



Walking pace is inversely associated with risk of death and cardiovascular disease: The Physicians' Health Study

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HIGHLIGHTS

- Walking pace is being increasingly used to assess functional status in ambulatory settings.
- It is simple to evaluate and can be performed with little time and cost in various settings.
- Walking pace was inversely associated with the risk of death and development of cardiovascular disease.

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ABSTRACT

Background: Walking pace is increasingly being used to assess functional status in ambulatory settings.

Methods: We conducted a prospective analysis within the Physicians' Health Study to examine whether walking pace is associated with mortality and incident cardiovascular disease (fatal or nonfatal myocardial infarction, coronary artery bypass grafting and percutaneous transluminal coronary angioplasty). Participants included 21,919 male physicians with a mean age of 67.8 ± 9.0 years.

Results: After a median follow-up of 9.4 years (IQR: 7.9–10.3), 3906 deaths and 2487 incident CVD events occurred. In a multivariable Cox proportional hazards model adjusting for age, body mass index, smoking, exercise frequency, and prevalent hypertension, diabetes mellitus, heart failure, peripheral vascular disease, cancer, and total weekly walking time, hazard ratios for mortality were 0.72 (95% CI: 0.64–0.81) for walking pace of 2–2.9mph, 0.63 (95% CI: 0.55–0.73) for walking pace of 3–3.9mph and 0.63 (95% CI: 0.48–0.83) for walking pace of ≥ 4 mph compared to the group that reported not walking regularly (p trend < 0.0001). Similar findings were observed for incident CVD: HRs were 0.88 (95% CI: 0.75–1.03) for a walking pace of 2–2.9mph, 0.75 (95% CI: 0.63–0.89) for a walking pace of 3–3.9mph and 0.70 (0.53–0.94) for a walking pace of ≥ 4 mph compared to the group that reported not walking regularly (p trend 0.0001). These associations persisted after excluding those who exercised regularly.

Conclusion: We found that walking pace is inversely associated with risk of mortality and CVD among US male physicians.

1. Introduction

Coronary heart disease is the leading cause of mortality in the United States [1]. Physical inactivity is among the modifiable risk factors for this disease. Walking, the most commonly performed physical activity, is associated with lower rates of coronary heart disease [2] and stroke [3]. Walking pace has important clinical utility in ambulatory settings. A slow walking pace is an indicator of a worse prognosis for those with severe

chronic conditions [4,5] and is associated with an increased risk of disability, mobility limitation, and mortality [6–8]. Patients who are unable to walk 400 m on the 6-min walk test (or slower than 24 min per mile) have the highest risk of increased mortality [9]. Gait speed measured at short intervals (4–6 m) has been suggested as a screening tool for mobility, disability, and frailty [7,10], and pooled data from nine cohort studies demonstrated a 10% increased risk in 5-year mortality with every 0.1 m/s decrease in walking speed [8].

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Few studies have examined whether walking intensity, as assessed by pace, is an important predictor of cardiovascular events in the general population, even after adjusting for total activity [11]. The National Walkers' Health Study, which included recreational walkers, found that the risk of mortality decreased with walking intensity, and was significantly increased for those with a pace > 24-min per mile (equivalent to 400 m in a 6 min walk test) even among those who exercised regularly [11]. Other studies have found that greater walking intensity was not associated with lower disease risk when adjusted for total energy expenditure [12]. Thus, we sought to address this knowledge gap by examining whether walking pace is associated with an elevated risk of cardiovascular events and mortality, even when accounting for the total walking time. If walking pace can help to identify individuals who are at elevated risk of cardiovascular events in the general population, it may have considerable public health utility.

2. Materials and methods

2.1. Study population

The Physicians' Health Study (PHS) is a longitudinal cohort study that includes adult male physicians between the ages of 40 and 84 years. In this study, participants were included from PHS I (clinicaltrials.gov; NCT00000500), a randomized trial of the efficacy of low-dose aspirin and beta carotene on cancer and cardiovascular disease (1982–1995) and from PHS II (clinicaltrials.gov; NCT00270647), a randomized trial to evaluate the effects of vitamin C, vitamin E, beta-carotene and multivitamins on the risk of cancer, cognitive decline, and cardiovascular disease (1997–2012). Detailed descriptions of these trials have been previously published [13,14]. For the current analysis, the follow-up period started when walking pace was asked in a validated questionnaire (2002). From a total of 26,395 participants from PHS I (those who continued to participate beyond 1995) and PHS II, twelve were excluded because they had died prior to the start of analysis; 4,456 participants did not have information on walking pace, and eight were excluded due to lower extremity amputation or hemiplegia. Thus, a total of 21,919 participants met criteria for analysis in our study for the primary outcome. For our second outcome of incident cardiovascular disease, those with pre-existing cardiovascular disease at baseline were excluded, thus leaving 18,862 participants for analysis. All participants gave written informed consent for participation in the study and the Brigham and Women's Hospital Institutional Review Board approved the study protocol.

2.2. Exposure

Walking pace was self-reported in a standardized questionnaire in 2002. The participants were asked "what is your usual walking pace: don't walk regularly, easy casual (< 2mph), normal average (2–2.9mph), brisk pace (3–3.9mph), very brisk, striding (4mph or faster)?" over the past twelve months. This questionnaire has been previously validated and used in other cohorts such as the Nurses' Health Study [15,16]. In addition, participants were also asked how many minutes they walk per week, and questions regarding the duration, frequency, consistency and intensity of physical activities during the week. They were asked "during the past year, what was your average time per week spent walking (include walking to work): none, 1–19 min, 20–59 min, 1 h, 1.5 h, 2–3 h, 4–6 h, 7 + hours."

2.3. Outcome

The outcomes were all-cause mortality and incidence of cardiovascular disease. Death was initially reported by the participants' family members or postal staff. After a report, the PHS endpoint committee obtained death certificates and/or autopsy reports. For those with unknown status, the National Death Index was used to identify and

confirm vital status. All-cause mortality includes both reported as well as confirmed death events. Incidence of cardiovascular disease was defined as fatal and non-fatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention or stroke. Myocardial infarction was confirmed by symptoms and cardiac enzyme level elevation or characteristic changes on electrocardiogram. For fatal myocardial infarction, the diagnosis was also accepted from autopsy reports [13]. Stroke was defined as a sudden neurological deficit, lasting more than 24 h and was classified according to the National Survey of Stroke criteria [17].

2.4. Ascertainment of clinical covariates

Covariates, ascertained via surveys in the Physicians' Health Study collected near the same time as walking pace, included demographic variables such as age (continuous), race (categorical), behavioral factors such as smoking (categories), alcohol (categories), walking time (minutes per week), exercise frequency (categories), and co-morbid conditions including heart failure (yes/no), peripheral vascular disease (yes/no), cancer (yes/no), renal disease (yes/no), and pulmonary disease (yes/no). Cigarette smoking was categorized as never smoker, former smoker or current smoker. Walking time was reported in minutes per week in the following categories: none, 1–19 min, 20–59 min, 1–3 h, and 4–7 or more hours. Exercise frequency was determined by days per week (none, < 1–2 days, ≥ 2–4 days, ≥ 4–7 days). Co-morbid conditions included prevalent heart failure, peripheral vascular disease, cancer, renal disease (chronic kidney disease), and pulmonary disease (chronic obstructive pulmonary disease, restrictive lung disease).

2.5. Statistical analysis

We stratified participants by categories of walking pace as follows: don't walk regularly, easy casual < 2mph, normal ≥ 2–2.9mph, brisk ≥ 3–3.9mph and very brisk ≥ 4mph. We examined baseline characteristics across the categories of walking pace by using the ANOVA test for continuous variables and the chi-square test for categorical variables. Person-time was calculated from baseline until the date of the event (death for the primary outcome or occurrence of a cardiovascular event for the second outcome) or censoring (the date of the last known information or death). Using Cox proportional hazards models, we computed hazard ratios (with 95% confidence intervals) of each group of walking pace, using the group that didn't walk regularly as the reference category. An initial model adjusted for age; a multivariable model adjusted for age and lifestyle factors (cigarette smoking, exercise frequency) and prevalent co-morbid conditions (heart failure, peripheral vascular disease, and cancer). Additional multivariable models adjusted for body mass index, hypertension, diabetes mellitus and weekly walking time.

For the second outcome of incident cardiovascular events, we repeated the analysis in 18,862 participants after excluding those who had prevalent cardiovascular disease (myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or stroke) at baseline. To test the robustness of our findings, we performed several sensitivity analyses excluding participants a) who reported regular weekly exercise 5–7 times/week, b) those age 75 years and older, c) those with chronic pulmonary disease, and d) those with congestive heart failure. We performed all analyses using SAS (version 9.4; SAS Institute), and considered an alpha of less than 0.05 to be statistically significant.

Kaplan-Meier curves were generated using the proc lifetest statement in the SAS software, which provides estimates of the survival probability. The strata statement was used to determine the survival estimates for each category of walking pace. The x-axis lists the follow-up times as person-years until the time of the event (either all-cause mortality for incident CVD) or censoring. The numbers below the figure denote the numbers of subjects at risk at a specific time.

Table 1
Baseline characteristics of 21,919 participants of the Physicians' Health Study by categories of walking pace.

	Do not walk regularly (n = 2,502)	Easy casual pace < 2mph (n = 2,569)	Normal 2-2.9mph pace (n = 9,647)	Brisk pace 3-3.9mph pace (n = 6,311)	Very brisk pace ≥ 4mph pace (n = 890)
Age, years	70.2 ± 9.8	72.6 ± 9.4	68.1 ± 8.7	65.1 ± 7.9	63.6 ± 7.2
Race					
White	91.6%	90.9%	91.8%	93.6%	92.6%
Smoking					
Never	47.2%	46.7%	52.7%	56.9%	60.1%
Former	49.1%	48.9%	44.5%	41.3%	39.3%
Current	3.7%	4.4%	2.9%	1.8%	0.7%
Walking time/wk					
None	43.5%	2.2%	0.9%	0.7%	1.1%
1–19 min	25.7%	17.9%	7.0%	4.9%	4.2%
20–59 min	13.5%	24.7%	19.7%	14.7%	10.5%
1–3.9 h	14.8%	40.7%	48.0%	48.4%	40.5%
4-7+ hrs	2.5%	14.6%	24.4%	31.3%	43.8%
Exercise frequency/wk					
None	57.9%	56.2%	36.4%	22.0%	8.7%
< 1–2 days	10.6%	13.1%	18.5%	17.0%	9.5%
3–4 days	19.6%	20.9%	29.8%	36.4%	39.2%
5–7 days	11.9%	9.9%	15.3%	24.7%	42.6%
Atrial fibrillation	13.0%	16.5%	9.8%	8.4%	6.0%
CHF	5.1%	6.9%	2.2%	1.0%	0.6%
CVD	17.7%	21.2%	13.4%	11.0%	9.2%
Valvular heart disease	2.2%	3.2%	2.2%	1.6%	1.4%
Diabetes mellitus type 2	12.3%	14.4%	8.4%	5.3%	3.4%
Liver disease	12.0%	12.8%	11.8%	11.1%	11.0%
Lung disease	9.8%	9.8%	7.4%	7.5%	4.8%
Peripheral arterial disease	6.2%	7.2%	2.9%	1.7%	0.9%
Renal disease	8.9%	8.6%	6.7%	5.4%	4.2%
Cancer	15.6%	17.6%	13.2%	9.7%	7.6%
Hypertension	59.0%	67.4%	53.8%	45.3%	37.3%

Column percentages are shown. CHF = congestive heart failure; CVD = cardiovascular disease.

From a total of 26,395 participants, 12 were excluded because they died prior the start of the study period; 4456 were missing information on walking pace; and 8 were excluded due to lower extremity amputation and hemiplegia, thus leaving 21,919 participants for analysis. Missing values for covariates were as follows: exercise frequency (298), smoking (137).

3. Results

Mean age was 67.8 ± 9.0 years among the 21,919 male physicians who met criteria for analysis. At baseline, 11% of participants didn't walk regularly, 12% walked at an easy casual pace (< 2mph), 44% had a normal walking pace (2-2.9mph), and 33% walked at a brisk pace (3-3.9mph) or very brisk pace (≥ 4mph) (Table 1). Those who did not walk regularly or had an easy casual pace were slightly older, more likely to be current smokers, and had less total minutes of weekly walking time than those in the normal and brisk walking pace categories.

After a median follow-up of 9.4 years (IQR: 7.9–10.3), 3,906 deaths and 2487 incident CVD events occurred. Fig. 1 shows the Kaplan-Meier curves illustrating the probability of death and cardiovascular disease by person-years to event for each category. The crude incidence rate/1000 person-years for mortality were 38.5 for the group that didn't walk regularly, 48.7 for walking pace of < 2mph, 19.0 for walking pace of 2-2.9mph, 10.3 for walking pace of 3-3.9mph and 7.8 for walking pace of ≥ 4mph. For incident CVD, a similar trend was observed with crude incidence rates of 23.8 for the group that didn't walk regularly, 25.6 for walking pace of < 2mph, 16.9 for walking pace of 2-2.9mph, 11.9 for walking pace of 3-3.9mph and 9.7 for walking pace of ≥ 4mph. In the fully adjusted multivariable model, we found that walking pace ≥ 4mph was associated with a 37% lower risk of mortality as compared to those who did not walk regularly. In a multivariable Cox proportional hazards model adjusting for age, body mass index, smoking, exercise frequency, and prevalence of hypertension, diabetes mellitus, heart failure, peripheral vascular disease, and cancer, and total weekly walking time, hazard ratios for mortality were 1.11 (95% CI: 0.99–1.24) for a walking pace < 2mph; 0.72 (95% CI: 0.64–0.81) for walking pace of 2–2.9 mph; 0.63 (95% CI: 0.55–0.73) for a walking pace of 3-3.9mph; and 0.63 (95% CI: 0.48–0.83) for a walking pace of

≥ 4mph compared to the group that reported not walking regularly (*p* trend < 0.0001) (Table 2). A similar trend was observed for incident CVD with HRs of 0.70 (95% CI: 0.53–0.94) for the very brisk pace category (> 4mph); 0.75 (95% CI: 0.63–0.89) for the brisk pace (3-3.9mph) category as compared to those who did not walk regularly (Table 3). After excluding those who exercised 5–7 times per week regularly, the HRs for all-cause mortality in the multivariable adjusted model were 0.95 (95% CI: 0.86–1.05) for walking pace of < 2mph; 0.60 (95% CI: 0.55–0.66) for walking pace of 2-2.9mph; 0.45 (95% CI: 0.40–0.52) for walking pace of 3-3.9mph; and 0.45 (0.31–0.64) for walking pace of ≥ 4mph compared to those who did not walk regularly.

For incident CVD, a similar trend was observed after excluding those who exercised 5–7 times per week regularly, with HRs of 0.89 (95% CI: 0.76–1.04) for walking pace of < 2mph; 0.77 (95% CI: 0.68–0.88) for walking pace of 2-2.9mph; 0.64 (95% CI: 0.55–0.75) for walking pace of 3-3.9mph; and 0.44 (95% CI: 0.31–0.64) for walking pace of > 4 mph. In a sensitivity analysis after excluding those with heart failure, cardiovascular disease or chronic pulmonary disease at baseline, and those older than age 75 years, the inverse association of those with a walking pace ≥ 4mph with mortality and risk of CVD persisted (Supplementary Table 1).

4. Discussion

Our study found that walking pace is inversely associated with risk of mortality and incident cardiovascular disease among US male physicians. This association persisted when adjusting for chronic medical illnesses and the total weekly walking time in the multivariable models. To our knowledge, this is the first study to evaluate the independent association of walking pace with risk of cardiovascular disease in adult men without pre-existing coronary artery disease or stroke.

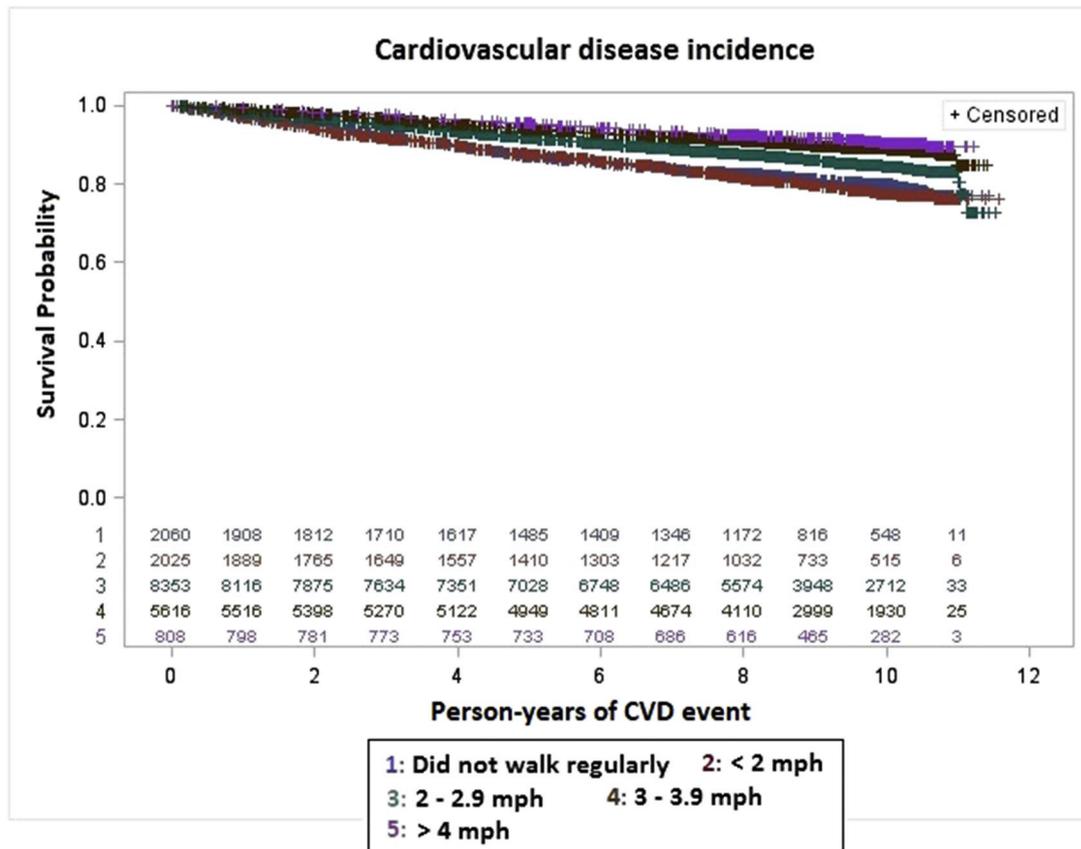
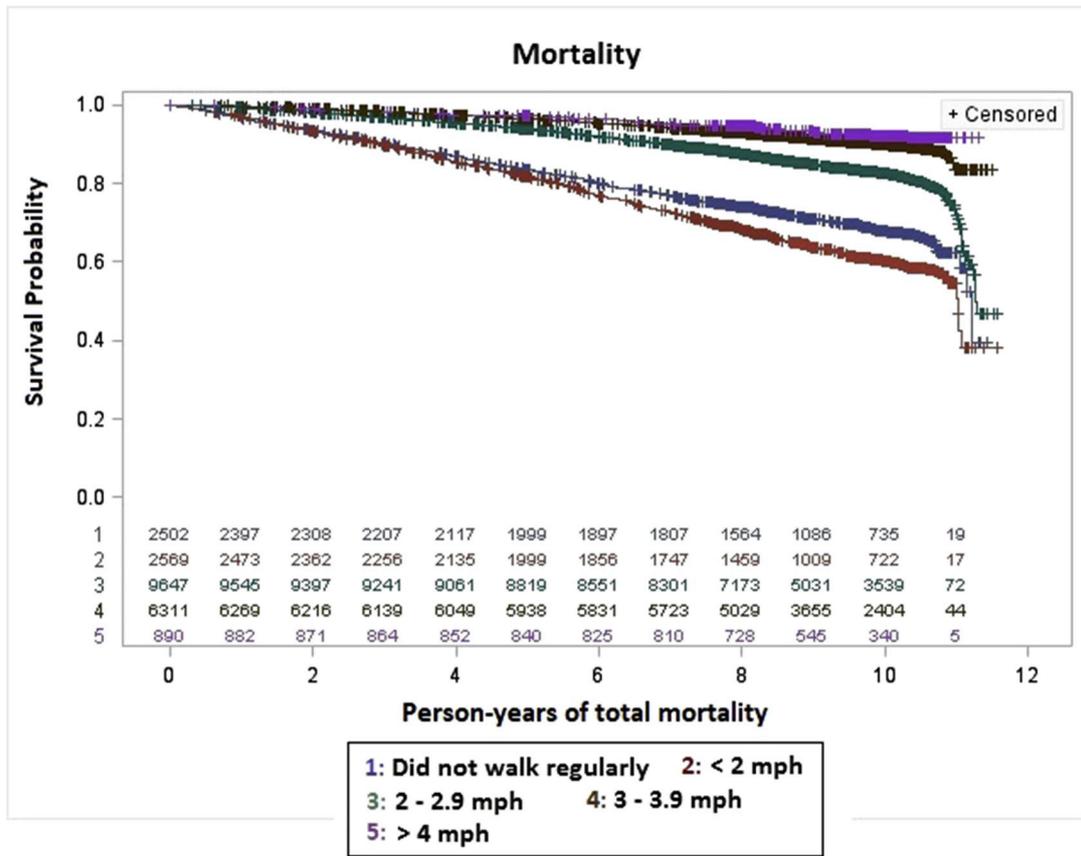


Fig. 1. Top: Survival probability by categories of walking pace (all-cause mortality). Bottom: Probability free of incident cardiovascular events by categories of walking pace (incident CVD).

Table 2

Hazard ratios (95% CI) of mortality according to walking pace in 21,919 participants of the Physicians' Health Study.

	Do not walk regularly	Easy casual < 2mph	Normal 2-2.9mph	Brisk 3-3.9mph	Very brisk ≥ 4mph	p for trend
Deaths/person-years	743/19,322	938/19,260	1,580/83,341	583/56,365	62/7,993	
Incidence rate/1000 PY	38.5	48.7	19.0	10.3	7.8	
Crude model	1.00 (ref)	1.28 (1.16–1.41)	0.48 (0.44–0.53)	0.26 (0.24–0.29)	0.20 (0.15–0.26)	< 0.0001
Age-adjusted model	1.00 (ref)	0.98 (0.89–1.08)	0.57 (0.52–0.62)	0.46 (0.41–0.51)	0.43 (0.33–0.56)	< 0.0001
Multivariable model 1 ^a	1.00 (ref)	0.99 (0.90–1.09)	0.63 (0.58–0.69)	0.55 (0.49–0.62)	0.55 (0.42–0.72)	< 0.0001
Multivariable model 2 ^b	1.00 (ref)	0.98 (0.89–1.09)	0.65 (0.59–0.71)	0.56 (0.50–0.64)	0.58 (0.44–0.76)	< 0.0001
Multivariable model 3 ^c	1.00 (ref)	1.11 (0.99–1.24)	0.72 (0.64–0.81)	0.63 (0.55–0.73)	0.63 (0.48–0.83)	< 0.0001

The reference category is the group that reported not walking regularly. PY = person years. CI = confidence interval.

The number of participants missing data on walking pace was 4456. Numbers of participants with missing covariates are as follows: smoking (298) and exercise frequency (137).

^a Adjusted for age (years), cigarette smoking, exercise frequency, heart failure, peripheral vascular disease and cancer.

^b Adjusted for all variables in multivariable model 1 plus body mass index, hypertension and diabetes mellitus.

^c Adjusted for all variables in multivariable model 2 plus weekly walking time.

Prior studies have found an inverse association with walking pace and mortality. In a pooled analysis of nine cohort studies that included individual data from 34,485 participants with a mean age of 73.5 ± 5.9 years, a decrease in mortality was noted per 0.1 m/s increase in walking pace (pooled HR per 0.1 m/s increase: 0.88, 95% CI: 0.87–0.90) [8]. The studies included in this analysis ranged from 6 to 21 years of follow-up [8]. In a study of 2,032 Chinese adults over 70 years old who were followed for three years, reduced walking speed and stride length were associated with higher risk of dependency and mortality (ROC: 0.71) [18]. In a prospective cohort of 472 Japanese patients with ST-segment elevation myocardial infarction, gait speed was found to be inversely associated with cardiovascular events (HR for 0.1 m/s increase of gait speed: 0.71, 95% CI: 0.63–0.81) [19]. Only one prior study evaluated gait speed as a composite of frailty components with regards to its' association with risk of developing cardiovascular disease [20]. The Pro VA study included 1,567 participants between the ages of 65–96 years without disability. After 4.4 years of follow-up, low energy expenditure, exhaustion and slow gait speed were found to be associated with higher risk of cardiovascular disease among those who met criteria for pre-frailty as defined by having 1 or 2 of the modified Fried criteria (low physical activity level, weakness, exhaustion, unintentional weight loss, and slow gait speed) compared to those who did not become frail [20]. Although a meta-analysis of nine studies (12,901 participants) found that a higher adjusted RR of all-cause mortality for those with a low walking pace as compared to those with the highest walking pace (1.89, 95% CI: 1.46–2.46) (which is in the same direction as our results), a subgroup analysis revealed that this association was not statistically significant among women (RR: 1.45, 95% CI: 0.95–2.20) [21]. This meta-analysis only included two studies that were conducted exclusively in women in the subgroup analysis. With a small sample size of women (2325 participants total), these two studies may not have been powered to detect modest associations.

In contrast to the previous findings, some studies did not report an inverse association between walking pace and mortality. In the

Translational Research Investigating Underlying Disparities in recovery from acute Myocardial infarction: Patients' Health status Registry study, 338 older adults (mean age: 75 years for slow gait and 72 years for preserved gait) underwent an in-home gait assessment one month after acute myocardial infarction. Adults with slow walking pace (< 0.8 m/s) were not found to have a significantly different one-year mortality and hospital readmission rate as compared to those with a pace of ≥ 0.8 m/s (HR: 1.23, 95% CI: 0.74–2.04) after adjusting for clinical factors and co-morbid conditions [22]. In this study, it may have been difficult to detect an association due to the relatively small sample size and fewer deaths. Also, the study population was different in that it included only patients who had an acute myocardial infarction, who may be more ill than the population in other studies.

Walking pace is thought to be a marker of vitality because it requires integration of multiple organ systems including the cardiovascular, pulmonary, nervous and musculoskeletal systems, in addition to support and balance [8]. Thus, a slower walking pace may reflect a disruption or less efficient organ systems due to disease, which may affect survival. Also, slower pace may lead to deconditioning or reduced activity, which may also impact longevity [23]. It has been postulated that higher oxidative stress and inflammation may be another mechanism of slower walking pace, thus contributing to cardiovascular disease. In the Framingham Offspring Study, a cross-sectional analysis of 1,919 participants found that slower walking pace was associated with elevation of makers of inflammatory and oxidative stress including interleukin-6, isoprostanes, LpPLA2 mass, and osteoprotegerin [24].

Our study has limitations. Walking pace was self-reported in a validated questionnaire. This could lead to some misclassification of the exposure if some participants do not accurately report their pace. However, self-reported walking pace has been shown to highly correlate with measured gait speed in prior studies of community dwelling older adults [6,25]. Also, those with faster walking pace may exhibit other healthy behaviors that may be part of a group of behaviors that

Table 3

Risk ratios (95% CI) of incidence of cardiovascular disease according to walking pace in 18,862 participants of the Physicians' Health Study.

	Do not walk regularly	Easy casual < 2mph	Normal 2-2.9mph	Brisk 3-3.9mph	Very brisk ≥ 4mph	p for trend
CVD incidence/person-years	352/14799	359/14048	1143/67526	565/47539	68/6992	
Incidence rate/1000 PY	23.8	25.6	16.9	11.9	9.7	
Crude model	1.00 (ref)	1.07 (0.93–1.24)	0.71 (0.63–0.80)	0.50 (0.44–0.57)	0.41 (0.32–0.53)	< 0.0001
Age-adjusted model	1.00 (ref)	0.92 (0.80–1.07)	0.75 (0.67–0.85)	0.62 (0.55–0.71)	0.55 (0.43–0.72)	< 0.0001
Multivariable model 1 ^a	1.00 (ref)	0.95 (0.82–1.11)	0.80 (0.71–0.91)	0.69 (0.60–0.79)	0.64 (0.49–0.83)	< 0.0001
Multivariable model 2 ^b	1.00 (ref)	0.91 (0.78–1.06)	0.84 (0.74–0.95)	0.73 (0.64–0.85)	0.72 (0.55–0.94)	0.0004
Multivariable model 3 ^c	1.00 (ref)	1.02 (0.86–1.21)	0.88 (0.75–1.03)	0.75 (0.63–0.89)	0.70 (0.53–0.94)	0.0001

PY = person years. CI = confidence interval.

^a Adjusted for age (years), cigarette smoking, exercise frequency, heart failure, peripheral vascular disease and cancer.

^b Adjusted for all variables in multivariable model 1 plus body mass index, hypertension and diabetes mellitus.

^c Adjusted for all variables in multivariable model 2 plus weekly walking time.

are inversely associated with mortality and cardiovascular disease. Residual confounding cannot be entirely excluded due to the observational nature of our study. Although reverse causation is a concern because those with chronic conditions may have a slower walking pace, we attempted to adjust for prevalent chronic and debilitating conditions in our analysis. It is noteworthy that our sensitivity analyses with a) exclusion of subjects who exercised 5–7 times per week and b) examination of the association in adults younger than age 75 years yielded similar conclusions. Since our study population includes US male physicians with higher educational attainment than the general population, the results of our study may not generalize to the public at large or to women. However, physiologic mechanisms of the effects of walking pace are not likely to be different across populations or gender.

Strengths of our study include a large sample size, which provides sufficient statistical power; a prospective design; incorporation of detailed lifestyle and behavioral factors and co-morbid conditions in the analysis; and adequate follow-up time. Contrary to other studies that were conducted primarily in older individuals, we included a wider age range among men with information on walking pace. Walking pace is a practical measure because it is simple to evaluate, can be performed in a timely fashion, and in various settings, with minimal to no additional cost. Thus, it may have significant public health utility.

4.1. Conclusion

Our findings suggest that walking pace is inversely associated with risk of mortality and risk of development of cardiovascular disease among US male physicians.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

TFI: design, statistical analysis, manuscript writing and revision; AO: critical review and revision of manuscript; JC: statistical analysis, critical manuscript revision; SS: critical review and revision of manuscript; JD: critical review and revision of manuscript; JMG: critical review and revision of manuscript; LD: input on design, critical review and revision of manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2019.08.001>.

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