diabetes prevention.

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Diabetes prevalence continues to increase, and the Centers for Disease Control and Prevention projected that the number of Americans with diabetes would reach 48.3 million by 2050 (1). Findings from Canada are similar, with a 27% increased diabetes prevalence from 2000 to 2005 (2). The growing rate of diabetes with its cardiovascular complications adds to the burden of direct health care costs, which ranges from 2.5 to 15% of health budgets globally (3).

Obesity and physical inactivity are two major contributors to type 2 diabetes in men and women (4–8). Because women newly diagnosed with diabetes have a higher relative risk for cardiovascular disease death than men with diabetes (9), it is important to investigate the associations among obesity, physical activity, and the risk of developing type 2 diabetes in women. Studies on the effects of obesity and physical activity on incident type 2 diabetes in women are limited, and the findings are inconsistent (5,6,8). Some reports show a greater magnitude of association between BMI and risk of type 2 diabetes than that for physical inactivity (5,8), whereas others do not (6). The differing results may be due to the misclassification of physical activity using self-report questionnaires, especially in women (10,11).

Cardiorespiratory fitness (CRF), which can be measured objectively in a laboratory and thereby provides quantifiable data that are correlated with habitual physical activity, is a stronger predictor of several health outcomes than self-reported physical activity (12). A few large longitudinal studies have related baseline measures of CRF with type 2 diabetes risk (13–17). However, three of these studies included only men (13,15,16), and the other two did not report sex-specific results (14,17). The current study was designed to determine the independent and joint associations of CRF, objectively measured by a maximal exercise test on a treadmill, and BMI on the incidence of type 2 diabetes in women in the Aerobics Center Longitudinal Study (ACLS).

RESEARCH DESIGN AND METHODS

— Participants were 6,249 women aged 20–79 years at baseline (mean 43.8 years) who completed at least one preventive evaluation at the Cooper Clinic in Dallas, Texas, between 1971 and 2004. At baseline, all participants were free of type 2 diabetes, cardiovascular disease (myocardial infarction and stroke), and cancer; had normal resting and exercise electrocardiograms; and were able to complete an exercise stress test to at least 85% of their age-predicted maximal heart rate. Most participants in this prospective study were white, well educated, and from middle to upper socioeconomic strata. The study protocol

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Abbreviations: ACLS, Aerobics Center Longitudinal Study; CRF, cardiorespiratory fitness.

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Table 1—*Baseline characteristics of women by type 2 diabetes status at follow-up: ACLS, 1971–2004*

	No diabetes	Diabetes	*P* value
n	6,106	143	
Age (years)	43.7 ± 9.9	46.5 ± 10.2	0.0008
Maximal METs	9.7 ± 2.2	8.7 ± 2.0	<0.001
Treadmill duration (min)	13.8 ± 4.6	11.5 ± 4.4	<0.001
BMI (kg/m^2)	22.6 ± 3.8	24.7 ± 5.3	<0.001
Waist girth (cm)	67.2 ± 20.2	73.7 ± 22.5	0.02
Lipid level (mmol/l)			
Total cholesterol	5.2 ± 1.0	5.7 ± 1.3	<0.001
HDL cholesterol	1.6 ± 0.4	1.4 ± 0.3	<0.001
Triglycerides	1.0 ± 0.6	1.3 ± 0.8	<0.001
Fasting blood glucose (mmol/l)	5.2 ± 0.5	5.5 ± 0.7	<0.001
Blood pressure (mmHg)			
Systolic	112 ± 14	117 ± 14	<0.001
Diastolic	75 ± 9	77 ± 9	0.01
Current smoker (%)	8.6	11.2	0.28
≥5 alcohol drinks per week (%)	19.3	16.8	0.45
Hypertension (%)	14.8	22.4	0.01
Pre-diabetes (%)*	21.8	43.4	<0.001
Family history of diabetes (%)	7.0	12.6	0.01

Data are means ± SD unless indicated otherwise. *Fasting glucose of 5.56–6.99 mmol/l (100–125.9 mg/dl).

was reviewed and approved annually by the Cooper Institute Review Board.

Clinical examination

The baseline examination was performed after participants gave written informed consent and included fasting blood chemistry analyses, personal and family health history, anthropometry, resting blood pressure, and a maximal graded exercise test. Details of the study design, population characteristics of the cohort, and baseline examination were available in earlier reports (16,18). Height and weight were measured using a stadiometer and standard physician's scale, and BMI (weight in kilograms divided by the square of height in meters) was calculated. The BMI groups were based on clinical definitions for normal weight (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Resting blood pressure was recorded as the first and fifth Korotkoff sounds by auscultatory methods after at least 5 min of rest. Two or more readings separated by 2 min were averaged. If the first two readings differed by >5 mmHg, additional readings were obtained and averaged (19). Serum samples were analyzed for lipids and glucose using standardized automated bioassays. Hypertension was defined as a history of physician diagnosis or a measured resting systolic or diastolic blood pressure of ≥140 or ≥90 mmHg, respectively. Information on smoking, alcohol intake, and family history of diabetes was obtained from a standardized questionnaire.

CRF was assessed as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol as described previously (18,20). Patients were encouraged to give maximal effort. The test end point was volitional exhaustion or termination by the physician for medical reasons. Exercise duration on this protocol is highly correlated with measured maximal oxygen uptake in women ($r = 0.94$) (21). We categorized women into thirds depending on age-specific (20–29, 30–39, 40–49, 50–59, and ≥60 years) distributions of treadmill time. We also expressed CRF as maximal metabolic units (1 MET = 3.5 ml O_2 uptake · kg^{-1} · min^{-1}) calculated from the final treadmill speed and grade (22).

Ascertainment of type 2 diabetes

We defined type 2 diabetes according to fasting plasma glucose criteria of the American Diabetes Association (23): fasting plasma glucose ≥7 mmol/l (126 mg/dl) at a follow-up clinic evaluation. Subjects who did not meet this criterion but who gave a history of diabetes (from responses to mail-back health surveys in 1982, 1986, 1990, 1999, and 2004 or from follow-up clinical visits) or reported current therapy with hypoglycemic medication also were considered to have diabetes. Patients with diabetes at baseline by any of these criteria were excluded from the current study. We used these same criteria to determine diabetes incidence during the follow-up. This method of case ascertainment has been used in our previous studies (16,24) and is similar to those used in other studies (5,15,17). Further, in a random sample of self-reported diabetes end points ($n = 52$), the percentage of agreement between reported events and medical record review was 92%. The aggregate survey response rate across all survey periods in the ACLS is ~65%. We believe that nonresponse bias is unlikely to be a major limitation in this study because baseline health histories and clinical measures were similar between responders and nonresponders and between early and late responders to the survey (25).

Data analysis

SAS (version 9.1; SAS Institute, Cary, NC) was used for statistical analysis. Standard *t* tests and χ^2 tests were used to compare the mean levels of continuous variables and the prevalence of categorical variables between subjects with and without incident type 2 diabetes. The Cox proportional hazards model was used to estimate the single or joint effect of different levels of CRF and BMI on the risk for the incidence of type 2 diabetes. To account for differences in survey response patterns among study participants and for the possibility that external events may have differentially affected their responses to the type 2 diabetes questions during the six survey periods, we created an indicator variable that showed the source of the outcome (26). To assess the shape of the CRF or BMI diabetes curve, we examined the incidence rate per 10,000 woman-years across increments of METs or BMI. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no appreciable violations were noted. *P* values are two sided, and $P < 0.05$ was accepted as statistically significant.

RESULTS — During a 17-year follow-up period (109,295 woman-years of exposure), 143 women developed type 2 diabetes. Compared with nondiabetic women, women who developed diabetes tended to be older, had lower CRF and higher BMI, had a higher prevalence of hypertension and family history of diabetes, and had unfavorable blood pressure and lipid profiles (Table 1).

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Table 2—*Event rates and HRs (95% CI) of incident type 2 diabetes according to baseline CRF and BMI in women: ACLS, 1971–2004*

	CRF thirds			
	Low	Middle	High	P_{trend}
n	2,075	2,091	2,083	
Cases of diabetes	71	45	27	
Woman-years of observation	41,791	35,861	31,682	
Event rate*	17.4	12.5	8.1	<0.001
HR (95% CI)				
Age adjusted	1.0 (referent)	0.72 (0.49–1.04)	0.46 (0.30–0.73)	<0.001
Multivariate adjusted†	1.0 (referent)	0.76 (0.52–1.11)	0.49 (0.31–0.77)	0.002
Multivariate adjusted including continuous BMI‡	1.0 (referent)	0.86 (0.59–1.25)	0.61 (0.38–0.96)	0.03

	BMI			
	<25.0 kg/m^2	25.0–29.9 kg/m^2	≥30.0 kg/m^2	P_{trend}
n	5,077	875	297	
Cases of diabetes	87	36	20	
Woman-years of observation	92,249	12,915	4,158	
Event rate*	10.0	25.1	44.8	<0.001
Age adjusted	1.0 (referent)	2.52 (1.70–3.73)	4.49 (2.76–7.32)	<0.001
Multivariate adjusted†	1.0 (referent)	2.60 (1.74–3.88)	4.62 (2.78–7.67)	<0.001
Multivariate adjusted HR including continuous treadmill test duration§	1.0 (referent)	2.34 (1.55–3.54)	3.70 (2.12–6.44)	<0.001

Data are *n* or HR (95% CI). *Rate is expressed as per 10,000 woman-years and adjusted for age. †Adjusted for age, current smoking, alcohol intake, hypertension, family history of diabetes, and survey response pattern. ‡Adjusted for age, current smoking, alcohol intake, hypertension, family history of diabetes, survey response pattern, and BMI. §Adjusted for age, current smoking, alcohol intake, hypertension, family history of diabetes, survey response pattern, and treadmill test duration.

Table 2 shows the age-adjusted incidence rates of type 2 diabetes, which were inversely associated with CRF and were positively associated with BMI ($P_{trend} < 0.001$ for each). After adjusting for covariables (age, survey response pattern, current smoking, alcohol intake, hypertension, and family history of diabetes), middle and higher thirds of CRF were associated with 24 and 51% lower risk of diabetes ($P_{trend} = 0.002$). The inverse association was slightly attenuated but remained significant after additional adjustment for BMI ($P_{trend} = 0.03$). Multivariate-adjusted (same covariables as for CRF) HRs for diabetes based on BMI levels of <25.0, 25.0–29.9, and ≥30.0 kg/m^2 were 1.00, 2.60, and 4.62 ($P_{trend} < 0.001$), respectively. After further adjustment for baseline CRF, the direct association decreased but remained significant ($P_{trend} < 0.001$).

To examine further the dose-response characteristics between CRF, BMI, and risk of type 2 diabetes, we computed the age-adjusted incidence rates (per 10,000 woman-years) for 1 MET increments of CRF across the range of 7 to 10 METs (Fig. 1*A*) and for categories of BMI (2.5 units) (Fig. 1*B*). An exercise capacity <7 METs was associated with a threefold higher diabetes risk compared with an exercise capacity of ≥10 METs ($P_{trend} < 0.001$). A BMI of ≥32.5 kg/m^2 was associated with a sixfold higher diabetes risk compared with a BMI of <22.5 kg/m^2 ($P_{trend} < 0.001$).

Finally, we examined the combined effects of CRF and BMI on risk for type 2 diabetes, where women in the referent group were normal weight (BMI < 25 kg/m^2) and fit (upper two-thirds of CRF) (Table 3). Among normal-weight women, being unfit (lower one-third of CRF) was not associated with increased risk (hazard ratio [HR] 1.05 [95% CI 0.67–1.65]) but was associated with higher risk among overweight/obese women (BMI ≥25 kg/m^2) (2.55 [1.49–4.37]), all relative to normal-weight fit women (Table 3). When fitness levels within BMI strata were compared, the unfit women had a significantly higher risk of type 2 diabetes than fit women in the overweight/obese group (multivariate adjusted HR 1.40 [95% CI 1.01–2.52]), but this was not significant in normal-weight subjects (1.25 [0.80–1.94]) (data not shown).

CONCLUSIONS — We addressed the single and joint associations of CRF and BMI for the risk of development of type 2 diabetes in women. Low fitness was associated with a significantly higher risk for type 2 diabetes in women, independent of age, smoking, alcohol intake, hypertension, family history of diabetes, and BMI at baseline. Overweight and obese women also had a higher risk of type 2 diabetes. The protective effect of CRF remained in overweight/obese women but not in the normal-weight women.

Previous observational studies have indicated that physical activity (4–8) or CRF (13–17) is inversely associated with the prevalence and incidence of diabetes. However, studies on the prospective association of CRF, an objective measure of physical activity habits that is less prone to misclassification, with diabetes risk in women are limited (14,17). There are only two studies that included women, but separate analyses for women and men were not performed. Carnethon et al. (14) reported a 15-year follow-up study in 2,478 young adults, during which 56 cases of type 2 diabetes were identified. After adjusting for confounders including BMI, participants with low fitness (<20th percentile) were two times more likely to develop type 2 diabetes than those with

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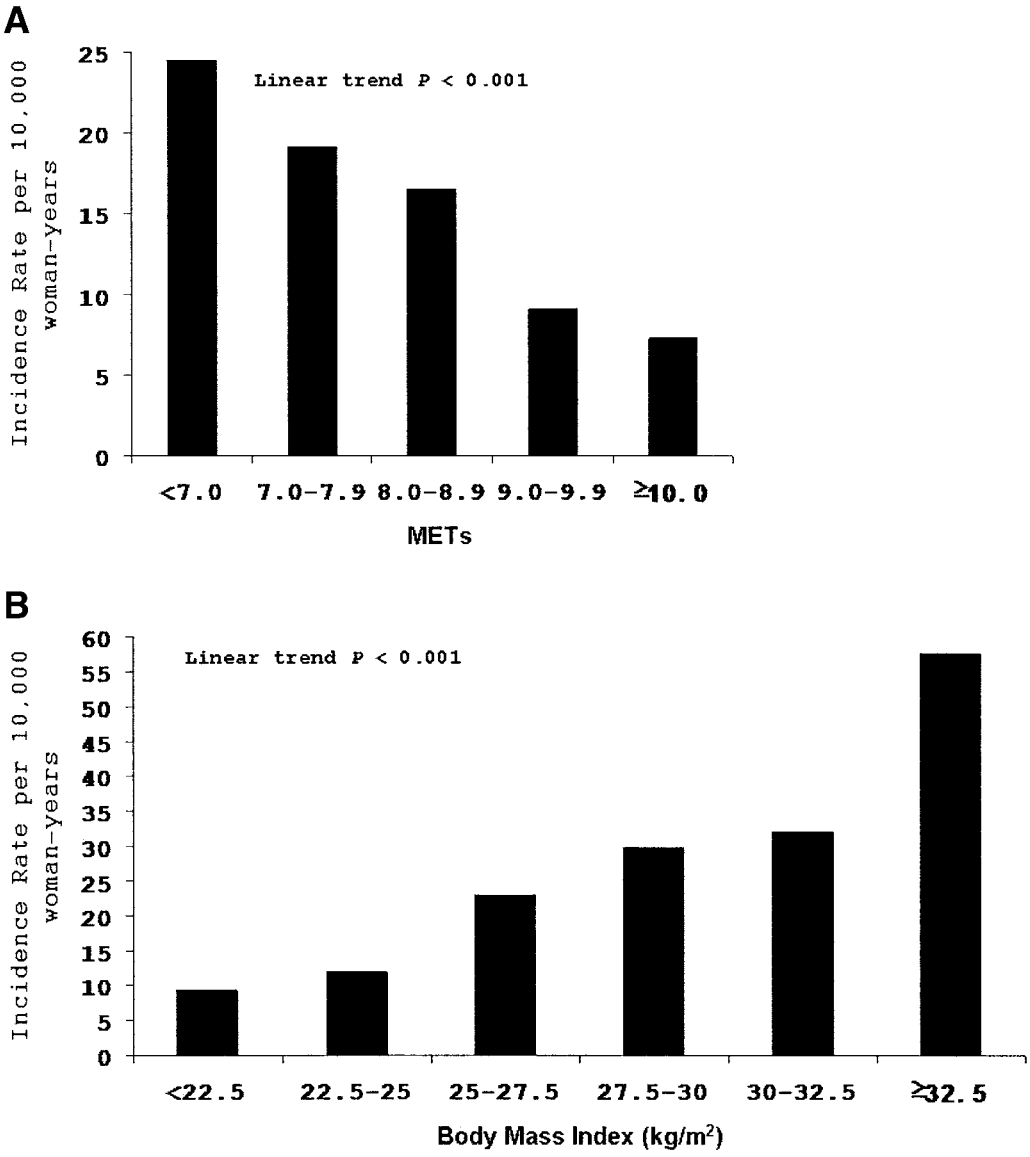

Figure 1— *Age-adjusted incidence rates (per 10,000 woman-years) of type 2 diabetes by CRF levels quantified in 1-MET increments obtained during a maximal treadmill test (A) and by BMI levels quantified in 2.5 kg/m^2 increments (B) in women. Number at risk (and number of cases) in <7.0, 7.0–7.9, 8.0–8.9, 9.0–9.9, and ≥10 METs were 556 (29), 631 (24), 1,575 (47), 993 (15), and 2,494 (28) and with BMI <22.5, 22.5–25, 25–27.5, 27.5–30, 30–32.5, and ≥32.5 kg/m^2 were 3,749 (59), 1,328 (28), 584 (22), 291 (14), 138 (7), and 159 (13), respectively.*

Table 3—*Event rates and HRs of type 2 diabetes by both BMI and CFR categories: ACLS, 1971–2004*

	Normal weight (BMI <25.0 kg/m^2)		Overweight (BMI ≥25.0 kg/m^2)	
Variable	Fit (upper two-thirds)	Unfit (lower one-third)	Fit (upper two-thirds)	Unfit (lower one-third)
No. women				
Total	3,665	1,412	509	663
With diabetes	56	31	16	40
Event rate*	9.4	11.0	21.4	34.9
Adjusted for age	1.00	1.17 (0.75–1.82)	2.27 (1.30–3.99)	3.70 (2.46–5.57)
Multivariate adjusted†	1.00	1.08 (0.69–1.69)	2.32 (1.31–4.10)	3.62 (2.39–5.48)
Multivariate adjusted‡	1.00	1.05 (0.67–1.65)	1.79 (0.95–3.38)	2.55 (1.49–4.37)

Data are *n* or HR (95% CI). *Per 10,000 woman-years with adjustment for age. †Adjusted for age, current smoking, alcohol intake, hypertension, family history of diabetes, and survey response pattern. ‡Adjusted for age, current smoking, alcohol intake, hypertension, family history of diabetes, survey response pattern, and BMI.

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high fitness (≥60th percentile). Katzmarzyk et al. (17) followed 1,543 adults aged 18–69 years for 15 years and found that physical fitness, but not physical activity, was a significant predictor of incident diabetes after adjustment for age, sex, and several covariates. We found 14 and 39% lower risks of diabetes for women in the middle and upper thirds of fitness, compared with women in the lower third of fitness group. The present study extends our previous findings in men (16) and is the first to report an inverse association between CRF and the risk for diabetes in overweight and obese women.

The protection against the development of type 2 diabetes by physical activity or CRF may be explained by enhanced glucose homeostasis (27). Structural changes (e.g., increased fiber size, capillary density, and blood flow) and biochemical changes (e.g., increased insulin and noninsulin signaling kinetics, enzymes related to glucose metabolism, and/or myoglobin) in skeletal muscle are two of the several mechanisms involved with the favorable effect that regular physical activity has on glucose (27). Other suggested mechanisms include systemic influences of physical activity such as improved oxygen uptake and functional capacity, better lipemic control, and lowered excessive hepatic secretion of glucose and VLDL (27).

Obesity is an independent risk factor for the development of type 2 diabetes in women (5,8,28). We observed low fitness in 28, 48, and 82% of women across normal-weight, overweight, and obese groups, respectively, and overweight/obese and low fit women had the highest risk of type 2 diabetes compared with other fitness and BMI combination groups (Table 3). Higher fitness was associated with a lower risk of type 2 diabetes in overweight/obese women but not in normal-weight subjects. The latter finding was inconsistent with two previous studies showing that the risk of diabetes could be reduced by higher physical activity in individuals with or without obesity (4,8) but was in accordance with another study (5). In fact, the joint association of physical activity and BMI on diabetes in women has been poorly understood, and the data are very limited (5,8). The Women's Health Study (5) reported a small and nonsignificant lower risk within the normal-weight, overweight, and obese groups when inactive and active participants were compared. Recently, the Nurses' Health Study (8) showed that slower walking pace was associated with higher risk of type 2 diabetes within the same BMI category, and the inverse association between pace and intensity of walking and risk of type 2 diabetes was most evident in overweight and obese women. There are several possible explanations for the differing results when we compare our findings with those of others. First, the measures of CRF used in this study may be a better marker for habitual levels of physical activity than less precise self-reported physical activity exposures, particularly in women (10,11). Second, the sample size and small number of events in the current study may not have been adequate to detect a significant effect of CRF in the normal weight individuals. The present study adds useful information, as no previous studies have examined the independent and joint association of CRF and BMI on the incidence of type 2 diabetes in women.

Although CRF has a genetic component (25–40%) (29,30), it is clear that usual physical activity habits are the primary determinant of fitness. Recently, Church et al. (31) reported that an activity level as low as 4 kcal · kg^{-1} · week^{-1} level (~72 min/week of moderate intensity walking) was associated with a significant improvement in CRF compared with women in the nonexercise control group.

The laboratory measurements of CRF and BMI as predictors and fasting blood glucose as the primary source for defining the study outcome are major strengths of the current study. Limitations are mainly those for epidemiological studies in general. The homogeneity of our population sample should not affect the internal validity but may limit the generalizability. Whether our results apply to men, women of other ethnic groups, or individuals of low socioeconomic status remains to be determined; however, our previous report (16) and other studies in men (15) on the association of CRF with diabetes are consistent with those reported here. Although women in this cohort tend to be healthier than those in the general population, the biological mechanisms that affect the development of type 2 diabetes are not likely to be different. We did not have sufficient information on hypertension medication usage, menopausal status, or dietary habits to include these in our analysis. We do not have data from an oral glucose tolerance test. Self-report of diabetes was one criterion used to categorize participants, and, consequently, we cannot verify that the participants had type 2 rather than type 1 diabetes. However, based on the current literature, >90% of adults with diabetes are estimated to have type 2 diabetes (32). Because this study consisted of middle-aged women, we suspect that most of the participants had type 2 diabetes. Therefore, our methods of ascertainment should not be less valid than those of other epidemiologic studies (5,33) in which self-reported diabetes was used.

In summary, this study demonstrated that both CRF and BMI are important in the development of diabetes in women. Our finding that high fitness was associated with a lower risk of type 2 diabetes in overweight/obese women further confirms the benefits of engaging in regular physical activity for these high-risk individuals. Our data also support the benefits of maintaining normal weight. Given the rapidly growing population prevalence of diabetes (34), the small improvement in physical activity over the past decade (34), and the continuing rise in obesity rates (35), the public health burden attributed to diabetes continues to be large and is likely to increase in coming years. We therefore believe health professionals should consider the potential benefits of greater CRF and aggressively counsel their sedentary obese patients to become more physically active and improve their CRF as a cornerstone of diabetes prevention.

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