ESC European Society of Cardiology

European Heart Journal (2021) **42**, 4565–4575
doi:10.1093/eurheartj/ehab580

CLINICAL RESEARCH
Epidemiology and prevention

Physical activity and fitness in the community: the Framingham Heart Study

Matthew Nayor [1,2]*, Ariel Chernofsky [3], Nicole L. Spartano [4], Melissa Tanguay[2], Jasmine B. Blodgett[2], Venkatesh L. Murthy [5,6], Rajeev Malhotra [2,7], Nicholas E. Houstis [2], Raghava S. Velagaleti[8], Joanne M. Murabito[9,10], Martin G. Larson[3,10], Ramachandran S. Vasan [10,11], Ravi V. Shah[2,12]†, and Gregory D. Lewis[2,13]†

[1]Sections of Cardiology and Preventive Medicine and Epidemiology, Department of Medicine, Boston University School of Medicine, 72 E Concord St, Suite L-514, Boston, MA 02118, USA; [2]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [3]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA; [4]Department of Medicine, Section of Endocrinology, Diabetes, Nutrition and Weight Management, Boston University School of Medicine, Boston, MA, USA; [5]Division of Cardiovascular Medicine, Department of Medicine, University of Michigan, Ann Arbor, MI, USA; [6]Frankel Cardiovascular Center, University of Michigan, Ann Arbor, MI, USA; [7]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA; [8]Cardiology Section, Department of Medicine, Boston VA Healthcare System, West Roxbury, MA, USA; [9]Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA; [10]Boston University's and National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, MA, USA; [11]Sections of Preventive Medicine and Epidemiology, and Cardiology, Department of Medicine, Department of Epidemiology, Boston University Schools of Medicine and Public Health, Center for Computing and Data Sciences, Boston University, Boston, MA, USA; [12]Vanderbilt Clinical and Translational Research Center, Cardiology Division, Vanderbilt University Medical Center, Nashville, TN; and [13]Pulmonary Critical Care Unit, Massachusetts General Hospital, Boston, MA USA

Received 23 March 2021; revised 14 June 2021; editorial decision 10 August 2021; accepted 10 August 2021; online publish-ahead-of-print 26 August 2021

See page 4576 for the editorial comment for this article 'Don't count the steps: make the steps count? Digging deeper into physical activity and fitness', by J.M. Letnes and B.M. Nes, https://doi.org/10.1093/eurheartj/ehab716.

Aims

While greater physical activity (PA) is associated with improved health outcomes, the direct links between distinct components of PA, their changes over time, and cardiorespiratory fitness are incompletely understood.

Methods and results

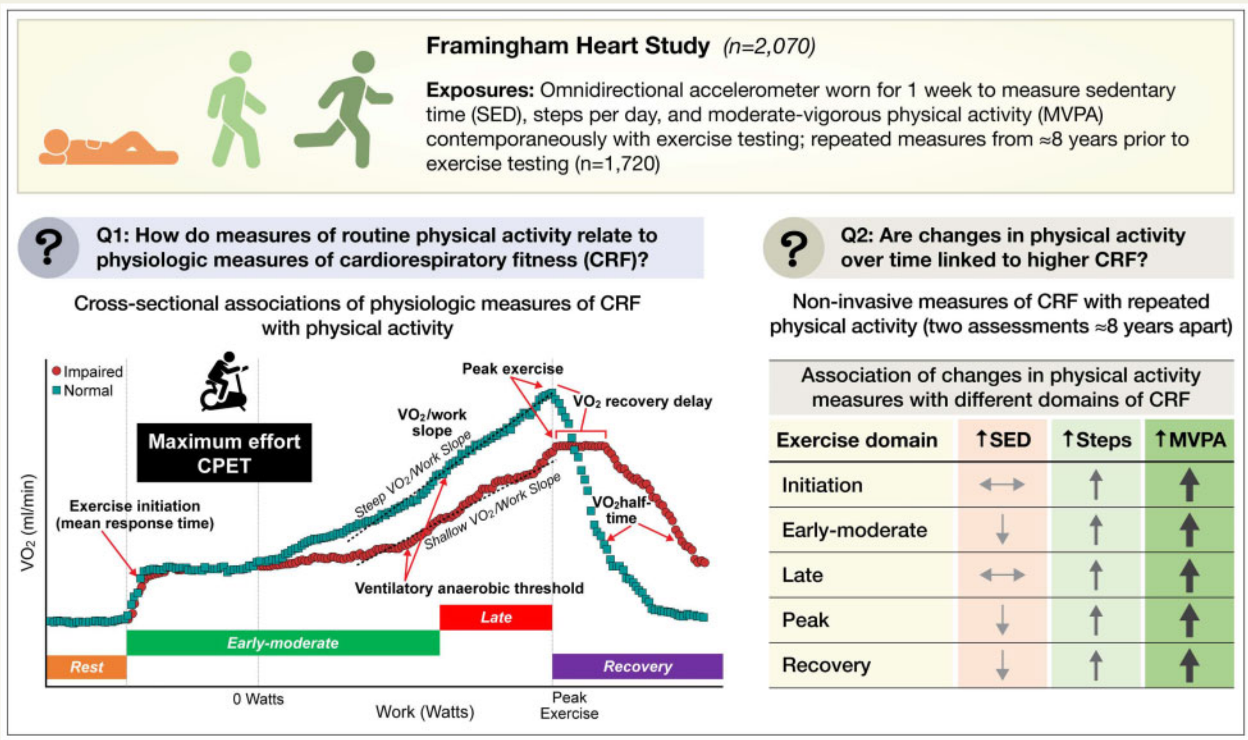
Maximum effort cardiopulmonary exercise testing (CPET) and objective PA measures [sedentary time (SED), steps/day, and moderate-vigorous PA (MVPA)] via accelerometers worn for 1 week concurrent with CPET and 7.8 years prior were obtained in 2070 Framingham Heart Study participants [age 54 ± 9 years, 51% women, SED 810 ± 83 min/day, steps/day 7737 ± 3520, MVPA 22.3 ± 20.3 min/day, peak oxygen uptake (VO_2) 23.6 ± 6.9 mL/kg/min]. Adjusted for clinical risk factors, increases in steps/day and MVPA and reduced SED between the two assessments were associated with distinct aspects of cardiorespiratory fitness (measured by VO_2) during initiation, early-moderate level, peak exercise, and recovery, with the highest effect estimates for MVPA (false discovery rate <5% for all). Findings were largely consistent across categories of age, sex, obesity, and cardiovascular risk. Increases of 17 min of MVPA/day [95% confidence interval (CI) 14–21] or 4312 steps/day (95% CI 3439–5781; ≈54 min at 80 steps/min), or reductions of 249 min of SED per day (95% CI 149–777) between the two exam cycles corresponded to a 5% (1.2 mL/kg/min) higher peak VO_2. Individuals with high (above-mean) steps or MVPA demonstrated above average peak VO_2 values regardless of whether they had high or low SED.

Conclusions

Our findings provide a detailed assessment of relations of different types of PA with multidimensional cardiorespiratory fitness measures and suggest favourable longitudinal changes in PA (and MVPA in particular) are associated with greater objective fitness.

* Corresponding author. Tel: 617-638-8771, Email: mnayor@bu.edu
†These authors contributed equally to this work.

Graphical Abstract



An overview of the study design is displayed. Cardiopulmonary fitness measures were associated with omnidirectional accelerometry data concurrent with exercise testing and from ≈8 years prior to evaluate the relations of physical activity and fitness.

Keywords Physical activity • Sedentary time • Cardiorespiratory fitness • Exercise

Introduction

Greater routine physical activity (PA) is associated with lower cardiovascular disease (CVD) risk[1–6] and improved longevity.[7–13] PA promotes cardiovascular health partly through positive effects on clinical CVD risk factors (e.g. weight, blood pressure, dysglycemia, and blood cholesterol[14,15]). However, the physiological and metabolic benefits of PA extend beyond its impact on standard risk factors[16,17] with favourable effects on multiple organ systems including the heart and vasculature, brain, muscle, bones, and kidneys.[18–21]

The 2018 Physical Activity Guidelines for Americans encourage several types of PA, including dedicated exercise [i.e. moderate-vigorous PA (MVPA)], lower-level activity (e.g. steps during routine ambulation), and minimization of sedentary time (SED), in accordance with growing evidence that each form of PA is associated with improved long-term health outcomes.[1–13,22] However, for individuals across the age, sex, and cardiovascular risk status spectrum, the relative impact of PA intensity and duration on physical fitness remains unclear. Cardiorespiratory fitness, as assessed by peak oxygen uptake (VO_2) during cardiopulmonary exercise testing (CPET), integrates global physiological function and is, therefore, ideally suited to investigate the relations of PA and metabolic health. CPET also provides measures of central cardiac and vascular function and VO_2 kinetics during different phases of exercise (including initiation, low-moderate intensity, peak exercise, and recovery), which may help to map how each component of habitual PA relates to changes in metabolic responses to exercise.

In the present investigation, we related different types of PA with components of cardiorespiratory fitness in 2070 predominantly middle-aged community-dwelling Framingham Heart Study (FHS) participants. One week of accelerometry-derived PA measures (SED, steps/day, and MVPA) and their changes over nearly a decade were related to CPET fitness measures assessed on a single occasion. Our relatively large sample size permitted assessment of how various combinations of SED, steps/day, and MVPA were related to cardiorespiratory fitness as well as enabling examination of how relations of PA and fitness measures varied across age, sex, and cardiovascular risk status.

Methods

Study sample

Detailed characteristics and enrolment procedures for the FHS Generation Three, Omni Generation Two, and New Offspring cohorts

Table 1 Methodological approaches for measuring cardiopulmonary exercise testing responses

CPET fitness measure	Exercise intensity	Physiological significance	Measurement methodology
Mean response time	Initiation-moderate	Exponential time constant of VO_2 onset kinetics	O_2 deficit/ΔVO_2, where O_2 deficit = time from rest to steady state $\times$ ΔVO_2-cumulative VO_2, and ΔVO_2 = VO_2 at steady state-VO_2 at rest[43]
O_2 uptake efficiency slope	Initiation-moderate	Reflects VO_2 kinetics	Slope of the regression line of VO_2 vs. $\log_{10}V_E$
VO_2 at the VAT	Moderate	VO_2 prior to onset of anaerobic metabolism	Measurement of VO_2 up to the VAT, measured using the V-slope method[44]
VO_2 at the VAT as % of peak VO_2	Moderate	Amount of total VO_2 (peak VO_2) that occurs prior to VAT	VO_2 at VAT/peak VO_2
VO_2/work	Moderate	Reflects metabolic cost of performing external work	$\Delta VO_2/\Delta$work during incremental exercise
Post-VAT VO_2	Late	Amount of VO_2 occurring during primarily anaerobic phases of exercise	Peak VO_2—VO_2 at the VAT
Peak VO_2	Peak	'Gold standard' assessment of cardiorespiratory fitness	Highest 30 s median value of VO_2 during the final minute of loaded exercise
% predicted peak VO_2	Peak	Comparison of peak VO_2 achieved with predicted value for age, sex, and body size	Using the Wasserman and Hansen formula[45,46]
Peak O_2 pulse	Peak	Reflects stroke volume and peripheral O_2 extraction	Peak VO_2/peak heart rate
VO_2 recovery delay	Recovery	VO_2 recovery kinetics reflect the metabolic deficit accrued during exercise (lower deficit observed with higher fitness)	Time from end of loaded exercise to when VO_2 permanently falls below peak VO_2
VO_2 half-time	Recovery		Time for VO_2 to decrease to 50% of peak VO_2 after adjustment for resting VO_2
% maximum predicted heart rate	Peak	Heart rate response to exercise	Predicted peak heart rate calculated using the Tanaka formula (peak heart rate = 208–0.7 $\times$ age)[47]
V_E/VCO_2 nadir	Low-moderate	Central cardiac and pulmonary vascular function and peripheral chemoreflexes[48,49]	The lowest 30 s average V_E/VCO_2 value during exercise
Mean arterial pressure at 75 W	Low-moderate	Blood pressure and vascular response to exercise	Diastolic blood pressure + 1/3(systolic–diastolic blood pressure)

CPET, cardiopulmonary exercise testing; O_2, oxygen; VAT, ventilatory anaerobic threshold; V_E/VCO_2, the ratio of minute ventilation to carbon dioxide production; VO_2, oxygen uptake.

have been described.[23,24] At their third examination cycle (exam 3; 2016–2019), all participants were offered participation in the CPET study, and information on their metabolic responses to exercise and ventilatory efficiency has been reported previously.[25–27] Accelerometry data were obtained during both the second (exam 2; 2008–2011) and the third (exam 3) examination cycles. At both examinations, participants were asked to wear the accelerometer for 8 days after their study visit. From a total of 3521 exam 3 participants, 3486 attended the research centre ($n = 35$ were home visits), and 3117 completed CPET, of whom 2408 individuals provided accelerometry data. Characteristics of individuals with and without accelerometry data at exam 3 were similar with slightly worse cardiometabolic risk profiles noted in those who did not provide accelerometry data (Supplementary material online, *Table S1*). The majority of participants resided in New England (84%). We excluded individuals with inadequate volitional effort during exercise (peak respiratory exchange ratio <1.0; $n = 41$), insufficient accelerometer wear time (fewer than 3 days with ≥10 h of wear time; $n = 182$), missing steps data ($n = 3$), missing CPET data or covariate information ($n = 108$), or outlier values likely to be a result of instrument error (five standard deviations [SD] above or below the mean) for PA measures ($n = 4$), yielding a final sample size of 2070 individuals for cross-sectional analyses of CPET and accelerometry measures (*Graphial Abstract*). For analysing the relations of CPET measures with the change in accelerometry measures from exam 2 to exam 3, we further excluded individuals without accelerometry data from exam 2 ($n = 350$), yielding an analytic subsample of 1720 individuals. This study was approved by the Institutional Review Boards at Boston University Medical Campus/Boston Medical Center and Massachusetts General Hospital. All participants provided written informed consent.

Cardiopulmonary exercise testing

Maximum effort incremental ramp CPET was performed on a cycle ergometer (Lode, Netherlands), as previously described.[26,27] Briefly, breath-

Table 2 Clinical characteristics of the study sample for cross-sectional analyses

Characteristic	Overall (*n* = 2070)	Men (*n* = 1006)	Women (*n* = 1064)
Age, years	54 (9)	54 (9)	53 (9)
Body mass index, kg/m^2	28.0 (5.3)	29.1 (4.7)	26.9 (5.5)
Resting systolic blood pressure, mmHg	124 (16)	129 (16)	121 (16)
Nonwhite race	183 (8.8)	88 (8.7)	95 (8.9)
Hypertension medication use	425 (21)	250 (25)	175 (16)
Current smoking	105 (5.1)	52 (5.2)	53 (5.0)
Former smoking	641 (31)	291 (29)	350 (33)
Diabetes	145 (7.0)	103 (10.2)	42 (3.9)
Prevalent cardiovascular disease	88 (4.3)	60 (6.0)	28 (2.6)
Residing in New England	1734 (84)	838 (83)	896 (84)
Wear time, h/day	14.2 (1.2)	14.3 (1.2)	14.1 (1.2)
Valid days of accelerometry data, days	6.9 (1.6)	7.0 (1.6)	6.9 (1.5)
Steps-per-day, steps	7737 (3520)	7828 (3468)	7651 (3568)
Sedentary time standardized to an 18-h day, min/day	810 (83)	810 (85)	810 (80)
Moderate-vigorous physical activity, min/day	22.3 (20.3)	22.5 (19.4)	22.2 (21.2)
Peak respiratory exchange ratio	1.23 (0.09)	1.24 (0.10)	1.21 (0.09)
Peak VO_2, mL/kg/min	23.6 (6.9)	26.2 (6.9)	21.0 (5.9)
% predicted peak VO_2, %	96.7 (20.1)	95.0 (18.5)	98.2 (21.3)
VO_2 at the VAT, mL/kg/min	12.8 (3.7)	13.8 (3.8)	11.9 (3.3)
VO_2 at the VAT as a % of peak VO_2, %	54.6 (7.6)	52.5 (7.0)	56.6 (7.5)
Post-VAT VO_2, mL/kg/min	11.0 (4.1)	12.7 (4.0)	9.4 (3.4)
VO_2/work, mL/kg/min per W	9.0 (0.9)	9.3 (0.9)	8.7 (0.9)
V_E/VCO_2 nadir	27.0 (2.8)	26.4 (2.7)	27.5 (2.8)
Peak oxygen pulse, mL/beat	12.5 (4.0)	15.5 (3.2)	9.6 (2.1)
Mean response time	28.1 (16.4)	25.6 (16.8)	30.4 (15.7)
O_2 uptake efficiency slope	2009 (602)	2421 (519)	1619 (371)
% of maximum predicted heart rate achieved, %	89.6 (9.8)	89.5 (10.2)	89.8 (9.5)
VO_2 recovery half time, s	77.2 (28.6)	69.5 (22.5)	84.5 (31.7)
VO_2 recovery delay, s	9.7 (10.0)	7.7 (8.3)	11.5 (11.1)
Mean arterial pressure at 75 W, mmHg	106 (11)	107 (11)	105 (12)

Characteristics are displayed as mean (standard deviation) for continuous variables or *n* (%) for categorical variables.
VAT, ventilatory anaerobic threshold; V_E/VCO_2, the ratio of minute ventilation to carbon dioxide production; VO_2, oxygen uptake.

by-breath gas exchange data were obtained by metabolic cart (Medgraphics, St. Paul, MN, USA) during four stages of exercise: (i) 2 min of rest, (ii) 3 min of unloaded ('freewheel') exercise, (iii) a maximum incremental ramp (15 or 25 W/min), and (iv) recovery with 3 min of unloaded cycling followed by 1 min of rest. The measurement approach for each CPET variable is detailed in *Table 1*.

Accelerometry assessment of physical activity

Participants attending exam 2 and exam 3 were asked to wear an omnidirectional accelerometer (Actical model no. 198-0200-00; Philips Respironics) for all hours (except when bathing) for 8 days on a belt worn around the waist.[16] Given difficulty in discriminating sleep from waking wear time, participants at exam 3 were asked to remove the device during sleep. Signals within 0.5–3 Hz and accelerations/decelerations of 0.05–2 *g* were grouped into 'counts' or 'steps' at 30-s intervals and averaged over 1 min. Processing of the data and quality control were performed using the SAS programming language and the first day of wear was removed from the dataset.[28] Non-wear time periods were removed and were defined by the Choi algorithm, as periods of consecutive zero counts lasting for at least 90 min with allowance of non-zero counts lasting up to 2 min as long as they were surrounded by 30 min intervals of consecutive zero counts.[29] We further removed 6 consecutive hours of wear with the lowest accumulated counts to exclude potential sleep time that was not removed through application of the Choi algorithm and to account for differences in wear time between the two examinations. 'SED' was defined as <100 counts per minute[30] and reported as a percent of wear time and then standardized to an 18-hour wear day. 'MVPA' was defined by >1535 counts per minute.[31]

Covariate ascertainment

Smoking was defined by self-report as current smokers (having smoked within the 1-year period preceding the study visit), former smokers (prior smoking but none in the last year), and never smokers. We defined diabetes as fasting blood glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, or use of medications for diabetes. Prevalent CVD was characterized as a history of myocardial infarction, stroke, or heart failure, or by self-report of taking medications for angina or chest pain, heart failure, atrial fibrillation or heart rhythm abnormality, stroke, claudication, or

Table 3 Cross-sectional associations of physical activity and cardiopulmonary exercise testing fitness measures

	Sedentary time			Steps/day			Log(moderate-vigorous PA)		
CPET fitness measure	Est. beta	SE	FDR-P	Est. beta	SE	FDR-P	Est. beta	SE	FDR-P
VO_2 kinetics									
Exercise initiation-moderate level									
Mean response time	0.030	0.022	0.20	-0.088	0.023	0.0002	-0.190	0.023	<0.0001
O_2 uptake efficiency slope	-0.035	0.015	0.024	0.122	0.015	<0.0001	0.172	0.016	<0.0001
Log(VO_2 at the VAT)	-0.079	0.017	<0.0001	0.168	0.017	<0.0001	0.205	0.018	<0.0001
VO_2 at the VAT as % of peak VO_2^a	0.023	0.022	0.32	-0.049	0.023	0.038	-0.145	0.023	<0.0001
VO_2/work	-0.084	0.021	0.0001	0.162	0.021	<0.0001	0.220	0.022	<0.0001
Late exercise									
Post-VAT VO_2	-0.051	0.017	0.003	0.144	0.017	<0.0001	0.236	0.017	<0.0001
Peak exercise									
Log(peak VO_2)	-0.078	0.015	<0.0001	0.171	0.015	<0.0001	0.257	0.015	<0.0001
% predicted peak VO_2	-0.103	0.022	<0.0001	0.246	0.021	<0.0001	0.356	0.021	<0.0001
Peak oxygen pulse	-0.042	0.014	0.004	0.130	0.015	<0.0001	0.183	0.015	<0.0001
Exercise recovery									
Square root (VO_2 recovery delay)	0.025	0.022	0.27	-0.076	0.023	0.0012	-0.106	0.023	<0.0001
VO_2 half-time	0.108	0.019	<0.0001	-0.174	0.020	<0.0001	-0.263	0.020	<0.0001
Central cardiac and vascular									
% maximum predicted heart rate	0.010	0.021	0.66	0.003	0.022	0.88	0.074	0.022	0.001
V_E/VCO_2 nadir	0.051	0.021	0.017	-0.044	0.022	0.047	-0.081	0.022	0.0004
Mean arterial pressure at 75 W	-0.038	0.015	0.016	-0.004	0.016	0.81	-0.043	0.016	0.010

Estimated beta coefficients represent the change in standardized CPET fitness measure for a 1-SD change in sedentary time (82.5 min/day standardized to an 18-h day), steps/day (3519 steps/day), or moderate-vigorous PA (1.0 in log moderate-vigorous PA). Models were adjusted for age, sex, cohort, season of device wear, location (New England vs. others), average minutes of device wear (for steps and MVPA), body mass index, resting systolic blood pressure, hypertension medication use, smoking (current/former/never), diabetes, and prevalent cardiovascular disease.
CPET, cardiopulmonary exercise testing; Est., estimated; FDR-P, false discovery rate adjusted *P*-value; PA, physical activity; SD, standard deviations; SE, standard error; VAT, ventilatory anaerobic threshold; V_E/VCO_2, the ratio of minute ventilation to carbon dioxide production; VO_2, oxygen uptake.
[a]Models for peak VO_2 at the VAT as % of peak VO_2 were restricted to individuals reaching a respiratory exchange ratio ≥1.1 ($n = 1917$) to ensure that adequate volitional effort was expended to allow accurate interpretation.

peripheral arterial disease. The 10-year atherosclerotic CVD risk was calculated using the Pooled Cohort Equations.[32]

Statistical analysis

After reviewing variable distributions for normality, peak VO_2, VO_2 at the ventilatory anaerobic threshold (VAT), and MVPA were natural-logarithmically transformed and VO_2 recovery delay was square root transformed prior to analysis to reduce the skewness of these variables. All CPET and PA variables were mean centred and standardized prior to analysis.

We evaluated the cross-sectional associations of CPET (dependent) variables with PA measures at exam 3 (independent variables) using multivariable linear regression models adjusted for age, sex, cohort, season of activity monitor wear (fall: September–November; winter: December–February; spring: March–May; Summer: June–August), location (New England vs. others, to account for geographic weather differences that may affect PA), average minutes of activity monitor wear (for steps and MVPA), body mass index (BMI), resting systolic blood pressure, hypertension medication use, smoking, diabetes, and prevalent CVD. We evaluated for the evidence of effect modification by clinical variables on the associations of PA measures and CPET variables using multiplicative interaction terms and the following categorical variables: age (> or ≤ the median age of 54 years), sex, BMI (three level categorical variable: <25, 25 to <30, and ≥30 kg/m^2), prevalent CVD or diabetes vs. those without prevalent CVD or diabetes, and CVD risk score (three-level categorical variable based on sex-specific tertiles from the Pooled Cohort Equations: for women <0.8%, 0.8–2.2%, and >2.2%; for men <3.4%, 3.4–7.7%, and >7.7%). Non-linearity of the relation of PA measures with peak VO_2 was assessed by examining the visual fit of generalized additive models with flexible splines for PA measures. To measure the associations of domains of cardiorespiratory fitness with changes in PA between exam 2 and exam 3 (defined as the exam 3–exam 2 value), linear regression models were constructed using covariate values at exam 3 with additional adjustment for the exam 2 (baseline) PA measure, interval between exams 2 and 3, and discordant season (which was defined as a binary variable with a value of '1' assigned if the accelerometer was worn for the summer months for one assessment and the winter months for the other and was otherwise assigned a value of '0').

A 5% false discovery rate (FDR; Benjamini–Hochberg) was used to determine statistical significance. All analyses were performed with R (The R Foundation for Statistical Computing, version 4.0.3; Vienna, Austria; http://www.rproject.org).

Results

Study sample characteristics

The characteristics of the study sample are shown in *Table 2*. The analytic sample ($n = 2070$) had a mean age of 54 ± 9 years and was

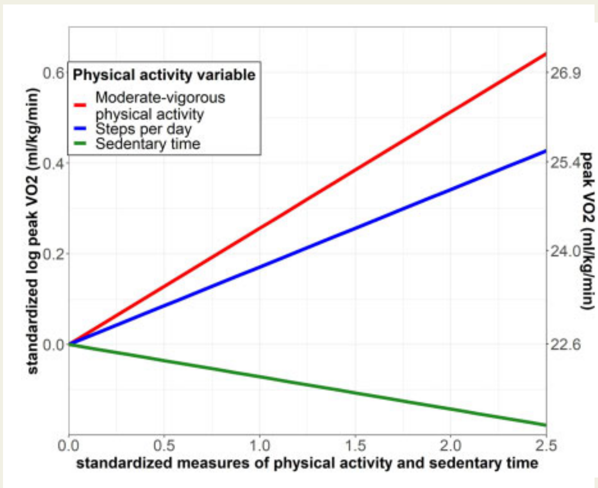


Figure 1 Relative associations of physical activity measures with cardiorespiratory fitness (peak oxygen uptake [VO_2]). Overlaid added variable plots are displayed for the association of standardized log(peak VO_2) and standardized steps per day, log(moderate-vigorous physical activity), and sedentary time. Each line was fitted individually adjusting for age, sex, cohort, season of device wear, location (New England/other), average minutes of device wear (except for sedentary time), body mass index, resting systolic blood pressure, hypertension medication use, smoking (current/former/never), diabetes, and prevalent cardiovascular disease.

evenly split between men and women, and the mean BMI was 28.0 ± 5.3 kg/m^2. Accelerometers were worn for an average of 14.2 ± 1.2 h/day, and participants took 7737 ± 3520 steps/day and spent 22 ± 20 min/day performing MVPA and 13.5 ± 1.4 h/day (standardized to an 18-h day) sedentary.

Associations of physical activity measures with multi-domain measures of cardiorespiratory fitness

Each PA measure demonstrated a modest linear relation with peak cardiorespiratory fitness (peak VO_2) in unadjusted analyses (Supplementary material online, *Figure S1*). In multivariable models adjusted for clinical risk factors, statistically significant associations for PA measures with different domains of fitness were observed (*Table 3*). Each of the PA measures was associated with VO_2 responses reflecting different components of exercise: initiation-moderate level, late exercise, peak exercise, and recovery (FDR <5% for all, *Table 3*). Notably, while steps/day was associated with numerous VO_2 measures, it was not significantly associated with heart rate or blood pressure exercise responses. The effect size for a 1-SD higher MVPA was greater for each of the fitness responses compared with SED and steps. A 5% higher peak VO_2 (corresponding to 1.18 mL/kg/min relative to the mean) was associated with daily averages of 96% higher MVPA [95% confidence interval (CI) 82–113%; e.g. 22 min more relative to the sample mean], 3458 more steps (95% CI 2942–4193; expected to take 40 min, assuming an average cadence of 80 steps/min[33]), and 182 min less SED (95% CI 131–301) (*Figure 1*). We did not observe clinically significant non-linearity in the association of the PA measures with peak VO_2 visually or by comparison of the model fit of linear vs. flexible regression models.

We then evaluated whether PA measures were complementary (i.e. additive) in their relations to peak VO_2. The marginal mean peak VO_2 was estimated for individuals with high vs. low values (in relation to the approximate sample means) for each of the three PA measures (*Figure 2*). Higher peak VO_2 values were observed in groups with greater than average steps/day or MVPA and low SED. Intriguingly, individuals with low steps/day or MVPA displayed estimated peak VO_2 values below the mean regardless of whether they had high or low SED, whereas individuals with high steps or MVPA demonstrated peak VO_2 values above the mean even with high SED.

Finally, to assess whether the associations of PA and fitness measures differed across categories of clinical variables, we evaluated for effect modification by age, sex, BMI, prevalent CVD or diabetes, and CVD risk (Supplementary material online, *Table S2*). Despite several significant interactions, the key findings were largely consistent across clinical categories (Supplementary material online, *Table S2* and Supplementary material online, *Figure S2*). We did, however, observe the evidence of effect modification by sex on the association of SED and peak VO_2, such that each 1-SD higher SED was associated with a larger decrement in the observed peak VO_2 in women compared with men (Supplementary material online, *Figure S2F*).

Associations of changes in physical activity measures over time and cardiorespiratory fitness

Next, we evaluated the associations of changes in PA measures over a median interval of 7.8 years (25th–75th percentile 7.5–8.1 years) in 1720 individuals who attended both exams 2 and 3 and had complete accelerometry and CPET measures (Supplementary material online, *Table S3*). Changes in PA measures were not associated with heart rate or blood pressure responses during exercise but were reflected in metrics of VO_2 kinetics in different domains of exercise (*Table 4*). Increases in average steps/day or MVPA and reductions in SED between the two exam cycles were related to favourable measures of each exercise domain, with the largest effect size observed for MVPA (*Table 4*). Overall, increases of 17 min of MVPA/day (95% CI 14–21) or 4312 steps/day (95% CI 3439–5781; ≈54 min at 80 steps/min), or reductions of 249 min of SED per day (95% CI 149–777) between the two exam cycles corresponded to a 5% higher peak VO_2 (i.e. 1.18 mL/kg/min relative to the mean).

Lastly, we estimated the marginal mean log peak VO_2 for individuals with PA values above or below the approximate sample mean at the two exam cycles (*Figure 3*). There was a stepwise increase in peak VO_2 from individuals with low steps/MVPA (or high SED) at both exams 2 and 3, to high steps/MVPA (or low SED) at one exam, to high steps/MVPA (or low SED) at both exam cycles. Notably, peak VO_2 was similar in the groups with high steps/MVPA (or low SED) at one of the exam cycles, regardless of whether it was the current exam when CPET was performed (exam 3) or the previous exam (exam 2).

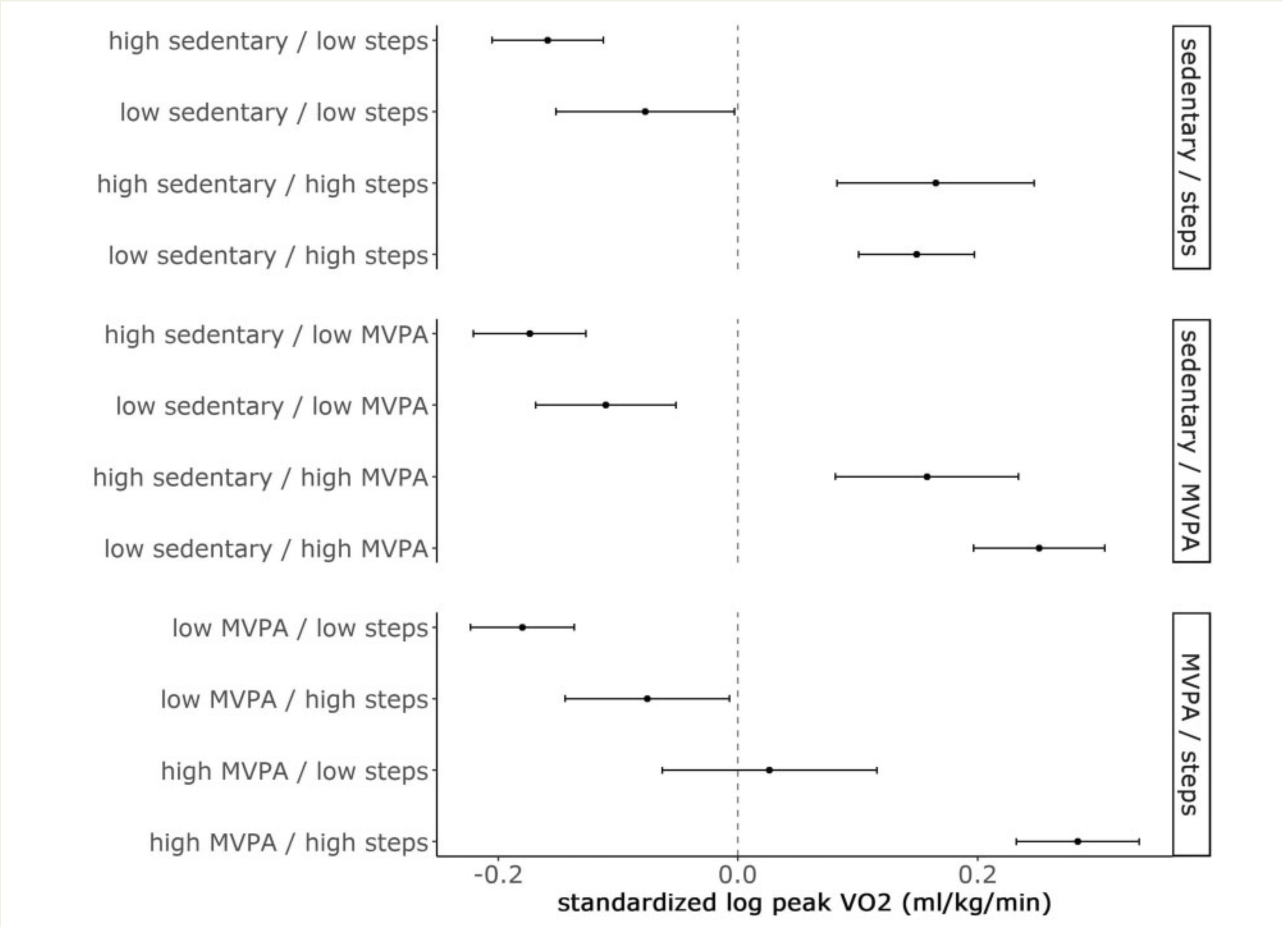


Figure 2 Marginal means of peak oxygen uptake (VO_2) by categories of high or low physical activity measures. The estimated marginal means of standardized log(peak VO_2) and 95% confidence intervals were plotted for each category of high or low physical activity measures defined as the following: sedentary time, <821 vs. ≥821 min; steps/day, <7500 vs. ≥7500 steps; moderate-vigorous physical activity, >21 vs. ≤21 min/day. Each marginal mean was fitted individually adjusting for age, sex, cohort, season of device wear, location (New England/other), average minutes of device wear (except for sedentary time), body mass index, resting systolic blood pressure, hypertension medication use, smoking (current/former/never), diabetes, and prevalent cardiovascular disease.

Discussion

The principal findings of our study are three-fold. First, in a large sample of community-dwelling individuals, we defined relative associations between three measures of routine PA (MVPA, steps, SED) and multiple dimensions of cardiorespiratory fitness. MVPA had the highest effect size for exercise response patterns throughout exercise relative to total steps/day and SED. Specifically, for each minute of increase in average MVPA, >3 min of intermediate cadence walking and >14 min less SED would be required for the equivalent changes in fitness. Second, we observed linearity in associations of PA measures and peak VO_2 and broad consistency of the associations among categories of age, sex, obesity, and CVD status. Third, the relation of steps and MVPA with peak VO_2 was additive, such that the highest peak VO_2 was observed in individuals with higher values for both MVPA and steps/day. Interestingly, higher activity levels (both moderate-to-vigorous and total activity by steps/day) were associated with greater than average fitness levels regardless of the amount of SED, and above average PA at 8 years prior to CPET and at the time of CPET similarly influenced fitness. Collectively, these findings not only provide a detailed assessment of the relation of PA to precise measures of fitness but are also consistent with the notion that antecedent PA and maintenance of PA over time (specifically MVPA) may preserve cardiorespiratory fitness.

Greater PA has been associated with higher levels of cardiorespiratory fitness,[34,35] but prior reports were mostly limited by relatively narrow inclusion criteria, small sample sizes, and lack of objective measurement of both PA and fitness. Detailed physiologic studies have demonstrated that physical inactivity (modeled as prolonged bedrest leading to both high SED and minimal PA) has a powerful deleterious effect on cardiovascular function and fitness.[36] Conversely, in sedentary middle-aged individuals, supervised exercise training can result in significant benefits in fitness.[37] Recently, investigators demonstrated that higher self-reported MVPA was associated with attenuation of age-related declines in peak VO_2 in ≈1500 middle-aged, community-dwelling individuals.[38] By relating different

Table 4 Associations of change in physical activity measures from exam 2 to exam 3 with cardiopulmonary exercise testing fitness measures at exam 3

CPET fitness measure	Δ Sedentary time			Δ Steps/day			Δ Moderate-vigorous PA		
	Est. beta	SE	FDR-P	Est. beta	SE	FDR-P	Est. beta	SE	FDR-P
Oxygen uptake kinetics									
Exercise initiation-moderate level									
Mean response time	0.019	0.027	0.53	-0.068	0.030	0.041	-0.170	0.028	<0.0001
$O_{2\ uptake}$ efficiency slope	-0.009	0.019	0.65	0.102	0.021	<0.0001	0.146	0.019	<0.0001
Log(VO_2 at the VAT)	-0.052	0.021	0.026	0.152	0.023	<0.0001	0.185	0.021	<0.0001
VO_2 at the VAT as % of peak VO_2[a]	-0.001	0.026	0.97	-0.049	0.031	0.15	-0.079	0.028	0.010
VO_2/work	-0.069	0.026	0.013	0.170	0.029	<0.0001	0.175	0.026	<0.0001
Late exercise									
Post-VAT VO_2	-0.038	0.021	0.10	0.139	0.023	<0.0001	0.198	0.021	<0.0001
Peak exercise									
Log(peak VO_2)	-0.054	0.019	0.008	0.158	0.021	<0.0001	0.206	0.018	<0.0001
% predicted peak VO_2	-0.066	0.026	0.023	0.225	0.029	<0.0001	0.292	0.026	<0.0001
Peak oxygen pulse	-0.029	0.018	0.14	0.127	0.020	<0.0001	0.166	0.018	<0.0001
Exercise recovery									
Square root (VO_2 recovery delay)	0.040	0.027	0.18	-0.071	0.030	0.032	-0.096	0.028	0.001
VO_2 half-time	0.092	0.024	0.0003	-0.177	0.027	<0.0001	-0.177	0.025	<0.0001
Central cardiac and vascular									
% maximum predicted heart rate	0.028	0.026	0.32	-0.038	0.029	0.23	0.003	0.027	0.93
V_E/VCO_2 nadir	0.038	0.026	0.18	-0.043	0.029	0.18	-0.030	0.027	0.31
Mean arterial pressure at 75 W	-0.033	0.019	0.120	-0.012	0.021	0.61	-0.046	0.020	0.032

Estimated beta coefficients represent the change in standardized CPET fitness measure for a 1-SD change in sedentary time (80.1 min/day standardized to an 18-h day), steps/day (4044 steps), or moderate-vigorous PA (20.7 min/day). Models were adjusted for age, sex, exam 2 PA measure, interval between exams, cohort, season of device wear, location (New England vs. others), discordant season, average minutes of device wear (for steps and moderate-vigorous PA), body mass index, resting systolic blood pressure, hypertension medication use, smoking (current/former/never), diabetes, and prevalent cardiovascular disease.
CPET, cardiopulmonary exercise testing; Est., estimated; SE, standard error; FDR-P, false discovery rate adjusted *P*-value; PA, physical activity; SD, standard deviations; VAT, ventilatory anaerobic threshold; VO_2, oxygen uptake; V_E/VCO_2, the ratio of minute ventilation to carbon dioxide production.
[a]Models for peak VO_2 at the VAT as % of peak VO_2 were restricted to individuals reaching a respiratory exchange ratio ≥1.1 (*n* = 1597) to ensure that adequate volitional effort was expended to allow accurate interpretation.

forms of objectively measured PA (SED, steps/day, MVPA) to multiple domains of VO_2 during exercise, our study builds on these prior reports and demonstrates that routine PA modalities (as opposed to dedicated exercise training, *per se*) are important in building and maintaining cardiorespiratory fitness throughout the life course.

Peak VO_2 is considered the gold standard measure of cardiorespiratory fitness and is closely related to health outcomes across the entire spectrum of health and disease.[39] In our sample, relative amounts of MVPA, moderate walking, and reduction in SED were associated with a clinically meaningful difference in fitness (>1–1.2 mL/kg/min of VO_2 relative to the mean peak VO_2 of 23.6 mL/kg/min) among community-dwelling middle-aged adults. Importantly, MVPA was linearly related to peak VO_2, indicating that while the guideline-recommended thresholds (≥150 min/week of MVPA[22,40]) may be a reasonable benchmark (and closely approximated mean MVPA levels of 156 min/week observed in our cohort), higher levels of MVPA would be expected to result in continued improvements in physical fitness with >3- and >14-fold greater efficiency in achieving higher fitness levels than moderate walking or reducing sedentary time. These associations were consistent among categories of age, sex, BMI, and CVD status, reinforcing the message that PA is associated with higher levels of fitness across age and health status.

A unique aspect of this study is the availability of PA measures across two times over nearly a decade, necessary to understand the benefits of maintenance of activity over time on cardiorespiratory fitness. Individuals with persistently low activity levels (or high SED) had lower cardiorespiratory fitness relative to individuals who displayed an improvement in activity levels over time, though we did not observe differences in peak VO_2 in those individuals with discordant MVPA at the two exam cycles (e.g. high MVPA at exam 2/low MVPA at exam 3 vs. low MVPA at exam 2/high MVPA at exam 3). Our findings suggest that cumulative exposure to PA may be related to long-term fitness levels.[41]

In addition to peak VO_2, we observed associations of PA measures with numerous CPET variables reflecting VO_2 during initiation-moderate level exercise, late exercise, peak exercise, and recovery. While MVPA would be expected to promote adaptation to high-intensity peak exercise (e.g. peak VO_2), we found higher relative effect sizes for MVPA compared to steps or SED in relation to CPET variables reflecting VO_2 throughout exercise, suggesting that MVPA may promote global adaptation to all intensity levels of exercise. Each

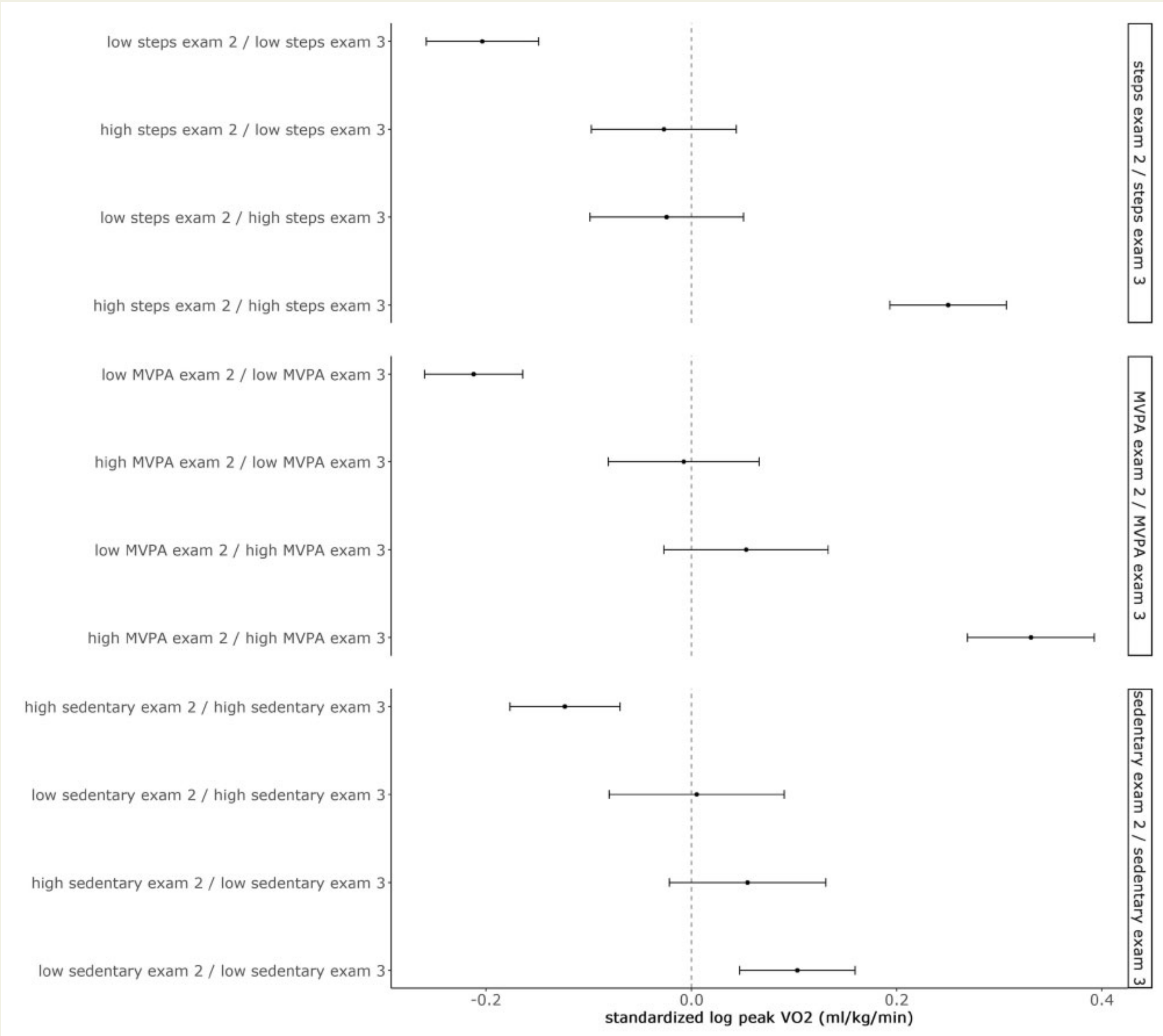


Figure 3 Marginal means of peak oxygen uptake (VO_2) by categories of high or low physical activity measures at examinations 2 and 3. The estimated marginal means of peak VO_2 (log transformed and standardized) with 95% confidence intervals were plotted for each category of high or low physical activity measures defined as the following: sedentary time, <821 vs. ≥821 min; steps/day, <7500 vs. ≥7500 steps; moderate-vigorous physical activity, >21 vs. ≤21 min/day. The marginal means were estimated by linear models adjusted for age, sex, cohort, season of device wear, location (New England/others), average minutes of device wear (except for sedentary time), body mass index, resting systolic blood pressure, hypertension medication use, smoking (current/former/never), diabetes, and prevalent cardiovascular disease.

form of PA was associated with CPET measures of VO_2 kinetics, but were less reliably associated with simple hemodynamic measures such as heart rate and blood pressure responses. While peak global cardiorespiratory fitness (peak VO_2) is closely related to changes in PA over time, it requires peak volitional effort for accurate ascertainment. Submaximal measures of VO_2 kinetics may therefore serve as sensitive measures (i.e. biomarkers) of the physiologic benefits of discrete PA interventions.

Our study has several limitations. The cross-sectional associations of PA with fitness measures may be affected by reverse causation. For example, individuals with lower fitness levels may be less likely (or unable) to perform PA. By investigating the associations of changes in PA over 8 years with fitness measures, the issue of reverse causation is partially addressed, but we still cannot exclude the potential for residual confounding by other determinants of health status that may simultaneously impact cardiorespiratory fitness and the propensity for PA. Our findings should be interpreted as cross-sectional associations; the precise mechanisms explaining the relations of greater PA and higher fitness should be assessed using different study designs and may include formal mediation analysis. Our sample was mostly middle-aged. Therefore, while we tested for effect modification by age, we cannot exclude that the associations of PA with fitness differ at the extremes of age. Moreover, our sample comprised community-dwelling, middle-aged individuals who displayed, on average, lower than expected fitness levels; whether these relations differ in more fit individuals should be explored in future studies. One potential explanation for the lower-than-expected peak VO_2 values is the use of cycle exercise, which is recognized to result in lower peak VO_2 measures compared to treadmill exercise.[42] Finally, our sample was primarily of European descent and generalizability to other populations is therefore unknown.

In conclusion, lower SED, and greater steps/day and MVPA (and their changes over time) were each associated with better cardiorespiratory fitness measures. The highest effect estimate was observed for MVPA, which was associated with favourable CPET fitness measures throughout various intensity levels of incremental exercise (i.e. from initiation to recovery). These findings are consistent with the notion that different forms of PA (especially MVPA) are associated with cardiorespiratory fitness in the general public regardless of one's age, sex, BMI, or CVD status. In addition, our data provide information regarding the relative modifiability of specific exercise responses and permit scaling of relative changes in SED, steps/day, and MVPA required to improve fitness.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The Framingham Heart Study is supported by the National Heart, Lung and Blood Institute (NHLBI) (Contracts N01-HC-25195, HHSN26 8201500001I, and 75N92019D00031). This work was supported by NIH grants K23-HL138260 (M.N.) and R01-HL131029 (R.S.V. and G.D.L.) and AHA grant 15GPSGC24800006 (G.D.L.). M.N. is supported by a Career Investment Award from the Department of Medicine, Boston University School of Medicine. R.S.V. is supported in part by the Evans Medical Foundation and the Jay and Louis Coffman Endowment from the Department of Medicine, Boston University School of Medicine.

Conflict of interest: R.V.S. is supported in part by grants from the National Institutes of Health and the American Heart Association. In the past 12 months, R.V.S. has served as a consultant for Myokardia (ongoing) and Best Doctors (ongoing), receives research funding from Amgen (concluded), and had minor stock holdings in Gilead, and his spouse has current stock holdings in Pfizer. R.V.S. is a co-inventor on a patent for ex-RNAs signatures of cardiac remodelling. G.D.L. acknowledges research funding from the National Institutes of Health and the American Heart Association as well as Amgen, Cytokinetics, Applied Therapeutics, AstraZeneca, and Sonivie in relation to projects and clinical trials investigating exercise capacity that are distinct from this work. He has served as a scientific advisor for Pfizer, Merck, Boehringer-Ingelheim, Novartis, American Regent, Relypsa, Cyclerion, Cytokinetics, and Amgen and receives royalties from UpToDate for scientific content authorship related to exercise physiology. N.L.S. acknowledges research support from the Alzheimer's Association and has also received funding from Novo Nordisk for a MD-initiated research grant unrelated to the current paper. J.M.M. has served as a guest lecturer/consultant at Merck. The other authors report no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author. FHS data are made publicly available and can be accessed through the National Institutes of Health database of genotypes and phenotypes (https://www.ncbi. nlm.nih.gov/gap/).

References

1. Lin H, Sardana M, Zhang Y, Liu C, Trinquart L, Benjamin EJ, Manders ES, Fusco K, Kornej J, Hammond MM, Spartano NL, Pathiravasan CH, Kheterpal V, Nowak C, Borrelli B, Murabito JM, McManus DD. Association of habitual physical activity with cardiovascular disease risk. *Circ Res* 2020;**127**:1253–1260.
2. Chen GC, Qi Q, Hua S, Moon JY, Spartano NL, Vasan RS, Sotres-Alvarez D, Castaneda SF, Evenson KR, Perreira KM, Gallo LC, Pirzada A, Diaz KM, Daviglus ML, Gellman MD, Kaplan RC, Xue X, Mossavar-Rahmani Y. Accelerometer-assessed physical activity and incident diabetes in a population covering the adult life span: the Hispanic Community Health Study/Study of Latinos. *Am J Clin Nutr* 2020;**112**:1318–1327.
3. Whitaker KM, Pettee Gabriel K, Buman MP, Pereira MA, Jacobs DR, Jr., Reis JP, Gibbs BB, Carnethon MR, Staudenmayer J, Sidney S, Sternfeld B. Associations of accelerometer-measured sedentary time and physical activity with prospectively assessed cardiometabolic risk factors: the CARDIA study. *J Am Heart Assoc* 2019; **8**:e010212.
4. LaCroix AZ, Bellettiere J, Rillamas-Sun E, Di C, Evenson KR, Lewis CE, Buchner DM, Stefanick ML, Lee IM, Rosenberg DE, LaMonte MJ; for the Women's Health Initiative (WHI). Association of light physical activity measured by accelerometry and incidence of coronary heart disease and cardiovascular disease in older women. *JAMA Netw Open* 2019;**2**:e190419.
5. Huai P, Han H, Reilly KH, Guo X, Zhang J, Xu A. Leisure-time physical activity and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Endocrine* 2016;**52**:226–230.
6. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 2002;**347**:716–725.
7. Wang Y, Nie J, Ferrari G, Rey-Lopez JP, Rezende LFM. Association of physical activity intensity with mortality: a national cohort study of 403 681 US adults. *JAMA Intern Med* 2021;**181**:203–211.
8. Zhao M, Veeranki SP, Li S, Steffen LM, Xi B. Beneficial associations of low and large doses of leisure time physical activity with all-cause, cardiovascular disease and cancer mortality: a national cohort study of 88,140 US adults. *Br J Sports Med* 2019;**53**:1405–1411.
9. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, Whincup P, Diaz KM, Hooker SP, Chernofsky A, Larson MG, Spartano N, Vasan RS, Dohrn IM, Hagstromer M, Edwardson C, Yates T, Shiroma E, Anderssen SA, Lee IM. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ* 2019;**366**:l4570.
10. Lee IM, Shiroma EJ, Evenson KR, Kamada M, LaCroix AZ, Buring JE. Accelerometer-measured physical activity and sedentary behavior in relation to all-cause mortality: the women's health study. *Circulation* 2018;**137**:203–205.
11. Kikuchi H, Inoue S, Lee IM, Odagiri Y, Sawada N, Inoue M, Tsugane S. Impact of moderate-intensity and vigorous-intensity physical activity on mortality. *Med Sci Sports Exerc* 2018;**50**:715–721.
12. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, Casanova A, Swaminathan S, Anjana RM, Kumar R, Rosengren A, Wei L, Yang W, Chuangshi W, Huaxing L, Nair S, Diaz R, Swidon H, Gupta R, Mohammadifard N, Lopez-Jaramillo P, Oguz A, Zatonska K, Seron P, Avezum A, Poirier P, Teo K, Yusuf S. The effect of physical activity on mortality and cardiovascular disease in 130000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet* 2017;**390**:2643–2654.
13. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of moderate to vigorous physical activity on all-cause mortality in middle-aged and older Australians. *JAMA Intern Med* 2015;**175**:970–977.
14. Tremblay A, Després JP, Leblanc C, Craig CL, Ferris B, Stephens T, Bouchard C. Effect of intensity of physical activity on body fatness and fat distribution. *Am J Clin Nutr* 1990;**51**:153–157.
15. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ* 2006;**174**:801–809.
16. Spartano NL, Stevenson MD, Xanthakis V, Larson MG, Andersson C, Murabito JM, Vasan RS. Associations of objective physical activity with insulin sensitivity and circulating adipokine profile: the Framingham Heart Study. *Clin Obes* 2017;**7**: 59–69.
17. Qi Q, Strizich G, Merchant G, Sotres-Alvarez D, Buelna C, Castaneda SF, Gallo LC, Cai J, Gellman MD, Isasi CR, Moncrieft AE, Sanchez-Johnsen L, Schneiderman N, Kaplan RC. Objectively measured sedentary time and cardiometabolic biomarkers in US Hispanic/Latino adults: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Circulation* 2015;**132**:1560–1569.

18. Andersson CL, Lyass A, Larson MG, Spartano NL, Vita JA, Benjamin EJ, Murabito JM, Esliger DW, Blease SJ, Hamburg NM, Mitchell GF, Vasan RS. Physical activity measured by accelerometry and its associations with cardiac structure and vascular function in young and middle aged adults. *J Am Heart Assoc* 2015;**4**:e001528.
19. Parvathaneni K, Surapaneni A, Ballew SH, Palta P, Rebholz CM, Selvin E, Coresh J, Grams ME. Association between midlife physical activity and incident kidney disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis* 2021;**77**:74–81.
20. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, Keadle SK, Arem H, Berrington de Gonzalez A, Hartge P, Adami HO, Blair CK, Borch KB, Boyd E, Check DP, Fournier A, Freedman ND, Gunter M, Johannson M, Khaw KT, Linet MS, Orsini N, Park Y, Riboli E, Robien K, Schairer C, Sesso H, Spriggs M, Van Dusen R, Wolk A, Matthews CE, Patel AV. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med* 2016;**176**:816–825.
21. Spartano NL, Demissie S, Himali JJ, Dukes KA, Murabito JM, Vasan RS, Beiser AS, Seshadri S. Accelerometer-determined physical activity and cognitive function in middle-aged and older adults from two generations of the Framingham Heart Study. *Alzheimers Dement (N Y)* 2019;**5**:618–626.
22. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The physical activity guidelines for Americans. *JAMA* 2018;**320**: 2020–2028.
23. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB, Sr., Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D. The third generation cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol* 2007;**165**:1328–1335.
24. Abraham TM, Massaro JM, Hoffmann U, Yanovski JA, Fox CS. Metabolic characterization of adults with binge eating in the general population: the Framingham Heart Study. *Obesity* 2014;**22**:2441–2449.
25. Shah RV, Schoenike MW, Armengol de la Hoz MA, Cunningham TF, Blodgett JB, Tanguay M, Sbarbaro JA, Nayor M, Rouvina J, Kowal A, Houstis N, Baggish AL, Ho JE, Hardin C, Malhotra R, Larson MG, Vasan RS, Lewis GD. Metabolic cost of exercise initiation in patients with heart failure with preserved ejection fraction vs community-dwelling adults. *JAMA Cardiol* 2021;**6**:653–660.
26. Nayor M, Xanthakis V, Tanguay M, Blodgett JB, Shah RV, Schoenike M, Sbarbaro J, Farrell R, Malhotra R, Houstis NE, Velagaleti RS, Moore SA, Baggish AL, O'Connor GT, Ho JE, Larson MG, Vasan RS, Lewis GD. Clinical and hemodynamic associations and prognostic implications of ventilatory efficiency in patients with preserved left ventricular systolic function. *Circ Heart Fail* 2020;**13**: e006729.
27. Nayor M, Shah RV, Miller PE, Blodgett JB, Tanguay M, Pico AR, Murthy VL, Malhotra R, Houstis NE, Deik A, Pierce KA, Bullock K, Dailey L, Velagaleti RS, Moore SA, Ho JE, Baggish AL, Clish CB, Larson MG, Vasan RS, Lewis GD. Metabolic architecture of acute exercise response in middle-aged adults in the community. *Circulation* 2020;**142**:1905–1924.
28. Glazer NL, Lyass A, Esliger DW, Blease SJ, Freedson PS, Massaro JM, Murabito JM, Vasan RS. Sustained and shorter bouts of physical activity are related to cardiovascular health. *Med Sci Sports Exerc* 2013;**45**:109–115.
29. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. *Med Sci Sports Exerc* 2011;**43**:357–364.
30. Wong SL, Colley R, Connor Gorber S, Tremblay M. Actical accelerometer sedentary activity thresholds for adults. *J Phys Act Health* 2011;**8**:587–591.
31. Colley RC, Tremblay MS. Moderate and vigorous physical activity intensity cut-points for the Actical accelerometer. *J Sports Sci* 2011;**29**:783–789.
32. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**:S49–73.
33. Tudor-Locke C, Han H, Aguiar EJ, Barreira TV, Schuna JM, Jr., Kang M, Rowe DA. How fast is fast enough? Walking cadence (steps/min) as a practical estimate of intensity in adults: a narrative review. *Br J Sports Med* 2018;**52**:776–788.
34. Kulinski JP, Khera A, Ayers CR, Das SR, de Lemos JA, Blair SN, Berry JD. Association between cardiorespiratory fitness and accelerometer-derived physical activity and sedentary time in the general population. *Mayo Clin Proc* 2014;**89**: 1063–1071.
35. Dehn MM, Bruce RA. Longitudinal variations in maximal oxygen intake with age and activity. *J Appl Physiol* 1972;**33**:805–807.
36. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas Bedrest and Training Study: I. Effect of age on the cardiovascular response to exercise. *Circulation* 2001;**104**: 1350–1357.
37. Howden EJ, Sarma S, Lawley JS, Opondo M, Cornwell W, Stoller D, Urey MA, Adams-Huet B, Levine BD. Reversing the cardiac effects of sedentary aging in middle age—a randomized controlled trial: implications for heart failure prevention. *Circulation* 2018;**137**:1549–1560.
38. Letnes JM, Dalen H, Aspenes ST, Salvesen O, Wisloff U, Nes BM. Age-related change in peak oxygen uptake and change of cardiovascular risk factors. The HUNT Study. *Prog Cardiovasc Dis* 2020;**63**:730–737.
39. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisloff U; American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as aa clinical vital sign: a scientific statement from the American Heart Association. *Circulation* 2016;**134**:e653–e699.
40. Pelliccia A, Sharma S, Gati S, Back M, Borjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M; ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;**42**:17–96.
41. Shortreed SM, Peeters A, Forbes AB. Estimating the effect of long-term physical activity on cardiovascular disease and mortality: evidence from the Framingham Heart Study. *Heart* 2013;**99**:649–654.
42. Maeder M, Wolber T, Atefy R, Gadza M, Ammann P, Myers J, Rickli H. Impact of the exercise mode on exercise capacity: bicycle testing revisited. *Chest* 2005;**128**: 2804–2811.
43. Chatterjee NA, Murphy RM, Malhotra R, Dhakal BP, Baggish AL, Pappagianopoulos PP, Hough SS, Semigran MJ, Lewis GD. Prolonged mean VO2 response time in systolic heart failure: an indicator of impaired right ventricular-pulmonary vascular function. *Circ Heart Fail* 2013;**6**:499–507.
44. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;**60**:2020–2027.
45. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984;**129**:S49–55.
46. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema K, Sun XG, Whipp BJ. Principles of Exercise Testing and Interpretation. 5th edition ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2012. p. 154–178.
47. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 2001;**37**:153–156.
48. Weatherald J, Sattler C, Garcia G, Laveneziana P. Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. *Eur Respir J* 2018;51.
49. Baratto C, Caravita S, Faini A, Perego GB, Senni M, Badano LP, Parati G. Impact of COVID-19 on exercise pathophysiology. A combined cardiopulmonary and echocardiographic exercise study. *J Appl Physiol* (1985) 2021.