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Cardiorespiratory Fitness and Incidence of Type 2 Diabetes in United States Veterans on Statin Therapy

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Abstract

Background: Impact of cardiorespiratory fitness on statin-related incidence of type 2 diabetes has not been assessed. We assessed the cardiorespiratory fitness and diabetes incidence association in dyslipidemic patients on statins.

Methods: We identified dyslipidemic patients with a normal exercise test performed during 1986 and 2014 at the Veterans Affairs Medical Centers in Washington, DC or Palo Alto, California. The statin-treated patients (n=4,092; age=58.8±10.9 years) consisted of 2,701 African-Americans and 1,391 Caucasians. None had evidence of type 2 diabetes prior to statin therapy. We formed four fitness categories based on age and peak Metabolic Equivalents achieved: Least-fit (n=954); Low-fit (n=1,201); Moderate-fit (n=1,242); and High-fit (n=695). The Non-statin treated cohort (n=3,001; age=57.2±11.2 years) with no evidence of type 2 diabetes prior to the exercise test served as controls.

Results: Diabetes incidence was 24% higher in statin-treated compared to non-statin treated patients (p<0.001). In the statin-treated cohort, 1075 (26.3%) developed diabetes (average annual incidence rate of 30.6 events/1,000 person-years). Compared to the Least-Fit, adjusted risk declined progressively with increasing fitness and was 34% lower for High-fit patients (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.53-0.82; p<0.001). Compared to the non-statin cohort elevated risk was only evident in the Least-Fit (HR 1.50; 95% CI 1.30-1.73; p<0.001) and Low-Fit patients (HR 1.22; 95% CI 1.06-1.41; p=0.006).

Conclusions: Risk of diabetes in statin-treated dyslipidemic patients was inversely and independently associated to cardiorespiratory fitness. The increased risk was evident only in relatively low fitness patients. Improving fitness may modulate the potential diabetogenic effects of statins.

Key Words: cardiorespiratory fitness, statins, type 2 diabetes incidence

Introduction

Statins have become the most widely prescribed medication in the US.[1] According to the 2013 ACC/AHA Task Force on treatment of cholesterol,[2] the number of US adults receiving or eligible for statin therapy would increase from 43.2 million (37.5%) currently to 56.0 million.[1] Observational studies and several meta-analyses of randomized controlled trials of statins have reported unfavorable glycemic homeostasis[3] and higher risk for developing type 2 diabetes in those treated with statins compared to placebo or standard care[4-6] The risk was found to be dose-related.[5] The mechanisms of statin-induced increase in dysglycemia and risk for type 2 diabetes have not been established. Results from a genetic analysis of samples available from 43 randomized statin trials showed that increased risk of type 2 diabetes with statins is at least partially explained by the inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase.[7] Body weight gain associated with insulin resistance might partly explain the higher risk of type 2 diabetes in statin-treated patients.[7,8]

Despite the statin-induced increased risk of type 2 diabetes and the increased cardiovascular disease risk associated with type 2 diabetes, the benefit of statin treatment for prevention of cardiovascular disease and all-cause mortality outweigh the risk, even among patients with existing type 2 diabetes[9-11] and statin use is not likely to decline. For this reason, lifestyle interventions such as optimization of body weight and adequate physical activity to improve cardiorespiratory fitness have been proposed as ways to counter the risk of type 2 diabetes in statin-treated patients.[7] Evidence from large epidemiologic studies strongly support an inverse, independent, and graded association between cardiorespiratory fitness, major cardiovascular events, all-cause mortality [12,13] and risk for developing certain chronic illnesses[14,15] including type 2 diabetes.[16-18] We have also shown that both statin therapy and increased cardiorespiratory fitness were independently associated with lower mortality risk in those treated and not treated with statins.[19] Additionally, the combination of statin therapy and increased cardiorespiratory fitness was more effective in lowering mortality risk than either alone.[11,19] However, the impact of increased cardiorespiratory fitness on the development of type 2 diabetes in statin-treated patients has not been examined. Furthermore, some [20,21] but not all studies [22-24] suggest that improvements in cardiorespiratory fitness in response to exercise training may be blunted by statin therapy. Therefore, in the current study we sought to assess the impact of cardiorespiratory fitness on the incidence of type 2 diabetes in dyslipidemic patients treated with statins.

METHODS

Study Population

This prospective cohort study included individuals from the Exercise Testing and Health Outcomes Study (ETHOS) at the Veterans Affairs Medical Centers, Washington, DC, and the Veterans Exercise Testing Study (VETS) at the Veterans Hospital in Palo Alto, CA. Both are prospective observational studies designed to address the impact of exercise capacity, clinical and lifestyle factors and their association with disease states and health outcomes. The cohort consisted of 21,890 individuals who completed a symptom-limited exercise tolerance test at two Medical Centers between 1986 and

2014, as part of a routine evaluation, clearance to participate in exercise, or assessment of suspected coronary artery disease.

From this cohort, we identified those with documented dyslipidemia treated with statins for at least 6 months and no clinical history of type 2 diabetes prior to the initiation of statin therapy and no evidence of ischemia during the exercise tolerance test. We excluded those with any of the following: 1) exercise capacity <2 Metabolic Equivalents; 2) body mass index <18.5 kg/m2; and 3) those with an implanted pacemaker, left bundle-branch block, chronic obstructive pulmonary disease, or musculoskeletal factors that prevented them from completing the exercise tolerance test and those with acquired immune deficiency syndrome or human immunodeficiency virus. After these exclusions, the participant group for the current study (n = 4,092) consisted of 2,701 African Americans (mean age=58.3 ±10.7 years) and 1,391 Caucasians and other ethnicities (mean age=59.6±11.1 years). In addition to the statin-treated cohort we identified 3,001 Veterans (age=57.2±11.2 years) not treated with statins who had a normal exercise test and no evidence of type 2 diabetes prior to the test to serve as controls. The institutional review board at each institution approved the study, and all patients gave written informed consent prior to their exercise tolerance test.

Assessments of Co-variables

Detailed information on relevant demographic, clinical history, concurrent medications and risk factors as defined by International Classification of Diseases-9 for all participants was obtained from electronic medical records at the time of the exercise tolerance test. Body weight and height were assessed with a standardized scale and recorded prior to exercise tolerance test. Body mass index was calculated as weight in kilograms divided by height squared in meters squared.

Assessments of Exercise Capacity

Cardiorespiratory fitness was assessed by a standard treadmill test using the Bruce protocol at the Veterans Affairs Medical Center in Washington, DC, and an individualized ramp protocol as described previously[20] for subjects assessed at the Veterans Affairs Health Care System Center in Palo Alto, CA. Peak exercise capacity (Metabolic Equivalents) was estimated by use of standardized equations.[20,21] One Metabolic Equivalent is defined as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 mL oxygen per kg body weight per minute. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping.[22] The use of handrails was allowed only if necessary for balance and safety and not support. Medications were not altered before testing.

Fitness Categories

We stratified the cohort into four age categories (<50; 50-59; 60-69 and ≥70 years) and identified those with an exercise capacity ≤25%; >25% to 50%; >50% to 75% ; and >75% of Metabolic Equivalents achieved within their respective age category, as described previously.[15,19] We then established the following four cardiorespiratory fitness categories based on age-stratified quartiles of peak Metabolic Equivalents achieved: Least-fit (4.8±1.2 Metabolic Equivalents; range: 2.0-7.8; n=954); Low-fit (6.5±1.1 Metabolic Equivalents; range: 4.5-8.9; n=1,201); Moderate-fit (8.0±1.1 Metabolic Equivalents; range: 5.5-10.9; n=1,242); and High-fit (10.3±2.1 Metabolic Equivalents; range: 7.0-19.0; n=695). The primary endpoint was the development of type 2 diabetes determined as of December 31, 2014. Type 2 diabetes diagnosis was based on International Classification of Diseases-9 obtained from each patient electronic medical record. Dates of the onset of type 2 diabetes were verified using the Computerized Patient Record System available within the Veterans Affairs Health Care System.

Statistical Analysis

Follow-up time was calculated from the date of statins therapy initiation to the date of the event (type 2 diabetes); and to the date of death or December 31, 2014, for those who did not develop type 2 diabetes. Follow-up time is presented as median and mean ± SD. Event rate was calculated as the ratio of type 2 diabetes by the person-years of observation. Continuous variables are presented as mean ± SD and categorical variables as relative frequencies (%). Baseline associations between categorical variables were tested with the χ^2 test. Analysis of variance was applied to evaluate mean differences of normally distributed variables between statin and non-statin-treated groups and cardiorespiratory fitness categories.

A fully adjusted Cox proportional hazards model was constructed to assess the risk of type 2 diabetes between the statin-treated and non-statin treated groups. Adjusted and unadjusted Cox proportional hazards models were also constructed to compare risks for developing type 2 diabetes across the four cardiorespiratory fitness categories within the statin treated group. In these analyses the Least-fit category served as the reference group. Finally, we compared the risk of the four statin-treated fitness categories to that of the entire non-statin-treated group. For this analysis, the entire non-statin-treated group was used as the reference group.

In all fully adjusted models the covariates were: age in years, peak Metabolic Equivalents (when appropriate), body mass index, race, gender, alcohol/drug abuse, smoking status, sleep apnea, hypertension, and anti-hypertensive/cardiac medications (β-blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors [ACEI], and angiotensin II receptor blockers [ARB]). All co-variables included in the models were based on the rationale of their clinical role on the outcome and the main factors of interest. The assumption of proportionality for the Cox proportional hazards models was graphically tested by plotting the logarithm of the cumulative hazards with time for each covariate; the proportionality assumption was fulfilled for each model. All hypotheses were 2 sided, and p-values <0.05 were considered statistically significant. All statistical analyses were performed with SPSS software version 24.0 (SPSS Inc, Armonk, NY: IBM Corp).

Results

The incidence of type 2 diabetes was 24% higher (HR 1.24; 95% CI 1.11-1.39; p<0.001) in statin-treated compared to non-statin treated patients. The non-statin cohort was younger than the statin-treated cohort (57.2 ±11.1 vs 58.7±10.9 vs years; p<0.001) had similar body mass index and higher cardiorespiratory fitness (7.9 ±2.9 vs 7.2 ±2.3 Metabolic Equivalents; p<0.001).

For the 4,092 (179 females) statin-treated patients the follow-up time ranged from 0.50 to 27.0 years (mean, 8.3±5.2 years). The median follow-up time was 8.3 years (4.3 and 12.3 for 25th, and 75th percentiles, respectively), comprising 35,177 person-years. In this cohort, there were 1,075 type 2 diabetes events (26.3%) with an average annual incidence rate of 30.6 events per 1,000 person-years. There were no interactions between site and Metabolic Equivalents (p=0.31) or race and Metabolic Equivalents (P=0.41); therefore, the data were not stratified by site or race.

Baseline demographic and clinical characteristics across cardiorespiratory fitness categories for the statin-treated group are presented in Table 1. Age was similar across all cardiorespiratory fitness categories. However, significant differences were evident across cardiorespiratory fitness categories. In general, body weight, body mass index, blood pressure, and lipoprotein-lipid profile were more favorable with increased cardiorespiratory fitness. Similarly, the prevalence of comorbidities, and the use of anti-hypertensive/cardiac medications were substantially lower or more favorable for individuals with increased cardiorespiratory fitness categories.

Predictors of Type 2 Diabetes

Multivariable Cox proportional hazards analysis revealed that body mass index, (HR 1.07; 95% CI 1.05-1.08; p<0.001), hypertension (HR 1.49; 95% CI 1.21-1.83; p<0.001), smoking (HR 1.89; 95% CI 1.66-2.14; p<0.001), sleep apnea (HR 1.35; 95% CI 1.15-1.59; p<0.001), and exercise capacity were strong predictors of type 2 diabetes incidence. For each 1 Metabolic Equivalent increase in cardiorespiratory fitness, the adjusted HR for incidence of type 2 diabetes was 6% lower (HR =0.94; CI 0.91-0.97; $p<0.001$).

The relative risks for developing type 2 diabetes across cardiorespiratory fitness categories are presented in Table 2 and Figure 1. In the fully adjusted model, type 2 diabetes risk progressively decreased as exercise capacity increased. The risk was not altered significantly when treatment with β-blockers and diuretics only (medications known to increase the incidence of diabetes) or when ACEIs and ARBs only were considered in a separate analyses (findings not included).

Finally, we performed an additional multivariable Cox proportional hazards analysis to further access the impact of cardiorespiratory fitness on the risk of developing diabetes. For this analysis, we used the non-statin treated cohort as the reference group and compared it with the aforementioned fitness categories of the statin-treated cohort. Diabetes incidence was significantly elevated for individuals in the Least-Fit (HR 1.50; 95% CI 1.30-1.73; $p<0.001$) and Low-Fit (HR 1.22; 95% CI 1.06-1.41; $p=0.006$) categories. For the Moderate and High-Fit individuals the risk was similar to those not treated with statins.

Discussion

The findings of the current study support that statins increase the risk for developing diabetes in United States veterans to a magnitude within the range reported by several studies.[6] However, the unique finding of the current study is that the increased risk for diabetes was only evident in individuals with poor cardiorespiratory fitness. This concept is supported by two findings. First, when compared to the Least-Fit individuals, the adjusted risks for developing type 2 diabetes declined progressively, with the risk being 18%; 24% and 34% lower for Low-Fit, Moderate-fit and High-fit individuals, respectively. Second, when compared to those not treated with statins, the higher risk for developing diabetes was only evident for those in the two lowest fitness categories (Least-Fit and Low-Fit). Specifically, the risk of incidental type 2 diabetes was 50% higher in Least-fit individuals treated with statins and 22% higher in the Low-fit individuals. The risk was virtually eliminated for the Moderate-fit and High-fit individuals (Figure 2). This suggests that the potential increased risk for developing type 2 diabetes associated with statin therapy may be modulated by increased cardiorespiratory fitness.

When considering the worldwide rise in type 2 diabetes incidence related, at least in part to the obesity epidemic and low physical activity and cardiorespiratory fitness as well as the pervasive use of statins worldwide, even a relatively minor tendency for statins to increase type 2 diabetes incidence can have significant implications on global health. Moreover, statins not only promote diabetogenesis, but also have a detrimental impact on glycemic control in established type 2 diabetes and type 1 diabetes mellitus patients, greatly increasing their pathophysiological influence.[25] In this regard, the findings of the current study support that adequate levels of physical activity to increase cardiorespiratory fitness provides a means to counteract the diabetogenic propensities of statin therapy. The cardiorespiratory fitness level necessary to lower the risk of type 2 diabetes significantly within the statin-treated group was approximately 8 Metabolic Equivalents (Table 2). Furthermore, at this fitness level, the higher incidence of diabetes observed in the Least and Low-fit patients when compared to the non-statin-treated group, was virtually eliminated (Figure 2). This cardiorespiratory fitness level is achievable by most middle-aged and older individuals by moderate levels of physical activity such as 30-40 minutes of brisk walk most days of week.[26,27] It is also well within the cardiorespiratory fitness level shown to work synergistically with statin therapy and most effectively lower mortality risk in dyslipidemic patients.[19] The interaction between cardiorespiratory fitness, type 2 diabetes, and statin use provides an additional impetus for health care providers to promote moderate physical activity in order to reduce the burden of type 2 diabetes.[26-28]

This study has several strengths and limitations inherent in prospective follow-up studies. Importantly, cardiorespiratory fitness levels were based on only 1 assessment, and follow-up data on cardiorespiratory fitness status of the participants was not available. The use of 2 different exercise protocols to assess cardiorespiratory fitness is also a potential limitation. Previous work suggests that the ramp protocol is somewhat more accurate in predicting estimated Metabolic Equivalents.[29,30] However, separate analyses from the 2 locations yielded similar results, suggesting that the differences in protocols had minimal impact.[29,31,32] We did not have an adequate number of participants to assess risk in those <30 years of age. Dietary information was also not available in our records. Finally, mostly male veterans were included, which limits the ability to generalize the findings to women and other non-veteran populations.

There are also certain attributes that make our findings unique and applicable to other populations. This was a comparatively large study to address the association between cardiorespiratory fitness status assessed objectively and incidence of type 2 diabetes in a clinically-referred cohort (n=7,093) with a follow-up of 81,768 person-years. Our cohort has equal access to care independent of a patient's financial status provided by the Veterans Health Administration. This permits epidemiologic evaluations while minimizing the influence of disparities in medical care.[33-35] In addition, the existence of electronic health records within the Veterans Affairs Healthcare System enables accurate identification of the onset of type 2 diabetes and the initiation or discontinuation of statin therapy, as well as detailed observation of prior history, medications, co-morbidities and alterations in health status. These attributes, allowed greater accuracy in defining our cohort, minimize the likelihood of reverse causality and support the validity of the cardiorespiratory fitness - type 2 diabetes risk association across the age spectrum. However, the current findings are based on epidemiologic data, derived form a cohort of veterans and should be interpreted with caution. Future studies are needed to validate and expand our findings to different populations.

Conclusions

The current of the current study suggest that the risk of type 2 diabetes incidence in dyslipidemic patients treated with statins may be significantly attenuated by moderate increases in cardiorespiratory fitness. Therapeutic interventions including increasing physical activity through rehabilitation or community exercise programs to improve cardiorespiratory fitness should be encouraged in high-risk individuals, especially those on statins. These results provide further support for health care professionals and health organizations to promote physical activity in order to reduce the public health care burden of type 2 diabetes and support the promotion of physical activity throughout the healthcare system and throughout the globe.[27,36,37]

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P.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Demographic and clinical characteristics according to fitness categories

	Least-fit	Low-fit	Moderate-fit	High-fit	p-value
n (%)	954	1,201	1,242	695	
Age (yrs)	58.2±10.9	58.8±11.0	58.8±10.7	59.5±10.9	0 .121
Weight (Kg)	94.0±20.2	92.2±17.6	89.3±15.1	85.5±13.7	<0.001
Body Mass Index (kg/m^2)	30.3±6.1	29.7±5.0	28.8±4.3	27.6±4.0	<0.001
Resting Heart Rate (beats/min)	73.7±14.0	71.6±13.1	68.4±11.8	67.3±12.4	<0.001
Rest Systolic Blood Pressure (mm Hg)	131.9±20.9	129.8±19.6	126.7±18.0	127.0±17.9	<0.001
Rest Diastolic Blood Pressure (mm Hg)	80.3±12.3	78.8±11.5	78.0±10.8	78.1±10.9	<0.001
Peak MET	4.8±1.2	6.5±1.1	8.0±1.1	10.3±2.1	<0.001
Total Cholesterol (mg/dL)	190.6±44.1	195.9±47.2	194.2±46.0	193.9±40.8	0.701
Triglycerides (mg/dL)	141.8±82.5	136.6±91.8	122.7±88.3	113.7±68.5	0.025
Low Density Liporoptein - Cholesterol (mg/dL)	118.5±36.8	126.0±86.2	123.7±41.4	129.4±40.7	0.081
High Density Lipoprotein - Cholesterol (mg/dL)	42.1±12.0	43.8±12.7	45.3±13.0	45.2±12.4	0.034
Glucose (mg/dL)	105.5±33.5	101.4±24.6	98.9±21.0	95.0±14.7	<0.001
Type 2 Diabetes Incidence (%)	444 (30.9)	449 (25.9)	288 (23.2)	123 (17.7)	<0.001
Hypertension (%)	824 (25.7)	984 (30.6)	957 (29.8)	447 (13.9)	<0.001
Smoking (%)	408 (30.8)	448 (33.8)	326 (24.6)	144 (10.9)	<0.001

Sleep Apnea (%)	113 (22.6)	168 (33.7)	171 (34.3)	47 (9.4)	<0.001
Antihypertensive/Cardiac agents (%)	879 (25.0)	1,089 (30.9)	1,058 (30.0)	496 (14.1)	<0.001
ACEI/ARBS (%)	71 (22.0)	116 (36.0)	99 (30.7)	36 (11.2)	0.006
β-blockers/diuretics (%)	243 (23.4)	295 (28.4)	330 (31.8)	169 (24.3)	0.621
Drug/Alcohol abuse (%)	108 (28.3)	130 (34.0)	105 (27.5)	39 (10.2)	0.001

Table 2. Risk for developing type 2 diabetes according to fitness categories

	Patients (n)	Type 2 Diabetes (n; %)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	p value†
Least-Fit (Referent; 4.8±1.2 Metabolic Equivalents)	954	395 (41.4%)	1	1	-
Low-Fit (6.5±1.1 Metabolic Equivalents)	1,201	420 (35.0%)	0.75 (0.64-0.87)	0.82 (0.70-0.95)	0.009
Moderate-Fit (8.0±1.1 Metabolic Equivalents)	1,242	378 (30.4%)	0.59 (0.50-0.69)	0.76 (0.65-0.90)	0.001
High-Fit (10.3±2.1 Metabolic Equivalents)	695	145 (20.9%)	0.41 (0.34-0.51)	0.66 (0.53-0.82)	<0.001

HR=hazard ratio

* Adjusted for age, body-mass index, race, gender, β blockers, calcium channel blockers, diuretics, angiotensin-converting enzymes, angiotensin II receptor blockers, smoking, hypertension, sleep apnea, and alcohol/drug abuse

†For fully adjusted HR

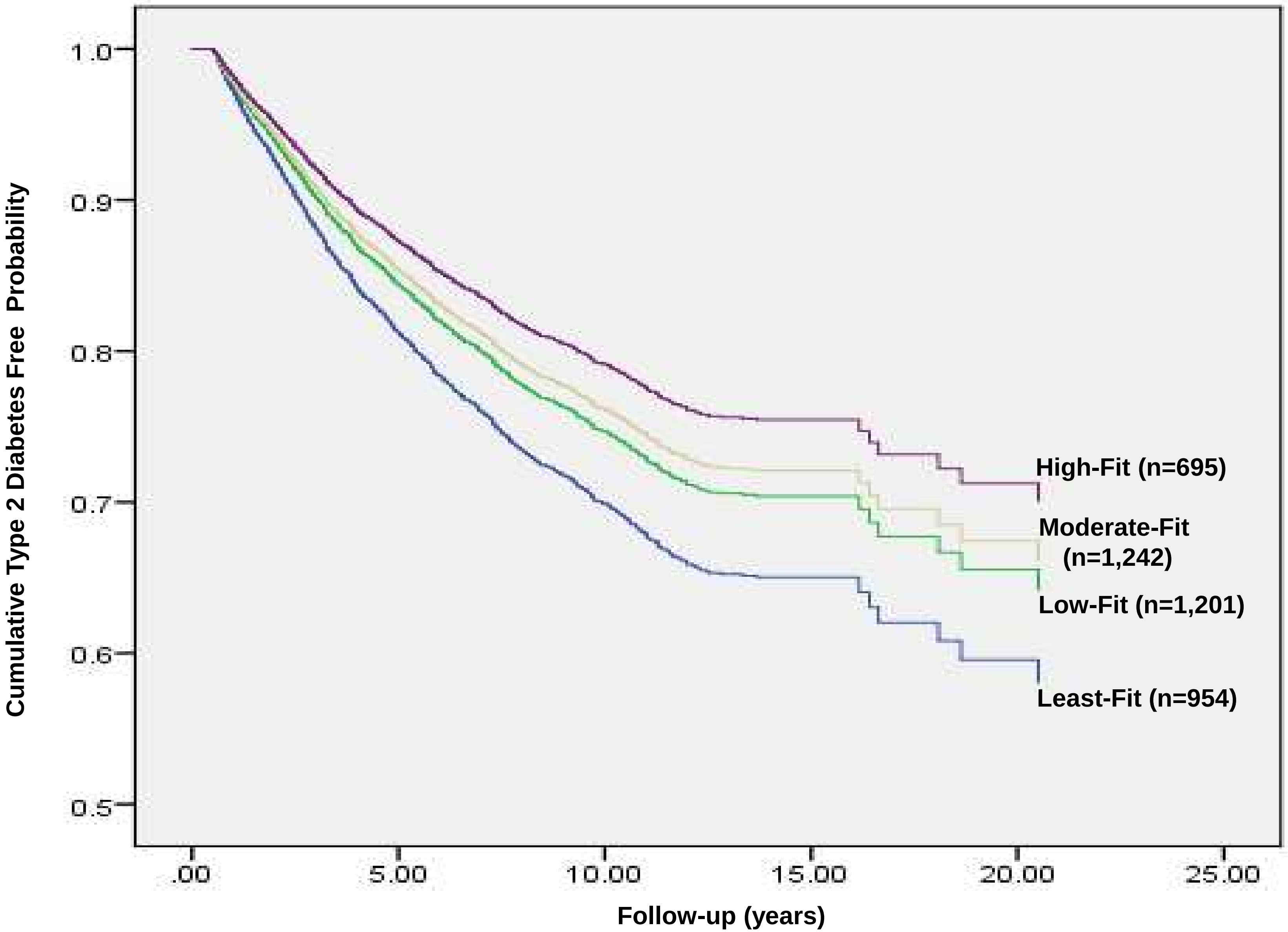

Figure 1. Relative risk for developing type 2 diabetes according to cardiorespiratory fitness categories

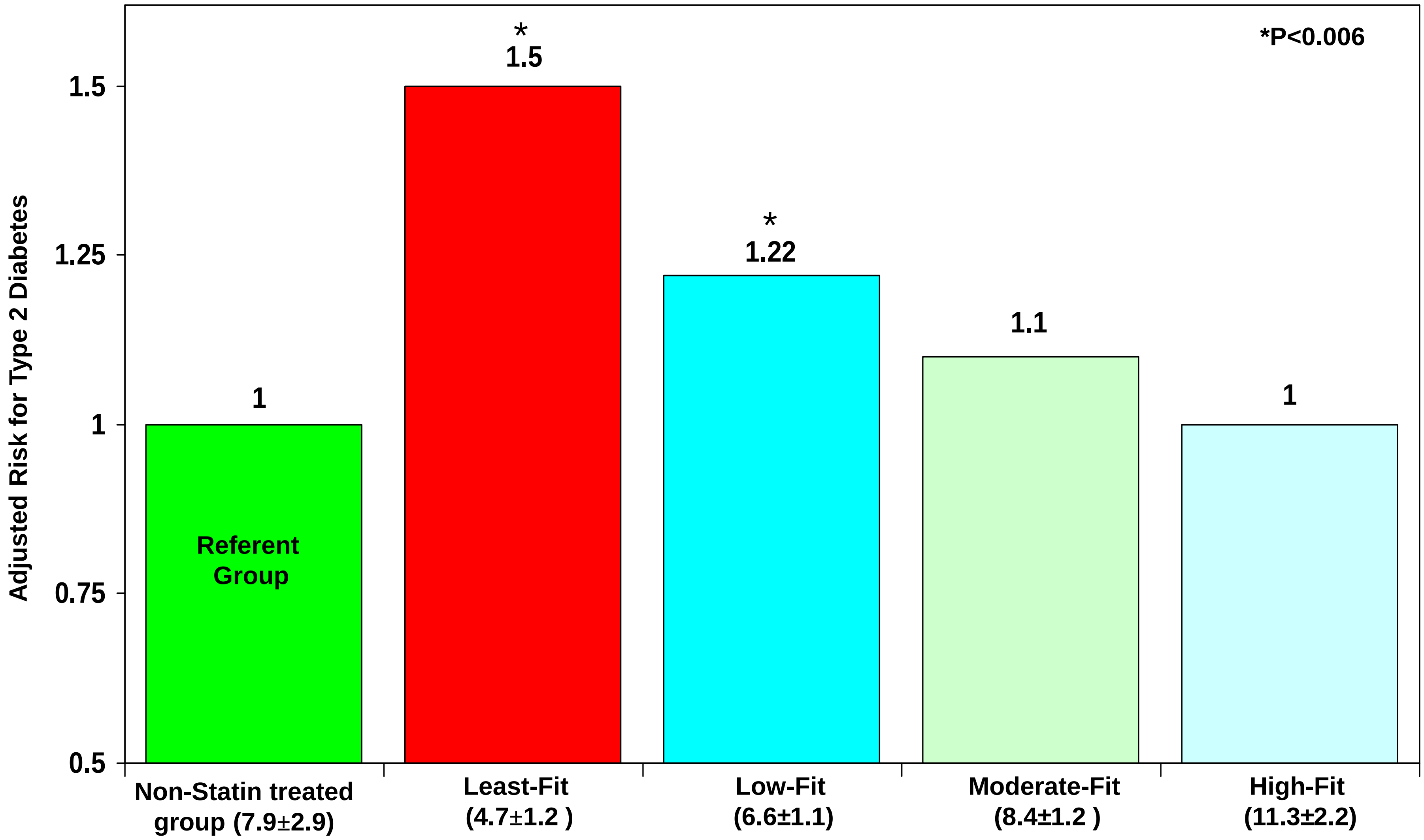

Figure 2 **Risk for developing type 2 diabetes according to fitness status in statin-treated patients with dyslipidemia compared to the non-statin treated group. Fitness categories represent individuals in the statin-treated group only. Numbers in parentheses denoting peak Metabolic Equivalents achieved.**

Clinical Significance

- Recent studies have shown an increase in the incidence of type 2 diabetes with statin therapy
- Since the use of statins is considerably high, ways to attenuate the incidence of Type 2 diabetes is clinically important
- Cardiorespiratory fitness improves metabolic parameters and attenuates the risk for developing Type 2 diabetes
- The findings of the current study support that cardiorespiratory fitness modulates the statin-associated risk for developing type 2 diabetes