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 physical activity 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 4,068 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%CI: 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.

Association of Physical Activity Volume and Intensity with Incident Cardiovascular Disease: a UK Biobank Study

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Abbreviations

CVD= cardiovascular disease; PA= physical activity; MVPA= moderate-to-vigorous intensity physical activity; LPA= light-intensity physical activity; PAEE= physical activity energy expenditure; %MVPA= fraction of PAEE from MVPA; ENMO= Euclidean Norm Minus One; MICE= Multiple Imputation by Chained Equations.

ABSTRACT

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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 physical activity 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 4,068 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%CI: 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.

INTRODUCTION

Regular physical activity (PA), particularly moderate-to-vigorous intensity physical activity (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 characterisation 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 to 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 seven consecutive days. Measured acceleration from this type of sensor contains three main components: movement-related acceleration, gravity, and noise. A movement metric (ENMO, Euclidean norm minus one) was generated by calibrating measured wrist acceleration to local gravity (within the +/-1g range and assuming sensor linearity to +/-8g), 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 m*g*, which was taken into consideration to minimise diurnal bias when summarising 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 physical activity 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) (Supplemental 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 (Supplemental Figure S1). We focussed on two key metrics (Supplemental Table S1) to summarize total PA volume and intensity, respectively:

- Average daily PAEE (kJ/kg/day) – calculated as the sum of physical activity-based energy expenditure from all intensity levels.

• 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 Supplemental 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 who did not experience a cardiovascular disease outcome were censored at death or the end of the study period, as appropriate (England 30/09/2021; Wales 28/02/2018; Scotland 31/07/2021).

Statistical analyses

All analyses were conducted using Stata v15.1 (StataCorp, 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 visualise causal assumptions and guide which covariates to progressively include in analyses *a priori* (see Supplemental 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 cardiovascular disease 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 physical activity and incident CVD, given its plausible bidirectional associations with physical activity (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 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 m*g*) 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, Supplemental 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 Supplemental 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. Supplemental Table S2 also shows baseline data by tertiles of %PAEE from MVPA. Mean age was 62 (SD, 8; range, 43-79) years; mean 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 (IQR: 6.2-7.3) years (584,568 person-years) of follow-up, 4,068 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 to 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. Supplemental 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 both men and women (Figure 3, Supplemental Figure S5 and Supplemental 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 (Supplemental Figure S6). Excluding participants who had a CVD event within two 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 physical activity, 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. 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 minimising 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 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 minimising 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 (44, 45). In

addition, higher intensity activities should theoretically provide greater stimuli (e.g. overload, specificity, and/or relative intensity) for physiological adaptation in functions recognized to specifically influence and maintain cardiorespiratory fitness and muscular/vascular function (18-21, 46-48). 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 (47-50). 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 Supplemental 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 Table S1), is easily interpretable, and potentially more applicable to wrist-worn wearable devices for personalised 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 Supplemental 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 minimise 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 (51) and the accelerometer sample may be subject to additional selection pressures (e.g., survival five years after baseline measurement and the requirement of a valid email address), which may impact further on generalisability. However, PA volumes are comparable to national estimates (52) and previous work suggests exposure-outcome associations found in UK Biobank provide valid estimates and are similar to results in more representative samples (51, 53). It should be noted that individuals who engage primarily in activities such as resistance exercise or cycling may not be appropriately characterised 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, 54, 55). 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 (56), 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 (57).

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.

DECLARATIONS

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.

Consent for publication

Not applicable

Availability of data and materials

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.

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Conflict of interest

The authors had financial support from the funders listed above for the submitted work. The authors declare that they have no conflicts of interests.

Authors' contributions

PCD, AR, TS, KW, SB, and TY formed the core working group and developed the research question. PCD and TS developed the analysis code, and TS independently replicated the results. PCD ran the final analysis and drafted the manuscript. All authors contributed to the interpretation and revised the manuscript for important intellectual content.

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

	Men (n=36,903; incident CVD events=2,364)			Women (n=51,509; incident CVD events=1,704)		
Characteristics	**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)*	1,119 (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	1,314 (9.5%)	797 (6.7%)	743 (6.7%)	1,441 (9.2%)	1,255 (7.1%)	1,159 (6.3%)
Any other qualification	6,254 (45.0%)	5,276 (44.4%)	5,277 (47.5%)	7,643 (49.1%)	8,684 (49.4%)	8,949 (48.8%)
Degree level or above	6,208 (44.7%)	5,736 (48.2%)	5,030 (45.2%)	6,352 (40.8%)	7,526 (42.8%)	8,126 (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 (%)	7,615 (54.9%)	7,765 (65.4%)	8,088 (72.9%)	8,052 (51.8%)	10,654 (60.7%)	12,262 (67.0%)
Cigarette smoking, n (%)						
Never	7,087 (51.0%)	6,476 (54.5%)	6,158 (55.4%)	9,253 (59.4%)	10,793 (61.4%)	11,424 (62.3%)
Previous	5,500 (39.6%)	4,527 (38.1%)	4,126 (37.1%)	5,206 (33.4%)	5,789 (32.9%)	6,022 (32.8%)
Current	1,259 (9.1%)	863 (7.3%)	814 (7.3%)	1,085 (7.0%)	955 (5.4%)	857 (4.7%)
Alcohol consumption, n (%)						
Never or previous	675 (4.9%)	494 (4.2%)	461 (4.1%)	1,178 (7.6%)	1,021 (5.8%)	1,082 (5.9%)
< Twice a week	5,661 (40.8%)	4,451 (37.4%)	4,287 (38.6%)	8,437 (54.2%)	8,859 (50.4%)	8,856 (48.3%)
At least three times a week	7,546 (54.3%)	6,939 (58.4%)	6,363 (57.2%)	5,952 (38.2%)	7,684 (43.7%)	8,396 (45.8%)
Added salt intake, n (%)						
Never/rarely	8,097 (58.3%)	7,018 (59.0%)	6,548 (58.9%)	9,423 (60.5%)	10,671 (60.7%)	11,335 (61.8%)
Sometimes or more frequent	3,801 (27.4%)	3,333 (28.0%)	3,123 (28.1%)	4,220 (27.1%)	4,861 (27.7%)	4,916 (26.8%)
Usually/Always	1,987 (14.3%)	1,537 (12.9%)	1,441 (13.0%)	1,932 (12.4%)	2,038 (11.6%)	2,091 (11.4%)
Oily fish consumption, n (%)						
More than once a week	7,543 (54.5%)	6,428 (54.2%)	6,001 (54.1%)	9,071 (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)
Mean sleep duration, n (%)						
<7 hours/day	2,920 (21.0%)	2,600 (21.9%)	2,702 (24.3%)	3,483 (22.4%)	3,757 (21.4%)	3,754 (20.5%)
7-8 hours/day	9,841 (70.8%)	8,691 (73.1%)	7,971 (71.7%)	10,682 (68.6%)	12,609 (71.7%)	13,678 (74.5%)
>8 hours/day	1,096 (7.9%)	585 (4.9%)	430 (3.9%)	1,351 (8.7%)	1,164 (6.6%)	870 (4.7%)
Parental history of cardiovascular disease or cancer, n (%)	9,974 (72.8%)	8,392 (71.5%)	7,520 (68.6%)	11,695 (76.2%)	12,824 (73.9%)	12,834 (70.8%)
Body mass index, n (%)						
Normal weight (<25 kg/m^2)	3,322 (23.9%)	3,699 (31.1%)	4,382 (39.4%)	5,266 (33.8%)	8,236 (46.9%)	10,956 (59.7%)
Overweight (25-30 kg/m^2)	6,772 (48.8%)	6,050 (50.9%)	5,337 (48.0%)	5,893 (37.8%)	6,433 (36.6%)	5,570 (30.4%)
Obese (≥30 kg/m^2)	3,754 (27.0%)	2,123 (17.9%)	1,388 (12.5%)	4,376 (28.1%)	2,885 (16.4%)	1,804 (9.8%)
Current prescription of blood pressure or cholesterol medicine, n (%)	4,575 (33.1%)	2,782 (23.5%)	1,810 (16.3%)	3,725 (24.0%)	2,773 (15.8%)	1,964 (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 (%)	1,806 (13.0%)	1,168 (9.8%)	874 (7.9%)	2,414 (15.5%)	2,178 (12.4%)	1,870 (10.2%)
Mobility limitation, n (%)	5,829 (42.0%)	4,000 (33.7%)	3,321 (29.9%)	6,124 (39.4%)	5,460 (31.1%)	4,630 (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= Euclidian Norm Minus One.

*Shows the number and crude incident CVD event rates per 1000 person-years.

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 Supplemental 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 Supplemental Figure S4. Season of accelerometer wear is described in Supplemental Figure S2.

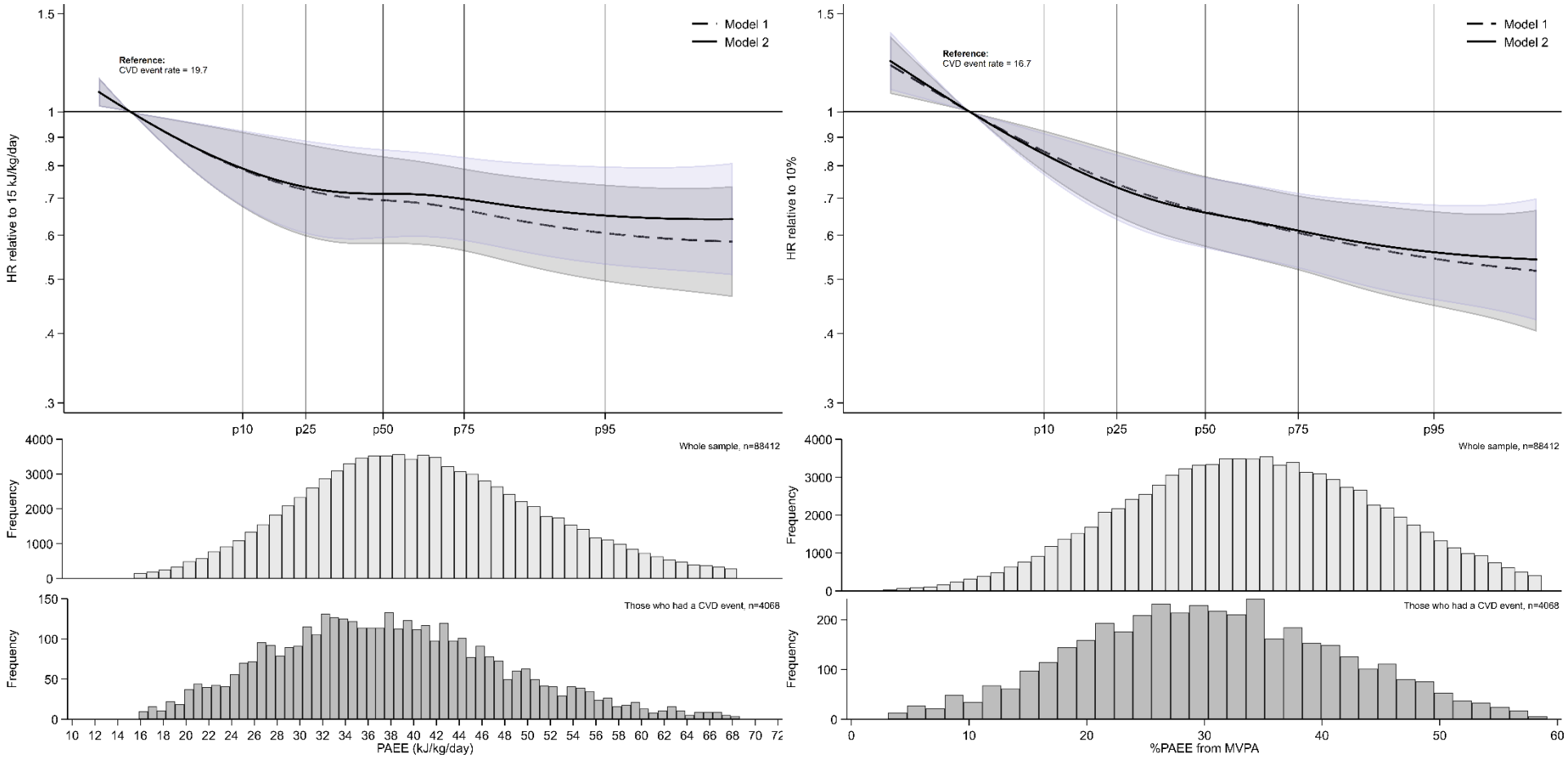

Figure 1. Baseline exposure distribution and adjusted hazard ratios of incident CVD comparing different volumes of PAEE and different fractions of PAEE from MVPA.

- %PAEE from MVPA models are additionally adjusted for PAEE.
- 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 CVD event.
- Reference CVD event rates depict the crude incident CVD event rate per 1000 person-years, buffered around the reference zone for each exposure (i.e., ≤17.5 kJ/kg/day and ≤15 %PAEE from MVPA).
- 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 Supplemental Figure S6.

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=4,068; 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 <2yr 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*	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 <2yr 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)

Note: Model 1b (n=77,606, no. of events=2,919); Model 1c (n=85,451, no. of events=3,891).

* %PAEE from MVPA models are additionally adjusted for PAEE. Models 1 and 2 are displayed on Figure 1.

- 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.

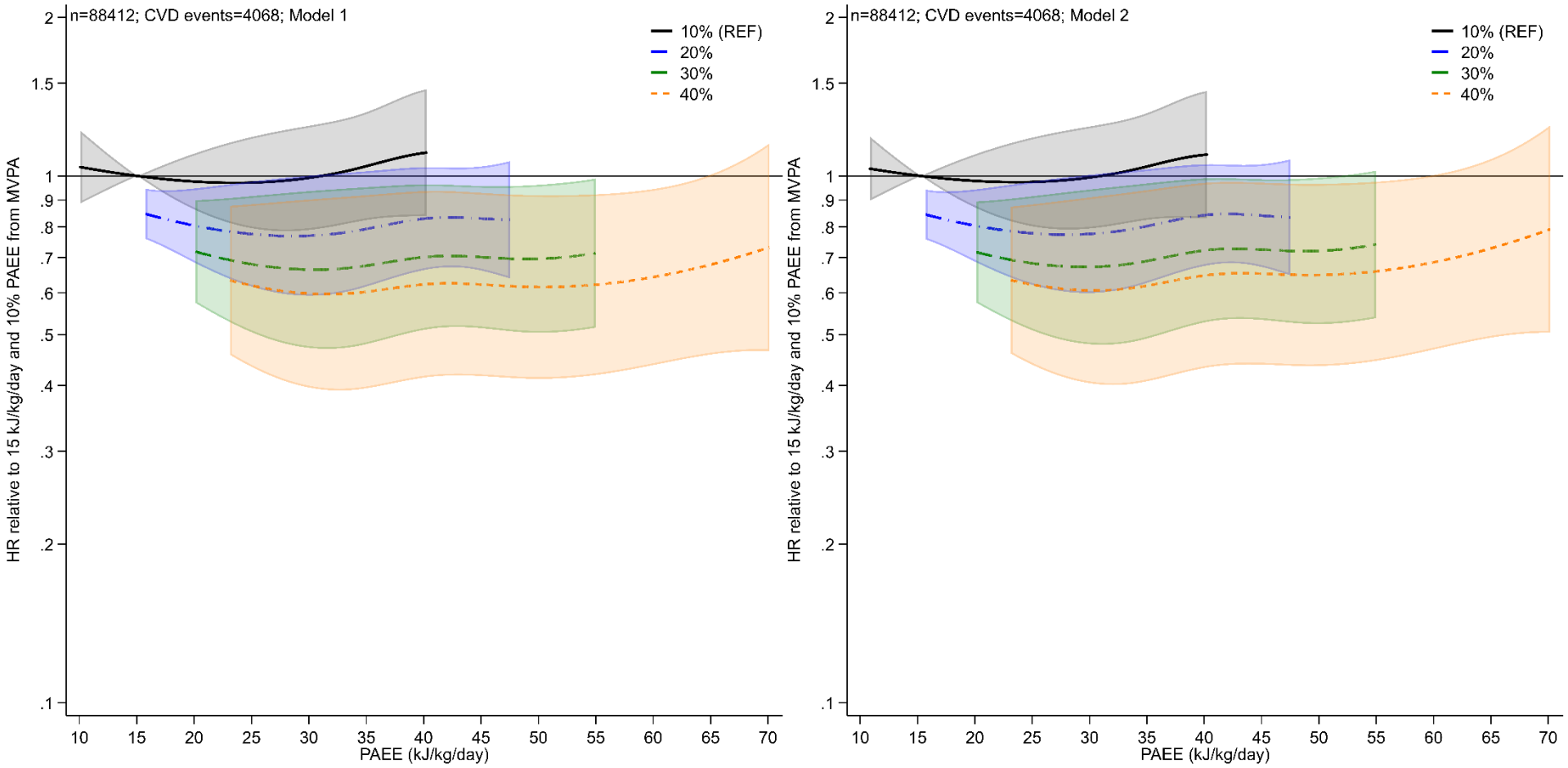

Figure 2. Associations of volume of PAEE and the %PAEE from MVPA with incident CVD.

- All hazard ratios are relative to a PAEE of 15 kJ/kg/day and 10% fraction from MVPA (i.e. hazard ratio, 1).
- Moving right along each line reflects the hazard ratio for a higher PAEE volume but a constant %PAEE from MVPA. A comparison between lines at a given point on the x-axis therefore reflects the hazard ratio for an increase in intensity but at a constant PAEE. Hazard ratios (95% CI) are shown for values between the 1st or 99th percentiles of the PAEE distribution among those who had a CVD 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.

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		88412		77606	85451
Person-years		584568		516559	565068
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.

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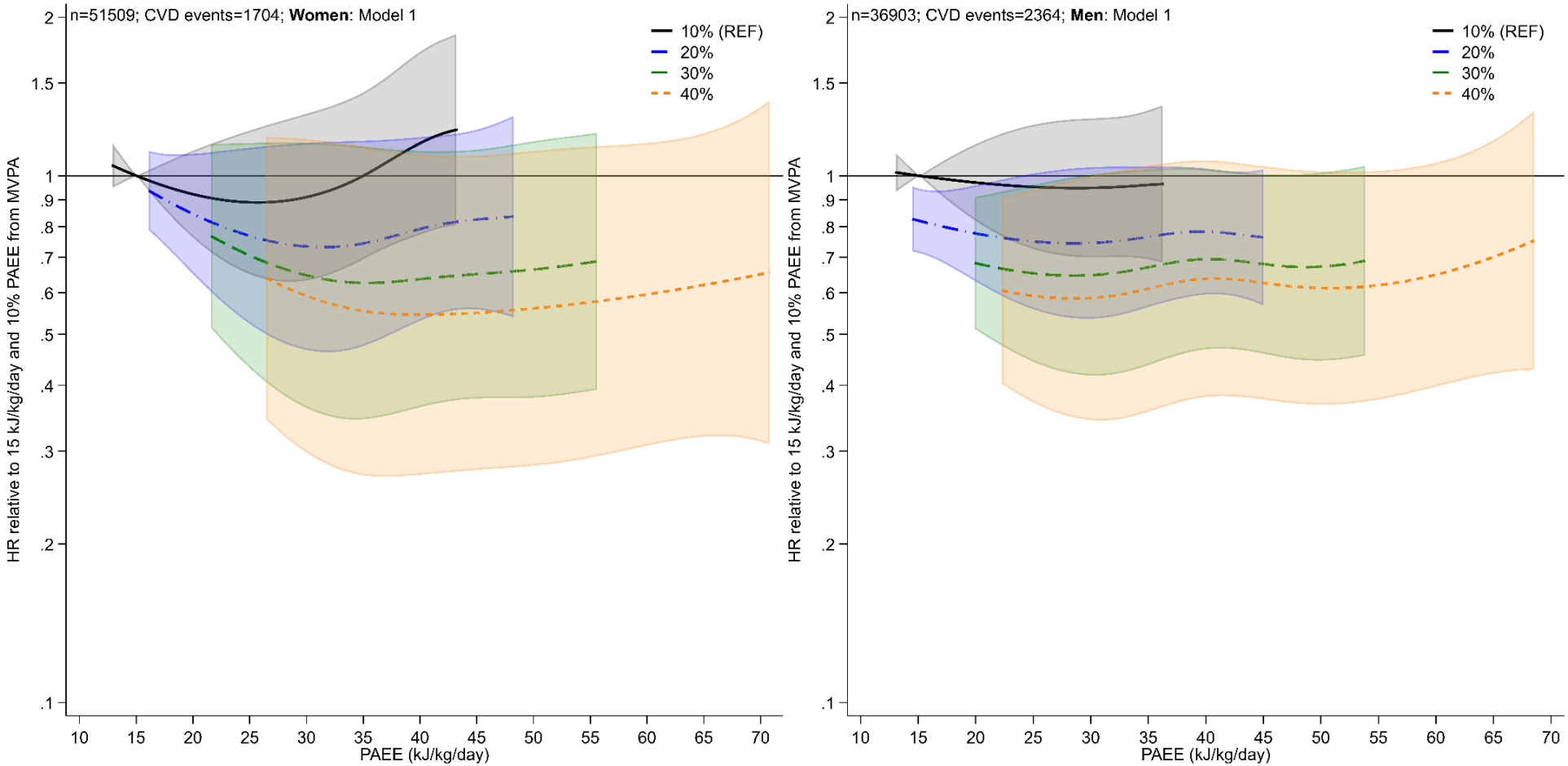


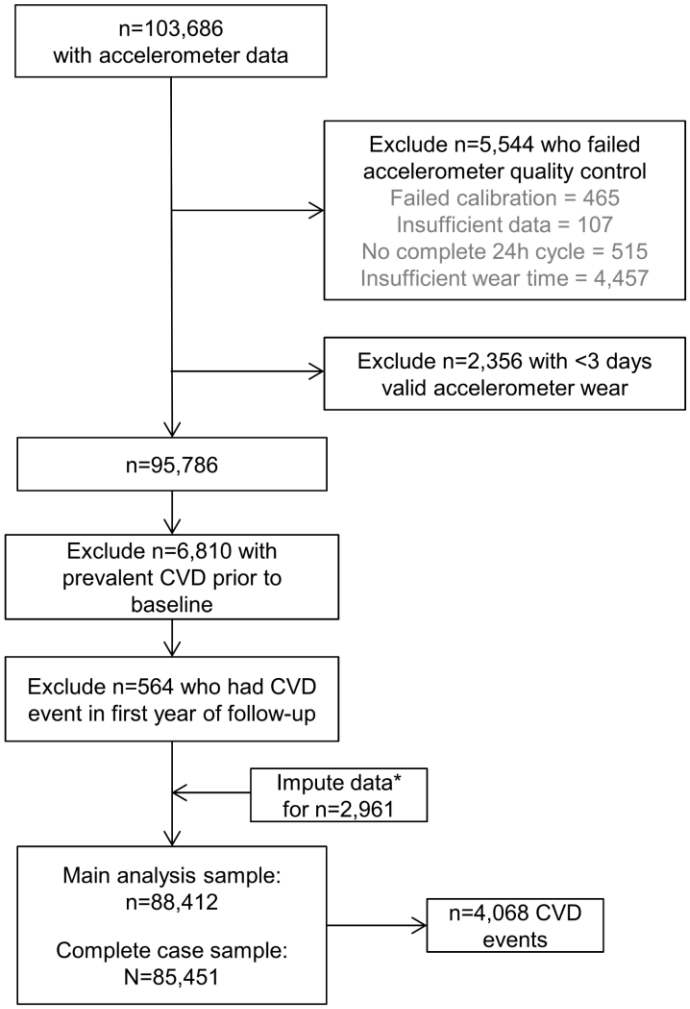
Figure 3. Associations of volume of PAEE the %PAEE from MVPA with incident CVD (model 1), by sex.

- All hazard ratios are relative to a PAEE of 15 kJ/kg/day and 10% fraction from MVPA. Moving right along each line reflects the hazard ratio for a higher PAEE volume but a constant %PAEE from MVPA. A comparison between lines at a given point on the x-axis reflects the hazard ratio for an increase in intensity, but a constant PAEE. Hazard ratios shown for values between the 1st or 99th percentiles of the PAEE distribution among those who had a CVD 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.
- Supplemental Figure S5 displays results for model 2. Further details are also shown in Supplemental Table S4.

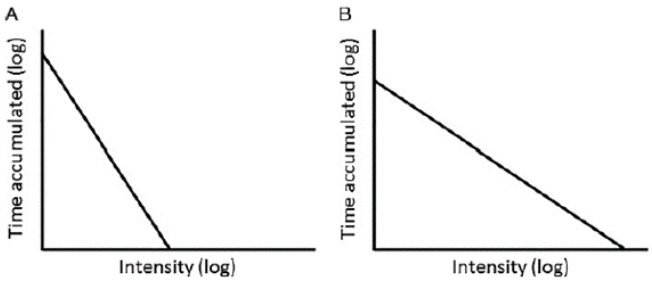
Supplemental Material

Supplemental Figure S1: Flowchart of participant exclusions.



***We used multiple imputation by chained equations (5 imputed datasets) for individuals with missing covariates (n=2961). 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.

Supplemental Table S1: Summary and description of PA volume and intensity variables**.**

Exposure	Description	Interpretation
Volume		
Physical activity energy expenditure (PAEE), kJ/kg/day	- Time spent in each accelerometer intensity level is converted into a value of PAEE (kJ/kg/day) using equations[1] derived from combined heart rate and trunk acceleration sensors, validated in UK age-matched samples against the gold-standard criterion of doubly labeled water (1, 2). - Predicted PAEE is calculated as the sum of energy expenditure from all intensity levels (3).	- A higher value indicates higher volume of PAEE. - note: PAEE and ENMO are very highly correlated metrics of overall PA volume (see *Supplemental Figure S4*)
Total PA – Euclidean Norm Minus One (ENMO), m*g*	- Based on the Euclidean Norm (vector magnitude) of the three processed acceleration signals Minus One (with negative values rounded to zero) derived from dominant wrist accelerometry, also referred to as ENMO (4-6). - Summarized as average 24-hour acceleration over all valid days (proxy for total PA).	- A higher value indicates higher total PA (acceleration).
Intensity		
%PAEE from MVPA	The fraction of PAEE from MVPA (3) is the sum of predicted energy expenditure from wrist-worn accelerometry above 3 METs[2] (threshold of 125 m*g*) divided by total PAEE, expressed as a percentage.	- A higher value indicates higher fraction of PAEE is spent in MVPA.
Intensity gradient, unitless	- The intensity gradient describes the negative curvilinear relationship between PA intensity and the time accumulated at that intensity (7) over 24-h. - The intensity gradient is always negative, reflecting the decrease in time accumulated as intensity increases.  **A)** A ***steeper, more negative (lower)*** gradient with a higher constant (y-intercept) showing a steep drop in time accumulated with increasing intensity (left)—a 'poorer' intensity profile. **B)** A ***shallower, less negative (higher)*** gradient with a lower constant (y-intercept) showing more time spread across the intensity range (right)—a 'better' intensity profile.	- a higher (less negative) value indicates proportionally more time is habitually spent in higher intensity activities (e.g., brisk walking), or more time spread across the intensity distribution.

[1] The quadratic equation from White et al. (1) converts dominant wrist accelerometry ENMO processed signal into activity-related energy expenditure measured in J/min/kg: -10.58 + 1.1176*(1.5 + .8517*x) + 2.9418*sqrt((1.5 + .8517*x)) - 0.00059277*((1.5 + .8517*x)^2), where x is the category midpoint in m*g*. This was derived through calibration to PAEE measured by combined heart rate and trunk acceleration in 1695 UK adults (2). This approach has subsequently been validated against total PAEE measured using gold-standard doubly-labelled water in 97 adults (r=0.676) (1).

[2] 1 MET is the standard resting metabolic rate defined as 1.0 kcal/kg/h (8).

References

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8. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-81.

Supplemental Table S2. Descriptive characteristics of the sample at baseline, by sex and tertiles of %PAEE from MVPA.

Characteristics	Men (n=36,903; incident CVD events=2,364)			Women (n=51,509; incident CVD events=1,704)		
	Tertile 1 (n=10,783)	Tertile 2 (n=12,217)	Tertile 3 (n=13,903)	Tertile 1 (n=18,688)	Tertile 2 (n=17,254)	Tertile 3 (n=15,567)
Follow-up time (years), median (IQR)	6.7 (6.1-7.2)	6.8 (6.2-7.3)	6.8 (6.2-7.3)	6.8 (6.2-7.3)	6.8 (6.2-7.3)	6.9 (6.3-7.4)
Person-years	69,297	80,373	92,215	122,859	114,916	104,909
Incident CVD events, n (rate)*	996 (14.4)	742 (9.2)	626 (6.8)	935 (7.6)	494 (4.3)	275 (2.6)
Age (years), mean (SD)	65.8 (7.0)	62.5 (7.8)	59.9 (7.8)	64.6 (7.2)	61.2 (7.5)	58.7 (7.4)
White ethnicity, n (%)	10,497 (97.7%)	11,812 (97.0%)	13,384 (96.6%)	18,127 (97.3%)	16,627 (96.6%)	14,953 (96.3%)
Highest educational level achieved, n (%)						
No qualification	1,089 (10.1%)	924 (7.6%)	841 (6.0%)	1,778 (9.5%)	1,199 (6.9%)	878 (5.6%)
Any other qualification	5,021 (46.6%)	5,632 (46.1%)	6,154 (44.3%)	9,555 (51.1%)	8,448 (49.0%)	7,273 (46.7%)
Degree level or above	4,584 (42.5%)	5,561 (45.5%)	6,829 (49.1%)	7,181 (38.4%)	7,489 (43.4%)	7,334 (47.1%)
Townsend indicator of multiple deprivation, median (IQR)	-2.57 (-3.88--0.47)	-2.60 (-3.92--0.39)	-2.40 (-3.80--0.13)	-2.47 (-3.80--0.27)	-2.43 (-3.82--0.16)	-2.31 (-3.73-0.08)
In employment, n (%)	5,593 (52.0%)	7,850 (64.4%)	10,025 (72.3%)	9,118 (48.9%)	10,868 (63.1%)	10,982 (70.7%)
Cigarette smoking, n (%)						
Never	5,163 (47.9%)	6,635 (54.3%)	7,923 (57.0%)	11,144 (59.6%)	10,625 (61.6%)	9,701 (62.3%)
Previous	4,507 (41.8%)	4,648 (38.0%)	4,998 (35.9%)	6,277 (33.6%)	5,671 (32.9%)	5,069 (32.6%)
Current	1,087 (10.1%)	900 (7.4%)	949 (6.8%)	1,225 (6.6%)	915 (5.3%)	757 (4.9%)
Alcohol consumption, n (%)						
Never or previous	580 (5.4%)	478 (3.9%)	572 (4.1%)	1,437 (7.7%)	1,016 (5.9%)	828 (5.3%)
< Twice a week	4,226 (39.2%)	4,766 (39.0%)	5,407 (38.9%)	9,867 (52.8%)	8,691 (50.4%)	7,594 (48.8%)
At least three times a week	5,973 (55.4%)	6,963 (57.0%)	7,912 (56.9%)	7,368 (39.4%)	7,534 (43.7%)	7,130 (45.8%)
Added salt intake, n (%)						
Never/rarely	6,077 (56.4%)	7,169 (58.7%)	8,417 (60.5%)	11,172 (59.8%)	10,519 (61.0%)	9,738 (62.6%)
Sometimes or more frequent	3,052 (28.3%)	3,390 (27.7%)	3,815 (27.4%)	5,129 (27.4%)	4,760 (27.6%)	4,108 (26.4%)
Usually/Always	1,653 (15.3%)	1,651 (13.5%)	1,661 (11.9%)	2,380 (12.7%)	1,967 (11.4%)	1,714 (11.0%)
Oily fish consumption, n (%)						
More than once a week	6,007 (55.8%)	6,521 (53.6%)	7,444 (53.7%)	11,135 (59.7%)	9,918 (57.6%)	8,617 (55.5%)
Fruit and vegetable intake score, mean (SD)	1.5 (1.1)	1.5 (1.1)	1.5 (1.1)	1.8 (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)	1.00 (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)
Mean sleep duration, n (%)						
<7 hours/day	2,458 (22.8%)	2,686 (22.0%)	3,078 (22.1%)	4,334 (23.2%)	3,666 (21.2%)	2,994 (19.2%)
7-8 hours/day	7,487 (69.4%)	8,821 (72.2%)	10,195 (73.3%)	12,809 (68.5%)	12,480 (72.3%)	11,680 (75.0%)
>8 hours/day	817 (7.6%)	684 (5.6%)	610 (4.4%)	1,476 (7.9%)	1,053 (6.1%)	856 (5.5%)
Parental history of cardiovascular disease or cancer, n (%)	7,878 (74.1%)	8,593 (71.3%)	9,415 (68.7%)	14,104 (76.6%)	12,557 (73.7%)	10,692 (69.6%)
Body mass index, n (%)						
Normal weight (<25 kg/m^2)	2,333 (21.6%)	3,600 (29.5%)	5,470 (39.3%)	6,729 (36.0%)	8,282 (48.0%)	9,447 (60.7%)
Overweight (25-30 kg/m^2)	5,226 (48.5%)	6,262 (51.3%)	6,671 (48.0%)	7,071 (37.8%)	6,199 (35.9%)	4,626 (29.7%)
Obese (≥30 kg/m^2)	3,189 (29.6%)	2,335 (19.1%)	1,741 (12.5%)	4,837 (25.9%)	2,749 (15.9%)	1,479 (9.5%)
Current prescription of blood pressure or cholesterol medicine, n (%)	3,931 (36.6%)	2,958 (24.3%)	2,278 (16.4%)	4,621 (24.8%)	2,438 (14.2%)	1,403 (9.0%)
Diagnosis of diabetes or insulin prescription, n (%)	854 (7.9%)	419 (3.4%)	278 (2.0%)	681 (3.6%)	275 (1.6%)	167 (1.1%)
Previous diagnosis of cancer, n (%)	1,510 (14.0%)	1,261 (10.3%)	1,077 (7.8%)	2,905 (15.6%)	2,069 (12.0%)	1,488 (9.6%)
Mobility limitation, n (%)	4,766 (44.2%)	4,296 (35.2%)	4,088 (29.4%)	7,358 (39.4%)	5,132 (29.8%)	3,724 (23.9%)
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 (6.6-7.0)	6.9 (6.7-7.0)
Valid wear-time, hr/day, median (IQR)	24.0 (23.7-24.0)	24.0 (23.8-24.0)	24.0 (23.8-24.0)	23.8 (23.5-24.0)	23.8 (23.6-24.0)	24.0 (23.6-24.0)
PAEE (kJ/kg/day), mean (SD)	31.29 (7.34)	39.16 (7.42)	49.22 (11.02)	34.23 (7.42)	42.31 (7.50)	52.29 (10.32)
%PAEE from MVPA, mean (SD)	22.77 (5.29)	34.50 (2.79)	47.40 (6.40)	22.46 (5.40)	34.40 (2.81)	46.65 (5.84)
ENMO (mg), mean (SD)	21.10 (4.72)	26.70 (4.90)	34.97 (8.96)	22.85 (4.75)	28.59 (4.92)	36.48 (7.92)
Intensity gradient, mean (SD)	-2.66 (0.15)	-2.51 (0.14)	-2.36 (0.19)	-2.71 (0.14)	-2.56 (0.11)	-2.41 (0.16)

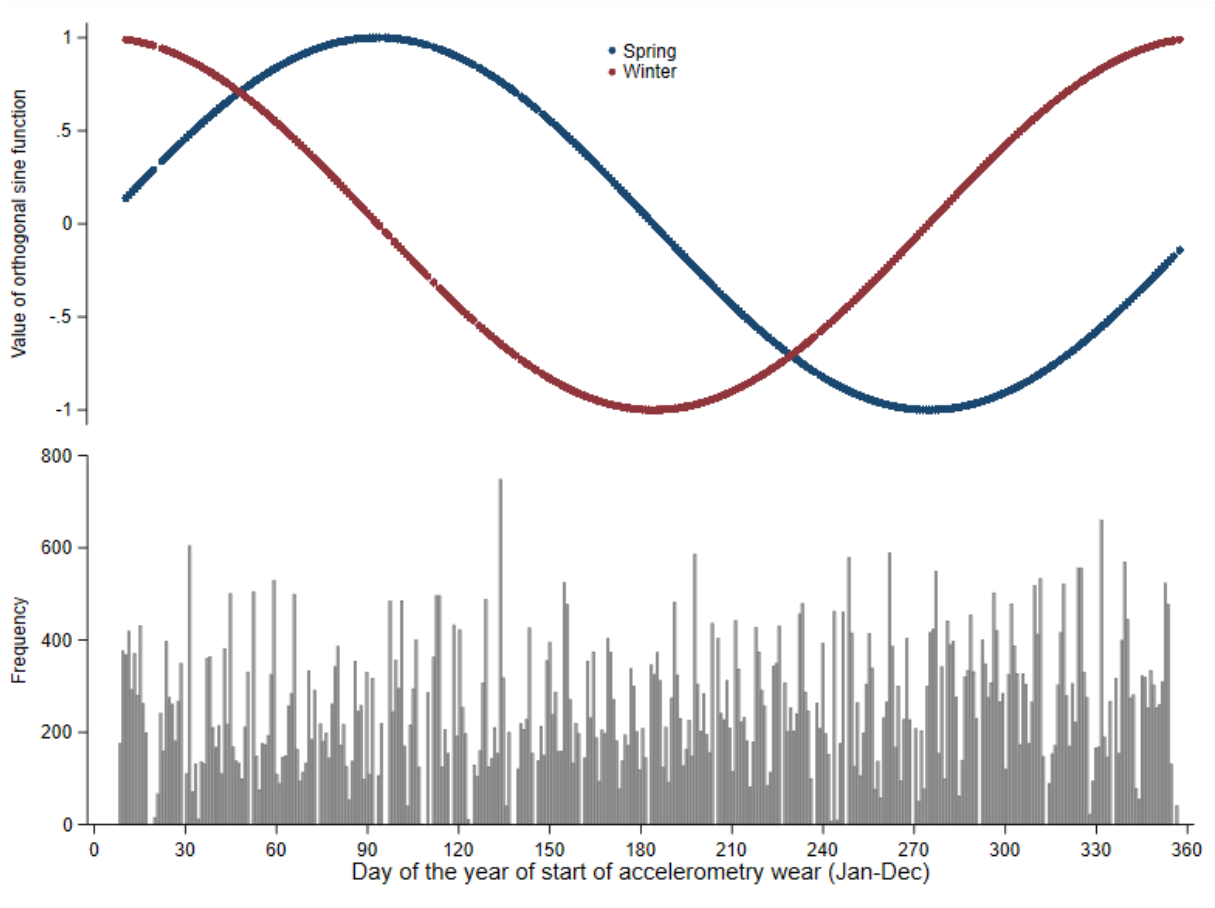
CVD= cardiovascular disease; MVPA= moderate-to-vigorous physical activity; PAEE= physical activity energy expenditure; ENMO= Euclidian Norm Minus One.

*Shows the number and crude incident CVD event rates per 1000 person-years.

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.

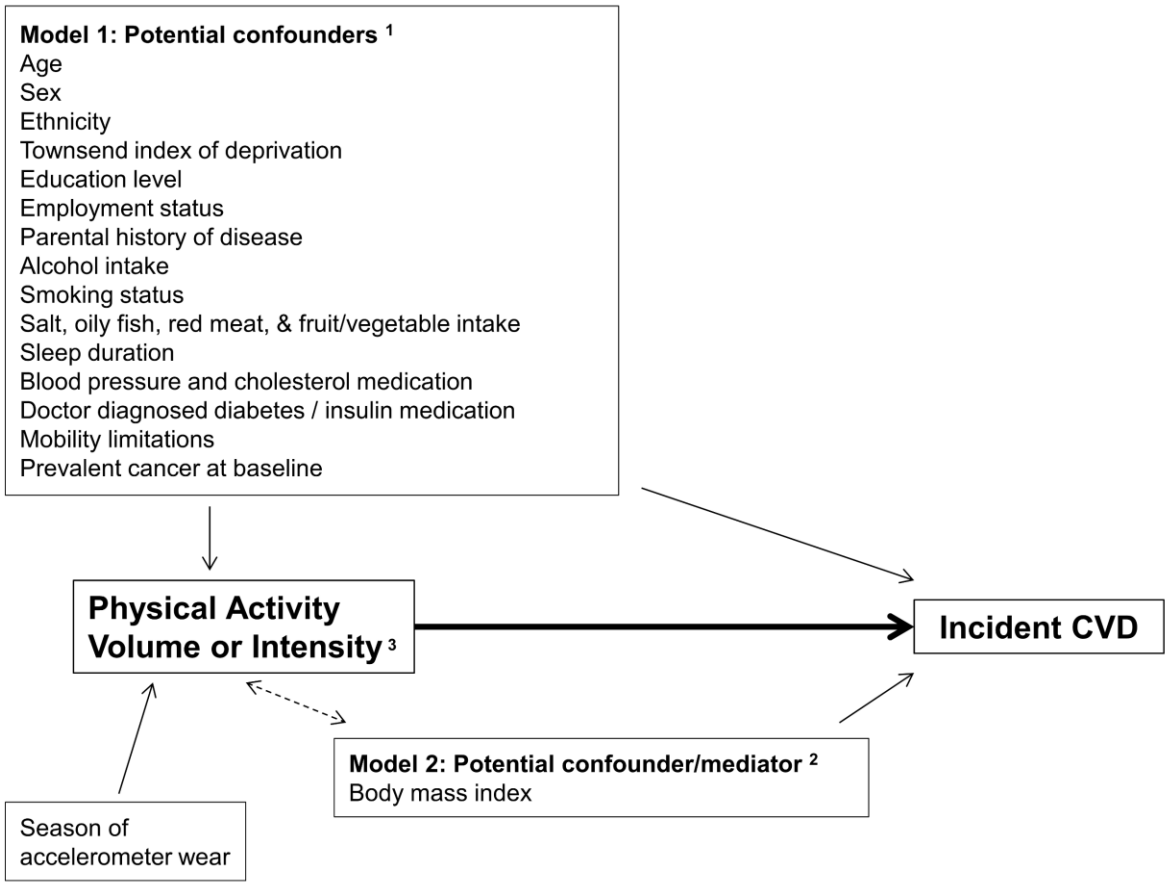
Season of accelerometer wear is described in Supplemental Figure S2.

Supplemental Figure S2: Descriptive statistics for the season of wear variable (n=88,412)



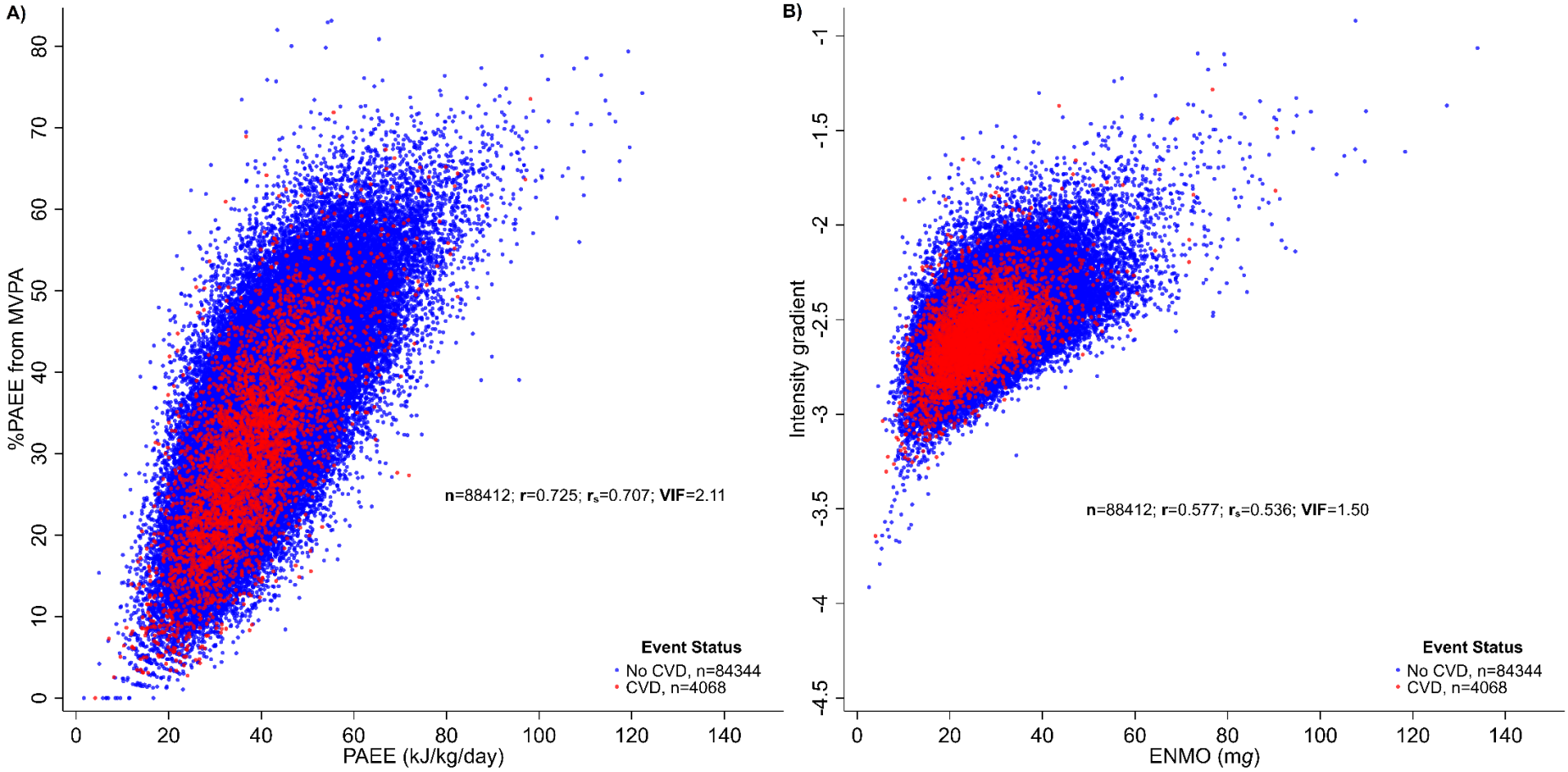
Orthogonal sine functions formulae:
spring = sin(2 * π * dayofyear / 365.25)
winter = cos(2 * π * dayofyear / 365.25)

Supplemental Figure S3: Directed Acyclic Graph representing the assumed relationships between the included variables.



[1] Plausible associations with both the exposure (physical activity) and outcome (incident CVD).
[2] Plausible associations with both the exposure (physical activity) and outcome (incident CVD), but also potential bi-directional associations with the exposure (physical activity).
[3] All %MVPA from PAEE models are adjusted for PAEE.

Supplemental Figure S4: Scatter plots showing the relationships between two metrics of PA volume (PAEE and ENMO) vs. intensity (%PAEE from MVPA and intensity gradient), respectively. Correlation coefficients are also displayed between all PA variables.



Pearson's (r)	ENMO	PAEE	IG	%MVPA from PAEE
ENMO	1			
PAEE	.966	1		
Intensity gradient	.577	.478	1	
%MVPA from PAEE	.763	.725	.738	1

Spearman's (r_s)	ENMO	PAEE	IG	%MVPA from PAEE
ENMO	1			
PAEE	.978	1		
Intensity gradient	.536	.465	1	
%MVPA from PAEE	.752	.707	.736	1

r=Pearson's correlation coefficient; r_s=Spearman's correlation coefficient; VIF=variance inflation factor; MVPA=moderate-to-vigorous intensity PA; PAEE=physical activity energy expenditure; ENMO=Euclidean Norm Minus One; IG=intensity gradient. See Table S1 for a more detailed description of the PA volume/intensity metrics.

Supplemental Table S3: Time-based equivalents at two intensity levels for different combinations of the PAEE and %PAEE from MVPA.

Assumptions	METs	mMETS	kJ/kg/h
LPA ("stroll")	2.5	1.5	6.3
MVPA ("brisk walk")	4	3	12.6

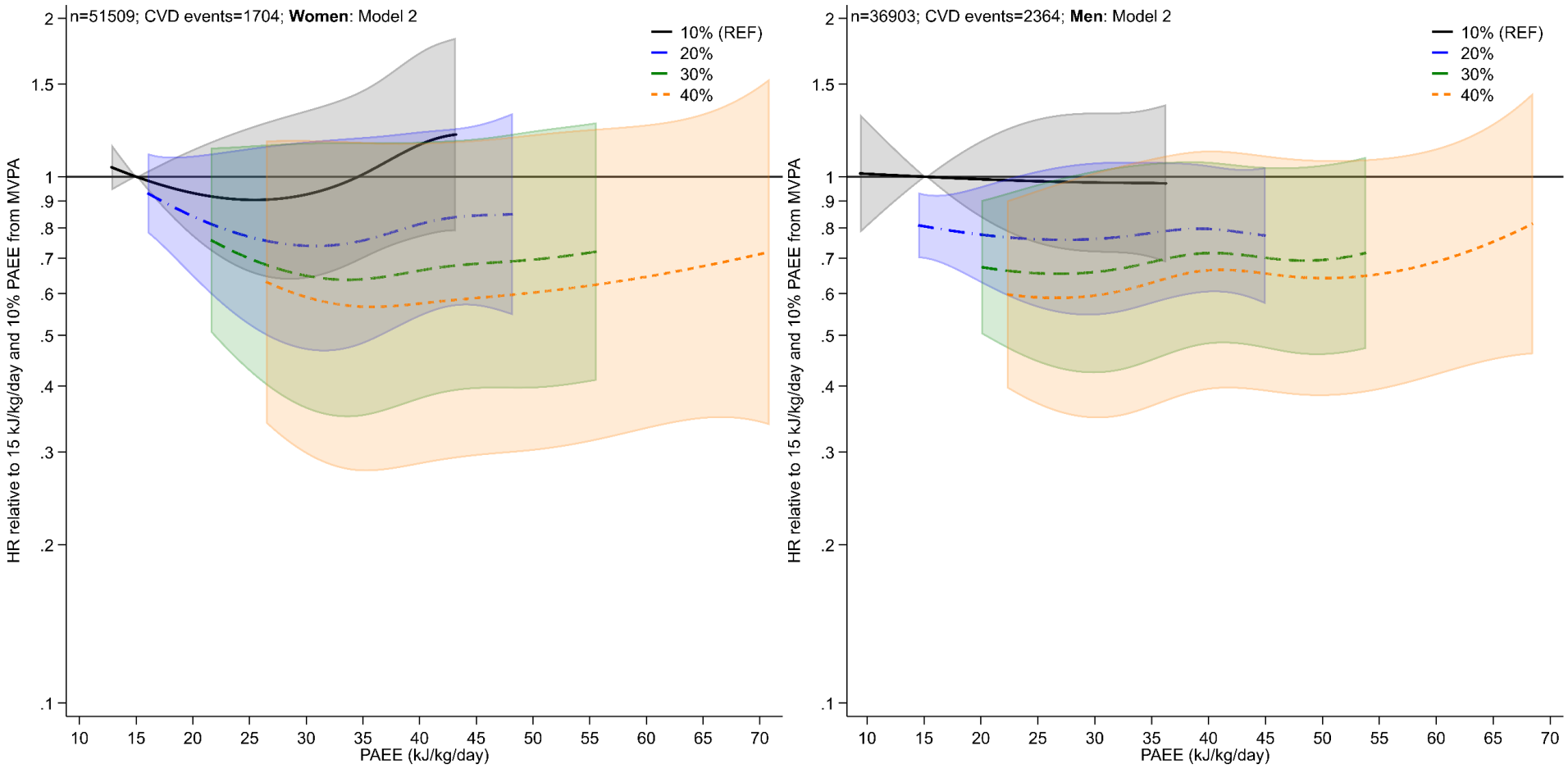
mMET = MET - 1
kJ/kg/h = mMET * 4.184 [1 kcal = 4.184 kJ]

PAEE (kJ/kg/d)	%PAEE from MVPA	EE from LPA (kJ/kg/d)	EE from MVPA (kJ/kg/d)	Absolute difference in MVPA EE compared to REF (kJ/kg/d)	LPA time equivalent (min)*	MVPA time equivalent (min)*	Difference in LPA (min) compared to REF	Difference in MVPA (min) compared to REF	Difference in time commitment (min) compared to REF	Plain language statement
15	10	13.5	1.5	***REF***	129	7	***REF***	***REF***	***REF***	
15	20	12	3	1.5	115	14	-14	7	-7	Convert 14 min stroll to 7 min brisk walk
15	30	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
15	40	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20	10	18	2	0.5	172	10	43	2	45	Add 43 min stroll & 2 min brisk walk
20	20	16	4	2.5	153	19	24	12	36	Add 24 min stroll & 12 min brisk walk
20	30	14	6	4.5	134	29	5	22	26	Add 5 min stroll & 22 min brisk walk
20	40	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
30	10	27	3	1.5	258	14	129	7	136	Add 129 min stroll & 7 min brisk walk
30	20	24	6	4.5	229	29	100	22	122	Add 100 min stroll & 22 min brisk walk
30	30	21	9	7.5	201	43	72	36	108	Add 72 min stroll & 36 min brisk walk
30	40	18	12	10.5	172	57	43	50	93	Add 43 min stroll & 50 min brisk walk
40	10	36	4	2.5	344	19	215	12	227	Add 215 min stroll & 12 min brisk walk
40	20	32	8	6.5	306	38	177	31	208	Add 177 min stroll & 31 min brisk walk
40	30	28	12	10.5	268	57	139	50	189	Add 139 min stroll & 50 min brisk walk
40	40	24	16	14.5	229	76	100	69	170	Add 100 min stroll & 69 min brisk walk
50	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
50	20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
50	30	35	15	13.5	335	72	206	65	270	Add 205 min stroll & 65 min brisk walk
50	40	30	20	18.5	287	96	158	88	246	Add 158 min stroll & 88 min brisk walk
60	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
60	20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
60	30	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
60	40	36	24	22.5	344	115	215	108	323	Add 215 min stroll & 108 min brisk walk

LPA= light-intensity PA; MVPA= moderate-to-vigorous PA; VPA= vigorous PA; mMET= marginal MET; EE= energy expenditure; REF= reference category
N/A= 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.

- EE from LPA calculated as: (1 - %MVPA / 100) * PAEE; EE from MVPA calculated as: (%MVPA / 100) * PAEE

*Time equivalents (min) given key intensity assumptions (kJ/kg/h) for LPA and MVPA.
- LPA time equivalent calculated as: (EE from LPA / LPA kJ/kg/h) * 60
- MVPA time equivalent calculated as: (EE from MVPA / MVPA kJ/kg/h) * 60



Supplemental Figure S5. Associations of volume of PAEE the %PAEE from MVPA with incident CVD (model 2), by sex.

- All hazard ratios are relative to a PAEE of 15 kJ/kg/day and 10% fraction from MVPA (i.e. hazard ratio, 1).
- Moving right along each line reflects the hazard ratio for a higher PAEE volume but a constant %PAEE from MVPA. A comparison between lines at a given point on the x-axis therefore reflects the hazard ratio for an increase in intensity but at a constant PAEE. Hazard ratios (95% CI) are shown for values between the 1st or 99th percentiles of the PAEE distribution among those who had a CVD event.

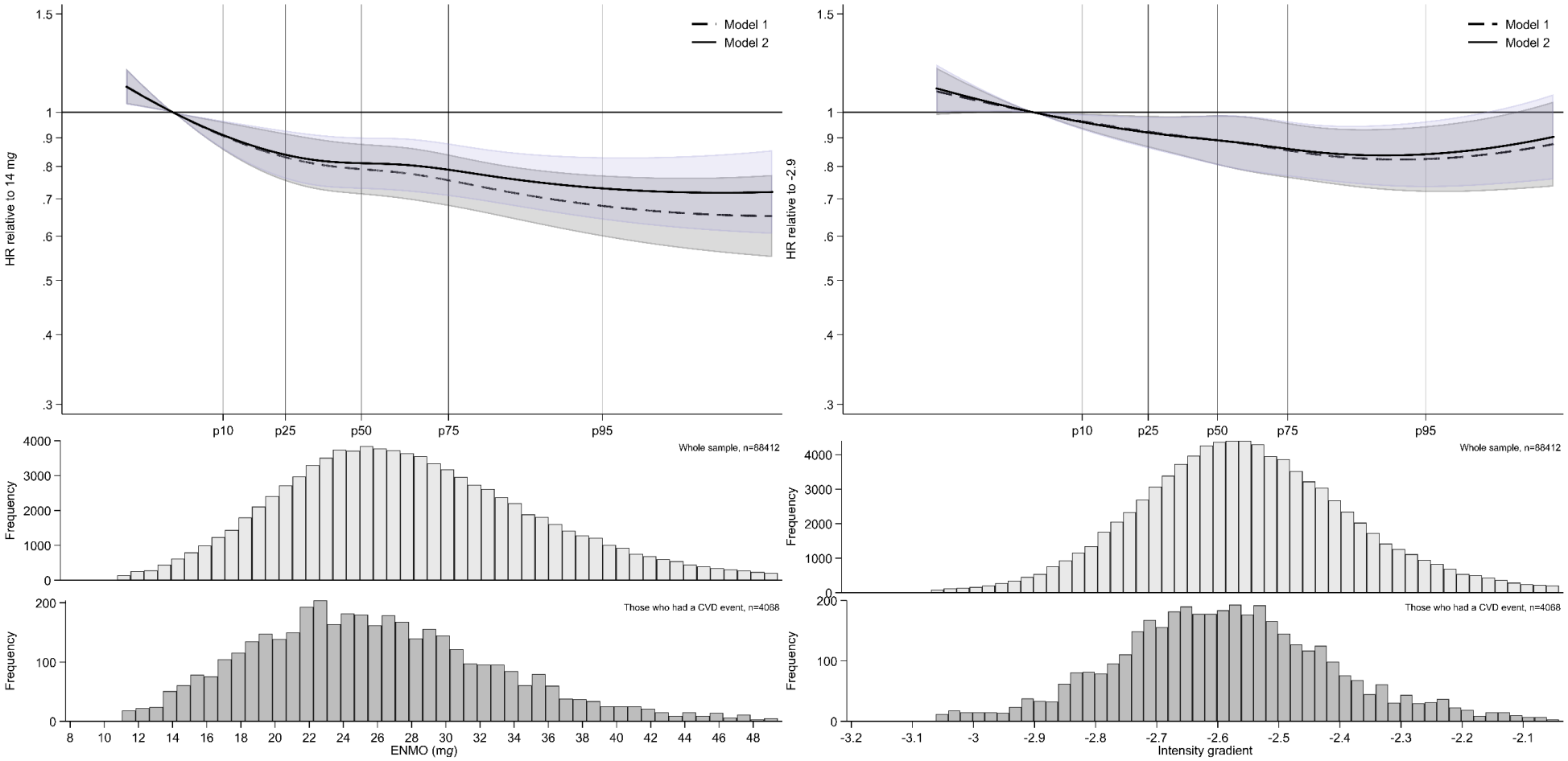
- Model 2 is adjusted for season of accelerometer wear (with age as the underlying time scale), ethnicity, education level, employment status, Townsend index of deprivation, dietary variables, alcohol intake, smoking status, average sleep duration, parental history of cardiovascular disease or cancer, blood pressure or cholesterol medication use, insulin prescription or diagnosed diabetes, mobility limitation, prevalent cancer, and body mass index.
- Figure 3 displays results for model 1. Further details are shown in Supplemental Table S4.

Supplemental Table S4. Adjusted hazard ratios of incident CVD for different values of volume of PAEE and the fraction of PAEE from MVPA, stratified by sex.

		Women		Men	
		Model 1	**Model 2**	**Model 1**	**Model 2**
n		51509		36903	
Person-years		342683		241884	
CVD events		1704		2364	
PAEE	**%PAEE from MVPA**				
15	10	1 (REF)	1 (REF)	1 (REF)	1 (REF)
	20	0.97 (0.82-1.14)	0.82 (0.71-0.95)	0.95 (0.81-1.13)	0.80 (0.70-0.93)
	30	N/A	N/A	N/A	N/A
	40	N/A	N/A	N/A	N/A
20	10	0.92 (0.77-1.11)	0.97 (0.82-1.15)	0.93 (0.77-1.13)	0.99 (0.83-1.17)
	20	0.85 (0.66-1.10)	0.78 (0.63-0.96)	0.84 (0.65-1.10)	0.78 (0.63-0.96)
	30	N/A	N/A	0.79 (0.55-1.14)	0.67 (0.50-0.90)
	40	N/A	N/A	N/A	N/A
30	10	0.91 (0.63-1.31)	0.95 (0.70-1.28)	0.93 (0.64-1.34)	0.98 (0.72-1.32)
	20	0.73 (0.47-1.15)	0.75 (0.54-1.04)	0.74 (0.47-1.17)	0.76 (0.55-1.06)
	30	0.65 (0.36-1.16)	0.65 (0.42-1.00)	0.65 (0.36-1.16)	0.66 (0.42-1.03)
	40	0.59 (0.30-1.17)	0.59 (0.34-1.00)	0.59 (0.30-1.17)	0.59 (0.35-1.02)
40	10	1.15 (0.77-1.72)	0.96 (0.65-1.42)	N/A	N/A
	20	0.79 (0.53-1.18)	0.78 (0.59-1.03)	0.81 (0.54-1.22)	0.80 (0.60-1.05)
	30	0.64 (0.36-1.11)	0.69 (0.47-1.03)	0.66 (0.38-1.17)	0.72 (0.48-1.07)
	40	0.54 (0.27-1.10)	0.64 (0.38-1.07)	0.57 (0.28-1.16)	0.66 (0.39-1.12)
50	10	N/A	N/A	N/A	N/A
	20	N/A	N/A	N/A	N/A
	30	0.66 (0.38-1.16)	0.67 (0.45-1.01)	0.70 (0.40-1.22)	0.70 (0.46-1.05)
	40	0.56 (0.28-1.11)	0.61 (0.37-1.02)	0.60 (0.30-1.20)	0.64 (0.38-1.08)
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	0.60 (0.31-1.15)	0.65 (0.40-1.06)	0.65 (0.33-1.26)	0.69 (0.42-1.13)

- 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 3 and Supplemental Figure S5.

- 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.



Supplemental Figure S6. Baseline exposure distribution and adjusted hazard ratios of incident CVD comparing different amounts of ENMO (a measure of total PA) and different levels of intensity gradient (a measure of the intensity distribution of PA).

- Intensity gradient models are additionally adjusted for total PA – defined here as Euclidean Norm Minus One (ENMO). A higher (less negative) intensity gradient (intensity distribution of PA) indicates more time is habitually spent in higher intensity activities (e.g., brisk walking) over a day.
- Models were fitted with the use of restricted 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 CVD 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.
- A higher (less negative) intensity gradient value indicates more time is habitually spent in higher intensity activities (e.g., brisk walking).
- See Supplemental 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 Supplemental Figure S4.