THE ASSOCIATIONS BETWEEN SHIFT WORK EXPOSURE AND SELECTED HEALTH OUTCOMES AMONG MIDDLE-AGED AND OLDER ADULTS, RESULTS FROM THE CANADIAN LONGITUDINAL STUDY ON AGING

DURDANA KHAN

A DISSERTATION SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN KINESIOLOGY AND HEALTH SCIENCE

YORK UNIVERSITY

TORONTO, ONTARIO

JULY 2023

Abstract

We live in a globalized 24-hour society, consuming services, products and entertainment around the clock. As a result, more and more people are working in shifts. Currently, one in every four Canadians is working in shifts other than regular daytime hours. At the same time, the working population is aging and are becoming more common in most developed nations, including Canada. Together with physiological and epidemiological data on the alarming relationships between shift work and various physical, social and mental health outcomes, there is reason to believe that shift work may become a major occupational health problem in the near future. This dissertation analyzed data from the Canadian Longitudinal Study on Aging (CLSA) and investigated the associations between shift work and three specific outcomes related to health of middle-aged and older adults, specifically variations in age at natural menopause, frailty and cognitive impairment. The primary exposure, shift work, was measured using three derived variables: ever exposed to shift work, shift work exposure in current job, and shift work exposure in longest job. Multivariable analysis revealed that exposure to shift work is significantly related to adverse health outcomes among middle-aged and older adults. These findings highlight how shift work affects the health of the aging labor force. It also serves as a reminder of the importance of taking modifiable risk factors like shift work into account when developing and implementing health interventions in old age. It is believed that shift work, through circadian misalignment and melatonin suppression, interfere with human homeostasis and wellbeing, however, further research is needed to confirm this.

Keywords: Shift work, night shift work, rotating shift work, occupational health, Canadian Longitudinal Study on Aging (CLSA), Age at natural menopause, frailty, cognition, circadian disruption, Canada

Dedication

This thesis is dedicated to all those millions of people around the world who devote their lives to an unusual working lifestyle to serve, protect, and maintain society's operations.

As a society, we should work towards health promotion and awareness of those who keep the shelves stocked, our water and electricity running through the night, keep the communities safe and look after the sick while we sleep, to name a few of the important jobs that deserve our thanks.

Acknowledgements

The completion of this work and dissertation would not have been made possible without the support, guidance, mentorship, and patience of many individuals especially throughout the trying times of the pandemic.

Firstly, I would like to thank my supervisor Dr. Hala Tamim. Over the past five years of working together, I have gained so much knowledge with you as my supervisor, also as a friend and mentor. Thank you so much for believing in and taking a chance on me and accepting me into your lab. You helped me develop my passion for health research all while doing such meaningful work. The growth I have experienced under your tutelage in writing, presenting, communicating, and critical thinking would be sufficient to justify the time I have spent in your lab. You have done amazing research over the past years and I am so proud to say I was a part of it.

I am also grateful and indebted to my advisory committee, Dr. Heather Edgell and Dr. Michael Rotondi. Thank you for your helpful feedback, data analyses advice and contributions throughout this process. And I could not have completed this journey without your guidance.

Thank you, Dr. Chris Verschoor, for your professional assistance and insightful advice. It was such a great learning experience to work with you on one of my publications.

I would like to express my gratitude to my mother who always believed in me, inspiring me to believe in myself and my abilities. I am forever grateful to my family for their tremendous love, continued patience and endless support over the years.

I want to thank Zeeshan, my husband, who have been my staunchest ally, the dearest friend, and the most reliable partner. You support me when I stumble, you applaud me when I achieve, and you adore me just the way I am. You push me to be better each and every day.

My three amazing kids, Momin, Haniya and Hafsa, thank you for giving me a space where I can forget about studying and just have fun.

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Foreword to the thesis

This thesis is organized as three separate manuscripts as described below, preceded by introductory chapters: 1. General introduction, prevalence, review of literature, rationale and objectives; 2. Overall methodology which includes the description of CLSA cohorts, its design, characteristics of study participants, data collection timelines, and confidentiality and ethics approval.

Chapter three, four and five which includes separate manuscripts are followed by a general discussion including pathophysiology, strength and limitations, implications and future directions, overall significance and conclusion (Chapter six). The thesis concludes with a detailed list of references and appendices relevant to the research studies.

The thesis consists of the following three manuscripts:

1. Associations between shift work exposure and variations in age at natural menopause at three years follow-up

2. Associations between shift work exposure and proportion of frailty at three years follow-up

3. Associations between shift work exposure and cognitive impairment at baseline

Chapter One: General Introduction

Shift work

Working eight hours, Monday through Friday, from 9 a.m. to 5 p.m. is referred as a 'classic work day'.[1,2] However, due to the development of new technologies and the expansion of basic services to a larger population, unconventional working shifts have acquired a growing importance. It is necessary for both consumers and producers to have access to goods and services, as well as the flexibility to do so at any time of day or night.[3] These developments demand constant human assistance and round-the-clock management of the work processes. As a result, working unconventional hours is becoming more prevalent.[4] The term *'shift work' (SW)* implies any work outside the regular daytime hours.[1,2,4] SW schedules are designed to maintain a continuous operation of goods and services. A full spectrum of SW comprises: (1) regular evening shift (beginning after 3 p.m., ending before midnight), (2) regular night shift (beginning after 11 p.m., ending before 11 a.m.), (3) rotating shift (day to evening and/or night), (4) on-call or casual shift (no pre-arranged schedule) and (5) irregular shifts.[2,5–7]

SW has increased globally in recent years, with an estimated 20% of the economically active population in North America and Europe engaged in some type of SW.[8] In Canada, more than a quarter of employees (28%) work outside traditional daytime hours.[24] More specifically, about two-third of protective service workers (police-officers, firefighters, and security guards), 45% of health workers, 40% of sales and service workers, and 42% of primary industry workers (i.e. farm workers, miners, forestry workers, etc.) are involved in SW.[1,4]

Prevalence of shift work

The number of workers exposed to SW in Canada is growing and there have been noticeable changes in the prevalence of SW exposure over time by sex, industry, and occupation. According to the latest Survey of Labour and Income Dynamics (SLID),[9] 15 million Canadians were employed in 2011. Overall, approximately 5.1 million or 34% of the working population were exposed to some type of SW. More specifically, 2.1% worked regular night shifts, 4.9% evening shifts, while 10% worked rotating shifts. An additional 2.6 million (17%) were exposed to unspecified shifts other than daytime work (i.e. split shifts, irregular schedules, on call shifts, or other). By occupation, the highest prevalence of SW exposure was in occupations in protective services (37%), health (35%), and machine operators and assemblers in manufacturing (24%).[9] Industries with the highest prevalence of SW were accommodation and food services (20%), natural resources (19%), and social assistance (18%).[9]

Similar trends in SW were also reported in other developed countries. Survey data from the United States use similar definitions of SW, and as a result, can readily be compared to Canadian estimates. Overall, the estimated prevalence of SW in the United States compared to Canada is low, where an estimated 17.7 % worked non-day shifts (evening, night, rotating, irregular or other).[10,11] By type of SW, 3.1 % worked night shifts, 6.8 % worked evening shifts, 2.7 % worked rotating shifts, and 5.1% worked employer-arranged irregular schedules or others.[10,11] Another survey examining working conditions in the European Union (EU)[12] found that between 6% and 30% of workers were exposed to SW across the EU countries in 2005. The prevalence of SW in Canada, particularly night SW, was comparable to that of Austria, Belgium, Greece, Switzerland, Ireland, and the Netherlands (estimates ranging from 12% to 13%).[12] While the rates were lower in Denmark, Poland, and Turkey (6-10%) but much higher in the remaining countries (ranging from 20% to 34%).[12] According to Working Time Arrangements Survey Australia

(2012),[13] 1.5 million employees (15% of the working population) worked SW in their main job, with the most common type of shift being a rotating shift (6.7%).

Surveys conducted in the EU (European Foundation, 2012),[14] the United States (Bureau of Labor Statistics, 2005),[10] and Australia (Australian Bureau of Statistics, 2013)[13] indicate that the prevalence of all types of SW is typically highest among younger workers. SW is more common among part-time workers in Australia and the United States, but in the EU it is more prevalent among full-time workers.[14] In Canada, overall, a greater proportion of male workers (12.4%) were exposed to night SW compared to female workers (10.7%).[9] However, a higher percentage of female employees who work night shifts are found in some industries particularly healthcare and social assistance (84%) as well as in accommodation and food services (55%).[9] A greater proportion of male night shift workers compared to female workers was observed in the United States[10] (6.5% and 4.9%) as well as in Australia[13] (8.3% and 4.5%). While rates of SW are almost similar among men and women in the EU.[14] Comparison of the overall rates of SW exposure, in particular across surveys, is challenging. Differences in the populations surveyed, as well as variations in the definitions of SW used may contribute to the observed global differences in the prevalence of SW exposure.

The main drivers of SW demand are globalization and technological advancement, which make it crucial for ongoing assistance (e.g. healthcare and public safety), convenient services (e.g. hospitality), and economic processes (e.g. production and manufacturing) to be available throughout the day and night.[2] Although SW may be a social and economic necessity, its negative effects on worker’s health cannot be ignored. The following section summarizes the existing evidence describing how SW exposure has affected workers' physical, social, and mental health.

Literature review

Shift work and physical health outcomes

Most of the health issues related to SW were attributed to sleep disorders like insomnia among shift workers.[15] The prevalence of insomnia or excessive sleepiness is 32% and 26% in night and rotating shift workers, respectively.[16] In recent years, the International Classification of Sleep Disorders has officially defined the Shift Work Sleep Disorder as one that *"consists of symptoms of insomnia or excessive sleepiness that occur as transient phenomena in relation to work schedules"*.[17] About 10% of night and rotating shift workers, aged between 18 and 65, are estimated to have a diagnosable Shift Work Sleep Disorder.[16] Sleep disorders among shift workers can be a greater risk for poor safety, performance, and health outcomes. In this way, exposure to rotating and night SW were related to high risk of work injury, particularly among women.[18] Night SW was associated with work injury in both women [odds ratio (OR)=2.04, 95% confidence interval [(95% CI), 1.13-3.69] and men (OR=1.91, 95% CI, 1.21-3.03), while rotating SW was associated with work injury in women (OR=2.29, 95% CI, 1.37-3.82).[18] All types of SW were associated with an increased risk of coronary events (RR=1.41, 95% CI, 1.13-1.76).[5] SW, specifically night and rotating shifts, has been identified as a risk factor for peptic ulcer (RR=2.00, 95% CI, 1.49-2.67) when compared with regular day workers.[19] An increased risk of developing type-2 diabetes have been reported among both night (OR=1.58, 95% CI, 1.25-1.99) and evening shift nurses (OR=1.29, 95% CI, 1.04-1.59) when compared to their day shift counterparts.[20] Moreover, the International Agency for Research on Cancer (IARC) has classified night shiftwork as a probable human carcinogen (Group 2A)[21,22] with evidence of an association with breast (HR=2.15, 95% CI, 1.23-3.73),[23] prostate (RR=1.24, 95% CI, 1.05-1.46),[24] and colorectal (OR=1.32, 95% CI, 1.12-1.55)[25] cancers.

Also, shift-working women have several gender-specific health concerns and has previously been associated with poor reproductive outcomes including menstrual cycle disorders,[26–28] preterm delivery[29] and miscarriages,[30] suggesting a possible effect of circadian disruption on ovulation and fertility.

Shift work and mental health outcomes

In addition to the impact of SW on physical health, the literature highlights how shift workers' disrupted sleeping patterns ultimately affect their mental health. The risk of poor mental health and, more specifically, symptoms of depression is increased for shift workers, and this is especially true for female shift workers.[31] Sleep disturbances are more common among shift workers than day workers.[32,33] Since SW typically involves working during sleeping hours, it is common to attribute sleep issues among shift workers to disruption of the circadian rhythm.[34] A meta-analysis of 11 observational studies found significant risk of depression among night shift workers (RR=1.43, 95% CI, 1.24-1.64).[35] Shift workers are more likely (OR = 2.05, 95% CI, 1.52-2.77) to suffer from mood disorders compared to day time workers.[36]

Shift work and social health outcomes

SW appears to be detrimental to psychosocial functioning and negatively impact social engagements[37] and family life.[38] According to Cheng and Drake's review of the psychological impact of SW, people who work shifts are more likely to feel socially isolated.[39] Another study found that evening (31%) and night shift workers (27%) endorsed feeling socially isolated.[37] Notably, increased social isolation may also deteriorate the sleep problems associated with SW; shift workers who were single had a 20% higher prevalence of sleep disorders than those who were partnered.[34] Similarly, shift workers had lower rates of intimate partnership (i.e. spouse, significant other, or otherwise regular partner) than day workers.[34]

The evidence that has been presented thus far, while limited, offers significant insights about the effects of SW on health. The brief rationale and dissertation objectives in the following section are based on knowledge gaps in the existing evidence.

Rationale and objectives

Given the world's growing labour force and aging population, it is critical to investigate modifiable risk factors such as SW. Although some workers still work traditional work hours (daytime working schedule), the demand for a "24/7" economy has led to the common exposure of SW in a variety of occupations and industries. With the substantial body of evidence, International Commission on Occupational Health has recently published a consensus statement and concluded that the strength of evidence linking SW and physical health issues like cardiovascular diseases, gastrointestinal and metabolic disorders (type 2 diabetes) was strong and persistent.[40] At the same time citing inconsistent findings reported for the impact of SW on mental and reproductive health, the commission advocated for further research.[40] While SW impacts worker's health significantly, there has been limited research studying effects of SW on an aging population. For instance, menopause, one of the most significant biological events in a woman's life, has received considerable attention in literature. Of particular concern is variations in age at natural menopause that has been found to negatively impact women's health.[41] The effect of occupational exposures on menopause is understudied, particularly the evidence related to SW exposures is inconclusive.[42] Moreover, frailty, a geriatric syndrome, increases an individual's vulnerability to dependency and death.[43,44] Evidence shows that it is not just the result of a decline in intrinsic capacity but is more affected by environmental/lifestyle factors.[43,44] However, to the best of our knowledge, the relationship of SW exposure with frailty has not been investigated. Lastly, another critical health issue among the aging population is progressive decline in cognitive functions. While environmental factors are thought to significantly affect cognitive functions,[45] there is a need to explore the role of SW in cognitive decline.[46,47] Individual rationales are discussed in depth in the corresponding chapters. With an aging labour force and global rise in life expectancy, new healthcare challenges are emerging. Exposures like SW may affect the biology of aging and need to be studied and quantified. This dissertation aims to address the following objectives:

Objective 1: To investigate the association between shift work exposure and the variations in age at natural menopause among middle-aged and older adults utilizing the Canadian Longitudinal Study on Aging database.

Objective 2: To investigate the association between shift work exposure and frailty among middle-aged and older adults utilizing the Canadian Longitudinal Study on Aging database.

Objective 3: To investigate the association between shift work exposure and cognitive impairment among middle-aged and older adults utilizing the Canadian Longitudinal Study on Aging database.

The following section covers overall methodology, which includes the description of CLSA cohorts, its design, characteristics of participants, the baseline inclusion/exclusion criteria, data collection timelines, and confidentiality and ethics approval.

Chapter Two: Overall Methodology

Data source and study participants

This dissertation used data from the Canadian Longitudinal Study on Aging (CLSA),[48–50] a large, national, long-term cohort study of adult development and aging. The ultimate aim of CLSA is to identify modifiable factors with the potential to develop interventions to improve the health of aging populations. Between 2011 and 2015, CLSA started recruiting and collecting information from more than 50,000 Canadian men and women aged 45 to 85 years at the time of recruitment (baseline). Overall the baseline inclusion criteria included community dwelling, cognitively unimpaired, and able to speak and understand English or French.[48] Exclusion criteria comprised being a resident of a federal First Nations reserve or other First Nations settlements in the provinces; being a full-time member of the Canadian Armed Forces; and not a permanent resident or Canadian citizen. Individuals living in long-term care institutions (i.e., those providing 24-hour nursing care) were excluded at baseline. However, those living in households and transitional housing arrangements (e.g., seniors' residences, in which only minimal care is provided) were included. CLSA cohort participants who become institutionalized during the course of the study continue to be followed either through personal or proxy interview. Interviewers were trained to identify cognitively impaired persons and exclude them from taking part in the interview.[48]

Participation in the CLSA cohort is voluntary and all individuals provided written informed consent.[48] The selection and recruitment process is detailed elsewhere,[48,51] but in brief, a random sample of eligible households was contacted, and if an eligible individual in the household was identified, they were asked to provide their information to the CLSA in order to be contacted for recruitment. Those who responded by providing their contact information were considered pre-recruits. These pre-recruits were then contacted, and those who underwent all required baseline interviews and assessments and provided written informed consent were enrolled into the cohort. The CLSA reported a 10% overall response rate.[51]

Baseline cohort participants were asked to provide a core set of information on demographic and lifestyle/behaviour, social, physical/clinical, psychological measures, economical indicators, health status and health services use. On the basis of sampling frame and measures used for data collection, the CLSA baseline cohort was divided into following two groups.[49]

Tracking cohort (TRM) consisted of 21,241 participants and provided the core set of information (60- to 70-minute interview) using computer-assisted telephone interviews (CATI) software. CATI is an interactive computer system that aids interviewers to ask questions over the telephone. The answers are keyed directly into the computer system immediately by the interviewer thus reducing the chance of transcription errors and maximizing data security.[48]

Comprehensive cohort (COM) consisted of 30,097 participants and provided the core information (45-minute interview) through computer-assisted personal interviews (CAPI) software. At the end of the home interview, the participants were scheduled for a visit to the data collection site (DCS). At DCS detailed physical examination was conducted for all participants and asked to provide blood and urine samples (approximately 120 minutes).[48]

Data collection timelines

Participants in both CLSA baseline cohorts undergo repeated waves of data collection every 3 years and will be followed for at least 20 years, or until death.[48] The three-year interval strikes a balance between the need for a short enough interval to capture significant changes and map trajectories and the practical consideration of the time required for a full wave of data collection. To maintain contact and minimize loss to follow-up, scheduled follow-up visits are supplemented with a brief inter-assessment telephone interview. The follow-up 1 (conducted between 2015 and 2018) and follow-up 2 (conducted between 2018 and 2021) are available, where the CLSA research team collected virtually the same set of information that was obtained at baseline.[48]

The CLSA research team includes experts from across Canada in biology, genetics, clinical research, social sciences, economics, psychology, nutrition, health services, statistics, epidemiology, and population health. This database provides the opportunities to understand the complex interplay between determinants of health and enable research to move beyond a snapshot of the adult Canadian population to observe and understand the disease, disability, and psychosocial processes that accompany aging. The CLSA is one of the most complete studies of its kind in Canada.[48]

Confidentiality and ethics approval

The CLSA provides researchers with the collected data accompanied by unique study identification numbers (de-identified data without name or contact information). Researcher will not be able to identify or link the information with the participants. The core CLSA study has been approved by McMaster University Health Integrated Research Ethics Board and by research ethics boards at all collaborating Canadian institutions.[48] This dissertation is a secondary analysis of fully de-identified CLSA data which has been approved by the York University, Office of Research Ethics (ORE) [STU 2020-123], see appendix A. As such, additional participant consent for this analysis was not required as all CLSA participants provided informed consent during primary data collection to have their de-identified data used in research. The dissertation now continues with the three described manuscripts.

Primary Exposure Shift work

Main exposure of interest is 'shift work'. Only a subset of respondents who self-reported as currently working or have worked at baseline were included in our study sample. All job-related information was captured, by utilizing following two CLSA modules.

1. Labour Force (LBF) module collects job-related information from participants that are currently working. They are asked to provide detailed information related to their 'current job' as well as the 'longest job' they performed so far.
2. Pre-Retirement Labour Force Participation (LFP) module collects job-related information from participants who are retired. They are also asked to provide detailed information related to their 'recent job' as well as the 'longest job' they had over their entire career.

Based on all job-related information from LBF and LFP following three variables were generated to measure SW exposure.

a. Ever exposed to SW

This binary variable 'ever exposed to SW' (yes/no) measured overall occurrence of SW. This variable reflected the effect of SW exposure regardless of type of exposure (night or rotating) or timing of occurrence (current or longest). All participants who reported ever working in any shift (evening/night/rotating shift) in any time period in their working career (current/longest job) were considered exposed and coded as 'yes'. All those who reported daytime work only, were coded as 'no'.

b. SW exposure in longest job

This categorical variable measured the longest exposure to SW. Participants were asked to think back over their entire career of the job that they have worked for the longest period of time and were categorized into day time work (reference category), night SW and rotating SW. This was done to better reflect duration of exposure in term of dose-response relationship, as those with SW schedules during their longest job, would have been exposed to shift work for a longer period of time. However, this variable did not capture exact timing of occurrence of longest SW exposure.

c. SW exposure in current job

This categorical variable captured the information of SW exposure in the current job. Participants were asked about their current job (currently working participants from LBF module) and categorized into following; day time work (reference category), night SW and rotating SW. This variable for SW only included participants who are currently employed and are currently exposed to SW. This was done to capture the recent/acute effect of SW and participants included in the analyses were workers who have been in the labour force for some period of time.

Chapter Three

The association between shift work exposure and the variations in age at natural menopause among adult Canadian workers: Results from the Canadian Longitudinal Study on Aging (CLSA)

Durdana Khan[1], MPH, Michael Rotondi[1], PhD, Heather Edgell[1], PhD, and Hala Tamim[1], PhD

[1]From the School of Kinesiology and Health Science, York University, Toronto, Canada

This manuscript has been published:

Khan D, Rotondi M, Edgell H, Tamim H. The association between shift work exposure and the variations in age at natural menopause among adult Canadian workers: results from the Canadian Longitudinal Study on Aging (CLSA). *Menopause*. 2022;29(7):795-804. doi:10.1097/GME.0000000000001981

Online abstract link

Video summary link

Abstract

Objective

A wide range of negative health outcomes have been associated with shift work (SW) particularly night and rotating SW. However, little is known about effects of SW exposure on reproductive health outcomes. The objective of our study is to prospectively investigate the association between SW exposure and the variations in age at natural menopause (ANM) among adult Canadian workers.

Methods

Secondary data analyses were performed using the Canadian Longitudinal Study on Aging (CLSA) database. Premenopausal women (N=3,688) at baseline were followed prospectively for three years. Three derived variables were used to measure SW primary exposure: 1) Ever exposed to SW, 2) SW exposure in current job and 3) SW exposure in the longest job. Cox proportional hazard regression models were used to evaluate risk of variations in ANM after adjusting for potential confounders.

Result

One out of five women (20%) reported to be ever exposed to SW during their jobs. Overall, women who were ever exposed to SW were significantly associated with a delayed onset of menopause compared to daytime workers (HR=0.77, 95% CI, 0.61-0.98). Particularly, when compared to daytime workers, rotating shift worker in the current and longest job were significantly related to delayed onset of menopause (HR=0.64, 95% CI, 0.46-0.89 and HR =0.65, 95% CI, 0.49-0.86), respectively.

Conclusion

Our results suggest a relationship between rotating shift and delayed onset of menopause. We speculate that disruptive circadian stimuli may play a role in menopausal onset and this warrants further investigation.

Key Words: Night shift, rotating shift, menopause, occupational health, circadian disruption, CLSA

Introduction

Working for eight hours from 9am to 5pm on weekdays is considered a regular daytime job.[1,2] However, in an economy with rising demands for goods production and provision of round the clock services, working non-traditional shifts remain common.[52] The term *'shift work (SW)'* is defined as any work outside the regular daytime hours.[1,2,4] A full spectrum of SW comprises: evening shift, night shift, rotating shift (day to evening and/or night), and other less specified shifts including on-call or casual shift (no pre-arranged schedule) and irregular shifts.[2,5–7] SW has increased globally in recent years, with an estimated 20% of the economically active population in North America and Europe engaged in some type of SW.[8] In Canada, more than a quarter of employees (28%) work outside traditional daytime hours.[2,4] SW may be a social and economic necessity, but its negative impact on workers' health cannot be overlooked. A recent meta-analysis of 34 studies showed that all types of SW were associated with an increased risk of coronary events and the highest point estimate was noted for night shifts (RR= 1.41, 95% CI, 1.13-1.76).[5] SW, specifically night and rotating shift, has been identified as a risk factor for peptic ulcer,[19] type-2 diabetes,[20] and cancers such as prostate,[24] colorectal,[25] and breast.[23] While SW significantly impacts worker's health, there has been inadequate research investigating effects of SW on middle-aged and older adults. Exposures like SW may affect the biology of aging and limited research has attempted to study or quantify these relationships.

Age at natural menopause (ANM) is a matter of concern for middle-aged and older women as both an early or late menopause may be a significant risk marker for subsequent morbidity and mortality.[53] Environmental factors such as smoking, parity and socioeconomic status have previously been identified to be strongly associated with variations in ANM.[54,55] A factor that may impact ANM is SW, as previous evidence from physiological studies has suggested a possible effect of circadian disruption on ovulation and fertility.[56] Increased risk of hormonally induced cancers such as endometrial[57] and breast cancer[58] among night shift workers, provide additional support to the hypothesis that circadian disruptions may alter reproductive functions and influence menopausal timing. Furthermore, excessive exposure of artificial light during dark hours has been documented to cause melatonin suppression, which in turn leads to disruption of ovarian activity.[59,60] Though causal relationships have not been yet completely demonstrated, evidence from these studies support the notion that disruption of circadian rhythm and melatonin suppression in shift workers could impact the timing of natural menopause.

There is a large gap in the literature regarding relationship between SW exposure and ANM. The only evidence was from a single observational study, that followed a cohort of nurses and concluded that overall, rotating night shift nurses had an increased risk of earlier menopause, compared to their day shift counterparts (HR=1.09, 95% CI, 1.02–1.16).[42] But, age-stratified analysis indicated that risk of early menopause was only significant for younger nurses (<45years) and not for nurses over the age of 45 years. Although the study was first to investigate effect of rotating night SW on variation in ANM, analysis was limited to only the nursing profession and utilized a non-standard operational definition for menopause.

Despite the importance of variations in ANM and its consequences on women's reproductive health, relationship between SW exposure and ANM remains unclear. It is imperative to assess and quantify this association using a nationally representative longitudinal data. Therefore, this study aims to prospectively investigate the association between SW exposure and the variations in ANM among adult Canadian workers.

Methodology

Study design and sample

Secondary data analyses were performed using the Canadian Longitudinal Study on Aging (CLSA) database, which is a large, Canada wide, longitudinal cohort that encompassed 51,338 adults between the ages of 45 and 85. The CLSA has two cohorts: A "comprehensive cohort" (30,097) provided self-reported health information through in-home personal interviews, and a "tracking cohort" (21,241) which provides all information through telephone interviews. For this study, we utilized the pooled dataset, (by combining the two cohorts) and the modules that were common in both cohorts were included and formed the basis of our analysis. CLSA excluded residents of institutions, the three territories, First Nations reserves; those who spoke neither English nor French; fulltime Canadian Armed Forces members; and individuals with cognitive impairment. CLSA study design has been previously described in detail elsewhere.[48,61]

Study participants

All male participants were excluded, and only female participants remained in the sample. Additional exclusions were applied and summarized in figure 1. All women who responded 'yes' to the following CLSA baseline question related to menopausal status: *"Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?",* were categorized as postmenopausal women and were excluded. Women were excluded if they reported; surgical menopause as their menopausal status was uncertain; not experiencing menopause by age of 62 because of any underlying pathologic conditions resulting in very late menopause or these values could be inaccurate;[62,63] a diagnosis with breast, ovarian, or female genital organ cancers because treatment for cancers might mask the true ANM;[64,65] all women who reported never worked in any job; and finally women who have missing information (refused to answer or don't know status of menopause or age of menopause) were

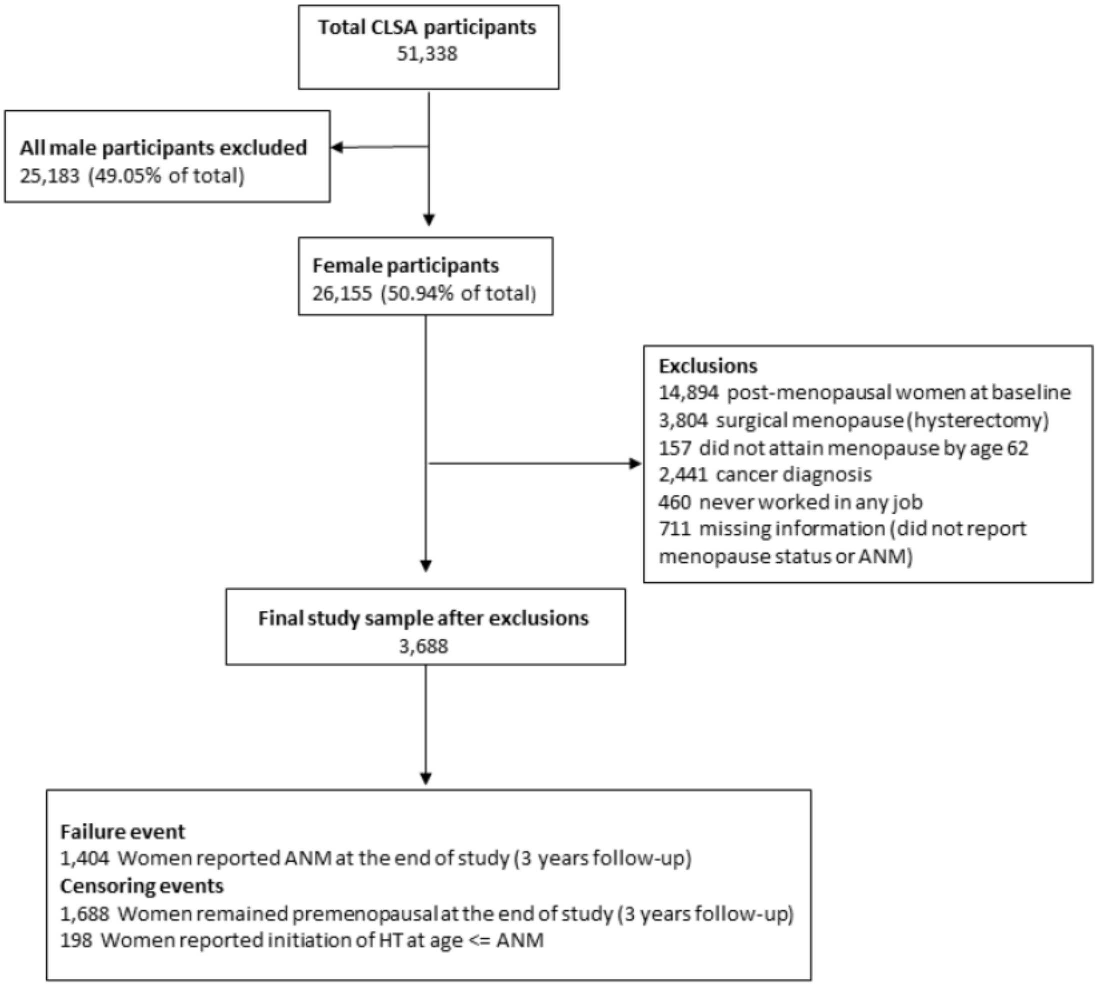

Figure 1. Canadian Longitudinal Study on Aging (CLSA) participant flowchart. ANM, age at natural menopause; HT, hormone therapy.

excluded. After these exclusions, our final study sample at baseline included 3,688 premenopausal women and were followed prospectively for three years (2015-2018).

Assessment of primary exposure (SW)

The primary exposure of interest 'SW' was self-reported and assessed in the CLSA baseline questionnaires. All study participants were asked '*Have you ever worked at a job or business?* (yes/no). The participants who reported 'yes' were asked '*Are you currently working at a job or business?* (yes/no). Participants who reported 'yes' were asked *"Which of the following best describes your working schedule?"* (daytime work, night shift, rotating shift). Participants were also asked about their longest job, *"Thinking about the job you worked at the longest, which of the following best describes your working schedule?"* (daytime work, night shift, rotating shift). Based on this job-related information, three variables were generated to measure SW exposure:

1. Ever exposed to SW

This variable measured overall occurrence of any SW. All participants who reported ever working in any shift (night/rotating) in their working career were considered exposed and coded as 'yes'. All those who reported only daytime work, were considered unexposed and coded as 'no'.

2. Exposure of SW in current job

This variable measured the exposure of SW among participants who reported currently working and categorized into; daytime work (reference category), night SW, rotating SW, currently not working.

3. Exposure of SW in longest job

This variable measured the exposure of SW during the longest job. SW in longest job was categorized into; day time work (reference category), night SW and rotating SW.

Assessment of outcome (ANM)

All premenopausal women at baseline were asked about their menopausal status after three years of follow-up to update the information, *"Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?"* (yes/no), women who answered *'yes'* were classified as naturally postmenopausal and further asked about age of natural menopause, "*How old were you when your menstrual periods stopped for at least one year and did not re-start?"* Exact age in years was taken as the main outcome variable and all participants who had reported attainment of natural menopause were considered to have the event, while those who remained premenopausal at follow-up were considered as censored observations.

Covariates

Sociodemographic variables included, ethnicity (white vs other), where 'other' included South Asian, Chinese, Filipino, Latin American, Japanese, Southeast Asian, Korean, Arab, West Asian and Black, education level (less than high school, high school to some college, bachelor's degree or higher), marital status (partner vs no partner), total annual household income in Canadian dollars (<20,000, 20,000-50,000, 50,000-100,000, >100,000). Lifestyle factors included smoking status (never, former, current), alcohol consumption (never, less than weekly, at least weekly), and frequency of leisure time physical activity in the past year (regular vs non-regular). Premenopausal clinical factors included self-reported status of type 2 diabetes, hypertension and CVD, categorized as (yes/no). Depression (yes/no) was ascertained by utilizing 'The Center for Epidemiological Studies short Depression (CES-D10) scale. A score ≥ 10 suggesting presence of depression.[66,67] Height and weight were used to calculate BMI in kg/m^2. A cut-off of 20 kg/m^2 was used for underweight, because most women were 45 and over, and were less likely to be very underweight.[62,68] In addition, reproductive factors, as they are significant components in studies related to ANM[69,68] included parity (i.e. number of pregnancies) categorized into nulliparous, 1-3, 3-5 and >5; age at first pregnancy (in years) and use of oral contraceptives (yes/no). All covariates (except reproductive factors) were measured at baseline.

Endpoints

Age in years was utilized as a time scale for survival analysis in the study. ANM was the primary outcome, but the analysis method allowed premenopausal women to contribute person-years even if they did not reach natural menopause during the study period. Participants were censored if they did not experience the event of interest (menopause) during the 3 years of follow-up period or women who reported initiation of hormone therapy (HT) before the event of interest. Endpoint age was defined as one of the following: (a) Self-reported ANM after 3 years of follow-up for postmenopausal women, (b) for those women who remained premenopausal (not experienced event of interest) at the end of study (3 years follow-up), their self-reported age at end of the study (follow-up interview), and (c) Self-reported age at initiation of HT among women who had used HT before menopause.

Analysis

Survival analysis was used for ANM (in years) in this study.[68,70] Nonparametric Kaplan-Meier cumulative survivor curves were used to assess the median ANM.[71] Then, unadjusted and adjusted Cox proportional hazard regression models were used to estimate the association between SW exposure and ANM. Three separate models were created, first with 'ever exposed to SW' (Model 1), then SW exposure in current job' (Model 2) and finally 'SW exposure in longest job' (Model 3). Multivariable-adjusted hazard ratios (HRs) and 95% CIs for ANM were estimated. HRs greater than 1 reflect earlier onset of menopause, and those with less than 1 reflect later age at menopause.[71] The proportional hazard assumption was checked using log-log plots of survival probabilities over time, and through visualizing plots of scaled Schoenfeld residuals. These did not indicate violation of the assumption. Interactions between BMI, hypertension and diabetes variables were tested, however no significance was found. The CLSA provides survey inflation weights and analytical weights, which were utilized for prevalence estimates and regression modelling respectively, that allow the results to reflect the population of Canada.[51] A p-value <0.05 considered statistically significant. All statistical data analyses were performed using STATA version 13.0.

Results

Figure 1 depicts a flow diagram summarizing the criteria used for exclusions. We compared the baseline characteristics of women excluded due to missing information (N=711) with the women included in our final study population (N=3,688). No significant differences were detected except for age and household income (i.e. women excluded were older ($P < 0.0001$) and reported to have low income ($P<0.0001$) than those included in study). Table 1 shows descriptive characteristics of the 3,688 (weighted N=1,412,705) premenopausal women at baseline that were included in our final study population. Their mean age at baseline interview was 48.9 years (SD 0.08) and the majority of women in the sample were white (94.3%) and with partner (81.1%). Over 50% of women had a high school to some college education, a household income of 100,000 CAD and more, and reported to be former smokers. More than 50% of women reported consuming alcohol at least weekly, and were not involved in regular physical activity in past year. The proportion of women whose BMI was considered overweight and obese were 28.5% and 24.5% respectively. Over 15% of women reported having hypertension, or depressive illness whereas less than 10% reported having type 2 diabetes or CVD. Considering reproductive factors, the majority of women (90%) reported having at least one child and the mean age at first pregnancy was 25.6 years (SD 0.21). At three years follow-up, 40.7% of pre-menopausal women reported to attain natural menopause, while 59.2% were censored. The median ANM of the sample was 54 years (interquartile range, IQR: 52-56).

Table 1: Baseline characteristics of premenopausal women in the Canadian Longitudinal Study on Aging, their menopause status and ANM at 3 years follow-up					
	Total sample		**Natural menopause**		**Median ANM**
Variables	**N[a]**	**%[a]**	**N**	**%[b]**	**Years (IQR)[c]**
Ever exposed to SW					
Never exposed to SW (Daytime work only)	1,053,666	79.93	1100	37.99	54(52-56)
Ever exposed to SW	264,563	20.06	198	32.54	55 (52-57)
SW exposure in current job					
Not exposed to SW (Daytime work)	904,010	67.33	925	35.64	54(52-56)
Night SW	49,388	3.67	29	44.02	53(50-57)
Rotating SW	108,940	8.11	90	28.96	55(53-57)
Currently not working	280,184	20.86	282	44.13	54(52-56)
SW exposure in longest job					
Not exposed to SW (Daytime work)	1,053,666	82.10	1100	37.99	54(52-56)
Night SW	60,404	4.70	37	42.88	54(51-55)
Rotating SW	169,258	13.18	136	29.14	55(52-57)
Socio-demographic factors					
Age at baseline in years [mean(SD)][a]	48.9	0.08	1404	40.74	54 (52-56)
Ethnicity					
White	1,332,117	94.32	1339	37.05	54(52-56)
Other[d]	80,219	5.67	63	36.35	53(52-56)
Marital status					
With partner	1,146,536	81.11	1066	36.86	54(52-56)
No partner	266,168	18.84	338	37.92	54(51-56)
Education level					
Less than high school	102,452	7.25	22	37.21	54(52-57)
High school to some college	920,699	65.17	735	39.18	54(52-56)
Bachelor's degree and higher	389,553	27.57	647	32.69	54(52-56)
Household income (CAD)					
Less than $20,000	43,973	3.23	38	42.02	53(50-56)
$20,000 or more, but less than $50,000	164,179	12.07	168	38.74	54(51-56)
$50,000 or more, but less than $100,000	459,484	33.73	411	35.94	54(52-57)
$100,000 and more	691,815	50.88	734	37.34	54(52-56)
Lifestyle factors					
Smoking					
Never	501,357	35.58	537	35.19	54(52-56)
Former	741,797	52.65	735	37.17	54(52-56)
Current	165,677	11.75	129	43.3	53(50-57)
Alcohol consumption					
Never	172,566	12.21	142	30.18	55(52-56)
Drinks less than weekly	514,084	36.39	513	38.94	54(51-56)
Drinks at least weekly	725,694	51.38	748	37.58	54(52-56)
Physical activity					
Non-regular	825,580	64.08	876	34.58	54(52-56)
Regular(daily)	462,747	35.91	499	41.51	54(51-56)
BMI (kg/m^2)					
20.0-24.99 (normal weight)	569,074	40.45	575	38.31	54(51-56)
Less than 20.00 (underweight)	85,054	6.04	89	43.21	53(51-55)
25.0-29.99 (overweight)	402,323	28.59	409	36.33	54(52-57)
More than 30.0 (obese)	350,315	24.90	326	34.98	55(52-56)
Chronic conditions					
Hypertension					

No	1,180,956	83.86	1166	35.94	54(52-56)
Yes	227,234	16.13	235	43.21	54(52-56)
CVD					
No	1,373,116	97.42	1372	37.1	54(52-56)
Yes	36,311	2.57	30	35.13	54(52-56)
Diabetes					
No	1,281,936	90.81	1293	37.15	54(52-56)
Yes	129,588	9.18	111	36.23	54(52-58)
Depression					
No(CES-D10 <10)	1,147,937	81.49	1147	36.23	54(52-56)
Yes(CES-D10 >=10)	260,742	18.50	255	40.78	54(51-56)
Reproductive history					
Age at first pregnancy in years [mean(SD)][a]	25.61	0.21	1215	37.24	54(52-56)
Parity (number of pregnancies)					
Nulliparous	126,834	10.55	182	35.31	54(51-56)
1 to less than 3	489,527	40.72	632	39.78	54(52-56)
3 to less than 5	460,529	38.31	462	35.5	55(52-56)
5 and more	125,004	10.40	127	33.13	55(52-58)
Contraceptive use					
No	204,099	16.96	264	49.71	54(52-56)
Yes	999,254	83.03	1140	34.95	54(51-56)

ANM, age at natural menopause; SW, shift work; BMI, body mass index; CAD, canadian dollars; CVD, cardiovascular disease; IQR, interquartile range; CES-D, the center for epidemiological studies depression scale; SD, standard deviation.
[a] Reported mean, SD and % are estimation for the study sample(N=3688) using survey inflation weights; figures do not always sum up to the total due to missing values
[b] Frequencies are row percentages estimated using analytical weights
[c] Calculated using Kaplan-Meier estimate
[d] Other included South Asian, Chinese, Filipino, Latin American, Japanese, Southeast Asian, Korean, Arab, West Asian and Black

Overall, one out of five women (20%) reported to be ever exposed to SW during their jobs. Specifically, 3.6% and 8.1% of the currently working women reported to be exposed to night and rotating SW respectively. Considering the job held the longest in their entire career, 4.7% and 13.1% of the women reported to be exposed to night and rotating SW respectively. Figure 2 summarized the comparison of reported ANM for primary SW variables using Kaplan-Meier cumulative estimates. Table 2 summarized results of the unadjusted and adjusted Cox regression analysis. Model 1 shows that women who were ever exposed to any SW (night/rotating) were more likely to have a later ANM compared to day time workers (HR=0.77, 95% CI, 0.61-0.98). Among currently working women (Model 2, Table 2), night shift workers had an increased risk of earlier menopause (HR=1.27, 95% CI, 0.72-2.24), while rotating shift workers were more likely to have a later menopause than day time workers (HR=0.64, 95% CI, 0.46-0.89). Similar results were noticed when considering SW exposure in longest job (Model 3, Table 2). Women who reported working in night shift during their longest job period were at higher risk of early menopause (HR=1.32, 95% CI, 0.92-1.91), while women who reported working in rotating shifts during their longest job period were associated with later menopause as compared to day time workers (HR=0.65, 95% CI, 0.49-0.86).

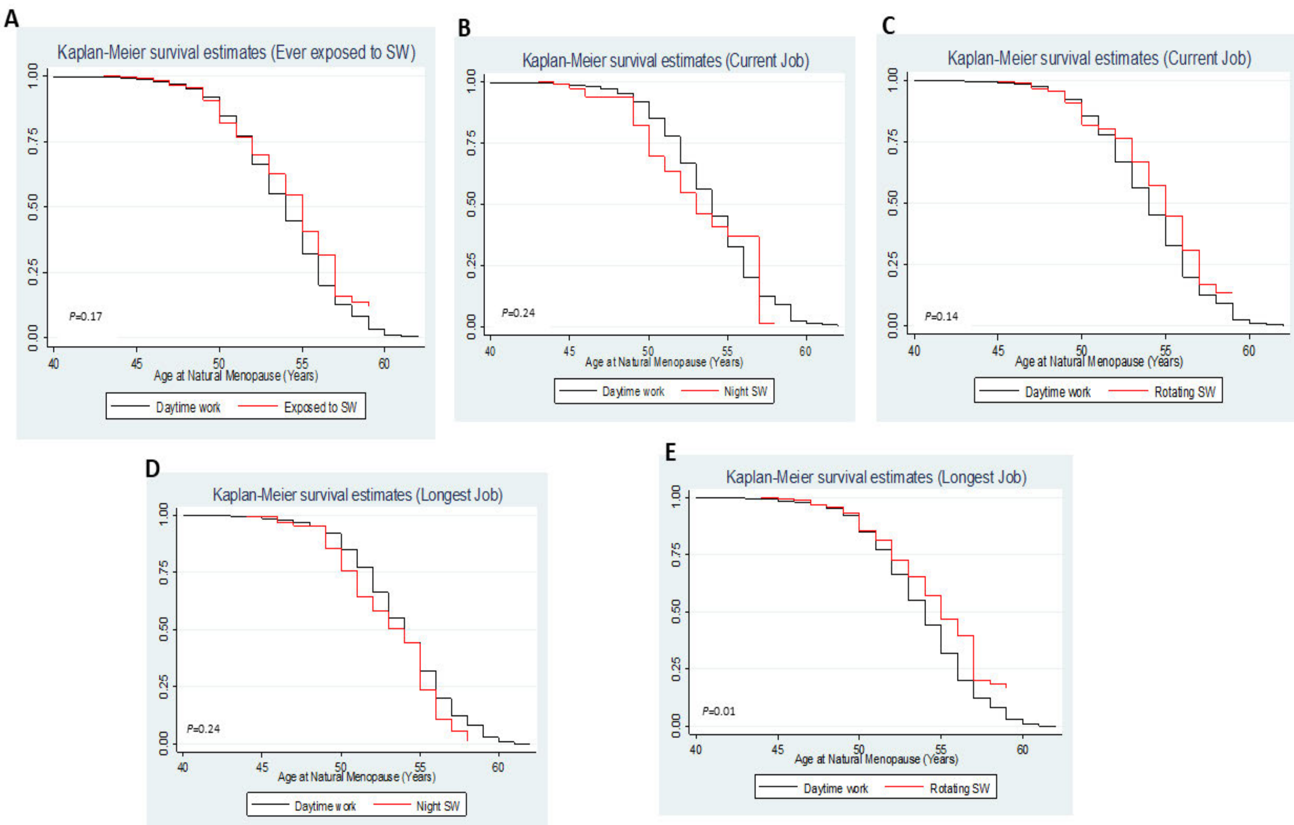

Figure 2. Kaplan-Meier (KM) cumulative estimates of age at natural menopause at three years follow-up. (A) KM curves for those who were ever exposed to SW vs. never exposed to SW (daytime work). (B, C) KM curves for night and rotating SW vs. daytime workers among currently working participants. (D, E) KM curves for night and rotating SW vs. daytime workers for the longest job.
SW, Shift work; P, p-value for log rank test

Table 2: Unadjusted and adjusted hazard ratios (HRs) and 95% Confidence Intervals (CI) for ANM				
	Unadjusted [a] HR(95% CI)	Adjusted[a,b] HR(95% CI)		
Variables		**Model 1** Ever exposed to SW	**Model 2** SW exposure in current job	**Model 3** SW exposure in longest job
Ever exposed to SW				
Never exposed to SW (Daytime work only)	1.00	1.00	---	---
Ever exposed to SW	0.87 (0.71-1.06)	**0.77 (0.61-0.98)**	---	---
SW exposure in current job				
Not exposed to SW (Daytime work)	1.00	---	1.00	---
Night SW	1.36 (0.82-2.28)	---	1.27 (0.72-2.24)	---
Rotating SW	0.81 (0.62-1.07)	---	**0.64 (0.46-0.89)**	---
Currently not working	1.02 (0.86-1.20)	---	0.92 (0.76-1.11)	---
SW exposure in longest job				
Not exposed to SW (Daytime work)	1.00	---	---	1.00
Night SW	1.35 (0.94-1.95)	---	---	1.32 (0.92-1.91)
Rotating SW	**0.74 (0.59-0.94)**	---	---	**0.65 (0.49-0.86)**
Socio-demographic factors				
Ethnicity				
White	1.00	1.00	1.00	1.00
Other	1.16 (0.84-1.61)	1.17 (0.76-1.80)	1.23 (0.83-1.84)	1.21 (0.80-1.83)
Marital status				
With partner	1.00	1.00	1.00	1.00
No partner	1.13 (0.97-1.32)	0.93 (0.75-1.16)	0.94 (0.76-1.17)	0.97 (0.79-1.20)
Education level				
Less than high school	0.98 (0.60-1.59)	1.04 (0.58-1.84)	0.91 (0.52-1.63)	1.12 (0.64-1.95)
High school to some college	1.10 (0.98-1.22)	1.10 (0.95-1.27)	1.12 (0.97-1.29)	1.12 (0.96-1.29)
Bachelor's degree and higher	1.00	1.00	1.00	1.00
Household income(CAD)				
Less than $20,000	**1.64 (1.01-2.67)**	1.84 (0.88-3.84)	**1.97 (1.00-3.86)**	1.84 (0.92-3.69)
$20,000-$50,000	1.07 (0.87-1.32)	1.02 (0.76-1.36)	1.02 (0.78-1.34)	0.88 (0.66-1.15)
$50,000-$100,000	0.97 (0.84-1.11)	0.95 (0.79-1.13)	0.94 (0.79-1.12)	0.97 (0.82-1.16)
More than $100,000	1.00	1.00	1.00	1.00
Lifestyle factors				
Smoking				
Never	1.00	1.00	1.00	1.00
Former	0.97 (0.86-1.11)	1.06 (0.90-1.25)	1.08 (0.91-1.26)	1.02 (0.87-1.20)
Current	**1.49 (1.15-1.93)**	**1.49 (1.09-2.03)**	**1.45 (1.06-1.98)**	1.36 (0.99-1.85)
Alcohol consumption				
Never	1.00	1.00	1.00	1.00
Drinks less than weekly	1.22 (0.97-1.52)	1.31 (0.99-1.73)	1.29 (0.98-1.68)	**1.39 (1.06-1.84)**
Drinks at least weekly	1.13 (0.91-1.40)	1.17 (0.88-1.54)	1.14 (0.87-1.49)	1.21 (0.93-1.59)
Physical activity				
Non-regular	1.00	1.00	1.00	1.00
Regular(daily)	**1.20 (1.05-1.37)**	**1.21(1.03-1.40)**	**1.20 (1.03-1.40)**	**1.20 (1.03-1.39)**
BMI(kg/m^2)				

20.0-24.99 (normal weight)	1.00	1.00	1.00	1.00
Less than 20.00 (underweight)	1.21 (0.93-1.59)	1.03 (0.76-1.40)	1.04 (0.77-1.41)	1.03 (0.75-1.40)
25.0-29.99 (overweight)	**0.85 (0.73-0.98)**	**0.76 (0.63-0.91)**	**0.77 (0.64-0.92)**	**0.78 (0.65-0.93)**
More than 30.0 (obese)	**0.79 (0.67-0.94)**	**0.77 (0.62-0.95)**	**0.76 (0.62-0.94)**	**0.79 (0.64-0.96)**
Chronic conditions				
Hypertension				
No	1.00	1.00	1.00	1.00
Yes	0.90 (0.77-1.06)	0.91 (0.74-1.13)	0.93 (0.75-1.15)	0.91 (0.74-1.12)
CVD				
No	1.00	1.00	1.00	1.00
Yes	0.92 (0.61-1.40)	1.01 (0.63-1.61)	1.12 (0.71-1.76)	1.03 (0.63-1.67)
Diabetes				
No	1.00	1.00	1.00	1.00
Yes	0.89 (0.69-1.13)	0.98 (0.72-1.34)	1.00 (0.73-1.35)	0.94 (0.69-1.29)
Depression				
No(CES-D10 <10)	1.00	1.00	1.00	1.00
Yes(CES-D10 >=10)	1.14 (0.96-1.35)	1.07 (0.87-1.31)	1.06 (0.86-1.29)	1.12 (0.91-1.36)
Reproductive history				
Age at first pregnancy in years	1.00 (0.99-1.02)	1.00 (0.98-1.01)	1.00 (0.98-1.01)	1.00 (0.98-1.01)
Parity				
Nulliparous	1.00	1.00	1.00	1.00
1 to less than 3	0.98 (0.80-1.20)	N/A	N/A	N/A
3 to less than 5	0.83 (0.67-1.02)	**0.83 (0.70-0.97)**	**0.84 (0.71-0.98)**	**0.82 (0.69-0.96)**
5 and more	**0.73 (0.53-0.98)**	0.82 (0.62-1.09)	0.80 (0.61-1.06)	0.79 (0.61-1.04)
Contraceptive use				
No	1.00	1.00	1.00	1.00
Yes	**0.83 (0.70-0.97)**	0.86 (0.70-1.06)	0.85 (0.69-1.04)	0.86 (0.70-1.05)

HRs, hazard ratios; 95% Confidence Intervals, CI; ANM, age at natural menopause; SW, shift work; BMI, body mass index; CAD, canadian dollars; CVD, cardiovascular disease; CES-D, the center for epidemiological studies depression scale.
[a] Calculated HR and 95% CI using survey analytical weights
[b] Hazard ratios adjusted for ethnicity, income, education, marital status, parity, contraceptive use, age at first pregnancy, smoking, alcohol, physical activity, CVD, diabetes, BMI, HTN, depression
N/A, Unable to calculate the HR due to lack of events
Bold numbers indicate the significant results with p-value <0.05

Results of the multivariate analysis also exposed significant associations between socio-demographic factors among working women and ANM. Overall, risk of early menopause was significantly higher among workers who were current smokers (HR=1.49, 95% CI, 1.09-2.03) and involved in regular physical activity (HR=1.21, 95% CI, 1.03-1.40). Whereas, significant risk of later menopause was found among workers who were overweight (HR=0.76, 95% CI, 0.63-0.91), obese (HR=0.77, 95% CI, 0.62-0.95) and with high parity (HR=0.83, 95% CI, 0.70-0.97).

Discussion

This study investigated the associations between SW exposure and ANM among working Canadian women. Results of the study revealed that SW, in particular rotating SW significantly influenced the timing of natural menopause. Overall, ever exposed to SW was significantly associated with later onset of menopause. Moreover, the study findings suggested that women who worked as a rotating shift worker in current job or in longest job, were significantly related to delayed onset of menopause. Investigating and identifying the modifiable factors of ANM like SW exposure among working populations is of clinical relevance given the potential adverse health outcomes associated with variations in menopausal timing. These preliminary study results would add insight on the impact of SW on reproductive function and further elucidate the role of circadian regulation on timing of natural menopause.

SW is prevalent throughout the world and consistent with the literature,[2,4] this study found that 20% of women were exposed to SW at some point in their careers. Similar trends were noticed in other developed countries like Japan,[72] France,[73] and throughout Europe,[74] and USA,[74] affecting 20% to 25% employees in different industries. In developing countries SW is expected to be higher for reasons such as lack of proper labour laws and poor socio-economic conditions leading to working irregular hours other than day time work.[75,76] Further, results of this study demonstrated that 11.9% of currently working population reported to be exposed to night (3.7%) and rotating (8.1%) SW. These findings are consistent with previously published trend analysis, that utilized Survey of Labour and Income Dynamics (SLID), and reported that approximately 1.8 million Canadians (12%) of the working populations were exposed to night (2.2%) and rotating (10%) SW; and that 45% were female.[9,18]

We also note that the women who reported to be ever exposed to SW were significantly associated with risk of delayed menopause as compared to day time workers (HR=0.77, 95% CI, 0.61-0.98). This relationship was found consistent among rotating shift workers in current job (HR=0.64, 95% CI, 0.46-

0.89) or in longest job (HR=0.65, 95% CI, 0.49-0.86). In contrast, Stock et al[42] followed a cohort of nurses for 22 years (1991-2013) and calculated the hazard of menopause among rotating night shift workers (defined as at least 3 nights in addition to day/evening SW) as both recent and lifelong exposures. Overall, the study indicated that nurses who worked in rotating night shifts, in previous 2 years, had an increased risk of early ANM (HR= 1.09, 95% CI, 1.02–1.16) compared to non-shift workers. However, it is worth noting that, the age-stratified analysis showed significant risk of early menopause among younger nurses (<45 years) for both recent (HR = 1.25, 95% CI, 1.08–1.46) and lifelong exposures (HR= 1.22, 95% CI, 1.03–1.44). Such significant relationship was not observed for those over the age of 45 years. Also, it's important to note that the Stock's analysis[42] was restricted to the nursing profession and not representative of workers from other occupations. Moreover, definition for menopause was limited to querying whether a woman's periods had ceased or not, in contrast to the standard World Health Organization definition[77] that requires periods to have ceased for 12 months as measured by CLSA questionnaire "*Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?*"

Circadian desynchronization experienced by shift workers is complex. Exact underlying mechanisms are unknown, rotating SW has been hypothesized to be more disruptive to circadian rhythm than regular night work and studied previously as a risk factor for adverse reproduction-related outcomes.[58,78,79] It is possible that rotating shift workers demonstrate greater difficulty in adapting to work schedules as they have to move from shift to shift compared to regular night shift workers. In addition, the delaying effect of rotating SW on ANM in our study might be due to effects of circadian disruption on estrogen production. For example, previous studies have shown that impaired pineal secretion of melatonin, due to light exposures among shift workers, may cause increased release of estrogen by the ovaries,[80–83] an indicator of delayed menopause.[55,84] In order to develop a more complete picture of the relationship between SW and ANM, additional studies will be needed to confirm the association as well as determine any physiological pathways that are influenced.

Results of the multivariate analysis also revealed substantial associations between socio-demographic factors among working women and ANM. Consistent with prior literature our study results found that working women who were current smokers[64,65,69,71,85–87] and with low household income[69,71,88] were at higher risk of early menopause. Polycyclic aromatic hydrocarbons in cigarette smoke have harmful effects on growth of ovarian follicles,[89] thus reducing the circulating estrogen and accelerating the onset of menopause. Also, employment and income levels are indicators of economic security as well as social and psychological stress, which can affect ovarian function and therefore, timing of natural menopause.[90,91] However, workers who consumed alcohol,[69,71,86,92] have children,[86,87,93–97] and have higher BMI[65,69,98] were associated with later ANM. An explanation for these findings is that moderate alcohol consumption increases estrogen levels[99], and increased estrone production in the adipose tissue of obese women might involve in delaying menopause onset.[100] Also, it has been found by Parazzini et al[87] and Soberon et al[101] that increased parity may be associated with delayed menopause. Further, the relationship of regular physical activity with the early onset of menopause among working women in our study is contrary to what previously reported.[69,92] However, this relationship remains vague with other studies finding no association[64,71] or a very small impact.[102]

This study had several strengths. First, to our knowledge, it is the first study to prospectively investigate the associations between SW exposure and ANM among diverse group of Canadian workers, using a large population based sample. Secondly, the CLSA questionnaire utilized standard measuring tools[50,61,62,77] compatible with other international surveys to capture all information related to SW exposure and ANM. Additionally, the simultaneous adjustment for multiple factors in the Cox models, while censoring at initiation of HT limited the potential for confounding bias due to HT use. Nonetheless, this study has several limitations. First, due to the number of events we pooled evening and night shift together as previously reported by some investigators.[4,6,18] Second, we were unable to capture some SW related information, as they were not recorded in the CLSA questionnaire, such as the type and direction of rotating shifts, number of consecutive night shifts worked, and the number of days off between shifts.[103] Related to longest job exposure, we were not able to capture the exact timing of occurrence of the exposure. Data related to early reproductive life circumstance like age at menarche and breastfeeding, which have been previously linked to ANM, were also not collected. In addition, most of the data were derived from questionnaires based on memory recall, raising the possibility of recall bias. The potential homogenous ethnicity (almost 95% white in our study sample) and the exclusion of women with surgical menopause and breast cancer, may affect the generalizability of our findings. Finally, there is a possibility of selection bias as the women excluded due to missing information were older and reported to have low income than those included in study.

Conclusion

In conclusion, based on our study results, SW exposure is significantly related to variations in ANM later in life. Although our findings do not offer conclusive evidence, they do suggest that a delaying effect of rotating SW exposure, on ANM might be plausible. This delaying effect of rotating SW on ANM has not been reported before. Therefore, further studies are warranted to clarify the basis for this association. Detailed information related to SW on scheduling, workplace and personal factors, is desirable for higher quality research related to shiftwork and reproductive health outcomes.

Chapter Four

The association between shift work exposure and frailty among middle-aged and older adults: Results from the Canadian Longitudinal Study on Aging (CLSA)

Durdana Khan[1], MPH, Chris Verschoor[2,3,4], PhD, Michael Rotondi[1], PhD, Heather Edgell[1], PhD, and Hala Tamim[1], PhD

[1]From the School of Kinesiology and Health Science, York University, Toronto, Canada

[2]Health Sciences North Research Institute, Sudbury, Canada

[3]Northern Ontario School of Medicine, Sudbury, Canada

[4]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

This manuscript has been published:

Khan D, Verschoor C, Edgell H, Rotondi M, Tamim H. The association between shift work exposure and frailty among middle-aged and older adults: results from the Canadian Longitudinal Study on Aging (CLSA). *J Occup Environ Med*. 2023; 65(5):355-361. doi:10.1097/jom.0000000000002806

Online abstract link

Video summary link

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Abstract

Objective: To investigate the association between shift work (SW) exposure and frailty

Methods: Longitudinal secondary data analyses were performed using Canadian Longitudinal Study on Aging. Individuals aged 45–85 years were included at baseline (N=47,740). Primary SW variables were derived at baseline: ever exposed to SW, SW exposure in longest job, and SW exposure in current job. Multinomial regression models were constructed to evaluate the association between SW and frailty at 3 years of follow-up.

Result: Participants who reported ever exposed to SW were associated with frailty compared to daytime workers. Particularly, female participants working in rotating shifts in their longest jobs were more likely to be classified as frail compared to daytime workers.

Conclusion: This study suggests that SW may play a role in development of frailty and this warrants further investigation.

Key Words: Aging – CLSA – Frailty – Shift work – Occupational health – Night shift work– Rotating shift work – Canadian workers

Introduction

Frailty is a concept that is frequently used to describe elderly people who are more susceptible to morbidity and mortality, and is gaining importance as a healthcare priority in countries with ageing populations.[104] Closely linked to advanced age and disease-related processes, frailty is defined as a *"medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death."*[105,106] It allows researchers to quantitatively summarize individual vulnerability, which cannot be inferred from chronological age alone. Those who are frail, are at increased risk of pre-mature mortality, institutionalisation and worsening disability.[106] While frailty naturally occurs with age, previous literature have consistently shown that women are more likely to be frail than men of the same age,[107–111] and is significantly related to lifestyle choices like physical activity, healthy diet,[104,112] and socio-demographic factors such as poverty, educational level, marital status,[112–115] and participation in social organizations.[43,116]

A factor that may impact development of frailty is shift work (SW), defined as any work outside the regular daytime hours.[1,2,4] A full spectrum of SW involves: 1) evening shift, 2) night shift, 3) rotating shift (day to evening and/or night), and 4) other less specified shifts including on-call or casual shift (no prearranged schedule) and irregular shifts.[2,5–7] SW has increased worldwide in recent years. In Canada, more than a quarter of employees (28%) work outside traditional daytime hours.[2,4] SW may be a social and economic necessity, but its adverse effect on workers' health cannot be ignored. Growing evidence suggest that a wide range of negative health outcomes have been associated with SW particularly night and rotating SW.[5,19,20,23–25] Although it is highly recommended that occupational factors throughout adulthood should be taken into consideration when exploring the frailty of older persons,[117,118] the role of SW on frailty development at advanced age has not yet explored.[119] Several mechanisms have been proposed that linked SW to disease process, including circadian misalignment, disrupted sleep, and light induced suppression of melatonin levels at night.[120,121] These mechanisms may contribute to the development of frailty by disturbing metabolic, hormonal and inflammatory responses.[120,122] Therefore, in the view of this assumption, the study aims to investigate the association between SW exposure and frailty among adult Canadians.

Methodology

Study design and sample

Secondary longitudinal data analyses were performed using the Canadian Longitudinal Study on Aging (CLSA) database, which is a large cohort that includes 51,338 adults between the ages of 45 and 85. The CLSA has two cohorts: A "comprehensive cohort" (30,097) that provided self-reported health information through in-home personal interviews, and a "tracking cohort" (21,241) which provided all information through telephone interviews. For this study, we combined both cohorts to increase sample size. CLSA excluded residents of institutions, the three territories, First Nations reserves; those who spoke neither English nor French; fulltime Canadian Armed Forces members; and individuals with cognitive impairment. CLSA study design has been previously described in detail elsewhere.[48,61]

Assessment of primary exposure (SW)

The primary exposure of interest 'SW' was self-reported and assessed in the CLSA baseline questionnaires. All study participants were asked *"Have you ever worked at a job or business?"* (yes/no). The participants who reported 'yes' were asked *"Are you currently working at a job or business?"* (yes/no). Participants who reported 'yes' were asked *"Which of the following best describes your working schedule?"* (daytime work, night shift, rotating shift). Participants were also asked about their longest job, *"Thinking about the job you worked at the longest, which of the following best describes your working* *schedule?"* (daytime work, night shift, rotating shift). Based on this information, three variables were generated to measure SW exposure:

Ever exposed to SW

This variable measured overall occurrence of any SW. All participants who reported ever working in any shift (night/rotating) in their working career were considered exposed to SW and coded as 'yes'. All those who reported only daytime work, were considered unexposed to SW and coded as 'no'.

Exposure of SW in longest job

This variable measured the exposure of SW during the longest job. SW in longest job was categorized into; daytime work (reference category), night SW and rotating SW.

Exposure of SW in current job

This variable measured the exposure of SW among participants who reported currently working and categorized into; daytime work (reference category), night SW, rotating SW.

Assessment of outcome (frailty)

Frailty index (FI) utilized in this study was based on standard procedures (Accumulation of Deficits Model),[123] recently applied by Pérez-Zepeda et al[109] to create population-based normative frailty values for Canada. All variables, selected to create FI, were available in both CLSA arms and could identify deficits in health including diseases, disability and mental health problems[124] Specific details regarding the CLSA variables employed to construct FI, deficit classification, and relevant summary statistics can be found in the appendix B. Additional information regarding screening procedures and construction of FI has been previously described in detail.[109] All 52 variables, selected to create FI, were transformed into a 0 (no deficit) to 1 (deficit) scale. Interval or ordinal variables with more than two responses were coded as a fraction of the complete deficit. To calculate each participant's FI score, we summed the deficits and divided that count by the total number of deficits measured, using the formula

$$\text{FI} = \frac{\textit{Number of deficits present on a determined individual}}{\textit{Number of deficits measured for that individual}}$$

Possible FI scores range from zero to one, with those individuals scoring zero having the lowest level of frailty. For instance, if an individual had 15 deficits of 52 considered, the FI score would be 15/52 = 0.29. We did not calculate FI scores for participants with missing values for ≥10 items (≥20% of the 52 items included in frailty index).[109] Although there is no single standard cut-off for defining frailty states, previously utilized cut-points[125–128] were applied to classify continuous FI scores into the following categories, robust/non frail (FI ≤ 0.10), mild frail (FI > 0.10 to FI< 0.20) and frail (FI ≥ 0.20). The frailty scores were calculated at baseline (covariate) and at three years follow-up (outcome).

Covariates

Sociodemographic variables included, sex, age in years, ethnicity, education level, marital status, total annual household income in Canadian dollars, retirement status and baseline frailty. Lifestyle factors specifically smoking status and alcohol consumption were also included. Height and weight were used to calculate BMI in kg/m^2. In addition, reproductive factors were included, as they are significant components in studies related to frailty in women.[129,130] Reproductive factors comprised parity (number of pregnancies), use of oral contraceptives, history of hormone therapy (HT) and menopause classification. All covariates were measured at baseline and their respective categories are summarized in Table 3.

Analysis

Baseline characteristics were presented as frequencies. Multinomial regression analyses were used because frailty has three categories (non frail, mild frail and frail). This analysis allowed to compare mild frail to non frail and frail to non frail in the same model and to estimate association between SW exposures and each level of frailty status at 3 years of follow-up. Separate models were generated for three primary SW exposures, stratified by sex, because of earlier findings on the sex differences in frailty.[107–111] First with "ever exposed to SW" (Model 1), then "SW exposure in longest job" (Model 2) and finally "SW exposure in current job" (Model 3). Odds ratios (OR) with 95% confidence interval (CI) were calculated for all models. The CLSA provides survey inflation weights (i.e. inverse probability weights) and analytical weights, which were utilized for prevalence estimates and regression modelling respectively to generalize results to the Canadian population.[51] A p-value <0.05 considered statistically significant. All statistical data analyses were performed using STATA version 13.0.

Results

For this study, the analysis was restricted to participants who self-reported as currently working or have worked. Figure 1 illustrates a flow diagram summarizing the criteria used for exclusions. Participants were excluded if they reported: never worked in any job, missing ≥20% of the 52 items included in frailty index;[109] working in unspecified schedules; and refused to answer or don't know their working schedules. Finally, 47,740 participants remained in the study sample at baseline which formed the basis of analysis.

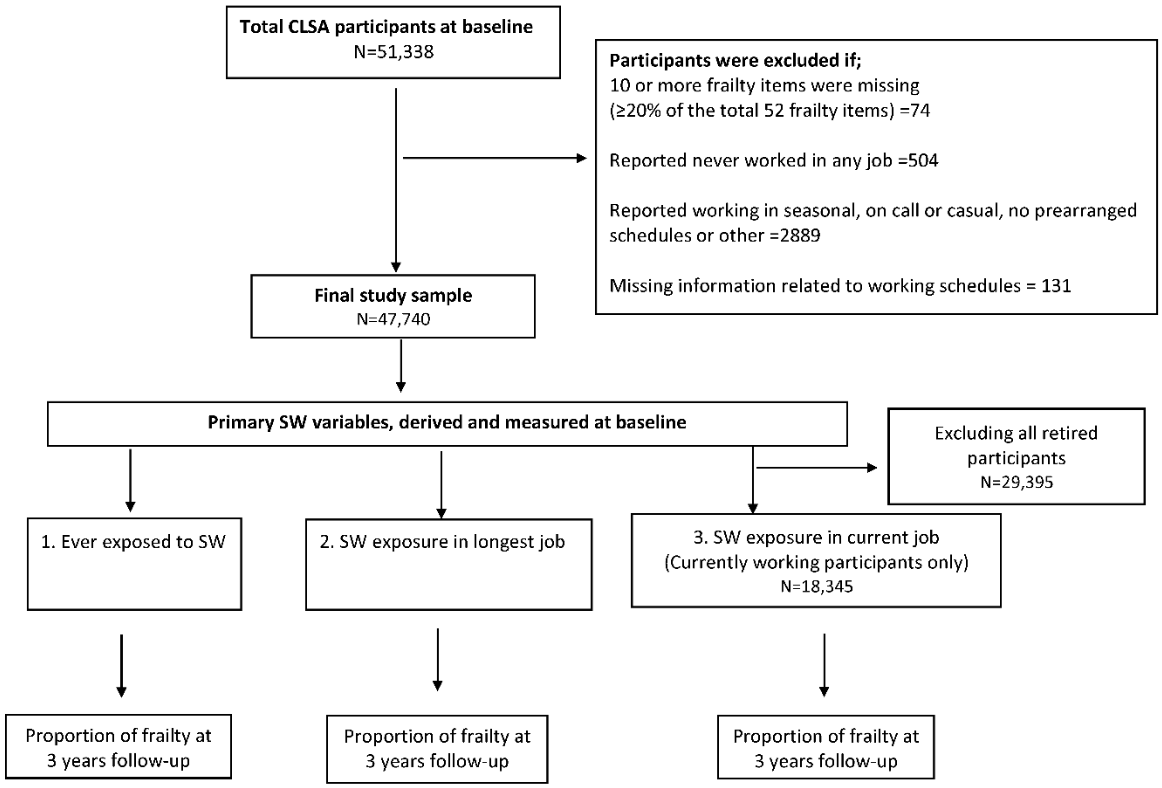

Figure 3. Canadian Longitudinal Study on Aging (CLSA) participant flowchart. SW shift work

Table 3: Baseline characteristics of study sample stratified by sex

Characteristics	Total N[a] (%)[b]	Males (%)[b]	Females (%)[b]	*P*-value
All study participants	12,623,776 (100)	48.60	51.40	
Age(years)				
45-54	4,885,111 (38.70)	19.07	19.63	<0.001
55-64	3,998,471 (31.67)	15.40	16.27	
65-74	2,366,008 (18.74)	9.04	9.70	
75+	1,374,183 (10.88)	5.09	5.79	
Ethnicity				
Whites	11,983,202 (95.01)	45.93	49.08	0.051
Other[c]	629,207 (4.98)	2.64	2.34	
Marital status				
With partner	9,611,163 (76.16)	39.77	36.89	<0.001
No partner	3,009,088 (23.84)	8.83	15.01	
Education level				

Less than high school	2,649,292 (20.99)	10.36	10.63	<0.001
High school to some college	7,514,756 (59.55)	27.85	31.70	
Bachelor's degree and Higher	2,454,830 (19.45)	10.39	9.06	
Household income (CAD)				
Less than $20,000	758,530 (6.34)	2.34	4.00	<0.001
$20,000 or more, but less than $50,000	3,101,121 (25.94)	11.57	14.36	
$50,000 or more, but less than $100,000	4,333,343 (36.24)	18.58	17.66	
$100,000 and more	3,763,102 (31.47)	16.87	14.60	
Retirement status				
Completely /partially retired	5,946,289 (47.34)	21.94	25.40	<0.001
Not retired	6,613,764 (52.65)	26.79	25.86	
Baseline frailty (covariate)				
Non frail (FI ≤ 0.10)	8,477,739 (67.16)	34.32	32.83	<0.001
Mild frail (FI > 0.10 to FI< 0.20)	3,467,282 (27.47)	12.22	15.25	
Frail (FI ≥ 0.20)	678,754 (5.38)	2.06	3.32	
Frailty at 3 years follow-up (outcome)				
Non frail (FI ≤ 0.10)	8,428,426 (66.77)	34.61	32.15	<0.001
Mild frail (FI > 0.10 to FI< 0.20)	3,286,169 (26.03)	11.41	14.63	
Frail (FI ≥ 0.20)	909,179 (7.20)	2.58	4.62	
Smoking				
Never	3,558,625 (28.26)	11.92	16.34	<0.001
Former	7,352,841 (58.40)	30.33	28.07	
Current	1,678,669 (13.33)	6.39	6.94	
Alcohol consumption				
Never	1,943,395 (15.41)	6.84	8.57	<0.001
Drinks less than weekly	4,039,891 (32.03)	12.53	19.50	
Drinks at least weekly	6,628,465 (52.56)	29.24	23.31	
BMI(kg/m^2)				
20.0-24.99 (normal weight)	3,830,525 (30.72)	12.66	18.06	<0.001
<20.00 (underweight)	419,089 (3.36)	0.74	2.62	
25.0-29.99 (overweight)	4,797,901 (38.47)	22.04	16.43	
>30.0 (obese)	3,422,752 (27.45)	13.05	14.40	
Primary SW exposures				
Ever exposed to SW				
Never exposed to SW (Daytime work only)	9,626,973 (78.82)	37.90	40.92	0.321
Ever exposed to SW	2,586,712 (21.18)	10.44	10.73	
SW exposure in current job[d]				
Not exposed to SW (Daytime work)	4,904,438 (84.65)	44.13	40.52	0.04
Night SW	216,157 (3.73)	1.60	2.13	
Rotating SW	672,829 (11.61)	6.29	5.32	
SW exposure in longest job				

Not exposed to SW (Daytime work)	9,615,937 (80.55)	38.77	41.78	<0.001
Night SW	458,907 (3.84)	1.53	2.31	
Rotating SW	1,862,517 (15.60)	8.23	7.37	
Reproductive history (Females only)				
Parity				
Nulliparous	--	--	10.86	
1 to less than 3	--	--	38.45	
3 to less than 5	--	--	39.01	
5 and more	--	--	11.67	
Contraceptive use	--	--		
No	--	--	25.39	
Yes	--	--	74.61	
History of HT	--	--		
No	--	--	62.07	
Yes	--	--	37.92	
Menopause classification	--	--		
Normal ANM (46-54 yrs)	--	--	46.27	
Premature ANM (30-39 yrs)	--	--	3.32	
Early ANM (40-45 yrs)	--	--	10.84	
Late ANM (55-62 yrs)	--	--	11.05	
Hysterectomy	--	--	17.92	
Pre-menopause	--	--	10.60	

CAD, Canadian dollars; BMI, body mass index; SW, shift work; HT, hormone therapy; ANM, age at natural menopause.
[a] Reported sample size is an estimation for the study sample (N=47,740) using survey inflation weights; figures do not always sum up to the total due to missing values
[b] Reported frequencies are column percentages, calculated using survey inflation weights
[c] Other included South Asian, Chinese, Filipino, Latin American, Japanese, Southeast Asian, Korean, Arab, West Asian, and Black.
[d] For current job, only those participants were included who reported currently working (not retired) at baseline (N=18,345)

Table 3 shows characteristics of 47,740 participants (weighted to represent 12,623,776 Canadians) at baseline. The mean age of participants at baseline was 59.7 years (SD 10.15), 51.4% were females. The majority (95 %) of participants were white, over 50% reported to be living with partners, having education of high school to some college level, former smokers, drinking at least weekly and had household income 50,000 CAD and above. Overall, one out of five participants (21.1%) reported to be ever exposed to SW during their jobs. Specifically, 3.7 % and 11.6 % of the currently working participants reported to be exposed to night and rotating SW respectively. Considering the job held the longest in their entire career, 3.8 % and 15.6% of the participants reported to be exposed to night and rotating SW respectively. Overall, at 3 years of follow-up, 66.8% participants were categorised as non frail/robust, 26% as mild frail, and 7.2% as frail. The proportion of frailty at 3 years follow-up among primary SW variables, stratified by sex are summarized in Table 4. Unadjusted multinomial regression analyses showed that SW exposures were associated to mild frailty and frailty at 3 years follow-up (Table 4).

Results of multivariate analyses suggested that SW exposure was related to increased odds of being frail at 3 years of follow-up, after adjustments for confounders (Table 5).

Table 4: Proportion of frailty and unadjusted multinomial regression [odds ratios (ORs) and 95% Confidence Intervals(CI)], at three years follow-up for primary SW variables stratified by sex

Primary SW variables	Proportion of Frailty at 3 years follow-up						Unadjusted multinomial regression at 3 years follow-up			
	Male			Female			Male		Female	
	Non frail (%)[a]	Mild frail (%)[a]	Frail (%)[a]	Non frail (%)[a]	Mild frail (%)[a]	Frail (%)[a]	Mild frail OR[b] (95% CI)	Frail OR[b] (95% CI)	Mild frail OR[b] (95% CI)	Frail OR[b] (95% CI)
Ever exposed to SW										
Never exposed to SW (Daytime work only)	72.21	23.23	4.56	63.96	27.69	8.35	1.00	1.00	1.00	1.00
Ever exposed to SW	68.82	23.29	7.89	58.44	30.63	10.92	1.17 (1.05-1.31)*	1.90 (1.57 -2.32)*	1.09 (0.99-1.21)	1.51 (1.29-1.77)*
SW exposure in longest job										
Not exposed to SW (Daytime work only)	72.22	23.23	4.55	63.92	27.72	8.36	1.00	1.00	1.00	1.00
Night SW	70.65	18.88	10.47	58.33	30.38	11.29	1.25 (0.92-1.69)	2.14 (1.42-3.24)*	1.11 (0.90-1.37)	1.95 (1.40-2.72)*
Rotating SW	67.35	24.76	7.89	57.75	31.34	10.92	1.18 (1.05-1.33)*	1.92 (1.54-2.39)*	1.13 (1.00-1.28)*	1.44 (1.21-1.72)*
SW exposure in current job[c]										
Not exposed to SW (Daytime work only)	84.48	14.07	1.45	78.27	20.06	1.67	1.00	1.00	1.00	1.00
Night SW	78.76	18.54	2.71	71.39	24.9	3.72	1.58 (1.05-2.37)*	3.22 (1.42-7.27)*	1.42 (0.99-2.03)	2.14 (0.87-5.29)
Rotating SW	82.76	15.58	1.27	69.41	25.59	5.00	1.19 (0.94-1.51)	1.87 (0.96-3.66)	1.14 (0.92-1.42)	2.04 (1.16-3.59)*

[a] The reported frequencies are row percentages utilizing survey inflation weights.
[b] The ORs and 95% CI were calculated using survey analytical weights.
[c] For current job, only those participants were included who reported currently working (not retired) at baseline (N=18,345)
* P value <0.05

Table 5: Adjusted multinomial regression longitudinal models, odds ratios (ORs) and 95% Confidence Intervals(CI) for proportion of frailty at 3 years follow-up

Primary SW exposures	Adjusted multinomial regression at 3 years follow-up			
	Male		Female	
	Mild frail OR[a,b] (95% CI)	Frail OR[a,b] (95% CI)	Mild frail OR[a,c] (95% CI)	Frail OR[a,c] (95% CI)
Model 1 Ever exposed to SW				
Never exposed to SW (Daytime work only)	1.00	1.00	1.00	1.00
Ever exposed to SW	1.05 (0.91-1.21)	1.30 (1.01-1.68)*	1.16 (1.01-1.34)*	1.41 (1.09-1.83)*
Model 2 SW exposure in longest job				
Not exposed to SW (Daytime work only)	1.00	1.00	1.00	1.00
Night SW	1.31 (0.93-1.86)	1.68 (0.95-2.97)	1.04 (0.77-1.40)	1.50 (0.92-2.45)
Rotating SW	1.02 (0.88-1.18)	1.29 (0.98-1.72)	1.28 (1.09-1.51)*	1.55 (1.17-2.07)*
Model 3 SW exposure in current job[d]				
Not exposed to SW (Daytime work only)	1.00	1.00	1.00	1.00
Night SW	1.33 (0.78-2.30)	1.08 (0.28-4.20)	1.14 (0.70-1.86)	1.49 (0.56-4.03)
Rotating SW	1.08 (0.82-1.43)	1.21 (0.62-2.62)	1.07 (0.82-1.40)	1.76 (0.87-3.61)

[a] The adjusted ORs and 95% CI were calculated using survey analytical weights.
[b] Models are adjusted for age, ethnicity, marital status, income, education, retirement status, baseline frailty, smoking, alcohol, BMI categories
[c] Models are adjusted for age, ethnicity, marital status, income, education, retirement status, baseline frailty, smoking, alcohol, BMI categories, contraceptive use, parity, HRT, menopause classification
[d] For current job, only those participants were included who reported currently working (not retired) at baseline (N=18,345)
*P value <0.05

Relationship between ever exposed to SW and frailty

After adjusting for covariates, it was found that the males who were ever exposed to SW were more likely to be frail than non frail (OR=1.30, 95% CI, 1.01-1.68) when compared to daytime workers (Table 5, Model 1). Females who were ever exposed to SW had significantly higher odds of being mild frail (OR=1.16, 95% CI, 1.01–1.34) and frail (OR=1.41, 95% CI, 1.09–1.83) vs. non frail relative to those never exposed to SW (daytime work only).

Relationship between SW exposure in longest job and frailty

Similar results were observed when considering SW exposure in longest job (Table 5, Model 2). Men who reported working in night shift during their longest job period were more likely to be frail than non frail (OR=1.68, 95% CI, 0.95–2.97) compared to daytime workers. Also, men who reported working in rotating shifts during their longest job period were associated with the odds of frail vs. non frail when compared with day time workers (OR=1.29, 95% CI, 0.98–1.72). Among female shift workers, the odds of being classified as frail relative to non frail were higher if participants reported working in night shift (OR=1.50, 95% CI, 0.92–2.45) or rotating shift (OR 1.55, 95% CI, 1.17–2.07) compared to daytime workers during the longest job period. In addition, female rotating shift workers were more likely to be mild frail vs. non frail (OR=1.28, 95% CI, 1.09–1.51) compared to day workers.

Relationship between SW exposure in current job and frailty

For the current job, only who reported currently working (not retired) at baseline (N=18,345) were included (Table 5, Model 3). After adjusting for confounders, results showed that the participants working in night shift were more likely to be classified as frail vs. non frail (OR_{male}=1.08, 95% CI, 0.28–4.20, OR_{female}=1.49, 95% CI, 0.56–4.03) compared to day workers. Similarly, for rotating shift both male and female current workers were more likely to be frail vs. non frail as compared to daytime workers (OR_{male}=1.21, 95% CI, 0.62–2.62 and OR_{female}=1.76, 95% CI, 0.87–3.61). However, the relationships between currently working population (for both night and rotating SW) and frailty were not statistically significant at the nominal 5% two-sided significance level.

Discussion

This study investigated the associations of SW exposure and frailty among adult Canadian workers. Results of the study revealed that ever exposed to SW was significantly associated with frailty at 3 years of follow-up. Particularly, exposure to rotating SW during longest job among females was significantly related to frailty. Investigating and identifying the modifiable factors of frailty like SW exposure among working populations is of clinical relevance. These study results would add insight on the impact of SW on frailty and further elucidate the role of circadian regulation on biology of aging which will assist in extending healthy active life expectancy.

SW has increased universally through years and consistent with the literature,[2,4] this study found that 21% of Canadian workers were exposed to SW at some point in their careers. Similar trends were identified in other developed countries like Japan,[72] France,[131] all over Europe[74] and the US,[74] affecting 20% to 25% of workers in different industries. This study reported that overall, 7.2% of the participants were categorized as frail and is consistent with the previously reported prevalence for frailty (7.6%) that utilized Canadian Health Measures Survey among adults of age 18-79 years.[132] Consistent with the literature, this study found that frailty was higher for older age groups,[109] and the high frailty scores among women compared to men is also in line with the well-described phenomenon that women tend to have more deficits than men but greater longevity.[109,113,133]

It was also noted that participants who were ever exposed to SW, were more likely to be frail compared to daytime workers. This relationship remained consistent for female participants who reported working in rotating shifts during their longest jobs, and were significantly classified as frail compared to daytime workers. However, the observed relationship between SW and frailty was not significant for current working participants (both night and rotating SW). This lack of association may be attributed to the healthy worker effect, with healthier individuals usually being recruited or choosing to work as shift workers, and less healthy workers being restricted to day work.[134,135] There is a large gap in the literature regarding the relationship between SW exposure and frailty as no previous studies have investigated this relationship. However, suggestive evidence has linked SW exposure to chronic disease risk. A recent meta-analysis of 34 studies showed that night SW was associated with an increased risk of coronary events (RR=1.41, 95% CI, 1.13-1.76).[5] SW has been identified as a risk factor for peptic ulcer, type-2 diabetes,[20] and cancers such as prostate,[24] colorectal,[25] and breast cancers,[23] when compared to their day shift counterparts. In addition, previous studies have also reported adverse effects of SW on mental health. A meta-analysis of eleven observational studies found significant risk of depression among night shift workers.[35] Also, shift workers are more likely to suffer from mood disorders compared to day time workers.[36]

Circadian desynchronization experienced by shift workers is complex. Exact underlying mechanisms for associations between SW and development of frailty are unknown. However, it has previously been observed that circadian misalignment affect body levels of cortisol,[136,137] and significantly increase pro- and anti-inflammatory proteins like plasma tumor necrosis factor-alpha (TNF-α), interleukin 10 (IL-10) and C-reactive protein (CRP).[122] Release of both cortisol and inflammatory proteins into the blood in response to stressors like SW exposure, may contribute to ongoing disease processes and could act as preliminary markers for occurrence of frailty. Also, previous studies have highlighted the role of disrupted sleep[138] and poor sleep quality[139] in development of frailty. Further research is thus needed to develop a complete picture of the relationship between SW and frailty, and to determine any physiological pathways that are influenced.

A major strength of this study is that, to our knowledge, it is the first study to investigate the associations between SW exposure and frailty. In addition, a large population based sample was utilized involving a diverse group of workers. There are limitations to this study that warrant mention. First, due to the number of events evening and night shifts were pooled together as previously reported by some investigators.[4,6,18] Second, some SW related information were not included, as they were not recorded in the CLSA questionnaire, such as the type and direction of rotating shifts, number of consecutive night shifts worked, and the number of days off between shifts.[103] In addition, most of the data were derived from questionnaires based on memory recall, raising the possibility of recall bias.

Conclusion

In conclusion, this study shows that female shift workers, specifically those who were exposed to rotating shifts in their longest job is significantly related to frailty later in life. This gender difference in risk of frailty supports the significance of considering gender when addressing frailty and targeting interventions in old age. Although these findings are preliminary, they suggest that circadian disruption may be an important factor and the role of SW exposure in the risk of frailty warrants further investigation.

Chapter Five

The association between shift work exposure and cognitive impairment among middle-aged and older adults: results from the Canadian Longitudinal Study on Aging (CLSA)

Durdana Khan[1], MPH, Heather Edgell[1], PhD, Michael Rotondi[1], PhD, and Hala Tamim[1], PhD

[1]From the School of Kinesiology and Health Science, York University, Toronto, Canada

This manuscript has been submitted to PLOS ONE and is under-review:

Khan D, Edgell H, Rotondi M, Tamim H. The association between shift work exposure and cognitive impairment among middle-aged and older adults: results from the Canadian Longitudinal Study on Aging (CLSA). *PLoS One*. 2023:Under-review. Manuscript No. PONE-D-23-11981

Abstract

Background: Shift work, especially rotating and night shift work, has been linked to a wide range of detrimental health outcomes. Occupational factors like shift work and their potential impact on cognitive functions have received little attention, and the evidence is inconclusive. The objective of our study is to explore associations between shift work exposure and cognitive impairment indicators based on comparisons with the normative standards from the Canadian population.

Methods: Cross-sectional analyses were performed using baseline Canadian Longitudinal Study on Aging database, including 47,811 middle-aged and older adults (45–85 years). Three derived shift work variables were utilized: ever exposed to shift work, shift work exposure in longest job, and shift work exposure in current job. Four cognitive function tests were utilized, Rey Auditory Verbal Learning Tests (immediate and delayed) representing memory domain, and Animal Fluency, and Mental Alteration, representing the executive function domain. All cognitive test scores included in study were normalized and adjusted for the participant's age, sex, education and language of test administration (English and French), which were then compared to normative data to create "cognitive impairment' variables. Unadjusted and adjusted multivariable logistic regression models were used to determine associations between shift work variables and cognitive impairment individually (memory and executive function domains), and also for overall cognitive impairment.

Result: Overall, one in every five individuals (21%) reported having been exposed to some kind of shift work during their jobs. Exposure to night shift work (both current and longest job) was associated with overall cognitive impairment. In terms of domain-based measures, night shift work (longest job) was associated with memory function impairment, and those exposed to rotating shift work (both current and longest job) showed impairment on executive function measures, when compared to daytime workers.

Conclusion: This study suggests disruption to the circadian rhythm, due to shift work has negative impact on cognitive function in middle-aged and older adults and this warrants further investigation.

Introduction

Cognitive impairment is a condition that indicates the transitional phase between normal cognitive function and dementia.[140] As the global population is aging, cognitive impairment has become a major health concern affecting independence and quality of life. Although it was believed that cognitive decline was an inevitable feature of the normal aging process,[141] evidence now reveals that cognitive functions are modifiable across the lifespan[142] A comprehensive meta-analysis of 247 studies examined key risk factors such as socio-economic and behavioural factors for cognitive impairment including dementia and found that lower educational attainment and physical activity were strong indicators of cognitive disorders.[143] Similarly, lack of availability of social support has been linked to poor cognitive function among middle-aged and older adults.[144]

Little attention has been paid to occupational factors like shift work (SW) and their potential role in cognitive performances. In general, SW refers to a work schedule that occurs outside the traditional daytime (9:00 a.m. to 5:00 p.m.) working hours.[1,2,4] The entire spectrum of SW comprises the following shifts: evening shift, night shift, rotating shift (day to evening and/or night), and other less defined shifts including on-call or casual shift (no set schedule) and irregular shifts.[2,5–7,145] A variety of negative health outcomes have been associated with SW, particularly night and rotating SW.[5,19,20,23–25,145] A meta-analysis of 34 studies showed that both types of SW, night and rotating, were associated with an increased risk of coronary events including myocardial infarction and ischaemic stroke; the highest point estimate was noted for night shifts (RR= 1.41, 95% CI, 1.13-1.76). [5] SW, specifically night and rotating shifts, has been identified as a risk factor for peptic ulcer when compared with regular day workers.[19] A Danish prospective study that followed a cohort of 20,000 nurses for 15 years concluded that night shift workers were at increased risk of developing type-2 diabetes when compared with their day shift counterparts.[20] A previous study investigated female shift workers and have suggested a connection between rotating SW and a delayed menopause.[145] Moreover, the International Agency for Research on Cancer (IARC) has classified night SW as a probable human carcinogen (Group 2A) [21,22] with evidence of an association with prostate (RR=1.24, 95% CI, 1.05-1.46),[24] colorectal (OR=1.32, 95% CI, 1.12-1.55),[25] and breast (HR=2.15, 95% CI, 1.23-3.73) [23] cancers.

Taken together, these studies support the concept that SW impacts worker's health significantly. While little is known about the physiological pathways underlying SW-related disease processes, several mechanisms have been hypothesized including circadian misalignment due to disturbed sleep, and light induced suppression of melatonin levels at night.[120,121] These factors, in turn, disrupt a number of physiological and behavioral processes that contribute to disease progression. Any interference in regular circadian rhythm, due to sleep restriction, could result in disturbed metabolic, hormonal and inflammatory responses.[146] Such misalignment has been found to disturb cortisol levels, and pro- and anti-inflammatory proteins,[122] contributing to the development of chronic diseases including cognitive impairment. Another mechanism is endogenous melatonin rhythm. Melatonin is a hormone secreted from the Pineal body, low during the daylight hours and at the highest levels during dark periods (night). [120,146,147] Exposure to light at night can reduce circulating melatonin levels.[148] If the light is bright, the levels can be completely suppressed, which may be a potential risk factor for chronic illnesses.[103] Shift workers experience substantial misalignment between circadian system of the body and unusual working schedules,[40] which exposes them to increased risk for health problems. One more important factor that contributes to circadian interruption among shift workers is their behavior/lifestyle. This includes eating at irregular timings, lower physical activity levels, and higher incidence of smoking and intake of alcohol.[149] These factors feed back into the circadian clock causing desynchronized rhythms and altered metabolic and body temperature cycles.[8,40,120] In short, the potential effects of SW on cognition are likely related to the circadian misalignment and melatonin suppression. However, it is possible that any or all of the mechanisms described above interact to influence shift worker's cognitive function.[40,149]

The existing body of literature supports the notion that SW plays a critical role in cognitive functions. For example, some studies have highlighted acute and short term negative effects of night SW and disturbed sleep on cognitive functions.[150–152] In addition, few studies have assessed consequences of repeated disruption of circadian rhythms on cognitive functioning, among shift workers over time. First population based study [47] that explored chronic consequences of SW on cognitive functioning utilized large cross-sectional sample (3,237 French workers of aged 32, 42, 52, and 62 years) from VISAT (Aging, Health and Work) cohort. SW were classified into 'current', 'former' and 'never' and cognitive performances were evaluated by measuring verbal memory and speed performances. This first work provides some evidence of adverse effects of SW exposure on cognitive functioning, especially for men who are current or past shift workers.[47] Later, a prospective cohort study utilized the same French VISAT data base and reported that rotating SW was linked to lower cognitive test scores (memory and speed performances).[153] According to the study, former shift workers who stopped working shifts within the previous five years showed improved cognitive functioning.[153] Furthermore, a cross-sectional Swedish EpiHealth cohort study (7,143 participants, aged between 45-75 years) investigated associations between history of SW (non-shift, past and current shift worker) and cognitive executive functions i.e., trail making test (TMT). The study revealed that current and former shift workers performed worse on TMT outcomes than non-shift workers.[154] More recently, analysis of 21,610 participants of aged 45-85 years, from the Canadian Longitudinal Study on Aging (CLSA) examined the cross-sectional relationship between SW (yes/no) and aspects of cognitive performance (declarative memory and executive functioning).[155] The study found that shift workers showed poorer cognitive scores on tests for executive functioning (mental alteration test and interference condition of stroop test) but not for declarative memory (immediate and delayed recall trial) compared to non-shift workers.[155]Contrary to the results previously described, there are studies[46,156] that did not find significant associations between SW and cognitive function. A sample of 595 participants with no dementia from a Swedish Adoption Twin Study of Aging (SATSA), were followed for 9 years.[46] No significant associations were reported between any types of SW (ever/never) and measures of cognitive performance (verbal, spatial, memory, processing speed, and general cognitive ability).[46] Similarly, The Nurse's Health Study [156] followed 16,190 female participants in the United States, aged 30–55 years, over a 6-year period with three repeated cognitive assessments. Overall, this study does not convincingly support the hypothesis that older persons' cognition is negatively affected by their midlife SW history.[156] These discrepancies could be attributed to lack of differentiation between SW schedules (night, rotating),[46] and restriction of study sample to highly educated participants, who held at least a registered nurse or bachelor's degree.[156]

Despite SW's significance and crucial part in cognitive impairment, there is still a dearth of evidence. Existing normative standards utilized to evaluate cognitive functions were based on non-Canadian samples,[46,47,153,154,157,158] which may be outdated, [47,157,158] and did not cover the full spectrum of ages from middle-aged to older adults. [47,153,156–158] Most previous studies [46,154,155] did not account for differentiation between SW schedules (night and rotating SW separately).[46,47,154–156] and educational differences [153] in their analyses. Considering that circadian rhythm regulates cognitive activities,[159,160] desynchronization of the circadian rhythms associated with SW might be one of the plausible mechanisms underlying this association. Given the mixed findings reported from the limited studies on SW in relation to cognitive performance, this study aims to examine the association between SW and cognitive impairment measures based on normative standards from the Canadian population.

Methodology

Study design and sample

Cross-sectional data analyses were performed using the Canadian Longitudinal Study on Aging (CLSA) database, which is a nationwide, epidemiological study of aging that includes 51,338 middle-aged and older adults (aged 45-85 years). Participants were recruited and baseline data was collected between 2010 and 2015. The CLSA has two cohorts: the “tracking cohort” (21,241) that provided all information through telephone interviews, and a “comprehensive cohort” (30,097) that provided self-reported health information through in-home personal interviews, also, during a site visit at their local data collection center, they provided data including the entire neuropsychological battery. For this study, we combined both cohorts to increase sample size. CLSA excluded residents of institutions, the three territories, First Nations reserves; those who spoke neither English nor French; fulltime Canadian Armed Forces members; and individuals with overt cognitive impairment. The CLSA study design has been previously described in detail elsewhere.[48,61] The core CLSA study has been approved by McMaster University Health Integrated Research Ethics Board and by research ethics boards at all collaborating Canadian institutions. The present study is a secondary analysis of fully de-identified CLSA data which has been approved by the York University, Office of Research Ethics (ORE) [STU 2020-123]. As such, additional participant consent for this analysis was not required as all CLSA participants provided informed consent during primary data collection to have their de-identified data used in research.

This study sample was limited to those who self-reported being currently employed or having previously worked. Figure 4 displays a flow diagram outlining the exclusion criteria. Participants were excluded if they reported: never working in any job; working in unspecified schedules; and refused to answer or do not know their working schedules. Finally, 47,811 participants remained in the study sample, which formed the basis of analysis.

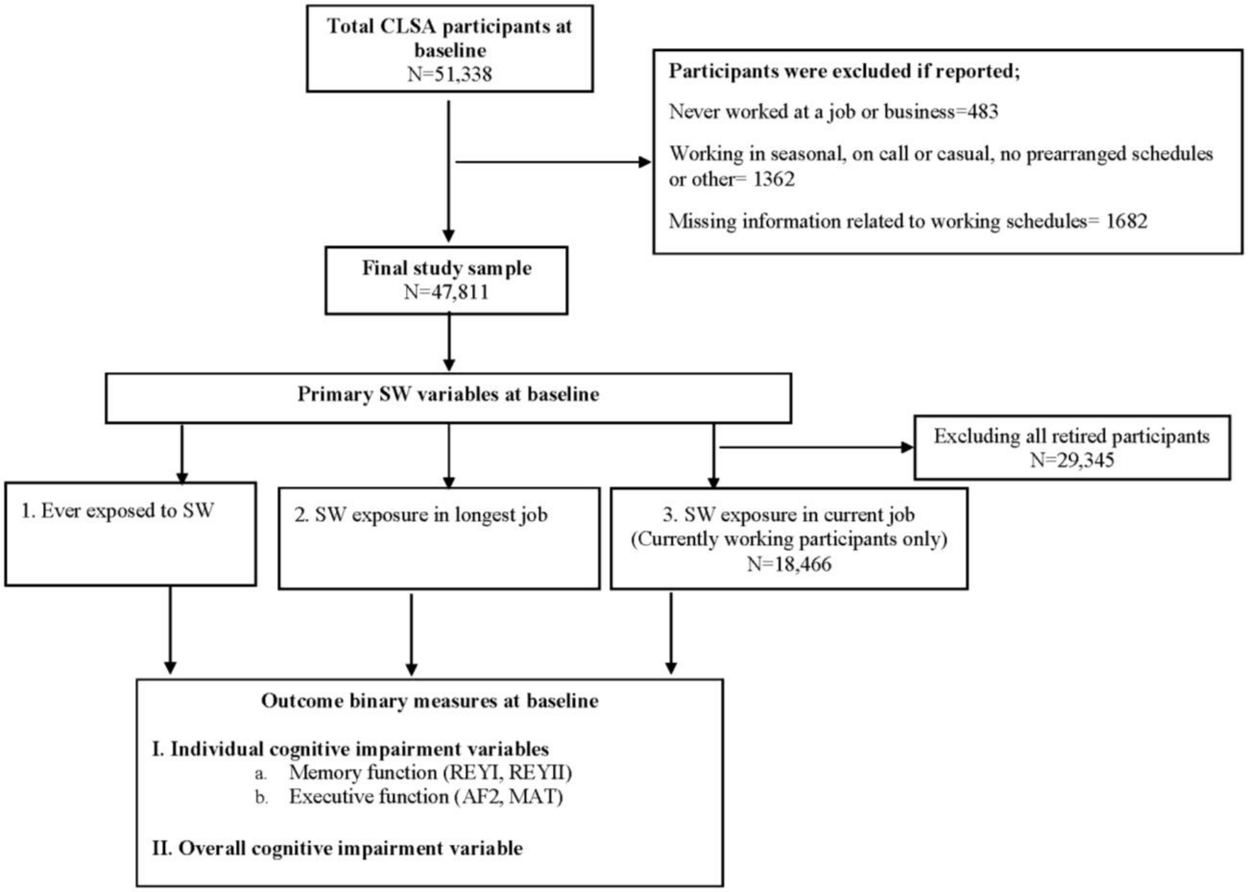

Figure 4: Canadian Longitudinal Study on Aging participant flowchart.

Assessment of primary exposure (SW)

The primary exposure of interest 'SW' was self-reported and assessed in the CLSA baseline questionnaires. All study participants were asked *"Have you ever worked at a job or business?"* (yes/no). The participants who reported 'yes' were asked *"Are you currently working at a job or business?"* (yes/no). Participants who reported 'yes' were asked *"Which of the following best describes your working schedule?"* (daytime work, night shift, rotating shift). Participants were also asked about their longest job, *"Thinking about the job you worked at the longest, which of the following best describes your working schedule?"* (daytime work, night shift, rotating shift). Based on this information, three variables were generated to measure SW exposure:[145]

Ever exposed to SW

This variable measured overall occurrence of any SW. All participants who reported ever worked in any shift (night/rotating) in their working career were considered exposed to SW and coded as 'yes'. All those who reported only daytime work, were considered unexposed to SW and coded as 'no'.

Exposure of SW in longest job

This variable measured the exposure of SW during the longest job. SW in longest job was categorized into; daytime work (reference category), night SW and rotating SW.

Exposure of SW in current job

This variable measured the exposure of SW among participants who reported currently working and categorized into; daytime work (reference category), night SW, rotating SW.

Primary outcome: Cognitive impairment

The primary outcome for this study is 'cognitive impairment', based on four cognitive function tests, including Rey Auditory Verbal Learning Tests (REYI and REYII) representing memory domain, with Animal Fluency (AF2), and Mental Alteration (MAT), representing the executive function domain of cognition. Details are summarized in Table 6. These domains were selected because they are present in both CLSA cohorts and each has been shown to correlate with everyday functioning (i.e. physical, behavioral, and social).[161–163] The CLSA working group created normalized scores from the original test scores as standardized z-scores that have a mean of zero and standard deviation of 1.0. All normed z-scores were adjusted for age, sex and education status, and norming is done separately for tests completed in English and French. In order to determine whether a person's performance is within the range of healthy cognitive performance, comparisons were made with normative data. Normative data were created by CLSA[164] and used as a comparison standard for an individual's performance.

Table 6. Description of cognitive function tests utilized by CLSA to create cognitive impairment variables

Cognitive domain assessed	Cognitive function tests	Cognitive function tests description	Individual impairment variables	Overall impairment variable
Memory This domain assesses both learning and retention	Rey Auditory Verbal Learning Test (Immediate) (REYI)	The REYI is a 15-item word learning exam that measures learning as well as retention. This test is divided into two trials. During the first trial, 15 words were read out to the participants, who were then asked to immediately recall as many of the 15 words as they could in 90 seconds. During second trial (REYII) participants were asked to recall as many of the 15 words from the first trial within 60 seconds after a 30 minutes delay. REY I and REY II were treated as separate memory tests. One point was allocated for each correctly recalled word in each of the tests.	Yes=Impaired on REYI if score is below the 5th percentile of healthy participants (normative data)	Based on four individual impairment variables i.e. REYI, REYII, AF2, & MAT and can only be calculated when all scores are available. Yes=Presence of two or more individual impaired scores are suggestive of overall impairment
	Rey Auditory Verbal Learning Test (Delayed) (REYII)		Yes=Impaired on REYII if score is below the 5th percentile of healthy participants (normative data)	
Executive Function This domain assesses many higher order mental processes and complex behaviours, including mental flexibility, abstract concept formation, problem-solving, and reasoning	Animal Fluency (AF2)	Scores on the Animal Naming Test were based on a 'lenient' scoring algorithm where participants received one point for each distinct animal named, even if the animals were members of the same species.	Yes=Impaired on AF2 if score is below the 5th percentile of healthy participants (normative data)	
	Mental Alteration (MAT)	Mental flexibility and processing speed are measured using the MAT. MAT involves a cognitive switching task that requires a participant to alternate between the numbers 1–26 and the letters of the alphabet (i.e. 1-A, 2-B, 3-C, etc.).	Yes=Impaired on MAT if score is below the 5th percentile of healthy participants (normative data)	

After comparisons, the following impairment variables were created and utilized as outcome variables in the study:

Individual cognitive impairment variables

Four binary-valued impairment variables (yes/no) were created, one for each of the cognitive function test i.e. REYI, REYII, AF2, and MAT. 'Yes' indicates that the participant's normed z-score falls in the lowest 5% of the neuro-healthy CLSA normative data.

Overall cognitive impairment variable

A binary-valued variable (yes/no) that indicates the participant's overall cognitive performance on the basis of four individual cognitive impairment variables and can only be calculated when all four are available i.e. REYI, REYII, AF2, and MAT.[164,165] The presence of two or more individual impaired scores are suggestive of overall cognitive impairment and coded as 'yes', whereas zero or one impaired score is suggestive of 'no' impairment overall.[164,165]

Detailed rationale for the selection of these measures of 'cognitive impairment' along with explanation of their implementation and validity of utilized base rate algorithms have been published elsewhere.[164,166–170]

Potential predictors

Multivariable models were adjusted for a relevant set of confounders. . Potential confounders were determined by consulting the existing literature on SW and cognitive impairment.[46,154–156] Sociodemographic variables included, sex, age in years, ethnicity, education level, marital status, total annual household income in Canadian dollars, retirement status[46,154–156].. Lifestyle factors comprised of smoking status and alcohol consumption. Height and weight were used to calculate body mass index (BMI) in kg/m^2. [46,154–156] Depression was ascertained by utilizing The Center for Epidemiological Studies short Depression scale (CES-D10). A score ≥10 suggests the presence of depression.[66,67] The measure of multi-morbidity was based on the standard definition[171] and included following chronic conditions: anxiety or mood disorder, Alzheimer's disease, arthritis, asthma, cancer, chronic obstructive pulmonary disease, diabetes, cardiovascular disease, and stroke. These chronic conditions were measured in the CLSA using the self-reported question, "*Has a doctor ever told you that you have . . . ?"* The presence of ≥2 chronic diseases were suggestive of multi-morbidity. CLSA measured Social Support Availability (SSA) by asking participants to rate their level of perceived support.[172] The measure contains 19 items rated on a 5-point Likert scale, from 1 (none of the time) to 5 (all of the time), with higher responses indicating better perceived support. 'Type of study cohort' is included as a covariate to represent the cohort membership, categorized into 'tracking' and 'comprehensive'.[173] Data from participants in the tracking cohort were collected over the phone, whereas data from participants in the comprehensive cohort were collected in-person.[167] Finally, the average SSA scores were used to create three categories, low, medium, and high.[144] All covariates were measured at baseline and their respective categories are summarized in Table 7.

Analysis

Baseline characteristics were presented as frequencies. Unadjusted and adjusted logistic regression models were used to determine associations between SW variables and cognitive impairment individually, and also for overall cognitive impairment. Separate models were generated for each outcome variable. Odds ratios (ORs) with 95% confidence interval (CI) were calculated for all models. The CLSA provides survey weights (i.e., inverse probability weights) and analytical weights, which were used for prevalence estimates and regression modeling respectively to generalize results to the Canadian population.[51] A P value less than 0.05 was considered statistically significant. To assess the robustness of our findings, we compared complete cases included in analysis to the excluded cases due to missing information related to

SW schedules, as well as cognitive impairment. Results from both sensitivity analyses are available in Appendix C. All statistical data analyses were performed using STATA version 13.0.

Results

Figure 4 depicts a flow diagram summarizing the criteria used for exclusions. We compared the baseline characteristics of participants excluded due to missing information related to SW schedules (N=1,682) with the participants included in our final study population (N=47,811). No significant differences related to cognitive impairment variables were found between two groups. However, the participants excluded tend to be male, older (65 plus), less educated, non consumer of alcohol, and belongs to comprehensive cohort. Details are available in Appendix C. We also compared the participants with missing information related to cognitive impairment (N=1,201) to the participants with complete cognitive impairment data (N=46,610). No significant differences were found related to SW exposure between two groups. However, the participants with missing information tend to be in older group (65 plus), retired and living without partner, belong to tracking cohort and low income group, consume less alcohol, have depression and multi morbidity. Details are available in Appendix C.

Table 7 shows summary statistics of 47,811 participants (weighted to represent 12,632,907 Canadians) at baseline. The mean age of participants was 59.7 years (SD, 10.15 years), and 51.4% were females. Most participants (95%) were White, more than 50% reported to be living with partners, having education of high school to some college level, former smokers, drinking at least weekly, still working (not retired) and had household income 50,000 CAD and more. Around 30% were obese, had multiple-morbidity, and reported low to medium SSA. Overall, one in every five individuals (21.1%) reported having been exposed to some kind of SW at work. 4% and 11.6% of currently working participants, respectively, reported being exposed to night and rotating SW. Considering the longest job held in their whole career, 3.9% and 15.6% of individuals reported being exposed to night and rotating SW, respectively.

Table 7: Baseline characteristics of study sample and proportion of cognitive impairment indicators						
Characteristics	**Total sample**	**Memory Function impairment**		**Executive Function impairment**		**Overall Impairment (%)** [c,d]
	N[a] **(%)**[b]	**REYI (%)**[c,d]	**REYII (%)**[c,d]	**AF2 (%)** [c,d]	**MAT (%)** [c,d]	
Total study participants	12,632,907 (100)	6.44	5.73	6.11	9.10	4.40
Age (years)						
45-54	4,887,556 (38.69)	7.29	6.7	7.99	9.74	5.52
55-64	4,000,705 (31.67)	5.68	5.28	5.35	8.00	3.98
65-74	2,367,052 (18.74)	5.28	5.79	4.60	8.79	3.56
75+	1,375,571 (10.89)	7.56	3.43	4.30	10.52	2.82
Sex						
Male	6,141,058 (48.61)	6.00	5.34	6.08	8.17	4.05
Female	6,491,848 (51.38)	6.86	6.10	6.13	9.98	4.73
Ethnicity						
Whites	11,989,923 (94.99)	6.12	5.44	5.49	8.58	3.86
Other[e]	631,617 (5.01)	12.49	11.13	17.71	19.91	14.46
Marital status						
With partner	9,614,721 (76.13)	5.96	5.51	5.72	8.39	3.99
No partner	3,014,661 (23.87)	7.99	6.45	7.38	11.42	5.74
Education level						
Less than high school	2,651,620 (20.99)	7.31	4.69	5.26	10.80	3.55
High school to some college	7,519,899 (59.55)	6.86	6.76	6.96	9.71	5.32
Bachelor’s degree and Higher	2,456,491 (19.45)	4.25	3.76	4.45	5.52	2.56
Household income (CAD)						
Less than $20,000	761,294 (6.36)	13.57	11.39	9.70	16.99	12.4
$20,000 or more, but less than $50,000	3,103,306 (25.94)	6.5	5.54	7.10	11.91	5.04
$50,000 or more, but less than $100,000	4,333,590 (36.22)	5.99	5.41	5.75	8.37	3.94
$100,000 and more	3,765,059 (31.47)	4.97	4.97	4.91	5.75	2.60
Smoking						
Never	3,560,312 (28.25)	5.99	5.23	5.85	8.73	4.65
Former	7,357,349 (58.39)	6.19	5.54	5.99	8.53	3.77
Current	1,681,606 (13.34)	8.41	7.60	7.24	12.56	6.52
Alcohol consumption						
Never	1,945,792 (15.41)	8.96	7.12	7.79	12.27	6.88
Drinks less than weekly	4,044,907 (32.05)	7.18	6.05	6.58	9.83	5.13
Drinks at least weekly	6,630,183 (52.53)	5.27	5.15	5.32	7.72	3.24
BMI (kg/m^2)						
20.0-24.99 (normal weight)	3,834,669 (30.73)	5.78	5.18	6.41	7.40	3.72

<20.00 (underweight)	419,736 (3.36)	10.95	7.59	7.74	12.65	9.1
25.0-29.99 (overweight)	4,800,165 (38.47)	6.75	5.57	6.20	8.65	4.23
>30.0 (obese)	3,423,626 (27.43)	6.17	6.39	5.34	11.04	4.67
Depression						
No (CES-D10 <10)	10,330,178 (81.77)	5.66	5.17	5.75	8.14	3.67
Yes (CES-D10 ≥ 10)	2,302,729 (18.22)	9.97	8.32	7.72	13.45	7.68
Multi-morbidity						
Yes (≥2 chronic diseases)	3,507,516 (27.76)	7.67	6.72	5.62	10.89	5.29
No (<2 chronic disease)	9,125,391 (72.23)	5.97	5.36	6.30	8.43	4.06
Social Support Availability (SSA)						
Low	4,009,023 (32.97)	8.55	6.68	7.30	10.93	5.99
Medium	3,878,890 (31.90)	5.62	4.75	5.73	8.43	3.57
High	4,271,457 (35.13)	5.07	5.50	5.28	7.74	3.55
Retirement status						
Completely /partially retired	5,951,165 (47.34)	6.31	5.54	4.85	9.44	4.13
Not retired	6,618,004 (52.65)	6.53	5.90	7.23	8.84	4.61
Type of study cohort						
Tracking	5,156,753 (40.82)	6.23	5.56	5.95	9.14	4.28
Comprehensive	7,476,154 (59.18)	7.07	6.26	6.57	8.98	4.72
Primary SW exposure variables						
Ever exposed to SW						
Never exposed to SW(Daytime work only)	9,631,177 (78.81)	6.12	5.43	5.89	8.29	4.04
Ever exposed to SW	2,589,578 (21.19)	7.89	7.24	7.31	12.21	6.10
SW exposure in longest job						
Not exposed to SW (Daytime work)	9,620,140 (80.54)	6.11	5.43	5.89	8.28	4.04
Night SW	460,950 (3.86)	9.74	9.03	7.69	13.22	8.68
Rotating SW	1,863,147 (15.60)	7.49	6.63	7.23	12.20	5.29
SW exposure in current job[f]						
Not exposed to SW (Daytime work)	4,905,640 (84.38)	5.72	5.36	7.00	7.18	3.90
Night SW	235,468 (4.05)	11.21	5.16	9.78	11.53	7.62
Rotating SW	672,753 (11.57)	8.3	6.43	7.37	12.02	5.26

[a] Reported sample size is an estimation for the study sample (N=47,811) using survey inflation weights; figures do not always sum up to the total due to missing values
[b] Reported frequencies are column percentages, calculated using survey inflation weights
[c] Reported frequencies are row percentages, calculated using survey inflation weights
[d] Prevalence of cognitive impairment was based on normalized scores with respect to participant's age, sex, education and within each language group (English and French).

[e] Other included South Asian, Chinese, Filipino, Latin American, Japanese, Southeast Asian, Korean, Arab, West Asian, and Black. [f] For current job, only those participants were included who reported currently working (not retired) at baseline (N=18,466) CAD, Canadian dollars; BMI, body mass index; CES-D, the Center for Epidemiological Studies Depression Scale SW, shift work; REY, Rey auditory verbal learning; AF, Animal fluency; MAT, Mental alteration.

The proportions for cognitive impairment (both individual and overall) are included in Table 7. Higher cognitive impairment was noted among those who reported ever exposed to any type of SW compared to those never exposed (daytime work only). Consistently, individuals who reported being exposed to night

Table 8: Unadjusted logistic regression [odds ratios (ORs) and 95% Confidence Intervals(CI)] for individual and overall cognitive impairment for primary SW variables

Primary SW variables	**Memory**		**Executive function**		**Overall**
	REYI	**REYII**	**AF2**	**MAT**	
	Impaired cognition OR (95% CI) [a]	Impaired cognition OR (95% CI) [a]	Impaired cognition OR (95% CI [a]	Impaired cognition OR (95% CI) [a]	Impaired cognition OR (95% CI) [a]
Ever exposed to SW					
Never exposed to SW (Daytime work only)	1.00	1.00	1.00	1.00	1.00
Ever exposed to SW	1.12 (0.98-1.29)	**1.23 (1.06-1.41)***	**1.36 (1.18-1.56)***	**1.41 (1.25-1.59)***	**1.42 (1.2-1.69)***
SW exposure in longest job					
Not exposed to SW (Daytime work)	1.00	1.00	1.00	1.00	1.00
Night SW	1.29 (0.96-1.73)	**1.79 (1.34-2.39)***	**1.74 (1.25-2.41)***	**1.78 (1.37-2.29)***	**2.26 (1.58-3.23)***
Rotating SW	1.09 (0.93-1.28)	1.11 (0.94-1.29)	**1.24 (1.07-1.45)***	**1.35 (1.18-1.54)***	**1.24 (1.02-1.49)***
SW exposure in current job[b]					
Not exposed to SW (Daytime work)	1.00	1.00	1.00	1.00	1.00
Night SW	**1.81 (1.25-2.62)***	**1.53 (1.01-2.31)***	**1.88 (1.26-2.79)***	**1.99 (1.36-2.93)***	**2.85 (1.74-4.67)***
Rotating SW	1.18 (0.90-1.55)	1.16 (0.88-1.51)	1.11(0.87-1.41)	**1.48(1.17-1.86)***	1.26 (0.92-1.73)

***** *P* value <0.05
[a] The ORs and 95% CI were calculated using survey analytical weights.
[b] For current job, only those participants were included who reported currently working (not retired) (N=18,466)

and rotating SW during current or longest job had a greater proportion of cognitive impairment compared to those who only reported daytime work. Unadjusted logistic regression analyses indicated that SW exposures were associated with high odds of cognitive impairment compared to those who were unexposed (Table 8). Results of multivariate analyses suggested that SW exposure was related to increased odds of cognitive impairment, after adjustments for confounders (Table 9).

Table 9: Adjusted logistic regression [odds ratios (ORs) and 95% Confidence Intervals(CI)] for individual and overall cognitive impairment for primary SW variables					
Primary SW variables	**Memory function**		**Executive function**		**Overall**
	REYI	**REYII**	**AF2**	**MAT**	
	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]
Ever exposed to SW					
Never exposed to SW (Daytime work only)	1.00	1.00	1.00	1.00	1.00
Ever exposed to SW	0.95 (0.81-1.11)	1.07 (0.92-1.25)	1.12 (0.96-1.30)	**1.14 (1.00-1.30)***	1.12 (0.93-1.36)
SW exposure in longest job					
Not exposed to SW (Daytime work)	1.00	1.00	1.00	1.00	1.00
Night SW	0.99 (0.71-1.39)	**1.45 (1.04-2.01)***	1.28 (0.92-1.77)	1.21 (0.91-1.61)	**1.53 (1.04-2.27)***
Rotating SW	0.96 (0.81-1.14)	0.99 (0.83-1.18)	1.06 (0.89-1.25)	**1.16 (1.01-1.34)***	1.02 (0.82-1.26)
SW exposure in current job[c]					
Not exposed to SW (Daytime work)	1.00	1.00	1.00	1.00	1.00
Night SW	1.49 (0.99-2.22)	1.29 (0.81-2.05)	1.32 (0.87-2.00)	1.31 (0.87-1.94)	**1.79 (1.09-2.98)***
Rotating SW	1.03 (0.77-1.4)	1.02 (0.77-1.36)	0.95 (0.72-1.25)	**1.35 (1.05-1.73)***	1.03 (0.73-1.46)

***** *P* value <0.05
[a] The ORs and 95% CI were calculated using survey analytical weights.
[b] Models are adjusted for age, sex, ethnicity, marital status, education, income, BMI, smoking, alcohol consumption, retirement status, depression , multi-morbidity, social support availability index , type of study cohort
[c] For current job, only those participants were included who reported currently working (not retired) (N=18,466),and the models are adjusted for all covariates mentioned above except for retirement status
SW, shift work; OR, odds ratio; CI, confidence interval.

Relationship between SW exposure and overall cognition impairment

Separate models were constructed to evaluate the associations between SW exposures and overall cognitive impairment. For ever exposed to SW, no significant associations was observed for overall impairment (OR, 1.12; 95% CI, 0.92–1.35). However, overall cognitive impairment was found significant among participants who reported to be exposed to night SW during their current job (OR, 1.79; 95% CI, 1.08–2.96) and, night SW during their longest job (OR, 1.53; 95% CI, 1.04–2.26) when compared to those who only reported day time work (Table 9).

Results of the multivariate analysis also exposed significant associations among employed participants between sociodemographic factors and overall cognitive impairment (estimators for confounders are not shown in Table 9, details are available in Appendix D). In general, overall cognitive impairment was significantly higher among non-white workers (OR, 4.83; 95% CI, 3.55–6.57), workers having depression (OR, 1.80; 95% CI, 1.38–2.34) and having education of high school to some college (OR, 2.37; 95% CI, 1.69–0.83). However, lower odds of overall cognitive impairment were noted for those workers who belong to older age groups (55 and plus) (OR, 0.65; 95% CI, 0.51–0.83), higher income groups (50,000 CAD and above) (OR, 0.48; 95% CI, 0.37–0.63), having some social support (OR, 0.81; 95% CI, 0.67–0.97), and drinks at least weekly (OR, 0.74; 95% CI, 0.59–0.91). Details of complete models including estimators for all confounders are presented in separate tables (Appendix D).

Relationship between SW exposure and memory function of cognition

The associations between SW exposures and memory function of cognitive impairment (REYI and REYII) were examined and separate models were constructed. For REYI measure of memory function, no statistically significant results were found across all primary SW variables (Table 9). Based on REYII measure of memory function (Table 9), participants who were exposed to night SW during their longest job were found significantly associated with cognitive impairment compared to those reported only daytime work (OR, 1.44; 95% CI, 1.03–2.01). The association remained non-significant for current night (OR, 1.28; 95% CI, 0.81–2.05) and rotating (OR, 1.03; 95% CI, 0.77–1.36) shift workers.

In addition, the multivariate analysis revealed substantial associations between sociodemographic characteristics and memory function impairment among employed participants (estimators for confounders are not shown in Table 9, details are available in Appendix D). Memory function impairment (both REYI and REYII) was significantly higher among non-white workers (OR, 2.12; 95% CI, 1.57–2.86), and workers having depression (OR, 1.31; 95% CI, 1.13–1.52). However, lower odds of memory function impairment (both REYI and REYII) were noted for those workers who belong to older age groups (OR, 0.46; 95% CI, 0.35–0.60), and higher income groups (20,000 CAD and above) (OR, 0.57; 95% CI, 0.44–0.73). REYI impairment reduced for those having social support (OR, 0.81; 95% CI, 0.70–0.94), having high education (OR, 0.74; 95% CI, 0.58–0.93) and those who drink at least weekly (OR, 0.75; 95% CI, 0.63–0.89). Details of complete models including estimators for all confounders are presented in separate tables (Appendix D).

Relationship between SW exposure and executive function of cognition

Separate models were generated to evaluate the relationships between SW exposures and executive function impairment (AF2 and MAT). For AF2 measure of executive function, no statistically significant results were noticed across all primary SW variables (Table 4). However, based on MAT measure of executive function (Table 9), cognitive impairment was associated with participants who reported ever exposed to any type of SW (OR, 1.14; 95% CI, 1.00–1.30), exposed to rotating SW in their current job (OR, 1.36; 95% CI, 1.06–1.74), and exposed to rotating SW in their longest job (OR, 1.16; 95% CI, 1.01–1.34) compared to those who had never been exposed to SW (daytime work only). For the AF2 measure of executive function, no statistically significant results were found across all primary SW variables (Table 9).

Furthermore, among participants who were employed, the multivariate analysis showed significant associations between sociodemographic factors and executive function impairment (estimators for confounders are not shown in Table 9, details are available in Appendix D). Executive function impairment (both AF2 and MAT) was significantly higher among non-white workers (OR, 3.06; 95% CI, 2.39–3.93), and workers having depression (OR, 1.34; 95% CI, 1.10–1.50). However, lower odds of executive function impairment (both AF2 and MAT) were noted for those workers who belong to older age groups (OR, 0.76; 95% CI, 0.64–0.91), and higher income groups (20,000 CAD and above) (OR, 0.57; 95% CI, 0.34–0.98). Also, MAT based cognitive impairment was found significantly higher for workers who are current smokers (OR, 1.34; 95% CI, 1.10–1.50), and obese (OR, 1.35; 95% CI, 1.08–1.68). Details of complete models including estimators for all confounders are presented in separate tables (Appendix D).

Discussion

The purpose of this study was to investigate the associations between SW exposure and cognitive impairment among middle-aged and older adults. The results of this study demonstrated that SW exposure has significant relationship with cognitive impairment. Overall cognitive impairment was evident for those exposed to night SW, both during current and longest job, compared to those who worked daytime shift only. In terms of domain-based measures, night SW exposure in longest job was related to memory function impairment and those exposed to rotating SW, both in current and longest job, were more likely than daytime workers to have impaired executive function. These findings are clinically relevant and support the notion that circadian misalignment would render shift workers more vulnerable to cognitive impairment. It is imperative to identify and comprehend modifying risk factors, like SW, associated with cognitive impairment, since this is critical for designing and implementing suitable prevention strategies. Globally, SW is prevalent and these study results are consistent with the literature[2,4,145] indicating that 21% of Canadians were exposed to some kind of SW during their career. Findings from other developed economies such as France,[131] Japan,[72] across Europe[74] and the United States,[74] also confirms similar pattern where 20% to 25% of workers were exposed to SW in various sectors. Moreover, this study reported the overall proportion of cognitive impairment as 4.4%, which is consistent with rates observed (5.3% and 2.8%) in some previous studies.[174,175] However, other studies,[176–178] have discovered higher rates (10.8%, 7%, 8.7%) of cognitive impairment. A major factor that may have influenced these differences is the CLSA study design, which included only persons without overt cognitive impairment at baseline.[165]

The study results suggest that the association between night SW (both in current and longest job) and overall cognitive impairment were significant. As far as domain-based measures are concerned, night SW (in longest job) and rotating SW (both in current and longest job) were more likely than daytime workers to have impaired memory (REYII) and executive function (MAT) respectively. These findings support evidence from previous research linking SW with cognitive impairment. A population based study[47] that explored chronic consequences of SW (current, former or never) reported that cognitive functions among former shift workers tends to be impaired. Later, a prospective cohort study also stated that rotating SW was associated with lower cognitive test scores.[153] Similarly, a cross-sectional Swedish study linked a history of any SW to lower cognitive performances and observed that current shift workers performed worse on the cognitive tests than non-shift workers.[154] Contrary to the results previously described[47,153,154] other studies[46,156] did not find significant associations between SW and cognitive function. Possible explanations for these contrasting results might be due to differences in the classification of SW[153,155] (unable to account for types of SW), age categorization[156] (did not cover full spectrum and limited to age group 58-68 years), and the use of a non-representative highly educated sample[156] (restricted to nurses).

Recently, Alonzo et al[155] documented lower performance on measures of executive function (MAT) among shift workers. However, the measures based on declarative memory (REYI and REYII) did not find any statistically significant results, whereas our adjusted analysis indicated that exposure to night SW during longest job is associated with impaired measure of memory function (REYII). The results of Alonzo et al[155] need to be interpreted with caution as several limitations have been identified. First, measures used to assess the cognitive function were based on scores without any demographic adjustments of age, sex, education and language. Exploration of cognition in an aging population without adjustment for demographic variables associated with healthy aging will produce misleading results due to measurement bias.[164,179] In contrast, our study utilized 'normalized cognitive scores' with respect to participant's age, sex, education and within each language group (English and French), hence reducing the chance of measurement bias.[164] Second, findings lacked comparisons with normative data, which is fundamental for the interpretation of neuropsychological test scores and determining whether a person's performance is below the range of healthy cognitive performance. Finally, their study[155] did not examine types of SW separately, i.e., night and rotating SW. In contrast, our analysis takes into account different types of SW (night and rotating SW) for both current and longest job. The relationship between SW and cognitive functions may not be same across different types of SW (night and rotating SW). Also, rotating SW has been hypothesized to be more disruptive to circadian rhythm than regular night work and it is possible that rotating shift workers demonstrate greater difficulty in adapting to work schedules as they have to move from shift to shift compared with regular night shift workers.[180]

Although the relationship between SW and cognitive performances is inconclusive[142] there are good reasons to believe that such a relationship may exist. One possible pathophysiological mechanism underlying the association between SW, and cognitive impairment has been thought to be the repeated desynchronization of body clock due to working and sleeping at the wrong circadian phase among shift workers.[153,181,182] This could demonstrate harmful impacts on health, such as sleep deprivation, daytime sleepiness, and brain inflammation, making people more susceptible to cognitive decline.[47,181,183–185] Another mechanism is the repeated physiological stress and increased levels of cortisol induced by circadian disruption, as evidenced by a previous study[186] which explored the influence of chronic jet lag on cognitive functions among airline cabin crew. Moreover, disturbed circadian rhythms have also been linked to neurodegeneration.[187,188] It is possible that impaired pineal secretion of melatonin, due to unusual light exposures among shift workers, may significantly impair the normal antioxidant defenses of the brain, contributing to cognitive impairment.[189] On balance, the literature supports the notion that circadian disruption due to SW plays a critical role in cognitive functions. However, additional studies are needed to confirm the association between SW and cognitive impairment, as well as any physiological pathways that underlie the mechanism.

Results of the multivariate analysis also revealed substantial associations between socio-demographic factors among shift workers and cognitive impairment (Appendix D). Consistent with literature [190,191] non-white ethnicity in our study sample was significantly associated with cognitive impairment. Similarly, workers who were current smokers,[192] have depression [193] and have higher BMI were associated with higher odds of cognitive impairment. An explanation for these findings is that the smoking can cause periventricular and subcortical white matter lesion progression,[194] cholinergic system in the basal forebrain can be effected by depression,[195] and obesity can cause local inflammation within the hypothalamus that alters synaptic plasticity, thus contributing to neurodegeneration.[196] In addition, high income groups and better social support were related to reduce cognitive impairment. Employment and income levels are indicators of economic security as well as social and psychological stress, which can affect brain function and cognition.[144,197,198] However, lower odds of cognitive impairment among older age groups in our study is contrary to what was previously reported.[45,46,154] This inconsistency may be due to exclusion of persons with overt cognitive impairment from CLSA database at baseline, as a result cognitively healthy subgroup of the population may have chosen to participate. This is probably why the overall proportion of participants with cognitive impairment decreases as age group increases.

There are some additional occupational characteristics (not included in this study) that have been linked to cognitive impairment. According to prior studies,[199,200] high mental demands at work are significantly associated with better cognitive functioning in old age. Despite the possibility that work-related stress brought on by complex work, such as inadequate job control, high job demands, a lack of social support, and manual labour, may raise the risk of dementia,[201,202] research revealed that high work complexity was associated with a lower risk of dementia.[203,204] Cognitive reserve in workers with higher work complexity can serve as a neuroprotective agent thus postponing the cognitive decline.[205] There is an increased risk of cognitive impairment due to certain occupational and environmental exposures that are neurotoxic to brain cells, such as lead,[206] organophosphate pesticides,[207] and magnetic fields among electronic workers.[208]

Our study had several strengths. A major strength of this study is that, to our knowledge, it is the first study to investigate the associations between different types of SW exposure (night and rotating shift), and cognitive impairment based on Canadian standards, which means that cognitive impairment was identified after comparisons with neuro-healthy normative data.[164,165] All cognitive test scores are normalized for the participant's age, sex, education level and language of test administration (English and French).[164] Such normalization of cognitive scores and comparisons with normative data were lacking in a previous study,[155] and are required to determine whether a person's performance falls within the range of healthy cognitive performance.[164] In addition, a large population based sample was used involving a wide range of participants. Nonetheless, there are limitations to this study that are worth noting. There were some differences in mode of data collection between tracking and comprehensive cohorts that is phone vs. in-person respectively. We controlled for type of study cohort in all adjusted models as this approach has been previously utilized, [173] reducing the potential for this to have affected the study findings. Due to the number of events evening and night shifts were pooled together as previously done by some researchers.[4,6,18] Some SW related information were not included, as they were not recorded in the CLSA questionnaire, such as the type and direction of rotating shifts, number of consecutive night shifts worked, and the number of days off between shifts [103]. Type and duration of job were not examined and the association between SW and cognitive functions may not be constant across all types and duration of job.[209,210] The lack of this information is a limitation and suggest potential areas for future investigation. Some participants were excluded from analysis due to missing information related to SW schedules (N=1,682; 3.2%) and cognitive impairment (N=1,201; 2.3%). Despite the relatively small proportion of missing data, there were some statistically significant differences between the missing and complete cases (Appendix C), which may result in potential bias. Respondents were free of overt cognitive impairment at baseline and are more likely healthier than the regular population possibly leading to an underestimation of the magnitude of some of our findings. In addition, generalizability of the results is limited to those healthier than the overall population. Moreover, due to the cross-sectional nature of our study, we are unable to assess temporality in the relationship between SW and cognitive impairment, raising the possibility of reverse causation.

Conclusion

These findings highlight the negative impact of SW on cognitive function in middle-aged and older adults. By taking this modifiable risk factor into account we may enable workers to reduce cognitive impairment both during their working lives and after retirement, and support "active aging" of the workforce. Although these findings are preliminary, they suggest that SW exposure and circadian disruption may be an important factor in the risk of cognitive impairment and warrants further investigation.

Chapter Six: General Discussion

Collectively, the findings of all three research projects show that SW is associated with adverse outcomes in the context of an aging Canadian population. These finding supports previous literature and fill existing gaps. While little is known about the physiological pathways underlying SW-related disease processes, several mechanisms have been proposed including circadian misalignment, disturbed sleep, and light induced suppression of melatonin levels at night.[120,121] These factors, in turn, disrupt a number of physiological and behavioral processes that contribute to disease progression. Some of these mechanisms are discussed in the following section.

Pathophysiology of shift work

The circadian timing system (CTS) is the mechanism that mediates the alignment of human physiology with the environment.[211] Circadian rhythms in physiological functions are crucial for survival. There is an endogenous 'clock' in supra-chiasmatic nuclei (SCN), located in the lower frontal hypothalamus, responsible for controlling CTS and maintains the 24-hour rhythms throughout the body.[211,212] When aligned appropriately to the environment, the 'clock' promotes sleep and related 'anabolic' functions at night (such as, immune functions and hormone release), and wakefulness and its related catabolic functions during the day (such as, diet intake and metabolism).[212,213] Any interference in regular circadian rhythm could result in disturbed metabolic, hormonal and inflammatory responses.[146] This misalignment has also been found to reduce cortisol levels and disturb levels of pro- and anti-inflammatory proteins,[122] contributing to the development of chronic diseases. Another mechanism also regulated by the SNC clock is endogenous melatonin rhythm. Melatonin is a hormone secreted from the Pineal body, low during the daylight hours and at the highest levels during dark periods (night).[120,146,147] Exposure to light at night can reduce circulating melatonin levels.[148] If the light is bright, the levels can be completely suppressed, which may be a potential risk factor for cancers.[103] Shift workers experience substantial misalignment between circadian system of the body and unusual working schedules,[40] which exposes them to increased risk for health problems. Another important factor that contributes to circadian interruption among shift workers is their behaviour/lifestyle. This includes eating at irregular timings, lower physical activity levels, and higher incidence of smoking and intake of alcohol. These factors feed back into the circadian clock causing desynchronised rhythms and altered metabolic and body temperature cycles.[8,40,120] In short, the potential effects of SW on health are likely related to the circadian misalignment and melatonin suppression. However, it is possible that any or all of the mechanisms described above interact to influence shift worker's health.[40,149]

The conceptual diagram (Figure 5) below is outlining the different pathways through which SW can impact different dimensions of health, specifically ANM, frailty and cognitive impairment.

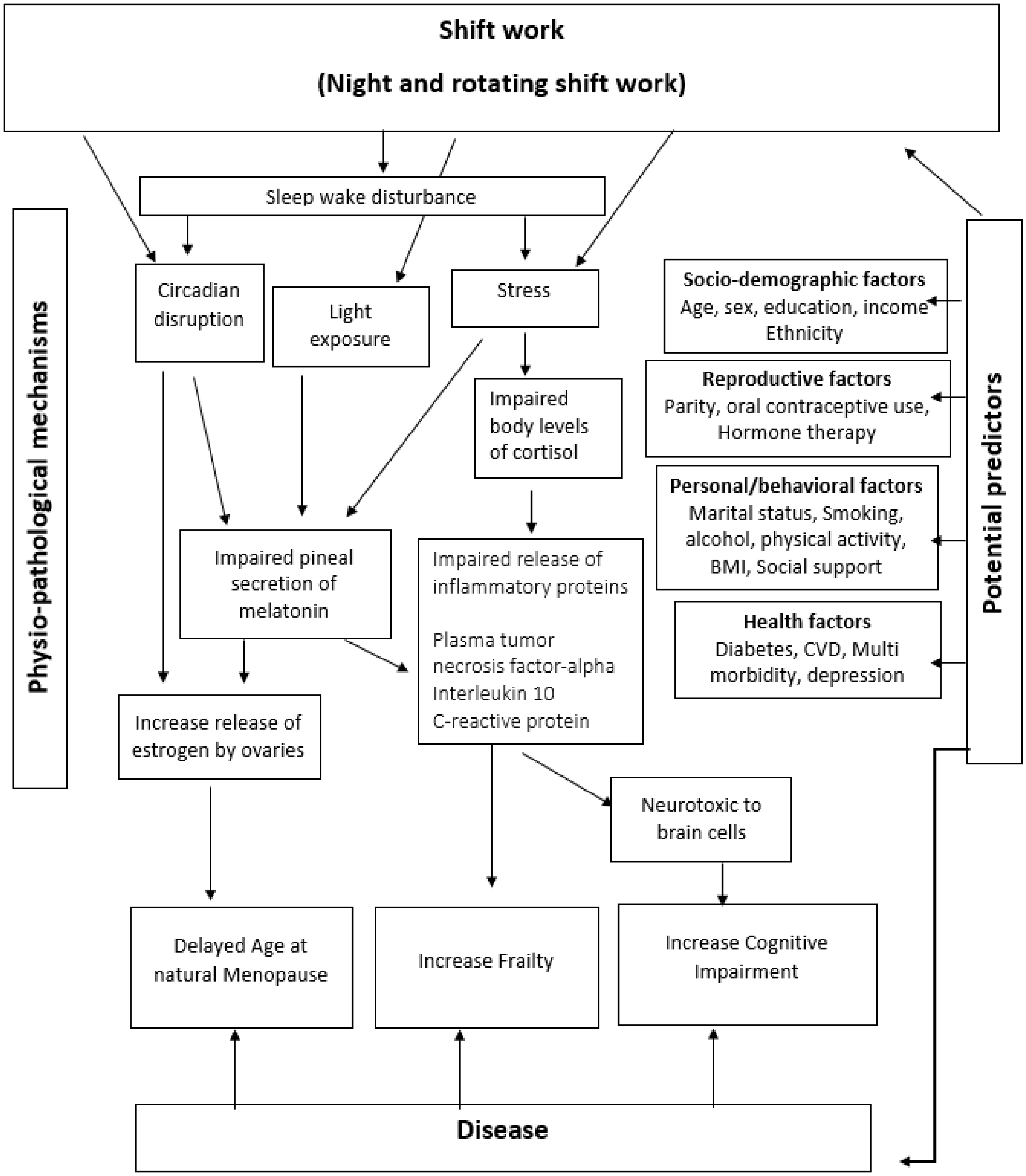

Figure 5: Conceptual diagram of the association between shift work and selected health outcomes

Strengths and Limitations

This dissertation has made significant contributions to research on the emerging role of SW in several ways. First, the thesis used the CLSA database, a large cohort that provides job-related information, from both current and retired labour force, including a variety of working schedules, and timing (current/longest) of performed job. Second, the dissertation included standardized measures for all outcome variables. ANM is documented according to the standard definition recommended by the World Health Organization (WHO)[214] and consistent with other studies.[64,215–217] Similarly, the assessment tools measuring frailty and cognitive impairment have been validated by the CLSA expert team. Third, the study participants recruited at the population level, rather than from narrow sub-groups of the population, thereby limiting selection bias and increasing generalizability.

Nonetheless, this dissertation has some potential limitations. First, due to the number of events, evening and night shift were pooled together as previously reported by some investigators.[6,18,4] Second, some SW related information was not captured, as they were not recorded in the CLSA questionnaire, such as the type and direction of rotating shifts, number of consecutive night shifts worked, and the number of days off between shifts [103]. Type and duration of jobs were not examined and the association between SW and selected health outcomes may not be constant across all types and duration of jobs. The lack of this information is a limitation and suggest potential areas for future investigation. Related to longest job exposure, the exact timing of occurrence of the exposure was not captured. Finally, the potential homogenous ethnicity (almost 95% white in study sample) and low response rate of CLSA (10%) may affect the generalizability of our findings.

Implications and future directions

SW schedules are an integral part of our economy and will continue to be used to ensure the continuous operation of goods and services. Therefore, the next step is to determine what can be done to lessen its potential negative health effects. SW tolerance varies widely among people, which may be a result of the interaction between individual characteristics, environmental, social and occupational factors.[218]

Education, counseling and health promotion

Primary prevention has different targets, such as adequately assessing the suitability for shift work, organising shifts according to ergonomic criteria, and adopting adequate compensatory measures to avoid significant disturbances in circadian rhythms, accumulation of sleep loss and conflicts in social life. Well-scheduled und targeted health programmes can change the lifestyle of shift working employees and the risk factors involved. It is also necessary that helpful information and suggestions should be given to workers on how to best cope with shift and night work, particularly concerning sleep, diet, stress control and good physical health. It has been shown that good social support from coworkers and supervisors at work, as well as from family members, is able to significantly improve adaptation and tolerance.[219,220] If shift workers' lifestyle habits are to be improved, it is imperative to identify the existing barriers. The most frequently cited perceived barriers in literature were a lack of breaks, shift patterns, poor food selection, inadequate cafeteria opening times, lack of time and tiredness due to long working hours.[32] The studies in this area highlight the need for workplace interventions that encourage well-designed work schedules and regular meal breaks, improved availability of healthy dining options and access to canteens at evenings and weekends.[32] In addition, opportunities for the provision of health promotion programs should be tailored to SW. For example, the workplace-based weight loss program targeting over-weight shift workers was feasible and efficacious and resulted in significant weight loss i.e. reducing weight, waist circumference, BMI, systolic blood pressure and resting heart rate, and improvement in health-related outcomes and behaviours.[221] For mental health reasons, it is important to emphasise the necessity of special programmes for advanced training (and education) to prevent mental illness in shift workers.[222] Cognitive and behavioral interventions can also be useful in coping with the effects of shift work.

Many workforces consist largely of women. For some women, the menopause may not present any major issues, but for others, it is known to present significant challenges in both their personal and professional lives. The transition to menopause is a significant occupational health concern. To assist women in navigating the menopause transition and sustaining wellbeing and productivity at work, it is advised to implement health promotion programs, improve the working environment, ventilation, and work policies, offer more flexibility in working hours, and raise awareness of the menopause. [223]

Health surveillance and work-fitness evaluation

Regular medical checks are recommended by International Labour Organization (ILO, 1990) prior to beginning SW (particularly night SW) and at regular intervals thereafter (i.e. every 2-3 years),[135,224] to determine the compatibility between health conditions and SW. This should be scheduled in accordance with the type of shift schedules, environmental conditions, work loads, and worker's characteristics (i.e. age, gender, health, and social), with the goal of detecting early signs of mal-adjustment or intolerance.[135,224] Health surveillance should address basic psycho-physiological status (sleep, digestion, women hormonal pattern, body mass index), life styles (i.e. diet, smoking, alcohol and coffee intake, physical activity), previous and current health issues (with particular reference to gastrointestinal, cardiovascular, endocrine, metabolic and neuro-psychic), current therapy, and absenteeism due to health impairment.[135] In order to define the nature and severity of the worker's health conditions, specialized medical visits, laboratory and instrumental tests, and clinical checks may be effectively supplemented. Given the possible association between night SW and breast cancer, which is the most commonly diagnosed cancer and the second leading cause of cancer mortality in Canadian females,[225] ongoing monitoring of these potentially high-risk groups of shift workers is important. Finally, to reduce risk of miscarriage, pregnant women should reduce SW to one night shift in a week.[226]

Organization of shift scheduling

Through training, better job design, and organizational improvements, many workplace challenges can be addressed. As proposed[227] efforts should focus on administrative controls related to shift scheduling and shift rotation, including:

i. Using forward shift rotations (clockwise — day to afternoon to night)
ii. Limiting consecutive evening or night shifts (maximum three)
iii. Minimizing the number of consecutive shifts on nights (8 hour shift for 5 nights, 10 hours shift for 4 nights, 12 hour shift for 3 nights)
iv. Providing adequate rest between shifts — more than 10 hours to allow for adequate sleep
v. Providing adequate recovery period between shift change (minimum 24 hrs)
vi. Avoiding early starts to day shift (before 6:00 am); and
vii. Limiting weekend work

Shift work regulations

Regulatory approaches for SW vary widely between countries, industry sectors, and companies. In Canada, just like many other occupational hazards, the most part of SW is governed by the general duty clause both in Ontario and for federally-regulated workplaces. Employers and workers must be adequately informed of these regulations.[227,228]

Ontario: Employers are required to identify workplace hazards and take every precaution reasonable in the circumstances for the protection of a worker [Section 25, 2(h), Occupational

Health and Safety Act (the Act)]. This must include protection from risk to health posed by SW. Employers are also required to provide information, instruction and supervision to protect the health or safety of the worker [Section 25(2) (a)]. Ontario's Employment Standards Act (ESA) addresses SW protection by mandating worker entitlements to "hours free from having to work." In most cases, workers must receive 11 consecutive hours off work in a day [Section 18(1), ESA]. They must get eight hours off between shifts unless the total time for two shifts does not exceed 13 hours [Section 18(3), ESA]. Workers are also entitled to 24 consecutive hours off work each work week or 48 consecutive hours of work in every period of two consecutive weeks [Section 18(4), ESA].[227,228]

Federal jurisdiction: Employers have a general duty to ensure the health and safety of their employees [Section 124, Canada Labour Code (the Code), Part II].[229] Workers are entitled to one full day of rest per week [Section 173, the Code, Part III].[230]

Overall significance and conclusion

This dissertation provides evidence of a potential association between SW and selected health outcomes particularly in the Canadian context. These findings may help inform and remind employers and health and safety policy committees to better design SW schedules that are less disruptive to the circadian rhythms. As the population continues to age, increased awareness about the effects of modifiable risk factors like SW may contribute to better health outcomes for middle-aged and older adults. More research on ways to mitigate the harmful effects of SW on health is needed. Consequently, detailed information related to SW scheduling, workplace and personal factors, including extended follow-up periods, is needed for higher quality research related to SW and health outcomes.

List of Abbreviations (listed alphabetically)

AF2	Animal Fluency
ANM	Age at natural menopause
BMI	Body mass index
CAD	Canadian dollar
CAPI	Computer-assisted personal interviews
CATI	Computer-assisted telephone interviews
CES-D	The center for epidemiological studies depression scale
CLSA	Canadian Longitudinal Study on Aging
COM	Comprehensive cohort
CRP	C-reactive protein
CTS	Circadian timing system
CVD	Cardiovascular disease
DCS	Data collection site
ESA	Ontario's Employment Standards Act
EU	European Union
FI	Frailty Index
HR	Hazard Ratio
HT	Hormone therapy
IL-10	Interleukin 10
ILO	International Labour Organization
IQR	Interquartile range
KM	Kaplan-Meier cumulative estimates
MAT	Mental Alteration
OR	Odds Ratio
ORE	Office of Research Ethics
REYI and REYII	Rey Auditory Verbal Learning Tests
RR	Relative Risk
SCN	Supra-chiasmatic nuclei
SD	Standard deviation
SLID	Survey of Labour and Income Dynamics
SSA	Social Support Availability
SW	Shift work
TNF-α	Plasma tumor necrosis factor-alpha
TRM	Tracking cohort
USA	United States of America
WHO	Word Health Organization
95% CI	95% confidence interval

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Appendices

Appendix A: Ethical approval certificate

YORK U UNIVERSITÉ UNIVERSITY

Certificate #:	STU 2020-123
Initial Approval:	12/09/20-12/09/21
Amendments:	
Renewals:	11/09/21-11/09/22 10/12/22-10/12/23
Current Approval Period:	10/12/22-10/12/23

OFFICE OF RESEARCH ETHICS (ORE)
309 York Lanes

4700 Keele St.
Toronto ON
Canada M3J 1P3
Tel 416 736 5914
Fax 416 736-5512
www.research.yorku.ca

ETHICS RENEWAL

To: **Durdana Khan - Graduate Student**
Department of Kinesiology
Faculty of Health
[redacted]

From: Alison M. Collins-Mrakas, Sr. Manager and Policy Advisor, Research Ethics
(on behalf of You-Ta Chuang, Chair, Human Participants Review Committee)

Date: Wednesday, October 12, 2022

Title: **The associations of shift work exposure and selected outcomes in Canadian Longitudinal Study of Aging**

Risk Level: ☒ Minimal Risk ☐ More than Minimal Risk

Level of Review: ☒ Delegated Review ☐ Full Committee Review

I am writing to inform you that this research project, **"The associations of shift work exposure and selected outcomes in Canadian Longitudinal Study of Aging"** has received ethics review and renewal by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines.

Note that renewal is granted for one year. Ongoing research – research that extends beyond one year – must be renewed prior to the expiry date.

Any changes to the approved protocol must be reviewed and approved through the amendment process by submission of an amendment application to the HPRC prior to its implementation.

Any adverse or unanticipated events in the research should be reported to the Office of Research ethics (ore@yorku.ca) as soon as possible.

For further information on researcher responsibilities as it pertains to this approved research ethics protocol, please refer to the attached document, **"RESEARCH ETHICS: PROCEDURES to ENSURE ONGOING COMPLIANCE".**

Please note that prior to commencing any research activities, researchers are advised to review the latest updates on research involving human participants at: *https://www.yorku.ca/research/researchers-faqs/*

Should you have any questions, please feel free to contact me at 416-736-5914 or via email at: acollins@yorku.ca.

Yours sincerely,

Alison M. Collins-Mrakas M.Sc., LLM
Director, Office of Research Ethics

RESEARCH ETHICS: PROCEDURES to ENSURE ONGOING COMPLIANCE

Upon receipt of an ethics approval certificate, researchers are reminded that they are required to ensure that the following measures are undertaken so as to ensure on-going compliance with Senate and TCPS ethics guidelines:

1. **RENEWALS:** Research Ethics Approval certificates are subject to annual renewal. **Failure to renew an ethics approval certificate or (to notify ORE that no further research involving human participants will be undertaken) will result in the closure of the protocol.** No further research activities may be undertaken until such time as a new protocol has been reviewed and approved. **Further, it may result in suspension of research cost fund and access to research funds may be suspended/withheld**;

2. **AMENDMENTS:** Amendments must be reviewed and approved **PRIOR** to undertaking/making the proposed amendments to an approved ethics protocol;

3. **END OF PROJECT**: ORE must be notified when a project is complete;

4. **ADVERSE EVENTS**: Adverse events must be reported to ORE as soon as possible;

5. **POST APPROVAL MONITORING:**
    a. More than minimal risk research may be subject to post approval monitoring as per TCPS guidelines;
    b. A spot sample of minimal risk research may similarly be subject to Post Approval Monitoring as per TCPS guidelines.

FORMS: As per the above, the following forms relating to on-going research ethics compliance are available on the Research website:

a. Renewal
b. Amendment
c. End of Project
d. Adverse Event

Appendix B: Summary of 52 Items utilized in construction of the Frailty Index

1. Self-rated health

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Poor	1	388687 (3.08)	264583 (2.54)
Fair	0.75	1244484 (9.87)	1104051 (10.58)
Good	0.5	3902446 (30.94)	3297144 (31.62)
Very good	0.25	4798372 (38.04)	4135792 (39.66)
Excellent	0	2279348 (18.07)	1625764 (15.59)
Total		12613337	10427334

2. Self-rated vision

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Poor	1	197216 (1.56)	180266 (1.74)
Fair	0.75	876346 (6.94)	851894 (8.21)
Good	0.5	4170058 (33.05)	3663415 (35.31)
Very good	0.25	4645736 (36.82)	3722272 (35.88)
Excellent	0	2726946 (21.61)	1957120 (18.86)
Total		12616304	10374967

3. Self-rated hearing (srau5)

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Poor	1	234705 (1.86)	210826 (1.74)
Fair	0.75	1222984 (9.69)	1152482 (8.21)
Good	0.5	4095573 (32.46)	3686790 (35.31)
Very good	0.25	4018396 (31.85)	3324282 (35.87)
Excellent	0	3045109 (21.13)	1997354 (18.86)
Total		12616767	10371734

4. Osteoarthritis

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	3165789 (25.09)	3137485 (30.28)
No	0	9449064 (74.90)	7225335 (69.72)
Total		12614853	10362820

5. Arthritis

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	2124347 (25.09)	1876890 (18.15)
No	0	10472627 (83.14)	8464941 (81.85)
Total		12596974	10341831

6. Chronic obstructive pulmonary disease

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	803294 (6.37)	791898 (7 65)
No	0	11799997 (93.63)	9552461 (92.34)
Total		12603291	10344359

7. High blood pressure

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	4421142 (35.09)	4021709 (38.89)
No	0	8176748 (64.91)	6320236 (61.11)
Total		12597890	10341945

8. Diabetes

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	2098236 (16.64)	2017076 (19.48)
No	0	10514212 (83.36)	8339774 (80.52)
Total		12612448	10356850

9. Heart diseases (heart failure)

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	1233647 (9.79)	1077732 (10.42)
No	0	11367668 (90.21)	9260873 (89.57)
Total		12601315	10338605

10. Angina

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	567071 (4.50)	470304 (4.55)
No	0	12035435 (95.50)	9875171 (95.45)
Total		12602506	10345475

11. Acute myocardial infarction

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	662300 (5.25)	568090 (5.50)
No	0	11946024 (94.75)	9767428 (94.50)
Total		12608324	10335518

12. Peripheral vascular disease

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	794482 (6.31)	740316 (7.16)
No	0	11789203 (93.69)	9590791 (92.83)
Total		12583685	10331107

13. Stroke

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	216897 (1.72)	208950 (2.02)
No	0	12391985 (98.28)	10146166 (97.98)
Total		12608882	10355116

14. Transient ischemic attack

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	347337 (2.76)	319537 (3.09)
No	0	12236418 (97.24)	10017568 (96.91)
Total		12583755	10355116

15. Memory problems (srmem)

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	268844 (2.13)	203695 (1.97)
No	0	12344318 (97.87)	10154561 (98.03)
Total		12613162	10358256

16. Parkinson’s disease

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	34395 (0.27)	36218 (0.35)
No	0	12586432 (99.73)	10329170 (99.65)
Total		12620827	10365388

17. Peptic-ulcer disease

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	969319 (7.69)	777860 (7.51)
No	0	11632305 (92.31)	9577229 (92.49)
Total		12601624	10355089

18. Colitis

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	1064040 (8.45)	1046381 (10.12)
No	0	11532281 (91.55)	9293770 (89.88)
Total		12596321	10340151

19. Bowel incontinence

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	249253 (1.97)	638777 (6.16)
No	0	12366004 (98.02)	9721298 (93.83)
Total		12615257	10360075

20. Urinary incontinence

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	1006879 (7.98)	1775267 (17.14)
No	0	11602550 (92.01)	8581931 (82.86)
Total		12609429	10357198

21. Cataract

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	2475818 (19.74)	2907572 (28.05)
No	0	10068582 (80.26)	7456258 (71.94)
Total		12544400	10363830

22. Glaucoma

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	523053 (4.15)	522566 (28.05)
No	0	12068197 (95.84)	9827971 (94.95)
Total		12591250	10350537

23. Macular degeneration

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	404825 (3.21)	448744 (4 35)
No	0	12183913 (96.78)	9875831 (95.65)
Total		12588738	10324575

24. Cancer

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	1613834 (12.79)	1612896 (15.58)
No	0	11004459 (87.21)	8736080 (84.41)
Total		12618293	10348976

25. Osteoporosis

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	1034535 (8.23)	955181 (9.27)
No	0	11534254 (91.77)	9343335 (90.72)
Total		12568789	10298516

26. Back pain

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	3250205 (25.77)	2904930 (28.11)
No	0	9359706 (74.22)	7431026 (71.89)
Total		12609911	10335956

27. Hypothyroidism

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	1311225 (10.48)	1249649 (12.16)
No	0	11197735 (89.52)	9030782 (87.84)
Total		12508960	10280431

28. Kidney fail

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	316437 (2.51)	344888 (3.33)
No	0	12295115 (97.49)	10003638 (96.67)
Total		12611552	10348526

29. Pneumonia

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	350787 (2.78)	370103 (3.57)
No	0	12266466 (97.22)	9991521 (96.43)
Total		12617253	10348526

30. Urinary tract infection

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	940180 (7.45)	832143 (8.03)
No	0	11671869 (92.54)	9526147 (91.96)
Total		12612049	10358290

31. Falls

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Two or more	1	80316 (0.70)	157880 (1.72)
Any one	0.5	515274 (4.48)	504353 (5.49)
None	0	10896376 (94.82)	8530898 (92.79)
Total		11491966	9193131

32. Walking

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	18273 (0.14)	17595 (0.17)
With help	0.5	169545 (1.34)	309073 (3.00)
Able	0	12421145 (98.51)	9972956 (96.83)
Total		12608965	10299624

33. Bathing

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	14174 (0.11)	11800 (0.11)
With help	0.5	136271 (1.08)	159794 (1.56)
Able	0	12470423 (98.81)	10125795 (98.33)
Total		12620868	10297389

34. Shopping

Categories	Code	At Baseline	At 3yrs follow-up
Unable		Weighted frequencies N (%)	Weighted frequencies N (%)
With help	1	19695 (0.16)	18579 (0.18)
Able	0.5	196942 (1.56)	222991 (2.17)
Unable	0	12400734 (98.28)	10052922 (97.65)
Total		12617371	10294492

35. Doing housework

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	64208 (0.51)	69779 (0.68)
With help	0.5	557863 (4.43)	560138 (5.45)
Able	0	11973453 (95.06)	9653118 (98.33)
Total		12595524	10283035

36. Effort

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
All of the time	1	659478 (5.23)	468193 (4.58)
Occasionally	0.66	1281772 (10.17)	971398 (9.51)
Some of the time	0.33	2531160 (20.09)	1840418 (18.02)
Rarely or never	0	8124576 (64.50)	6934361 (67.89)
Total		12596986	10214370

37. Felt lonely

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
All of the time	1	345913 (2.74)	292527 (2 86)
Occasionally	0.66	1008641 (7.99)	798868 (7 83)
Some of the time	0.33	1553491 (12.32)	1180131 (11.56)
Rarely or never	0	9703748 (76.94)	7937546 (77.74)
Total		12611793	10209074

38. Could not get going

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
All of the time	1	438441 (3.48)	407821 (3.99)
Occasionally	0.66	1392924 (11.05)	1135082 (11.13)
Some of the time	0.33	2513901 (19.94)	2034996 (19.95)
Rarely or never	0	8260531 (65.53)	6620176 (64.92)
Total		12605797	10198075

39. Alzheimer´s disease

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	22263 (0.18)	17421 (0.17)
No	0	12598500 (99.82)	10347456 (99.83)
Total		12620763	10364877

40. Dressing

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	12035 (0.09)	8748 (0.08)
With help	0.5	103736 (0.82)	96558 (0.94)
Able	0	12497197 (99.08)	10199838 (98.98)
Total		12612968	10305144

41. Grooming

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	2160 (0.02)	2210 (0.02)
With help	0.5	29152 (0.23)	19909 (0.19)
Able	0	12591742 (99.75)	10139419 (99.78)
Total		12623054	10161538

42. In/out of bed

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	5132 (0.04)	5268 (0.05)
With help	0.5	77139 (0.61)	75974 (0.74)
Able	0	12539142 (99.35)	10223899 (99.21)
Total		12621413	10305141

43. Using the phone

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	1894 (0.01)	112 (0.00)
With help	0.5	43791 (0.35)	26357 (0.25)
Able	0	12576727 (99.64)	10274914 (99.74)
Total		12622412	10301383

44. Using transport

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	5462 (0.04)	9089 (0.09)
With help	0.5	128595 (1.02)	181274 (1.76)
Able	0	12483165 (98.94)	10094932 (98.15)
Total		12617222	10285295

45. Cooking

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	13581 (0.12)	31063 (0.30)
With help	0.5	87958 (0.69)	106314 (1.03)
Able	0	12516355 (99.19)	10158516 (98.66)
Total		12617894	10295893

46. Taking medicine

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	1598 (0.01)	2307 (0.02)
With help	0.5	55339 (0.44)	65774 (0.64)
Able	0	12564009 (99.55)	10137560 (99.33)
Total		12620946	10205641

47. Managing money

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Unable	1	5170 (0.04)	5864 (0.05)
With help	0.5	49524 (0.39)	61100 (0.59)
Able	0	12563653 (99.57)	10235880 (99.35)
Total		12618347	10302844

48. Hyperthyroidism

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	263890 (2.11)	231335 (2.25)
No	0	12245865 (97.89)	10029705 (97.74)
Total		12509755	10261040

49. Verbal fluency (zverbalfl_comb_FI)

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	406131 (4.28)	427637 (3.38)
No	0	9071118 (95.71)	12196138 (96.61)
Total		9477249	12623775

50. Executive function (zexecutive_comb_FI)

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	637252 (5.59)	372313 (4.12)
No	0	10768496 (94.41)	8651634 (95.87)
Total		11405748	9023947

51. Immediate recall (zimmrec_comb_FI)

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	1426944 (11.95)	187292 (1.92)
No	0	10508953 (88.04)	9540338 (98.07)
Total		11935897	9727630

52. Delayed Recall (zdelrec_comb_FI)

Categories	Code	At Baseline	At 3yrs follow-up
		Weighted frequencies N (%)	Weighted frequencies N (%)
Yes	1	635703 (5.38)	537395 (5.61)
No	0	11172594 (94.62)	9043233 (94.39)
Total		11808297	9580628

Appendix C: Comparisons of complete versus missing cases.

Comparison of baseline properties of cases included for analysis (N=47,811) versus cases with missing information related to shift work exposure (N=1,682)				
Baseline characteristics	**Cases included (N=47811) N (%)[a]**	**Missing cases (N=1682) N (%)[a]**	**Statistics[b]**	**P-value**
Age (years)			12.83	<0.05
45-54	12,623 (26.41)	407 (24.20)		
55-64	15,427 (32.27)	507 (30.14)		
65-74	11,141 (23.31)	428 (25.45)		
75+	8,610 (18.01)	340 (20.21)		
Sex			31.79	<0.05
Male	23,461 (49.07)	943 (56.06)		
Female	24,350 (50.93)	739 (43.94)		
Ethnicity			0.002	0.96
Whites	45,784 (95.87)	1,610 (95.89)		
Other[c]	1,974 (4.13)	69 (4.13)		
Marital status			1.16	0.28
With partner	32,930 (68.90)	1,138 (67.66)		
No partner	14,867 (31.10)	25.95 (32.34)		
Education level			17.79	<0.05
Less than high school	3,759 (7.87)	174 (10.36)		
High school to some college	24,564 (51.40)	792 (47.14)		
Bachelor's degree and Higher	19,467 (40.73)	714 (42.50)		
Household income (CAD)			12.40	0.10
Less than $20,000	2,567 (5.73)	128 (8.09)		
$20,000 or more, but less than $50,000	11,233 (25.09)	435 (27.48)		
$50,000 or more, but less than $100,000	16,101 (35.96)	511 (32.28)		
$100,000 and more	14,869 (33.21)	509 (32.15)		
Smoking			0.40	0.81
Never	14,667 (30.76)	520 (30.99)		
Former	28,511 (59.79	1,007 (60.01)		
Current	4,510 (9.46)	151 (9.00)		
Alcohol consumption			23.12	<0.05
Never	6,946 (14.53)	294 (17.51)		
Drinks less than weekly	14,607 (30.56)	501 (29.84)		
Drinks at least weekly	26,237 (54.90)	884 (52.65)		
BMI (kg/m^2)			3.13	0.37
20.0-24.99 (normal weight)	14,056 (29.65)	473 (28.43)		
<20.00 (underweight)	1,466 (3.09)	57 (3.43)		
25.0-29.99 (overweight)	18,945 (38.96)	653 (39.24)		
>30.0 (obese)	12,938 (27.29)	481 (28.91)		
Depression			0.076	0.78
No (CES-D10 <10)	39,901 (83.46)	1,408 (83.46)		
Yes (CES-D10 ≥ 10)	7,910 (16.54)	274 (16.29)		

Multi-morbidity			3.10	0.08
Yes (≥2 chronic diseases)	14,363 (30.04)	539 (32.05)		
No (<2 chronic disease)	33,448 (69.96)	1,143 (67.95)		
Social Support Availability (SSA)			0.54	0.76
Low	16,396 (35.47)	573 (36.20)		
Medium	15,148 (32.77)	520 (32.85)		
High	14,681 (31.76)	490 (30.95)		
Retirement status			0.90	0.34
Completely/partially retired	26,940 (56.51)	927 (55.34)		
Not retired	20,729 (43.49)	748 (44.66)		
Type of study cohort			49.09	<0.05
Tracking	19,515 (40.82)	543 (32.28)		
Comprehensive	28,296 (59.18)	1,139 (67.72)		
REYI impairment			0.03	0.86
No	42,594 (94.18)	1,502 (94.29)		
Yes	2,630 (5.82)	91 (5.71)		
REYII impairment			10.61	0.06
No	42,382 (94.56)	1,520 (96.45)		
Yes	2,436 (5.44)	56 (3.55)		
AF2 impairment			3.94	0.06
No	42,501 (94.54)	1,529 (95.68)		
Yes	2,456 (5.46)	69 (4.32)		
MAT impairment			0.054	0.82
No	39,619 (91.92)	1,391 (91.75)		
Yes	3,482 (8.08)	125 (8.85)		
Overall impairment			1.02	0.31
No	39,092 (96.22)	1,392 (96.73)		
Yes	1,536 (3.78)	47 (3.76)		

[a] Reported frequencies are column percentages
[b] The statistic reported for all variables was the chi-square value
[c] Other included South Asian, Chinese, Filipino, Latin American, Japanese, Southeast Asian, Korean, Arab, West Asian, and Black.
CAD, Canadian dollars; BMI, body mass index; CES-D, the Center for Epidemiological Studies Depression Scale SW, shift work; REY, Rey auditory verbal learning; AF, Animal fluency; MAT, Mental alteration.

Comparison of baseline properties of complete cases of cognitive impairment variables included for analysis (N=46,610) versus cases with missing information (N=1,201)				
Baseline characteristics	**Cases included (N=46,610) N (%)[a]**	**Missing cases (N=1,201) N (%)[a]**	**Statistics [b]**	**P-value**
Age (years)			44.76	<0.05
45-54	12,377 (26.55)	246 (20.65)		
55-64	15,071 (32.33)	356 (29.89)		
65-74	10,839 (23.25)	302 (25.36)		
75+	8,323(17.86)	287 (24.10)		
Sex			0.83	0.36
Male	22,856 (49.04)	605 (50.37)		
Female	23,754 (50.96)	596 (49.63)		
Ethnicity			8.80	0.16
Whites	44,656 (95.91)	1,128 (95.87)		
Other[c]	1,905 (4.09)	69 (5.76)		
Marital status			23.28	<0.05
With partner	32,179 (69.06)	751 (62.53)		
No partner	14,417 (30.94)	450 (37.47)		
Education level			47.69	<0.05
Less than high school	3,614 (7.75)	145 (12.29)		
High school to some college	23,924 (51.33)	640 (54.24)		
Bachelor's degree and Higher	19,072 (40.92)	395 (33.47)		
Household income (CAD)			46.17	<0.05
Less than $20,000	2,476 (5.66)	91 (8.63)		
$20,000 or more, but less than $50,000	10,914 (24.97)	319 (30.27)		
$50,000 or more, but less than $100,000	15,727 (35.98)	374 (35.48)		
$100,000 and more	14,599 (33.40)	270 (25.62)		
Smoking			2.38	0.31
Never	14,314 (30.79)	353 (29.42)		
Former	27,791 (59.78)	720 (60)		
Current	4,383 (9.43)	127 (10.58)		
Alcohol consumption			21.21	<0.05
Never	6,724 (14.43)	222 (18.52)		
Drinks less than weekly	14,222 (30.53)	385 (32.11)		
Drinks at least weekly	25,645 (55.04)	592 (49.37)		
BMI (kg/m^2)			7.24	0.07
20.0-24.99 (normal weight)	13,735 (29.71)	321 (27.30)		
<20.00 (underweight)	1,417 (3.07)	49 (4.17)		
25.0-29.99 (overweight)	18,472 (39.96)	473 (40.22)		
>30.0 (obese)	18,472 (27.27)	333 (28.32)		
Depression			10.55	<0.05
No (CES-D10 <10)	38,940 (83.54)	961 (80.02)		
Yes (CES-D10 ≥ 10)	7,670 (16.46)	240 (19.98)		
Multi-morbidity			5.04	<0.05
Yes (≥2 chronic diseases)	13,967 (29.97)	396 (32.97)		
No (<2 chronic disease)	32,643 (70.03)	805 (67.03)		
Social Support Availability (SSA)			10.19	<0.05

Low	15,949 (35.36)	447 (39.98)		
Medium	14,806 (32.82)	342 (30.59)		
High	14,352 (31.82)	329 (29.43)		
Retirement status			28.19	<0.05
Completely /partially retired	26,173 (56.32)	767 (64.02)		
Not retired	20,298 (43.68)	431 (35.98)		
Type of study cohort			35.91	<0.05
Tracking	18,924 (40.60)	591 (49.21)		
Comprehensive	27,686 (59.40)	610 (50.79)		
Ever exposed to SW			0.097	0.75
Never exposed to SW(Daytime work only)	37,433 (82.94)	939 (82.59)		
Ever exposed to SW	7,701 (17.06)	198 (17.41)		
SW exposure in longest job			2.72	0.26
Not exposed to SW (Daytime work)	37,392 (84.54)	937 (83.51)		
Night SW	1,217 (2.75)	26 (2.32)		
Rotating SW	5,622 (12.71)	159 (14.17)		
SW exposure in current job			3.73	0.15
Not exposed to SW (Daytime work)	15,720 (86.86)	307 (83.79)		
Night SW	601 (3.32)	15 (4.08)		
Rotating SW	1,777 (9.82)	46 (12.50)		

[a] Reported frequencies are column percentages
[b] The statistic reported for all variables was the chi-square value
[c] Other included South Asian, Chinese, Filipino, Latin American, Japanese, Southeast Asian, Korean, Arab, West Asian, and Black.
CAD, Canadian dollars; BMI, body mass index; CES-D, the Center for Epidemiological Studies Depression Scale SW, shift work; REY, Rey auditory verbal learning; AF, Animal fluency; MAT, Mental alteration.

Appendix D: Adjusted logistic regression models with estimates for all covariates

Memory Function Impairment (REYI)			
Adjusted logistic regression models [odds ratios (ORs) and 95% Confidence Intervals(CI)] for Memory Function Impairment (REYI)			
	Model 1	**Model 2**	**Model 3**
	Ever exposed to SW	**SW exposure in longest job**	**SW exposure in current job**
	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]
Ever exposed to SW			
Never exposed to SW (Daytime work only)	1.00	—	—
Ever exposed to SW	0.95 (0.81-1.11)	—	—
SW exposure in longest job			
Not exposed to SW (Daytime work)	—	1.00	—
Night SW	—	0.95 (0.67-1.33)	—
Rotating SW	—	0.97 (0.82-1.16)	—
SW exposure in current job[c]			
Not exposed to SW (Daytime work)	—	—	1.00
Night SW	—	—	1.47 (0.97-2.21)
Rotating SW	—	—	1.06 (0.79-1.41)
Potential predictors			
Age (years)			
45-54	1.00	1.00	1.00
55-64	**0.67 (0.57-0.78)***	**0.67 (0.56-0.78)***	**0.72 (0.60-0.87)***
65-74	**0.64 (0.52-0.80)***	**0.65 (0.52-0.81)***	**0.59 (0.38-0.93)***
75+	**0.72 (0.56-0.92)***	**0.73 (0.57-0.93)***	**0.39 (0.17-0.92)***
Sex			
Male	1.00	1.00	1.00
Female	0.93 (0.82-1.05)	0.93 (0.82-1.05)	1.05 (0.87-1.27)
Ethnicity			
Whites	1.00	1.00	1.00
Other	**1.89 (1.50-2.37)***	**1.89 (1.50-2.38)***	**2.12 (1.57-2.86)***
Marital status			
With partner	1.00	1.00	1.00
No partner	0.99 (0.85-1.14)	0.98 (0.84-1.14)	0.93 (0.75-1.15)
Education level			
Less than high school	1.00	1.00	1.00
High school to some college	1.19 (0.97-1.47)	1.18 (0.95-1.46)	1.07 (0.71-1.61)

Bachelor's degree and Higher	**0.74 (0.58-0.93)***	**0.73 (0.58-0.93)***	0.69 (0.45-1.05)
Household income (CAD)			
Less than $20,000	1.00	1.00	1.00
$20,000 or more, but less than $50,000	**0.53 (0.41-0.67)***	**0.53 (0.41-0.67)***	0.81 (0.41-1.58)
$50,000 or more, but less than $100,000	**0.49 (0.38-0.63)***	**0.50 (0.39-0.65)***	0.70 (0.36-1.36)
$100,000 and more	**0.42 (0.32-0.55)***	**0.42 (0.32-0.56)***	0.62 (0.32-1.19)
Smoking			
Never	1.00	1.00	1.00
Former	1.12 (0.98-1.28)	1.12 (0.98-1.28)	1.17 (0.96-1.42)
Current	1.10 (0.89-1.35)	1.10 (0.89-1.35)	0.99 (0.73-1.35)
Alcohol consumption			
Never	1.00	1.00	1.00
Drinks less than weekly	0.96 (0.80-1.14)	0.94 (0.79-1.13)	1.08 (0.82-1.44)
Drinks at least weekly	**0.75 (0.63-0.89)***	**0.73 (0.61-0.87)***	**0.74 (0.57-0.97)***
BMI (kg/m^2)			
20.0-24.99 (normal weight)	1.00	1.00	1.00
<20.00 (underweight)	1.20 (0.86-1.68)	1.25 (0.89-1.74)	1.08 (0.63-1.83)
25.0-29.99 (overweight)	1.06 (0.91-1.24)	1.07 (0.92-1.25)	1.18 (0.94-1.48)
>30.0 (obese)	0.92 (0.78-1.08)	0.93 (0.78-1.10)	1.00 (0.78-1.28)
Depression			
No (CES-D10 <10)	1.00	1.00	1.00
Yes (CES-D10 ≥ 10)	**1.31 (1.13-1.52)***	**1.29 (1.10-150)***	**1.30 (1.04-1.63)***
Multi-morbidity			
Yes (≥2 chronic diseases)	1.00	1.00	1.00
No (<2 chronic disease)	0.93 (0.81-1.07)	0.94 (0.82-1.09)	0.96 (0.77-1.19)
Social Support Availability (SSA)			
Low	1.00	1.00	1.00
Medium	**0.81 (0.70-0.94)***	**0.81 (0.70-0.94)***	0.93 (0.74-1.15)
High	**0.75 (0.65-0.88)***	**0.75 (0.64-0.88)***	**0.66 (0.53-0.82)***
Retirement status			
Completely /partially retired	1.00	1.00	—
Not retired	1.04 (0.88-1.23)	1.04 (0.88-1.23)	—
Type of study cohort			
Tracking	1.00	1.00	1.00
Comprehensive	1.11 (0.98-1.25)	1.12 (0.99-1.27)	**1.28 (1.07-1.54)***

***** *P* value <0 05
[a] The ORs and 95% CI were calculated using survey analytical weights
[b] Models are adjusted for age, sex, ethnicity, marital status, education, income, BMI, smoking, alcohol consumption, retirement status, depression , multi-morbidity, social support availability index , type of study cohort
[c] For current job, only those participants were included who reported currently working (not retired) (N=18,466),and the models are adjusted for all covariates mentioned above except for retirement status
SW, shift work; OR, odds ratio; CI, confidence interval

Memory Function Impairment (REYII)			
Adjusted logistic regression models [odds ratios (ORs) and 95% Confidence Intervals(CI)] for Memory Function Impairment (REYII)			
	Model 1	**Model 2**	**Model 3**
	Ever exposed to SW	**SW exposure in longest job**	**SW exposure in current job**
	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]
Ever exposed to SW			
Never exposed to SW (Daytime work only)	1.00	—	—
Ever exposed to SW	1.08 (0.92-1.26)	—	—
SW exposure in longest job			
Not exposed to SW (Daytime work)	—	1.00	—
Night SW	—	**1.44 (1.03-2.01)***	—
Rotating SW	—	0.99 (0.82-1.16)	—
SW exposure in current job[c]			
Not exposed to SW (Daytime work)	—	—	1.00
Night SW	—	—	1.28 (0.81-2.05)
Rotating SW	—	—	1.03 (0.77-1.36)
Potential predictors			
Age (years)			
45-54	1.00	1.00	1.00
55-64	0.88 (0.75-0.78)	0.88 (0.75-1.03)	0.91 (0.76-1.09)
65-74	0.94 (0.76-1.16)	0.94 (0.75-1.17)	1.21 (0.77-1.90)
75+	**0.46 (0.35-0.59)***	**0.46 (0.35-0.60)***	**0.21 (0.62-0.68)***
Sex			
Male	1.00	1.00	1.00
Female	1.03 (0.91-1.17)	1.03 (0.90-1.16)	0.90 (0.74-1.08)
Ethnicity			
Whites	1.00	1.00	1.00
Other	**1.82 (1.41-2.35)***	**1.75 (1.35-2.27)***	**1.94 (1.36-2.76)***
Marital status			
With partner	1.00	1.00	1.00
No partner	0.87 (0.74-1.02)	0.87 (0.74-1.2)	0.94 (0.74-1.20)
Education level			
Less than high school	1.00	1.00	1.00
High school to some college	**1.52 (1.18-1.93)***	**1.52 (1.19-1.96)***	1.44 (0.89-2.32)
Bachelor's degree and Higher	0.99 (0.76-1.30)	1.01 (0.77-1.33)	0.84 (0.51-1.39)

Household income (CAD)			
Less than $20,000	1.00	1.00	1.00
$20,000 or more, but less than $50,000	**0.57 (0.44-0.74)***	**0.57 (0.44-0.73)***	0.78 (0.38-1.59)
$50,000 or more, but less than $100,000	**0.45 (0.35-0.60)***	**0.44 (0.34-0.58)***	0.70 (0.35-1.42)
$100,000 and more	**0.44 (0.33-0.60)***	**0.43 (0.32-0.58)***	0.74 (0.36-1.52)
Smoking			
Never	1.00	1.00	1.00
Former	1.01 (0.86-1.16)	1.02 (0.89-1.17)	1.08 (0.88-1.31)
Current	1.16 (0.94-1.43)	1.12 (0.90-1.38)	1.14 (0.85-1.53)
Alcohol consumption			
Never	1.00	1.00	1.00
Drinks less than weekly	0.91 (0.75-1.09)	0.92 (0.76-1.10)	0.82 (0.60-1.10)
Drinks at least weekly	0.90 (0.75-1.07)	0.90 (0.75-1.07)	0.74 (0.57-0.97)
BMI (kg/m^2)			
20.0-24.99 (normal weight)	1.00	1.00	1.00
<20.00 (underweight)	1.27 (0.86-1.86)	1.37 (0.93-2.00)	**1.90 (1.12-3.22)***
25.0-29.99 (overweight)	1.14 (0.98-1.32)	**1.20 (1.04-1.40)***	1.09 (0.88-1.36)
>30.0 (obese)	1.12 (0.94-1.31)	1.16 (0.98-1.37)	1.13 (0.89-1.44)
Depression			
No (CES-D10 <10)	1.00	1.00	1.00
Yes (CES-D10 ≥ 10)	**1.31 (1.11-1.53)***	**1.31 (1.12-1.53)***	1.23 (0.97-1.57)
Multi-morbidity			
Yes (≥2 chronic diseases)	1.00	1.00	1.00
No (<2 chronic disease)	0.97 (0.84-1.12)	1.00 (0.86-1.15)	0.96 (0.75-1.22)
Social Support Availability (SSA)			
Low	1.00	1.00	1.00
Medium	0.89 (0.77-1.04)	0.90 (0.70-0.94)	1.03 (0.83-1.28)
High	0.95 (0.82-1.11)	0.96 (0.64-0.88)	0.66 (0.53-1.22)
Retirement status			
Completely /partially retired	1.00	1.00	—
Not retired	1.13 (0.96-1.33)	1.14 (0.96-1.34)	—
Type of study cohort			
Tracking	1.00	1.00	1.00
Comprehensive	1.06 (0.94-1.21)	1.07 (0.94-1.22)	1.08 (0.89-1.30)

***** *P* value <0 05
[a] The ORs and 95% CI were calculated using survey analytical weights
[b] Models are adjusted for age, sex, ethnicity, marital status, education, income, BMI, smoking, alcohol consumption, retirement status, depression , multi-morbidity, social support availability index , type of study cohort
[c] For current job, only those participants were included who reported currently working (not retired) (N=18,466),and the models are adjusted for all covariates mentioned above except for retirement status
SW, shift work; OR, odds ratio; CI, confidence interval

Executive Function Impairment (AF2)			
Adjusted logistic regression models [odds ratios (ORs) and 95% Confidence Intervals(CI)] for Executive Function Impairment (AF2)			
	Model 1	**Model 2**	**Model 3**
	Ever exposed to SW	**SW exposure in longest job**	**SW exposure in current job**
	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]
Ever exposed to SW			
Never exposed to SW (Daytime work only)	1.00	—	—
Ever exposed to SW	1.12 (0.96-1.30)	—	—
SW exposure in longest job			
Not exposed to SW (Daytime work)	—	1.00	—
Night SW	—	1.27 (0.92-1.76)	—
Rotating SW	—	1.07 (0.90-1.26)	—
SW exposure in current job[c]			
Not exposed to SW (Daytime work)	—	—	1.00
Night SW	—	—	1.32 (0.87-1.99)
Rotating SW	—	—	0.95 (0.73-1.26)
Potential predictors			
Age (years)			
45-54	1.00	1.00	1.00
55-64	**0.65 (0.56-0.75)***	**0.64 (0.55-0.75)***	**0.63 (0.52-0.76)***
65-74	**0.56 (0.45-0.70)***	**0.57 (0.45-0.71)***	**0.45 (0.28-0.69)***
75+	**0.51 (0.39-0.67)***	**0.51 (0.39-0.67)***	**0.27 (0.12-0.63)***
Sex			
Male	1.00	1.00	1.00
Female	0.98 (0.86-1.12)	0.97 (0.85-1.11)	1.10 (0.92-1.33)
Ethnicity			
Whites	1.00	1.00	1.00
Other	**3.27 (2.70-3.98)***	**3.30 (2.72-4.01)***	**4.24 (3.32-5.40)***
Marital status			
With partner	1.00	1.00	1.00
No partner	0.92 (0.79-1.07)	0.91 (0.78-1.06)	0.91 (0.72-1.15)
Education level			
Less than high school	1.00	1.00	1.00
High school to some college	**1.53 (1.18-1.97)***	**1.52 (1.17-1.97)***	1.84 (0.71-1.61)

Bachelor's degree and Higher	0.90 (0.68-1.18)	0.89 (0.67-1.18)	1.02 (0.58-1.80)
Household income (CAD)			
Less than $20,000	1.00	1.00	1.00
$20,000 or more, but less than $50,000	0.81 (0.63-1.03)	0.85 (0.66-1.11)	0.73 (0.42-1.28)
$50,000 or more, but less than $100,000	**0.64 (0.50-0.83)***	**0.65 (0.51-0.86)***	0.64 (0.38-1.08)
$100,000 and more	**0.47 (0.36-0.62)***	**0.48 (0.36-0.63)***	**0.45 (0.26-0.76)***
Smoking			
Never	1.00	1.00	1.00
Former	1.05 (0.91-1.19)	1.05 (0.92-1.20)	1.13 (0.94-1.36)
Current	1.04 (0.84-1.28)	0.99 (0.80-1.23)	1.23 (0.92-1.65)
Alcohol consumption			
Never	1.00	1.00	1.00
Drinks less than weekly	0.84 (0.70-1.00)	0.85 (0.71-1.02)	1.03 (0.78-1.35)
Drinks at least weekly	**0.78 (0.66-0.92)***	**0.78 (0.66-0.93)***	0.96 (0.74-1.23)
BMI (kg/m^2)			
20.0-24.99 (normal weight)	1.00	1.00	1.00
<20.00 (underweight)	0.96 (0.65-1.41)	0.97 (0.65-1.43)	1.06 (0.63-1.76)
25.0-29.99 (overweight)	1.13 (0.97-1.32)	1.01 (0.95-1.30)	1.16 (0.94-1.43)
>30.0 (obese)	0.97 (0.82-1.15)	0.98 (0.83-1.17)	0.95 (0.78-1.20)
Depression			
No (CES-D10 <10)	1.00	1.00	1.00
Yes (CES-D10 ≥ 10)	1.15 (0.98-1.34)	1.13 (0.96-1.32)	1.17 (0.94-1.46)
Multi-morbidity			
Yes (≥2 chronic diseases)	1.00	1.00	1.00
No (<2 chronic disease)	1.06 (0.92-1.24)	1.07 (0.91-1.25)	1.17 (0.90-1.50)
Social Support Availability (SSA)			
Low	1.00	1.00	1.00
Medium	**0.85 (0.73-0.98)***	**0.84 (0.73-0.97)***	0.89 (0.72-1.09)
High	**0.84 (0.71-0.99)***	**0.83 (0.70-0.98)***	0.87 (0.68-1.06)
Retirement status			
Completely /partially retired	1.00	1.00	—
Not retired	1.09 (0.93-1.27)	1.10 (0.93-1.25)	—
Type of study cohort			
Tracking	1.00	1.00	1.00
Comprehensive	1.03 (0.91-1.17)	1.04 (0.91-1.18)	1.07 (0.89-1.28)

***** *P* value <0 05
[a] The ORs and 95% CI were calculated using survey analytical weights
[b] Models are adjusted for age, sex, ethnicity, marital status, education, income, BMI, smoking, alcohol consumption, retirement status, depression , multi-morbidity, social support availability index , type of study cohort
[c] For current job, only those participants were included who reported currently working (not retired) (N=18,466),and the models are adjusted for all covariates mentioned above except for retirement status
SW, shift work; OR, odds ratio; CI, confidence interval

Executive Function Impairment (MAT)			
Adjusted logistic regression models [odds ratios (ORs) and 95% Confidence Intervals(CI)] for Executive Function Impairment (MAT)			
	Model 1	**Model 2**	**Model 3**
	Ever exposed to SW	**SW exposure in longest job**	**SW exposure in current job**
	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]
Ever exposed to SW			
Never exposed to SW (Daytime work only)	1.00	—	—
Ever exposed to SW	**1.14 (1.00-1.29)***	—	—
SW exposure in longest job			
Not exposed to SW (Daytime work)	—	1.00	—
Night SW	—	1.20 (0.90-1.60)	—
Rotating SW	—	**1.16 (1.01-1.34)***	—
SW exposure in current job[c]			
Not exposed to SW (Daytime work)	—	—	1.00
Night SW	—	—	1.31 (0.87-1.99)
Rotating SW	—	—	**1.36 (1.06-1.74)***
Potential predictors			
Age (years)			
45-54	1.00	1.00	1.00
55-64	**0.73 (0.63-0.84)***	**0.73 (0.63-0.84)***	**0.76 (0.64-0.91)***
65-74	**0.74 (0.61-0.89)***	**0.73 (0.60-0.87)***	**0.61 (0.41-0.91)***
75+	0.87 (0.70-1.08)	0.86 (0.69-1.07)	0.58 (0.28-1.20)
Sex			
Male	1.00	1.00	1.00
Female	1.03 (0.92-1.16)	1.03 (0.93-1.17)	1.07 (0.91-1.27)
Ethnicity			
Whites	1.00	1.00	1.00
Other	**2.77 (2.28-3.36)***	**2.79 (2.30-3.40)***	**3.06 (2.39-3.93)***
Marital status			
With partner	1.00	1.00	1.00
No partner	0.88 (0.76-1.01)	0.89 (0.77-1.02)	**0.70 (0.56-0.88)***
Education level			
Less than high school	1.00	1.00	1.00
High school to some college	**1.23 (1.03-1.49)***	**1.26 (1.04-1.52)***	**1.54 (1.03-2.32)***
Bachelor's degree and Higher	**0.76 (0.61-0.93)***	**0.76 (0.62-0.94)***	1.14 (0.75-1.72)

Household income (CAD)			
Less than $20,000	1.00	1.00	1.00
$20,000 or more, but less than $50,000	**0.66 (0.53-0.83)***	**0.67 (0.54-0.83)***	0.91 (0.52-1.57)
$50,000 or more, but less than $100,000	**0.46 (0.37-0.58)***	**0.47 (0.38-0.59)***	**0.57 (0.34-0.98)***
$100,000 and more	**0.34 (0.26-0.43)***	**0.34 (0.27-0.44)***	**0.37 (0.21-0.64)***
Smoking			
Never	1.00	1.00	1.00
Former	1.01 (0.89-1.14)	1.01 (0.90-1.15)	1.11 (0.94-1.33)
Current	**1.34 (1.12-1.61)***	**1.30 (1.08-1.57)***	**1.34 (1.03-1.74)***
Alcohol consumption			
Never	1.00	1.00	1.00
Drinks less than weekly	1.02 (0.87-1.19)	1.03 (0.88-1.22)	1.09 (0.84-1.43)
Drinks at least weekly	1.01 (0.86-1.19)	1.02 (0.87-1.20)	1.16 (0.90-1.50)
BMI (kg/m^2)			
20.0-24.99 (normal weight)	1.00	1.00	1.00
<20.00 (underweight)	**1.63 (1.20-2.19)***	**1.60 (1.18-2.17)***	1.18 (0.70-1.97)
25.0-29.99 (overweight)	1.13 (0.98-1.29)	**1.14 (0.99-1.30)***	1.20 (0.98-1.45)
>30.0 (obese)	**1.23 (1.06-1.43)***	**1.23 (1.06-1.43)***	**1.35 (1.08-1.68)***
Depression			
No (CES-D10 <10)	1.00	1.00	1.00
Yes (CES-D10 ≥ 10)	**1.29 (1.123-1.48)***	**1.31 (1.14-1.50)***	**1.34 (1.10-1.64)***
Multi-morbidity			
Yes (≥2 chronic diseases)	1.00	1.00	1.00
No (<2 chronic disease)	0.93 (0.82-1.04)	0.94 (0.83-1.07)	1.06 (0.86-1.32)
Social Support Availability (SSA)			
Low	1.00	1.00	1.00
Medium	0.94 (0.83-1.08)	0.95 (0.83-1.08)	0.89 (0.72-1.08)
High	0.98 (0.85-1.13)	0.98 (0.84-1.13)	0.87 (0.68-1.06)
Retirement status			
Completely /partially retired	1.00	1.00	—
Not retired	1.02 (0.89-1.19)	1.02 (0.89-1.18)	—
Type of study cohort			
Tracking	1.00	1.00	1.00
Comprehensive	0.97 (0.87-1.09)	0.98 (0.88-1.10)	1.03 (0.87-1.22)

***** *P* value <0 05
[a] The ORs and 95% CI were calculated using survey analytical weights
[b] Models are adjusted for age, sex, ethnicity, marital status, education, income, BMI, smoking, alcohol consumption, retirement status, depression , multi-morbidity, social support availability index , type of study cohort
[c] For current job, only those participants were included who reported currently working (not retired) (N=18,466),and the models are adjusted for all covariates mentioned above except for retirement status
SW, shift work; OR, odds ratio; CI, confidence interval

Overall cognitive impairment			
Adjusted logistic regression models [odds ratios (ORs) and 95% Confidence Intervals(CI)] for Overall cognitive impairment			
	Model 1	**Model 2**	**Model 3**
	Ever exposed to SW	**SW exposure in longest job**	**SW exposure in current job**
	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]	Impaired cognition OR (95% CI) [a,b]
Ever exposed to SW			
Never exposed to SW (Daytime work only)	1.00	—	—
Ever exposed to SW	1.12 (0.92-1.35)	—	—
SW exposure in longest job			
Not exposed to SW (Daytime work)	—	1.00	—
Night SW	—	**1.53 (1.04-2.26)***	—
Rotating SW	—	1.02 (0.83-1.27)	—
SW exposure in current job[c]			
Not exposed to SW (Daytime work)	—	—	1.00
Night SW	—	—	**1.79 (1.08-2.96)***
Rotating SW	—	—	1.04 (0.73-1.17)
Potential predictors			
Age (years)			
45-54	1.00	1.00	1.00
55-64	**0.63 (0.52-0.77)***	**0.63 (0.51-0.76)***	**0.65 (0.51-0.83)***
65-74	**0.58 (0.44-0.77)***	**0.58 (0.44-0.77)***	0.82 (0.48-1.43)
75+	**0.44 (0.31-0.62)***	**0.44 (0.31-0.63)***	0.66 (0.24-1.86)
Sex			
Male	1.00	1.00	1.00
Female	0.89 (0.76-1.05)	0.89 (0.75-1.04)	0.93 (0.73-1.17)
Ethnicity			
Whites	1.00	1.00	1.00
Other	**3.88 (3.04-4.94)***	**3.88 (3.05-4.94)***	**4.83 (3.55-6.57)***
Marital status			
With partner	1.00	1.00	1.00
No partner	0.87 (0.73-1.06)	0.90 (0.74-1.07)	0.80 (0.60-1.06)
Education level			
Less than high school	1.00	1.00	1.00
High school to some college	**2.26 (1.63-3.13)***	**2.37 (1.69-3.32)***	**2.15 (1.17-3.98)***

Bachelor's degree and Higher	1.06 (0.73-1.52)	1.11 (0.78-1.61)	0.98 (0.51-1.88)
Household income (CAD)			
Less than $20,000	1.00	1.00	1.00
$20,000 or more, but less than $50,000	**0.45 (0.34-0.58)***	**0.48 (0.37-0.63)***	0.59 (0.32-1.16)
$50,000 or more, but less than $100,000	**0.32 (0.24-0.43)***	**0.34 (0.25-0.45)***	**0.44 (0.23-0.84)***
$100,000 and more	**0.22 (0.16-0.31)***	**0.23 (0.16-0.32)***	**0.30 (0.15-0.58)***
Smoking			
Never	1.00	1.00	1.00
Former	0.99 (0.84-1.19)	1.00 (0.84-1.19)	1.01 (0.78-1.30)
Current	1.25 (0.98-1.60)	1.20 (0.94-1.54)	1.23 (0.87-1.76)
Alcohol consumption			
Never	1.00	1.00	1.00
Drinks less than weekly	0.84 (0.68-1.04)	0.87 (0.70-1.07)	0.89 (0.63-1.24)
Drinks at least weekly	**0.72 (0.59-0.89)***	**0.74 (0.59-0.91)***	0.81 (0.58-1.12)
BMI (kg/m^2)			
20.0-24.99 (normal weight)	1.00	1.00	1.00
<20.00 (underweight)	1.48 (0.95-2.27)	**1.60 (1.18-2.17)***	1.33 (0.70-2.54)
25.0-29.99 (overweight)	1.10 (0.90-1.34)	1.14 (0.99-1.30)	1.21 (0.92-1.60)
>30.0 (obese)	1.10 (0.88-1.37)	1.23 (1.06-1.43)	1.25 (0.92-1.71)
Depression			
No (CES-D10 <10)	1.00	1.00	1.00
Yes (CES-D10 ≥ 10)	**1.55 (1.29-1.86)***	**1.53 (1.28-1.84)***	**1.80 (1.38-2.34)***
Multi-morbidity			
Yes (≥2 chronic diseases)	1.00	1.00	1.00
No (<2 chronic disease)	0.97 (0.80-1.17)	0.99 (0.82-1.20)	1.22 (0.91-1.64)
Social Support Availability (SSA)			
Low	1.00	1.00	1.00
Medium	**0.80 (0.67-0.97)***	**0.81 (0.67-0.97)***	0.91 (0.69-1.20)
High	0.90 (0.74-1.10)	0.93 (0.76-1.13)	0.89 (0.67-1.19)
Retirement status			
Completely /partially retired	1.00	1.00	—
Not retired	1.07 (0.87-1.32)	1.08 (0.88-1.34)	—
Type of study cohort			
Tracking	1.00	1.00	1.00
Comprehensive	1.01 (0.86-1.19)	1.03 (0.88-1.21)	1.12 (0.88-1.42)

***** *P* value <0 05
[a] The ORs and 95% CI were calculated using survey analytical weights
[b] Models are adjusted for age, sex, ethnicity, marital status, education, income, BMI, smoking, alcohol consumption, retirement status, depression , multi-morbidity, social support availability index , type of study cohort
[c] For current job, only those participants were included who reported currently working (not retired) (N=18,466),and the models are adjusted for all covariates mentioned above except for retirement status
SW, shift work; OR, odds ratio; CI, confidence interval

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The association between shift work exposure and the variations in age at natural menopause among adult Canadian workers: results from the Canadian Longitudinal Study on Aging (CLSA)

Author: Durdana Khan, Michael Rotondi, Heather Edgell, et al

Publication: Menopause

Publisher: Wolters Kluwer Health, Inc.

Date: Jul 1, 2022

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Wolters Kluwer

The Association Between Shift Work Exposure and Frailty Among Middle-Aged and Older Adults: Results From the Canadian Longitudinal Study on Aging

Author: Durdana Khan, Chris Verschoor, Heather Edgell, et al

Publication: Journal of Occupational and Environmental Medicine

Publisher: Wolters Kluwer Health, Inc.

Date: Oct 3, 2023

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