OSTEOARTHRITIS AND CARDIOVASCULAR DISEASE RISK

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CARDIOVASCULAR RISK IN INDIVIDUALS WITH AND WITHOUT OSTEOARTHRITIS USING THE CANADIAN LONGITUDINAL STUDY ON AGING

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Title: Cardiovascular Risk in Individuals with and without Osteoarthritis Using the Canadian Longitudinal Study on Aging

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Lay Abstract

Osteoarthritis (OA) and cardiovascular disease (CVD) are two of the most prevalent comorbidities that affect the aging population. Surrogate measures of CVD, such as CVD risk scores and carotid intima-media thickness, have rarely been examined in individuals with OA despite studies showing elevated CVD risk in individuals with OA. We used baseline and 3-year follow-up data collected by the Canadian Longitudinal Study on Aging to study CVD risk factors in older individuals with and without OA, with considerations given to the site of OA and to menopause, which are additional non-modifiable factors known to influence vascular outcomes. We hypothesized that individuals with OA have greater CVD risk and odds of developing CVD compared to individuals without OA. We found that individuals with OA have greater CVD risk and odds of developing CVD at 3-year follow-up, with no influence of OA site on CVD outcomes, and post-menopausal women with OA have greater odds of developing CVD than post-menopausal women without OA. Our findings suggests that aspects of the OA pathology play a role in increasing CVD risk, which are partially explained through shared risk factors and etiology.

Abstract

Osteoarthritis (OA) is a prevalent and progressive musculoskeletal condition characterized by the degradation of the cartilage and bone and is often comorbid with cardiovascular disease (CVD), with both disease prevalence's increasing with age. Several factors, such as the site of OA and the menopause transition, are known to independently influence both conditions. OA and CVD share overlapping risk factors and proposed mechanisms, though it is not well understood how these mechanisms influence the risk of comorbidity. This thesis examines the relationship of CVD risk factors, sites of OA, and menopausal variables on CVD risk in individuals with OA.

The first aim of this thesis was to examine preclinical markers of CVD risk, namely the carotid intima-media thickness (cIMT) and cardiovascular risk scores, the Framingham risk score (FRS) and the InterHeart risk score (IHRS), in individuals with and without OA to examine differences in CVD risk profiles. Additional considerations were given to the site of OA, as well as non-specific CVD risk factors (such as social disadvantage and frailty). Risk factors were compared between age- and sex-matched individuals with and without OA and between weight-bearing and non-weight bearing OA. Individuals with OA had significantly greater cIMT, FRS, and IHRS, though no differences were found when comparing the site of OA. Unadjusted and multivariate adjusted odds ratios (OR) calculated odds of CVD at 3-year follow-up in the same cohorts. There was a significantly unadjusted ($p<0.001$, OR:1.70) and adjusted ($p<0.001$, OR ranging from 1.67-1.70) influence of OA diagnosis on odds of CVD at 3-year follow-up. There was no significant unadjusted or adjusted difference in odds of CVD at 3-year follow-up when comparing different sites of OA (p ranging from 0.24-0.75, OR ranging from 0.69-0.71).

The second aim of this thesis was to study CVD risk in post-menopausal women. CVD risk factors and the IHRS were used to calculate differences between age-matched post-menopausal women. Unadjusted and multivariable adjusted ORs calculated odds of CVD at 3-year follow-up. There was a significant unadjusted influence of OA diagnosis ($p=0.03$, OR:1.34) on CVD outcomes, though the effect of OA diagnosis became non-significant after adjusting for the IHRS ($p=0.25$, OR:1.36) and the IHRS with menopausal variables ($p=0.22$, OR:1.40).

Although OA is a multifaceted condition, it has often been viewed as a joint-centric disease. The elevated risk of CVD individuals with OA suggests that additional aspects of the OA pathology, such as inflammation and frailty, may drive the increase in risk of CVD independent of age, sex, or menopausal status.

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Preface

This Master's thesis contains two manuscripts that will be submitted to journals for publication and is formatted as a "sandwich" thesis. The first chapter provides background of the thesis topics and reviews previous literature. The second and third chapters contain the two manuscripts, which contains introduction, methods, results, and discussion sections. As the manuscripts follow similar research methodology and use the same dataset, there is overlap in the methods and limitations sections. At the time of submission of this thesis, the manuscripts are being prepared for submission to peer-reviewed journals. A comprehensive table of contents begins on page vii.

Disclaimer: The opinions expressed in these manuscripts are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

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List of Abbreviations

BMI	Body mass index
cIMT	Carotid intima-media thickness
CLSA	Canadian Longitudinal Study on Aging
cm	Centimetres
CVD	Cardiovascular disease
FRS	Framingham Risk Score
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
hsCRP	High-sensitivity C-reactive protein
HT	Hormone therapy
IHRS	InterHeart Risk Score
kg	Kilograms
LDL	Low-density lipoprotein
m	Metres
OA	Osteoarthritis
OR	Odds ratio
PASE	Physical Activity Scale for the Elderly
SD	Standard deviation
SDS	Social disadvantage score
TUG	Timed-up-and-go
WH ratio	Waist-to-hip ratio
%	Percentage

Declaration of Academic Achievement

I, Yixue Mei, declare this thesis work to be my own. I assisted with creating the study design, and for both the manuscripts I performed the data extraction, statistical analysis, interpretation of results, and writing of this thesis document, including the two manuscripts.

My supervisor, Dr. Al-Khazraji, and Dr. Dylan Kobsar led the creation of the study design for manuscript 1 (Chapter 2). Dr. Al-Khazraji has provided detailed guidance and feedback throughout the entire process, and along with Dr. Kobsar will have provided edits and meaningful feedback on the study design, results, and manuscript upon submission, and are therefore listed as co-authors of manuscript 1.

Dr. Al-Khazraji provided feedback for the study design for manuscript 2 (Chapter 3), and detailed guidance and feedback during the study process. Dr. Maureen MacDonald (committee member), and Dr. Alison Shea have provided edits and meaningful feedback regarding the study design and manuscript, and are listed as co-authors of manuscript 2.

Chapter 1 – Literature Review

1.1 Cardiovascular Physiology and Pathophysiology

The cardiovascular system is comprised of the heart and blood vessels, and is responsible for transporting blood containing nutrients and oxygen throughout the body.[1] The heart and vasculature work closely together to ensure that the tissues and organ systems in the body receive adequate nutrients and remove appropriate waste products. This coordination occurs as a response to stimuli, such as changes in blood pressure, hormones, and other signalling molecules.[1]

The nervous system and the respiratory system work closely with the cardiovascular system. The nervous system has baroreceptors that detect changes in pressure and chemoreceptors that detect changes in chemical signals in the blood. Working synonymously, these systems interact to adapt blood flow patterns to internal and external stimuli. Similarly, the respiratory system interacts with the nervous and cardiovascular system in the form of blood gasses. Particularly, carbon dioxide and oxygen concentrations in the blood alter blood flow patterns to ensure that adequate oxygen in the blood is maintained and distributed to other tissues and organ systems. Waste products such as carbon dioxide and other metabolites signal the body to change blood flow patterns. This can be through increasing or decreasing blood flow by means of vasoconstriction or vasodilation, as well as changes in the heart's regulation of heart rate and stroke volume.[1]

At the cellular level, signalling molecules and proteins work to maintain blood flow and vascular function in response to changes in blood gasses and signalling molecules, particularly with the endothelium. The endothelium is the layer of cells within vessels, and plays a large role in

regulating blood flow and vascular tone.[2] Nitric oxide (NO), catalyzed by endothelial NO synthase (eNOS), is a biological messenger that acts in the cardiovascular system to manage vascular tone, contractility, and inflammation by means of inflammatory markers adhering to the endothelium.[3] The endothelium is a target for inflammation and oxidative stress, and factors like obesity, smoking, stress, and high glucose intake may result in endothelial dysfunction.[2] Endothelial dysfunction, which can be screened using the Flow Mediated Dilation (FMD) method, is often a consequence of chronic inflammation.[4] Continuous repair and remodelling of the arterial wall further exacerbates dysfunction and increases the risk for atherosclerosis, which is a precursor to vascular-related diseases.[4]

Pathophysiology often occurs when there is a lacking of sufficient homeostatic mechanisms that regulate the cardiovascular system, such as changes in neural control, cardiac function, and/or as a result of vascular dysfunction (e.g., endothelial dysfunction).[2] Aging and inflammation have both been implicated in the damage to vascular structure. Vascular walls naturally thicken with age, which results in decreases in elasticity and increase the risk for conditions such as hypertension and atherosclerosis,[4] subsequently increasing the risk for future cardiovascular related events (e.g., heart failure, myocardial infarctions, strokes).[4,5] Cardiovascular disease (CVD) is an umbrella term encompassing pathologies related to the heart and vasculature, and is a leading cause of morbidity and mortality in the older population, accounting for over 17 million deaths per year and expected to increase to over 24 million by 2030.[6,7] Generally, men have higher prevalence of CVD compared to pre-menopausal women, and following the menopausal transition, the risk for CVD in women increases and may surpass age-matched men.[7,8]

Various factors, such as circulating sex hormones, are thought to underly sex differences in CVD risk.[8]

Different CVDs have different etiology, including beginning with atherosclerosis that results from the interaction of factors including inflammation and endothelial dysfunction, which marks the early stage of CVD pathology.[9] CVD diagnosis includes physical exams, imaging (e.g., electrocardiogram), expression of symptoms (e.g., chest pain), or presence of risk factors.[9] Following suspected or established diagnosis, many individuals are encouraged to address modifiable risk factors, such as stopping smoking, increasing physical activity, consuming a healthy diet, and avoiding/addressing obesity.[9]

1.2 Osteoarthritis Pathophysiology

With the growing number of older adults in the population, there is an increase in the proportion of individuals who live with physical disability.[10] Osteoarthritis (OA) is a highly prevalent musculoskeletal condition that has negative implications on the mobility, independence, and quality of life of individual affected.[11] The majority of individuals over 65 have some evidence of OA pathology in their joints, with around 1 in 4 people receiving a formal diagnosis, making OA among the most common causes of disability in the older population.[12,13] OA is characterized by the progressive breakdown of supporting tissues in the joints, namely the cartilage and bone.[14] It has often in literature been cited as a “wear and tear” disease, as one of the speculated causes of OA is overuse or injury to the joint that cannot be rectified by the body’s homeostatic properties. However, OA has been noted to have other causes as well, such as damage accrued by the

accumulation of metabolic by-products.[15] OA affects many different sites of the body, including the hand, hip, and knee.

OA results from the structural and functional damage to the affected joint(s), often by trauma or overloading[11,16], which can introduce various adverse symptoms, namely pain and swelling that lead to reduced movement.[16] Factors such as female sex, increased age, and obesity are found to increase the likelihood of developing OA.[16] OA can be diagnosed by a physician clinically (through symptoms) and radiographically (through medical imaging).[16] Specifically, diagnosis by a physician is often initiated by symptoms of OA, and can be confirmed through X-rays.[16,17]

Several treatment options are prescribed to minimize pain, improve function, and slow progression of OA. Non-pharmacological interventions include weight loss in obese individuals and increased physical activity to manage pain and improve function.[16] However, as physical activity and rehabilitation is often associated with pain in individuals with OA, more common treatment options are pharmacological avenues to control pain (e.g., non-steroidal anti-inflammatory drugs), with more severe progressions needing surgery (i.e., joint replacement).[16]

1.3 Markers of CVD risk

1.3.1 Carotid Intima-Media Thickness

The thickness between the intima and media layers of the artery, or the intima-media thickness (IMT), is a physiological measure of the vascular system that has been implicated in studies to be representative of cardiovascular health, and a surrogate for CVD risk.[18] The common site of IMT measures occurs at the carotid artery as carotid IMT (cIMT) is easily imaged through

ultrasonography, which produces high-resolution ultrasound images of the cross-section of the cIMT that can be analyzed for thickness.[19]

Studies have found increases in IMT values in men and women with increasing age.[20] Higher IMT values have also been implicated in increased risk of atherosclerosis, and may be a result of increased stress on the vascular system.[18] Importantly, these higher IMT values associated with increased disease risk are independent of age-related IMT changes,[18,20] and IMT is considered an important technique for identifying CVD risk.[19]

1.3.2 CVD Risk Scores

Various factors increase the risk for cardiovascular disease. Composite risk scores have been created in the last few decades to represent multiple variables for CVD as a single, holistic score. This approach is advantageous for examining CVD, as often it is not only one or two variables that predict increased CVD risk, but the interaction or influence of several.

The Framingham risk score (FRS) was developed in the late 1990s using data collected by the Framingham Heart Study that initially assessed risk for coronary heart disease.[21] The FRS considered variables known to influence heart disease: age, sex, blood pressure, total cholesterol, high- and low-density lipoprotein, smoking behaviour, and diabetes. Predictive equations were implemented to create a score that estimated the risk of heart disease in 5 and 10 years.[21]

The FRS is used by clinicians and patients to estimate the risk of developing heart disease by evaluating known risk factors. It has been reported that the FRS performs reasonably well when discriminating between individuals who are at high risk versus low risk, though concerns still exist surrounding the general predictive capacity of the score.[22] A cited limitation is that the FRS was

originally developed and validated in a middle-class white American population, which limits the generalizability of the score to other groups.[22] However, follow-up studies have found that the FRS performs reasonably well when applied to other populations (such as Hispanic men, Black men and women), though there was found to be an over-estimation of risk of heart disease.[22]

A newer risk score is the InterHeart risk score (IHRS), which was created using data collected from 52 countries, strengthening the generalizability of the CVD risk score to a vaster cohort of individuals. In addition to the CVD risk factors considered by the FRS (e.g., age, sex, cholesterol, hypertension, smoking), the IHRS incorporates several important modifiable risk factors (e.g., diet, physical activity), as well as considering other known factors that influence CVD risk (e.g., psychosocial stress).[23,24]

The original IHRS development study examined the probability of CVD onset for 1 and 3.25 year(s) follow-up, which is a shorter time interval compared with the FRS.[23,24] The IHRS was originally validated in 2010 to detect myocardial infarction worldwide in both sexes and all ages,[23] and later validated to predict general CVD events with a similarly high degree of accuracy.[23] Additionally, the researchers also developed a non-laboratory IHRS that excludes biomarkers (LDL, HDL) and results in a similar predictive accuracy, which is advantageous for accessibility and implementation in community-based populations.[25]

1.4 Osteoarthritis and Cardiovascular Disease Intersection

OA is highly comorbid with CVD, particularly in the aging population.[26] Approximately a quarter of the older population is diagnosed with OA, and having OA has been proposed as being an independent risk factor for CVD.[27] Collectively, OA and CVD are independently two of the

leading causes of morbidity and mortality in older individuals.[28] Hawker and colleagues[33] found that OA has a high rate of comorbidities, where up to 90% of patients with OA have at least one comorbid, chronic condition, the most frequent of which is CVD. Other reviews and meta-analyses found OA to be a strong indicator for cardiovascular-related events, where the risk of CVD was significantly increased in those with OA in comparison to those without.[28,29] The literature surrounding the relationship between OA and CVD has been abundant, with many studies and reviews speculating the directionality of the relationship and the associated underlying mechanisms. In the following sections, shared risk factors that influence the risk for and progression of OA and CVD are highlighted.

1.4.1 Aging

Age-related wear on the heart and vasculature can disturb regulation of vascular repair and homeostasis.[28] Vascular repair by means of intimal and medial thickening result in increased stiffness and subsequent loss of elasticity, and occurs due to plaque build-up, or atherosclerosis.[30] Atherosclerosis is facilitated by inflammatory cells and lipid debris,[30] which presents clinically as hypertension and increases the risk for CVD.[28] Increased cIMT is strongly associated with age, even in a healthy aging population.[20] Higher cIMT is also a surrogate for vascular risk, and has been found to be associated with increased CVD.[18,31]

The stiffening of the vessels subsequently influences nutrient delivery to tissues, which affects the bone and joints. Particularly in individuals with or at-risk of OA, stress on the joint in addition to age-related loss of homeostatic capacity can occur to compound the symptoms of OA.[28] Additionally, aging studies in OA found low-grade chronic inflammation associated with OA pathology, and the increased oxidative stress may disrupt bone health regulation.[32] The elevated

risk for older adults to develop OA and CVD independently may contribute to the increased comorbidity of the two conditions in the aging population.

1.4.2 Sex Differences and Menopause

Circulating sex hormones play a role in regulating aspects of the body, particularly in adipose tissues. Increased adiposity may be seen in women compared to men, due to higher concentrations of circulating estrogen and progesterone in the blood. Alterations in adiposity and circulating sex hormones has been suggested to play a role in a higher risk of OA in women, particularly after menopause, compared with men.[33] Estrogen's role in regulating bone health has been documented, with estrogen regulating calcium signalling, decreasing inflammation, and regulating bone turnover.[34] After the menopause transition, studies have determined an association between decreased circulating estrogen and increased risk for OA.[35,36]

Similarly, changes because of menopause have been linked to increasing CVD risk. Estrogen plays a cardioprotective effect in vascular health through various pathways including increasing NO production, reducing oxidative stress, and protecting against vascular injury.[37,38] Dramatic decreases in endogenous estrogen following menopause have been associated with increased progression of cIMT and greater risk of atherosclerosis, which increases the risk for CVD events.[39,40] The role of estrogen in adipose tissue, and the protective effects on bone and vascular health help explain sex differences in the prevalence and risk for OA and CVD, and the menopause transition and subsequent decline in sex hormones account for the increase in risk for both conditions in women.

1.4.2.1 Hormone therapy

In post-menopausal women, hormone therapy (HT) is a commonly prescribed treatment for vasomotor symptoms associated with the sharp decline in circulating sex hormones. There is literature to suggest that HT, particularly estrogen therapy, may help preserve joint health through maintaining healthy bone turnover.[35] The role of HT in CVD risk has also been examined, and found that the benefits of HT are greatest when started within 10 years of the menopausal transition.[8,41] Literature has been more mixed with the use of HT and CVD risk, particularly in 10+ years post-menopausal women, where studies found no change or increased CVD risk with the use HT.[42] However, the use of HT on the interaction between OA and CVD risk, particularly with regards to the type, duration, and route of administration, remains unclear.[34] Whether HT elevates or decreases the risk for OA and CVD as comorbidities or drives an increase in CVD risk in women with OA using HT requires further consolidation of literature.

1.4.3 Inflammation

Inflammation in the joints, as a result of cytokines and adipokines, contributes to the shared pathology of CVD and OA.[43] Chronic, low-grade inflammation plays a role in the progression of OA, potentially beginning following trauma or increased loading in the joints. After the initial damage, inflammation becomes chronic, as the joint experiences a self-perpetuating cycle of inflammation and repair, causing OA to be progressive.[44] Inflammatory cytokines have been associated with OA pathology, where markers including C-reactive protein (CRP) and interleukin-6 (IL-6) were found to be elevated with inflammation in individuals with OA.[15,45] Additionally, there is a proposed link between IL-6 and obesity and insulin resistance, which also are related to

elevated CVD risk.[15] These inflammatory cytokines may result in damage to the arterial wall, which accelerates the progression of atherosclerosis, subsequently increasing CVD risk.[46] Specifically, inflammatory factors reduce the expression of eNOS, and results in excess amounts of circulating NO that is implicated in endothelial dysfunction.[46]

Obesity results in chronic inflammation in the adipose tissues as they release adipokines.[47] Adipokines play a role in the vascular wall and endothelial function, and overexpression of pro-inflammatory adipokines result in increased risk for atherosclerosis and subsequent CVD.[48] Joint-related pain associated with OA is often accompanied by decreased physical activity, which increases the occurrence of increased obesity[49] and thus the circulation of adipokines. The chronic inflammation in OA pathology acting as a risk factor for CVD suggests the shared etiology may be a driving factor for the high prevalence of the conditions as comorbidities.

1.4.4 Drug and substance use

1.4.4.1 Smoking

Smoking has been implicated as a risk factor for various health concerns. Specifically, cigarette smoking has been linked to chronic musculoskeletal conditions, though the relationship between smoking and OA has been largely mixed.[50] One study examined the relationship between smoking and cartilage loss in men, and found current smokers to be less physically active, have greater knee pain, and at increased risk for cartilage loss compared to non-smokers.[50] Smoking can increase oxidative stress,[51] which can lead to additional cartilage loss, with additional mechanisms needing further consolidation.

Smoking and smoking exposure has been associated with increased risk for CVD and CVD-related mortality.[52] Studies have found negative impacts of smoking on endothelial function, possibly as a result of oxidative and inflammatory processes.[53] Second-hand exposure has been associated with increased toxic particulate matter (such as metals)[54] on cardiovascular health, and even short periods of smoking exposure has been linked to increases in endothelial dysfunction and risk for vascular conditions.[55,56] Collectively, smoking as a modifiable risk factor for OA and CVD explain some of the overlapping risk that result in elevated occurrences of the two conditions.

1.4.4.2 Medication

Disease management methods, such as the use of non-steroidal anti-inflammatory drugs (NSAIDs) are common in individuals with OA. NSAIDs are frequently prescribed for pain and inflammation and may act through several pathways depending on the type. NSAIDs act to inhibit the cyclooxygenase (COX) enzyme, which is required in the production of prostaglandins.[57] Prostaglandins play an important role in vasodilation in the vascular smooth muscle.[58,59] One study examining causes of mortality in individuals with knee or hip OA found that CVD was significantly associated with NSAID use.[60] This suggests the use of NSAIDs in individuals with OA may have a mediating role in the increased risk of CVD.

1.4.5 Physical inactivity

OA, particularly in the weight-bearing joints (i.e., the knee or the hip), is often accompanied with pain during movement. This causes difficulty during daily activities such as walking and going up steps, which often results in individuals with OA being less likely to be physically active.[61] As a result, increased sedentary behaviour is often associated with OA.[61] Decreased physical activity is

often linked with increased abdominal obesity, which are both risk factors for CVD.[49] Decreased physical activity results in lower muscle tone and increases the risk for frailty, which is independently associated with OA and CVD.[62,63] Increased obesity increases the inflammatory markers that circulate the system, which have negative implications on vascular[46] and joint[44] health.

Physical activity improves the health of the vasculature and may delay or prevent development of atherosclerosis.[64] These changes result from the role physical activity plays in modifying blood lipids, improvements in endothelial function (e.g., increasing the bioavailability of NO), and up-regulation of healthy arterial remodeling.[65] Acute bouts of exercise also result in decreases in oxidative stress and increases in markers (e.g., interleukin-6) that reduce chronic inflammation.[66] Thus, physical inactivity in individuals with OA result in increased risk for CVD, though physical activity as a modifiable risk factor improves the pathology of OA and risk for CVD.

1.4.6 Nutrition and Biomarkers

OA is often comorbid with type 2 diabetes mellitus (T2D), with the relationship proposed to be a result of shared risk factors such as age, obesity, lipid metabolism, and glucose control.[67] Particularly in obese individuals with larger adipocytes, there are associations with insulin resistance and poor cartilage regulation.[67] Hemoglobin A1c (HbA1c) is a biomarker that reflects glucose concentration in the blood, and higher values are indicative of possible diabetes.[68] However, the relationship between HbA1c and OA pathology is mixed,[69,70] and it is unclear whether there are associations between OA and higher levels of HbA1c. Diabetes is also comorbid with CVD, and they share similar risk factors including obesity and poor lipid metabolism.[68] Independent of diabetes diagnosis, HbA1c has been found to be associated with the risk of CVD.[71]

This suggests there may be a role of poor glucose control in the shared pathology between OA and CVD.

There is evidence for the general role of nutrition on OA risk and progression. Poor diet (possibly due to lifestyle choices or social disadvantage) may lead to increased obesity,[72] which furthers CVD risk through pathways such as inflammation from adipokines. Consumption of high cholesterol and fat diets may also cause inflammation and metabolic syndrome, a risk factor for CVD characterized by high blood pressure, obesity, and poor glucose and cholesterol regulation.[15,72]

There is some literature that suggests high cholesterol may have a role in musculoskeletal disorders such as OA.[15] OA has often been viewed as a mechanical loading or joint-centric condition, though there are studies that show the metabolic role of OA progression where several risk factors, such as cholesterol, interact in the pathogenesis of OA.[15] Cholesterol accumulation (specifically low-density lipoprotein) may create an inflammatory environment, increasing CVD risk.[15] Recent studies have recognized the role of metabolic risk factors in inducing OA, and suggest that the development and progression of OA may share similar pathways with precursors to CVD (such as atherosclerosis) through changes in blood vessel formation and health.[15,73]

Other biomarkers, such as leptin, a pro-inflammatory adipokine, have been cited in OA pathology, where higher levels of leptin in obese mice were associated with higher risk for OA whereas obese mice without leptin were not at risk.[74] Leptin is generally elevated with obesity, and is associated with cartilage degradation.[75] The role of leptin in CVD risk has also been examined in the context of homeostasis in the vascular system, where leptin resistance or signaling deficiency increases the risk for vascular dysfunction and heart failure.[76]

Nutrition and biomarker availability work to increase or decrease the risk for OA and CVD as independent conditions and as comorbidities. Factors such as glucose control, cholesterol, leptin, and inflammatory markers likely interact to result in changes in risk, making nutrition an important modifiable risk factor for OA and CVD pathology.

1.4.7 Social disadvantage

In addition to biomedical determinants of health, the role of non-physiological factors such as social inequalities have been show to influence an individual's biology and disease risk.[50] Considering the influence of non-biomedical factors on health and disease, social disadvantage has recently been studied in both OA and CVD outcomes. Research has found that lower socioeconomic status is associated with greater likelihood of OA outcomes, independent of influence from factors such as sex and aging.[77] In particular, factors such as ethnicity, pain perception, and socioeconomic variables have been proposed to influence risk and progression of OA.[77] There is a proposed relationship between occupation and OA outcome, such that in physically-demanding work (which has been associated with greater physical demand and lower socioeconomic status[78]), there is an increase biomechanical loading at the joint and greater incidence of OA.[77] Studies suggest that prolonged standing and labour-intensive tasks are associated with increased risk and prevalence of OA of the knee and hip.[78] It is postulated that factors such as socioeconomic status may influence pain perception,[50] though it is unclear whether this relationship holds true in women.

Studies have found similar results in CVD risk, where social disadvantage is an independent predictor of CVD.[79] Higher social disadvantage was associated with increased age, and was more commonly found in women than in men. Risk factors for CVD were also found to be more prevalent

in individuals with greater social disadvantage.[79] Specifically, these individuals were more likely older, women, greater body weight, and greater levels of inflammation, suggesting that social disadvantage results in lifestyle and social factors that are associated with greater CVD risk.[79]

Social disadvantage is not frequently studied, possibly due to the less understood and complicated interactions that social determinants of health have on physiology and progression of pathophysiology. However, there is literature that proposes social disadvantage may be a shared factor between OA and CVD (in addition to other conditions, such as obesity), suggesting social determinants of health should be examined when considering the comorbidities.

1.4.8 Frailty

Factors such as age, physical disease and comorbidity, and cognitive health and satisfaction intersect to influence an individual's quality of life.[80] Frailty is the age-related decline in physiological and functional capacity, resulting in increased vulnerability and negative implications on quality of life.[81] Individuals with OA often have joint-related pain as a result of the OA pathology, which in turn acts to decrease physical activity and quality of life.[82] OA is associated with frailty, and the two conditions often result in similar health-related consequences (e.g., disability, pain).[82] A study found significant associations between joint-related pain in individuals with OA and increased prevalence of frailty, and that pain in individuals with OA of the knee or hip are at risk for developing frailty.[82]

In individuals with CVD, there is an increased prevalence of frailty, and the two conditions share similar risk factors.[62] However, the directionality of the relationship remains unclear, with studies suggesting that frailty increases the risk for more severe CVD consequences,[62,83] though

whether frailty increases the risk for CVD alone is not well understood.[84] Physical inactivity, obesity, and dietary factors all increase the risk for both CVD and frailty.[62]

Frailty is independently associated with OA and CVD, and share common risk factors that suggest an increased risk for frailty in individuals with OA or CVD.[62,82] Using comprehensive assessment tools, such as a frailty index, may provide a better understanding of the underlying mechanisms between OA and CVD, as well as the potential role of frailty in the relationship between OA and increased risk for CVD.

1.5 Clinical Epidemiology Studies and Approaches

1.5.1 Significance of epidemiological studies

Clinical epidemiology studies have long-since been cited to examine variables on health and risk, and allow clinicians and researchers to better understand individual and population-level health.[85,86] Preclinical changes may be observed in populations, and early interventions and preventative measures can be taken before major structural or function damage occurs. This proactive approach will aid in prolonged quality of life as well as decreased burden on the healthcare system.

1.5.2 Statistics in clinical epidemiology

Studies in clinical epidemiological research often use case-control designs, where one "case" (e.g., an individual with OA) is matched (attributes like age, sex, etc.) to one or more "controls" (e.g., an individual without OA).[87] Within a larger dataset, these case-control studies are nested within the larger cohort of cases based on their disease characteristics.

A common approach for examining larger population-based data include use of proportions and ratios. By examining differences in proportions either cross sectionally or longitudinally, the differences in risk and group prevalence are better understood. From the population proportions, ratios can be calculated to allow for comparisons between groups (e.g., relative proportions). This provides further information on how proportions differ between groups, particularly in larger-scale studies that examine the prevalence and incidence of diseases.

Another means of analyzing large datasets is studying relationships at follow-up time points. For example, through matching cases and controls within the large dataset, a nested case-control study can help achieve greater precision when calculating odds ratios.[87,88] Odds ratios can be calculated through unadjusted and adjusted (i.e., incorporating covariates) logistic regression models. Logistic regression is a statistical approach used to examine the relationship between one or many variables and a dichotomous outcome, such as disease status (i.e., CVD or no CVD).[89] This technique is advantageous, as researchers can study the relationship between multiple variables (independently, interactions, and parallel to each other) and the binary outcome variable.[90] From the logistic regression analysis, odds ratios can be calculated by exponentiating the coefficient returned by the logistic regression (the logit, or the log of the odds ratio). The odds ratio can then be used to determine the change in the outcome variable for a 1-unit increase in a categorical variable (e.g., 1 year of age) or against a reference level (e.g., no OA and OA).[90] This aids in the interpretability of the results, and allows for incorporation of multiple explanatory variables in the model.[89]

1.5.3 Working with CLSA: a large longitudinal aging dataset

The Canadian Longitudinal Study on Aging is a national research study designed to collect data over the course of two decades to support a wide array of research questions targeted to better understanding aspects of the aging population.[91,92] A total of 51,338 Canadians aged 45-85 years were enrolled into the cohort at baseline (between 2010-2015), of which 21,241 participants were in the Tracking cohort and 30,097 were in the Comprehensive cohort. Both cohorts had comprehensive questionnaire data administered at baseline and at follow-up time points (approximately 3 years apart), and the Comprehensive cohort had additional physical assessments and biological samples collected to supplement the interview questionnaires. All individuals tracked by the CLSA are contacted for 3-year follow-ups, with the final follow-up projected to complete in 2033 or when the participant passes on.[91]

Participants were recruited from 10 provinces, and efforts were taken to ensure appropriate representation, particularly in areas that were identified as under-represented in population-based studies. More information on the recruitment and eligibility of participants can be found in the CLSA cohort study.[91] Multidisciplinary fields were incorporated into the design and decision of the variables collected. As a result, the data includes variables to better understand interdisciplinary aspects of aging, ranging from biological and clinical outcomes, functional measures and lifestyle habits, sociodemographic factors, to medications used. Several specific types of variables taken relevant to this study include ultrasound images of the carotid artery and blood biomarkers.

Survey weights were calculated using the CLSA dataset to maximize the generalizability of the study results to the Canadian population. Survey weights aim to correct for bias in the data collection (i.e., corrections for over- and under-sampling), and allows for comparisons of key

variables and outcomes to the aging population in Canada. There were two types of weights calculated to ensure the generalizability of the data: inflation weights and analytic weights. Inflation weights were used to represent descriptive variables, such as the proportion of people in the CLSA with a certain condition. These inflation weights dictate how many people a single collected individual can represent, with the 50,000 individuals included in the CLSA representing approximately around 13 million Canadians. Inflation weights reduce the sampling bias when examining proportions (i.e., for disease), as they correct for over- or under-sampling at a population level. For regression analyses, analytic weights are similarly applied, where over- or under-sampled locations are adjusted to reduce these sampling biases in statistical analyses. More information about sampling weights, how they were created, and how they should be used can be found in the data support documentation provided by the CLSA.

A key strength of using CLSA data is the breadth of the data included in the longitudinal data collection.[91] The data is comprehensive, with many different fields of variables collected, and the generalizability of the data and results generated aids the in producing more accurate results specific to the Canadian population. However, some considerations include possible recruitment bias, as individuals recruited had to have means to participate in the study, express written permission in French or English, and the Comprehensive cohort required individuals to visit the data collection centres. Thus, there may be a "healthy volunteer" bias and individuals who were not proficient in French or English may be under-represented. However, it appears there is still validity in examining relationships between disease and external variables, and conclusions are still widely generalizable.[91,93]

1.6 Purpose & Objectives

There is a cited relationship between OA and CVD pathologies. However, what remains unknown is specifically which aspects of the shared mechanisms drive the increase in risk for CVD in individuals with OA, and whether preclinical changes occur in individuals with OA that resemble CVD pathology to a greater extent than individuals without existing OA. The purpose of this study is to examine risk factors for and markers of cardiovascular disease in individuals with osteoarthritis using data collected by the Canadian Longitudinal Study on Aging.

The first objective, covered in the manuscript in Chapter 2, will examine cIMT, FRS, IHRS, and other CVD risk factors in individuals with and without OA, with considerations given to the site of OA, and how these factors influence CVD incidence at a 3-year follow-up. The second objective, covered in the manuscript in Chapter 3, will examine sex differences and menopause on CVD risk in individuals with and without OA, and how these factors influence CVD incidence at a 3-year follow-up.

Chapter 2 – Predictors of CVD risk in the OA population using the Canadian Longitudinal Study on Aging

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2.1 Introduction

Osteoarthritis (OA) is a musculoskeletal condition characterized by a progressive degradation of the cartilage and joint.[1] OA is a progressive and chronic disease associated with prolonged morbidity and decreased quality of life, impacting factors that can affect daily quality of life including risk of frailty and reduced mobility.[2,3] Over 650 million people currently live with OA worldwide, rendering OA as one of the highest contributors to disease and disability, particularly in the older demographic.[4] OA is highly comorbid with cardiovascular disease (CVD),[5,6] and collectively, OA and CVD increase all-cause mortality and result in decreased quality of life and general health in those affected.[5,7,8] The nature of the relationship between OA and CVD is presently unclear, though a large body of literature demonstrates a higher risk and incidence of CVD in the OA population.[6–9] The two pathologies share several common risk factors which include physical inactivity, systemic inflammation, disease management methods, and lifestyle habits, all of which contribute to the high comorbidity between the two conditions.[10,11]

OA affects different sites in the body, with hand, knee, and hip being the most common joints for OA to occur.[1] Interestingly, the site of OA is differentially associated with CVD risk, where studies have found OA of the knee and hip to be highly associated with increased CVD risk, while literature surrounding the influence of hand OA on CVD is more mixed.[11,12] However, the majority

of literature confirms a general relationship between an OA diagnosis and CVD risk and incidence, particularly increasing with OA severity,[13] suggesting that aspects of the OA pathology may put individuals with OA at a greater risk for comorbidities such as CVD. A recent cross-sectional study examining CVD risk in individuals with OA using baseline data found contributions of systemic inflammation, sex differences, and the sites of OA on CVD risk profiles among older adults.[14] It is therefore of great interest to identify early risk factors and pre-clinical changes to inform how factors interact with CVD risk differently depending on the site of OA, and how they influence CVD outcomes to take preventative approaches in the treatment of both conditions.

A subclinical marker of cardiovascular health is the carotid intima-media thickness (cIMT)[15], with many studies and systematic reviews reporting associations of cIMT with future cardio- and cerebrovascular events.[15,16] Interestingly, though higher cIMT values have been linked to increased cardiovascular risk,[15] this subclinical measure of vascular health has only seldom been examined in the OA population despite the existing and evident comorbidity.[17] Specifically, cIMT was significantly higher in patients with OA, and it was also found that greater cIMT values were associated with greater disease severity (measured through disease duration and the Kellgren-Lawrence grading scale).[17]

Development of various CVD risk scores account for various CVD risk factors and are used as tools to predict future CVD events. These CVD risk scores provide a validated method for identifying populations at risk of CVD, thereby assisting with prevention and early intervention.[18] The Framingham Risk Score (FRS) is a commonly used method to identify CVD risk in the population.[19,20] Notably, one study examined the FRS in the OA population, and found associations between OA and higher FRS values, specifically finding the prevalence of OA to be higher in those

with greater CVD risk.[8] This finding demonstrates a possible meaningful relationship between an OA diagnosis and CVD risk quantified by the FRS, which provides rationale for further examination of CVD risk in the OA population.

In addition to cIMT, other risk factors including age, sex, waist-to-hip ratio, cholesterol (total, high- and low-density lipoprotein), and physical activity levels are also markers of health and CVD risk.[21] Many risk factors (e.g., glucose control,[21] pro-inflammatory cytokines[22]) interact to affect CVD onset and progression by influencing factors or physiologic processes that may result in endothelial dysfunction.[22] Beyond the risk factors included in the FRS, physical activity, diet, and stress also influence the risk of CVD.[23] These modifiable lifestyle risk factors are especially of interest to researchers and clinicians, as they have the potential to influence the behaviour and treatment of patients and can be addressed often without pharmaceutical or medical intervention.[24] Similar to the FRS, the InterHeart Risk Score (IHRS) was developed as a tool to estimate CVD risk.[24,25] The IHRS score is relatively novel in comparison to the FRS; however, its well-rounded construction with additional modifiable risk factors and the validation of the IHRS on a more diverse cohort suggests that the IHRS may also be a good predictor of CVD risk.[24] Specifically, using the IHRS as a tool to examine CVD risk in the OA population could provide further insight on the factors driving the two comorbidities as a complement to the risk analysis provided by FRS.

Used together, cIMT and CVD risk scores have been demonstrated to yield some predictive power for identifying CVD risk.[19] Incorporating both cIMT as a subclinical marker of CVD risk and the FRS and/or IHRS as a comprehensive profile of CVD risk factors may provide a more comprehensive account of CVD risk. A recent study found that the combination of cIMT and CVD

risk scores (e.g. FRS) improved risk prediction in individuals with low CVD risk.[19] The combination of cIMT and FRS/IHRS for CVD risk assessment in the OA population could provide a holistic understanding of how CVD risk presents in individuals with OA. Improved quantification of CVD risk could also help address the relationship between two of the most prevalent and significant health conditions.[5]

Additional risk factors not specific to CVD, such as inflammation, general frailty, and social disadvantage have been shown to influence the risk for both OA and CVD risk and diagnosis. Inflammatory pathways have been highlighted by literature as a key mechanism of the overlapping etiology between OA and CVD.[26] Chronic inflammation in the joint, often as a result of trauma or overloading, drives the progression of OA.[27] Inflammation is associated with the development of atherosclerosis, potentially through processes such as the induction of endothelial dysfunction and dyslipidemia.[28] This relationship has been documented in individuals with OA, where OA of the knee, hip, and hand were associated with atherosclerosis, and OA of the knee and hip were associated with subsequent CVD consequences.[29] Additionally, OA is a common cause of disability, with studies showing that OA is associated with increased frailty regardless of the joint affected (hand or hip or knee OA).[30] There is a proposed bi-directional relationship between frailty and CVD outcomes, where frailty increases the risk of CVD and poor CVD outcomes, and having a CVD condition may cause or exacerbate frailty.[31] Frailty has also been suggested to worsen the prognosis in individuals with both OA and CVD independently, which raises cause for examining a measurement of frailty in CVD risk with individuals with and without OA. Finally, social disadvantage, sometimes considered through combinations of variables including socioeconomic status, ethnicity, and pain, has also been linked to both OA[32] and CVD[33] independently. Specifically,

social disadvantage has been speculated to increase both OA prevalence and severity/progression, particularly considering factors such as education level, employment status, and income.[34]

What remains unknown is how all the CVD risk factors discussed above present in individuals with OA, how CVD risk differs between different sites of OA, and how these risk factors affect odds of developing CVD. The purpose of this study was to examine surrogate measures of CVD risk (cIMT, IHRS, FRS) and additional risk factors (e.g., frailty, social disadvantage, inflammation, age, sex) in a population with known CVD risk (i.e., individuals with an OA diagnosis but no existing CVD) and a healthy control cohort (i.e., individuals with no OA or CVD diagnoses). The primary aim was to examine measures of CVD risk (cIMT, IHRS, FRS) in a population with OA (but no existing CVD) and a healthy control cohort (with no OA or CVD diagnoses). The secondary aim of this study was to compare the CVD risk between a sub-population of individuals with weight-bearing OA to non-weight bearing OA. These aims were addressed by the following objectives:

Objective 1: Examine proportions of CVD in individuals with or without OA at baseline and 3-year follow-up. This will examine the comorbidity of OA and CVD, specifically to observe the frequency of CVD in individuals with versus without an existing OA diagnosis.

Objective 2: Compare group demographics of CVD risk factors, cIMT, the FRS, and the IHRS between individuals without CVD, and either with or without OA.

Objective 3: Examine associations between cIMT, FRS, and IHRS with odds of CVD at 3-year follow-up in individuals with or without OA who did not have CVD at baseline. Using baseline CVD risk profiles in an isolated age- and sex- matched sub-cohort of individuals with or without OA, CVD at 3-year follow-up (measured through answering “Yes” to any of the previously defined CVD

variables) will be studied as the outcome of interest. The logistic regression models will systematically include variables (exposure) to assess how odds ratio of CVD at 3-year follow-up is impacted by:

1. OA status
2. OA status + cIMT
3. OA status + cIMT + known CVD risk factors [age, sex, waist-to-hip ratio, frailty index]
4. OA status + cIMT + FRS
5. OA status + cIMT + IHRS

Objective 4: Compare group demographics of CVD risk factors, cIMT, the FRS, and the IHRS between weight-bearing and non-weight-bearing OA. The possible influence of the type of OA will be examined in individuals with only weight-bearing (hip and knee) OA and individuals with only non-weight-bearing (hand) OA. The CVD risk profiles will be compared in the two cohorts to determine the role of the site of OA on CVD risk.

Objective 5: Examine the associations between cIMT, FRS, and IHRS with odds of CVD at 3-year follow-up in weight-bearing and non-weight-bearing OA cohorts who did not have CVD at baseline. Using baseline CVD risk profiles in a sub-cohort of age- and sex-matched individuals with either weight-bearing or non-weight-bearing OA, CVD at 3-year follow-up (measured through answering "Yes" to any of the previously defined CVD diagnoses) will be studied as the outcome of interest. The logistic regression models will systematically include variables (exposure) to assess how odds ratio of CVD at 3-year follow-up is impacted:

1. OA type

2. OA type + cIMT
3. OA type + cIMT + known CVD risk factors [age, sex, waist-to-hip ratio, frailty index]
4. OA type + cIMT + FRS
5. OA type + cIMT + IHRS

The specific sub-cohorts can be found in Figure 1. We hypothesize that: Objective 2 - markers of CVD risk (cIMT, FRS, IHRS, CVD risk factors) will be elevated in individuals with OA; Objective 3 - individuals with OA have significantly greater odds of developing CVD at 3-year follow-up compared to individuals without OA, which can partially be explained by determinants of CVD risk (e.g., cIMT, FRS, IHRS); Objective 4 - markers of CVD risk (cIMT, FRS, IHRS, CVD risk factors) will be elevated in individuals with weight-bearing compared to non-weight-bearing OA; and Objective 5 - individuals with weight-bearing OA have greater odds of developing CVD at 3-year follow-up compared to individuals with non-weight-bearing OA, which can be partially explained by determinants of CVD risk (e.g., cIMT, FRS, IHRS).

2.2 Methodological Approach

2.2.1 Study design and population

Baseline (n = 30,097) and 3-year follow-up (n = 27,765) data from the Comprehensive cohort collected by the Canadian Longitudinal Study on Aging (CLSA) was examined. Further details surrounding the CLSA design are described elsewhere.[35,36] The study was approved by the CLSA scientific advisory board and received ethics from the McMaster Research Ethics Board (protocol #4912). Illustrative outline highlighting Inclusion of participants into sub-cohorts used for analyses can be found in Figure 1.

2.2.2 Osteoarthritis status

Self-reported osteoarthritis status was used to group participants based on OA diagnosis using baseline data. Participants who answered "yes" to having been diagnosed with hand, knee, or hip OA by a physician were characterized as having "Any OA". Participants who responded "no" to hand, knee, and hip OA were characterized as "No OA". Participants who answered "yes" to having been diagnosed with knee or hip OA, and answered "no" to having been diagnosed with hand OA by a physician were characterized as having weight-bearing OA ("wbOA"). Participants who answered "yes" to having been diagnosed with hand OA, and answered "no" to having been diagnosed with knee and hip OA by a physician were characterized as having non-weight-bearing OA ("nwbOA").

2.2.3 Cardiovascular disease (CVD) status

The primary outcome variable was self-report of having received a physician's diagnosis of CVD, defined as heart disease (HD), cerebrovascular accident (CVA), transient ischemic stroke (TIA), high blood pressure (HBP), angina, peripheral vascular disease (PVD), or acute myocardial infarction (AMI).[37] For analyses examining CVD risk or development at 3-year follow-up, participants who reported "no" to all CVD conditions at baseline were included, and their 3-year follow-up CVD incidence data were analyzed. CVD development at 3-year follow-up was defined as having answered "no" to all of the CVD conditions at baseline, and "yes" to having been diagnosed with any of the conditions by a physician at 3-year follow-up.

2.2.4 Cardiovascular risk

The Framingham Risk Score (FRS) is a commonly used method to identify CVD risk in the population.[19,20] The FRS calculation can be found in the Appendix (Supplementary Table 1). Age and sex were self-reported. high-density lipoprotein (HDL) and total cholesterol were collected from non-fasting blood samples.[38] Systolic blood pressure was collected, and self-reported medication to treat high blood pressure was included. Self-reported smoking status as a binary variable ("yes" or "no"). Self-reported diabetes was based on previous physician diagnosis.

The InterHeart risk score (IHRS) was developed using data collected from 52 countries as a tool to predict the risk of a CVD event.[24,25] A non-laboratory IHRS was later validated and determined to be of similar predictive accuracy, which excluded blood cholesterols and considered a family history of myocardial infarction.[39] For the purposes of this study, the non-laboratory IHRS was modified to adapt to the available CLSA variables (Psychosocial factors: self-rated mental health and physicians diagnosis of mental illness; Dietary factors, Physical activity) and the calculations can be found in the Appendix (Supplementary Table 2)[24]. For variables that assigned scores based on quantiles (e.g., waist-to-hip ratio), a healthy control cohort[25] (n = 13,561) of no existing OA and CVD was isolated from CLSA to determine new quantile values representative of the CLSA cohort. Age and sex were self-reported. Smoking variables were accounted for using self-reported smoking and second-hand smoking behaviours. Diabetes and high blood pressure were self-reported based on previous physician diagnosis. Psychosocial factors were defined as self-rated mental health and self-reported cases of mood disorders (including clinical depression, bipolar disorder, mania, or dysthymia) previously diagnosed by a physician. Dietary factors were self-reported frequencies of consuming salty foods, fried snacks, fruit, vegetables, and meat. Physical

activity was estimated using participant responses to the Physical Activity Scale for the Elderly (PASE), where a PASE score of <120 for females and <140 for males was considered sedentary activity.[40]

2.2.5 Carotid Intima-Media Thickness (cIMT)

High quality left cIMT values were included in the analyses, as selected by the image quality rating variable (IMT_L_QUALITY_COM), where only values that reported "good" for quality were included in analyses. Right cIMT values did not have quality ratings and thus were excluded from analysis.

2.2.6 Statistical analyses

Descriptive statistics, expressed as means and standard deviations, were used to describe continuous variables. Counts, frequencies, and proportions were used to describe categorical variables such as disease frequency in a population. In the sub-cohorts, a nested, age- and sex-matched case-control population was used for analysis. Multivariable logistic regressions were used to determine unadjusted and adjusted odds ratios, presented as the odds ratio of the grouping variable (i.e., OA diagnosis) using 95% confidence intervals [95% CI]. Age, sex, waist-to-hip ratio, a Frailty Index,[41] cIMT, IHRS, and FRS were included as covariates in the different logistic regression models to yield adjusted odds ratio calculations. Individuals with missing values for one or more of the variables of interest were excluded from the logistic regression analyses. When appropriate and feasible, samples were 1 OA: 2 No OA age-matched in 10-year intervals. When variance was unequal, non-parametric Welch's t-tests were used to compare medians of unadjusted, raw continuous variables (Supplementary tables). Student's t-tests were used to

compare means of adjusted continuous variables. Alpha level of significance was set to 0.05, where test outcomes less than the alpha level were deemed significant. All statistical analyses were conducted using sampling weights with appropriate methods for the analysis of survey data. All data analyses were conducted using Python (version 3.0 via Jupyter Lab) and Jamovi (version 1.8).

2.3 Results

Proportion of CVD in individuals with any OA at baseline

All individuals in the comprehensive cohort collected by the CLSA (n = 30,097) were included in the frequency analysis of CVD at baseline (Figure 1) (Table 1.1.1a). Of the entire sample, 7,922 had OA and 22,175 did not have OA. A total of 13,231 individuals had a CVD condition at baseline (44% of all individuals), of which 4,437 had OA (54% of all people with OA) and 9,204 did not have OA (40% of all people without OA).

Next, a smaller cohort of individuals at baseline (n = 6,365) who had complete data for the primary variables of interest (high quality cIMT, FRS, IHRS, and individuals with 3-year follow-up data) were examined for diagnosis frequency (Figure 1) (Table 1.1.1b). Of all the individuals in this cohort, 1,694 had OA and 4,671 did not have OA. A total of 2,923 individuals had a CVD condition at baseline (46% of all individuals), of which 957 had OA (56% of all people with OA) and 1,966 did not have OA (42% of all people without OA).

Proportion of CVD in individuals with OA at 3-year follow-up with no CVD at baseline

A total of 3,442 individuals were included in the frequency analysis of CVD at follow-up (Figure 1). From the sub-cohort of individuals who had complete data for the primary variables of interest, individuals who had any type of CVD event at baseline were excluded. From the sub-cohort, 3-year follow-up CVD was examined (Table 1.1.2). Of the 3442 individuals without CVD at baseline, 737 had OA and 2705 did not have OA. A total of 383 individuals developed a CVD condition at 3-year follow-up (11% of all individuals), of which 112 had OA (15% of all people with OA) and 271 did not have OA (10% of all people without OA).

Participant demographics and CVD risk in individuals with and without OA

The raw (Supplementary Table 4) and adjusted (Table 1.2) baseline demographics of the sex- and age-matched cohort were examined in a sub-cohort of 1706 individuals (Figure 1). Where possible, an individual with OA was matched to two individuals without OA. There were 618 individuals with OA and 1088 individuals without OA. Following application of survey weights, significantly greater age (OA: 60.82 ± 9.14; No OA: 58.56 ± 8.81), greater timed-up-and-go (OA: 9.39 ± 3.22; No OA: 8.87 ± 1.51), greater BMI (OA: 27.39 ± 5.16; No OA: 26.05 ± 4.68), greater frailty (OA: 0.09 ± 0.05; No OA: 0.07 ± 0.04), greater social disadvantage (OA: 0.55 ± 0.85; No OA: 0.42 ± 0.75), greater non-laboratory IHRS (OA: 7.43 ± 5.14; No OA: 6.61 ± 5.25), greater FRS (OA: 10.11 ± 4.57; No OA: 9.23 ± 4.6), and greater cIMT (OA: 0.72 ± 0.15; No OA: 0.70 ± 0.15) were observed in individuals with OA compared to individuals without OA (Table 1.2).

Greater odds of CVD at 3-year follow-up in individuals with OA

The same sub-cohort of 1706 individuals were examined at 3-year follow-up (Figure 1). The odds of developing CVD at 3-year follow-up were significantly greater in individuals with OA compared to individuals without OA (defined by "Any OA" in tables) alone ($p<0.001$, Any OA Odds ratio: 1.72 [1.29-2.28]) (Table 1.3.1) and after adjusting for cIMT ($p<0.001$, Any OA Odds ratio: 1.71 [1.29-2.28]) (Table 1.3.2). After accounting for cIMT in addition to other CVD risk factors (age, frailty, waist-to-hip ratio, sex) (Table 1.3.3), the odds of developing CVD remained significantly greater in individuals with OA ($p<0.001$, Any OA Odds ratio: 1.70 [1.27-2.28]). The odds of developing CVD after accounting for cIMT in conjunction with FRS (Table 1.3.4) and IHRS (Table 1.3.5) were both significantly greater in individuals with OA ($p<0.001$, Any OA Odds ratio: 1.63 [1.22-2.17]; $p<0.001$, Any OA Odds ratio: 1.67 [1.26-2.23], respectively). 116 individuals who did not have OA at baseline (10.7%) developed CVD at 3-year follow-up, and 105 individuals who had OA at baseline (16.9%) developed CVD at 3-year follow-up. 3 individuals who did not have OA at baseline out of 1088 developed OA by the follow-up time-point.

Participant demographics and CVD risk in weight-bearing and non-weight bearing OA

The raw (Supplementary Table 5) and adjusted (Table 1.4) baseline demographics of the sex- and age-matched sub-cohort of 318 weight-bearing and non-weight-bearing OA (Figure 1) were examined. There were 159 individuals with weight-bearing OA and 159 individuals with non-weight-bearing OA. Following application of survey weights, there was greater timed-up-and-go (wbOA: 10.24 ± 6.48; nwbOA: 8.76 ± 1.25), greater BMI (wbOA: 27.39 ± 4.73, nwbOA: 25.43 +

3.74), and lower frailty (wbOA: 0.08 ± 0.05; nwbOA: 0.09 ± 0.04) in individuals with weight-bearing OA compared to individuals with non-weight-bearing OA (Table 1.4).

No difference in CVD risk at 3-year follow-up in individuals with weight-bearing OA compared to non-weight bearing OA

The same sub-cohort of 318 individuals were examined at 3-year follow-up (Figure 1). The odds of developing CVD at 3-year follow-up were not different in individuals with weight-bearing OA compared to individuals with non-weight-bearing OA alone (defined by "Type of OA" in tables) (p=0.28, Type of OA Odds ratio: 0.71 [0.38-1.32]) (Table 1.5.1) and after adjusting for cIMT (p=0.275, Type of OA Odds ratio: 0.71 [0.38-1.31]) (Table 1.5.2). After accounting for cIMT in addition to other CVD risk factors (age, frailty, waist-to-hip ratio, sex) (Table 1.5.3), the odds of developing CVD were not different between individuals with weight-bearing and non-weight-bearing OA (p=0.273, Type of OA Odds ratio: 0.70 [0.37-1.32]). The odds of developing CVD after accounting for cIMT in conjunction with FRS (Table 1.5.4) and IHRS (Table 1.5.5) were not different between weight-bearing and non-weight-bearing OA (p=0.263, Type of OA Odds ratio: 0.70 [0.38-1.30]; p=0.236, Type of OA Odds ratio: 0.69 [0.37-1.28], respectively). Twenty-one individuals who had weight-bearing OA (13.2%) at baseline developed CVD at 3-year follow-up, and 28 individuals who had non-weight-bearing OA (17.6%) at baseline developed CVD at 3-year follow-up. Thirty-two individuals in either the weight-bearing or non-weight-bearing OA groups received an additional diagnosis of OA after baseline and thus had both weight-bearing and non-weight-bearing OA at follow-up.

2.4 Discussion

The measures of CVD risk examined in this study were cIMT, FRS, and IHRS. Through quantifying CVD risk in an OA population and comparing to individuals without OA, the differences in CVD risk with or without the influence of OA pathology can be examined. Baseline and 3-year follow-up data from the CLSA were used to examine measures of CVD risk in individuals with and without OA, with further analyses concerning CVD risk in individuals with weight-bearing and non-weight bearing OA. For Objective 1, we found that OA (hand and/or knee and/or hip) was present in 26% of the baseline CLSA comprehensive cohort. There are no studies examining pooled total OA prevalence in the population, though previous literature reported prevalence of knee OA as 23% in individuals over 40, with prevalence increasing in age, which is comparable to our findings.[4] The frequency of CVD was 54% in individuals with OA and 40% in individuals without OA, which is also consistent with research suggesting that the prevalence for overall CVD was elevated in individuals with OA.[5] For Objective 2, we hypothesized that individuals with OA would have significantly greater markers of CVD risk compared to age- and sex- matched individuals without OA, and we found significantly greater TUG, higher BMI, greater Frailty Index, and greater SDS values in individuals with OA compared to individuals without. Additionally, we found individuals with OA had higher cIMT, FRS, and IHRS compared to individuals without OA. . For Objective 3, we hypothesized that the odds of developing CVD were greater in individuals with OA. At 3-year follow-up, we found that individuals with OA had significantly elevated odds of developing CVD, even after accounting for markers of CVD risk. For Objective 4, we hypothesized that markers of CVD risk would be elevated in individuals with weight-bearing compared to non-weight-bearing OA and found significantly greater TUG and BMI and significantly lower HDL and Frailty Index in

individuals with weight-bearing OA; however, we did not find cIMT, IHRS, or FRS were different between groups. For Objective 5, we hypothesized that individuals with weight-bearing OA would experience greater odds of developing CVD compared to individuals with non-weight-bearing OA; but, found no significant influence of the site of OA on odds of CVD, with no differences between weight-bearing and non-weight bearing OA when examining CVD at 3-year follow-up.

The unadjusted odds ratio suggests that the odds of CVD at 3-year follow-up is significantly higher in individuals with OA and aligns with previous findings, where a meta-analysis reported individuals with OA had at a higher relative risk ($p<0.001$, relative risk: 1.24 [1.12-1.37] of experiencing heart failure and ischemic heart disease.[5] Interestingly, this meta-analysis did not find a significant difference in individuals with or without OA when examining myocardial infarction and stroke risk, which may suggest that the type of vascular disease interacts differently with the OA pathology.[5] Specifically, we did not examine the interaction between the type of CVD with OA, and by grouping all the vascular conditions collected by the CLSA into one umbrella variable, the nuanced interaction between specific vascular-related disorders and OA pathology may have been masked.

Influences of cIMT, FRS, and IHRS

cIMT increases as a result of natural aging, higher values of cIMT have been found to be associated with atherosclerotic risk, with this relationship holding true after accounting for the effects of aging.[15,42] Additionally, cIMT is measured through non-invasive techniques, making it an accessible surrogate of vascular health.[19,43,44] Individuals with OA had significantly greater cIMT measures when compared to individuals without OA, though no significant differences between

individuals with weight-bearing and non-weight-bearing OA. The odds ratio of developing CVD at 3-year follow-up remained significant after accounting for cIMT, which suggests other factors may a role in the odds of developing CVD in individuals with and without OA. Literature examining cIMT in individuals with OA is sparse, though there are studies that found that patients with OA have increased cIMT values.[17,45,46] A study comparing cIMT in a smaller sample (12 individuals with OA, 13 individuals without OA) found significantly greater IMT values in individuals with OA, aligning with our findings.[45] It is important to consider the effects of aging on cIMT; however, despite the individuals in the analyzed cohorts in our study being age-matched, differences still persisted, suggesting cIMT as a surrogate measure of CVD risk is influenced by OA pathology. One study comparing the association between cIMT and the presence of OA stratified by sex, and only found associations between IMT and prevalence of hand OA in women.[46] A different study examining a population of healthy age- and sex-matched individuals with and without OA (30 OA females, 11 control females, 10 OA males, 4 control males).[17] They found significant associations between severity of OA and higher IMT values; however, they excluded individuals with hypertension, diabetes, and selected for individuals with only primary OA (i.e., OA with no known cause as opposed to trauma, infection, etcetera).[17] It is possible that when considering our results examining the influence of the site of OA, the cohorts compared did non differ significantly in OA pathology, which may explain the lacking of differences in cIMT seen between weight-bearing and non-weight-bearing OA.

The Framingham Risk Score (FRS) is a commonly used method to identify CVD risk in the population.[19,20] The FRS was originally developed as a 10-year risk tool for coronary heart disease with a 4-12 year predictive capacity, and after its development, it was then validated as a 5-year

tool. A limitation of the FRS is the generalizability of the score; as it was originally developed and validated in a population of primarily middle-class white men, the application of the FRS to other ethnic populations requires adjustments and additional considerations.[20,47,48] There were significantly greater FRS values found in individuals with OA compared to individuals without OA, though no significant differences when considering the site of OA. The odds of developing CVD at 3-year follow-up remained the same before and after accounting for the FRS. The increased FRS in individuals with OA aligns to other research examining the FRS in the OA population, which has found associations between OA and higher FRS values.[8] However, similar to cIMT, it is possible that by controlling for the variability of age and sex, the FRS was not significantly different between the types of OA pathology (weight-bearing versus non-weight-bearing OA).

Similar to the FRS, the InterHeart Risk Score (IHRS) was developed using data collected from 52 countries as a tool to calculate CVD risk.[24,25] The IHRS was used for detecting myocardial infarction worldwide in both sexes and all ages,[24] and later validated to predict general CVD events with a similarly high degree of accuracy.[24] A non-laboratory IHRS was later validated and determined to be of similar predictive accuracy, which is advantageous for accessibility and implementation in community-based populations.[39] In addition to the CVD risk factors that are accounted for by the FRS, factors such as physical activity, diet, and stress have also been demonstrated to influence the risk of CVD.[23] These modifiable, lifestyle risk factors are especially of interest to researchers and clinicians alike, as they have the potential to influence the behaviour and treatment of patients and can be addressed often without pharmaceutical or medical intervention.[24] A strength of using the IHRS in the CLSA cohort specifically is the narrower window of prediction time (~1.25-3 years, compared to 5-10 years by the FRS). In our study, we found

significantly greater IHRS when comparing individuals with OA to individuals without OA, with no significant differences in weight-bearing and non-weight-bearing OA. Additionally, the odds of developing CVD at 3-year follow-up remained significant after accounting for the IHRS. There are no existing research studies examining the IHRS as a means to quantify CVD risk in individuals with OA, though the well-rounded construction and validation of the IHRS on a more diverse cohort suggests that the IHRS may also be a good predictor of CVD risk in populations including the CLSA cohort.[24] However, similar to cIMT and FRS, lacking of differences between weight-bearing and non-weight-bearing OA may also be attributed to the effects of age- and sex-matching, as accounting for the variation of age and sex factors may result in more similar disease phenotypes.

The combination of cIMT and FRS/IHRS for CVD risk assessment in the OA population has been suggested to have potential to provide a holistic understanding of how CVD risk presents in individuals with OA.[19] However, the odds of developing CVD at 3-year follow-up were significantly higher in individuals with OA, and not different between weight-bearing and non-weight-bearing OA both before and after accounting for the combination of cIMT and FRS/IHRS. This suggests that a different aspect of OA pathology may be driving the increase in CVD risk in individuals with OA, such as the potential interactions between the risk factors accounted for in CVD risk scores and non-specific risk factors such as inflammation and frailty. Additionally, increasing age and the female sex (particularly after the menopause transition) are well documented to be associated with increased risk and prevalence for both OA and CVD.[8,9,26] Through using matching criteria prior to analysis, the bias of the independent influences of age and sex are decreased. Lack of significant differences between individuals with and without OA when considering CVD risk scores may in part result from how age and sex interact with other risk factors to elevate CVD risk in individuals

with OA. Future studies may include sex-stratified analyses for examining factors such as body adiposity (e.g., through BMI or waist-to-hip ratio), frailty, social disadvantage, and other variables that are influenced by sex differences.

Influence of other risk factors on CVD risk in OA

We examined inflammation, measured through C-reactive protein, in individuals with and without OA. High-sensitivity C reactive protein (hsCRP) is a marker that interacts with other cytokines to elevate inflammation, and has potential implications in atherosclerosis through altering endothelial function.[49] There were no significant differences found between individuals with and without OA in our study, though there is literature to suggest that hsCRP levels are elevated in individuals with OA,[50,51] and high levels are also independently associated with predicting long-term CVD.[49] Notably, the first study to examine CVD risk in age- and sex-matched individuals with and without OA in the CLSA reported systemic inflammation (measured through hsCRP) and disturbed metabolism acting to increase the occurrence of elevated CVD risk in individuals with OA, and potentially to a greater extent in women.[14] Our study did not stratify these CVD risk factors by sex, which may provide rationale for this evidence gap. However, interpretations of hsCRP must be made with additional considerations, as the high sensitivity nature of hsCRP levels may be influenced by additional factors, such as acute trauma or infection that may result in a short-term inflammatory response and subsequent elevations of hsCRP levels in the blood.[52] Thus, it is important to note that hsCRP does not provide a complete inflammatory profile, and additional markers such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α are also independently implicated in OA[53] and CVD[54] pathologies. Adipokines, produced by adipose

tissue, results in inflammation that negatively impacts joint health.[55] Adipokines are often associated with obesity, which also negatively impact cardiovascular health,[56] which provides rationale to suspect a role of adipokines in mediating the relationship between OA and CVD. Collectively these additional inflammatory markers can be used to provide a more holistic understanding of the role of inflammation with CVD risk in individuals with OA.

Physical inactivity and poor performance in other functional measures have been associated with OA and risk for CVD. Increased pain during movement as a result of OA is a potential facilitating mechanism for CVD.[26] We examined timed-up-and-go (TUG) and the Physical Activity Scale for the Elderly (PASE) as functional measures to compare the differences between groups. We found that PASE was not significantly different between individuals with and without OA and was not significantly different between weight-bearing and non-weight-bearing OA, though TUG was significantly greater in individuals with OA and individuals with weight-bearing OA. However, these measures are not considered robust measures of activity or mobility and are therefore limited in the application. Though they provide some insight into the functional status of the individual, neither test can be used to represent complete functional ability. The reliability of the TUG test in individuals with OA, particularly knee OA, is not well established.[57] Additionally, literature suggests that the PASE score cannot be used to predict healthy physical metrics.[40] The PASE score is a questionnaire that can be used as a tool to survey physical activity in adults 65 years and older.[40] Individuals collected in the CLSA are aged 45-85 years, and thus the application of the PASE questionnaire within the analyses must be interpreted with caution, as a portion of the sub-cohort is below 65 years old.

In individuals with OA (specifically knee OA), a study found that there was overlap of waist-to-hip ratio and BMI, particularly in women, providing rationale to examine these surrogates of body composition in our study.[58] Increased sedentary behaviour, seen with individuals with OA,[59] may further lead to increased body adiposity, which is also associated with increased risk of CVD.[26] Increased adiposity has been associated with increased risk for CVD through mechanisms such as through inflammatory adipokines, which play a role in increasing hypertension, atherosclerosis, poor cholesterol regulation, and subsequent CVD outcomes.[56] Thus, obesity is a notable risk factor for adverse CVD events.[56] Interestingly, we found no significant differences when comparing waist-to-hip ratio in individuals with OA compared to individuals without OA, and we found that individuals with weight-bearing OA had no differences in waist-to-hip ratio compared to individuals with non-weight-bearing OA. However, BMI was significantly greater in individuals with OA, and significantly greater in individuals with weight-bearing OA. BMI and waist-to-hip ratio are both used as approximations body fat.[60,61] A study comparing measures of adiposity using the CLSA found BMI to be highly correlated with %body fat, and found waist-to-hip ratio to have a weaker relationship and influenced by sex differences when approximating %body fat.[60] Additionally, waist-to-hip ratio did not significantly affect odds of developing CVD at 3-year follow in individuals with and without OA and individuals with weight-bearing and non-weight-bearing OA. A different study examining BMI and waist-to-hip-ratio in evaluating obesity indices found that these measures did not add to CVD prediction in healthy middle-aged and older adults.[62] BMI and waist-to-hip ratio are estimations of body composition, and a possible explanation for the lacking of differences in waist-to-hip ratio particularly in individuals with OA may be that these estimations alone are not sensitive to only detecting body adiposity (apart from muscle mass) or individual

anatomical differences. Additionally, it is possible that body composition measures may only be a risk factor when other mechanisms are interacting, such as increased inflammation and low physical activity. The differences observed in BMI between age- and sex-matching individuals with OA, particularly in weight-bearing OA, may therefore be influenced by decreased physical activity, as literature suggests individuals with OA of the knee or hip often have pain associated with movement, and therefore increased sedentary behaviour.[26,63] Further, as our study did not conduct sex-stratified analyses of CVD risk, the influence of body adiposity, inflammation, and other risk factors reported to contribute to elevated CVD risk in previous studies[14] did not consider the influence of sex.

Blood biomarkers have been cited in studies examining CVD risk. In particularly, glucose control, which can be measured through hemoglobin A1c (HbA1c) levels, is strongly associated with an increased risk of CVD.[64] HbA1c is a marker of the average blood glucose concentration, with elevations in HbA1c levels often associated with diabetes, which is can result in obesity and hypertension, risk factors for CVD.[65] We found no significant differences in HbA1c levels when comparing individuals with and without OA, and no significant differences when comparing the site of OA. There is no literature suggesting that individuals with OA have elevated HbA1c levels, and as significant elevations were not found in our cohorts, this suggests that though higher HbA1c are associated with CVD, it is possible they are not caused by OA pathology as a linking mechanism between OA and CVD risk. Blood cholesterol is another factor associated with CVD risk, where LDL plays an atherogenic role in increasing CVD risk, and anti-atherogenic effects of HDL may mediate decreases in CVD risk.[66] We found significantly greater HDL values in individuals without OA, which has been suggested to have protective effects on CVD.[67] However, it is important to note that

concentration alone does not translate into functionality, and elevated HDL levels may not always result in clinically beneficial results.[66] Additionally, there were no significant differences in LDL between individuals with and without OA, and no significant differences in HDL or LDL levels between weight-bearing and non-weight-bearing OA. Again, this suggests that though dyslipidemia is associated with CVD, it is possible that OA pathology does not directly result in dyslipidemia, and CVD risk is merely elevated in populations with dyslipidemia regardless of OA status.

We found frailty, measured through a modified Frailty Index, a holistic metric created using CLSA data to capture frailty, to be significantly higher between age- and sex-matched individuals with OA and individuals with non-weight-bearing OA. Frailty has a bi-directional relationship with CVD, which when contextualized within our results helps to explain the increased risk for CVD in individuals with OA. Higher frailty is observed in individuals with OA, which may be a result of greater physical and cognitive frailty measured through the Frailty Index.[41] Physical frailty often leads to lower physical activity, which may result in muscle weakness, lower cardiovascular health, increased adiposity, and a subsequent increased risk of CVD.[26,68] The elevated frailty in non-weight-bearing OA may suggest a role of inflammation as opposed to decreased functional capacity driving frailty, which further implicates frailty not only influenced by and resulting in physical impairments.

The influence of SDS on CVD at 3-year follow-up was not studied, however we did examine group differences of SDS. We found the SDS to be significantly higher in individuals with OA compared to individuals without OA in an age- and sex matched cohort. This aligns with the literature surrounding social disadvantage and OA,[34] though it is important to note that the SDS

does not encompass all aspects of social disadvantage. However, there were no significant differences in the SDS value between individuals with weight-bearing OA compared to non-weight-bearing OA. The study that developed the social disadvantage index found that social disadvantage specifically in individuals CVD increased with age and varied by sex and ethnicity.[33] When considering individuals with and without OA in our cohort, differences exist after age- and sex-matching the groups, though ethnicity was not considered, which prompts future questions targeting the role of ethnicity in OA and CVD risk. Further, as there were no differences between the site of OA and SDS despite literature suggesting more influence of SDS on weight-bearing OA,[34] an aspect that can be considered in the future is also the role of ethnicity and the site of OA on CVD risk.

Influence of OA site on CVD outcomes

We found no significant influence of site (weight-bearing vs non-weight-bearing) of OA on CVD at 3-year follow-up. This is in contrast to many existing studies that suggest a stronger relationship of weight-bearing OA with CVD compared to non-weight-bearing OA.[11,12,29] Additionally, literature finds that as weight-bearing OA will influence aspects such as physical activity, the association with CVD outcomes is more apparent.[26,68] A study found that individuals with weight-bearing OA (specifically knee OA) spent over two-thirds of their daily time sedentary, which was also related to worse physical function.[63] Thus, it may not be the specific site of OA that results in different CVD risk, but rather the additional consequences of having weight-bearing or non-weight bearing OA. Factors such as age, sex, physical activity, and body composition may interact and result in elevated CVD risk in individuals with weight-bearing OA in current literature.

Limitations & Strengths

A limitation of this study is the self-reported nature of survey data. All OA and CVD diagnoses were self-reported of physician diagnoses, which may influence the validity of the results, which must be considered when interpreting the results from survey data. Additionally, several variables underwent minor adjustments in score calculations, such as for the IHRS (Supplementary Table 1), the Frailty Index (Supplementary Table 3), and the SDS. Due to the design of CLSA, there are limitations in the inclusion criteria of the cohort collected (e.g., English-speaking, individuals residing in the 10 provinces) that may slightly alter the demographic characteristics. Further considerations must be taken and possibly examined as potential avenues for future directions, including the role of OA severity on increased CVD risk,[69] and a potential mediating role of joint replacement.[11] Both OA severity and the occurrence of joint replacement surgeries may affect functional limitations of OA that cause greater CVD risk.[12] OA has been cited to affect specific types of CVD, such as heart failure, with weaker associations with ischaemic heart disease and transient ischemic attacks.[5] Future directions could thus include examining the specific sub-cohorts of CVD type with OA. The time of the most recent CVD event was also not collected and considered, which could explain fewer differences found between the groups, as individuals may begin to exhibit increased risk for CVD (regardless of OA status) prior to the CVD event. With these variables, Cox proportional hazards regressions can be analyzed to provide information on survival or differences in time-to-event for CVD in OA and non-OA groups. Though our study age- and sex-matched individuals with and without OA, we did not sex-match within each group (i.e., male participants with OA were matched to male participants without OA, but not to female participants with OA). Thus, a sex-stratified analysis will provide additional information on the specific influence

of sex on CVD outcomes. A more complete inflammatory profile that includes both chronic and transient inflammatory markers could provide a better idea of the role of inflammation in the two pathologies. Medications used, such as non-steroidal anti-inflammatory drugs (NSAIDs), were not considered in this study, though they have been implicated as a mechanism between individuals with OA and CVD.[26] Finally, nutrition is a factor that is associated with increased CVD, and though diet was considered in the IHRS, the role of healthy and unhealthy dietary patterns could be further examined in future studies.[70]

A strength of this study results from the generalizability of findings of the CLSA cohort to the Canadian aging population. In addition to using a large longitudinal dataset, survey weights were applied to minimize sampling bias in the analysis and allow for better generalizability of the findings. This study examined a novel combination of variables, investigating CVD risk by means of cIMT, FRS, and IHRS in individuals with OA, who have been reported by literature as high-risk for CVD. Specifically, the FRS and IHRS are both holistic measures of CVD risk, which are advantageous examine in a cohort where cross-sectional variables are used to calculate the scores, and the influence on longitudinal time-points can be studied. The non-laboratory IHRS provides additional modifiable risk factors of CVD risk while increasing the application potential of the score in settings where it is not feasible to have participants enter a lab for blood work. Finally, we performed random frequency-matching of age and sex within our analysis cohorts to narrow the scope of our analysis and remove possible biasing effects of age and sex between the groups.[71] We also included a diverse array of risk factors, and considering variables including inflammation, social disadvantage, and frailty in the context of CVD risk in relation to OA.

Conclusion

Using a nested, age- and sex-matched, case-control sub-cohort from the CLSA, this study found greater odds of CVD in individuals with OA compared to individuals without OA, and no significant effect of cIMT, FRS, or IHRS on odds of CVD, though significantly elevated values of cIMT, FRS, and IHRS in individuals with OA at baseline compared to individuals without OA. Additionally, we found no significant differences in odds of CVD at 3-year follow-up in weight-bearing and non-weight-bearing OA, and no significant effect of cIMT, FRS, or IHRS on odds of CVD. There were significant differences when examining factors such as frailty and social disadvantage at baseline between individuals with and without OA. This study provides rationale for future studies to further examine type of OA with type of CVD, with considerations given to a more comprehensive panel of risk factors such as frailty and social disadvantage. The global disease burden of OA and CVD are significant, making it of great interest for clinicians and patients alike to take early measures towards preserving health and furthering the understanding of disease onset and progression. Examining markers of CVD risk in an at-risk population with osteoarthritis will help further research targeting strategies to decrease the occurrence and burden of disease and comorbidity. Thus, researching the best approaches for early detection of CVD risk will play an important role in prevention and quality of life, particularly in the aging population.

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2.6 Figures and Tables

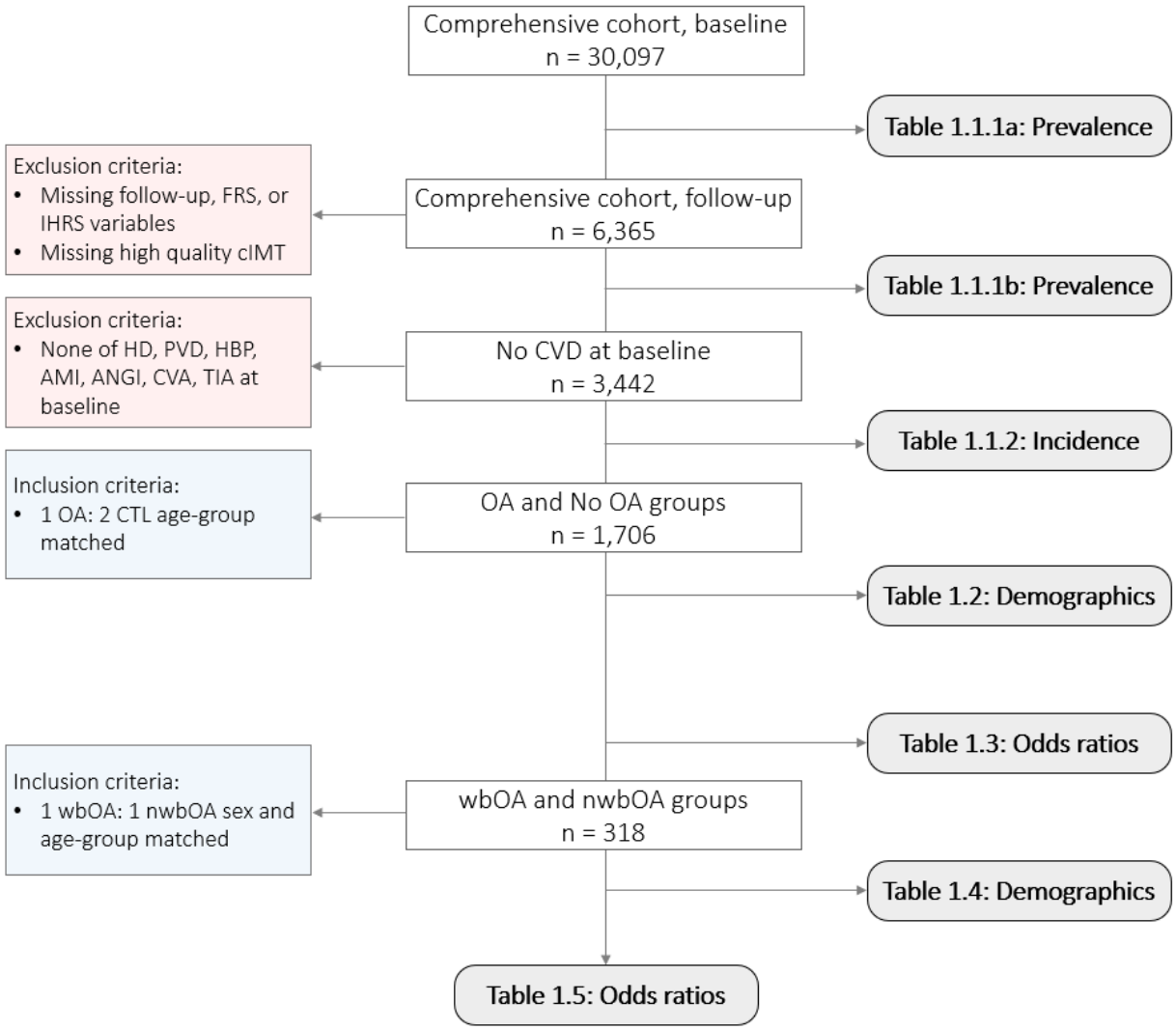

Figure 1. Flowchart of individuals included in this study (Chapter 2) from baseline and 3-year follow-up in the CLSA Comprehensive cohort. SDS: social disadvantage score; IHRS: INTERHEART risk score; HD: heart disease; PVD: peripheral vascular disease; HBP: high blood pressure; AMI: acute myocardial infarction; ANGI: angina; CVA: cerebrovascular accident; TIA: transient ischemic accident; OA: osteoarthritis; wbOA: weight-bearing OA; nwbOA: non-weight-bearing OA.

Table 1.1.1a. CVD frequency in individuals with OA (hand OR hip OR knee OA) compared to individuals with no OA diagnoses at baseline using CLSA data.

	OA diagnosis n (GP)	**No OA diagnosis** n (GP)	**RP** OA/ No OA	**Total prevalence** n (OA + No OA prevalence)
Total n =	*7922*	*22175*		*30097*
Hand OA	3857 (0.49)	0 (0)		3857 (0.1262)
Knee OA	4499 (0.57)	0 (0)		4499 (0.1495)
Hip OA	2499 (0.32)	0 (0)		2499 (0.083)
Any CVD diagnosis	**4437 (0.54)**	**9204 (0.40)**	**1.35**	**13231 (0.44)**
HD	1176 (0.15)	2327 (0.10)	1.41	3503 (0.12)
PVD	639 (0.08)	1007 (0.05)	1.78	1646 (0.05)
HBP	3655 (0.46)	7446 (0.34)	1.37	11101 (0.37)
AMI	434 (0.05)	1027 (0.05)	1.18	1460 (0.05)
ANGI	492 (0.06)	832 (0.04)	1.18	1324 (0.4)
CVA	180 (0.02)	342 (0.02)	1.47	522 (0.02)
TIA	358 (0.05)	607 (0.03)	1.65	965 (0.03)

GP: group proportion; RP: relative proportion; OA: osteoarthritis; CVD: cardiovascular disease; HD: heart disease; PVD: peripheral vascular disease; HBP: high blood pressure; AMI: acute myocardial infarction; ANGI: angina; CVA: cerebrovascular accident; TIA: transient ischemic accident

Table 1.1.1b. CVD frequency in individuals with OA (hand OR hip OR knee OA) compared to individuals with no OA diagnoses at baseline who have complete data for cIMT, FRS, and IHRS using CLSA data.

	OA diagnosis n (group prevalence)	**No OA diagnosis** n (group prevalence)	**Relative proportions** OA/No OA	**Total prevalence** n (OA + No OA prevalence)
Total n =	*1694*	*4671*		*6365*
Hand OA	827 (0.49)	0 (0)		827 (0.13)
Knee OA	983 (0.58)	0 (0)		983 (0.15)
Hip OA	534 (0.32)	0 (0)		534 (0.08)
Any CVD diagnosis	**957 (0.56)**	**1966 (0.42)**	**1.33**	**2923 (0.46)**
HD	247 (0.15)	487 (0.10)	1.50	734 (0.12)
PVD	120 (0.07)	193 (0.04)	1.75	313 (0.05)
HBP	813 (0.48)	1624 (0.35)	1.37	2437 (0.38)
AMI	86 (0.05)	211 (0.05)	1.00	297 (0.05)
ANGI	95 (0.06)	164 (0.04)	1.50	259 (0.04)
CVA	40 (0.02)	59 (0.01)	2.00	99 (0.02)
TIA	74 (0.04)	106 (0.02)	2.00	180 (0.03)

GP: group proportion; RP: relative proportion; OA: osteoarthritis; CVD: cardiovascular disease; HD: heart disease; PVD: peripheral vascular disease; HBP: high blood pressure; AMI: acute myocardial infarction; ANGI: angina; CVA: cerebrovascular accident; TIA: transient ischemic accident

Table 1.1.2. CVD frequency at 3-year follow-up in individuals with OA (hand OR hip OR knee OA) compared to individuals with no OA diagnoses at baseline who have complete data for cIMT, FRS, and IHRS using CLSA data.

	OA diagnosis n (GI)	**No OA diagnosis** n (GI)	**RP** OA/No OA	**Total incidence** n (OA + No OA prevalence)
Total n =	*737*	*2705*		*3442*
Hand OA	362 (0.49)	0 (0)		362 (0.11)
Knee OA	400 (0.54)	0 (0)		400 (0.12)
Hip OA	207 (0.28)	0 (0)		207 (0.06)
Any CVD diagnosis	**112 (0.15)**	**271 (0.10)**	**1.50**	**383 (0.11)**
HD	31 (0.04)	68 (0.03)	1.41	482 (0.14)
PVD	15 (0.02)	34 (0.01)	1.33	49 (0.01)
HBP	62 (0.08)	167 (0.06)	1.33	229 (0.07)
AMI	8 (0.011)	18 (0.007)	1.57	26 (0.01)
ANGI	7 (0.01)	9 (0.003)	3.33	16 (0.00)
CVA	2 (0.003)	8 (0.003)	1.00	10 (0.00)
TIA	6 (0.008)	17 (0.006)	1.33	23 (0.01)

GI: group proportion at 3-year follow-up; OA: osteoarthritis; CVD: cardiovascular disease; HD: heart disease; PVD: peripheral vascular disease; HBP: high blood pressure; AMI: acute myocardial infarction; ANGI: angina; CVA: cerebrovascular accident; TIA: transient ischemic accident

Table 1.2. Participant demographics using baseline CLSA data.

	OA Diagnosis	# Missing (% total)	No OA Diagnosis	# Missing (% total)	p-value
Total n	618	---	1088	---	---
Age (years)	60.82 [9.14]	0	58.56 [8.81]	0	**<.001**
PASE	151.75 [74.7]	5 (< 1%)	156.94 [73.22]	10 (1%)	0.163
TUG (s)	9.39 [3.66]	7 (1%)	8.87 [1.51]	20 (2%)	**<.001**
BMI (kg/m^2)	27.39 [5.16]	0	26.05 [4.68]	2	**<.001**
WH ratio	0.87 [0.1]	0	0.87 [0.1]	0	1
HbA1c (%)	5.53 [0.7]	2 (< 1%)	5.48 [0.57]	11 (1%)	0.110
hsCRP (mg/L)	2.06 [2.81]	1 (< 1%)	1.92 [3.54]	1 (< 1%)	0.399
HDL (mmol/L)	1.61 [0.5]	0	1.63 [0.5]	0	0.427
LDL (mmol/L)	2.98 [0.92]	0	2.94 [0.87]	0	0.372
Frailty Index	0.09 [0.05]	0	0.07 [0.04]	0	**<.001**
SDS	0.55 [0.85]	32 (5%)	0.42 [0.75]	59 (5%)	**0.001**
Non-lab IHRS[39]	7.43 [5.14]	0	6.61 [5.25]	0	**0.002**
FRS	10.11 [4.57]	0	9.23 [4.6]	0	**<.001**
cIMT	0.72 [0.15]	0	0.70 [0.15]	0	**0.01**

P values are calculated through Student's t-test between OA and No OA individuals. Data is matched 1 OA: 2 No OA. n = 690 male participants, n = 1016 female participants. OA: osteoarthritis; PASE: Physical Activity Scale for the Elderly; TUG: timed-up-and-go; BMI: Body Mass Index; WH: waist-to-hip ratio; HbA1c: hemoglobin A1c; HSCRP: high sensitivity C-Reactive Protein; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; *SDS – Social Disadvantage Score, modified from Anand et al (2020)[72], calculated by income less than 20,000 CAD assigned a score of two, income between 20,000 CAD and 50,000 CAD assigned a score of one, and living without a partner assigned a score of one. The maximum SDS was three, and the lowest possible SDS was zero; IHRS – InterHeart risk score (non-lab); FRS: Framingham risk score; cIMT: carotid intima-media thickness (left side).

Table 1.3.1 Unadjusted odds ratio of CVD at 3-year follow-up in OA and No OA

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-2.126	0.0982	-21.64	**<.001**	0.119	0.0984	0.145
Any OA:							
OA – No OA	0.539	0.1453	3.71	**<.001**	1.715	1.2899	2.280

Note. Estimates represent the log odds of "fCVD = CVD" vs. "fCVD = No CVD"

Total n = 1706 (n = 618 OA, age- and sex-matched n = 1,088 No OA). OA: osteoarthritis; fCVD: cardiovascular disease at follow-up.

Table 1.3.2 Adjusted odds ratio of CVD at 3-year follow-up in OA and No OA – cIMT

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-2.034	0.173	-11.773	**<.001**	0.131	0.0932	0.184
Any OA:							
OA – No OA	0.538	0.145	3.704	**<.001**	1.713	1.2885	2.278
cIMT	-0.138	0.216	-0.639	0.523	0.871	0.5707	1.330

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 1706 (n = 618 OA, age- and sex-matched n = 1,088 No OA). OA: osteoarthritis; cIMT: carotid intima-media thickness; fCVD: cardiovascular disease at follow-up.

Table 1.3.3. Adjusted odds ratio of CVD at 3-year follow-up in OA and No OA – cIMT and CVD risk factors

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.9142	0.2271	-8.430	**<.001**	0.147	0.0945	0.230
Any OA:							
OA – No OA	0.5312	0.1486	3.575	**<.001**	1.701	1.2712	2.276
cIMT	1.3554	0.5292	2.561	**0.010**	3.878	1.3748	10.942
Age	-0.0255	0.0107	-2.391	**0.017**	0.975	0.9546	0.995
Frailty Index	2.6325	1.5722	1.674	0.094	13.909	0.6383	303.079
WH ratio	-0.1460	0.5998	-0.243	0.808	0.864	0.2667	2.800
Sex:							
M – F	0.4672	0.1619	2.886	**0.004**	1.595	1.1618	2.191

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 1706 (n = 618 OA, age- and sex-matched n = 1,088 No OA). OA: osteoarthritis; WH ratio: waist-to-hip ratio; cIMT: carotid intima-media thickness; WHR: waist-to-hip ratio; fCVD: cardiovascular disease at follow-up.

Table 1.3.4. Adjusted odds ratio of CVD at 3-year follow-up in OA and No OA – cIMT and FRS

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-2.1781	0.1773	-12.29	**<.001**	0.113	0.0800	0.160
Any OA:							
OA – No OA	0.5115	0.1466	3.49	**<.001**	1.668	1.2512	2.223
cIMT	-1.1138	0.3148	-3.54	**<.001**	0.328	0.1772	0.608
FRS	0.0884	0.0175	5.04	**<.001**	1.092	1.0555	1.131

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 1706 (n = 618 OA, age- and sex-matched n = 1,088 No OA). OA: osteoarthritis; cIMT: carotid intima-media thickness; FRS: Framingham Risk Score; fCVD: cardiovascular disease at follow-up.

Table 1.3.5. Adjusted odds ratio of CVD at 3-year follow-up in OA and No OA – cIMT and IHRS

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	**Estimate**	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-2.0480	0.1730	-11.83	**<.001**	0.129	0.0919	0.181
Any OA:							
OA – No OA	0.5196	0.1459	3.56	**<.001**	1.681	1.2631	2.238
cIMT	-0.5466	0.2582	-2.12	**0.034**	0.579	0.3490	0.960
IHRS (non-lab)	0.0452	0.0135	3.35	**<.001**	1.046	1.0189	1.074

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 1706 (n = 618 OA, age- and sex-matched n = 1,088 No OA). OA: osteoarthritis; cIMT: carotid intima-media thickness; IHRS: InterHeart Risk Score (non-laboratory); fCVD: cardiovascular disease at follow-up.

Table 1.4 Participant demographics using baseline CLSA data in weight-bearing and non-weight-bearing OA

	wbOA	# Missing (% total)	nwbOA	# Missing (% total)	p-value
Total n	159	---	159	---	---
Age (years)	60.88 [9.05]	0	60.63 [9.25]	0	0.808
PASE	156.04 [82.7]	0	151.5 [67.86]	1 (< 1%)	0.593
TUG (s)	10.24 [6.48]	0	8.76 [1.35]	4 (3%)	**0.005**
BMI (kg/m^2)	27.39 [4.73]	0	25.43 [3.74]	0	**<.001**
WH ratio	0.88 [0.1]	0	0.86 [0.1]	0	0.076
HbA1c (%)	5.6 [0.94]	1 (< 1%)	5.47 [0.51]	0	0.126
hsCRP (mg/L)	1.99 [2.85]	1 (< 1%)	2.02 [3.37]	0	0.932
HDL (mmol/L)	1.58 [0.5]	0	1.72 [0.51]	0	**0.014**
LDL (mmol/L)	2.94 [0.98]	0	3.01 [0.83]	0	0.492
Frailty Index	0.08 [0.05]	0	0.09 [0.04]	0	**0.050**
SDS	0.54 [0.8]	9 (6%)	0.65 [0.93]	6 (4%)	0.259
Non-lab IHRS[39]	7.21 [5.39]	0	6.68 [4.95]	0	0.362
FRS	10.22 [4.89]	0	9.56 [4.52]	0	0.212
cIMT	0.72 [0.14]	0	0.69 [0.14]	0	0.057

P values are calculated through Student's t-test between weight-bearing (wbOA) and non-weight-bearing (nwbOA) osteoarthritis (OA). Data is matched 1 wbOA: 1 nwbOA. n = 54 male participants per group, n = 105 female participants per group. PASE: Physical Activity Scale for the Elderly; TUG: timed-up-and-go; BMI: Body Mass Index; WH: waist-to-hip ratio; HbA1c: hemoglobin A1c; HSCRP: high sensitivity C-Reactive Protein; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; *SDS – Social Disadvantage Score, modified from Anand et al (2020)[72], calculated by income less than 20,000 CAD assigned a score of two, income between 20,000 CAD and 50,000 CAD assigned a score of one, and living without a partner assigned a score of one. The maximum SDS was three, and the lowest possible SDS was zero; IHRS – InterHeart risk score (non-lab); FRS: Framingham risk score; cIMT: carotid intima-media thickness (left side).

Table 1.5.1. Unadjusted odds ratio of CVD at 3-year follow-up in weight-bearing OA (wbOA) and non-weight-bearing OA (nwb OA)

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.543	0.208	-7.41	<.001	0.214	0.142	0.321
Type of OA:							
wbOA – nwbOA	-0.340	0.313	-1.08	0.278	0.712	0.385	1.316

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 318 (n = 159 nwbOA, age- and sex-matched n = 159 wbOA). wbOA: weight-bearing osteoarthritis; nwbOA: non-weight-bearing osteoarthritis; cIMT: carotid intima-media thickness; fCVD: cardiovascular disease at follow-up.

Table 1.5.2. Adjusted odds ratio of CVD at 3-year follow-up in weight-bearing OA (wbOA) and non-weight-bearing OA (nwb OA) – cIMT only

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.5899	0.389	-4.090	<.001	0.204	0.0952	0.437
Type of OA:							
wbOA - nwbOA	-0.3430	0.314	-1.091	0.275	0.710	0.3833	1.314
cIMT	0.0756	0.527	0.143	0.886	1.079	0.3840	3.029

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 318 (n = 159 nwbOA, age- and sex-matched n = 159 wbOA). wbOA: weight-bearing osteoarthritis; nwbOA: non-weight-bearing osteoarthritis; cIMT: carotid intima-media thickness; fCVD: cardiovascular disease at follow-up.

Table 1.5.3. Adjusted odds ratio of CVD at 3-year follow-up in weight-bearing OA (wbOA) and non-weight-bearing OA (nwb OA) – cIMT and CVD risk factors

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.7851	0.5048	-3.536	**<.001**	0.168	0.0624	0.451
Type of OA:							
wbOA - nwbOA	-0.3557	0.3245	-1.096	0.273	0.701	0.3709	1.324
cIMT	2.8439	1.2588	2.259	**0.024**	17.182	1.4574	202.560
Age	-0.0226	0.0228	-0.990	0.322	0.978	0.9348	1.022
Frailty Index	5.3207	4.0927	1.300	0.194	204.524	0.0671	623015.672
WHR	-1.5477	1.3202	-1.172	0.241	0.213	0.0160	2.829
Sex:							
M – F	1.0307	0.3447	2.990	**0.003**	2.803	1.4264	5.508

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 318 (n = 159 nwbOA, age- and sex-matched n = 159 wbOA). wbOA: weight-bearing osteoarthritis; nwbOA: non-weight-bearing osteoarthritis; cIMT: carotid intima-media thickness; WHR: waist-to-hip ratio; fCVD: cardiovascular disease at follow-up.

Table 1.5.4. Adjusted odds ratio of CVD at 3-year follow-up in weight-bearing OA (wbOA) and non-weight-bearing OA (nwb OA) – cIMT and FRS

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.7835	0.4154	4.294	**<.001**	0.168	0.0745	0.379
Type of OA:							
wbOA - nwbOA	-0.3536	0.3159	-1.119	0.263	0.702	0.3780	1.304
cIMT	-0.5290	0.6637	-0.797	0.425	0.589	0.1605	2.164
FRS	0.0675	0.0382	1.768	0.077	1.070	0.9927	1.153

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 318 (n = 159 nwbOA, age- and sex-matched n = 159 wbOA). wbOA: weight-bearing osteoarthritis; nwbOA: non-weight-bearing osteoarthritis; cIMT: carotid intima-media thickness; FRS: Framingham Risk Score; fCVD: cardiovascular disease at follow-up.

Table 1.5.5. Adjusted odds ratio of CVD at 3-year follow-up in weight-bearing OA (wbOA) and non-weight-bearing OA (nwb OA) – cIMT and IHRS

Model Coefficients - fCVD

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-1.6552	0.3974	4.165	**<.001**	0.191	0.0877	0.416
Type of OA:							
wbOA - nwbOA	-0.3759	0.3173	-1.185	0.236	0.687	0.3687	1.279
cIMT	-0.3218	0.5958	-0.540	0.589	0.725	0.2255	2.330
IHRS (non-lab)	0.0547	0.0302	1.810	0.070	1.056	0.9955	1.121

Note. Estimates represent the log odds of "fCVD = 1" vs. "fCVD = 0"

Total n = 318 (n = 159 nwbOA, age- and sex-matched n = 159 wbOA). wbOA: weight-bearing osteoarthritis; nwbOA: non-weight-bearing osteoarthritis; cIMT: carotid intima-media thickness; IHRS: InterHeart Risk Score (non-laboratory); fCVD: cardiovascular disease at follow-up.

Chapter 3 – The association between OA, menopause, and the risk for CVD in the Canadian Longitudinal Study on Aging

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3.1 Introduction

Osteoarthritis (OA) is a progressive musculoskeletal disease characterized by the degradation of cartilage and bone, resulting in pain and disability and affects approximately 654 million people worldwide.[1,2] The prevalence of OA is greater in women than in men (~22%, ~12%, respectively), and becomes more apparent after the sixth decade of life, where OA prevalence in women surpasses that in men.[2] The increased prevalence of OA in older women is partially explained by the occurrence of the menopause transition, or the sudden decrease in circulating sex hormones, estrogen (i.e., 17β-estradiol) and progesterone associated with the menstrual cycle.[3]

Cardiovascular disease (CVD), encompassing pathologies of the heart and vascular system, is also a leading cause of morbidity and mortality, contributing to over 17.3 million deaths worldwide each year.[4] While men have higher CVD prevalence and incidence earlier in life, the risk for women developing CVD after menopause is elevated, as estimated with the available risk scoring mechanisms and by evidence of CVD incidence.[5] OA and CVD are often comorbid, thereby increasing burden on the aging demographic and the surrounding society.[6] However, the joint in which osteoarthritis develops seems to matter when considering the shared risk profile between

cardiovascular disease and osteoarthritis. Specifically, compared to hand OA, studies have found a greater association of knee and hip OA with higher CVD risk.[7,8] It is of interest to further understand the relationship between weight-bearing OA and CVD risk.

The role for menopausal hormone therapy (HT) in the absence of contraindications, when started within 10 years of menopause, has been shown to decrease the risk for CVD.[9] Likewise, the estrogen component of HT, has shown promise in managing symptoms and progression of OA due to its protective effects on bone and surrounding tissue.[10,11] However, results from the Women's Health Initiative and Heart and Estrogen/progestin Replacement Study suggested that HT may increase the risk for CVD.[12,13] Since these studies were done, a "timing hypothesis" has emerged that describes HT as beneficial to women for reducing CVD disease during a specific window (i.e., within 10 years of menopause onset). It is possible that the same principles of the timing hypothesis may apply to OA disease risk, where using HT within 10 years of menopause onset may have protective effects for OA diagnosis and progression.

Furthermore, additional factors such as body adiposity (e.g., measured through body mass index or waist-to-hip ratio, BMI and WH ratio respectively) and physical activity all contribute to CVD risk.[14] Blood biomarkers, including inflammatory markers (e.g., C-reactive protein, or CRP), cholesterol (e.g., high- and low-density lipoproteins, HDL and LDL respectively), and glucose control (e.g., hemoglobin A1c, orHbA1c), also play a role in CVD risk.[15–17] Social disadvantage, often approximated through a combination of socioeconomic factors and social support, has been found to be significantly higher in women, and is also associated with CVD risk.[18] These risk factors have all been observed in individuals with OA, providing rationale for exploring the overlapping etiology.[19,20] Further, the decrease in circulating estrogen as a result of menopause has been

suggested to contribute to elevations in these risk factors among post-menopausal women.[21] CVD risk scores have been created to provide a holistic score for CVD risk using common CVD risk factors. Notably, the InterHeart risk score (IHRS) uses a combination of general and modifiable risk factors to quantify CVD risk of future CVD events.[19,22] However, the IHRS has not been used to examine CVD risk in individuals with OA.

To our knowledge, no prior research has examined the interaction between HT use, OA diagnosis, and CVD risk in post-menopausal women. The aim of this study is to examine sex differences and the potential role of menopause on CVD risk in a population with known CVD risk (i.e., individuals with an OA diagnosis but no existing CVD) and a healthy control cohort (i.e., individuals with no OA or CVD diagnoses), while considering additional CVD risk variables and the IHRS. These aims will be addressed by the following objectives:

Objective 1: Examine proportions of CVD in male and female participants with and without OA at baseline and 3-year follow-up. This will examine the comorbidity of OA and CVD, specifically to observe the frequency of CVD in individuals with versus without an existing OA diagnosis stratified by sex to examine sex differences

Objective 2: Compare group demographics of CVD risk factors and the IHRS between post-menopausal women with and without OA. CVD risk profiles will be compared between a sub-group of age-matched post-menopausal female participants with and without OA diagnosis to examine the CVD risk profiles in the two cohorts.

Objective 3: Examine the associations between menopausal variables and odds CVD at 3-year follow-up in post-menopausal women with and without OA. Using baseline CVD risk profiles in an isolated population of post-menopausal female participants, the odds of CVD (measured

through answering "Yes" to any of the previously defined CVD diagnosis variables at 3-year follow-up) will be compared in age-matched female participants with and without OA as the outcome of interest. The logistic regression models will systematically include variables (exposure) to assess how odds ratio of CVD incidence is impacted by:

1. OA status alone
2. OA status with IHRS and interaction effects between IHRS and OA status
3. OA status with age, years since menopause, HT use, and IHRS, with interaction effects between IHRS and OA status

The specific sub-cohorts can be found in Figure 1. We hypothesize that: Objective 2 - individuals with OA will have greater CVD risk profiles when examining demographics than individuals without OA; Objective 3 - in the sub-cohort of age-matched post-menopausal female participants with and without OA, post-menopausal female participants with OA will have greater CVD risk profiles when examining demographics; and Objective 4 - that post-menopausal female participants with OA will have greater odds of CVD at 3-year follow-up, which is partially explained by menopausal variables and CVD risk.

3.2 Methodological Approach

3.2.1 Study design and population

Baseline (n = 30,097) and follow-up 1 (n = 27,765 after 3 years) data from the Comprehensive cohort collected by the Canadian Longitudinal Study on Aging (CLSA) was used for secondary analysis. Further details surrounding the CLSA design are described elsewhere.[23,24] Cross-sectional and longitudinal studies were conducted using physiological and sociocultural data relevant to

health and aging collected from participants aged 45-85 years old sampled from 11 data collection sites across 7 Canadian provinces. The study was approved by the CLSA scientific advisory board and received ethics from the McMaster Research Ethics Board (protocol #4912). The flowchart of the sub-cohorts used for each analysis can be found in Figure 1.

3.2.2 Osteoarthritis status

Self-reported weight-bearing osteoarthritis status was used to group participants based on OA diagnosis. Participants who answered "yes" to having been diagnosed with knee or hip OA by a physician were characterized as having OA. Participants who responded "no" to both knee and hip OA were characterized as No OA. Although hand OA was also a collected variable, self-reported hand OA was not factored into the OA definition. Thus, individuals with hand OA were not excluded in the weight-bearing OA definition.

3.2.3 Menopausal status and hormone therapy (HT) use

Self-reported data on reproductive variables, such as menopause and HT use, have been examined in previous studies and found to be reliable and acceptable.[25,26] Self-reported menopausal status was used, defined as having stopped menstruation for at least one year without restarting. Individuals who reported undergoing a hysterectomy were excluded, as neither data regarding date of the hysterectomy nor the occurrence of an oophorectomy were available. Those who reported being post-menopausal were further asked the age of menopause onset, specifically the age at which the participants menstrual periods stopped for at least one year and did not restart. Using the participants' age and age of menopause onset, the number of years since menopause

was calculated as a variable in the analyses. Self-reported HT use was included as a variable in the analyses, included as a binary variable with “ever used” and “never used”.

3.2.4 Cardiovascular risk

The IHRS was developed using data collected from 52 countries as a tool to predict the risk of a CVD event.[19,22] A non-laboratory IHRS was later validated and determined to be of similar predictive accuracy, which excluded blood cholesterols and considered a family history of myocardial infarction.[27] For the purposes of this study, the non-lab IHRS was modified to adapt to the available CLSA variables, and the calculations can be found in the Appendix (Supplementary Tables 1)[22]. The methodology for calculating the IHRS in CLSA data can be found elsewhere (Chapter 2).

3.2.5 Cardiovascular disease (CVD) status

The primary outcome variable was CVD. Participants who answered “yes” to having been diagnosed with the following conditions by a physician, were characterized as having CVD: self-reported heart disease (HD), cerebrovascular accident (CVA), transient ischemic stroke (TIA), high blood pressure (HBP), angina, peripheral vascular disease (PVD), or acute myocardial infarction (AMI).[28] For analyses examining CVD at 3-year follow-up, participants who reported “no” to all CVD conditions at baseline were included, and their 3-year follow-up CVD data was subsequently analyzed.

3.2.6 Statistical analyses

Descriptive statistics, expressed as means and standard deviations, were used to describe continuous variables and stratified by sex, menopause status, and disease. Counts, frequencies,

and proportions were used to describe categorical variables such as disease frequencies. Multivariable logistic regressions were calculated using covariates and interactions to determine adjusted odds ratios, presented using 95% confidence intervals [95% CI]. Age, years since menopause, HT use and type,[29] and the IHRS were included as covariates in the adjusted odds ratio calculations. Individuals with missing values for one or more of the variables of interest were excluded from the analyses. When appropriate and feasible, samples were 1 OA: 2 No OA age-matched in 10-year intervals. Non-parametric Welch's t-tests were used to compare medians of unadjusted, raw continuous variables (Supplementary tables), and Student's t-tests were used to compare means of adjusted continuous variables. Alpha level of significance was set to 0.05, where test outcomes less than the alpha level were deemed significant. All statistical analyses were conducted using appropriate sampling weights with appropriate methods for the analysis of survey data. All data analyses were conducted using Python (version 3.0 via Jupyter Lab) and Jamovi (version 1.8).

3.3 Results

Proportion of CVD in individuals with OA at baseline

A total of 17,217 participants (Figure 2) were included in the frequency analysis of CVD in participants that were stratified based on diagnosis, sex, and menopausal status (Table 2.1). This cohort had complete data for IHRS and 3-year follow-up data. At baseline, there were 3,502 total people with OA (n = 1,401 male participants, n = 2,101 female participants), and 13,715 people without OA (n = 7,030 male participants, n = 6,685 female participants). Of the 2101 female participants with an OA diagnosis, 142 were pre-menopausal and 1,533 were post-menopausal.

Of the 6,685 female participants without an OA diagnosis, 1,249 were pre-menopausal and 4,386 were post-menopausal. A total of 7,753 individuals had a CVD condition at baseline (45% of all individuals), of which 1,986 had OA (57% of all people with OA) and 5,767 did not have OA (42% of all people without OA). When comparing people with OA to people without OA, CVD diagnosis was consistently greater in all individuals with OA (relative proportion: 1.10 – 1.76), regardless of sex or menopausal status.

Proportion of CVD in individuals with OA at 3-year follow-up with no CVD at baseline

A total of 9,464 individuals (Figure 2) were included in the frequency analysis at follow-up. From the sub-cohort of individuals who had complete data for the primary variables of interest, individuals who had any type of CVD event at baseline were excluded. From the sub-cohort, 3-year follow-up CVD diagnosis was examined, stratified based on diagnosis, sex, and menopausal status (Table 2.2). At baseline, there were 1,516 total people with OA (n = 565 male participants, n = 951 female participants), and 7,948 people without OA (n = 3,760 male participants, n = 4,188 female participants). Of the 951 female participants with an OA diagnosis, 78 were pre-menopausal and 721 were post-menopausal. Of the 4,188 females without an OA diagnosis, 993 were pre-menopausal and 2,685 were post-menopausal. A total of 1,146 individuals developed a CVD condition at 3-year follow-up (12% of all individuals), of which 244 had OA (16% of all people with OA) and 902 did not have OA (11% of all people without OA). When comparing people with OA to people without OA, CVD diagnosis at 3-year follow-up had relative proportions of 1.03 – 2.3 in individuals with OA (regardless of sex or menopausal status) compared to individuals without OA.

Participant demographics and CVD risk in post-menopausal female participants with or without OA

The raw (Supplementary Table 7) and adjusted (Table 2.3) demographic characteristics of the age-matched cohort of post-menopausal female participants with and without OA were examined (Figure 2). There were 711 post-menopausal female participants with OA and 1,405 age-matched post-menopausal female participants without OA. Following the adjustments of survey weights, greater age (OA: 64.0 ± 8.15; No OA: 63.22 ± 8.15), greater BMI (OA: 27.71 ± 5.52; No OA: 25.93 ± 4.58), and greater waist-to-hip ratio (OA: 0.83 ± 0.06; No OA: 0.82 ± 0.06) was observed in post-menopausal female participants with OA compared with post-menopausal female participants without OA (Table 2.3)

Greater unadjusted odds of CVD at 3-year follow-up in post-menopausal female participants with OA, with no significant differences after considering covariates.

The odds of developing CVD at 3-year follow-up were significantly greater in post-menopausal female participants with OA compared to post-menopausal female participants without OA (Figure 2) (p=0.03, Odds ratio: 1.34 [1.03-1.74]) (Table 2.4.1). After adjusting for the IHRS and considering the interaction between IHRS and OA diagnosis, the odds of developing CVD at 3-year follow-up were not significantly different between the groups (p=0.246, Odds ratio: 1.37 [0.81-2.27]) (Table 2.4.2), with no significant interaction effect of IHRS with OA diagnosis and a significant main effect of IHRS. After adjusting for the effects of age, years since menopause, HT use, the IHRS, and considering the interaction between IHRS and OA diagnosis, the odds of developing CVD at 3-year follow-up remained not different between groups (p=0.217, Odds ratio: 1.40 [0.82-2.40]) (Table

2.4.3), with no significant interaction effect of IHRS with OA diagnosis and significant effects of age, years since menopause, HT use, and the IHRS. Of this sub-cohort, 39 post-menopausal female participants who did not have OA at baseline out of 1436 developed OA at 3-year follow-up.

3.4 Discussion

This study examined the relationship between weight-bearing OA and CVD in post-menopausal women by using baseline and 3-year follow-up data from the CLSA. To our knowledge, this study is the first to examine CVD risk (measured through the IHRS) and the influence of menopause on CVD incidence among those with a diagnosis of OA. For Objective 2, we hypothesized that in an age-matched sub-cohort of post-menopausal women, individuals with OA will have greater risk than individuals without OA, and we found significantly higher age, BMI, and waist-to-hip ratio in post-menopausal women with OA. For Objective 3 we hypothesized that post-menopausal women will have greater odds of CVD at 3-year follow-up, which could be partially explained through menopausal variables and IHRS. We found that post-menopausal women with OA have greater odds of CVD at 3-year follow-up compared to post-menopausal women without OA, which becomes non-significant after accounting for interaction effects of IHRS and OA diagnosis and main effects of menopausal variables. This suggests that age, years since menopause, HT use, and the interaction of IHRS and OA diagnosis account for the some of the elevated risk of CVD in post-menopausal women.

The results from the current study show a higher proportion of CVD events at a cross-sectional time-point among a sub-cohort with existing OA, as compared with a sub-cohort without OA, which aligns with previous work.[30,31] Men and post-menopausal women had increased

frequencies of both OA and CVD diagnoses in this population. The 3-year follow-up data demonstrated that there was a higher incidence of CVD in individuals with OA, a higher proportion among males compared with women, and a higher proportion in post-menopausal versus pre-menopausal women. The group frequency of CVD at 3-year follow-up was comparable between men and post-menopausal women, supporting previous work indicating that sex hormones prior to the menopausal transition play a protective role for pre-menopausal women.[32]

To better understand the relationship between menopause and OA in CVD risk, a sub-cohort of age-matched female participants were examined at baseline and followed to 3-year follow-up. Interestingly, few differences were observed between post-menopausal women with and without OA, as only age, BMI, and waist-to-hip ratio were significantly greater in the OA group. This aligns with a previous study examining OA and CVD risk in baseline CLSA data that found BMI to be the largest contributor of CVD risk, predominantly in females.[33] After examining how menopausal variables influence CVD risk at follow-up, we found that post-menopausal women with OA are at higher odds of developing CVD than post-menopausal women without OA (Table 5.1), even after accounting for age, years since menopause, use of HT, and the IHRS (Table 5.2). Thus, despite few significant differences between post-menopausal women with and without OA at baseline, primarily surrounding surrogate measures of body adiposity, there is an elevated risk for CVD in postmenopausal women with OA at 3-year follow up, which suggests that menopausal variables and CVD risk (measured through the IHRS) may be at play to explain the difference in CVD risk for postmenopausal women with and without OA.

Influence of age

The post-menopausal women with OA were significantly older than post-menopausal women without OA following the application of survey weights. However, the clinical significance of this difference may be speculated, as there is less than one year difference between the two cohorts after this adjustment. The adjusted odds of developing CVD at 3-year follow-up show a main effect of age, suggesting that age explains some of the differences in CVD outcomes at 3-year follow-up. Increased age has been implicated as a factor that affects the risk of CVD independent of OA, possibly resulting from age-related decline of endothelial health.[34] The main effect of age may also be mediated through factors such as the age-related increase of carotid intima-media thickness, which is a marker for CVD.[35]

Influence of menopausal variables

There are associations between HT use and years since menopause and increased risk of CVD at 3-year follow-up. There is rationale for post-menopausal women to use HT due to previous health conditions and risks,[36] and these significant results of HT use with CVD outcomes further prompt examination of HT type and route of administration on CVD risk in post-menopausal females with and without OA. Years since menopause is used as a surrogate of age to predict risk of CVD, where studies have found that increased age and years since menopause were associated with greater CVD incidence.[37] Our results show significant main effects for both HT use and years since menopause with CVD outcomes at 3-year follow-up.

Influence of IHRS

The adjusted odds of developing CVD at 3-year follow-up show a main effect of IHRS. The interaction effect of the IHRS and OA diagnosis both alone and with other menopausal variables further explains some of the relationship between CVD outcomes in post-menopausal women. When considering a comprehensive score such as the IHRS, several CVD risk factors are included in the composition of the score. Another commonly used CVD score is the Framingham risk score (FRS), provides a 10-year risk score for CVD.[38,39] One of the shortcomings of the FRS is the original population demographic; as it was originally developed and validated in a population of primarily middle-class white men, the generalizability of the score to other populations requires adjustments and consideration.[40–42] In contrast to the FRS, the IHRS was created using multi-ethnic data collected from 52 countries, and incorporates several modifiable risk factors (e.g., diet, physical activity) that the FRS does not account for.[19,22] Additionally, the original IHRS study examined the probability of CVD onset for 1-3.25 year follow-up, which is a shorter time interval compared with the 10-year estimation of the FRS[19,22], and aligns with the timeframe of the follow-up data which was collected 3 years from baseline. As OA and CVD share many overlapping risk factors, it is expected that the IHRS explained some of the CVD risk differences between individuals with and without OA.

There is a strong association between OA and CVD in the literature which can partially be explained through shared risk factors and disease etiology.[6,43,44] Aging, higher inflammation and body adiposity, and general lifestyle habits all contribute to the risk for both OA and CVD. Aging negatively influences the cardiovascular system, which subsequently increases the risk of developing vascular-related conditions.[43] Regulation of blood glucose, measured through HbA1c

levels, plays a role in CVD risk as high levels of HbA1c are strongly associated with an increased risk of CVD.[17] Inflammation, often measured through high-sensitivity C-reactive protein (hsCRP), plays a role in the degradation of joint health in OA pathology.[15] Likewise, high levels of hsCRP are implicated in the development of CVD, specifically as a potential indicator for atherosclerosis, a precursor to CVD-related events.[6,43] Further, body adiposity is an indicator of health and disease risk, and increased adiposity can act through inflammation and endothelial dysfunction to increase the risk of both OA and CVD independently.[43] Despite the limitations of the body mass index (BMI) (i.e., oversimplification of body adiposity across sex, age, and distribution), it is still one of the most widely used indices of body composition.[45] Recent studies have used waist-to-hip ratio and waist circumference as better candidates to understanding body adiposity, particularly when examining adiposity as a risk factor for OA[46] and CVD[45,47]. Both BMI and waist-to-hip ratio were included in the study examine measures of body composition, with distinct differences found between the groups of post-menopausal women with and without OA. Additionally, studies have begun to incorporate measures of social disadvantage in understanding health and disease in the population. A modified social disadvantage score (described elsewhere)[18] was incorporated in the study.

Modifiable lifestyle habits such as physical activity, diet, and smoking have been implicated in elevating OA and CVD risk independently by influencing both endothelial and general vascular health.[19,48] To consider the effects of interacting risk factors, the IHRS provides a holistic profile of CVD risk.[19,22] The original study on which the IHRS is created examined the probability of CVD onset for 1 and 3.25-year follow-up, which may be a smaller and more sensitive window to detect CVD

risk compared with other CVD risk scores (e.g., the Framingham risk score which is based on a 10-year risk of CVD).[19]

After accounting for OA diagnosis in age-matched post-menopausal women, our study found the presence of weight bearing OA at baseline increased future CVD events. However, after including the main effects of age, years since menopause, HT use, and the IHRS and the interacting effect of IHRS and OA diagnosis with CVD outcomes at 3-year follow-up, the difference is no longer significant. This indicates that menopausal variables and IHRS can help explain why OA pathology plays a role in increasing CVD risk in older women.

Limitations & Strengths

There are several limitations to consider when interpreting findings from this study. Self-reported data were collected in the CLSA for several variables of interest, which may play a role in the validity of the results. For example, OA was a self-reported variable of physician diagnosis that did not distinguish radiographic or symptomatic OA and did not report on OA severity. There is a known association between increased OA severity and increased CVD risk,[49] but we did not have this information to incorporate this information into our analyses. It is important to note that hand OA has been presented by some studies to play a role on CVD risk, and as having OA was only classified as knee and/or hip OA in this study, the influence of hand OA was not studied.[50,51] Possible effects of joint replacement surgeries as a result of OA were also not considered.[7] These considerations of OA pathology are additional avenues for future research questions. Additionally, inflammation was considered solely through the content of hsCRP within the blood, which is not a complete inflammatory profile due to the transient nature of the marker, as elevations of hsCRP may occur in the blood during periods of acute trauma or infection.[52] However, additional

inflammatory markers were not available for usage within the baseline CLSA data, though incorporating a panel of inflammatory markers would provide a better profile for inflammation. Due to the design of the CLSA, certain populations were not collected, including individuals living on federal First Nations reserves and those who were unable to respond in English or French.[53] Several variables included in the IHRS calculation were not exact, such as the adjustments of cholesterol values due to the lacking of apolipoproteins measured. Additional minor modifications made to the IHRS include slight re-definitions of psychosocial questions and second-hand smoking. These adjustments are reflected in Supplementary Table 1. The prescribed use of HT works best with individualized care, and factors such as type, dose, and duration of use are often not considered in studies, making it difficult to translate the results of specific studies to populations.[36] These limitations may also result in reverse causality, where post-menopausal females who are at higher risk for CVD take HT to manage other symptoms, and more healthy post-menopausal females are not using HT. Further, time of/since event for menopause, OA, and CVD was not included in the analysis, which may influence the interpretation of results. In particular, there is an association between early menopause and increased risk of CVD,[54] as well as early CVD events resulting in early menopause.[55] These variables can provide further understanding of the relationship between menopause and CVD, particularly in a population with OA who is known to be at elevated CVD risk. Time to event will also provide information on the "timing hypothesis" as women within the first 10 years of menopause are at greatest risk of CVD (which may be decreased by HT).[56] Finally, the physiological differences between sex and gender may influence disease risk. There is research to suggest feminine gender, and not female sex, influence CVD risk,[57] which suggests a role of gender (and possibly complex interactions between social determinants of

health) in CVD pathology which may also extend to OA. CLSA baseline data collected information on sex, which was used in the subsequent analyses; however, given the role of gender, future research should seek to further examine the relationship between gender and disease.

A key strength of this study is the use of large, weighted, and longitudinal cohort data that is representative of the Canadian population. Survey weights adjust for biases in sampling and data collected, which allowed for increased generalizability of our findings. The sub-cohorts that underwent further risk analysis (i.e., through logistic regression models) were age-matched, which though reduces the total n in the sample, help reduce bias within the analysis. Age was still included as a covariate, as matching does not remove variability or the influence of the matched variables as covariates.[58] In addition, the IHRS provided a holistic representation of CVD risk in the population, and the employment of a CVD risk score allows for an accessible and well-rounded measurement of CVD risk. Specifically using a non-laboratory IHRS in this and other studies is advantageous as it increases the accessibility and therefore the use of the score, as individuals do not have to enter a lab to have this CVD profile generated.[27] Additionally, comparable to the cohort that was used to create the IHRS, the CLSA contains a multi-ethnic Canadian population,[53] making the IHRS a suitable score to apply on the cohorts analyzed. Including both cross-sectional and longitudinal results allowed for a unique and thorough examination of the roles of risk factors on outcomes. Particularly considering menopausal variables, examining factors known to influence CVD risk in a large aging dataset with focus given to a known high-risk population (i.e., individuals with OA) shows how menopause influences and perhaps augments CVD risk in individuals with existing OA. The use of HT on OA and CVD as comorbidities is not well known, and results from

this study provides further rationale to examine HT as a holistic variable (i.e., type, duration of use, etc.) in post-menopausal women who experience elevated disease risk and.

Conclusion

This study suggests that having OA increases the risk of CVD in post-menopausal females, and this relationship is no longer significant after accounting for the effects of CVD risk factors, such as HT and the IHRS. Additionally, when considering CVD risk factors between the two cohorts, surrogate measures of body adiposity were elevated in post-menopausal women with OA, perhaps signifying a relationship between OA pathology and CVD relating to inflammation, diet, physical activity, or a combination of these factors. The study is one of the first to examine the effects of OA, menopause, and HT on CVD incidence, and informs future studies and clinical practices on the potential changes to CVD risk and incidence following the menopause transition and particularly in females with OA. The results demonstrate that sex differences exist in CVD risk, which is also influenced by OA status. Particularly in post-menopausal females, OA diagnosis is linked with CVD risk and higher odds of developing CVD at 3-year follow-up compared to individuals without OA, and both menopausal variables and CVD risk factors explain some of this relationship. Future studies should further examine sex-stratified analyses CVD risk within individuals with and without OA, with considerations to the type and severity of OA, as well as sex-specific cutoffs for adiposity surrogates.[59] Studies should also target the role of the menopause transition, and how factors such as hormone therapy type, duration, and route of administration interact with OA to alter CVD risk.

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3.6 Figures and Tables

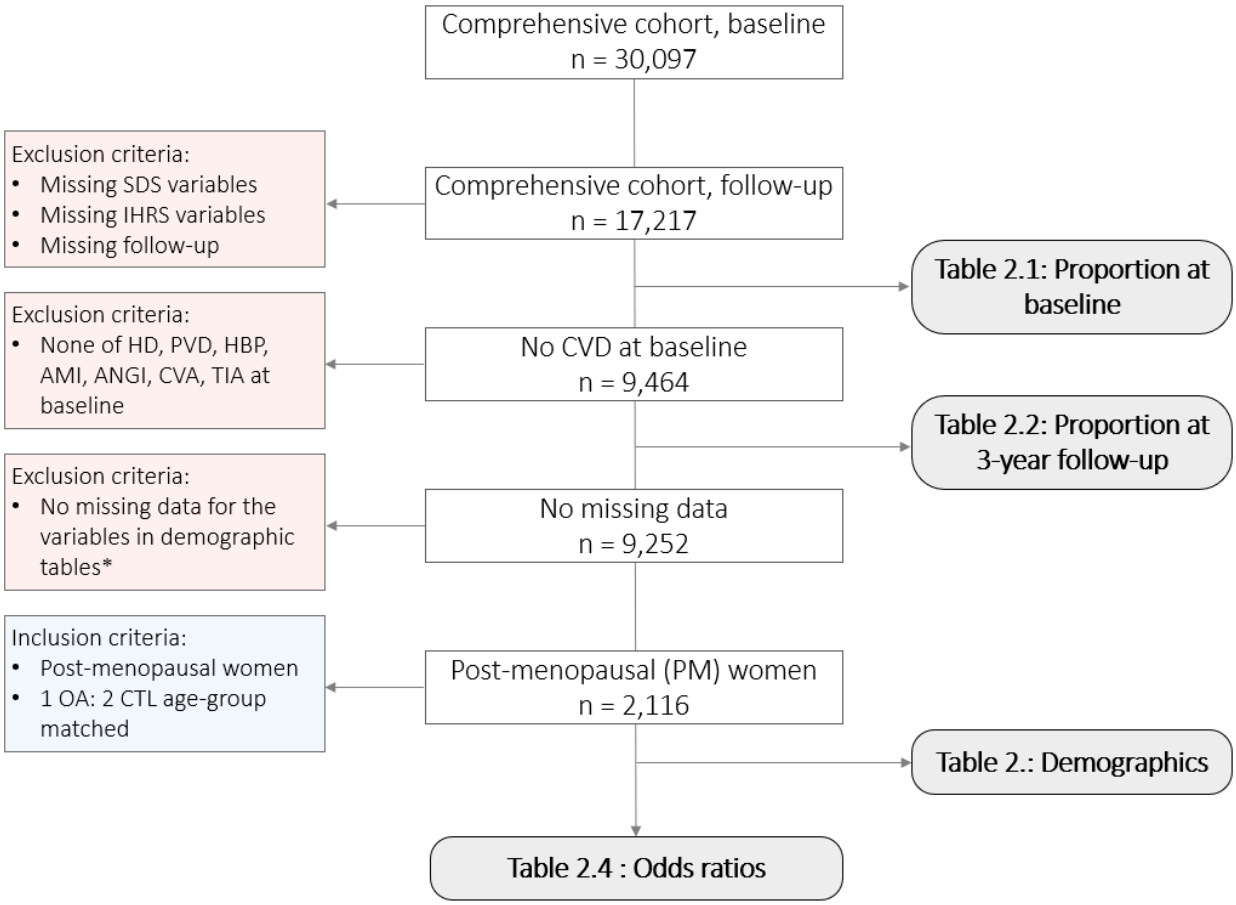

Figure 2. Flowchart of individuals included in this study (Chapter 3) from baseline and 3-year follow-up in the CLSA Comprehensive cohort. SDS: social disadvantage score; IHRS: InterHeart risk score; HD: heart disease; PVD: peripheral vascular disease; HBP: high blood pressure; AMI: acute myocardial infarction; ANGI: angina; CVA: cerebrovascular accident; TIA: transient ischemic accident; PASE: Physical Activity Scale for the Elderly; OA: osteoarthritis. *Excludes Physical Activity Scale for the Elderly.

Table 2.1. CVD frequency at baseline in OA and No OA (CTL) groups stratified by sex (M/F).

	OA Diagnosis							No OA Diagnosis											
	Total n (GP)	Male n (GP)	Female n (GP)			RP (MP^{POS}/ MP^{PRE})	RP (OA^{M}/ OA^{F})	Total n (GP)	Male n (GP)	Female n (GP)			RP (MP^{POST}/ MP^{PRE})	RP (CTL^{M}/ CTL^{F})	RP (OA^{M}/ CTL^{M})	RP (OA^{F}/ CTL^{F})	RP (OA^{PR}/ CTL^{PR})	RP (OA^{PO}/ CTL^{PO})	RP (OA^{T}/ CTL^{T})
			Total n (GP)	MP^{PRE} n (GP)	MP^{POST} n (GP)					Total n (GP)	MP^{PRE} n (GP)	MP^{POST} n (GP)							
Total n	*3502*	*1401*	*2101*	*142*	*1533*			*13715*	*7030*	*6685*	*1249*	*4386*							
Knee OA	2645 (0.76)	1062 (0.76)	1583 (0.75)	109 (0.77)	1142 (0.74)	0.96	1.01	0	0	0	0	0							
Hip OA	1446 (0.41)	512 (0.37)	934 (0.44)	57 (0.40)	685 (0.45)	1.13	0.82	0	0	0	0	0							
Any CVD diagnosis	1986 (0.57)	836 (0.60)	1150 (0.55)	64 (0.45)	812 (0.53)	1.18	1.09	5767 (0.42)	3270 (0.47)	2497 (0.37)	256 (0.20)	1701 (0.39)	1.95	1.25	1.28	1.47	2.25	1.36	1.35
HD	509 (0.15)	270 (0.19)	239 (0.11)	10 (0.07)	163 (0.11)	1.57	1.69	1412 (0.10)	969 (0.14)	443 (0.07)	27 (0.02)	316 (0.07)	3.50	2.08	1.40	1.72	3.50	1.57	1.41
PVD	267 (0.08)	105 (0.07)	162 (0.08)	8 (0.06)	114 (0.07)	1.17	0.97	603 (0.04)	287 (0.04)	316 (0.05)	48 (0.04)	212 (0.05)	1.25	0.86	1.84	1.63	1.50	1.40	1.73
HBP	1649 (0.47)	673 (0.48)	976 (0.46)	54 (0.38)	679 (0.44)	1.16	1.03	4699 (0.34)	2629 (0.37)	2070 (0.31)	193 (0.15)	1416 (0.32)	2.13	1.21	1.28	1.50	2.53	1.38	1.37
AMI	171 (0.05)	113 (0.08)	58 (0.03)	1 (0.01)	41 (0.03)	3.00	2.92	609 (0.04)	480 (0.07)	129 (0.02)	3 (0.002)	92 (0.02)	10.00	3.54	1.18	1.43	5.00	1.50	1.10
ANGI	213 (0.06)	121 (0.09)	92 (0.04)	2 (0.01)	65 (0.04)	4.00	1.97	526 (0.04)	367 (0.05)	159 (0.02)	5 (0.004)	104 (0.02)	5.00	2.19	1.66	1.84	2.50	2.00	1.58
CVA	83 (0.02)	40 (0.03)	43 (0.02)	0 (0.00)	38 (0.02)	---	1.40	185 (0.01)	113 (0.02)	72 (0.01)	6 (0.005)	49 (0.01)	2.00	1.49	1.78	1.90	---	2.00	1.76
TIA	142 (0.04)	53 (0.04)	89 (0.04)	2 (0.01)	64 (0.04)	4.00	0.89	332 (0.02)	188 (0.03)	144 (0.02)	11 (0.01)	100 (0.02)	2.00	1.24	1.42	1.97	1.00	2.00	1.72

GP: group proportion; RP: relative proportion; MP^{PRE}: pre-menopausal female participants; MP^{POST}: post-menopausal female participants; OA^{M}: male participants with OA; OA^{F}: female participants with OA; CTL^{M}: male participants without OA diagnosis; CTL^{F}: female participants without OA diagnosis; OA^{PR}: pre-menopausal female participants with OA; CTL^{PR}: pre-menopausal female participants without OA; OA^{PO}: post-menopausal female participants with OA; CTL^{PO}: post-menopausal female participants without OA; OA^{T}: total OA; CTL^{T}: total without OA; OA: osteoarthritis; CVD: cardiovascular disease; HD: heart disease; PVD: peripheral vascular disease; HBP: high blood pressure; AMI: acute myocardial infarction; ANGI: angina; CVA: cerebrovascular accident; TIA: transient ischemic accident

Table 2.2. CVD frequency at 3-year follow-up in OA and No OA (CTL) groups without CVD at baseline stratified by sex (M/F).

	OA Diagnosis							No OA Diagnosis											
	Total n (GI)	Male n (GI)	Female n (GI)			RP (MP^{POST}/ MP^{PRE})	RP (OA^{M}/ OA^{F})	Total n (GI)	Male n (GI)	Female n (GI)			RP (MP^{POST}/ MP^{PRE})	RP (CTL^{M}/ CTL^{F})	RP (OA^{M}/ CTL^{M})	RP (OA^{F}/ CTL^{F})	RP (OA^{PR}/ CTL^{PR})	RP (OA^{PO}/ CTL^{PO})	RP (OA^{T}/ CTL^{T})
			Total n (GI)	MP^{PRE} n (GI)	MP^{POST} n (GI)					Total n (GI)	MP^{PRE} n (GI)	MP^{POST} n (GI)							
Total n	*1516*	*565*	*951*	*78*	*721*			*7948*	*3760*	*4188*	*993*	*2685*							
Any CVD diagnosis	244 (0.16)	98 (0.17)	146 (0.15)	8 (0.10)	106 (0.15)	1.50	1.13	902 (0.11)	489 (0.13)	413 (0.10)	64 (0.06)	278 (0.10)	1.67	1.30	1.31	1.50	1.67	1.50	1.42
HD	62 (0.04)	29 (0.05)	33 (0.03)	2 (0.03)	26 (0.04)	1.33	1.67	206 (0.03)	124 (0.03)	82 (0.02)	9 (0.01)	56 (0.02)	2.00	1.50	1.67	1.50	3.00	2.00	1.58
PVD	44 (0.03)	11 (0.02)	33 (0.03)	1 (0.01)	22 (0.03)	3.00	0.67	117 (0.01)	39 (0.01)	78 (0.02)	21 (0.02)	45 (0.02)	1.00	0.50	1.67	1.50	0.50	1.50	1.97
HBP	134 (0.09)	57 (0.10)	77 (0.08)	6 (0.08)	56 (0.08)	1.00	1.25	550 (0.07)	317 (0.08)	233 (0.06)	33 (0.03)	165 (0.06)	2.00	1.33	1.25	1.33	2.67	1.33	1.28
AMI	12 (0.01)	9 (0.02)	3 (0.003)	0 (0.00)	2 (0.003)	---	6.67	47 (0.01)	37 (0.01)	10 (0.002)	1 (0.001)	9 (0.003)	3.00	5.00	2.00	1.50	---	1.00	1.34
ANGI	15 (0.01)	7 (0.01)	8 (0.01)	0 (0.00)	4 (0.01)	---	1.00	34 (0.004)	20 (0.01)	14 (0.003)	3 (0.003)	8 (0.003)	10.00	3.33	1.00	3.33	---	3.33	2.30
CVA	6 (0.004)	2 (0.004)	4 (0.004)	0 (0.00)	2 (0.003)	---	1.00	31 (0.004)	12 (0.003)	19 (0.005)	1 (0.001)	13 (0.005)	5.00	0.60	1.33	0.80	---	0.60	1.03
TIA	21 (0.01)	8 (0.01)	13 (0.01)	0 (0.00)	9 (0.01)	---	1.00	53 (0.01)	29 (0.01)	24 (0.01)	0 (0.00)	19 (0.007)	0.00	1.00	1.00	1.00	---	1.43	2.07

GI: group proportion at 3-year follow-up; MP^{PRE}: pre-menopausal female participants; MP^{POST}: post-menopausal female participants; OA^{M}: male participants with OA; OA^{F}: female participants with OA; CTL^{M}: male participants without OA diagnosis; CTL^{F}: female participants without OA diagnosis; OA^{PR}: pre-menopausal female participants with OA; CTL^{PR}: pre-menopausal female participants without OA; OA^{PO}: post-menopausal female participants with OA; CTL^{PO}: post-menopausal female participants without OA; OA^{T}: total OA; CTL^{T}: total without OA; OA: osteoarthritis; CVD: cardiovascular disease; HD: heart disease; PVD: peripheral vascular disease; HBP: high blood pressure; AMI: acute myocardial infarction; ANGI: angina; CVA: cerebrovascular accident; TIA: transient ischemic accident

Table 2.3. Participant demographics of post-menopausal female participants with and without OA. Values represent mean [SD].

	OA Diagnosis	No OA Diagnosis	p-value
Total n	711	1405	---
Age (years)	64.00 [8.15]	63.22 [8.15]	**0.038**
PASE	132.85 [65.05]	138.23 [64.83]	0.072
BMI (kg/m^2)	27.71 [5.53]	25.93 [4.58]	**<0.001**
WH ratio	0.83 [0.06]	0.82 [0.06]	**<0.001**
HbA1c (%)	5.50 [0.55]	5.46 [0.45]	0.074
hsCRP (mg/L)	2.47 [2.78]	2.19 [4.98]	0.164
HDL (mmol/L)	1.78 [0.51]	1.77 [0.49]	0.612
LDL (mmol/L)	3.15 [0.85]	3.20 [0.89]	0.215
SDS	0.70 [0.91]	0.65 [0.88]	0.222
Non-lab IHRS[27]	6.07 [3.73]	5.76 [3.87]	0.078

P values are calculated through Student's t-test between OA and No OA post-menopausal female participants. Data is matched 1 OA: 2 No OA. PASE: Physical Activity Scale for the Elderly – missing 6 (< 1%) for OA diagnosis, missing 11 (< 1%) for No OA diagnosis; BMI: Body Mass Index; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; high sensitivity C-Reactive Protein; *SDS – Social Disadvantage Score, modified from Anand et al (2020)[60], calculated by income less than 20,000 CAD assigned a score of two, income between 20,000 CAD and 50,000 CAD assigned a score of one, and living without a partner assigned a score of one. The maximum SDS was three, and the lowest possible SDS was zero; IHRS – InterHeart risk score.

Table 2.4.1. Unadjusted odds ratio of CVD at 3-year follow-up in OA and No OA post-menopausal female participants.

Model Coefficients - CVD incidence

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-2.055	0.0832	-24.71	<.001	0.128	0.109	0.151
GROUP:							
OA – No OA	0.291	0.1344	2.16	**0.030**	1.338	1.028	1.741

Note. Estimates represent the log odds of "CVD incidence = CVD" vs. "CVD incidence = No CVD"

Total n = 2154 (n = 718 OA, age-matched n = 1,436 No OA)

Table 2.4.2. Adjusted odds ratio of CVD at 3-year follow-up in OA and No OA post-menopausal female participants.

Model Coefficients - CVD incidence

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-2.48766	0.1584	-15.704	<.001	0.0831	0.0609	0.113
GROUP:							
OA – No OA	0.30498	0.2628	1.160	0.246	1.3566	0.8105	2.271
Non-lab IHS	0.06708	0.0196	3.416	**<.001**	1.0694	1.0290	1.111
Non-lab IHS ✻ GROUP:							
Non-lab IHS ✻ (OA – No OA)	-0.00375	0.0327	-0.115	0.909	0.9963	0.9344	1.062

Note. Estimates represent the log odds of "CVD incidence = CVD" vs. "CVD incidence = No CVD"

Total n = 2154 (n = 718 OA, age-matched n = 1,436 No OA)

Table 2.4.3. Adjusted odds ratio of CVD at 3-year follow-up in OA and No OA post-menopausal female participants.

Model Coefficients - CVD incidence

						95% Confidence Interval	
Predictor	Estimate	SE	Z	p	Odds ratio	Lower	Upper
Intercept	-4.57080	0.57009	-8.018	<.001	0.0103	0.00339	0.0316
GROUP:							
OA – No OA	0.33910	0.27486	1.234	0.217	1.4037	0.81905	2.4056
Non-lab IHS	0.05938	0.02085	2.848	**0.004**	1.0612	1.01869	1.1054
Age	0.03463	0.00818	4.233	**<.001**	1.0352	1.01877	1.0520
mYears	-0.00146	3.99e-4	-3.657	**<.001**	0.9985	0.99776	0.9993
HT:							
No HT – HT	-0.31816	0.13385	-2.377	**0.017**	0.7275	0.55962	0.9457
Non-lab IHS ✻ GROUP:							
Non-lab IHS ✻ (OA – No OA)	-0.01082	0.03449	-0.314	0.754	0.9892	0.92458	1.0584

Note. Estimates represent the log odds of "CVD incidence = CVD" vs. "CVD incidence = No CVD"

Total n = 2154 (n = 718 OA, age-matched n = 1,436 No OA); mYears: years since menopause; HT – hormone therapy; IHRS – InterHeart risk score.

Chapter 4 – Conclusions

4.1 Summary of Findings and Implications

Analysis of baseline and 3-year follow-up data of the Comprehensive cohort collected by the CLSA revealed elevated odds of developing CVD in individuals with OA. The study design for both manuscript 1 (Chapter 2) and manuscript 2 (Chapter 3) were nested case-control, with age- and sex-matching performed for manuscript 1 and age-matching performed for manuscript 2.

For manuscript 1, there were greater unadjusted and adjusted odds of CVD at 3-year follow-up in individuals with OA, with significant differences at baseline for cIMT, FRS, or IHRS but no significant influence of odds in cIMT, FRS, or IHRS. Factors including TUG, BMI, frailty, and social disadvantage were significantly different at baseline in individuals with and without OA. There were no differences with odds of CVD at 3-year follow-up in weight-bearing and non-weight-bearing OA, though BMI was found to be significantly greater in individuals with weight-bearing OA at baseline. Our findings suggest that although individuals with OA are at an elevated risk of CVD compared to individuals without OA, markers of CVD risk (cIMT, FRS, IHRS) alone did not account for the differences of odds of developing CVD between the groups.

For manuscript 2, there were greater unadjusted odds of CVD at 3-year follow-up in post-menopausal females with OA. The adjusted odds of CVD after accounting for IHRS, the interaction of IHRS and OA diagnosis, and menopausal variables were no longer significantly different between post-menopausal females with and without OA. This suggests that the elevation in CVD following the menopause transition is augmented by OA pathology interacting with menopausal variables, such as hormone therapy use and years since menopause.

This thesis provides novel information on how CVD risk presents in individuals with OA, with considerations given to the site of OA and menopausal transition. Collectively, findings from manuscripts 1 and 2 suggest that there may be additional and interacting aspects of OA pathology that increase CVD risk. For example, it is known that factors such as smoking, obesity, and high-fat and high-cholesterol diets are associated with increased inflammation, which is a driver of increased CVD risk. It is possible that these risk factors alone are not independent determinants of health outcomes, but rather act synergistically to alter CVD risk profiles, particularly in an elevated-risk group such as OA.

4.2 Future Directions and Conclusions

The results from this thesis provide rationale to explore several additional avenues for examining the relationship between OA and CVD. The roles of OA severity and occurrence of joint replacement have been demonstrated to influence CVD risk. As CVD pathology is different between specific diseases (e.g., stroke versus heart failure), the influence of OA pathology on difference CVDs may also differ, prompting further investigations on OA and type of CVD. Many risk factors, including as diet, physical activity, smoking, and obesity are all associated with increased inflammation, suggesting that examining a holistic inflammatory profile may provide further understanding of underlying mechanisms. Specifically with regards to women's health, examining sex differences before and after the menopause transition as well as examining the changes in OA pathology and CVD risk factors across the menopause transition will address the specific role of menopause in altering CVD risk. Additional variables associated with menopause, such as HT use, have also been implicated in independently influencing the risk for OA and CVD,

and warrants further exploration. Through examining key mechanisms underlying the shared pathology, early risk identification may improve to help reduce disease burden and preserve the quality of life of aging individuals.

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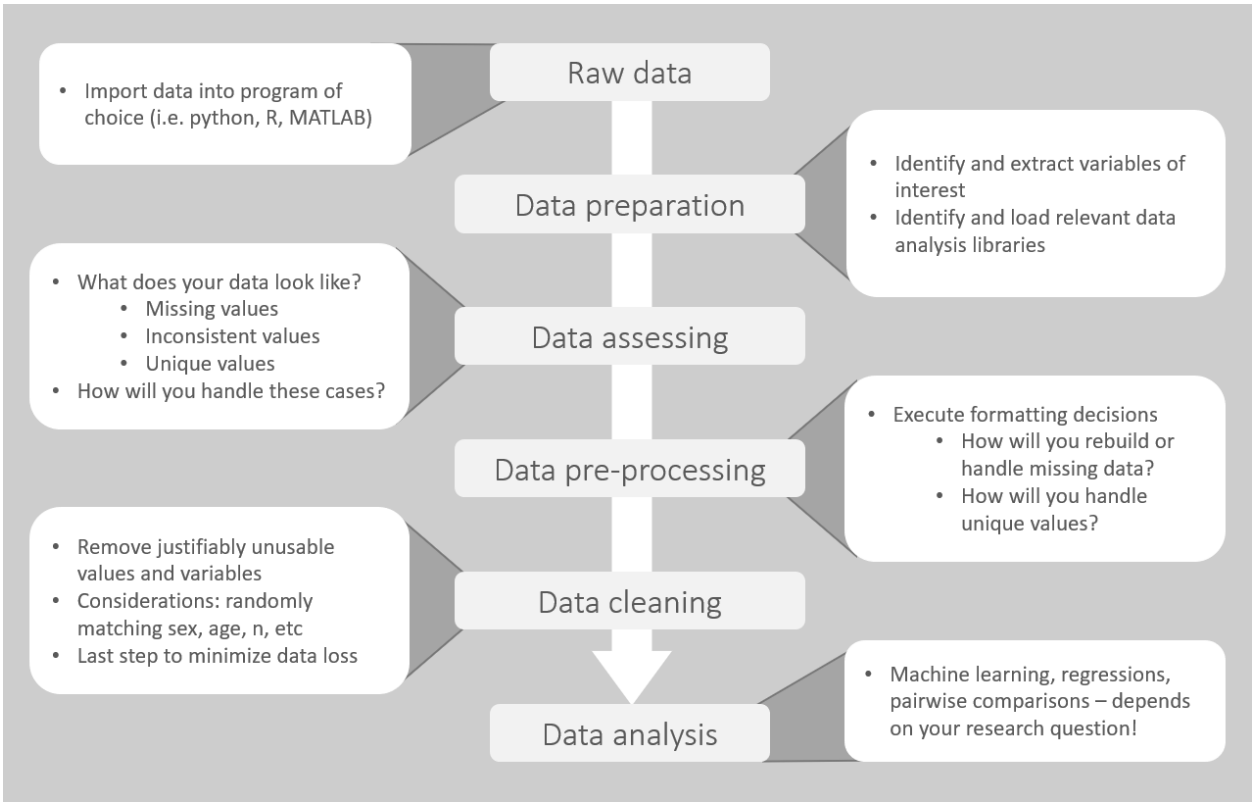
Supplementary Figure



Supplementary Figure 1. Approaches to working with large datasets

Supplementary Tables

Supplementary Table 1. Framingham Risk Score Table (modified based on variables available from CLSA)

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

Supplementary Table 2. Non-Laboratory InterHeart Score Table (modified based on variables available from CLSA)

Risk Factor	Question		Points for the answer	Points for each section
Age	Are you a man 55 years or older OR woman 65 years or older?		2	Points:
	OR Are you a man younger than 55 years or woman younger than 65 years		0	
Smoking. Pick the description which matches you best:	I never smoked OR I've smoked less than 100 cigarettes in my life		0	Points:
	OR I am a former smoker (last smoked more than 12 months ago)		2	
	OR I am a current smoker or I smoked regularly in the last 12 months, and I smoke…	1-5 cigarettes/d	2	
		6-10 cigarettes/d	4	
		11-15 cigarettes/d	6	
		16-20 cigarettes/d	7	
		More than 20 cigarettes/d	11	
Second hand smoke	Over the past 12 months, what has been your typical exposure to other people's tobacco smoke?	Once a month or less	0	Points:
		OR at least once a week or more	2	
Diabetes	Do you have diabetes mellitus?	Yes	6	Points:
		No or unsure	0	
High blood pressure	Do you have high blood pressure?	Yes	5	Points:
		No or unsure	0	
Waist to hip ratio	Pick one only:	Q1: less than 0.81	0	Points:
		Q2: 0.81 – 0.887	1	
		Q3: 0.887 – 0.965	2	
		Q4: greater than or = 0.965	3	
Psychosocial factors	How is your self-rated mental health?	Never or some periods	0	Points:
		OR Several periods of stress or permanent stress	3	
	Has a doctor ever told you that you suffer from clinical depression or a mood disorder?	Yes	3	
		No	0	
	Do you eat salty food or snacks one	Yes	1	Points:
		No	0	

Dietary factors. Pick one answer for each food group mentioned	or more times a day?			
	Do you eat fried foods or snacks or fast foods (French fries, pan-fried potatoes, poutine) 3 or more times a week?	Yes	1	
		No	0	
	Do you eat fruit one or more times daily?	Yes	0	
		No	1	
	Do you eat vegetables one or more times daily?	Yes	0	
		No	1	
	Do you eat meat and/or poultry 2 or more times daily?	Yes	2	
		No	0	
Physical activity	How active are you during your leisure time?	I am mainly sedentary or perform low level exercise (PASE < 120 for females; PASE < 140 for males)	2	Points:
		OR I perform moderate to high level exercise (PASE > 120 for females; PASE > 140 for males)	0	

Supplementary Table 3. Frailty Index calculations (modified to exclude OA as a variable).

Domain	Item	Question	Scoring
Self-rated health, vision, hearing	Health gen_hlth_com	In general, would you say your health is excellent, very good, good, fair or poor?	0= excellent 0.25= very good 0.5= good 0.75= fair 1= poor
	Vision vis_sght_com	Is your eyesight, using glasses or corrective lens if you use them: excellent, very good, good, fair or poor?	0= excellent 0.25= very good 0.5= good 0.75= fair 1= poor
	Hearing hrg_hrg_com	Is your hearing, using a hearing aid if you use one: excellent, very good, good, fair or poor?	0= excellent 0.25= very good 0.5= good 0.75= fair 1= poor
Chronic conditions	Arthritis ccc_ra_com, cct_otart_com	Has a doctor ever told you that you have rheumatoid arthritis or another type of arthritis?	0= no 1= yes
	COPD ccc_copd_com	Has a doctor told you that you have/had any of the following: emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD) or chronic changes in lungs due to smoking?	0= no 1= yes
	COPD ccc_copd_com	Has a doctor told you that you have/had any of the following: emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD) or chronic changes in lungs due to smoking?	0= no 1= yes
	HBP ccc_hbp_com	Has a doctor ever told you that you have high-blood pressure or hypertension?	0= no 1= yes
	Diabetes Mellitus dia_diab_com	Has a doctor ever told you that you have diabetes, borderline	0= no 1= yes

		diabetes or that your blood sugar is high?	
	Chronic Heart Failure ccc_heart_com	Has a doctor ever told you that you have heart disease (including congestive heart failure, or CHF)?	0= no 1= yes
	Angina ccc_angi_com	Has a doctor ever told you that you have angina (or chest pain due to heart disease)?	0= no 1= yes
	Acute Myocardial Infarction ccc_ami_com	Has a doctor ever told you that you have had a heart attack or myocardial infarction?	0= no 1= yes
	Peripheral Vascular Disease ccc_pvd_com	Has a doctor ever told you that you have peripheral vascular disease or poor circulation in your limbs?	0= no 1= yes
	Stroke ccc_cva_com	Has a doctor ever told you that you have experienced a stroke or CVA (cerebrovascular accident)?	0= no 1= yes
	Transient Ischemic Attack ccc_tia_com	Has a doctor ever told you that you have experienced a mini-stroke or TIA? (Transient Ischemic Attack)?	0= no 1= yes
	Memory Problem ccc_mempb_com	Has a doctor ever told you that you have a memory problem?	0= no 1= yes
	Parkinson's Disease ccc_park_com	Has a doctor ever told you that you have Parkinson's disease?	0= no 1= yes
	Peptic Ulcer Disease ccc_ulcr_com	Has a doctor ever told you that you have intestinal or stomach ulcers?	0= no 1= yes

	Colitis ccc_ibdibs_com	Has a doctor ever told you that you have a bowel disorder such as Crohn's Disease, ulcerative colitis, or Irritable Bowel Syndrome?	0= no 1= yes
	Bowel Incontinence ccc_bowinc_com	Has a doctor ever told you that you experience bowel incontinence?	0= no 1= yes
	Urinary Incontinence ccc_uriinc_com	How often do you wet or soil yourself (either day or night)?	0= no 1= yes
	Cataract icq_catrct_com	Has a doctor ever told you that you have cataracts?	0= no 1= yes
	Glaucoma icq_glauc_com	Has a doctor ever told you that you have glaucoma?	0= no 1= yes
	Macular Degeneration ccc_macdeg_com	Has a doctor ever told you that you have macular degeneration?	0= no 1= yes
	Cancer ccc_canc_com	Has a doctor ever told you that you have cancer?	0= no 1= yes
	Osteoporosis ccc_ostpo_com	Has a doctor ever told you that you have osteoporosis, sometimes called low bone mineral density, or thin, brittle, or weak bones?	0= no 1= yes
	Back Pain ccc_bckp_com	Has a doctor ever told you that you have back problems, excluding fibromyalgia and arthritis?	0= no 1= yes
	Hypothyroidism ccc_uthyr_comMissing	Has a doctor ever told you that you have an UNDER-active thyroid gland (sometimes called hypothyroidism or myxedema)?	0= no 1= yes
	Hyperthyroidism	Has a doctor ever told you that you have an	0= no 1= yes

	ccc_othyr_com	OVER-active thyroid gland (sometimes called hyperthyroidism or Graves' disease)?	
	Kidney Failure ccc_kidn_com	Has a doctor ever told you that you have kidney disease or kidney failure?	0= no 1= yes
	Pneumonia ccc_drpneu_com	In the past year, have you seen a doctor for pneumonia?	0= no 1= yes
	Urinary Tract Infection ccc_druti_com	In the past year, have you seen a doctor for urinary tract infection?	0= no 1= yes
	Falls fal_nmbr_nb_com	How many times have you fallen in the past 12 months?	0= none 0.5= only one 1= two or more
Activities of daily living	Walking adl_ablwk_com, adl_hpwk_com, adl_unwk_com	Can you walk without help?	0= able 0.5= with help 1= unable
	Bathing adl_ablbt_com, adl_hpbt_com, adl_unbt_com	Can you take a bath or shower without help?	0= able 0.5= with help 1= unable
Instrumental activities of daily living	Shopping ial_ablgro_com, ial_hpgro_com, ial_ungro_com	Can you go shopping for groceries or clothes without help (taking care of all shopping needs yourself)?	0= able 0.5= with help 1= unable
	Doing housework ial_ablwrk_com, ial_hpwrk_com, ial_unwrk_com	Can you do your housework without help (i.e., you can clean floors, etc.)?	0= able 0.5= with help 1= unable
Cognitive function	Verbal fluency cog_aft_score_1_com	As many names of animals, the participant recalls in 1 minute	0= no 1= yes
Mental health	Effort dep_ffrt_com	How often did you feel that everything you did was an effort	0= rarely or never 0.33= some of the time 0.66= occasionally

			1= all of the time
	Felt lonely dep_lonly_com	How often did you feel lonely?	0= rarely or never 0.33= some of the time 0.66= occasionally 1= all of the time
	Could not get going dep_gtgo_trm (com not given)	How often did you feel that you could not 'get going'?	0= rarely or never 0.33= some of the time 0.66= occasionally 1= all of the time

Supplementary Table 4. Raw participant demographics using baseline CLSA data.

	OA Diagnosis	# Missing (% total)	No OA Diagnosis	# Missing (% total)	p-value
Total n	618	---	1088	---	---
Age (years)	63.19 [9.22]	0	61.61 [9.08]	0	**<0.001**
PASE	146.62 [72.38]	5 (< 1%)	147.93 [72.27]	10 (1%)	**0.003**
TUG (s)	9.35 [2.67]	7 (1%)	9.04 [1.62]	20 (2%)	**0.012**
BMI (kg/m^2)	27.30 [5.06]	0	26.20 [4.64]	2	**<0.001**
WH ratio	0.87 [0.10]	0	0.88 [0.10]	0	0.236
HbA1c (%)	5.56 [0.67]	2 (< 1%)	5.52 [0.55]	11 (1%)	0.160
hsCRP (mg/L)	2.16 [3.01]	1 (< 1%)	2.10 [4.73]	1 (< 1%)	0.774
HDL (mmol/L)	1.60 [0.49]	0	1.62 [0.50]	0	0.562
LDL (mmol/L)	2.96 [0.89]	0	2.95 [0.88]	0	0.769
Frailty Index	0.62 [0.88]	0	0.54 [0.83]	0	**<.001**
SDS	0.09 [0.05]	32 (5%)	0.08 [0.05]	59 (5%)	0.069
Non-lab IHRS[25]	7.57 [5.16]	0	7.27 [5.28]	0	0.263
FRS	10.79 [4.56]	0	10.26 [4.62]	0	**0.024**
cIMT	0.74 [0.15]	0	0.72 [0.15]	0	**0.039**

P values are calculated through Student's t-test between OA and No OA individuals. Data is matched 1 OA: 2 No OA. n = 690 male participants, n = 1016 female participants. OA: osteoarthritis; PASE: Physical Activity Scale for the Elderly; TUG: timed-up-and-go; BMI: Body Mass Index; WH: waist-to-hip ratio; HbA1c: hemoglobin A1c; HSCRP: high sensitivity C-Reactive Protein; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; *SDS – Social Disadvantage Score, modified from Anand et al (2020)[94], calculated by income less than 20,000 CAD assigned a score of two, income between 20,000 CAD and 50,000 CAD assigned a score of one, and living without a partner assigned a score of one. The maximum SDS was three, and the lowest possible SDS was zero; IHRS – InterHeart risk score (non-lab); FRS: Framingham risk score; cIMT: carotid intima-media thickness (left side).

Supplementary Table 5. Raw participant demographics using baseline CLSA data in weight-bearing and non-weight-bearing OA

	wbOA	# Missing (% total)	nwbOA	# Missing (% total)	p-value
Total n	159	---	159	---	---
Age (years)	62.74 [9.21]	0	63.01 [9.24]	0	0.794
PASE	147.45 [79.61]	0	149.63 [70.15]	1 (< 1%)	0.063
TUG (s)	9.64 [4.15]	0	8.98 [1.54]	4 (3%)	**0.03**
BMI (kg/m^2)	27.27 [4.85]	0	25.55 [3.80]	0	**<0.001**
WH ratio	0.87 [0.09]	0	0.86 [0.09]	0	0.416
HbA1c (%)	5.58 [0.79]	1 (< 1%)	5.54 [0.63]	0	0.647
hsCRP (mg/L)	2.16 [3.20]	1 (< 1%)	2.09 [3.65]	0	0.845
HDL (mmol/L)	1.61 [0.49]	0	1.69 [0.48]	0	0.129
LDL (mmol/L)	2.84 [0.89]	0	2.97 [0.85]	0	0.162
Frailty Index	0.62 [0.85]	0	0.62 [0.90]	0	0.362
SDS	0.09 [0.05]	9 (6%)	0.09 [0.05]	6 (4%)	0.993
Non-lab IHRS[25]	7.50 [5.65	0	6.97 [4.97]	0	0.376
FRS	10.50 [4.91]	0	10.35 [4.53]	0	0.776
cIMT	0.73 [0.14]	0	0.72 [0.15]	0	0.521

P values are calculated through Student's t-test between weight-bearing (wbOA) and non-weight-bearing (nwbOA) osteoarthritis (OA). Data is matched 1 wbOA: 1 nwbOA. n = 54 male participants per group, n = 105 female participants per group. PASE: Physical Activity Scale for the Elderly; TUG: timed-up-and-go; BMI: Body Mass Index; WH: waist-to-hip ratio; HbA1c: hemoglobin A1c; HSCRP: high sensitivity C-Reactive Protein; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; *SDS – Social Disadvantage Score, modified from Anand et al (2020)[94], calculated by income less than 20,000 CAD assigned a score of two, income between 20,000 CAD and 50,000 CAD assigned a score of one, and living without a partner assigned a score of one. The maximum SDS was three, and the lowest possible SDS was zero; IHRS – InterHeart risk score (non-lab); FRS: Framingham risk score; cIMT: carotid intima-media thickness (left side).

Supplementary Table 6. Raw participant demographics using baseline CLSA data, stratified by OA diagnosis, sex, and menopausal status.

	OA Diagnosis					No OA Diagnosis				
	Total	Male	Female			Total	Male	Female		
			Total	PRE	POST			Total	PRE	POST
Total n	*1430*	*596*	*834*	*86*	*753(6?)*	*7822*	*3958*	*3864*	*1038*	*2797*
Age (years)	63.79 [9.05]	63.71 [9.09]	63.84 [9.02]	52.23 [7.46]	65.19 [8.19]	59.25 [9.20]	59.80 [9.35]	58.68 [9.00]	49.78 [3.48]	62.05 [8.11]
PASE	140.59 [70.74]	157.59 [74.89]	128.53 [65.05]	144.56 [78.14]	126.79 [63.29]	155.68 [75.73]	164.83 [78.14]	146.35 [72.02]	167.35 [79.60]	138.58 [67.35]
BMI (kg/m^2)	28.25 [5.53]	28.35 [4.82]	28.17 [5.99]	30.29 [8.27]	27.92 [5.62]	26.75 [4.70]	27.17 [4.16]	26.32 [5.15]	26.62 [5.90]	26.21 [4.84]
WH ratio	0.89 [0.09]	0.97 [0.06]	0.83 [0.06]	0.83 [0.08]	0.83 [0.06]	0.89 [0.10]	0.96 [0.06]	0.82 [0.06]	0.81 [0.06]	0.82 [0.07]
HbA1c (%)	5.54 [0.61]	5.57 [0.67]	5.52 [0.56]	5.41 [0.54]	5.53 [0.56]	5.49 [0.55]	5.54 [0.61]	5.44 [0.48]	5.32 [0.43]	5.49 [0.48]
hsCRP (mg/L)	2.46 [4.06]	2.11 [4.09]	2.70 [4.01]	3.87 [6.61]	2.56 [3.57]	2.08 [4.18]	1.93 [3.88]	2.24 [4.47]	2.17 [3.50]	2.26 [4.79]
HDL (mmol/L)	1.58 [0.49]	1.35 [0.38]	1.75 [0.49]	1.58 [0.40]	1.76 [0.50]	1.56 [0.48]	1.37 [0.39]	1.75 [0.49]	1.71 [0.47]	1.77 [0.49]
LDL (mmol/L)	3.04 [0.86]	2.93 [0.86]	3.11 [0.86]	2.92 [0.79]	3.13 [0.87]	3.04 [0.89]	2.97 [0.88]	3.12 [0.90]	2.91 [0.84]	3.20 [0.91]
SDS*	0.64 [0.91]	0.40 [0.75]	0.82 [0.97]	0.58 [0.89]	0.85 [0.97]	0.52 [0.81]	0.42 [0.75]	0.63 [0.87]	0.41 [0.73]	0.71 [0.90]
Non-lab IHRS[25]	7.57 [4.29]	9.36 [4.29]	6.29 [3.80]	5.95 [3.86]	6.33 [3.80]	7.07 [4.41]	8.59 [4.26]	5.52 [4.01]	4.58 [3.93]	5.86 [3.96]

PRE: pre-menopausal female participants; POST: post-menopausal female participants; OA: osteoarthritis; PASE: Physical Activity Scale for the Elderly; TUG: timed-up-and-go; BMI: Body Mass Index; WH: waist-to-hip ratio; HbA1c: hemoglobin A1c; HSCRP: high sensitivity C-Reactive Protein; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; *SDS – Social Disadvantage Score, modified from Anand et al (2020)[94], calculated by income less than 20,000 CAD assigned a score of two, income between 20,000 CAD and 50,000 CAD assigned a score of one, and living without a partner assigned a score of one. The maximum SDS was three, and the lowest possible SDS was zero; IHRS – InterHeart risk score (non-lab); FRS: Framingham risk score; cIMT: carotid intima-media thickness (left side).

Supplementary Table 7. Raw participant demographics of post-menopausal females with and without OA. Values represent mean [SD].

	OA Diagnosis	No OA Diagnosis	p-value
Total n	711	1405	
Age (years)	65.20 [8.12]	64.75 [8.13]	0.224
PASE	127.39 [63.18]	134.41 [64.48]	**0.018**
BMI (kg/m^2)	27.93 [5.64]	26.06 [4.65]	**<0.001**
WH ratio	0.83 [0.06]	0.82 [0.07]	**0.028**
HbA1c (%)	5.53 [0.56]	5.49 [0.45]	0.053
hsCRP (mg/L)	2.49 [2.94]	2.27 [5.33]	0.291
HDL (mmol/L)	1.77 [0.50]	1.79 [0.48]	0.505
LDL (mmol/L)	3.13 [0.84]	3.20 [0.90]	0.067
SDS	0.83 [0.95]	0.77 [0.91]	0.199
Non-lab IHRS[25]	6.26 [3.72]	6.02 [3.86]	0.168

P values are calculated through Student's t-test between OA and No OA post-menopausal female participants. Data is matched 1 OA: 2 No OA. PASE: Physical Activity Scale for the Elderly – missing 6 (< 1%) for OA diagnosis, missing 11 (< 1%) for No OA diagnosis; BMI: Body Mass Index; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; high sensitivity C-Reactive Protein; *SDS – Social Disadvantage Score, modified from Anand et al (2020)[94], calculated by income less than 20,000 CAD assigned a score of two, income between 20,000 CAD and 50,000 CAD assigned a score of one, and living without a partner assigned a score of one. The maximum SDS was three, and the lowest possible SDS was zero; IHRS – InterHeart risk score.