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ORIGINAL RESEARCH

Midlife Cardiorespiratory Fitness and the Development of Peripheral Artery Disease in Later Life

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BACKGROUND: Data are sparse on the prospective associations between physical activity and incidence of lower extremity peripheral artery disease (PAD).

METHODS AND RESULTS: Linking participant data from the CCLS (Cooper Center Longitudinal Study) to Medicare claims files, we studied 19 023 participants with objectively measured midlife cardiorespiratory fitness through maximal effort on the Balke protocol who survived to receive Medicare coverage between 1999 and 2009. The study aimed to determine the association between midlife cardiorespiratory fitness and incident PAD with proportional hazards intensity models, adjusted for age, sex, body mass index, and other covariates, to PAD failure time data. During 121 288 person-years of Medicare follow-up, we observed 805 PAD-related hospitalizations/procedures among 19 023 participants (21% women, median age 50 years). Lower midlife fitness was associated with a higher rate of incident PAD in patients aged 65 years and older (low fit [quintile 1]: 11.4, moderate fit [quintile 2 to 3]: 7.8, and high fit [quintile 4 to 5]: 5.7 per 1000 person years). After multivariable adjustment for common predictors of incident PAD such as age, body mass index, hypertension, and diabetes, these findings persisted. Lower risk for PAD per greater metabolic equivalent task of fitness was observed (hazard ratio [HR], 0.93 [95% CI, 0.90–0.97]; P<0.001). Among a subset of patients with an additional fitness assessment, each 1 metabolic equivalent task increase from baseline fitness was associated with decreased risk of incident PAD (HR, 0.90 [95% CI, 0.82–0.99]; P=0.03).

CONCLUSIONS: Cardiorespiratory fitness in healthy, middle-aged adults is associated with lower risk of incident PAD in later life, independent of other predictors of incident PAD.

Key Words: cardiorespiratory fitness ■ midlife ■ peripheral artery disease

Peripheral artery disease (PAD) is a global health problem, with over 200 million people worldwide affected, with increasing prevalence in people with diabetes, renal insufficiency, and smoking.[1–5] PAD, defined as an ankle-brachial index (ABI) ≤0.90, may or may not cause symptoms. Although asymptomatic PAD observed on an ABI may indicate a patient is at high risk of morbidity, the evidence underlying treatment options in asymptomatic PAD is unclear.[6] In comparison, symptomatic PAD, ranging from intermittent claudication to severe, limb-threatening ischemia with significant resultant morbidity and mortality, has many procedural and medical therapies.[7] Given the significant morbidity and mortality from PAD, factors that reduce or attenuate the risk of developing PAD are likely to have large public health importance.

Although lower fitness in patients with PAD is associated with increased rates of mortality and mobility loss,[8] and supervised exercise programs are first-line therapy for the symptomatic treatment of patients with PAD,[9–11] the association of fitness and incident PAD is not well understood. There are few longitudinal

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CLINICAL PERSPECTIVE

What Is New?

- In this large population of 19 023 healthy individuals followed for an average of 17.5 years, higher midlife cardiorespiratory fitness was associated with a lower incidence of peripheral artery disease–related hospitalizations and/or procedures decades later.
- Improvement in cardiorespiratory fitness during midlife was associated with reduced risk of peripheral artery disease–related events.

What Are the Clinical Implications?

- Changes in physical activity levels in the population could have a robust impact on the population burden of peripheral artery disease.
- The future role of exercise and fitness for prevention of peripheral artery disease will need prospective evaluation.

Nonstandard Abbreviations and Acronyms

CCLS	Cooper Center Longitudinal Survey
CMS	Centers for Medicare and Medicaid Services

studies[12–14] illustrating higher activity levels associated with diminished PAD incidence. However, these studies either rely on self-reported fitness data or include both asymptomatic and symptomatic PAD as assessed through ABI measurement. Given that most of the morbidity, mortality, and health care cost is from symptomatic PAD, objective data analyzing the relationship between fitness and incidence of symptomatic PAD are needed.

The CCLS (Cooper Center Longitudinal Study) offers the opportunity to characterize the associations of objectively measured cardiorespiratory fitness during midlife and the development of morbid outcomes later in life.[15–17] We sought to assess the association between objectively measured cardiorespiratory fitness during midlife and the development of symptomatic, severe PAD later in life.

METHODS

The authors will not make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results because the data are owned by the Cooper Clinic.

Study Population

The CCLS consists of a large cohort of individuals who completed a preventive medicine examination at the Cooper Clinic in Dallas, Texas, from its inception in 1970 through 2009. Participants are generally healthy, community-dwelling individuals who are self-referred or referred by their employer for preventive health examinations. Patients who are part of the CCLS receive a comprehensive clinical examination that includes detailed personal and family history assessments, standardized medical examination by a physician, anthropometric measurements, fasting laboratory studies, and a maximal treadmill exercise test. Participants provide written informed consent for inclusion in the research database. The study is reviewed and approved annually by the institutional review board of the Cooper Institute. Longitudinal follow-up was obtained by combining data from the CCLS with Medicare data from the Centers for Medicare and Medicaid Services (CMS).

Among 73 439 participants in the CCLS who had complete data for the analysis, 27 453 were eligible to receive Medicare fee-for-service coverage between January 1, 1999 and December 31, 2009 and had no evidence of self-reported atherosclerotic disease at baseline. We excluded 2951 participants with missing or incomplete treadmill exercise data and 3831 participants with missing demographic and baseline clinical data. Lastly, we excluded 1648 participants with a CCLS examination after enrollment into a Medicare fee-for-service plan. The final sample included 19 023 participants.

Ascertainment of Exposure Variables

The primary exposure variable was cardiorespiratory fitness, as assessed by maximal effort using the modified Balke protocol.[18] In this protocol, treadmill speed is set initially at 88 m/min. In the first minute, the grade is set at 0% followed by 2% in the second minute and an increase of 1% for every minute thereafter. After 25 minutes, the grade remains unchanged, but the speed is increased 5.4 m/min for each additional minute until the test is terminated. A subgroup of CCLS participants had a second fitness measurement assessed through the modified Balke protocol at a later visit.

Other variables were ascertained from the CCLS examination, as described previously,[15–17,19] including age, smoking status, alcohol intake, education level, systolic blood pressure, body mass index, total cholesterol, and fasting glucose. Height, weight, and body mass index were measured using a standard clinical stadiometer and scale. Resting systolic blood pressure was assessed with a calibrated sphygmomanometer. All laboratory studies were performed after a 12-hour fast and included fasting blood glucose and cholesterol profiles, performed in accordance with standard procedures.

In accordance with standard approaches to the analysis of fitness data,[19,20] each participant's treadmill time was classified into age- and sex-specific mutually exclusive quintiles of fitness, with low fitness corresponding to quintile 1, moderate fitness to quintiles 2 and 3, and high fitness to quintiles 4 and 5. Fitness level in metabolic equivalents task (METs) was determined from the treadmill times using regression equations, as previously described.[21]

Ascertainment of Outcome Variables

The primary outcome variable of interest was lower extremity PAD-related hospitalizations and/or lower extremity surgical or endovascular procedure. PAD was defined as arterial disease of the infrarenal aorta and lower extremities. This was ascertained using CMS files between 1999 (the first year CMS data were available for public use when the data set was acquired) and 2009. Inpatient hospitalization files from CMS provide all individual records for each medical service billed to Medicare, the date of service, primary diagnosis, and up to 8 secondary diagnoses and procedure codes. Because coding standards are not distinct for PAD-related treatment, we used a previously described algorithm to assess PAD-related claims in both inpatient and outpatient settings, as initially developed by Margolis et al[22] and subsequently modified by Hirsch and colleagues.[23] Briefly, patients with PAD were identified from claims using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes (440.0, 440.20–24, 440.31, 440.9, 442.3, 443.9, 444.2, 444.81) and procedure codes (38.08, 38.13, 38.18, 39.25, 39.26, 39.50, 39.90) from an inpatient or outpatient medical claim or *Current Procedural Terminology* (*CPT*) codes for a PAD-related procedure (noncoronary and extracranial thrombectomy, embolectomy, angioplasty, atherectomy, bypass graft, or stenting).

Statistical Analysis

Mean (SD) and percentage were reported for continuous and categorical variables, respectively. Cumulative incidence rates were obtained using the Kaplan-Meier approach. Because patients enter the Medicare claims data at various ages and for varying durations, the data are subject to censoring on the right and truncation on the left, with the possibility of multiple events per patient. To include at most 1 PAD event per patient, Medicare claims surveillance was censored beyond the earliest of the first event, death, or December 31, 2009.

The association between midlife cardiorespiratory fitness and first PAD-related hospitalization/procedure after age 65 years was assessed by applying a proportional hazards intensity model to the failure time data. We used attained age as the time scale and entered midlife fitness as the independent covariate. This was assessed as both a categorical variable (low, moderate, and high fit) and a continuous variable (METs achieved). Models were also adjusted for age at baseline examination, sex, smoking status, total cholesterol, baseline systolic blood pressure, baseline diabetes, and baseline body mass index. An interaction term between smoking and fitness was also assessed. Population attributable risk (PAR) for low fitness and smoking was estimated from the proportional hazards model using the formula of Levin,[24] and CIs were calculated on the logit scale.[25]

In a subgroup of CCLS participants who had their fitness tested again at a later visit, the association between the continuous change in fitness (ie, per MET) and PAD-related hospitalizations/procedures was assessed by applying a proportional hazards intensity model to the failure time data adjusted for age, sex, baseline fitness, time between exams, smoking status, body mass index, diabetes, and resting systolic blood pressure.

All analyses were programmed in SAS/STAT version 9.4 (SAS Institute, Cary, NC). All *P* values were 2-tailed, with statistical significance set at 0.05, and all CIs were calculated at a 95% confidence level.

RESULTS

A total of 19 023 participants were included, with a mean (SD) interval of 17.5 (7.6) years between the baseline exam and entry into the Medicare claims surveillance period. Most participants (median age, 50.0 years) were White (98.3%), with 21.1% women and 15.6% actively smoking at the baseline exam. Baseline characteristics of the sample by category of midlife fitness are listed in Table 1. Low-fit participants had a higher body mass index, less self-reported physical activity, and a higher prevalence of active smoking at baseline compared with the other 2 groups. Additionally, low-fit participants had higher prevalence of diabetes, hypertension, and elevated cholesterol.

After 121 288 person-years of Medicare follow-up to the first PAD event, we observed 805 PAD-related hospitalizations/procedures, with an overall incidence rate of 6.6 events per 1000 person-years of follow-up. The age-adjusted incidence of PAD events was 7.4 per 1000 person-years in men and 3.9 per 1000 person-years in women. We observed a consistent association between lower levels of fitness at baseline and a higher long-term incident PAD event rate in both men and women (Figure 1). The incidence in men declined from 11.4 per 1000 person-years in the low-fit quintile to 5.4 per 1000 person-years in the high-fit quintile. Similarly,

Table 1. Baseline Characteristics of the Study Population (N=19 023)

Characteristics	Low fit, N=3130	Moderate fit, N=7644	High fit, N=8249
Sociodemographics			
Baseline age, y, mean (SD)	47.3 (8.7)	49.8 (8.8)	51.9 (8.4)
Medicare age, y, mean (SD)	67.8 (4.8)	67.9 (5.1)	67.7 (4.9)
Women	17.1%	19.3%	24.3%
White race	98.2%	98.3%	98.6%
Education level, y (SD)*	15.3 (2.7)	15.9 (2.6)	16.2 (2.6)
Alcohol intake, drinks/wk (SD)	8.5 (10.9)	8.7 (11.3)	8.5 (10.6)
Current smoking	29.4%	18.0%	8.2%
Body mass index, kg/m^2 (SD)	27.4 (4.8)	25.9 (3.5)	24.3 (2.9)
Physical activity/cardiorespiratory fitness			
Physical activity index (SD)†	0.5 (0.9)	1.0 (1.0)	2.0 (1.1)
Fitness, METs (SD)	8.0 (1.4)	9.8 (1.5)	12.2 (2.2)
Treadmill time, min (SD)	10.1 (3.0)	14.1 (3.2)	19.5 (4.4)
Medical history			
Diabetes	7.2%	3.7%	1.9%
Hypertension	42.3%	34.8%	28.3%
Laboratory and other measurements			
Systolic blood pressure, mm Hg (SD)	123.6 (15.0)	121.5 (14.6)	120.0 (14.8)
Diastolic blood pressure, mm Hg (SD)	82.5 (10.0)	81.1 (9.7)	79.8 (9.3)
Total cholesterol, mg/dL (SD)	217 (41.2)	215 (39.1)	206 (37.1)
Glomerular filtration rate, mL/min (SD)‡	64.0 (14.3)	63.0 (13.5)	63.3 (12.2)

Numbers represent median (SD) for continuous variables and percent for binary or categorical variables. METs indicates metabolic equivalents task.
*Only 20% of participants reported educational level.
†Physical Activity Index is a self-reported scale, for which 0 indicates no regular physical activity; 1, some physical activity other than walking, running, or jogging; 2, walking, jogging, or running <16 km/week; 3, walking, jogging, or running 16 to 32 km/week; and 4, walking, jogging, or running >32 km/week.
‡Calculated using the Modification of Diet in Renal Disease equation.

the incidence rate declined from 5.1 per 1000 person-years in the low-fit quintile to 3.2 per 1000 person-years in the high-fit quintile in women.

After multivariable adjustment, high midlife fitness was associated with a lower risk for incident PAD compared with low midlife fitness (hazard ratio [HR], 0.71 [95% CI, 0.57–0.88]; *P*=0.002) (Figure 1). Every additional MET at baseline was associated with lower risk of PAD (HR, 0.93 [95% CI, 0.90–0.97]; *P*<0.001). Smoking at baseline was associated with a higher risk for incident PAD decades later (HR, 1.58 [95% CI, 1.34–1.86]; *P*<0.001) (Table 2). There was no significant interaction with fitness and smoking (smoking×fitness, *P*=0.3). The estimated PAR for both smoking and low fitness in age-adjusted models was similar (smoking: 9.32%, low fitness: 8.55%) (Figure 2). However, in multivariable-adjusted models, the PAR for low fitness was lower, whereas the PAR for smoking remained unchanged (smoking: 9.36%, low fitness: 5.45%).

Table S1 shows changes in baseline parameters and fitness data between visit 1 and visit 2. Overall, 8759 participants had fitness data from a later visit (mean difference in time between visit 1 and visit 2 of 4.23 years). The majority of participants were high fit at baseline and remained high fit at visit 2 (N=7331). Three hundred sixty-two participants remained low fit at visit 2 (visit 1, 8.0 METs) with average change in fitness of +0.1 METs. Nine hundred nine participants improved their fitness level (visit 1, 8.4 METs) with average change in fitness of +1.9 METs. Lastly, 157 participants decreased their fitness level with average change in fitness of −1.9 METs. After multivariable adjustment, each 1-MET increase from baseline fitness was associated with a decreased risk of incident PAD (HR, 0.90 [95% CI, 0.822–0.990]; *P*=0.03) (Table 3).

DISCUSSION

The results of this cohort study of 19 023 healthy individuals followed for a mean interval of 17.5 years until entry into the Medicare surveillance period with 805 initial lower-extremity PAD-related hospitalizations/procedures indicate that higher midlife cardiorespiratory fitness is associated with a lower incidence of PAD-related hospitalizations/procedures decades later. Furthermore, each MET improvement from baseline of cardiorespiratory fitness at a subsequent visit was associated with a ≈10% reduction in the risk of developing a PAD-related event. The PAR of fitness was half

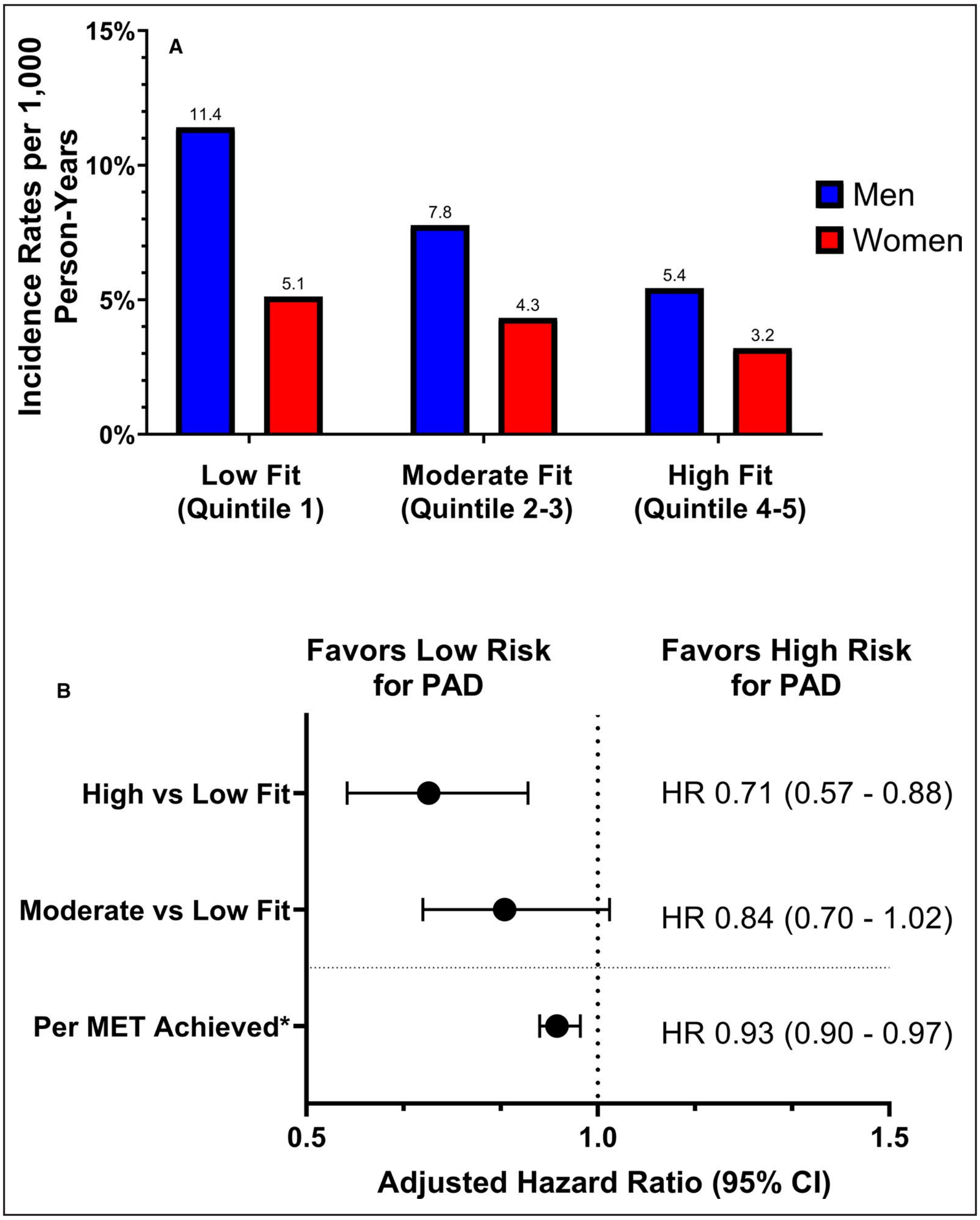

Figure 1. Relationship between midlife cardiorespiratory fitness and incidence of peripheral artery disease (PAD) for men and women (A) and adjusted association between cardiorespiratory fitness and PAD (B).
Incidence rates in (**A**) adjusted for age, whereas associations in (**B**) were adjusted for body mass index, age, sex, systolic blood pressure, diabetes, cholesterol, and smoking. HR indicates hazard ratio; and MET, metabolic equivalent task. *Modeled separately with METs achieved as a continuous variable.

that of smoking after adjustment for age, sex, and clinical comorbidities.

Although fitness is associated with other disease states, the relationship between fitness and incident PAD is relatively unknown.[15,16] The vast majority of studies use self-reported physical activity[12–14,26–31] or assessment of daily activity through accelerometry.[32–34] Most previous studies also used ABI as the primary outcome of PAD without assessment of patient symptoms. These studies find an association between measured/assessed activity levels and PAD. For example, Delaney et al studied 5656 participants from the MESA (Multi-Ethnic Study of Atherosclerosis) study and noted intentional reported exercise from the Typical Week Physical Activity Survey, used to calculate metabolic equivalent–minutes per week of activity, was associated with a lower likelihood of ABI progression over 2 to 5 years of follow-up.[30] Fewer studies

Table 2. Multivariable Adjusted Associations Between Midlife Fitness and Incident Peripheral Artery Disease

Predictors	Primary model, HR (95% CI)*
Moderate vs low fit	0.84 (0.70–0.1.02); *P*=0.071
High vs low fit	0.71 (0.57–0.88); *P*=0.002
Per MET achieved†	0.93 (0.90–0.97); *P*<0.001
Male sex	1.45 (1.16–1.82); *P*=0.001
Diabetes	1.58 (1.34–1.86); *P*<0.001
Current smoking	1.58 (1.34–1.86); *P*<0.001
Body mass index, per 3 kg/m^2 increase	1.07 (1.00–1.15); *P*=0.045
Systolic blood pressure, per 20 mm Hg increase	1.17 (1.06–1.29); *P*=0.002
Cholesterol, per 40 mg/dL increase	1.08 (1.01–1.16); *P*=0.037

Low fit: defined as quintile 1; moderate fit: defined as quintiles 2 and 3; high fit: defined as quintiles 4 and 5. HR indicates hazard ratio; and MET, metabolic equivalent task.

*Model adjusted for body mass index, age, sex, systolic blood pressure, diabetes, cholesterol, and smoking status. Low fit was used as the referent group.

†Modeled separately with MET achieved as a continuous variable.

used a clinical definition of PAD[12–14,31] assessing either ABI and/or clinical symptoms or receipt of endovascular procedure or surgery. Of these 4 studies, only Garg et al did not find a statistically significant association between physical activity and PAD.[31]

In comparison, the present study uses Medicare administrative claims data with a large cohort of healthy men and women with objectively measured fitness levels, providing an efficient strategy to examine the association between midlife fitness and the development of clinical, symptomatic PAD decades later. To our knowledge, the current study is the first to demonstrate a relationship between midlife objectively measured cardiorespiratory fitness and incident PAD years later. One of the strengths of this analysis is the use of a validated objective definition for ascertaining clinical, symptomatic, incident PAD within an administrative data set with a large number of clinically significant observed events (805 PAD-related hospitalizations/procedures) as compared with measurement of ABIs, which may include both asymptomatic and symptomatic patients.[23] Because the majority of health care resource use in patients with PAD is related to procedural care, and patients with severe symptomatic disease face the highest morbidity and mortality from PAD, assessing for predictive factors in this cohort has large public health ramifications.[22,23]

The mechanism of the interaction between physical activity and incident PAD is currently unknown.[35] Physical exercise may have preventive actions because of the control of atherosclerotic risk factors, such as dyslipidemia, insulin resistance, and arterial hypertension.[36] However, beyond these risk factors, exercise itself has been shown to have many actions on the cardiovascular system, such as the prevention of endothelial dysfunction and maladaptive vascular remodeling.[37] The understanding of both the cellular and functional alterations as a result of physical activity require further research in an effort to isolate avenues for both treatment and prevention of PAD. Furthermore, prescription of purposeful exercise as a treatment for prevention of PAD in high-risk individuals will need prospective evaluation.

Assessment of the effects of cardiorespiratory fitness on incident PAD can be confounded by reverse causality, that is, did participants with lower fitness have either covert or overt PAD at the time of enrollment, thus resulting in lower performance on the treadmill? Although this cannot be conclusively ruled out, a number of factors argue against this phenomenon in the present study. First, CCLS participants were not referred specifically for exercise testing, because this was performed as part of a preventive health evaluation. Second, the fitness level of the CCLS population was in the normal range (10.5 METs). Even in the low-fit group, the mean fitness level was 8.0 METs, which is significantly higher than reported previously in patients with PAD.[8,38] Moreover, the vast majority of participants remained high fit at visit 2, and patients who had a positive change (improvement) in fitness had a lower risk of developing incident PAD during long-term follow-up. Lastly, our study had a long delay between fitness ascertainment and Medicare enrollment. This accentuates our findings, which showed that difference in fitness within the normal range translated into PAD many decades later.

In the current study, the PAR of smoking for incident PAD was lower than previously reported,[39] likely reflecting the relatively low burden of smoking exposure within a healthy population. Nevertheless, given the established contribution of smoking on PAD, this provides important context for our findings related to the PAR for fitness. In our study, the PAR for fitness was about one-half the PAR for smoking, suggesting that changes in physical activity levels in the population could have a similarly robust impact on the population burden of PAD as public health efforts to reduce smoking.

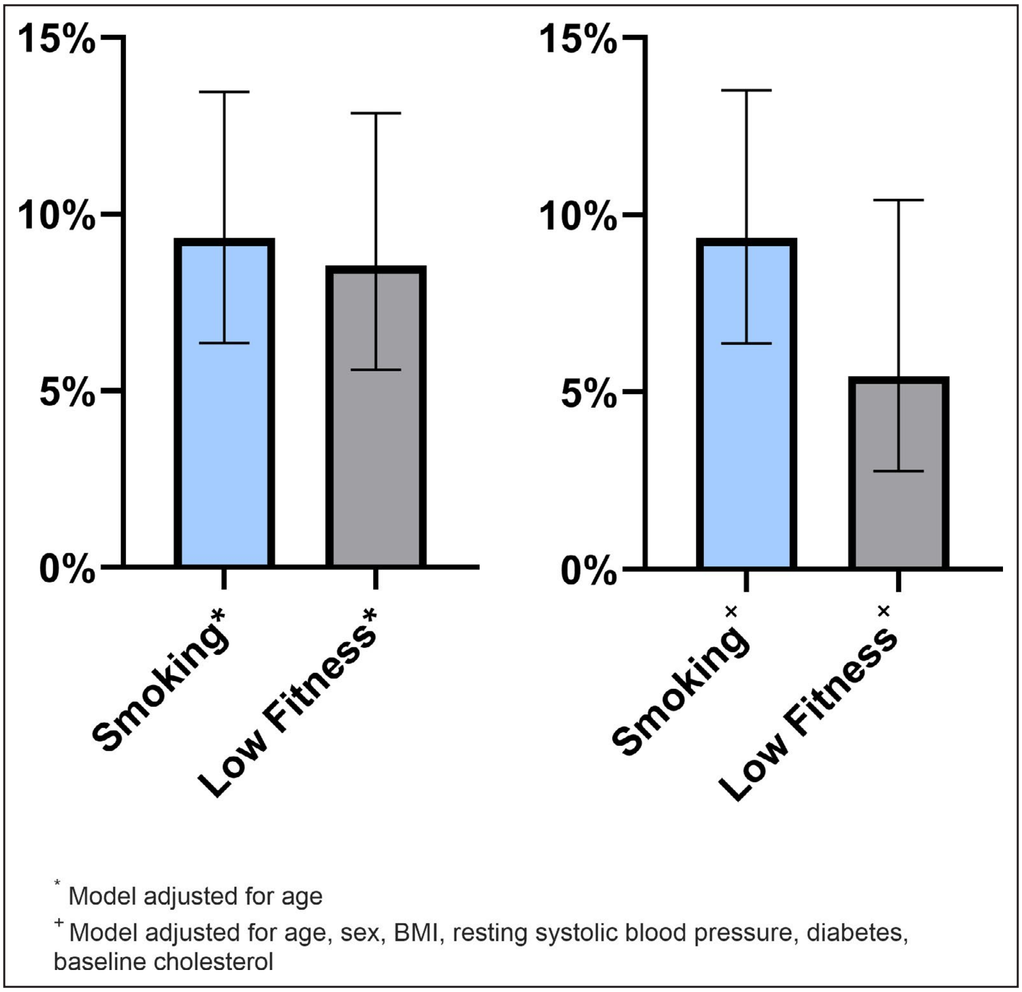

Figure 2. Population attributable risk of smoking and low fitness to the incidence of peripheral artery disease.
BMI indicates body mass index.

This study has limitations. The use of an administrative data set from CMS for ascertainment of outcomes rather than adjudicated clinical diagnoses is a possible limitation, because PAD cases could have been missed or may have been overcounted. However, CMS data are reliable sources of information for multiple outcomes.[40,41] We also used a validated algorithm to ascertain PAD based on *ICD-9-CM* diagnosis and procedure codes and *CPT* codes.[23] Another limitation is that by linking individual-level data from CCLS with CMS claims files, we were unable to capture outcomes that occurred between study entry and onset of Medicare eligibility. Additional factors, such as dietary patterns and medication use,[42] were not available for analysis and may have led to unmeasured and residual confounding. Lastly, nearly all participants in CCLS were White (98.3%). This stands in stark contrast to previously published epidemiologic assessments of PAD incidence showing that the rate of PAD in the Black population was 2-fold that of the non-Hispanic White population.[2] This limits the generalizability off these findings to other racial or ethnic groups. Participants in the CCLS have a higher socioeconomic and educational status and a lower prevalence of traditional risk factors as compared with the general population. Thus, PAD incidence may be higher in the general population.

Table 3. Multivariate Models for Incident Peripheral Artery Disease and Change in Fitness in a Subgroup of Cooper Center Longitudinal Survey Participants With 2 Visits (N=8759)

	HR (95% CI)	C^2	*P* value
Per 1 MET higher baseline CRF	0.97 (0.90–1.04)	0.84	0.36
Per 1 MET increase in METs	0.90 (0.82–0.99)	4.70	0.03

Model adjustment: exam year, sex, age, body mass index, diabetes, resting systolic blood pressure, smoking status. CRF indicates cardiorespiratory fitness; HR, hazard ratio; and MET, metabolic equivalent task.

In conclusion, higher midlife cardiorespiratory fitness is associated with a lower incidence of lower extremity PAD-related hospitalizations/procedures in men and women aged >65 years, independent of other common predictors of PAD. Furthermore, changes in midlife fitness were similarly associated with a reduction in risk for PAD.

ARTICLE INFORMATION

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Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Demographics of Participants with Fitness Change Data (N=8,759)

	Low to Low (N =362)	Low to High (N = 909)	High to Low (N = 157)	High to High (N = 7331)	P value
Socio-demographic					
Baseline Age (years, SD)	45.26 (7.48)	45.80 (7.98)	46.80 (8.49)	48.68 (8.28)	<0.0001
Medicare Entry Age (years, SD)	67.48 (4.29)	68.13 (4.96)	67.61 (4.84)	67.97 (4.94)	0.1459
Caucasian (%)	98.3	97.5	95.5	98.4	<0.0001
Female Sex (%)	10.8	13.1	17.2	16.3	0.0038
Time between Visit 1 and Visit 2 (Years, SD)	3.30 (3.57)	4.53 (4.70)	4.94 (4.91)	4.22 (4.03)	<0.0001
Cardiorespiratory Fitness Data					
METs at 1st Visit (Mean, SD)	8.02 (1.33)	8.44 (1.26)	9.91 (1.42)	11.47 (2.11)	<0.0001
METs at 2nd Visit (Mean, SD)	8.11 (1.29)	10.30 (1.68)	7.98 (1.41)	11.83 (1.28)	<0.0001
Average Difference in Mets between Visit 1 and Visit 2 (Mean, SD)	0.09 (1.03)	1.86 (1.46)	-1.94 (1.47)	0.36 (1.46)	<0.0001
Laboratory and other measurements at baseline exam					
Systolic blood pressure (mm Hg, SD)	123.58 (13.65)	122.73 (15.32)	122.66 (13.67)	120.80 (13.98)	<0.0001
Diastolic blood pressure (mm Hg, SD)	83.67 (9.91)	82.27 (10.14)	82.49 (9.86)	80.38 (9.35)	<0.0001
Total cholesterol (mg/dL, SD)	221.19 (46.27)	221.90 (39.48)	215.70 (40.16)	212.94 (37.91)	<0.0001

SD – standard deviation; MET – metabolic equivalent of task

Numbers represent median (standard deviation) for continuous variables, and % for binary or categorical variables. p-values were obtained with Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.