The Influence of Genetics and Psychosocial Factors on Cardiovascular Diseases

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ABSTRACT

Background: Cardiovascular disease (CVD) can be subcategorized into heart-related disorders (HRD) and peripheral/vascular-related disorders (PVRD). Genome-wide association studies (GWAS) have mainly identified genetic variants associated with HRD that can be used to develop a polygenic risk score (PRS) to quantify genetic risk. While GWAS have mainly been conducted in middle-aged adults, previous research suggests that genetics may have less of an influence on the risk of chronic diseases among the elderly and non-genetic factors may play a larger role. This includes psychosocial factors (PSFs) such as depression and social isolation that have been associated with CVD. Although gene-environment interactions studies have reported that a healthy lifestyle may mitigate polygenic risk of CVD, PSFs as moderators of polygenic risk of CVD have not been explored.

Methods This cross-sectional study analyzed baseline data (n=9,892) from the Canadian Longitudinal Study on Aging. A PRS for CVD was constructed with 39 single nucleotide polymorphisms. Depressive symptoms assessed by the Center for Epidemiological Studies – Depression Scale were categorized into: "none" (Group 1, reference), "current" (Group 2), "clinical depression with no current symptoms" (Group 3) and "potential, recurrent depression" (Group 4). Social isolation index as a binary variable was comprised of marital status, living arrangements, retirement status, contacts, and social participation. The outcome measures were heart-related disorders (HRD: myocardial infarction, angina and heart disease) and peripheral/vascular-related disorders (PVRD: stroke, peripheral vascular disease and hypertension). Logistic regression was performed to generate adjusted odds ratios (ORs) for individual and interactive associations of PRS and PSFs on CVD, according to middle-aged (45-69 years) and elderly (≥70 years) subgroups.

Results After adjusting for age, biological sex, total household income, education, smoking status, immigration status, province, urban/rural classification and the first five principal components of ancestry, PRS associated with HRD and PVRD among middle-aged participants (OR (95% confidence interval) (HRD: 1.06 (1.03-1.08) and PVRD: (1.02 (1.00-1.03)) but only with HRD among elderly (1.06 (1.03-1.08)). Among middle-aged participants, compared to the reference (group 1), the higher depressive symptoms groups associated with both HRD and PVRD, respectively (group 3: 1.21 (1.21-2.01), 1.49 (1.28-1.74); group 4: 1.75 (1.28-2.39), 1.73 (1.41-2.12)), while group 2 of depressive symptoms associated with only PVRD (1.28 (1.07-1.53)). Among elderly participants, only group 4 compared to reference associated with PVRD (1.69 (1.08-2.64)). Social isolation associated with only PVRD among middle-aged participants (1.84 (1.04-3.26)). No significant PRS*PSFs interactions were observed.

Conclusion: This study suggests that PSFs may not act as moderators for polygenic risk of CVD. However, genetics and PSFs are individually associated with CVD, which may vary according to the stage of the life course and anatomical location of CVD outcome.

RÉSUMÉ

Contexte: Les maladies cardiovasculaires (MCV) peuvent être subdivisées en maladies liées au cœur (MLC) et maladies vasculaires périphériques (MVP). Les études d'association à l'échelle du génome (EAEG) ont principalement identifié des variantes génétiques associées au MLPV qui peuvent être utilisées pour développer un score de risque polygénique (SRP) pour quantifier le risque génétique. Bien que le EAEG ait été principalement mené chez des adultes d'âge moyen, des recherches antérieures suggèrent que la génétique peut avoir moins d'influence sur le risque de maladies chroniques chez les personnes âgées et que des facteurs non génétiques peuvent jouer un rôle plus important. Cela comprend les facteurs psychosociaux (FPS) tels que la dépression et l'isolement social qui ont été associés aux MCV. Bien que études des interactions gènes-environnement aient montré qu'un mode de vie sain peut atténuer le risque polygénique de MCV, les FPS en tant que modérateurs du risque polygénique de MCV n'ont pas été explorés.
Méthodes: Cette étude transversale a analysé les données de base (n = 9,892) de l'Étude Longitudinale Canadienne sur le Vieillissement. Un score de risque polygénique (SRP) pour MCV a été construit avec 39 polymorphismes mononucléotidiques. Les symptômes dépressifs évalués par l'Échelle de Dépression du Centre d'Études Épidémiologiques- ont été classés en: « aucun » (groupe 1, référence), « actuel » (groupe 2), « dépression clinique sans symptômes actuels » (groupe 3) et « potentiel, dépression récurrente » (Groupe 4). L'indice d'isolement social en tant que variable binaire comprenait l'état matrimonial, les conditions de vie, le statut de retraité, les contacts et la participation sociale. Les variables dépendantes étaient: les maladies liées au cœur (MLC: infarctus du myocarde, angine et maladies cardiaques) et maladies vasculaires périphériques (MVP: accident vasculaire cérébral, maladie vasculaire périphérique et hypertension). Une régression logistique a été effectuée pour générer des rapports de cotes (OR)

ajustés pour les associations individuelles et d'interaction des SRP et des PSFs sur les MCV, selon les sous-groupes d'âge moyen (45-69 ans) et de personnes âgées (≥70 ans).

Résultats: Après ajustement pour l'âge, le sexe biologique, le revenu total du ménage, l'éducation, le statut de fumeur, le statut d'immigration, la province, la classification urbaine / rurale et les cinq premières composantes principales de l'ascendance, la SRP était associée au MLC et au MVP chez les participants d'âge moyen (OR (95 % intervalle de confiance) (MLC: 1.06 (1.03-1.08) et MVP: (1.02 (1.00-1.03)), mais uniquement avec MLC chez les personnes âgées (1.06 (1.03-1.08)). Parmi les participants d'âge moyen, le groupe 2 de symptômes dépressifs par rapport à la référence était associée au MVP (1.28 (1.07-1.53)), le groupe 3 par rapport à la référence était associée au MLC (1.56 (1.21-2.01)) et au MVP (1.49 (1.28-1.74)) et le groupe 4 par rapport à la référence était associée au MLC (1.75 (1.28-2.39)) et MVP (1.73 (1.41-2.12)). Parmi les participants âgés, seulement le groupe 4 par rapport à la référence était associée à MVP (1.69 (1.08-2.64)). L'isolement social était associé à seulement MVP parmi les participants âgés (1.84 (1.04-3.26)). Aucune interaction significative SRP*FPS n'a été observée.

Conclusion: Cette étude suggère que les FPS peuvent ne pas agir comme modérateurs du risque polygénique de MCV. Cependant, la génétique et les FPS sont individuellement associés aux MCV qui peuvent varier en fonction du stade du cycle de vie et l'emplacement anatomique des MCV.

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CONTRIBUTION OF AUTHORS

Gabriella Menniti (MSc Candidate) was mainly responsible for merging of datasets (genotypic and phenotypic data), data cleaning and statistical analysis. The candidate wrote this thesis and prepared all figures and tables.

Dr. Daiva Nielsen (Supervisor of Candidate, Assistant Professor, School of Human Nutrition, McGill University): provided access to the CLSA database, obtained ethics approval, and provided continuous research guidance and feedback for data analysis and creation of this manuscript. Dr. Nielsen thoroughly contributed to the editing of this thesis manuscript.

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LIST OF ABBREVIATIONS

CVD	Cardiovascular disease
HRD	Heart-related disorders
PVRD	Peripheral/vascular-related disorders
PRS	Polygenic risk score
GWAS	Genome-wide association studies
PSF	Psychosocial factor
MI	Myocardial infarction
CVA	Cerebrovascular accident
SNP	Single nucleotide polymorphism
PCA	Principal components of ancestry
BMI	Body mass index
CAD	Coronary artery disease
CHD	Congenital heart disease
PVD	Peripheral vascular disease
T2D	Type 2 Diabetes Mellitus
ARIC	Atherosclerosis Risk in Communities
WGHS	Women's Genome Health Study
MDCS	Malmö Diet and Cancer Study
RR	Relative risk
HR	Hazard ratio
FRS	Framingham Risk Score
HDL	High density lipoprotein
NRI	Net reclassification index
BMD	Bone mineral density
CES-D	Center for Epidemiology Studies Depression scale
CI	Confidence interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
CDK	China Kadoorie Biobank
DFTJ	Dongfeng-Tongji
HPA	Hypothalamic-pituitary-adrenal
CLSA	Canadian Longitudinal Study on Aging
MOS	Medical Outcome Study
AF	Atrial fibrillation
SMI	Statistical multiple imputation
FCS	Fully conditional method
CCA	Complete case analysis
OR	Odds ratio
DCS	Data collection sites
TMPLR	The Manitoba Personalized Lifestyle Research

Chapter 1

Rationale and Objectives

1.1 Rationale

Canada is experiencing an unprecedented change in the makeup of its population and undergoing a process of population aging. Greater longevity is associated with increasing rates of chronic conditions, including cardiovascular disease (CVD), which is among the leading causes of death among elderly people in Canada (1). Two of the most common types of cardiovascular disease include myocardial infarction (MI) and cerebrovascular accident (CVA), both of which may lead to death (1). There are many factors that increase the risk of CVD in an aging population, both modifiable and non-modifiable (1). Some modifiable risk factors include but are not limited to nutritional status, alcohol consumption and smoking (2). Contrarily, non-modifiable risk factors of CVD include but are not limited to age and biological sex (2). Another non-modifiable risk factor of CVD that has been gaining increased attention in health research is genetics (2).

The genetic makeup of an individual leads to a predisposed increased risk of CVD that may manifest itself over the lifecourse (3). Genome-wide association studies (GWAS) have found several genetic variants known as single nucleotide polymorphisms (SNPs) that have been linked to an increased risk of CVD (4). SNPs are the most common type of genetic variant (5). SNPs occur when a nucleotide in DNA making up a gene is replaced by another nucleotide and thus, can be considered a variation in the code of a gene, which may lead to altered function of that gene (5). They occur almost once in every 1,000 nucleotides on average, which means there are roughly 4 to 5 million SNPs in a person's genome (5). Consequently, the more of these SNPs are found in an individual's genome, the more susceptible they may be to developing CVD. This

has allowed for the formation of a polygenic risk score (PRS), which quantifies an individual's genetic risk for CVD based on the number of SNPs present in their genome (6-7). Several studies have reported that a PRS created for SNPs related to CVD are predictive of the occurrence of CVD in middle-aged adults (6-7).

Although PRS are reported to be clinically useful in middle-aged adults, the ability for PRS to predict risk of chronic diseases may be less useful in the elderly. Recent evidence suggests that genetic risk may become less important in older age, if good health has been maintained earlier in the lifecourse (8). Previous studies have shown that both PRS related to bone mineral density (BMD) and fracture risk (9) as well as PRS related to body mass index (BMI) in middle-aged adults become less clinically useful in their predictive abilities as individuals' age (10). Interestingly, it has been suggested that lifestyle factors may be able to interact with genetic risk in order to influence disease-related outcomes (11). Therefore, lifestyle factors such as diet and physical activity are recognized as important to take into consideration when assessing the likelihood of CVD occurrence in the aging population and that a PRS alone may not be as clinically useful (11).

Lifestyle and environmental factors may counteract genetic risk for CVD. Although lifestyle factors such as obesity, smoking status, physical activity and diet have been studied with respect to their influence on genetic risk for CVD (7,12), no study has yet examined whether psychosocial factors may moderate genetic risk for CVD. However, several studies have shown that psychosocial factors, specifically measures of psychological well-being (i.e. depressive symptoms) (13-16) as well as social functionality (i.e. social support, network and social participation) (17-19) may influence the risk of CVD. These studies have shown that a favorable psychosocial profile, which consists of higher psychological well-being and increased social

functionality may lower the risk for CVD (13-19). Studies have also shown that psychosocial factors may influence lifestyle, therefore psychosocial factors may represent an important upstream environmental factor for the assessment of gene-environment interactions on the risk of CVD (20-24). Therefore, it is of particular relevance to investigate how psychological and social characteristics interact with polygenic risk to influence the likelihood of CVD. More specifically, to determine whether having higher levels of psychological and social functioning could potentially mitigate the occurrence of CVD in individuals with higher polygenic risk.

1.2 Thesis Objectives

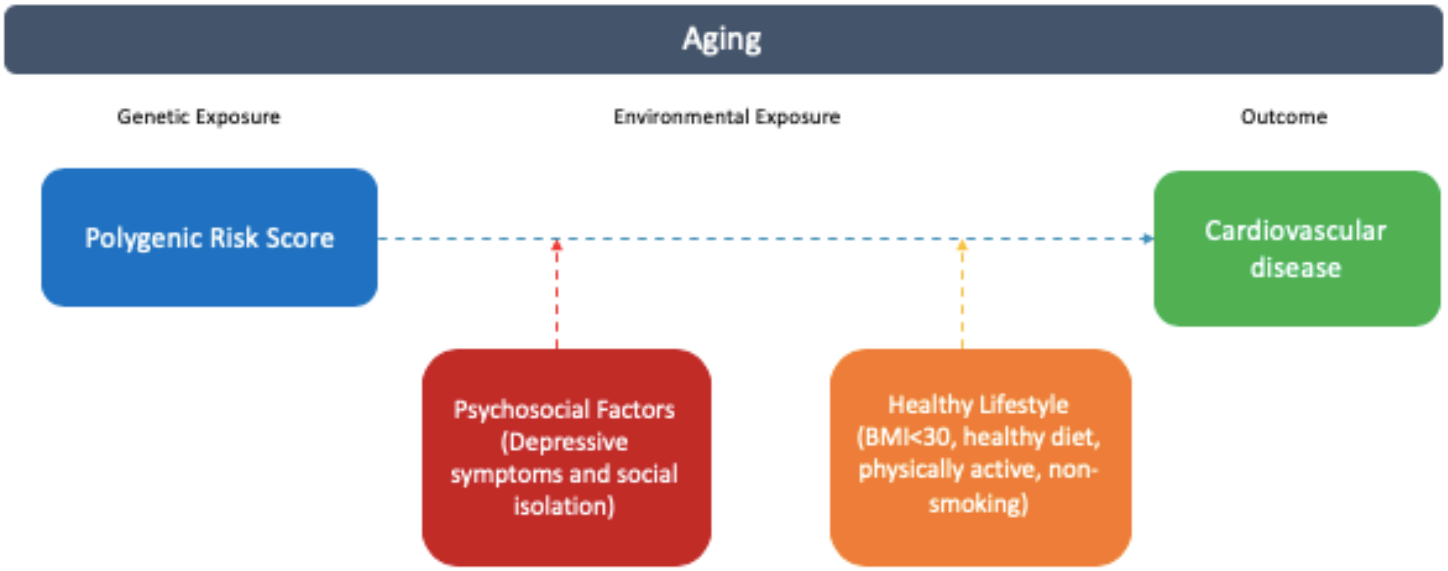
Primary: To investigate individual and combined associations between polygenic risk of CVD and psychosocial factors (depression and social isolation) on physician-diagnosed heart-related disorders (HRD) and peripheral/vascular-related disorders (PVRD) in the Canadian population.
Secondary: Conduct analyses separately in between middle-aged (45-69 years old) and elderly (70 years old and more) participants to determine whether associations vary according to age group.

1.3 Thesis Hypothesis

Hypotheses are the following:

i) There is a significant combined association between polygenic risk of CVD and psychosocial factors (depression and social isolation), such that higher genetic risk of CVD outcomes is mitigated by favorable psychosocial status when compared to lower genetic risk of CVD outcomes.
ii) Associations between PRS and CVD outcomes (HRD and PVRD) will be more pronounced among middle-aged (45-69 years old) compared to elderly (70+ years old) participants.

Figure 1.1 Psychosocial factors as moderators of polygenic risk of CVD upstream of lifestyle factors



Chapter 2

Literature Review

2.1 Cardiovascular Disease

2.1.1 Overview of Cardiovascular Disease

Cardiovascular disease accounts for 17.9 million deaths per year making up 31% of all deaths (25). More than 85% of deaths related to CVD are due to myocardial infarction (heart attack) or cerebrovascular accident (stroke) (25). In fact, every hour 12 Canadians over the age of 20 years old who are diagnosed with cardiovascular disease die (26).

Myocardial infarction (MI) is caused by a build-up of plaque, which are fatty deposits that accumulate in the walls of coronary arteries (27). Coronary arteries are the blood vessels located within the heart that supply blood and therefore oxygen and nutrients to the heart muscle itself and allows for it to remain viable (27). When this build-up of plaque occurs, it reduces and eventually completely hinders blood flow and results in a lack of oxygen and nutrients reaching the heart muscle (27). Without oxygen or nutrients provided by blood flow, the cells making up the heart tissue begin to die, and the result is a heart attack (27). This build-up of plaque in the walls of coronary arteries (also known as atherosclerosis) does not happen instantly but rather progressively worsens over several years (27).

A cerebrovascular accident (CVA) occurs when blood flow to a region of the brain is obstructed resulting in a lack of oxygen and nutrients reaching the nerve cells located within this region (28). Without oxygen or nutrients, the neurons die, resulting in a stroke (28). There are two main types of cerebrovascular accidents: ischemic stroke and hemorrhagic stroke (28). Ischemic stroke is the most common type accounting for approximately 80% of stroke cases

(28). Ischemic strokes occur when the presence of a blood clot in an artery located in the brain results in the obstruction of blood flow (28). These blood clots may form in the arteries of the brain or they may form in other arteries located around the body and travel to the brain (28). Conversely, hemorrhagic strokes occur when a blood vessel breaks and bleeds into the brain (28). Additionally, an individual can also experience a transient ischemic attack (i.e. mini stroke), which is when blood supply is blocked to a region of the brain for only a few minutes (28).

2.1.2 Risk Factors for CVD

There are many factors that increase the risk of cardiovascular disease, which are categorized into modifiable and non-modifiable risk factors. Non-modifiable risk factors are those that cannot be altered by an individual, yet they increase the risk of CVD (29). The first non-modifiable risk factor of CVD is age, where the risk of CVD increases as an individual's age increases, as do the rates of many chronic diseases (29). Additionally, biological sex is a non-modifiable risk factor where men are at an increased risk of CVD compared to women (29). In fact, men tend to develop CVD earlier than women because there seems to be a protective effect of estrogen against the development of CVD in pre-menopausal women (30). Even after menopause when the risk of CVD increases for women, it is still lower than that of men (29). However, women are at a greater risk of mortality from CVD (29). Traditionally, a third non-modifiable risk factor has been ethnicity (29,31) although there has been a growing movement to avoid labelling participants according to ethnic backgrounds in research studies (32-33). In the field of genetics, an alternative approach to collecting self-reported ethnicity information has been the application of principal component analysis (PCA) to genome-wide data that enables grouping of shared genetic variants reflective of ancestry due to common patterns of inheritance

(34). A final non-modifiable risk factor for CVD is genetics, which will be discussed in more detail in a subsequent section.

Modifiable risk factors are mainly lifestyle factors that influence risk of CVD (29). One modifiable risk factor is smoking status, where smokers have an increased risk of CVD compared to non-smokers (29). Cigarette smoking is an independent risk factor for CVD, but it also may interact with other risk factors to even further increase the risk of CVD (29). Another modifiable risk factor is alcohol consumption, where an increase in the frequency and amount of alcohol intake can also increase the risk of CVD (29). Several studies have shown that consuming more than 5 drinks per episode of drinking or more than 3 drinks a day increases the risk of CVD (35). Physical activity level is another modifiable risk factor, where those who perform a lower amount of physical activity have an increased risk of CVD (29). Studies have shown that there is a pertinent indirect dose-response relationship between higher levels of physical activity and lower rates of CVD (29). The American Heart Association makes recommendations for the amount of physical activity to reduce the risk of CVD, which is 30 minutes 5 times a week of moderate exercise (36). Another important modifiable risk factor is dietary intake pattern, where the American Heart Association suggests the consumption of a healthy dietary pattern consisting of high intake of fruits and vegetables, whole grains and low-fat dairy products and to limit intake of sweets, sugar-sweetened beverages and red meats (37). While diet may be a modifiable risk factor of CVD, there are several factors that may limit an individual's ability to adhere to public health recommendations for healthy eating such as lower household income, nutrition literacy and food literacy (38-40). These are important constraints to take into account when determining the extent to which diet can be modified. Lastly, an important modifiable risk factor is body mass index (BMI), where those with BMI greater than

30.0 kg/m^2 (i.e. Obesity Class I) have an increased risk of CVD (41). The recommendation for decreasing the risk of CVD is to maintain a BMI in the normal range from 18.5-24.9 kg/m^2 (41).

2.1.3 Different Types of CVD

There are many different types of cardiovascular diseases. The word "cardiovascular" can be divided into "cardio" referring to diseases specific to the heart and "vascular" referring to diseases related to the vascular system meaning all blood vessels outside of the heart (i.e periphery) (42). Cardiovascular diseases can thus be further subcategorized into heart-related disorders (HRD) and peripheral/vascular-related disorders (PVRD) (43). HRD mainly include MI, angina, coronary artery disease (CAD), congenital heart disease (CHD), cardiac arrythmias, cardiomyopathy, valvular heart disease, pericardial disease and heart failure (44). PVRD mainly include cerebrovascular accident (CVA), transient ischemic attack (i.e. mini stroke), hypertension, peripheral vascular disease (PVD), aneurysm, cerebral vascular disease and pulmonary embolism (44-45). Although these cardiovascular diseases are subcategorized based on anatomical location, these cardiovascular diseases all share a common pathophysiology of atherosclerosis (see section 2.1.1) and common risk factors (see section 2.1.2) (46).

2.2 Genetics of CVD

2.2.1 Overview of Genetic Risk of CVD

An important non-modifiable risk factor of CVD is genetics, specifically genetic variants (29). Single nucleotide polymorphisms (SNPs) are one of the most common types of genetic variants (5). They occur when a nucleotide found in DNA is replaced by another nucleotide, for example if there is meant to be an adenosine (A) in a particular location of DNA making up a gene and it is replaced by a guanine (G) (5). This causes a variation in the code of a gene, which may lead to altered function of that gene (5). SNPs occur very frequently within the genome

where each person has approximately 4 to 5 million SNPs in their genome (5). However, certain SNPs located in certain genes found on different chromosomes have been associated with an increased risk for several chronic diseases. In fact, several genome-wide association studies (GWAS) have been conducted to identify possible SNPs located in genes associated with an increased risk of CVD (4, 47-51). Since 2007, these GWAS have identified SNPs found in more than 50 different individual loci that have been associated with an increased risk of CVD (7) and have been combined into a PRS that is predictive of CVD outcomes (7). SNPs are named according to a Reference SNP cluster ID (rsID), denoted "rs" followed by a unique identifier number and each have an associated gene locus that can be found in Table S1 (7). These genes have a wide range of functions, some of which have been mechanistically related to CVD development (e.g. *PCKS9* codes for proprotein convertase subtilisin/kexin type 9, which plays a role in cholesterol and fatty acid metabolism (52)) while for others further investigation to uncover mechanisms still remains (53).

2.2.2 Polygenic Risk Score (PRS) for CVD

The identification of approximately 50 SNPs from GWAS that have been associated with CVD has led to the development a polygenic risk score (PRS) for CVD (7). A PRS is an additive model that allows for the quantification of genetic risk based on the amount of SNPs present in an individual's DNA (54). A PRS is the sum of the product of the number of risk alleles for each SNP (0, 1 or 2) and weighted risk estimate (natural logarithm of the published odds ratio for that SNP with CVD) (7). This means the more SNPs associated with CVD are found in an individual's genome, the higher the PRS, the higher the risk of developing CVD at one point over the lifecourse (7).

Several studies have looked at the association between a PRS created for SNPs associated with CVD and the risk of CVD (6). One study conducted in a Danish prospective cohort (n=6041) evaluated the association between a PRS containing 45 genetic variants with the risk of MI and CAD (6). For every unit increase in the PRS, the risk of MI significantly increased by 5% in a model adjusted only for age and sex and 6% in a model adjusted for age, sex, BMI, smoking status and type 2 diabetes mellitus (T2D) (6). However, there were no significant associations between the PRS and CAD. Similarly, a cross-sectional study conducted using a cohort of participants from three prospective cohort studies including 7,814 participants in the Atherosclerosis Risk in Communities (ARIC) study, 21,222 in the Women's Genome Health Study (WGHS) and 22,389 in the Malmö Diet and Cancer Study (MDCS) evaluated the association between a PRS comprised of 50 SNPs and CVD (7). Participants were categorized into high polygenic risk (highest quintile of polygenic scores), intermediate polygenic risk (quintile 2 to 4) and low polygenic risk (lowest quintile of polygenic scores) (7). CVD was defined as any of the following: MI, coronary revascularization and death from coronary causes (7). The investigators reported that those with a high polygenic risk (highest quantile of polygenic scores) had a 91% higher relative risk (RR) of developing CVD than those with a low polygenic risk (lowest quantile of polygenic scores) in a model controlling for age, sex, education and the first five principal components of ancestry (clusters of inherited SNPs that are shared among participants of similar genetic ancestry (34)) (7). Another prospective cohort study that occurred over a roughly 4-year follow-up period (n=10,612) looked at several different PRS, one of which was specific for coronary heart disease and contained 46 SNPs identified by the CARDIoGRAMplusC4D consortium (55). Participants were categorized into quartiles based on genetic risk score where the first quartile contained the lowest polygenic scores and the fourth

quartile contained the highest polygenic scores (55). The hazard ratio (HR) between the fourth and first quartile was 1.52 ($P<0.0001$) indicating a higher risk of CVD for those with higher polygenic scores (55).

Just as PRS have been associated with CVD outcomes, evidence also suggests that adding a PRS to a predictive model of CVD may be able to significantly improve prediction (55-60). The Framingham risk score (FRS) is one of the most commonly used validated tools to measure 10-year CVD risk in clinical settings (61). This score is calculated based on traditional risk factors separately for men and women where the higher the values of the risk factors, the more points towards the total score (61). This includes age, high-density lipoprotein (HDL) levels (mmol/L), total cholesterol levels (mmol/L), systolic blood pressure (mmHg) with points differing if treated or not, smoking status (smokers receive more points) and presence of T2D (those with diabetes receive more points) (61). Overall FRS then corresponds to a percentage of 10-year CVD risk, where FRS less than 10% means low risk, between 10-19% means intermediate risk and greater than or equal to 20% means higher risk (61). Specific treatment options and target ranges of blood cholesterol levels to reduce risk can then be advised based on the FRS of each individual (61).

The current FRS does not consist of any genetic or psychosocial measures. However, studies have looked at how incorporating genetics into the FRS alters its predictive ability in terms of predicting the risk of CVD. This was seen in the previously mentioned study by Ganna et al. (55), where adding the genetic risk score for 46 SNPs relating to coronary heart disease to a model that predicted the risk based on the Framingham risk factors led to a statistically significant net reclassification improvement (NRI) of 4.2% (55). Therefore, adding this PRS to the model improved the prediction of coronary heart disease compared to when only traditional

FRS risk factors are considered (55). Similar results have been seen in a variety of other studies where adding a PRS containing SNPs associated to CVD to a model predicting CVD including traditional risk factors significantly improves the prediction of CVD (55-60).

2.2.3 Clinical Utility of PRS with Age

Most studies that have assessed the ability of a PRS to predict the risk of various chronic diseases have been conducted in middle-aged adults, with very few studies being conducted in the elderly population (55-60). A recent proposition is that the influence of polygenic risk may diminish as an individual ages', if good health has been maintained over the life course (11). Three studies summarized below have looked at the association of PRS (generated from cohorts of middle-aged participants) with chronic disease risk among older adults over the age of 65 years old.

First, a cross-sectional study looking at participants from three separate prospective cohort studies (n=8,067) of elderly subjects over the age of 65 years old, aimed to look at two PRS (9). One PRS was composed of 63 bone mineral density (BMD)-associated SNPs known as the GRS63 and the other was compared of 13 SNPs relating to fracture risk known as the GRS13 (9). The study aimed to determine whether these PRS would be able to predict BMD, BMD change and fracture risk in elderly subjects (9). The results of this study showed that the GRS63 was significantly associated with BMD, however it was not significantly associated with BMD change (9). Although both GRS63 and GRS13 were significantly associated with fracture risk, both were unable to predict fracture risk when added to a basic model including age, weight, height and BMD (9). Therefore, the complete usefulness of these PRS in elderly subjects could not be determined (9).

Similarly, two studies have examined the relationship between PRS containing SNPs related to BMI at different stages over the life course (10). One study looked at two cohorts, female registered nurses from the Nurses' Health Study (n=9,971) and male professionals from the Health Professionals' Follow Up Study (n=6,405) who had been genotyped when the studies originally began in 1976 and 1986, respectively (10). Both cohorts reported their height and weight at baseline and then were asked to recall their weight at 18 and 21 years old for women and men, respectively (10). They were then followed-up at 5-year intervals from 45 to 85 years old (10). The PRS contained 97 SNPs and higher scores indicated higher genetic risk of developing obesity over the life course (10). The association between PRS and BMI change was examined over three periods of life: early adulthood (18-45 years old), middle adulthood (45-65 years old), and late adulthood (65-80 years old) (10). In women, PRS was positively associated with BMI across all ages, however the association was strongest up until approximately 45 years old and remained unstable until 60 years old, after which the association progressively weakened (10). The mean BMI difference per 10-allele increment reached its peak of 1.30 kg/m^2 at 45 years old, after which it declined to 0.86 kg/m^2 at 80 years old (10). Although not statistically significant, this same pattern was seen in men, with associations becoming progressively weaker after 45 years old (10). Thus, the association between PRS and BMI may be less pronounced as individuals' age (10).

Lastly, a cross-sectional study examined the association between PRS created using BMI-associated SNPs and "body fatness" in 181 middle aged (30-64 years old) and elderly (65-79 years old) Japanese men (11). Body fatness was described as a combination of BMI, total abdominal fat and visceral fat (11). The results of this study showed that this PRS was not associated with any of the components of body fatness in elderly subjects, however the PRS was

strongly associated with all components in middle-aged men (11). In the middle-aged group, PRS was the strongest predictor of BMI ($p<0.0001$), total abdominal fat ($p=0.001$) and visceral fat ($p=0.003$). However, PRS was not significantly associated with BMI ($p=0.752$), total abdominal fat ($p=0.633$) or visceral fat ($p=0.968$) in elderly subjects (11). Alternatively, level of physical activity was significantly negatively associated with total abdominal fat ($p=0.024$) and visceral fat ($p=0.046$) in the elderly subjects (11). Similarly, fat intake (% energy) was significantly positively associated with BMI ($p=0.037$), total abdominal fat ($p=0.001$) and visceral fat ($p<0.001$) in the elderly subjects (11). The authors note that lifestyle risk factors rather than genetic risk seem to be more important to take into consideration when assessing the risk of obesity in the elderly population (11). In fact, they state that based on their results, genetic influence on BMI may lessen with age and thus environmental factors may have stronger effects on BMI in older individuals (11).

Therefore, it is unclear whether PRS created to predict the risk of chronic diseases have similar clinical utility in elderly subjects as they do in middle-aged adults. Further studies are required to examine the clinical utility of PRS at different stages over the lifecourse, as the literature on this manner is still contradictory.

2.3 Psychological Well-Being and CVD

There are many factors that influence the risk of CVD, however the role of psychosocial factors such as mental health and social functioning status have been recognized as becoming increasingly relevant. Recent research has suggested that an individual's psychosocial characteristics may influence their risk for various diseases, one of which is CVD. Psychosocial profiles can be defined in terms of the level of psychological well-being (i.e. depressive symptoms) and level of social functionality (i.e. social isolation).

2.3.1 Depressive Symptoms

The role of psychological well-being in the risk of CVD has been most extensively studied in terms of the presence of negative mood states. One of the most studied negative mood states in relation to CVD is the presence of depressive symptoms. A meta-analysis of thirty prospective cohort studies conducted in 2014 aimed to look at the association between the presence of depressive symptoms and the risk of CVD (13). The assessment of depressive symptoms varied across studies, where a total of nine different self-reported symptom scales were used (13). The most commonly used validated questionnaire that was used in twelve of the included studies was the Center for Epidemiological Studies - Depression scale (CES-D) (13). Twenty-four of the studies looked at CHD as the primary outcome and twelve of the studies looked at MI as the primary outcome (13). To be consistent across studies, presence of depressive symptoms (yes/no) and presence of CHD and MI outcomes were dichotomized (yes/no) (13). Results of this meta-analysis showed a pooled RR of CHD for depressive symptoms of 1.30 (95% confidence interval (CI): 1.22-1.40) indicating that those with depressive symptoms had a 30% higher RR of developing CHD compared to those without depressive symptoms (13). Similarly, the pooled RR of MI for depressive symptoms was also 1.30 (95% CI: 1.18-1.44) indicating that those with depressive symptoms had a 30% higher relative risk of developing MI compared to those without (13). Therefore, overall conclusions drawn from this meta-analysis of thirty prospective cohort studies is that the presence of depressive symptoms seems to increase the risk of CHD and MI (13).

More recent research shows similar results for the relationship between the presence of depressive symptoms and the risk of CVD (14). A cross-sectional study conducted in 2018 looked at a cohort of participants from twenty-four primary care facilities in Latvia (n=1,569)

(14). Depression was assessed using the Patient Health Questionnaire-9, which is a 9-item self-reported screening tool for clinical symptoms of depression based on diagnostic criteria for major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (14). Presence of symptoms of clinical depression was based on a score of 10 (14). 10-year risk of fatal CVD including CVA, MI and aneurysm of the aorta was assessed using the validated SCORE system where a score of 10% indicates a very high CVD mortality risk (14). Results from this cross-sectional study showed that those with the presence of symptoms of clinical depression (score of 10 or more) had a 57% increase in the odds of having a very high CVD mortality risk (SCORE $\geq$ 10%) compared to those without depressive symptoms (OR=1.57, 95% CI: 1.06-2.33) (14).

Similarly, a prospective cohort study published in 2019 using data from the China Health and Retirement Longitudinal Study aimed to look at incidence of physician-diagnosed CVD in middle-aged and older Chinese adults (n=12,417) over a 4 year follow up period (15). Physician-diagnosed CVD included both heart disease and stroke and depressive symptoms was assessed using the CES-D10 Scale (15). In a well-adjusted statistical model including demographics, lifestyle factors, anthropometrics, disease status, and medication use, having a higher level of depressive symptoms was independently associated with an increased risk of CVD (HR=1.39, 95% CI: 1.22-1.58) (15). Lastly, a very recently published study in February 2020, assessed the relationship between presence of depressive symptoms and CVD mortality in two cohort populations (16). One cohort was from the China Kadoorie Biobank (CDK) study (n=512,712) over a 12-year follow-up period of individuals aged 30 to 79 years old and another cohort was from the Dongfeng-Tongji (DFTJ) study (n=26,298) over a 8-year follow up period of individuals 32 to 104 years old (16). Both studies assessed presence of symptoms using self-

reported questionnaires and followed participants to track deaths associated with CVD (16). Using multi-variate adjusted Cox proportional hazards regression models, the risk of CVD mortality was 22% higher for those with depressive symptoms compared to those without (HR=1.22, p=0.002) in the cohort from the CDK study and the risk of CVD mortality was 32% higher for those with depressive symptoms compared to those without (HR=1.32, p<0.001) in the cohort from the DFTJ study (16). Therefore, all of these studies similarly conclude that those with depressive symptoms may be at an increased risk of CVD and mortality from CVD.

2.3.2 Depressive Symptoms in the Canadian Population

Notably, the association between depressive symptoms and CVD has been previously studied in the Canadian population, using baseline data from the Canadian Longitudinal Study on Aging (CLSA) (43). This cross-sectional study looked 29,328 individuals ranging from 45 to 85 years old categorized into four categories based on depression status (43). The four categories were based on a combination of self-reported clinical depression (yes/no) and presence of depressive symptoms assessed via the CES-D10 scale where a score of 10 indicated presence of depressive symptoms (43). Group 1 had no depression (no clinical depression and CES-D10 score < 10), Group 2 had current depressive symptoms (no clinical depression but CES-D10 score 10), Group 3 had self-reported depression with no current symptoms (clinical depression with CES-D10 score < 10) and Group 4 had self-reported depression with current symptoms (clinical depression with CES-D10 score ≥ 10) (43). CVD was categorized into two related-disorders categories including heart-related disorders (HRD), i.e. heart disease, myocardial infarction and angina, and peripheral/vascular-related disorders (PVRD), i.e. hypertension, stroke and peripheral vascular disease (43). Comparing the no depression to the highest level of depression categories, those with self-reported depression and current symptoms (Group 4) had

31% higher odds of HRD (OR=1.31, $p<0.01$) and 17% higher odds of developing PVRD (OR=1.17, $p<0.05$) compared to those with no depression (Group 1) (43). Therefore, this shows that the relationship between the presence of depressive symptoms and the risk of CVD has been previously seen in the Canadian population as well.

In all, the literature shows an association between the presence of depressive symptoms and an increased risk of CVD. Depressive symptoms as a negative mood state may be a useful measure of one's level of psychological well-being. Studies have shown a possible biological mechanism underlying the relationship between depressive symptoms and CVD may be the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (62). Hyperactivity of the HPA axis leads to higher levels of stress hormones (i.e. cortisol) in the bloodstream, which has both been seen in patients with depressive symptoms and also shown to be associated with an increased risk of CVD (62). Therefore, having a more favorable level of psychological well-being by minimizing one's negative mood state (i.e. lower levels of depressive symptoms) may be an important preventive measure of CVD occurrence.

2.4 Social Considerations and CVD

While mood states have been seen to be important in relation to CVD, it is also important to evaluate social considerations that may or may not be linked to mood. An individual's social milieu can be defined as their level of social networks and their level of social participation. These aspects of one's social milieu have been studied in relation to the risk of CVD. Although the literature on social functionality in relation to CVD risk is limited in comparison to depressive symptoms, research suggests that having a more favorable social functioning status may be associated with a reduced risk of CVD especially in the elderly population.

2.4.1 Social Networks and Participation

Social networks are important aspects of an individual's social functionality and contribute to a social support system. This includes social contacts meaning actually having individuals whether it be family or friends that are physically present (i.e. having people in one's life) and feelings of perceived support and care if need be (i.e. feeling supported by the people in one's life) (63). Having an extensive social network and social support system have been studied in relation to the risk of CVD in all adults with some studies mainly focusing on the elderly population who may have lower social functionality (17-19).

One cross-sectional study examined the relationship between social networks and risk factors for CVD in a cohort (n=1,012) over the age of 65 years old (17). This study defined social networks in terms of current marital status, living arrangements, widowhood and number of times participants interacted with or participated in activities with family, friends and community (17). Results of this study showed interesting trends that specifically in men, having a higher level of social networks was associated with a decrease in the risk factors for CVD (17). Particularly, being married was associated with a significant increase in HDL cholesterol levels and not living alone was associated with a significant decrease in systolic blood pressure (17). Therefore, having higher levels of social networks in elderly men may be associated with a decreased risk of CVD (17).

A prospective cohort study with more promising results looked at social networks as a combination of social contacts and perceived social support in a cohort of adults (n=29,179) in association with mortality from CVD (63). Social contacts included level of contact with family and friends and marital status (63). Over a follow-up of approximately 14 years, mortality of participants from various diseases including all-cause CVD and heart disease were assessed (63).

One significant result was that those in the highest social network group had a decreased risk of all-cause CVD mortality (63). Those in the highest social network group also had a lower risk of mortality from heart disease (63). This study shows that having higher levels of social networks may be important to improve prognosis of CVD (63).

Lastly, a prospective cohort study of participants (n=44,152) aged 40 to 69 years old also looked at both level of social contacts and perceived social support (18). The outcome measures were incidence and mortality from stroke and CHD (18). This study showed that having a lower amount of social contacts and no perceived social support were both associated with an increased risk of stroke mortality in men and women (18). Therefore, this study showed that having social networks that contributes to a well-built support system is important for decreasing the risk of CVD and mortality from CVD (18).

Based on these studies, social networks as a measure of social functionality may be an important factor when assessing the risk of CVD, however the literature is still limited. Another important measure of social functionality is level of social participation. Studies that have been conducted looking at the association between social participation and CVD are even more limited. However, of the studies that have been conducted, interesting results do arise.

A study using data from the Health and Retirement Study for a cohort of participants (n=7,803) aged 51 years old or older aimed to look at social participation (i.e. volunteering) and risk factors for CVD (64). In middle aged adults (51-64 years old), those who volunteered were less likely to have high-risk central adiposity including those with even a moderate level of volunteering (1-99 hours) (64). Additionally, those who volunteered were seen to have higher levels of HDL, especially if they volunteered more than 100 hours (64). Lastly, those who volunteered were less likely to have MetS2, which was described as having high risk central

adiposity plus two out of four of the additional risk factors of CVD (64). Therefore, social participation was seen to decrease risk factors for CVD in middle-aged adults. Among the elderly (65 years old and more), volunteering was associated with a decrease in the risk of hypertension, especially for those who volunteered for 100 hours or more (64). Therefore, social participation may decrease the risk of CVD in both middle-aged and elderly adults (64).

Furthermore, a prospective cohort study looked at the association between social participation and incident CVD or CVD mortality (19). This study examined a cohort (n=4,775) aged 51 years old and older (19). Social participation included: volunteering, frequency of attendance to religious services and frequency of attendance to social group meetings (19). The outcome of interest was the combination of incident CVD and CVD mortality (19). Findings from this study showed that higher levels of social participation, particularly volunteering was associated with a decrease in the incidence of CVD and mortality from CVD (19). Therefore, this prospective cohort study shows the potential of social participation, especially volunteering as being protective against either the diagnosis of CVD or improving the prognosis of CVD (19).

Overall, these studies do show promising results that social participation with an emphasis on level of volunteering may be associated with a decrease in the risk of CVD and mortality from CVD and thus would be an important factor to take into consideration when measuring the level of social functionality.

2.4.2 Social Isolation Index

As there have been studies that have looked at the relationship between the risk of CVD with social networks and social participation separately, recent research has combined both of these aspects of social functionality into one score known as a social isolation index. Social isolation index has been used as an overall measure of social functioning status by including

measures on level of social networks including number of social contacts (with friends, family, coworkers) and presence of a support system (marital status, living arrangements, etc), with level of social participation (participation in community-related activities) all together into a score, which then is dichotomized into socially isolated and not socially isolated (65-66).

Recently, a social isolation index based on data from the Canadian Longitudinal Study on Aging (CLSA) was created by Menec et al. (65). This social isolation index contained measures of social networks including marital status, living arrangements, frequency of social contacts with friends/neighbours, relatives/siblings and children, and retirement status as well as measures of social participation based on participation in church or family and friend based activities, religious activities, sports or physical activities, educational and cultural activities and more (65).

Another social isolation index created by Wister et al. using data from the CLSA included social networks based on level of social contact with friends, family and community, living arrangements, and marital status, social participation, the Medical Outcome Study (MOS) Social Support Survey Scale to capture social support and a single item as a measure of loneliness (66). This single item comes from the CES-D10 depression scale, whose overall score is used to assess the presence of current depressive symptoms (66). Although social isolation and depression may be related, they are not necessarily consistently correlated where depression seems to be more of an emotional state and social isolation seems to be more of a circumstantial state (67-68). Therefore, including a measure of depressive symptoms in the social isolation index may not be the most accurate way to assess social isolation as a circumstantial state rather than emotional. For this reason, the social isolation index by Menec et al., which reflects more of a circumstantial state, may be the better instrument to measure social isolation in its truest form (65).

Although the social isolation index by Menec et al. (65) has not been tested in relation to CVD risk in the Canadian population (i.e. CLSA), a previous study conducted in China looked at another social isolation index that is very similar, which was created using the exact same measures of social functionality and how they related to the risk of CVD, particularly stroke (69). This prospective cohort study was conducted using data from China Health and Retirement Longitudinal Study conducted from 2011 to 2015 on a cohort (n=12,662) over the age of 45 years old during a 4-year follow-up period (69). The outcome of interest was physician-diagnosed stroke, where if the person responded "yes" to being diagnosed then it was considered incident stroke (69). Social isolation was assessed at baseline (2011) and after the first follow up in 2013 (69). The social isolation index used in this study was similar to that in Menec et al. (65) where it was based on social networks defined by marital status, living arrangements and frequency of seeing or contacting parents, children and friends as well as social participation defined as participation in activities including clubs, groups and committees (69). This social isolation index was used to dichotomize participants into being socially isolated or not socially isolated (69). Depressive symptoms were also assessed using the CES-D10 scale in order to see if social isolation independent of depressive symptoms related to the risk of stroke (69). Results from this study showed that social isolation independent of depression (after adjusting for it) had a direct association with the risk of stroke (69). Those who were socially isolated had 139% higher odds of having a stroke (OR=2.39, 95% CI: 1.49-3.82) compared to those who were not socially isolated (69). Therefore, this study reported that a social isolation index similar to the one created using the CLSA data was associated with the risk of stroke and consequently, may be useful to assess the relationship between social functionality and CVD in the Canadian population (69).

As with depressive symptoms, social isolation has also been shown to influence biological markers, which increase the risk of CVD (70). However, adherence to medication and medical advice is another link between social isolation and CVD. Studies have shown that patients who are socially isolated tend to experience more difficulty adhering to and complying with medical directives (i.e. taking medications, following a prescribed diet, etc.), which may increase the risk of CVD and mortality from CVD (70-72).

2.5 Gene-Environment Interaction

Overall, previous research has reported independent associations between both polygenic risk and psychosocial factors with CVD. However, the interaction between genetics and psychosocial factors is of interest due to emerging research that suggests that polygenic risk of CVD may be modified by lifestyle or environmental factors (7,12,73-75). A review by Said et al. conducted in 2019 summarized the current literature that has been published looking at the interaction between genetic risk and lifestyle factors on the risk of CVD (73). Although the research has been limited, the review identifies a few noteworthy studies that have reported that lifestyle factors may interact with genetic risk in order to influence CVD-related outcomes (73).

The first study that was conducted to look at the gene-environment was a study by Khera et al. that aimed to demonstrate whether lifestyle factors would be able to offset genetic risk of coronary artery events, including MI, coronary revascularization and death from coronary causes (7). This study analyzed data mainly from three prospective cohort studies: The Atherosclerosis at Risk in Communities (ARIC) Study (n=7814), the Women's Genome Health (WGS) Study (n=21,222) and the Malmo Diet and Cancer Study (n=22,389). A polygenic risk score was calculated for all participants in these three studies based on a total of approximately 50 SNPs that had previously been associated with CAD in GWAS studies (7). Participants were then

separated into low (quintile 1 of PRS), intermediate (quintile 2 to 4 of PRS) and high (quintile 5 of PRS) genetic risk categories (7).

Participants in each study were categorized as having either a favorable, intermediate or unfavorable lifestyle based on four lifestyle factors (7). The healthy lifestyle factors included: no smoking, no obesity (BMI<30), physical activity at least once weekly and a healthy dietary pattern (7). A participant was considered to have a healthy dietary pattern if they adhered to at least half of the aspects of a healthy diet including consuming high levels of fruit and vegetable intake, nuts, whole grains, fish and dairy products and low levels of refined grains, processed meats, unprocessed red meats and sugar-sweetened beverages (7). Afterwards, participants were categorized as having a favorable lifestyle if they had at least three of the healthy lifestyle factors and an unfavorable lifestyle if they had no or only one healthy lifestyle factor. Intermediate lifestyle was any other combination of the healthy lifestyle factors (7).

The results of this study indicated that across all three cohort studies, those in the high genetic risk category (highest quintile of PRS) had a 91% increased relative risk of coronary events than those in the low genetic risk (lowest quintile of PRS) category (HR=1.91, 95% CI: 1.75-2.09) (7). Interestingly, of those who were in the high genetic risk category, those who also had a favorable lifestyle had a 46% lower relative risk of coronary events compared to those who had an unfavorable lifestyle (HR=0.54, 95% CI: 0.47-0.63) (7). In fact, of those in the high genetic risk category, having an unfavorable lifestyle lead to a 10-year standardized coronary events rate of 10.7%, 4.6% and 8.2% in the ARIC, WGS and Malmo cohorts, respectively, whereas having a favorable lifestyle lead to a 10-year standardized coronary events rate of 5.1%, 2.0% and 5.3% in the respective cohorts (7). Similarly, the results showed that of those who were in the low genetic risk category, those who also had an unfavorable lifestyle had a 10-year

standard rates of coronary events that was higher than if they had a favorable lifestyle in all three cohorts (7). Consequently, the findings from this study indicate that there may be a significant interaction between genetic risk and lifestyle (7). This means that having a more favorable lifestyle may counteract polygenic risk and decrease the risk of CVD, which may be particularly beneficial for those at an increased polygenic risk (7).

Additionally, another study conducted by Said et al. also looked at the interaction between genetics and lifestyle on the risk of CVD (12). This prospective cohort study utilized data from the UK Biobank (n=339,003) over a 4-year follow up period (12). A PRS was created separately for each of the CVD outcomes including CAD, atrial fibrillation (AF), stroke and hypertension (12). For each of the outcomes, the PRS was separated into quintiles where those in quintile 1 were in the low, those in quintile 2 to 4 were in the intermediate and those in quintile 5 were in the high genetic risk categories. Lifestyle was categorized in a similar manner as seen in Khera et al. (7) based on smoking status, BMI, dietary pattern and physical activity level (12). Participants were then categorized into ideal (having 3 or more healthy lifestyle factors), poor (having 3 or more poor lifestyle factors) or intermediate (any other combination) (12).

Results from this study are similar to those of Khera et al. (7) where those in the high genetic risk category had an increased risk of incident CAD (HR=1.86, 95% CI: 1.74-1.98), incident AF (HR=2.33, 95% CI: 2.16-2.52), incident stroke (HR=1.24, 95% CI: 1.12-1.38) and incident hypertension (HR=1.44, 95% CI: 1.36-1.53) (12). However, the interesting results of this study is when looking at the different combinations of genetic and lifestyle factors together. First, looking at the outcome of incident CAD, comparing those in the high genetic/ideal lifestyle category to the low genetic/ideal lifestyle category, the risk of incident CAD increases by 79% (HR=1.79, 95% CI: 1.48-2.16) (12). However, when comparing those in the high genetic/poor

lifestyle category to the low genetic/ideal lifestyle category, the risk of incident CAD increases by 354% (HR=4.54, 95% CI: 3.72-5.54) (12). This shows that when comparing low vs. high genetic risk by just changing the lifestyle from healthy to poor the risk of incident CAD increases dramatically (12). This similar pattern can be seen for AF, where the high genetic/ideal lifestyle group has a 158% increase in the risk of incident AF compared to the low genetic/ideal lifestyle group (HR=2.58, 95% CI: 2.09-3.19) but the high genetic/poor lifestyle has a 441% increase in the risk of incident AF compared to the low genetic/ideal lifestyle group (HR=5.41, 95% CI: 4.29-6.81) (12). Additionally, the high genetic/ideal lifestyle group has a 52% increase in the risk of incident hypertension compared to the low genetic/ideal lifestyle group (HR=1.52, 95% CI: 1.29-1.79) whereas the high genetic/poor lifestyle group has a 368% increase in the risk of incident hypertension compared to the low genetic/ideal lifestyle group (HR=3.85-5.69) (12). Overall, the findings of this study show that in those that are in the ideal lifestyle group, having a higher genetic risk will increase the risk of CVD (12). However, if not only does one have a high genetic risk, but they also have a poor lifestyle compared to ideal, they will even further increase the risk of incident CVD (12). Therefore, the interplay between genetic and environmental factors is important to take into consideration when assessing the risk of CVD (12).

These two studies by Khera et al. (7) and Said et al. (12) are the largest studies conducted to date looking at the gene-environment interaction on the risk of CVD. A few other studies have examined the interaction between particular SNPs related to risk factors of CVD (i.e. blood lipid levels) and a lifestyle factor (i.e. physical activity). One study (n=250,564) reported that certain SNPs at *CLASP1*, *LHX1*, and *SNTA1* loci were associated with higher levels of HDL and for those where these SNPs were present in their genome, having higher levels of physical activity even further increased levels of HDL (74). Similarly, a SNP at the *CNTNAP2* loci was associated

with lower levels of LDL and the addition of higher levels of physical activity even further decreased the levels of LDL (74). Other studies have also shown interaction between genetics and other single lifestyle factors, including smoking status (75) and BMI (76). Therefore, based on previous research, it is evident that there may be a gene-environment interaction on the risk of CVD and thus, the combination of both genetic and lifestyle factors should be taken into consideration when assessing the likelihood of CVD occurrence in the population.

2.6 Summary

After a thorough review of the literature, previous research has identified several risk factors that may influence the risk of CVD. Although there are various risk factors for CVD, genetic risk may be particularly important. GWAS have identified several SNPs that reach genome-wide significance in association with the risk of CVD (7). Identification of these SNPs has allowed for the development of a PRS, which quantifies genetic risk (7). Studies that have looked at this relationship between a PRS and CVD risk have shown that these PRS may be associated with an increased risk of CVD and be able to predict those who are at increased risk for CVD in middle-aged adults (6-7,55-60). However, several studies testing different PRS for chronic diseases, which have previously been shown to be useful in middle-aged adults, demonstrate that the influence of genetic risk may dampen as individuals' age if good health has been maintained over the life course (9-11). Therefore, other non-genetic factors are also important to take into consideration.

In particular, psychosocial factors including psychological well-being and social functionality have recently been recognized as relevant in relation to CVD. The most studied measure of psychological well-being is presence of depressive symptoms in association with the risk of CVD. Specifically, studies have shown that more favorable psychological well-being

defined by lower depressive symptoms may decrease the risk of CVD (13-16, 43). Similarly, measures of social functionality, which can all be combined into a social isolation index including both social networks and social participation has been associated with the risk of CVD (17-19, 63-64, 69). Research in this regard has shown that more favorable social functionality defined by not being socially isolated (i.e. higher levels of social networks and participation) may decrease the risk of CVD (17-19, 63-64, 69). Thus, previous literature suggests that having an overall more favorable psychosocial status may decrease the risk of CVD.

Previous studies have examined interactions between genetic risk and lifestyle factors such as BMI, diet, physical activity and smoking, and shown that having a less favorable lifestyle in terms of these four factors may exacerbate the risk for CVD, which particularly affects those with higher genetic risk (7,12,73-76). Therefore, having a more favorable lifestyle consisting of no smoking, lower BMI, higher level of physical activity, and healthy dietary pattern may decrease the likelihood of developing CVD and would be particularly beneficial for those at higher genetic risk (7,12,73-76). In addition, other environmental factors such as psychosocial factors have been shown to play a role in the risk of CVD, where previous research has detected a potential beneficial effect of having a more favorable psychosocial status on the risk of CVD. Nevertheless, no previous study has included psychosocial factors in the assessment of the interaction between lifestyle/environmental factors and genetics on the risk of CVD. The interaction between genetics and psychosocial factors merits further exploration to assess the plausibility that having more favorable psychosocial status (i.e. higher levels of psychological well-being and social functionality) could counteract high genetic risk and thereby decrease the likelihood of developing CVD that may manifest itself over the life course.

Chapter 3

Manuscript

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Multiscale risk factors of cardiovascular disease: a cross-sectional analysis of genetic and psychosocial contributors among Canadian adults

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3.1 Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and the second leading cause of death in Canada (25-26). CVD can be categorized into heart-related disorders (HRD) including myocardial infarction, angina and heart disease and peripheral/vascular-related disorders (PVRD) including cerebrovascular accident (CVA), hypertension and peripheral vascular disease (43). Multiscale risk factors consider combinations of factors that are involved along the pathway of disease pathogenesis and represent a more all-encompassing approach to studying disease risk (77). This investigation assessed the associations between CVD and multiscale risk factors of genetics, psychosocial factors (PSFs) and life course stage.

Genome-wide association studies (GWAS) have identified SNPs associated with an increased risk of CVD (4,47). From these, polygenic risk scores (PRS) have been developed to quantify genetic disease risk according to the number of SNP alleles carried by an individual (7). GWAS have primarily focused on SNPs associating with HRD (7) and to a lesser extent with PVRD (78), although the genetic predisposition may differ between types of CVD (54). While GWAS have overwhelmingly been conducted among cohorts of middle-aged individuals, emerging evidence suggests that effects of genetic risk on health outcomes may dampen as individuals approach the later stages of the life course if good health has been maintained (11). Non-genetic risk factors may increasingly play a role in chronic disease risk among the elderly who have entered the later stages of life with overall good health as experience and environmental exposure cumulate over a person's lifecourse (9-11,79), underscoring the importance of assessing the performance of PRS in elderly groups. Moreover, recent gene-environment interaction studies provide supportive evidence that non-genetic factors (e.g. healthy lifestyle) may counteract polygenic risk of chronic diseases and may be particularly beneficial for subgroups at highest

polygenic risk (7,12, 73-76). While lifestyle is an important modifiable risk factor, no previous study has examined psychosocial factors (PSFs) as possible moderators of polygenic risk of CVD despite robust evidence for individual associations between PSFs and CVD risk/outcomes. In particular, depression (13-16,43) and social isolation (17-19,63-64,69) have both been consistently associated with CVD. While they can be related constructs, social isolation does not consistently correlate with depression (67) as it more often reflects a circumstantial state rather than an emotional state (such as loneliness, a strong risk factor for depression) (68) These PSFs can influence lifestyle (20-24) and thus represent an important upstream environmental factor for assessing gene-environment interactions on CVD risk.

Therefore, the objective of the present study is to assess the individual and interaction associations of PSFs (depression and social isolation) and polygenic risk of CVD with CVD outcomes among middle-aged and older adults.

3.2 Subjects and Methods

3.2.1 Study design and cohort

This cross-sectional study used baseline data from the Canadian Longitudinal Study on Aging (CLSA). Phenotypic data from 50,000 Canadian individuals between the ages of 45-85 years old upon recruitment was collected (80). The first phase in which baseline data were collected between 2010 to 2015. These 50,000 individuals (forming the CLSA Tracking and Comprehensive Cohorts) were selected via random digit dialing and had information collected via telephone survey on the demographic, behavioural/lifestyle, physical/clinical, economic, psychological and social aspects of their lives (80). Additionally, the subset known as the CLSA Comprehensive Cohort made up of 30,000 of the participants have in-depth information collected through further interviews and in-person physical examinations and biospecimen sample

collections. CLSA Comprehensive participants must go to data collection sites (DCS) every 3 years to have information collected on physical function, clinical variables, anthropometrics and to undergo a neuropsychological assessment (80). Out of the CLSA Comprehensive Cohort, 9,896 randomly sampled participants had genome-wide genotyping performed on DNA samples (80).

3.2.2 Polygenic Risk Score

Genome-wide genotyping of 9,896 participants was performed using the Affymetrix UK Biobank Axiom array (81). Out of 50 SNPs previously used to create a PRS by Khera et al (7), 39 were present in the CLSA genotyping data and were used to generate the PRS. The PRS was made by multiplying the number of CVD risk alleles by their weighted risk estimate (natural log of published odds ratio) for each of the SNPs seen in Supplementary Table S1 (7). These values were then summed across all SNPs and multiplied by the value of the total number of SNPs divided by the sum of the weighted risk estimates to obtain the PRS. The resulting PRS used in the present investigation ranged from a score of 0 (no SNPs) to 78 (all 39 SNPs).

3.2.3 Depressive Symptoms

Depressive symptoms were assessed using the short form of the Center for Epidemiological Studies – Depression (CES-D10) Scale. Scores ranged from 0 to 30, where a score of greater than 10 indicated current depressive symptoms (positive screen for depression) and a score of less than 10 indicating no evidence of current depressive symptoms (negative screen) (82). Additionally, participants were assessed for presence of clinical depression by being asked “Has a doctor ever told you that you suffer from clinical depression?” (82). Based on these two assessments of depressive symptoms, participants were categorized into four groups as previously described by Liu et al. (4). Group 1 had no evidence of any depressive symptoms with a negative screen of depressive symptoms and a negative response to the question on clinical depression. Group 2 are

considered to have *current* depressive symptoms with a positive screen of depressive symptoms but a negative response to the question on clinical depression. Group 3 are diagnosed as clinically depressed but without any current depressive symptoms with a negative screen of depressive symptoms but a positive response to the question on clinical depression. Group 4 have potential, recurrent depression with both a positive screen of depressive symptoms and a positive response to the question on clinical depression.

3.2.4 Social Isolation Index (SII)

SII was created according to methods developed using CLSA data by Menec et al. (65). This index was created using responses to five sets of questions in regard to marital status, living arrangements, social contacts, retirement status and social participation. The index was scored between 0 and 5 with higher scores indicating higher levels of social isolation (65). A social isolation score from 0 to 2 was classified as not socially isolated (coded as 0) and a score from 3 to 5 was classified as socially isolated (coded as 1) (65).

3.2.5 Outcome Measures

The outcome measures are defined in the same manner as Liu et al. (43). for consistency of methods. The six CLSA questions for physician-diagnosed CVD were subdivided into two groups. The primary outcome measure was heart-related disorders (HRD), which is composed of heart disease, myocardial infarction and angina. These were each assessed with the following questions: “Has a doctor ever told you that you have… i) heart disease (including congestive heart failure or chronic heart failure)?; ii) a heart attack or myocardial infarction?”; iii) angina (or chest pain due to heart disease)?” The secondary outcome measure was peripheral/vascular-related disorders (PVRD), which is composed of hypertension, cerebrovascular accident and peripheral vascular disease. These were each assessed with the follow questions: “Has a doctor ever told you

that you have… i) high blood pressure or hypertension?"; ii) experienced a stroke or cerebrovascular accident (CVA)?"; iii) peripheral vascular disease or poor circulation in your limbs?" These CVD subgroups share common risk factors and pathophysiology (i.e. atherosclerosis) with the major point of convergence being anatomical location (46).

3.2.6 Covariates

The following continuous co-variates were incorporated: age (years) and the first five principal components of ancestry. The following categorical co-variates were included: biological sex (male *vs*. female), education level (< secondary school; secondary school graduate but no post-secondary education; post-secondary education but below bachelor's degree; bachelor's degree; and > bachelor's degree), province at recruitment (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Quebec, Saskatchewan), total household income ($20,000 or more, but less than $50,000; $50,000 or more, but less than $100,000; $100,000 or more, but less than $150,000; $150,000 or more), smoking status (current smoker; former smoker; and never smoked), urban/rural classification (urban; rural; postal code link to dissemination area and immigration status (immigrant *vs.* not an immigrant).

3.2.7 Multiple Imputation Analysis

A statistical multiple imputation (SMI) was performed using SAS 9.4 to minimize bias due to missing data. Missing data was not substantial with the exception of one variable used to construct the SII, "social contacts with children", which had n=1,488 observations missing (15%). The fully conditional method (FCS) was used to impute missing variables since the outcome variables (HRD and PVRD) are binary (83). In this case, the FCS method which uses separate conditional distributions for each variable instead of assuming a joint distribution is most appropriate (83). SMI was performed using 20 imputation datasets. Results reported herein were

generated with the use of SMI. Corresponding results generated from a complete case analysis (CCA) are included as Supplementary material.

3.2.8 Statistical Analysis

Using SAS 9.4, multi-variable logistic regression models were used to test the main and interactive associations of PRS and PSFs with HRD as the primary outcome measure and PVRD as the secondary outcome measure. Separate models were run for depression and SII. For depressive symptoms, the reference category was Group 1 (no depressive symptoms). The reference category for the social isolation variable was not socially isolated (coded as 0). These five logistic regression models were performed for all available participants (n=9,892), and also for a predefined subgroup analysis stratified by age: middle-aged participants between 45-69 years old (n=7,155) and older participants aged 70 years old and above (n=2,737).

As a sensitivity analysis, the continuous PRS was separated into quintiles with roughly equal number of participants (~n=2000). The quintiles of the PRS were used to test the interaction association between extreme categories of PRS and the PSFs. PRS quintile 1 (lowest scores of PRS) was compared to the reference PRS quintile 5 (highest scores of PRS) since previous research indicates that grouping a PRS into categories can enable detection of associations that are present between the extremes of PRS (i.e. lowest vs. highest genetic risk) (7). The corresponding complete case analysis was also performed for this sensitivity analysis (see Appendix).

3.3 Results

3.3.1 Population Characteristics

Our analytic sample included n=9,892 of the 9,896 participants who had data available for the exposure (PRS and PSFs) and outcomes variables (HRD and PVRD) upon statistical imputation. Four participants had genetic data missing for principal component analysis of

ancestry. Among our analytic sample 49.2% were male, 72.3% were middle-aged adults (45-69 years old), and 27.7% were elderly adults (70 years old and more). Table 1 shows the characteristics of this sample based on the SMI analysis. The mean PRS was similar across the total sample and pre-specified age subgroups (middle-aged and elderly). The majority of the sample fell within Group 1 of depressive symptoms (no depressive symptoms): 73.2% for the total sample, 71.3% for the middle-aged subgroup, and 78.2% for the elderly subgroup. Similarly, most of the participants were considered not socially isolated: 98.8% of the total sample, 99.0% of middle-aged adults, and 98.2% of elderly adults. The proportion of those who reported at least one CVD outcome was higher among the elderly subgroup (HRD:24.1%, PVRD: 56.7%) than among the middle-aged subgroup (HRD: 8.1%, PVRD: 33.6%). These descriptive statistics were similar in the CCA (see Supplementary Table S2).

3.3.2 Genetic Risk of CVDs

Table 2 reports the main effect associations of the PRS with HRD and PVRD. Among the total sample, PRS was significantly associated with HRD such that the adjusted odds of HRD increased by 6% per one unit increase in the PRS (OR=1.06, 95% CI: 1.04 to 1.07, $p<0.0001$). The PRS was also significantly associated with HRD in the middle-aged (OR=1.06, 95% CI: 1.03 to 1.08, $p<0.0001$) and elderly (OR=1.06, 95% CI: 1.03 to 1.08, $p<0.0001$) subgroups. For the secondary outcome, among the total sample PRS was significantly associated with PVRD such that the adjusted odds of PVRD increased by 1% per one unit increase in the PRS (OR=1.01, 95% CI: 1.00 to 1.02, $p=0.0127$). The PRS was significantly associated with PVRD in the middle-aged subgroup (OR=1.02, 95% CI: 1.00 to 1.03, $p=0.0127$), but not significantly associated with PVRD in the elderly subgroup (OR=1.01, 95% CI: 0.99 to 1.02, $p=0.6312$).

3.3.3 Depressive Symptoms and CVDs

The main effect associations between depressive symptoms (Group 1-4) and CVD outcomes are also reported in Table 3. Group 1 was the reference group in all models. Among the total sample, the adjusted odds of HRD were 41% and 57% higher in Group 3 and Group 4 compared to Group 1, respectively (OR=1.41, 95% CI: 1.15 to 1.75, p=0.0013 and OR=1.57, 95% CI: 1.20 to 2.04, p=0.0008, respectively). However, Group 2 was not significantly different from Group 1 (OR=1.01, 95% CI: 0.82 to 1.26, p=0.9001). Among the middle-aged subgroup, the adjusted odds of HRD was 56% higher in Group 3 (OR=1.56, 95% CI: 1.21 to 2.01, p=0.0006) and 75% higher in Group 4 (OR=1.75, 95% CI: 1.28 to 2.40, p=0.0005) compared to Group 1. The adjusted odds of HRD was not significantly different between Group 2 and Group 1 (OR=1.10, 95% CI: 0.82 to 1.49, p=0.5218). However, among the elderly subgroup, the adjusted odds of developing HRD were not significantly different for any of the depressive symptoms groups compared to Group 1 (Group 2: OR=0.96, 95% CI: 0.71 to 1.31, p=0.8039, Group 3: OR=1.11, 95% CI: 0.76 to 1.62, p=0.5920, Group 4: OR=1.26, 95% CI: 0.78 to 2.04, p=0.3488).

For the secondary outcome, among the total sample the adjusted odds of developing PVRD was 22% higher for Group 2 (OR=1.22, 95% CI: 1.05 to 1.40, p=0.0080), 42% higher for Group 3 (OR=1.42, 95% CI: 1.23 to 1.63, p<0.0001) and 68% higher for Group 4 (OR=1.68, 95% CI: 1.40 to 2.02, p<0.0001) compared to Group 1. A similar pattern was observed among the middle-aged subgroup, where the adjusted odds of developing HRD was 28% higher for Group 2 (OR=1.28, 95% CI: 1.07 to 1.53, p=0.0058), 49% higher for Group 3 (OR=1.49, 95% CI: 1.28 to 1.74, p<0.0001) and 73% higher for Group 4 (OR=1.73, 95% CI: 1.41 to 2.12, p<0.0001) compared to Group 1. The odds of developing PVRD in the elderly subgroup was

only significantly different between Group 4 compared to Group 1 (OR=1.67, 95% CI: 1.08 to 2.64, p=0.0226). However, the odds of developing PVRD did not significantly differ for either Group 2 or Group 3 compared to Group 1 among the elderly subgroup (Group 2: OR=1.13, 95% CI: 0.88 to 1.46, p=0.3275, Group 3: OR=1.17, 95% CI: 0.85 to 1.61, p=0.3264).

3.3.4 Social Isolation and CVDs

Social isolation was not significantly associated with HRD among the total sample (OR=0.98, 95% CI: 0.58 to 1.65, p=0.9352), the middle-aged subgroup (OR=1.59, 95% CI: 0.82 to 3.10, p=0.1738) or the elderly subgroup (OR=0.58, 95% CI: 0.26 to 1.30, p=0.1828). However, for the secondary outcome, significant associations were observed between social isolation and PVRD among the total sample and middle-aged subgroup. Those who were socially isolated had 65% higher adjusted odds of PVRD compared to those who were not socially isolated (OR=1.65, 95% CI: 1.07 to 2.56, p=0.0251). Among the middle-aged subgroup those who were socially isolated had 84% higher adjusted odds of PVRD compared to those who were not socially isolated. (OR=1.84, 95% CI: 1.04 to 3.26, p=0.0361). The association between social isolation and PVRD was not significant among the elderly subgroup (OR=1.41, 95% CI: 0.70 to 2.83, p=0.3362) (Table 4).

3.3.5 PRS x Psychosocial Factors Interaction on CVDs

When PRS was modelled as a continuous variable, there were no statistically significant interactions between the PRS and either PSF (depressive symptoms and social isolation) among the total sample or age subgroups. PRS was also modelled as a categorical variable by quintiles since gene-environment interactions may be more detectable when comparing extremes of genetic risk (lowest vs. highest) (7). No significant (or borderline significant) interactions were observed between the extreme quintiles (i.e. quintile 1 vs. quintile 5) for either PRS*depressive

symptoms or PRS*social isolation among the total analytical sample. Corresponding results in the CCA were very similar to the analysis using MI (Supplementary Tables S3-7).

Table 1 Participant Characteristics

Variable	Total (n=9,892)	Middle-Aged (n=7,155)	Elderly (n=2,737)
Age	63.0 (10.2)	57.9 (6.6)	76.3 (4.2)
Biological sex (Male)	49.2%	48.6%	50.6%
Total Household Income ($)			
Less than $20,000	5.6%	5.2%	6.7%
$20,000 or more, but less than $50,000	23.5%	17.9%	38.2%
$50,000 or more, but less than $100,000	35.2%	34.4%	37.4%
$100,000 or more, but less than $150,000	19.8%	22.6%	12.4%
$150,000 or more	15.9%	19.9%	5.4%
Self-Reported Ethnicity			
Caucasian	92.0%	90.9%	94.7%
Any other racial or cultural origin	8.0%	9.1%	5.3%
Smoking Status			
Current smoker	9.5%	11.2%	5.0%
Non-smoker	47.1%	48.3%	43.9%
Former smoker	43.4%	40.5%	51.1%
Education Level			
Less than secondary school graduate	5.5%	3.7%	10.2%
Secondary school graduate but no post-secondary education	9.8%	9.1%	11.8%
Post-secondary education but below a bachelor's degree	40.0%	39.8%	40.6%
Bachelor's degree	23.1%	25.5%	16.7%
Higher than a bachelor's degree	21.5%	21.8%	20.7%
Province at recruitment			
Alberta	9.7%	9.7%	9.7%
British Columbia	20.9%	20.6%	21.6%
Manitoba	10.3%	10.3%	10.1%
Newfoundland and Labrador	7.3%	7.4%	7.1%
Nova Scotia	10.1%	10.2%	10.0%
Ontario	21.3%	21.0%	22.3%
Quebec	20.4%	20.8%	19.3%
Urban vs. Rural Classification			
Rural	7.7%	8.3%	6.3%
Urban	90.9%	90.6%	91.8%
Postal code link to dissemination area	1.4%	1.2%	1.9%
Immigration Status			
Immigrant	17.7%	15.7%	23.1%
Not an immigrant	82.3%	84.3%	76.2%

Polygenic Risk Score (PRS)	37.7 (4.2)	37.8 (4.2)	37.6 (4.1)
Depressive Symptoms			
Group 1: No depressive symptoms	73.2%	71.3%	78.2%
Group 2: Current depressive symptoms	10.0%	9.4%	11.4%
Group 3: Clinically depressed but without any current depressive symptoms	10.7%	12.3%	6.7%
Group 4: Potential, recurrent depression	6.1%	7.0%	3.7%
Social Isolation			
Not socially isolated	98.8%	99.0%	98.2%
Socially isolated	1.2%	1.0%	1.8%
Heart-Related Disorders (HRD)			
At least one of the heart-related disorders	13.0%	8.8%	24.1%
None of the heart-related disorders	87.0%	91.2%	75.8%
Peripheral/Vascular-Related Disorders (PVRD)			
At least one of the peripheral/vascular-related disorders	40.0%	33.6%	56.7%
None of the peripheral/vascular-related disorders	60.0%	66.4%	43.3%

*cells indicate mean (standard deviation) unless otherwise specified

Table 2 Main Effects of PRS on CVDs with Multiple Imputation

	Outcome							
	HRD				*PVRD*			
Polygenic Risk Score	OR	95% CI		P-value	OR	95% CI		P-value
Total (n=9,892)	1.06	1.04	1.07	<0.0001	1.01	1.00	1.02	0.0127
Middle-Aged (n=7,155)	1.06	1.03	1.08	<0.0001	1.02	1.00	1.03	0.0127
Elderly (n=2,737)	1.06	1.03	1.08	<0.0001	1.01	0.99	1.02	0.6312

Table 3 Main Effects of Depressive Symptoms on CVDs with Multiple Imputation

		Outcome							
		HRD				*PVRD*			
	Depressive Symptoms*	OR	95% CI		P-value	OR	95% CI		P-value
Total (n=9,892)	1	1.00				1.00			
	2	1.01	0.82	1.26	0.9001	1.22	1.05	1.40	0.008
	3	1.41	1.15	1.75	0.0013	1.42	1.23	1.63	<0.0001
	4	1.57	1.57	2.04	0.0008	1.68	1.40	2.02	<0.0001
Middle-Aged (n=7,155)	1	1.00				1.00			
	2	1.10	0.82	1.49	0.5218	1.28	1.07	1.53	0.0058
	3	1.21	1.21	2.01	0.0006	1.49	1.28	1.74	<0.0001
	4	1.75	1.28	2.39	0.0005	1.73	1.41	2.12	<0.0001
Elderly (n=2,737)	1	1.00				1.00			
	2	0.96	0.71	1.31	0.8039	1.13	0.88	1.46	0.3275
	3	1.11	0.76	1.62	0.5920	1.17	0.85	1.61	0.3264
	4	1.26	0.78	2.04	0.3488	1.69	1.08	2.64	0.0226

*Each group of depressive symptoms is compared to the reference (Group 1)

Table 4 Main Effects of Social Isolation on CVDs with Multiple Imputation

	Outcome							
	HRD				*PVRD*			
*Social Isolation (1 vs. 0)**	OR	95% CI		P-value	OR	95% CI		P-value
Total (n=9,892)	0.98	0.58	1.65	0.9352	1.65	1.07	2.56	0.0251
Middle-Aged (n=7,155)	1.59	0.82	3.10	0.1738	1.84	1.04	3.26	0.0361
Elderly (n=2,737)	0.58	0.26	1.30	0.1828	1.41	0.70	2.83	0.3362

*Those who are socially isolated (coded as 1) are compared to the reference not socially isolated (coded as 0)

Table 5 Interactive Effects of PRS and PSFs on CVDs with Multiple Imputation

		Outcome							
		HRD				*PVRD*			
	PRS*PSFs	OR	95% CI		P-value	OR	95% CI		P-value
Continuous PRS									
Total (n=9,892)	PRS*Dep 1	1.00				1.00			
	PRS*Dep 2[+]	1.04	0.98	1.09	0.1789	0.97	0.93	1.00	0.0577
	PRS*Dep 3	1.00	0.95	1.05	0.9242	1.01	0.98	1.04	0.5683
	PRS*Dep 4	0.99	0.93	1.06	0.8366	1.00	0.95	1.04	0.8926
Middle-Aged (n=7,155)	PRS*Dep 1	1.00				1.00			
	PRS*Dep 2	1.05	0.97	1.13	0.2299	0.97	0.93	1.02	0.2142
	PRS*Dep 3	0.99	0.94	1.06	0.8243	1.01	0.98	1.05	0.5429
	PRS*Dep 4	0.76	0.90	1.05	0.4706	1.00	0.95	1.05	0.9455
Elderly (n=2,737)	PRS*Dep 1	1.00				1.00			
	PRS*Dep 2	1.03	0.95	1.11	0.4717	1.13	0.90	1.02	0.1380
	PRS*Dep 3	1.01	0.92	1.10	0.8558	1.17	0.93	1.07	0.9899
	PRS*Dep 4	1.04	0.92	1.18	0.5047	1.69	0.87	1.08	0.5925
Total (n=9,892)	PRS*SII 1’	1.06	0.93	1.20	0.3732	1.08	0.97	1.21	0.1691
Middle-Aged (n=7,155)	PRS*SII 1	1.04	0.87	1.24	0.6661	1.13	0.96	1.33	0.1304
Elderly (n=2,737)	PRS*SII 1	1.07	0.89	1.27	0.4736	1.03	0.89	1.20	0.6600
Extreme Quintiles of PRS (PRS 1 vs. 5)[$]									
Total (n=9,892)	PRS 1*Dep 1	1.00				1.00			
	PRS 1*Dep 2	0.76	0.37	1.56	0.4535	1.27	0.81	2.00	0.3025
	PRS 1*Dep 3	1.01	0.53	1.95	0.9693	0.91	0.59	1.40	0.6584
	PRS 1*Dep 4	1.43	0.56	3.64	0.4566	1.03	0.58	1.83	0.9154
Total (n=9,892)	PRS 1*SII 1	0.53	0.09	3.35	0.5029	0.47	0.11	2.04	0.3124

[+]Dep is the depressive symptoms group that is compared to reference (group 1)
‘Social isolation index (SII) compares those who are socially isolated (coded as 1) to the reference not socially isolated (coded as 0)
[$]PRS quintile 1 (lowest scores of PRS) is compared to the reference PRS quintile 5 (highest scores of PRS).

3.4 Discussion

This observational study investigated main and interactive associations of polygenic risk and PSFs on CVD outcomes by age using baseline data from a Canadian cohort. This represented a multiscale approach that assessed combinations of risk factors with CVD outcomes, and to our knowledge is the first such investigation evaluating genetic, psychosocial, and biological (age) risk factors with CVD. The findings indicate that polygenic risk and PSFs individually associate with CVD outcomes, but that these relationships may differ according to stage of the life course. GWAS have increasingly implicated common SNPs as risk factors for CVD, however, GWAS cohorts to date have been restricted to middle-aged adults (4). While our results suggest that a PRS for CVD associates with HRD to a similar extent among both middle-aged and elderly individuals, the association was attenuated for PVRD among elderly. Future studies would be warranted to evaluate the performance of PRS among different age groups, particularly because a nascent but growing body of evidence suggests that the influence of genetic risk may differ across the life course (9-11,84). In addition, PRS was strongly associated with HRD, but the association was much weaker with PVRD. This suggests that a different set of SNPs may be implicated with PVRD and so future research on constructing PRS for CVD risk assessment should consider CVD outcomes with different anatomical locations separately (46).

Among PSFs, various degrees of depressive symptoms were significantly associated with HRD and PVRD among middle-aged adults, but only the most severe depressive group (potential, recurrent depression) was associated with PVRD alone among elderly adults. These findings replicate recent results reported by Liu et al who investigated depression and CVD in the CLSA Comprehensive Cohort (43). However, our findings align with the previous report to suggest that depressive symptoms play a greater role at the mid-stage of the life course. Indeed, considering

stage of the life course is important because older adults have been described to exhibit differential stability of emotional experience such that positive states are maintained longer, and negative states are more quickly dismissed (85). This aging-related motivational shift may explain why depressive symptoms did not associate with CVD outcomes among the elderly subgroup to the same degree that we observed among the middle-aged subgroup.

Social isolation was significantly associated with increased risk of PVRD among the middle-aged subgroup, but not the elderly subgroup. This finding was unexpected since elderly adults have been identified as more vulnerable to social isolation (69). However, a likely explanation for our finding is an under-representation of socially isolated CLSA participants in the subset that had genome-wide genotyping performed, which may have impacted statistical power particularly among the elderly subgroup of our analysis that had a very low prevalence of social isolation. Menec et al. recently reported the prevalence of social isolation in the overall CLSA (n=47,752) to be 5.1% (65). The prevalence in our analytic sample, comprised of the 9,892 participants who had genotyping data available, was remarkably lower at 1.2%. The Comprehensive Cohort was chosen based on proximity and ability to be present at a CLSA data collection site (DCS) where blood samples were collected. Participants who were unable or unwilling to go to a DCS were excluded (86). CLSA participants who are socially isolated likely could not visit a DCS due to access barriers (e.g. living outside of proximity buffer or not being able to access transportation). CLSA follow-up efforts may benefit from incorporating mobile examination centres so that physical assessments and biospecimen collection can be obtained from a greater proportion of socially isolated participants, particularly as results from the present investigation and other studies (17-19,62-63,69) indicate that social isolation is a risk factor for CVD. Indeed, other population-based studies such as NHANES (87) have used mobile

examination centres to better reach participants who are unable or unwilling to go to a DCS (87-88).

Strengths of this investigation include the use of a national cohort with detailed data on participant genetics, health and lifestyle, and psychosocial factors. Additionally, we applied methods used in previous related studies for consistency, including our construction of a PRS for CVD (7) and our use of the same CVD outcomes (43), depressive symptoms (43) and SII (65) groupings that were utilized by separate investigations conducted with CLSA data. A potential limitation is the non-specific format of CLSA questions about participant CVD diagnosis history (e.g. only providing a response option for heart disease rather than specifying coronary or congenital heart disease) and that diagnosis was not ascertained could introduce response bias. To account for this measurement error, we categorized CVD variables into broad groupings rather than individual CVD outcomes (43). Potential survival bias in the CLSA cohort may have prevented certain associations from being detected. For example, if mortality from CVD is truly higher among elderly individuals with less favorable psychosocial status, elderly participants who have been diagnosed with CVD and are also socially isolated or present with depression would be underrepresented in CLSA (89). We did not correct for multiple testing and so it is possible that some of our findings represent false positives. While a stringent Bonferroni correction may not be the most appropriate for our investigation (owing to the possible interrelationship between PSFs), lowering our alpha to 0.01 does not materially alter our overall findings. Moreover, due to the cross-sectional nature of the study the directionality of associations between PSFs (particularly depression (90)) and CVD outcomes cannot be determined. Lastly, lack of genetic data for a larger sample of socially isolated participants may have also affected statistical power to detect certain associations.

This study provides evidence that polygenic risk and PSFs independently associate with CVD outcomes, but that stage of the life course and type of CVD are important considerations underscoring the importance of a multiscale risk factor approach. Future studies that explore the possible bidirectional nature of depression and CVD and possible mediators of associations between PSFs and CVD are warranted in order to provide insight into novel targets for strategies to prevent CVD.

Chapter 4

Discussions, Limitations and Future Directions

4.1 General Summary

This cross-sectional study examined the main and interaction associations between genetics and psychosocial factors on the risk of two subgroups of cardiovascular diseases, heart-related disorders (HRD) and peripheral/vascular-related disorders (PVRD) using baseline data from the CLSA (n=9,892). The findings indicate that polygenic risk is associated with both HRD and PVRD in middle-aged adults, however only HRD in the elderly. Among middle-aged participants, all groups of depressive symptoms compared to the reference group 1 (no depressive symptoms) were significantly associated with PVRD. Group 3 (clinical depression without current symptoms) and group 4 (potential, recurrent depression) compared to no depressive symptoms were significantly associated with HRD in middle-aged adults. Among the elderly, only the highest level of depressive symptoms (group 4) compared to no depressive symptoms was significantly associated with PVRD. This supports the findings presented in Liu et al. (43) that self-reported depression is associated with an increased risk of CVDs in those over the age of 45 years old (43). Our findings align with the previous investigation by demonstrating that depressive symptoms may be particularly important in middle-aged adults rather than elderly (defined as aged 70 years and older). Similarly, among middle-aged participants, social isolation significantly associated with PVRD. These results suggest that genetics and psychosocial factors are individually associated with CVDs.

Although genetics and psychosocial factors individually related to CVD, no statistically significant interaction was observed between genetics and psychosocial factors (depression or social isolation) with HRD or PVRD. Previous studies have shown that an interaction between genetic and non-genetic risk factors (i.e. healthy lifestyle) may be significant when PRS is evaluated as categories rather than as a continuous variable (7). In fact, non-genetic risk factors may influence polygenic risk of CVD, which may be particularly evident among those in the highest PRS category (7). PRS was separated into quintiles to look at the interaction associations with psychosocial factors (depression and social isolation). PRS quintile 1 (lowest scores of PRS) compared to quintile 5 (the highest scores of PRS) was assessed in the total sample. No significant interactions in the anticipated pattern (PRS quintile 1 vs. 5) were observed between PRS and psychosocial factors on either HRD or PVRD. Previous studies that have evaluated lifestyle factors as moderators of genetic risk have reported that a favorable lifestyle was able to decrease the risk of CVD, which was particularly beneficial among those with a high PRS (7). Similar patterns of association were thought to occur in regard to psychosocial factors as moderators of genetic risk. The presence of no depressive symptoms was thought to possibly have an effect on reducing the risk of CVDs in those with a high PRS compared to a low PRS. However, the results when looking at the interaction between PRS as extreme quintiles and depressive symptoms did not follow this expected pattern. Therefore, it appears that psychosocial factors as moderators of genetic risk may have low biological plausibility and that genetics and psychosocial factors may impact CVD risk independently (*see Sections 2.2 to 2.4)*. However, future studies conducted in different study populations are still necessary in order to confirm that in fact these significant interactions do not exist.

Furthermore, sensitivity analyses included a complete case analysis to compare with the results of the statistical imputation. The complete case analysis was done by removing observations that had missing values for any variable included in the model. For the models including PRS and depressive symptoms, there were few missing observations (see Table S2) and therefore results were similar to that of the multiple imputation analysis. This includes PRS being significantly associated with HRD and PVRD for middle-aged adults and with HRD for the elderly. All significant associations of depressive symptoms groups compared to reference for both HRD and PVRD in middle-aged and elderly participants were the same between the complete case analysis and multiple imputation. All interactions between PRS and psychosocial factors were not statistically significant as was seen for the multiple imputation analysis.

However, the results for social isolation varied between the complete case analysis and the multiple imputation analysis. This was mainly due to the vast amount of missing data for observations in the calculation of the social isolation index. The degree of missingness for the social isolation variables included in the creation of the index went up to 15% for one variable on social contacts. There was a total of 16 variables included in the formation of the social isolation index and if a participant was missing a value for even one of these variables then their social isolation index could not be calculated since missing data would lead to an underestimation of their social isolation score. This led to a reduction in sample size by 3,633 participants (40% decrease) for the total sample. With this markedly smaller sample size compared to the multiple imputation analysis, there was a substantial decrease in the statistical power to detect significant associations given the low prevalence of social isolation within the analytical sample. Therefore, in the complete case analysis there was no significant association between social isolation and PVRD among middle-aged adults as was detected with the multiple imputation analysis. The use

of a statistical multiple imputation increased the statistical power to enable the detection of a significant association, which explains the difference in findings between the two approaches.

4.2 Strengths and Limitations

This investigation has both its strengths and limitations. The strengths include the examination of novel interaction associations between polygenic risk, psychosocial factors and the prevalence of physician diagnosed HRD and PVRD. In fact, this study uses aspects from various previous related investigations enabling consistency in methodologies, including the construction of a PRS based on Khera et al. (7), a social isolation index created by Menec et al. (65), and groups of depressive symptoms formed by Liu et al. (43). The latter two of these previous studies also examined baseline data from the CLSA cohort and the subgroups of CVD, which included HRD and PVRD, were also based on the previous work by Liu et al. (43). Another strength of this study is the utilization of comprehensive data from a national cohort that contained variables that are not often measured together (i.e. genetic data, health and lifestyle and psychosocial factors). A final strength of this study is that potential bias owing to missing data for the exposures, outcomes and co-variates was mitigated by the use of statistical multiple imputation. This is a widely accepted approach for dealing with missing data as a complete case analysis with large amounts of missing data can lead to biased estimates and loss of a significant amount of statistical power (91).

Limitations of this investigation include its cross-sectional nature making it difficult to determine the directionality of significant associations. This study looked at psychosocial factors as the exposures and CVDs as the outcome measures, however it may be that diagnosis of CVDs led to less favorable psychosocial status or that CVDs and less favorable psychosocial status occur concurrently. A longitudinal study would need to be performed to look at the direction of

these associations, especially between depressive symptoms and CVDs. An additional limitation is the possibility of selective survival bias within the CLSA cohort such that seniors diagnosed with CVDs may have overall healthier lifestyles, which is why they have survived to this older age (89). If seniors with less favorable psychosocial factors who were diagnosed with CVD died more often, then the frequency of elders with less favorable psychosocial status diagnosed with CVD would be underrepresented within this cohort (89). This would prevent detection of possible significant associations between psychosocial factors and CVD among the elderly population (89), which may have been the case with our findings for social isolation. Therefore, the possibility of selective survival bias is a limitation of this study. Another limitation was the non-specific format of CLSA questions about physician-diagnosed CVD that may have introduced response bias (43). For example, participants were asked about if a doctor had informed them that they had heart disease but failed to specify coronary artery disease or congenital heart disease (43). CVD was categorized into these two broad groupings of HRD and PVRD rather than individual CVD outcomes to account for the possible measurement error that would accompany lack of specificity (43). A fourth limitation is the low prevalence of socially isolated individuals in our analytical sample of CLSA participants with genome-wide genotyping (1.2%), which led to decreased statistical power to detect significant associations between social isolation and CVDs. Lastly, a final limitation is that survey weights were not applied in this analysis as they were not available for the genotyped cohort, therefore this sample is not a representation of the Canadian population. In addition, CLSA does not recruit individuals living on federal First Nations reserve (92), who are known to be vulnerable to psychosocial (93-95) and chronic disease outcomes (96-97). While this analysis contributes to furthering the

understanding of relationships between psychosocial variables and CVD, the broader social determinants of health were not examined.

4.3 Future Directions

GWAS have identified genetic variants that are associated with an increased risk of CVD, however GWAS have mainly been performed in middle-aged adults (4). In this study, polygenic risk was significantly associated with PVRD among middle-aged participants, however the association was attenuated in the elderly. This finding adds to the growing evidence that genetics may have varying influence on the risk of chronic diseases at different stages over the life course (9-11). Future studies conducted examining the association between genetic risk and CVD may want to further examine how these associations vary according to different age groups. Additionally, findings from this study show that the PRS was strongly associated with HRD and to a much lesser extent with PVRD in middle-aged participants. As the SNPs used to construct this PRS were mainly associated with HRD in previous studies (7), the weaker associations with PVRD may suggest that a different set of SNPs are be implicated with PVRD. Future studies may want to take this into consideration when developing PRS for CVD outcomes. It may be more beneficial to construct PRS separately for CVD outcomes of different anatomical locations (46).

The availability of genome-wide genotyping also enabled adjustment for principal components of ancestry in place of using self-reported ethnicity as a covariate in analyses. This is a method used to capture genetic ancestry of participants that involves identifying patterns of inheritance of genetic variants (i.e. SNPs) where individuals who have inherited common sets of SNPs share a common ancestry (34). This approach is not a measure of ethnicity as ethnicity is not simply a biological trait but rather includes cultural heritage, language, social practice,

traditions and geopolitical factors that are not captured by the principal component analysis for genetic ancestry (33). However, limitations are present in self-reported measures of ethnicity that are commonly used as part of population survey studies. Participant confusion of labels that were used in questions that asked for self-reporting of ethnicity has been reported (98), highlighting the possibility for inaccuracy in self-reported ethnicities.

Furthermore, the association between depressive symptoms and CVDs was only significant among middle-aged participants. Studies have shown that compared with younger adults, older adults show differential stability of emotional experience such that positive states are maintained longer, and negative states are more quickly dismissed (85). This aging-related motivational shift can be a powerful influence on health (85). Consequently, fewer individuals may experience depressive symptoms in their older age resulting in less of an impact on CVD (85). This study further supports this notion by demonstrating that among the elderly, there is an attenuation of the association between all groups of depressive symptoms compared to no depressive symptoms and HRD and only the highest depressive symptoms group compared to no depressive symptoms was associated with PVRD. The associations between groups of depressive symptoms compared to none with HRD and PVRD were more pronounced in middle-aged participants. This suggests a possible benefit of including some consideration of an individual's psychosocial status in CVD risk screening tools for middle-aged adults. The gold standard CVD risk screening tool used currently to assess 10-year CVD risk is the Framingham Risk Score (FRS) (99). However, findings from this this study are suggestive of the possible utility of implementing, alongside or within the FRS, these simple measures of depressive symptoms to improve the assessment of the risk of CVD, especially among middle-aged adults.

Furthermore, social isolation was significantly associated with PVRD in middle-aged adults only. However, the prevalence of social isolation in this analytical sample of CLSA participants with genome-wide genotyping data was 1.2%, substantially lower than the proportion in the overall CLSA (5.1%). A potential explanation for this discrepancy in the proportions of those socially isolated may be due to the difference in recruitment methods for the CLSA Tracking cohort and Comprehensive cohort. For the Tracking cohort, who undergo solely telephone interviews, the participants were randomly selected across the 10 provinces (86). For the Comprehensive cohort, participants were selected to go to data collection sites (DCS) for in-person interviews and physical assessments including collection of biospecimen samples (blood and urine) based on proximity to the DCS (86). These participants were randomly selected from within 25-50 km of one of the eleven DCS located within their province (86). From the Comprehensive cohort who provided blood samples, 9,896 participants were randomly selected for genome-wide genotyping on DNA samples (100). This method of selection of participants meant those who did not live in close proximity to the DCS or were unable or unwilling to transport themselves to the DCS, which would be plausible for socially isolated individuals would not be included in the Comprehensive cohort. Contrarily, collecting information via telephone interviews as seen for the Tracking cohort is much more accommodating to those who may be socially isolated and therefore may capture more of these individuals. This possibly explains why the proportion of those who were socially isolated in the entire CLSA cohort used by Menec et al. (65) is much higher than in our analytical sample. The CLSA recruitment methods may have resulted in an underrepresentation of socially isolated individuals specifically in the Comprehensive cohort. Follow-up efforts to correct for the underrepresentation of socially isolated individuals in the Comprehensive cohort due to inability to be present at DCS may be to

use mobile examination centers as done by NHANES, a large longitudinal study to assess health and nutrition in the United States (87). Mobile examination centres have also been incorporated into The Manitoba Personalized Lifestyle Research (TMPLR) study protocol where participants will complete questionnaires, undergo health assessments and provide biospecimen samples within these travelling research units so that more individuals in Manitoba can be reached to participate in the study (88). CLSA follow-up efforts may benefit from providing mobile examination centres so that participants who are not in close proximity to the DCS, unable or unwilling to travel can also be included in the Comprehensive cohort and therefore allow for a more representative sample including those who may be socially isolated.

Although genetics and psychosocial factors individually related to CVD, no statistically significant interaction was observed between genetics and psychosocial factors (depression or social isolation) with HRD or PVRD. Lifestyle may be a potential mediator in the relationship between psychosocial factors and CVDs. Psychosocial factors have been shown in the literature to be associated with lifestyle, although the association between depression and lifestyle compared to social isolation and lifestyle may differ. Depression and social isolation are related constructs of psychosocial status; however, they are not consistently correlated (67). A major risk factor of depression is loneliness, which therefore makes depression more of an emotional state (68). The relationship between depression and lifestyle may in fact be bidirectional. Some studies report that the presence of depression is associated with a more sedentary lifestyle and higher rates of obesity (23-24). Other studies report that an unhealthy dietary pattern including a high consumption of red meat and/or processed meat, refined grains, sweets, high-fat dairy products, low intake of fruits and vegetables, etc. and higher rates of obesity are associated with an increased risk of depression (21-22, 24). Therefore, the relationship between depression and

lifestyle can occur in either direction. On the other hand, social isolation seems to be more of a circumstantial rather than an emotional state and therefore a separate construct of psychosocial status (67). The relationship between social isolation and lifestyle may be more unidirectional. Studies have mainly shown that those who are socially isolated are more likely to eat lower amounts of fruits and vegetables and engage in physical activity less often than those who are not socially isolated in the elderly population (101) as well as across all ages (20). Thus, the relationships between depression and social isolation with lifestyle may differ further demonstrating that these are independent constructs of psychosocial status. Nevertheless, a commonality between both psychosocial factors is that previous research indicates that they both influence lifestyle (20-24). Additionally, unfavorable lifestyle composed of obesity (BMI>30), smoking, unhealthy dietary pattern and physical inactivity is associated with an increased risk of CVDs (7). Therefore, lifestyle factors may present themselves as mediators in the relationship between psychosocial factors and CVD and consequently, it would not be appropriate to include these as co-variates in the logistic regression models since they may sit on the causal pathway between psychosocial factors and CVDs. However, this may be a possible explanation for no significant interactions being observed between genetic risk and psychosocial factors on CVDs. Psychosocial factors may not act as moderators of polygenic risk of CVD themselves, but rather are upstream of lifestyle which is a likely moderator in the relationship between genetic risk and CVD (7). For example, having a more favorable psychosocial status may lead to a healthier lifestyle, which may counteract high polygenic risk of CVD and therefore decrease the risk of CVD. Although no significant interactions were seen between psychosocial factors and genetics, further investigations are required in different study populations to confirm that these interactions do not exist and an assessment of lifestyle as a mediator of the relationship between

psychosocial factors and genetic risk of CVD is warranted. In addition, other psychosocial factors might be important to consider in future research such as life satisfaction (102-104) personality (105) and perceived social support (18,63).

To summarize, future directions based off of findings from this observational study include consideration of stage of life and anatomical location of CVD when assessing the relationship between polygenic risk and CVD, incorporation of measures of depressive symptoms into CVD risk assessment of middle-aged adults, refinement of CLSA methods to include more socially isolated individuals and examining the mediator/moderator relationships between genetic and environmental exposures on CVDs.

4.4 Conclusion

In all, this study furthers the understanding of the role of genetic and non-genetic (i.e. environmental) risk factors of CVDs. Specifically, findings from this study suggest that polygenic risk and psychosocial factors are independently associated with CVD outcomes (HRD and PVRD). However, these associations may vary depending on stage of the life course and anatomical location of CVD outcomes. Although significant, the directionality of the associations between psychosocial factors, especially depression and CVD require further clarification. In fact, the relationship between depression and chronic disease may actually be bidirectional (90). Similarly, this study does not report any significant interactions, however, replication of this analysis is needed in other study populations to confirm that an interaction does not exist. Therefore, future studies should further explore these relationships focusing on their directionality in order to provide insight into novel targets to prevent CVD.

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APPENDIX

Supplementary Material

Missing Data Estimated with Multiple Imputation Analysis

The highest proportion of missing observations was one of the variables used in the SII, specifically for last get together with children outside of house with 1,488 missing observations out of 9,892 (15%). After this, the amount of missing observations for each variable goes as follows: last get together with neighbours (n=1,224), last get together with siblings (n=874), total household income (n=616), last get together with friends outside of the house (n=594), current marital status (n=582), urban/rural classification (n=138), last get together with relatives outside of house (n=82), physician-diagnosed high blood pressure (n=57), physician-diagnosed peripheral vascular disease (n=56), physician-diagnosed angina (n=56), CESD-10 screen for depression (n=50), physician-diagnosed heart disease (n=48), physician-diagnosed myocardial infarction (n=47), physician-diagnosed cerebrovascular accident (n=38), retirement status (n=36), participation in service clubs or fraternal organizations (n=28), education level (n=21), participation in neighborhood, community or professional activities (n=23), participation in any other recreational activities (n=22), participation in church or religious activities (n=21), participation in educational or cultural activities (n=18), participation in sport or physical activities (n=18), participation in volunteering or charity activities (n=17), participation in family or friend based activities (n=16), number of people living in household (n=8) and immigration status (n=2). The following variables had no missing observations: biological sex, age, smoking status, province at recruitment, PRS, and first five principal components of ancestry. The degree of missingness ranged from 0-15%. The rule of thumb is that the number of imputed datasets

chosen is based on the percentage of missingness in the dataset. In order to remain on the side of caution, a total of 20 imputed datasets was chosen (38).

Complete Case Analysis

Before multiple imputation was performed, a complete case analysis was run where missing observations were not included in the analysis. For the primary outcome of HRD, this resulted in a total sample size of n=7,319 with n=5,479 individuals in the middle-aged group (45-69 years old) and n=1,840 in the elderly group (70 years old and more). For analysis run using depressive symptoms as the main independent variable, there were even fewer observations with n=7,285 in the total sample, where n=5,460 were in the middle-aged group and n=1,825 were in the elderly group. For the secondary outcome of PVRD, the total sample size was n=7,320 participants with n=5,476 in the middle-aged group and n=1,844 in the elderly group. For the analysis run with depressive symptoms as the primary predictor variable, the total sample was n=7,287 participants with n=5,457 in the middle-aged group and n=1,830 in the elderly group.

Supplementary Tables

Table S1 Single Nucleotide Polymorphisms (n=39) used to create Polygenic Risk Score for Cardiovascular Disease

Gene Locus	SNP	Ln (Published Odds Ratio)
SORT1	rs599839	0.104
PPAP2B	rs17114036	0.104
PCKS9	rs11206510	0.077
IL6R	rs4845625	0.039
MIA3	rs17465637	0.131
GGCX/VAMP8	rs1561198	0.049
ABCG8	rs6544713	0.058
APOB	rs515135	0.077
ZEB2-AC074093.1	rs2252641	0.039
WDR12	rs6725887	0.113
MRAS	rs9818870	0.068

SLC22A4/SLC22A5	rs273909	0.086
KCNK5	rs10947789	0.058
ANKS1A	rs17609940	0.068
PHACTR1	rs12526453	0.095
SLC22A3/LPAL2/LPA	rs2048327	0.058
LPA	rs3798220	0.412
HDAC9	rs2023938	0.068
BCAP29	rs10953541	0.077
ZC3HC1	rs11556924	0.086
TRIB1	rs2954029	0.039
CDKN2BAS	rs3217992	0.148
CDKN2A	rs4977574	0.255
ABO	rs579459	0.068
KIAA1462	rs2505083	0.058
CXCL12	rs501120	0.068
LIPA	rs2246833	0.058
CYP17A1	rs12413409	0.113
APOA5	rs964184	0.122
HNF1A	rs2259816	0.077
SH2B3	rs3184504	0.068
FLT1	rs9319428	0.049
COL4A1	rs4773144	0.068
HHIPL1	rs2895811	0.058
RASD1	rs12936587	0.058
SMG6	rs216172	0.068
UBE2Z	rs46522	0.058
LDLR	rs1122608	0.095
KCNE2	rs9982601	0.122
Total	39	3.517

Table S2 Participant Characteristics for Complete Case Analysis

Variable	**Total (n=9,892)**	**Middle-Aged (n=7,155)**	**Elderly (n=2,737)**
Age	63.0 (10.2)	57.9 (6.6)	76.3 (4.2)
Biological sex (Male)	49.2%	48.6%	50.6%
Total Household Income ($)			
Less than $20,000	5.5%	5.1%	6.7%
$20,000 or more, but less than $50,000	23.0%	17.7%	37.4%
$50,000 or more, but less than $100,000	35.3%	34.4%	37.8%
$100,000 or more, but less than $150,000	20.1%	22.8%	12.7%
$150,000 or more	16.2%	20.1%	5.8%
Missing	n=616	n=346	n=270
Self-Reported Ethnicity			

Caucasian	92.0%	90.9%	94.7%
Non-Caucasian	8.0%	9.1%	5.3%
Missing	n=78	n=61	n=17
Smoking Status			
Current smoker	9.5%	11.2%	5.0%
Non-smoker	47.0%	48.3%	43.9%
Former smoker	43.4%	40.5%	51.1%
Education Level			
Less than secondary school graduate	5.5%	3.7%	10.1%
Secondary school graduate but no post-secondary education	9.8%	9.1%	11.8%
Post-secondary education but below a bachelor's degree	40.1%	39.8%	40.6%
Bachelor's degree	23.1%	25.5%	16.8%
Higher than a bachelor's degree	21.5%	21.8%	20.7%
Missing	n=21	n=7	n=14
Province at recruitment			
Alberta	9.7%	9.7%	9.7%
British Columbia	20.9%	20.6%	21.6%
Manitoba	10.3%	10.3%	10.1%
Newfoundland and Labrador	7.3%	7.4%	7.1%
Nova Scotia	10.1%	10.2%	10.0%
Ontario	21.3%	21.0%	22.3%
Quebec	20.4%	20.8%	19.3%
Urban vs. Rural Classification			
Rural	7.7%	8.3%	6.3%
Urban	90.9%	90.6%	91.8%
Postal code link to dissemination area	1.4%	1.2%	1.9%
Immigration Status			
Immigrant	17.7%	15.7%	23.1%
Not an immigrant	82.3%	84.3%	76.9%
Missing	n=2	n=1	n=1
Polygenic Risk Score (PRS)	37.7 (4.2)	37.8 (4.2)	37.6 (4.1)
Depressive Symptoms			
Group 1: No depressive symptoms	73.3%	71.4%	78.4%
Group 2: Current depressive symptoms	9.9%	9.4%	11.4%
Group 3: Clinically depressed but without any current depressive symptoms	10.8%	12.3%	6.7%
Group 4: Potential, recurrent depression	6.0%	6.9%	3.6%
Missing	n=76	n=36	n=40
Social Isolation			
Not socially isolated	99.2%	99.4%	98.7%
Socially isolated	0.8%	0.6%	1.3%
Missing	n=3,924	n=2,735	n=1,189
Heart-Related Disorders (HRD)			

At least one of the heart-related disorders	13.3%	9.0%	24.6%
None of the heart-related disorders	86.7%	91.0%	75.4%
Missing	n=72	n=39	n=33
Peripheral/Vascular-Related Disorders (PVRD)			
At least one of the peripheral/vascular-related disorders	40.1%	33.7%	56.8%
None of the peripheral/vascular-related disorders	59.9%	66.3%	43.2%
Missing	n=76	n=46	n=30

*cells indicate mean (standard deviation) unless otherwise specified

Table S3 Main Effects of PRS on CVDs for Complete Case Analysis

	Outcome								
	HRD				*PVRD*				
Polygenic Risk Score	OR	95% CI		P-value		OR	95% CI		P-value
Total (n=9,188)	1.06	1.04	1.07	<0.0001	Total (n=9,187)	1.01	1.00	1.02	0.0231
Middle-Aged (n=6,766)	1.05	1.03	1.07	<0.0001	Middle-Aged (n=6,759)	1.01	1.00	1.03	0.0306
Elderly (n=2,422)	1.06	1.02	1.07	<0.0001	Elderly (n=2,428)	1.00	0.99	1.03	0.5507

Table S4 Main Effects of Depressive Symptoms on CVDs for Complete Case Analysis

		Outcome							
		HRD				*PVRD*			
Depressive Symptoms*	Obs.	OR	95% CI		P-value	Obs.	OR	95% CI		P-value
1	Total (n=9,138)	1.00				Total (n=9,137)	1.00			
2		1.06	0.85	1.32	0.6375		1.19	1.03	1.39	0.0223
3		1.51	1.11	1.86	0.0001		1.40	1.22	1.62	<0.0001
4		1.55	1.55	2.04	0.0017		1.66	1.37	2.01	<0.0001
1	Middle-Aged (n=6,741)	1.00				Middle-Aged (n=6,734)	1.00			
2		1.12	0.83	1.53	0.4634		1.30	1.09	1.56	0.0043
3		1.65	1.28	2.12	0.0001		1.46	1.25	1.72	<0.0001
4		1.74	1.26	2.42	0.0009		1.66	1.34	2.05	<0.0001
1	Elderly (n=2,397)	1.00				Elderly (n=2,403)	1.00			
2		1.02	0.74	1.41	0.9185		1.02	0.78	1.34	0.8914
3		1.19	0.81	1.75	0.3866		1.17	0.84	1.63	0.3531
4		1.23	0.73	2.05	0.4376		1.96	1.20	3.20	0.0076

*Each group of depressive symptoms is compared to the reference (Group 1)

Table S5 Main Effects of Social Isolation on CVDs for Complete Case Analysis

	Outcome								
	HRD				*PVRD*				
*Social Isolation (1 vs. 0)**	OR	95% CI		P-value		OR	95% CI		P-value
Total (n=5,555)	0.75	0.30	1.87	0.5316	Total (n=5,553)	2.42	1.18	4.97	0.0156
Middle-Aged (n=4,182)	1.64	0.56	4.78	0.3648	Middle-Aged (n=4,180)	2.07	0.88	4.84	0.0941
Elderly (n=1,373)	0.20	0.03	1.60	0.1298	Elderly (n=1,373)	4.21	0.92	19.21	0.0631

*Social isolation index is those who are socially isolated (coded as 1) compared to the reference not socially isolated (coded as 0)

Table S6 Interaction Effects of PRS and Depressive Symptoms on CVDs for Complete Case Analysis

		Outcome								
		HRD					*PVRD*			
	PRS*Dep[+]	OR	95% CI		P-value		OR	95% CI		P-value
Total (n=9,138)	PRS*1	1.00				Total (n=9,137)	1.00			
	PRS*2	1.02	0.97	1.08	0.4645		0.97	0.93	1.00	0.0594
	PRS*3	0.99	0.95	1.05	0.8054		1.02	0.98	1.05	0.3273
	PRS*4	0.98	0.92	1.05	0.6368		1.00	0.95	1.04	0.8514
Middle-Aged (n=6,741)	PRS*1	1.00				Middle-Aged (n=6,734)	1.00			
	PRS*2	1.02	0.95	1.10	0.5515		0.97	0.93	1.02	0.2370
	PRS*3	1.00	0.94	1.06	0.8917		1.01	0.98	1.05	0.5215
	PRS*4	0.96	0.89	1.04	0.2822		1.00	0.95	1.06	0.9031
Elderly (n=2,397)	PRS*1	1.00				Elderly (n=2,403)	1.00			
	PRS*2	1.02	0.94	1.10	0.6424		0.95	0.89	1.01	0.1052
	PRS*3	1.00	0.91	1.09	0.9115		1.04	0.96	1.12	0.3618
	PRS*4	1.06	0.92	1.22	0.3967		0.97	0.86	1.09	0.5721

[+]Dep is the depressive symptoms group that is compared to reference (group 1)

Table S7 Interaction Effects of PRS and Social Isolation on CVDs for Complete Case Analysis

		Outcome								
		HRD					*PVRD*			
	PRS*SII[+]	OR	95% CI		P-value		OR	95% CI		P-value
Total (n=5,555)	PRS*1	0.96	0.77	1.21	0.7566	Total (n=5,553)	1.12	0.93	1.35	0.2408
Middle-Aged (n=4,182)	PRS*1	0.98	0.74	1.30	0.8805	Middle-Aged (n=4,180)	1.19	0.88	1.43	0.1656
Elderly (n=1,373)	PRS*1	1.04	0.66	1.63	0.8766	Elderly (n=1,373)	1.03	0.74	1.44	0.8669

[+]SII is those who are socially isolated (coded as 1) compared to the reference not socially isolated (coded as 0)