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Abstract

Aims: Previous prospective studies of the association between mortality and physical activity (PA) have generally not fully accounted for the interplay between movement behaviors. A compositional data modelling approach accounts for relative scale and co-dependency in time-use data across PA behaviors of the 24-hour day.

Methods and Results: A prospective analysis of NHANES 2005-06 on N=1468 adults (d=135 deaths) between ages 50-79 was undertaken using compositional Cox regression analysis. Daily time spent in sedentary behavior (SB), light intensity (LIPA) and moderate-to-vigorous physical activity (MVPA) was determined from waist-mounted accelerometer data (Actigraph 7164) and supplemented with self-reported sleep data to determine the daily time-use composition. The composition of time spent in SB, LIPA, MVPA and Sleep was associated with mortality rate after allowing for age and sex effects ($p < 0.001$), and remained significant when other lifestyle factors were added ($p < 0.001$). This was driven primarily by the preponderance of MVPA, however significant changes are attributable to LIPA relative to SB and Sleep, and SB relative to Sleep. The final ratio ceased to be statistically significant after incorporating lifestyle factors. The preponderance of MVPA ceased to be statistically significant after incorporating health at outset and physical limitations on movement.

Conclusions: An association is inferred between survival rate and the PA composition of the day. The MVPA time share is important, but time spent in LIPA relative to SB and Sleep is also a significant factor. Increased preponderance of MVPA may have detrimental associations at higher levels of MVPA.

Keywords: survival analysis, compositional data analysis, 24 hour time use, accelerometry, physical activity, sedentary behavior

1. Introduction

Extensive literature supports the health benefits of moderate-to-vigorous physical activity (MVPA) (1), and current public health guidelines recommend spending time daily engaging in MVPA at all ages (2). Nevertheless, MVPA represents a small part of the 24 hour day and, increasingly, evidence points to an association between time spent in lower intensity daily movement behaviors with health and wellbeing (3). Time spent in sedentary behavior (SB) has been found to be detrimental to health (4) whereas time spent in light-intensity physical activity (LIPA), incidental to daily living, appears to have a positive effect on cardiometabolic health and mortality, unless it displaces MVPA (5). The associations of sleep time with all-cause mortality are mixed (6). Alternative divisions of the 24 hour day are possible and a number of studies have gone further in considering the possibility that the deleterious effects of sedentary behavior are exacerbated by longer bout lengths (7).

Any increase in the time spent in one of these behaviors over a given day necessarily reduces the time spent in other behaviors, and the change in some health outcome associated with this increase will also depend on the behavior displaced. It is therefore more meaningful to consider the overall time-use composition, rather than analyzing behaviors in isolation. This requires breaking down the composition of the day into a series of nested subcompositions and investigating the associations of the relative allocations of time between them. This methodology has been successfully applied previously to cross-sectional studies on biomarkers of cardio metabolic health (8–11), but to date has not been applied to mortality risk analysis. We propose

to model the association between mortality and the time-use composition of the 24-hour day, then use this model to demonstrate the beneficial associations of replacing non-active behaviors with LIPA whilst allowing for the impact of the allocation of time to MVPA relative to all other behaviors.

This analysis is part of the open science project "Million Days of Mortality" (www.opencoda.net) aimed at investigating the relation between daily time use composition and mortality through a global federated analysis.

2. Materials and Methods

2.1. Participants

Participants are from the 2005-2006 wave of the National Health and Nutrition Examination Survey (NHANES), a stratified, multistage probability sample representative of the civilian non-institutionalized U.S. population. The survey has been described in detail elsewhere (12). A subset of the individuals included are linked to death records from the National Death Index through December 31, 2011 (13), which provide vital status. If deceased, length of time (in months) between the NHANES examination and the subject's death is provided, as well as cause of death. Our modelling is restricted to adults between ages 50 and 79 in line with previous work done on NHANES data to avoid violations of the proportional hazards assumption (14).

2.2. Ethical Approval

This study involved secondary analysis of publicly available data only. The original study was approved by the ethics committee of the Centers for Disease Control and Prevention (CDC) and all participants gave informed consent. NHANES operates under the approval of the National

Center for Health Statistics Research Ethics Review Board, Protocols #98-12, #2005-06, and #2011-17.

2.3. Assessment of the 24 hour time-use composition

The time-use composition of the 24-hour day was defined as the proportions of time spent in the aforementioned four movement behaviors: MVPA, LIPA, SB and Sleep.

Time spent in SB, LIPA and MVPA was assessed objectively following the protocol detailed previously [15,17], using an ActiGraph AM-7164 accelerometer (ActiGraph, LLC, Fort Walton Beach, Florida). Participants were instructed to wear the device on a belt around the waist for seven consecutive days, except when sleeping or bathing. The resulting acceleration counts integrated over 1 minute epochs, were processed according to the Center for Disease Control's standard quality assurance procedures (15,16). Days when the accelerometer was worn for at least 10 hours were considered valid (based on prior simulation studies using NHANES data (17)) and participants were included if they accumulated at least one valid day of activity as in previous studies (14,18). Each minute epoch was classified using standard count per minutes thresholds as SB(<100 counts/min), LIPA (100 to 2020 counts/min) or MVPA (>2020counts/min) (19). Minutes spent in each of these three behaviors were tallied per day and averaged over all available valid days.

Sleep duration was self-reported to the nearest hour in response to the question "How much sleep do you actually get at night on weekdays or workdays". Sleep time was then expressed as a proportion of 24 hours, and the remaining proportion of 24 hours was allocated between SB, LIPA and MVPA in proportion to the total time recorded for each behavior.

2.4. Covariates

Based on previous research on the associations of physical activity, sedentary behavior and sleep with health in adults and older adults as well as data availability in the NHANES, a number of covariates were included in the analyses to control for confounding effects.

Demographic covariates considered for inclusion in the model included age (years), sex (male, female), ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other including mixed race), education (less than 9th grade, 9-11th grade, high school, college or AA degree, college graduate, refuse to answer, do not know), marital status (married, widowed, divorced, separated, never married Living with partner, refused, don't know), and family income to poverty ratio (continuous from 0 to 4.99, values are 5 if the ratio is 5 or over). Health behavior covariates considered for inclusion in the model included smoking status (yes, no, former), average alcohol consumption (number of drinks per day over last 12 months), average dietary intake (kCal/day), average saturated fat intake (g/day), average caffeine intake (mg/day). Health status covariates considered for inclusion in the model included previous diagnosis of stroke (yes, no), previous diagnosis of cancer (yes, no), previous diagnosis of diabetes (yes, no), self-assessed health (poor, fair, good, very good, excellent), use of medication to control blood pressure (yes, no), and physical limitations on movement (yes, no). All covariates were measured via self-report as part of the interview.

2.5. Statistical Analysis

Data were analyzed within a compositional data analysis framework (20,21). Data analysis follow the Compositional Cox regression method developed by McGregor et al. 2019 (22) and performed using codes authored by McGregor (and available on www.opencoda.net). This model is based on using isometric log-ratio (ilr) coordinates of the time-use composition, along with

other covariates and confounding factors, as explanatory variables and the time of exit (either observed or censored) as response variable. This way the association of each movement behavior with the outcome is adequately measured in terms relative to the other behaviors (formally through log-ratios between them) in accordance to the intrinsic relative scale and co-dependence between the corresponding amounts of time derived from the 24-hour constraint.

Firstly, the composition of time spent in MVPA, LIPA, SB, and Sleep (S) was considered. A set of three ilr-coordinates $\boldsymbol{z} = (z_1, z_2, z_3)$ was obtained from the 4-part composition. They were constructed by sequential binary partition (23) giving rise to the following vector of ilr-coordinates:

$$\boldsymbol{z} = \left(\sqrt{\frac{3}{4}} \ln \frac{MVPA}{(S \cdot SB \cdot LIPA)^{1/3}}, \sqrt{\frac{2}{3}} \ln \frac{LIPA}{(S \cdot SB)^{1/2}}, \sqrt{\frac{1}{2}} \ln \frac{S}{SB} \right) \quad (1)$$

A Cox proportional hazards regression model was then fitted by maximum likelihood to this set of ilr-coordinates along with the covariates. Once the proportional hazards assumption was confirmed, the analysis focused on the statistical significance of the association between the hazard function and the overall composition of the day, as represented by $\boldsymbol{z}$, assessed using a likelihood ratio test (LRT). Moreover, note that the first coordinate z_1 represents time spent in MVPA relative to the (geometric) average of all the other behaviors. The second coordinate z_2 is the balance between time allocated to LIPA and time allocated to (the geometric average of) SB and sleep. The third coordinate z_3 accounts for the balance of time between Sleep and SB. The model coefficients associated to these individual ilr-coordinates were assessed for statistical significance using ordinary Wald test statistics to determine main drivers of the association.

All statistical analyses and graphical representations were produced using the R system for statistical computing (R 3.4.1, R Foundation for Statistical Computing, Vienna, Austria, 2017). Statistical test significance was concluded at the usual 0.05 significance level.

Our initial analysis incorporated the full set of covariates listed in Section 2.4. Backwards elimination was performed from the full model aiming to minimize Akaike's information criterion (AIC), coupled with manual testing with the ordering of the covariates, and reintroducing previously eliminated covariates. Finally, the average change in AIC associated with each covariate across all possible models was considered. This procedure (24,25) suggested that the major contributors were age, gender, smoker status, alcohol intake, energy intake, self-assessed health, and physical limitations on movement, and we opted to explore three nested Cox model formulations:

- Model 1: composition of the 24-hour day (on ilr-coordinates) + age and gender.
- Model 2: Model 1 + smoker, alcohol intake and energy intake.
- Model 3: Model 2 + self-assessed health and physical limitations on movement.

Model 1 includes the minimum set of plausible covariates. Model 2 incorporates three significant lifestyle factors. Model 3 incorporates the individual's (self-assessed) state of health at the start of the follow-up period.

The reasonability of the proportional hazards assumption underlying our model was assessed both graphically and using the Grambsch-Therneau test (26). Further details are provided in Supplementary Materials S1.

3. Results

3.1. Data

The complete NHANES database included 10,348 individual records. A subsample of N=5,560 adults (over 18 years) were eligible for follow up, and of these, 1,820 were within the age range (50-79) of this study. This study's analysis dataset comprises of 1,594 of these individuals who had valid accelerometer data and the full set of covariates, although a further two records were removed from the final analysis due to cause of death (accidental death). The data flow is illustrated in Figure 1. The characteristics of the final sample analyzed are summarized in Table 1, including standard summary statistics for the key categorical, continuous, and compositional variables. We also note that around 86% of the observed total variation in the compositional variables can be attributed to the first ilr-coordinate, indicating time spent in MVPA relative to other behaviors is the predominant source of variability in the composition data. Around 9% is attributable to the second ilr-coordinate, and the remaining 5% is attributable to the third.

[Figure 1]

[Table 1]

3.2. Cox regression analysis results

The results from the first Cox regression analysis, focused on the association between the (MVPA, LIPA, SB, S) daily composition and mortality outcome, are shown in Table 2. All three models considered, including nested sets of potential confounding variables, indicate that the movement behavior time-use composition of the day as a whole has a statistically significant association with mortality rates (LRT $p<0.001$). If we examine the p-values associated with the z_1 coordinate, we observe that the ratio of time spent in MVPA to average time spent in other behaviors has a statistically significant negative association with mortality in Models 1 ($p=0.001$)

and 2 (p=0.020), but it ceases to be statistically significant (strictly speaking at the usual 5% level) when the individual's physical limitations and state of health at the start of the observation period are accounted for (p=0.093). The negative association of time spent in LIPA relative to other behaviors, excluding MVPA, with mortality is statistically significant in Models 1, 2 and 3 (p=0.004, p=0.001, and p=0.006 respectively). Lastly, note that the balance of time spent in Sleep relative to the time spent in sedentary behavior has a marginally statistically significant negative association with mortality in Model 1 (p=0.040). However, this is no longer the case after allowing for basic lifestyle factors in Model 2 (p=0.219) and the individual's starting state of health in Model 3 (p=0.600).

[Table 2]

[Figure 2]

Figure 2 shows ternary diagrams accounting for the expected hazard ratio as predicted from Model 3, using the average movement behavior composition observed in the dataset, (MVPA, LIPA, SB, S) = (0.2, 6.3, 10.5, 7.0) hours, as the reference composition. Each ternary diagram considers one of the four possible 3-part subcompositions based on our initial time-use partitioning of the day. In each case, one component is held fixed, and the expected hazard ratio is shown for a range of possible combinations of the remaining three components. The relative importance of MVPA in the time-use composition dominates the results in the first three graphs (Figures 2a, b and c). The last one (Figure 2d), which leaves MVPA fixed, illustrates most clearly the effect of substitutions between the remaining components of the daily movement behavior time-use composition.

3.3. Estimation of size of association

Based on our models, we calculated the expected hazard ratio (with respect to change from the observed average time-use composition) associated with the range of compositions arising from two-way reallocations of time (expressed in minutes). The results for Model 3 are shown in Figure 3. For example, Figure 3a shows hazard ratio against time allocated to MVPA assuming that the only permitted reallocations are fixed amounts of time between MVPA and each of the remaining individual components in turn. Thus, the green line in Figure 3a indicates the hazard ratio associated with different levels of MVPA and SB, with Sleep and LIPA fixed at their compositional average. Similarly, Figures 3b, 3c and 3d show the expected hazard ratio against time allocated to, respectively, LIPA, SB, and Sleep. In each case, time is exchanged between the component displayed on the x-axis and the component indicated by the line (labelled as replaced behavior). It is worth remarking that these lines are often cut short over the displayed range because it is not possible to have a negative allocation of time to a component. The results for models 1 and 2 are very similar, but plots are included in the Supplementary Materials S2 and S3.

[Figure 3]

4. Discussion

The association between mortality and the movement behavior time-use composition of the 24 hour day was statistically significant for all three models considered in this study ($p<0.001$), indicating that the relative distribution of daily time across movement behaviors is important to mortality risk. This study supports the hypothesis that the most potent element of the movement behavior time-use composition is MVPA when accounting for its synergies with time spent in all other behaviors. After allowing for the dominant association of MVPA time, relative to the other

235 behaviors, with mortality risk, it was found that the balance of LIPA to Sleep and SB had a
236 beneficial association with mortality. This is consistent with health benefits from exchanging
237 time spent seated or lying down with light activity. This has been demonstrated in experimental
238 studies (27) but prospective studies are more mixed (5), potentially due to the issues with non-
239 compositional analyses not allowing correctly for codependency between the different behaviors.

240 Interestingly, the association of mortality with MVPA relative to other behaviors was only
241 confirmed to be statistically significant for Models 1 and 2, although the overall composition
242 remained significant. The distinctive feature of Model 3 was that it allowed for the state of health
243 of the individual at the start of observation and physical limitations on movement, indicating that
244 although lower mortality rates were still associated with higher levels of MVPA, the association
245 was weaker, and was not statistically significant at the 5% level after allowing for pre-existing
246 conditions at the outset of the study. Previous studies using conventional (non-compositional)
247 approaches have found similar results (e.g. (28) found no statistically significant association
248 between fatal myocardial infarction (MI) and self-reported physical activity and for individuals
249 with previous incidents of MI). These covariates are likely to be strongly associated with the
250 individual's MVPA, and it is then reasonable that incorporating them downplays the association.
251 This may suggest that a large part of the beneficial association of MVPA with mortality is
252 attributable to higher levels of MVPA being indicative of a lack of mobility issues and
253 comorbidities, or that it is accumulated in earlier life, or at least over a longer period than the 5-6
254 year follow-up period of this study. Another possible explanation is that population with mobility
255 issues and comorbidities seldom engage in MVPA (29) resulting in lower fitness levels and
256 therefore light activity (which is statistically significant in Model 3) requires a level of effort
257 sufficient to confer significant health benefits. Another consideration is the choice of

accelerometer threshold for MVPA. For older individuals there is some evidence that a lower threshold is more appropriate than the standard (30). In addition, the metabolic cost of movement is higher (31) for people with movement disability and comorbidities. In any case, the sign of the association found between mortality and MVPA in Model 3 is certainly in the expected direction, and we should be careful of placing too much weight on a relatively borderline p-value (p=0.093).

An interesting feature of Model 3, which is particularly apparent in Figures 3a and 3b, is that the reduction in mortality risk associated with increased levels of MVPA appears to attenuate at higher levels of MVPA. In fact, if we examine the line in Figure 3a showing the hazard ratio for increasing MVPA out of LIPA (cyan-colored line) we observe the hazard ratio eventually stops falling and actually starts to increase slowly, indicating individuals with lower LIPA and higher MVPA are expected to have higher levels of mortality risk beyond a certain threshold. However, this reversal occurs at high levels of MVPA (1.5 hours per day) that are not widely present in the data, and the deleterious association is close to zero (i.e. a very small increase in hazard ratio). The unbalanced design, specifically the sparsity of data at higher levels of MVPA, means we should be careful of attaching great importance to this finding. Nevertheless, the notion that there is a level of MVPA that is excessive and potentially harmful is not inherently unreasonable, and this was previously observed in pooled prospective analysis (32), albeit at a higher value of MVPA which was probably because of the self –reported nature of the data used. A reversal in the direction of the association of replacing LIPA with MVPA recalls the previously noted inconsistency in published findings related to this reallocation in the same dataset (14,18). In practice, this seems unlikely to be related, as the levels of MVPA in the NHANES dataset are generally very low. We previously noted that the fixed accelerometer threshold for MVPA

might underestimate the daily time spent in MVPA for older adults though, so it might merit re-examination in a future study.

It is also worth remarking that the majority of variation observed in the compositional data arises from the ratio of MVPA to the other components (around 86% of the total variation as observed in Section 3.1). Generally, a majority of people spend a very small amount of time in MVPA, so it would be relatively easy to make dramatic changes in proportional terms. The other behaviors (LIPA, SB, sleep) make up a much larger portion of the day, and then major proportional changes are harder to achieve. Accordingly, our findings suggest that individuals with very low levels of MVPA can achieve dramatic benefits from small relative increases in time allocated to MVPA, which is interesting of itself. Such a finding would not be possible using conventional linear analyses, although some non-compositional studies of leisure time physical activity using cubic splines seem to suggest a similar pattern (e.g. (33)).

A key strength and novelty of this report is the application of a novel compositional approach to survival data analysis in a prospective study design. It considers the relative scale of time shares and allows for synergies and co-dependencies between times distributed across the common array of movement behaviors over the 24 hours day. Establishing the precise effects of LIPA has commonly proven difficult due to small effect sizes (34) so using the most meaningful available modelling approach is highly recommended in our view.

A limitation of this study is the lack of longitudinal data. Although using a prospective measure such as mortality (combined with covariates linked to the individual's state of health at commencement) provides stronger support for a causal relationship than an ordinary cross-sectional study, the possibility remains that population effects are being conflated with, or

confused for, a causal effect. Recent work (35) suggests that the health benefits of physical activity have limited duration, and it is plausible the levels of physical activity for individuals in the NHANES study will have declined at different rates as the individuals age, making the need for longitudinal data even greater. In addition, the absence of objective data on sleep time has compelled us to rely on a mixture of self-reported data and accelerometer data that are probably not wholly consistent, leading to potential inaccuracies in the individual compositions. We have not included detailed nutrition data in our modelling, in view of the reported shortcomings in the NHANES nutrition data (36). Interaction between diet and physical activity may play an important role in mortality risk and inclusion of accurate nutrition data could alter the results significantly. Lastly, the limitations around accelerometer data should be acknowledged. In particular, we have relied on fixed thresholds that do not account for the age of the individual, and have not accounted for the context in which the movement behavior is performed (although we would expect the work/leisure divide to be of less significance for older adults). Additionally, hip-worn accelerometers do not measure postural sitting, and therefore some quiet standing may have been incorrectly allocated to SB (37,38).

5. Conclusions

Our results demonstrate an association between mortality risk and movement behavior time-use composition of the day. This association was statistically significant after allowing for individuals' states of health at the outset and physical limitations on their movement. Our results support that this association is driven primarily by time spent in MVPA relative to all the other movement behaviors, although the association ceased to be statistically significant after allowing for individuals' states of health at the outset and physical limitations on their movement. In addition, there is some suggestion that beyond some threshold level of MVPA higher levels of

MVPA and lower levels of LIPA may be associated with higher mortality. They also reveal a significant role of time spent in LIPA relative to SB and Sleep after allowing for MVPA.

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Bibliography

1. World Health Organization. *Global recommendations on physical activity for health.* https://www.who.int/dietphysicalactivity/publications/9789241599979/en/. Geneva, 2010. Accessed March 6, 2018.
2. Department of Health and Social Care. *Start active, stay active: a report on physical activity from the four home countries' Chief Medical Officers*. https://www.gov.uk/government/publications/start-active-stay-active-a-report-on-physical-activity-from-the-four-home-countries-chief-medical-officers. UK, 2011. Accessed March 6, 2018.
3. Buman MP, Winkler EAH, Kurka JM, Hekler EB, Baldwin CM, Owen N, Ainsworth BE,

Healy GN, Gardiner PA. Reallocating Time to Sleep, Sedentary Behaviors, or Active Behaviors: Associations With Cardiovascular Disease Risk Biomarkers, NHANES 2005–2006. *Am J Epidemiol.* 2014;179(3):323–334.

4. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults. *Ann Intern Med.* 2015;162(2):123.

5. Chastin SFM, De Craemer M, De Cocker K, Powell L, Van Cauwenberg J, Dall P, Hamer M, Stamatakis E. How does light-intensity physical activity associate with adult cardiometabolic health and mortality? Systematic review with meta-analysis of experimental and observational studies. *Br J Sports Med.* 2019;53:370-376.

6. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep.* 2010;33(5):585–92.

7. Diaz KM, Howard VJ, Hutto B, Colabianchi N, Vena JE, Blair SN, Hooker SP. Patterns of Sedentary Behavior in US Middle-Age and Older Adults: The REGARDS Study. *Med Sci Sports Exerc.* 2016;48(3):430–438.

8. Chastin SFM, Palarea-Albaladejo J, Dontje ML, Skelton DA. 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(10):e0139984.

9. McGregor DE, Palarea-Albaladejo J, Dall PM, Stamatakis E, Chastin SFM. Differences in physical activity time-use composition associated with cardiometabolic risks. *Prev Med Rep*. 2018;13:23-29.

10. Dumuid D, Pedišić Ž, Stanford TE, Martín-Fernández JA, Hron K, Maher CA, Lewis LK, Olds T. The compositional isotemporal substitution model: A method for estimating changes in a health outcome for reallocation of time between sleep, physical activity and sedentary behaviour. *Stat Methods Med Res*. 2019; 28(3):846-857.

11. Rosenberger ME, Buman MP, Haskell WL, McConnell M V, Carstensen LL. Twenty-four Hours of Sleep, Sedentary Behavior, and Physical Activity with Nine Wearable Devices. *Med Sci Sports Exerc.* 2016;48(3):457–65.

12. US Department of Health and Human Services Centers for Disease Control and Prevention. *National Health and Nutrition Examination Survey.* Accessed November 1, 2018. Available from: http://www.cdc.gov/nchs/nhanes.htm.

13. US Department of Health and Human Services Centers for Disease Control and Prevention. *National Health and Nutrition Examination Survey NHANES (1999-2010) Public-use Linked Mortality Files (2011).* Hyattsville, MD2015. Accessed March 5, 2015. Available from: https://www.cdc.gov/nchs/data-linkage/index.htm.

14. Fishman EI, Steeves JA, Zipunnikov V, Koster A, Berrigan D, Harris TA, Murphy R. Association between Objectively Measured Physical Activity and Mortality in NHANES. *Med Sci Sports Exerc.* 2016;48(7):1303–11.

15. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, Troiano RP. Amount of Time Spent in Sedentary Behaviors in the United States, 2003-2004. *Am J Epidemiol.* 2008;167(7):875–81.

16. Troiano RP, Berrigani D, Dodd KW, Masse LC, Tilert T, McDowell M, Troiano RP, Berrigan D, Dodd KW, Mâsse LC, et al. Physical Activity in the United States Measured by Accelerometer. *Med Sci Sport Exerc.* 2008;40(1):181–8.

17. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, Owen N. Objectively measured light-intensity physical activity is independently associated with 2-h plasma glucose. *Diabetes Care.* 2007;30(6):1384–9.
18. Schmid D, Ricci C, Leitzmann MF. Associations of Objectively Assessed Physical Activity and Sedentary Time with All-Cause Mortality in US Adults: The NHANES Study. Newton RL, editor. *PLoS One.* 2015 Mar 13;10(3):e0119591.
19. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med Sci Sports Exerc.* 1998;30(5):777–81.
20. Aitchison J. The Statistical Analysis of Compositional Data. *J R Statist Soc B.* 1982;44(2):139-177.
21. Pawlowsky-Glahn V, Egozcue JJ, Tolosana-Delgado R. *Modelling and analysis of compositional data*. Chichester: John Wiley & Sons; 2015.
22. McGregor D, Palarea-Albaladejo J, Dall P, Hron K, Chastin SFM. Cox regression survival analysis with compositional covariates: application to modelling mortality risk from 24-hour physical activity patterns. *Stat Methods Med Res.* 2019;In Press.
23. Egozcue, J.J., Pawlowsky-Glahn, V. Isometric Logratio Transformations for Compositional Data Analysis *Math Geol.* 2005;37:795-828.
24. Burnham KP, Anderson DR. Basic Use of the Information-Theoretic Approach. In: Model Selection and Multimodel Inference. New York: Springer; 2004. p. 98–148.
25. Barton K. *R-Forge: MuMIn - multi-model inference: Project Home.* Accessed Feb 28, 2019. Available from: http://r-forge.r-project.org/projects/mumin/.
26. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3):515–26.

27. Chastin SFM, Egerton T, Leask C, Stamatakis E. Meta-analysis of the relationship between breaks in sedentary behavior and cardiometabolic health. *Obesity.* 2015;23(9):1800-1810.
28. Ejlersen H, Andersen ZJ, Von Euler-Chelpin MC, Johansen PP, Schnohr P, Prescott E. Prognostic impact of physical activity prior to myocardial infarction: Case fatality and subsequent risk of heart failure and death. Eur J Prev Cardiol. 2017;24(10):1112–9.
29. Loprinzi PD, Sheffield J, Tyo BM, Fittipaldi-Wert J. Accelerometer-determined physical activity, mobility disability, and health. *Disabil Health J.* 2014;7(4):419–25.
30. Schrack JA, Cooper R, Koster A, Shiroma EJ, Murabito JM, Rejeski WJ, Ferrucci L, Harris TB. Assessing Daily Physical Activity in Older Adults: Unraveling the Complexity of Monitors, Measures, and Methods. *Journals Gerontol Ser A Biol Sci Med Sci.* 2016;71(8):1039–1048.
31. Knaggs JD, Larkin KA, Manini TM. Metabolic cost of daily activities and effect of mobility impairment in older adults. *J Am Geriatr Soc.* 2011;59(11):2118–2123.
32. Arem H, Moore SC, Patel A, Hartge P, Berrington De Gonzalez A, Visvanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, et al. Leisure time physical activity and mortality: A detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* 2015;175(6):959-67.
33. Cheng W, Zhang Z, Cheng W, Yang C, Diao L, Liu W. Associations of leisure-time physical activity with cardiovascular mortality: A systematic review and meta-analysis of 44 prospective cohort studies. Eur J Prev Cardiol. 2018;25(17):1864–72.
34. del Pozo-Cruz J, García-Hermoso A, Alfonso-Rosa RM, Alvarez-Barbosa F, Owen N, Chastin S, del Pozo-Cruz B. Replacing Sedentary Time: Meta-analysis of Objective-

Assessment Studies. *Am J Prev Med.* 2018;55(3):395–402.

35. Engeseth K, Prestgaard EE, Mariampillai JE, Grundvold I, Liestol K, Kjeldsen SE, Bodegard J, Erikssen JE, Gjesdal K, Skretteberg PT. Physical fitness is a modifiable predictor of early cardiovascular death: A 35-year follow-up study of 2014 healthy middle-aged men. Eur J Prev Cardiol. 2018;25(15):1655–63.
36. Archer E, Hand GA, Blair SN. Validity of U.S. Nutritional Surveillance: National Health and Nutrition Examination Survey Caloric Energy Intake Data, 1971–2010. PLoS One. 2013;8(10):e76632.
37. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing sedentary behavior. Med Sci Sports Exerc. 2011;43(8):1561–1567.35. Sellers C, Dall P, Grant M, Stansfield B. Validity and reliability of the activPAL3 for measuring posture and stepping in adults and young people. Gait Posture. 2016;43:42–47.

Figure Legends

Figure 1: Consort diagram illustrating flow of data in this study using NHANES 2005-06.

Figure 2: Heatmap ternary diagrams of expected hazard ratios based on Model 3 against different percentage time allocations of the movement behavior time-use composition, with fixed (a) Sleep = 29.1%, (b) SB = 44.4%, (c) LIPA = 25.9%, and (d) MVPA = 0.7%. The blue point indicates the reference average movement behavior time-use composition.

Figure 3: Expected hazard ratios based on Model 3 against daily time (in minutes) spent in (a) MVPA, (b) LIPA, (c) SB, and (d) Sleep. Time is exchanged between the component on the x-axis and the component indicated by the line, whilst holding the remaining components fixed at their value in the average time-use composition.

Table 1: Summary statistics for the final analysis sample from NHANES 2005-06.

Categorical Covariates	**Category**	**Proportion in category (%)**
Gender	Male Female	51.7 48.3
Smoking status	Current Former Never Unknown	19.5 35.6 44.8 0.1
Current state of health (self assessment)	Excellent (1) Very good (2) Good (3) Fair (4) Poor (5) Unknown	8.1 26.5 35.0 21.4 4.1 4.9
Physical limits on movement	True False	21.2 78.8
Continuous Covariates	**Mean (± s.e.)**	**Median**
Age at baseline (years)	63.1 (± 0.2)	63
Alcohol consumption (drinks/day)	1.8 (± 0.1)	1
Mean energy intake (kCal/day)	1,940 (± 21)	1,826
Compositional Variables	**Compositional mean**	**Arithmetic mean**
Sleep (hrs)	7.0	6.9
Sedentary Behaviour (hrs)	10.5	10.4
Light Intensity Physical Activity (hrs)	6.3	6.4
Moderate to Vigorous Physical Activity (hrs)	0.2	0.3

Table 2: Compositional Cox regression model coefficient estimates and 95% confidence limits using Models 1, 2, and 3.

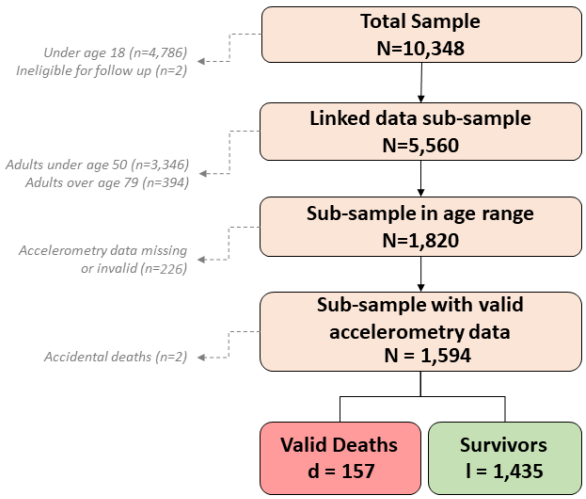
Model	Ilr-coord. ‡	exp(γ)*	Lower Bound	Upper Bound	p-value †
1	z_1	0.7725	0.6595	0.9049	0.001
	z_2	0.5346	0.3498	0.8171	0.004
	z_3	0.5263	0.2850	0.9719	0.040
	Overall	-	-	-	<0.001
2	z_1	0.8249	0.7010	0.9706	0.020
	z_2	0.4957	0.3245	0.7573	0.001
	z_3	0.6813	0.3696	1.2558	0.219
	Overall	-	-	-	<0.001
3	z_1	0.8680	0.7359	1.0239	0.093
	z_2	0.5447	0.3539	0.8383	0.006
	z_3	0.8479	0.4580	1.5697	0.600
	Overall	-	-	-	<0.001

* Exponential of the Cox regression coefficient – indicates proportional change in hazard function per unit increase in the associated ilr-coordinate.

† p-values for individual ilr-coordinates are based on Wald tests, p-value for the overall composition based on likelihood ratio test.

‡ $\boldsymbol{z}$ is defined in Equation 1.

477 **Figure 1**



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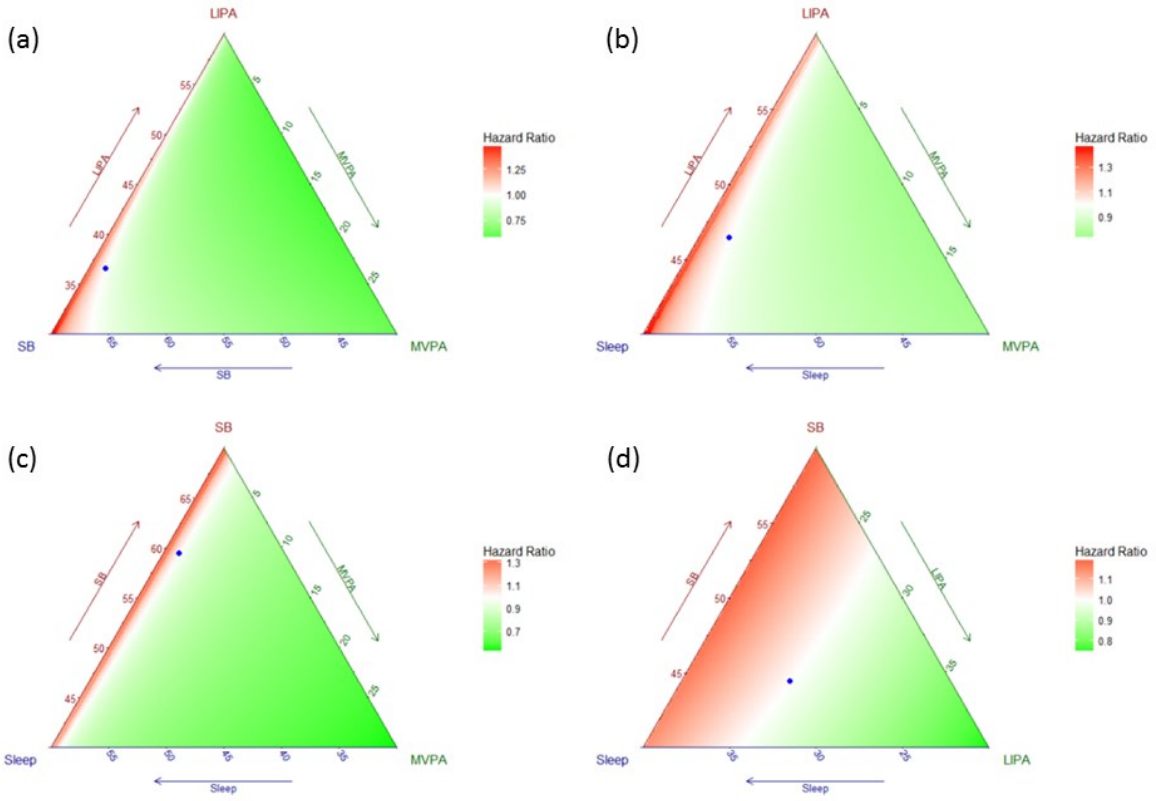
480 **Figure 2**



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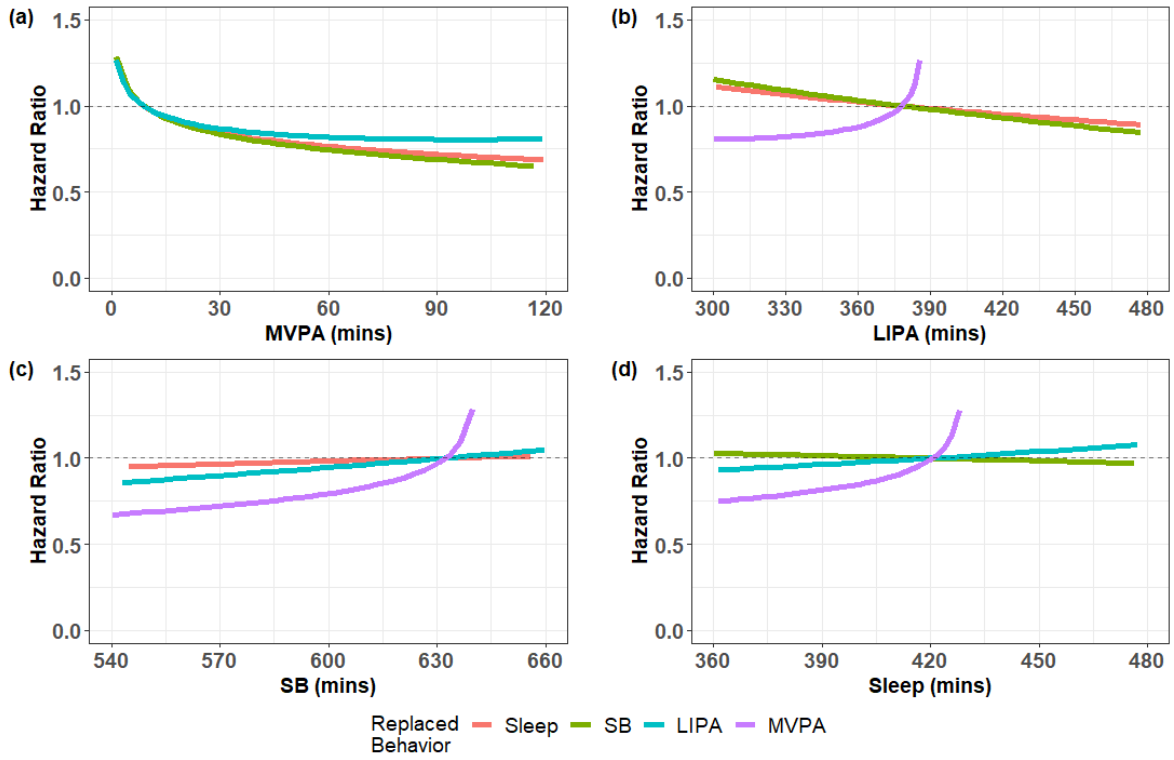
483 **Figure 3**



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Supplemental Materials

Contents

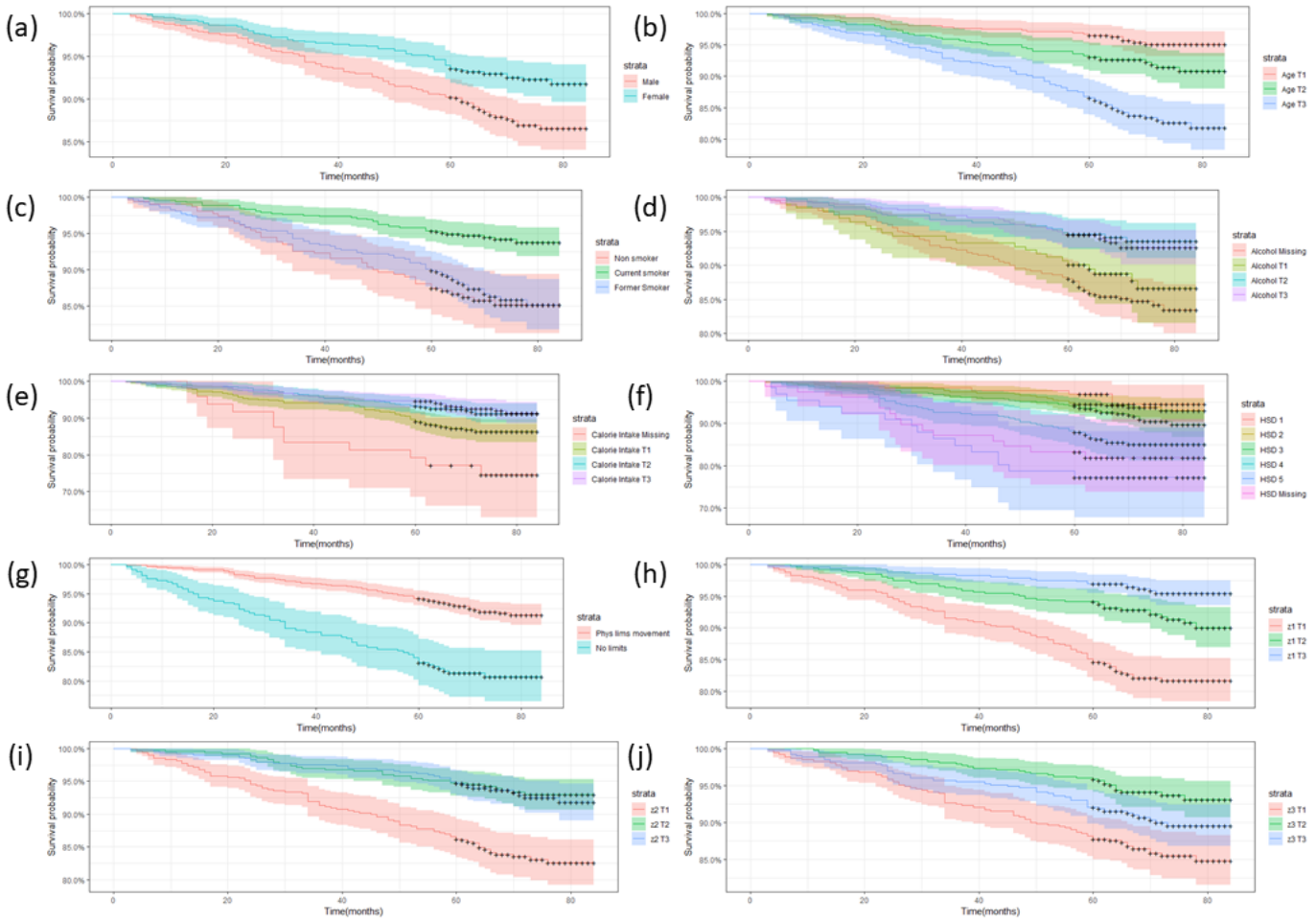
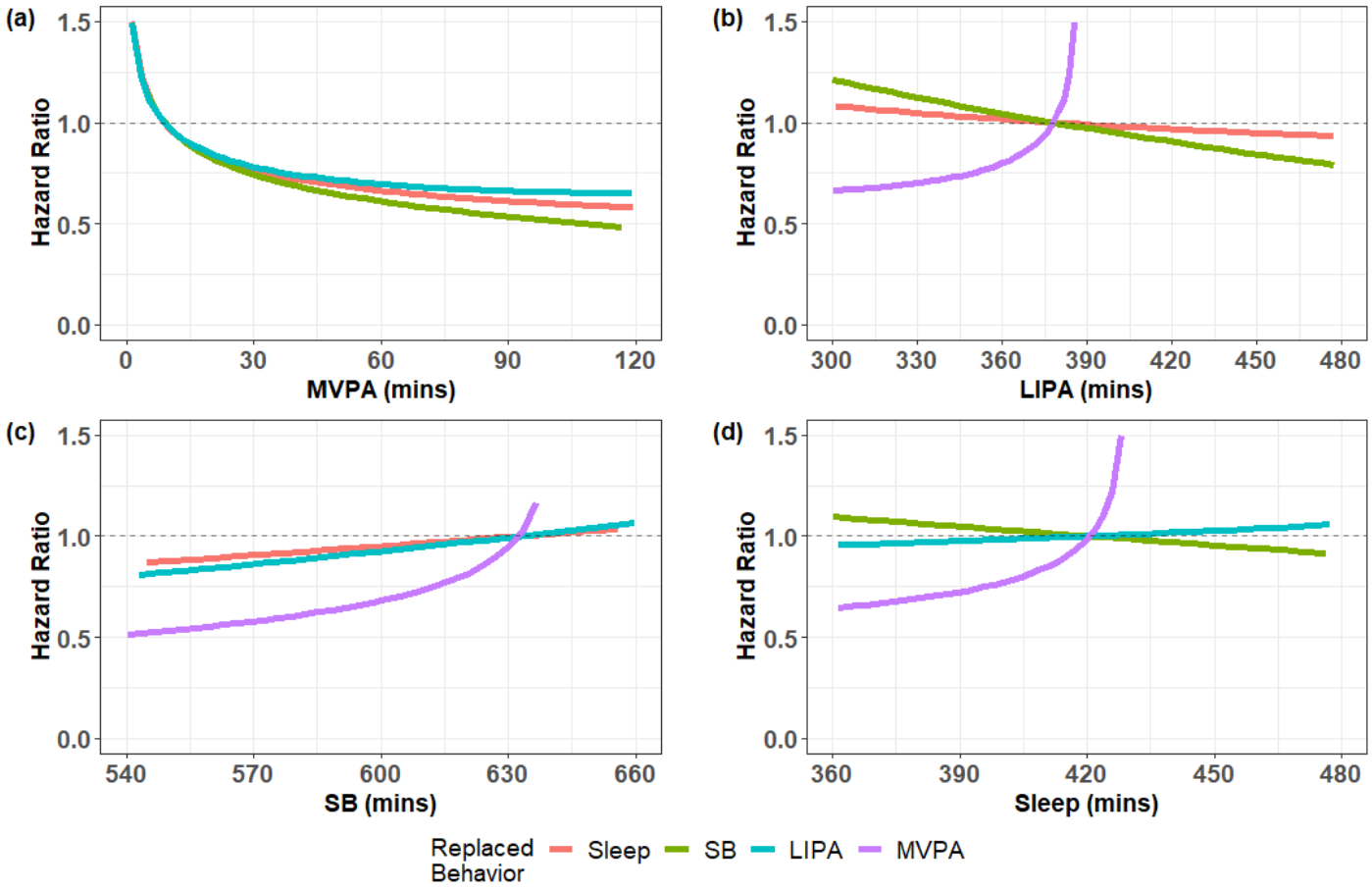


Figure S1: Kaplan-Meier survival curves for subset of NHANES 05-06 data stratified by (a) gender, (b) age tertile, (c) smoker status, (d) alcohol intake tertile, (e) calorie intake tertile, (f) self-assessed health status, (g) physical limitations on movement, and (h)-(j) the tertiles of the three ilr coordinates (+ symbols indicate an observation ceasing on an individual rather than a death).

Testing the Proportional Hazards Assumption

The proportional hazards assumption underlying our model was assessed graphically, and with reference to the Gramsch-Therneau test for violations of the proportional hazards assumption (based on hypothesized time dependence scaled with reference to the Kaplan-Meier curve). Based on this hypothesis, we obtained a test p-value equal to 0.266 for model 2 and 0.242 for model 3 indicating an absence of evidence for rejecting the proportional hazards assumption underlying these models at the 5% level. For model 1 the test p-value was 0.014 indicating a violation of the proportional hazards assumption. Examining Figure S1, in particular the age tertiles, it seems likely this is attributable to a small number of early deaths, however we have avoided drawing conclusions based on model 1 for this reason.



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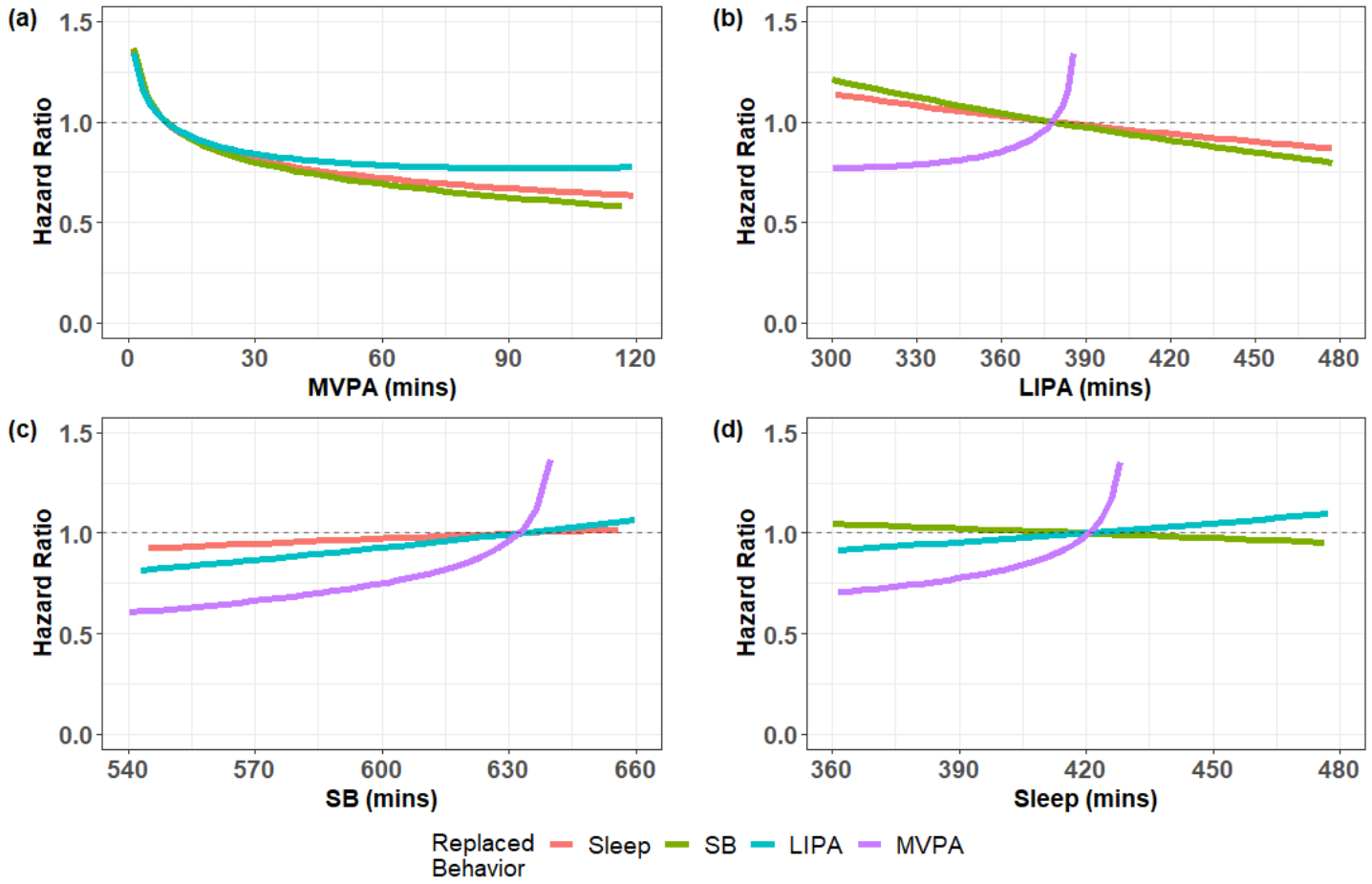
519 **Figure S2: Expected hazard ratios based on Model 1 against daily time (in minutes) spent in (a) MVPA, (b) LIPA, (c)**

520 **SB, and (d) Sleep. Time is exchanged between the component on the x-axis and the component indicated by the line,**

521 **whilst holding the remaining components fixed at their value in the average time-use composition.**



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523 **Figure S3: Expected hazard ratios based on Model 2 against daily time (in minutes) spent in (a) MVPA, (b) LIPA, (c)**
524 **SB, and (d) Sleep. Time is exchanged between the component on the x-axis and the component indicated by the line,**
525 **whilst holding the remaining components fixed at their value in the average time-use composition.**

Reading Ternary Plots

A ternary plot is used to display the values of a composition consisting of three components with a fixed sum constraint (e.g. 100% if expressed in percentages); that is, points on a 3-dimensional simplex. Proximity to one of the vertices indicates how close the composition is to being wholly composed of that component, e.g. the x vertex below at the peak of the triangle corresponds to 100% component x and 0% components y and z. To read off the x-value of any point we draw a horizontal line from the point to the left-hand axis.

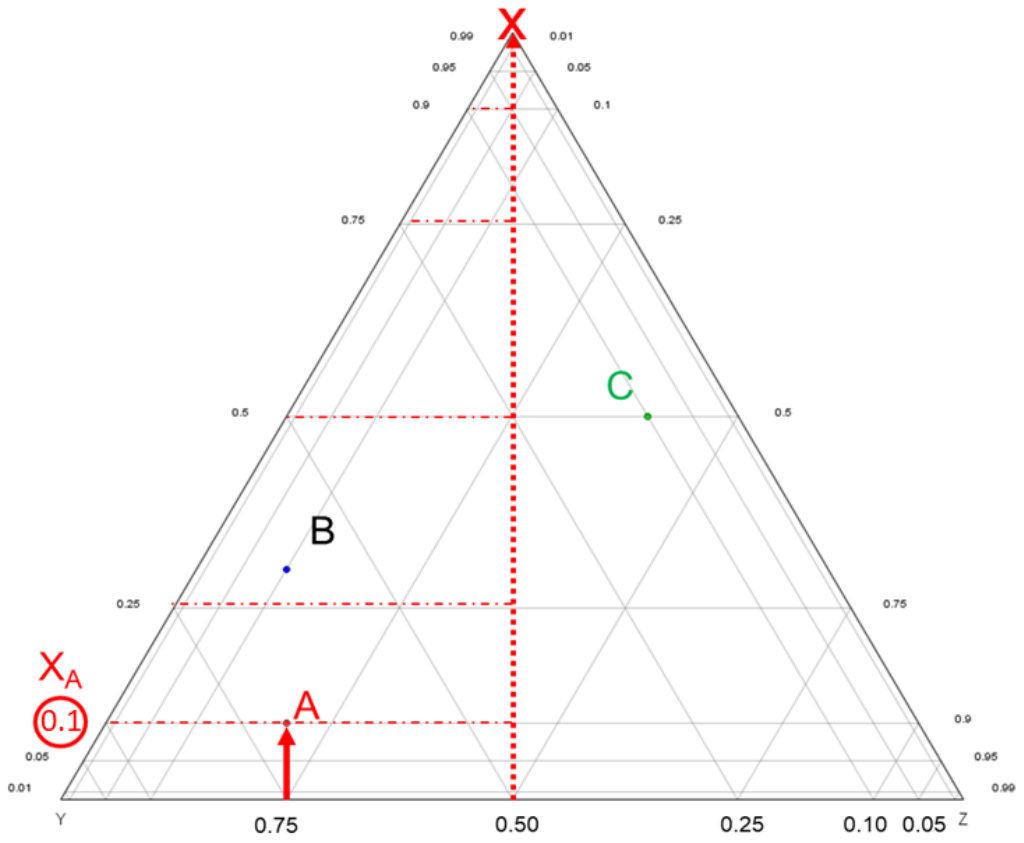
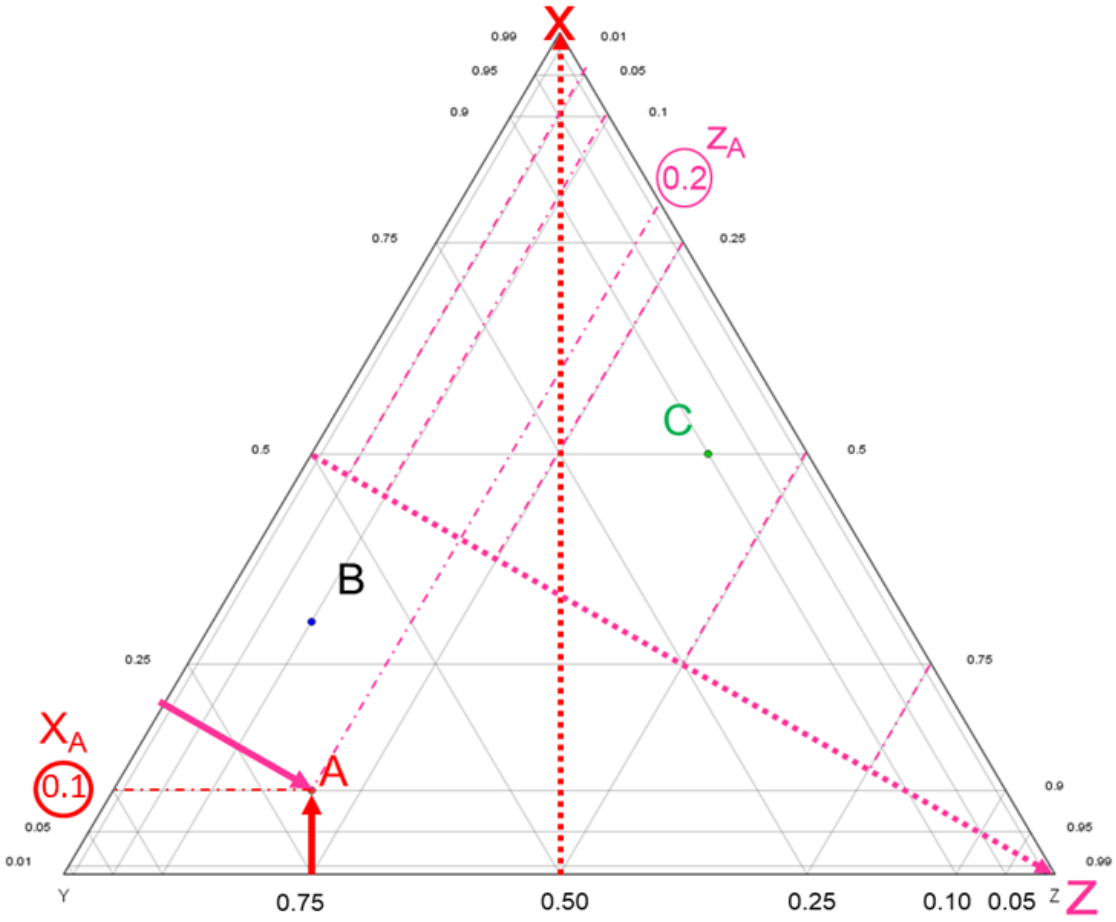


Figure S4: Sample ternary plot

535 Similarly, the z component is read off from the right-hand side axis.



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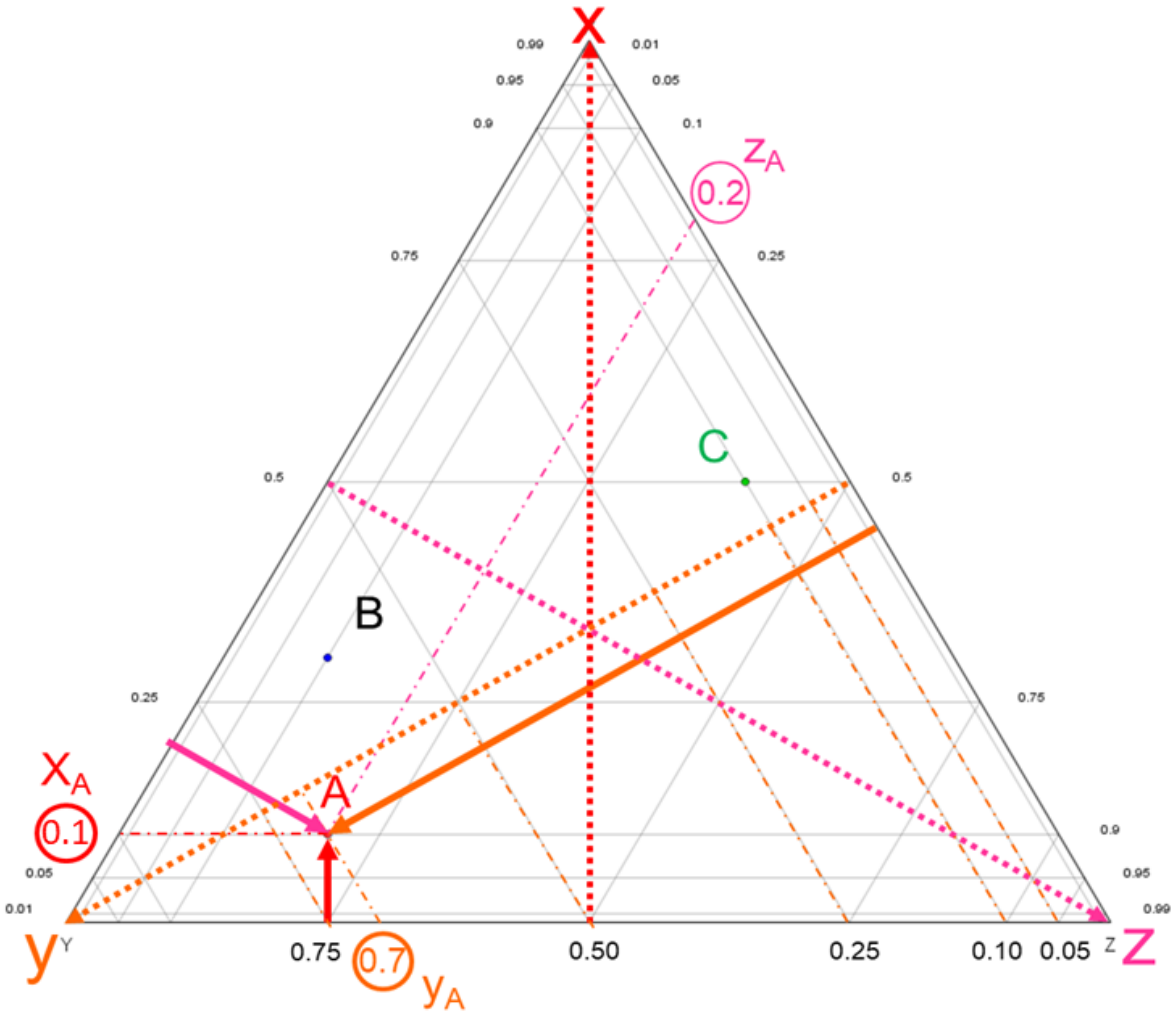
537 **Figure S5: Sample ternary plot**

538 And the y component is read off the bottom scale.



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540 **Figure S6: Sample ternary plot**

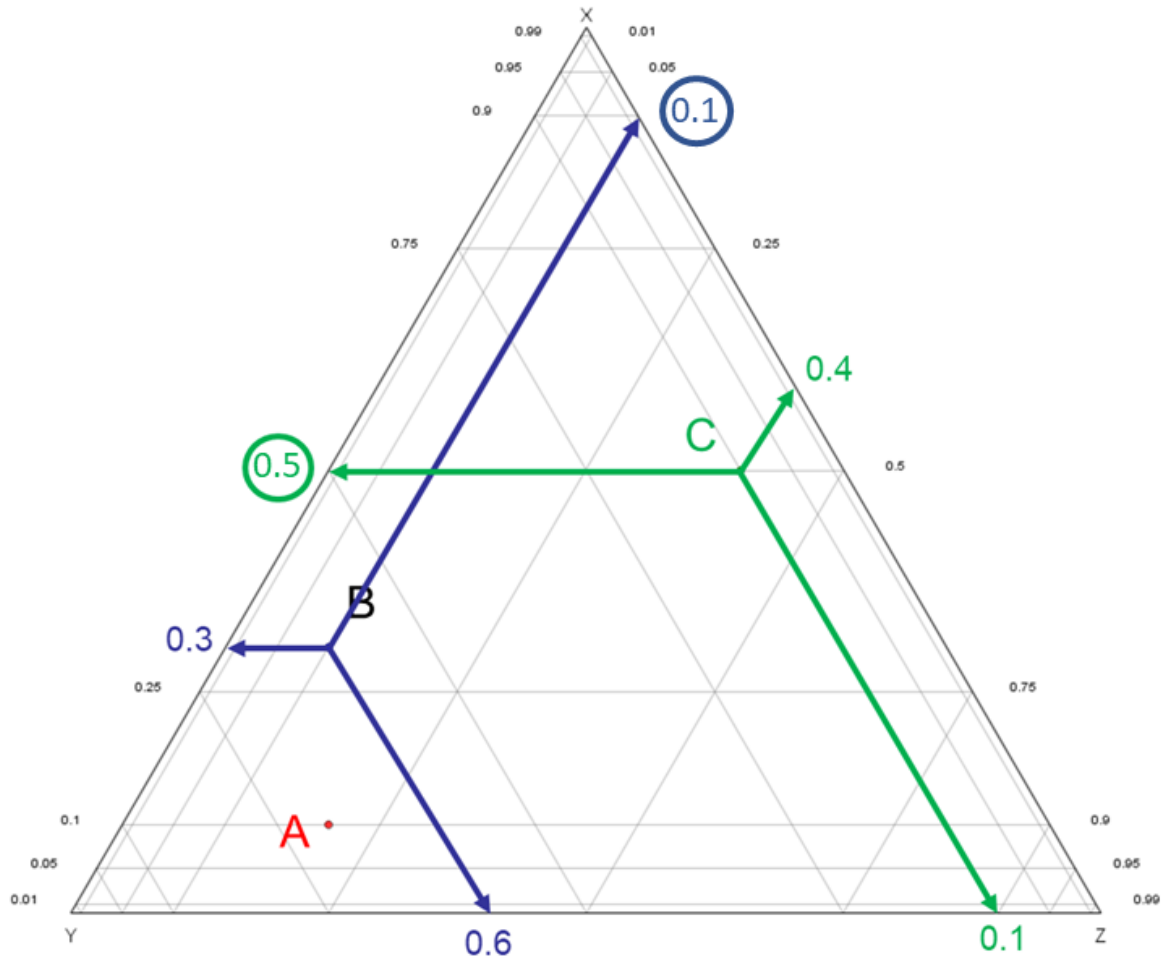

Figure S7: Sample ternary plot

Point	X	Y	Z
A	0.1	0.7	0.2
B	0.3	0.6	0.1
C	0.5	0.1	0.4

Table S8: Simplicial coordinates of points on sample ternary plot

Reading Isotemporal Substitution Plots

The objective of isotemporal substitution plots is to show the hypothetical outcome of two-way substitution of time between behaviors.

Considering Figure S8, the crossover point for the three lines at hazard ratio = 1.0 represents the average composition used as reference. The position on the x-axis indicates the time spent in the day on the behavior type indicated on the x-axis label. The color of the line indicates the behavior that time is being reallocated to/from to alter the x-axis behavior. For example, the purple line in plot (d) in Figure S3 corresponds to two-way substitution of time between MVPA and Sleep. Thus, the mortality risk for an individual at the average composition who replaces 30 minutes of sleep (reduction) by 30 minutes of MVPA (increase) per day, is expected to be lower by a factor of 0.76.

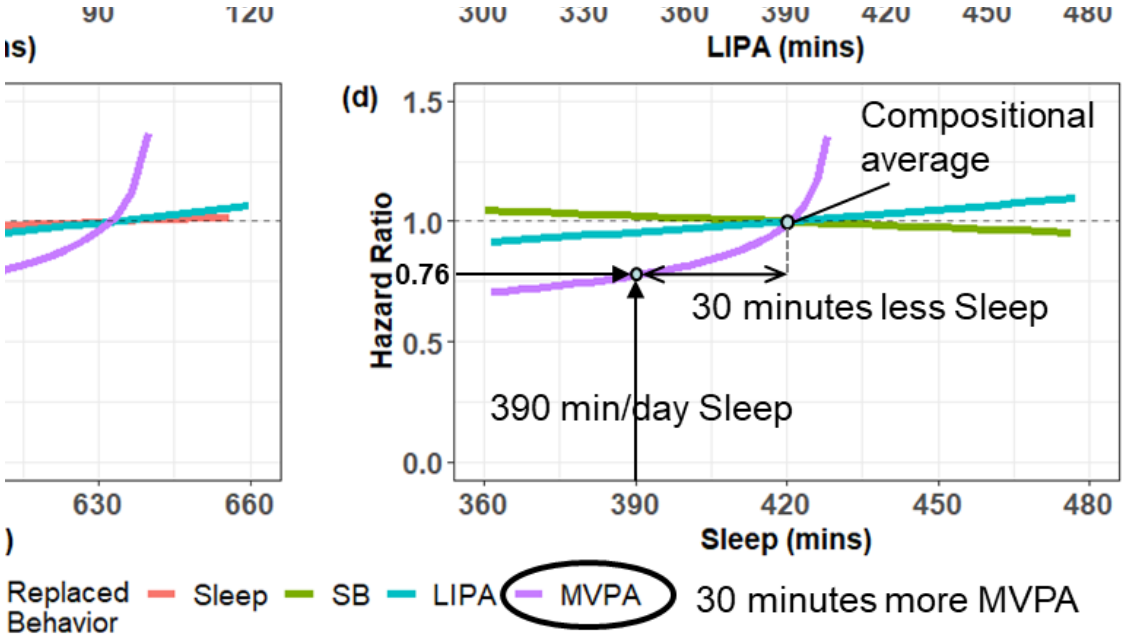

Figure S8: Magnified section of Figure S3(d) with annotations