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Association between Physical Activity and Peripheral Artery Disease and Carotid Artery Stenosis in a self-referred population of 3 Million Adults

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Abstract

Objective—While the relationship between physical activity and coronary heart disease is well characterized, a paucity of data exists regarding physical activity and vascular disease in other arterial territories. This study examined the prevalence of peripheral artery disease (PAD) and carotid artery stenosis (CAS) in association with physical activity.

Approach and Results—The association between physical activity and vascular disease was examined in more than 3 million self-referred US participants in the United States from 2003–2008 who completed a medical and lifestyle questionnaire in the Life Line screening program. All subjects were evaluated by screening ankle brachial indices <0.90 for PAD and ultrasound imaging for CAS >50%. Multivariable logistic regression modeling was used to estimate odds of disease. Among 3,250,350 subjects, 63% of the population engaged in some leisure time vigorous physical activity. After adjustment for age, sex, race/ethnicity, hypertension, hypercholesterolemia, smoking status, diabetes, body mass index and family history of cardiovascular disease, subjects who reported any physical activity had a significantly lower odds of PAD (OR 0.64, 95% CI 0.63 – 0.65) and CAS (OR 0.80, 95% CI 0.79 – 0.81). The association between physical activity with PAD and CAS was robust when stratified by sex, race and age

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categories. Physical activity intensity frequency was associated with lower PAD and CAS in a graded manner (p trend <0.0001 for both). Findings appeared unaffected by confounding by comorbidity or indication.

Conclusions—In a large population based study, higher levels of physical activity were independently associated with lower odds of vascular disease in the lower extremities and carotid arteries.

The association of regular physical activity with reduced risk of coronary heart disease has been extensively evaluated in prior studies.[1–3] A systematic evidence review by the Physician Activity Guidelines Advisory Committee of the U.S. Department of Health and Human Services noted consistent findings in 20 observational cohort studies, which included more than 141,000 men and 263,000 women, supporting an inverse relationship between increased physical activity and risk of coronary heart disease.[4] A meta-analysis including 9 studies with quantitative estimates of physical activity demonstrated a dose-response between physical activity and coronary heart disease.[5]

In contrast, the association of physical activity and vascular disease in other arterial territories has been relatively under studied and is far from certain. In 1996 the Surgeon General's report on Physical Activity and Health was unable to support an association between physical activity and risk of stroke.[6] More recently, in 2011 the American Heart Association and American Stroke Association concluded that the data supported a reduction in risk of stroke with increased physical activity.[7] However, the relationship between carotid artery stenosis (CAS) – an important risk factor for stroke[8] – and physical activity is unknown. There is even less known about the relationship between physical activity and lower extremity peripheral artery disease (PAD).[9] While some data suggest an association between physical activity and PAD, conflicting data remains.[10–15] Prior data from our group found that the population attributable risk for physical inactivity ranged between 5% to 20% across different phenotypes of peripheral vascular disease.[16] A community based intervention of increased physical activity was able to increase levels of physical activity and reduce disability related to PAD.[17] To date, the Physical Activity Guidelines Advisory Committee of the U.S Department of Health and Human Services was unable to conclusively support the association between physical activity and PAD.[4]

To address the paucity of data on the association between a history of physical activity and different phenotypes of prevalent vascular disease, the current study hypothesized a relationship between physical activity and prevalence of vascular disease in the carotid and lower extremity circulation. We examined the prevalence of PAD and CAS in association with engagement in vigorous leisure time physical activity, including the frequency and relative intensity of physical activity, in the Life Line Screening Cohort of approximately 3 million US adults.

MAETERIALS and METHODS

Materials and Methods are available in the online-only Data Supplement.

RESULTS

A total of 3,250,350 individuals were included in the analyses. Overall, the mean age was 63.1 and 65% were female. The mean body mass index (BMI) was 27.7 and 28% of participants were obese (BMI >30kg/m^2). Sixty three percent of the population engaged in some leisure time vigorous physical activity (64% in males and 62% in women). The baseline characteristics of the study population stratified by their physical activity are summarized in table 1. Subjects who reported some physical activity were younger, less frequently female, had a lower BMI, and had better risk factor profiles than inactive subjects. Baseline characteristics stratified by sex is noted in Supplementary Table 1.

Peripheral Artery Disease was identified in 124,866 (4.1%) subjects. Among subjects who reported any vigorous physical activity, the prevalence of PAD was 3.1% versus 5.3% in subjects who reported no vigorous physical activity (P<0.0001, Table 2). After adjustment for age, sex, race/ethnicity, smoking status, hypertension, hypercholesterolemia, diabetes, BMI and family history of cardiovascular disease, subjects who reported any physical activity had a 36% lower odds of PAD (OR 0.65, 95% CI 0.64 – 0.66). The association between physical activity and PAD was not clinically different when stratified by sex, race and different age categories. (Table 2)

Carotid artery stenosis was found in 104,631 (3.3%) subjects. Among subjects who reported any vigorous physical activity, the prevalence of CAS was 2.9% versus 3.8% in subjects who reported no vigorous physical activity (P<0.0001, Table 2). After adjustment for age, sex race/ethnicity, smoking status, hypertension, hypercholesterolemia, diabetes, BMI and family history of cardiovascular disease, subjects who reported any physical activity had a 20% lower odds of CAS (OR 0.80, 95% CI 0.78 – 0.81). The association between physical activity and PAD was not clinically different when stratified by sex, race and different age categories. (Table 2)

Frequency of Physical Activity

Frequency of physical activity was also associated with prevalence of PAD (Table 3, Figure X). In multivariable adjusted analyses, compared with no physical activity, individuals reporting 1X/week, 2X/week, 3X/week, and>3X/week had 26%, 31%, 39%, and 45% lower odds of PAD, respectively (P for trend < 0.0001). Frequency of physical activity was also associated with prevalence of carotid artery disease. In multivariable adjusted analyses, compared with no physical activity, individuals reporting 1X/week, 2X/week, 3X/week, and >3X/week had 16%, 21%, 24%, and 23% lower odds of carotid artery disease, respectively (P for trend < 0.0001; Table 3).

Type of Physical Activity

Each type of physical activity defined as representing an increased intensity[18] was associated with significantly lower odds of vascular disease in both the lower extremities and carotid arteries (Table 3). Since walking is a form of aerobic activity and is one of the easiest ways to get exercise, we note the association between walking and different phenotypes of vascular disease. After multivariable adjustment, walking was associated with a significantly lower odds of PAD (OR 0.61, 95% CI 0.60 – 0.62) and carotid artery disease (OR 0.80, 95% CI 0.79 – 0.82). For individuals who walk once per week, a lower odds of vascular disease was observed; however, the strength of the association was somewhat attenuated (OR 0.73, 95% CI 0.70–0.76 for PAD and OR 0.85, 95% CI 0.81–0.88 for carotid artery). The most intense type of physical activity was running and was associated with a significantly lower odds of PAD (OR 0.40, 95% CI 0.38 – 0.43) and carotid artery disease (OR 0.65, 95% CI 0.61 – 0.66).

Sensitivity Analyses

To assess confounding by physical activity limitation, we excluded individuals with comorbidities that could significantly limit activity, including claudication, angina, and lower extremity neuropathy. Results were not greatly altered, with lower odds of vascular disease in multivariable adjusted analyses with any vigorous physical activity (OR 0.65, 95% CI 0.63–0.66 for PAD and OR 0.80, 95% CI 0.79–0.82 for carotid artery disease). We next evaluated the extent to which observed relationships between physical activity and PAD or carotid artery disease might be mediated by a prior history of coronary artery disease. After multivariable adjustment including history of prior coronary artery disease, association between physical activity and vascular disease was similar (OR 0.64, 95% CI 0.63–0.65 for PAD and OR 0.80, 95% CI 0.79–0.81 for carotid artery disease). After excluding subjects with a history of coronary artery disease, physical activity was still associated with a lower odds of PAD (OR 0.64, 95% CI 0.63–0.65) and carotid artery disease (OR 0.0.80, 95% CI 0.78–0.81).

Since the study population is a self-referred population who paid out of pocket for their screening test, we evaluated confounding using measures of socioeconomic status (SES). After multivariable adjustment including SES, association between physical activity and vascular disease was similar (OR 0.66, 95% CI 0.65–0.67 for PAD and OR 0.81, 95% CI 0.80–0.82 for carotid artery disease). When stratified by degree of SES, the association between physical activity and vascular disease was robust across different SES strata (Supplementary Figure 1).

DISCUSSION

In this large cross sectional study of more than 3.2 million women and men across the US, a significantly lower prevalence of PAD and CAS was seen with participation in vigorous leisure time physical activity, with stronger associations seen for increased frequency of physical activity. The strength of the association between physical activity and prevalence of PAD and CAS did not noticeably change after adjustment for baseline demographics, body mass index and clinical risk factors, and was present when stratified by sex, race/ethnicity and different age groups. A significant association was seen with any leisure time physical activity on a regular basis suggesting the importance of any physical activity on the risk of vascular disease. These observations suggest that physical activity has significant independent associations with vascular disease in the lower extremities and carotid arteries.

The inverse relationship between physical activity and coronary heart disease morbidity and mortality is well-known.[1–3] Previous studies have also found a significant association between physical activity and improved survival in subjects with PAD.[19] In the current study, we extend the protective benefit of physical activity to lower prevalence of vascular disease in the lower extremities and carotid arteries. Prior studies were limited by several design issues, such as small sample size, lack of objectively measured vascular disease in all subjects, limiting physical activity to walking duration and frequency, and lack of information on clinical symptoms.[4, 10, 13, 14, 20] In a cross-sectional population-based study in 3,786 individuals >49 years, randomly selected in 28 primary care centers in Barcelona (Spain), walking > 7 hours per week was associated with a lower odds of PAD; however, this failed to reach statistical significance in men.[10] Conversely, investigators from the Edinburgh Artery Study found an inverse association between physical activity and PAD in male smokers and not in male non-smokers or women.[13] In a cross sectional study of 4,470 men from Australia, physical activity was reported in 76% of the population. Physical inactivity increased the odds of PAD by 40 percent.[11] In a Danish cohort of 2,589 women and men followed up for 7.2 years, no significant associations were seen between sedentary lifestyle and risk of PAD,[12] but daily work and leisure time activity was combined into a single variable of sedentary activity. In a French cohort of 3,805 middle-aged participants followed for 6-years noted a graded increased trend of PAD among those who were less physically active, which did not reach statistical significance.[15] While prior studies have noted a weak relationship between carotid intima media thickness and physical activity,[14] no prior studies have assessed the relationship between physical activity and CAS.

The biological mechanism for the inverse relationship between physical activity and atherosclerotic disease in the coronary arteries would apply to atherosclerotic disease in the lower extremities and carotid arteries. There is a well-known beneficial effect of physical activity on established cardiovascular risk factors such as dyslipidemia, hypertension, and diabetes mellitus.[21–24] We previously demonstrated that approximately 20 percent of vascular disease could be attributed to hypertension, ≈12 percent to hyperlipidemia and ≈6 percent to diabetes.[16] Thus, by reducing certain modifiable risk factors, a reduction in vascular disease is certainly plausible. In addition to traditional risk factors, physical activity has been found to improve endothelial function, vascular inflammation, platelet aggregation and vascular oxidative stress.[25–28]

To better understand the association between physical activity and peripheral vascular diseases, potential confounding by underlying comorbidity was assessed. Some individuals have comorbidities that limit their physical activity due to their vascular disease. PAD in particular is well associated with a large decrease in peak exercise performance and 6-minute walking distance compared with an age-matched healthy population.[29, 30] In contrast carotid artery stenosis, in the absence of a debilitating stroke, is not known to impact daily physical activity. Thus the associations of physical activity and prevalent PAD (but presumably not prevalent CAS) could be confounded by the exercise limitation in PAD. Conversely, other individuals may increase their physical activity in response to diagnosis of a condition that also increases risk of vascular disease (confounding by indication), which would cause physical activity to appear less favorable than the true association. Multivariable adjustments are one method to decrease such confounding. Exclusion of all subjects with any comorbidity is another method to address such potential confounding. When subject to a series of sensitivity analyses, the physical activity associations did not appear to be attributable to confounding by presence of comorbid conditions (such as preexisting coronary heart disease or cerebrovascular disease), symptoms (such as angina, claudication, or atypical lower extremity symptoms), or socioeconomic status (such as wealth or education). Notably, the relationships between physical activity and vascular disease of the lower extremities and carotid arteries were not clinically different in multivariable-adjusted analyses and after excluding those subjects, which suggests that confounding alone would not fully account for the observed relationships.

Limitations

Several limitations should be considered when interpreting the results of this study. As in any cross sectional study, we cannot exclude the possibility that health differences between physically active and sedentary subjects explain the inverse association between physical activity and peripheral vascular disease. This is unlikely, however, for several reasons. First, all participants were screened from the community and were relatively healthy. Also, the exclusion of participants with established cardiovascular disease and those with symptoms that may limit their physical activity did not alter the inverse association between physical activity and prevalence of PAD and CAS. Nonetheless, this study should be considered “hypothesis generating” and should be repeated in a prospective design. Additionally, the lack of information on duration of each physical activity did not allow the authors to calculate weekly physical activity in MET-hours for each subject.

The study population is a self-referred population who were relatively healthy and paid out of pocket for their screening test, raising the issue of selection bias, which may limit the generalizability of these findings. Nonetheless, as reported previously, the prevalence of different cardiovascular risk factors in this population database were similar to those of the general US population.[31] Moreover, the prevalence of PAD and CAS was similar to other representative cohorts demonstrating good external validity (Supplementary Figure 2). Physical activity was self-reported and assessed average activity. While the physical activity survey was not validated, the questions and response choices are similar to those used in prior studies.[32–35] In the current study, the ABI was measured using the posterior tibial artery; the dorsalis pedis artery was used only when the posterior tibial artery was inaudible. The highest of the dorsalis pedis or posterior tibial artery pressures at the ankle traditionally is used to form the calculation.[36] However, a recent report compared this traditional method with an alternative method using the lower of the two ankle artery pressures, and both methods had similar diagnostic and predictive accuracy for all-cause and cardiovascular mortality, suggesting the utility of the alternate method in identifying a clinically meaningful population with PAD.[37] Finally, while residual confounding from unmeasured variables may additionally modify the association of physical activity and peripheral vascular disease, these findings are consistent with observational studies showing lower incidence of coronary artery disease and improved risk factor profile with increased physical activity. Importantly, the latter relationship has been confirmed in randomized, clinical trials.

The present study also has several strengths, including a very large number of women and men and subjects of different race/ethnicities across the United States. The large number of subjects with PAD and carotid artery disease allows excellent power and facilitates adjustment for multiple covariates. Standardized assessment of ankle brachial indices and duplex carotid artery ultrasound was performed in every subject, thereby using a simple noninvasive validated procedure for the diagnosis of PAD and CAS that have high sensitivity and specificity.[38, 39]

Conclusions

The current study of over 3 million subjects demonstrates a significant association between increased physical activity and a lower prevalence of PAD and CAS. These data add important new information to the existing literature of physical activity and atherosclerotic disease by demonstrating a robust and significant inverse relationship between physical activity frequency and prevalence of vascular disease in the lower extremities and carotid arteries. The findings were not clinically different when stratified by sex, race/ethnicity and age suggesting the importance of physical activity in different demographic groups. Importantly, our findings that self-described vigorous walking may be sufficient to obtain meaningful benefits with regard to PAD and CAS are consistent with the previously described benefits of this activity with regard to coronary heart disease.[2] Our data suggest that vigorous leisure time physical activity may be a particularly effective and simple strategy of lowering atherosclerotic disease in the lower extremities and carotid arteries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PAD	peripheral artery disease
CAS	carotid artery stenosis
BMI	body mass index
OR	odds ratio
CI	confidence interval
US	United States

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Significance

While the relationship between physical activity and coronary heart disease is well characterized, a paucity of data exists regarding physical activity and vascular disease in other arterial territories. In a large population based study of more than 2.5 million subjects, higher levels of physical activity were independently associated with lower odds of vascular disease in the lower extremities and carotid arteries. The strength of the association between physical activity and prevalence of peripheral artery disease and carotid artery stenosis did not noticeably change after adjustment for baseline demographics, body mass index, cardiovascular risk factors and clinical history, and was present when stratified by different demographic groups.

Table 1

Baseline characteristics participants according to physical activity

	Overall (n=3,250,350)	No Physical Activity (n=1,149,535)	Physical Activity (n=1,942,535)
Age, mean (SD)	63.1(10.5)	63.2 (10.8)	62.8 (10.2)
<40	1.3	1.4	1.2
41–50	8.6	8.9	8.5
51–60	28.1	28.3	28.5
61–70	35.2	33.7	36.4
71–80	20.2	19.9	19.9
>80	6.7	7.9	5.5
Women	65.5	66.5	64.5
Race			
White	88.9	87.3	90.4
Black	3.2	3.5	2.9
Asian	2.1	2.3	1.8
Hispanic	2.5	2.9	2.2
Native American	2.7	3.3	2.2
Other	0.6	0.7	0.5
BMI, mean (SD)	27.7(5.8)	28.9 (6.3)	27.0 (5.3)
Smoking Status			
Current smoker	24.5	26.5	23.5
Former smoker	23.5	22.2	24.2
Never	52	51.3	52.4
Diabetes	9.9	11.4	9.0
Hypertension	46.1	48.8	44.2
Hypercholesterolemia	51.3	51.5	52.3
Family History of Cardiovascular disease	22.6	22.8	22.4

BMI, body mass index (kg/m^2)

Table 2

Prevalence and adjusted odds ratios for PAD and CAS according to physical activity

	Number	Physical Activity	No Physical Activity	Adjusted OR (95% Confidence Interval)
		Peripheral Artery Disease Prevalence (%)		
All Subjects	3,250,350	3.14 (3.12,3.17)	5.33 (5.29,5.37)	0.65 (0.64–0.66)
Sex				
Women	2,067,816	3.54 (3.5,3.57)	6.03 (5.97,6.08)	0.65 (0.64–0.66)
Men	1,087,571	2.40 (2.36,2.44)	3.91 (3.84,3.97)	0.64 (0.63–0.66)
Race/Ethnicity				
White	2,785,618	3.01 (2.98,3.03)	5.17 (5.13,5.22)	0.64(0.63–0.65)
Black	98,735	5.97 (5.73,6.14)	9.04 (8.75,9.33)	0.71 (0.67–0.75)
Asian	64,524	2.37 (2.21,2.53)	3.36 (3.13,3.59)	0.68 (0.61–0.77)
Hispanic	78,744	2.53 (2.37,2.68)	3.56 (3.36,3.77)	0.70 (0.63–0.78)
NA	85,247	5.28 (5.06,5.51)	7.78 (7.5,8.07)	0.68 (0.64–0.73)
Other	19,914	4.15 (3.75,4.55)	5.56 (5.05,6.06)	0.76 (0.64–0.90)
Age				
<40	37,021	1.64 (1.46,1.82)	2.32 (2.06,2.58)	0.70(0.58–0.84)
41–50	250,801	1.60 (1.53,1.66)	2.42 (2.32,2.52)	0.73 (0.68–0.78)
51–60	823,524	1.83 (1.79,1.86)	3.10 (3.04,3.17)	0.64 (0.62–0.67)
61–70	1,032,105	2.71 (2.67,2.75)	4.72 (4.65,4.79)	0.642 (0.60–0.63)
71–80	593,499	4.94 (4.86,5.01)	8.07 (7.95,8.19)	0.64 (0.62–0.65)
>80	195,491	10.85 (10.64,11.05)	15.00 (14.74,15.26)	0.71 (0.69–0.74)
		Carotid Artery Stenosis Prevalence (%)		
All Subjects	3,250,350	2.92% (2.9,2.95)	3.78% (3.75,3.82)	0.80 (0.78–0.81)
Sex				
Women	1,909,413	2.68 (2.65,2.70)	3.65 (3.60,3.69)	0.78 (0.76–0.79)
Men	1,022,494	3.36 (3.31,3.4)	4.01 (3.95,4.08)	0.82 (0.8–0.84)
Race/Ethnicity				
White	2,598,625	2.96 (2.93,2.98)	3.87 (3.83,3.91)	0.79 (0.78–0.81)
Black	91,077	2.02 (1.9,2.14)	2.34 (2.19,2.5)	0.84 (0.76–0.93)
Asian	58264	1.70 (1.56,1.84)	1.90 (1.73,2.07)	0.78 (0.67–0.90)
Hispanic	71515	1.81 (1.68,1.94)	1.96 (1.81,2.11)	0.88 (0.78–1.00)
NA	75589	4.59 (4.39,4.8)	5.66 (5.42,5.9)	0.81 (0.75–0.87)
Other	17784	2.43 (2.12,2.73)	2.98 (2.61,3.35)	0.80 (0.65–0.99)
Age				
<40	33,749	0.64 (0.53,0.75)	0.67 (0.54,0.81)	1.04 (0.77–1.41)
41–50	234,066	0.75 (0.71,0.8)	0.89 (0.83,0.95)	0.87 (0.79–0.97)
51–60	775,895	1.37 (1.33,1.4)	1.81 (1.76,1.86)	0.79 (0.76–0.82)
61–70	965,654	2.95 (2.9,2.99)	3.86 (3.8,3.93)	0.78 (0.76–0.8)
71–80	539,468	5.25 (5.18,5.33)	6.46 (6.36,6.57)	0.80 (0.78–0.82)

	Number	Physical Activity	No Physical Activity	Adjusted OR (95% Confidence Interval)
>80	171,088	7.45 (7.28,7.62)	8.61 (8.41,8.8)	0.83 (0.79–0.86)

NA, Native American

Table 3

Prevalence and adjusted odds Ratios for PAD and CAS according to physical activity frequency and type

	Number	PAD Prevalence (%)	Adjusted OR (95% Confidence Interval)
Physical Activity Frequency			
None	1,095,265	5.33 (5.29,5.37)	Reference
1X/week	219,699	3.44 (3.36,3.52)	0.74 (0.72–0.76)*
2X/week	338,796	3.21 (3.15,3.27)	0.69 (0.67–0.71)*
3X/week	507,220	2.99 (2.94,3.04)	0.61 (0.60–0.63)*
>3X/week	614,714	2.66 (2.62,2.71)	0.56 (0.55–0.57)*
Physical Activity Type			
None	1,055,365	5.32 (5.28,5.37)	Reference
Walk	1,063,302	3.15 (3.12,3.18)	0.63 (0.62–0.64)
Run	95,636	1.19 (1.12,1.26)	0.39 (0.36–0.42)
Bicycle	134,833	2.84 (2.75,2.93)	0.63(0.6–0.65)
Tennis	31,147	1.96 (1.8,2.11)	0.43 (0.39–0.47)
Swim	106,477	4.03 (3.91,4.14)	0.7 (0.67–0.72)
Other	282,577	3.91 (3.84,3.98)	0.74 (0.72–0.76)
	Number	**CAS Prevalence (%)**	**Adjusted OR (95% Confidence Interval)**
Physical Activity Frequency			
None	1,123,110	3.78 (3.75,3.82)	Reference
1X/week	225,148	2.81 (2.74,2.87)	0.84 (0.81–0.87)*
2X/week	347,455	2.69 (2.64,2.74)	0.79 (0.77–0.81)*
3X/week	521,564	2.81 (2.77,2.86)	0.77 (0.75–0.79)*
>3X/week	633,731	2.89 (2.85,2.94)	0.76 (0.75–0.78)*
Physical Activity Type			
None	1,081,932	3.76 (3.72,3.8)	Reference
Walk	109,2672	3.02 (2.99,3.06)	0.80 (0.79–0.82)
Run	98,660	1.63 (1.55,1.71)	0.66 (0.63–0.67)
Bicycle	139,235	2.75 (2.67,2.84)	0.74 (0.71–0.77)
Tennis	32,148	2.31 (2.14,2.47)	0.62 (0.57–0.68)
Swim	109,887	3.30 (3.19,3.41)	0.82 (0.78–0.85)
Other	289,863	3.22 (3.16,3.29)	0.835 (0.81–0.85)

*P for trend <0.00001