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Fitness Change Effects on Midlife Metabolic Outcomes: The CARDIA Study

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Abstract

Purpose—Fitness decline, high BMI, and insulin resistance (IR) are associated with worsening cardiometabolic risk factors prospectively; modification of the fitness change effect by BMI and IR remains unknown.

Methods—Participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study without diabetes at Year 0 (Y0) [n=2048, 43.4% men, mean age 25] had fitness quantified by treadmill at Y0 and Y20. Y0 BMI was normal (nBMI<25 kg/m²) or high (hBMI ≥ 25 kg/m²). Y0 insulin resistance status was insulin sensitive [IS: HOMA-IR <1.84 (75%tile)] or insulin resistant [IR: HOMA-IR ≥ 1.84]. 4 groups were established: nBMI/IS, hBMI/IS, nBMI/IR, hBMI/IR. Y0 fitness was low (<33%tile for sex) or average-high (≥ 33%tile for sex). Fitness change (Treadmill time: Y20-Y0) was maintained [increase or decline < 20%tile for sex] or decreased [decline >20%tile for sex]. The outcomes were incident diabetes and percent change over 25 years in weight, waist girth, blood pressure, and lipid profile. Analysis was by multiple linear regression and proportional hazards regression with adjustment for individual characteristics.

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The results of the present study do not constitute endorsement by ACSM.

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Results—Maintained fitness after 20 years was associated with greater increase in HDL-C and less increase in weight, waist girth, blood pressure, and triglycerides than decreased fitness, similarly for the groups defined by BMI and IR. Maintained fitness reduced the rate of incident diabetes in IS but not IR participants.

Conclusions—Maintained fitness after 20 years was associated with more favorable middle age cardiometabolic risk factors than decreased fitness; this benefit might be blunted by baseline IR.

Keywords

Body Mass Index; Insulin Resistance; Cardiometabolic Risk Factors; Cardiorespiratory Fitness

Introduction

Americans are becoming increasingly obese and sedentary. In 2011, the majority of Americans reported either no or low physical activity.(10) Consequently, there is growing interest in the role of physical activity and fitness in reducing the morbidity and mortality associated with the obesity epidemic.

Physical activity has an established dose-response relationship with fitness.(11) Moderate to high fitness level, as measured by cardiorespiratory fitness (CRF) from exercise testing, has many established benefits. In several prospective studies, higher baseline CRF was associated with lower risk of future coronary heart disease,(2) metabolic syndrome,(8) diabetes(29) and total mortality.(2, 4) The implications of fitness, as described by a single measurement of CRF, (2, 4, 29) has been subsequently complemented by studies examining the effects of CRF change. Compared with peers with longitudinal CRF decrease, individuals with longitudinal CRF improvement or maintenance over time had lower risk of hypertension,(26) metabolic syndrome,(8, 26) hyperlipidemia,(26) diabetes,(9) cardiovascular mortality,(3)and total mortality.(3) Several factors, however, limit our understanding of CRF change and health outcomes. Most(3, 26) but not all(9) of the current literature has focused on a predominantly white male population, reducing generalizability. The time interval for measuring CRF change has varied greatly, typically spanning 5–7 years.(3, 8, 26) Although it had been previously shown in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort that participants who developed diabetes over 20 years had larger declines in fitness after 20 years than those who did not develop diabetes,(9) whether certain subpopulations, as described by body mass index (BMI) or insulin resistance, might be particularly affected remains unknown.

Since improving fitness on a population level is challenging and expensive, identification of populations at high risk for metabolic complications from either low baseline or decreased fitness over time would enhance the impact of fitness interventions. Antecedent obesity (21) and insulin resistance (13) increases the risk for adverse cardiometabolic outcomes, yet the health outcomes in common subgroups such as the “metabolically obese, normal-weight” (34) [~ 28% of the US population age 20 and older (40)] or “obese but metabolically healthy”(30) [8% of the US population age 20 and older(40)] remain less well described. Fitness may contribute to the “obese, metabolically healthy” phenotype,(30) however, the relative contribution of fitness change remains less understood.

The CARDIA cohort presents a unique opportunity to address this knowledge gap. CARDIA is a 25-year biracial prospective cohort study that has collected both fitness and cardiometabolic data over 25 years by standardized protocols with stringent quality control. Previously in CARDIA, it has been shown that young adults with elevated metabolic risk (as defined from a composite of blood pressure, glucose, insulin, high density lipoprotein cholesterol, triglycerides, and waist girth) had lower baseline CRF compared with young adults with normal metabolic risk; however, the rate of CRF decline after 20 years was similar between the two groups.⁽⁷⁾ As this earlier CARDIA study did not describe the relationship between change in long-term fitness and change in cardiometabolic risk factors,⁽⁷⁾ and another earlier CARDIA study did not subdivide by BMI and insulin resistance status,⁽⁹⁾ we will extend these previous findings by specifically examining fitness change from Y0 to Y20 and outcome change from Y0 to Y25, to see whether the association between young adult body mass index (BMI)/insulin resistance status and middle age metabolic consequences may be influenced by interim fitness change while controlling for baseline fitness. We hypothesize that interim fitness change alters the association between young adult BMI/insulin resistance status and middle age cardiometabolic outcomes, with participants who maintained or increased fitness having more favorable alterations in cardiometabolic measures than participants with decreased fitness, independent of baseline fitness.

Methods

Participants

The CARDIA study is a prospective, multicenter, 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 at Y0) were recruited and examined in 1985–1986 from 4 US communities (Birmingham, AL; Chicago, IL; Minneapolis, MN, and Oakland, CA) and balanced on age, race, sex and educational attainment as previously described.⁽¹⁸⁾ A total of 5115 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 analysis, participants were excluded if they had elevated fasting glucose 7 mmol/L ($n=31$) at baseline. Of the remaining 5084 participants, an additional 2288 participants were excluded if they were missing fitness testing at Y0 ($n=150$) or Y20 ($n=2138$) or if they had incomplete outcome data at Y20 ($n=23$ participants not previously excluded) or Y25 ($n=725$ participants not previously excluded). In total, 2048 (59% of CARDIA Y25 participants) participants met the study criteria for the analysis.

Designation of Y0 body mass index (BMI) and insulin resistance

Y0 BMI was categorized as either normal ($nBMI < 25 \text{ kg/m}^2$) or high ($hBMI \geq 25 \text{ kg/m}^2$). Y0 insulin resistance status was measured by the homeostatic model assessment (HOMA-IR).⁽⁵⁾ Participants were considered either insulin sensitive [IS: $HOMA-IR < 75\%$ tile (< 1.84)]

or insulin resistant [IR: HOMA-IR 75%tile (1.84)], similar to previous studies.(1, 33) We used Y0 BMI and insulin resistance status to classify participants into one of 4 groups: 1) normal BMI/insulin sensitive (nBMI/IS); 2) high BMI/insulin sensitive (hBMI/IS); 3) normal BMI/insulin resistant (nBMI/IR); 4) high BMI/insulin resistant (hBMI/IR) (Table 1).

Measurement of cardiorespiratory fitness

The CARDIA study measured CRF at Y0 and Y20 by symptom-limited graded treadmill exercise testing using a modified Balke protocol.(35) Briefly, the exercise test protocol was designed to assess maximal, symptom-limited performance. After baseline measurement of pulse, blood pressure, and EKG, the participant started the protocol. The protocol consisted of nine stages (2 minutes each, maximum of 18 minutes total) of progressively increasing difficulty, with the first 6 stages generally performed by walking. Stage 1 was 3.0 miles per hour at 2% grade [4.1 Metabolic equivalent (MET)], progressing to stage 9 at 5.6 miles per hour at 25% grade (19.0 MET). Y0 fitness was classified as either low (<33%tile for sex) or average-high (33%tile for sex), similar to previous literature.(36) (Table 1). As we were interested in the effects of long-term fitness change, only fitness data from the Y0 and Y20 time points were used. Fitness change (Y20 treadmill time-Y0 treadmill time) was considered either maintained [increase or decline 20%tile for sex] or decreased [decline >20%tile for sex](Table 1). This 20%tile cutoff was derived from the observation that the mean age-related decline in fitness(16) is approximately 10% (5% per decade) from age 30 to age 50 in men and women.(16) In our statistical analysis, we adjusted for baseline fitness by incorporating the Y0 treadmill time as a covariate.

Measurement of cardiometabolic risk factors

Cardiometabolic risk factors were measured using standardized protocols across field centers and examinations with quality control monitoring.(12, 18) Briefly, body weight was measured in light clothing to the nearest 0.2 pound using a balance beam scale; waist girth was measured midway between the xyphoid process and the umbilicus.(12) Blood pressure was measured three times after a 5-minute rest using a Hawksley random zero sphygmomanometer (WA Baum Company, Copague, NY, USA) on the right arm of the seated participant at Y0 and a standard automated aneroid monitor (*OmRON* model HEM907XL) at Y20. For each visit, the average of the last two measures was used.(12) Fasting plasma blood samples were sent to the Northwest Lipid Research Laboratories, University of Washington (Seattle, WA, USA) for lipid determination. Total cholesterol and triglycerides (TG) were measured enzymatically, (38) high-density lipoprotein-cholesterol (HDL-C) was determined after dextran sulfate–magnesium chloride precipitation,(39) and low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald equation. (17) Serum glucose concentrations were measured using the hexokinase method at Linco Research Inc. (St Charles, MO, USA). Serum insulin was measured by immunoassay.(12) HbA1c samples were sent to the University of Minnesota (Minneapolis, MN, USA) and were measured using the Tosoh G7 high-performance liquid chromatography instrument. Incident diabetes in non-pregnant participants was determined at each follow-up visit (Years 7, 10, 15, 20, or 25) if any of the following criteria was met: fasting glucose 7 mmol/L, use of medications for diabetes treatment, 2-hour glucose tolerance test 11.1 mmol/L

(performed at Y10, Y20, Y25), or hemoglobin HbA1c $\geq 6.5\%$ (48 mmol/mol) (performed at Y20, Y25).

Outcomes

The primary outcomes were percentage change ($100 \times [Y25 - Y0] / Y0$) in weight and in waist girth between Y0 and Y25, as well as incident diabetes by Y25. The secondary outcomes were percentage change in cardiometabolic risk factors including: mean arterial pressure (MAP: $[2 \times \text{DBP} + \text{SBP}] / 3$), LDL-C, TG and HDL-C.

Other measurements

Covariates were selected as possible confounders in our analysis because of their clinical relevance and association with BMI, insulin resistance, or fitness.(7, 8, 16) Relevant covariates were measured at Y0 and included: age, sex, race (black vs. white), field center and lifestyle factors (physical activity, smoking, energy intake, alcohol intake, education level) These covariates were measured by trained and certified staff using standardized protocols across field centers and examinations with QC monitoring.(12, 18) Age, race and sex were confirmed during the clinic visits. Educational attainment was based on self-reported number of years of schooling and the highest degree earned at the last follow-up examination attended. Elapsed time between examinations was calculated using the baseline and follow-up examination dates. Physical activity level (reported as exercise units: EU) was measured using the CARDIA physical activity history questionnaire, an interviewer-based self-report of duration and intensity of participation in 13 categories of exercise over the previous 12 months.(22) For reference, 300 EU approximates 150 minutes of moderate-intensity activity (3–5 METs) per week or 30 minutes of moderate-intensity activity five days per week.(32) Diet was quantified (including total energy intake) using a semi-quantitative, interviewer-administrated, validated diet history food frequency questionnaire.(28)

Statistical analysis

All analyses were conducted by using SAS (version 9.2 - SAS institute, Inc., Cary, North Carolina). Baseline characteristics were summarized for participants across the baseline groups using ANOVA (for continuous characteristics) and Fisher's exact test or Pearson's chi-squared test as appropriate (for categorical characteristics).

We used 2 multiple linear regression models (described below) to examine the associations of each of fitness change and baseline BMI/insulin resistance status with % change from baseline in cardiometabolic outcomes at Y25. Since there was no overall statistically significant interaction between fitness change and BMI/insulin resistance status on any of the continuous cardiometabolic outcomes, the interaction term (fitness change*BMI/insulin resistance status) was not included in the final models and subgroup analysis for this interaction was not reported. Cox proportional hazards regression was used to examine the relationships between incident diabetes and exposures. Time-to-diabetes was approximated as the difference between baseline and the first follow-up visit with a report of diabetes. Because the interaction between fitness change and BMI/insulin resistance status was statistically significant for incident diabetes, this interaction term was retained in the 2

models for this outcome only. The proportional hazards assumption was tested using Schoenfeld residuals.(37) Model 1, for both continuous and incident diabetes outcomes, included Y0 BMI/insulin resistance status, age, race, sex and field center, fitness change (maintained vs. decreased), and Y0 fitness (treadmill duration). Model 2 further adjusted for other relevant covariates measured at Y0: education (highest year of school completed), cigarette smoking (current/former/never), alcohol consumption (mL/day), total physical activity intensity score (in exercise units with >800 exercise units being very high activity), (22) and energy intake (total kcal/day).

Results

Baseline characteristics for participants as separated by young adult BMI, insulin resistance status

The mean age ranged from 23 to 26 years old at baseline (Y0) across BMI and insulin resistance groups. The sex distribution was similar across all four categories (nBMI/IS, hBMI/IS, nBMI/IR, hBMI/IR). Table 2 reports the baseline values (mean $\pm$ SD if continuous variables, percentages if categorical). In the hBMI/IR group, there were fewer participants who had education beyond high school (62%) and white race (37%). Caloric intake and alcohol use were similar across BMI and insulin resistance groups.

The hBMI/IR participants (n=305) had the highest mean weight (88.5 $\pm$ 16.3kg), waist girth (91 $\pm$ 12 cm), BMI (30.4 $\pm$ 5 kg/m²), mean arterial pressure (85 $\pm$ 9 mmHg), fasting glucose (4.8 $\pm$ 0.4 mmol/l), LDL-C (3.13 $\pm$ 0.78 mmol/l), TG (1.05 $\pm$ 0.77 mmol/l) and HOMA-IR (2.8 $\pm$ 1.1). The hBMI/IR participants had the lowest physical activity (355 $\pm$ 263 exercise units), baseline treadmill exercise time (501 $\pm$ 158 sec) and HDL-C (1.22 $\pm$ 0.28 mmol/l). In terms of baseline fitness, the hBMI/IR participants had the highest percentage of low fit participants (71%), followed by hBMI/IS (43%), nBMI/IR (33%) and nBMI/IS (21%).

Across BMI and insulin resistance groups, 16–25% of participants maintained fitness after 20 years. The hBMI/IS participants had the lowest percentage of maintained fitness (16%) and greatest decline in fitness (–189 $\pm$ 121 seconds) compared with the other groups. The nBMI/IR had the highest percentage of maintained fitness (25%) and least decline in fitness (–154 $\pm$ 123 seconds) compared with the other groups.

Fitness Change after 20 years by baseline BMI/insulin resistance status and fitness

Within the CARDIA cohort, 20.6% maintained fitness after 20 years. Maintained fitness was less common in participants with average-high baseline fitness [7% (hBMI/IR) to 17% (nBMI/IS and nBMI/IR groups)] than participants with low baseline fitness [25% (hBMI/IS) to 41% (nBMI/IR)]. Among participants with average-high baseline fitness, treadmill times generally decreased in those who maintained fitness [–12 $\pm$ 62 seconds (nBMI/IS) to –40 $\pm$ 54 seconds (hBMI/IS)]. Among participants with low baseline fitness, treadmill times generally increased in those who maintained fitness [+5 $\pm$ 82seconds (nBMI/IS) to +17 $\pm$ 126 (nBMI/IR)] with the exception of the hBMI/IR group (–21 $\pm$ 52 seconds). Consequently, the number of participants who had average-high baseline fitness and maintained fitness after 20

years was low across the BMI/insulin resistance status groups (nBMI/IS: n=157, nBMI/IR: n=25, hBMI/IS: n=19, hBMI/IR: n=6).

Effect of fitness change on mid-life cardiometabolic outcomes (Table 3)

Associations between fitness change and any of the continuous cardiometabolic outcomes did not differ by baseline BMI/insulin resistance status after controlling for baseline fitness level. Consequently, we present the results from fitness change controlling for BMI/IR (Table 3).

Participants with maintained fitness gained significantly less weight and waist girth by middle age (Y25) than participants with decreased fitness ($p<0.0001$ maintained vs decreased fitness, Model 1 and Model 2). In terms of the lipid profile, participants with maintained fitness had higher HDL ($p<0.0001$ maintained vs decreased fitness, Model 1 and Model 2), lower LDL ($p=0.02$ for Model 1, $p=0.03$ for Model 2 maintained vs decreased fitness) and lower triglycerides ($p<0.0001$ maintained vs decreased fitness, Model 1 and Model 2) than those with decreased fitness. Maintained fitness was also associated with less increase in blood pressure, as measured by MAP, than decreased fitness ($p=0.001$ for Model 1, $p=0.01$ for Model 2 maintained vs decreased fitness).

Effect of young adult BMI/insulin resistance status and fitness change on incident diabetes by middle age

In the CARDIA cohort, 11.5% of the young adults in CARDIA (n=236) developed incident diabetes by middle age (Y25). Because a statistically significant interaction was observed between BMI/insulin resistance status and incident diabetes by fitness change, we present stratum-specific results for this outcome. The incidence rate was 12.4% in participants with decreased fitness (n=201 out of 1626) and 8.3% in participants with maintained fitness (n=35 out of 422) ($p=0.02$). In young adults who were insulin sensitive at baseline, the hazard ratio (HR) for incident diabetes was higher with decreased fitness given normal BMI (HR 6.7, 95% CI of 2.1–21.8, $p<0.01$ decreased vs maintained) or high BMI (HR 4.5, 95% CI of 1.4–14.6, $p=0.01$ decreased vs maintained). In young adults who were insulin resistant at baseline, the HR for incident diabetes was not statistically different between decreased fitness and maintained fitness given normal BMI (HR 1.4, 95% CI of 0.5–3.5, $p=0.51$ decreased vs maintained), and was borderline statistically significant given high BMI (HR 1.5, 95% CI of 0.9–2.5, $p=0.08$ decreased vs maintained). Relative to a referent group of nBMI/IS/maintained fitness (HR=1), insulin resistant participants who maintained fitness were at higher risk for developing incident diabetes if normal BMI (HR 7.7, HR 1.9–30.8, $p=0.004$ compared with nBMI/IS/maintained fitness) or high BMI (HR 18.1, HR 5.4–61.0, $p<0.001$ compared with nBMI/IS/maintained fitness).

Discussion

We were interested in whether the association between young adult body mass index (BMI)/insulin resistance status and middle age metabolic consequences may be influenced by interim fitness change. Adjusting for baseline fitness, we found that participants with maintained fitness had more favorable alterations in cardiometabolic measures than

participants with decreased fitness. The main findings from this study include: 1) A greater percentage of maintained fitness was observed in participants with low baseline fitness than participants with average-high baseline fitness; 2) Maintained fitness was less common in hBMI participants than nBMI participants; 3) Participants with maintained fitness after 20 years had less increase in weight gain, waist girth, LDL, triglycerides and blood pressure and greater increase in HDL than participants with decreased fitness; 4) Although maintained fitness reduced the rates of incident diabetes in the insulin sensitive participants, this was not observed in the insulin resistant participants.

Currently, it remains highly debated whether obesity itself or low cardiorespiratory fitness/inactivity plays a greater role in the adverse metabolic consequences associated with obesity. The benefits of physical activity on improving cardiometabolic risk factors in patients at risk for developing diabetes have been shown by interventional studies. (24, 31) Subsequent follow up after these interventions (10–20 years later) found lower rates of incident diabetes in the intervention group than the placebo group. (25, 27) The clinical significance of these benefits, however, remains unknown. In the Look AHEAD study, overweight/obese patients with type 2 diabetes (age 45–75, mean age 58) received intensive lifestyle intervention and were followed clinically (median follow-up: 9.6 years). Although the intervention improved fitness, reduced weight, reduced waist circumference and reduced glycated hemoglobin, cardiovascular morbidity and mortality remained unchanged and the study was terminated early based on a futility analysis. (19) These observations are consistent with our findings that maintained fitness may be less effective in reducing cardiometabolic outcomes in high-risk populations. Our study extends the current literature by examining the long-term effects of fitness change using a younger cohort well balanced by sex and race.

Although the response of fitness to physical activity is generally dose related, (11) genetics(6) may influence the magnitude of the response. Since exercise therapy, without concomitant dietary therapy, produces minimal weight loss, (41) much of the metabolic benefits from maintained fitness likely arises from alterations in body composition. Short term, weight stable, exercise training reduces hepatic fat and visceral fat. (23) Reduction in fat mass is associated with improved insulin sensitivity(14) and incident diabetes. (20) Our study suggests that 20 years of maintained fitness is associated with less adiposity, as approximated by changes in weight and waist girth. However, the beneficial effect of maintained fitness was blunted in the presence of insulin resistance, particularly within the context of high BMI. Consequently, in young adults with insulin resistance, reduction in weight and adiposity may be insufficient to improve cardiometabolic risk factors, and other mechanisms such as ectopic fat deposition or systemic inflammation may need to be addressed.

This study is clinically relevant for several reasons. Although we advocate that increased fitness is an important and laudable goal, relatively few participants in the CARDIA study increased fitness by 20 years and the reality is maintained fitness. This study examined the implications of maintained fitness, while adjusting for baseline fitness, and found that young adults who maintained fitness had improved cardiometabolic risk factors by middle age, although the results may be blunted by baseline insulin resistance. In addition, our observations complement previous findings that body fat, fitness and lifestyle in adolescence

(age 13) all independently increase the development of metabolic syndrome by young adulthood (age 36). (15) Since we found that young adults with insulin resistance had less benefit from maintained fitness in reducing incident diabetes, reducing insulin resistance prior to young adulthood may be particularly impactful.

This study had several strengths. This study focused on a key demographic: young adults (age 18–30), who were prospectively followed into middle age (age 43–55). This study capitalizes on several key features of CARDIA, specifically the prospective measurement of fitness by treadmill testing, balanced cohort in terms of sex and race, outcome measurements using standardized protocols with rigorous quality control and frequent in-person follow-up visits to ascertain incident diabetes. Certainly, some limitations need to be considered. Given the limitations of an observational study, only association and not causation can be shown. The effects of fitness change on cardiometabolic parameters may vary depending on whether the observed interval is between young adulthood and middle age or between middle age and older age. The categorization of fitness change (20%tile as maintained fitness) is arbitrary, but parallels well with observed age-associated decline in fitness (0.5–1% decline per year). (16) We acknowledge that participants with maintained fitness may be a very heterogeneous group, with maintained fitness easier to attain in participants with low baseline fitness than participants with high baseline fitness. However, we adjusted for this difference in baseline fitness by incorporating baseline fitness in both of our models. Although the number of participants who developed incident diabetes was low in certain subgroups of young adult BMI/insulin resistance status/fitness change, CARDIA remains as one of the best cohorts available to address this issue given its objective measures of fitness change and standardized long-term follow-up. Whether increased fitness may be more significant than maintained fitness cannot be determined at this time, as only a small number of CARDIA participants increased fitness after 20 years. Lastly, we acknowledge the risk factors of an overweight individual is likely less adverse than an obese individual, which may be masked by the categorization of the overweight and obese participants into the high BMI group. However, we could not separately analyze the obese young adults given the young age of the CARDIA population at the time of recruitment in 1985–1986 and relatively rare prevalence of obesity at the time of recruitment [n=598/5115 (11.7%, of total CARDIA cohort), n = 175/2048 (8.5% of the analyzed cohort)].

Generally speaking, young adults with maintained fitness after 20 years had more favorable middle age cardiometabolic risk factors than their peers with decreased fitness. However, young adults who were insulin resistant were at higher risk for developing incident diabetes than young adults who are insulin sensitive, even with maintained fitness. We advocate the importance of maintained fitness, and in young adults who are insulin resistant, the additional need for reducing insulin resistance to improve middle age cardiometabolic outcomes.

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Table 1

Definition of terms used in paper

Term	Definition
normal BMI/Insulin sensitive (nBMI/IS)	BMI<25, HOMA IR< 75%tile for cohort (<1.84)
high BMI/Insulin sensitive (hBMI/IS)	BMI ≥25, HOMA-IR< 75%tile for cohort (<1.84)
normal BMI/Insulin resistant (nBMI/IR)	BMI<25, HOMA-IR ≥75%tile for cohort (≥ 1.84)
high BMI/Insulin resistant (hBMI/IR)	BMI ≥25, HOMA-IR ≥75%tile for cohort (≥ 1.84)
low baseline fitness	Y0 treadmill time < 33%tile for sex (<676 sec for men, < 468 sec for women)
average-high baseline fitness	Y0 treadmill time ≥33%tile for sex (≥ 676 sec for men, ≥ 468 sec for women)
maintained fitness	Change in treadmill time (Y20–Y0): Increase or decline ≤20%tile for sex (increase or decline ≤112 sec in men, ≤60 sec in women)
decreased fitness	Change in treadmill time (Y20–Y0): Decline >20%tile for sex (decline >112 sec in men, >60 sec in women)

Table 2

Baseline variables by baseline BMI/insulin resistance status

Variable (SD)	nBMI		hBMI		pvalue
	IS	IR	IS	IR	
n	1190	212	341	305	
Age (yrs)	25.2 (3.5)	23.9 (4.0)	25.9 (3.2)	25.2 (3.8)	<0.01
Gender (% Men)	495 (42%)	90 (43%)	168 (49%)	139 (46%)	0.07
Race (% white)	806 (68%)	105 (50%)	190 (56%)	112 (37%)	<0.01
Weight (kg)	63.1 (9.5)	65.4 (8.6)	80.4 (10.9)	88.5 (16.3)	<0.01
Waist Girth (cm)	72 (7)	74 (6)	84 (8)	91 (12)	<0.01
Body Mass Index (kg/m2)	21.7 (1.9)	22.4 (1–7)	27.7 (3.0)	30.4 (5.0)	<0.01
Smoking (% Never Smoked)	717 (61%)	145 (68%)	206 (61%)	214 (71%)	0.01
Caloric Intake (kcal)	2691 (1400)	2892 (1457)	2814 (1589)	2685 (1367)	0.17
Alcohol Consumption (ml of alcohol/day)	12 (18)	10 (21)	13 (20)	11 (24)	0.31
Level of Education (% more than high school education)	847 (71%)	145 (68%)	239 (70%)	190 (62%)	0.03
Study Center					
Birmingham	267 (22%)	42 (20%)	71 (21%)	86 (28%)	<0.01
Chicago	292 (24%)	49 (23%)	95 (28%)	80 (26%)	
Minneapolis	278 (23%)	39 (18%)	97 (28%)	67 (22%)	
Oakland	353 (30%)	82 (39%)	78 (23%)	72 (24%)	
Total Activity (exercise units)	443 (291)	396 (288)	467 (335)	355 (263)	<0.01
Baseline Treadmill Time (seconds)	648 (157)	601 (153)	581 (166)	501 (158)	<0.01
Mean Arterial Pressure (mmHg)	81 (8)	82 (9)	83 (8)	85 (9)	<0.01
Glucose (mmol/L)	4.4 (0.4)	4.8 (0.4)	4.5 (0.4)	4.8 (0.4)	<0.01
Low Density Lipoprotein (mmol/L)	2.72 (0.75)	2.87 (0.88)	2.95 (0.78)	3.13 (0.78)	<0.01
High Density Lipoprotein (mmol/L)	1.45 (0.34)	1.40 (0.31)	1.32 (0.28)	1.22 (0.28)	<0.01
Triglycerides (mmol/L)	0.71 (0.31)	0.83 (0.46)	0.82 (0.44)	1.05 (0.77)	<0.01
HOMA-IR	1.22 (0.30)	2.28 (0.58)	1.38 (0.29)	2.77 (1.11)	<0.01
Population with Low Fitness at baseline (n, % of BMI/insulin sensitivity category) (<33%tile of sex-specific treadmill time)	247 (21%)	69 (33%)	146 (43%)	216 (71%)	<0.01
Population with Maintained Fitness (n, % of BMI/insulin sensitivity category) * (increased or decreased 20%tile for sex) *this is change in fitness over 20 years [(Y20–Y0)/Y0]	250 (21%)	53 (25%)	56 (16%)	63 (21%)	<0.01
Decline in Fitness (seconds: Y20 exercise duration-Y0 exercise duration)	–169 (123)	–154 (123)	–189 (121)	–179 (116)	<0.01

Table 3

Effects of fitness change on mid-life cardiometabolic outcomes

% change by Y25 from Y0 (Mean, SE)		Decreased Fitness	Maintained Fitness	P value (decreased fitness Vs maintained fitness)
Weight	Model 1	26.2 (0.5)	11.8 (1.0)	<0.0001
	Model 2	25.7 (0.6)	11.4 (1.0)	<0.0001
Waist Girth	Model 1	23.9 (0.4)	12.3(0.7)	<0.0001
	Model 2	23.8 (0.5)	12.4 (0.8)	<0.0001
HDL-C	Model 1	7.2 (0.8)	18.9 (1.4)	<0.0001
	Model 2	8.0 (0.9)	19.7 (1.5)	<0.0001
LDL-C	Model 1	5.0 (0.9)	0.8 (1.6)	0.02
	Model 2	4.5 (1.0)	0.6 (1.7)	0.03
MAP	Model 1	8.7 (0.4)	5.9 (0.8)	0.001
	Model 2	9.5 (0.5)	7.2 (0.8)	0.01
Triglycerides	Model 1	75.2 (2.6)	37.2 (4.9)	<0.0001
	Model 2	72.6 (3.0)	35.1 (5.1)	<0.0001

Model 1 included Y0 BMI/insulin resistance status, age, race, sex and field center, fitness change (maintained vs. decreased), Y0 fitness (treadmill duration).

Model 2 further adjusted for other relevant covariates measured at Y0: education (highest year of school completed), cigarette smoking (current/former/never), alcohol consumption (mL/day), total physical activity intensity score and energy intake (total kcal/day).

Abbreviations: high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), mean arterial pressure (MAP)