INDEPENDENT AND JOINT EFFECTS OF SITTING TIME WITH LIFESTYLE FACTORS ON MORTALITY, IN POST-MENOPAUSAL, U.S. WOMEN

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Abstract

Prolonged sitting has been linked to cardiovascular disease, diabetes, obesity, cancer and early mortality, independent of physical activity. As a result, it would be beneficial from a public health standpoint to examine the impact of sitting time amongst older populations who are prone to sitting. We grouped post-menopausal women of the Women's Health Initiative (n= 84 865; 50-79 years of age) into quartiles of total daily sitting time (Q1: ≤5; Q2: 6-9; Q3: 10-13; Q4: 14+ hrs. /day). We also examined the joint effects of sitting time with other well-known risk factors on mortality. The two highest quartiles of sitting time had significantly higher all-cause (Q3: HR: 1.13, 95% CI: 1.04-1.22); (Q4: 1.26, 95% CI: 1.11-1.44) and cancer mortality (Q3: HR:1.17, 95% CI: 1.04-1.31); (Q4: 1.38, 95% CI: 1.13-1.67) risk in comparison to our referent group who sat less than or equal to 5 hours daily. Additionally, individuals who at baseline were smokers, or inactive in conjunction with high levels of sitting, were also at a considerably higher risk of all-cause and cancer mortality compared to women with a more optimal risk profile (non-smoker, or active and low sitting). These findings suggest that in older, post-menopausal women, limiting sitting time throughout the day may be a positive strategy to improve one's longevity. Further, high-risk individuals such as older women who exhibit high sitting with other behaviours such as, smoking, or inactivity should be of priority to limit sitting time.

Keywords:

Physical activity, lifestyle, risk factors

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Abbreviations

AusDiab	Australian Diabetes, Obesity and Lifestyle
BMI	Body Mass Index
BP	Blood Pressure
CCHS	Canadian Community Health Survey
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
CSEP	Canadian Society of Exercise Physiology
CVD	Cardiovascular Disease
EPIC-Norfolk Study	The EPIC-Norfolk Prospective Population Study
HDL	High Density Lipoprotein
$HOMA_{IR}$	Homeostasis Model-Estimated Insulin Resistance
HR	Hazard Ratio
ICD	International Classification of Diseases
IPAQ	International Physical Activity Questionnaire
KCal	Kilocalorie
LDL	Low Density Lipoprotein
MET	Metabolic Equivalent of Task
MetS	Metabolic Syndrome
NHANES	National Health and Nutritional Examination Survey
OR	Odds Ratio
OS COHORT	Observational Study Cohort
Q1,Q2,Q3,Q4	Quartile 1 through 4
RR	Relative Ratio
SE	Standard Error
SES	Socioeconomic Status
T2DM	Type II Diabetes
TG	Triglyceride
TV	Television
WC	Waist Circumference
WHI	Women's Health Initiative

Table of Contents

List of Tables and Figures

Extended Discussion

Introduction

Physical inactivity is currently a growing public health concern not only in the United States and Canada (Troiano et al., 2008) but globally. Worldwide, 31% of adults aged 15 years or older were reported as insufficiently active in 2008 (World Health Organization, 2011). In Canada, data from the 2007-2009 Canadian Health Measures Survey (CHMS) suggest that only 15% of Canadian adults accumulate sufficient moderate physical activity on a weekly basis (Colley et al., 2011). Moreover, in the 2010 Canadian Community Health Survey, more than 60% of women 65 years or older were inactive (Gilmour, 2007). The dangers of physical inactivity include increased risk of major chronic conditions such as diabetes (Sigal et al., 2006), obesity (Fox & Hillsdon, 2007), cardiovascular disease (CVD) (Kohl, 2001), osteoporosis (Grahn, 2013) and some cancers (Thune & Furberg, 2001). A relationship with mortality was also found early on in the double-decker bus study where London bus drivers had greater CVD mortality rates than the more active conductors (Morris et al., 1953). Ever since, there has been accumulating evidence of the influence physical inactivity can have on lifespan and long-term health as it is responsible for approximately 1in 10 premature deaths annually (Lee et al., 2012). Inactivity also poses a sizable economic burden on the Canadian and US Health Care System, accounting for approximately $6.8 billion CDN (Janssen, 2012) annually, in direct ($2.4 billion) and indirect ($4.3) health care costs in Canada. Meanwhile, in the United States, physical inactivity, overweight, and obesity accounted for 27% of national health care charges (Anderson et al., 2005).These expenses can be attributed to health care for the prevention, diagnosis and treatment of chronic conditions related to inactivity, in addition to the value of lost wages by people unable to work because of illness and disability (US Department of Health and Human Services, 2008). Defined as less than 30 minutes of moderate activity 5 days a week or 20 minutes of vigorous activity 3 times a week (US Department of Health and Human Services, 2008), physical inactivity was used interchangeably with the term "sedentary" behaviour and conceptualized to represent the very low end of the physical activity continuum. However, sedentary time has evolved to mean any waking behaviour done in a sitting or reclining posture that is characterized by little physical movement and low energy expenditure (Sedentary Behaviour Research Network, 2012). Researchers have also found sedentary behaviour to embody a number of distinct effects on metabolism, health and physical functioning beyond that of physical inactivity (Harris et al., 2007; Gustat et al., 2002; Kronenberg et al., 2000). In this way, sedentary behaviour may be of even greater concern than physical inactivity, because of its high prevalence and pervasiveness throughout the day. Where physical activity can encompass a more modest portion of an individual's waking hours, sedentary time can occur continuously, and in collective bouts throughout the whole day. For example, a recent survey showed that worldwide, people spend about 300 minutes or 20% of their day sitting (Bauman et al., 2011). In another study by Colley et al. (2011), Canadian adults 20-79 y were reported to be sedentary for an average of 9.5 hours each day, while children and youth spent an average of 8.6 hours engaged in sedentary activities such as watching television. Moreover, in an evaluation of NHANES 03-04 of participants aged 6 years and older, being white, female and aged 50+ was linked to one of the highest reported sitting times at approximately 8.6 hrs. /day (Matthews et al., 2008). As a result, many studies link major health risks to sitting time that are irrespective of physical activity (de Heer et al., 2012; Owen et al., 2010; Proper et al., 2011). However, studies focusing strictly on older and American female samples are limited, despite the likely tendencies of this demographic to sit (Matthews et al., 2008).

Review of the Literature

Prevalence

The prevalence of sedentary behaviour can vary from country to country, but recent accounts suggest universally high levels. In a study involving 4000 French women, aged 45 years and older, it was reported that 34% of adults spent between 2-3 hours per day watching TV, and 33% spent more than 3 hours per day watching TV (Bertrais et al., 2004). Meanwhile in the United States, an investigation of the 2003–2004 National Health and Nutrition Examination Survey (NHANES) found that overall, participants spent 7.7 hours/day in sedentary pursuits (Matthews et al., 2008). Similarly, Canadian children and youth spend 8.6 hours per day or 62% of their waking hours in sedentary pursuits (Colley et al., 2011). The comparable prevalence of sitting time (despite cultural and socio-demographic differences across countries) is most likely due to its ubiquitous nature. Sedentary behaviour can comprise a number of domains, most often described as "screen time" (watching television, playing video games, using the computer), but can also occur during the commute and at the work place (Owen et al., 2011). In fact, for most white collared and office-type jobs, occupational sitting can contribute to more than half of the daily sitting an individual can experience. For example, in a study of Australian workers, full-time employees accumulated an average of 4.2 hours of sitting at work and 2.9 hours during their leisure time (Brown et al., 2003). Self-reported data from the Australian Longitudinal Study on Women's Health also found women born between 1946-1951 to have a mean sitting time of 5.70 hours/day (van Uffelen et al., 2012).

Measurement

Traditional methods for capturing sedentary time involve the use accelerometers and/or self-report surveys. Accelerometers are small mechanical devices typically attached around the hip and worn for a number of consecutive days measuring the intensity, duration, and frequency of walking and running movements. The absence of these movements can be used to derive sedentary time. This 'objective' method is commonly considered a more reliable measurement tool than self-report. Still, accelerometers have their disadvantages. First, it cannot distinguish between types of sedentary behaviour (e.g., TV viewing vs. computer use), or different postures (e.g., sitting vs. standing still), as standing can elicit higher energy expenditure. They are also more expensive and resource-intensive than self-report measures and have greater participant burden, which may impact on studies that require repeated and/or long term-wear (Ainsworth & Macera, 2011). Although there are reports of disparities between the two measures (Prince et al., 2008), several studies do exist which report considerable agreement between subjective and objective measures when tracking sedentary time. In one report, total sitting time calculated from a domain-specific questionnaire (i.e. time spent sitting whilst travelling to and from places, at work, watching TV, using a computer at home, and during leisure time), did not differ significantly from accelerometer-determined sedentary time on weekdays (mean difference [±SE] = –14 ± 28 mins/day) and weekend days (–4 ± 45 mins/day, both $P > .05$) (Clemes et al., 2012). Additionally, in a study involving endometrial cancer survivors and age-matched controls, self-reported exercise-bout duration matched accelerometer duration 93% of the time for survivors, and 99% of the time for the controls (Jovanovic et al., 2011). Studies involving either method have also found positive associations between sitting time with various detrimental outcomes, including a study evaluating the cardio-metabolic dose-response for sedentary behaviour between 7–day accelerometer and questionnaire-based measures (IPAQ) (Celis-Morales et al., 2012). Here, both measures resulted in significant relationships between sitting time with all measured risk factors [glucose, triglyceride (TG) and total, LDL and HDL cholesterol concentrations, homeostasis model-estimated insulin resistance ($HOMA_{IR}$),waist circumference (WC), BMI, body fat percentage and blood pressure (BP)]. Therefore together, evidence suggests that in the absence of objective measurement, assessment of sedentary time by self-report is an adequate proxy for health-related research in population-based settings.

A Distinct Definition

Currently, the Sedentary Behaviour Research Network (sedentarybehaviour.org) is advising researchers to formally define sedentary behaviour as any waking behaviour characterized by an energy expenditure $\leq$ 1.5 MET while in a sitting or reclining posture. In contrast, they propose that authors and researchers use the term "inactive" to describe those who are performing insufficient amounts of moderate-vigorous physical activity (i.e., not meeting specified physical activity guidelines)(Sedentary Behaviour Research Network, 2012). Other differences also exist which may drive the need for a distinct identification. For instance, methods to reduce sedentary behaviour involve different levels of planning and preparation. According to one author (Tremblay et al., 2010), the promotion of physical activity normally requires organized and structured programs which often face financial and time constraints that are difficult to overcome. On the other hand, reductions in sedentary behaviour could be achieved by minimal changes to the environment, while providing a wealth of micro-intervention opportunities designed to promote energy expenditure. A simple example involves implementing walking meetings over the traditional sit-down arrangement. Another includes designing desks/tables that have height adjusting features to provide the option of working while standing up or sitting down (Owen et al., 2010). In fact, studies that have investigated these interventions involving employees found workers adjusted their desk on average 3.6 times per day, with 91% of participants adjusting it at least once per day (Nerhood& Thompson, 1994) and increasing standing frequency of 2.5 times per day (Dainoff, 2002).

The effects of sedentary behaviour are now also believed to impact longevity and quality of life differently as well. For instance, in a study investigating the association between sedentary behaviour and successful aging (physical, psychological, and social) among older adults, compared to those who were sedentary (4 hours or more/day), participants who were moderately (2–4 hours/day) and least sedentary (<2 hours/day) were 38% (OR: 1.38, 95% CI: 1.12–1.69) and 43% (OR: 1.43, 95% CI: 1.23–1.67) more likely to age successfully, regardless of physical activity levels (Dogra & Stathokostas, 2012). In another study on 1 367 men and women (60 y+), a higher percentage of sedentary time and fewer sedentary breaks were associated with a noticeably greater likelihood of metabolic syndrome, even after adjustment for age, sex, ethnicity, education, alcohol consumption, smoking, BMI, diabetes, heart disease, and physical activity (Bankoski et al., 2011). Moreover, a recent analysis by Katzmarzyk and Lee (2012) revealed that the estimated gains in life expectancy in the US population were 2 years for reducing excessive sitting to <3h/day, and a gain of 1.38 years from reducing excessive television viewing to <2h/day. Finally, an earlier study by the same author (Katzmarzyk et al., 2009), reported a progressively higher risk of mortality across higher levels of sitting time for both CVD [HR: 1.00 (none of the time); HR: 1.01, 95% CI: 0.77-1.31 (1/4 of the time); HR: 1.22, 95% CI: 0.94-1.60 (1/2 of the time); HR:1.47, 95% CI: 1.09-1.96 (3/4 of the time); HR: 1.54, 95% CI: 1.09-2.17 (almost all of the time)]; and all causes [HR: 1.00; HR:1.00, 95% CI: 0.86-1.18;

HR: 1.11, 95% CI: 0.94-1.30; HR: 1.36, 95% CI: 1.14-1.63; HR: 1.54, 95% CI: 1.25-1.91]. In light of these findings, researchers are proposing the well-established physical activity-health framework to integrate the role of sedentary behaviour (Katzmarzyk, 2010),which may in turn improve and expand our understanding of health.

Sedentary Patterns in Older and Aging Women

There is a strong inverse association between aging and physical activity (DiPietro et al., 1993), with steady declines in leisure-time physical activity, beginning in midlife, and growing steeper at progressively older ages (Shaw et al., 2010). Specifically, older, post-menopausal and retired women are a demographic highly susceptible to a decline in physical activity with only a small percentage (39.3%) of American adults aged 65 years and older meeting current physical activity guidelines (Centers for Disease Control and Prevention (US), 2010). Various accounts however now report ties between aging and increased sitting time. In fact, for most studies investigating sedentary time in adults, females and individuals over the age of 60 are reported to record the highest sitting times (Salmon et al., 2003; Martínez-González et al., 1999). Results from NHANES 2003-2004 for instance, show that adults 70–85 years were the most sedentary group in that population with these women spending approximately 9.1 hours/day sitting (Matthews et al., 2008). Also, in a study excluded to individuals 75 years and older of the Australian Longitudinal Study on Women's Health, more than half reported sitting for between 4 and 8 hrs/day (55%), and <5% for more than 11 hrs./day (Pavey et al., 2012). These accounts are particularly concerning as sitting time has been reported to compromise one's health. A recent study on the WHI cohort for example, found sedentary time to be strongly associated with diminished physical function and most pronounced among older women and those exhibiting the greatest sedentary time (Seguin et al., 2012). Moreover, in a study conducted on the same Australian Longitudinal Study cohort (Pavey et al., 2012), compared with participants who sat <4 h/day, those who sat 8–11 h/day had an 1.45 times higher risk of death and 1.6 times higher for those who sat ≥11 h/day.

Health Outcomes

Prolonged sitting at the workplace and during leisure time has been linked to cancer, CVD, diabetes, obesity and premature mortality, even in the presence of adequate physical activity (Proper et al., 2011; Thorp et al., 2011; Tremblay et al., 2010). In a recent meta-analysis, greater time spent in sedentary pursuits was found to be associated with higher odds of metabolic syndrome (MetS; OR:1.73, 95% CI: 1.55–1.94), results that remained largely unchanged after conducting a sensitivity analysis of those studies which adjusted for physical activity (OR:1.73, 95% CI: 1.54–1.97) (Edwardson et al., 2012). Also in a case-control study, standing or intense occupational activity was associated with a lower risk of colon or rectal cancer compared to individuals employed in primarily sitting jobs (Levi et al., 1999). Finally, 7-day data from 1 906 participants aged 50 and over from the U.S. National Health and Nutrition Examination Survey (NHANES 2003–2004), found participants in the third (HR: 4.05, 95%CI:1.55–10.60) and fourth quartile (HR:5.94, 95%CI: 2.49–14.15) of sedentary time to have significantly higher risk of death compared to those in the lowest quartile (Koster et al., 2012). However, studies linking sitting time to mortality in a strictly older, American and female subset during the time of post-menopause is limited and warrant further study.

Interactions between Sedentary Time and Various Risk Factors

With the continuing emergence of studies on sedentary behaviour and its associated health risks, it would be insightful to examine the effects it can have on health when in the presence of other major risk factors. Sedentary behaviours tend to exist within clusters of other harmful conditions and behaviours such as poor diet, excess weight, inactivity and smoking which can intensify health risks (van Uffelen et al., 2012). To illustrate, in a recent meta-analysis, sedentary behaviour was found to be clearly associated with elements of a less healthy diet (including lower fruit and vegetable consumption; higher consumption of energy-dense snacks, drinks, and fast foods; and higher total energy intake), regardless of age. For example, TV viewing was found to be positively linked to snacking ($p<0.01$), frequency of meals ($p<0.01$) and soft drinks ($p<0.01$)(Cleland et al., 2008). Additionally, women who ate while watching television were less likely to consume two or more servings of vegetables per day (Crawford et al., 2007). Results from the 2007 Canadian Community Health Survey (CCHS)(Katzmarzyk et al., 2009), also link television viewing and computer use to obesity in both males and females. Among women, the prevalence of obesity rose from 11% in those reporting five or fewer hours, to 24% in those reporting 21 or more hours of television viewing per week. Additionally, for both sexes, those who used computers for at least six hours per week had higher odds of being obese (20% higher odds for men and 30% higher odds for women), compared with those who averaged five or fewer hours (Koster et al., 2012). Finally, television time in Australian adults has been linked to low levels of activity (Salmon et al., 2012; Sugiyama et al., 2008) and positively associated with other types of sedentary behaviours.

Therefore, to fully understand the sedentary-health relationship, it is necessary to characterize sedentary behaviours across different health risk factors (e.g. by physical activity, diet, BMI, and smoking). However, such assessments in strictly older, female samples, particularly at the time of post-menopause is limited.

Summary

A growing collection of studies is illustrating not only the immediate but longer-term impacts of sedentary time on our health. Women at the time of post-menopause are prone to adopting these sedentary tendencies. In addition, sedentary behaviour is likely to coexist with other patterns of unhealthy behavioural factors such as smoking and obesity. As such, it would be beneficial to assess these relationships within high risk groups to aid in refining current sedentary guidelines.

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Objectives

To estimate the association between sedentary behaviour and mortality in post-menopausal women of the Women's Health Initiative (WHI).

Specific Aims:

Aim 1: To assess distinct strata of sitting time (low (quartile 1/Q1), low-moderate (quartile 2/Q2), moderate (quartile 3/Q3) and high volumes (quartile 4/Q4) and their association with mortality from all-cause, CVD and cancer.

Hypothesis: Individuals in higher quartiles of sitting time will have greater risks of mortality from all-cause, CVD and cancer.

Aim 2: To explore the combined contributions of these sitting groups with age and other major risk factors of health (BMI, smoking, alcohol, physical activity, sleep and diet) and the corresponding mortality risks across those levels.

Hypothesis: Individuals in higher quartiles of sitting time who also exhibit poor health habits (high BMI, currently smoking, no or excess alcohol consumption, inadequate physical activity, low or overabundance of sleep hours, and inadequate fruit & vegetable consumption) will experience the greatest mortality risk.

INDEPENDENT AND JOINT EFFECTS OF SITTING TIME WITH LIFESTYLE FACTORS ON MORTALITY, IN POST-MENOPAUSAL, U.S. WOMEN

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Abstract

Objective: To examine the all-cause, CVD and cancer mortality risk across different volumes of daily sitting time and to assess how the interaction of sitting with age and other known risk factors (physical activity, smoking history, alcohol consumption, BMI, sleep and fruit & vegetable consumption) further contributes to those risks.

Design: A 15-year prospective study of post-menopausal women from the Women's Health Initiative (WHI)-observational study, was acquired from the National Heart, Lung and Blood Institute.

Subjects: After exclusions, a final sample of 84 865 female participants, (50-79 y) remained for analysis.

Methods: Cox proportional hazards regression was used to assess the relationship between all-cause, CVD and cancer mortality with sitting time, after adjusting for potential confounders. Interactions between sitting time with age and other well-established modifiable risk factors were explored, and analyses repeated after cross-classification of sitting time with sleep duration, alcohol consumption, physical activity, fruit and vegetable consumption, body mass index and smoking history. All data analysis was conducted using SAS v9.3 (SAS, Inc, Cary, NC), with statistical significance set at alpha <0.05.

Results: 5 458 deaths were reported at the time of follow-up. Compared to women within the lowest quartile of sitting time, participants within quartile 3 and 4 had an elevated risk of all-cause (Q3: HR: 1.13, 95% CI: 1.04-1.22; Q4: HR: 1.26, 95% CI: 1.11-1.44) and cancer mortality (Q3: HR: 1.17, 95% CI: 1.04-1.31; Q4: HR:1.38, 95% CI: 1.13-1.67). Those in the top quartile of sitting time who were also inactive in their leisure time had a (HR: 1.63, 95% CI: 1.39-1.90) and (HR: 1.84, 95% CI: 1.46-2.32) of all-cause and cancer mortality respectively, compared to their active, lowest sitting counterparts. Furthermore, current smokers who experienced the most sitting time throughout the day had a more than 3-fold elevation in all-cause (HR: 3.41, 95% CI: 2.51-4.63) and cancer mortality (HR: 3.93, 95% CI: 2.54-6.07), compared to the lowest sitting group with no history of smoking (referent). No significant interactions were seen between sitting time with alcohol history, BMI, sleep and fruit & vegetable consumption. ***Conclusion:*** Prolonged sitting was a significant predictor of mortality from all-cause and cancer. In the presence of smoking or physical inactivity, the mortality risk was further amplified.

Keywords:

Body mass index, retirement, aging, mortality

Introduction

Current physical activity guidelines in the United States suggest at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity each week in order to reap major health benefits (US Department of Health and Human Services, 2008). Worldwide, over 31% of adults 15 and older, fail to meet the minimal guidelines, however, and are therefore considered physically inactive (World Health Organization, 2011). In the past, the term physical inactivity was used interchangeably with 'sedentary behaviour', and conceptualized in national surveys related to screen time (i.e., television viewing, computer use, video games) (Ottevaere et al., 2011). However, sedentary behaviour is distinct from physical inactivity in that a person can accumulate the daily recommended physical activity levels despite leading a sedentary lifestyle. To illustrate, the "active couch potato" can perform one bout of structured physical activity, but then decide to be completely sedentary for the rest of their waking hours (Tremblay et al., 2010).

Activities with an energy expenditure equal to or under the resting level of 1.5 metabolic equivalent of task (MET) constitute sedentary behaviour (Sedentary Behaviour Research Network, 2012).This may include prolonged sitting at work, home, travel and/or performing other tasks that require very little energy expenditure (Katzmarzyk, 2010). Appropriately, the Canadian Society for Exercise Physiology (CSEP) released the very first evidence-based sedentary guidelines for children and youth in early 2011. These guidelines advise children to minimize sedentary behaviour by means of reducing screen time to no more than 2 hours per day (Tremblay et al., 2011).

Regardless of leisure-time physical activity levels, sedentary time has been shown to be a predictor of various health risks such as type 2 diabetes mellitus (T2DM) (Hu et al., 2003), metabolic syndrome (Bankoski et al., 2011), and cancer (Cohen et al., 2013). In one study of women aged 50-79, sitting ≥ 10 hrs./day compared to ≤ 5 hrs/day was associated with increased CVD risk (HR: 1.18, 95% CI: 1.09-1.29), independent of physical activity levels (Chomistek et al., 2013). In another, the author linked more than 40 hrs. of television per week to a nearly threefold increase in the risk of T2DM compared with those who spent less than one hour per week watching TV (Hu et al., 2003). And finally, sitting has been implicated in certain site-specific cancers. In an Australian study for example, participants who spent 10 or more years in sedentary work had almost twice the risk of distal colon cancer and a 44% increased risk of rectal cancer (Boyle et al., 2011) .

Despite these associations, literature examining the joint effect of sedentary time with other known risk factors of health are limited (Katzmarzyk et al., 2009), particularly, in mid-to-older aged adults. Increases in sitting time are commonly paralleled by other unhealthy behavioural patterns, and to date, it is not yet clear the extent to which sitting time may interact with other known risk factors to contribute to all-cause, CVD, and cancer mortality.

Therefore, the objective of the present analysis is i) to describe the sedentary-based risk factor profiles in a cohort of post-menopausal women and ii) to quantify the joint effects of sitting time and other known risk factors on all-cause, CVD and cancer mortality.

Methods

Study Sample

Socio-demographics, health behaviours, and medical and family history were collected by interview or use of self-administered questionnaires from the Women's Health Initiative (WHI).

WHI is a longitudinal health study focusing on the risk factors, antecedents, and treatment of cancer, cardiovascular disease, and osteoporotic injury amongst a sample of post-menopausal American women. WHI has over 15 years of follow-up (1992 to 2008) data from 161 808 (age 50 to 79 y) participants. All exposure variables in this analysis were collected at baseline and at year 3 clinic visit during which medical and physiological measurements were collected by certified personnel. Additional data were collected through annual self-administered questionnaires from year 3 to the end of the study. Participants with missing values for the exposure or outcome variables were excluded from the analysis. From the original sample of 161 808 participants, we obtained data from the Observational Study (OS) cohort, consisting of 93 676 individuals who were recruited from 1993 to 1998. Of that sample, those who were underweight (N=1020) or had missing values [(BMI (N=1 847), physical activity (N=507), education (N=1 954), alcohol (N=1 182), sitting time (N=719), fruit & vegetable (N=117), ethnicity (N=242), hormone use (N=1 218), general health (N=401), and physical limitations (N=624)] were excluded, providing a sample of 84 865 participants for final analysis. This working sample was indeed representative of the original as confirmed by a missing value analysis (Appendix E).

Women's Health Initiative Questionnaire

Sitting time: Participants documented their total daily sitting time in the baseline questionnaire (i.e. "During a usual day and night, about how many hours do you spend sitting? Be sure to include the time you spend sitting at work, sitting at the table eating, driving or riding a car or bus, and sitting up watching TV or talking"). Response options were (<4, 4-5, 6-7, 8-9, 10-11, 12-13,14-15, 16+hrs/day, and missing). For this analysis, participants are divided into quartiles of sitting time categories i.e. (Q1: ≤5; Q2: 6-9; Q3: 10-13; Q4: 14+ hrs./day), based on previous studies (Katzmarzyk et al., 2009; Koster et al., 2012; Warren et al., 2010).

Modifiable risk factors: To assess the joint effect of other modifiable risk factors along with sitting time, the following variables were used: **Physical activity**: self-reported weekly physical activity participation at baseline based from various questions on energy expenditure from recreational physical activity (physically active: at least 500 MET-min/week; inactive: less than 500 MET-min/week)(Nelson et al., 2007); **Sleep duration**: self-reported daily hours spent sleeping or lying down at baseline (low ≤7, normal 8-9, high ≥10) (Tamakoshi et al., 2004; Cappucio et al., 2010); **Smoking history:** self-reported history at baseline (never smoked, past smoker, current smoker) (Shavelle et al., 2008); **Alcohol consumption:** self-reported history at baseline [non-drinker, past drinker (during entire life, consumed at least 12 drinks of any kind of alcoholic beverage), moderate current drinker (≤7 drinks/week), and heavy current drinker (>7 drinks/week)] (Thun et al., 1997; Gaziano et al., 2000; Fuchs et al., 1995); **Daily fruit and vegetable intake:** self-reported daily fruit and vegetable consumption at baseline, classified as inadequate (0-6 servings) or meets requirements (≥7 servings) (Health Canada, 2011); Body mass index **(BMI)** at baseline, classified as normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥30 kg/m^2) (Health Canada, 2003).

Confounding Variables: In addition to physical activity, smoking history, BMI and alcohol consumption, the following factors were treated as potential confounders in all analyses: age at baseline (years), education (less than high school degree, high school diploma, some college, college graduate or more) total family income (< $35 000, $35 000-74 999, or >$75 000), ethnicity (White, African American, Hispanic/Latino, or other), general health (based on a quality of life subscale ranging from 0 to 100, with a higher score indicating a more favourable health state), physical limitations (based on a quality of life subscale on role limitations due to physical health ranging from 0 to 100 with a higher score indicating a more favourable health state), and use of female hormones ever (yes, no).

Mortality: Endpoints were death from all-cause, CVD and Cancer. Trained physician adjudicators established the endpoints from records (hospitalizations, emergency room, death certificates, and autopsy and coroner's reports). Cause-specific mortality categorizations were based on the cause of death, rather than the immediate or contributing cause of death. CVD mortality (ICD-9 codes 390-449) included death from coronary heart disease, cerebrovascular disease, pulmonary embolism, congestive heart failure, and other cardiovascular causes. Cancer mortality (ICD -9 codes 140-239) included all carcinomas, lymphomas, sarcomas (including metastatic cancer from unknown primaries), and hematologic malignancies (including blood, bone marrow, and lymph nodes).

Statistical Analysis

Cox proportional hazards regression was used to quantify the relationship between all-cause, CVD and cancer mortality with sitting time, after adjusting for potential confounders. Covariate selection was based on previous analyses to facilitate comparison of results (Katmarzyk et al., 2009; Matthews et al., 2008; Pavey et al., 2012). Analyses were stratified by age to test for potential interactions. Two-way interactions between sitting time and other modifiable risk factors were also explored in each model (i.e. sitting x BMI). Subsequently, analyses were repeated after cross-classification of sitting time with physical activity and smoking history. Two models were used to measure the association of joint categories of sitting time and other modifiable risk factors on all-cause mortality. To determine whether the assumption of proportionality for the Cox model was met, time dependent covariates were included in the model and visual inspection of the log-by-log plots was performed. A Pearson correlation coefficient of R <0.85, was used as the basis to include both education and income variables within our multivariate analyses. All data analyses were performed with SAS v9.3 (SAS, Inc, Cary, NC), with statistical significance set at alpha <0.05.

Results

Baseline Characteristics

At the end of 2008 follow-up period, there were 5 458 deaths from all causes among the study participants. **Table 1** provides descriptive characteristics of the study participants according to their daily sitting time, categorized in quartiles. On average, participants in Q4 were roughly three years younger than those in Q1 (61.43±7.51 vs. 64.27±7.17 years, $p<0.001$). BMI was also highest and physical activity levels lowest among those in Q4 of total daily sitting time ($p<0.001$). Never or past history of smoking was most common in Q1 and Q2 while no alcohol use was most frequent among those in Q1. Finally, 10-16 hours of sleep and inadequate fruit and vegetable consumptions were more common among the two higher quartiles when compared to the lower two.

Relationship between Sitting Time, CVD, Cancer and All-Cause Mortality

To quantify the relationship of sitting time with CVD, cancer, and all-cause mortality, hazard ratios were calculated for model 1: unadjusted; model 2: adjusted for age, income, education, ethnicity; model 3: additionally adjusted for alcohol history, leisure time physical activity, BMI, smoking; model 4: additionally adjusted for general health, hormone use, physical limitations but not physical activity and smoking; and model 5: all adjusted **(Table 2).** Fully adjusted results revealed those in Q3 and Q4 were at higher risk for all-cause (Q3: HR: 1.13, 95% CI: 1.04-1.22; Q4: HR: 1.26, 95% CI: 1.11-1.44) and cancer mortality (Q3: HR: 1.17, 95% CI: 1.04-1.31; Q4: HR: 1.38, 95% CI: 1.13-1.67) compared to Q1. No significant increase in risk was found between sitting time and CVD mortality after adjusting for age, SES, ethnicity, BMI, leisure time physical activity, smoking, alcohol hormone use, general health and physical limitations. There were also significant interactions of sitting time with all-cause and cancer mortality within subgroups of age (p for interaction 0.02 and 0.03, respectively. Accordingly, **Table 3** displays the mortality risk for mortality by age category. Individuals in quartile 3 and 4 were at increased mortality risks for all-cause (Q3: HR: 1.11, 95% CI: 1.01-1.22; Q4: 1.30, 95% CI: 1.10-1.53) and cancer mortality (Q3: HR: 1.20, 95% CI: 1.03-1.39; Q4: 1.30, 95% CI: 1.02-1.71) respectively, if they were 65 years of age or older.

Sitting Time and Risk Factors

Figure 1 presents the relationship between sitting time and all-cause, CVD and cancer mortality stratified by physical activity level. Significant interactions of sitting time with physical activity were reported for all-cause (p-interaction=0.002) and cancer (p-interaction=0.02) but not CVD mortality (p-interaction=0.24). For consistency however, we present the CVD data as well. A significant all-cause and cancer mortality risk was seen for sitting time amongst physically inactive individuals **(Figure 1: A&C)**. Additionally, the risk increased in a dose response pattern across sitting time quartiles. For instance, those in the Q4/physically inactive category had a (HR: 1.64, 95% CI: 1.39-1.90) of all-cause and (HR: 1.84, 95% CI: 1.46-2.32) and cancer mortality compared to those who were in the Q1/physically active group. Next, **Figure 2** presents the relationship between sitting time and all-cause, CVD and cancer mortality stratified by smoking history. Significant interactions of sitting time with smoking history were reported for all-cause (p-interaction=0.03) and cancer (p-interaction=0.04) but not CVD mortality (p-interaction=0.32). Again, for consistency sake, we present the CVD data as well. Similar to results in Figure 1, a significant all-cause and cancer mortality risk was seen for sitting time amongst those with a history of smoking **(Figure 2: A&C).** The risk also increased in a dose response manner across sitting time quartiles. To illustrate, Q4/current smokers had over a 3 fold increase in all-cause (HR: 3.41, 95% CI: 2.51-4.63) and cancer (HR: 3.93, 95% CI:2.54-6.07) mortality risk compared to Q1/never smokers. No other risk factors assessed yielded significant interactions for all-cause, CVD or cancer mortality.

Discussion

In this large prospective cohort of post-menopausal women, sitting time was positively linked to all-cause and cancer mortality. Individuals within the two highest quartiles of sitting time exhibited elevated mortality risks compared to those in the lowest quartile. These relationships persisted even after adjustments for related covariates (leisure time physical activity, BMI, age, ethnicity, alcohol and smoking history, education, income, hormone use, general health and physical limitations).

These findings are generally consistent with previous reports which assessed the sitting-mortality relationship in younger cohorts (Katzmarzyk et al., 2009; Koster et al., 2012; Wijndaele et al., 2011). To illustrate, in a large prospective cohort of 53 400 men and 69 776 women, time spent sitting (≥ 6 vs. <3 hours/day) was associated with mortality in both women (RR:1.34) and men (RR:1.17) (Patel et al., 2010). Furthermore, in Australian adults ≥ 25 years of age, each 1-hour increment in television viewing time per day was associated with an increased mortality risk of 1.11, 1.18 and 1.09 for mortality from all-cause, CVD and cancer, respectively (Dunstan et al., 2010). These findings in conjunction to ours continue to underline the importance of minimizing sedentary behaviour throughout the day.

Our results also target certain types of profiles over others. In essence, individuals with the greatest mortality rates were those who exhibited high volumes of daily sitting but were also either categorized as a smoker or physically inactive. However, physical activity (>=500 MET-min/week) offset the mortality risk associated with sitting time. Similar results were found in an analyses of the Australian Longitudinal Study on Women's Health (Pavey et al., 2012), where no significant interactions between sitting time and mortality were seen for individuals who met physical activity guidelines. Additionally, earlier studies have found the greatest mortality risks for individuals who did not meet or only met the minimum physical activity guidelines (Katzmarzyk et al, 2009; Matthews et al, 2012; van der Ploeg et al, 2012). For the most part, the principal message from the results seem to be the potential risks of excess sitting when present in individuals exhibiting other unhealthy patterns. Individuals who either smoke, or are physically inactive should therefore be of priority in limiting sitting time throughout the day. Moreover, for the majority of the cross analyses, mortality risk increased with each increasing level of sitting time regardless of risk factor category, thus supporting the benefit of limiting sitting time in these subgroups. When we stratified by age group (<65 vs. ≥65 years of age) we found that only individuals 65years and older had significant mortality risks for all-cause and cancer mortality suggesting the relationship is mostly driven by women of the retirement age. This may be due to differences in body composition and diet although we cannot say for certain as we did not assess this. In addition, our sitting time variable which included both sitting during occupational and leisure time hours may explain this relationship. In essence, the sitting time within our older subgroup, may have been composed of more television watching because they are more likely to be retired than the younger group (Chomistek et al., 2013) .Consequently, sitting while watching television has been found to be more harmful than overall sitting time (Matthews et al., 2012). Together, these findings reinforce the importance of adding sitting time guidelines to current public health initiatives.

The descriptive characteristics of our analytical sample also revealed some interesting patterns. Namely, higher BMI and lower leisure time physical activity levels were present with each increasing quartile of sitting time. This is consistent with the literature and continues to show a correlation between sitting time and other health patterns and behaviours. For instance, women aged 65-74 who reported high TV time, were more likely to engage in lower levels of physical activity (<200 min/week) vs. ≥510 min/week (Kikuchi et al., 2013). Our results further revealed an increase in BMI with increasing sitting time. This is supported by various studies illustrating an association of sedentary behaviours with increased adiposity, and other markers of obesity. For example, in a cross-sectional study of 3 136 people ≥65 years of age, women who sat in excess of four hours per day and walked less than one hour were at an increased risk of overweight-obesity (1.5 fold) and over fat (1.4 fold) compared with those who spent sitting less than four hours per day(Gomez-Cabello et al., 2012). Additionally, in a cross-sectional analyses of 466 605 generally healthy participants from China, (Du et al., 2013), for any given physical activity level, greater sedentary time was associated with a greater prevalence of increased BMI, as was lower physical activity for any given sedentary time. In addition to obesity (Shields & Tremblay, 2008; Mortensen et al.,2006; Patrick et al., 2004), sedentary behaviour has also been associated with smoking; both of which are known to have ties with various diseases and premature death (Gellert et al., 2012; Solomon & Manson, 1997).

In regards to cause of death, it was surprising to note that sitting time was more closely linked to mortality from all-cause and cancer than CVD in our study. Most studies have found significant relationships for all-cause and CVD but not cancer mortality. In our study however, trends for CVD mortality were not significant once fully adjusted for related covariates. For example, an analysis of the Ausdiab study found that compared with a television viewing time of less than two hours per day, the fully adjusted hazard ratios for all-cause mortality were (HR: 1.13, 95% CI: 0.87-1.36 for $\geq$2 to <4 h/d ; HR: 1.46, 95% CI: 1.04-2.05 for $\geq$4 h/d) and (HR: 1.19, 95% CI: 0.72-1.99 and HR: 1.80, 95% CI: 1.00-3.25) for CVD mortality (Dunstan et al.,2010). Moreover, in the Canada Health Survey, there was a dose response relationship between sitting and mortality from all-cause and CVD but not cancer (Katzmarzyk et al., 2009). Even so, literature suggesting no relationship between sitting and CVD incidence does exist in a study of middle aged women (Herber-Gast et al., 2013). Investigators have also found CVD mortality to not always be linked to sedentary behaviour (Katzmarzyk, 2010; Warren et al., 2010). The lack of association in our study however may also be explained by the characteristic profile of this sample. Over 60% of women who were recruited into this study were in fact taking postmenopausal hormones, a preventative intervention for coronary disease, at baseline. In conjunction with this benefit, women choosing to take hormones possess more optimal health profiles and make healthier decisions than women who do not (Langer et al., 2003). Moreover, a growing body of evidence is supporting a link between sedentary behaviour and various cancer outcomes in women. For example, watching TV/sitting per day has been linked to endometrial (Friberg et al., 2006) and ovarian cancer (Patel et al., 2006). In addition, sitting for at least six hours per day was associated with a 30% increased odds of cancer mortality compared to women who sat less than three (Patel et al., 2010).

Findings from this study also suggest that a minimum threshold of 10 hours of daily sitting (Table 2: Q3 and Q4) must be met to be at increased risk for all-cause and cancer mortality. Similar thresholds have also been reported in other cohorts. In a study of older Australian women, they found a range of between 7 and 9 hours of sitting per day, above which sitting was associated with an increased risk of all-cause mortality (Pavey et al., 2012). In another, only individuals who sat for at least 7 hours were at elevated risks for mortality from all-cause, CVD and cancer (Matthews et al., 2008).

Strengths and Limitations

There are several strengths and limitations of this study that warrant discussion. First, data collection involved self-reported measures of sitting and physical activity by means of questionnaires. Although self-report carries its benefits such as low cost and accessibility, it bears many disadvantages which may compromise the validity and reliability of the study

(Austin et al., 1998; Fan et al., 2006). Self-report methods have the capacity to over- or underestimate true physical activity energy expenditure and rates of inactivity (Prince et al., 2008).They also often contain issues of recall and response bias (e.g. social desirability, inaccurate memory) and the inability to capture the absolute level of activity (Prince et al., 2008). However, a few studies have discovered considerable agreement between accelerometer and self-reported data on sedentary time and physical activity in active (Hart et al., 2011; Hagstromer et al., 2010) and sedentary cohorts. Also, having only used baseline data for sitting time and physical activity, we may have missed out on some noticeable changes across time which could have influenced the relationship. Finally, women in the Observational Cohort (OS) were likely to be taking hormone therapy, have low dietary intake and have a cluster of other healthy behaviours (Langer et al., 2003). As a result, the generalizability of the results beyond the WHI study sample to the broader US or Canadian population is unclear.

Implications and Future Directions

Together, our findings add to the current body of literature outlining the potential dangers of extensive sitting time. Consistent with analyses of different cohorts, our study suggests higher levels of sitting to have stepwise increases in mortality risk. In our age and gender specific cohort, mortality risk was further amplified when sitting occurred simultaneously with other unhealthy behaviours such as smoking and physical inactivity. For that reason, public health initiatives should include the promotion of not only physical activity but guidelines for making reductions to sitting time as well.

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Figure Legends

Table 1: Baseline Characteristics of Women's Health Initiative Participants (n=84 865) by Sitting Quartile

Characteristics	Sitting Time (Hours/day)					p-Value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Overall	
N (%)	29 386(34.63)	34 763(40.96)	17 185(20.25)	3 531 (4.16)	84 865	<.0001
Death (n, %)	1 824 (33.42)	2 276 (41.70)	1 091 (19.99)	267 (4.89)	5 458(6.43)	0.01
Follow Up Time (Mean Years)	5.24 (2.33)	5.14 (2.26)	5.26 (2.33)	5.10 (2.26)	5.19 (2.36)	<.0001
Age (Years)	64.27 (7.17)	64.23 (7.25)	61.61 (7.37)	61.43 (7.51)	63.60 (7.35)	<.0001
Physical Activity (MET-min/wk)	907.8 (955.8)	794.4 (834.6)	688.2 (761.4)	543 (694.8)	801.6 (865.2)	<.0001
Physical Activity Level (n, %)						
<500MET-min/wk	12 915(31.94)	16 286(40.27)	9 025(22.32)	2 213(5.47)	40 439(47.65)	<.0001
≥500MET-min/wk	16 471(37.08)	18 477(41.59)	8 160(18.37)	1 318(2.97)	44 426(52.35)	<.0001
BMI (kg/m^2)	26.70 (4.98)	27.16 (5.29)	27.73 (5.71)	28.98 (6.28)	27.19 (5.35)	<.0001
BMI Category(n, %)						
Normal	12 659(36.97)	14 044(41.02)	6 483(18.94)	1 051(3.07)	34 237(40.46)	<.0001
Overweight	10 422(35.23)	12 230(41.34)	5 752(19.44)	1 179(3.99)	29 583(34.96)	<.0001
Obese	6 235(29.97)	8 390(40.32)	4 889(23.50)	1 293(6.21)	20 807(24.59)	<.0001
Smoker (n, %)						
Never	15 798(36.59)	17 687(40.97)	8 107(18.78)	1 578(3.66)	43 170(50.87)	<.0001
Past	11 941(32.79)	14 979(41.13)	7 862(21.59)	1 634(4.49)	36 416(42.91)	<.0001
Current	1 647(31.20)	2 097(39.72)	1 216(23.03)	319 (6.04)	5 279(6.22)	<.0001
Alcohol (n, %)						
Never	4 086(43.48)	3 527(37.53)	1 438(15.30)	347(3.69)	9 398(11.11)	<.0001
Past	5 667(35.85)	6 263(39.62)	3 117(19.72)	759 (4.80)	15 806(18.69)	<.0001
Current (1-7 drinks/week)	15 990(32.85)	20 314(41.73)	10 370(21.30)	2 005(4.12)	48 679(57.56)	<.0001
Current (>7 drinks/week)	3 501(32.77)	4 566 (42.74)	2 204(20.63)	413(3.87)	10 684(12.63)	<.0001
Education (n, %)						
<High school	2 203(52.44)	1 440(34.28)	440 (10.47)	118(2.81)	4 201(4.99)	<.0001
High school graduate	5 202(37.89)	5 678(41.35)	2 397(17.46)	453(3.30)	13 730(16.31)	<.0001
Some college	10 937(35.47)	12 509(40.57)	6 100(19.78)	1 289(4.18)	30 835(36.62)	<.0001
College graduate	10 778(30.41)	12 908(42.07)	8 114(22.90)	1 638(4.62)	35 438(42.09)	<.0001
Income (n, %)						
<19 999	6 533(40.83)	6 329(39.56)	2 540(15.88)	597(3.73)	15 999(18.85)	<.0001
$20 000-$74 999	16 697(33.25)	20 986(41.78)	10 442(20.79)	2 099(4.18)	50 224(59.18)	<.0001
≥$75 000	5 054(31.24)	6 515(40.27)	3 858(23.85)	750(4.64)	16 177(19.06)	<.0001
Don't know	3 501(32.77)	4 566(42.74)	2 204(20.63)	413(3.87)	10 684(12.63)	<.0001
Sleep Hours(n,%)						

0-7	12 752(41.09)	11 172(35.99)	5 649(18.20)	1 465(4.72)	31 038(36.64)	<.0001
8-9	12 433(32.10)	16 831(43.45)	8 129(20.99)	1 341(3.46)	38 734(45.72)	<.0001
10-16	4 131(27.64)	6 708(44.88)	3 387(22.66)	720(4.82)	14 946(17.64)	<.0001
Fruit and Vegetable Consumption (n,%)						
Inadequate	26 082(34.23)	31 171(40.91)	15 670(20.57)	3 265(4.29)	76 188(89.78)	<.0001
Meets Requirements	3 304(38.08)	3 592(41.40)	1 515(17.46)	266(3.07)	8 677(10.22)	<.0001

Means (SD), Frequencies (%)-Chi-Square and ANOVA comparisons

p for trend across quartiles of daily sitting time

Abbreviations: N, Sample Size; MET-min/week, metabolic equivalent of task per min per week; BMI, Body Mass Index

Quartiles: 1, ≤5 daily hours of sitting; 2, 6-9 daily hours of sitting; 3, 10-13 daily hours of sitting; 4, 14+ daily hours of sitting

Table 2: Risk of All-Cause, Cardiovascular Disease and Cancer Related Mortality associated with Total Daily Sitting Time (Quartiles)

Death Cause	**Sitting Time (Hours/day)**				
All-Cause	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-value**
Model 1 HR(95% CI)	1.00(Ref)	1.03 (0.97-1.10)	0.98 (0.91-1.05)	1.19*(1.04-1.35)	0.13
Model 2 HR(95% CI)	1.00(Ref)	1.07(1.00-1.14)	1.26*(1.17-1.36)	1.52*(1.34-1.73)	<.0001
Model 3 HR(95% CI)	1.00(Ref)	1.03(0.96-1.09)	1.14*(1.06-1.24)	1.32*(1.16-1.50)	<.0001
Model 4 HR(95% CI)	1.00(Ref)	1.04 (0.98-1.11)	1.19 *(1.10-1.29)	1.37*(1.20-1.56)	<.0001
Model 5 HR(95% CI)	1.00(Ref)	1.02 (0.96-1.08)	1.13*(1.04-1.22)	1.26*(1.11-1.44)	<.0001
CVD					
Model 1 HR(95% CI)	1.00(Ref)	0.98(0.87-1.10)	0.86*(0.75-0.99)	1.12(0.88-1.42)	0.80
Model 2 HR(95% CI)	1.00(Ref)	1.02(0.91-1.14)	1.20*(1.04-1.39)	1.53*(1.20-1.95)	<.0001
Model 3 HR(95% CI)	1.00(Ref)	0.98 (0.87-1.10)	1.07(0.92-1.24)	1.28*(1.01-1.64)	0.03
Model 4 HR(95% CI)	1.00(Ref)	0.99 (0.89-1.12)	1.10 (0.95-1.28)	1.31*(1.03-1.68)	0.007
Model 5 HR(95% CI)	1.00(Ref)	0.97(0.86-1.09)	1.04(0.90-1.21)	1.21(0.95-1.54)	0.08
Cancer					
Model 1 HR(95% CI)	1.00(Ref)	1.07(0.98-1.18)	1.07(0.96-1.20)	1.32*(1.10-1.60)	0.02
Model 2 HR(95% CI)	1.00(Ref)	1.09(0.99-1.20)	1.28*(1.14-1.44)	1.59*(1.31-1.93)	<.0001
Model 3 HR(95% CI)	1.00(Ref)	1.05(0.95-1.15)	1.17*(1.05-1.32)	1.40*(1.15-1.69)	0.0002
Model 4 HR(95% CI)	1.00(Ref)	1.07 (0.97-1.17)	1.23*(1.10-1.38)	1.49*(1.23-1.80)	<.0001
Model 5 HR(95% CI)	1.00(Ref)	1.04(0.95-1.15)	1.17*(1.04-1.31)	1.38*(1.13-1.67)	0.0004

model 1: unadjusted
model 2: age, income, education, ethnicity
model 3: age, income, education, ethnicity, alcohol history, leisure time physical activity, BMI, smoking
model 4: age, income, education, ethnicity, alcohol history, BMI, general health, hormone ever, physical limitations
model 5: age, income, education, ethnicity, alcohol history, leisure time physical activity, BMI, smoking, general health, hormone ever, physical limitations

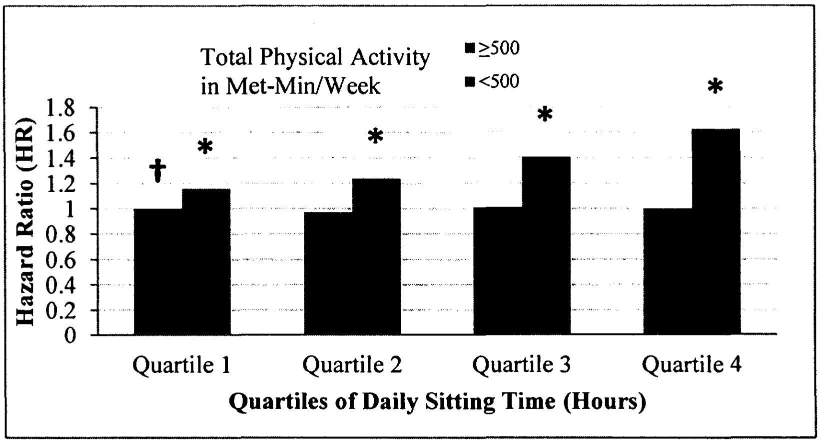
Quartiles: 1, ≤5 daily hours of sitting; 2, 6-9 daily hours of sitting; 3, 10-13 daily hours of sitting; 4, 14+ daily hours of sitting;
Abbreviations: BMI, Body Mass Index; CI, Confidence interval
All covariates collected at the period of baseline

Table 3: Risk of All-Cause, Cardiovascular Disease and Cancer Related Mortality associated with Total Daily Sitting Time by Age Category

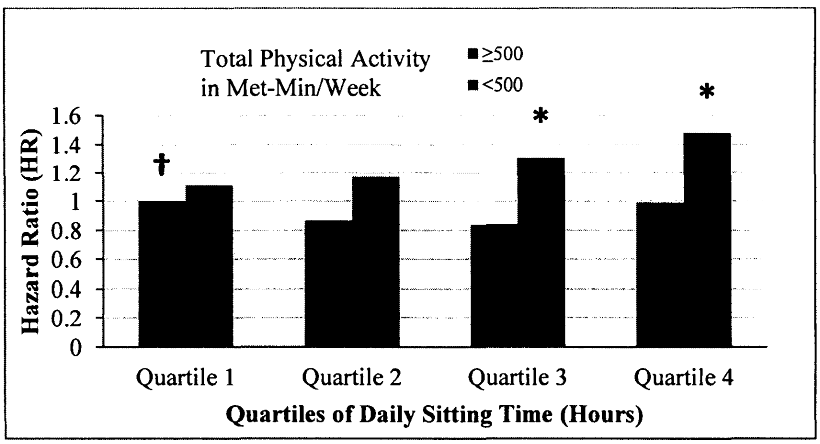
	Quartiles of Daily Sitting Time				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
All Cause					p-value
Aged <65	1.00	1.03(0.91-1.16)	1.07 (0.94-1.23)	1.12 (0.90-1.39)	0.15
Aged ≥65	1.00	1.02 (0.95-1.11)	1.11*(1.01-1.22)	1.30*(1.10-1.53)	0.0004
CVD					
Aged <65	1.00	1.12 (0.84-1.47)	0.99 (0.72-1.36)	0.79 (0.45-1.37)	0.72
Aged ≥65	1.00	0.95 (0.83-1.07)	1.04 (0.88-1.22)	1.37 (1.00-1.80)	0.05
Cancer					
Aged <65	1.00	1.00 (0.84-1.19)	1.07 (0.89-1.29)	1.34 (1.00-1.77)	0.11
Aged ≥65	1.00	1.06(0.95-1.19)	1.20*(1.03-1.39)	1.30*(1.02-1.71)	0.006

Cox Proportional Hazards Regression modelled with Quartile 1 (≤ 5 hours of daily sitting) as referent; p< 0.05
Presented as HR + 95% CI
Model adjusted for income, education, ethnicity, alcohol history, leisure time physical activity, BMI, smoking history, general health, physical limitations and hormone ever
Quartiles: 1, ≤5 daily hours of sitting; 2, 6-9 daily hours of sitting; 3, 10-13 daily hours of sitting; 4, 14+ daily hours of sitting;
Abbreviations: BMI, Body Mass Index; CI, Confidence interval
All covariates collected at the period of baseline

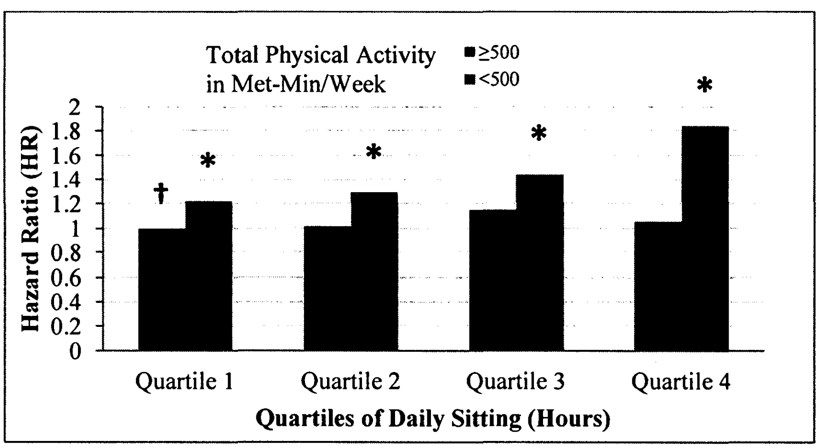
Figure 1: Risk of All-Cause, Cardiovascular Disease and Cancer Related Mortality associated with Total Daily Sitting Time by Physical Activity Level



A)



B)



C)

*Figure 1: A) All-Cause Mortality, B) CVD Mortality, C) Cancer Mortality. Figures adjusted for age, income, education, ethnicity, alcohol history, BMI, smoking history, general health, physical limitations and hormone ever Quartiles: 1, ≤5 daily hours of sitting; 2, 6-9 daily hours of sitting; 3, 10-13 daily hours of sitting; 4, 14+ daily hours of sitting. *P<.05 compared with reference group. † Reference group.*

Figure 2: Risk of All-Cause, Cardiovascular Disease and Cancer Related Mortality associated with Total Daily Sitting Time by Smoking History

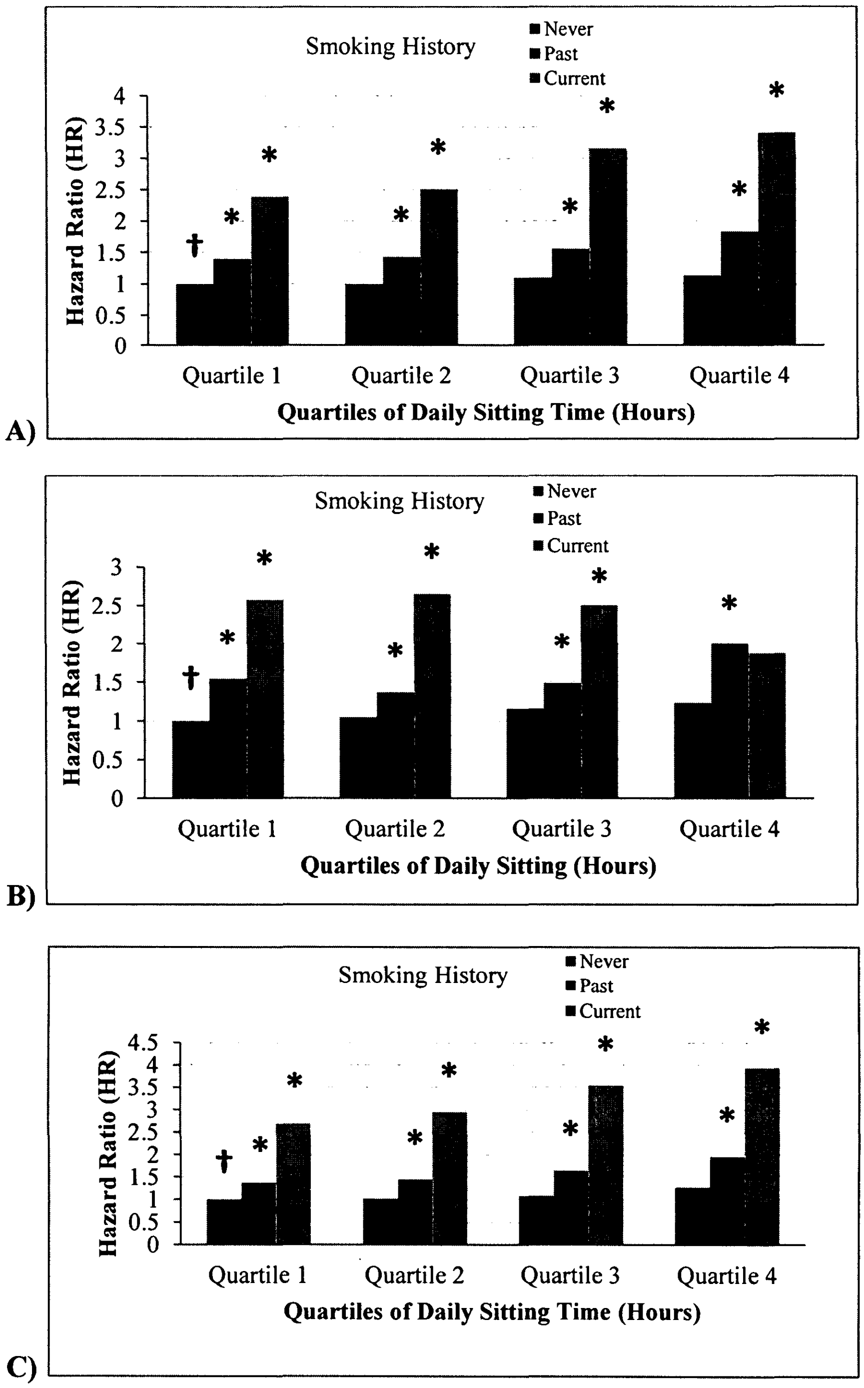


*Figure 2: A) All-Cause Mortality, B) CVD Mortality, C) Cancer Mortality. Figures adjusted for age, income, education, ethnicity, alcohol history, BMI, physical activity level, general health, physical limitations and hormone ever; Quartiles: 1, ≤5 daily hours of sitting; 2, 6-9 daily hours of sitting; 3, 10-13 daily hours of sitting; 4, 14+ daily hours of sitting. *P<.05 compared with reference group. † Reference group.*

Extended Discussion

Results from this study reveal that sitting time was positively associated with mortality from all-cause and cancer. Study participants who at baseline sat for 10-13 (Q3) and 14+ (Q4) hours had a 13% and 26% increased risk from all-cause, and a 17% and 38% increased risk from cancer compared to the least sedentary. Moreover, when in combination with one of the following lifestyle risk factors (i.e. smoking, leisure-time physical inactivity) the mortality risk associated with excess sitting was elevated even further. For instance, women who did not engage in at least 500 MET-min of energy expenditure per week and sat in excess of 14 hours daily had a 63% greater risk of all-cause mortality compared to those who were active and reported low sitting time. These elevated risks however, were absent in women who were non-smokers or physically active. These results are contradictory to much of the literature which finds sedentary time to exert its effects on health and mortality regardless of other factors.

As such, a major limitation of our study was the crude nature of the variables in question, especially the sitting time and physical activity variable. For this study, we investigated these variables at baseline and the resulting mortality risk at follow-up. Therefore, we were unable to track and account for potential changes in activity patterns over the years. Rather than stay static, activity patterns are dynamic and known to fluctuate across time (Picavet et al., 2011; Paffenbarger et al., 1993; Schnohr et al., 2003). This is particularly important for older women, as they are a demographic highly vulnerable to a decline in activity, with only a small fraction (39.3%) of American adults aged 65 years and older meeting current physical activity guidelines (Centers for Disease Control and Prevention (US), 2010). Several studies have also found that leisure time physical activity levels (Sallis et al., 2000; Caspersen et al., 2000; Ingram, 2000) and total energy expenditure (Gordon-Larsen et al., 2004; Manini, 2010) decline with age. This trend is especially concerning, as post-menopausal women have greater risk of atherosclerosis, angina and hypertension (Meadows & Vaughan, 2011; Colombel & Charbonel, 1997), which may be exacerbated by lower activity levels.

Many studies have also investigated changes in physical activity over time (Steffen-Batey et al., 2000; Matthews et al., 2008; Warren et al., 2010; Gregg et al., 2003), the majority of which find that increasing energy expenditure have favourable returns on health, while decreases tend to have a negative impact; to date however, only one other study on 2 635 Spanish persons aged 60 and older (León-Muñoz et al., 2013) has assessed changes in sedentary time and their impending mortality risks. In this study, compared to persons who were consistently sedentary, only those who remained consistently non-sedentary had significantly lower mortality risks (HR: 0.75, 95% CI: 0.62-0.90).

Thus, to not only compare but to investigate this further, a preliminary analysis of changes in sedentary time between baseline and follow-up at year 6 was conducted in the WHI sample.

For purposes of this analysis, the sitting variable was dichotomized as 'low to moderate' (≤9 hours of daily sitting) or 'high' (≥10 hours of daily sitting). These cut-offs were based on the earlier analysis wherein stronger relationships between sitting time and mortality were seen for participants who sat in excess of 9 hours. To test for changes in sitting volumes and corresponding mortality risk, we compared 4 groups; the referent group which were women considered high sitting time at both baseline and follow-up ("stayed high"; RR:1.00), women who were considered low-moderate sitters at both baseline and follow-up ("stayed low"), women who went from low-moderate at baseline to high at follow-up ("increased sedentary"), and women who went from high at baseline to low-moderate at the follow-up ("decreased sedentary")(Gregg et al., 2003).

Compared to participants who stayed high at both time points (HR:1.00), all-cause mortality risk was roughly 38% higher for women who increased their sitting time over time **(Table 2).** Women however who sustained low sitting time during the follow-up period had a modest decrease in risk by 16%. Additionally, only women who stayed at low levels of sitting time had lower levels of cancer mortality at 31%, and in fully adjusted models, no significant results were found for mortality from CVD.

To determine whether differences in age modified the relationship between changes in sitting time and mortality, results were presented separately for those less than and at least 65 years of age (**Table 3**). Women in both age groups who increased sedentary throughout the follow-up had a (<65: HR: 1.58, 95% CI: 1.10-2.28) and (≥65: HR: 1.36, 95% CI: 1.07-1.75) for all-cause mortality, compared to those who remained high at both time points. This was an interesting outcome as the results suggest increasing sitting levels over time may be more harmful than sustaining high levels itself. In contrast, only women who remained low and were at least 65 years of age saw protective effects from all-cause.

When we stratified by physical activity levels **(Table 4)**, inactivity either at baseline or year 6 resulted in an increased mortality risk if one increased their sitting time over the follow up period, (baseline: HR: 1.29, 95% CI: 1.02-1.66; year 6: HR: 1.39, 95% CI: 1.11-1.74). In contrast, individuals who met recommended physical activity levels at baseline were at a 53%

increased risk of mortality if they increased their sitting time. Moreover, individuals had a 20% and 17% lower risk of mortality if they sustained low levels of sitting time regardless if they were active at baseline or follow-up. Again, results were somewhat surprising as a physically active status at baseline resulted in a greater risk than being inactive. In addition, only women who were inactive at either time points and remained low sedentary had their risk reduced. These results may suggest that when it comes to changes in activity patterns across time, sitting time may have a stronger influence on life expectancy than physical activity.

Finally, we conducted logistic regressions to predict the odds of 1) maintaining low sitting levels and 2) maintaining *or* lowering sitting time. Covariates in this analysis included age, sex, education, income, ethnicity, physical activity, BMI, smoking history and alcohol consumption. In general, abstainers from alcohol were 30% more likely to maintain and/or lower their sitting when compared to regular drinkers. As anticipated, individuals who stayed below the threshold of 500 met-min/week were also 32% less likely to reach the low sitting category compared to individuals who became active (HR: 1.00). Additionally, maintainers of adequate physical activity were 34% more likely to maintain low sitting levels.

When compared to the only other study which assessed changes in sitting time, both studies found that when compared to those who stayed sedentary at both time points, individuals who maintained low levels at both times reaped the most favourable survival rates. However, we also had significant increases in all-cause mortality risk for individuals who increased their sitting volumes over time whereas the Spanish cohort did not. Our results therefore stress the importance of maintaining low levels throughout time not only to prevent an elevation in risk but to also see protective gains.

Table 1: Characteristics of Study Population by Change in Sitting between Baseline and Follow-up at Year 6

		High Sitting at Baseline		Low to Moderate Sitting at Baseline		p-value
Characteristics	**Total 68 652**	**Stayed High 7 361**	**Lowered Sedentary 9 759**	**Increased Sedentary 5 887**	**Stayed Low 45 645**	
Death	1 542(2.25)	211(13.68)	196(12.71)	226(14.66)	909(58.95)	<.0001
Age (years), mean (SD)	63.19(7.21)	60.47(7.41)	61.68(6.96)	63.40(7.71)	63.92(7.00)	<.0001
Body Mass Index, mean (SD)	27.13(5.53)	28.61(6.64)	27.51(5.72)	28.05(6.06)	26.69(5.14)	<.0001
Physical Activity at Baseline						
Inactive	31628(46.07)	4 265(13.48)	4 748(15.01)	3 127(9.89)	19 488(61.62)	<.0001
Active	37024(53.93)	3 096(8.36)	5 011(13.53)	2 760(7.45)	26 157(70.65)	<.0001
Physical Activity at Follow-up						
Inactive	32945(47.99)	4 337(13.16)	4 663(6.79)	3 405(4.96)	20 540(29.92)	<.0001
Active	35707(52.01)	3 024(8.47)	5 096(14.27)	2 482(6.95)	25 105(70.31)	<.0001

**Data are presented as number (percentage) unless otherwise indicated and are based on information collected at baseline visit except for death and physical activity status at follow-up. P<.0001 in a test for heterogeneity across groups for all variables.*
Body mass index is calculated as weight in kilograms divided by the square of height in meters.
>=500 MET minutes per week is deemed physically active.

Table 2: Mortality Risk by Change in Sitting Time at 6 Year Follow-up

Cause of Death	**High Sitting at Baseline**		**Low to Moderate Sitting at Baseline**		**p-value**
	Stayed High	**Lowered Sedentary**	**Increased Sedentary**	**Stayed Low**	
All-Cause					
Model 1	1.00	0.83(0.68-1.01)	1.49*(1.23-1.80)	0.83(0.71-0.96)	0.03
Model 2	1.00	0.79*(0.64-0.96)	1.14(0.93-1.38)	0.64*(0.55-0.75)	0.19
Model 3	1.00	0.86(0.70-1.05)	1.10(0.90-1.34)	0.72*(0.61-0.84)	0.37
Model 4	1.00	1.02(0.83-1.26)	1.38*(1.13-1.69)	0.84*(0.71-0.98)	0.28
CVD					
Model 1	1.00	0.78(0.52-1.18)	1.86*(1.28-2.70)	0.97(0.71-1.32)	0.005
Model 2	1.00	0.71(0.45-1.09)	1.32(0.89-1.95)	0.72*(0.52-0.99)	0.43
Model 3	1.00	0.79(0.51-1.23)	1.28(0.86-1.90)	0.86 (0.61-1.19)	0.31
Model 4	1.00	0.83(0.53-1.31)	1.31(0.88-1.97)	0.97(0.69-1.36)	0.18
Cancer					
Model 1	1.00	0.90(0.68-1.20)	1.10(0.82-1.49)	0.70*(0.56-0.87)	0.15
Model 2	1.00	0.91(0.68-1.21)	0.92(0.67-1.25)	0.57*(0.45-0.73)	0.002
Model 3	1.00	0.98(0.73-1.30)	0.91(0.67-1.24)	0.63*(0.50-0.81)	0.006
Model 4	1.00	1.13(0.84-1.51)	1.14(0.83-1.57)	0.69*(0.54-0.88)	0.08

**Data are presented as hazard ratios (95% confidence intervals). Covariates were reported at baseline unless indicated otherwise.*
model 1: unadjusted
model 2: age, income at year 6, education, ethnicity
model 3: age, income at year 6, education, ethnicity, alcohol consumption at year 6, leisure time physical activity at year 6, BMI, smoking at year 6
model 4: age, income at year 6, education, ethnicity, alcohol consumption at year 6, leisure time physical activity at year 6, BMI, smoking at year 6, physical limitations, hormone use ever, history of CVD, cancer and diabetes
Cox Proportional Hazards Regression modelled with(Stayed High) as referent; $p< 0.05$
Abbreviations: BMI, Body Mass Index; CI, Confidence interval; CVD, Cardiovascular disease

Table 3: Hazard Ratios for All-Cause Death Associated with Changes in Sitting, Stratified by Age

	High Sitting at Baseline		Low to Moderate Sitting at Baseline		p-value
	Stayed High	**Lowered Sedentary**	**Increased Sedentary**	**Stayed Low**	
Aged <65					
Model 1	1.00	1.30 (0.93-1.82)	1.58*(1.10-2.28)	1.18(0.89-1.56)	0.07
Aged ≥65					
Model 1	1.00	0.94(0.72-1.24)	1.36*(1.07-1.75)	0.77*(0.63-0.96)	0.34

**Data are presented as hazard ratios (95% confidence intervals). Covariates were reported at baseline unless indicated otherwise.*
Model 1: Adjusted for income at year 6, education, ethnicity, alcohol consumption at year 6, leisure time physical activity at year 6, BMI, smoking at year 6, physical limitations, hormone use ever, history of CVD, cancer and diabetes
Cox Proportional Hazards Regression modelled with (Stayed High) as referent; p< 0.05
Abbreviations: BMI, Body Mass Index; CI, Confidence interval; CVD, Cardiovascular disease

Table 4: Hazard Ratios for All-Cause Death Associated with Changes in Sitting, Stratified by Physical Activity

Baseline	**High Sitting at Baseline**		**Low to Moderate Sitting at Baseline**		**p-value**
	Stayed High	**Lowered Sedentary**	**Increased Sedentary**	**Stayed Low**	
Model 1					
Inactive	1.00	1.05(0.81-1.35)	1.29*(1.02-1.66)	0.80*(0.65-0.98)	0.79
Active	1.00	0.79(0.55-1.14)	1.53*(1.08-2.17)	0.82(0.62-1.08)	0.17
Follow-up	**High Sitting at Baseline**		**Low to Moderate Sitting at Baseline**		**p-value**
	Stayed High	**Lowered Sedentary**	**Increased Sedentary**	**Stayed Low**	
Model 1					
Inactive	1.00	1.02(0.79-1.30)	1.39*(1.11-1.74)	0.83*(0.68-0.98)	0.25
Active	1.00	0.96(0.64-1.43)	1.40(0.89-2.20)	0.89(0.63-1.26)	0.59

**Data are presented as hazard ratios (95% confidence intervals). Covariates were reported at baseline unless indicated otherwise.*
Model 1: Adjusted for baseline age, income at year 6, education, ethnicity, alcohol consumption at year 6, BMI, smoking at year 6, physical limitations, hormone use ever, history of CVD, cancer and diabetes
Cox Proportional Hazards Regression modelled with (Stayed High) as referent; p< 0.05
Abbreviations: BMI, Body Mass Index; CI, Confidence interval; CVD, Cardiovascular disease

Conclusion

The aim of this study was to highlight the potentially dangerous implications of prolonged sitting on our life expectancy. Consistent with earlier studies on different cohorts, analysis on our post-menopausal sample also provides evidence of a harmful relationship between sedentary time and mortality. Women within the two highest quartiles of daily sitting had marked mortality risks from all-cause and cancer compared to women in the lowest. These outcomes are especially troubling as women are inclined to sit more frequently as they age (Matthews et al., 2008). Additionally, increases in sitting time are likely paralleled by decreases in physical activity (Charansonney, 2011), further amplifying the risk associated with lack of activity. In our cross analyses (Figure 1), we considered the interaction of sitting time with other lifestyle components. We found that participants in Q4 who were also either smoking at baseline or were classified as physically inactive experienced clear elevations in risk compared to those who made healthier decisions. To date, only a few studies have surfaced looking at the influence of sitting time in conjunction with other risk factors on our health. It follows that sedentary behaviour exist in the presence of other unhealthy patterns such as over-eating and smoking (Katzmarzyk, 2010; Ottevaere et al., 2011; Al-Hazzaa et al., 2011; Le Marchand et al., 1997. Our results therefore reflect on the importance of assessing how sedentary time may interact with other behavioural elements to augment any risk. Given the probable changes to sedentary behaviour and physical activity over time, our assessment on the change of sedentary behaviour from baseline and year 6 suggests that women who sustained low sedentary levels throughout were at 16% and 31% lower all-cause and cancer mortality risks respectively, compared to women whose sedentary time stayed high.

Moreover, women who increased their sitting levels markedly increased their mortality risks. Ultimately, this suggests the importance of maintaining low levels of sedentary behaviour across time to maximize life expectancy.

For future analyses, efforts should be made to evaluate these components across longer time periods in conjunction with other major lifestyle factors to better understand this complex relationship; these relationships should also be assessed in other demographic cohorts to identify how sedentary behaviour affects groups differently.

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Appendices

Appendix A-Baseline Variables

Explanatory variables of interest in addition to related covariates were collected at baseline in the form of a self-administered questionnaire.

Number of hours spent sitting

During a usual day and night, about how many hours do you spend sitting? Be sure to include the time you spend sitting at work, sitting at the table eating, driving or riding in a car or bus, and sitting up watching TV or talking.

- Less than 4 hours
- 4-5 hours
- 6-7 hours
- 8-9 hours
- 10-11 hours
- 12-13 hours
- 14-15 hours
- 16 or more hours
-

For the purposes of this study, sedentary categories were collapsed into the following quartiles based on their daily reported sedentary hours.

- Less than or equal to 5 hours
- 6-9 hours
- 10-13 hours
- 14 or more hours

Leisure time physical activity

Total leisure time physical activity was calculated in MET-min/week and based from various questions on energy expenditure from recreational physical activity (includes walking, mild, moderate and strenuous physical activity in kcal/week/kg). Participants were subsequently classified as physically active: at least 500 MET-min/week; inactive: <500 MET-min/week)

Sample questions

1.1. MILD EXERCISE. For example, slow dancing, bowling, golf.

- None
- 1 day per week
- 2 days per week
- 3 days per week
- 4 days per week
- 5 or more days per week

1.2. How long do you usually exercise like this at one time?

- Less than 20 minutes
- 20-39 minutes
- 40-59 minutes
- 1 hour or more

2.1. STRENUOUS OR VERY HARD EXERCISE (You work up a sweat and your heart beats fast.) For example, aerobics, aerobic dancing, jogging, tennis, swimming laps.

- None
- 1 day per week
- 2 days per week
- 3 days per week
- 4 days per week
- 5 or more days per week

2.2. How long do you usually exercise like this at one time?

- Less than 20 minutes
- 20-39 minutes
- 40-59 minutes
- 1 hour or more

Appendix B- Physical Activity Compendium

MET (Metabolic Equivalent)

The ratio of the work metabolic rate to the resting metabolic rate. One MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly. A MET also is defined as oxygen uptake in ml/kg/min with one MET equal to the oxygen cost of sitting quietly, equivalent to 3.5 ml/kg/min.

Physical Activity	Major Heading	MET
Light Intensity Activities		**<3**
Sleeping	Inactivity quiet/light	1.0
Sitting quietly and watching television	Inactivity quiet/light	1.3
Light office work	Volunteer activities	1.5
Walking, less than 2.0 mph, level, strolling, very slow	Walking	
Moderate Intensity Activities		**3-6**
Walking for transportation, 2.8-3.2 mph, level, moderate pace, firm surface	Transportation	3.5
Home exercise, general	Conditioning	3.8
Bicycling, <10 mph, leisure, to work or for pleasure	Bicycling	4.0
Ballet, modern, or jazz, general, rehearsal or class	Dancing	5.0

Vigorous Intensity Activities		**>6**
Racquetball, general	Sports	7.0
Calisthenics (e.g., push ups, sit ups, pull-ups, jumping jacks), vigorous effort	conditioning exercise	8.0
Running, 6mph (10 min/mile)	Running	9.8
Rope skipping, general	conditioning exercise	12.3

Appendix C-Mortality (ICD Codes)

Endpoints were death from all-cause, CVD and Cancer. Trained physician adjudicators established the endpoints from records (hospitalizations, emergency room, death certificates, and autopsy and coroner's reports). Cause-specific mortality categorizations were based on the cause of death, rather than the immediate or contributing cause of death. All deaths were defined by the International Classification of Diseases, Ninth Revision.

Cancer mortality (ICD-9 codes 140–239)

Breast cancer (174)

Ovarian cancer (183)

Endometrial cancer or cancer of the uterus (179)

Colon, recto sigmoid junction, or rectal cancer (154)

Other cancer (190-199)

Unknown cancer site (190-199)

CVD mortality (ICD-9 codes 390–449)

Atherosclerotic cardiac disease (414)

Cerebrovascular disease (430-438)

Pulmonary embolism (415.19)

Possible coronary heart disease (414.9)

Other cardiovascular disease (420-429)

Appendix D-The Women's Health Initiative

The Women's Health Initiative (WHI) was a longitudinal health study, exploring prevention and treatment methods for some of the most common causes of disease and death among American postmenopausal women, such as cancer, cardiovascular disease, and osteoporotic injuries. The 15 year project which ran from 1992 to 2008, involved an overall number of 161 808 women ranging in age from 50 to 79. It was composed of a randomized clinical trial (CT), a longitudinal cohort observational study (OS), and community prevention study (CPS). The CT enrolled 68 132 participants and were composed of three interventions: Hormone Therapy (HT), Dietary Modification, and Calcium/Vitamin D supplementation.

Women ineligible or unwilling to participate in the CT were invited to enrol in the OS, which served to do the following:

- To give reliable estimates of the extent to which known risk factors to predict heart disease, cancers and fractures;
- To identify "new" risk factors for these and other diseases in women;
- To compare risk factors, presence of disease at the start of the study, and new occurrences of disease during the WHI across all study components; and
- To create a future resource to identify biological indicators of disease, especially substances and factors found in blood.

Approximately, 93 676 women were recruited into the OS at 40 clinical centers throughout the United States. Clinical centers used in person contacts, mailings and telephone calls to enlist participants.

Clinical and Questionnaire Measures

Women in the OS had a baseline-screening visit, administered by trained and certified staff, that included the following elements: physical measurements (height, weight, blood pressure, heart rate, waist and hip circumferences), collection of blood specimens (stored as serum, plasma, and buffy coat), a medication/supplement inventory, and completion of questionnaires related to medical, family and reproductive history, lifestyle/behavioural factors, and quality of life. In addition, the OS questionnaire ascertained additional exposures, including geographic residence history, passive smoking exposure in childhood and adulthood, early life exposures, details of physical activity, weight cycling history, and occupational exposures. Three years post entry into the program; participants were mailed self administered questionnaires on an annual basis, to update their exposure and medical status. In addition, at that three year mark, all OS participants completed a clinical center visit which included physical measures and additional questionnaires. All participants in the WHI gave informed consent and were followed prospectively for up to 9 years. Details of the scientific rationale, eligibility requirements, and baseline characteristics of the WHI participants have been published elsewhere.

Appendix E-Missing Value Analysis

Table: Comparison of Baseline Characteristics (Original Sample vs. Working Sample)

Variables	Original Sample	Working Sample
Sample Size (N)	(93676)	(84 865)
Age (Years)	63.62 (7.37)	63.60 (7.35)
Total MET-Hours Per Week	13.36 (14.50)	13.37 (14.42)
Total Sitting Per Day (Hours)	3.38 (1.64)	3.38 (1.63)
Blood Pressure (mmHg)	126/74	126/74
Smoking at Baseline	5790 (6.27)	5 279 (6.22)
Alcohol Intake (1-6 drinks per week/protective)	23 824 (25.62)	21 797 (25.77)
BMI (kg/m^{2})	27.25 (5.70)	27.19 (5.35)
Follow Up Time(Years)	7.01 (1.63)	7.02 (1.60)
Number of Deaths	6260 (6.68)	5 458 (6.43)
Diabetes Ever	5318 (5.68)	4 656 (5.49)
Breast Cancer	3877 (4.16)	3 536 (4.19)

Means (SD), Frequencies (%)