THE COMPOSITIONAL ASSOCIATIONS OF TIME SPENT IN SLEEP, SEDENTARY BEHAVIOUR AND PHYSICAL ACTIVITY WITH ALL-CAUSE MORTALITY

by

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A thesis submitted to the Department of Public Health Sciences

In conformity with the requirements for

the degree of Master of Science

Queen's University

Kingston, Ontario, Canada

(September, 2020)

Abstract

INTRODUCTION: Daily time spent in sleep, sedentary behaviour (SED), light intensity physical activity (LIPA), and moderate-to-vigorous intensity physical activity (MVPA) are compositional, co-dependent variables. The objective of this study was to use compositional data analysis (CoDA) to examine the relationship between the movement behaviour composition (daily time spent in sleep, SED, LIPA, and MVPA) and all-cause mortality risk.

METHODS: 2,838 adult participants from the 2005-2006 cycle of the U.S. National Health and Nutrition Examination Survey were studied. Daily time spent in SED, LIPA, and MVPA were objectively determined by accelerometer. Time spent sleeping per night was self-reported. Survey data were linked with mortality data through to the end of December 2015. CoDA was used to investigate relationships between the movement behaviour composition and mortality.

RESULTS: The movement behaviour composition was significantly associated with mortality risk. Time spent in MVPA relative to other movement behaviours was negatively associated with mortality risk (HR=.74; 95% CI [.67, .83]) while relative time spent in SED was positively associated with mortality risk (HR=1.75; 95% CI [1.10, 2.79]). Time displacement estimates revealed that the greatest changes in mortality risk occurred when time spent in MVPA was decreased and replaced with sleep, SED, LIPA, or a combination of these behaviours (HRs of 1.76 to 1.80 for 15 minute/day displacements).

CONCLUSION: The daily movement behaviour composition was related to survival. Replacing MVPA or SED with any other movement behaviour was associated with an increase and decrease in mortality risk, respectively.

Co-Authorship

This thesis was prepared by Anna Clarke under the supervision of Dr. Ian Janssen. The data used in this thesis are from the National Health and Nutrition Examination Survey (NHANES) cycles 2005-2006. This data is publicly available. The conceptualization of this thesis was a collaboration between Anna Clarke and Dr. Ian Janssen. Anna Clarke conducted the literature review, database manipulation, relevant analyses, interpretation of results, and writing of this document. Dr. Janssen provided continual feedback, guidance and editing of this thesis.

Acknowledgements

First and foremost, I would like to thank my supervisor, Dr. Ian Janssen, for his ongoing guidance and feedback throughout the past two years. I consider myself incredibly fortunate to have worked with such a helpful, supportive, and knowledgeable supervisor who provided countless opportunities for me to learn and grow as an epidemiologist.

I would like to acknowledge the faculty and staff in the department of Public Health Sciences for providing a friendly and caring community to learn in. I would like to thank my MSc epidemiology classmates and physical activity epidemiology labmates for their support throughout this degree. A special thank you to Lindey and Haley for their help and friendship during my time at Queen's. Thank you to all of those who graciously welcomed me and helped make Kingston my home these past two years. I would also like to thank my former colleagues and mentors at the University of Ottawa Heart Institute for inspiring me to pursue graduate training in epidemiology and continuing to encourage me in my academic and career pursuits.

I would like to acknowledge Queen's University, the McLaughlin Fellowship, and the Public Health Agency of Canada in partnership with the Canadian Society for Exercise Physiology for financial assistance during my MSc training.

Finally, thank you to my family and friends (near and far) for their continual love and support throughout the past two years. I am truly grateful for all of you.

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List of Abbreviations

BMI: Body mass index

CoDA: Compositional data analysis

ilr: Isometric log ratio

LIPA: Light intensity physical activity

MVPA: Moderate-to-vigorous intensity physical activity

NHANES: National Health and Nutrition Examination Survey

SED: Sedentary behaviour

US: United States

Chapter 1

Introduction

1.1 Overview

From a movement perspective, the 24-hour day is made up of time spent in various movement behaviours, namely sleep, sedentary behaviour (SED), light intensity physical activity (LIPA), and moderate-to-vigorous intensity physical activity (MVPA). Movement behaviours are mutually exclusive, and time spent in these behaviours makes up the finite 24-hour day. Insufficient sleep, extensive time spent being sedentary, and inadequate participation in physical activity is pervasive in the Canadian population.[1,2] Indeed, 35.2% of Canadian adults are not meeting sleep guidelines and as many as 82.5% fail to meet physical activity guidelines.[2,3] Currently there are no formal guidelines for SED, but the average Canadian adults spends 9.6 hours being sedentary each day.[3] This is troubling as time spent in each of these movement behaviours are associated with morbidity and mortality.[3–5]

Previous research has largely studied the associations between movement behaviours and health outcomes, such as mortality, in isolation.[3] Recently, there has been an interest in examining how combinations of movement behaviours are associated with health.[6] This has typically been done using a regression model that includes two or more movement behaviours as *independent* variables.[7] This regression approach is problematic for three main reasons. First, regression models treat time spent in movement behaviours as being *independent* of each other, when they are *codependent* variables.[8] For example, if time spent in MVPA changes (increases or decreases), an equal but opposite change must occur in time spent in one or more of the remaining movement behaviours.[8] Second, traditional regression approaches assume the

exposure variables are unconstrained and free to range in standard real space (from - ∞ to + ∞).[8] This is not the case for movement behaviours, which are compositional variables confined to a 24-hour day.[8] Third, when all movement behaviours are included in a single regression model, multi-collinearity is a significant statistical concern due to their intrinsic *co-dependency*.[8,9] Using standard regression methods to study movement behaviours is a flawed technique that may lead to erroneous conclusions.[8,10,11]

Compositional data analysis (CoDA) is a statistical approach that can be used to overcome the three problems noted above. Specifically, CoDA methods were designed to be used with codependent data that are proportions of a finite whole (e.g., time spent in movement behaviours that adds up to a 24-hour day).[8] In movement behaviour studies, CoDA can be used to examine associations for the collective 24-hour movement behaviour composition, the relative importance of individual movement behaviours, and time reallocations between movement behaviours.

A new systematic review of studies using CoDA revealed that the entire movement behaviour time-use composition should be considered when evaluating health outcomes.[12] The review also showed that relative time spent in MVPA was favourably associated with health outcomes. For time displacement estimates, reallocating time to MVPA (from the other movement behaviours) or from SED (to the other movement behaviours) was favourably associated with health outcomes.

Studies in the movement behaviour field that have used CoDA are few in number. In fact, the review found only 8 studies have examined the association between the full 24-hour movement behaviour composition and health outcomes in adults.[12] Furthermore, existing studies have largely been cross-sectional in nature, with only a single study examining potential

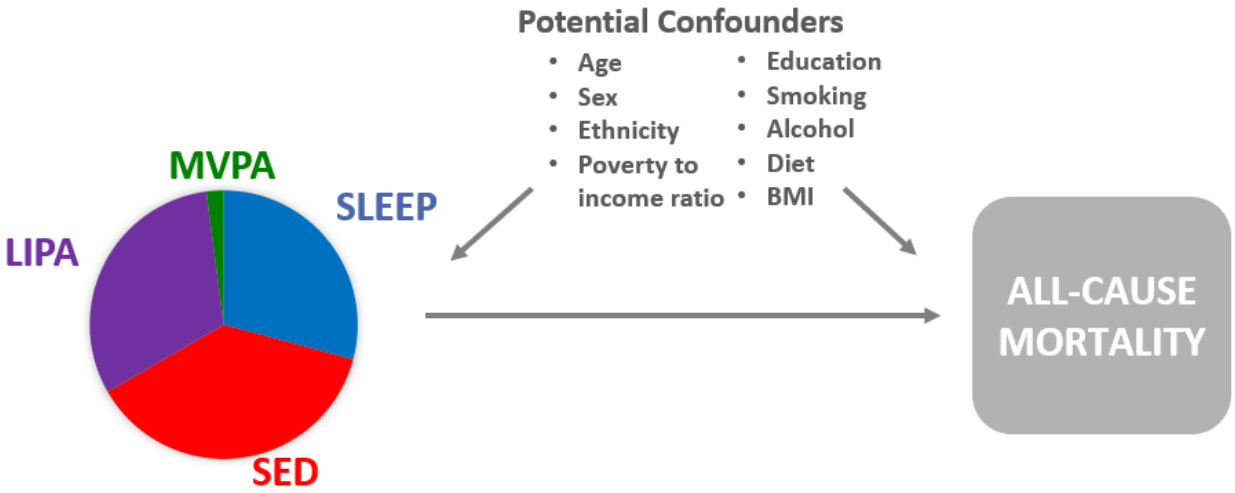
temporal relationships with morbidity or mortality endpoints.[12] Cross-sectional study designs have limited ability to establish temporal relationships and are at risk of reverse-causality.

1.2 Objectives & Hypotheses

The objectives of my thesis research will be to use a compositional data analysis approach to: (1) investigate whether the composition of time spent in sleep, SED, LIPA, and MVPA is associated with all-cause mortality risk; and, (2) estimate the degree to which changing time in any given movement behaviour (sleep, SED, LIPA, or MVPA) within the movement behaviour composition is associated with changes in risk of all-cause mortality.

It is hypothesized that: (1) the composition of time spent in sleep, SED, LIPA and MVPA will be significantly associated with all-cause mortality risk; (2) the relative amount of time spent in MVPA, LIPA, and sleep will be beneficially associated with mortality risk while relative time spent in SED will be detrimentally associated with mortality risk; and, (3) the estimated change in mortality risk associated with displacing SED with MVPA will be greater than that associated with displacing SED with LIPA or sleep.

Figure 1.1, which is shown immediately below, is a conceptual model of the associations between the composition of time spent in sleep, SED, LIPA, and MVPA with all-cause mortality risk



1.3 Scientific and Public Health Significance

Public health guidelines for movement behaviours have traditionally focused on recommendations concerning individual movement behaviours in isolation. Individuals may seek to change the amount of time they spend in a given movement behaviour to meet these individual guidelines (e.g. increase time spent in MVPA). However, a change (e.g., increase) in one movement behaviour must correspond to an equivalent and opposite change (e.g., decrease) in one or more of the remaining movement behaviours because movement behaviours are intrinsically *codependent*. Future public health guidelines should account for the entire movement behaviour composition, acknowledging that sleep, SED, LIPA, and MVPA are all relative parts of the 24-hour day. This thesis research considers the compositional nature of movement behaviours and their associations with mortality. It is hoped that the findings from this thesis will contribute to the growing integration of movement behaviours in future public health guidelines, policies, and interventions.

1.4 Thesis Organization

This thesis adheres to the guidelines provided by the School of Graduate Studies at Queen's University for a manuscript-based thesis document. The second chapter consists of a literature review examining associations between individual, combinations of, and the composition of movement behaviours (sleep, SED, LIPA and MVPA) and mortality. Methodological issues pertaining to measurement as well as the statistical approaches that have been applied in the field of movement behaviour epidemiology are also discussed. The third chapter is the main manuscript, investigating the compositional associations of time spent in sleep, SED, LIPA and MVPA with all-cause mortality. The fourth chapter concludes with a general discussion of the key findings, strengths and limitations, public health implications, and suggested directions for future research.

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Chapter 2

Literature Review

2.1 Introduction

The purpose of this literature review is to summarize existing evidence examining associations between movement behaviours and all-cause mortality. This review begins by defining key terms and concepts and providing an overview of common methods used to measure movement behaviours. A description of the evidence for associations between time spent in movement behaviours and mortality is then given. This is followed by a summary of the research investigating relationships between time spent in combinations of movement behaviours and mortality, accompanied by a critique of common methodological approaches for studying movement behaviour time-use. Finally, a description of compositional data analysis (CoDA) and its application in movement behaviour epidemiology is provided. Key gaps and limitations in the existing literature are highlighted throughout this review.

It is important to note that this review focusses on the *time* spent in different movement behaviours. There are many other movement behaviour characteristics that may be important for health that fall outside the scope of my thesis research and which are therefore not critiqued in this literature review chapter. Some of these other movement behaviour characteristics include: the quality of sleep, the timing on when one goes to bed and gets up in the morning (e.g., night owl vs. morning lark), the patterns in which sedentary time (e.g., prolonger vs. breaker) and physical activity time (e.g., bouts of activity vs. intermittent activity) are accumulated, the type of sedentary behaviour (e.g., screen time) and physical activity (e.g., sport, active transportation, occupational, etc.), and the timing of when sedentary behaviour and physical activity occurs (e.g., watching TV or exercising immediately before bed).

2.2 Key Movement Behaviour Terms and Concepts

Sleep duration is typically defined as the total amount of sleep obtained, either overnight or across the entire 24-hour day.[1] *Sedentary behaviour (SED)* is defined as any waking behaviour that requires very low energy expenditure (i.e., <50% above resting energy expenditure) while sitting, reclining or lying down.[2] Some examples of common sedentary behaviours include driving to work, sitting and working on a computer, and watching television while sitting or lying down. *Light intensity physical activity (LIPA)* is generally classified as waking behaviours performed at an intensity of between 50-299% above resting energy expenditure and includes activities such as standing, casual walking, and light housework.[3,4] *Moderate-to-vigorous intensity physical activity (MVPA)* is classified as waking behaviours performed at an intensity of at least 300% above resting energy expenditure levels and includes activities such as brisk walking, running and cycling.[4]

2.3 Common Measures of Movement Behaviours

There are several methods for measuring movement behaviours, each with their own considerations, which will be discussed below. For this review, I will focus on relevant measurement methods appropriate for observational research in large epidemiological settings. This is not an exhaustive list and there are other means to measures movement behaviours not discussed, such as those used in lab-based and clinical environments (e.g., doubly labelled water, room calorimetry, polysomnography). Some measurement methods better capture particular movement behaviours than others. The appropriate tool depends on several factors including the available study funds, number of participants, duration of study participation, participant burden, etc.[5] More than one method of measurement can be used in combination when appropriate and feasible.

2.3.1 Self-Reported Measures

2.3.1.1 Questionnaires

For many years, researchers have measured movement behaviours using questionnaires (e.g., the International Physical Activity Questionnaire, Sedentary Behaviour Questionnaire, Pittsburgh Sleep Quality Index, etc,).[6–8] Questionnaires may assess individual movement behaviours based on a single question (e.g., average time spent sitting per day) or they may be composite measures (e.g., several questions about multiple domains of SED are summed to produce total sitting time per day). Composite item questionnaires have been shown to perform better than single item questionnaires.[9] Questionnaires tend to better capture activities that are longer in duration (e.g., going for a 30-minute run) rather than brief or intermittent activities (e.g., a 5 minute walk to the bus stop). These self-reported measures are subject to recall error or bias and are affected by social desirability.[5] Furthermore, many questionnaires used in research studies have not been validated. For example, in a critical appraisal of 54 recent studies of SED, a staggering 59% used self-reported measurements of SED that had not been validated.[10] Even among questionnaire measurements of total SED that have been evaluated, a recent review found many yield only poor-to-moderate agreement with objective criterion measures such as accelerometers or inclinometers.[11] Poor validity of questionnaire measures likely results in non-differential misclassification and biases associations between movement behaviours and health outcomes towards the null. These limitations can obscure the true relationship between movement behaviours and mortality, producing biased effect estimates.

2.3.1.2 Logs

Logs can be used to capture time spent in movement behaviours (i.e., sitting, sleeping or being physically active). These logs are typically completed daily throughout study participation (e.g.,7 days). Participants are asked to report the current or previous day's activities, often broken up into time periods (e.g., every 15 minutes or every hour). Other logs are simplified to focus on a particular movement behaviour (e.g., reporting daily time spent sleeping). Logs are self-reported measurement tools and subject to potential misclassification since participants may struggle to accurately remember what they were doing throughout each day and when. Indeed, a systematic review of SED measurement methods found a high degree of variability within and between studies that compared SED estimates from logs/diaries with device-based measures (some studies suggested logs/diaries under-reported, were comparable, or over-reported average SED estimates when compared to device-based measures).[11] Detailed time-use logs can also be cumbersome both on participants and researchers conducting analyses on large samples. The use of logs in the movement behaviour field has predominantly been used in sleep research, and, to a lesser extent, studies of SED.

2.3.2 Device Based Measures

With advances in technology, researchers have used device-based methods to objectively classify movement behaviours of all intensities and overcome issues inherent in self-reported measurement tools. For example, a recent systematic review found self-reported measures underestimated SED by 1 hour 45 minutes (CI: 0:83, 2:07 [hours: minutes]) compared with device-based methods.[9] However, device-based measures remain imperfect measurement tools. For instance, most devices used by researchers are not waterproof (and removed when they could get wet), so activities such as swimming are not captured. When feasible, researchers may choose to supplement the use of device-based measures with self-reported questionnaires or logs

to further validate movement behaviour classification, especially if devices are removed while sleeping. Device-based measures can be more difficult to apply in large epidemiological study settings as they can be costly, time-intensive, and intrusive for participants.

2.3.2.1 Pedometers

Pedometers are small devices that use spring-based mechanisms to estimate steps from forces generated by movement in the vertical axis.[12] They can be useful for measuring total volume of physical activity (i.e., number of steps), but do not typically provide information regarding time-use (duration of activities). As a result, most pedometers cannot be used to capture time spent in different intensities of movement (e.g., LIPA, SED, or MVPA). However, more sophisticated emerging devices may include an internal clock and memory that allow for classification of time spent in waking movement behaviours using step-rate thresholds.[13,14] Pedometers detect movement in the vertical axis alone and have not been used to measure sleep.

2.3.2.2 Accelerometers

Accelerometers are small devices (about 5 X 5 X 2 cm) typically worn on an elastic belt around the waist during waking hours that continuously measure acceleration or change in velocity to detect and quantify movement or lack thereof. The accelerations captured over pre-set intervals, which are typically 1 minute in length, are summed into count values and established cut-points are used to quantify whether that minute was spent in SED, LIPA or MVPA. Because accelerometers are typically worn for 7 consecutive days and measure 1-minute intervals, 10,080 distinct movement data points are captured for each participant. These 10,080 data points are generally processed and then summarized into a few key variables that reflect average daily time spent at different intensities of movement.

In recent decades, accelerometers have increasingly been used in physical activity research to expand upon previous self-reported findings. Accelerometer measurements do not have the same potential for recall error or recall bias present with self-reported tools. The increased use and availability of accelerometers has allowed researchers to better capture intermittent or sporadic bouts of activity as well as time spent in LIPA (e.g., walking around the house). These activities are often more difficult to accurately recall.[15–18] However, accelerometers do not provide postural information and have difficulty distinguishing between activities at the lower end of the energy expenditure spectrum, such as sitting and standing.[2,9] This can introduce misclassification. Both sitting and standing are low energy expenditure activities, but only the former complies with the consensus definition of SED.[2] Therefore, while accelerometers are helpful in better classifying higher intensity-level physical activities, they provide imperfect measures of movement behaviours at the lower end of the energy expenditure continuum. Furthermore, accelerometers best capture step-based movements. As such, physical activities stemming from non step-based movements, such as cycling or resistance training, may not be accurately classified.

When used to measure sleep, accelerometers are typically worn on the wrist to detect arm movements (or lack thereof) and differentiate sleep time from wake time.[19] Specialized algorithms are used to generate sleep parameter estimates, such as sleep duration and sleep efficiency. Sleep duration estimates from accelerometers have consistently been shorter than self-reported measures which may in part be due to difficulty accurately recalling sleep time and differentiating between time spent sleeping and time in bed.[19–21] Advantages of using accelerometers to quantify sleep include the objective nature of the measure. Furthermore, they are less costly, burdensome, and intrusive than polysomnography.

2.3.2.3 Inclinometers

Inclinometers are instruments that measure slope or tilt, often worn on the thigh. They provide additional postural information (i.e., sitting, standing, or lying down) to distinguish between movement behaviours.[22] Inclinometers can be helpful in differentiating between lower energy expenditure activities, including some forms of SED and LIPA (e.g., sitting versus standing). Indeed, these devices emerged from research pertaining to SED to address challenges in accurately measuring SED by self-reported or accelerometer methods alone. However, inclinometers do not adequately differentiate physical activity intensity.[23] To address this limitation, some devices contain both an inclinometer and accelerometer (e.g., activPAL) to capture both postural information and movement intensity.

2.4 Associations Between Time Spent in Movement Behaviours and Mortality

2.4.1 Sleep Duration

The National Sleep Foundation recommends adults aged 18-64 years obtain 7-9 hours of sleep per night.[24,25] A nationally representative cohort of American adults found that those who meet these guidelines have a 19% (95% CI: 0.67-0.99) reduction in risk of all cause-mortality.[26] Data from the Canadian Health Measures Survey indicate that 35.2% of Canadian adults 18-64 years of age are not meeting these guidelines.[27]

Multiple systematic reviews and meta-analyses demonstrate that both shortened and prolonged sleep duration have detrimental associations with all-cause mortality.[28–33] A recent meta-analysis of 43 prospective studies that included 2.4 million participants used a restricted spline model that showed a U-shape association between sleep duration and all-cause mortality.[30] The lowest risk of all-cause mortality corresponded with approximately 7 hours of sleep per

day.[30] In comparison to 7 hours of sleep per day, results indicated a 1.06 times greater risk of all-cause mortality (95% CI: 1.04-1.07) per 1-hour reduction in sleep when sleep was <7 hours per day and a 1.13 times greater risk of all-cause mortality (95% CI: 1.11-1.15) per 1-hour increase in sleep when sleep was >7 hours per day.[30] While both short and long sleep durations are associated with a greater risk of mortality, the underlying mechanisms for this increased risk differ.[28–33] It has been hypothesized that short sleep itself is a risk factor for mortality.[29,34] Proposed biological mechanisms include an increase in cardiometabolic risk via disruptions in metabolic systems, endothelial function, the autonomic nervous system, insulin and glucose regulation, and inflammation.[29,34–36] Conversely, rather than long sleep duration itself being a true risk factor, researchers believe long sleep duration may be reflective of underlying morbidity or subclinical disease that leads to a greater risk of mortality.[30,32,36,37] However, a known limitation of sleep research is the limited feasibility and consequently availability of experimental evidence. For example, at most a few studies have attempted to experimentally examine acute health effects related to sleep by restricting or prolonging time in bed.[38–40]

A study by Kim et al. is a good example of the study design, measurement methods and limitations of the studies that have examined the association between sleep and mortality.[41] These authors prospectively followed a large cohort of 135,685 participants aged 45-75 years for an average period of 12.9 years.[41] A self-reported questionnaire was used to collect baseline data on average sleep per day and potential confounders.[41] Among those who reported sleeping ≤5 hours per day, a 15% increased risk in men (HR=1.15; 95% CI:1.06,1.23) and 14% increased risk in women (HR=1.14; 95% CI:1.06,1.23) was observed compared to those sleeping 7 or 8 hours per day.[41] Consistent with the overwhelming majority of epidemiological studies, sleep duration was assessed using self-reported tools, which typically capture *time in bed* rather than

accurately quantifying *sleep duration*. Participants struggle to differentiate total *sleep duration* from *time in bed*, the later of which generally fails to account for differences in sleep latency and efficiency.[21] Greater availability of electronic wearable devices, such as accelerometers, to estimate sleep may permit more accurate and reliable measurements of sleep duration within the resource confines of some large epidemiological studies. Sleep estimates from accelerometer measurements have consistently been shorter than self-reported sleep measurements.[19–21] Optimal *sleep duration* estimates guided by studies using self-reported rather than objective measures may be misleading since, as discussed, these studies more accurately capture *time in bed* rather than *sleep duration*, which may explain some of the discrepancy between these methods of measurement. Assessing sleep by questionnaire may result in non-differential misclassification of *sleep duration*, provided that misclassification occurs to the same extent in both those who do and do not survive. If this is the case, studies using self-reported measures of *sleep duration* have underestimated the true relationship between sleep and mortality.

A further limitation of the studies investigating the relationship between *sleep duration* and all-cause mortality is the inadequate consideration of and adjustment for other movement behaviours (SED, LIPA, MVPA).[28–33] Few past studies have adjusted for any other movement behaviours and those that did tended to only adjust for MVPA.[30] Sleep researchers are calling for the conceptualization of sleep as a modifiable component of time-use alongside other movement behaviours in the 24-hour time-use profile when assessing relationships between sleep and health.[42]

2.4.2 Sedentary Behaviour

Data from the Canadian Health Measures Survey indicate that Canadian adults 18-79 years of age spend an average of 9.6 hours being sedentary each day.[43] Increasing evidence has demonstrated SED is a risk factor for several chronic diseases and mortality.[44] A recent meta-analysis of 13 prospective cohort studies including 828,690 unique participants that examined the relationship between time spent sitting and all-cause mortality (by self-report in all but one study) while adjusting for MVPA, reported a hazard ratio (HR) of 1.22 (95% CI: 1.09-1.41) for individuals with the highest versus lowest time spent sitting.[45] Patterson et al. further examined the dose-response relationship of SED and mortality risk, adjusting for MVPA, and found a non-linear relationship.[44] Specifically, at lower exposure levels (<8 hours per day spent sitting), there were small increases in risk as sitting time increased while at higher exposure levels (≥8 hours per day spent sitting), the risk increased more rapidly.[44] Below 8 hours per day spent sitting, a 1.01 times greater risk of all-cause mortality (95% CI=1.00-1.01) was found for each additional hour of sitting per day.[44] Above 8 hours per day spent sitting, there was a 1.04 times greater risk in all-cause mortality (95% CI 1.03-1.05) for each additional hour of sitting per day.[44] Four other meta analyses have further demonstrated a significant curvilinear dose-response relationship between SED and all-cause mortality.[46–49]

Matthews et al. published one of the earlier studies investigating the relationship between SED and mortality in a large cohort of American adults aged 50-71 years enrolled in the NIH-AARP Diet and Health Study.[50] They followed 240,819 participants for an average of 8.5 years who reported no history of cancer, cardiovascular disease or respiratory disease at baseline. Mortality status was obtained from the National Death Index.[50] Participants were asked to report how much time they spent sitting during a typical 24-hour period over the past 12 months (<3, 4-5, 5-6, 6-7, 7-8, or ≥9 hours per day).[50] Analyses revealed an associated 1.30 times greater risk of

mortality (95% CI: 1.22, 1.38) for those sitting ≥9 hours per day compare to <3 hours per day, but when MVPA was adjusted for this fell to only a 1.19 times greater mortality risk in (95% CI: 1.12, 1.27).[50] A limitation of this study is the way in which MVPA was measured and controlled for. Rather than adjusting for MVPA duration as another component of time-use, models adjusted for frequency of MVPA (average number of times spent per week in activities of at least a moderate intensity over the past 10 years: never, rarely, <1/week, 1-3 times/week, 4-7 times/week, >7 times per week).[50] Thus, MVPA may be misclassified and not appropriately controlled for (e.g., consider a brisk walk 4 times a week for 10 minutes in compared with running 3 times a week for an hour). Furthermore, this study assessed SED from a single question, yet composite measures have been shown to yield greater validity.[9] This study is typical of many SED investigations embedded within large cohort studies of health where competing research priorities may sway how many questions are allotted to different domains of interest.

A recent systematic review and meta-analysis looked at the relationship between objectively measured sedentary time, captured by accelerometer, and mortality risk.[48] The authors included individual level data from 36,383 adults (mean age 63 years) with a median follow up of 6.8 years.[48] A 2.63 (95% CI: 1.94-3.56) times greater risk of all-cause mortality was found for those in the highest versus lowest quartile of sedentary time after adjusting for sex, age, body mass index, socioeconomic position and wear time.[48] The corresponding hazard ratio from a recent meta-analysis that included studies that relied on self-reported measures of sitting time was 1.22 (95% CI: 1.09-1.41).[45] This discrepancy in risk estimates supports the argument that it is important to use accurate measures of movement behaviours and that biased estimates

of sedentary behaviour have greatly influenced the observed associations SED and health outcomes.

Inclinometers have not yet been used to assess long-term associations between SED and mortality risk. However, a recent study by Edwardson et al. published in 2020 compared measurements of SED by accelerometer and inclinometer when investigating associations between SED and cardiometabolic health markers.[51] Significant associations were found for both accelerometer and inclinometer derived measures of SED with BMI, waist circumference, body fat percentage, high density lipoprotein (HDL) cholesterol, triglycerides, and cardiometabolic risk score.[51] The authors reported these association were in the same direction (negative for HDL cholesterol and positive for all other markers) and of similar magnitude.[51] Though the Beta coefficient values were only reported visually, the magnitude of these associations did consistently appear slightly stronger when measured by inclinometer compared to accelerometer estimates.[51] Relationships may potentially be found to be even stronger as SED measurement continues to improve (i.e., self-report versus accelerometer versus inclinometer), though more research is needed to examine this.[51]

2.4.3 Light Intensity Physical Activity (LIPA)

Results from the Canadian Health Measure Survey indicate that Canadian adults aged 18-79 years old spend an average of 3 hours and 39 minutes per day engaged in LIPA.[52] Most research to date in the field of physical activity has centred on the health benefits of MVPA, despite the fact that physical activity intensity is on a continuum.[53,54] Furthermore, in the average person a substantially greater proportion of the day is spent in LIPA than MVPA (an estimated 219 versus 26 minutes per day for the average Canadian adult) making it an additional behaviour

to potentially target for public health guidelines. Increasing LIPA may be a more feasible means of increasing total activity because it can be incorporated into one's incidental daily activities without formal exercise knowledge or skills by adding light movements and reducing sedentary time.[55]

Four systematic reviews have described a significant inverse association between high amounts of LIPA and all-cause mortality risk.[3,16,48,56] In 2019, a harmonized meta-analysis found a 62% reduction (HR=0.38; 95% CI= 0.28-0.51) in all-cause mortality risk associated with greater time spent in daily light activity (highest compared to lowest quartile of time spent in LIPA).[48] However, the authors failed to adjust for MVPA in this pooled analysis (let alone other movement behaviours), which is concerning.[48] Shortly thereafter, a meta-analysis was published in which all included studies adjusted for MVPA.[56] This meta-analysis indicated a 44% lower risk (HR=0.56; 95% CI: 0.44-0.71) of mortality for participants who accumulated >7 compared to only <3 hours per day of LIPA.[56] It is important to consider other parts of the movement behaviour composition to ensure effect estimates for LIPA are not biased.

A study by Matthews et al. was one of the first to consider if objective measures of LIPA are associated with mortality.[57] These authors followed 4,840 adults aged 40 years and older over an average of 6.6 years.[57] Using a restricted cubic splines modelling, they reported an associated 40% lower risk (HR=0.60; 95% CI: 0.40-0.89) of mortality for participants who accumulated 6 compared to only 3 hours of LIPA, but when MVPA was controlled for, a weaker, non-significant association with mortality was revealed (HR=0.89; 95% CI:0.60-1.30).[57] It is important to note this study used alternative cut-points for LIPA and MVPA wherein LIPA was defined as ≥100 counts per minute and <760 counts per minute and MVPA was defined as ≥760

counts per minute.[57] In contrast, most studies use a cut point of 2020 counts per minute to differentiate LIPA from MVPA. The authors contrasted these two LIPA classifications in supplemental materials using a linear model which revealed an associated 16% reduced risk of mortality (HR=0.84; 95% CI:0.75-0.95) for every additional hour spent in LIPA using the 760 counts per minute delineation compared to an associated 21% reduced risk (HR=0.79; 95% CI:0.72,0.87) when the 2020 counts per minute delineation was used (both models adjusted for MVPA).[57] This suggests that higher intensities of LIPA may confer additional benefits than lower intensities of LIPA. A key limitation of this study includes over-adjusting for covariates that lie on the causal pathway of this relationship (history of diabetes, coronary heart disease, stroke, and cancer) which could bias results towards the null and obscure relationships. In addition, participants with as little as one day of valid accelerometer data were included. This may not reflect their habitual movement patterns and could result in misclassification.[58,59]

2.4.4 Moderate-to-Vigorous Intensity Physical Activity

The Canadian Physical Activity Guidelines recommend adults accumulate at least 150 minutes of MVPA per week, in bouts of at least 10 minutes, to achieve health benefits.[60] An estimated 82.5% of Canadian adults (aged 18-79 years) do not meet these guidelines, indicating that MVPA levels are low among the Canadian population.[43] There is overwhelming evidence of the health benefits associated with MVPA. Hundreds of prospective cohort studies summarized in dozens of reviews have consistently demonstrated an inverse relationship between MVPA and all-cause mortality.[53,61–67] A recent overview of systematic reviews investigating the dose-response relationship between physical activity and health status demonstrated strong evidence for an association between regular MVPA and a reduction in all-cause mortality.[63] Studies included in the overview demonstrate this relationship is non-linear such that the largest relative

reduction in risk is seen at lower levels of MVPA (i.e., moving from inactive to accumulating some amount of MVPA) and this beneficial risk reduction attenuates at higher levels of MVPA (i.e. moving from participating in high amounts of MVPA to even higher amounts of MVPA).[63]

A 2015 pooled analysis of six prospective cohort studies from the National Cancer Institute Cohort Consortium included self-reported physical activity data from 661, 137 adults.[64] It revealed a 37% reduction in mortality risk associated with participating in 2-3 times the minimum recommended amounts of leisure-time MVPA compared to those that did not report engaging in any leisure-time MVPA (HR=0.63; 95% CI=0.62-0.65).[64] The additional benefit of participating 3-5 times the recommended physical activity versus meeting the recommended minimum 7.5 MET hours per week of MVPA was modest (31% versus 39% reduction in risk compared to non-active individuals).[64] Other meta-analyses corroborate these findings.[53,65] In comparison, a prospective study that objectively measured physical activity by accelerometer observed a 78% reduction in all-cause mortality risk (HR=0.22 95% CI 0.11-0.44) for the highest compared to lowest MVPA quintile.[68] Misclassification of MVPA resulting from self-reported measurements may underestimate the true association between MVPA and mortality.

Saint-Maurice et al. recently published a study investigating the relationship between MVPA and all-cause mortality in a large American representative sample of 4,840 adults aged 40 years and older.[69] Specifically, they assessed the potential importance of accumulating MVPA in bouts or chunks of time (e.g., periods of at least 5 or 10 consecutive minutes).[69] The authors found both MVPA accumulated sporadically or in bouts of 5 or 10 minutes were similarly and strongly associated with reductions in mortality risk (HR=0.21-0.23 for the highest versus lowest quartile of MVPA).[69] Although current guidelines in Canada recommend accumulating MVPA

in bouts of at least 10 minutes or more, this stipulation has been removed from American guidelines.[60,70] A limitation of this study includes its selection of confounders. No other movement behaviours were adjusted for as fellow time-use components nor was there a measure of diet quality, yet several variables that lie on the causal pathway of this relationship were adjusted for (diagnosis of diabetes, coronary artery disease, stroke, and cancer).[69] MVPA was measured by waist worn accelerometers, which underestimate participation in activities that are not step-based, such as cycling and swimming.[69] This may introduce non-differential misclassification and has the potential to bias results towards the null.

2.5 Associations Between Combinations of Movement Behaviours and Mortality

2.5.1 Covariate Approach

Researchers have commonly examined associations of specific movement behaviours with health outcomes *independent* of other movement behaviours.[16,30,45,61] This has primarily been done by including two or more movement behaviours of interest as *independent* variables in the same regression model. Often only two of the movement behaviours are included in the model, yet all have the potential to confound the relationship of interest. For example, Stamatakis et al. recently investigated the relationship between self-reported time spent sitting and self-reported time in MVPA with all-cause mortality in a large Australian cohort.[71] Both variables (and several confounders) were included as covariates in a Cox Proportional Hazards regression model.[71] LIPA and sleep were not accounted for. These authors reported a 14% greater risk of all-cause mortality (HR=1.14; 95% CI: 1.04-1.23) for participants who sat for more than 8 hours per day compared to those that sat less than 4 hours per day after adjusting for MVPA and other covariates.[71] They expanded on this analysis by exploring joint associations of

sitting time and MVPA together on all-cause mortality risk.[71] Sitting for more than 8 hours per day was associated with an increased risk of all-cause mortality in those who accumulated 0, 1-149 or 150-299 minutes per week of MVPA (HRs and 95% CIs: 1.61 [1.32-1.96]; 1.43 [1.24-1.65]; 1.31 [1.11-1.56]).[71] However, this association was no longer significant among those that accumulated 300-419 or ≥420 minutes per week of MVPA (HRs and 95% CIs: 1.06 [0.83-1.35]; 0.97 [0.83-1.13]).[71] A key limitation of this study is that time spent in each movement behaviour was obtained from self-reported responses to a single question item per behaviour.[71] These questions were not validated and similar questions in other studies yielded poor correlations with accelerometry.[71] This may have resulted in non-differential misclassification and biased results towards the null.[71]

2.5.2 Iso-temporal Substitution Approach

Iso-temporal substitution modelling (ISM) is an expansion of the regression approach discussed in the previous paragraph. This approach has been used to estimate the extent to which replacing one movement behaviour with another (e.g. substituting 30 minutes of sleep with 30 minutes of MVPA) is associated with changes in a health outcome of interest.[72] ISM models the relationship both of a given behaviour being performed and another being displaced for an equal amount of time, controlling for confounding by other time-use behaviours and capturing the results of substitution.[72–74] The covariates in an ISM approach include time spent in each movement behaviour individually (e.g. sleep, SED, and MVPA) and total time spent in all the movement behaviours together (sleep+SED+MVPA).[72] To estimate how the relationship with the outcome would change if a particular movement behaviour is replaced (e.g. 30 minutes of sleep is lost), that behaviour is removed from the model.[72] For example, if sleep is removed from the regression model, the coefficients for the remaining movement behaviours estimate the

effect of replacing 1 unit (e.g. 30 minutes) of sleep with each respective movement behaviour, while adjusting for the remaining movement behaviours and keeping total time constant.

Several studies have used ISM to investigate the theoretical change that would occur to associated mortality risk if time spent in different movement behaviours were substituted for each other.[71,73,75–80] Loprinzi et al. estimated that replacing 30 minutes/day of SED with 30 minutes/day of MVPA would be associated with an 81% reduction in mortality risk (HR=0.19; 95% CI=.06-.60) in the NHANES 2003-2006 cycles followed up for mortality assessment through to 2011.[75] Others researchers have also found significant reductions in mortality risk associated with replacing SED with MVPA.[76,78–80] However, when stratified by physical activity status, Rees-Punia et al. noted that while this association persisted among the least active (≤17 minutes/day; HR=0.55; 95% CI=0.47-0.62) and moderately active (>17 to ≤38 minutes/day; HR=0.83; 95% CI=0.76-0.88) participants, it was absent in participants that were the most active (>38 minutes of MVPA/day; HR=0.99; 95% CI=0.95-1.02).[76] Weaker significant associations with a reduction in mortality risk have also been shown when sedentary behaviour was replaced with LIPA (HRs of 0.83-0.89), though again this disappeared for participants that were most active (HR=1.0; CI=0.97-1.03) in Rees-Punia et al.'s stratified analysis.[76,78–80] Although most studies have focussed on replacing SED, Schmid et al. assessed LIPA displacement and found a 42% reduction in mortality risk (HR=0.58; 95% CI=0.36-0.93) associated with replacing 30 minutes of LIPA with MVPA.[80]

2.5.3 Problems with Covariate and ISM Approaches

The covariate and ISM framework provide easily interpretable methods of examining how individual movement behaviours relate to mortality risk either on their own or when

replacing other movement behaviours. However, both are problematic for three reasons. First of all, these approaches treat movement behaviours as *independent* absolute values rather than relative components of fixed total time use (e.g. 24-hour day).[10,81,82] Movement behaviours are more accurately classified as *co-dependent*, since a change in one movement behaviour (e.g. increase in MVPA) must displace an equal amount of time spent in one or more of the remaining movement behaviours (e.g. decrease in SED and LIPA).[83] Secondly, since movement behaviours capture relative amounts of time, (i.e. proportions of a 24-hour day), their *co-dependent* nature introduces severe multi-collinearity when all these behaviours (sleep, SED, LIPA, and MVPA) are included as covariates in a single regression model.[83,84] Multicollinearity can occur when covariates are highly correlated, or when one covariate can be predicted as a function of one or more of the remaining covariates. One movement behaviour variable (e.g., daily sleep duration) can be predicted by summing daily time spent in the remaining movement behaviour variables (e.g., SED, LIPA, and MVPA), which introduces perfect multi-collinearity. Multi-collinearity can result in poor statistical adjustment and imprecise parameter estimation. Finally, movement behaviours are not continuous variables free to range in standard real space (from $-\infty$ to $+\infty$), but rather time-use components constrained to a finite whole (i.e. 24 hours). Geometrically speaking, movement behaviours are compositional data that occupy the D-part simplex, a subset of quotient space, which is governed by Aitchison geometry rather than the classical geometry of real space.[85] Standard regression techniques are designed to manipulate data existing in standard real space and as such are inappropriate for movement behaviour data. [83] The use of covariate and ISM approaches may lead to erroneous conclusions.[10,81]

2.6 Compositional Data Analysis (CoDA)

Researchers are moving away from conceptualizing sleep, SED, LIPA and MVPA as individual exposures that are *independent* of each other and shifting towards considering movement behaviours collectively as compositional variables.[10,83,84] In this context, the inter-relationships between multiple behaviours are investigated instead of studying a single behaviour in isolation, focussing on relative information rather than absolute. An individual movement behaviour is meaningful in relation to time spent in the remaining movement behaviours: the ratios between behaviours are of primary interest.[83]

To avoid misleading results, statistical approaches suitable for compositional data (i.e., CoDA) should be used to analyze movement behaviour data.[10,83,85] CoDA has been used for years in other research disciplines such as nutrition, microbiome data, and geochemistry.[85–88] CoDA can be used to avoid the main problems (described above) that arise with the covariate and ISM approaches. The CoDA approach involves transforming compositional movement behaviour data, typically using a log-ratio transformation, so it maps onto standard real space.[85,89] After this transformation, standard regression methods commonly used in health research can then be applied (e.g., Cox's proportional hazards regression) and collinearity is no longer a concern.[85,89]

As noted in a new systematic review, studies to date in the field of movement behaviour epidemiology using CoDA have largely been cross-sectional and examined relationships with a small range of health indicators in adults such as adiposity, cardio-metabolic health markers, and mental health.[90] An important finding from this review is that the daily composition of time spent in movement behaviours is associated with a variety of health outcomes.[90] The authors reported

time spent in MVPA relative to sleep, SED, and LIPA was favourably with health.[90] They also found that time reallocation estimates consistently revealed beneficial associations across health outcomes when time was reallocated to MVPA (from sleep, SED, or LIPA) and unfavourable associations when MVPA was removed and replaced with any of the other movement behaviours.[90] In contrast, estimates showed associations with health outcomes were favourable when time was reallocated from SED to LIPA or MVPA and unfavourable when time was reallocated to SED from LIPA or MVPA.[90]

This review included a cross-sectional study by McGregor et el. that used CoDA and data from the Canadian Health Measures Survey to examine associations between the 24-hour movement behaviour composition and health indicators.[91] In this study, time spent in MVPA, relative to the remaining movement behaviours was beneficially associated with reductions in BMI, waist circumference, glucose, insulin, triglycerides, and c reactive proteins and increases in high density lipoprotein cholesterol (all p values <.001).[91] Associations between time spent in LIPA relative to the remaining movement behaviours varied by health outcome (e.g., associated with reductions in triglycerides, but not adiposity measures). [91] No associations were observed between relative time spent in SED and any of the investigated health indicators.[91] Relative time spent in sleep was associated with increases in insulin and c reactive proteins and reductions in high density lipoprotein cholesterol and low-density lipoprotein cholesterol (all p values<.001). No time reallocation findings were presented.[91]

In the fall of 2019, McGregor et al. published the first study that used CoDA to examine temporal relationships between the full composition of movement behaviours (sleep, SED, LIPA, MVPA) across the 24-hour day and mortality outcomes. They studied 1,592 adults aged 50-79 years who were followed for 6 to 7 years.[92] The daily composition (proportion of time spent in

each movement behaviour) was log-transformed (via iso-metric log ratio transformation) to map onto standard real space.[92] This facilitated the use of Cox regression analysis, which revealed the 24-hour movement behaviour composition was significantly associated with all-cause mortality risk.[92] The relationship between the amount of time spent in MVPA relative to the remaining movement behaviours and mortality risk was not statistically significant in the fully adjusted model, though there was a trend towards significance (p=.09) for a reduction in mortality risk.[92] Relative associations between sleep, SED, or LIPA and mortality were not reported.[92] The authors did perform time substitutions using regression coefficients that estimated changes in mortality risk associating with reallocating time spent in one behaviour to another movement behaviour (e.g. removing 15 minutes per day of sleep and adding 15 minutes per day to SED). These time displacement estimates showed replacing equivalent time spent in sleep, SED. or LIPA with MVPA was associated with a reduced mortality risk and reallocating time into SED from any of the remaining movement behaviours was associated with greater mortality risk (the time displacement finding were only presented graphically so specific hazard ratio values could not be abstracted).[92]

There were several limitations to McGregor et al., 2019 study. A key limitation of this study pertains to the measurement reliability of the movement behaviour composition. Only one day of valid accelerometry data (out of seven) was required for participants to be included in this study.[92] This could result in misclassification of participants' typical movement behaviour composition as a single day may not accurately or reliably reflect habitual movement patterns.[58,59] Research suggests at least four days of valid accelerometer data are needed to attain a reliability coefficient ≥70.[59] Confounder selection in this study also warrants further examination. For example, the study failed to include a comprehensive measure of diet quality,

yet of the 17 potential covariates considered, six of these were “health status covariates” that lie on the causal pathway for the relationship of interest and thus should not be considered true confounders (including self-assessed health and physical limitations on movement which were both included in the final fully adjusted model).[92] This over adjustment may bias results towards the null and mask the true nature of relationships.

Rosen et al. published a study examining the relationship between the waking movement behaviour composition and all-cause mortality risk, but did not include sleep data.[93] The authors found time spent in SED relative to LIPA and MVPA was significantly associated with a higher mortality risk (HR=2.24; 95% CI: 1.41-3.56; p<.001). They also showed that replacing SED with LIPA or MVPA was associated with lower mortality risk. Not including sleep when studying associations between the movement behaviour composition and health is a key limitation of this study. Sleep is an important co-dependent component of daily time use that should be accounted for alongside SED, LIPA, and MVPA.

2.7 Summary and Conclusions

The composition of movement behaviours in the population is likely far from ideal. Few Canadian adults meet physical activity guidelines (17.5%), large proportions of the day are spent being sedentary (9.6 hours per day on average) and many fail to get appropriate amounts of sleep (35.2%).[27,43] There are several methods commonly used to measure movement behaviours, each with their own nuances and considerations. Researchers have typically examined independent associations between movement behaviours and mortality using conventional regression techniques. This is a flawed approach since movement behaviours are *codependent* time-use components that together make up total time use. They are not free to range in standard real

space meaning conventional regression techniques are inappropriate. Furthermore, when all movement behaviours are put into a regression model together, severe multi-collinearity is introduced. The relationship between movement behaviours and health outcomes, such as mortality, needs to be further studied using statistical approaches that account for the compositional and codependent nature of movement behaviours, such as CoDA.

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Chapter 3

Compositional associations of time spent in sleep, sedentary behaviour and physical activity with all-cause mortality

3.1 Abstract

INTRODUCTION: Daily time spent in sleep, sedentary behaviour (SED), light intensity physical activity (LIPA), and moderate-to-vigorous intensity physical activity (MVPA) are compositional, co-dependent variables. The objective of this study was to use compositional data analysis (CoDA) to examine the relationship between the movement behaviour composition (daily time spent in sleep, SED, LIPA and MVPA) and all-cause mortality risk.

METHODS: 2,838 adult participants from the 2005-2006 cycle of the U.S. National Health and Nutrition Examination Survey were studied. Daily time spent in SED, LIPA and MVPA were objectively determined by accelerometer. Time spent sleeping per night was self-reported. Survey data were linked with mortality data through to the end of December 2015. CoDA was used to investigate relationships between the movement behaviour composition and mortality.

RESULTS: The movement behaviour composition was significantly associated with mortality risk. Time spent in MVPA relative to other movement behaviours was negatively associated with mortality risk (HR=.74; 95% CI [.67, .83]) while relative time spent in SED was positively associated with mortality risk (HR=1.75; 95% CI [1.10, 2.79]). Time displacement estimates revealed that the greatest changes in mortality risk occurred when time spent in MVPA was decreased and replaced with sleep, SED, LIPA or a combination of these behaviours (HRs of 1.76 to 1.80 for 15 minute/day displacements).

CONCLUSION: The daily movement behaviour composition was related to survival. Replacing MVPA or SED with any other movement behaviour was associated with an increase and decrease in mortality risk, respectively.

3.2 Introduction

Sleep, sedentary behaviour (SED), light intensity physical activity (LIPA), and moderate-to-vigorous intensity physical activity (MVPA) are movement behaviours and time spent in these behaviours adds up to a constant 24-hour per day sum.[1] Data from the Canadian Health Measures Survey indicate that 35.2% of Canadian adults are not meeting sleep guidelines and a staggering 82.5% are not meeting physical activity guidelines.[2,3] Although formal SED guidelines have not yet been established, Canadians adults are sedentary for an average of 9.6 hours per day.[3] Movement behaviours are related to mortality risk. Short and long sleep durations and greater time spent in SED have been associated with an increased risk of mortality whereas more time spent being physically active has been associated with reduced mortality risk.[4–9] Previous studies have largely explored associations between individual movement behaviours and mortality in isolation. Recently, researchers have explored how multiple movement behaviours, such as the combination of high SED and low MVPA, influence mortality. For example, Stamatakis et al. reported that sitting for ≥8 hours per day is significantly associated with greater all-cause mortality risk in those who accumulate <300 minutes per week of MVPA, but not for those who accumulated ≥300 minutes per week of MVPA.[10]

The relationships between multiple movement behaviours with morbidity and mortality have generally been studied using standard regression techniques that include movement behaviours as *independent* variables in a model.[10,11] While this has shed additional light on how combinations of movement behaviours influence health, the statistical approaches used in these studies were flawed for three main reasons. First, these approaches treat movement behaviours as being *independent* of each other when they are *co-dependent* variables.[1] They are co-dependent because movement behaviours are compositional variables confined to a 24-hour day.[1] Thus,

time spent in one movement behaviour must displace time spent in any of the remaining movement behaviours. For instance, if time spent in MVPA is increased, it must be accompanied by a corresponding decrease in one or more of the remaining movement behaviours. Second, traditional regression techniques assume variables are free to take on any value in standard real space (from $-\infty$ to $+\infty$), yet movement behaviours can only assume finite time values from 0 to 24 hours. Third, multi-collinearity is a significant statistical concern when all movement behaviours are included in a single regression model due to their intrinsic *co-dependency*.[1,12] In short, using standard regression techniques to study movement behaviours is inherently flawed and may lead to erroneous conclusions.[1,13,14]

To avoid the above noted problems, compositional data analysis (CoDA) can be used. CoDA is a statistical approach suitable for co-dependent variables that are relative components of a finite sum, such as time spent in movement behaviours adding up to the 24-hour day.[1] As noted in a new systematic review, the few movement behaviour studies that have used CoDA have largely been cross sectional in nature and limited to examining a small selection of health indicators such as adiposity, cardio-metabolic risk factors, and measures of mental health.[15] A key conclusion from this review is that the daily movement behaviour composition is associated with a variety of health outcomes.[15] The authors reported relative time spent in MVPA was favourably associated with health outcomes and associations for time reallocation estimates were consistently favourable when time was reallocated to MVPA (from other movement behaviours) and unfavourable when MVPA was removed and replaced with sleep, SED or LIPA.[15] These estimates also revealed favourable associations for health outcomes when time was removed from SED and replaced with LIPA or MVPA.[15]

To our knowledge, only one longitudinal study has used CoDA to examine the association between the full 24-hour movement behaviour composition and health.[16] The authors also used data from the NHANES and found that the composition of time spent in sleep, SED, LIPA, and MVPA was significantly associated with risk of all-cause mortality during a 5-6 year follow-up.[16] They showed in graphic format that replacing time spent in any movement behaviour with MVPA was associated with a lower mortality risk.[16] Replacing time spent in sleep or SED with LIPA and replacing time spent in SED with sleep were also favourable.[16] A key limitation of this study was the inclusion of participants with as little as one valid day of accelerometry data. A single day may not accurately or reliably reflect participants' habitual movement patterns and could result in misclassification of their movement behaviour composition.[17,18] Studies have shown four days of accelerometer data are necessary to obtain reliable measures of physical activity (ICC $\geq$ 0.80).[17,18] Another limitation was the short follow-up and number of deaths, as such the study may not have had adequate power to detect associations for all movement behaviours.[16] Furthermore, the time displacement findings were only presented graphically, so readers are unable to extract specific hazard ratio values corresponding to time displacement estimates. Confounder selection in this study is also concerning. A comprehensive measure of diet quality was missing, yet two health status covariates that lie on the causal pathway between movement behaviours and mortality were included.[16]

The objectives of this study were to use a CoDA approach to: (1) investigate whether the composition of time spent in sleep, SED, LIPA, and MVPA was associated with all-cause mortality risk; and, (2) estimate the degree to which changing time in any given movement

behaviour (sleep, SED, LIPA, or MVPA) within the movement behaviour composition was associated with changes in risk of all-cause mortality.

3.3 Study Design and Methods

3.3.1 Data Source and Study Participants

The study sample relied on data from the 2005-2006 cycles of the U.S. National Health and Nutrition Examination Survey (NHANES). The NHANES is a series of surveys and physical health measures that aim to assess the health and nutritional status of the American population.[19] The NHANES surveys a nationally representative sample using a stratified, multistage probability design of civilian, non-institutionalized participants.[19] NHANES data are publicly accessible and include survey and interview data collected in a home interview, physical and biological measures obtained in a mobile exam centre visit and follow-up record linkage for mortality.[19] Unlike other cycles of the NHANES, the 2005-2006 cycle collected objective waking movement behaviour data and information on sleep duration, which allowed us to evaluate the entire 24-hour movement behaviour composition.

Ethics approval was obtained from the National Centre for Health Statistics. Participants provided written, informed consent. Additional ethics approval for the analyses performed in this thesis was obtained from the Queen's University Health Sciences Research Ethics Board (see Appendix A).

To be included in this study, NHANES participants were required to be at least 20 years old and eligible for mortality follow-up and not pregnant at the time of their mobile examination centre visit (n=4641). Participants were excluded if they had less than four days of valid accelerometry data (defined as ≥10 hours of wear time, n=1691) or were missing self-reported

sleep data (n=4). One participant missing education covariate data was excluded. Participants who suffered an accidental death (n=15) during the follow-up period were excluded because these were not expected to be related to the movement behaviour composition. Furthermore, participants who died prior to one year of follow up (n=27) were excluded to maintain a relevant exposure time window and reduce the potential for misclassification of habitual movement behaviour patterns which may have been altered close to death. Finally, participants that reported sleeping 10 or more hours per night were excluded (n=65). Although both short and long sleep durations are associated with an increased mortality risk, the underlying mechanisms for this increased risk differ.[4,5,20–23] Long sleep duration may be indicative of underlying morbidity or subclinical disease that leads to increased mortality risk rather than long sleep duration itself being a true risk factor.[4,20,24] There were not enough long sleepers (n=65) to power a separate analysis, so the present analysis was limited to participants who reported obtaining <10 hours of sleep per night. This left a final study sample of 2,838 adult participants. A flowchart outlining participant inclusion in this study can be seen in Figure 1.

3.3.2 Exposure Variable: Movement Behaviour Composition

The exposure of interest was participants' baseline movement behaviour composition as assessed in 2005-2006. Participants were asked to wear a uniaxial accelerometer (Actigraph PAM-7164, Pensacola, FL) on their right hip for 7 consecutive days.[25] The accelerometers were programmed to start recording at 12:01AM the day after the mobile exam centre visit.[25] Participants were instructed to remove the accelerometers at bedtime and to keep them dry (e.g., remove when swimming or bathing).[25] Participants were given postage-paid padded envelopes to return the accelerometers and were remunerated $40 USD upon their return.[25] The accelerometers recorded movement intensity (magnitude of acceleration) over 10,080

consecutive 1-minute intervals – one interval for each minute of the week - and these data were used to objectively determine time spent in SED, LIPA, and MVPA.[19]

Accelerometer processing began by using an algorithm to determine non-wear time (i.e., when participants were not wearing the accelerometer). Non-wear time was defined as ≥90 consecutive minutes where the intensity count was equal to zero, allowing for up to 2 consecutive minutes with intensity counts between 1-99.[26] The next step involved removing invalid accelerometer collection days (i.e., wear time <10 hours) and participants with insufficient valid accelerometer data (i.e., < 4 valid days). [26–30] The remaining accelerometer count data was used to determine average daily time spent in SED (<100 counts per minute), LIPA (100-2019 counts per minute), and MVPA (≥2020 counts per minute).[26–30]

Information on sleep duration to the nearest hour was gathered from responses to the computer-assisted personal interview item "How much sleep do you actually get at night on weekdays or workdays?"[31] Responses were rounded to the nearest hour and could range from 1 to 12 hours/night.[31] Average sleep duration was expressed as a proportion of 24 hours. The remaining proportion of 24 hours (i.e. 24 hours minus self-reported sleep duration), was used to normalize average time spent in SED, LIPA and MVPA per day, which was then expressed as a proportion of the full 24-hour day. Any zero values for average daily time spent in SED, LIPA or MVPA were assigned the smallest possible value that we could have detected (one minute per week or ~8.6 seconds/day) to allow for a compositional approach to be used. This only applied to 8 participants.

3.3.3 Outcome Variable: Mortality

NHANES survey data were linked with mortality data through December 31st, 2015 using probabilistic record matching with the National Death Index, a database of all U.S. deaths. The National Death Index has a sensitivity of 87-98% and specificity of 99-100%.[32] Other sources of mortality information were also used including linkage with Social Security administration and active follow-up. The public-use linked mortality file was used to obtain vital status (assumed alive or assumed deceased), leading underlying cause of death and follow-up time in person-months from the date of the mobile examination centre visit to the date of death or end of the follow-up period.

3.3.4 Covariates

Covariates were investigated as possible confounders based on their known association with mortality and at least one movement behaviour, but only if they did not lie on the causal pathway. Covariate measures were obtained using self-reported questionnaires, in person interviews (including 24-hour food recalls), and direct physical measures. Several potential covariates were considered including age (continuous), sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other Hispanic, other race including multi-racial), smoking status (non-smoker, former smoker, current smoker), highest level of education (<high school, high school, college degree), family poverty-to-income ratio, body mass index (BMI) category, alcohol consumption, and diet quality. Family poverty-to-income ratio was determined by dividing family income by poverty guidelines (according to the Department of Health and Human Services) specific to family size, year and state.[33] Poverty-to-income ratio values were categorized into weighted quartiles. BMI was calculated from height and weight measurements collected by health technicians and categorized into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese class I (30-

34.9 kg/m^2), and obese class II or higher (≥35kg/m^2).[34] Alcohol consumption was categorized as non-drinkers, light-to-moderate drinkers (1-14 drinks/week for men, 1-7 drinks/week for women), and heavy drinkers (>14 drinks/week for men, >7 drinks/week for women) based on guidelines from the US National Institute on Alcohol Abuse and Alcoholism.[35] A healthy eating index score, a diet quality tool that measures conformance with the 2010 Dietary Guidelines for Americans, was derived for each participant using several dietary variables that were captured from two 24-hour food recall assessments and a food frequency questionnaire.[36] Weighted quartiles of the healthy eating index scores were calculated. A 'missing' category for participants with missing values was created for some variables (family poverty-to-income ratio, BMI, alcohol consumption, and diet quality) to avoid removing these observations from the analyses and help preserve power.

3.3.5 Analysis Strategy

Statistical analyses were performed in SAS version 9.4 (SAS Inc., Carry, NC). NHANES survey design and sample weights were accounted for in the analyses using SURVEY functions. Conventional descriptive statistics were derived (e.g., means, proportions, death rates) for the variables of interest. CoDA was used to describe the movement behaviour variables, to determine their codependence, and to assess the association between the movement behaviour composition and its components with all-cause mortality risk. CoDA is suitable for data that make up portions of a finite whole (i.e., movement behaviours in a 24-hour day).[1] Geometric means for time spent in each movement behaviour were calculated (adjusted to collectively add to 100% or 24 hours) as they better capture the central tendency of compositional data than conventional arithmetic means.[37]

The codependence between movement behaviours was assessed using pair-wise log ratio variances between all behaviours (e.g. variance of ln(sleep/SED)) and scaled to aid in interpretation [($e^{-\frac{t^2}{2}}$) where t is any log ratio variance).[1] Values for these pair-wise log ratio variances could range from zero to one; values closer to one indicated a higher codependence. Cox proportional hazards regression models were used to examine the association between the movement behaviour composition and mortality risk. Prior to fitting the regression models, the movement behaviour variables were transformed from their natural space, the constrained simplex (i.e., a 24-hour day) onto standard real space. For this step, *isometric log ratio (ilr)* transformations were used to express the movement behaviour composition as ratios of its parts (i.e., *absolute* time spent in sleep, SED, LIPA and MVPA). This transformation generated *ilr* coordinates in real space based on a sequential partition of one movement behaviour to the remaining movement behaviours (e.g., time spent in sleep *relative* to SED, LIPA and MVPA).[12] Daily activity composition allotted into four parts (sleep, SED, LIPA and MVPA) was expressed as three *ilr* coordinates $[z_{i1}, z_{i_2}, z_{i3}]$. These *ilr* coordinates captured the combined distribution of all parts of the composition (time spent in sleep, SED, LIPA, and MVPA). For example, *ilr* coordinates for sleep's relative contribution were found as follows:

$$z_{i1} = \sqrt{\frac{3}{4}} \ln\left(\frac{sleep_i}{\sqrt[3]{SB_i \cdot MVPA_i \cdot LIPA_i}}\right),\ z_{i2} = \sqrt{\frac{2}{3}} \ln\left(\frac{SB_i}{\sqrt{MVPA_i \cdot LIPA_i}}\right), and\ z_{i3} = \sqrt{\frac{1}{2}} \ln\left(\frac{MVPA_i}{\sqrt{LIPA_i}}\right)$$

After movement behaviour data were *ilr* transformed, Cox proportional hazards regression models estimating survival were built using the corresponding set of three *ilr* coordinates for each movement behaviour and the confounding variables as explanatory variables. Overall maximum likelihood test statistics from the robust regression models were used to assess the significance of the entire movement behaviour composition. The coefficient and p-value

corresponding to the first *ilr* coordinate variable were used to assess if that specific movement behaviour was significantly associated with mortality, *relative* to time spent in the remaining movement behaviours. Only the first *ilr* coordinate variable in each model was interpreted as it contained all the relevant information regarding a participant's movement behaviour composition (e.g. sleep relative to the remaining movement behaviours).[1,12] The second and third *ilr* coordinate variables were used to fit the model, but not meaningfully interpreted. A backward elimination approach with a liberal p-value (0.20) was used to remove covariates unrelated to mortality. Proportional hazards were assessed by including time-dependent covariates in the model and by visual inspection of log(-log(survival)) curves versus log survival time charts. The proportional hazards assumption held for the final models. Statistical interactions by sex and age were investigated based on their a priori consideration as potential effect modifiers. This was done by including product terms between sex and age with each movement behaviour.

The Cox proportional hazard regression parameters of the *ilr* coordinates are difficult to interpret without a back transformation. To present the results of the Cox models in a more meaningful and interpretable way, we used the results from these models to estimate the extent to which displacing time spent in one movement behaviour with one or more of the remaining movement behaviours predicted changes in mortality.[1,12] For example, we estimated the HR associated with removing 15 minutes/day from the average time spent in MVPA and adding 15 minutes/day to the average time spent in sleep. Because compositional data are relative, the time displacement predictions must be made in relation to a reference point.[1,12] We used the study sample mean movement behaviour composition as the reference point.

3.4 Results

3.4.1 Descriptive Characteristics

Descriptive baseline sociodemographic and health behaviour characteristics are summarized in Table 1. On average, participants were aged 46.4 years at baseline. There was a roughly even distribution of males and females (51.8% female). The majority (71.7%) were non-Hispanic white, high school graduates (85%), had overweight or obesity (66%), were non- or former smokers (79%), and were non-drinkers or light-to-moderate drinkers (86.6%).

The geometric means for sleep, SED, LIPA and MVPA were (in hours:minutes per day) 6:58, 10:05, 6:40, and 0:17, respectively. On average 29% of the 24-hour day was spent sleeping, 42% was spent in SED, 28% was spent in LIPA, and 1% was spent in MVPA. Values for the pair-wise log ratio variances could range from 0 (lowest codependence) to 1 (highest codependence). The greatest pair-wise log ratio variances were between sleep and SED (0.99), followed by sleep and LIPA (0.98), and LIPA and SED (0.95). The lowest variances were between MVPA and SED (0.08), MVPA and sleep (0.17), and MVPA and LIPA (0.34). Therefore, MVPA had the least co-dependency with the other movement behaviours.

3.4.2 Follow Up

The follow-up length ranged from 1 to 11 years and was 9.7 years on average. During the 26,730 person-years of follow up, a total of 393 deaths occurred for a death rate of 147 per 10,000 person-years.

All-cause mortality risk estimates associated with each movement behaviour relative to the remaining movement behaviours are presented in Table 2. After backwards elimination, the final regression models were adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption, and diet quality. The 24-hour movement behaviour composition was significantly associated with mortality risk ($p<.0001$ for the overall model fit). The HRs for these models can be interpreted as proportional change in mortality risk associated

with an increase in time spent in that behaviour relative to time spent in the remaining movement behaviours. Time spent in MVPA relative to the other movement behaviours was associated with a reduction in mortality risk (HR=.74; 95% CI = .67, .83, p<0.0001). Relative time spent in LIPA was associated with a reduction in mortality risk, although this did not reach statistical significance (HR=.75; 95% CI=.54, 1.04, p=.08). Relative time spent in SED was associated with an increase in mortality risk (HR=1.75; 95% CI= 1.10, 2.79, p=0.02). Relative time spent in sleep was not associated with mortality risk (HR=1.02; 95% CI=0.64, 1.63, p=0.90).

3.4.3 Interactions

Statistical interactions by sex and age were investigated. For sex, none of the interaction terms were statistically significant. For age, only the interaction term containing LIPA relative to the remaining movement behaviours was statistically significant (p=.002). Based on existing literature, we hypothesised that this difference in the strength of the association between relative LIPA and mortality across different ages was attributable to variations in MVPA levels and not truly a differential association.[38] Indeed, in the present study when adults accumulated similar amounts of MVPA per day, associations for LIPA relative to the remaining movement behaviours were in the same direction regardless of age. For example, when participants obtained <5 minutes per day of MVPA, relative LIPA was associated with lower mortality risk among both participants under 60 years old and participants 60 years of age and older. In contrast, when participants obtained 15 or more minutes per day of MVPA on average, this was not seen. As such, analyses are presented in all ages combined.

3.4.4 Compositional Isometric Substitution Modelling

Figures 2 and 3 depict how parameter estimates from the regression models were used to estimate changes in mortality risk associated with equivalent time displacements from the mean movement behaviour composition. Figure 2 shows predicted changes in mortality risk associated with replacing time spent in one movement behaviour with another movement behaviour (e.g., removing 15 minutes/day of sleep and adding 15 minutes/day of SED). Figure 3 depicts estimated changes in mortality risk associated with displacing time spent in one movement behaviour to or from a combination of the remaining movement behaviours based on the relative proportional daily contribution of behaviours. For example, when 15 minutes/day was removed from the mean time spent in MVPA (Table 3, Figure 3), 15 minutes/day was proportionally redistributed to the remaining movement behaviours such that 4.4 minutes were added to sleep, 6.4 minutes were added to SED and 4.2 minutes were added to LIPA. Values for estimated HRs associated with 15-minute/day time displacements can be seen in Tables 3 and 4. Additional hazard ratios for time displacement estimates ranging from 15 minutes per day to 120 minutes per day can be found in Appendix C.

Estimates revealed an increased mortality risk associated with reallocating 15 minutes/day of MVPA into sleep (HR=1.78; 95% CI=1.47, 2.15), SED (HR=1.80; 95% CI=1.46, 2.22), LIPA (HR=1.76; 95% CI=1.46, 2.13), or a combination of sleep, SED, and LIPA (HR=1.78; 95% CI=1.47, 2.15). Conversely, reallocating time out of sleep, SED, LIPA, or their combinations into MVPA was associated with a reduction in mortality risk (HRs for 15-minute/day displacements ranged from 0.84-0.86). SED predictions showed that decreasing SED by 15 minutes/day by increasing time spent in any of the other movement behaviour was associated with a lower mortality risk (HRs=0.84-0.99), whereas increasing SED by 15 minutes/day from time spent in any other movement behaviour was associated with greater risk

(HRs=1.01-1.80). Reallocating 15 minutes per day to LIPA from sleep or SED was estimated to be associated with a lower mortality risk (HR=0.99; 95% CI=0.99, 0.99 and HR=0.98; 95% CI:=0.96, 1.00, respectively). The predictions also suggested that redistributing 15 minutes to sleep from SED was not associated with a change in mortality risk (HR=0.99; 95% CI=0.97, 1.01), but when sleep replaced MVPA or LIPA it was associated with an increased mortality risk (HR=1.78; 95% CI=1.47, 2.15 and HR=1.01; 95% CI= 1.01, 1.01). The estimates in Figures 2 and 3 also suggest the relationship between changes in MVPA and mortality risk is asymmetrical. For instance, reallocating 15 minutes of MVPA to the remaining movement behaviours (Figure 3) was associated with a larger increase in risk (78%; 95% CI=46%, 117%) than the reduction in risk (15%; 95% CI=10%, 20%) associated with redistributing 15 minutes of time from the remaining movement behaviours into MVPA.

3.5 Discussion

This study used a compositional data analysis framework to investigate the relationship between the daily movement behaviour composition and all-cause mortality. The composition of daily time spent in sleep, SED, LIPA, and MVPA was significantly associated with mortality risk. The amount of time spent in MVPA relative to the remaining behaviours was significantly associated with a lower mortality risk whereas relative time spent in SED was significantly associated with an increased mortality risk. Estimates suggest reallocating time into MVPA from any of the other movement behaviours would be associated with a lower risk of mortality. Correspondingly, removing time from MVPA and adding this to any other movement behaviour would be associated with a greater risk of mortality. This relationship was asymmetrical, such that removing MVPA was associated with a greater reduction in mortality risk than the corresponding increase in mortality risk associated with adding MVPA. This asymmetrical

relationship is consistent with other studies that have examined relationships between MVPA relative to the remaining movement behaviours and health outcomes.[1,39]

In 2019, McGregor et al. published the only study to date using CoDA to examine the relationship between the 24-hour movement behaviour composition and all-cause mortality.[16] Similar to this paper, McGregor et al. used data from the NHANES and found that the movement behaviour composition was significantly associated with mortality over five to six years in a sample of 1,592 Americans 50-79 years of age.[16] Though there was no statistically significant association between the amount of time spent in MVPA relative to the remaining behaviours and all-cause mortality in the fully adjusted model, the association did show a trend towards significance (p=.09) in a direction consistent with the present study.[16] This difference can potentially be explained by the smaller sample size and shorter follow up in McGregor et al.'s study and over adjustment for two covariates (self-assessed health and physical limitations on movement) that lie on the causal pathway between movement behaviours and all-cause mortality.[16] Over adjustment for factors that lie on the casual pathway is a problem because it can bias effect estimates (HRs in this case) and distort the true relationship between an exposure and outcome.[40] Typically, this kind of over adjustment could bias results towards the null, so true relationships may be obscured.[40] This paper further reports on associations between relative time spent in sleep, SED and LIPA and all-cause mortality, which are not reported by McGregor et al.

One other study by Rosen et al. investigated the relationship between the waking movement behaviour composition and all-cause mortality but did not include sleep data.[41] Lacking information on sleep limited the ability of these authors to consider all co-dependent parts of the 24-hour movement behaviour composition within a compositional analysis paradigm.[41] They found that time spent in SED relative to LIPA and MVPA was significantly

associated with greater mortality risk (HR=2.24; CI=1.41, 3.56). Replacing SED with LIPA or MVPA was associated with reductions in mortality risk. The present study expanded on this by measuring all parts of the full 24-hour movement behaviour composition, including sleep.

Key implications of our study include recommendations to preserve time spent in MVPA over time spent in other movement behaviours, especially for those with low levels of MVPA. Among those spending little to no time in MVPA, large reductions in mortality risk can occur by increasing time in MVPA regardless of which other movement behaviour that time is taken from. Limiting time spent in SED when possible is also recommended; reducing SED would reduce mortality risk irrespective of what movement behaviour that time is reallocated to. Insufficient levels of sleep should be addressed by reallocating time to sleep from SED, but not from physical activity (especially MVPA).

Key strengths of this study include its objective measurement of physical activity and SED, its ability to examine the temporal relationship between the daily movement behaviour composition and all-cause mortality due to the prospective cohort study design, and the use of a novel analytic approach to analyze 24-hour movement behaviour data in a large sample of adults. Moreover, this study used data from a nationally representative sample of Americans and the results should be generalizable to similar populations. There are also several limitations. Accelerometers, while an improvement over self-reported data, are imperfect measurement tools. The waist-worn accelerometers used in NHANES best measure step-based movements.[42] MVPA would be underestimated if it stemmed from participation in certain activities such as cycling, resistance training or swimming. Non-differential misclassification could occur in this case, which may have attenuated our effect estimates towards the null. Furthermore, a cut-point of <100 activity counts per minute was used to classify SED. This would have resulted in non-

differential misclassification of some LIPA, such as time spent standing, being categorized as SED. This may have biased the relative importance of LIPA and the relative importance of SED towards the null. Accelerometers were removed at night and sleep duration was self-reported. This is likely to result in non-differential sleep misclassification, which may have attenuated associations for the relative importance of sleep. Furthermore, a large proportion of NHANES participants (36.4%) were removed from the analyses due to insufficient accelerometer data. If the relationship between daily movement behaviour composition and all-cause mortality risk was different between those with and without adequate accelerometer data, our results may be biased. Lastly, the movement behaviour composition was assessed using 4-7 days of accelerometer data. This time period may not reflect some of the participants' habitual movement patterns.

More research is needed applying CoDA techniques in movement behaviour research to further explore associations with health. For example, exploring potential differences in work-related SED and leisure-time and/or screen-time related SED. This could help elucidate possible differential effects of separate domains of SED. LIPA could also be broken up into lighter intensity LIPA and higher intensity LIPA to delve further into the importance of various behaviour intensities. Future studies should aim to objectively measure all parts of the movement behaviour composition in conjunction with self-reported time-use logs to reduce the potential for misclassification. Researchers should also consider collecting repeated measures of the movement behaviour composition to better capture habitual movement patterns over time and further elucidate temporal relationships.

3.6 Conclusion

CoDA can help provide insight into the co-dependent relationships between movement behaviours and survival. In this study, the relative amount of time spent in MVPA and SED was

significantly associated with a reduction and increase in mortality risk, respectively. Our estimates suggest replacing time spent in sleep, SED, or LIPA with MVPA or replacing time spent in SED with any other movement behaviour would be associated with lower mortality risk. Our results also suggest that insufficient sleep duration should be addressed by reallocating time into sleep from SED but not from LIPA or MVPA.

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Table 1. Participant characteristics

Variable	n	%	Weighted N	Weighted %
Sex				
Male	1,461	51.5	98,445,733	48.2
Female	1,377	48.5	105,912,178	51.8
Age				
20-39	829	29.2	77,648,076	38.0
40-60	995	35.1	81,118,121	39.7
≥60	1,014	35.7	45,591,714	22.3
Race/Ethnicity				
Mexican American	573	20.2	16,113,144	7.9
Other Hispanic	82	2.9	7,252,096	3.5
Non-Hispanic white	1,453	51.2	146,521,928	71.7
Non-Hispanic black	620	21.9	23,438,894	11.5
Other (including multi-racial)	110	3.9	11,031,849	5.4
Education				
< High school	726	25.6	30,712,002	15.0
High school	1,513	53.3	118,267,386	57.9
College graduate	599	21.1	55,378,522	27.1
Poverty-to-income ratio				
Below poverty threshold (<1)	395	13.9	17,970,937	8.8
At or above poverty threshold (≥1)	2,327	82.0	180,200,584	88.2
Missing	116	4.1	6,186,389	3.0
BMI Category				
Underweight	36	1.3	3,117,177	1.5
Normal weight	817	28.8	65,554,605	32.1
Overweight	993	35.0	66,951,444	32.8
Obese class I	580	20.4	38,713,305	18.9
Obese class II +	401	14.1	29,269,908	14.3
Missing	11	0.4	751,472	0.4
Alcohol consumption				
Non-drinker	935	33.0	56,036,438	27.4
Light-to-moderate drinker	1,536	54.1	120,840,686	59.1
Heavy drinker	188	6.6	16,811,619	8.2
Missing	179	6.3	10,669,167	5.2
Smoking status				
Non-smoker	1,496	52.7	108,550,690	53.1
Former smoker	787	27.7	529,45,457	25.9
Current smoker	555	19.6	428,61,763	21.0
Healthy eating index				
Poor (<50)	1,250	44.1	95,280,809	46.6
Needs improvement (50-80)	1,418	50.0	97,650,947	47.8
Good (80-100)	79	2.8	5,915,565	2.9
Missing	91	3.2	5,510,589	2.7

Table 2. Compositional Cox regression model estimates

Model	Sleep		SED		LIPA		MVPA	
p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
<.0001	1.02 (.64, 1.63)	0.9	1.75 (1.10, 2.79)	0.02	0.75 (.54, 1.04)	0.08	0.74 (.67, .83)	<.0001

Note: Adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption, and diet quality. Hazard ratios can be interpreted as proportional change in mortality risk associated with an increase in time spent in that behaviour relative to time spent in the remaining movement behaviours.

Table 3. Estimated hazard ratios for displacing 15 minutes between movement behaviours

Remove 15 minutes per day from	Add 15 minutes per day to			
	Sleep	SED	LIPA	MVPA
Sleep	--	1.01 (0.99, 1.03)	0.99 (0.99-0.99)	0.85 (0.81, 0.89)
SED	0.99 (0.97, 1.01)	--	0.98 (0.96, 1.00)	0.84 (0.78, 0.90)
LIPA	1.01 (1.01, 1.01)	1.02 (1.00, 1.04)	--	0.86 (0.82, 0.90)
MVPA	1.78 (1.47, 2.15)	1.80 (1.46, 2.22)	1.76 (1.46, 2.13)	--

Note: Data presented as hazard ratio (95% confidence interval). All estimates have been adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption, and diet quality. Hazard ratios reflect the estimated change in mortality risk associated with reallocating 15 minutes from the movement behaviour in the column to the movement behaviour in the row using the mean movement behaviour composition as the reference.

Table 4. Estimated hazard ratios for reallocating 15 minutes from one movement behaviour to the remaining movement behaviours proportionally (and vice versa)

Movement behaviour	Remove 15 minutes of column behaviour and add to remaining behaviours	Add 15 minute to column behaviour from remaining behaviours
Sleep	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
SED	0.98 (0.96, 1.00)	1.02 (1.00, 1.04)
LIPA	1.01 (1.00, 1.03)	0.99 (0.98, 1.00)
MVPA	1.78 (1.46, 2.17)	0.85 (0.80, 0.90)

Note: Data presented as hazard ratio (95% confidence interval). All estimates have been adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption and diet quality. Hazard ratios reflect the estimated change in mortality risk associated with reallocating time from one movement behaviour to the remaining movement behaviours proportionally (or vice versa) using the mean movement behaviour composition as the reference.

Figure 1. Flowchart of study participants

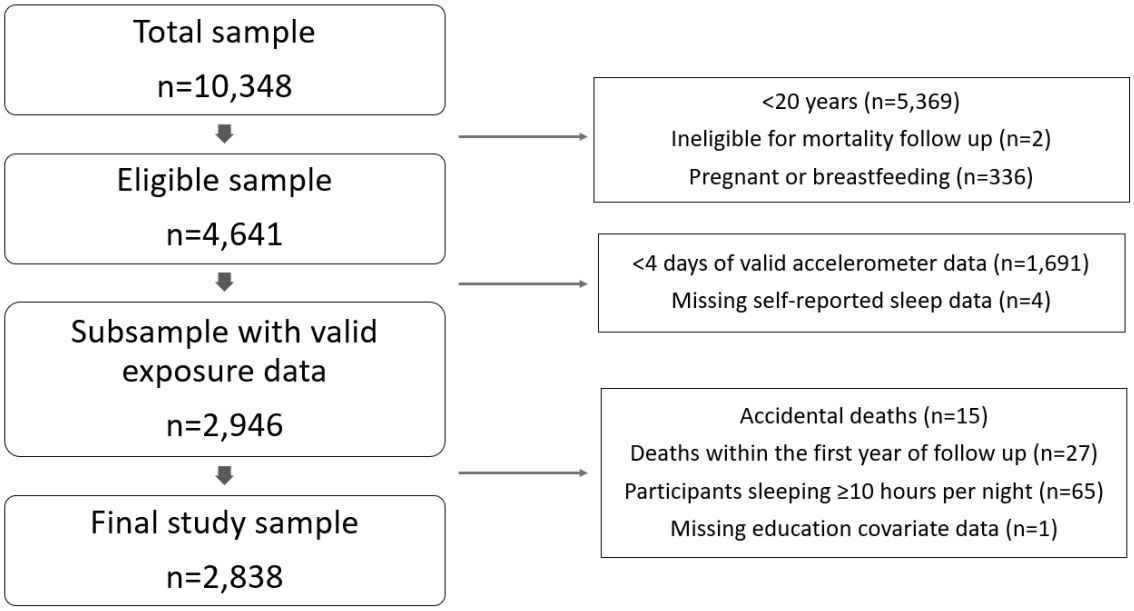
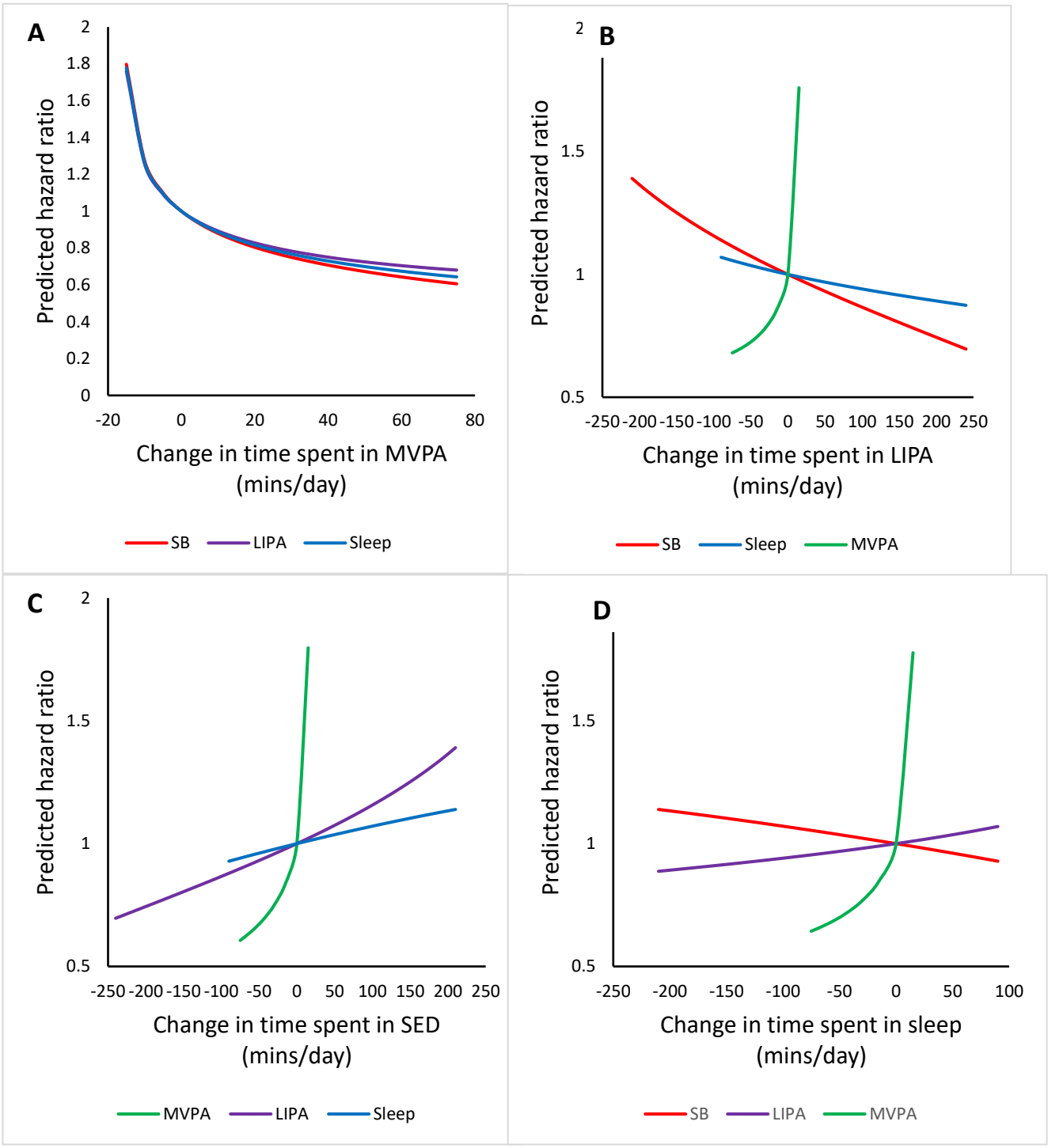


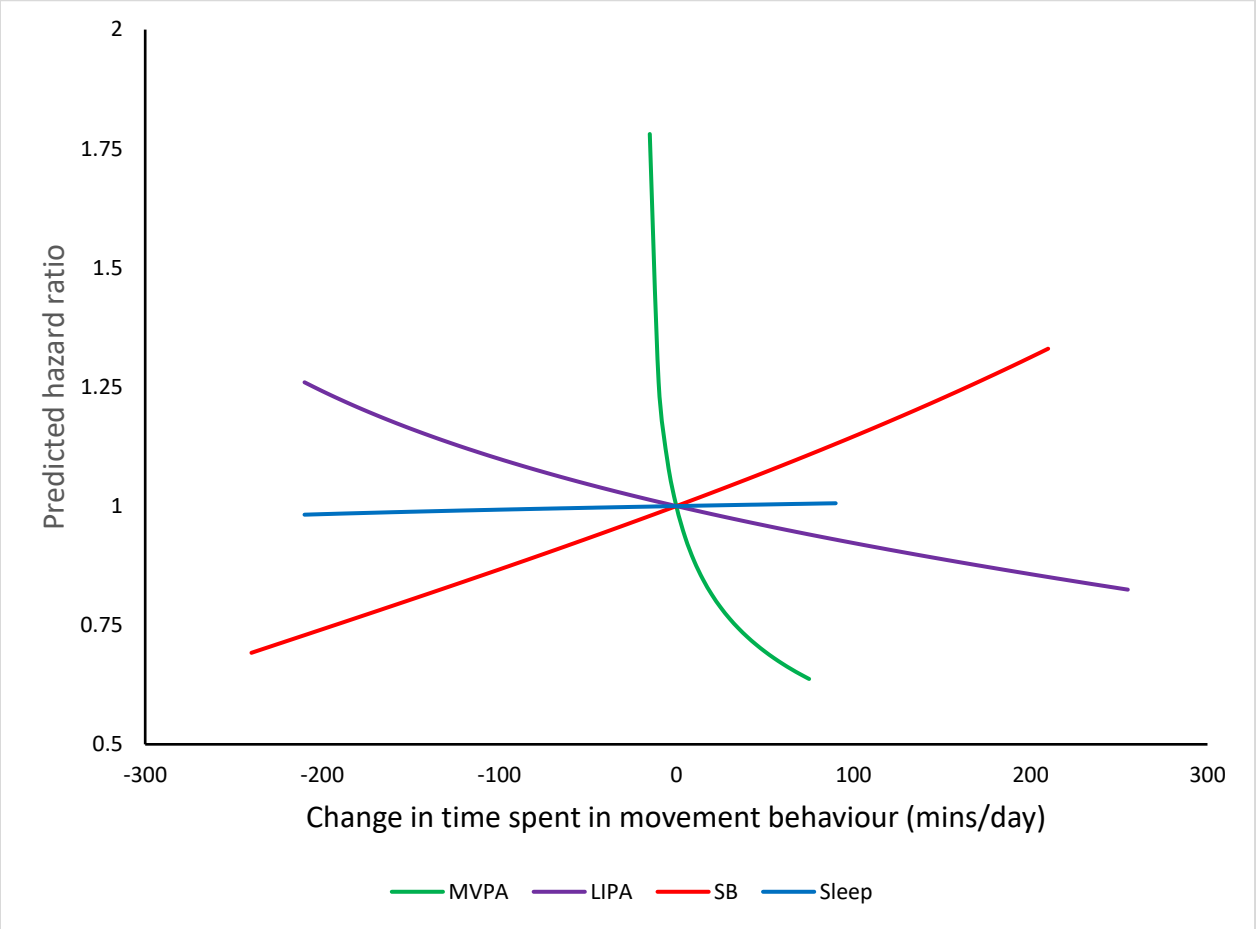
Figure 2. Estimated hazard ratios associated with hypothetical time displacements from one movement behaviour to another



Note: All estimates have been adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption and diet quality. Hazard ratios reflect the hypothetical change in estimated mortality risk associated with reallocating time spent in a) MVPA, b) LIPA, c) SED, and, d) sleep based on parameter estimates from compositional regression. The difference in minutes/day are

modelled around the mean movement behaviour composition (reference). Time is substituted between the movement behaviour on the x-axis and the movement behaviour indicated by the line. For example, the top right shows estimated hazard ratios associated with hypothetically changing the mean amount of time spent in LIPA. As more minutes are added to LIPA (positive x-axis), it is estimated that the associated hazard ratio will increase if this time is taken from MVPA, but decrease if this time is taken from sleep or SED. Substitutions were not made beyond the range of the 2.5^{th} to 97.5^{th} percentile of minutes per day spent in each movement behaviour (e.g. no more than 75.4 minutes per day were added to the mean 16.8 minutes per day spent in MVPA).

Figure 3. Estimated hazard ratios associated with hypothetical time displacements from one movement behaviour to the remaining movement behaviours (and vice versa)



Note: All estimates have been adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption and diet quality. Hazard ratios reflect the hypothetical change in estimated mortality risk associated with reallocating time between one movement behaviour and the remaining movement behaviours based on parameter estimates from compositional regression. The difference in min/day are modelled around the mean movement behaviour composition (reference). For example, if more time is hypothetically allocated to LIPA and removed from the remaining movement behaviours (positive x axis; purple line), the estimated hazard ratio for this association decreases. Substitutions were not made beyond the range of the 2.5th to 97.5th percentile of minutes per day spent in each movement behaviour (e.g. no more than 75.4 minutes per day were added to the mean 16.8 minutes per day spent in MVPA).

Chapter 4

General Discussion

4.1 Study Summary

The purpose of this thesis was to investigate the relationship between the 24-hour movement behaviour composition and all-cause mortality using a compositional data analysis (CoDA) approach. Data were obtained from the 2005-2006 cycle of the U.S. National Health and Nutrition Examination Survey (NHANES), which surveys a representative sample of the American population. Our study included 2,838 adult participants (≥20 years) who were followed for an average of 9.7 years. Waking measures of movement behaviours including sedentary behaviour (SED), light intensity physical activity (LIPA), and moderate-to-vigorous intensity physical activity (MVPA) were obtained directly by waist worn accelerometers. Measures of sleep duration were obtained from self-reported questionnaire responses. Isometric log ratio transformations were performed to facilitate the use of traditional regression techniques with compositional data. Cox regression models were fit using the transformed coordinates that account for all aspects of the movement behaviour composition. Model p-values were used to assess whether the movement behaviour composition was significantly associated with all-cause mortality risk. Associations between each movement behaviour relative to the remaining movement behaviours and mortality risk were assessed. Model coefficients were used to estimate changes in mortality risk associated with displacing time spent in one movement behaviour to or from one or more of the remaining movement behaviours.

4.2 Summary of Major Findings

A key finding of this study is that the composition of daily time spent in sleep, SED, and different intensities of physical activity was significantly associated with all-cause mortality risk. This means that the distribution of time spent in movement behaviours throughout the 24-hour day is important for survival.

The amount of time spent in MVPA relative to time spent in the other movement behaviours was associated with a significant reduction in mortality risk. Conversely, the amount of time spent in SED relative to time spent in the other movement behaviours was associated with a significant increase in mortality risk. Relative time spent in LIPA tended to be associated with a reduction in mortality risk, whereas relative time spent in sleep was not meaningfully or significantly associated with mortality risk. This suggests that in terms of daily waking movement, a priority should be placed on participating in physical activities, including higher intensities of activity when possible, and limiting time spent in SED.

Time displacement estimates revealed reallocating time into MVPA was consistently associated with reduced mortality risk irrespective of which movement behaviour(s) this time was taken from. Correspondingly, an associated increase in mortality risk was observed when time was removed from MVPA and reallocated to any of the other movement behaviours. This increased risk was especially sharp among those with low initial levels of MVPA which is in line with other movement behaviour literature.[1,2] This suggests that time spent in MVPA should be preserved over time spent in other movement behaviours, especially for those with low levels of existing MVPA. When MVPA is low, an increase in MVPA may be accompanied by a large reduction in mortality risk, regardless of which other movement behaviour that time is taken from. Displacing time spent in SED with an equal amount of time spent in any of the other

movement behaviours was associated lower mortality risk, whereas adding time to SED from sleep, LIPA, or MVPA was associated with greater mortality risk. This indicates reducing SED would reduce mortality risk irrespective of what movement behaviour that time is reallocated to and conversely increasing time spent in SED would increase mortality risk regardless of which other movement behaviour that time is taken from. Reallocating time to LIPA from sleep or SED was associated with lower mortality risk and reallocating time to sleep was favourably associated with survival when this time came from SED, but not when time was taken out of LIPA or MVPA. These findings suggest inadequate levels of sleep should be met by reallocating time to sleep from SED, but not from LIPA or MVPA. The main findings from this research are consistent with other studies exploring compositional associations of movement behaviours with health.[3]

4.3 Strengths

This thesis has several strengths. First, a novel analytic approach suitable for compositional movement behaviour variables was applied in a large sample of adults. To date, only a small selection of studies have used CoDA to examine relationships between the full 24-hour movement behaviour composition and health indicators.[3] Furthermore, our study applied a prospective cohort design allowing us to assess potential temporal relationships between the 24-hour movement behaviour composition and health. Currently, this has only been explored in one other longitudinal study.[4] The present study expanded on this previous longitudinal study by including a greater sample size and longer follow-up duration to enhance our power to detect associations, improving confounder selection, and using a more valid approach of assessing habitual movement patterns.[4–6] A further strength of this thesis includes its reliance on objective measures of waking movement behaviours to overcome limitations inherent in self-reported

estimates. Moreover, this study used data from a nationally representative sample of Americans and the results should be generalizable to comparable adult populations.

4.4 Internal Validity

Internal validity is defined as how accurately the results of a study reflect what is truly happening in the sample population, assuming the results are not due to chance.[7] In epidemiological studies, prominent threats to internal validity include selection bias, information bias, and confounding.

4.4.1 Chance

Due to random sampling error, in any study the observed results may differ from truth simply because by chance the people who were in the study differed in some way from the population average.[7] In this thesis, the potential for chance to explain our results was assessed using confidence intervals and p-values. The probability that our results were observed due to chance is very low for investigations between all-cause mortality and the entire 24-movement behaviour composition, relative MVPA, relative SED, and fairly low for relative LIPA ($p<.001$; $p<.001$; $p=.02$; $p=.08$). However, results for the relationship between sleep relative to the remaining movement behaviours and mortality risk have a high probability of being seen by chance ($p=0.9$).

4.4.2 Selection Bias

Selection bias can occur when participants included in the study sample are systematically different than the population they represent, in this case adults in the United States (≥20 years old) who are not pregnant or breastfeeding.[7] Given the objectives of this thesis were to investigate an etiological relationship, the potential for selection bias is only a concern if the

relationship between time spent in movement behaviours and mortality risk differed as a result of study selection (i.e., the study population differed systematically from the population it represented on the basis of both the exposure and outcome).

A common source of selection bias is *volunteer bias*, whereby those who elect to participate in a study differ systematically from those who do not participate.[7] While the NHANES is not a volunteer sample in the traditional sense (a pre-defined sample of U.S. residents were asked to participate), those that agreed to participate could differ systematically from those who did not agree to participate. To mitigate this potential, cash incentives and repeated calls were used to encourage survey participation.[8] The overall unweighted response rate of those that participated in the mobile examination centre visit was 77.4%.[9] The NHANES dataset provides sample weights for participants who completed this visit that reflect the unequal probability of selection, adjustment for non-responders and adjustment to independent population controls.[8] Perhaps the bigger concern around selection bias for my thesis project was that a large proportion of eligible NHANES participants (38.8%) were excluded from the analyses. These participants were primarily excluded due to insufficient accelerometer data (36.4% of the eligible sample). If the relationship between daily movement behaviour composition and all-cause mortality risk was different between those with and without adequate accelerometer data, our results may be biased. Compared to those who were excluded, participants included in our final study sample were, on average, significantly older ($p<.001$), with higher diet quality ($p<.001$), and family poverty-to-income ratio values ($p<.001$). More participants included in our study sample were non-Hispanic white (51.2% versus 49.5%) completed post-secondary education (21.1% versus 17.1%), were never smokers (52.7% versus 49.8%), and non-drinkers (35.2% versus 33%). To mitigate the potential for bias, I adjusted the

sample weighting for those with complete exposure (accelerometer and sleep) data. This weighting accounts for differences in age, sex, and ethnicity. Furthermore, a large body of evidence has shown the relationships between movement behaviours and mortality are consistent across many different populations, genders, ages, races/ethnicities, and socio-economic levels.[10,11] As this is an etiological relationship that holds true across many different populations, we are confident of our findings.

Another potential source of selection bias is *loss to follow up bias*, whereby participants lost to follow up have differential movement behaviour levels and mortality rates than those remaining in the study. Because follow up was obtained via linkage with the National Death Index, it was extremely complete. In fact, of the 10,348 original NHANES 2005-2006 cycle participants, only two could not be linked due to insufficient identifying data. The potential for *loss to follow up bias* in this study is extremely low.

4.4.3 Information Bias

Information error can occur when any intentional or unintentional error is made in measuring an exposure, covariate, or outcome.[7] It can lead to information bias if these errors are made systematically.[7] When information error and resulting misclassification occur equally across comparison groups, it is considered to be non-differential. Typically, non-differential misclassification tends to bias effect estimates towards the null and reduces the power of a study to detect a significant association. Conversely, when misclassification occurs to a greater extent in a particular comparison group, it is considered differential. This could bias effect estimates away from or towards the null.

Exposure measurement: As discussed, this study objectively measured all waking parts of the movement behaviour composition using an accelerometer and sleep duration was obtained from self-reported responses. The movement behaviour composition was assessed using 4-7 days of accelerometer data. Though it is possible that this time period may not reflect some participants' habitual movement patterns, studies have shown four days of accelerometer data are sufficient to obtain reliable measures of physical activity (ICC $\geq$ 0.80).[12,13] While 7 days of data may slightly increase reliability (ICC=0.90), more than 7 days has not been shown to further improve the reliability of physical activity estimates in a meaningful way.[12]

Measures of sleep, SED, LIPA, and MVPA were only collected at a single time point, yet our true exposure time window of interest is habitual movement patterns throughout adult life. The accelerometer data captured at study onset is intended to not only reflect habitual movement at the time of data collection, but also be a proxy for lifetime movement patterns. Movement behaviour levels may have changed throughout the follow-up period, which was not be captured and may contribute to potential misclassification of habitual movement patterns throughout the study duration.

Accelerometers are considered the 'gold standard' for measuring physical activity in natural settings, but they are by no means a perfect measurement tool.[14] Accelerometers best capture step-based movements and underestimate the intensity of some physical activities stemming from non-step-based movements such as cycling, resistance training and swimming. This would tend to lead to an underestimation of MVPA level and non-differential misclassification, which could attenuate potential associations. MVPA was likely underestimated to a similar extent of that which is typical in the literature. This misclassification could only be differential if those who died during follow-up were also more or less likely than those who did

not die to partake in movements such as cycling, resistance training, or swimming. There is no known evidence to date of this occurring, so misclassification of accelerometer measured MVPA in this study is likely to be non-differential.

Accelerometers were also used to measure SED. Using this method, time spent in SED was inferred from a lack of movement detected by the waist-worn accelerometer. The consensus definition of SED stipulates that this very low energy expenditure activity takes place in a sitting or reclining position.[15] It was not possible to determine postural information from the accelerometer devices, so some LIPA may have been misclassified as SED. This is of particular concern for very light activities such as quiet standing, when there is little movement at the hip and may lead to standing time being misclassified as SED. Misclassification would most likely have affected all participants regardless of if they subsequently died during follow-up and thus been non-differential. As a result of this misclassification, associations for relative SED and LIPA were likely biased towards the null.

Accelerometer "reactivity" is another potential form of information bias wherein participants are conscious of the fact they are wearing a device that measures movement which may incite them to alter their movement behaviours in a socially desirable manner (e.g., be more physically active than usual).[16] To mitigate the potential for this behaviour adaptation to occur, the accelerometers used in this study provided no feedback or output (e.g., step count) to participants. In this respect, the monitors are starkly different from common consumer-grade monitors, such as the Apple Watch or Fitbit, where real-time feedback is provided and where participants can be prompted to move. Although examining accelerometer "reactivity" is commonly raised as a potential concern, studies have shown there is little evidence of it occurring.[16,17] For example, a study by Davis et. al. revealed limited evidence of potential

reactivity pertaining to total daily step count which only occurred when the first day of monitoring was a Monday (4-4.5% average decrease in step count on subsequent days).[16] More importantly for this thesis, their study showed no evidence of reactivity in adults pertaining to MVPA levels.[16]

Sleep duration was measured from self-reported responses of typical sleep per day. These types of tools generally capture time in bed rather than accurately quantifying sleep duration. Participants struggle to differentiate total sleep duration from time in bed, the latter of which typically fails to account for differences in sleep latency and efficiency.[18] Furthermore, reported typical sleep per night may not be reflective of average sleep length over the days when study accelerometers were worn. Consequently, it is likely that there was some misclassification of sleep time. This was likely non-differential and would have tended to bias associations for relative sleep towards the null.

Outcome measurement: All-cause mortality status was obtained via linkage with the National Death Index, a database containing all deaths in the United States. A comparative review found the National Death Index to have a high sensitivity (87-98%) and specificity (99-100%).[19] The sensitivity and specificity were likely even higher in the present study as additional sources of mortality information were also used in the NHANES to complement linkage with the National Death Index including linkage with Social Security administration and active follow-up. There is no reason to believe any measurement error in mortality status would be differential with respect to participants' movement behaviour profiles.

4.4.4 Confounding

Confounding can occur when the relationship between an exposure and outcome is distorted or masked by the effects of another variable that is related to both the exposure and outcome, but does not lie on the causal pathway for the relationship of interest.[7] Analyses conducted in this study controlled for several potential confounders previously identified in the literature including age, gender, education, family poverty-to-income ratio, body mass index, smoking status, alcohol consumption, and diet quality. However, it is possible that the observed results in this study were skewed due to residual confounding caused by imprecise measurement of confounding variables.

4.5 External Validity

External validity refers to whether study results can be generalized to other populations outside of the sample population.[7] This study relied on data from the 2005-2006 cycles of the NHANES, a nationally representative sample using a stratified, multistage probability design of civilian, non-institutionalized participants.[20] The present study used statistical procedures that accounted for the complex survey design. Assuming results are internally valid, they should be generalizable to civilian, non-institutionalized American adults who met our inclusion criteria (i.e., were not pregnant and were at least 20 years of age). Furthermore, the relationship between movement behaviours and mortality risk is biologic in nature and consistent in people of different genders, ages, races/ethnicities, and socioeconomic circumstances.[10,11] Therefore, the results are likely also generalizable to adults in comparable countries.

4.6 Causation

In 1965, Sir Bradford-Hill proposed nine criteria meant to help assess whether an observed relationship was likely to be causal. Five of these criteria remain widely used in epidemiological research today and are discussed below in relation to my findings.

4.6.1 Temporality

Temporality refers to the necessity of an exposure to precede the development of the outcome of interest in order to be considered potentially causal.[7] This is the only Bradford-Hill criterion considered an absolute requirement to establish causality. This longitudinal study assessed movement behaviour patterns at baseline while all participants were still living and before follow-up began. Therefore, we have strong reason to be confident that this criterion was met.

4.6.2 Strength of Association

The stronger an observed association, quantified in this study by the hazard ratio, the less likely it is a result of bias or confounding.[7] In the present CoDA-based study, there were 25 parameters to interpret: 1) one result reflecting whether the 24-hour movement behaviour composition as a whole is related to mortality risk; 2) four results pertaining to whether the relative contributions of time spent in MVPA, LIPA, SED, and sleep are associated with all-cause mortality risk; and, 3) twenty results pertaining to whether different time reallocations are associated with changes in mortality risk (e.g., reallocating time from MVPA to SED, reallocating time from SED to MVPA, reallocating time from LIPA to all the other movement behaviours proportionally, etc.). Because of all these results, the strength of observed associations between the movement behaviour composition and all-cause mortality risk varied

depending on the specific parameter under investigation. Firstly, the collective 24-hour movement behaviour composition was strongly associated with all-cause mortality. Second, relative time spent in both MVPA and SED were strongly associated with mortality risk, relative time spent in LIPA showed a modest association and relative time spent in sleep showed no association. Reallocating time between MVPA and any or all of the remaining behaviours was strongly associated with changes in mortality risk. Reallocating time between LIPA and SED was associated with modest to moderate changes in mortality risk (associations were stronger when longer amounts of time were reallocated). Associations were also modest to moderate when time was reallocated between LIPA or SED and the other movement behaviours proportionally (again, associations were stronger when longer amounts of time were reallocated). Reallocating time between sleep and LIPA showed modest associated changes in mortality risk and reallocating time between SED and sleep weak associated changes. Reallocating time between sleep and the other movement behaviours proportionally did not reveal meaningful associations. Overall, the strength of associations varied by the parameter of interest, where some were more strongly associated with mortality risk than others. Results revealed even small changes in the amount of time spent in MVPA were strongly associated with changes in mortality risk.

4.6.3 Consistency

An association found consistently across a range of study types and populations provides assurance that the observed association is not artefact.[7] It is important to keep in mind differences in the statistical significance of associations alone does not dictate a set of studies are inconsistent. Effect estimates may be quite similar even if some are significant and others are not. Such variations in statistical significance may arise from differences in standard errors and

study sample sizes.[7] Only one other study to date has examined the relationship between the full 24-hour movement behaviour composition and all-cause mortality risk using CoDA.[4] Of the regression estimates that were reported by the authors, comparable estimates were found in the present study.[4] Furthermore, in a recent systematic review of studies that examined relationships between the movement behaviour composition and health indicators, the overall direction of relationships for each movement behaviour relative to the remaining behaviours were comparable with those in the present study.

Our findings for MVPA are consistent with the immense body of literature that has continually demonstrated higher levels of MVPA are significantly associated with reductions in mortality risk.[10,11,21–26] Our study is in agreement with a substantial amount of evidence that shows greater time spent in SED is associated with higher mortality risk and considerable evidence that reveals greater LIPA participation is associated with reductions in mortality risk.[27–33] The relative contribution of sleep was not associated with mortality, however, replacing sleep with SED (but not physical activity), was associated with greater mortality risk. This is consistent with previous sleep literature wherein lower levels of sleep are associated greater mortality risk. It is important to note that the previous evidence typically examined associations between these individual movement behaviours and mortality without considering their co-dependence on the other movement behaviours.

4.6.4 Dose-Response Relationship

If an exposure is causal, then the risk of developing an outcome may likely be related to the amount or 'dose' of exposure.[7] This is called the dose-response relationship (or biological gradient). The time reallocation estimates found in the present study revealed a curvilinear

relationship between relative MPVA and all-cause mortality risk, where greater reductions in risk were observed when time spent in MVPA was increased among those with low MVPA levels (regardless of what movement behaviour MVPA replaced). When time spent in LIPA or sleep was replaced with SED a fairly linear increase in mortality risk was observed, though this increased risk appears to become slightly sharper at the upper limits of time spent in SED. These are consistent with other findings.[4]

4.6.5 Biological Plausibility

This criterion proposes that when assessing the potential for causality, the plausibility of a relationship of interest should be considered.[7] Relationships between movement behaviours and mortality risk are biologically plausible. A plethora of health benefits associated with participating in physical activity have been identified. The effects of physical activity are seen all throughout the body (acting on metabolic systems, in cells, in tissues etc.) and these play a role in the prevention of numerous diseases and conditions that can lead to death. For example, plausible mechanisms by which physical activity may protect against coronary heart disease morbidity and mortality include improving endothelial function, reducing plaque progression, stabilizing vulnerable plaques to prevent their rupture, reducing myocardial oxygen demand, decreasing thrombosis, enhancing collateralization to restore blood flow, and decreasing the release of inflammatory mediators from skeletal muscle and adipose tissue.[34] Suggested mechanisms for how SED relates to mortality risk include changes in cardiovascular risk factors (glucose tolerance, blood pressure, high-density-lipoprotein cholesterol) and impairments in vascular health. For example, prolonged sitting is associated with changes in hemodynamic stimuli, such as shear stress, which can mediate vascular dysfunction.[35] Furthermore, the presence of low-grade inflammation and metabolic disruptions associated with prolonged sitting

may also contribute to impairments in vascular health.[35] Proposed biological mechanisms by which short sleep duration is related to mortality include an increase in cardiometabolic risk via disruptions in metabolic systems, endothelial function, the autonomic nervous system, insulin and glucose regulation, and inflammation.[36–39]

4.7 Public Health Implications

Public health guidelines for sleep, SED and physical activity have historically focussed on recommendations for individual movement behaviours in isolation. Likewise, most movement behaviour interventions have centred on changing time spent in physical activity, SED, or sleep as separate individual components while neglecting their compositional nature. However, a change in one movement behaviour (e.g., increase in sleep) must correspond to an equal and opposite change in one or more of the remaining movement behaviours (e.g. decrease in SED). Future public health guidelines should account for the entire movement behaviour composition, acknowledging that sleep, SED, LIPA, and MVPA are all relative parts of the 24-hour day. In fact, a substantial portion of my student funding stemmed from conducting research to inform the upcoming Canadian 24-Hour Movement Guidelines for Adults and this thesis evolved out of that project. This thesis took the compositional and constrained nature of daily movement behaviours into consideration.

A key implication of this thesis research is that time spent in MVPA should be preserved over time spent in other movement behaviours, especially for those with existing low levels of MVPA. Among those spending little to no time in MVPA, substantial reductions in mortality risk may occur by increasing time spent in MVPA irrespective of which other movement behaviour that time is taken from. Limiting time spent in SED when possible and replacing time spent in SED with any other movement behaviour is also recommended to reduce mortality risk.

When sleep levels are insufficient, findings from this study recommend reallocating time to sleep from SED, but not from physical activity (especially MVPA).

4.8 Future Research Directions

This research contributes to the growing literature base applying CoDA techniques in movement behaviour epidemiology. More research using CoDA methodology to study movement behaviours is needed to further explore associations with health, including more longitudinal studies from a variety of populations on a variety of health outcomes. For instance, investigating potential differences in work-related SED and leisure-time and/or screen-time related SED could help elucidate potential differential effects of distinct domains of SED. LIPA could also be separated into lighter intensity LIPA and higher intensity LIPA to further explore the importance of various behaviour intensities. Future studies should aspire to objectively measure the entire movement behaviour composition in combination with self-reported time-use logs to minimize the potential for misclassification. Researchers should aim to collect repeated measures of movement behaviours when possible to better capture habitual movement patterns over time and further elucidate temporal relationships.

4.9 Summary of MSc Experience

My MSc experience in epidemiology has greatly expanded my knowledge and skills in epidemiology, biostatistics, and public health. In my first year of coursework, I gained a fundamental understanding of epidemiological methods and appropriate statistical techniques. In my second year, this was refined further while working as a teaching assistant and lab instructor for a fourth-year undergraduate course in biostatistics. Upon completion of my coursework, I conceptualized, conducted, and critically evaluated my own thesis research using data from the

NHANES. During this process I conducted a thorough review of relevant literature to inform my study hypotheses and analysis plan. I gained extensive technical skills with SAS statistical software in order to perform dataset merging, accelerometer processing, data cleaning, and variable manipulation. I conducted appropriate statistical analyses within a compositional framework while accounting for a complex survey design. I interpreted the results of my findings and prepared my research for this written thesis and submission for peer-reviewed journal publication. Throughout my degree I completed a research fellowship with my supervisor wherein I contributed to a systematic review related to integrated movement behaviours to help inform the Canadian 24-hour Movement Guidelines for Adults. I gained firsthand experience applying epidemiological methods to perform article screening, data extraction, and quality assessment. I attended Consensus Panel meetings where the 24-hour Movement Guidelines were developed and had an opportunity to meet and learn from leading experts in the field of movement behaviour epidemiology. I was also given the opportunity to lead a paper pertaining to adherence to the upcoming proposed Canadian 24-hour Movement Guidelines for Adults and associations with mortality risk currently in preparation. Collectively, these experiences have given me a strong foundation to successfully work in and contribute to the field of epidemiology and public health.

4.10 Conclusion

In summary, this study will contribute to the growing body of evidence examining relationships between the daily movement behaviour composition and health. In this study, the relative amount of time spent in MVPA and SED were significantly associated with a reduction and increase in mortality risk, respectively. Our estimates suggest reallocating time to MVPA from sleep, SED, or LIPA or reallocating time from SED to any of the other movement

behaviours would be associated with reduced mortality risk. Our results also indicate that inadequate levels of sleep duration should be met by reallocating time into sleep from SED but not from LIPA or MVPA. Future studies should aim to collect repeated objective measures of all parts of the movement behaviour composition in combination with time-use logs to minimize the potential for misclassification and further explore temporal relationships.

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Appendix A

Ethics letter of approval for thesis

Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB)

HSREB Initial Ethics Clearance

August 01, 2019

Ms. Anna Clarke
Faculty of Health Sciences
Queen's University

TRAQ #: 6027194
Department Code: EPID-673-19
Study Title: "EPID-673-19 The compositional associations of time spent in sleep, sedentary behaviour and physical activity with all-cause mortality"
Supervisor: Dr. Ian Michael Janssen
Review Type: Delegated
Date Ethics Clearance Issued: August 01, 2019
Ethics Clearance Expiry Date: August 01, 2020

Dear Ms. Clarke:

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

- Protocol: v.2019JUL26

Documents Acknowledged:
- Department Reviewers (Committee) Approval of Thesis Proposal
- Household interview consent form 2003 – 2004 & 2005-2006 cohorts
- Examination consent form 2003-2004 & 2005-2006 cohorts
- CORE Certificates: Janssen, Clarke

Amendments: No deviation from, or changes to the protocol, informed consent form and conduct of study should be initiated without prior written clearance or an appropriate amendment from the HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the study.

Renewals: An annual renewal event form or a study closure event form must be submitted annually as per the TCPS 2 2014 Article 6.14. As a courtesy, the Office of Research Ethics may send reminders

30 days in advance of the ethics clearance expiry date. All lapses in ethics clearance will be documented on the annual renewal clearance letter. Suspension letters may be issued for lapses in ethics clearances one day or greater, with subsequent termination and closure of the ethics file for lapses greater than 10 business days. Terminations should be reported to applicable regulatory authorities (e.g., Health Canada, FDA).

Completion/Termination: The HSREB must be notified of the completion or termination of this study through the submission of a study closure event in TRAQ.

Reporting of Serious Adverse Events: Any unexpected serious adverse events occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint.

Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Investigators please note that if your study is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.

Regards,

Albert F. Clark, PhD
Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2014); the international Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Product Regulations; Part 3 of the Medical Devices Regulations, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#: 00004184, IRB#: 00001173. HSREB members involved in the research project do not participate in the review, discussion or decision.

Appendix B

A priori power calculation

The following formula was used to calculate power:

$$Power = 1 - \beta = \Phi\left(z - z_{1-\frac{\alpha}{2}}\right) + \Phi\left(-z - z_{1-\frac{\alpha}{2}}\right); \quad where\ z = (\ln(\vartheta) - \ln(\theta_1))\sqrt{np_A p_B p_E}$$

θ=the hazard ratio (1.25, 1.5 and 2.0 respectively)
θ_1=the hazard ratio under the null hypothesis=1
n=total sample size = 3000 participants
p_A=proportion of the sample size allotted to group A =0.5
p_B=proportion of the sample size allotted to group B =0.5
p_E=overall probability of death occurring in the study period = 0.07
$z_{1-\frac{\alpha}{2}}$=1.96 (α=0.05)

For example, when the hazard ratio (θ) equals 2, the estimated power is:

$z = (\ln(\vartheta) - \ln(\theta_1))\sqrt{np_A p_B p_E}$=$(\ln(2) - \ln(1))\sqrt{3000(.5)(.5)(0.07)}$=6.96

$$Power = 1 - \beta = \Phi\left(z - z_{1-\frac{\alpha}{2}}\right) + \Phi\left(-z - z_{1-\frac{\alpha}{2}}\right) = \Phi(6.96 - 1.96) + \Phi(-5.13 - 1.96) = 1.0$$

Appendix C

Supplementary results

Supplemental Table 1. Estimated hazard ratios for displacing time between movement behaviours

Predicted hazard ratios

Remove time from:	Add time to MVPA (minutes)				
	15	30	45	60	75
SED	0.84 (0.78, 0.90)	0.75 (0.67, 0.84)	0.69 (0.59, 0.80)	0.64 (0.53, 0.78)	0.61 (0.49, 0.75)
LIPA	0.86 (0.82, 0.90)	0.78 (0.73, 0.84)	0.74 (0.67, 0.80)	0.70 (0.64, 0.78)	0.68 (0.61, 0.75)
Sleep	0.85 (0.81, 0.89)	0.77 (0.71, 0.83)	0.71 (0.65, 0.78)	0.67 (0.61, 0.75)	0.64 (0.57, 0.72)

Add time to:	Remove time from MVPA (minutes)				
	15	30	60	90	120
SED	1.80 (1.46, 2.22)				
LIPA	1.76 (1.46, 2.13)				
Sleep	1.78 (1.47, 2.15)				

Remove time from:	Add time to LIPA (minutes)				
	15	30	60	90	120
SED	0.98 (0.96, 1.00)	0.96 (0.92, 1.00)	0.92 (0.84, 1.00)	0.88 (0.77, 1.00)	0.84 (0.71, 1.00)
Sleep	0.99 (0.99, 0.99)	0.98 (0.98, 0.98)	0.96 (0.96, 0.97)	0.95 (0.95, 0.95)	0.93 (0.93, 0.93)
MVPA	1.76 (1.46, 2.13)				

Add time to:	Remove time from LIPA (minutes)				
	15	30	60	90	120
SED	1.02 (1.00, 1.04)	1.04 (1.00, 1.09)	1.09 (1.00, 1.19)	1.14 (1.00, 1.30)	1.19 (1.00, 1.42)
Sleep	1.01 (1.01, 1.01)	1.02 (1.02, 1.03)	1.04 (1.03, 1.06)	1.07 (1.05, 1.09)	
MVPA	0.86 (0.82, 0.90)	0.78 (0.73, 0.84)	0.70 (0.64, 0.78)		

Remove time from:	Add time to SED (minutes)				
	15	30	60	90	120
MVPA	1.80 (1.46, 2.22)				
LIPA	1.02 (1.00, 1.04)	1.04 (1.00, 1.09)	1.09 (1.00, 1.19)	1.14 (1.00, 1.30)	1.19 (1.00, 1.42)
Sleep	1.01 (0.99, 1.03)	1.02 (0.98, 1.06)	1.04 (0.97, 1.13)	1.06 (0.95, 1.19)	1.08 (0.93, 1.27)

Add time to:	Remove time from SED (minutes)				
	15	30	60	90	120
MVPA	0.84 (0.78, 0.90)	0.75 (0.67, 0.84)	0.64 (0.53, 0.78)		
LIPA	0.98 (0.96, 1.00)	0.96 (0.92, 1.00)	0.92 (0.84, 1.00)	0.88 (0.77, 1.00)	0.84 (0.71, 1.00)
Sleep	0.99 (0.97, 1.01)	0.98 (0.94, 1.02)	0.95 (0.88, 1.03)	0.93 (0.83, 1.04)	

Remove time from:	Add time to sleep (minutes)				
	15	30	60	90	120
SED	0.99 (0.97, 1.01)	0.98 (0.94, 1.02)	0.95 (0.88, 1.03)	0.93 (0.83, 1.04)	
LIPA	1.01 (1.01, 1.01)	1.02 (1.02, 1.03)	1.04 (1.03, 1.06)	1.07 (1.05, 1.09)	
MVPA	1.78 (1.47, 2.15)				

Add time to:	Remove time from sleep (minutes)				
	15	30	60	90	120
SED	1.01 (0.99, 1.03)	1.02 (0.98, 1.06)	1.04 (0.97, 1.13)	1.06 (0.95, 1.19)	1.08 (0.93, 1.27)
LIPA	0.99 (0.99, 0.99)	0.98 (0.98, 0.98)	0.96 (0.96, 0.97)	0.95 (0.95, 0.95)	0.93 (0.93, 0.93)
MVPA	0.85 (0.81, 0.89)	0.77 (0.71, 0.83)	0.67 (0.61, 0.75)		

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

Note: Data presented as hazard ratio (95% confidence interval). All estimates have been adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption, and diet quality. Hazard ratios reflect the estimated change in mortality risk associated with reallocating time increments between movement behaviours using the mean movement behaviour composition as the reference.

Supplemental Table 2. Estimated hazard ratios for displacing time between one and the remaining movement behaviours proportionally

Predicted hazard ratios

Remove time from	Minutes				
	15	30	60	90	120
MVPA	1.78 (1.46, 2.17)				
LIPA	1.01 (1.00, 1.03)	1.03 (1.00, 1.05)	1.06 (1.00, 1.11)	1.09 (1.01, 1.18)	1.12 (1.01, 1.25)
SED	0.98 (0.96, 1.00)	0.96 (0.92, 1.00)	0.92 (0.84, 1.00)	0.88 (0.77, 1.01)	0.84 (0.70, 1.01)
Sleep	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)	1.00 (0.96, 1.04)	0.99 (0.93, 1.06)	0.99 (0.91. 1.08)

Add time to	Minutes				
	15	30	60	90	120
MVPA	0.85 (0.80, 0.90)	0.76 (0.70, 0.84)	0.67 (0.58, 0.77)		
LIPA	0.99 (0.98, 1.00)	0.98 (0.95, 1.00)	0.95 (0.91, 1.00)	0.93 (0.87, 0.99)	0.91 (0.83, 0.99)
SED	1.02 (1.00, 1.04)	1.04 (1.00, 1.09)	1.09 (1.00, 1.18)	1.13 (1.00, 1.28)	1.18 (0.99, 1.40)
Sleep	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)	1.00 (0.97, 1.04)	1.01 (0.95, 1.06)	

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

Note: Data presented as hazard ratio (95% confidence interval). All estimates have been adjusted for age, sex, education, family poverty-to-income ratio, BMI, smoking status, alcohol consumption and diet quality. Hazard ratios reflect the estimated change in mortality risk associated with reallocating time increments from one movement behaviour to the remaining movement behaviours proportionally (or vice versa) using the mean movement behaviour composition as the reference.