Job strain, depressive symptoms, and cardiovascular disease: cross-sectional and longitudinal associations in community samples

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Abstract

Background: Job strain is associated with cardiovascular disease (CVD). Job strain and depression are closely related and are both risk factors for CVD, yet few studies have included an assessment of depressive symptoms in examination of the association between job strain and CVD. It remains unclear whether job strain is still associated with CVD when depression is controlled for. Depression is more prevalent in women and has a higher comorbidity in female CVD. Previous studies have failed to assess whether there are different associations between job strain, depressive symptoms, and CVD for males and females. Both education and occupation type have been associated with and CVD separately. Occupational type as classified by education/skill level (occupational skill level) has also been associated with CVD. However, no previous study has investigated whether occupational skill level varies the association between job strain and CVD.

Objectives: The aims of the first manuscript are to 1) investigate the cross-sectional association between job strain and CVD risk score as measured by the Framingham Risk Score and 2) to examine whether this association is different for either sex. The aims of the second manuscript are 1) to prospectively examine the association between job strain and the risk of developing heart disease; 2) to assess whether this association is different for either sex and; 3) to explore the association between job strain and heart disease according to occupational skill level.

Methods The first manuscript contains data from the CARTaGENE study, a community health survey of adults in Québec, including 7,848 working adults aged 40 to 69 years (2009-2010). Multiple linear regression analyses were conducted to examine the association between job strain and CVD risk score, controlling for depressive symptoms, and other factors. The second manuscript also used data from the CARTaGENE study which was linked to administrative health insurance data (RAMQ) in order to investigate the association between job strain and the incidence of heart disease (n = 8,073) over a seven year time interval. Cox proportional hazards regression models were used to examine the association of job strain and heart disease. Both analyses were adjusted for various sociodemographic characteristics, behavioral and clinical factors, and depressive symptoms.

Results: In the first study (manuscript 1), job strain was associated with Framingham Risk Score, controlling for depressive symptoms in overall, male, and female samples. Further adjustment for lifestyle factors did not change this association. There was no interaction effect between job strain and depressive symptoms in the association with Framingham Risk Score. In the second study (manuscript 2) models adjusted for age, education, and ethnicity found that job strain was associated with the risk of heart disease in the female sample only, not in the male sample. The association remained in the female sample even after adjustment for depressive symptoms and other lifestyle and biological factors. High job strain and heart disease were most prevalent in individuals with occupations of the lowest skill level. There was no interaction between job strain and occupational skill level in the association between job strain and CVD.

Conclusion: A cross-sectional association between job strain and Framingham Risk Score, independent of depressive symptoms was observed. Results of longitudinal analyses indicate that job strain is associated with increased risk of heart disease in females even when depressive symptoms are controlled for. Job strain does not appear to be a major risk factor for heart disease in males. The association between job strain and CVD did not vary according to occupational skill level however the highest rate of heart disease occurred in individuals with jobs of the lowest occupational skill level.

Résumé

Contexte : On associe le stress au travail avec la maladie cardiovasculaire (MCV). Le stress au travail et la dépression étant étroitement liés, tous les deux sont reconnus indépendamment comme facteurs de risque de maladies cardiovasculaires. Pourtant, peu d'études ont inclus une évaluation des symptômes dépressifs dans l'examen de leur association. Il reste à savoir si l'association entre le stress au travail et les MCV est toujours probante lorsque la dépression est prise en compte. La dépression est plus répandue chez les femmes, et sa comorbidité est aussi plus élevée chez les femmes atteintes de MCV. La littérature sur le sujet n'est pas parvenue à démontrer la relation spécifique entre le stress au travail, la dépression et les MCV, et ce tant chez les hommes que les femmes. Le niveau de scolarité et le type d'occupation sont des facteurs connus de risques de maladie cardiovasculaire. Pourtant, aucune autre étude n'a pu examiner spécifiquement comment le stress au travail et la MCV peuvent varier selon le niveau de qualification professionnel.

Objectifs : Les objectifs du premier manuscrit sont de :1) examiner l'association transversale entre le stress au travail et la cote de risque de MCV mesurée par le score de Framingham; 2) examiner les différences dans cette association entre les hommes et les femmes. Les objectifs du deuxième manuscrit sont de 1) examiner l'association entre le stress au travail et le risque de développer une maladie cardiaque ; 2) d'en évaluer la disparité entre les sexes ; 3) explorer le lien entre le stress au travail et la maladie cardiaque selon le niveau de qualification professionnel.

Méthodes : Les données utilisées dans le premier manuscrit proviennent du sondage CARTaGENE. Cette enquête a été portée sur 7 848 travailleurs au Québec âgés entre 40 et 69 ans. Une analyse à régression linéaire a été effectuée pour examiner l'association entre le stress au travail et la cote de risque de MCV, le tout ajusté pour la dépression et d'autres facteurs. Le

deuxième manuscrit croise les données du sondage CARTaGENE à celles recueillies par la RAMQ, afin d’estimer l’association entre le stress au travail et l’incidence de la maladie cardiaque (n = 8,073). Les modèles de régression aléatoire proportionnelle de Cox ont été utilisés pour examiner l’association entre le stress au travail et la maladie cardiaque.

Résultats : Dans la première étude, le stress au travail était associé avec le score du risque de Framingham, ajusté pour la dépression chez les femmes, les hommes, et l’échantillon global. Aucun effet d’interaction n’a pu être démontré par leur association avec le score du risque de Framingham. Dans la deuxième étude, les modèles ajustés ont démontré que le stress au travail est associé avec le risque de maladie cardiaque chez les femmes, mais pas les hommes. L’association persiste même après l’ajustement pour les symptômes de dépression et d’autres facteurs. Un niveau de stress élevé au travail est plus fréquemment rapporté par les individus dont l’emploi se classifie au bas niveau de scolarité. Cependant, aucune interaction n’a pu être établie entre le stress au travail et le niveau de qualification professionnel, dans leur association avec la maladie cardiaque.

Conclusion : Une association transversale entre le stress au travail et le score du risque de Framingham, indépendamment des symptômes de la dépression, a été observé. Les résultats indiquent que le stress au travail mène à un risque plus élevée de la maladie cardiaque chez les femmes même quand les symptômes de la dépression sont contrôlés. Il ne semble pas que le stress au travail soit un facteur de risque majeur pour la maladie cardiaque chez les hommes. L’association entre le stress au travail et la maladie cardiaque n’a pas varié selon l’emploi classifié par le niveau de scolarité.

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Preface and contribution of authors

The thesis contains seven chapters. Chapter one is the introduction which outlines the rationale and objectives of this thesis. The second chapter includes background information on cardiovascular disease, job strain, depression, and occupational skill types. The third chapter is composed of the first manuscript, a cross-sectional examination of the association between job strain, depressive symptoms and CVD risk. Chapter four serves to connect the two manuscripts and to transition to the second objective. Chapter five contains the second manuscript, a longitudinal investigation between job strain and heart disease. The sixth chapter consists of a summary of the research findings, strengths and limitations of the thesis, clinical implications, future directions for research, and a conclusion. Chapter seven contains the references including those for both manuscripts. Appendix I includes supplemental information on calculation of Framingham Risk Score points. Appendix II includes supplemental information on calculation of Framingham Risk Score (10 year risk %). Appendix III includes additional analyses for the second manuscript. Both manuscripts have been submitted for publication.

As first author, I (Niamh Power) have contributed to the development of objectives and hypotheses, research design, statistical analyses, data interpretation, and have drafted and revised both manuscripts in the present thesis. Dr. Norbert Schmitz, as thesis supervisor, and co-author on both manuscripts contributed to the conceptualization of the hypotheses, study design, analytic strategy, interpretation of results, providing critical revision to both manuscripts, and obtaining both the CARTaGENE and administrative health insurance (RAM-Q) datasets. Dr. Sonya Deschênes, as thesis committee member, and co-author on both manuscripts has provided substantial contributions regarding manuscript preparation and provided critical revisions.

Floriana Ferri (B.Sc.), as co-author on both manuscripts, has contributed to the interpretation of results and provided critical revisions.

List of abbreviations and acronyms

CVD – Cardiovascular Disease

CHD - Coronary Heart Disease

NOC – National Occupation Classification

CAD – Coronary Artery Disease

HPA – Hypothalamic Pituitary Adrenal

AMI – Acute Myocardial Infarction

CIDI – Composite International Diagnostic Interview

SCID – 5 -Structured Clinical Interview for DSM-5

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1. Introduction

1.1 Rationale

Cardiovascular disease (CVD) that is the number one cause of death worldwide (1). Diseases of the heart are a consistently leading cause of death in Canada accounting for 53,134 deaths in 2018 (2). Given the prevalence of CVD, it is important to gain a better understanding of psychosocial risk factors, such as stress (3). Job strain, which is a form of work stress conceptualized as the combination of high occupational demands and low control (4), has been demonstrated to be associated with CVD incidence (5) as well as CVD risk as indexed by the Framingham Risk Score (6). However, the association between job strain and CVD continues to be marked by heterogeneity with some studies observing no relationship between these factors (7, 8).

There exist few previous studies that include an assessment of depression in examination of the association between job strain and CVD. Job strain is associated with increased risk for depression (9, 10) and depression is an established risk factor for CVD (11). Yet no previous studies have evaluated whether there is *still* an association between job strain and CVD when depressive symptoms are controlled for. Additionally, there is a lack of Canadian data on the association between job strain and CVD, with previous studies conducted in this context subject to methodological limitations.

Previous cross-sectional studies have looked at the association between job-strain and (diagnosed) CVD (12), however here the temporal association is not clear, it is possible that job strain starts after the onset of CVD. Therefore, the aim of the first manuscript of this thesis was to look at the association between job strain and CVD risk, controlling for depressive symptoms using a well validated risk tool in a community sample in Québec. Previous prospective studies investigating job strain and CVD have used self-reported incidences of heart diseases however it has been demonstrated that administrative data is more accurate in identifying cases of heart disease (13). Therefore the main aim of the second manuscript of this thesis was to investigate the prospective association between job strain and heart disease, controlling for depressive symptoms using administrative health insurance data to identify heart disease in a community sample in Québec.

There are sometimes differences observed between men and women in the association between job strain and CVD. Some studies have reported stronger associations for females (14), and others for males (15), whereas other studies have not observed differences between the sexes (16). Depressive symptoms may explain some of the variance in the association between job strain and CVD between males and females as depression is more prevalent in females (17) and depression comorbidity is more common in female CVD than male CVD (18). However no previous studies have investigated whether the association between job strain and CVD, controlling for depressive symptoms is different for males and females. Therefore the current thesis additionally aimed to investigate whether there were sex differences in: the association between job strain and CVD risk, controlling for depressive symptoms (manuscript 1); the association between job strain and incident heart disease, controlling for depression (manuscript 2).

Low socio-economic status appears to be associated with a higher risk for CVD (19). The association between indices of socio-economic status such as education and occupation type have been previously investigated, with both of these factors demonstrating associations with CVD (20, 21). The association between job strain and CVD may vary according to occupation type (22). Given the observed associations between education and CVD, it is important to assess occupation type categorized according to educational skill level (*occupational skill level*). Occupational skill level is a measure of occupation type that is classified according to the education or skill level that is associated with the occupation (23). No previous study has assessed the association between job strain and heart disease according to occupational skill level in Canadian samples. Therefore an additional aim of the second manuscript of this thesis was to investigate the association between job strain and heart disease according to occupational skill level.

1.2 Thesis objectives

This thesis was comprised of five objectives. The objectives addressed in manuscript 1 were: 1) to estimate the cross-sectional association between job strain and CVD risk as indexed by the Framingham Risk Score, controlling for depressive symptoms and; 2) to assess whether the association is different for either sex. The objectives addressed in manuscript 2 were: 3) to investigate the association between job strain and heart disease, controlling for depressive symptoms; 4) to assess whether these associations differ according to sex and; 5) to examine if the association between job strain and heart disease varies according to occupational skill level.

2. Review of the literature

2.1 Cardiovascular disease

2.1.1 Definition of cardiovascular diseases

Cardiovascular disease (CVD) is estimated to account for 17.9 million deaths each year (31% of all deaths worldwide) (24). Cardiovascular disease is an umbrella term comprising diseases of the heart as well as diseases of blood vessels such as high blood pressure and peripheral artery disease (25). There are many different cardiovascular disease conditions. Heart disease is a sub group of cardiovascular disease conditions that referring to conditions that affect the structure and functioning of the heart itself e.g. arrhythmias and valve/wall abnormalities. Coronary heart disease (CHD) is a type of heart disease that develops when the arteries that supply the heart cannot deliver enough oxygen rich blood (26). The terms "cardiovascular disease" and "heart disease" are both used throughout this thesis and refer to the definitions previously mentioned.

2.1.2 Risk factors for cardiovascular disease and heart disease

Established risk factors for CVD include diabetes, abdominal obesity, dyslipidemia, and smoking (27-30). Increased fruit and vegetable consumption and physical activity have also been associated with a reduced risk of CVD (31). There exists a heterogeneous association between alcohol consumption and CVD (32) with some studies reporting that low or moderate consumption may be beneficial (33). Age is a major non-modifiable risk factor for CVD with the likelihood of disease development increasing with age. Ethnicity is another non-modifiable risk factor for CVD. Though higher rates of disease have been reported in South Asian groups and lower rates in Hispanics/Latinos (34, 35), there exists much heterogeneity across the research findings reported on this subject. Ethnic differences may be due to differences in genetic susceptibility or differences in the prevalence of CVD risk factors amongst different racial and ethnic groups (36, 37). The prevalence of CVD risk factors have also been observed to cluster in groups according to social determinants such as educational attainment (34).

However, as previously mentioned, there are different types of CVD conditions. The establishment of the above risk factors for CVD has been done under the assumption that these risk factors contribute similarly to different types of CVD conditions. However certain risk factors may contribute differentially to specific CVD conditions, such as heart disease. Although there are similarities in the risk factors for CVD and heart disease e.g. age, dyslipidemia, smoking, and diabetes (38), there is some evidence to suggest that there are also differences. For instance, hypertension is preferentially associated with incidence of stroke, whereas hypercholesterolemia may play a more important role in the development of CHD (39).

2.1.3 Framingham Risk Score

The Framingham Risk Score is an algorithm used to estimate the 10 year CVD risk of an individual (40). It was developed in 1998 and is based on data from the Framingham Heart Study, an ongoing cardiovascular cohort study that began in 1948 in Framingham, Massachusetts (41). The score is computed via points that are allocated to the individual based on age, total cholesterol, smoking, HDL cholesterol, and systolic blood pressure. Point allocation is sex specific, e.g. a female with untreated systolic blood pressure that is 160mm Hg or higher obtains a score of 4, whereas a male with the same systolic blood pressure status obtains a score of 2. Scores are then used to derive the following risk categories: (i) low risk (10% or less ten year risk for coronary heart disease [CHD]); (ii) intermediate risk (10-20% ten year risk for CHD) and; (iii) high risk (20% or more ten year risk for CHD). Supplementary information about the calculation of the Framingham Risk Score points and risk categories is provided in the appendix (42).

2.1.4 Stress and cardiovascular disease

An increasing amount of evidence asserts the association between psychosocial factors and CVD, with psychosocial stress emerging as a primary factor of investigation (3, 43). Different forms of stress interact with CVD in different ways. Early life stressors such as repeated childhood adversity have been associated with an increased risk of heart disease (44), as well as other chronic stressors such as social isolation and loneliness experienced in adulthood (45). Acute stress such as the death of a significant person appears to operate via the acute triggering of cardiac events (46). In contrast, more chronic forms of stress appear to be associated with the long term development of CVD (31).

The link between stress and the heart operates via the physiological stress response. The hypothalamic–pituitary–adrenocortical (HPA) and sympatho–adrenomedullary axes are the principal biological systems activated during the stress response (47, 48). Elements of the biological response to stress that seem to contribute to CVD include raised blood pressure, reduced insulin sensitivity, increased hemostasis, and endothelial dysfunction (47).

Allostatic load is a concept that has been developed to explain how *chronic* or *long term* stress increases the risk of CVD (49). Perceived stress initiates a series of physiologic responses resulting in a state of allostasis which is the process by which the body attempts to return to a state of homeostatis. Allostatis results in the activation of the sympathetic-adrenal medullary system, the hypothalamic pituitary adrenal cortical axis, and cardiovascular, metabolic, neural, endocrine, and immune systems (50). Allostasis is an adaptive process in the short term that helps the individual deal with the stressor. For example, the “fight or flight response” is initiated in allostasis and results in physiologic responses that help the individual deal with a stressor such as increased heart rate, immune system activation. However, repeated allostasis in the long term causes allostatic load, a state in which the normal allostatic processes wear out or fail to disengage and therefore, the physiological systems are not able to adapt (50, 51). E.g. blood pressure levels vary continuously throughout the day in response to stressors (allostasis), however if blood pressure is repeatedly elevated (allostatic load) it has been proposed that this increases atherosclerotic plaques which leads to a greater risk for CVD (52). Dysregulation of the HPA axis in allostatic load is associated with the development of metabolic syndrome (53) which is a risk factor for CVD (54). Dysregulation of the HPA axis in allostatic load is also associated with disturbances in the circadian rhythm of cortisol. Cortisol serves to reduce inflammation in the body. Regulation of cortisol is also important for the maintenance of normal blood pressure (an element of the metabolic syndrome) (55).

Other inflammatory processes may also be implicated in the association between stress and CVD. Activation of the HPA axis by stress induces pro inflammatory responses. Chronic stress may result in chronic low grade inflammatory load (56) which may be linked to the development of CVD (57). Two important biomarkers of systematic inflammation IL-6 and CRP have been associated with atherosclerosis (58, 59).

2.2 Job strain

2.2.1 Definition of work stress and job strain

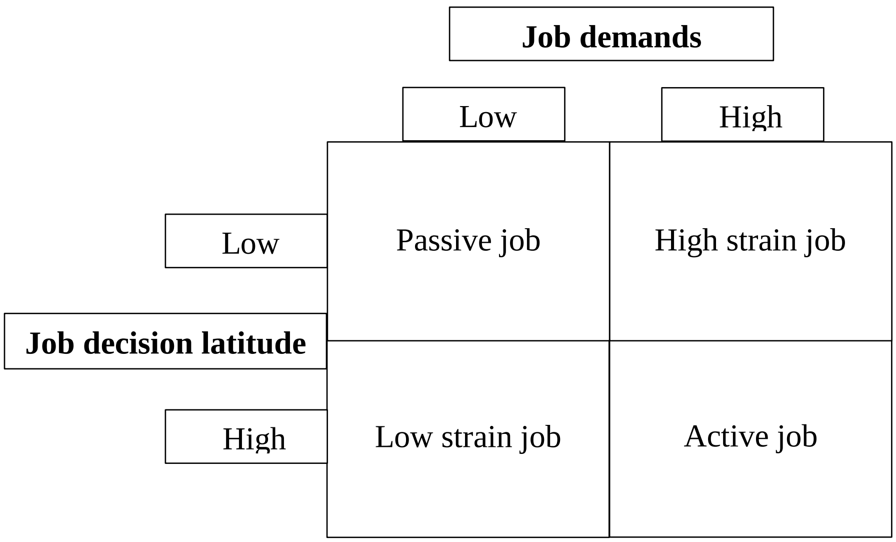
Amongst all forms of chronic stress potentially associated with CVD, work related stress has been most extensively investigated. Work related stress is highly prevalent, it has been estimated that 62% of Canadian workers report work as their main source of stress (60). The association between various stressors related to work such as long working hours and job security have been explored in relation to CVD (61, 62). However, *job strain*, as conceptualized by the "Job Demand Control Model", developed by Karasek, is the most commonly tested model of occupational stress (4) that encompasses a wide range of stressors related to work. The model consists of two main elements: job demands (e.g. workload, pace of work) and job control (control the employee has over their work). Job control is sometimes alternately referred to as "decision latitude" in the literature on job strain (63). The main premise of the Job Demand Control Model is that the most stressful or "high strain" jobs are those which involve high levels of demands for the employee accompanied by little control over their work (64).

The most widely adopted questionnaires that measure dimensions of demand and control are the Job Content Questionnaire (JCQ) and the Demand Control Questionnaire (DCQ) (65). The number of items chosen to measure demand and control varies with some studies using shortened versions. A comparison of alternate versions of the job demand-control scales found that in comparison with scores from complete scale, agreement between job strain definitions was still good when at least three scale items were included (66).

2.2.2 Measurement of job strain

The Job Demand Control model proposes four different types of "job" or job situation based on a combination of job demands and job control as follows: (i) passive job (low job demands and low job control); (ii) low-strain (low job demands and high job control); (iii) high-strain (high job demands and low job control); and active job (high job demands and high job control). These jobs are often summarized visually using quadrants (Figure 1).

Figure 1 Quadrants of Job Demand Control Model (2.2.2 Measurement of job strain)



Previous studies investigating job strain and CVD outcomes have chosen to use various formulations of job strain (67). Some studies compare outcomes in each group according to the four job strain categories (68, 69). Other studies have used a dichotomy, comparing the outcome in those with high job strain compared to those without high job strain. High job strain is a combination of high demands and low control derived from demand and control summary scores which are dichotomized as high/low according to median cut off scores (70). Most studies have measured job strain using a job strain ratio variable derived from the ratio of job demands summary score to job control summary score (71, 72).

2.2.3 The association between job strain and CVD

Previous cross-sectional studies examined the association between job-strain (conceptualized by the “Job Demand Control Model”) and (diagnosed) CVD (12). However, the temporal association is not clear. It is possible that job strain starts after onset of CVD. A meta-analysis investigated the cross-sectional association between job strain and CVD risk factors instead of diagnosed CVD. An overall cross-sectional association was found between job strain and CVD risk factors such as diabetes, blood pressure, pulse pressure, lipid fractions, smoking, alcohol consumption, physical inactivity, obesity, as well as overall CVD risk as indexed by the Framingham Risk Score (6). However there is a lack of this type of data in Canadian samples and there is still some heterogeneity in this association as demonstrated by a recent cross-sectional sectional study that did not find an association between job strain and the Framingham Risk Score (8).

There is evidence for a longitudinal association between job strain and CVD. A large scale meta-analysis comprising over 197,000 participants from 13 European cohort studies found that after adjustment for age and sex, the hazard ratio for job strain versus no job strain was 1·23 (95% CI 1·10-1·37) with adjustment for socio-economic status attenuating the association 1·17 (1·05–1·31). However, psychosocial factors such as depression were not adjusted for in this analysis (5).

In general, there exists evidence for an association between job strain and CVD incidence (5) yet it appears there is still more to be understood about the relationship between job strain and CVD incidence as some longitudinal studies have not observed an association between these factors (73-75). In a review of the association between work related stress and coronary heart disease (CHD) it was observed that amongst 19 studies that measured work stress using the job strain model, only 8 found an association between job strain and CHD (76). Thus the inconsistency observed in the association between job strain and CVD incidence indicates that the nature of this relationship has yet to be fully elucidated. Previous studies of job strain and CVD incidence are subject to the following limitations: (i) there is lack of assessment of psychosocial factors such as depression in the job strain-CVD association; (ii) there is a paucity of Canadian data that addresses the longitudinal association between these factors; (iii) previous studies have relied on self-reported CVD incidence as an outcome measure. Addressment of these limitations may provide a better understanding of the association between job strain and CVD incidence.

2.2.4 Mechanisms underpinning the job strain-CVD association

Biological mechanisms proposed to underlie the association between job strain and CVD are similar to those proposed for stress and CVD. Work related stress is an indicator of long term stress and is associated with allostatic load (77). As mentioned previously, allostatic load is a biological mechanism that links long term stress to CVD. Allostatic load seems to be implicated in the relationship between job strain and CVD through similar processes to those involved in the relationship between stress and CVD. As explained previously, allostatic load is associated with metabolic syndrome and disruption of cortisol. Work stress has been associated with the risk for metabolic syndrome (53) and longer duration of work-related stress was found to be associated with a greater morning rise in cortisol level and reduced heart-rate variability (78). Similarly, there appears to be similar pro-inflammatory processes linking stress to CVD and job strain to CVD. For instance, associations between job strain and similar inflammatory markers to those implicated in the relationship between stress and CVD (CRP and IL-6, and fibrinogen) have been observed (79). However, there is still no single biological mechanism asserting the link between job strain and CVD (80).

Job strain may also be associated with CVD indirectly by increasing health risk behaviours. Lifestyle risk factors for CVD such as physical activity, alcohol consumption, and smoking are also associated with job strain (81-83).

2.2.5 Covariates of the job strain - CVD association

Biological risk factors for CVD such as blood pressure, cholesterol, and diabetes are also associated with job strain (70, 84, 85). Lifestyle risk factors for CVD such as physical activity, alcohol consumption, and smoking have also been associated with job strain (81-83). Thus it is important to include these factors as covariates in assessment of the association between job strain and CVD. Job strain and CVD may share other common psychosocial risk factors, such as depression (9, 11). In review of previous literature, depression has been scarcely considered as a covariate within the job strain-CVD association.

2.3. Depression

2.3.1 Definition and measurement of depression

Depression is a common mental disorder characterized by persistent sadness and a lack of interest or pleasure. Depression can disturb sleep, appetite, sleep, and concentration. Depression affects more than 264 million people worldwide (86). Diagnosis of depression using structured clinical interviews such as the Composite International Diagnostic Interview (CIDI) and the Structured Clinical Interview for DSM-5 (SCID-5) remains the optimal method of diagnosing clinical depression (87, 88). Depressive symptom rating scales are commonly employed in epidemiological studies to assess the presence and severity of depression symptoms, with higher scores on these scales indicating greater severity of depressive symptoms. These rating scales can be completed by the respondent and are less time-consuming and expensive than structured clinical interviews (89). Additionally, these scales tend to have moderate to excellent validity (89). One such scale is the Patient Health Questionnaire (PHQ-9), a nine item questionnaire that measures depressive symptoms over the last two weeks. Respondents are asked "*Over the last two weeks, how often have you been bothered by any of the following problems*?" Examples of items include: "*Trouble falling or staying asleep, or sleeping too much*" and "*Feeling bad about yourself or that you are a failure or have let yourself or your family down*". The score can range from 0 to 27 as each item can be scored from 0 ("*not at all"*) to 3 ("*nearly every day"*). The PHQ-9 is a valid and reliable measure and demonstrates good agreement with clinical diagnosis of major depressive disorder (90). A cut off score of ≥10 indicating moderate to severe depressive symptoms has been recommended and has been used in studies on CVD. (91-94).

2.3.2 Depression and job strain

Major depression is prevalent amongst the working population. Previous research has suggested that depression is prevalent amongst 4.6% of Canadian workers (72). Depression and job strain are related, with strong evidence for an association between job strain and the risk for major depressive disorder (9, 95, 96). High job strain has also been related to greater risk of depressive symptoms (96). The precise pathway through which job strain is related to depression remains unknown. Previous research has shown that job strain is associated with social and behavioral risk factors for depression such as social isolation (97) and leisure time physical inactivity (98). Other perspectives suggest that exposure to chronic stressors such as job strain can induce dysregulation of the hypothalamic– pituitary–adrenal axis and subsequent physiological changes that are involved in the pathophysiology of depression (99). There may be some crossover with respect to symptomatology in job strain and depression.

2.3.3 Depression and cardiovascular disease

Depression is an established psychosocial risk factor for CVD incidence, independent of traditional risk factors (11, 100) and is associated with worse prognosis in existing CVD (101). The mechanism through which this association operates appears to be complex. Numerous biological theories have been proposed to underlie this association from those involving alterations in the autonomic nervous system, to platelet receptors and function (101). Inflammatory processes have also been proposed to underpin the depression-CVD association (102, 103).

2.3.4 Job strain, depressive symptoms and CVD

As highlighted above, job strain and depression closely related conceptually and as such, can be difficult to disentangle. Additionally, both job strain and depression seem to be associated with inflammatory pathways that are implicated in CVD (56, 102). Previous studies have examined each factor's independent association with CVD (5, 11) however these factors are rarely considered together in relation to CVD. There may be some overlap in between job strain and depression, in relation to CVD. It is thus necessary to understand whether job strain is associated with CVD even when depressive symptoms are controlled for.

As mentioned above, there is a lack of previous research investigating the association between job strain and CVD that controls for psychosocial factors such as depression. A sub analysis within the Women's Health Study investigated the association between job strain and CVD incidence controlled for depressive and anxiety symptoms. A 4 item measure was used to assess depression and anxiety. Inclusion of these factors as covariates resulted in a slight attenuation of the association between job strain and CVD incidence. However, this analysis was limited as it consisted of a female sample only (104).

Investigations of this kind are even scarcer in Canadian samples. A recent study in a Canadian sample investigating the association of work stressors on the risk of heart disease *did* adjust for depressive symptoms however this study used self-reported heart disease as an outcome measure. This is an important limitation given that self-report data has been demonstrated to be less accurate in identifying heart disease than administrative data (13).

2.4 Sex differences

2.4.1 Cardiovascular disease

Cardiovascular disease, specifically ischemic heart disease is the number one cause of death in both males and females worldwide (105) . A 2018 update demonstrates that mortality rates for CVD are currently similar in male and female populations (106). There are sex differences in the occurrence of different CVD conditions. The risk for heart disease higher for men than women, especially at a younger age (107) whereas there is evidence for an increased propensity of stroke in females (108). However, with age, the risk for heart disease increases in females who demonstrate similar rates to males in later life, particularly post-menopause (109-112).

Recent evidence suggests that the gap between female and male heart disease prevalence is increasingly narrow and not only in older populations. In a community based study of over 23,000 patients hospitalized with Acute Myocardial Infarction (AMI) over the course of nineteen years, it was observed that the proportion of young AMI hospitalizations remained fairly stable across 1995 to 2014 among men, and steadily increased among women (113). In addition, findings from the National Health and Nutrition Examination Surveys (NHANES) indicate that the prevalence of myocardial infarctions increased in midlife (35 to 54 years) in women, and declined in similarly aged men (112).

It appears that females have not benefited from the overall decline in heart disease mortality that has occurred in the last four decades (114), but rather some findings suggest that female heart disease mortality rates are stagnant rather than in decline, particularly amongst younger females (115).

2.4.2 Job strain and cardiovascular disease

Previous research indicates that there is an association between job strain and CVD for both males and females (5). Yet it remains unknown whether there are sex differences in the association between job strain and CVD with some studies stronger associations for males and others for females. In a Canadian study, it was observed that amongst a large sample of men and women with white-collar jobs, job strain was more strongly associated with an increase in hypertension over approximately 7.5 years in men (RR=1.33, 95% CI: 1.01 – 1.76) than in women (RR =1.15, 95% CI: 0.93 – 1.41) (116). In contrast, a Swedish study of employed individuals observed that females with job strain reported an increased prevalence of hypertension compared to males with job strain (70). Findings from the INTERHEART study suggest a stronger association between work stress and acute myocardial infarction for males (15) whereas another study found a stronger association between job strain and cardiovascular events in females (RR=6.66, 95% CI: 0.93-47.70) than in males (RR = 1.75, 95% CI: 0.49-6.29).

2.4.3 Depression and cardiovascular disease

A greater prevalence of depression in females is consistently reported across cultures (17, 117), with women approximately twice as likely as men to be diagnosed with depression (118). Social, cultural, and biological factors have been proposed to underlie this difference (119). Additionally, several studies have demonstrated that the co-occurrence of depression and CVD is more common in females than males. Female coronary artery disease (CAD) patients experience higher levels of depression than men (120) and depression is associated with a greater incidence of CAD in women (18, 121). Numerous biological and psychosocial mechanisms have been proposed in attempt to explain this higher comorbidity of depression and CVD in females. Some elements of metabolic syndrome such as diabetes, low HDL cholesterol, and high triglycerides may contribute more to women than men's CVD risk (122). Greater exposure to chronic stressors, interpersonal stress responsiveness, and internalized coping styles are also said to be implicated operating via cardiovascular, endocrinological, and immunological activity (123).

2.4.4. Job strain and depression

As previously mentioned, there may be some overlap in symptomatology for job strain and depressive symptoms and this might vary according to sex. A study utilizing population attributable risk methods to estimate the proportion of depression attributable to job strain found that the proportion of depression attributable to job strain is higher in females (17.2%) than in males (13.2%). However, this was not examined within the context of CVD (124). There is a lack of studies that investigate the association between job strain and CVD controlling for depressive symptoms in both sexes. Previous studies that controlled for depression in investigation of the association between job strain and CVD incidence, were limited with one study assessing this association in females only (104). Another study measured heart disease incidence using self-reported heart disease as a measure of incident heart disease (7, 13).

2.5 Occupational skill level

2.5.1 Inverse social gradient in cardiovascular disease

Findings from previous studies investigating risk factors for CVD indicate an inverse social gradient i.e. low socio-economic status is associated with an increased risk for CVD (125) (19). This appears to be in some part due to an increased prevalence of CVD risk factors (e.g. poor diet and obesity) in people of lower socio-economic status(126). Both occupation type and educational attainment are strong indices of socio-economic difference and lower levels of both factors have demonstrated associations with increased CVD risk respectively (20, 21). Occupation type refers to the different type of jobs that individuals are employed in often classified by sector e.g. farming, fishing and forestry, and business and financial operations (127). Results from a Canadian study exploring heart disease and occupational risk factors exhibited a trend toward an association between heart disease and occupation type classified by sector (128). However this study did not elucidate the mechanisms that may underpin the association between occupational type and CVD such as stress or job strain.

2.5.2 National Occupation Classification (NOC)

Both education and occupational type been considered in relation to CVD separately. In addition, these two factors have also been assessed together (occupational skill level) - a Canadian study investigating cause specific mortality by skill level used the NOC to measure occupational skill level with each occupation assigned to one of the following categories according largely to the education/skill level associated with each occupation type: (i) professional; (ii) managerial; (iii) skilled/technical/supervisory; (iv) semi-skilled; or (v) unskilled. Results demonstrated that the risk of mortality by heart disease was highest in those with unskilled jobs, followed by semi- skilled, skilled/technical/supervisory, and managerial, compared to those in professional jobs (129). A more recent version of the NOC was developed in 2011. Similar to the NOC 1990 classification this system groups jobs together based on educational qualification and/or skill level required. There are five categories (A, B, C, D, 0). The "0" category refers to management jobs, such as restaurant managers, mine managers, shore captains (fishing). The "A" category refers to professional jobs that usually call for a degree from a university, such as: doctors, dentists, architects. The "B" category refers to technical jobs and skilled trades that usually call for a college diploma or training as an apprentice, such as: chefs, plumbers, electricians. The "C" category refers to intermediate jobs that usually call for high school and/or job-specific training, such as: industrial butchers, long-haul truck drivers, and food and beverage servers. The "D" category refers to labour jobs that usually give on-the-job training, such as: fruit pickers, cleaning staff, oil field workers (23).

2.5.3 Occupational skill level and job strain

The association between job strain and CVD may differ according to occupational skill level. A previous study assessed the association between job strain and coronary heart disease with the analysis stratified for occupational type classified by sector. Results found an association between high job strain in manual and non-manual workers, however, there was no association for managers and proprietors (22). Other studies have assessed the association between job strain and CVD risk factors in specific occupational groups (130, 131), yet overall there appears to be a dearth of research studies that consider the role of occupational skill level within the association between job strain and heart disease incidence.

3 MANUSCRIPT 1: Job strain, depressive symptoms, and cardiovascular disease risk score: a cross-sectional analysis from a population based study

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Key words: job strain, cardiovascular disease, depression, work, Framingham Risk Score

3.1 Abstract

Objective: Job strain (high psychological demands and low decision control) has been associated with cardiovascular disease (CVD). It is unclear if job strain is associated with CVD risk score independently of depression, an established risk factor for CVD. This study investigated whether there is an association between job strain and CVD risk score, when depressive symptoms are controlled for. Sex differences were examined.

Methods: Data came from the CARTaGENE study, a community health survey of adults in Québec, Canada (n=7,848). Participants were working adults aged 40 to 69 years. CVD risk was estimated using the Framingham Risk Score. Job strain was measured as the ratio of job demands to control using questions from the Job Content Questionnaire. Depressive symptoms were assessed using the Patient Health Questionnaire. Regression analyses were conducted to examine the association between job strain and CVD risk score, controlling for depressive symptoms.

Results: High levels of job strain were reported in approximately 21% of participants, high Framingham Risk Score was observed in approximately 9%. Job strain was significantly associated with the Framingham Risk Score ($B = 0.73$, $p < 0.001$, adjusted for age, sex, and education) and controlling for depressive symptoms did not significantly change the association ($B= 0.59$, $p < 0.001$).

Conclusion: Results suggest job strain is associated with CVD risk score and that this association is not significantly explained by depressive symptoms. Job strain is independently associated with CVD risk score, controlling for depressive symptoms.

Key words: job strain, cardiovascular disease, depression, work, Framingham Risk Score

3.2 Introduction

Cardiovascular disease (CVD) is the primary cause of death globally (132) and a leading cause of death in Canada (133). Job strain, characterized by the joint effects of demands at work (heavy workload, fast working pace) and the range of decision making freedom (control) available to the worker facing those demands (4) is a form of psychosocial occupational stress that is associated with CVD. Work stress has been demonstrated to be associated with incident CVD (5) and CVD risk as indexed by the Framingham Risk Score (134). However, there remains some inconsistency regarding the strength of the relationship between job strain and CVD with some previous studies not reporting a positive association (74, 135). It is therefore necessary to gain an understanding of the risk factors that may determine this association. The majority of previous research that examines the association between job strain and CVD has adjusted for socioeconomic status, lifestyle, and other conventional risk factors. A greater understanding of non-conventional risk factors may help to understand the conditions under which the association between job strain and CVD does and does not take place (76).

Depression has been demonstrated to be an independent psychosocial risk factor for CVD (11, 75) and may play an important role in the association between job strain and CVD: job strain and depression appear to be interrelated as job strain has been associated with increased risk of major depressive disorder (9, 95). There is thus potential overlap between the constructs of depression and job strain. However, the association between job strain and CVD that is independent of overlap with depression has yet to be examined. It remains unclear whether the association between job strain and CVD takes place independently of depressive symptoms.

Cross-sectional associations between job strain and lifestyle risk factors such as physical inactivity and alcohol intake have been reported (82, 136). A previous meta-analysis investigated the association of job strain with CVD risk factors as indexed by the Framingham Risk Score. The Framingham Risk Score is a commonly used indicator of CVD risk which has previously been used to investigate job strain (134) and depressive symptoms as potential associated factors (137). However, to our knowledge no previous study has estimated the association between job strain and CVD risk (as indexed by the Framingham Risk Score) controlling for depressive symptoms.

There is a greater prevalence of depression in females than males (17) and there is a higher comorbidity of depression and CVD in females (123). A study that used population attributable risk methods found that the proportion of depression attributable to job strain is higher in females (17.2%) than in males (13.2%) (124). Higher levels of depression have also been observed in females who reported higher levels of job strain (138). However one meta-analysis found that there was no differential gender effect of adverse job conditions on depressive symptoms (139). A systematic review of gender inequalities in occupational health suggested that women had poorer self-perceived mental health than men (140). Thus previous studies have sought to understand potential sex differences in the relationship between job strain and depression; however this has yet to be understood within the context of CVD. It remains unknown whether there are sex differences in the association between job strain and CVD, controlling for depressive symptoms.

The relationship between job strain and depression has been examined, with higher job strain being associated with an increased risk of developing depression, and both factors separately have been associated with an increased CVD risk score. However, to our knowledge, no other previous study has considered these two factors together in relation to CVD risk score. The primary objective of the present study was to estimate the cross sectional association between baseline job strain and CVD risk score, controlling for depressive symptoms. It was expected that controlling for baseline depressive symptoms would explain a significant amount of the association between job strain and CVD risk score. The second objective was to investigate the interaction between job strain and depressive symptoms in the association with CVD risk score. The final objective was to examine potential sex differences within the association between job strain, depressive symptoms, and CVD risk score.

3.3 Methods

3.3.1 Study Sample

Cross-sectional data were from the CARTaGENE study, a community health survey of adults in Québec conducted in 2009-2010 (Phase A, n= 20,004). Details of the survey methods and sampling results have previously been published (141). Subjects were randomly selected from the public health insurance database in Québec (Régie de l'Assurance Maladie de Québec). The age range of participants was between 40 and 69 years (142). For the present study we included participants who were working part-time or full-time and who had no heart disease at baseline (n=4,764 males and n=5,070 females). All variables used for the current analysis were measured at baseline only.

3.3.2 Measures

Job Strain

Job strain was operationalized using a ratio of job demands to job control. Measures of demands and control were derived from the Job Contents Questionnaire (4) which has been shown to be a reliable measure of psychosocial job characteristics. For the current study, a ten item version of the scale was chosen based on shortened versions of the Job Content Questionnaire (143) that has demonstrable reliability and validity (66), and has been previously used in demographic samples similar to that in the current study (144). The French version of this scale has also been validated (145). Job demands was assessed with five questions dealing with work pace, workload, time-pressure, conflicting demands, and effort: My job requires working very fast; I am asked to do an excessive amount of work; I have enough time to get the job done; I receive conflicting demands from others; My job requires working very hard; (α = 0.75). Decision latitude or job control was assessed with five questions dealing with learning new things, skill level, task repetitiveness, independent decision-making, and participation in planning the work: *My job requires that I learn new things*; *My job requires a high level of skill*; *My job involves a lot of repetitive work*; *I have a lot of say about what happens on my job*; *On my job, I have the freedom to decide how I do my work*; (α = 0.68). Responses were coded from 1 (Strongly disagree) to 4 (Strongly agree) and a summary score was computed for both scales to compute the final measure for job strain derived by the ratio of job demands to decision control. High scores indicate a greater imbalance between the summary scores for demands and control (demands are much greater than control). A low score indicates less of an imbalance (demands are not much greater than control and vice versa).

Depressive Symptoms

Depressive symptoms experienced over the past two weeks were assessed with the 9-item Patient Health Questionnaire (PHQ-9). Items are rated on a 4-point scale ranging from 0 *"not at* *all"* to 3 *"nearly every day".* The PHQ-9 has good validity and reliability (146) and has shown good agreement with clinical diagnosis of major depressive disorder (90). The internal consistency for the current sample was $\alpha = 0.80$. In the present study, moderate to severe depressive symptoms were indicated by a score of ≥10 (91). The summary score was a continuous score ranging from 0 to 27.

CVD risk score

CVD risk score was measured using the Framingham Risk Score, a sex specific algorithm that combines age, total and HDL cholesterol, smoking status, and systolic blood pressure to estimate the 10 year CVD risk of an individual (40). The measure has demonstrated good validity and reliability (147). The methods used to measure the variables included in the Framingham Risk Score have been described elsewhere (141). "High" overall CVD risk score was defined as a Framingham Risk Score of 20% or higher. The measure has shown good accuracy in predicting CVD risk amongst men and women (148).

Covariates

Alcohol consumption was measured by response to the following question: "*About how often during the past 12 months did you drink alcohol?*" Responses were recoded to derive a binary categorical variable indicating daily or non- daily alcohol consumption. Information was on physical activity was only available for 82% of the sample, therefore missing values were imputed for physical activity using SPSS.

3.3.3 Data analysis

Primary analysis consisted of multiple linear regression to investigate: 1) the association between job strain and Framingham Risk Score and 2) whether the strength of this association changed when depressive symptoms were included in the model. In model 1, the association between job strain (continuous) and Framingham Risk Score (continuous) was modelled adjusting for age, sex, and education. In model 2, PHQ-9 summary score was additionally included as a covariate. In model 3, physical activity and alcohol consumption were adjusted for. An interaction term for job strain by PHQ-9 summary score was entered in the regression model in addition to covariates in order to assess the interaction between job strain and depressive symptoms and its association with CVD risk score. The interaction term job strain by PHQ-9 summary score was derived from the product of centred job strain ratio and centred PHQ-9 summary score variables. In addition to regression coefficients, adjusted R^2 values are reported as a measure of effect size reflecting the proportion of variance explained in the outcome (Framingham Risk Score) by each model. All analyses were stratified by sex in a second step. Analyses were conducted using SPSS software.

3.4 Results

The CARTaGENE sample included 9,834 working individuals. A total of 7,848 individuals had complete information on job strain and CVD risk (49.5% female; mean age of 50.2, SD = 6.0). High job strain was reported in 21.2% of the sample (n =1666, 24.7% of females and 17.8% of males). PHQ-9 score ≥10 was reported in 3.9% of participants (n=303, 3.1% of males and 4.6% of females). The proportion of participants who scored “high” on the Framingham Risk Score was 8.5% with a greater proportion of males (15.8%) than females (1.0%) categorized as being at high CVD risk. No significant sex differences were observed with respect to smoking status, alcohol consumption, or physical activity. The sample consisted predominantly of ethnically white (88.3%) and highly educated participants, with 81.6% of the sample having attained a college degree or higher. Sociodemographic and clinical characteristics of the sample are presented in Table 1. There was a positive correlation between job strain and PHQ-9 summary score ($r = 0.27$, $p < 0.01$). Characteristics of the sample according to Framingham Risk category are presented in Table 2.

Multiple Linear Regression

Results of the multiple linear regression models are presented in Table 3. Job strain was significantly associated with Framingham Risk Score ($B = 0.73$, $p < 0.001$, adjusted $R^2 = 0.50$). There was not a significant change in the association between job strain and the Framingham Risk Score when depressive symptoms were entered into the model ($B = 0.59$, $p < 0.001$, adjusted $R^2 = 0.50$), as indicated by a less than 10% change in the adjusted R^2 value. Adjustment for physical activity and alcohol consumption resulted in a 1% increase in adjusted R^2 (0.51), and a slight attenuation of the association between both job strain and Framingham Risk Score ($B = 0.57$, $p < 0.05$) and the association between PHQ-9 score and Framingham Risk Score ($B = 0.04$, $p < 0.05$).

Job strain was significantly associated with Framingham Risk Score for males ($B = 1.17$, $p < 0.01$) and females ($B = 0.52$, $p < 0.05$). Similarly, there was not a significant change in these associations when depressive symptoms were entered in model 2 ($B = 0.91$, $p < 0.05$ and $B = 0.40$, $p = 0.54$ respectively) indicated by a change in adjusted R^2 value that was less than 10% for either sex (from 0.368 to 0.369 in males and from 0.253 to 0.254 in females). When physical activity and alcohol consumption were adjusted for in the female sample, the association between job strain and Framingham Risk Score was weakened ($B = 0.35$, $p = 0.10$, adjusted $R^2 =$

0.259), and there was no significant change in the association between PHQ-9 score and Framingham Risk Score. There was no significant change in association between either job strain or PHQ-9 score and Framingham Risk Score when physical activity and alcohol were controlled for in the male sample.

Interaction Models

The interaction term for job strain by depressive symptoms was not significantly associated with Framingham Risk Score when controlling for age, sex, and education (B=0.05, p=0.214). Similar results were found for males and females (B=0.05, p =0.499, and B=0.03, p=0.408, respectively).

3.5 Discussion

In this cross-sectional study, there was an association between job strain and CVD risk score, independent of depressive symptoms. Models adjusted for age, sex, and education suggested a significant linear association between job strain and CVD risk score in the full sample, and separately for males and females in age and education adjusted models. Controlling for depressive symptoms in model 2 did not result in a significant change in association between job strain and CVD risk score in either sex. There was not a significant interaction effect between job strain and PHQ-9 on CVD risk score, indicating that the association of job strain and CVD risk score does not depend on depressive symptoms.

The results of the current analysis were consistent with previous studies that also found an association between job strain and Framingham Risk Score (134). Previous studies had looked CVD risk score associations between job strain and depressive symptoms separately (134, 137). The current population based study provides an estimate of the cross-sectional association between job strain and CVD risk score that it is independent of depressive symptoms for either sex, thus helping to understand job strain as an independent predictor of CVD risk score.

By controlling for PHQ-9 summary score, the current study minimized the variability in CVD risk score which could have been attributed to depression, a known risk factor for CVD. Although a significant association between job strain and CVD risk score was observed independently of depressive symptoms, significant associations between PHQ-9 score and Framingham Risk Score were observed in the results of the multiple linear regression analyses (model 2) for all samples. This iterates depressive symptoms as an important correlate of CVD risk score.

There were no sex differences in the association between job strain, depressive symptoms, and CVD risk score for either sex. A significantly higher Framingham Risk Score in males with depressive symptoms has been reported (137). However no previous study had provided information about potential sex differences in how *both* job strain and depressive symptoms are associated with CVD risk score.

Both job strain and depressive symptoms appear to be associated with CVD risk score; however the two factors may relate to CVD outcomes in different ways. Lifestyle and behavioural factors (e.g. reduced activity) may be more implicated within the depression-CVD risk score association (149), whereas the job strain-CVD risk score association might be more subject to acute stress response processes (3, 150). Optimal CVD risk assessment requires acknowledgement of disparate elements of job strain and depressive symptoms and consequently, how they may relate to CVD risk score in different ways.

The cross-sectional findings reported in this paper are important in so far as they provide information about the association between job strain and 10 year CVD risk estimation in a population who were working at the time of baseline measurement. The current study provides an alternative means of assessing CVD risk to longitudinal methods where participants can be subject to termination and/or change of employment.

3.5.1 Strengths and Limitations

The current study utilized a large working sample with no CVD reducing the chance of confounding due to existing CVD. Numerous studies have previously examined job strain and depressive symptoms separately as risk factors for CVD score. To our knowledge, no previous study has investigated how these factors, taken together, are associated with CVD risk score. The results of the current study help to differentiate two related risk factors for CVD.

The results of the current study must be interpreted with certain limitations. Measures of job strain and depressive symptoms were via self-report. Although PHQ-9 score was controlled for, the negative cognitive bias often present in cases of depression may influence how an individual perceives stress experienced at work (151). However, high psychological job demands have been shown to be associated with a twofold increased risk of major depression even when negative affectivity was controlled for (152). This was a middle-aged sample so the results are not adaptable to younger workers. This was a relatively homogenous, overall highly educated, and largely ethnically white sample. Type of job was not controlled for in the current analysis, e.g. physical labour vs administrative work. Cases of severe depression may not have been fully accounted for in the current relatively healthy working sample. The cross-sectional design of this study does not permit causal conclusions to be made about job strain, depressive symptoms, and CVD.

3.5.2 Conclusion

The results of the current study found that job strain was associated with CVD risk score in both males and females and that controlling for depressive symptoms did not significantly change this association. Optimal estimation of CVD risk should consider both job strain and depressive symptoms and how these factors may relate to CVD.

3.6. Tables

TABLE 1 Sample characteristics stratified by sex

Sample characteristics	Full sample (n=7,848)	Males (n=3,965)	Females (n=3,883)
Age, Mean (SD)	50.5 (6.0)	50.5 (6.2)	50.5 (5.8)
Education, %			
Less than high school	0.5	0.6	0.4
High school	17.7	18.0	17.4
College/University/Graduate Studies	81.6	81.1	81.9
Ethnicity, %			
White	88.3	86.7	90.0
Smoking status, %			
Current smoker	17.3	18.6	15.9
Former smoker	37.4	36.3	38.6
Never smoker	45.1	44.9	45.3
Alcohol Consumption, %			9.0
Daily	11.5	13.9	
Days of activity, %			
No physical activity	16.0	12.9	19.1
HDL cholesterol (mmol/L), Mean (SD)	48.9 (16.5)	41.6 (12.7)	56.4 (16.5)
Total cholesterol (mmol/L), Mean (SD)	200.5 (37.4)	199.4 (39.2)	201.7 (35.5)
Systolic blood pressure, Mean (SD)	122.2 (14.9)	127.1 (13.7)	117.1 (14.4)
Diastolic blood pressure, Mean (SD)	74.0 (10.1)	76.2 (10.0)	71.8 (9.8)

Job strain ratio, n (%)			
High strain	1666 (21.2)	705 (17.8)	961 (24.7)
Framingham Risk Categories, %			
Low risk	70.4	51.2	89.9
Intermediate risk	21.1	32.9	9.1
High risk	8.5	15.8	1.0
PHQ-9 summary score, Mean (SD)	2.5 (3.2)	2.3 (3.3)	2.8 (3.3)
Elevated symptoms (PHQ-9 ≥ 10), %	3.9	3.1	4.6

TABLE 2 Sample characteristics stratified by Framingham Risk Categories

	Low risk (n=5,522)	**Intermediate risk (n=1,659)**	**High risk (n=667)**
Age, Mean (SD)	49.0 (5.3)	53.2 (5.9)	56.8 (5.9)
Sex %			
Women	63.2	21.3	6.0
Education, %			
Less than high school	0.3	0.6	1.8
High school	15.4	22.7	24.1
College/University/Graduate Studies	84.1	76.4	73.6
Ethnicity, %			
White	88.3	88.2	89.1
Smoking status, %			
Current smoker	10.9	26.4	47.3
Former smoker	38.2	38.5	28.9
Never smoker	50.8	34.9	23.4
Alcohol Consumption, %			
Daily	9.7	14.5	18.4
Days of activity, %			
No physical activity	15.7	16.4	17.1
HDL cholesterol (mmol/L), Mean (SD)	52.5 (16.5)	41.6 (13.5)	37.5 (11.5)
Total cholesterol (mmol/L), Mean (SD)	197.1 (34.4)	207.7 (41.5)	211.0 (45.9)

Systolic blood pressure, Mean (SD)	117.2 (12.2)	131.6 (13.0)	139.7 (15.1)
Diastolic blood pressure, Mean (SD)	71.5 (9.2)	78.8 (9.7)	82.2 (10.1)
Job strain ratio, n (%)			
High strain	1240 (22.5)	311(18.7)	115 (17.2)
PHQ-9 summary score, Mean (SD)	2.6 (3.10)	2.5 (3.5)	2.3 (3.2)
Elevated symptoms (PHQ-9 ≥ 10), %	3.8	4.3	3.4

TABLE 3 Results of multiple linear regression analyses for the association between job strain and Framingham Risk Score

	Model 1				Model 2				Model 3			
	B (95% CI)	β	p	R^2 adj	B (95% CI)	β	p	R2 adj	**B (95% CI)**	**β**	**p**	**R^2 adj**
Job strain	0.73 (0.30, 1.16)	0.03	<0.001	0.503	0.59 (0.14, 1.03)	0.02	<0.001	0.503	0.57 (0.12, 1.03)	-0.021	0.014	0.508
Age	0.53 (0.51, 0.54)	0.46	<0.001		0.53 (0.51, 0.54)	0.46	<0.001		0.53 (0.51, 0.54)	0.46	<0.001	
Sex	-7.45 (-7.67, -7.23)	-0.54	<0.001		-7.47 (-7.69, 7.25)	-0.54	<0.001		-7.61 (-7.84, -7.39)	-0.078	<0.001	
Education	-0.59 (-0.70, -0.48)	-0.09	<0.001		-0.58 (-0.69, -0.47)	-0.08	<0.001		-0.55 (-0.66, -0.43)	-0.021	<0.01	
PHQ-9					0.05 (0.01, 0.08)	0.02	<0.05		0.04 (0.01, 0.08)	0.019	<0.05	
Physical activity									0.59 (0.28, 0.89)	0.031	<0.001	
Alcohol									-0.10 (-0.16, -0.05)	-0.029	<0.001	

Model 1 = adjusted for baseline age, sex, education; model 2 = adjusted for PHQ-9 summary score; model 3 = adjusted for physical activity and alcohol consumption

4. Bridge

The first manuscript describes the cross-sectional association between job strain and CVD risk as indexed by the Framingham Risk Score, controlling for depressive symptoms. Results from this study indicate an association between job strain and Framingham Risk Score, independent of depressive symptoms in overall, male, and female samples. This finding provides an estimate of CVD risk in working participants at one time point. Although the Framingham Risk measure is a widely utilized measure that demonstrates good predictive accuracy for CVD risk amongst males and females, it provides an estimate of the *10 year risk of CVD* only (153). Not everybody with a high risk score will develop CVD. In order to assess the risk for the *development* of CVD, longitudinal data is necessary.

The second manuscript differs from the first in a number of ways. Firstly, the second manuscript assessed the prospective association between job strain and incident heart disease by linking survey data with longitudinal data whereas the first manuscript assessed the cross-sectional association between job strain and CVD risk score using cross-sectional data only.

Secondly, the outcome in the second manuscript refers to heart disease only whereas the outcome in the first manuscript refers to cardiovascular disease generally, as indexed by a risk measure (Framingham Risk Score). Heart disease refers to one subgroup of CVD only. The Framingham Risk Score, which estimates the risk for all forms of CVD including conditions of cerebral circulation the blood vessels such as stroke and cerebrovascular disease, as well as heart disease. Thus the outcome measure in the first manuscript involved a more global measure of CVD than that in the second manuscript which involved a more focused measure of a specific CVD condition (heart disease).

Thirdly, the first manuscript assessed a single occupational factor "job strain" and its association with CVD, whereas an analysis included in the second manuscript assessed two occupational factors - job strain and occupation skill level and their association with CVD. Thus one component of the second manuscript involves a wider assessment of occupational factors in relation to CVD than that in the first manuscript.

5. MANUSCRIPT 2: Job strain and the incidence of heart diseases: a prospective community study

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5.1 Abstract

Background: Job strain (high psychological demands and low decision control) is associated with cardiovascular diseases, however it remains unclear if the associations are explained by depressive symptoms, and whether there are sex differences. The aim of the present study was to evaluate the association between job strain and heart diseases in a middle-aged population-based cohort.

Methods: Baseline data were from CARTaGENE, a community survey of adults aged 40-60 years in Quebec, Canada. Heart diseases incidence was examined in 8,073 individuals by linking survey data with administrative data. Cox regression models were used to examine the association between job strain and heart disease, adjusting for sociodemographic characteristics, behavioral and clinical factors, and depressive symptoms.

Results: In total, 557 (6.9%) participants developed heart diseases over an average follow-up of 6.6 years. Job strain was associated with an increased risk of heart diseases in women (adjusted HR = 1.63, 95% CI 1.02-2.64) after controlling for depressive symptoms, behavioral and clinical factors. There was no overall association between job strain and heart diseases in men (adjusted HR = 0.96, 95% CI 0.62-1.49); an association was observed only in men aged 50 years and older. Incidence of heart diseases and high job strain was highest in those with labour jobs, and lowest in those with professional jobs.

Conclusion: Job strain was associated with an increased risk of heart diseases in middle-aged women and in men aged 50 years and older. This association was not accounted for by depressive symptoms or sociodemographic, clinical, and behavioral factors.

5.2 Introduction

Heart diseases are the number one cause of death globally (154) and among the primary causes of death in Canada (155). Job strain, characterized by the joint effects of demands at work (e.g. heavy workload, fast working pace) and job control (i.e. decision-making freedom) available to the worker facing those demands (4), is a form of psychosocial occupational stress. Previous research indicates an overall association between job strain and cardiovascular diseases (CVD) (5); however, the association remains inconsistent: in a review of prospective studies of work stress and coronary heart diseases (CHD), 9 out of 19 studies did not observe an association between high job strain and incident CVD (76). Several methodological factors might explain the heterogeneity in results, including study design, sample characteristics, and outcome measures. For example, many studies have used self-report measures for the incidence of CVD (7, 14, 73, 74). Self-report data has been demonstrated to be less accurate in identifying heart diseases than administrative data (13). Individuals who develop a severe cardiovascular condition might be less likely to participate in a follow-up survey, resulting in a risk of selection bias. Furthermore, individuals with high level of job strain and chronic stress might be more likely to report physical symptoms such as chest pain and tightness, which might be unrelated to CVD (76).

The role of depression in the association between job strain and the incidence of CVD is also not clear. Job strain and depression are closely linked – job strain has been associated with depressive symptoms (156) and chronic stress at work has been associated with an elevated risk of major depressive disorders (9). Depression is an established risk factor for heart diseases (11) and it is possible that the observed association between job strain and CV may be attributable to underlying psychological problems like depression. Only one out of the 19 studies included in the review by Sara et al. (76) controlled for depressive symptoms, and this study consisted of a female only sample (104).

Furthermore, there might be different associations between job strain, depression, and heart diseases between men and women. Men are more likely to develop CVD than women (157), but a higher prevalence of depression is typically found in women (17). Depression is also associated with a greater incidence of CAD in women (18). A Swedish study found that women reported higher levels of job strain than men, although job strain was as strongly related to depressive symptoms among men as among women (158). It is therefore important to gain a better understanding of potential sex-specific differences in the association between job strain, depression and onset of CVD.

There is also existing evidence for an inverse social gradient in CVD (125), that is, lower socio-economic status carries greater risk for heart disease. Employment grade and educational attainment are strong indices of socio-economic difference, and lower levels of both factors have been associated with greater CVD incidence respectively (20, 21). Thus, consideration of occupational grade according to skill level may help to provide a better understanding of the association between job strain and heart disease. The skill required for different occupations may influence job demands and control, and consequently, the association between job strain and heart disease. The association between job strain and heart diseases may differ according to occupational skill level, however, this has yet to be investigated, especially in Canadian samples.

The objectives of the current study were: (i) to investigate the association between job strain and heart diseases for men and women; (ii) evaluate if the associations remain after controlling for depressive symptoms and other behavioral, clinical, and sociodemographic risk factors; (iii) to explore the interaction between job strain and occupational skill level and its association with heart diseases in a sub-sample.

5.3 Methods

5.3.1 Study Sample

Baseline data were from the CARTaGENE cohort study (2009-2010, https://cartagene.qc.ca/), a population-based health survey of residents in Quebec, Canada, (Phase A, *n* = 20,004). Participants were recruited from the public health insurance database in Quebec, the *Régie de l'Assurance Maladie du Quebec* (RAMQ) (159) (aged 40-69 years at baseline). Follow-up data referring to heart diseases were obtained by linking CARTaGENE participants with diagnostic codes from the RAMQ billing database (160). This study was approved by the Douglas Mental Health University Institute Research Ethics Board and the St. Justine Hospital Research Ethics. Only participants aged 40 to 60 years who were working part-time or full-time were included. Participants with self-reported heart diseases at baseline were excluded based on a positive response to any of the following three questions: 'Has a doctor ever told you that you have had a myocardial infarction or a heart attack? Has a doctor ever told you that you had angina? Has a doctor ever told you that you have had a stroke?'

The final sample for the current study was n = 8,073 (Figure 2).

5.3.2 Measures

Job strain was measured using the Job Contents Questionnaire (4). A ten item version of the scale was chosen based on shortened versions (161) with demonstrated reliability and validity (66) in demographic samples similar to that in the current study (144). The scale has been validated and demonstrates sound psychometric properties (145). The scale assesses job demands and job control.

Job demands was measured with 5 questions dealing with work pace, workload, time-pressure, conflicting demands, and effort: *"My job requires working very fast"* ; *"I am asked to do an excessive amount of work"*; *"I have enough time to get the job done"*; "*I receive conflicting demands from others*"; "*My job requires working very hard"*, ($\alpha = 0.75$) .

Job control was measured with 5 questions dealing with learning new things, skill level, task repetitiveness, independent decision-making, and participation in planning the work: "*My job requires that I learn new things*"; "*My job requires a high level of skill*"; "*My job involves a lot of repetitive work*"; "*I have a lot of say about what happens on my job*"; "*On my job, I have the freedom to decide how I do my work*" ($\alpha = 0.68$).

Responses to questions on job demands and control were coded from 1 (Strongly disagree) to 4 (Strongly agree) and a summary score was computed for both scales to build a continuous job strain ratio variable whose value was derived by the ratio of job demands to job control (162). High scores indicate a greater imbalance between the summary scores for demands and control (demands are much greater than control). A categorical job strain variable was computed based on the values of the job strain ratio variable with a value ≥ 1.00 categorized as "high job strain" and a value < 1.00 categorized as "low job strain".

Depressive symptoms experienced in the past two weeks were assessed with the Patient Health Questionnaire (PHQ-9). Items are rated on a 4-point scale ranging from 0 "*not at all*" to 3 "*nearly every day*". The PHQ-9 has demonstrated validity reliability (146), good agreement with clinical diagnosis of major depressive disorder (90), and showed good internal consistency in our sample (α = 0.80).

Heart diseases were assessed using diagnostic codes for coronary heart disease or heart failure in the RAMQ billing database (ICD-9 codes 410 [acute myocardial infarction], 411 [other acute and subacute forms of ischemic heart disease], 413 [angina pectoris], 414 [other acute and subacute forms of ischemic heart disease], and 428 [heart failure] or ICD-10 codes I21 [acute myocardial infarction] and I23 [hemopericardium as current complication following acute myocardial infarction]) (160). First diagnosis or hospital admission was recorded.

Sociodemographic characteristics (age, sex, ethnicity, and education) were included as covariates in addition to variables known a priori to be associated with heart diseases including smoking, alcohol consumption, physical activity (behavioural factors) and HDL cholesterol, blood pressure, and diabetes status (biological factors) (163, 164) . Education was defined as: "less than high school"; "high school"; "college/graduate studies/ university". Self-reported smoking status was defined as: "daily smoker"; "occasional smoker"; "former smoker"; "never smoker". Self-reported alcohol consumption was based on a response to the following question "About how often during the past 12 months did you drink alcohol?". Physical activity was measured by asking participants how many days in the last week they engaged in moderate/vigorous activity. Assessment of diabetes status and high blood pressure was via self-report or diagnosis from a health professional. Abnormal cholesterol was defined as low levels of high-density lipoprotein (< 1.03 mmol/l in men and < 1.30 mmol/l in women) or self-reported cholesterol problems ("*Has a doctor ever told you that your blood cholesterol was high?*") for those participants with missing blood samples.

The proportion of missing values for the covariates described above was generally low (<6%), with one exception: information on physical activity was only available for 82% of the participants. We therefore imputed missing values for physical activity using the PROC MI procedure in SAS.

Occupational skill level was measured using the National Occupation Classification (NOC) codes (2011) for current jobs. Each job category (A, B, C, D, 0) is differentiated by the level of qualification or skill required for the job: "0" are management jobs, e.g. restaurant managers. "A" are professional jobs requiring a university degree, e.g. doctor. "B" are technical jobs and skilled trades requiring a college diploma or training as an apprentice, e.g. chefs. "C" are intermediate jobs requiring high school and/or job-specific training, e.g. butchers. "D" are labour jobs that give on-the-job training, e.g. fruit pickers (165). Information on job categories was available in about 70% of the sample.

5.3.3 Data analysis

Cox proportional hazards regression models were used to examine the association between job strain (continuous ratio variable) and heart diseases adjusted for age, sex, education, and ethnicity (model 1). In a next step (model 2), depressive symptoms were adjusted for. Further adjustments for smoking status, alcohol consumption, physical activity, cholesterol, diabetes, and blood pressure were made (model 3). Analyses were conducted using SPSS and SAS software. Hazard ratios (HR) with 95% confidence intervals are reported. Person-years were calculated using the date of the CARTaGENE baseline interview to the first date of diagnosis of a heart disease, death (any cause), or the end of the follow up period.

5.4 Results

In total, 8,073 individuals (4014 men and 4059 women) were followed for a total of 53,120 person-years. There were 557 (6.9%) incident cases of heart diseases (8.5% in men and 5.3% in women) over a mean follow-up period of 6.58 (SD = 1.70) years. High job strain was reported in 21.8% of the sample (18.2% in men and 25.4% in women) and a high level of depressive symptoms (PHQ-9 score ≥ 10) in 4% of the sample (3.2 % in men and 4.7% in women). The correlation between job strain and depressive symptoms was 0.27. Sociodemographic and clinical characteristics of participants are presented in Table 1.

Table 2 describes the HRs for women. The HR for job strain was 1.96 (95% CI 1.27-3.10) when adjusted for age, education and ethnicity (model 1), 1.63 (95% CI 1.03-2.56) when additionally adjusted for depressive symptoms (model 2), and 1.63 (95% CI 1.02-2.60) when additionally adjusted for depressive symptoms and other behavioral and clinical factors (model 3). Depressive symptoms (PHQ-9) were associated with an increased risk of heart diseases.

Table 3 describes the HRs for men (n = 4,014). The HR's for job strain were much lower for men compared to women. When adjusted for depressive symptoms and behavioral and clinical factors, the HR was close to 1. Depressive symptoms were associated with the incidence of heart diseases.

We found no interaction between job strain and depressive symptoms, neither for men nor for women. A significant interaction between age and job strain was observed for men in exploratory analyses (p = 0.02): the adjusted HR for job strain for men aged 50 years and older was 1.72 (95% CI 1.05, 2.82) while the adjusted HR for job strain for men younger than 50 years was 0.58 (95% CI 0.27, 1.25).

In the sub-analysis (Table 4), incident heart diseases were highest in men with labour jobs (category D) and in women with management jobs (category 0). High job strain was reported most often in those with labour jobs (category D). Occupational skill level was only weakly associated with the incidence of heart diseases in age-adjusted models in men: using the professional job category (A) as the reference, adjusted HRs for men were 1.28 (95% CI 0.87-1.87) for category B, 1.50 (95% CI 0.97-2.31) for category C, 1.43 (95% CI 0.72-2.82) for category D, and 0.89 (95% CI 0.54-1.47). Adjusted HRs for women were 1.02 (95% CI 0.65-1.59), 1.02 (95% CI 0.63-1.64), 1.09 (95% CI 0.39-3.04) and 1.17 (95% CI 0.66-2.10) for categories B, C, D and 0, respectively. There were no statistically significant interactions between job strain and job categories on the incidence of heart diseases when job strain and interaction terms were added into the models (all interaction terms: $p > 0.1$).

5.5 Discussion

This prospective community cohort study from Quebec, Canada, investigated the longitudinal association between job strain and the risk of heart diseases in 8,073 working adults without heart diseases at baseline. Results suggest an important association between job strain and heart diseases in women even after controlling for depressive symptoms, behavioral and clinical risk factors. In men, job strain was only associated with heart diseases for those aged 50 years and older.

The results are in line with a meta-analysis of prospective cohort studies where the risk of coronary heart diseases was increased in those with high job strain (RR=1.26; 95% CI 1.12-1.41), although the review did not find significant differences between men and women and did not control for depression (166).

Women hold greater domestic responsibility than men and may struggle more with work-life balance which might compound the overall negative effects of stress on health outcomes (167). As women rates of heart diseases such as myocardial infarction increase compared to men's rates (113), the findings of this study are valuable toward understanding the complexities of women risk for heart disease. An overall higher rate of heart disease was reported in men; however results do not suggest a general association between job strain and heart diseases in men. An association was only observed for men aged 50 years and older. It is not clear why job strain was a risk factor for heart diseases in those elderly men. It possible that lifestyle, sociodemographic, and clinical factors might play a role: compared to men aged 40-50 years, those 50 to 60 years old men were more likely to be physically inactive (13.9% vs. 11.6%), were more often divorced, separated or widowed (18.8% vs. 12.4%), and were more often diagnosed with diabetes (6.6% vs 3.5%). Those factors might affect coping with stress, especially in older men.

The current study provided an exploration of the association between job strain and heart diseases according to occupational skill level. There was no significant interaction effect between job strain and occupational skill level, however the greatest rate of heart diseases and high job strain was reported by those in the lowest occupational skill level category with the lowest rate reported in those in the highest. This may indicate an inverse social gradient in relation to occupational skill level and heart diseases incidence.

To our knowledge, this study is the first to provide information about the association between job strain and heart disease, independent of depressive symptoms, in both men and women, in a Canadian sample. A previous study had found an association between job strain incident CVD while controlling for depression (104), however this was a female only sample.

5.5.1 Strengths and Limitations

This study utilised a large sample with no heart diseases at baseline, with up to seven years of follow-up data. This study combined survey and administrative data to evaluate the association of job strain and depressive symptoms on heart diseases in middle aged working individuals in whom the risk of heart diseases is the greatest. The study comprised objective information on occupational skill level.

Certain limitations of this study warrant consideration. Self-report measures were used to obtain information about job strain and depressive symptoms. Questions assessing depressive symptoms were limited to symptoms experienced in the last two weeks. There was no distinction between part-time and full-time workers. The current sample was highly educated and predominantly of white ethnicity.

5.5.2 Conclusions

Job strain is associated with the incidence of heart diseases in middle-aged women; an association in men was only found for those 50 years and older at baseline. The association remained when controlling for depressive symptoms, sociodemographic, clinical, and behavioral risk factors; suggesting that job strain is another psychosocial risk factor in addition to depression. The highest rate of job strain and heart diseases was in individuals with jobs of the lowest occupational skill level.

5.6 Tables and Figures

Table 1 Sample characteristics stratified by heart diseases status and sex

		Participants who did not develop heart disease (n = 7,516)		**Participants who did develop heart disease (n = 557)**	
	Full sample (n = 8,073)	**Men (*n* = 3,674)**	**Women (*n* = 3,842)**	**Men (*n* = 340)**	**Women (*n* = 217)**
Age (Mean, SD)	49.5 (4.9)	49.3 (5.0)	49.4 (4.8)	51.2 (5.1)	50.9 (4.9)
Education					
<High school % (*n*)	0.5 (41)	0.6 (22)	0.4 (16)	0.9 (3)	0.0 (0)
High school, % (*n*)	17.8 (1,434)	18.0 (662)	17.0 (652)	23.0 (78)	19.4 (42)
>High school % (*n*)	81.7 (6,585)	81.4 (2,985)	82.6 (3,167)	76.1 (258)	80.6 (175)
Ethnicity					
White, % (*n*)	88.3 (7,127)	86.4 (3,175)	89.9 (3,452)	88.5 (301)	91.7 (199)
Smoking					
Current, % (*n*)	17.9 (1,446)	19.0 (697)	16.7 (640)	21.0 (71)	17.5 (38)
Former, % (n)	36.8 (2,968)	34.8 (1,277)	38.2 (1,466)	41.5 (140)	39.2 (85)
Never, % (n)	45.2 (3,642)	46.2 (1,693)	45.1 (1,729)	37.4 (126)	43.3 (94)
Alcohol consumption					
Daily, % (*n*)	10.7 (859)	12.8 (469)	8.5 (326)	12.7 (43)	9.7 (21)
Physical activity					
No moderate/vigorous activity % (*n*)	15.7 (1,267)	12.7 (468)	18.7 (717)	10.9 (37)	20.7 (45)
High blood pressure % (*n*)	14.8 (1189)	16.0 (583)	12.3 (470)	24.9 (84)	24.2 (52)
Abnormal cholesterol, % (*n*)	44.8 (3,535)	48.8 (1,763)	39.7 (1,483)	54.2 (181)	51.9 (108)
Diabetes, % (*n*)	5.0 (400)	4.3 (159)	4.7 (181)	11.0 (37)	10.6 (23)
High job strain (binary), % (*n*)	21.8 (1,761)	18.2 (670)	25.1 (965)	18.2 (62)	29.5 (64)
Depressive Symptoms					
PHQ-9 (Mean, SD)	2.6 (3.2)	2.3 (3.0)	2.8 (3.3)	2.7 (3.4)	3.5 (3.8)

Table 2 HR and 95% CIs for association with new heart diseases in women (n=4,059)

	Model 1	**Model 2**	**Model 3**
	HR (95%CI)	**HR (95%CI)**	**HR (95%CI)**
Job strain ratio	1.85 (1.19, 2.90)	1.54 (0.98, 2.43)	1.63 (1.02, 2.60)
Age	1.06 (1.04, 1.09)	1.06 (1.04, 1.09)	1.06 (1.03, 1.09)
Ethnicity (white)	0.99 (0.61, 1.61)	1.04 (0.64, 1.68)	1.08 (0.65, 1.78)
Education (>high school)	1.03 (0.74, 1.46)	1.06 (0.75, 1.50)	1.14 (0.81, 1.62)
PHQ-9 summary score		1.05 (1.02, 1.09)	1.04 (1.01, 1.08)
Smoking (current)			0.95 (0.66, 1.36)
Alcohol consumption (daily)			1.26 (0.78, 2.04)
Physical activity (moderate/vigorous)			0.55 (0.39, 0.79)
Abnormal cholesterol			1.77 (1.32, 2.37)
High Blood pressure			1.51 (1.08, 2.12)
Diabetes			1.50 (0.95, 2.39)

Note: in order to allow the regression model to run, education variable was recoded to include two categories instead of three (less than high school and high school were included in the same category)

Model 1 = adjusted for baseline age, education, ethnicity; model 2 = adjusted for PHQ-9 summary score; model 3 = adjusted for smoking status, alcohol consumption, physical activity, cholesterol, blood pressure, and diabetes

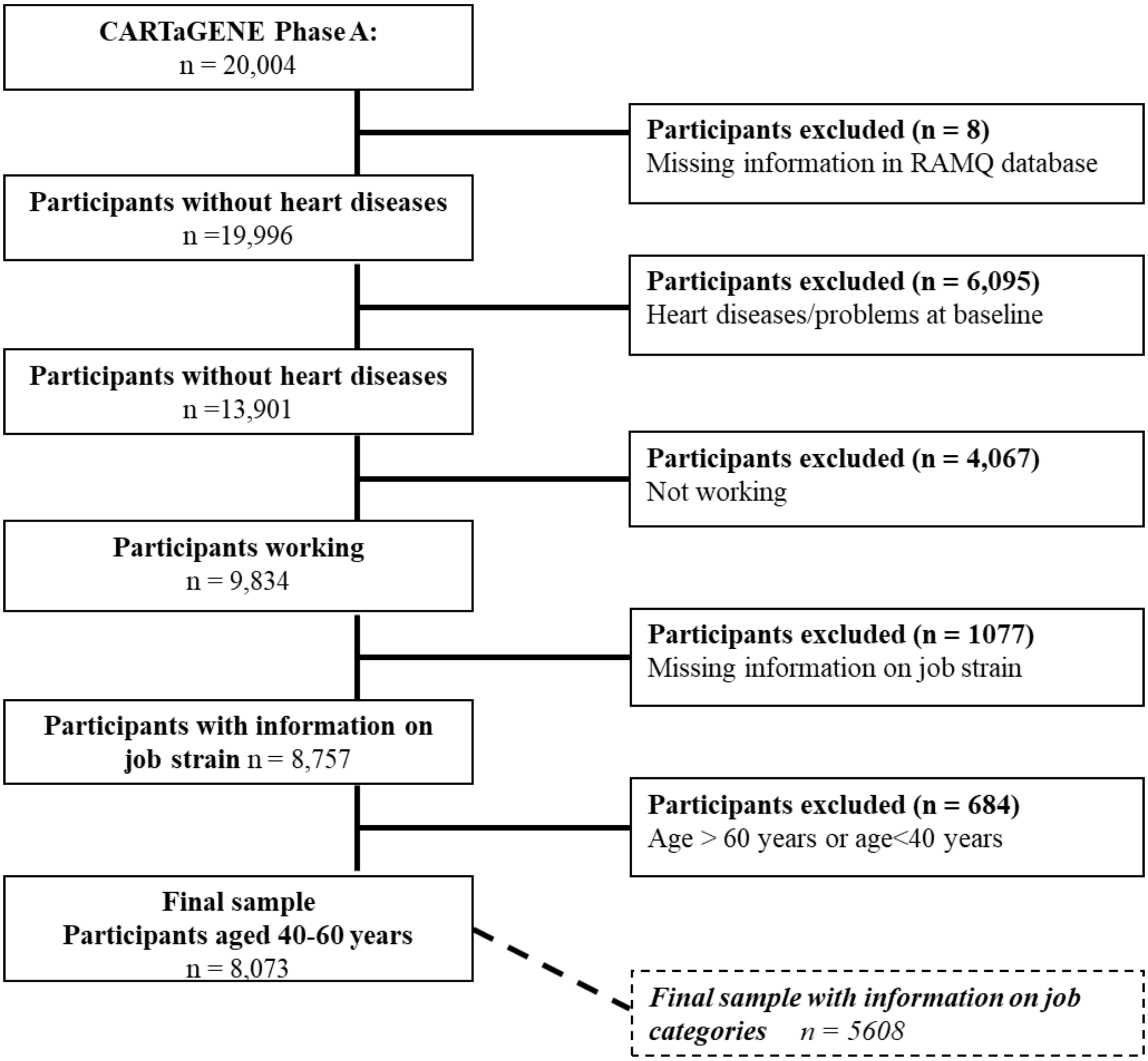
Table 3 HR and 95% CIs for association with new heart diseases in men (n = 4,014)

	Model 1	**Model 2**	**Model 3**
	HR (95%CI)	**HR (95%CI)**	**HR (95%CI)**
Job strain ratio	1.22 (0.81, 1.84)	1.05 (0.69,1.61)	0.96 (0.62, 1.49)
Age	1.07 (1.04, 1.09)	1.07 (1.04, 1.09)	1.06 (1.04, 1.09)
Ethnicity	0.94 (0.67, 1.31)	0.92 (0.66, 1.29)	0.93 (0.66, 1.31)
Education (>high school)	0.89 (0.69, 1.15)	0.90 (0.70, 1.16)	0.95 (0.73, 1.24)
PHQ-9 summary score		1.05 (1.01, 1.08)	1.03 (1.00, 1.06)
Smoking (current)			1.17 (0.89, 1.54)
Alcohol consumption (daily)			0.96 (0.68, 1.34)
Physical activity (moderate/vigorous)			0.79 (0.55, 1.15)
Abnormal cholesterol			1.42 (1.13, 1.78)
High Blood pressure			1.16 (0.89, 1.52)
Diabetes			1.89 (1.32, 2.72)

Table 4 Prevalence of heart diseases according to occupational skill level (NOC classification)

NOC 2011 Skill Levels Categories	Men (n=2,391)		Women (n=2,391)	
	High job strain	**Incidence Heart disease**	**High job strain**	**Incidence Heart disease**
A (Professional; University degree), (*n = 1,514*)	9.1 %	7.0 %	16.4 %	4.9 %
B (Technical jobs/skilled trades; College Diploma), (*n =1,373*)	15.7 %	9.0 %	23.4 %	5.2 %
C (Intermediate jobs; high school/job-specific training), (*n = 864*)	27.0 %	10.3 %	31.0 %	5.8 %
D (Labour jobs; on-the-job training), (*n = 163*)	31.3 %	12.1 %	63.8 %	5.0 %
0 (Management jobs), (*n = 576*)	12.7 %	6.8 %	16.9 %	6.8 %

Figure 2: Flow chart of participants excluded from analysis



6. DISCUSSION

6.1 Restatement of objectives

Job strain (high demands and low decision control) (4) is associated with CVD (5) however there is not always a relationship observed between these factors (7, 8). Depression and job strain are related (9) and depression is an established risk factor for CVD (11), yet there is a lack of studies that have assessed whether job strain is *still* associated with CVD when depressive symptoms are controlled for.

It appears that the disparity between the risk for CVD between men and women has reduced (113). Depression is more prevalent in females and co-occurs more frequently in female CVD than in male CVD (17, 120, 121). Yet previous studies have failed to assess whether there are differences between males and females in the association between job strain and CVD, when depressive symptoms are controlled for. Additionally, there is a lack of Canadian data that assesses the association between job strain and CVD, controlling for depressive symptoms.

Occupational skill level has been associated with mortality by heart disease however no previous study has investigated whether the association between job strain and heart disease varies according occupational skill level. The current thesis aimed to address these gaps in the literature with the development of five objectives outlined below. The first manuscript focused on general CVD risk whereas the second manuscript focused on the incidence of a subgroup of CVD conditions (heart diseases).

The first objective of this thesis was to estimate the cross-sectional association between job strain and CVD risk score, controlling for depressive symptoms. This objective was addressed in the first manuscript by investigating the cross-sectional association between job strain and CVD risk factors as measured by the Framingham Risk Score. The second objective of this thesis was to assess whether the association between job strain and CVD risk score, controlling for depressive symptoms is different for either sex. This objective was also addressed in the first manuscript by investigating the cross-sectional association between job strain and CVD risk factors as measured by the Framingham Risk Score for males and females separately (stratified analysis).

The third objective of this thesis was to investigate the association between job strain and heart disease, controlling for depressive symptoms. This objective was addressed in the second manuscript by assessing the longitudinal association between job strain and heart disease incidence, controlling for depressive symptoms. The fourth objective of this thesis was to investigate whether the association between job strain and heart disease is different for either sex. This objective was addressed in the second manuscript by investigating the longitudinal association between job strain and heart disease incidence for males and females separately (stratified analysis). The fifth and final objective of this thesis was to examine if the association between job strain and heart disease varies according to occupational skill level. This objective was addressed in the second manuscript by investigating the interaction effect between job strain and occupational skill level (measured by NOC skill category) in the association with heart disease incidence.

6.2 Summary of findings

In manuscript 1, it was found that job strain was associated with CVD risk score as indexed by the Framingham Risk Score even when controlling for depressive symptoms, physical activity, and alcohol consumption. Similar associations were observed for males and females in the stratified analysis. There was no interaction effect between job strain and depressive symptoms in the association with Framingham Risk Score.

In manuscript 2, in models adjusted for age, education, and ethnicity only, it was found that there was a longitudinal association between job strain and heart disease for females but not for males. An association between job strain and heart disease was observed in men aged 50 years and older only. Controlling for depressive symptoms in model 2 attenuated the association in both sexes, however there was still an association between job strain and heart disease in the female sample and this association remained even after further adjustment for sociodemographic, clinical, and behavioral risk factors. High job strain and heart disease was most prevalent in those with jobs of the lowest occupational skill level category ("D" labour jobs). Heart disease was least prevalent in those with jobs of the highest occupational skill level category ("A" professional jobs). There was no interaction effect between job strain and occupational skill level in the association with heart disease.

Thus in investigation of the association between job strain and CVD there were differences observed between CVD risk (assessed in manuscript 1) and heart disease incidence (assessed in manuscript 2). In the first manuscript, job strain was associated with CVD risk in both male and female samples, whereas in the second manuscript job strain was associated with heart disease in females only. These observed differences might be understood in relation to differences between the outcome measures that were utilized in manuscript 1 and manuscript 2. The Framingham Risk Score was used as an outcome measure in manuscript 1 and is an indicator of the estimated 10 year risk for CVD that includes a wide range of CVD conditions, whereas the outcome measure used in manuscript 2, incident heart disease, refers to one specific subgroup of CVD conditions (heart diseases). The findings in the male sample indicate that job strain is related to risk factors for CVD differently from how job strain is related to heart disease incidence in men. In males, job strain may be more related to risk factors for a broader range of

CVD conditions and less related to the incidence of heart disease, a specific subgroup of CVD conditions

The findings in the female sample indicate that job strain is associated with both risk factors for CVD conditions as well as heart disease, even when depressive symptoms are controlled for. In females, job strain may be related to both risk factors for a broad range of CVD conditions as well as to the incidence of heart disease, a specific subgroup of CVD conditions. Additionally, the Framingham Risk Score is a sex specific measure and is scored differently for males than for females, based on differential risk profiles. Heart disease incidence is not a sex specific measure. Thus the lack of sex difference between males and females in the association between job strain and CVD risk score may have been partly attributable to the sex-specificity that is inherent in the scoring of Framingham Risk measure. The difference between males and females observed in the association between job strain and heart disease cannot be attributed to any sex specificity inherent in the heart disease incidence outcome measure.

The difference in association of job strain and heart disease observed between men and women (manuscript 2) may be attributable to enduring differences in social roles between males and females. Women hold greater domestic responsibility than men, and may struggle more with work-life balance, which might compound the overall negative effects of stress on health outcomes (167). Other differences in working conditions and coping styles may explain this difference. Men are subject to more favorable work conditions and so they might respond better to job strain than they do to depressive symptoms. Men are less likely to seek treatment for depression and respond to negative emotions with more externalising behaviors (168).

The rate of heart disease was greater in males however results of the current analysis suggest that job strain was associated with heart disease in older men only. Differences in clinical, sociodemographic, and clinical factors between men aged between 40-50 years and men older than 50 years may explain this finding. Men aged 50-60 years were more likely to be physically inactive, more frequently divorced, separated or widowed, and were more often diagnosed with diabetes. These factors may affect how older men cope with stress. The association between job strain and heart disease in men aged less than 50 years appears to be more greatly determined by depressive symptoms and traditional risk factors (HDL cholesterol levels, diabetes status).

6.3 Strengths and limitations

The samples utilized in both manuscripts consisted of large samples with no CVD at baseline, reducing the chance of confounding due to existing CVD. Manuscript 2 combined survey and administrative data with up to seven years of follow- up information. This provides valuable information about the longitudinal association between job strain, depressive symptoms, and heart disease in a Canadian sample. This type of information was limited in previous studies. A recent study in a Canadian sample had assessed the association between work stressors and heart disease, controlling for depressive symptoms but had used self-reported heart disease as an outcome measure (7). Administrative data is more accurate in identifying heart disease than self-report data (13). Individuals with heart disease are more likely to drop out of a study as they may not be able to participate in follow-ups due to mortality and illness.

Manuscript 1 assessed the association between job strain and CVD risk factors using a risk estimate measure in working individuals at an age when risk for CVD is highest (middle age). This cross-sectional information serves as a valuable supplement to longitudinal assessments of job strain and CVD which could be limited by termination or change of employment.

The analyses conducted in both manuscripts provide insight into the association between job strain and CVD that is independent of depression. This helps to distinguish two closely related psychosocial CVD risk factors from each other, in relation to their association to CVD. Previously, there were very few studies that included an assessment of depression, and those studies were subject to limitations. One study that had controlled for depressive symptoms within the association between job strain and CVD had measured depression and anxiety symptoms using a shortened 4 item version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) in a female only sample (104). The current thesis provides information about the association between job strain and CVD, controlling for depressive symptoms in both sexes. Another study that had controlled for depressive symptoms in assessment of the association between work stressors and incident heart disease had used self-reported heart disease as an outcome measure rather than administrative data as used in manuscript 2 of the current thesis (7, 13). Objective information on occupational skill level was available in the survey data. Information of this type is rare in large scale surveys.

Despite these strengths, it must be considered that the studies presented in this thesis are subject to several limitations. Both job strain and depressive symptoms were measured using self-report measures. The PHQ-9 scale is a rating scale that assesses self-reported depressive symptoms in the last two weeks and is therefore, not a measure of clinical depression. Depression history and cases of treated depression (with anti-depressants) were not captured in the current analyses. Severe cases of depression may not have been captured in the current analysis as these individuals may not have been working when the survey data was taken. Lifestyle and biological variables were largely measured via self-report which may have contributed to bias. The regression analyses adopted in manuscripts 1 and 2 did not allow conclusions to be made about the exact proportion of risk for CVD risk score/heart disease that is attributable to depression versus job strain. The samples in manuscript 1 and 2 consisted of predominantly white and highly educated participants living in Québec thus limiting the generalizability of these findings to other populations. The current analyses did not differentiate between full time and part time workers. Other psychosocial factors such as social support and social isolation may be implicated within the job strain-CVD association and were not controlled for in the studies presented in this thesis (169, 170).

6.4 Implications of findings

By assessing the association between job strain, depressive symptoms, and CVD, the findings of this thesis add to extant literature on non-conventional risk factors for both CVD risk (manuscript 1) and CVD incidence (manuscript 2). Consequently, this provides suggestion for future researchers or clinicians to further develop knowledge of non-conventional risk factors for CVD. Furthermore, manuscript 2 included the exploration of two types of occupational factors (job strain and occupational skill level) in relation to CVD which may encourage further inquiry into other occupational factors. These efforts may help to inform CVD preventive measures.

The findings reported in manuscript 1 help to understand the association between job strain and CVD risk that is independent of depressive symptoms. This may have implications for future research studies that may choose to include an assessment of depression when investigating the cross-sectional association between work stress and CVD risk. Similarly, the findings reported in manuscript 2 provide insight into the association between job strain and heart disease incidence that is independent from depressive symptoms. This also may encourage future research studies to consider including an assessment of depression when investigating the longitudinal association between job strain and heart disease incidence. Analyses conducted in manuscript 1 and manuscript 2 taken together, help to distinguish the association between job strain and depressive symptoms and risk factors for a broad range of CVD conditions (manuscript 1) from the association between job strain and depressive symptoms and heart disease incidence (manuscript 2).

The findings reported in the second manuscript provide evidence toward a stronger association between job strain and CVD, independent of depressive symptoms, for females than for males. This finding highlights the importance of job strain as an important independent risk factor for female heart disease. As female rates of heart disease such as myocardial infarction increase compared to male rates (113), this type of information is valuable toward understanding the complexities of female risk for heart disease incidence. These findings should be replicated in other samples. Providing sex specific information about risk factors for heart disease could help to inform future general CVD risk assessment. Previous studies that had similarly found stronger associations between job strain and CVD for females may have attributed this difference to the greater propensity of depression in females. Seen as depressive symptoms were controlled for in this analysis, this finding helps to assert job strain as an especially important independent risk factor for heart disease in females versus males.

Exploration of occupational skill level within the job strain-CVD association indicates a greater prevalence high job strain and heart disease in individuals with jobs of lower occupational skill level. This finding helps to highlight the differences in job strain and CVD risk between individuals with different occupational skill levels. This type of information, if replicated, may be useful to CVD prevention as a means to identify groups of workers at increased risk.

6.5 Future directions

There are a number of ways that future studies could further elucidate the complex relationship between job strain, depression, and CVD. Firstly, the current studies measured depressive symptoms via a self-rated scale. Future studies could consider the use of structural clinical interviews to assess clinically diagnosed depression.

Secondly, future research could extend the occupational variables explored in this thesis by examining other work related variables such as commute time/mode. Distinctions between type of workers (e.g. full time, part time, shift, and remote worker) could also contribute to understanding how the relationship between job strain, depression, and CVD operates under different work situations. These variables could also be assessed within the context of increasingly automated workplaces.

These results should be replicated in other samples. Future research should extend knowledge about the mechanisms through which potential sex differences in the association between job strain, depressive symptoms, and heart disease operate. Future studies may benefit from investigating other factors that may contribute to female work stress. Some evidence suggests that there are sex-based differences in the experiences of stress that could lead to differences in the response to surveys (171). Domestic responsibility and work-life balance may also be implicated (167). Assessment of the responsibility of childcare may help to further explain the association between job strain and CVD. The accessibility and quality of childcare services available to the parent while they are at work may influence how they perceive work stress.

Indeed more prospective studies are necessary to determine the causal relationships between job strain, depression, and CVD. The adoption of mediator and moderator analyses might be strategies to consider.

6.6 Conclusion

In conclusion, the results presented in this thesis provide evidence for an association between job strain and CVD risk factors that is independent of depressive symptoms. This finding helps to distinguish two closely related factors in their association with CVD risk. Prospective analyses demonstrated that in females, there was an important association between job strain and heart disease incidence even when controlling for depressive symptoms, sociodemographic, lifestyle, and biological variables, but this was not observed for males. This finding provides insight into the potential sex difference in the association between job strain and heart disease, when controlling for depression. Finally, the findings of the current thesis provide novel information about occupational skill level within the association between job strain and heart disease incidence. It was demonstrated that the greatest prevalence of both high job strain and heart disease was in individuals with jobs of the lowest occupational skill level.

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Appendix

Appendix I: Supplemental information on calculation of Framingham Risk Score points

Risk Factor		**Risk Points**			
		Men		**Women**	
Age					
30-34		0		0	
35-39		2		2	
40-44		5		4	
45-49		7		5	
50-54		8		7	
55-59		10		8	
60-64		11		9	
65-69		12		10	
70-74		14		11	
75+		15		12	
HDL-Cholesterol (mmol/L)					
>1.6		-2		-2	
1.3-1.6		-1		-1	
1.2—1.29		0		0	
0.9-1.19		1		1	
<0.9		2		2	
Total Cholesterol					
<4.1		0		0	
4.1-5.19		1		1	
5.2-6.19		2		3	
6.2-7.2		3		4	
>7.2		4		5	
Systolic Blood Pressure (mmHg)		**Not treated**	**Treated**	**Not treated**	**Treated**
<120		-2	0	-3	-1
120-129		0	2	0	2
130-139		1	3	1	3
140-149		2	4	2	5
150-159		2	4	4	6
160+		3	5	5	7
Smoker	Yes	4		3	
	No	0		0	
Diabetes	Yes	**Statin-indicated condition**			
	No	0		0	
Total points					

Appendix II: Supplemental information on calculation of Framingham Risk Score (10 year risk %)

Total Points	10-Year CVD Risk %	
	Men	**Women**
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.51
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

Using 10-Year CVD Risk % (above) patient is categorized as low, moderate, or high risk

High risk = FRS ≥ 20 %

Intermediate risk = FRS 10-19%

Low risk = FRS < 10%

Appendix III: Supplemental table (manuscript 2)

HR and 95% CIs for association with new cardiovascular disease (heart_disnew) full sample (n = 8,073)

	Model 1		**Model 2**		**Model 3**	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**
Job strain ratio	1.46(1.08,1.97)	0.013	1.25 (0.92,1.70)	0.210	1.18 (0.86, 1.62)	0.306
Age	1.07 (1.05, 1.08)	0.000	1.07 (1.05, 1.08)	0.000	1.06 (1.04, 1.08)	0.000
Sex (male)	1.59 (1.34, 1.89)	0.000	1.62 (1.37, 1.92)	0.000	1.59 (1.32, 1.90)	0.000
Ethnicity (white)	0.96 (0.73, 1.27)	0.793	0.96 (0.730, 1.27)	0.793	0.99 (0.74, 1.31)	0.94
Education (college/graduate school/ university)	0.94 (0.77, 1.16)	0.573	0.96 (0.78, 1.18)	0.690	1.01 (0.81, 1.24)	0.964
PHQ-9 summary score			1.05 (1.03, 1.07)	0.000	1.04 (1.010, 1.061)	0.005
Smoking status						
Smoking former					1.10 (0.90, 1.33)	0.355

Smoking occasional					1.34 (0.91, 1.98)	0.141
Smoking daily					1.09 (0.83, 1.42)	0.551
Alcohol consumption (daily)					1.04 (0.79, 1.37)	0.785
Physical activity imputed (active moderate/vigorous)					0.66 (0.51, 0.85)	0.001
Low HDL cholesterol (yes)					1.54 (1.29, 1.84)	0.000
Blood pressure						
Diagnosed and not treated					1.44 (1.04, 2.00)	0.030
Treated					1.21 (0.94, 1.54)	0.133
Diabetes						
Diagnosed and not treated					1.90 (1.23, 1.95)	0.004
Treated					1.67 (1.17, 2.38)	0.005

Note: There were 0 female participants who had the event and were had “less than high school” on education variable. “less than high school” and “high school” placed in the same category in order to facilitate the running of the regression model