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Physical activity intensity profiles associated with cardiometabolic risk in middle-aged to older men and women

Paddy C. Dempsey [a,b,c,*], Eivind Aadland [d], Tessa Strain [a], Olav M. Kvalheim [e], Kate Westgate [a], Tim Lindsay [a], Kay-Tee Khaw [a], Nicholas J. Wareham [a], Søren Brage [a], Katrien Wijndaele [a]

[a] MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, UK
[b] Physical Activity & Behavioural Epidemiology Laboratories, Baker Heart & Diabetes Institute, Melbourne, Australia
[c] Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK
[d] Faculty of Education, Arts and Sports, Department of Sport, Food and Natural Sciences, Campus Sogndal, Western Norway University of Applied Sciences, Sogndal, Norway
[e] Department of Chemistry, University of Bergen, Bergen, Norway

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ABSTRACT

Accelerometers provide detailed data about physical activity (PA) across the full intensity spectrum. However, when examining associations with health, results are often aggregated to only a few summary measures [e.g. time spent "sedentary" or "moderate-to-vigorous" intensity PA]. Using multivariate pattern analysis, which can handle collinear exposure variables, we examined associations between the full PA intensity spectrum and cardiometabolic risk (CMR) in a population-based sample of middle-aged to older adults. Participants ($n = 3660$; mean ± SD age = 69 ± 8y and BMI = 26.7 ± 4.2 kg/m^2; 55% female) from the EPIC-Norfolk study (UK) with valid accelerometry (ActiGraph-GT1M) data were included. We used multivariate pattern analysis with partial least squares regression to examine cross-sectional multivariate associations (r) across the full PA intensity spectrum [minutes/day at 0–5000 counts-per-minute (cpm); 5 s epoch] with a continuous CMR score (reflecting waist, blood pressure, lipid, and glucose metabolism). Models were sex-stratified and adjusted for potential confounders. There was a positive (detrimental) association between PA and CMR at 0-12 cpm (maximally-adjusted $r = 0.08$ (95%CI 0.06–0.10). PA was negatively (favourably) associated with CMR at all intensities above 13 cpm ranging between $r = -0.09$ (0.07–0.12) at 800-999 cpm and $r = -0.14$ (0.11–0.16) at 75–99 and 4000-4999 cpm. The strongest favourable associations were from 50 to 800 cpm ($r = 0.10$–0.12) in men, but from ≥2500 cpm ($r = 0.18$–0.20) in women; with higher proportions of model explained variance for women ($R^2 = 7.4\%$ vs. 2.3%). Most of the PA intensity spectrum was beneficially associated with CMR in middle-aged to older adults, even at intensities lower than what has traditionally been considered "sedentary" or "light-intensity" activity. This supports encouragement of PA at almost any intensity in this age-group.

1. Introduction

Recent research utilising wearable devices (accelerometers) has shown physical activity (PA) intensity may play a role in mortality risk over and above total PA volume (Strain et al., 2020). Accelerometers provide high resolution time-stamped data on both total PA volume and across the full spectrum of PA intensities (Doherty et al., 2017; Golubic et al., 2014; Berkemeyer et al., 2016; Lindsay et al., 2019). However, one barrier to investigating the full PA intensity spectrum in relation to health outcomes is that time spent at different intensities are highly correlated with each other (i.e. multicollinearity) and thus challenging to model together. Although compositional data analysis approaches can address co-dependency of PA intensities, it remains common to collapse detailed PA intensity information into broad summary variables (e.g. time spent in moderate-to-vigorous intensity activity, sedentary time) using pre-defined cutpoints to give behavioural and biological meaning (Whitaker et al., 2019; Swindell et al., 2018; Powell et al., 2018; LaMonte et al., 2017; Alessa et al., 2017; Brocklebank et al., 2015; Henson et al., 2013; Healy et al., 2008; Healy et al., 2007). While this approach can lead to more easily interpretable messages, it can lead to loss of information and, importantly, pre-supposes which intensities are most important to examine with respect to health, rather than letting

* Corresponding author at: MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, UK.
E-mail address: Paddy.Dempsey@mrc-epid.cam.ac.uk (P.C. Dempsey).

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this information arise in a data-driven manner (Rowlands, 2018; Troiano et al., 2014; Trost, 2007).

Whilst several analytical or data-driven approaches attempt to address issues around cutpoints by examining accumulation of activity in different intensities and/or by deriving metrics to represent intensity distributions (e.g. (Rantalainen et al., 2021; Rowlands et al., 2018)), most analytical approaches at present give limited consideration to collinearity issues (Aadland et al., 2019a). Multivariate pattern analysis, a method previously applied in biomedical and pharmaceutical research to handle multicollinearity issues between explanatory variables (Rajalahti et al., 2010; Rajalahti and Kvalheim, 2011), allows for simultaneous examination of multiple highly correlated accelerometer intensity variables which parameterise the whole intensity spectrum. This method uses a different analytical approach (partial least squares regression) to identify and model regions of the PA intensity spectrum most strongly associated with health (Aadland et al., 2019b; Migueles et al., 2021). Multivariate pattern analysis was recently applied to examine associations of multiple accelerometer-derived PA intensity variables across the spectrum with cardiometabolic risk (CMR) factors in a sample of 841 Norwegian children (Aadland et al., 2018a) and over 4000 children from the International Children's Accelerometry Database (ICAD) database (Aadland et al., 2020a). Results suggested that associations were strongest for time spent at the more 'vigorous' end of the intensity spectrum, with weaker associations for 'moderate' intensities, and more trivial associations for time spent 'sedentary' or in 'light-intensity' activities in this age-group.

However, it is unclear whether the relative importance of more vigorous intensity activity seen in children holds true in middle-aged to older adults, who generally accumulate much less vigorous PA (Strain et al., 2020; Whitaker et al., 2019; Swindell et al., 2018; Powell et al., 2018; LaMonte et al., 2017; Alessa et al., 2017; Brocklebank et al., 2015; Henson et al., 2013; Healy et al., 2008; Healy et al., 2007). The influence of confounding factors on PA intensity associations with CMR, as well as potential sex differences, may also be more pertinent factors to consider in adult populations. Indeed, which PA intensities are most important for CMR has not been studied using this high-resolution intensity spectrum approach. We therefore aimed to establish which intensity regions are most important for CMR, using multivariate pattern analysis, in a well-phenotyped, population-based sample of middle-aged to older adults.

2. Methods

2.1. Participants and procedures

We used data collected as part of the European Prospective Investigation of Cancer (EPIC) Norfolk Study (Hayat et al., 2014). In brief, 25,639 participants were recruited from 35 general practices and invited to attend a clinic assessment between 1993 and 1997. The participating cohort at initial recruitment was similar to the national population studied in the Health Survey for England in terms of anthropometry, serum lipids and blood pressure (Hayat et al., 2014). At the 3rd health examination in EPIC-Norfolk (2004–2011), 8623 participants, then aged 48–92 years, attended a central research clinic for questionnaire assessment and biomedical examination (including anthropometry, blood pressure and venous blood sampling). The present study uses data from a subsample of 4142 participants aged 49–91 years from this 3rd health check who were also asked to wear an accelerometer (randomly sampled based on monitor availability), the descriptive epidemiology of which has been previously described (Berkemeyer et al., 2016). The final sample size was 3660 (1634 men and 2026 women) after excluding those with insufficient valid wear time ($n = 91$) or missing data on any of the covariates or outcomes of interest ($n = 391$). The Norfolk Local Research Ethics and East Norfolk and Waveney NHS Research Governance Committee (05/Q0101/191) approved the study and signed informed consent was obtained from all participants.

2.2. Physical activity

Participants wore a uniaxial accelerometer (ActiGraph GT1M [default filter setting; i.e., not the low-frequency extension setting], Pensacola, USA) on their right hip for seven consecutive days, except during water activities (e.g. swimming, showering) or while sleeping. Accelerometers were initialised to record data in 5 s resolution, with counts stored per epoch. Data was downloaded and the 5 s data was also collapsed to 60 s epochs prior to processing; we expressed movement intensity as counts-per-minute (cpm) for both 5 s and 60s time resolutions. Non-wear time was defined as time segments with ≥90 min of continuous zero activity counts (Berkemeyer et al., 2016; Choi et al., 2011). Participants with ≥4 days, each consisting of ≥10 h/day of valid wear time, were included. When daily wear time was ≥19 h (indicating monitor wear during sleep), wear time and time spent in the lowest intensity category (i.e. 0-12 cpm) were truncated to 19 h/day.

The intensity spectrum was summarised as the time distribution (minutes/day) across m = 22 systematically spaced intensity intervals (bins), chosen *a priori*. As a greater proportion of time was spent at the lower end of the intensity spectrum, we used a gradually decreasing resolution (i.e., increasing bin size) with higher intensities (0–12, 13–24, 25–49, 50–74, 75–99, 100–124, 125–149, 150–199, 200–299, 300–399, 400–499, 500–799, 800–999, 1000–1499, 1500–1999, 2000–2499, 2500–2999, 3000–3499, 3500–3999, 4000–4499, 4500–4999, ≥5000 cpm) to capture relevant information in the best possible way. Typically used thresholds for 'sedentary', 'light-intensity' and 'moderate-to-vigorous intensity' activity are also displayed in Supplemental Fig. S6, for illustrative purposes.

2.3. Continuous cardiometabolic risk

Trained research staff measured height, weight and waist circumference according to standardised procedures (Hayat et al., 2014). Systolic and diastolic blood pressure were measured in duplicate using an Accutorr sphygmomanometer (Datascore, UK) after three minutes of sitting, with the average taken. The non-fasting venous blood sample was examined for serum triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) using an RA1000 auto-analyzer (Bayer Diagnostics, UK). Glycated haemoglobin (HbA1c) was measured using Diamat ion exchange HPLC (Bio-Rad Laboratories, UK). A continuously distributed CMR score was computed using continuous indicators of waist circumference; blood pressure (average of systolic and diastolic); TG; TC:HDL-C; and, HbA1c. After log-normalisation of TG, TC:HDL-C and HbA1c, all five cardiometabolic variables were standardised [z = (value-mean)/SD)] in sex-specific strata. The CMR score was then calculated by summing all sex-standardised scores and dividing this sum by five. A higher CMR score indicates higher cardiometabolic disease risk. We confirmed face validity of this CMR score in the present population by examining its prospective association with incident cardiovascular disease, the risk of which was estimated to be 47% higher per 1 unit in the CMR score in a linear manner (see Supplemental Analysis S1).

2.4. Potential confounding variables

Age, gender, education level (none, General Certificate of Education (GCE) Ordinary Level, GCE Advanced Level, bachelor's degree, and above), smoking status (current, former and never), alcohol intake (units/week), baseline history of diabetes mellitus or anti-diabetic medications (yes, no), anti-hypertensive medication (yes, no), medication for dyslipidaemia (yes, no) were self-reported via a standardised health and lifestyle questionnaire. Habitual diet was assessed using a 130-item semi-quantitative food frequency questionnaire which asked about participants' average intake of food items over the past year. Adherence to the Mediterranean diet pyramid was derived based on 15 components on the pyramid for which continuous scores from 0 to 1

were assigned for each component. This Mediterranean diet score (range 0–15) was used as an overall measure of diet quality, while accounting for absolute levels of dietary consumption (Tong et al., 2016; Bingham et al., 2001). Information on prevalent heart disease and stroke was collected up until the 3rd health assessment via either self-report or record linkage with hospital episode statistics.

2.5. Statistical analyses

Prior to running all analyses, the CMR score was residualized to adjust for important sources of variation and confounding (decided upon *a priori*) by regressing the CMR score on all covariates, then adding the residual value from each participant to the analytical sample mean of predicted values (Willett and Stampfer, 1986). Residualization of covariates was executed on two levels. Model 1 adjusted for age and sex only. Model 2 additionally adjusted for education level, smoking status, alcohol intake, baseline history of diabetes, anti-hypertensive and dyslipidaemia medications, and prevalent heart disease/stroke.

Associations between the individual PA intensity variables (minutes/day at each intensity bin in cpm) and CMR were separately examined using Spearman's rank correlation coefficients (r_s). Partial least squares (PLS) regression analyses (Wold et al., 1984) were then used to determine the associations between the PA intensity variables and CMR, which included all PA intensity variables as exposures in the same model (Aadland et al., 2019b; Aadland et al., 2018a). PA variables were standardised prior to analyses to account for variation in bin widths and distributions. PLS regression handles the collinearity by decomposing the exposure variables into orthogonal linear combinations (PLS components or latent variables) while maximising the covariance with the outcome variable. Models were validated using Monte-Carlo resampling (Kvalheim et al., 2018) with 100 repetitions to select the optimal number of PLS components, by randomly keeping 50% of participants as an external validation set. The number of components was determined as the model providing the lowest prediction error over the repeated runs, taking into account the confidence limit of the prediction and to balance the risk of over- or underfitting the model (Kvalheim et al., 2018).

To summarize the overall explained variance (R^2) in each model from the combined PA intensity variables, a single predictive component was then calculated by means of target projection, expressing all the predictive variances in the PA variables related to the CMR response variable in a single vector (Rajalahti and Kvalheim, 2011). Next, selectivity ratios were calculated for each PA intensity variable as its explained predictive variance on the target-projected component divided by the total variance (Rajalahti and Kvalheim, 2011; Aadland et al., 2019b; Rajalahti et al., 2009a; Rajalahti et al., 2009b). Thus, for example, a selectivity ratio of 0.50 and a total model R^2 of 10% means the variable explains 5% of the actual outcome. Multivariate correlation coefficients (r) with 95% confidence intervals (CIs) were then calculated as: $r = \sqrt{selectivity\ ratio * explained\ variance\ in\ the\ outcome}$. These multivariate r can be interpreted on a similar scale as Pearson correlation coefficients or standardised regression coefficients, but in contrast to coefficients from standard multiple linear regression, these associations should not be interpreted as 'independent' contributions of each PA intensity variable to CMR (Aadland et al., 2019b). Given the strong correlations among PA intensity variables, focusing on each PA variable's unique association with the outcome is not meaningful. Thus, the multivariate r provides the relative importance of each PA variable for the CMR outcome, given the total association pattern of the explanatory variables as predicted by the model (Aadland et al., 2019b; Aadland et al., 2020a).

Main analyses focussed on the associations of m = 22 PA intensity variables with CMR and were conducted both in the overall sample (models 1 and 2) and stratified by sex (model 2 only). Since activity can be distributed differently across intensity bins depending on epoch resolution (Orme et al., 2014), we present 5 s and 60 s epoch data to allow comparison of overall intensity profiles with other studies. Sensitivity analyses were also conducted to examine the potential influence of using more PA intensity bins at more regularly spaced intervals (i.e. (+33% increments; by generating m = 37 and m = 57 PA intensity bins). Further sensitivity analyses were also run separately with additional adjustment for diet quality, due to a larger amount of missing data for this variable (n = 290 missing, see Supplemental Table S1 for all missing data).

Dataset/variable preparation and covariate adjustments were performed using Stata v15.1 (StataCorp LLC, College Station, TX) and multivariate pattern analyses using Sirius v11.0 (Pattern Recognition Systems AS, Bergen, Norway).

3. Results

3.1. Descriptive characteristics of the sample

As previously reported (Berkemeyer et al., 2016), participants with valid accelerometer data did not differ significantly from those who did not wear an accelerometer in terms of age, sex, BMI, education level and self-rated health. Socio-demographic attributes, health-related factors

Table 1
Sociodemographic characteristics, behavioural and health-related variables of the total sample and stratified by sex.

	Total sample (n = 3660)	Males (n = 1634)	Females (n = 2026)
Age (years)	69 ± 8	70 ± 8	68 ± 7
Education level, n (%)			
No formal qualification	922 (25.2)	326 (20.0)	596 (29.4)
Secondary school qualification (~16 years)	449 (12.3)	179 (11.0)	270 (13.3)
Higher secondary or college qualification (~18 years)	1641 (44.8)	807 (49.4)	834 (41.2)
Bachelor's degree and above	648 (17.7)	322 (19.6)	326 (16.1)
Cigarette smoking, n (%)			
Current	149 (4.1)	65 (4.0)	84 (4.0)
Former	1658 (45.3)	926 (56.7)	732 (36.3)
Never	1853 (50.6)	643 (39.3)	1210 (59.7)
Alcohol intake (units/week), median (IQR)	4.0 (0.0–8.0)	6.0 (1.4–12.0)	2.3 (0.0–7.0)
Mediterranean diet score (0–15)*	8.7 ± 1.3	8.4 ± 1.3	9.0 ± 1.2
History of diabetes or taking diabetes medications, n (%)	172 (4.7)	106 (6.5)	66 (3.3)
History of heart disease/stroke, n (%)	798 (21.8)	459 (28.1)	339 (16.7)
Anti-hypertensive medication, n (%)	1358 (37.1)	678 (41.5)	680 (33.6)
Lipid-lowering medication, n (%)	848 (23.2)	471 (28.8)	377 (18.6)
Total physical activity (average cpm/day)	258.2 ± 118.4	257.6 ± 127.0	258.7 ± 111.0
Cardiometabolic risk variables			
Waist circumference (cm)	94.4 ± 12.0	100.6 ± 9.4	89.5 ± 11.6
Body mass index (kg/m^2)	26.7 ± 4.2	27.1 ± 3.6	26.5 ± 4.6
Systolic blood pressure (mm hg)	136.2 ± 15.9	136.3 ± 14.9	136.2 ± 16.7
Diastolic blood pressure (mm hg)	78.3 ± 9.3	79.7 ± 9.6	77.1 ± 8.9
Triglycerides (mmol/L), median (IQR)	1.5 (1.0–2.0)	1.5 (1.1–2.1)	1.4 (1.0–2.0)
Total/HDL-cholesterol (mmol/L), median (IQR)	3.6 (3.0–4.3)	3.7 (3.1–4.5)	3.4 (2.9–4.1)
HbA1c (%), median (IQR)	5.7 (5.5–6.0)	5.7 (5.5–6.0)	5.7 (5.5–6.0)
Continuous *cardiometabolic risk score*	−0.01 ± 0.56	−0.02 ± 0.55	−0.01 ± 0.58

Data are means ± SD, unless otherwise indicated (i.e. n (%), or median (IQR).
* n = 3370 with valid data in included sample; the diet score variable was calculated based on the Mediterranean dietary pyramid (range 0–15), adjusted to a 2000 kcal/day (8.37 MJ/day) diet using the residuals method to assess diet quality independent of diet quantity.

and CMR variables for the analytical sample are shown in Table 1. The mean (±SD) age of the participants was 69 ± 8 years and 55% were women. Women tended to have a more favourable CMR profile and took fewer medications than men. Compared with eligible participants included in the analytical sample, eligible participants who were excluded due to missing covariate/outcome data (n = 391) took more blood pressure and lipid-lowering medications, had lowed physical activity, and had slightly poorer CMR profiles overall (see Supplemental Table S1).

3.2. Physical activity intensity distributions

Fig. 1 displays the PA intensity distributions using m = 22 intensity bins (overall, sex-stratified, and by 5 s and 60 s epoch length), with accumulated time (min/day) estimates normalised to 12.5 cpm bin width (the smallest used) to allow for relative comparison across the different PA intensities (more detail provided in Figure footnotes). Supplemental Fig. S1 displays the equivalent non-normalised distributions across these same PA intensity bins. The mean (±SD) accelerometer wear time of the analytical sample was 867 ± 61 min/day.

The profile of time spent in each PA intensity bin varied by epoch duration (Fig. 1; panels a and b vs. c and d), with more activity accumulated in the lower intensity ranges for 5 s epoch. Sex-stratified activity intensity distribution profiles were mostly similar (Fig. 1; panels b and d), but women appeared to spend slightly more time in PA at intensities ≥13 cpm and slightly less time at very low intensity (i.e. <13 cpm).

3.3. Bivariate correlations between PA intensity and cardiometabolic health

The Spearman rank correlation coefficients, showing the relationship between each of the PA intensity categories with CMR, were positive (detrimental) for 0-12 cpm (r_s = 0.09 and 0.14 for 5 s and 60 s epoch, m = 22 intensity bins, respectively) and negative (beneficial) correlations for the remaining PA intensity categories (r_s range = −0.1 to −0.19 and − 0.08 to −0.18 for 5 s and 60 s epoch, m = 22 intensity bins, respectively; Supplementary Fig. S2, plot 1). These trends were also evident when using m = 37 and m = 57 intensity bins (Supplementary Fig. S2; plots 2–3).

3.4. Multivariate association profiles between PA intensity and cardiometabolic health

The strength of the association between each of the PA intensity variables (using m = 22 PA intensity bins), relative to time spent in other bins in the multivariate space, and the CMR score is shown in Fig. 2. Similar to the Spearman rank correlation coefficients, there was a positive (detrimental) correlation with CMR for 0-12 cpm and a negative (favourable) correlation for all intensity bins ≥13 cpm. This was evident across all models (whole sample and sex-stratified, age/sex and confounder adjusted, 5 s and 60 s epochs).

In the whole sample 5 s epoch models, the magnitude of the correlation coefficients was slightly higher in the 13–200 and 2000-5000 cpm ranges (r = 0.13–0.14) than the 200-2000 cpm range (r = 0.09–0.11). In the 60 s epoch models, the association for 0-12 cpm and CMR was stronger than for 5 s (confounder adjusted r = 0.13 and 0.08, respectively) and the associations were also slightly weaker in the 13-200 cpm range (r = 0.07–0.08). Additional adjustment for potential confounders (model 2) attenuated the associations slightly, more so at the middle-to-upper end (≥800 cpm) and lowest end (0-12 cpm) of the intensity spectrum, with slightly more deviation in the magnitude of the correlation coefficients between models 1 and 2 in the 5 s epoch data.

In sex-stratified results, the proportion of variance explained by the models were R^2 = 7.0/7.4% for women and R^2 = 1.9/2.3% for men. The strongest favourable associations for men were evident in the 50-800 cpm range (r = 0.10–0.12) and the weakest associations in the highest intensity categories, while the strongest favourable associations for women were at higher intensities (r = 0.18–0.20 for bins >2500 cpm). These patterns were also evident in the 60 s epoch data.

Sensitivity analyses that additionally adjusted for diet quality had minimal impact on association patterns in the overall sample for model 2 (n = 3370; Supplemental Fig. S4.1–3; panels a and c). The total explained variances for the overall (R^2 range = 4.3–5.4%) and sex-specific models (men R^2 range = 1.9–2.3%; women R^2 range = 7.0–7.4%) were not materially different when the data were modelled using higher (m = 37 and 57) PA intensity resolutions (Supplemental Fig. S3.1–2). The shape and interpretation of the overall intensity profile associations with CMR were also similar.

Finally, unstandardised multivariate correlation coefficients for the associations between CMR and PA intensity expressed per minute/day of PA were relatively stronger at the higher intensities, particularly for women (Supplemental Fig. S5.1–3). These results should be considered alongside the intensity bin distributions shown in Fig. S1 and their variance, as for example 1 min of PA is much less frequently undertaken at the higher end of the intensity spectrum than the lower end. The magnitude and stability of these unstandardised coefficients is also influenced by the different PA intensity bin widths used for the different resolutions (i.e. m = 22, m = 37 and m = 57).

4. Discussion

In this large population-based cohort of UK middle-aged to older men and women, we observed that most of the PA intensity spectrum was beneficially associated with CMR, even at intensities much lower than what has traditionally been considered “sedentary” or “light-intensity” activity. Some variations in PA intensity association patterns were also observed between men and women, particularly at the highest intensities.

Epidemiological studies using multivariate pattern analysis to examine PA intensity profiles have so far only been applied in children. These studies suggest that associations with CMR are strongest for time spent at the ‘vigorous’ end of the intensity spectrum, with weaker associations for ‘moderate’ intensities, and more trivial associations for time spent in ‘light’ intensity or ‘sedentary’ activities (Aadland et al., 2018a; Aadland et al., 2020a; Aadland et al., 2018b; Aadland et al., 2019c). The current findings in middle-aged to older adults are consistent with recent guidelines (Dempsey et al., 2020; Bull and Willumsen, 2020; UK Chief Medical Officers' Physical Activity Guidelines, 2019; Piercy et al., 2018), and previous research using more traditional analytical approaches, and support the potential benefits to cardiometabolic health of encouraging both light and moderate-to-vigorous intensity PA (Whitaker et al., 2019; Swindell et al., 2018; Powell et al., 2018; LaMonte et al., 2017; Healy et al., 2007). Notably, the analytical approach used here allowed us to model relationships with CMR across the full PA intensity spectrum in more detail than has previously been done in adults, without the implications associated with only using a few pre-defined PA intensity categories covering wide ranges (Rowlands, 2018; Troiano et al., 2014; Aadland et al., 2019a). Indeed, the ‘switch’ in CMR associations from positive to negative for intensities between 0 and 12 and 13-24 cpm illustrates how wider intensity categories (e.g. <100 cpm typically used for ‘sedentary’ time; see Supplemental Fig. S6 for illustration) for waist-worn accelerometry could be missing relevant information or behaviors (e.g. standing or sit-to-stand transitions) that may be distinctly related to cardiometabolic health (Aguilar-Farías et al., 2014; Jain et al., 2021). Future research utilising this method, alongside thigh-worn devices or algorithms (e.g. deep learning) better equipped to distinguish posture (Aguilar-Farías et al., 2014; Jain et al., 2021; Nakandala et al., 2021), or the use of raw acceleration measurement coupled with low-frequency extension filtering for greater sensitivity to low-intensity activities of older-aged sub-groups (Cain et al., 2013), could help interrogate these aspects further.

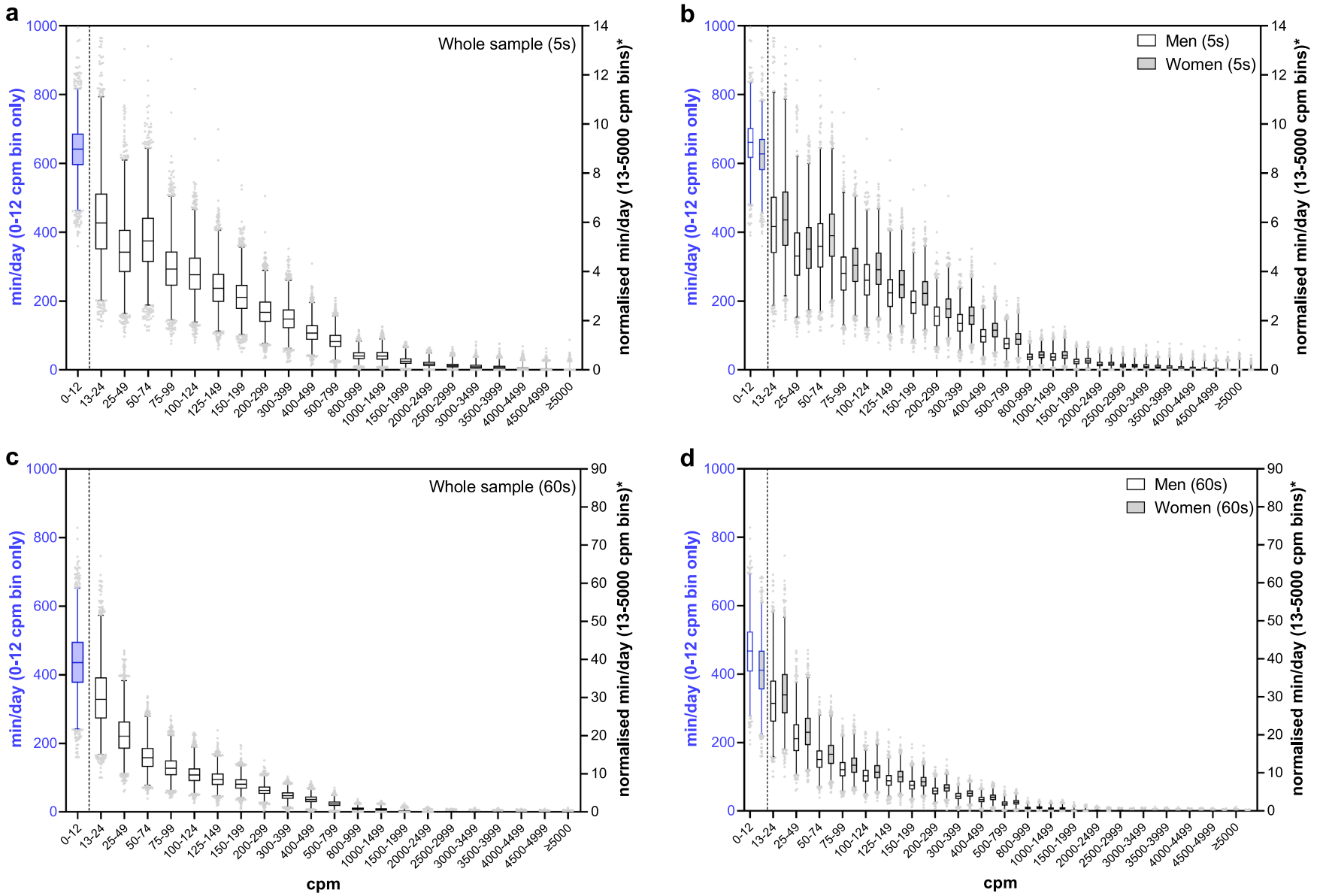

Fig. 1. Relative distribution of accelerometer-derived movement intensity variables for the whole sample (panels a and c) and by sex (panels b and d). Physical activity variables are shown for 5 s (panels a and b) and 60 s (panels c and d) epoch resolutions. Data for each PA variable are displayed as median and interquartile range (IQR), with whiskers from the 1st to 99th percentiles. *Note:* intensity variables with a bin width > 12 cpm were normalised to a 12 cpm bin width (e.g. 150-199 cpm width = 49/12 = 4.08; so divide the time in this bin by 4.08 to 'normalise' it) to allow for relative comparisons across all intensity variables. The equivalent non-normalised/raw PA variables are displayed in *Supplemental Fig. S1*.

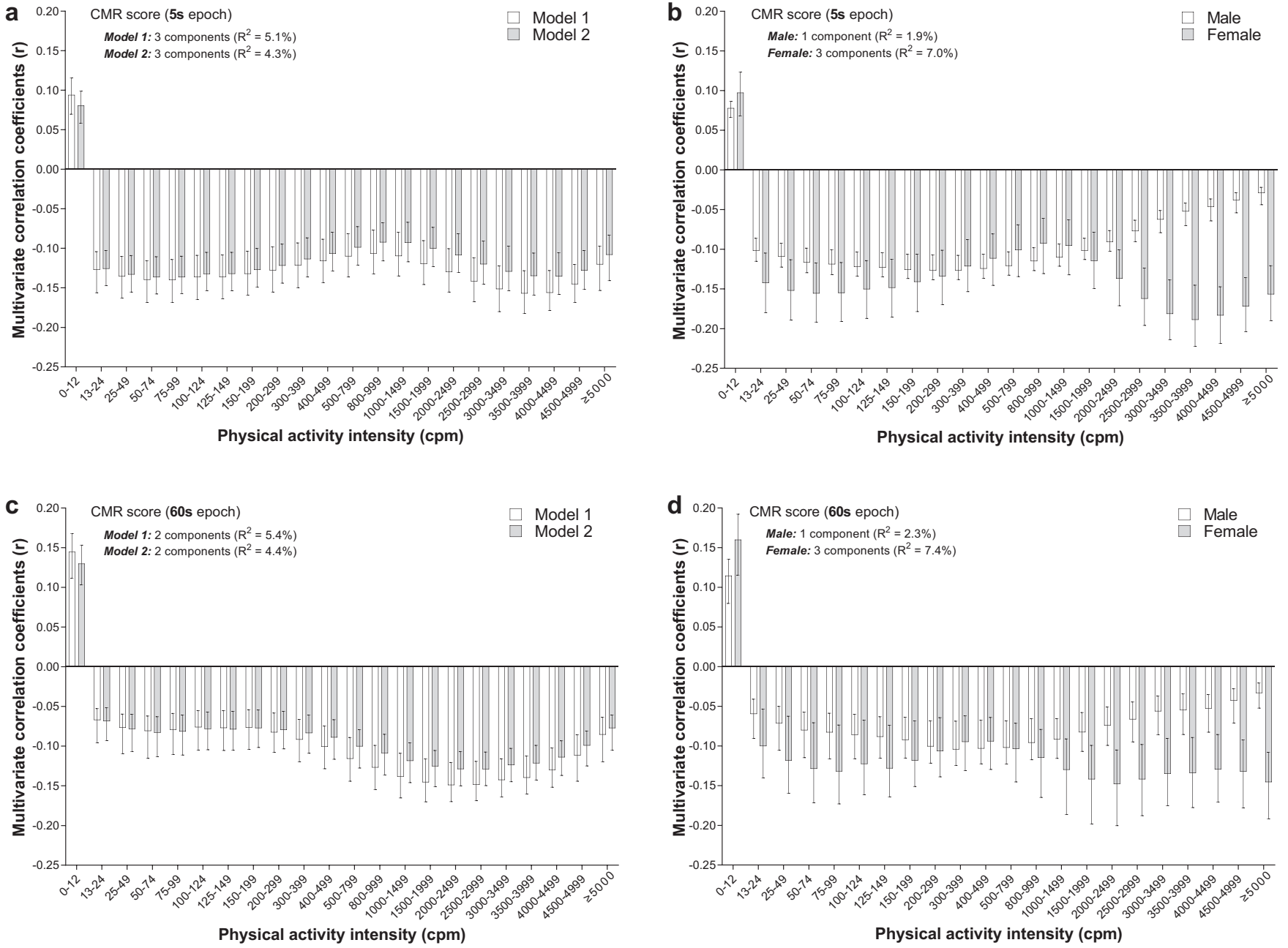

Fig. 2. Multivariate PA intensity profile associated with the CMR score. Multivariate correlation coefficients with 95% CIs from the multivariate model including m = 22 PA intensity variables are displayed for the whole sample (panels a and c) and by sex (panels b and d). Physical activity variables are shown for 5 s (panels a and b) and 60 s (panels c and d) epoch resolution. Model 1 adjusted for age and sex. Model 2 additionally adjusted for potential confounders (education level, smoking status, alcohol intake, baseline history of diabetes, anti-hypertensive and dyslipidaemia medications, and prevalent heart disease/stroke). Sex-specific models are based on model 2 (with no adjustment for sex). The number of PLS components and total explained variance (R^2) for each model are also displayed. A negative bar implies a more favourable association with the CMR score. *Note:* equivalent plots are displayed for higher intensity resolutions (m = 37 and 57 PA variables) in *Supplemental Fig. S3.1–2*, and for illustration only in m = 3 PA variables (*Supplementary Fig. S6*).

The reason for some variations in the PA intensity association patterns with CMR in sex-specific models is not entirely clear. It is plausible that these association patterns reflect differences in the underlying activity patterns not adequately characterised by waist-worn accelerometry alone or captured differentially by sex, such as potential differences in relative intensity or movement patterns, walking pace, or activities of daily living at the lower or higher intensities within the PA intensity spectrum (e.g. gardening, housework, cycling) (Strain et al., 2016; Dyrstad et al., 2014). Alternatively, differences could be related to age or sex-specific factors such as differences in body composition, hormonal responses or menopausal status (although most women in this sample were likely post-menopausal), or underlying variations in unmeasured variables or residual confounding. It is also possible that women's activity patterns are more stable than men's, meaning that a 1-week snapshot captures a higher proportion of variance in habitual (latent) activity; this would result in less regression dilution bias, compared to that observed in men. Future research should seek to confirm and further interrogate potential sex differences in association patterns in different cohorts to determine the extent to which any differences are behaviorally or biologically plausible, or perhaps spurious. Indeed, the sex-stratified results presented in this paper are descriptive, and interactions not formally tested. Thus, these results should be interpreted with caution.

As anticipated, PA intensity association patterns were influenced by epoch length, but only to a small degree in this older population. Slightly stronger associations with CMR were observed for 5 s compared to 60 s epoch duration for intensity ranges $\geq$13 cpm, while slightly weaker associations were observed for $<$13 cpm. The impact on model total explained variance between epoch durations was minimal. This parallels somewhat with previous studies in children, where short bursts of activity (albeit particularly at more vigorous intensities for children) seem to be of greater importance to cardiometabolic health (Aadland et al., 2018b; Aadland et al., 2020b). Additionally, the impact of lowering PA intensity resolution in $\pm$33% increments (i.e. reducing and widening the number of intensity bins from m = 57 to 37 to 22) on total model explained variance, and on overall association patterns with CMR, was minimal for standardised coefficients. This indicates simpler models may be sufficient in future research (Aadland et al., 2020b), although it should be noted that our simplest model still uses 5 times more intensity bins than what is typically used (e.g. Supplemental Fig. S6 for illustration).

The use of accelerometer-based PA monitoring in a highly compliant, well-characterised, and large population-based cohort is a strength of this work, allowing for more detailed evaluation of different methodological choices, as well as examination of potential confounding structures and sex-specific association patterns. However, there are also several limitations to this work. Although we have shown that our specific CMR score is strongly associated with future CVD, associations with PA may be subject to reverse-causality bias due to the cross-sectional design. The use of uniaxial accelerometry could lead to loss of information compared to triaxial accelerometry or multi-sensor arrays (Aadland et al., 2018b; Aadland et al., 2019c). Associations with CMR should also be interpreted with caution given some limitations of uniaxial waist-worn accelerometry (and associated algorithms) to classify non-wear, different postures and activity types (e.g. standing/sitting/cycling) as previously mentioned, including activity at very high intensities (Troiano et al., 2014; Migueles et al., 2017). Further confounding may also exist from unmeasured factors and included variables measured with substantial error, for example diet quality and other factors that may influence the non-fasted triglycerides measurements. Additionally, the sample was not population representative and there may be some selection biases. In particular, the analysis focused on a healthier sample within the third wave of a cohort that, like many others, had some loss to follow-up and there were some differences between participants included and those excluded due to missing outcome data, with potential consequences both to internal and external validity.

Some limitations of the multivariate pattern analysis approach should also be mentioned. This data-driven approach is more hypothesis generating in terms of identifying predictive association patterns and specific intensity regions of importance for health. However, it could be combined with specific replication analyses of identified PA intensity regions in independent samples or experimental studies. This approach may also facilitate the translation of the intensity profile findings into public heath action, since dose-response relationships are not immediately discernible from the pattern analysis presented herin. In addition, we also only consider the intensity profiling in the time-domain, but applying the approach in other domains (e.g. activity energy expenditure) may also yield new insights. Analysis of formal group*PA interactions with CMR and time-to-event outcomes (e.g. survival analysis) are also a promising areas for future research, but are not possible at present using this specific approach.

5. Conclusions

We examined the PA intensity profile associated with cardiometabolic disease risk in a large, population-based cohort of UK middle-aged to older men and women. Most of the PA intensity spectrum was beneficially associated with CMR in middle-aged to older adults, even at intensities much lower than what has traditionally been considered “sedentary” or “light-intensity” activity. This reiterates current PA guidelines on the potential benefits to cardiometabolic health of encouraging PA of all intensities (i.e. “every move counts”). Some differences in association pattern were observed between men and women, but further investigation is required to better understand potential sex differences; including potential interactions between accelerometer intensity and measurement (i.e. type/epoch) resolutions. In future work, multivariate pattern analysis could be applied to activity data generated by other wearable sensors, alongside other analytical approaches/techniques and study designs to examine longitudinal associations.

Authors' contributions

PCD, EA, OK and KWi conceived and designed the research question. PCD analysed and interpreted the data and wrote the manuscript. EA, TS, OK, KWe, TL, KK, NW, SB and KWi provided critical review for intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Norfolk District Local Research Ethics and East Norfolk and Waveney NHS Research Governance Committee (05/Q0101/191) approved the study and signed informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Individual-level data are available from the European Prospective Investigation Into Cancer and Nutrition–Norfolk Management Committee (contact via epic-norfolk@mrc-epid.cam.ac.uk) for researchers who meet the criteria for access to confidential data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2022.106977.

References

Aadland, E., Kvalheim, O.M., Anderssen, S.A., Resaland, G.K., Andersen, L.B., 2018a. The multivariate physical activity signature associated with metabolic health in children. Int. J. Behav. Nutr. Phys. Act. 15 (1), 77.

Aadland, E., Andersen, L.B., Anderssen, S.A., Resaland, G.K., Kvalheim, O.M., 2018b. Associations of volumes and patterns of physical activity with metabolic health in children: a multivariate pattern analysis approach. Prev. Med. 115, 12–18.

Aadland, E., Kvalheim, O.M., Anderssen, S.A., Resaland, G.K., Andersen, L.B., 2019a. Multicollinear physical activity accelerometry data and associations to cardiometabolic health: challenges, pitfalls, and potential solutions. Int. J. Behav. Nutr. Phys. Act. 16 (1), 74.

Aadland, E., Andersen, L.B., Resaland, G.K., Kvalheim, O.M., 2019b. Interpretation of multivariate association patterns between multicollinear physical activity accelerometry data and cardiometabolic health in children-A tutorial. Metabolites. 9 (7).

Aadland, E., Kvalheim, O.M., Anderssen, S.A., Resaland, G.K., Andersen, L.B., 2019c. The triaxial physical activity signature associated with metabolic health in children. Med. Sci. Sports Exerc. 51 (10), 2173–2179.

Aadland, E., Kvalheim, O.M., Hansen, B.H., Kriemler, S., Ried-Larsen, M., Wedderkopp, N., et al., 2020a. The multivariate physical activity signature associated with metabolic health in children and youth: an international Children's Accelerometry database (ICAD) analysis. Prev. Med. 141, 106266.

Aadland, E., Andersen, L.B., Anderssen, S.A., Resaland, G.K., Kvalheim, O.M., 2020b. Accelerometer epoch setting is decisive for associations between physical activity and metabolic health in children. J. Sports Sci. 38 (3), 256–263.

Aguilar-Farías, N., Brown, W.J., Peeters, G.M., 2014. ActiGraph GT3X+ cut-points for identifying sedentary behaviour in older adults in free-living environments. J. Sci. Med. Sport 17 (3), 293–299.

Alessa, H.B., Chomistek, A.K., Hankinson, S.E., Barnett, J.B., Rood, J., Matthews, C.E., et al., 2017. Objective measures of physical activity and cardiometabolic and endocrine biomarkers. Med. Sci. Sports Exerc. 49 (9), 1817–1825.

Berkemeyer, K., Wijndaele, K., White, T., Cooper, A.J., Luben, R., Westgate, K., et al., 2016. The descriptive epidemiology of accelerometer-measured physical activity in older adults. Int. J. Behav. Nutr. Phys. Act. 13, 2.

Bingham, S.A., Welch, A.A., McTaggart, A., Mulligan, A.A., Runswick, S.A., Luben, R., et al., 2001. Nutritional methods in the European prospective investigation of cancer in Norfolk. Public Health Nutr. 4 (3), 847–858.

Brocklebank, L.A., Falconer, C.L., Page, A.S., Perry, R., Cooper, A.R., 2015. Accelerometer-measured sedentary time and cardiometabolic biomarkers: a systematic review. Prev. Med. 76, 92–102.

Bull, F., Willumsen, J., 2020. World Health Organization. Guidelines on Physical Activity and Sedentary Behaviour. World Health Organization, Geneva, Switzerland.

Cain, K.L., Conway, T.L., Adams, M.A., Husak, L.E., Sallis, J.F., 2013. Comparison of older and newer generations of ActiGraph accelerometers with the normal filter and the low frequency extension. Int. J. Behav. Nutr. Phys. Act. 10, 51.

Choi, L., Liu, Z., Matthews, C.E., Buchowski, M.S., 2011. Validation of accelerometer wear and nonwear time classification algorithm. Med. Sci. Sports Exerc. 43 (2), 357–364.

Dempsey, P.C., Biddle, S.J.H., Buman, M.P., Chastin, S., Ekelund, U., Friedenreich, C.M., et al., 2020. New global guidelines on sedentary behaviour and health for adults: broadening the behavioural targets. Int. J. Behav. Nutr. Phys. Act. 17 (1), 151.

Doherty, A., Jackson, D., Hammerla, N., Plotz, T., Olivier, P., Granat, M.H., et al., 2017. Large scale population assessment of physical activity using wrist worn accelerometers: the UK biobank study. PLoS One 12 (2), e0169649.

Dyrstad, S.M., Hansen, B.H., Holme, I.M., Anderssen, S.A., 2014. Comparison of self-reported versus accelerometer-measured physical activity. Med. Sci. Sports Exerc. 46 (1), 99–106.

Golubic, R., Martin, K.R., Ekelund, U., Hardy, R., Kuh, D., Wareham, N., et al., 2014. Levels of physical activity among a nationally representative sample of people in early old age: results of objective and self-reported assessments. Int. J. Behav. Nutr. Phys. Act. 11 (1), 58.

Hayat, S.A., Luben, R., Keevil, V.L., Moore, S., Dalzell, N., Bhaniani, A., et al., 2014. Cohort profile: a prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3). Int. J. Epidemiol. 43 (4), 1063–1072.

Healy, G.N., Dunstan, D.W., Salmon, J., Cerin, E., Shaw, J.E., Zimmet, P.Z., et al., 2007. Objectively measured light-intensity physical activity is independently associated with 2-h plasma glucose. Diabetes Care 30 (6), 1384–1389.

Healy, G.N., Wijndaele, K., Dunstan, D.W., Shaw, J.E., Salmon, J., Zimmet, P.Z., et al., 2008. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian diabetes, obesity and lifestyle study (AusDiab). Diabetes Care 31 (2), 369–371.

Henson, J., Yates, T., Biddle, S., Edwardson, C., Khunti, K., Wilmot, E., et al., 2013. Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health. Diabetologia. 56 (5), 1012–1020.

Jain, P., Bellettiere, J., Glass, N., LaMonte, M.J., Di, C., Wild, R.A., et al., 2021. The relationship of accelerometer-assessed standing time with and without ambulation and mortality: the WHI OPACH study. J. Gerontol. A Biol. Sci. Med. Sci. 76 (1), 77–84.

Kvalheim, O.M., Arneberg, R., Grung, B., Rajalahti, T., 2018. Determination of optimum number of components in partial least squares regression from distributions of the root-mean-squared error obtained by Monte Carlo resampling. J. Chemom. 32 (4), e2993.

LaMonte, M.J., Lewis, C.E., Buchner, D.M., Evenson, K.R., Rillamas-Sun, E., Di, C., et al., 2017. Both light intensity and moderate-to-vigorous physical activity measured by accelerometry are favorably associated with cardiometabolic risk factors in older women: the objective physical activity and cardiovascular health (OPACH) study. J. Am. Heart Assoc. 6 (10), e007064.

Lindsay, T., Westgate, K., Wijndaele, K., Hollidge, S., Kerrison, N., Forouhi, N., et al., 2019. Descriptive epidemiology of physical activity energy expenditure in UK adults (the fenland study). Int. J. Behav. Nutr. Phys. Act. 16 (1), 126.

Migueles, J.H., Cadenas-Sanchez, C., Ekelund, U., Delisle Nystrom, C., Mora-Gonzalez, J., Lof, M., et al., 2017. Accelerometer data collection and processing criteria to assess physical activity and other outcomes: a systematic review and practical considerations. Sports Med. (Auckland, NZ). 47 (9), 1821–1845.

Migueles, J.H., Aadland, E., Andersen, L.B., Brond, J.C., Chastin, S.F., Hansen, B.H., et al., 2021. GRANADA consensus on analytical approaches to assess associations with accelerometer-determined physical behaviours (physical activity, sedentary behaviour and sleep) in epidemiological studies. Br. J. Sports Med. (bjsports-2020-103604), https://bjsm.bmj.com/content/early/2021/04/14/bjsports-2020-103604.citation-tools.

Nakandala, S., Jankowska, M.M., Tuz-Zahra, F., Bellettiere, J., Carlson, J.A., LaCroix, A.Z., et al., 2021. Application of convolutional neural network algorithms for advancing sedentary and activity bout classification. J. Meas. Phys. Behav. 4 (2), 102–110.

Orme, M., Wijndaele, K., Sharp, S.J., Westgate, K., Ekelund, U., Brage, S., 2014. Combined influence of epoch length, cut-point and bout duration on accelerometry-derived physical activity. Int. J. Behav. Nutr. Phys. Act. 11 (1), 34.

Piercy, K.L., Troiano, R.P., Ballard, R.M., Carlson, S.A., Fulton, J.E., Galuska, D.A., et al., 2018. The physical activity guidelines for Americans. JAMA. 320 (19), 2020–2028.

Powell, C., Herring, M.P., Dowd, K.P., Donnelly, A.E., Carson, B.P., 2018. The cross-sectional associations between objectively measured sedentary time and cardiometabolic health markers in adults - a systematic review with meta-analysis component. Obes. Rev. 19 (3), 381–395.

Rajalahti, T., Kvalheim, O.M., 2011. Multivariate data analysis in pharmaceutics: a tutorial review. Int. J. Pharm. 417 (1–2), 280–290.

Rajalahti, T., Arneberg, R., Kroksveen, A.C., Berle, M., Myhr, K.-M., Kvalheim, O.M., 2009a. Discriminating variable test and selectivity ratio plot: quantitative tools for interpretation and variable (biomarker) selection in complex spectral or chromatographic profiles. Anal. Chem. 81 (7), 2581–2590.

Rajalahti, T., Arneberg, R., Berven, F.S., Myhr, K.-M., Ulvik, R.J., Kvalheim, O.M., 2009b. Biomarker discovery in mass spectral profiles by means of selectivity ratio plot. Chemom. Intell. Lab. Syst. 95 (1), 35–48.

Rajalahti, T., Kroksveen, A.C., Arneberg, R., Berven, F.S., Vedeler, C.A., Myhr, K.-M., et al., 2010. A multivariate approach to reveal biomarker signatures for disease classification: application to mass spectral profiles of cerebrospinal fluid from patients with multiple sclerosis. J. Proteome Res. 9 (7), 3608–3620.

Rantalainen, T., Ridgers, N.D., Gao, Y., Belavý, D.L., Haapala, E.A., Finni, T., 2021. Physical activity accumulation along the intensity spectrum differs between children and adults. Eur. J. Appl. Physiol. 121 (9), 2563–2571.

Rowlands, A.V., 2018. Moving forward with accelerometer-assessed physical activity: two strategies to ensure meaningful, interpretable, and comparable measures. Pediatr. Exerc. Sci. 30 (4), 450–456.

Rowlands, A.V., Edwardson, C.L., Davies, M.J., Khunti, K., Harrington, D.M., Yates, T., 2018. Beyond cut points: accelerometer metrics that capture the physical activity profile. Med. Sci. Sports Exerc. 50 (6), 1323–1332.
Strain, T., Fitzsimons, C., Foster, C., Mutrie, N., Townsend, N., Kelly, P., 2016. Age-related comparisons by sex in the domains of aerobic physical activity for adults in Scotland. Prev. Med. Rep. 3, 90–97.
Strain, T., Wijndaele, K., Dempsey, P.C., Sharp, S.J., Pearce, M., Jeon, J., et al., 2020. Wearable-device-measured physical activity and future health risk. Nat. Med. 26 (9), 1385–1391.
Swindell, N., Mackintosh, K., McNarry, M., Stephens, J.W., Sluik, D., Fogelholm, M., et al., 2018. Objectively measured physical activity and sedentary time are associated with cardiometabolic risk factors in adults with prediabetes: the PREVIEW study. Diabetes Care 41 (3), 562–569.
Tong, T.Y., Wareham, N.J., Khaw, K.T., Imamura, F., Forouhi, N.G., 2016. Prospective association of the Mediterranean diet with cardiovascular disease incidence and mortality and its population impact in a non-Mediterranean population: the EPIC-Norfolk study. BMC Med. 14 (1), 135.
Troiano, R.P., McClain, J.J., Brychta, R.J., Chen, K.Y., 2014. Evolution of accelerometer methods for physical activity research. Br. J. Sports Med. 48 (13), 1019–1023.
Trost, S.G., 2007. State of the art reviews: measurement of physical activity in children and adolescents. Am. J. Lifestyle Med. 1 (4), 299–314.
UK Chief Medical Officers' Physical Activity Guidelines, 2019. Department of Health and Social Care, Llwodraeth Cymru Welsh Government, Department of Health Northern Ireland and the Scottish Government.
Whitaker, K.M., Pettee Gabriel, K., Buman, M.P., Pereira, M.A., Jacobs Jr., D.R., Reis, J. P., et al., 2019. Associations of accelerometer-measured sedentary time and physical activity with prospectively assessed cardiometabolic risk factors: the CARDIA study. J. Am. Heart Assoc. 8 (1), e010212.
Willett, W., Stampfer, M.J., 1986. Total energy intake: implications for epidemiologic analyses. Am. J. Epidemiol. 124 (1), 17–27.
Wold, S., Ruhe, A., Wold, H., Dunn III, W.J., 1984. The collinearity problem in linear regression. The partial least squares (PLS) approach to generalized inverses. SIAM J. Sci. Stat. Comput. 5 (3), 735–743.