



Cardiorespiratory Fitness and Incident Diabetes: The FIT (Henry Ford Exercise Testing) Project

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OBJECTIVE

Prior evidence has linked higher cardiorespiratory fitness with a lower risk of diabetes in ambulatory populations. Using a demographically diverse study sample, we examined the association of fitness with incident diabetes in 46,979 patients from The Henry Ford Exercise Testing (FIT) Project without diabetes at baseline.

RESEARCH DESIGN AND METHODS

Fitness was measured during a clinician-referred treadmill stress test performed between 1991 and 2009. Incident diabetes was defined as a new diagnosis of diabetes on three separate consecutive encounters derived from electronic medical records or administrative claims files. Analyses were performed with Cox proportional hazards models and were adjusted for diabetes risk factors.

RESULTS

The mean age was 53 years with 48% women and 27% black patients. Mean metabolic equivalents (METs) achieved was 9.5 (SD 3.0). During a median follow-up period of 5.2 years (interquartile range 2.6–8.3 years), there were 6,851 new diabetes cases (14.6%). After adjustment, patients achieving ≥ 12 METs had a 54% lower risk of incident diabetes compared with patients achieving < 6 METs (hazard ratio 0.46 [95% CI 0.41, 0.51]; P -trend < 0.001). This relationship was preserved across strata of age, sex, race, obesity, hypertension, and hyperlipidemia.

CONCLUSIONS

These data demonstrate that higher fitness is associated with a lower risk of incident diabetes regardless of demographic characteristics and baseline risk factors. Future studies should examine the association between change in fitness over time and incident diabetes.

Diabetes is a widely prevalent disease that affects over 20.4 million adults in the U.S. (1) and over 170 million people throughout the world (2). Furthermore, it is a significant contributor to mortality and was predominantly responsible for ~ 4 million deaths worldwide in 2010 (3). Numerous cross-sectional studies have described a relationship between reduced cardiorespiratory fitness and glucose intolerance (4) or diabetes (5–7). Furthermore, large cohort studies have demonstrated that low fitness may precede the development of insulin resistance and diabetes (8–15). However, it remains unknown how demographic characteristics (age, sex, and race) or other diabetes-related risk factors (obesity, hypertension, and

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hyperlipidemia) alter the association between fitness and incident diabetes. For example, there is emerging evidence to suggest that fitness is not a significant risk factor among obese people (11,16). Moreover, this association has never been examined in the elderly or compared across black and white races.

The purpose of this study was to 1) examine the prospective relationship between cardiorespiratory fitness and incident diabetes among patients without a diagnosis of diabetes at baseline and 2) examine whether the prospective relationship between cardiorespiratory fitness and incident diabetes differed across demographic characteristics or diabetes-related risk factors. We hypothesized that a higher level of fitness would be inversely associated with incident diabetes, independent of demographic characteristics or risk factors for diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The Henry Ford Exercise Testing (FIT) Project is comprised of 69,885 patients who underwent physician-referred treadmill stress testing at Henry Ford Health System Affiliated Subsidiaries in metropolitan Detroit, MI between 1991 and 2009. Details of the study are described elsewhere (17). In brief, the study population was limited to patients who were at least 18 years of age at the time of stress testing. Patients were excluded if the testing protocol was not the standard Bruce protocol. We further excluded patients who had a history of coronary artery disease (CAD; $n = 10,190$), heart failure ($n = 877$), and diabetes ($n = 10,619$) and patients missing data from covariates used in our regression models ($n = 1,220$) at the time of treadmill testing.

Known CAD was defined as an existing history of any of the following: myocardial infarction, coronary angioplasty, coronary artery bypass surgery, or documented obstructive CAD on angiogram. Heart failure was defined as a prior clinical diagnosis of systolic or diastolic heart failure (heart failure with reduced or preserved left ventricular function). Diabetes was defined as a prior clinical diagnosis of diabetes, use of antihyperglycemic medications including insulin, or an electronic medical record (EMR) or problem list–based diagnosis of diabetes.

After exclusions, our analytic sample included 46,979 patients. The Henry Ford Hospital Institutional Review Board approved The FIT Project.

Treadmill Stress Testing and Metabolic Equivalents

Study patients underwent routine clinical treadmill stress testing using the standard Bruce protocol between 1 January 1991 and 28 May 2009. The day the treadmill test was performed served as the baseline for this study. A treadmill test would be terminated by the supervising clinician if the patient had exercise-limiting chest pain, shortness of breath, or other limiting symptoms independent of the achieved heart rate. Furthermore, testing could also be terminated early at the discretion of the supervising clinician for significant arrhythmias, abnormal hemodynamic responses, or diagnostic ST-segment changes or if the participant was unwilling or unable to continue.

Resting heart rate and blood pressure were measured in the seated position prior to treadmill testing. The percent of maximal heart rate achieved was based on the age-predicted maximal heart rate formula: $220 - \text{age}$. Cardiorespiratory fitness, expressed in metabolic equivalents (METs), was based on the workload derived from the maximal speed and grade achieved during the total treadmill time. MET results were categorized into four groups based on the distribution of the data as follows: <6 , $6-9$, $10-11$, and ≥ 12 METs.

Primary Outcomes: Prevalent and Incident Diabetes

Incident diabetes was determined among patients without diabetes at baseline by ascertainment of problem list diagnoses in the EMR as well as through linkage with administrative claims files from services delivered by the Henry Ford physician group practice or reimbursed by the patient's health care insurer. A new diagnosis was considered present when a diagnosis of diabetes (ICD-9 250.XX) was listed in at least three separate encounters. Time-to-incident diabetes was based on the time between treadmill testing and the date of the first encounter with a new diabetes diagnosis. Patients who did not develop diabetes were censored at their last contact with the integrated Henry Ford group practice, when ongoing

coverage with their health care insurance could no longer be confirmed (i.e., death or loss to follow-up), or at the end of the study period (28 May 2009).

Other Measurements

Nurses and/or exercise physiologists collected additional health history data immediately prior to the stress test. Age, sex, and race were self-reported. Risk factors were based on both self-report and retrospective search of the EMR.

Hypertension was defined as a prior diagnosis of hypertension, use of antihypertensive medications, or an EMR problem list–based diagnosis of hypertension at the time of stress testing (study baseline). Hypertension medication use was determined in aggregate (any hypertension medication) as well as for individual classes, including ACE inhibitors, angiotensin receptor blockers (ARBs), β -blockers, and diuretic medications. Dyslipidemia was defined by prior diagnosis of any major lipid abnormality, use of lipid-lowering medications, or problem list–based diagnosis of hypercholesterolemia or dyslipidemia in the EMR. Obesity was defined by self-report and/or assessment by the clinician historian. Family history of CAD in a first-degree relative was based on self-report. Current smoking was informally assessed and was considered affirmative if patients were still smoking at the time of the test appointment. Physical activity was also informally assessed by asking patients if they regularly exercised (yes or no).

Medication use history was based on self-report prior to the stress test, the EMR, as well as pharmacy claims files from enrollees in the health system's integrated health plan. Medications were categorized as any hypertension medication use, ACE inhibitors, ARBs, β -blockers, diuretic medications, lipid-lowering medications, statin medications, medications for lung diseases (e.g., chronic obstructive pulmonary disease), or medications for depression.

Indication for stress test referral was provided by the referring physician and subsequently categorized into the most common indications (chest pain, shortness of breath, "rule out" ischemia, or other).

Hemoglobin A_{1c} or BMI measurements, measured within 1 year of treadmill testing, were available in the EMR for a subset of the study population.

Statistical Analysis

Means and proportions of the study population were calculated for study patients, both overall and by category of METs. Nested Cox proportional hazards models were used to examine the association between fitness and incident diabetes. Model 1 was adjusted for age, sex, and race (white, black, or other). Model 2 was adjusted for model 1 covariates as well as history of hypertension, hypertension medication use, ARB use, β -blocker use, diuretic medication use, history of hyperlipidemia, lipid-lowering medication use (including statins), statin use, history of obesity, family history of coronary heart disease, and current smoking status. Model 3 was adjusted for covariates of model 2 and physical activity, pulmonary disease medication use, depression medication use, and indication for stress testing. Cumulative incidence was depicted at 5-, 10-, and 15-year intervals via a bar graph as well as continuously via Kaplan-Meier curves. We also plotted a restricted cubic spline model to show the shape of the continuous relationship between METs and incident diabetes after adjustment for covariates.

We assessed for effect modification in strata of age (<40, 40–49, 50–59, or ≥ 60 years), sex, race (black, white, or other), history of obesity, history of hypertension, and history of hyperlipidemia. These findings were adjusted for the covariates above and presented as a forest plot. Interaction terms were determined via Wald tests and *F* statistics. We also examined the association between METs and incident diabetes in the subset of patients with a hemoglobin A_{1c} measurement ($n = 4,946$) by strata of hemoglobin A_{1c}: <5.7% (<39 mmol/mol; normal), 5.7–6.4% (39–47 mmol/mol; prediabetic), and $\geq 6.5\%$ (≥ 48 mmol/mol; diabetic), defined by the American Diabetes Association (18). Moreover, we conducted sensitivity analyses restricted to patients with a hemoglobin A_{1c} <6.5% (<48 mmol/mol; $n = 4,287$). Finally, we conducted a sensitivity analysis adjusting for BMI in the subpopulation with BMI data ($n = 11,750$).

All analyses were performed with STATA version 11.1 (Stata Corporation, College Station, TX). Statistical significance was defined as $P \leq 0.05$.

RESULTS

Population Characteristics

Study patients without diabetes ($n = 46,979$) had an average age of 52.5 years (Table 1). The study population was 48% women and 27% black. The most common indications for stress testing were chest pain (52%), “rule out” ischemia (11%), and shortness of breath (9%). Demographic characteristics, past medical history, and medications used by patients in this study were all significantly associated with METs achieved. Further, most indications for stress testing (with the exception of “rule out” ischemia) were associated with METs achieved.

Incident Diabetes

Over a median follow-up period of 5.2 years (interquartile range 2.6–8.3 years), 6,851 or 14.6% of patients without a history of diabetes at baseline were newly diagnosed with diabetes. The unadjusted 5-year cumulative incidences across categories of METs (<6, 6–9, 10–11, and ≥ 12) were 19.5, 15.6, 10.4, and 5.2%, respectively (Supplementary Fig. 1A). Examination of the crude association between categories of METs and risk of diabetes using a Kaplan-Meier cumulative incidence curve revealed a significant trend across categories of METs (log-rank test, $P < 0.001$) (Supplementary Fig. 1B). There was a significant association between categories of METs and risk of incident diabetes after adjustment for demographic characteristics (model 1, P -trend < 0.001) (Table 2). This trend was attenuated but remained significant after adjustment for diabetes risk factors (models 2 and 3; P -trends < 0.001).

Compared with patients achieving <6 METs, patients achieving ≥ 12 METs had a 54% lower risk of incident diabetes even after full adjustment (model 3 hazard ratio [HR] 0.46 [95% CI 0.41, 0.51]; P -trend < 0.001). Similarly, as a continuous variable with adjustment for all covariates, every 1 MET higher achieved at baseline was associated with an 8% lower risk (HR 0.92 [95% CI 0.91, 0.93]; $P < 0.001$) for incident diabetes (model 3). Using spline models, we observed an inverse, nonlinear relationship between baseline MET achievement and risk of diagnosed diabetes (Fig. 1). This association was greatest when MET achievement was >8.

Effect Modification

We assessed for effect modification of the relationship between METs and incident diabetes by strata of diabetes risk factors (Fig. 2). We found that older age, a positive history of hypertension, and a history of hyperlipidemia attenuated the association between fitness and incident diabetes, whereas white race strengthened the association between fitness and incident diabetes. Neither sex nor history of obesity significantly altered the relationship between fitness and incident diabetes. Despite the significant effect modification observed in this study, the inverse relationship between fitness and incident diabetes remained significant regardless of age, sex, race (black or white), or comorbidities.

Sensitivity Analyses

We examined the association between METs and incident diabetes in strata of hemoglobin A_{1c} (Supplementary Table 1). There was no statistical difference across strata of hemoglobin A_{1c} (P -interaction = 0.29). However, regardless of hemoglobin A_{1c} strata, METs achieved was inversely associated with incident diabetes (P -trends < 0.03 in all three strata). Furthermore, the strata were not statistically different from each other. A sensitivity analysis, restricted to patients with a hemoglobin A_{1c} <6.5%, showed strong associations between METs achieved and incident diabetes even with full adjustment (model 3) (Supplementary Table 2). Finally, in the subgroup with BMI measurements, adjustment for BMI attenuated, but did not meaningfully change, our findings (Supplementary Table 3).

CONCLUSIONS

This study represents one of the largest longitudinal studies on the association between fitness and incident diabetes. Higher fitness was strongly associated with a lower risk of diabetes among patients without a diagnosis of diabetes at baseline, such that a higher fitness of 1 MET was associated with an 8% lower risk of developing diabetes. These associations were observed regardless of age, sex, and other common diabetes risk factors.

The association between fitness and diabetes is well-established (19). Several small cross-sectional studies have shown that exercise capacity is inversely associated with impaired glycemic control (4,20,21), the metabolic syndrome

Table 1—Baseline population characteristics by METs, mean (SD), or %

	Patients without diagnosed diabetes at baseline					P across METs*
	Overall (n = 46,979)	<6 METs (n = 5,158)	6–9 METs (n = 11,588)	10–11 METs (n = 17,876)	≥12 METs (n = 12,357)	
Age, years	52.5 (12.6)	64.5 (12.6)	57.5 (11.9)	50.9 (10.7)	45.1 (10.1)	<0.001
Female, %	48.4	67.0	65.6	50.3	21.9	<0.001
Race, %						
White	66.5	59.9	61.7	66.6	73.5	<0.001
Black	26.6	36.1	32.7	26.0	17.7	<0.001
Other	7.0	4.0	5.6	7.4	8.8	<0.001
History of hypertension, %	56.5	79.0	68.1	53.8	40.1	<0.001
History of hyperlipidemia, %	40.1	39.3	43.6	41.0	36.1	<0.001
History of obesity, %	20.3	22.4	29.5	21.9	8.4	<0.001
Family history of coronary heart disease, %	52.2	46.0	52.1	53.6	53.0	<0.001
Current smoking status, %	41.7	42.9	43.6	43.0	37.4	<0.001
Regular exercise (yes or no), %	27.7	29.7	35.3	29.7	16.7	<0.001
Hypertension medication use, %	37.7	61.2	50.0	34.6	20.8	<0.001
ACE inhibitor use, %	12.1	19.2	15.9	11.2	7.0	<0.001
ARB use, %	1.9	2.4	2.5	1.9	0.9	<0.001
β-Blocker use, %	15.4	23.4	20.2	14.5	8.9	<0.001
Diuretic use, %	16.2	29.9	23.9	14.2	6.2	<0.001
Lipid-lowering medication use, %	16.1	18.3	20.4	16.2	11.2	<0.001
Statin use, %	14.7	16.8	18.9	14.7	9.8	<0.001
Pulmonary disease medication use, %	8.6	13.2	10.1	8.2	5.9	<0.001
Depression medication use, %	7.6	8.1	9.1	8.3	5.0	<0.001
Reason for stress test, %						
Chest pain	52.1	45.3	52.6	54.4	51.3	<0.001
Shortness of breath	8.8	11.7	9.0	7.9	8.9	<0.001
Rule out ischemia	10.6	10.8	10.5	10.7	10.6	0.943
Other	28.4	32.2	28.0	27.0	29.3	0.009
Peak METs achieved	9.5 (3.0)	4.2 (1.2)	7.0 (0.2)	10.0 (0.0)	13.2 (0.8)	—

*P values for trends across METs determined via linear and logistic regression.

(22), or diabetes (5–7) and positively associated with glucose disposal rate (23) and insulin sensitivity (24). Unfortunately, prospective studies examining the relationship between measured fitness and incident diabetes (8–15) have in general been small and confined to

limited demographic settings (single sex, racial group, or age-group). We have shown in a large and demographically diverse cohort that fitness, estimated by METs using a standard test (Bruce protocol), is associated with incident diabetes.

The mechanism behind the observed relationship between fitness and incident diabetes is a subject of much discussion. There is evidence to suggest that higher fitness, reflecting physical activity, is casual in deterring the pathogenesis of diabetes (25,26). It is

Table 2—Association between METs achieved and incident diabetes among patients without a diagnosis of diabetes at baseline (HRs, 95% CI), n = 46,979

Categories of fitness (METs)	HR (95% CI)		
	Model 1	Model 2	Model 3
<6	1.0 (reference)	1.0 (reference)	1.0 (reference)
6–9	0.96 (0.90, 1.04)	0.95 (0.88, 1.02)	0.96 (0.89, 1.03)
10–11	0.71 (0.66, 0.77)	0.76 (0.70, 0.82)	0.77 (0.71, 0.83)
≥12	0.38 (0.34, 0.42)	0.45 (0.41, 0.50)	0.46 (0.41, 0.51)
P trend across categories as ordinal variable	<0.001	<0.001	<0.001
METS per 1 unit	0.91 (0.90, 0.91)	0.92 (0.91, 0.93)	0.92 (0.91, 0.93)
P value	<0.001	<0.001	<0.001

Note that fitness was assessed during treadmill tests conducted between 1991 and 2009. Model 1, adjusted for age, sex, and race; model 2, adjusted for model 1 covariates as well as history of hypertension, hypertension medication use, ACE inhibitor use, ARB use, β-blocker use, diuretic use, history of hyperlipidemia, lipid-lowering medication use, statin use, history of obesity, family history of coronary heart disease, and current smoking status; model 3, adjusted for model 2 covariates as well as physical activity, pulmonary disease medication use, depression medication use, and indication for stress testing.

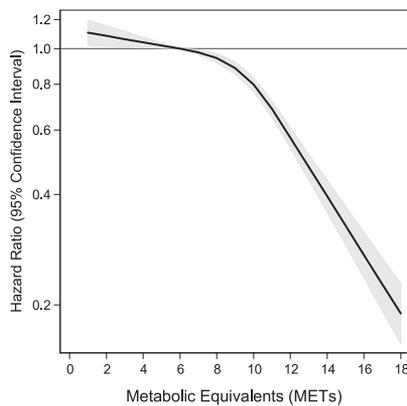


Figure 1—Adjusted HRs (solid line) from a restricted cubic spline model for incident diabetes using categories of baseline peak METs achieved. Shaded region represents the 95% CIs. The models were expressed relative to a MET value of 6 with knots specified at MET values of 6, 10, and 12. Model was adjusted for age, sex, race, history of hypertension, hypertension medication use, ACE inhibitor use, ARB use, β -blocker use, diuretic use, history of hyperlipidemia, lipid-lowering medication use, statin use, history of obesity, family history of coronary heart disease, current smoking status, physical activity, pulmonary disease medication use, depression medication use, and indication for stress testing.

thought that this relationship is mediated by positive changes in one's body tissue profile, namely, 1) reduced adiposity, an important risk factor for diabetes (27,28), and 2) increased skeletal muscle, a critical tissue in postprandial glucose uptake (23,29,30). Moreover, higher fitness has been shown to directly increase insulin sensitivity and glucose disposal (31–33). However, it is also possible that fitness partly reflects one's native genetic state (34) independent of physical activity. For example, several studies have shown that impaired oxidative respiration (35,36) due to mitochondrial dysfunction (37–40) underlies the pathogenesis of diabetes. Such a state would also manifest as reduced fitness independent of one's physical activity (15).

In this study, we observed fitness to be inversely associated with incident diabetes across age-groups, in both males and females, and in both white and black patients. Prior studies have shown fitness to be inversely associated with incident diabetes in young adults (11), men (8,10,14,15), and women (13). However, our study is the first to specifically evaluate the elderly and compare both black and white patients. Interestingly, we found that greater fitness at a younger

age was associated with the lowest risk of developing diabetes. This may imply that there is greater benefit to being fit at a young age. However, adults over the age of 60 years still show a significant inverse relationship between fitness and incident diabetes, suggesting that fitness is important among the elderly as well.

With regard to race, a lower risk of incident diabetes was observed among the more fit white versus more fit black patients. The reason for this observation is unclear. We can speculate that other risk factors for diabetes among black patients (e.g., genetic predisposition, lifestyle, and socioeconomic status) may diminish the association of fitness with diabetes risk. Additional research should examine this interaction more closely.

We also examined the association of fitness with incident diabetes in strata of obesity, hypertension, and hyperlipidemia. With regard to obesity, obesity status had very little influence on the relationship between fitness and incident diabetes. This was consistent with some (12–14), but not all (11,16), prospective studies examining obesity and fitness and may suggest that the associations between fitness and diabetes risk are indeed independent of obesity. In contrast, a history of hypertension or hyperlipidemia attenuated, but did not negate, the association between fitness and incident diabetes. This implies that greater fitness is associated with lower risk of diabetes even among people with risk factors for diabetes.

We found that fitness was associated with incident diabetes across strata of hemoglobin A_{1c}. This suggests that fitness is an important indicator of diabetes risk regardless of patients' underlying insulin resistance, including patients with normal blood glucose levels, similar to prior evidence (9).

This study has a number of important limitations. First, incident diabetes was based on medical records and administrative claims files, data which were not originally collected with the intent of examining diabetes. As a result, our study did not include study protocol-based direct measurements of hemoglobin A_{1c}, blood glucose, or oral glucose tolerance testing. Because of this, a number of people with undiagnosed diabetes may have been included in our study population or missed as incident cases, attenuating our results. Second,

our assessment of baseline fitness was based on a single measurement so we could not assess changes in fitness over time or issues related to within-person variability. Although we believe a single measure of fitness is informative as to subsequent fitness during one's lifetime, we cannot substantiate this assumption in our study. This may contribute to misclassification of patients' fitness, attenuating our findings. Third, physical activity was assessed via a single, nonstandardized question about exercise. Furthermore, sedentary behavior was not assessed. These have been found to be independently associated with cardiovascular health and may represent the causal behaviors contributing to fitness. Unfortunately we are unable to formally assess these behaviors in our study. This precludes a formal assessment of the relationship of self-reported physical activity with incident diabetes. Fourth, our study population was comprised of people referred for stress testing, which undoubtedly carries a higher burden of cardiovascular disease at baseline than the general population. This limits our study's generalizability. Fifth, treadmill machines were not standardized, e.g., some had handrails, which could have artificially increased the METs achieved. This would attenuate our findings. Sixth, specific forms of diabetes were not ascertained, limiting our ability to explore potential mechanisms between fitness and the pathogenesis of diabetes. Finally, residual confounding is always a concern with observational studies, especially with covariates assessed via self-report or medical records rather than direct measurement. This is particularly true with our retrospective cohort study.

This study has a number of strengths. The clinical standard for stress testing, the Bruce protocol treadmill test, was used to characterize fitness. This is readily interpreted in clinical settings. Further, our study sample was large and diverse and included a wide range of indications for treadmill testing. Moreover, our study has the advantage of having been reviewed by clinical practitioners responsible for the medical record entry or claims data.

In conclusion, greater fitness is associated with a lower risk of developing diabetes regardless of age or sex. Further, fitness demonstrated the strongest

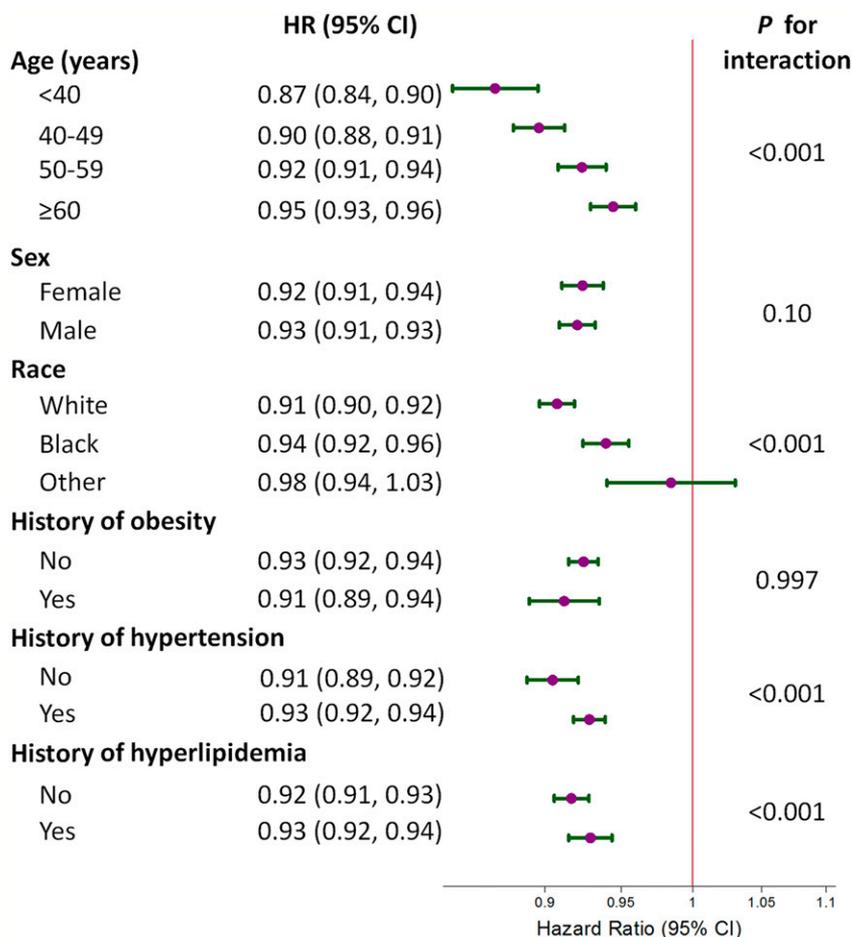


Figure 2—Forest plot portraying the HR and 95% CI of the association between baseline peak METs (per 1 MET) and incident diabetes. Strata were age (<40, 40–49, 50–59, and ≥60 years), sex (female or male), race (white, black, or other), history of obesity (no or yes), history of hypertension (no or yes), or history of hyperlipidemia (no or yes). In general, all models were adjusted for age, sex, race, history of hypertension, hypertension medication use, ACE inhibitor use, ARB use, β -blocker use, diuretic use, history of hyperlipidemia, lipid-lowering medication use, statin use, history of obesity, family history of coronary heart disease, current smoking status, physical activity, pulmonary disease medication use, depression medication use, and indication for stress testing. Models were not adjusted for the covariate pertaining to its strata. With regard to the interaction analysis, the age variable was replaced with a simplified variable (<40, 40–49, 50–59, and ≥60) to reflect the categories of age used in the stratified analysis. *P* values were determined via Wald tests and *F* statistics. (A high-quality color representation of this figure is available in the online issue.)

relationship with incident diabetes even in patients without evidence of impaired glucose homeostasis. Clinicians should be sensitive to fitness status, implementing clinical steps to reduce the likelihood of diabetes in patients with low fitness. Future studies should examine the role of physical activity in improving fitness and the relationship of this change in fitness with incident diabetes.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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