Association between physical activity and all-cause mortality: a 15-year follow-up using a compositional data analysis

Running title: Physical activity and all-cause mortality

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Abstract
The association between the composition of movement behaviours and mortality risk, acknowledging the composition nature of daily time data, is limited explored. The aim was to investigate how the composition of time spent in sedentary behaviours (SB), light intensity physical activity (LIPA) and moderate-to-vigorous physical activity (MVPA) is associated with all-cause mortality, in a cohort with 15 years follow-up time, using compositional data analysis. Eight hundred fifty-one participants (56% women, mean age 53 years) provided objectively assessed physical activity data using an Actigraph accelerometer and were followed for 15 years. Association of daily time composition of movement behaviours with risk of mortality were explored using compositional data analysis and hazard ratios (HR) of mortality were estimated based on a cox regression model. A significant (p<0.001) positive association between time spent in SB relative to time in other behaviours, and a significant (p=0.018) negative association between time spent in LIPA relative to time in other behaviours, with all-cause mortality, was found. Substituting time spent in LIPA or MVPA with time in SB increased the hazard for all-cause mortality, with greater effect found for MVPA (20 min replacement; HR 1.26, 95% CI 1.04-1.52) than for LIPA (20 min replacement; HR 1.06, 95% CI 0.65-1.73). In a public health perspective, it is recommended to substitute SB with either LIPA or MVPA, but for individuals with little time spent in MVPA, the most important message may be to try to maintain that behaviour.

Keywords: accelerometry, isotemporal substitution model, longitudinal, movement behaviour

INTRODUCTION
Physical activity represents a wide range of behaviours associated with multiple health benefits, such as reducing the risk of non-communicable diseases, improving subjective health and decreasing mortality risk.1-4 More time in moderate-to-vigorous physical activity (MVPA) has been associated with lower risk of cardiovascular disease and all-cause mortality.5,6 Time in light intensity physical activity (LIPA) has been associated with improved glycaemic control, reduced risk of developing type 2 diabetes and all-cause mortality,7-9 even if evidence is inconclusive.10 In addition, the adverse health effects and mortality risk associated with time spent in sedentary behaviour (SB), e.g. activities with < 1.5 MET, has been highlighted.11-13
Still, most studies have separately investigated the effect of movement behaviours such as SB, LIPA and MVPA as independent entities, and not considered that the portions of time spent on each activity represent relative information of the complete day. Recent evidence suggest that time spent in different behaviours are related, and thus time use in one behaviour also depends on the time it displaced from another behaviour. Consequently, the effect of different behaviours needs to be explored in relation to other behaviours since they are all inherently co-dependent.

To explore the theoretical effect of substituting time in one behaviour with another, isotemporal substitution method has been developed and applied frequently in the field of physical activity research last years. For instance, utilizing isotemporal substitution models we showed that substituting sedentary time with MVPA is associated with reduced cardiovascular disease mortality. Other reports have shown that substituting time in LIPA with MVPA is associated with more favourable waist circumference or HDL cholesterol and substituting SB with standing or stepping activity is associated with improved cardio-metabolic health. However, isotemporal substitution methods have been criticised for using absolute measures and not consider the compositional structure of time-use data. To handle the limitation of isotemporal substitution models, compositional data analysis is suggested, treating time-use data as relative values, and thus acknowledge the composition nature of daily time data.

To further clarify the association between the relative time of different behaviours and associated health consequences, prospective studies using compositional data analysis is needed. Additionally, there is lack of studies using objectively measured physical activity with longer follow-up time, since the majority of studies have less than seven years of follow-up. From a public health point of view, understanding the associated health benefits of allocating time between behaviours such as SB or LIPA is also highly important. Consequently, this study aims to provide all of that, by investigating how the composition of time spent in different behaviours (SB, LIPA, MVPA) is associated with all-cause mortality, in a cohort with 15 years follow-up time, using compositional data analysis.

MATERIALS AND METHOD
Study population and design
This prospective cohort study used data of the 2001-2002 Sweden Attitude Behaviour and Change (ABC) study. In the ABC study, a random sample of 3300 adults of age 18–75 years was selected from the Swedish population register and 2262 were reached. Of the eligible population, 1556 (69%) agreed to participate and 1221 (55% women) provided objective physical activity data. Detailed information about the survey has previously been described.29 The present study included participants ≥ 50 years at follow-up in 2015 with self-reported baseline data and objectively measured physical activity data,23 resulting in a final sample of 851 participants. The study was approved by the Regional Ethical Review Board at the Karolinska Institutet (Dnr 378/02, 2012/707 31/1, 2015 1578/32).

Data collection
Demographic and anthropometric data were self-reported and obtained from the baseline questionnaire sent by mail to the participants. Data collected from this questionnaire and used in this study consist of data on sex, age, BMI, education (University, High school, Primary school), smoking status (never/former or current), and history of chronic disease (hypertension, heart disease, diabetes, and cancer). Register data of mortality of 2002–2015 were collected from the National Board of Health and Welfare’s Cause of Death Register and the Swedish Cancer Registry in 2016. Data on cause-of death were obtained from The Cause of Death Register.

Time in different behaviours were assessed using the uniaxial ActiGraph accelerometer model 7164 (ActiGraph, Pensacola, FL, US), measuring time-varying acceleration in the vertical axis expressed as counts. Thereby, an objective measure of the duration and intensity of physical activity as well as sedentary time throughout a day could be captured. The accelerometers were mailed to the participants, and returned in a prepaid envelope. All participants were instructed to wear the accelerometer on the lower back, using an accompanying elastic belt, for seven consecutive days except during sleep, bathing or swimming activities. The device was set to sampling counts per 1-minute epochs and non-wear time were defined as periods of at least 60 consecutive min of zero counts, allowing for 2 min of counts between zero and 100.29 Data from participants with at least one valid day, including 10 hours or more of wear time,23 were included. In average, the participants had 6.4 days of accelerometer data. Zero values of MVPA (n=5) were imputed based on maximum likelihood estimation.30 Cut-points to estimate time spent in different...
behaviours were chosen in accordance with previous population-based studies: SB (0-99 counts/min), LIPA (100-2019 counts/min) and MVPA (≥ 2020 counts/min). The daily time spent in SB, LIPA and MVPA were normalized to the total wear time in each day and averaged over the number of valid days. The software ActiLife 6 (ActiGraph, Pensacola, FL, US) was used to extract and process the accelerometer data.

**Data analysis**

The compositional mean was determined by adjusting the geometric mean of each behaviour (SB, LIPA, MVPA) to the total wear time. For each participant, time spent in SB, LIPA and MVPA was transformed into isometric log-ratio (ilr) coordinates. Since we use a 3-part composition (SB, LIPA, MVPA), each movement behaviour is then represented by two ilr-variables $z_1$ and $z_2$. Ilr-coordinate $z_1$ represents the relative importance of one component (e.g., SB) relative to the geometric average of the other components (e.g., LIPA and MVPA). For instance, SB relative to LIPA and MVPA is isolated as:

$$z_1 = \frac{1}{\sqrt{3}} \ln \frac{SB}{\sqrt{LIPA \cdot MVPA}}$$

$$z_2 = \frac{1}{\sqrt{2}} \ln \frac{LIPA}{MVPA}$$

By orthogonal rotation it is possible to isolate LIPA or MVPA relative to the other components as well. Therefore, a total of six ilr-variables were constructed with pair of two variables (e.g., $z_1$, $z_2$) for each component (SB, LIPA, MVPA).

Cox proportional-hazard models using compositional methods were conducted to estimate HRs of all-cause mortality with 95% confidence intervals (CIs). Participants were followed from the first day of accelerometer assessment until the date of death or censoring on December 31, 2015. A pair of isometric log-ratios (ILRs) variables were entered as independent variables along with covariates, considered as possible confounders, that is, age, sex, smoking (never/former or current), history of chronic disease and education. Selection of these confounders was based on assumed association between these specific variables and mortality risk. The methodological approach allowed all three pairs of ILRs (one pair at a time) to act as independent variables, adjusting for the time spent in the other behaviours, without changing the model fit. Final model
was stratified for sex and age tertiles to fulfil the proportional-hazard assumption, and included ILRs and independent variables, that is, education, smoking, and chronic disease. A sensitivity analysis was conducted by randomly removing 10% of cases and evaluated its effect on the model parameters in order to assess the robustness of the results.

The HRs of the ILRs represent the direction and strength of the association. For instance, a HR value $>1$ for $z_1$, could be interpreted as when time spent in SB is increasing relative to time spent in LIPA and MVPA, the hazard for all-cause mortality is increased. To simplify the interpretation further, the association of substituting time in one behaviour for another was explored following the approach described by McGregor et al. The compositional mean of each of the three behaviours was used as a reference and HR was predicted based on the final Cox regression model. Then the effect of allocating time up to 90 minutes between behaviours were explored and HR values were again predicted. The ratio of HRs between the new time composition dataset and the reference dataset was calculated. Finally, an isotemporal plot was constructed to illustrate the effect on HR associated with allocating time between behaviours. A p value $\leq 0.05$ was considered as statistically significant. All analyses were conducted using the R statistical system version 3.5.1.

RESULTS

At the average follow-up time of 5197 days, a total of 79 deaths had occurred. The deaths were related to cardiovascular disease (n=24), cancer (n=27), other causes (n=28) and none to accidents. Based on unadjusted compositional mean values, the all-cause mortality group spent less time in LIPA, MVPA and more time in SB, compared to the non-death cases. Baseline characteristics of the study population are presented in Table 1 and the proportion time spent in SB, LIPA and MVPA, stratified by non-death/all-cause mortality, is presented in a ternary plot (Figure 1).

Please insert Table 1 here

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Adjusting for education, smoking, hypertension, heart disease, cancer, diabetes, with stratification by sex and age tertiles, the cox regression model showed more time spent in SB relative to time in other behaviours was significantly (p<0.001) positively associated with all-cause mortality (HR 2.24, 95% CI 1.41-3.56). Time spent in LIPA relative to time in other behaviours was significantly (p=0.018) negatively associated with all-cause mortality (HR 0.49, 95% CI 0.27-0.89), whereas no significant (p=0.419) effect was found for time spent in MVPA relative to time in other behaviours (Table 2). The sensitivity analysis showed no statistically significant change in the model when 10% of the cases were randomly removed (supplementary file).

The theoretical consequences of substituting time, centred around the compositional mean for each movement behaviour, were explored. Substituting time spent in LIPA or MVPA with time in SB increased the hazard for all-cause mortality, with higher hazard values for substituting time spent in MVPA (20 min replacement; HR 1.26, 95% CI 1.04-1.52) than for LIPA (20 min replacement; HR 1.06, 95% CI 0.65-1.73). At the same time, substituting time spent in SB with time in LIPA or MVPA was associated with reduced hazard of all-cause mortality (Figure 2). Substituting time spent in MVPA with time in SB or LIPA, keeping the total volume of MVPA below the compositional mean of MVPA (21.5 minutes), increased hazard for all-cause mortality.
DISCUSSION

In this study, we explored the effect of allocating time to SB, LIPA and MVPA on all-cause mortality, in a cohort with 15 years follow-up time, using compositional data analysis. Overall, we found statistically significant associations between time spent in SB relative to time in other behaviours with all-cause mortality, and between time spent in LIPA relative to time in other behaviours.

Extending upon previous work of substituting time with another type of activity,\textsuperscript{21,23,26,27} the present study is one of the first to employ a compositional data analysis approach to model mortality risk by substituting time spent in one behaviour with another. A compositional data analysis approach treats time-use data as relative values, considers behaviours as co-dependent while modelling the relative distribution of time spent in different behaviours and thereby acknowledges the composition nature of daily time data.\textsuperscript{17} In this study, a lack of a symmetric effect on substituting time between different behaviours and mortality risk was found, ie., the effect was different when allocating time between two behaviours depending on which behaviour that increased or decreased. For instance, substituting time spent in MVPA with time in SB increased mortality risk to a larger effect (20 min replacement; HR 1.26) compared to when time spent in SB was substituted with time in MVPA (20 min replacement; HR 0.92)

Our results confirm the findings of the 2018 Physical Activity Guidelines Advisory Committee Scientific Report that small increases in time spent in MVPA, for a participant with little time in MVPA, may be associated with great health benefits.\textsuperscript{4} Even though the relative time spent in
MVPA had no significant effect in this study, our results resemble other findings\textsuperscript{34-36} that even low doses of MVPA seem to affect mortality risk. For instance, substituting time spent in MVPA, with time in SB or LIPA, was associated with a relative rapid increased risk of all-cause mortality. Interestingly, the threshold level of MVPA identified in this study is in line with the recommended guidelines for physical activity of 150 minutes per week of MVPA\textsuperscript{4}.

It is worth acknowledging that the time spent in MVPA relative to the other behaviours had no significant effect on all-cause mortality and substituting time spent in LIPA with time in MVPA did not reduce the risk further. This may be explained by misclassification of accelerometer data. For instance time spent in LIPA might for older and more fragile participants be as demanding as time in MVPA for healthier and younger subjects. It is also possible that some parts of the recorded time spent in MVPA is associated with high level of occupational physical activity that has been shown to increase the risk of early mortality\textsuperscript{37}. In addition, due to limitations with accelerometry as a proxy for physical activity and the cut-off point based approach, type of activity such as swimming, bicycling or strength exercises could not be recorded as activities with higher intensities, even if time spent in these behaviours is likely associated with reduced mortality risk. By monitoring type of activity, clearer relationship between behaviours and mortality risk may be identified.

Compared to results from isotemporal substitution methods we found smaller effect sizes for substituting time with another type of behaviour. For instance, utilizing isotemporal substitution methods and substituting 30 minutes of SB with MVPA has been showed to decrease hazard of all-cause mortality with 19-50\%.\textsuperscript{23,27,38} Consequently, our estimates based on a compositional data analysis approach resulted in a smaller reduced mortality risk, possibly related to difference in follow-up time or in the way behaviours were defined. The difference may also be related to that isotemporal substitution methods use absolute measures and do not model the relative distribution of time spent in different behaviours\textsuperscript{19}. In addition, we used the compositional mean of behaviours as reference, whereas isotemporal substitution methods are based on classical regression techniques. More studies are needed comparing isotemporal substitution methods to compositional data analysis to fully understand the difference in estimates between the two methods.
Based on our findings, the average participant should substitute time spent in SB with time in LIPA or MVPA to reduce mortality risk. Time spent in LIPA or MVPA should not be substituted with each other, as displaced time spent in LIPA and MVPA was associated with no change in mortality risk and increased mortality risk, respectively. Therefore, time spent in LIPA or MVPA should only displace time spent in SB. Even if time spent in MVPA relative to time spent in other behaviours was not significantly associated with all-cause mortality, our findings suggest the importance of not decreasing time spent in MVPA.

The strength of this study is related to the objectively measured behaviours in a large nationally representative sample with 15 years’ follow-up. The compliance to accelerometer-wearing per day must be considered to be high with an average wear time of 14.5 hours/day, covering a high proportion of awake time. By analysing data in a compositional data analysis perspective our estimates are adjusted for all time use and associations of different behaviours in relation to each other could be explored. In addition, we used reliable register data on mortality and cause of death, where no deaths were related to accidents, making the cause of event less diverse. The main limitation of this study is related to our sample size and even if we had a long follow-up, we had quite few events compared to other population-based studies. We did not assess physical activity data repeatedly during follow-up and therefore we do not know if any participants changed their behaviour composition dramatically. However, a previous report on the same cohort, with six years follow-up, showed only small changes in physical activity composition. No data on sleep was obtained and consequently the accelerometer captured data represent the composition of awake time and not for all 24 hours of a given day. There are also limitations associated with the data collection method. All covariates were self-reported, which may bias our estimates and is likely less accurate than objective measured physical activity data. In addition, we did not set individual thresholds for different behaviours and thereby older and participants with illness may receive a lower time in more intensive behaviours in relation to time in less intensive behaviours, compared to younger and healthier participants. Future studies should monitor time spent sleeping/in bed to capture all 24 hours of a day. In addition, monitoring type of activity and not only time in different movement behaviours may increase our understanding of what activities are most relevant for decreasing mortality risk.

PERSPECTIVE
Across a day, time spent in different behaviours is intrinsically compositional and thus time use in one behaviour also depends on the time it displaced from another behaviour. These issues can be addressed using compositional data analysis. When a compositional data analysis perspective was applied in a national representative sample with 15 years follow-up time, a significant positive association was found between more time spent in SB relative to time other behaviours and all-cause mortality. In addition, a significant negative association was demonstrated, between more time spent in LIPA relative to time in other behaviours. Consequently, substituting time spent in LIPA or MVPA with time in SB increased the mortality risk, with the greatest effect found for MVPA. It is therefore recommended to substitute SB with either LIPA or MVPA, but for an individual with little time spent in MVPA, the most important message may be to try to maintain that behaviour.

References


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Table 1. Baseline characteristics of the total study population, stratified by non-death/all-cause mortality.

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n=851)</th>
<th>Non-death (n=772)</th>
<th>All-cause mortality (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>476 (55.9)</td>
<td>444 (57.5)</td>
<td>32 (40.5)</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>52.8 (10.2)</td>
<td>51.7 (9.8)</td>
<td>63.5 (8.0)</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>25.6 (3.6)</td>
<td>25.5 (3.6)</td>
<td>26.2 (3.0)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>227 (26.8)</td>
<td>206 (26.8)</td>
<td>21 (26.6)</td>
</tr>
<tr>
<td>Chronic disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>159 (18.7)</td>
<td>140 (18.1)</td>
<td>19 (24.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>117 (16.0)</td>
<td>110 (16.4)</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>29 (4.0)</td>
<td>22 (3.3)</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (2.9)</td>
<td>17 (2.5)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Cancer</td>
<td>23 (3.2)</td>
<td>18 (2.7)</td>
<td>5 (8.5)</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>224 (26.4)</td>
<td>189 (24.6)</td>
<td>35 (44.3)</td>
</tr>
<tr>
<td>High school</td>
<td>360 (42.5)</td>
<td>332 (43.2)</td>
<td>28 (35.4)</td>
</tr>
<tr>
<td>University</td>
<td>263 (31.1)</td>
<td>247 (32.2)</td>
<td>16 (20.3)</td>
</tr>
<tr>
<td>SB (min/day)</td>
<td>500.5 (90.9)</td>
<td>497.9 (91.4)</td>
<td>522.1 (84.9)</td>
</tr>
<tr>
<td>LIPA (min/day)</td>
<td>341.7 (93.2)</td>
<td>347.8 (91.6)</td>
<td>284.7 (95.0)</td>
</tr>
<tr>
<td>MVPA (min/day)</td>
<td>21.5 (31.2)</td>
<td>22.7 (32.0)</td>
<td>12.5 (20.3)</td>
</tr>
<tr>
<td>Days followed (SD)</td>
<td>5197.2 (703.5)</td>
<td>5378.5 (130.9)</td>
<td>3426.0 (1311.7)</td>
</tr>
<tr>
<td>Wearing time, h/day</td>
<td>14.5 (1.3)</td>
<td>14.5 (1.3)</td>
<td>13.7 (1.5)</td>
</tr>
<tr>
<td>Days with accelerometer data (SD)</td>
<td>6.4 (1.1)</td>
<td>6.4 (1.1)</td>
<td>6.2 (1.2)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD), counts (percentages) or by compositional means. 
BMI, body mass index; LIPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity; SB, sedentary behaviour.
Table 2. Showing hazard ratios (95% confidence interval), standard errors (SE) and p-values for isometric log-ratios for combinations of SB, LIPA and MVPA, based on the final cox regression model. The table shows all combinations of ilr variables. In the cox regression model, two ilr variables (e.g., SB vs. LIPA, MVPA; LIPA vs. MVPA) were used at a time to clarify the interpretation of the model.

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>HR (95% CI)</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB vs. LIPA, MVPA</td>
<td>2.24 (1.41-3.56)</td>
<td>0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LIPA vs. MVPA</td>
<td>0.70 (0.45-1.09)</td>
<td>0.22</td>
<td>0.111</td>
</tr>
<tr>
<td>LIPA vs. SB, MVPA</td>
<td>0.49 (0.27-0.89)</td>
<td>0.30</td>
<td>0.018</td>
</tr>
<tr>
<td>SB vs. MVPA</td>
<td>1.68 (1.31-2.15)</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MVPA vs. SB, LIPA</td>
<td>0.91 (0.73-1.14)</td>
<td>0.11</td>
<td>0.419</td>
</tr>
<tr>
<td>SB vs. LIPA</td>
<td>2.40 (1.32-4.38)</td>
<td>0.31</td>
<td>0.004</td>
</tr>
</tbody>
</table>

The model is stratified by sex and age tertiles, adjusted for education, smoking, presence of hypertension, heart disease, cancer and diabetes.

SB, sedentary behaviour; LIPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity.

Figure legends

Figure 1. Ternary plot depicting the proportion time (%) of SB (sedentary behaviour), LIPA (light intensity physical activity) and MVPA (moderate-to-vigorous physical activity), stratified by a) non-death and b) all-cause mortality. Every case, showed as circles, represent the proportion of time spent in SB, LIPA and MVPA using barycentric
coordinates where the perpendicular distance from any circle to one of the bases describe the proportion of time for each behaviour. Note that the axis of LIPA and MVPA is limited to 80% to simplify the interpretation.

**Figure 2.** Illustrating the effect on hazard of all-cause mortality of substituting time spent in different behaviours with time spent in another behaviour. Reference behaviour composition (compositional mean) in minutes: sedentary behaviour (SB), 500.5; light intensity physical activity (LIPA), 341.7; moderate-to-vigorous physical activity (MVPA), 21.5.