Association of 20-Year Changes in Cardiorespiratory Fitness With Incident Type 2 Diabetes

The Coronary Artery Risk Development in Young Adults (CARDIA) fitness study

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OBJECTIVE — To test the association of fitness changes over 7 and 20 years on the development of diabetes in middle age.

RESEARCH DESIGN AND METHODS — Fitness was determined based on the duration of a maximal graded exercise treadmill test (Balke protocol) at up to three examinations over 20 years from 3,989 black and white men and women from the Coronary Artery Risk Development in Young Adults study. Relative fitness change (percent) was calculated as the difference between baseline and follow-up treadmill duration/baseline treadmill duration. Diabetes was identified as fasting glucose ≥126 mg/dl, postload glucose ≥200 mg/dl, or use of diabetes medications.

RESULTS — Diabetes developed at a rate of 4 per 1,000 person-years in women ($n = 149$) and men ($n = 122$), and lower baseline fitness was associated with a higher incidence of diabetes in all race-sex groups (hazard ratios [HRs] from 1.8 to 2.3). On average, fitness declined 7.6% in women and 9.2% in men over 7 years. The likelihood of developing diabetes increased per SD decrease (19%) from the 7-year population mean change (−8.3%) in women (HR 1.22 [95% CI 1.09–1.39]) and men (1.45 [1.20–1.75]) after adjustment for age, race, smoking, family history of diabetes, baseline fitness, BMI, and fasting glucose. Participants who developed diabetes over 20 years experienced significantly larger declines in relative fitness over 20 years versus those who did not.

CONCLUSIONS — Low fitness is significantly associated with diabetes incidence and explained in large part by the relationship between fitness and BMI.

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Randomized trials and other short-term clinical studies demonstrate that increased physical activity is accompanied by decreases in glucose and insulin and a lowered risk of development of type 2 diabetes (1–7). Although fitness normally declines with age (8), there is marked variation in the degree of decline as determined by physical activity behaviors, body composition, and other clinical characteristics (9,10). Few longitudinal studies of healthy adults have included multiple measures of objectively determined fitness over an extended period of time. In an earlier study, we reported that stable or improved fitness over 7 years was associated with a lower likelihood of development of diabetes compared with decreasing fitness in middle-aged young adults (11). To date, no studies have investigated whether changes in fitness that correspond with the long latency period for the development of diabetes are associated with incident diabetes in healthy young to middle-aged adults. We built upon our previous analysis to test the hypotheses that baseline fitness and the relative changes in fitness over 7 years are inversely associated with the development of diabetes over 20 years. Because physical functioning, including fitness, is known to decline in the presence of chronic diseases and obesity (10), we also tested whether participants who developed diabetes over follow-up experienced greater declines in fitness over 20 years compared with participants who remained free of diabetes.

RESEARCH DESIGN AND METHODS

— The Coronary Artery Risk Development in Young Adults (CARDIA) study is a longitudinal study of lifestyle and the evolution of cardiovascular disease risk factors over time in 5,115 adults initially aged 18–30 years in 1985–1986. A stratified sample of black and white men and women were randomly recruited from census tracks in Minneapolis, Minnesota, and Chicago, Illinois; by telephone exchanges within the Birmingham, Alabama, city limit; and from participant lists of a large health maintenance organization in Oakland, California (12). Participant recruitment was balanced by age, race, sex, and education level. Participants were reexamined 2, 5, 7, 10, 15, and 20 years after baseline. Retention rates declined from 90 to 72% across examinations. Details of study recruitment and design have been published (12,13). All participants provided written informed consent, and institutional review boards from each field

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center and the coordinating center approved the study annually.

Participants who had diabetes at baseline, who did not have valid fitness test data, or who did not attend at least one follow-up examination were excluded. Our sample sizes for analyses of baseline fitness, 7-year changes, and 20-year changes included 3,989, 1,808, and 2,231 participants, respectively. Our sample size at year 7 was smaller because participants from Minnesota were determined to have violated the exercise test protocol at year 7 by holding on to the handrails, leading to artificially elevated treadmill test times, so all data from that field center were excluded (14).

Measurements

Standardized protocols for data collection were used across study centers and examinations. Participants were asked to fast for at least 12 h before examination and to avoid smoking or engaging in heavy physical activity for at least 2 h before the examination.

Fitness assessment

Eligible participants underwent symptom-limited maximal graded exercise treadmill testing according to a modified protocol by Balke (15) at the baseline, 7-year, and 20-year follow-up examinations (16). Participants were eligible for graded exercise treadmill testing if they had no history of ischemic or congenital heart disease, were not using cardiovascular medications other than antihypertensive drugs, had blood pressure <160/90 mmHg, and had no concurrent febrile illness. Every 2 min for up to 18 min, the speed or grade of the treadmill increased to a maximum speed of 5.6 miles/h and a 25% grade (16). Participants were encouraged to exercise to maximal exertion. Heart rate and blood pressure were measured at the end of each stage and once a minute for 3 min after cessation of the test. Exercise test data were determined to be valid if participants achieved ≥85% of their age-predicted maximum heart rate determined using the Tanaka formula (208 – 0.7 × age) (17). At baseline, year 7, and year 20, 81, 93, and 79% of examinees, respectively, achieved 85% of their age-predicted maximum. Cardiorespiratory fitness was determined based on the duration that participants were able to walk or run on the treadmill. We calculated the relative fitness change as the difference between fitness measured at baseline and follow-up (examination year 7 or 20) divided by baseline fitness. We studied the association between diabetes and relative fitness change per SD change from the sample mean.

Diabetes assessment

Blood was drawn and processed at the central laboratory according to standard procedures (13). Glucose was assayed using the hexokinase method. Diabetes was determined based on a combination of measured fasting glucose levels (≥7.0 mmol/l) at examination years 7, 10, 15, or 20; self-report of oral hypoglycemic medications or insulin (all examinations); or a 2-h postload glucose ≥11.1 mmol/l at examination years 10 and 20. The incidence of diabetes over 20 years was determined among participants who did not have diabetes at baseline based on fasting glucose levels. The 13-year incidence of diabetes was determined among participants who did not have prevalent diabetes through the year 7 follow-up examinations, but who developed diabetes at examination years 10, 15, or 20. Follow-up time was calculated from the baseline examination until diabetes was identified or until the last examination, whichever came first.

Other measurements

Age, race, education, cigarette smoking status, and medication use were ascertained by interview at all examinations. Height, weight, and waist circumference were measured, and BMI was calculated (weight in kilograms divided by the square of height in meters). Self-reported physical activity was assessed by a validated interview-administered questionnaire (18). The average of the last two seated resting (at least 5 min) blood pressure measurements was used to determine systolic and diastolic blood pressure (13). Fasting insulin was analyzed with a radioimmunoassay technique that used an overnight equilibrium incubation (17,18).

Statistical analysis

All analyses were stratified by sex. Before modeling, we tested and confirmed that the proportional hazards assumption was valid using time × fitness interaction terms ($P > 0.05$). Next, we evaluated the presence of effect modification by race, obesity, and impaired fasting glucose at baseline status using multiplicative interaction terms in a Cox proportional hazards model. Because the interaction between race and baseline fitness in men was statistically significant ($P < 0.05$), we calculated race- and sex-specific hazard ratios (HRs) and 95% CIs for the association between baseline fitness (per 2-min decrement) and the 20-year incidence of diabetes. No interactions by race were observed for analyses of the 7- or 20-year changes in fitness, so analyses are pooled by race. To compare the relative strength of association of each covariate with incident diabetes, we calculated HRs for each continuously measured covariate per SD of change from the mean value (i.e., standardized coefficients). We used ANOVA modeling to test whether the mean relative change in fitness between baseline and examination year 20 differed between participants who developed incident diabetes over follow-up and those who did not. After testing the univariate association between incident diabetes and fitness change, we statistically adjusted for age and baseline measures of BMI, treadmill duration, smoking status, and physical activity participation. Statistical significance was determined as $P < 0.05$. All analyses were conducted using the SAS system (SAS Institute, Cary, NC).

RESULTS

— Baseline characteristics of the analysis sample stratified by sex have been reported previously (11). In brief, women and men in the cohort were ~24.9 years old at baseline. Baseline treadmill test duration was highest in white men (12.5 ± 2.7 min) followed by black men (11.8 ± 2.9 min), white women (9.5 ± 2.9 min), and black women (7.5 ± 2.3 min). On average, black women were overweight (BMI 25.5 kg/m^2), whereas black men, white men, and white women had BMIs of 24.6, 24.3, and 23 kg/m^2, respectively. White and black men had the highest levels of baseline fasting glucose (4.7 and 4.6 mmol/l, respectively) followed by white women (4.5 mmol/l) and black women (4.4 mmol/l).

Over 20 years, the rate of diabetes (per 1,000 person-years) was higher in black women (5.8) and men (4.7) than in white men (3.4) and women (2.5). Baseline fitness (per 2-min decrement) was inversely associated with diabetes incidence in all race-sex groups after adjustment for age, smoking, family history of diabetes, and baseline fasting glucose (Table 1). With the exception of white men, treadmill duration at baseline was not associated with the incidence of diabetes after adjustment for baseline BMI. Heterogeneity by race among men ($\chi^2 = 17.9$, $P < 0.001$) was most evident after statistical

Table 1—*Association of baseline fitness and other covariates with the development of incident diabetes over 20 years by race-sex group*

	White men	Black men	White women	Black women
n	1,026	806	1,119	1,035
Model 1				
Treadmill test duration (per −2.7 min)	3.36 (2.44–4.63)	1.80 (1.26–2.58)	3.15 (2.03–4.87)	2.03 (1.41–2.91)
Age (per 3.6 years)	1.43 (1.04–1.95)	0.95 (0.73–1.24)	0.93 (0.69–1.25)	0.99 (0.80–1.21)
Ever vs. never smoked	0.88 (0.51–1.51)	1.41 (0.83–2.41)	1.04 (0.58–1.87)	1.87 (1.23–2.87)
Family history of diabetes (yes vs. no)	1.38 (0.66–2.89)	1.93 (1.03–3.62)	3.20 (1.68–6.07)	2.33 (1.49–3.64)
Physical activity (per 299 EU)	0.95 (0.69–1.30)	0.98 (0.78–1.24)	1.13 (0.78–1.65)	1.05 (0.80–1.39)
Baseline fasting glucose (per 0.45 mmol/l)	1.56 (1.20–2.03)	1.52 (1.18–1.95)	1.33 (1.01–1.75)	1.96 (1.62–2.37)
Model 2				
Treadmill test duration (per 2.7 min)	2.30 (1.52–3.48)	0.79 (0.51–1.25)	1.57 (0.92–2.67)	1.48 (0.95–2.31)
Age (per 3.6 years)	1.34 (0.97–1.86)	0.83 (0.63–1.09)	0.88 (0.65–1.20)	0.97 (0.79–1.19)
Ever vs. never smoked	0.96 (0.55–1.66)	1.84 (1.05–3.22)	0.99 (0.54–1.80)	1.87 (1.22–2.88)
Family history of diabetes (yes vs. no)	1.26 (0.59–2.70)	2.15 (1.12–4.14)	3.12 (1.62–6.01)	2.20 (1.42–3.47)
Physical activity (per 299 EU)	0.87 (0.62–1.20)	0.92 (0.72–1.17)	1.06 (0.71–1.57)	1.01 (0.76–1.34)
Baseline fasting glucose (per 0.45 mmol/l)	1.39 (1.06–1.84)	1.50 (1.15–1.97)	1.20 (0.89–1.60)	1.88 (1.55–2.29)
Baseline BMI (per 4.7 kg/m^2)	1.79 (1.31–2.45)	2.51 (1.83–3.44)	1.81 (1.38–2.38)	1.23 (1.03–1.47)

Data are HRs (95% CI). All continuously measured covariates (i.e., treadmill duration, age, physical activity, fasting glucose, and BMI) are presented per SD change from the mean. *P* values for race interaction using model 2: in men, black vs. white $\chi^2 = 17.9$, $P < 0.001$; in women, black vs. white $\chi^2 = 2.31$, $P = 0.13$. EU, exercise units (100 EU is roughly equivalent to participant in a vigorous activity, 2 or 3 h/week for 6 months of the year (18).

adjustment for baseline BMI when the hazard ratio for fitness attenuated and the direction of association changed. Findings were similar when we adjusted for waist circumference instead of BMI or when we used BMI values at the time of diabetes identification or last follow-up visit. Neither the magnitude nor the direction of association between fitness and incident diabetes changed when we restricted analyses to the 98% of participants who had normal fasting glucose at baseline.

Baseline obesity did not modify the association between fitness and incident diabetes in white participants, whereas it was a significant effect modifier in black men and a borderline modifier in black women. There were 40 cases of diabetes in 725 black men who were not obese at baseline and 21 cases in 81 black men who were obese at baseline. Fitness per 2.7-min duration decrement was not associated with the development of diabetes in either nonobese (HR 0.98 [95% CI 0.57–1.70]) or obese (0.60 [0.24–1.49]) black men, although the interaction term was statistically significant (χ^2 interaction 11.5, $P < 0.01$). In contrast, lower fitness (per 2 min) was only associated with incident diabetes ($n = 57$) in 823 black women who were not obese at baseline (1.92 [1.09–3.39]). There was no association between fitness and incident diabetes ($n = 41$) in 190 black women who were obese at baseline (0.92 [0.43–1.96]; χ^2 interaction = 3.2, $P = 0.08$).

Over 7 years, treadmill duration declined from an average of 8.8 to 8.1 min in women (relative change −7.6 ± 21%) and from 12.3 to 11.1 min (relative change −9.2 ± 16) in men. Baseline treadmill duration was modestly, but significantly ($P < 0.001$), correlated with the relative 7-year change in duration in women ($r = −0.16$) and men ($r = −0.21$). The adjusted hazard of developing diabetes was 50% higher in women and double in men per 19% decline in relative treadmill duration over 7 years (Table 2). Baseline treadmill duration was at least as strong a predictor of incident diabetes as change in duration. The addition of baseline BMI to the models had little additional influence on the estimates.

Treadmill duration declined 27.5 ± 19.9 and 27.3 ± 17.5% over 20 years in women and men, respectively. Baseline fitness was correlated with relative changes in fitness over 20 years in men ($r = −0.14$, $P < 0.0001$) but not women ($r = −0.03$, $P = 0.31$). At the 20-year follow-up examination, the incidence of diabetes was 7.2% ($n = 89$) in women and 7.3% ($n = 73$) in men. In unadjusted models, women who developed diabetes during follow up experienced larger ($P < 0.01$) declines in fitness (−34.9%) than women who did not (−27.0%). Similarly, men who developed diabetes also experienced a significantly ($P < 0.01$) greater decline in fitness (−37.9%) than men who did not (−26.5%). After adjustment for age, race, smoking status, baseline physical activity, BMI, and treadmill test duration, findings were similar and remained statistically significant (Fig. 1).

CONCLUSIONS — A single measure of cardiorespiratory fitness in young adulthood and changes in fitness over 7 years were each significantly inversely associated with the development of diabetes over 20 years, an observation that was largely accounted for by baseline BMI. Participants who developed diabetes over 20 years experienced greater declines in fitness than their counterparts who remained free of diabetes. Sex is an established determinant of fitness; however, we report with few exceptions that the magnitude of association between fitness and diabetes incidence is similar for women and men.

Our findings were consistent with those of other observational studies reporting inverse associations of fitness with incident diabetes (11,19–22). Mechanisms by which fitness may protect against diabetes development include weight loss, improved muscle insulin sensitivity, improved endothelial function and autonomic function, and reduced inflammation and oxidative stress (19,23). Most likely, these related factors are highly correlated with each other and with adiposity and combine to lower diabetes risk in the presence of increased activity or improved fitness.

We observed a marked attenuation in the association of fitness with diabetes in-

Table 2—*Incidence of diabetes from 1992–1993 through 2005–2006 by 7-year relative declines in fitness by sex*

	Women	Men
n	948	860
Model 1		
7-year change in treadmill test duration (per −19%*)	1.51 (1.19–1.92)	2.02 (1.46–2.79)
Baseline fitness (per 4.3 min)	2.56 (1.69–4.00)	2.86 (1.89–4.35)
Age (per 3.6 years)	0.87 (0.67–1.12)	0.98 (0.72–1.34)
Race (black vs. white)	1.32 (0.71–2.46)	0.79 (0.42–1.46)
Ever vs. never smoked	1.43 (0.82–2.50)	1.47 (0.80–2.69)
Family history of diabetes (yes vs. no)	1.89 (1.06–3.38)	1.64 (0.73–3.68)
Baseline fasting glucose (per 0.46 mmol/l)	1.64 (1.31–2.06)	1.17 (0.88–1.56)
Model 2		
7-year change in treadmill test duration (per −19%*)	1.46 (1.15–1.85)	2.03 (1.43–2.87)
Baseline fitness (per 4.3 min)	1.89 (1.14–3.11)	2.01 (1.24–3.25)
Age (per 3.6 years)	0.85 (0.65–1.10)	0.90 (0.66–1.24)
Race (black vs. white)	1.39 (0.74–2.60)	0.69 (0.37–1.31)
Ever vs. never smoked	1.44 (0.82–2.52)	1.72 (0.93–3.19)
Family history of diabetes (yes vs. no)	1.87 (1.05–3.35)	1.69 (0.74–3.86)
Baseline fasting glucose (per 0.46 mmol/l)	1.59 (1.26–2.01)	1.11 (0.83–1.48)
Baseline BMI (per 4.7 kg/m^2)	1.27 (1.02–1.58)	1.77 (1.28–2.46)

Data are HRs (95% CI). Model 1 adjusts for age, race, smoking, family history of diabetes, and baseline treadmill duration. Model 2 adjusts for model 1 + baseline BMI. *Relative change per SD from the population mean (−8.3%).

cidence when we statistically adjusted for BMI or waist circumference at the time of the fitness measurement. When the relative strength of association of baseline BMI and fasting glucose are compared using standardized coefficients, baseline BMI appears relatively more strongly associated with the incidence of diabetes than baseline fasting glucose or baseline fitness (in black men and white women). Despite similar baseline BMI between black and white men, BMI was more strongly associated with the development of diabetes in black men as evidenced by attenuation and a reversal in the direction of the effect estimate once BMI is included in the model.

Previous findings in this cohort suggested that the association of fitness with diabetes incidence was only present among participants who were not obese (BMI <30 kg/m^2) at baseline (11). In the present study, which includes longer follow-up time and stratification by sex and race, we observed this pattern only among black women in the cohort. These findings suggest that the mechanism by which fitness decreases risk for diabetes is through the regulation of body mass.

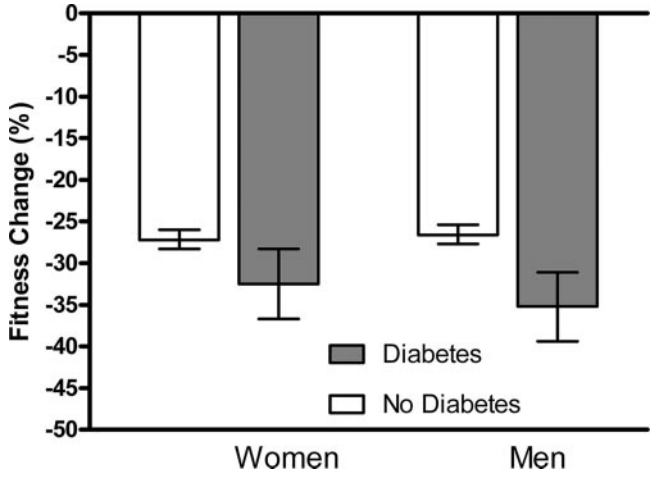

Figure 1—*Mean (95% CI) changes in relative fitness over 20 years by incident diabetes (1985/1986–2005/2006), adjusted for age, race, baseline smoking status, BMI, physical activity, and treadmill test time.*

Fitness is expected to decline with aging (8,20); however, there was a marked variation in fitness change in our sample as evidenced by the large SD. It was not surprising that marked declines in fitness were associated with a greater incidence of diabetes. Although we did not test the hypothesis that maintaining or increasing physical activity to sustain or improve fitness could prevent some proportion of incident diabetes, evidence from clinical trials including the Diabetes Prevention Program suggests that this effect is plausible (1,3).

The influence of fitness on diabetes risk was similar by sex. Our finding of no interaction by sex is noteworthy because fitness is lower in women than in men. Although some proportion of fitness is due to biological and structural differences between sexes, physical activity behaviors are the principal modifiable determinate of fitness. National reports and findings in the CARDIA study indicate that women are less physically active than men (21,22). Consequently, a substantial number of women are not achieving their sex-based potential for fitness and according to our findings could be at risk for developing diabetes.

Strengths and limitations

Strengths of our study include extended follow-up, diabetes determination based on measured glucose, a study sample balanced by race and sex, and most importantly, the use of objective measures of fitness at multiple time points. Fitness is a physiological state that reflects a combination of factors including physical activity, genetics, body composition, and other physical factors. By studying fitness in relation to diabetes incidence, we increased the precision of our primary exposure measure and reduced the error associated with measuring physical activity using recall methods. Our study represents the longest observational study of a population-based sample of adults who have objective measures of both fitness and diabetes incidence.

Despite the availability of diet history data at three time points during the study, we did not incorporate estimates into our study because of its complex association with activity levels and body composition. Instead, we chose to focus on fitness,

which is measured with greater precision and validity than self-reported diet or physical activity levels. Finally, although we statistically adjusted for BMI or waist circumference (in our secondary analyses) in an attempt to tease apart the role of fitness versus body composition on diabetes incidence, BMI is not a direct measure of adiposity or lean mass. Further, the ability of BMI to accurately estimate fat mass may vary by age, sex, and race group (24). Prior studies in this cohort demonstrated that the percentage of body fat that is metabolically active visceral fat is lower in black men than in white men even when corrected for total body fatness, whereas differences among black and white women were eliminated after adjustment for total body fatness (25). Consequently, our findings, particularly those stratified by race and sex should be carefully considered before and after adjustment for BMI.

Implications

Regular physical activity to improve and maintain cardiorespiratory fitness is an important component of a healthy lifestyle. Unfortunately, national statistics indicate that physical activity levels decline with age and are lower in women than in men (21). One consequence is that older adults and women are at risk for having lower fitness and have an increased risk for developing diabetes. By describing the association of changes in fitness over time with the long-term development of diabetes, we have identified one risk factor that, if modified, could lower the incidence of diabetes in the population.

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