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Twenty year fitness trends in young adults and incidence of prediabetes and diabetes: the CARDIA study

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Abstract

Aims/hypothesis—The prospective association between cardiorespiratory fitness (CRF) measured in young adulthood and middle age on development of prediabetes, defined as impaired fasting glucose and/or impaired glucose tolerance, or diabetes by middle age remains unknown. We hypothesised that higher fitness levels would be associated with reduced risk for developing incident prediabetes/diabetes by middle age.

Methods—Participants were from the Coronary Artery Risk Development in Young Adults (CARDIA) study who were free from prediabetes/diabetes at baseline (year 0 [Y0]: 1985–1986).

CRF was quantified by treadmill duration (converted to metabolic equivalents [METs]) at Y0, Y7 and Y20 and prediabetes/diabetes status was assessed at Y0, Y7, Y10, Y15, Y20 and Y25. We use an extended Cox model with CRF as the primary time-varying exposure. BMI was included as a time-varying covariate. The outcome was development of either prediabetes or diabetes after Y0. Model 1 included age, race, sex, field centre, CRF and BMI. Model 2 additionally included baseline (Y0) smoking, energy intake, alcohol intake, education, systolic BP, BP medication use and lipid profile.

Results—Higher fitness was associated with lower risk for developing incident prediabetes/ diabetes (difference of 1 MET: HR 0.99898 [95% CI 0.99861, 0.99940], $p < 0.01$), which persisted (difference of 1 MET: HR 0.99872 [95% CI 0.99840, 0.99904], $p < 0.01$] when adjusting for covariates.

Conclusions/interpretation—Examining participants who had fitness measured from young adulthood to middle age, we found that fitness was associated with lower risk for developing prediabetes/diabetes, even when adjusting for BMI over this time period. These findings emphasise the importance of fitness in reducing the health burden of prediabetes and diabetes.

Keywords

Introduction

Americans are becoming increasingly obese and sedentary [1], and this parallels the increasing epidemic of diabetes [2]. As physical activity is inversely associated with incident diabetes[3], the metabolic syndrome [4] and mortality [5], there is mounting interest in reducing morbidity and mortality by increasing physical activity and reducing sedentary time [6]. Although not equivalent due to genetics and behaviour effects, physical activity is directly related to cardiorespiratory fitness (CRF) [7]. Several prospective studies have observed higher CRF to be associated with lower future risk of coronary heart disease [8], the metabolic syndrome [9], diabetes [10] and total mortality[8].

Yet the benefits of higher CRF in young adulthood are not necessarily maintained across the lifespan. Compared with decreases in CRF over time, longitudinal improvement in CRF or maintenance of CRF through adulthood are associated with lower risk of hypertension [11], the metabolic syndrome [9], hyperlipidaemia [11], diabetes [10], cardiovascular mortality [12] and total mortality [13]. This literature, however, remains limited for several reasons. Much [12, 13], but not all [10, 11], of the current literature on CRF change has been focused on men, with either varying duration between CRF assessments [11, 12], or a limited period (5–7 years) between CRF assessments [10, 13]. Although it is generally presumed that higher fitness is associated with lower rates of prediabetes, defined as impaired fasting glucose and/or impaired glucose tolerance, or diabetes prospectively, we present a unique opportunity to address this presumption using the Coronary Artery Risk Development in Young Adults (CARDIA) study (ClinicalTrials.gov: NCT00005130). The CARDIA study objectively documented fitness by using treadmill exercise testing to measure CRF at baseline (year 0 [Y0]: age 18–30 years), in early adulthood (Y7: age 25–37 years) and again

at middle age (Y20: age 38–50 years), with documentation of incident prediabetes/diabetes over 25 years. This project extends a previous CARDIA analysis that reported that higher CRF in young adulthood and less CRF decline (over 7 years) reduce the 20 year risk for developing incident diabetes [10]. We hypothesised higher fitness levels, even after adjusting for changes in BMI, would be associated with reduced risk for developing incident prediabetes/diabetes.

Methods

Participants

The CARDIA study is a prospective, multicentre, cohort study designed to investigate trends and determinants of coronary heart disease risk factors in young adults. Black and white women and men (ages 18–30 years at Y0) were recruited and examined in 1985–1986 from four US communities (Birmingham, AL; Chicago, IL; Minneapolis, MN and Oakland, CA) and balanced on age, race, sex and educational attainment as previously described [14]. A total of 5,115 participants were enrolled at baseline (Y0) with follow-up examinations at 2, 5, 7, 10, 15, 20 and 25 years after baseline, with retention of 91%, 86%, 81%, 79%, 74%, 72% and 72% of the surviving cohort, respectively. All participants provided written informed consent. The study was approved by the Institutional Review Boards from each participating institution. For this particular study, we excluded participants that did not have baseline treadmill results ($n = 69$ excluded) or diabetes assessment at baseline (additional $n = 80$ excluded). We also excluded the CARDIA participants who had a diagnosis of prediabetes at Y0 (additional $n = 105$ excluded) and diabetes (additional $n = 28$ excluded) or did not have at least one follow-up visit documenting prediabetes/diabetes status (additional $n = 460$ excluded). After application of exclusion criteria, 4,373 CARDIA participants were available for analysis. Participants who did not develop prediabetes/diabetes by the time of their last available examination visit were censored.

CRF

A symptom-limited graded treadmill exercise testing using a modified Balke protocol [15] was used to assess CRF in the CARDIA study. The test protocol was designed to assess maximal, symptom-limited performance. After baseline measurement of pulse, BP and ECG, the participant started the protocol. The protocol consisted of nine stages (2 min/stage, maximum 18 min/test) of progressively increasing difficulty, with the first six stages generally performed by walking. Stage 1 was 4.8 km/h at 2% grade (4.1 metabolic equivalents [METs]), progressing to stage 9 at 9.0 km/h at 25% grade (19.0 METs). The exercise test was terminated either due to fatigue (82.5%), shortness of breath (7.5%), abnormal ECG response (1%), medical reasons (5.3%), participant refusal (1.6%) or completion of the entire protocol (0.2%) [15]. As previously described, treadmill duration as assessed by the Balke protocol has been shown to be highly predictive ($r = -0.94$) of maximum oxygen uptake ($\dot{V}O_{2max}$) [16]. Treadmill duration was converted to equivalent METs using a previously published conversion formula [15]. In the CARDIA cohort, the treadmill test was performed at Y0, Y7 and Y20. Because of an identified systemic protocol violation at Y7 at one site [17], the treadmill results from Y0, Y7 and Y20 were used when appropriate (three sites). In the extended Cox model, fitness prior to Y7 was represented by

Y0 CRF (all sites), fitness between Y7 and Y20 was represented by Y7 CRF (for the three valid sites: $n = 2,415$, otherwise Y0 CRF was used for the remaining site: $n = 1,195$) and fitness between Y20 and Y25 was represented by Y20 CRF (all sites).

Ascertainment of prediabetes and diabetes

At Y0, Y7, Y10, Y15, Y20 and Y25, prediabetes and diabetes status were assessed. The outcome was development of either prediabetes or diabetes (described as prediabetes/ diabetes) after Y0. Once a participant developed either documented prediabetes or diabetes after Y0, they were considered to have an event and were subsequently censored. The outcome for the extended Cox model was time to development of incident prediabetes/ diabetes. This was calculated as the time to the CARDIA follow-up visit where the diagnosis was made. Participants were classified as having prediabetes if they met any of the following criteria: fasting glucose 5.6–6.9 mmol/l; 2 h OGTT glucose 7.8–11.1 mmol/l or HbA$_{1c}$ 5.7– 6.4% (39–46 mmol/mol IFCC). Participants were classified as having diabetes if any of the following criteria was met: fasting glucose 7 mmol/l; use of medications for diabetes treatment; 2 h GTT 11.1 mmol/l or HbA$_{1c}$ 6.5% (48 mmol/mol IFCC) [10]. Serum glucose concentrations were measured using the hexokinase method.

Covariates

Covariates were selected in our analysis due to their clinical relevance and association with diabetes and/or CRF. Relevant covariates measured at Y0 included age, sex, race, field centre, BMI, smoking (current/former/never), energy intake (kJ/day), alcohol intake (ml/ day) and education level (highest year of school completed). To quantify physical activity (reported as exercise units [EU]), the CARDIA physical activity history questionnaire was used, which was an interviewer-based self-report of duration and intensity of participation in 13 categories of exercise over the previous 12 months [18]. As a reference, 300 EU approximates to 150 min of moderate-intensity activity (3–5 METs, with 1 MET defined as energy expenditure at rest or 3.5 ml O_2/kg) per week or 30 min of moderate-intensity activity 5 days per week [19]. These covariates were measured by trained and certified staff, using standardised protocols across field centres and examinations with quality control monitoring [14, 20]. Age, race and sex were confirmed during the clinic visits. Diet was measured using an interviewer-administrated, validated, semi-quantitative, food frequency questionnaire [21].

Body weight was measured with light clothing to the nearest 0.09 kg, body height without shoes was measured to the nearest 0.5 cm and BMI was calculated from these measures in units of kg/m^2 [20]. Because time-varying BMI was included in the analysis, we used Y0 BMI as a predictor for outcomes between Y0 and Y7, Y7 BMI as a predictor for outcomes between Y7 and Y10, Y10 BMI for outcomes between Y10 and Y15, Y15 BMI for outcomes between Y15 and Y20 and Y20 BMI for outcomes between Y20 and Y25.

We also used several cardiometabolic risk factors (systolic BP [SBP], medication treatment of hypertension, HDL-cholesterol and LDL-cholesterol) in the analysis. Cardiometabolic risk factors were measured using standardised protocols across field centres and examinations with quality control monitoring [14, 20]. BP was measured three times after a

5 min rest, using a Hawksley random zero sphygmomanometer (WA Baum Company, Copaigue, NY, USA) on the right arm of the seated participant. The average of the last two measures of three was used for Y0 SBP [20]. Fasting plasma blood samples were sent to the Northwest Lipid Research Laboratories, University of Washington (Seattle, WA, USA) for lipid determination. Total cholesterol and triacylglycerol (TG) were measured enzymatically [22]. HDL-cholesterol was determined after dextran sulfate–magnesium chloride precipitation [23] and LDL-cholesterol was calculated using the Friedewald equation [24].

Statistical analysis

In Table 1, participant Y0 characteristics are presented by whether they developed incident prediabetes/diabetes by Y25, using means and SD for continuous variables and percentages for categorical variables. Two-sample t tests and χ^2 tests were performed for continuous variables and categorical variables, respectively, to compare the two groups.

Modelling was performed using an extended Cox regression analysis, with inclusion of fitness and BMI as time-varying covariates. The outcome was incidence of prediabetes or diabetes as documented at Y7, Y10, Y15, Y20 or Y25. Model 1 included age, race, sex, field centre, time-dependent CRF and time-dependent BMI. Model 2 additionally included Y0 lifestyle factors (smoking, energy intake, alcohol intake, education, SBP, medication for hypertension, LDL-cholesterol and HDL-cholesterol). For both Model 1 and Model 2, we examined whether there was significant interaction between race and sex. As interaction between race and sex was not significant, this was therefore not included in Model 1 and Model 2. The extended Cox regression modelling approach eliminates the need to test for proportional hazards because the models are not restricted to baseline values of the exposures of interest. All analyses were performed using Statistical Analysis Software (version 9.3; SAS Institute, Cary, NC, USA).

Results

Subject characteristics

Compared with CARDIA participants who did not develop prediabetes or diabetes by Y25 (Table 1), the participants who developed prediabetes or diabetes by Y25 tended to be older, black race and male sex, were more likely to take blood pressure medication, more likely to smoke, have higher weight, BMI, waist circumference, SBP, LDL, daily alcohol intake and daily energy intake, and show a decline in treadmill duration over 20 years. Compared with CARDIA participants who did not develop prediabetes or diabetes by Y25, the participants who developed prediabetes or diabetes by Y25 group had lower Y0 CRF (as quantified by Y0 treadmill duration and converted to Y0 treadmill energy expenditure in METs), lower HDL-cholesterol, lower Y7 CRF (as quantified by Y7 treadmill duration and converted to Y7 treadmill energy expenditure in METs), lower Y20 CRF (as quantified by Y20 treadmill duration and converted to Y20 treadmill energy expenditure in METs) and a lower proportion who increased their CRF over 20 years. There was no difference in educational level or physical activity level between the two groups.

Subjective physical activity obtained by questionnaire was related to objectively measured CRF as follows: Y0 physical activity correlated with Y0 CRF (METs) ($r = 0.39$, $p < 0.01$, all sites used); Y0 CRF (METs) correlated with Y7 CRF (METs) ($r = 0.76$, $p < 0.01$, 3 sites used); Y0 CRF (METs) was correlated with Y20 CRF (METs) ($r = 0.69$, $p < 0.01$, all sites used).

Association of CRF with development of prediabetes/diabetes by Y25

In this study (N = 4,373), 1,927 (44.1%) participants did not develop either prediabetes or diabetes by Y25. By Y25, 1,941 (44.5% participants developed prediabetes and 505 (11.5%) participants developed diabetes.

We examined associations between CRF (METs) with the development of prediabetes or diabetes by Y25 (Table 2). While taking the time-varying aspect of BMI into account, we observed that higher CRF (per 1 MET increment) was associated with lower risk for developing incident prediabetes/diabetes (0.99898 [95% CI 0.99861, 0.99940]), which persisted (0.99872 [95% CI 0.99840, 0.99904]) after accounting for Y0 lifestyle factors (smoking, energy intake, alcohol intake, education) SBP, medication for blood pressure, LDL-cholesterol levels and HDL-cholesterol levels.

Discussion

As the benefit of high levels of fitness in young adulthood is well documented in current literature, this study evaluated the association between prospectively measured CRF over 20 years on incident prediabetes or diabetes by middle age. We found that CRF was associated with lower risk for developing prediabetes/diabetes, even when adjusting for BMI over this time period. These findings emphasise the importance of continued lifelong fitness in reducing the risk for developing prediabetes/diabetes.

Given high baseline levels of fitness, the prospective health benefits are well established [8, 13], with CRF mitigating the risk for developing impaired fasting glucose and type 2 diabetes even in obese participants [25]. The natural extension of this literature is to evaluate the metabolic impact of fitness, objectively quantified prospectively. By leveraging the unique design of CARDIA, this study complements and extends the current literature [10–13] by examining the association of changes in fitness over 20 years, from young adulthood to middle age, on developing prediabetes/diabetes, while considering concurrent changes in BMI.

There are several mechanisms by which continued fitness may reduce the risk for prediabetes and diabetes. Twenty weeks of supervised exercise training has been shown to improve the components of the metabolic syndrome, such as reduced TG, fasting glucose, waist circumference and improved HDL-cholesterol levels[4]. One mechanism may arise from the effect of exercise on visceral fat. Compared with subcutaneous fat, accumulation of visceral fat is associated with more adverse metabolic risk factors [26] and higher risk of diabetes [27]. With ageing, muscle mass declines[28, 29] and visceral fat increases [30, 31]. Since exercise training, depending on type, duration and intensity, reduces visceral fat and increases muscle mass [32, 33], this may be a significant protective mechanism. In addition,

type 2 diabetes is associated with low-grade systemic inflammation [34]. Potentially, another mechanism may arise from the anti-inflammatory effect of exercise [35, 36]. Short-term (20 weeks) supervised exercise training has been shown to reduce C-reactive protein (median 1.34 mg/l reduction) in participants with the highest level of C-reactive protein (> 3.0 mg/l) prior to training [37]. In the absence of weight change, smaller clinical studies have shown that exercise training improving fitness, as measured by $\dot{V}O_{2max}$, and insulin sensitivity, as measured by the gold standard hyperinsulinaemic–euglycaemic clamp [38, 39]. Our findings support the long-term implications of these short-term mechanistic findings.

This study is clinically relevant as it provides evidence to support commonly accepted dogma that fitness is beneficial in reducing the risk for prediabetes/diabetes. As this benefit remained significant even when adjusting for BMI, exercise programmes remain critically important for reducing the adverse health impact of prediabetes, diabetes, and their associated complications. From a clinical standpoint, the amount of physical activity required to increase an individual's fitness by 1 MET (3.5 ml O_2 kg^{-1} min^{-1}) depends on multiple factors, which include the age, health and baseline activity of the individual as well as the duration, intensity and form of the exercise. As a reference, the STRRIDE-AT/RT (Studies Targeting Risk Reduction Interventions through Defined Exercise-Aerobic Training and/or Resistance Training) study found that sedentary obese/overweight men and women (mean age 51 years, baseline $\dot{V}O_{2max}$ 27.1 ml O_2 kg^{-1} min^{-1}) increased $\dot{V}O_{2max}$ by 3.9 ml O_2 kg^{-1} min^{-1} with 8 months of aerobic training (0.06 mJ (14 kcal)/kg per week) and by 4.1 ml O_2 kg^{-1} min^{-1} with 8 months of combined aerobic and resistance training (0.06 mJ (14 kcal)/kg per week + 180 min resistance training per week) [40]. The high rate of incident prediabetes in this cohort additionally highlights the preventative aspect of fitness in reducing prediabetes, which predicts and precedes the development of diabetes.

This study has several strengths. It focuses on an important demographic—young adults (age 18– 30 years) followed prospectively through to middle age (age 43–55 years). It also capitalises on several key features of CARDIA, specifically the prospective objective measurement of CRF by treadmill testing, balanced cohort in terms of sex, race and educational attainment, outcome measurements using standardised protocols with rigorous quality control and frequent in-person follow-up visits to ascertain incident prediabetes/ diabetes. Consequently, the ability to quantify time to event, on the scale of the CARDIA study, is a study strength. Because of its objective measures of CRF over several time points and standardised long-term follow-up, CARDIA is a unique resource with which to address the relative association of prospective measures of fitness with prospective development of incident prediabetes/diabetes.

This study also has several limitations. CRF is not equivalent to physical activity and has a significant genetic component [41]. However, physical activity has been shown to have a dose–response relationship to cardiovascular CRF, with physical activity positively correlated with CRF [7]. We also saw a modest correlation between baseline physical activity and fitness in our data. In CARDIA, CRF was measured by treadmill duration and did not account for weight, with the possibility that reduced treadmill duration is not necessarily due to reduced CRF but rather weight gain. We adjusted for this possibility by including time-varying BMI in our modelling. We also acknowledge that participants,

particularly in the group that developed prediabetes/diabetes by Y25, may terminate the treadmill test due to reasons other than reaching their full physical capability. Although this may reduce the quantification of CRF by treadmill duration, early test termination, even if participants are physically capable, still remains an adverse prognostic indicator. We also acknowledge the presence of the 'healthy cohort' phenomenon, such that participants who can be followed up are generally healthier than those lost to follow-up. This limitation would tend to underestimate the observed associations by excluding those more likely to develop prediabetes/diabetes and less likely to maintain fitness levels.

In summary, by examining participants who had fitness measured from young adulthood to middle age, we found that fitness was associated with lower risk for developing prediabetes/ diabetes, even when adjusting for BMI over this time period. These findings emphasise the importance of fitness in reducing the health burden of prediabetes/diabetes.

Acknowledgments

Abbreviations

CARDIA	Coronary Artery Risk Development in Young Adults
CRF	Cardiorespiratory fitness
MET	Metabolic equivalent
SBP	Systolic BP
TG	Triacylglycerol

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Table 1

Baseline (Y0) characteristics of CARDIA participants comparing those who did and did not develop incident prediabetes/diabetes by middle age (Y25)

Characteristic	Absence of prediabetes/diabetes by Y25 (n=1,927)	Development of incident prediabetes/diabetes by Y25 (n=2,446)	p value
Age (years)	24.4±3.7	25.2±3.6	<0.01
Race, white	1,090 (56.6)	1,105 (45.2)	<0.01
Sex, female	1,213 (63)	1,200 (49.1)	<0.01
Weight (kg)	66.9±14.0	74.0±16.6	<0.01
BMI (kg/m^2)	23.2±4.2	25.3±5.2	<0.01
Waist circumference (cm)	75.0±9.7	79.9±11.7	<0.01
SBP (mmHg)	109.0±10.4	112±10.9	<0.01
No medications for BP	1,895 (98.4)	2,378 (97.3)	0.02
LDL-cholesterol (mmol/l)	2.7±0.8	2.9±0.8	<0.01
HDL-cholesterol (mmol/l)	1.4±0.3	1.3±0.3	<0.01
Y0 Education level, >12 years	1,208 (62.7)	1,501 (60.4)	0.36
Cigarette smoking			0.01
Never	1,123 (58.6)	1,380 (56.8)	
Former	275 (14.4)	301 (12.4)	
Current	518 (27.0)	748 (30.8)	
Alcohol (ml/day)	10.7±20.4	12.5±21.9	<0.01
Physical activity intensity score (EU)	418±288	421±304	0.77
Total energy intake (mJ/day)	11.7±6.2	12.6±7.6	<0.01
Total energy intake (kcal/day)	2,791±1,493	3,021±1,809	<0.01
Y0 treadmill duration, all sites (s)	590±180	575±187	0.005
Y0 treadmill energy expenditure, all sites (METs)	11.8±2.9	11.5±3.0	<0.01
Y7 treadmill duration, three sites (s)	558±174[a]	527±177[b]	<0.01
Y7 treadmill energy expenditure, three sites (METs)	11.3±2.7[a]	10.8±2.8[b]	<0.01
Y20 treadmill duration, all sites (s)	460±158[c]	407±159[d]	<0.01
Y20 treadmill energy expenditure, all sites (METs)	9.8±2.5[c]	8.9±2.6[d]	<0.01
Y20–Y0 change in treadmill duration (s)	−148±135[c]	−182±134[d]	<0.01
Participants who increased CRF over 20 years	119 (10.8)	111 (6.8)	<0.01

Data are means ± SD for continuous variables or number (%) for categorical variables, N=4,373

[a] n=1,018

[b] n=1,397

[c] n=1,097

[d] n=1,632

Table 2

Association of CRF change from young adulthood to middle age with development of prediabetes/diabetes by middle age

CRF	Model 1[a]		Model 2[b]	
	HR (95% CI)	*p value*	HR (95% CI)	*p value*
CRF (per 1 MET increment)	0.99898 (0.99861, 0.99940)	<0.01	0.99872 (0.99840, 0.99904)	<0.01

[a]Model 1 included age, race, sex, field centre, CRF (measured in METs, time-varying at Y0, Y7 [when available] and Y20) and BMI (time-varying at all time points)

[b]Model 2 as for Model 1, additionally including the following Y0 variables: smoking, energy intake, alcohol intake, education, SBP, medication for blood pressure, LDL-cholesterol levels and HDL-cholesterol levels