Original Article

Carotid femoral pulse wave velocity in type 2 diabetes and hypertension: capturing arterial health effects of step counts

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Objective: Optimal medication use obscures the impact of physical activity on traditional cardiometabolic risk factors. We evaluated the relationship between step counts and carotid-femoral pulse wave velocity (cfPWV), a summative risk indicator, in patients with type 2 diabetes and/or hypertension.

Research design and methods: Three hundred and sixty-nine participants were recruited (outpatient clinics; Montreal, Quebec; 2011–2015). Physical activity (pedometer/accelerometer), cfPWV (applanation tonometry), and risk factors (A1C, Homeostatic Model Assessment–Insulin Resistance, blood pressure, lipid profiles) were evaluated. Linear regression models were constructed to quantify the relationship of steps/day with cfPWV.

Results: The study population comprised 191 patients with type 2 diabetes and hypertension, 39 with type 2 diabetes, and 139 with hypertension (mean ± SD: age 59.6 ± 11.2 years; BMI 31.3 ± 4.8 kg/m^2; 54.2% women). Blood pressure (125/77 ± 15/9 mmHg), A1C (diabetes: 7.7 ± 1.3%; 61 mmol/mol), and low-density lipoprotein cholesterol (diabetes: 2.19 ± 0.8 mmol/l; without diabetes: 3.13 ± 1.1 mmol/l) were close to target. Participants averaged 5125 ± 2722 steps/day. Mean cfPWV was 9.8 ± 2.2 m/s. Steps correlated with cfPWV, but not with other risk factors. A 1000 steps/day increment was associated with a 0.1 m/s cfPWV decrement across adjusted models and in subgroup analysis by diabetes status. In a model adjusted for age, sex, BMI, ethnicity, immigrant status, employment, education, diabetes, hypertension, medication classes, the mean cfPWV decrement was 0.11 m/s (95% confidence interval −0.2, −0.02).

Conclusions: cfPWV is responsive to step counts in patients who are well controlled on cardioprotective medications. This ability to capture the 'added value' of physical activity supports the emerging role of cfPWV in arterial health monitoring.

Keywords: accelerometer, applanation tonometry, arterial stiffness, diabetes mellitus, hypertension, pedometer, physical activity

Abbreviations: A1C, hemoglobin A1C; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; cfPWV, carotid-femoral pulse wave velocity; HOMA-IR, Homeostatic Model Assessment–Insulin Resistance; MVPA, moderate to vigorous physical activity; PWV, pulse wave velocity; r, Pearson correlation coefficient; SD, standard deviation; VO$_{2peak}$, peak oxygen uptake

INTRODUCTION

Self-monitoring of glucose levels [1] and blood pressure [2,3] has allowed patients to make concrete connections between medication adherence and vascular health in type 2 diabetes and hypertension. Although guidelines also emphasize the importance of optimizing health behaviors such as physical activity, implementation has lagged behind that of medication-based approaches [4–6].

Novel physical activity monitoring devices offer the opportunity for higher levels of patient engagement and collaboration to increase physical activity levels [7]. Longitudinal investigations [8–10] demonstrate that regular walking leads to a greater than 40% reduction in mortality and vascular event rates over the following decade. Pedometers and accelerometers capture 'steps' in real time. A longitudinal evaluation in prediabetes (9306 participants in 40 countries) demonstrated that a 2000 steps/day baseline increment led to a 10% reduction in vascular complications over an average of 6 years [11].

The impact of physical activity is not entirely explained by effects on individual vascular risk factors [12]; more

comprehensive assessment of vascular health could better reflect physical activity's favourable effects. Carotid-femoral pulse wave velocity (cfPWV), the gold standard measure of arterial stiffness, provides a summative measure of vascular health [13–15]. In a meta-analysis of cohort studies, a 1 m/s increment in cfPWV corresponded to a 15% risk increase in vascular events and mortality [16]. In the Rio de Janeiro diabetes cohort study, a 1 m/s cfPWV increment corresponded to a 13% increase in a composite of fatal and nonfatal cardiovascular events and all-cause mortality [17].

In the present study, we estimated the association between steps and cfPWV in patients treated for type 2 diabetes and/or hypertension. Our overarching aim was to determine if cfPWV would reflect step count levels in a patient population on cardioprotective medications.

RESEARCH DESIGN AND METHODS

This is a cross-sectional examination of baseline data from the SMARTER trial for which recruitment has been completed and interventions are ongoing (SMARTER – Step Monitoring to improve ARTERial health; Clinicaltrials.gov NCT01475201; registered 16 November 2011) [18]. The protocol was approved by McGill University's Faculty of Medicine Institutional Review Board (A08-M76–11B) and participating institutions (McGill University Health Centre, St Mary's Hospital, Sir Mortimer General Jewish General Hospital, Institut De Recherches Cliniques De Montreal). All participants completed informed consent procedures. The study design and methods have been previously described [18]. Between March 2012 and March 2015, 80 collaborating physicians identified potentially eligible participants during routine clinic visits. Eligibility was based on diagnosis of type 2 diabetes, hypertension, or both; age 18 years or above; BMI between 25 and 40 kg/m^2; and absence of gait impairment. Excluded were individuals with comorbid conditions with potential to impact procedures/outcomes (e.g. active malignancy, pregnancy) and those in whom cfPWV could not be assessed (e.g. atrial fibrillation or other arrhythmias). In terms of physical activity, candidates were excluded if they reported 150 min or more of leisure time physical activity per week or if pedometer-recorded step counts were 10 000/day or more during the 1-week evaluation phase with a pedometer prior to randomization, described below.

Measurements

Steps/day and physical activity intensity
Participants wore a Yamax SW-701 pedometer at the waist for 1 week. The viewing window was concealed with a snap-on cover and tamper-proof seal [18]. In addition to the pedometer, participants wore an accelerometer (Actigraph GT3x+). For accelerometer measures, wear time was defined as at least 60 consecutive minutes of nonzero accelerometer counts, with allowance for 1–2 min of counts between 0 and 100 (i.e. spike tolerance). A valid wear day was defined as 10 or more hours of wear time; accelerometer data were used for participants with 4 or more valid wear days. Thresholds for physical activity intensity were: sedentary at less than 200 counts/min; light at 200–

1999 counts/min; moderate at 2000–3999 counts/min; and vigorous at 4000 or more counts/min [19]. Time at moderate to vigorous physical activity (MVPA) intensity per day was derived from accelerometer data. We evaluated the correlation between pedometer and accelerometer-assessed step counts, which was high with a Pearson correlation coefficient of 0.63. Pedometer-assessed step counts were used in the main analysis as complete data were available for all participants.

Arterial stiffness and vessel hemodynamic measurements
Peripheral blood pressure and heart rate were measured using an automated oscillometric BpTru Blood Pressure Monitor (BpTru Medical Devices Ltd, British Columbia, Canada) [20]. Six automated measures of systolic and diastolic blood pressure were taken at 1-min intervals, the first values were discarded, and the averages of the final five systolic and five diastolic blood pressure values were separately computed by the device. cfPWV was measured in duplicate and values were averaged through applanation tonometry (SphygmoCor system, AtCor Medical, Sydney, Australia) after a 10-min rest (supine position) [14,21,22]. Specifically, a micromanometer-tipped tonometer (SPC-301; Millar Instruments, Houston, Texas, USA) was placed over the carotid artery in the neck and the femoral artery (crease of the leg) in order to obtain the waveforms. Using the tonometer and a three-lead ECG, the PWV was automatically calculated from measurements of the pulse transit time and the distance between the two recording sites, carotid and femoral [PWV = distance (m)/transit time (s)] [14,21,22]. The transit time was measured from the foot of the carotid waveform to that of the femoral waveform (foot-to-foot method) using sequential recordings referenced to the ECG. In all participants, the distance was defined as (distance from the suprasternal notch to femoral artery) − (distance from carotid artery to the suprasternal notch), and was measured directly with a measuring tape [14,21,22]. This distance measurement method is termed the subtraction method. As confirmed by an MRI-based study, the subtraction method slightly overestimates the distance in comparison to an alternative method that is based on computing 80% of the direct measurement of the distance between sites [23]. However, both these methods (subtraction and 80% of direct measurement) are recommended by the American Heart Association [21].

All measurements were performed in our state-of-the art Vascular Lab at McGill University Health Center, which is a temperature (20 ± 1°C) and humidity (60 ± 5%) controlled environment. All participants were assessed at approximately the same time during the morning to minimize the effect of the circadian cycle [24]. Participants were fasting and were specifically instructed to abstain from any caffeinated beverages, ethanol intake, and smoking for at least 12 h prior to the assessments.

Other assessments
Participants completed questionnaires querying demographic factors, health behaviors, and medical history. A research assistant recorded antihyperglycemic, antihypertensive, and lipid-lowering medications. Type 2 diabetes,

hypertension, and dyslipidemia status were defined as participant-reported physician diagnosis and/or use of relevant medications. Participants enrolled prior to September 2015 completed a fitness assessment; VO_{2peak} was evaluated during treadmill testing (model VMax229LV; Sensorsmedics, Yorba Linda, California, USA; Med-TrackCR60 Treadmill; Quinton, Bothell, Washington, USA; Bruce ramp protocol). Anthropometric measures were performed using standard procedures (height, weight, waist, and hip circumferences). With fasting venous blood samples, we assessed total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, low-density lipoprotein cholesterol (LDL-C) (calculated using the Friedewald equation), apolipoproteins A1 and B, hemoglobin A1c (in diabetes patients), and high-sensitivity C-reactive protein. In patients not on insulin therapy, fasting glucose and insulin values were assessed and the Homeostatic Model Assessment–Insulin Resistance (HOMA-IR) was computed [25].

Statistical analyses

Means, standard deviations (SDs), number, and proportions were calculated, as appropriate, for all variables measured, both overall and separately for those with and without type 2 diabetes. Step counts were plotted against cfPWV, HOMA-IR, A1C, systolic blood pressure, and LDL-C; and Pearson correlation coefficients were computed with 95% confidence intervals (CIs).

Given that the plot of steps vs. cfPWV suggested that a linear model was reasonable and there was an inverse correlation between these two variables, a series of linear regression models was constructed to evaluate the relationship in greater detail. First, an unadjusted model was constructed; next, the model was adjusted for age and sex. We then added BMI, followed by a separate model that included waist circumference instead of BMI. Subsequently, we added other variables to each of these models, including demographic factors, type 2 diabetes and hypertension status, each medication category [i.e. antihyperglycemic categories (metformin, sulfonylureas, insulin); antihypertensive categories (angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB); β-blocker; calcium channel antagonist; diuretic; other] and lipid-lowering therapies (statins, other). We opted not to include other cardiometabolic risk factors in the models as we considered these to lie along the hypothesized causal pathway from step counts to cfPWV; moreover, these factors did not demonstrate an important correlation with cfPWV in this clinical cohort (see 'Relationship between step counts and cardiometabolic risk factors and cfPWV' subsection under the 'Results' section).

We repeated the above series of models with additional adjustment for MVPA and also considered models that included MVPA but not step counts.

RESULTS

The study cohort included 369 adults (Fig. 1; mean age 60 years, 200 women; Table 1 and Supplementary Table 1, http://links.lww.com/HJH/A730), most of whom were educated beyond high school (72.4%). Over 60% of participants

TABLE 1. Demographic characteristics, physical activity and fitness, anthropometric measures, and past medical history

Demographic characteristics	Overall (N = 369)
Age, years, mean (SD)	59.6 (11.2)
Women, no. (%)	200 (54.2)
Postsecondary education, no. (%)	254 (72.4)
White, no. (%)	221 (60.2)
Immigrant, no. (%)	172 (46.6)
Married/common-law, no. (%)	246 (74.8)
Full time or part time work or student, no. (%)	215 (59.2)
Physical activity and fitness	
Steps/day, mean (SD)	5165 (2722)
Moderate to vigorous activity, h/day, mean (SD)	0.82 (0.89)
Total activity, kcal/day, mean (SD)	571 (460)
Fitness, VO$_2$ peak percentile <10%, number (%)	159 (67.4)
Anthropometric measures, mean (SD)	
Women	
Body mass index (kg/m^2)	32.2 (4.5)
Waist circumference (cm)	101.3 (10.7)
Waist/hip	0.90 (0.1)
Men	
Body mass index (kg/m^2)	31.3 (4.8)
Waist circumference (cm)	107 (11.6)
Waist/hip	0.99 (0.1)
Smoking history, no. (%)	
Current smoker	21 (5.7)
Past smoker	129 (35.1)
Diabetes, no. (%)	230 (62.3)
Diabetes duration (years) mean (SD)	10.5 (7.9)
Antihyperglycemic therapy, no. (%)	
Metformin	199 (86.5)
Sulfonylurea	80 (34.8)
Insulin	68 (29.6)
Gestational diabetes history (in women with previous pregnancy; n = 155)	39 (25)
Hypertension, no. (%)	330 (89.4)
Hypertension duration, years, mean (SD)	12.4 (10.8)
Antihypertensive agents, no. (%)	
Angiotensin-converting enzyme inhibitor or receptor blocker	260 (70.4)
Calcium channel blocker	113 (30.6)
β-blocker	105 (28.5)
Diuretic	165 (44.5)
Hypertensive disorder of pregnancy (in women with previous pregnancy; n = 155)	35 (22.6)
Dyslipidemia, no (%)	254 (68.8)
Dyslipidemia duration, years, mean (SD)	9.5 (8.2)
Dyslipidemia therapy, number (%)	
HMGCoA reductase inhibitor (statin)	214 (58.0)
Cardiovascular disease	67 (18.2)
Menopause (women)	147 (73.5)
Antiplatelet agent	155 (42.0)

Missing values for education (18; 15 in diabetes), ethnocultural background (2; 1 in diabetes), marital status (40; 24 in diabetes), and work status (6; 4 in diabetes). Forty-two participants did not have valid accelerometer data (33 in diabetes). Exercise stress tests were not conducted in 133 participants (84 in diabetes).

had type 2 diabetes, nearly 90% had hypertension, and approximately 70% were treated for dyslipidemia. Nearly one-fifth had clinically diagnosed cardiovascular disease (18.2%). Overall, approximately 40% were non-white and over half were immigrants. Both men and women were on average at the stage 1 level of obesity with abdominal obesity; 73.5% of women were in menopause. Higher proportions of those with type 2 diabetes were men, were working, and were non-white. Blood pressure was well controlled (mean 125/77 ± 15 mmHg; Table 2); people with
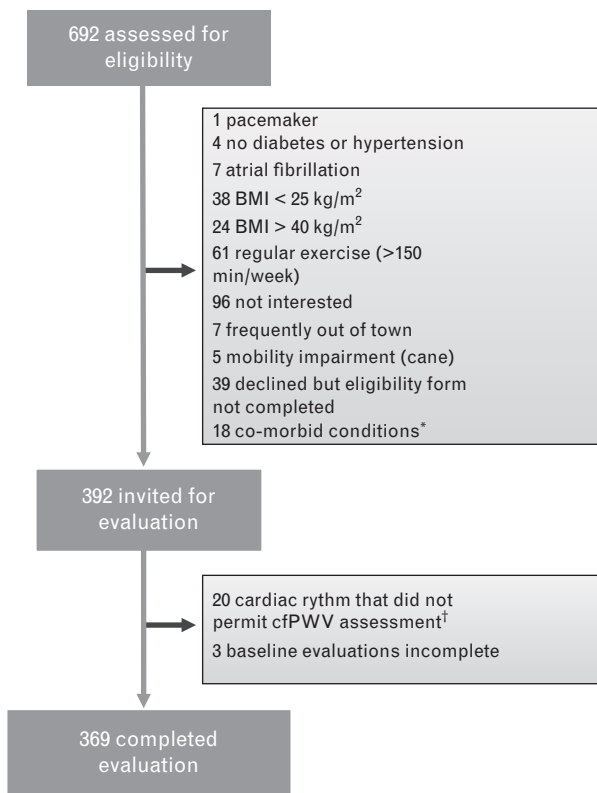
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┌─────────────────────┐
│ 692 assessed for    │
│ eligibility         │
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          │
          │      ┌──────────────────────────────────────┐
          ├─────▶│ 1 pacemaker                          │
          │      │ 4 no diabetes or hypertension        │
          │      │ 7 atrial fibrillation                │
          │      │ 38 BMI < 25 kg/m²                    │
          │      │ 24 BMI > 40 kg/m²                    │
          │      │ 61 regular exercise (>150            │
          │      │ min/week)                            │
          │      │ 96 not interested                    │
          │      │ 7 frequently out of town             │
          │      │ 5 mobility impairment (cane)         │
          │      │ 39 declined but eligibility form     │
          │      │ not completed                        │
          │      │ 18 co-morbid conditions*             │
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┌─────────────────────┐
│ 392 invited for     │
│ evaluation          │
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          ├─────▶│ 20 cardiac rythm that did not        │
          │      │ permit cfPWV assessment†             │
          │      │ 3 baseline evaluations incomplete    │
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│ 369 completed       │
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FIGURE 1 Participant flow.

type 2 diabetes had somewhat lower values (mean 123/77 ± 15 mmHg). A1C values averaged 7.7 ± 1.3% (61 mmol/mol) in patients with type 2 diabetes. Participants were in general on appropriate cardioprotective medications (e.g. ACEi or ARB treatment: over 70% overall and 73.9% with type 2 diabetes; statin therapy: 58% overall and 72.2% with type 2 diabetes). Close to one-third of participants with type 2 diabetes were on insulin therapy and 86.5% were taking metformin. Among the women with a past pregnancy, over one-fifth had a history of a hypertensive disorder of pregnancy and one-quarter had a history of gestational diabetes. Mean HOMA-IR was high (>2.7) [26] in both those with and

TABLE 2. Direct measures of arterial health and cardiometabolic risk factors

	Overall ($N = 369$)
Carotid femoral pulse wave velocity (m/s)	9.8 (2.2)
Systolic/diastolic blood pressure, mean (SD) (mmHg)	125 (15)/77 (9.0)
Heart rate (b.p.m.)	72 (12)
Hemoglobin A1C, %, mean (SD) in those with type 2 diabetes	7.7 (1.3)
HOMA-IR, mean (SD)	
Type 2 diabetes not on insulin therapy	4.5 (3.5)
No diabetes	3.0 (2.0)
Lipid profile, mean (SD)	
Total cholesterol (mmol/l)	4.54 (1.3)
HDL (mmol/l)	1.25 (0.33)
LDL (mmol/l)	2.54 (1.0)
C-reactive protein, mean (SD) (mg/l)	4.8 (13)

HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment–Insulin Resistance; LDL, low-density lipoprotein.

without type 2 diabetes, but, as expected, higher in those with type 2 diabetes.

The average step count was 5125 ± 2722 steps/day (i.e. in low active range) overall with a slightly lower value in those with type 2 diabetes (5010 ± 2800 steps/day) compared to those without type 2 diabetes (5420 ± 2600 steps/day) [27]. More than three-fourths of time was at the sedentary intensity (accelerometer measures) with an average of 48 min per day of MVPA. Fitness was poor (67.4% less than age-specific 10th percentile VO$_{2peak}$ value). The average cfPWV was elevated at 9.8 ± 2.2 m/s, with a value of 10.0 ± 2.3 m/s in those with type 2 diabetes and 9.4 ± 2.0 m/s in those without type 2 diabetes.

Relationship between step counts and cardiometabolic risk factors and carotid-femoral pulse wave velocity

In this cohort, plots (Fig. 2) of steps vs. systolic blood pressure ($r = -0.05$, 95% CI -0.15, 0.05) and steps vs. HOMA-IR ($r = -0.09$, 95% CI -0.2, 0.02) were consistent with an inverse relationship, but this finding was not conclusive. Plots of steps vs. LDL ($r = 0.01$, 95% CI -0.10, 0.11) and steps vs. A1C ($r = 0.03$, 95% CI -0.1, 0.16) did not suggest a relationship.

In contrast, an inverse linear relationship between steps and cfPWV was evident ($r = -0.24$, 95% CI -0.34, -0.14). A 1000 increment in steps/day was associated with a 0.2 m/s decrement (95% CI -0.28, -0.12) in cfPWV in an unadjusted linear regression model. In a model adjusted for age, sex, BMI, ethnicity, immigrant status, employment, education, type 2 diabetes, hypertension, medication classes, and MVPA, the mean cfPWV decrement was 0.10 m/s (95% CI -0.19, -0.02) for each 1000 steps/day increment. There was an approximately 0.1 m/s decrement in cfPWV across the 19 adjusted models examined (Table 3 and Supplementary Table 3, http://links.lww.com/HJH/A730); adjustment for MVPA did not alter the association between step counts and cfPWV. MVPA did not demonstrate an association in this cohort with cfPWV in either univariate or adjusted models (per 1-h increment in MVPA/day: -0.16 m/s, 95% CI -0.44, 0.12; Supplementary Table 3, http://links.lww.com/HJH/A730). When we adjusted for heart rate and mean arterial pressure (analyses not shown), the magnitude of association between step counts and cfPWV was halved and the findings were no more statistically significant.

Subgroup analyses (e.g. by sex, type 2 diabetes status) demonstrated similar findings for the association between step counts and cfPWV: in models adjusted for age, BMI, ethnicity, immigrant status, employment, and education, a 1000 increment in steps/day was associated with a 0.13 m/s decrement (95% CI -0.24, -0.02) in men overall, a 0.12 m/s decrement (95% CI -0.24, -0.005) in women overall, and a 0.13 m/s decrement (95% CI -0.2, -0.02) in type 2 diabetes. Further adjustments in these subanalyses yielded inconclusive results.

Other predictors of cfPWV

We identified independent relationships between step counts and age, BMI, and waist circumference. In fully adjusted models (age, sex, BMI, ethnicity, immigrant status,
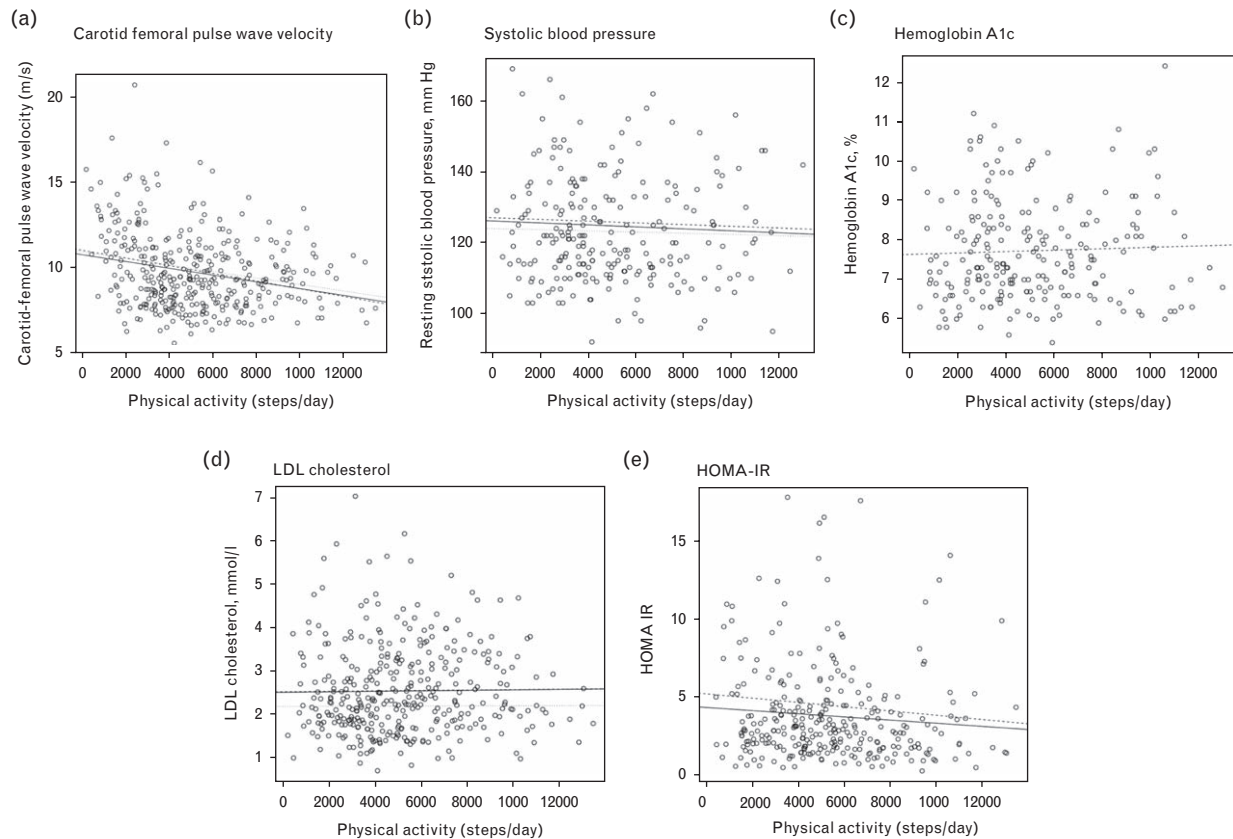
FIGURE 2 Step counts in increments of 1000 steps/day vs. (a) carotid femoral pulse wave velocity, (b) systolic blood pressure, (c) hemoglobin A1C, (d) LDL cholesterol, and (e) HOMA-IR. Overall (solid lines), type 2 diabetes (dashed lines), and hypertension (dotted lines). A1C, hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment–Insulin Resistance; LDL, low-density lipoprotein.

employment, education, type 2 diabetes, hypertension, medication classes, MVPA), a 1-year age increment was associated with a 0.09 increment in cfPWV (95% CI 0.06, 0.1), and a $1 kg/m^2$ BMI increment was associated with a 0.06 m/s increment in cfPWV (95% CI 0.02, 0.11). In the fully adjusted model that included waist circumference instead of BMI, a 1 cm increment in waist circumference was associated with a 0.04 m/s increment in cfPWV (95% CI 0.02, 0.06). Values were similar for women and men across models (not shown).

TABLE 3. Change in carotid femoral pulse wave velocity per 1000 steps/day

Model	cfPWV change, m/s (95% CI) per 1000 steps/day	Other variables in model
1	−0.20 (−0.28, −0.12)	Unadjusted
2	−0.14 (−0.21, −0.07)	+Age, sex
3	−0.12 (−0.16, −0.04)	+BMI
4	−0.13 (−0.2, −0.05)	+Ethnicity, immigrant status, employment, education
5	−0.11 (−0.2, −0.02)	+Type 2 diabetes, hypertension
6	−0.11 (−0.2, −0.02)	+Medication classes[a]

cfPWV, carotid-femoral pulse wave velocity; CI, confidence interval.
[a]The medication classes are specific categories of antihyperglycemic (metformin, sulfonylureas, insulin), antihypertensive (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, calcium channel antagonist, diuretic, other), and lipid-lowering therapies (statins, other).

DISCUSSION

We demonstrated a consistent inverse relationship between step counts and cfPWV in adults with type 2 diabetes and/or hypertension. A 1000 steps/day increment is associated with a 0.1 m/s decrement in cfPWV across adjusted models. The relationship remains robust even after accounting for a variety of covariates and potential confounders, including age and other demographic factors, anthropometric measures, use of cardioprotective medications, and physical activity intensity. Furthermore, the direction and magnitude of the relationship remained unaltered in subgroup analyses, by sex, diabetes status, and hypertension status. In fully adjusted models, age and anthropometric measures demonstrated independent relationships with step counts. A 1-year age increment, $2 kg/m^2$ higher BMI or 3 cm increase in waist circumference, and a 1000 steps/day decrement were each associated with a 0.1 m/s higher cfPWV.

The decrement of 0.1 m/s cfPWV that we observed to be associated with a 1000 step/day increment was identified in a patient population with well controlled cardiometabolic risk profiles (e.g. mean BP 125/77 mmHg).

Whereas a 1000 steps/day increment is associated with a 0.1 m/s cfPWV decrement, a higher step count increment would be linked to a greater cfPWV decrement. Meta-analyses indicate that pedometer-based interventions lead to an average step count increase of 2000 steps/day [28–30].

Based on our findings, such an increase would correspond to a 0.2 m/s cfPWV reduction. Extrapolating from meta-analyses evaluating relationships between cfPWV and vascular events and mortality [16], a 0.2 m/s reduction in cfPWV would be estimated in turn to lead to a 3% decrease in vascular events and mortality. A 0.2 m/s reduction corresponds to 50% of the cfPWV reduction observed with supervised exercise programs in one meta-analysis [31,32]

In a previous study addressing the association between step counts and cfPWV in type 2 diabetes [33], there was a conclusive difference in cfPWV at step count extremes (<5000 steps/day vs. >10 000 steps/day; 11 vs. 10.2 m/s), although an inverse linear relationship between steps and cfPWV was not observed. The absence of a linear relationship at baseline in this previous study may be related to a higher mean step count compared to our study (7863 vs. 5170 steps/day in our study). At 4 years follow-up [34], there was slower progression of cfPWV for those with higher baseline step counts; specifically, the increase in cfPWV was 0.1 m/s less per 1000 steps/day baseline increment. The magnitude and direction of this were notably similar to our findings, lending support to the 1000 steps/day increment to 0.1 m/s cfPWV decrement relationship that we observed.

In one pedometer-based intervention meta-analysis [28], interventions led to a 3.8 mmHg systolic blood pressure reduction. Similarly, in a previous cohort study in type 2 diabetes, we determined a 1000 daily step increment to be associated with 2.6 mmHg decrement in women [35]. In the SMARTER cohort, however, we did not detect a relationship between step counts and blood pressure. Notably, in this cohort, mean systolic blood pressure was 125 mmHg across the range of step counts, in contrast to our prior study in which values ranged from 144 mmHg in quartile 1 to 131 mmHg in quartile 4. The lower blood pressure in the SMARTER cohort may be a result of participation of patients more adherent to treatments, use of multiple automated measurements, and tighter management of blood pressure in recent years. Similarly, we did not observe a relationship between A1C and step counts in type 2 diabetes patients; this is consistent with the findings of a meta-analysis of pedometer-based interventions [29]. The authors note that baseline A1C values were well controlled (6.64–8.0%), possibly limiting ability to detect an impact of interventions on A1C. Despite an absence of relationship between step counts to systolic blood pressure and A1C in the SMARTER cohort, we have demonstrated a relationship between step counts and cfPWV; this underscores the potential benefit of using cfPWV to capture impacts of health behaviors that may otherwise be obscured by pharmacotherapy.

Whereas we did not identify a relationship between steps and individual cardiovascular risk factors, these all likely contributed, over time, to an impact on cfPWV. We conceptualized the relationship of step counts to cfPWV to be mediated at least partly through individual cardiovascular risk factors and thus did not adjust for variables 'along the causal pathway.' Indeed, as expected, when we adjusted for heart rate and mean arterial pressure (MAP; analyses not shown), the magnitude of association between step counts and cfPWV was halved.

We did not observe a relationship between physical activity intensity and cfPWV independent of the relationship between step counts and cfPWV. In a younger general population cohort [36] (Framingham Heart Study third generation cohort; mean age 47 years), a 10-min increment in MVPA was associated with a 0.5 m/s decrement in cfPWV. Whereas some studies observed added benefit to increasing intensity, and also volume of physical activity [32,37], this was not apparent in our cohort. Moreover, in older patients with type 2 diabetes and hypertension, a focus on increasing step counts may be a more realistic and practical option than increasing intensity, as suggested by evaluations of patient preferences [38]. Consistent with this, previous evidence suggests that even habitual physical activity is associated with decreased arterial stiffness [37,39–41]. Several changes in arterial structure with aging or presence of cardiovascular risk factors may contribute to increased arterial stiffness, including fragmentation of elastin, deposition of collagen, and smooth muscle hypertrophy as a result of exposure to free radicals and inflammatory cytokines [42], and also reduced nitric oxide and increased vasoconstrictors (angiotensin, endothelin, prostaglandins) [43]. The beneficial effect of higher physical activity levels on arterial stiffness can be attributed to different mechanisms involved in both the function and structure of the arteries. These mechanisms include anti-oxidant effects (through up-regulation of superoxide dismutases and down-regulation of NAD(P)H oxidase) [44], anti-inflammatory effects (by increasing anti-inflammatory cytokines, e.g. interleukin (IL)-4, IL-10), and reduction of proinflammatory cytokines [IL-6 and tumour necrosis factor (TNF)-α]. Furthermore, physical activity is known to have direct effects on the endothelium leading to increased nitric oxide production, and decreased release of vasoconstrictor agents. Specifically, increased production of nitric oxide is believed to have antimitogenic effects that inhibit vascular smooth muscle proliferation and cause vasorelaxation [45]. Nitric oxide also plays an important role in counterbalancing the vasoconstrictive actions of endothelin by inhibiting its synthesis in endothelial cells [46]. Structurally, physical activity has been shown to mitigate the cross-linking of structural proteins by advanced glycation products within the arterial wall and inhibits the smooth muscle-mediated synthesis of collagen, both key contributors to arterial stiffness [47].

Our study has several strengths, including the objective measurement of physical activity, the use of a validated measure of arterial stiffness, with which we have extensive experience in our Vascular Lab [22,48–51], and our ability to account for a variety of demographic factors, and also specific antihypertensive, antihyperglycemic, and lipid-lowering therapies.

An aspect that could be interpreted as a limitation is the high level of blood pressure control in our study cohort, as we have previously discussed. Indeed, the mean cfPWV observed in our cohort was identical to that of study participants with optimized risk factors and behaviors in the Maine-Syracuse Longitudinal Study and lower than those in that study with less optimal risk factors in whom cfPWV averaged 11.7 m/s [52]. Despite this, we identified an inverse relationship between steps and cfPWV. This

is arguably additional evidence of the importance of physical activity in the management of patients with hypertension, diabetes, or additional cardiometabolic profile abnormalities.

The cross-sectional design of the present analysis is a limitation to making causal inferences. Nonetheless, we believe that our findings nonetheless support the responsiveness of cfPWV to step counts in type 2 diabetes and hypertension, when interpreted in the context of prior studies. Participating individuals are enrolled in our clinical trial and thus may represent a more motivated group who may have higher step counts than the less motivated; despite this possibility, average step count values were in the sedentary to low active range. Our analyses demonstrate that in patients with type 2 diabetes and/or hypertension, cfPWV values distinguish those with higher and lower step counts, even when cardiometabolic risk factors are well controlled across step count values, as a result of pharmacotherapy.

In conclusion, the integration of physical activity promotion strategies into hypertension and diabetes clinical management has been historically limited by a paucity of monitoring tools. Pedometers and accelerometers now allow the objective capture of physical activity data. Capturing arterial health impact, however, is challenging in the context of cardioprotective medications with direct impacts on cardiometabolic risk factors. Our analyses demonstrate that cfPWV captures the 'added value' of physical activity effects on arterial health, in contrast to traditional cardiometabolic risk factors, in patients with type 2 diabetes and hypertension. cfPWV is advocated by European and American guidelines as a means of monitoring vascular health [21,53]. We acknowledge that at the present time, cfPWV remains dependent on expensive equipment and technical expertise. However, we anticipate that the technology will evolve to become cheaper, simpler, and thus more accessible in the coming years. As pedometer and accelerometer technologies are integrated into patient management, cfPWV measurements may eventually allow physicians and patients to tailor physical activity strategies for maximal arterial health benefits.

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Conflicts of interest

There are no conflicts of interest related to the content of this manuscript.

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Reviewers' Summary Evaluations

Referee 1

Strengths
The main finding of the present study is that aortic stiffness, measured as carotid-femoral PWV, is responsive to step counts. Despite the cross-sectional design and the relatively small size, the study is interesting because of its novel findings in patients who are well controlled on cardio-protective medications

Limitations
After adjustment for heart rate and mean arterial pressure (analyses not shown), estimates were no more statistically significant.

Referee 2
Strength: in this study, the authors demonstrate that more physical activity is associated with better carotid to femoral pulse wave velocity in diabetic subjects.

Weakness: being observational, this study does not provide evidence for causality and/or mechanisms. A randomized controlled trial testing the effect of exercise on pulse wave velocity in diabetic patients would be needed.