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Physical activity volume, intensity, and incident cardiovascular disease

Paddy C. Dempsey [1,2,3,4]*, Alex V. Rowlands [1,4†], Tessa Strain [2†], Francesco Zaccardi [1,5], Nathan Dawkins [1,6], Cameron Razieh [1,4,5], Melanie J. Davies [1,4], Kamlesh K. Khunti [1,5], Charlotte L. Edwardson [1,4], Katrien Wijndaele [2†], Soren Brage [2†], and Tom Yates [1,4†]

[1]Diabetes Research Centre, College of Life Sciences, University of Leicester, Gwendolen Road, Leicester, LE54PW, UK; [2]MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK; [3]Baker Heart and Diabetes Institute, Melbourne, Australia; [4]NIHR Leicester Biomedical Research Centre, Leicester, UK; [5]Leicester Real World Evidence Unit, Diabetes Research Centre, University of Leicester, Leicester, UK; and [6]School of Social and Health Sciences, Leeds Trinity University, Leeds, UK

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Abstract

Aims The interplay between physical activity (PA) volume and intensity is poorly understood in relation to cardiovascular disease (CVD) risk. This study aimed to investigate the role of PA intensity, over and above volume, in relation to incident CVD.

Methods and results Data were from 88 412 UK Biobank middle-aged adults (58% women) without prevalent CVD who wore accelerometers on their dominant wrist for 7 days, from which we estimated total PA energy expenditure (PAEE) using population-specific validation. Cox proportional hazards regressions modelled associations between PAEE (kJ/kg/day) and PA intensity (% MVPA; the fraction of PAEE accumulated from moderate-to-vigorous-intensity PA) with incident CVD (ischaemic heart disease or cerebrovascular disease), adjusted for potential confounders. There were 4068 CVD events during 584 568 person-years of follow-up (median 6.8 years). Higher PAEE and higher %MVPA (adjusted for PAEE) were associated with lower rates of incident CVD. In interaction analyses, CVD rates were 14% (95% confidence interval: 5–23%) lower when MVPA accounted for 20% rather than 10% of 15 kJ/kg/d PAEE; equivalent to converting a 14 min stroll into a brisk 7 min walk. CVD rates did not differ significantly between values of PAEE when the %MVPA was fixed at 10%. However, the lowest CVD rates were observed for combinations of both higher PAEE and %MVPA.

Conclusion Reductions in CVD risk may be achievable through higher PA volume and intensity, with the role of moderately intense PA appearing particularly important. This supports multiple approaches or strategies to PA participation, some of which may be more practical or appealing to different individuals.

* Corresponding author. Email: paddy.dempsey@mrc-epid.cam.ac.uk
† Formed the core working group along with the first author and contributed equally to the work.

Structured Graphical Abstract

Key Question

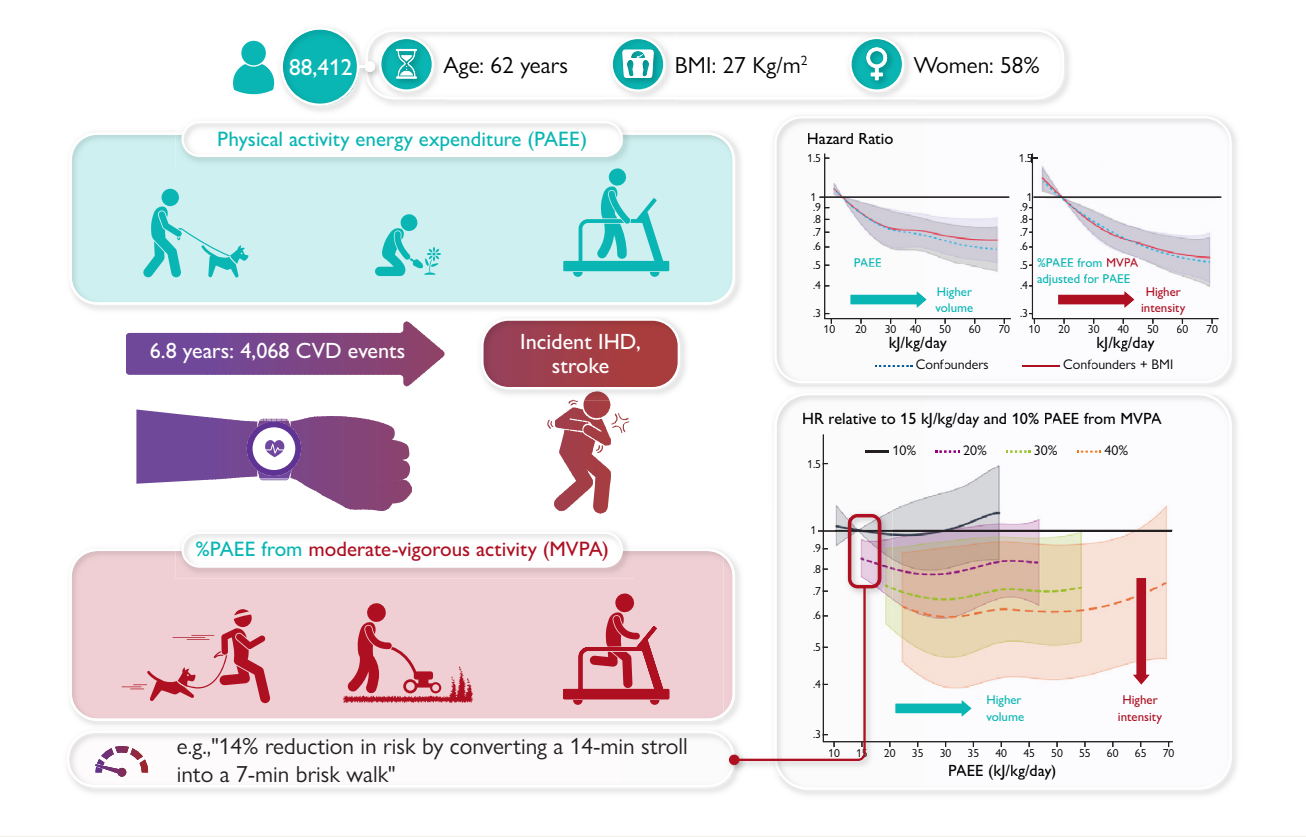
What is the association between device-based physical activity volume and intensity with cardiovascular disease (CVD)? Does physical activity energy expenditure (PAEE) derived from moderate to vigorous activity confer any additional benefits to incident CVD risk?

Key Finding

Higher volumes of PAEE were associated with lower CVD risk, while achieving the same PAEE through higher intensity activity was associated with even greater benefits. Achieving both was optimal.

Take Home Message

Findings support simple behaviour-change messages that encourage increasing overall physical activity, and if possible, doing so by incorporating more moderately intense activities (converting a short stroll into a brisk walk).



Keywords Physical activity • Exercise • Intensity • Volume • Accelerometer • Cardiovascular disease • Mortality

Introduction

Regular physical activity (PA), particularly moderate-to-vigorous intensity PA (MVPA), is associated with a myriad of health benefits, including lower risk of cardiovascular disease (CVD), cancer, and all-cause mortality.[1–3] However, epidemiological evidence used to inform current PA guidelines has relied mostly on self-reported estimates of leisure-time PA or aerobic MVPA,[4–6] which comprise only a very small proportion of the day and are prone to recall bias and measurement error.[7,8] In contrast, device-based measures of PA can more accurately capture sporadic activity of different intensities throughout the whole waking day, which could enable more specific, targeted, or indeed more flexible PA recommendations.

Several cohort studies are now starting to report findings on the associations between device-based measures of PA with mortality,[9–13]

but fewer have examined associations with CVD risk. In these studies, higher durations of PA volume and/or time spent in MVPA have been associated with lower risks of incident CVD.[14–17] However, it is not clear whether the intensity of the activity is important, or whether simply that undertaking large durations of MVPA contributes to a high overall PA volume. In other words, are there similar CVD health benefits to accumulating the same PA volume via a large amount of light-intensity PA (e.g. 'pottering about'), or through short periods of higher intensity PA (e.g. 'an exerciser' or 'active commuter'). Elucidating these relationships can be challenging, since PA volume is, by definition, intensity multiplied by time, making volume and intensity intrinsically linked as nested constructs (i.e. intensity within volume). Indeed, simultaneously analysing total PA and MVPA, whether expressed as volume or duration, is problematic due to collinearity issues. This means that when examining *integrated* intensity/volume associations, it is necessary to use alternative analytical approaches to purely time-based PA exposures.

We have previously proposed an approach by simultaneously analysing PA volume and the proportion of that volume obtained through MVPA,[9] which honours the nested nature of intensity within volume. This characterization of intensity as the relative contribution to total volume does not stand alone as a measure of the absolute amount of MVPA undertaken. Rather, when considered alongside PA volume, it provides an indication of how the activity was accumulated. Using this method, we recently showed that higher contributions of MVPA to a given volume of PA may play a role for all-cause mortality risk; however, it is unclear whether this applies to incident CVD in the same way. There are supporting mechanisms suggesting that PA intensity may play a specific role in CVD risk, over and above volume, potentially due to greater stimulation and adaptation of cardiorespiratory-related pathways.[18–22] Therefore, the specific interplay between PA volume and intensity warrants further robust investigation in association with CVD outcomes. Here, we investigate how device-based estimates of PA volume and different PA intensity profiles are associated with incident CVD in UK Biobank, the largest study of accelerometer-measured PA to date.

Methods

Data source and study population

We used data from UK Biobank (application #33266), a population-based prospective cohort study of over 500 000 adults aged 40–69 years, recruited between 2006 and 2010 from across the UK. Methods have been described in detail previously.[23] In brief, a sub-sample of 103 686 participants responded to an email for the accelerometer sub-study between June 2013 and December 2015, with PA measurement a median of 5.3 years after their recruitment into the main study.[24] The UK Biobank study received ethical approval from the Northwest England Research Ethics Committee (reference 16/NW/0274). Participants gave informed consent before participation.

Physical activity volume and intensity derived from wrist acceleration

Accelerometry subsample participants were asked to wear a triaxial accelerometer (AX3, Axivity, UK) on their dominant wrist continuously (24 h/day) for 7 consecutive days. Measured acceleration from this type of sensor contains three main components: movement-related acceleration, gravity, and noise. A movement metric (Euclidean norm minus one, ENMO) was generated by calibrating measured wrist acceleration to local gravity (within the +/−1 g range and assuming sensor linearity to +/−8 g), filtering out sensor noise as a high-frequency signal component, and subtracting gravity.[25,26] Non-wear was quantified as time periods of ≥60 min where the standard deviation of acceleration in each of the three axes was <13 mg, which was taken into consideration to minimize diurnal bias when summarizing the 5-s epoch time-series to average movement volume and distribution of intensity.[25,26] The average ENMO over 5-s epochs (the intensity time-series) was summarized into average proportions of daily time spent at different movement intensity levels.[24] We estimated instantaneous PA energy expenditure (PAEE) from wrist movement intensity,[27] the time integral of which constitutes total volume of activity as PAEE, as validated against the gold-standard criterion of doubly-labelled water[28] (see Supplementary material online, *Table S1*). Participants were excluded if their accelerometer record failed calibration (including those not calibrated on their own data), had <3 days of valid wear (defined as >16 h/day), or wear data were not present for each 15-min period of the 24-h cycle (see Supplementary material online, *Figure S1*). We focussed on two key metrics (see Supplementary material online, *Table S1*) to summarize total PA volume and intensity, respectively: (i) Average daily PAEE (kJ/kg/day)—calculated as the sum of PAEE-based energy expenditure from all intensity levels and (ii) Fraction of PAEE from MVPA (%MVPA)—calculated as the sum of energy expenditure from any activity above 125 mg (equivalent to 3 METs) divided by total PAEE.

Covariate measurement

All participants completed a touchscreen questionnaire and anthropometric assessment at recruitment into the main study, and some participants took part in up to two further touchscreen interviews. Since the accelerometry time-point was used as the analytical baseline for this study, covariate data from the interview undertaken closest to the accelerometry were used.[9] Exceptions were: sex and Townsend Index of deprivation (based on postcode) that were only obtained at recruitment baseline; ethnicity (assumed not to have changed) and family medical history where a condition was counted if it was reported at any measurement point.

Covariates for this analysis included demographic and lifestyle related characteristics of age, sex, ethnicity (white/non-white), Townsend Index of deprivation (based on postcode), highest educational level achieved (degree or above/any other qualification/no qualification), employment status (unemployed/in paid or self-employment), parental history of CVD or cancer, season of accelerometry wear (using two orthogonal sine functions; described in Supplementary material online, *Figure S2*), alcohol drinking status (never/previous/current), salt added to food (never/sometimes), oily fish intake (never/sometimes), fruit and vegetable intake (a score from 0–4 taking into account questions on cooked and raw vegetables, fresh and dried fruit consumption), processed and red meat intake (average weekly frequency in days per week), and sleep duration (<7, 7–8, >8 h) and a diagnosis of cancer prior to baseline. Prevalent CVD and cancer variables were derived from the self-reported history of heart attack, angina, stroke, or cancer variables and from hospital episode data (corresponding ICD-10 codes for CVD or cancer I20–25, I60–69, or C00–99 and ICD-9 codes 410–414, 430–439, or 140–199, 201–208, 209.1–209.3, 209.7–209.9). Health-related covariates included blood pressure or cholesterol medications, an insulin prescription or a self-report of doctor diagnosed diabetes, mobility limitations (self-reported longstanding illness or disability or chest pain at rest), and body mass index (BMI) in three categories (<25, 25–30, ≥ 30 kg/m^2). We used multiple imputation by chained equations (MICE; 5 imputed datasets) for individuals with missing covariates. All covariates were included in the imputation model, as well as the Nelson-Aalen estimate of cumulative baseline hazard of CVD, and the incident CVD variable.[29]

Ascertainment of incident CVD

Incident non-fatal/fatal CVD was defined as the first appearance of ischaemic heart disease (ICD-10/9 codes I20–25/410–414) or cerebrovascular disease (ICD-10/9 codes I60–69/430–438.9), identified from linkages to Hospital Episode Statistics (HES) or the national death index. Participants

Table 1 Descriptive characteristics of the whole sample at baseline, by sex and tertiles of PAEE

Characteristics	Men (*N* = 36 903; incident CVD events = 2364)			Women (*N* = 51 509; incident CVD events = 1704)		
	Tertile 1 (*N* = 13 891)	Tertile 2 (*N* = 11 892)	Tertile 3 (*N* = 11 120)	Tertile 1 (*N* = 15 580)	Tertile 2 (*N* = 17 578)	Tertile 3 (*N* = 18 350)
Follow-up time (years), median (IQR)	6.7 (6.1–7.3)	6.8 (6.2–7.3)	6.8 (6.2–7.3)	6.7 (6.2–7.3)	6.8 (6.2–7.3)	6.9 (6.3–7.3)
Person-years	90 157	78 209	73 519	102 652	116 951	123 080
Incident CVD events, *n* (rate)[a]	1119 (12.4)	727 (9.3)	518 (7.1)	736 (7.2)	551 (4.7)	417 (3.4)
Age (years), mean (SD)	64.6 (7.6)	62.3 (7.9)	60.1 (7.8)	63.7 (7.5)	61.8 (7.6)	59.8 (7.6)
White ethnicity, *n* (%)	13 491 (97.5%)	11 528 (97.3%)	10 674 (96.4%)	15 092 (97.2%)	17 008 (97.0%)	17 607 (96.2%)
Highest educational level achieved, *n* (%)						
No qualification	1314 (9.5%)	797 (6.7%)	743 (6.7%)	1441 (9.2%)	1255 (7.1%)	1159 (6.3%)
Any other qualification	6254 (45.0%)	5276 (44.4%)	5277 (47.5%)	7643 (49.1%)	8684 (49.4%)	8949 (48.8%)
Degree level or above	6208 (44.7%)	5736 (48.2%)	5030 (45.2%)	6352 (40.8%)	7526 (42.8%)	8126 (44.3%)
Townsend indicator of multiple deprivation, median (IQR)	−2.50 (−3.85–0.23)	−2.59 (−3.89–0.40)	−2.47 (−3.85–0.27)	−2.32 (−3.71–0.09)	−2.46 (−3.82–0.25)	−2.44 (−3.81–0.18)
In employment, *n* (%)	7615 (54.9%)	7765 (65.4%)	8088 (72.9%)	8052 (51.8%)	10 654 (60.7%)	12 262 (67.0%)
Cigarette smoking, *n* (%)						
Never	7087 (51.0%)	6476 (54.5%)	6158 (55.4%)	9253 (59.4%)	10 793 (61.4%)	11 424 (62.3%)
Previous	5500 (39.6%)	4527 (38.1%)	4126 (37.1%)	5206 (33.4%)	5789 (32.9%)	6022 (32.8%)
Current	1259 (9.1%)	863 (7.3%)	814 (7.3%)	1085 (7.0%)	955 (5.4%)	857 (4.7%)
Alcohol consumption, *n* (%)						
Never or previous	675 (4.9%)	494 (4.2%)	461 (4.1%)	1178 (7.6%)	1021 (5.8%)	1082 (5.9%)
< Twice a week	5661 (40.8%)	4451 (37.4%)	4287 (38.6%)	8437 (54.2%)	8859 (50.4%)	8856 (48.3%)
At least three times a week	7546 (54.3%)	6939 (58.4%)	6363 (57.2%)	5952 (38.2%)	7684 (43.7%)	8396 (45.8%)
Added salt intake, *n* (%)						
Never/rarely	8097 (58.3%)	7018 (59.0%)	6548 (58.9%)	9423 (60.5%)	10 671 (60.7%)	11 335 (61.8%)
Sometimes or more frequent	3801 (27.4%)	3333 (28.0%)	3123 (28.1%)	4220 (27.1%)	4861 (27.7%)	4916 (26.8%)
Usually/always	1987 (14.3%)	1537 (12.9%)	1441 (13.0%)	1932 (12.4%)	2038 (11.6%)	2091 (11.4%)
Oily fish consumption, *n* (%)						
More than once a week	7543 (54.5%)	6428 (54.2%)	6001 (54.1%)	9071 (58.4%)	10 231 (58.3%)	10 368 (56.6%)
Fruit and vegetable intake score, mean (SD)	1.4 (1.1)	1.5 (1.1)	1.6 (1.1)	1.7 (1.1)	1.8 (1.1)	1.9 (1.2)
Weekly frequency of red or processed meat intake, median (IQR)	1.00 (0.63–1.38)	0.88 (0.63–1.25)	0.88 (0.63–1.25)	0.63 (0.50–1.13)	0.63 (0.50–1.13)	0.63 (0.50–1.00)

Continued

Table 1 *Continued*

Characteristics	Men (*N* = 36 903; incident CVD events = 2364)			Women (*N* = 51 509; incident CVD events = 1704)		
	Tertile 1 (*N* = 13 891)	Tertile 2 (*N* = 11 892)	Tertile 3 (*N* = 11 120)	Tertile 1 (*N* = 15 580)	Tertile 2 (*N* = 17 578)	Tertile 3 (*N* = 18 350)
Mean sleep duration, *n* (%)						
<7 h/day	2920 (21.0%)	2600 (21.9%)	2702 (24.3%)	3483 (22.4%)	3757 (21.4%)	3754 (20.5%)
7–8 h/day	9841 (70.8%)	8691 (73.1%)	7971 (71.7%)	10 682 (68.6%)	12 609 (71.7%)	13 678 (74.5%)
>8 h/day	1096 (7.9%)	585 (4.9%)	430 (3.9%)	1351 (8.7%)	1164 (6.6%)	870 (4.7%)
Parental history of cardiovascular disease or cancer, *n* (%)	9974 (72.8%)	8392 (71.5%)	7520 (68.6%)	11 695 (76.2%)	12 824 (73.9%)	12 834 (70.8%)
Body mass index, *n* (%)						
Normal weight (<25 kg/m^2)	3322 (23.9%)	3699 (31.1%)	4382 (39.4%)	5266 (33.8%)	8236 (46.9%)	10 956 (59.7%)
Overweight (25–30 kg/m^2)	6772 (48.8%)	6050 (50.9%)	5337 (48.0%)	5893 (37.8%)	6433 (36.6%)	5570 (30.4%)
Obese (≥30 kg/m^2)	3754 (27.0%)	2123 (17.9%)	1388 (12.5%)	4376 (28.1%)	2885 (16.4%)	1804 (9.8%)
Current prescription of blood pressure or cholesterol medicine, *n* (%)	4575 (33.1%)	2782 (23.5%)	1810 (16.3%)	3725 (24.0%)	2773 (15.8%)	1964 (10.7%)
Diagnosis of diabetes or insulin prescription, *n* (%)	937 (6.7%)	376 (3.2%)	238 (2.1%)	592 (3.8%)	285 (1.6%)	246 (1.3%)
Previous diagnosis of cancer, *n* (%)	1806 (13.0%)	1168 (9.8%)	874 (7.9%)	2414 (15.5%)	2178 (12.4%)	1870 (10.2%)
Mobility limitation, *n* (%)	5829 (42.0%)	4000 (33.7%)	3321 (29.9%)	6124 (39.4%)	5460 (31.1%)	4630 (25.3%)
Axivity accelerometer						
Valid wear days, median (IQR)	6.9 (6.7–7.0)	6.9 (6.7–7.0)	6.9 (6.7–7.0)	6.9 (6.6–7.0)	6.9 (6.7–7.0)	6.9 (6.6–7.0)
Valid wear-time, hr/day, median (IQR)	24.0 (23.8–24.0)	24.0 (23.8–24.0)	24.0 (23.8–24.0)	23.8 (23.6–24.0)	23.8 (23.6–24.0)	23.8 (23.6–24.0)
PAEE (kJ/kg/day), mean (SD)	29.67 (4.93)	40.68 (2.65)	54.34 (8.24)	30.35 (4.62)	40.75 (2.65)	54.19 (7.77)
%PAEE from MVPA, mean (SD)	27.76 (8.88)	36.42 (7.92)	45.61 (8.87)	24.59 (8.24)	32.83 (7.70)	42.46 (8.67)
ENMO (mg), mean (SD)	20.39 (3.47)	27.91 (2.54)	38.20 (7.68)	20.61 (3.20)	27.58 (2.32)	37.18 (6.52)
Intensity gradient, mean (SD)	−2.59 (0.19)	−2.50 (0.16)	−2.39 (0.20)	−2.68 (0.17)	−2.58 (0.15)	−2.47 (0.17)

CVD = cardiovascular disease; MVPA = moderate-to-vigorous physical activity; PAEE = physical activity energy expenditure; ENMO = Euclidean norm minus one.
Townsend score = a composite area-level measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding; a higher score indicates higher deprivation. See Supplementary material online, *Table S1* for a more detailed description of the PA volume and intensity metrics and the methods used. The relationships between the different PA volume/intensity metrics are also displayed in Supplementary material online, *Figure S4*. Season of accelerometer wear is described in Supplementary material online, *Figure S2*.
[a]Shows the number and crude incident CVD event rates per 1000 person-years.

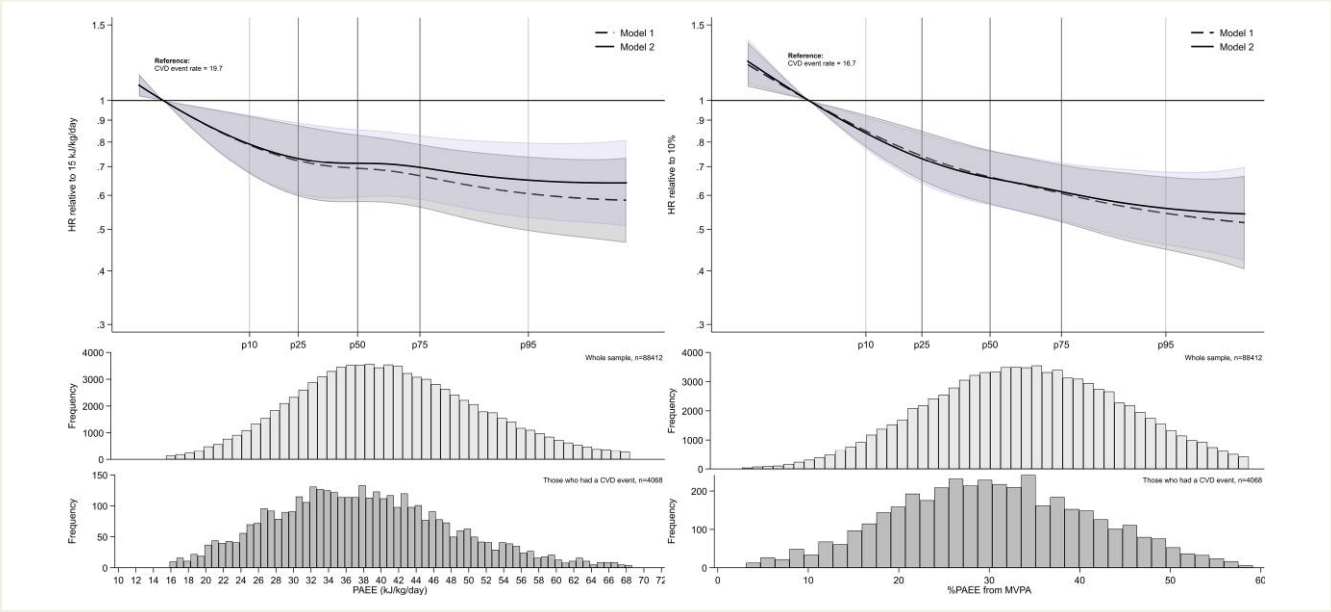


Figure 1 Baseline exposure distribution and adjusted hazard ratios of incident cardiovascular disease comparing different volumes of physical activity energy expenditure and different fractions of physical activity energy expenditure from moderate-to-vigorous intensity physical activity. %Physical activity energy expenditure from moderate-to-vigorous intensity physical activity models are additionally adjusted for physical activity energy expenditure. Models were fitted using cubic splines (3 evenly spaced knots). Adjusted hazard ratios and histogram data shown for values between the 1st or 99th percentiles of the exposure distribution among those who had a cardiovascular disease event. Reference cardiovascular disease event rates depict the crude incident cardiovascular disease event rate per 1000 person-years, buffered around the reference zone for each exposure (i.e. ≤17.5 kJ/kg/day and ≤15%physical activity energy expenditure from moderate-to-vigorous intensity physical activity). Model 1 is adjusted for sex (with age as the underlying time scale), season of accelerometer wear, ethnicity, education level, employment status, Townsend index of deprivation, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of cardiovascular disease or cancer, blood pressure or cholesterol medication use, insulin prescription or diagnosed diabetes, mobility limitation, and prevalent cancer. Model 2 adjusts for covariates in model 1, with additional adjustment for body mass index. Further sensitivity analyses are detailed in *Table 2* and Supplementary material online, *Figure S6*.

who did not experience a CVD outcome were censored at death or the end of the study period, as appropriate (England 30/09/2021; Wales 28/02/2018; Scotland 31 July 2021).

Statistical analyses

All analyses were conducted using Stata v15.1 (StataCorp, College Station, TX, USA) and statistical significance was set at $P < 0.05$ (two-tailed); results are reported with 95% confidence interval (CI). Participants with CVD prior to accelerometer wear were excluded. We also excluded those who had a CVD event ($n = 564$) within the first year of follow-up, to reduce the risk of reverse causality bias (i.e. participants experiencing CVD events close to baseline may have had an underlying health condition, or poor health, leading to lower levels of activity). Using Cox proportional hazard regression models, we first investigated the associations of PAEE and fraction of PAEE from MVPA (the latter adjusted for PAEE) with incident CVD. These models used age as the underlying timescale and modelled exposures using cubic splines with three evenly spaced knots. Exposure reference values were chosen as the nearest 5 kJ/kg/day or 5% to the first percentile of the distribution among those who had a CVD event.

Directed acyclic graphs[30] were used to visualize causal assumptions and guide which covariates to progressively include in analyses *a priori* (see Supplementary material online, *Figure S3*). As per STROBE recommendations, Model 0 adjusted for sex and season of accelerometer wear, with age as the underlying time scale. Model 1 was the main confounder-adjusted model and further adjusted for ethnicity, education level, employment status, Townsend index of deprivation, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of CVD or cancer, blood pressure or cholesterol medication use, diabetes diagnosis or insulin prescription, mobility limitation, and prevalent cancer. Model 2 additionally adjusted for body mass index, which may be considered to be a potential confounder, but also a potential mediator, in the association between PA and incident CVD, given its plausible bidirectional associations with PA.[31] We checked the proportional hazard assumptions for categorical covariates using log–log plots, with those variables failing to meet the assumptions used to stratify the baseline hazards. The log-linear relationship between continuous covariates and hazard of incident CVD was checked using fractional polynomials, with all variables meeting the linearity assumption.

Interactions between PA volume and intensity were investigated by fitting a spline regression for PAEE and log-transformed %PAEE from MVPA, including interaction terms between the four orthogonal spline variables and %PAEE from MVPA. Using the coefficients, we plotted the fitted spline functions showing the association between PAEE and CVD risk for incremental fractions of PAEE from MVPA (10, 20, 30, and 40%). A 15 kJ/kg/day and 10% PAEE from MVPA reference was chosen for these models. Due to known differences in activity levels by sex in this cohort,[24] interaction analyses were also sex-stratified to investigate integrated volume/intensity associations for women and men separately.

Sensitivity analyses

Several additional sensitivity analyses were performed, adjusting for covariates in Model 1. To further investigate potential reverse causality bias, we excluded those who had a CVD event/death within 2 years of follow-up or with prevalent cancer at baseline. We also investigated whether results differed when performing complete-case analysis (i.e. without imputation of

Table 2 Adjusted hazard ratios for incident CVD by volume of PAEE and different fractions of PAEE from MVPA

	Incident CVD (*N* = 88 412; no. of events = 4068; person years = 584 568)					
PAEE (kJ/kg/day)	15	20	30	40	50	60
Model 0	1	0.80 (0.73–0.87)	0.57 (0.47–0.69)	0.50 (0.42–0.59)	0.44 (0.37–0.52)	0.40 (0.33–0.49)
Model 1	1	0.88 (0.80–0.96)	0.73 (0.60–0.88)	0.69 (0.58–0.82)	0.64 (0.53–0.76)	0.60 (0.49–0.73)
Model 2	1	0.88 (0.80–0.96)	0.74 (0.61–0.89)	0.71 (0.60–0.85)	0.67 (0.56–0.81)	0.65 (0.52–0.80)
Model 1b excluding CVD event/death <2 yr or prevalent cancer	1	0.86 (0.77–0.96)	0.70 (0.55–0.87)	0.67 (0.54–0.82)	0.65 (0.52–0.81)	0.61 (0.48–0.78)
Model 1c complete-case analysis	1	0.88 (0.81–0.97)	0.74 (0.61–0.90)	0.69 (0.58–0.83)	0.65 (0.54–0.78)	0.61 (0.50–0.75)
%PAEE from MVPA[a]	10	20	30	40	50	60
Model 0	1	0.71 (0.63–0.79)	0.56 (0.49–0.63)	0.47 (0.42–0.53)	0.42 (0.36–0.48)	0.39 (0.31–0.48)
Model 1	1	0.78 (0.69–0.88)	0.66 (0.57–0.77)	0.59 (0.51–0.70)	0.54 (0.45–0.66)	0.52 (0.39–0.67)
Model 2	1	0.77 (0.68–0.87)	0.66 (0.57–0.77)	0.60 (0.51–0.71)	0.56 (0.46–0.68)	0.54 (0.41–0.71)
Model 1b excluding CVD event/death <2 yr or prevalent cancer	1	0.83 (0.72–0.96)	0.72 (0.60–0.86)	0.68 (0.56–0.82)	0.65 (0.51–0.82)	0.58 (0.42–0.80)
Model 1c complete-case analysis	1	0.78 (0.69–0.88)	0.67 (0.57–0.77)	0.60 (0.51–0.71)	0.55 (0.45–0.68)	0.53 (0.40–0.69)

Model 1b (*n* = 77 606, no. of events = 2919); Model 1c (*n* = 85 451, no. of events = 3891). Model 0 is adjusted for sex (with age as the underlying time scale) and season of accelerometer wear. Model 1 is adjusted for sex (with age as the underlying time scale), season of accelerometer wear, ethnicity, education level, employment status, Townsend index of deprivation, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of cardiovascular disease or cancer, blood pressure or cholesterol medication use, insulin prescription or diagnosed diabetes, mobility limitation, and prevalent cancer. Model 2 adjusts for covariates in model 1, with additional adjustment for body mass index.
[a]%PAEE from MVPA models are additionally adjusted for PAEE. Models 1 and 2 are displayed on *Figure 1*.

missing covariate data). Finally, to assess whether the derived measures of PAEE and %PAEE from MVPA used in this analysis provided a similar dose-response association with CVD incidence as more direct measures of PA using acceleration only, we repeated analyses using alternative exposure definitions of PA volume (average ENMO in mg) and intensity (intensity gradient; a unitless integrated measure which describes the negative curvilinear relationship between PA intensity and the time accumulated at that intensity[32]). As mentioned, Supplementary material online, *Table S1* provides an overview and more detailed description of all the PA metrics used and the methods to calculate them. The relationships between the different PA volume and intensity metrics are also displayed in Supplementary material online, *Figure S4*.

Results

Descriptive characteristics

Descriptive characteristics of the 88 412 participants at baseline are shown in *Table 1*, by sex and tertiles of PAEE. Supplementary material online, *Table S2* also shows baseline data by tertiles of %PAEE from MVPA. Mean age was 62 (SD, 8; range, 43–79) years; mean body mass index (BMI) was 26.6 (SD, 4.5) kg/m^2; and 58% were women. The age range was similar across sexes, but a higher proportion of women had a BMI in the normal range, had never smoked, took medications, or reported markers of poor health. Activity profiles between sexes were similar on average, but men had slightly lower overall PA volume and spent more time in higher intensity activities. During a median of 6.8 (interquartile range [IQR]: 6.2–7.3) years (584 568 person-years) of follow-up, 4068 CVD events occurred.

Associations of PA volume and intensity

Adjusted for potential confounders and prevalent cancer (model 1), both higher PAEE and %PAEE from MVPA (adjusted for PAEE) were inversely associated with rates of incident CVD (*Figure 1*; *Table 2*). Compared with 15 kJ/kg/d, a PAEE of 20 kJ/kg/d was associated with 12% (95%CI: 4–20%) lower rates. PAEE values of 30, 40, and 50 kJ/kg/d were associated with 26% (11–39%), 29% (15–40%), and 33% (19–44%) lower rates, respectively. Compared to accruing 10% of PAEE from MVPA, accruing 20% was associated with 23% (13–32%) lower rates. Accruing 30, 40, and 50% of PAEE from MVPA were associated with 34% (23–43%), 40% (29–49%), and 44% (32–54%) lower rates, respectively. Additional adjustment for BMI (model 2) attenuated all associations, but only slightly.

Interaction between PA volume and intensity

In joint volume-intensity analyses, CVD rates were 14% (5–23%) lower when MVPA accounted for 20% rather than 10% of a fixed volume level of 15 kJ/kg/d PAEE (*Figure 2*; *Table 3*). CVD rates did not differ significantly with higher values of PAEE when the %PAEE from MVPA was fixed; however, the combination of higher PAEE and %PAEE from MVPA was associated with lower CVD rates. For example, rates were 19% (5–31%) lower for 20 kJ/kg/d PAEE with 20% from MVPA, 23% (0–41%) lower for 30 kJ/kg/d PAEE with 20% from MVPA, and 40% (10–60%) lower for 30 kJ/kg/d with 40% from MVPA (all compared to 15 kJ/kg/d PAEE with 10% MVPA). There was considerable uncertainty around levels of PAEE beyond 40 kJ/kg/day with a > 20% fraction of MVPA. Additional adjustment for BMI (model 2) slightly attenuated the associations. Supplementary material online, *Table S3* presents time-based units (assuming walking activities at two intensity levels) for the different combinations of PAEE and %PAEE from MVPA, to aid further translation.

Sex-stratified interaction analyses showed a broadly similar pattern of PAEE and %PAEE from MVPA associations with CVD rates for

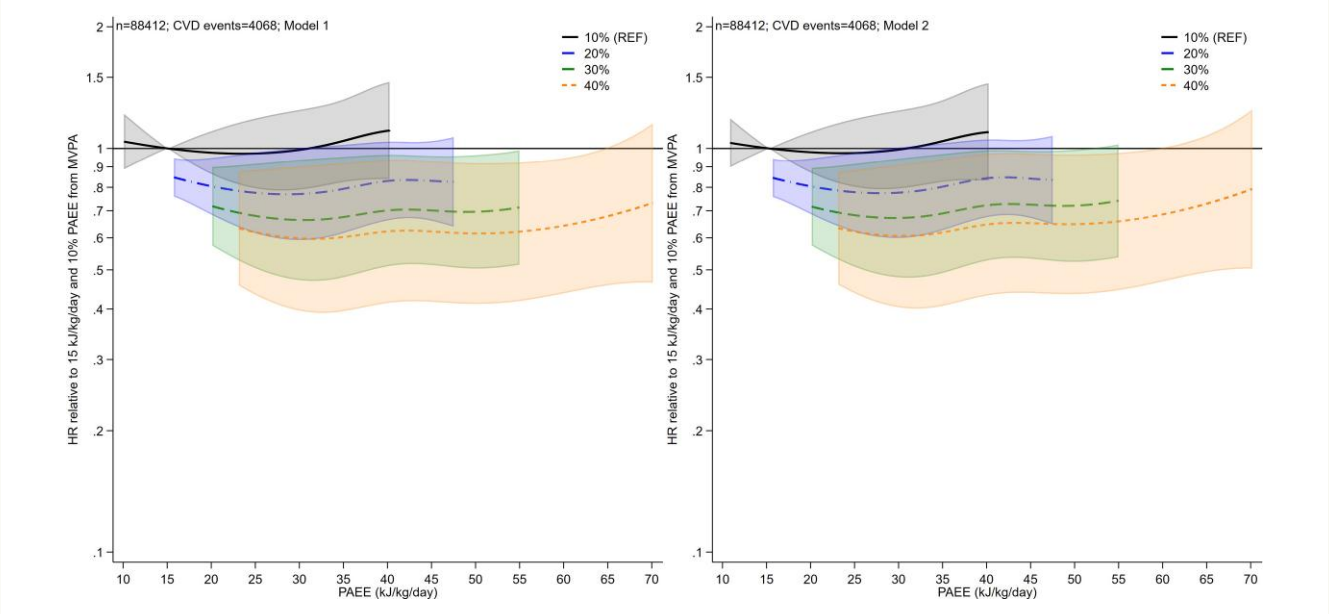


Figure 2 Associations of volume of physical activity energy expenditure and the %physical activity energy expenditure from moderate-to-vigorous intensity physical activity with incident cardiovascular disease. All hazard ratios are relative to a physical activity energy expenditure of 15 kJ/kg/day and 10% fraction from moderate-to-vigorous intensity physical activity (i.e. hazard ratio, 1). Moving right along each line reflects the hazard ratio for a higher physical activity energy expenditure volume but a constant %physical activity energy expenditure from moderate-to-vigorous intensity physical activity. A comparison between lines at a given point on the x-axis therefore reflects the hazard ratio for an increase in intensity but at constant physical activity energy expenditure. Hazard ratios (95% confidence interval) are shown for values between the 1st or 99th percentiles of the physical activity energy expenditure distribution among those who had a cardiovascular disease event. Model 1 is adjusted for sex (with age as the underlying time scale), season of accelerometer wear, ethnicity, education level, employment status, Townsend index of deprivation, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of cardiovascular disease or cancer, blood pressure or cholesterol medication use, insulin prescription or diagnosed diabetes, mobility limitation, and prevalent cancer. Model 2 adjusts for covariates in model 1, with additional adjustment for body mass index. Further details are shown in *Table 3*.

both men and women (*Figure 3*; see Supplementary material online, *Figure S5* and Supplementary material online, *Table S4*), with the lowest rates of CVD seen with higher levels of both PAEE and %PAEE from MVPA.

Sensitivity analyses

The direction and strength of associations for PAEE and %PAEE from MVPA with CVD rates were consistent when analyses were conducted using acceleration-defined metrics of ENMO and intensity gradient (see Supplementary material online, *Figure S6*). Excluding participants who had a CVD event within 2 years of follow-up or with prevalent cancer resulted in similar to slightly attenuated associations (*Tables 2* and *3*). In addition, results did not materially differ in complete-case analyses.

Discussion

In this large population-based cohort study of middle-aged adults with objective measurement of PA, we found that a higher volume of PAEE was associated with lower rates of incident CVD. We also investigated the influence of accumulating more of this PA volume through MVPA—demonstrating an important role for activity intensity in future CVD risk. For example, when PAEE was fixed at 15 kJ/kg/d, accumulating 20% rather than 10% through MVPA was associated with a 14% lower CVD rate. This is equivalent to converting a 14-min stroll into a brisk 7-min walk; both have the same volume, but the higher intensity of the latter was associated with lower CVD rates (*Structured Graphical Abstract*). Although largely consistent with the latest PA guidelines for both primary and secondary prevention[1,2,33]—which are supportive of messages that 'every move counts' for improving health outcomes—these findings provide further evidence that PA intensity may play an important role in minimizing CVD risk, over and above total PA volume.

In interaction analyses, the role of intensity appeared to be particularly important, such that it diminished the previously demonstrated association between PA volume and incident CVD. Our interpretation is, therefore, that promoting MVPA is a priority for future CVD risk. Theoretically, our results support guidance that encourages individuals to undertake a given task more intensely (i.e. maintaining a comparable total PA volume but increasing the contribution of MVPA). Nevertheless, there are two main reasons not to ignore the role of PA volume. Firstly, we demonstrated a strong inverse association between PAEE and incident CVD. Secondly, the lowest CVD rates were evident amongst those undertaking higher levels of PAEE with greater proportions from MVPA. For example, compared to a combination of 15 kJ/kg/d PAEE with 10% from MVPA, we observed a 40% lower CVD rate amongst those with a combination of 30 kJ/kg/d PAEE with 40% PAEE from MVPA. In addition, given that intense activity may not be pleasurable, preferable, or advisable for all individuals,[34–36] our results support added flexibility in options through guidance that encourages multiple PA pathways to reducing CVD risk.

Our findings extend upon previous studies using self-reported[10,37–41] and accelerometer derived[9,10,12,15,42] measures of PA by examining in

Table 3 Adjusted hazard ratios of incident CVD for different values of PAEE and the fraction of PAEE from MVPA

		Model 1	Model 2	Model 1 excluding CVD event/death <2yr or prevalent cancer)	Model 1 complete-case analysis
n		88 412		77 606	85 451
Person-years		584 568		516 559	565 068
CVD events		4068		2919	3891
PAEE (kJ/kg/day)	**%PAEE from MVPA**				
15	10	1 (REF)	1 (REF)	1 (REF)	1 (REF)
	20	0.86 (0.77–0.95)	0.85 (0.76–0.95)	0.97 (0.85–1.10)	0.83 (0.74–0.93)
	30	N/A	N/A	N/A	N/A
	40	N/A	N/A	N/A	N/A
20	10	0.98 (0.86–1.10)	0.98 (0.87–1.10)	0.95 (0.82–1.09)	0.98 (0.87–1.12)
	20	0.81 (0.69–0.95)	0.80 (0.69–0.94)	0.85 (0.71–1.02)	0.80 (0.68–0.94)
	30	0.72 (0.58–0.90)	0.72 (0.58–0.89)	0.80 (0.62–1.04)	0.71 (0.56–0.89)
	40	N/A	N/A	N/A	N/A
30	10	0.99 (0.79–1.25)	0.99 (0.79–1.24)	0.90 (0.68–1.20)	1.00 (0.79–1.27)
	20	0.77 (0.59–1.00)	0.78 (0.60–1.01)	0.74 (0.55–1.00)	0.78 (0.60–1.02)
	30	0.66 (0.47–0.94)	0.67 (0.48–0.94)	0.66 (0.44–0.99)	0.67 (0.47–0.96)
	40	0.60 (0.40–0.90)	0.61 (0.40–0.91)	0.61 (0.37–0.99)	0.61 (0.40–0.93)
40	10	1.11 (0.84–1.46)	1.10 (0.83–1.45)	0.97 (0.70–1.36)	1.09 (0.82–1.45)
	20	0.83 (0.66–1.04)	0.84 (0.67–1.05)	0.78 (0.60–1.02)	0.83 (0.66–1.04)
	30	0.70 (0.51–0.96)	0.72 (0.53–0.99)	0.69 (0.48–1.01)	0.70 (0.51–0.98)
	40	0.62 (0.41–0.94)	0.65 (0.43–0.97)	0.63 (0.39–1.03)	0.63 (0.41–0.95)
50	10	N/A	N/A	N/A	N/A
	20	N/A	N/A	N/A	N/A
	30	0.70 (0.50–0.96)	0.72 (0.52–0.99)	0.72 (0.49–1.06)	0.69 (0.50–0.97)
	40	0.62 (0.41–0.92)	0.65 (0.44–0.97)	0.65 (0.40–1.04)	0.62 (0.41–0.95)
60	10	N/A	N/A	N/A	N/A
	20	N/A	N/A	N/A	N/A
	30	N/A	N/A	N/A	N/A
	40	0.64 (0.44–0.94)	0.69 (0.47–1.00)	0.68 (0.43–1.08)	0.64 (0.43–0.96)

N/A indicates the specific combination of exposures not between the 1st and 99th percentiles of the PAEE distribution among those who had a CVD event for that %PAEE from MVPA value. All hazard ratios are relative to a PAEE of 15 kJ/kg/day mg and a %PAEE from MVPA of 10%. Models 1 and 2 are displayed on *Figure 2*. Model 1 is adjusted for sex (with age as the underlying time scale), season of accelerometer wear, ethnicity, education level, employment status, Townsend index of deprivation, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of cardiovascular disease or cancer, blood pressure or cholesterol medication use, insulin prescription or diagnosed diabetes, mobility limitation, and prevalent cancer. Model 2 adjusts for covariates in model 1, with additional adjustment for body mass index.

more detail the interplay between PA volume and intensity. Using simple, continuous accelerometer-derived metrics of total PAEE and fraction of PAEE from MVPA, we provide a more detailed and integrated perspective on associations with CVD risk, which were previously ambiguous concerning the interactive role of intensity over and above PA volume.[15] As noted, a key observation was that when exposures were combined in interaction analyses, the association between PAEE and CVD risk at a given value of %PAEE from MVPA was weaker than when PAEE was the only exposure. Comparing these results with those from similar analyses for all-cause mortality,[9] this finding suggests that intensity may be particularly important in minimizing CVD risk.

We had anticipated strong evidence of an association with PA intensity for incident CVD. This is consistent with previous research showing that self-reported walking pace, a measure of habitual movement intensity and function, is a stronger predictor of CVD mortality than other PA exposures (i.e. volume) or lifestyle-related factors.[43,44] In addition, higher intensity activities should theoretically provide greater stimuli (e.g. overload, specificity, and/or relative intensity) for physiological

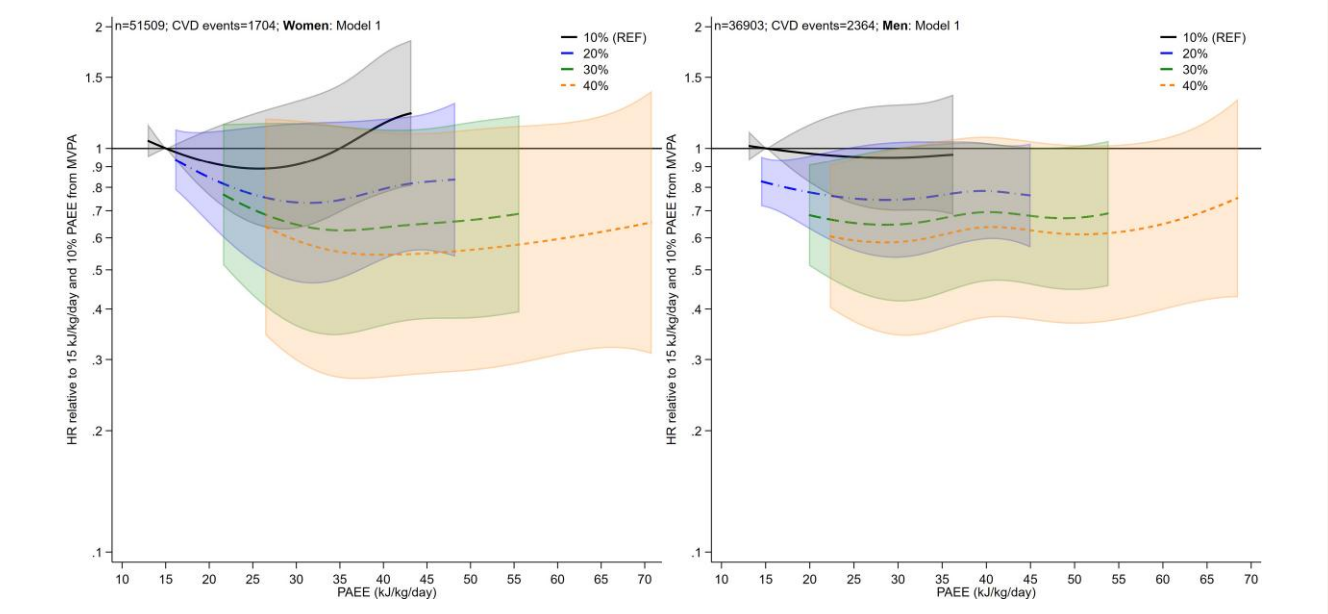


Figure 3 Associations of volume of physical activity energy expenditure the %physical activity energy expenditure from moderate-to-vigorous intensity physical activity with incident cardiovascular disease (model 1), by sex. All hazard ratios are relative to a physical activity energy expenditure of 15 kJ/kg/day and 10% fraction from moderate-to-vigorous intensity physical activity. Moving right along each line reflects the hazard ratio for a higher physical activity energy expenditure volume but a constant %physical activity energy expenditure from moderate-to-vigorous intensity physical activity. A comparison between lines at a given point on the x-axis reflects the hazard ratio for an increase in intensity, but a constant physical activity energy expenditure. Hazard ratios shown for values between the 1st or 99th percentiles of the physical activity energy expenditure distribution among those who had a cardiovascular disease event. Model 1 is adjusted for season of accelerometer wear (with age as the underlying time scale), ethnicity, education level, employment status, Townsend index of deprivation, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of cardiovascular disease or cancer, blood pressure or cholesterol medication use, insulin prescription or diagnosed diabetes, mobility limitation, and prevalent cancer. Supplementary material online, *Figure S5* displays results for model 2. Further details are also shown in Supplementary material online, *Table S4*.

adaptation in functions recognized to specifically influence and maintain cardiorespiratory fitness and muscular/vascular function.[18–21,45–47] Indeed, it has previously been noted that cardiorespiratory fitness is a cardiovascular vital sign, which has been shown to respond particularly to intensity and less so to volume.[46–49] Therefore, it is possible that the relative importance of intensity observed in this study is mediated in part by improvements in cardiorespiratory fitness and vascular structure/function.

Although it is important to note the inherent inter-relationships between PA volume and intensity (i.e. a higher PAEE is generally achieved with a higher %PAEE from MVPA; see Supplementary material online, *Figure S4*), our findings suggest that focusing on increasing MVPA and the intensity of habitual PA, such as walking, regardless of the overall daily volume of PA, could have relevance for CVD prevention or targeting for future interventions. Taken together, the public health message is therefore to increase overall volume of activity and, if possible, do so by incorporating more intense activities. Indeed, for any given activity volume (e.g. walking to the bus stop, or the completion of a set list of manual chores), accumulating this volume at higher intensity (e.g. walking faster to the bus stop, or completing tasks/chores more intensely) would also take up less time, which may be particularly attractive for time-poor individuals or for intervention strategies aimed at freeing up time to increase overall PA levels.[19]

Strengths and limitations

A key strength of this study is its large sample size, allowing sufficient variation to investigate interactions across the distributions of PA volume and intensity with incident CVD. In addition, the accelerometer-derived metric of PAEE has a strong validation foundation[24,25] (see Supplementary material online, *Table S1*), is easily interpretable, and potentially more applicable to wrist-worn wearable devices for personalized prevention. Although translation of wrist-worn acceleration to energy expenditure does have some limitations, associations with CVD were consistent when analyses were repeated using purely acceleration-based measures of PA volume and intensity (albeit on different exposure scales; see Supplementary material online, *Figure S6*), providing further confidence in our results. The extensively phenotyped population allowed a comprehensive investigation into possible confounding or mediating influences on the associations between PA volume or intensity with incident CVD; however, residual bias may also have occurred via some unmeasured factors and/or included variables measured with substantial error. We performed several additional sensitivity analyses to investigate and help minimize the potential for reverse causality biases (an important limitation of any observation study) but acknowledge that we cannot fully ameliorate this concern.

Further limitations include the single time-point measure of PA and the non-concurrent measurement of covariates and accelerometry. Although we adjusted for season, the single time-point limits any potential inferences related to within-person changes or variability in PA over time. In addition, UK Biobank is not a population-representative cohort[50] and the accelerometer sample may be subject to additional selection pressures (e.g. survival 5 years after baseline measurement and

the requirement of a valid email address), which may impact further on generalizability. However, PA volumes are comparable to national estimates[51] and previous work suggests exposure-outcome associations found in UK Biobank provide valid estimates and are similar to results in more representative samples.[50,52] It should be noted that individuals who engage primarily in activities such as resistance exercise or cycling may not be appropriately characterized by wrist accelerometry, and the potential impact of different domains of PA (e.g. occupational) on the associations with incident CVD were not directly addressed. Moreover, we only considered intensity at an absolute level, while intensity relative to maximal capacity may be more critical to driving physiological adaptations.[18,53,54] However, we did adjust for mobility limitations that are associated with low physical capacity, and different MVPA thresholds yielded similar results. Differences in associations for CVD outcomes relative to all-cause mortality[9] could also be related to variations in follow-up time and/or greater exclusions for prevalent disease,[55] although further sensitivity analyses did not indicate this to be a major factor.

Future directions

Future pooled research should aim to confirm these findings in younger age groups and other populations. It should also consider including repeated accelerometer PA exposures and aspects of PA type/domain, while incorporating other biomarkers and disease endpoints (including different CVD sub-types or severity) to shed further light on potential mechanisms. Examination of activity volume and intensity interactions in the context of differing levels of adiposity status (variously defined) would also provide valuable insights.[56]

Conclusion

In this large population-based cohort, we show that both higher volumes of PA, and a greater proportion of that volume accumulated as at least moderate intensity, are associated with lower rates of incident CVD in both men and women. The role of activity intensity, over and above its contribution to total PA volume, also appears to be particularly relevant for CVD risk. These findings support simple behaviour change messages that encourage MVPA, such as converting a short stroll into a brisk walk. However, they also support broader guidance that more movement of any intensity is beneficial (i.e. 'every move counts'). A variety of approaches or strategies should therefore be promoted to support PA participation, and help individuals find whichever is most practical or appealing to them.

Author contributions

P.C.D., A.R., T.S., K.W., S.B., and T.Y. formed the core working group and developed the research question. P.C.D. and T.S. developed the analysis code, and T.S. independently replicated the results. P.C.D. ran the final analysis and drafted the manuscript. All authors contributed to the interpretation and revised the manuscript for important intellectual content.

Supplementary material

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

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Conflict of interest: None declared.

Data availability

The UK Biobank resource can be accessed by researchers on application. Variables derived for this study will be returned to the UK Biobank for future applicants to request. No additional data are available.

Ethics approval and consent to participate

The UK Biobank study received ethical approval from the Northwest England Research Ethics Committee (reference 16/NW/0274). Participants gave informed consent before participation.

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