The GRANADA consensus on analytical approaches to assess associations with accelerometer-determined physical behaviours (physical activity, sedentary behaviour, and sleep) in epidemiological studies

Jairo H. Migueles[1,2], Eivind Aadland[3], Lars B. Andersen[3], Jan Christian Brønd[4], Sébastien F. Chastin[5,6], Bjørge H. Hansen[7,8], Kenn Konstabel[9,10,11], Olav M. Kvalheim[12], Duncan E. McGregor[5,13], Alex V. Rowlands[14,15,16], Séverine Sabia[17,18], Vincent T. van Hees[19,20], Rosemary Walmsley[21], Francisco B. Ortega[1,22] and external review group*

Note: Except for the first and last author, contributing authors are listed in alphabetic order.

[1] PROFITH "PROmoting FITness and Health through physical activity" Research Group, Sport and Health University Research Institute (iMUDS), Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain.
[2] Department of Health, Medicine and Caring Sciences, Linköping University, 581 83, Linköping, Sweden.
[3] Faculty of Education, Arts and Sports, Western Norway University of Applied Sciences, Sogndal, NORWAY.
[4] Department of Sport Science and Biomechanics, University of Southern Denmark, Odense, Denmark.
[5] School of Health and Life Science, Glasgow Caledonian University, Glasgow, UK.
[6] Department of Movement and Sport Science, Ghent University, Belgium.
[7] Department of Sports Medicine, Norwegian School of Sport Sciences, PO Box 4014, Ullevål Stadion, 0806 Oslo, Norway.
[8] Departement of Sport Science and Physical Education, University of Agder, Norway
[9] Department of Chronic Diseases, National Institute for Health Development, Hiiu 42, Tallinn, Estonia.
[10] School of Natural Sciences and Health, Tallinn University, Tallinn, Estonia.
[11] Institute of Psychology, University of Tartu, Tartu, Estonia.
[12] Department of Chemistry, University of Bergen, Bergen, Norway.
[13] Biomathematics and Statistics Scotland, Edinburgh, UK.
[14] Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK.
[15] NIHR Leicester Biomedical Research Centre, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK.
[16] Alliance for research in Exercise, Nutrition and Activity (ARENA), Sansom Institute for Health Research, Division of Health Sciences, University of South Australia, Adelaide SA 5001, Australia.
[17] Université de Paris, Inserm U1153, Epidemiology of Ageing and Neurodegenerative diseases, 75010 Paris, France.
[18] Department of Epidemiology and Public Health, University College London, London, UK.
[19] Accelting, Almere, The Netherlands.

[20] Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Public and Occupational Health, Amsterdam Public Health research institute, The Netherlands.
[21] Nuffield Department of Population Health, University of Oxford, Oxford, OX3 7LF, UK.
[22] Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden.

***External review group:** Alexander Burchartz[1], Cain Clark[2], Paddy Dempsey[3,4,], Aiden Doherty[5,6], Ulf Ekelund[7], Timothy Olds[8], Eric J. Shiroma[9], Emmanuel Stamatakis[10], Richard P. Troiano[11], Stewart Trost[12,13] and Vadim Zipunnikov[14].

Note: Listed in alphabetic order.

[1]Institute for Sports and Sports Science, Karlsruhe Institute of Technology, Karlsruhe, Germany.
[2]Centre for Sport, Exercise and Life Sciences, Coventry University, Coventry, CV1 5FB, UK.
[3]MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, UK.
[4]Physical Activity & Behavioural Epidemiology Laboratories, Baker Heart and Diabetes Institute, Melbourne, Australia.
[5]Nuffield Department of Population Health, Big Data Institute, University of Oxford, Oxford, UK.
[6]NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK.
[7]Department of Sports Medicine, Norwegian School of Sport Sciences, PO Box 4014, Ullevål Stadion, 0806 Oslo, Norway.
[8]Alliance for Research in Exercise, Nutrition and Activity, University of South Australia, Adelaide, Australia.
[9]Laboratory of Epidemiology and Population Science, National Institute on Aging, Baltimore, Maryland.
[10]Charles Perkins Centre, Prevention Research Collaboration, Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia.
[11]Division of Cancer Control and Population Sciences, National Cancer Institute, NIH, HHS, Rockville, MD.
[12]Institute of Health and Biomedical Innovation at Queensland Centre for Children's Health Research, Queensland University of Technology, South Brisbane, Australia.
[13]Faculty of Health, School of Exercise and Nutrition Sciences, Queensland University of Technology, Brisbane, Australia.
[14]Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University.

Appendix 1

Contents

Accelerometer data descriptors

Modern accelerometers collect raw accelerations (measured in *G*'s) at sample frequencies typically varying from 20 to 100 Hz. As an example, raw data from a thigh-worn accelerometer is presented in **Figure A1**. This raw signal is usually filtered and aggregated to remove the gravitational acceleration and the noise effects on the signal [1]. Examples of common accelerometer data aggregation metrics are activity counts (brand-specific and proprietary aggregation metrics), Euclidean Norm Minus One with negative values rounded to 0 (ENMO), Mean Amplitude Deviation (MAD), Monitor Independent Motion Summary (MIMS) units, Activity Index (AI_0), or steps, among others (hereinafter we refer collectively to them as 'acceleration metrics'). With regard to MIMS it should be noted that the claim that it is accelerometer brand independent has so far not been demonstrated, only sensor from the Actigraph brand were used in the study by John and colleagues [2]. Further, other metrics like MAD and AI_0 can also be brand independent, although this has not been formally tested yet. MIMS applies a narrow frequency filter by which its potential lack of sensitivity to differences in the monitor comes at the cost of lower sensitivity to movements in the low- and high frequency range. In-depth discussions about the influence that these aggregation metrics on the final estimates have been published elsewhere [1,3–5]; we focus our discussion on the conversion of such acceleration metrics to descriptors at a day or person level. Given the numerous versions of accelerometer data descriptors presented in the literature, we decided to focus on those descriptors representative of physical activity (PA) volume, type, and intensity since they are the most frequently-used in public health guidelines.

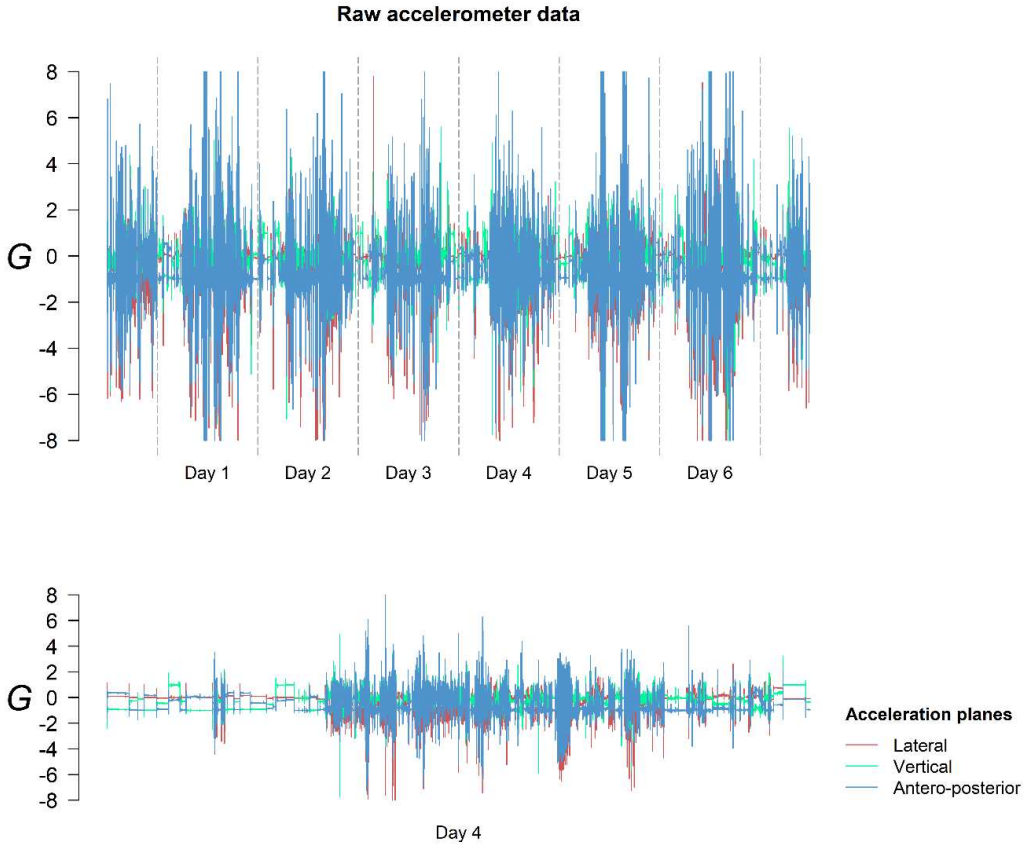

Figure A1. Sample raw accelerometer data recording from a thigh-worn accelerometer. Accelerometer model: Axivity AX3, sampling frequency: 30 Hz, body attachment site: thigh; 24h/day recording protocol.

1.1 Average acceleration or steps per day

Average acceleration over a 24 h period is directly derived from the processed acceleration and can be used as a proxy for total daily PA-related energy expenditure [6]. This single estimate indicates the overall activity level and/or the volume of activity. The same can be obtained from the total number of steps per day, which is also widely used in the field [7,8]. It is usually expressed in m*g* or a manufacturer-provided acceleration metric (usually

counts). Average acceleration usually has a moderate correlation with PA-related energy expenditure (r ~ 0.3-0.5), which can be improved by considering body weight, body composition, and activity type in the models [9,10]. Given that the correlation is not high, it is often used as a direct measure of movement, without making inferences about PA-related energy expenditure.

1.2 Time-use behaviours

Various descriptors quantify the daily time spent in a set of behaviours e.g. time spent in certain activity intensities (e.g., light, moderate or vigorous PA) or types (e.g., sitting, standing, walking). In this regard, cut-points represented one of the first developed and most frequently used methods for assessing the time spent sedentary and in light PA, moderate PA and vigorous PA using the acceleration metric [11]. The identified linear association between acceleration and energy expenditure was used to determine cut-points based on linear absolute metabolic equivalents (METs) thresholds (e.g., sedentary behaviour (SB), ≤1.5; light PA, >1.5 and <3.0; moderate PA, ≥3.0 and <6.0; vigorous PA, ≥6.0 [12]). Thresholds have been also proposed for walking cadence based on the estimation of steps per minute [13,14]. **Figure A2** graphically represents a cut-point-based classification of the acceleration recorded during one day without any definition of bouts. Cut-points can be derived with linear statistical procedures such as linear regression or receiver operating characteristic (ROC) curves, which assume a linear relationship between magnitude of acceleration and METs. However, non-linear approaches have also been used. Otherwise, classification of activity types usually relies on thresholds applied to the device angle variability, usually from thigh- or wrist-placed accelerometers [15,16]. Similarly, thresholds have been applied to acceleration metrics and accelerometer angles to detect

sleep from the accelerometer signal [15,17,18]. More sophisticated models have used the acceleration signal to detect whether the activity performed is locomotion or not, and then applied specific regression models for each activity type (locomotion vs. not locomotion) [19]. Machine learning (ML) methods have gained momentum to classify both activity intensities and types from an accelerometer time series [20]. Classifying behaviours or estimating energy expenditure using a supervised ML approach requires data labelled with 'true' intensity or type (as measured with indirect calorimetry, direct observation, heart rate monitors, among others) [21–25], which is used to iteratively improve classification/estimation. Alternatively, unsupervised ML methods can be used to define "states" in the accelerometer signal pattern that can be interpreted as specific behaviours [26].

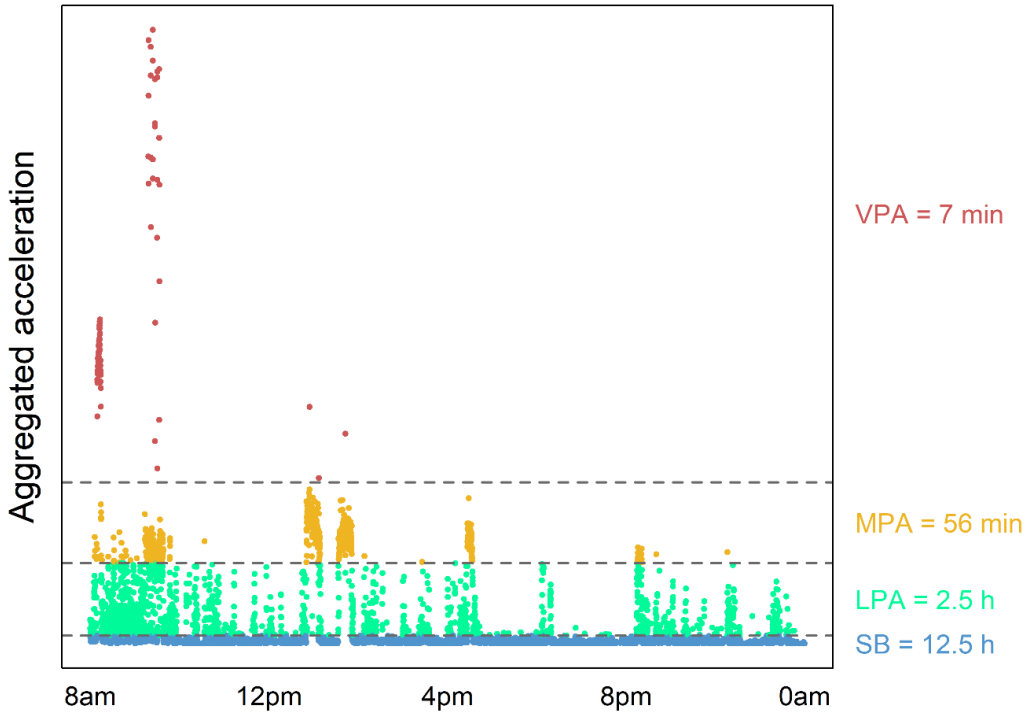

Figure A2. Graphical representation of cut-point-based metrics without bout-specification. Accelerometer model: ActiGraph GT3X+, sampling frequency: 100 Hz, body attachment site: hip; only awake time represented. SB: sedentary behaviour; LPA: light physical activity; MPA: moderate physical activity; VPA: vigorous physical activity.

Independently of the method used to derive these descriptors, they estimate daily time devoted to a specific behaviour. Descriptors of time spent in different PA intensities were first developed to assess objectively the information gained from questionnaire data (the source of most knowledge on the benefits of PA). Use of these time estimates in recent research has confirmed the benefits of PA for health and demonstrated stronger effects of PA than observed with self-report [27].

1.3 Time-use descriptor (intensity spectrum)

The intensity spectrum is also quantified as daily time spent in certain categories, so it is a time-use descriptor. Specifically, time acceleration metric signal over time is classified based on increasing acceleration bands (e.g., time spent from 0-50, 50-100, 100-150, … counts or m*g* or steps per minute). Thus, the intensity spectrum uses a wider range of narrower equally-sized bands for increased resolution of the data [28]. The definition of the bin size is arbitrary, might not directly relate to energy expenditure and does not make any assumption on the behaviour underlying the intensity bin (its purpose is purely descriptive). It can also be regarded as a discretisation of a functional representation of the intensity distribution. The idea behind this approach is to avoid exaggerated aggregation of data (into only 3-4 categories) leading to loss of information. Thus, the number of bands should be large enough to incorporate all essential features in the accelerometer signal.

1.4 Intensity gradient

The intensity gradient describes the negative curvilinear shape of the intensity spectrum (i.e., the higher the intensity the less time spent at this intensity) [29]. The regression coefficient from a linear regression of time spent in an intensity bin on intensity, both on a logarithmic scale, is used as a scalar descriptor of this curvilinear relationship. It is always negative, reflecting the drop-in time accumulated as intensity increases; a more negative (lower) gradient reflects a steeper drop with a large proportion of time accumulated at lower intensities, while a less negative (higher) gradient reflects a shallower drop with time accumulated at higher intensities (**Figure A3**).

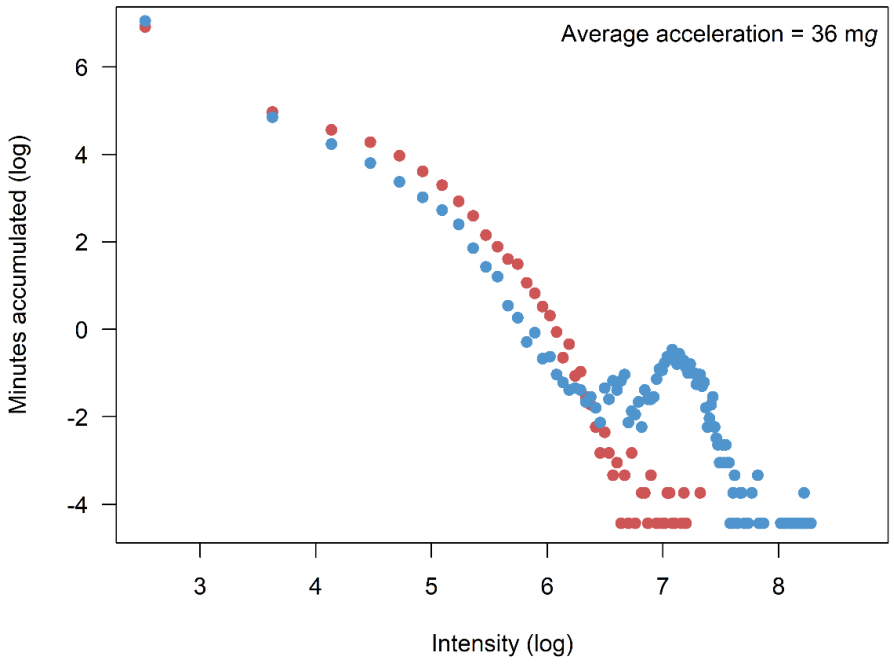

Figure A3. Example of intensity gradients from different participants with a similar average acceleration but discordant intensity distribution (i.e., intensity gradient). Accelerometer model: ActiGraph GT3X+, sampling frequency: 100 Hz, body attachment site: non-dominant wrist.

99

1.5 MX metrics - acceleration values corresponding to a set of percentiles

100 Time-use descriptors were based on the time accumulated in a series of a priori defined
101 behaviours/bands. An alternative is to turn this approach on its head and describe the
102 acceleration intensity distribution in terms of linearized periods of time or fractions of the
103 24 h day (percentiles). The acceleration for each epoch during the day is ranked in
104 descending order to obtain the acceleration above which the person's most active X
105 minutes are accumulated [29]. Therefore, instead of reporting the minutes above a given
106 acceleration threshold, the minimum acceleration achieved for a given duration is reported
107 (the unit of measurement is often m*g* or counts). MX, where X refers to the duration, e.g.
108 M30, refers to the minimum acceleration for the most active 30 min (~percentile 98^{th}) of
109 the day. The MX metrics focus on a person's most active periods of the day, with the active
110 minutes accumulated in any way across the day. For example, if a child had an M60 value
111 of 230 m*g*, the child accumulated 60 min of PA at accelerations (intensity) greater than 230
112 m*g* across the day. Similarly, the periods with the lowest recorded activity can be defined.
113 Similar estimates have been proposed for steps per minute (cadence), being typically
114 referred to as peak-X min (e.g., peak-30 min) [30].

115 A range of MX metrics covering short to long time durations can be used to aid
116 interpretation of the volume and intensity of the 24 h profile of physical activity. Using the
117 MX metrics facilitates interpretation in terms of time spent in indicative activities (e.g.,
118 brisk walking) or above cut-points for different intensities of activity, e.g., moderate-to-
119 vigorous PA (MVPA) or vigorous PA. Plotting a broad range of MX variables on a radar
120 plot illustrates the intensity and volume of the 24h activity profile (**Figure A4**), facilitating

e.g., translation of results from analyses investigating the relative contributions of average acceleration and intensity gradient to markers of health, and/or comparisons between and within groups. For example, the M120, M60, M45, M30, M15, M10, M5 and M2 illustrate the more active periods of the day, while M8h refers to the most active 8 h of the day.

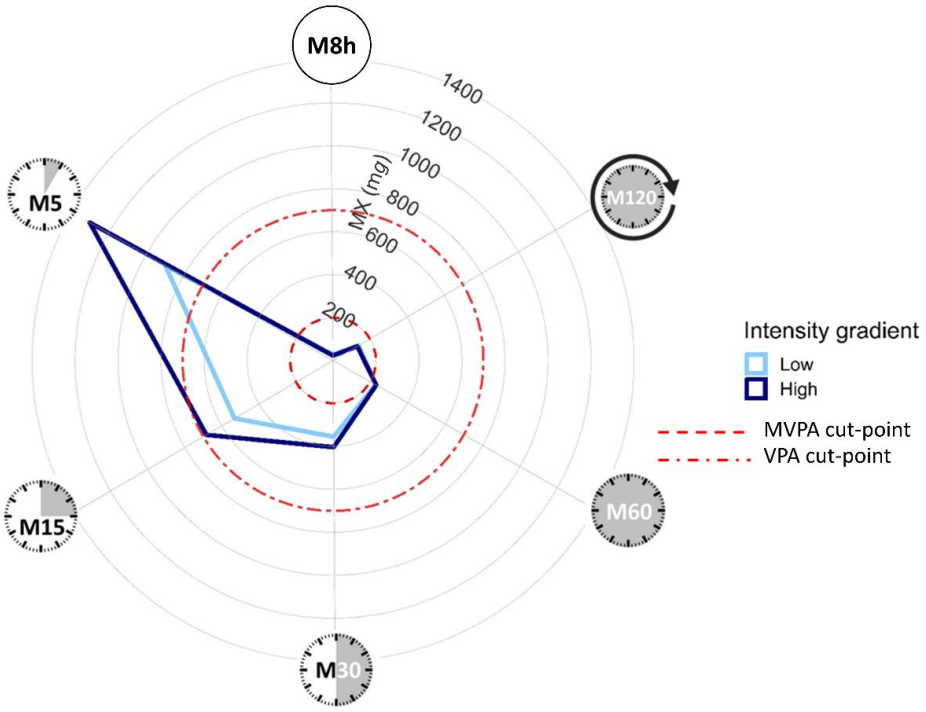

Figure A4. MX metrics example from two participants with similar average acceleration but different intensity gradient. Accelerometer model: ActiGraph GT9X, sampling frequency: 100 Hz, body attachment site: non-dominant wrist. Adapted from Rowlands et al. [31] with the permission from the publisher. IG: intensity gradient; MVPA: moderate-to-vigorous physical activity; VPA: vigorous physical activity.

1.6 Acceleration functions

While the above-mentioned descriptors are represented by scalar numbers, acceleration can also be described using a function. For example, the intensity gradient (described above) can be defined by its function instead of only reporting the beta coefficient. Other functions of interest could be the acceleration over time of the day [32] or the acceleration distribution (**Figure A5**) [33]. Acceleration functions seek a more detailed description of behaviours without making a priori assumptions. For example, while time in light activities assumes that all of the data between two cut-points (e.g., 0.05 to 0.10 *g*) relates similarly to health outcomes, analysis of acceleration functions could detect that a group tend to do more activities at acceleration less than 0.0 m*g* or more activities at acceleration above 0.07 *g*.

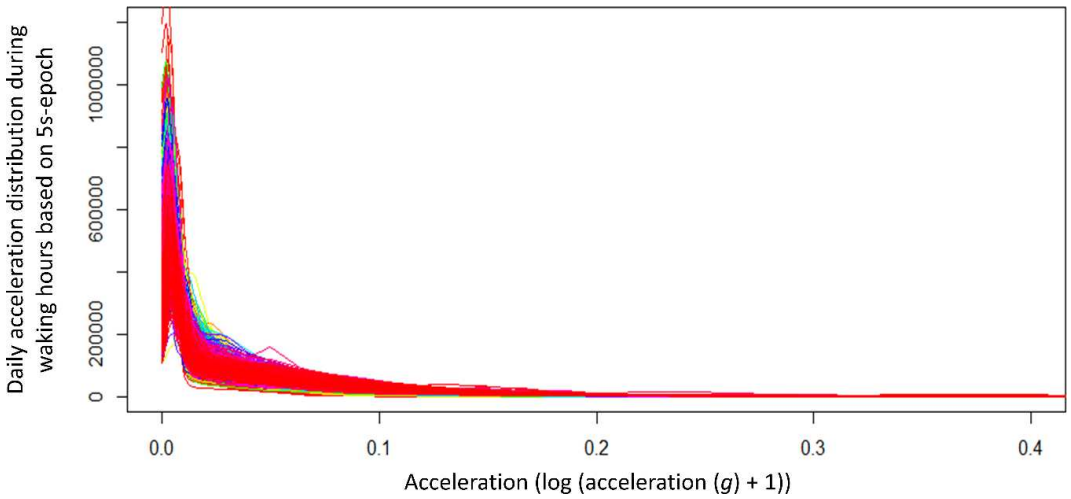

Figure A5. Sample of accelerometer-based distribution as a function of acceleration and time. Accelerometer model: GeneActiv, sampling frequency: 85.7 Hz, body attachment site: non-dominant wrist; 24h/day recording protocol.

1.7 Indicators of movement behaviour patterns and quality

All the above-mentioned descriptors are time-based (time-use behaviours and intensity spectrum) or acceleration-based (average acceleration, MX metrics, acceleration functions) descriptors. That is, they either measure time in a given behaviour or acceleration in a certain time interval. Other descriptors of movement behaviour quality and patterns can be obtained thanks to the time-stamped data derived from accelerometers. Time-stamped accelerometer data can be used to derive certain characteristics of the PA and SB patterns throughout the day, such as the time accumulation in bouts of PA intensities or types. Time-stamped data also provides insight on timing of behaviours, domain (school/work or leisure), and circadian rhythmicity. For example, fragmentation of PA and sleep, sedentary breaks, intradaily variability, interdaily stability, sleep efficiency, or waking periods after sleep onset are frequently used in the field to assess the quality and patterns of PA, SB, and sleep.

Mathematical treatment of descriptors (compositional data analysis)

This section focuses on mathematical treatments to account for the specific singularities of the descriptors presented above. Time-use behaviours and the intensity spectrum consist of a set of components that represent parts of some finite total. This total may be explicit (e.g., complete 24-hour data) or it may arise through interpretation of the data as proportions (e.g., waking day data). Therefore, these descriptors can be considered as compositional data. Each part is called a component and the proportional distribution is called composition. So, for a composition with *i* components:

$$\sum_i Component_i = 1 = 100\% = Whole$$

Compositional data analysis (CoDA) is an approach to analyse compositional data. Its birth is often attributed to Pearson's paper on spurious forms of correlation in ratio data [34]. Arguably the father of CoDA is John Aitchison, who developed comprehensive statistical frameworks to deal with compositional data [35]. CoDA is an established branch of statistics and has been used in many fields of research such as geosciences, nutrition, the study of the microbiome and gene sequencing. In the last five years CoDA has been applied in the field of 'physical behaviour epidemiology' to study the association between daily time use and health (**Figure A6**) [36–38].

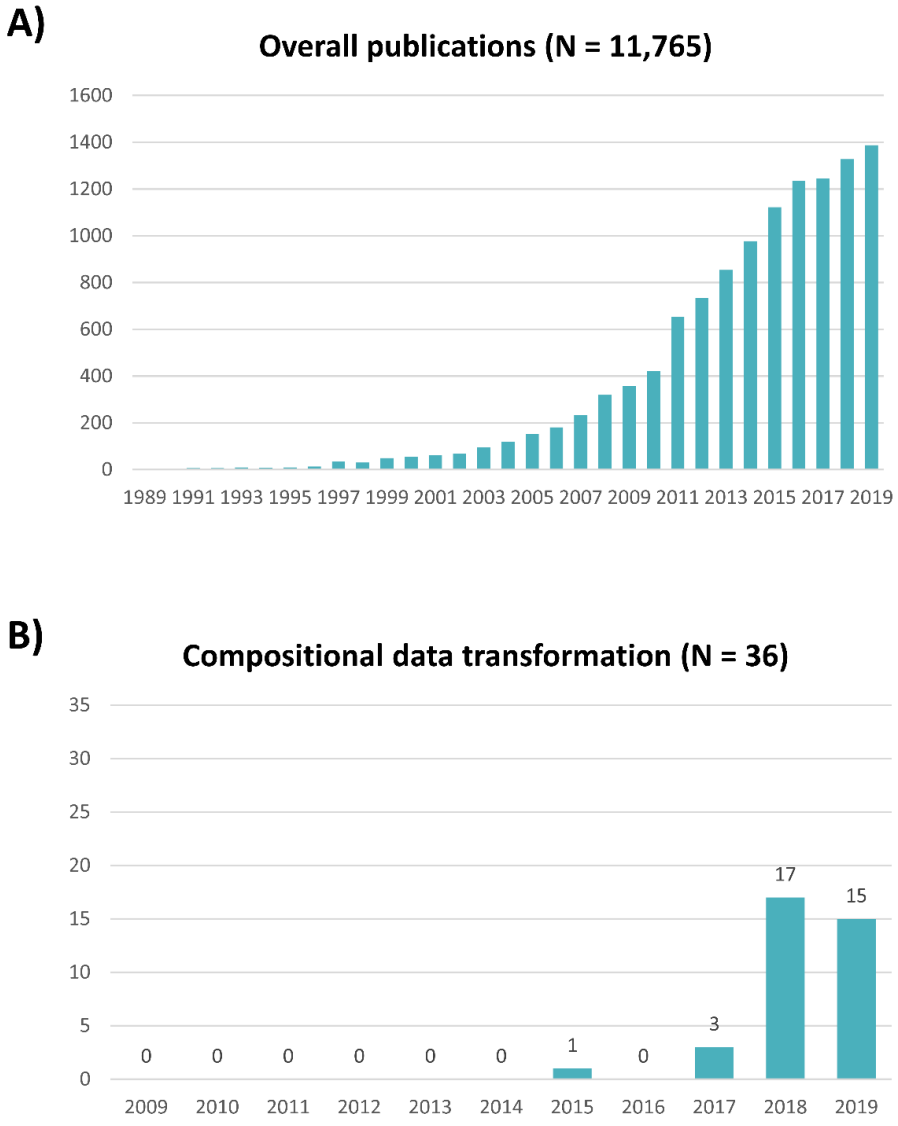

Figure A6. Overall number of publications using accelerometer-determined PA (panel A) and number of publications using compositional data transformations from inception to December 31st, 2019. Search syntax introduced in the Web of Science: Panel A: (((((("physical activity")) OR "sedentary")) AND ((acceleromet*) OR actigraph*)); Panel B: (((((("physical activity")) OR "sedentary")) AND ((acceleromet*) OR actigraph*) AND ("compositional data analysis")).

1.8 Compositional data transformation

Time-use descriptors of physical behaviours are by nature compositional when they describe a time or energy budget (**Figure A7**). Hence the sum of time spent in each behaviour will be the period of interest (24 hours, waking period, week, wear time) and the proportions will sum to 100% of this period. In this example, the composition is made of four components over 24 hours: sleep, SB, light PA and MVPA.

$$t_{sleep} + t_{SB} + t_{LPA} + t_{MVPA} = 24\ hours$$

This is also true if we consider part of the day, such as the composition of movement behaviours during the waking day. Though waking hours are typically not fixed, we can still carry out a compositional data analysis of the proportions.

$$t_{SB} + t_{LPA} + t_{MVPA} = waking\ hours$$

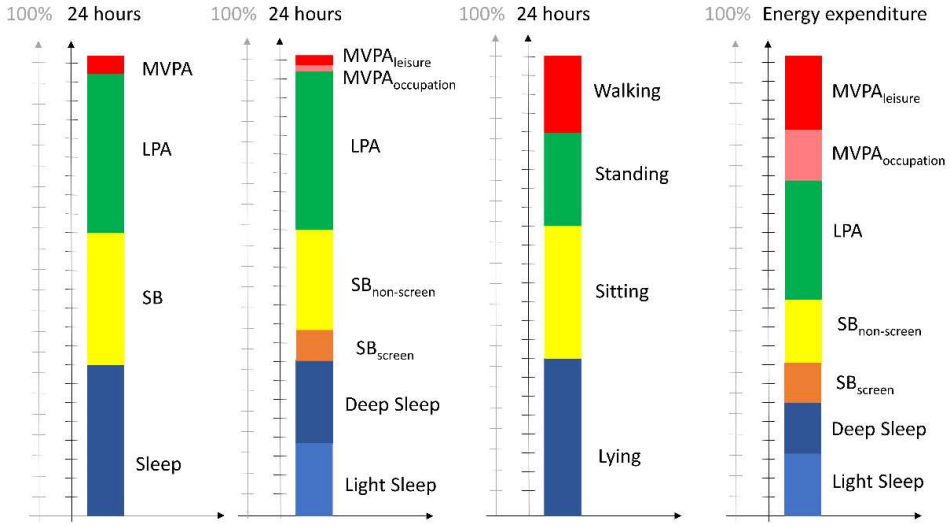

Figure A7. Visualization of the compositional nature of physical behaviour data. SB: sedentary behaviour; LPA: light physical activity; MVPA: moderate-to-vigorous physical activity.

192 A composition can have an unlimited number of parts that can be defined by intensity
193 band,activity type, context information or a combination of those, provided they are
194 mutually exclusive. As a consequence of the fact they describe mutually exclusive
195 components of a time or energy budget, each part only contains relative information rather
196 than an absolute value and, then, the interpretation of compositional data is in terms of
197 relative time spent in the different behaviours. If the data is regarded as a composition;
198 mathematical transformation of the data is required prior to introducing the variables in a
199 statistical model. For some applications, the absolute time may be important, in which case
200 it would not be appropriate to apply the compositional transformation.

201 Compositional data transformations are simple and rely on logarithmic transformations.
202 The purpose of this transformation is to resolve the difficulties around co-dependency and
203 spurious correlation associated with the compositional nature of these descriptors.
204 Statistical models can, therefore, be adjusted for all physical behaviour components without
205 incurring perfect collinearity. Specifically, the data transformations that have been used so
206 far in 'physical behaviour epidemiology' are the centred log ratio (CLR) [39,40] and the
207 isometric-log ratio (ILR) [37,41–43]. Using the CLR method, each component is centred
208 according to the mean logarithm of all the components [35]. The CLR-transformation is
209 mathematically expressed as:

210 $z_i = \ln \frac{t_i}{\sqrt[D]{\prod_{j=1}^{D} t_j}}$ with i indicating each component

211 The sum of the D (number of components) CLR-transformed variables is 0. This fixed sum
212 means they are singular, and cannot be used in regression models. However, we can apply
213 an additional transformation to the CLR components to obtain a D-1 dimensional space

without this constraint. This is referred to as the ILR-transformation when the new space uses an orthonormal basis. There are multiple such bases (and hence ILR transformations) however the most common approach in physical behaviour epidemiology research is shown below (e.g., SB, light PA, MVPA and sleep):

$$z_{SB} = \left(z_1 : \sqrt{\frac{3}{4}} ln \frac{SB}{(LPA \cdot MVPA \cdot Sleep)^{1/3}}, z_2 : \sqrt{\frac{2}{3}} ln \frac{LPA}{(MVPA \cdot Sleep)^{1/2}}, z_3 : \sqrt{\frac{1}{2}} ln \frac{MVPA}{Sleep} \right) (1)$$

$$z_{LIPA} = \left(z_1 : \sqrt{\frac{3}{4}} ln \frac{LPA}{(MVPA \cdot Sleep \cdot SB)^{1/3}}, z_2 : \sqrt{\frac{2}{3}} ln \frac{MVPA}{(Sleep \cdot SB)^{1/2}}, z_3 : \sqrt{\frac{1}{2}} ln \frac{Sleep}{SB} \right) (2)$$

$$z_{MVPA} = \left(z_1 : \sqrt{\frac{3}{4}} ln \frac{MVPA}{(Sleep \cdot SB \cdot LPA)^{1/3}}, z_2 : \sqrt{\frac{2}{3}} ln \frac{Sleep}{(SB \cdot LPA)^{1/2}}, z_3 : \sqrt{\frac{1}{2}} ln \frac{SB}{LPA} \right) (3)$$

$$z_{Sleep} = \left(z_1 : \sqrt{\frac{3}{4}} ln \frac{Sleep}{(SB \cdot LPA \cdot MVPA)^{1/3}}, z_2 : \sqrt{\frac{2}{3}} ln \frac{SB}{(LPA \cdot MVPA)^{1/2}}, z_3 : \sqrt{\frac{1}{2}} ln \frac{LPA}{MVPA} \right) (4)$$

Thus, the ILR produces a set of coordinates for each component (i.e., z_1, z_2 and z_3 in each component of the example above) that should be introduced together as covariates in any statistical model (see section 2.3 for considerations on the statistical model selection). The main difficulty associated with these transformations is in interpreting the results; this is a problem similar to (for example) in linear regression when a variable is log-transformed. For compositional data, a solution is to find an appropriate graphical representation of the results, keeping in mind the co-dependence of the parts and using model predictions rather than deriving the estimate directly from model coefficients. Another difficulty arising from these mathematical transformations is related to having zeros or values close to zero in any of the components. This can happen in certain populations which may not perform vigorous PA or even MVPA. Considering very low values in a composition could lead to spurious

correlations [44], usually, these values are either ignored in the analysis or imputed to stabilize the models [37].

Statistical modelling

The third and last step of the analytical process relates to the decisions on how to model the associations between the selected descriptor(s) (with or without mathematical transformations) and health. As far back as the 1950's [45,46], many studies have investigated the epidemiological associations of physical behaviours with health outcomes. The use of accelerometers confirmed some of these associations, and allowed a better characterisation of the dose-response curve overcoming the cognitive biases of self-reports. However, most studies have solely focused on basic descriptors of one behaviour in isolation (e.g., MVPA). Out of the 11,765 publications identified in a search in the Web of Science on physical activity and accelerometers (**Figure A6, Panel A**), only 125 studies explored the interdependencies among physical behaviours using isotemporal substitution models, multivariate pattern analysis or functional data analysis (**Figure A8**) [47]. This consensus group believes that now is the right time to move to more detailed and informative studies on the combined effects and interactions across physical behaviours on health outcomes.

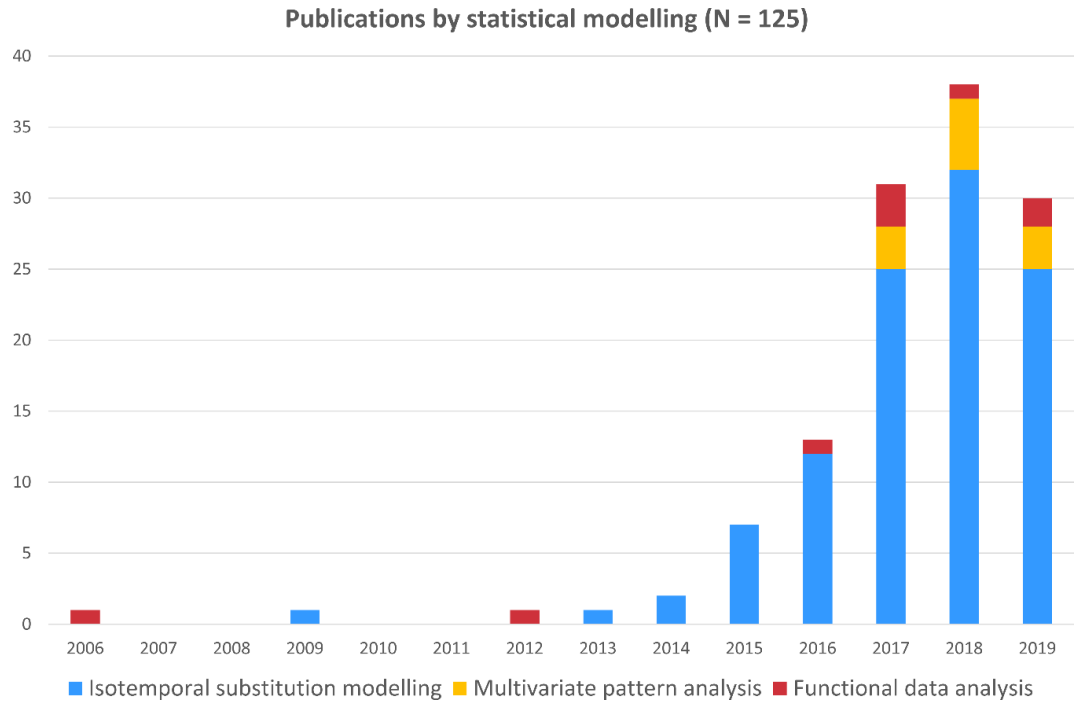

Figure A8. Number of publications using some of the approaches described in the present document from inception to December 31st, 2019. Search syntax introduced in the Web of Science: isotemporal substitution models: (((((("physical activity")) OR "sedentary")) AND ((acceleromet*) OR actigraph*) AND ("isotemporal substitution")); multivariate pattern analysis: (((((("physical activity")) OR "sedentary")) AND ((acceleromet*) OR actigraph*) AND ("Physical activity signature" OR "multivariate pattern analysis")); functional data analysis: (((((("physical activity")) OR "sedentary")) AND ((acceleromet*) OR actigraph*) AND ("Physical activity signature" OR "functional data analysis")).

1.9 Linear regression modelling

Linear regression is the most frequently used statistical model in the field, often including the physical behaviour descriptor as a continuous exposure variable in a linear, logistic or Cox regression (depending on the outcome of interest). Linear regression models are

interpreted in terms of the (theoretical) effect of increasing the explanatory variable on the outcome, under a linear relationship. Standard linear regression models are usually adjusted for the covariates that could influence the association of interest. Highly correlated explanatory variables result in multicollinearity, which is a phenomenon in which redundant information carried by predictors leads to erratic estimation of the models [48].

Linear regression models can also be used with compositional ILR-transformed descriptors, which may eliminate that part of the collinearity which arises from the fixed sum (or closure) constraint [37,38]. In this case, the model coefficients are interpreted in terms of time replacements across behaviours. For example, the estimate for the z_1 coordinate of the z_{SB} equation presented above represents the effect of increasing SB while proportionally reducing the time in light PA, MVPA and sleep. The dose-response association between a specific behaviour and the health outcome is assumed to be logarithmic (curvilinear) using compositionally-transformed descriptors. Likewise, the regression model predictions (using compositional data) can be used to estimate the time replacement between pairs of behaviours (e.g., reallocating time from SB to MVPA). This results in a similar interpretation to the isotemporal substitution models presented in the section 2.3.2. When examining longitudinal associations, advanced regression models (e.g., survival analysis using Cox regression) may be used with either absolute descriptors [27,49,50] or compositional ILR-transformed descriptors [42].

1.10 Isotemporal substitution models

The isotemporal substitution modelling framework considers potential outcomes of increasing one behaviour at the expense of another and whether the strength of the association is dependent on the behaviour being displaced. Isotemporal substitution models

are linear regressions in which all-but-one of the time-use behaviours are introduced as the exposure (together with the pertinent covariates) and the health outcome is the dependent variable. These models examine the estimated effects of replacing time spent in one behaviour (the missing behaviour in the model) with an equal amount of time spent in another, while keeping monitor wear time constant. They do so by dropping the behaviour of interest from the model (otherwise, the model would suffer from perfect collinearity). The linear effects of the pair-wise reallocations are then estimated from the model coefficients. Similar interpretations of time replacement between pairs of behaviours can be obtained from applying linear regression over compositional data (see section 2.3.1).

1.11 Multivariate pattern analysis and other dimension reduction models

Multivariate pattern analysis can handle completely collinear explanatory variables by combining the data into orthogonal latent variables [51]. Thereby, this method tackles collinearity as a dimension reduction problem, rather than a data transformation (as CoDA does). Multivariate pattern analysis is especially well-suited to analyse a wide range of collinear descriptors, such as the intensity spectrum, without requiring any data transformation [28,52], although transformations can be done to make distributions within bands more normal and linearly associated with the outcome. Another important feature is that the models are optimized for predictive ability by Monte-Carlo resampling whereby half of the data are repeatedly used for modelling and half for prediction [53]. In this way, the optimal number of latent variables can be determined and only relevant features in the descriptor retained.

Multivariate pattern analysis uses partial least squares (PLS) regression modelling [51], or other latent-variable regression models [54], to determine the multivariate association

pattern. PLS regression decomposes the explanatory variables into orthogonal linear combinations (PLS components), while simultaneously maximizing the covariance with the outcome variable. Similar procedures to reduce the data can be observed in factor analysis, principal component analysis, or JIVE models. Multivariate pattern analysis differs from these others by creating components that maximize the covariation with the outcome, not internally among the explanatory variables. JIVE models seek to maximize the variance explained across explanatory variables assuming that they come from different dimensions (e.g., PA, sleep, and circadian rhythms) and improving the within and between dimension representation [55]. The procedure for obtaining the multivariate patterns is completely data-driven, with no assumptions on variable distributions or degree of collinearity among variables. Selectivity ratios are calculated to express and rank each single explanatory variables' association with the outcome [56,57]. The selectivity ratio represents each explanatory variable's ratio of explained to residual variance in relation to the outcome (**Figure A9**). By replacing residual variance with total variance in the denominator, a straight-forward measure of explained variance can be obtained [58]. Multivariate pattern analysis has been applied with time-use descriptors and intensity spectrum in both their absolute scale and with the compositional CLR-transformation [39]. Since multivariate pattern analysis can handle singular data (e.g., CLR-transformed data), the ILR-transformation is not necessary if modelling compositional data.

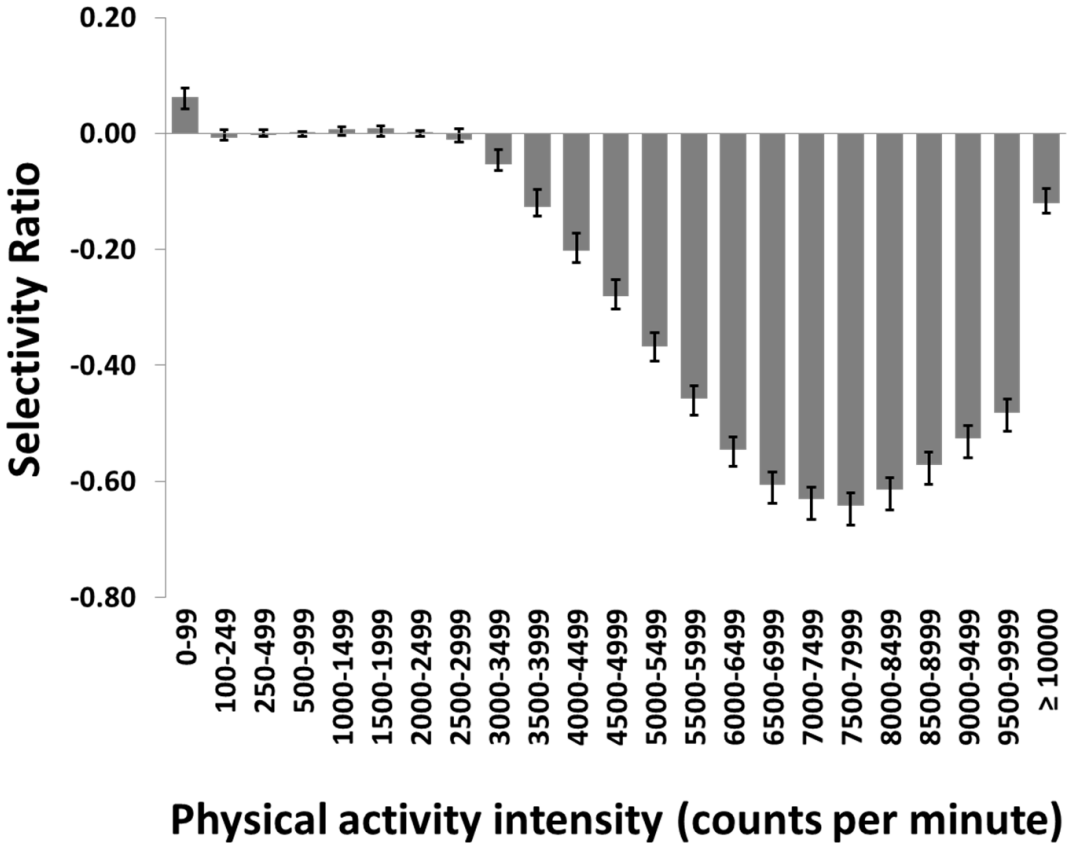

Figure A9. Multivariate pattern analysis example. Accelerometer model: ActiGraph GT3X+, sampling frequency: 30 Hz, body attachment site: right hip; awake time recording protocol. Selectivity ratio represents the explained-to-total outcome variance ratio. Adapted from Aadland et al. [39] with permission from the publisher.

1.12 Functional data analysis

Functional data analysis is an extension of linear regression analysis where the exposure or the outcome (or both) is a function instead of a scalar [59–61]. In physical behaviour epidemiology, the rationale of functional data analysis in the context of accelerometer data comes from the availability of moment-by-moment acceleration data allowing the use of the entire range of accelerations, whatever the aggregated metric used (e.g., counts, ENMO,

MAD) [62,63]. The acceleration functions described in section 2.1.6 can be used in functional data analysis. A first step often consists in smoothing the function of interest so that the smoothed function can then be used in functional data analysis, although some approaches do not smooth the data at subject level and rather pool the data across subjects to avoid the loss of information from the accelerometer signal. For example, when the interest is in the distribution of acceleration over time of the day, one can reduce data into 10 minute epochs as the objective is to assess when individuals are more or less active at each time of the day [64]. When the function of interest is the acceleration density distribution, Gaussian Kernel smoothing methods can be used (**Figure A10**) [65]. In that case, careful attention should be given to the number and place of nodes for acceleration values: a higher number of nodes should be present in the acceleration range where most of the time is spent. Then, the smoothed function of interest can be used for further analysis as an outcome variable (Function-on-scalar analysis), an exposure (Scalar-on-function analysis), or both (Function-on-function analysis) using functional data analysis regression techniques.

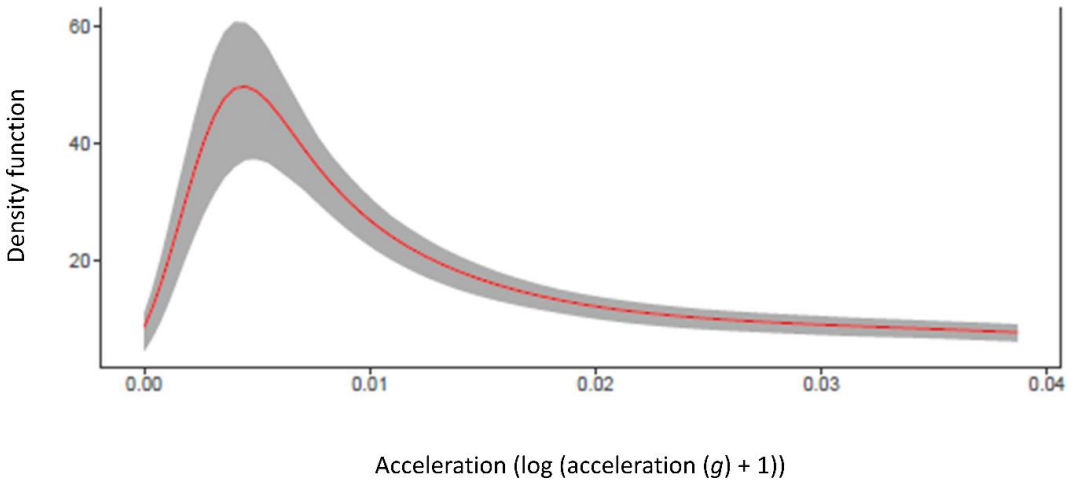

Figure A10. Smooth mean and interquartile acceleration density function. Red curve represents the mean density function of the study population and the grey area the interquartile range.

1.13 Machine learning for epidemiological analysis

ML methods provide a broad range of techniques to identify patterns in data. Although it has been increasingly used to derive descriptors from raw accelerometer data [20], ML has rarely been applied to the study of the associations of accelerometer data descriptors (examples of ML for health association analysis using physical behaviour data include [66,67]). As ML methods typically emphasise prediction or data reduction, they are most often relevant for hypothesis generation and data exploration. While there is no clear distinction between conventional statistical methods and ML, there is typically a different emphasis, and so they can be difficult to apply directly to problems requiring statistical inference. Bi et al. discuss possible epidemiologic applications of a wide range of machine learning methods in detail [68]. Examples of ML methods which could be applied to health association analysis using accelerometer data include Decision Trees/ Random Forests, Support Vector Machines and Neural Networks.

References

1 van Hees VT, Gorzelniak L, Dean León EC, *et al.* Separating Movement and Gravity Components in an Acceleration Signal and Implications for the Assessment of Human Daily Physical Activity. *PLoS One* 2013;**8**:1–10. doi:10.1371/journal.pone.0061691

2 John D, Tang Q, Albinali F, *et al.* An Open-Source Monitor-Independent Movement

Summary for Accelerometer Data Processing. *J Meas Phys Behav* 2019;**2**:268–81. doi:10.1123/jmpb.2018-0068

3 Migueles JH, Cadenas-Sanchez C, Rowlands A V, *et al.* Comparability of accelerometer signal aggregation metrics across placements and dominant wrist cut points for the assessment of physical activity in adults. *Sci Rep* 2019;**9**:18235. doi:10.1038/s41598-019-54267-y

4 Migueles JH, Cadenas-Sanchez C, Ekelund U, *et al.* Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. *Sports Med* 2017;**47**:1821–45. doi:10.1007/s40279-017-0716-0

5 Vähä-Ypyä H, Vasankari T, Husu P, *et al.* A universal, accurate intensity-based classification of different physical activities using raw data of accelerometer. *Clin Physiol Funct Imaging* 2015;**35**:64–70. doi:10.1111/cpf.12127

6 Bouten C V, Verboeket-van de Venne WP, Westerterp KR, *et al.* Daily physical activity assessment: comparison between movement registration and doubly labeled water. *J Appl Physiol* 1996;**81**:1019–26. doi:10.1152/jappl.1996.81.2.1019

7 Saint-Maurice PF, Troiano RP, Bassett DR, *et al.* Association of Daily Step Count and Step Intensity With Mortality Among US Adults. *JAMA* 2020;**323**:1151–60. doi:10.1001/jama.2020.1382

8 Lee IM, Shiroma EJ, Kamada M, *et al.* Association of Step Volume and Intensity with All-Cause Mortality in Older Women. *JAMA Intern Med* 2019;**02215**. doi:10.1001/jamainternmed.2019.0899

9 Migueles JH, Rowlands A V., Huber F, *et al.* GGIR: A Research Community–Driven Open Source R Package for Generating Physical Activity and Sleep Outcomes From Multi-Day Raw Accelerometer Data. *J Meas Phys Behav* 2019;**2**:188–96. doi:10.1123/jmpb.2018-0063

10 Brage S, Westgate K, Franks PW, *et al.* Estimation of free-living energy expenditure by heart rate and movement sensing: A doubly-labelled water study. *PLoS One* 2015;**10**:1–19. doi:10.1371/journal.pone.0137206

11 Freedson PS, Melanson E, Sirard JR. Calibration of the computer science and applications, Inc. accelerometer. *Med Sci Sports Exerc* 1998;**30**:777–81. doi:10.1097/00005768-199805000-00021

12 Garber CE, Blissmer B, Deschenes MR, *et al.* Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;**43**:1334–59. doi:10.1249/MSS.0b013e318213fefb

13 Tudor-Locke C, Aguiar EJ, Han H, *et al.* Walking cadence (steps/min) and intensity in 21-40 year olds: CADENCE-adults. *Int J Behav Nutr Phys Act* 2019;**16**:8. doi:10.1186/s12966-019-0769-6

14 Tudor-Locke C, Schuna JM, Han H, *et al.* Cadence (steps/min) and intensity during ambulation in 6-20 year olds: the CADENCE-kids study. *Int J Behav Nutr Phys Act* 2018;**15**:20. doi:10.1186/s12966-018-0651-y

15 Van Hees VT, Sabia S, Anderson KN, *et al.* A novel, open access method to assess sleep duration using a wrist-worn accelerometer. *PLoS One* 2015;**10**:1–13.

415 doi:10.1371/journal.pone.0142533

416 16 Crowley P, Skotte J, Stamatakis E, *et al.* Comparison of physical behavior estimates
417 from three different thigh-worn accelerometers brands: a proof-of-concept for the
418 Prospective Physical Activity, Sitting, and Sleep consortium (ProPASS). *Int J Behav*
419 *Nutr Phys Act* 2019;**16**:65. doi:10.1186/s12966-019-0835-0

420 17 Sadeh A, Sharkey KM, Carskadon MA. Activity-based sleep-wake identification: an
421 empirical test of methodological issues. *Sleep* 1994;**17**:201–7. doi:7939118

422 18 Cole RJ, Kripke DF, Gruen W, *et al.* Automatic sleep wake identification from wrist
423 activity - Cole et al 1992.pdf. Sleep. 1992;**15**:461–9.

424 19 Crouter SE, Kuffel E, Haas JD, *et al.* Refined two-regression model for the
425 ActiGraph accelerometer. *Med Sci Sports Exerc* 2010;**42**:1029–37.
426 doi:10.1249/MSS.0b013e3181c37458

427 20 Narayanan A, Desai F, Stewart T, *et al.* Application of Raw Accelerometer Data and
428 Machine-Learning Techniques to Characterize Human Movement Behavior: A
429 Systematic Scoping Review. *J Phys Act Health* 2020;**17**:360–83.
430 doi:10.1123/jpah.2019-0088

431 21 Doherty A, Smith-Byrne K, Ferreira T, *et al.* GWAS identifies 14 loci for device-
432 measured physical activity and sleep duration. *Nat Commun* 2018;**9**:5257.
433 doi:10.1038/s41467-018-07743-4

434 22 Willetts M, Hollowell S, Aslett L, *et al.* Statistical machine learning of sleep and
435 physical activity phenotypes from sensor data in 96,220 UK Biobank participants.
436 *Sci Rep* 2018;**8**:1–10. doi:10.1038/s41598-018-26174-1

23 Ellis K, Kerr J, Godbole S, *et al.* Hip and wrist accelerometer algorithms for free-living behavior classification. *Med Sci Sports Exerc* 2016;**48**:933–40. doi:10.1249/MSS.0000000000000840

24 Ellis K, Kerr J, Godbole S, *et al.* A random forest classifier for the prediction of energy expenditure and type of physical activity from wrist and hip accelerometers. *Physiol Meas* 2014;**35**:2191–203. doi:10.1088/0967-3334/35/11/2191

25 Staudenmayer J, He S, Hickey A, *et al.* Methods to estimate aspects of physical activity and sedentary behavior from high-frequency wrist accelerometer measurements. *J Appl Physiol* 2015;**119**:396–403. doi:10.1152/japplphysiol.00026.2015

26 van Kuppevelt D, Heywood J, Hamer M, *et al.* Segmenting accelerometer data from daily life with unsupervised machine learning. *PLoS One* 2019;**14**:e0208692. doi:10.1371/journal.pone.0208692

27 Ekelund U, Tarp J, Steene-Johannessen J, *et al.* Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ* 2019;**366**:l4570. doi:10.1136/bmj.l4570

28 Aadland E, Kvalheim OM, Anderssen SA, *et al.* The multivariate physical activity signature associated with metabolic health in children. *Int J Behav Nutr Phys Act* 2018;**15**:1–11. doi:10.1186/s12966-018-0707-z

29 Rowlands A V., Edwardson CL, Davies MJ, *et al.* Beyond Cut Points: Accelerometer Metrics that Capture the Physical Activity Profile. *Med Sci Sports*

Exerc 2018;**50**:1323–32. doi:10.1249/MSS.0000000000001561

30 Tudor-Locke C, Brashear MM, Katzmarzyk PT, *et al.* Peak stepping cadence in free-living adults: 2005-2006 NHANES. *J Phys Act Health* 2012;**9**:1125–9. doi:10.1123/jpah.9.8.1125

31 Rowlands A V., Dawkins NP, Maylor B, *et al.* Enhancing the value of accelerometer-assessed physical activity: meaningful visual comparisons of data-driven translational accelerometer metrics. *Sport Med - Open* 2019;**5**. doi:10.1186/s40798-019-0225-9

32 Goldsmith J, Zipunnikov V, Schrack J. Generalized multilevel function-on-scalar regression and principal component analysis. *Biometrics* 2015;**71**:344–53. doi:10.1111/biom.12278

33 Benadjaoud MA, Menai M, van Hees VT, *et al.* The association between accelerometer-assessed physical activity and respiratory function in older adults differs between smokers and non-smokers. *Sci Rep* 2019;**9**:1–9. doi:10.1038/s41598-019-46771-y

34 Pearson K. Mathematical contributions to the theory of evolution.-On a form of spurious correlation which may arise when indices are used in the measurement of organs. *Proc R Soc London* 1897;**60**:489–98. doi:10.1098/rspl.1896.0076

35 Aitchison J. The statistical analysis of compositional data. *J R Stat Soc* 1982;**44**:139–77.

36 McGregor DE, Palarea-Albaladejo J, Dall PM, *et al.* Cox regression survival analysis with compositional covariates: Application to modelling mortality risk from

24-h physical activity patterns. *Stat Methods Med Res* 2019;**29**:096228021986412. doi:10.1177/0962280219864125

37 Chastin SFM, Palarea-Albaladejo J, Dontje ML, *et al.* Combined effects of time spent in physical activity, sedentary behaviors and sleep on obesity and cardio-metabolic health markers: A novel compositional data analysis approach. *PLoS One* 2015;**10**:e0139984. doi:10.1371/journal.pone.0139984

38 Dumuid D, Stanford TE, Martin-Fernández JA, *et al.* Compositional data analysis for physical activity, sedentary time and sleep research. *Stat Methods Med Res* 2018;**27**:3726–38. doi:10.1177/0962280217710835

39 Aadland E, Kvalheim OM, Anderssen SA, *et al.* Multicollinear physical activity accelerometry data and associations to cardiometabolic health: challenges, pitfalls, and potential solutions. *Int J Behav Nutr Phys Act* 2019;**16**:1–14. doi:10.1186/s12966-019-0836-z

40 Hinkle J, Rayens W. Partial least squares and compositional data: problems and alternatives. *Chemom Intell Lab Syst* 1995;**30**:159–72. doi:10.1016/0169-7439(95)00062-3

41 Egozcue JJ, Pawlowsky-Glahn V, Mateu-Figueras G, *et al.* Isometric Logratio Transformations for Compositional Data Analysis. *Math Geol* 2003;**35**:279–300. doi:10.1023/A:1023818214614

42 McGregor DE, Palarea-Albaladejo J, Dall PM, *et al.* Compositional analysis of the association between mortality and 24-hour movement behaviour from NHANES. *Eur J Prev Cardiol* 2019;:204748731986778. doi:10.1177/2047487319867783

43 Migueles JH, Cadenas-Sanchez C, Esteban-Cornejo I, *et al.* Associations of objectively-assessed physical activity and sedentary time with hippocampal gray matter volume in children with overweight/obesity. *J Clin Med* 2020;**9**. doi:10.3390/jcm9041080

44 Skala W. Some effects of the constant-sum problem in geochemistry. *Chem Geol* 1979;**27**:1–9. doi:10.1016/0009-2541(79)90099-8

45 Rook A. An investigation into the longevity of Cambridge sportsmen. *Br Med J* 1954;**1**:773–7. doi:10.1136/bmj.1.4865.773

46 Morris JN, Heady JA, Raffle PA, *et al.* Coronary heart-disease and physical activity of work. *Lancet (London, England)* 1953;**262**:1111–20; concl. doi:10.1016/s0140-6736(53)91495-0

47 Ekelund U, Dalene KE, Tarp J, *et al.* Physical activity and mortality: What is the dose response and how big is the effect. *Br J Sports Med* 2020;**0**:5–6. doi:10.1136/bjsports-2019-101765

48 Stanton JM. Galton, Pearson, and the Peas: A Brief History of Linear Regression for Statistics Instructors. *J Stat Educ* 2001;**9**. doi:10.1080/10691898.2001.11910537

49 Tarp J, Hansen BH, Fagerland MW, *et al.* Accelerometer-measured physical activity and sedentary time in a cohort of US adults followed for up to 13 years: The influence of removing early follow-up on associations with mortality. *Int J Behav Nutr Phys Act* 2020;**17**:1–8. doi:10.1186/s12966-020-00945-4

50 Lee I-M, Shiroma EJ, Evenson KR, *et al.* Accelerometer-Measured Physical Activity and Sedentary Behavior in Relation to All-Cause Mortality: The Women's Health

Study. *Circulation* 2018;**137**:203–5. doi:10.1161/CIRCULATIONAHA.117.031300

51 Wold S, Ruhe A, Wold H, *et al.* The Collinearity Problem in Linear Regression. The Partial Least Squares (PLS) Approach to Generalized Inverses. *SIAM J Sci Stat Comput* 1984;**5**:735–43. doi:10.1137/0905052

52 Aadland E, Kvalheim OM, Anderssen SA, *et al.* The Triaxial Physical Activity Signature Associated with Metabolic Health in Children. *Med Sci Sports Exerc* 2019;**51**:2173–9. doi:10.1249/MSS.0000000000002021

53 Kvalheim OM, Arneberg R, Grung B, *et al.* 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* 2018;**32**:1–12. doi:10.1002/cem.2993

54 Rajalahti T, Kvalheim OM. Multivariate data analysis in pharmaceutics: A tutorial review. *Int J Pharm* 2011;**417**:280–90. doi:10.1016/j.ijpharm.2011.02.019

55 Di J, Spira A, Bai J, *et al.* Joint and Individual Representation of Domains of Physical Activity, Sleep, and Circadian Rhythmicity. *Stat Biosci* 2019;**11**:371–402. doi:10.1007/s12561-019-09236-4

56 Kvalheim OM, Karstang T V. Interpretation of latent-variable regression models. *Chemom Intell Lab Syst* 1989;**7**:39–51. doi:10.1016/0169-7439(89)80110-8

57 Rajalahti T, Arneberg R, Kroksveen AC, *et al.* Discriminating variable test and selectivity ratio plot: Quantitative tools for interpretation and variable (biomarker) selection in complex spectral or chromatographic profiles. *Anal Chem* 2009;**81**:2581–90. doi:10.1021/ac802514y

58 Aadland E, Andersen LB, Resaland GKKK, *et al.* Interpretation of Multivariate Association Patterns between Multicollinear Physical Activity Accelerometry Data and Cardiometabolic Health in Children-A Tutorial. *Metabolites* 2019;**9**:1–14. doi:10.3390/metabo9070129

59 Ramsay J, Silverman B. *Functional Data Analysis*. 2nd Editio. New York: 2005. doi:10.1007/978-3-540-32691-5_16

60 Reiss PT, Goldsmith J, Shang HL, *et al.* Methods for scalar-on-function regression. *Int Stat Rev* 2017;**85**:228–49. doi:10.1111/insr.12163

61 Morris JS. Comparison and Contrast of Two General Functional Regression Modeling Frameworks. *Stat Modelling* 2017;**17**:59–85. doi:10.1177/1471082X16681875

62 Augustin NH, Mattocks C, Cooper AR, *et al.* Modelling fat mass as a function of weekly physical activity profiles measured by Actigraph accelerometers. *Physiol Meas* 2012;**33**:1831–9. doi:10.1088/0967-3334/33/11/1831

63 Augustin NH, Mattocks C, Faraway JJ, *et al.* Modelling a response as a function of high-frequency count data: The association between physical activity and fat mass. *Stat Methods Med Res* 2017;**26**:2210–26. doi:10.1177/0962280215595832

64 Goldsmith J, Liu X, Jacobson JS, *et al.* New Insights into Activity Patterns in Children, Found Using Functional Data Analyses. *Med Sci Sports Exerc* 2016;**48**:1723–9. doi:10.1249/MSS.0000000000000968

65 Chacón JE, Duong T. Multivariate plug-in bandwidth selection with unconstrained pilot bandwidth matrices. *Test* 2010;**19**:375–98. doi:10.1007/s11749-009-0168-4

569 66 Hua A, Quicksall Z, Di C, *et al.* Accelerometer-based predictive models of fall risk
570 in older women: a pilot study. *npj Digit Med* 2018;**1**. doi:10.1038/s41746-018-0033-
571 5

572 67 Alaa AM, Bolton T, Angelantonio E Di, *et al.* Cardiovascular disease risk prediction
573 using automated machine learning: A prospective study of 423,604 UK Biobank
574 participants. *PLoS One* 2019;**14**:1–17. doi:10.1371/journal.pone.0213653

575 68 Bi Q, Goodman KE, Kaminsky J, *et al.* What Is Machine Learning: a Primer for the
576 Epidemiologist. *Am J Epidemiol* Published Online First: 11 September 2019.
577 doi:10.1093/aje/kwz189

578