THE EPIDEMIOLOGY OF OSTEOARTHRITIS AND ITS ASSOCIATION

WITH CARDIOVASCULAR DISEASE AND DIABETES

by

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ABSTRACT

Background: Osteoarthritis (OA) is a highly prevalent chronic condition and the most common form of rheumatic disease. The relationship between OA and cardiovascular disease (CVD) and diabetes has not been observed prospectively and the data on descriptive epidemiology of administratively defined OA are limited.

Objectives: 1) to determine whether OA increases the risk of CVD (myocardial infarction, ischemic heart disease, congestive heart failure, and stroke) and diabetes; 2) to examine the association between OA and prevalent CVD; 4) to estimate the prevalence, incidence, and trends of OA; and 5) to validate the administrative diagnosis of OA.

Methods: Using a random sample (n = 640,000) from the British Columbia administrative database during the period 1991-2009, the crude and age-standardized incidence rates and the prevalence of OA were calculated. Administrative OA Definition 1 required at least one physician diagnosis or hospital admission, and Definition 2 required, at least two physician diagnoses in two years or one hospital admission. The relative risks (RR) of CVD and diabetes in persons with OA, compared to age-sex matched non-OA individuals, were estimated using Cox proportional hazards models. Based on the Canadian Community Health Survey (CCHS) data, odds ratio (OR) between OA and heart disease was obtained. The validity of the two administrative definitions was determined using four clinical reference standards.

Results: The overall prevalence of OA on March 2009, was 19.7%, and the incidence rate in the year 2008/09 was 14.6/1000 person-years under Definition 1. The adjusted RRs (95% CI) for

CVD were 1.26 (1.13-1.42), 1.17 (1.07-1.26), 1.08 (0.97-1.19), and 1.15 (1.04-1.27), among

younger women, older women, younger men, and older men, respectively. For diabetes, adjusted

RRs (95% CI) were 1.27 (1.18-1.38), 1.23 (1.12-1.34), 1.19 (1.09-1.29), and 0.94 (0.82-1.09) for

younger women, older women, younger men, and older men, respectively. In the CCHS sample,

ORs (95% CI) for heart disease were 1.35 (1.21-1.50) among men and 1.51 (1.39-1.64) among

women.

Conclusions: These novel findings update current knowledge of OA epidemiology and highlight

the risks of CVD and diabetes among persons with OA. These data are useful in formulating

public health policies around OA treatment and prevention.

PREFACE

Osteoarthritis (OA) is referred to as a complex and degenerative joint disease. OA is a leading cause of disability among the elderly and therefore a major burden on health care and social care systems. With the increase of overall life expectancy and the non-fatal nature of this condition, individuals will live for many years in a lasting state of disability, thus contribute to other co-morbid conditions. In recent years, OA has become an important public health issue. However, data on the incidence, prevalence, and trends of overall OA in any joint estimated form administrative health records are limited. Despite some suggestions that OA may increase the risk of cardiovascular disease (CVD) and diabetes, this relationship has not been investigated prospectively. Previous studies regarding the epidemiology of OA and the relationship between OA and the co-morbid conditions were mostly cross-sectional and were based on small samples.

This thesis describes the epidemiology of OA and its link to severe comorbidity such as cardiovascular conditions and diabetes. Using a random sample from the population-based administrative data, and the self-reported Canadian Community Health Survey (CCHS) data, I obtained the descriptive epidemiology of OA and estimated the association of OA with CVD and diabetes. These include estimating the prevalence and incidence rates of OA, calculating the trends in OA incidence, estimating the odds ratio and relative risks of developing CVD, and estimating the relative risks of diabetes among OA cases. Two different administrative definitions were used to identify OA cases from physician billing claims and hospital records. I have analyzed the validity of both case definitions using clinical, radiographic, and MRI-based diagnoses using a population-based cohort linked to the administrative data.

Five chapters of this thesis have been published or submitted for possible publication as multi-authored papers in the peer-reviewed medical/scientific journals where I am the first author. In these chapters the subject "I" has been replaced by the subject "we" to reflect the team effort in this work. Authors' contributions on these papers are provided below.

A version of Chapter 4 has been accepted for publication in the Journal of Rheumatology 2014. Authors include Rahman MM, Cibere J, Goldsmith CH, Anis AH, and Kopec JA. The title is "Osteoarthritis incidence and trends in the administrative health records from British Columbia, Canada". I am the first author. I contributed to the concept and design of the study, data acquisition, and statistical analyses. I did the literature search and wrote the manuscript and also contributed to the critical revision of the manuscript. Dr. Cibere contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Goldsmith contributed to the concept and design of the study, statistical analyses, and the critical revision of the manuscript. Dr. Anis contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Kopec contributed to the concept and design of the study, data acquisition and statistical analyses, and the critical revision of the manuscript.

A version of Chapter 6 has been submitted for possible publication in a peer-reviewed journal. Authors include, Rahman MM, Kopec JA, Goldsmith CH, Anis AH, and Cibere J. The title is "Validation of administrative case definitions for osteoarthritis using a clinical and radiological cohort". As the first author of this manuscript, I contributed to the concept and design of the study, data acquisition and statistical analyses, literature search, manuscript writing, and the critical revision of the manuscript. Dr. Kopec contributed to the concept and design of the study,

data acquisition and statistical analyses, and the critical revision of the manuscript. Dr. Goldsmith contributed to the concept and design of the study, statistical analyses, and the critical revision of the manuscript. Dr. Anis contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Cibere contributed to the concept and design of the study, data acquisition and statistical analyses, and the critical revision of the manuscript.

A version of Chapter 7 has been published in BMJ Open. Full citation of the paper is, Rahman MM, Kopec JA, Cibere J, Goldsmith CH, and Anis AH. The relationship between osteoarthritis and cardiovascular disease in a population health survey: a cross-sectional study. BMJ Open 2013; 3: e002624. As a first author of this paper, I contributed to the concept and design of the study, data acquisition, statistical analyses, literature search, writing the manuscript, and the critical revision of the manuscript. Dr. Kopec contributed to the concept and design of the study, statistical analyses, and the critical revision of the manuscript. Dr. Cibere contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Goldsmith contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Anis contributed to the concept and design of the study and the critical revision of the manuscript.

A version of Chapter 8 has been published in Arthritis Care & Research. Full citation of the article is, Rahman MM, Kopec JA, Cibere J, Anis AH, Goldsmith CH. The risk of cardiovascular disease in patients with osteoarthritis: a prospective longitudinal study. Arthritis Care & Research (Hoboken): 2013;65:1951-8. I am the first author of the article and I contributed to the concept and design of the study, data acquisition and statistical analyses, literature search,

manuscript writing, and the critical revision of the manuscript. Dr. Kopec contributed to the concept and design of the study, data acquisition and statistical analyses, and the critical revision of the manuscript. Dr. Cibere contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Anis contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Goldsmith contributed to the concept and design of the study and the critical revision of the manuscript.

A version of Chapter 9 has been submitted for possible publication to a peer-reviewed journal. Authors include, Rahman MM, Cibere J, Anis AH, Goldsmith CH, Kopec JA. The title is "Risk of type 2 diabetes among osteoarthritis patients in a prospective longitudinal study". As a first author of this manuscript, I contributed to the concept and design of the study, data acquisition, statistical analyses, literature search, manuscript drafting, and the critical revision of the manuscript. Dr. Kopec contributed to the concept and design of the study, data acquisition and statistical analyses, and the critical revision of the manuscript. Dr. Goldsmith contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Anis contributed to the concept and design of the study and the critical revision of the manuscript. Dr. Cibere contributed to the concept and design of the study and the critical revision of the manuscript.

Ethics approval for the studies contained in this thesis was obtained from the University of British Columbia Behavioral Research Ethics Board (certificate number H03-80134) and the Clinical Research Ethics Board (certificate number H02-70200).

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AOA1	At least one visit to a health professional or one hospital admission for osteoarthritis
AOA2	At least two visits to health professionals in two years or one hospital admission for osteoarthritis
ARC	Annual Relative Change
BC	British Columbia
BMI	Body Mass Index
BMD	Bone Mineral Density
CCHS	Canadian Community Health Survey
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
Def1	At least one visit to a health professional or one hospital admission for osteoarthritis
Def2	At least two visits to health professionals in two years or one hospital admission for osteoarthritis
HR	Hazard Ratio
ICD-9	International Classification of Disease 9th Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IHD	Ischemic Heart Disease
K-L	Kellgren-Lawrence
LR+	Positive Likelihood Ratio
LR-	Negative Likelihood Ratio
MI	Myocardial Infarction
MPC	Metacarpophalageal
MRI	Magnetic Resonance Imaging
MSP	Medical Services Plan
NPV	Negative Predictive Value
NHANES	National Health and Nutrition Examination Survey

NSAID	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OR	Odds Ratio
OS	Orthopaedic Surgeon
PH	Proportional Hazard
PHN	Personal Health Numbers
PPV	Positive Predictive Value
RR	Relative Risk
SES	Socio-economic Status
TJR	Total Joint Replacement

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DEDICATION

To my parents and other family members who were very helpful during my studies.

CHAPTER 1 INTRODUCTION

1.1 Overview

Osteoarthritis (OA) is the most common form of rheumatic disease, a highly prevalent chronic condition among the elderly, and a leading cause of disability (1–3). OA is characterized by loss or failure of the functional, biomechanical, and biochemical integrity of a joint that may be caused by progressive cartilage loss, subchondral bone remodeling, osteophyte formation and synovial inflammation. The symptoms of OA include pain, joint stiffness and dysfunction. Although in principle, any joint in the body can be affected, OA commonly affects the hands, feet, spine, and the large weight bearing joints, such as the hips and knees (4,5). Studies show that approximately 10–12 percent of the global population have OA (5–8). Economic cost analysis of musculoskeletal disorders in industrialized countries such as Australia, Canada, France, United Kingdom, and United States have found a rising trend in costs attributable to OA. Annually, these costs amount reaches between 1% and 2.5% of the gross domestic product of these countries (9). The total cost of musculoskeletal disorders in Canada was estimated at $25.6 billion in 1994 Canadian dollars (10). In its advanced stage, OA severely limits mobility and physical activity (11,12). In recent years, this condition has been recognized as an inflammatory disease (13) as well as a metabolic disease (14,15). Furthermore, muscle weakness is a frequent symptom observed among individuals with OA (16). Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat OA-related pain. Therefore, OA may contribute to other chronic health issues, such as cardiovascular disease (CVD), diabetes, obesity, and other conditions. Despite this, population-based data on the analytic epidemiology of OA are limited, and little is known about the risk of developing CVD and diabetes among individuals with OA. Currently, other than the total joint replacement, there is no specific treatment option for OA.

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Therefore, identifying the risks of these chronic conditions among OA cases is of paramount importance from a biological, physiological, and epidemiological point of view.

Epidemiology

Population-based epidemiologic data on chronic diseases such as OA are of great importance with regard to maintaining public health. These data are useful in describing geographic and demographic variations in the prevalence and incidence estimates, examining long-term trends, and identifying at-risk groups. They are also useful in predicting the potential effects of a particular chronic disease on severe comorbid conditions and mortality at the population level. This information is essential in formulating public health policy around chronic disease treatments and preventions and evaluating the effectiveness of population-based health promotion and disease prevention strategies. Administrative data have been used in numerous population-based studies and are potentially valuable tools for understanding chronic disease epidemiology. These data are relatively easy to access and can be used to monitor the relationship of a particular disease with co-morbidity as well as provide both cross-sectional and longitudinal information about the entire population. In this thesis, I have used administrative data from British Columbia (BC), Canada, and in particular, the health records of a random sample of 640,000 BC residents over the period 1991-2009.

Unfortunately, data on the incidence and prevalence of OA from administrative health records are limited. Studies have shown that the disease frequency of OA varies depending on the age and sex of the population under study, the method of case identification used, and the specific joint sites studied. Furthermore, the incidence and prevalence rates of administrative OA depend

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on the length of the observation records (6). Based on 10 years of administrative health records, the overall prevalence of OA was estimated at 10.8%, and the overall incidence in any joint was 11.7 per 1000 person-years in BC (6). Compared to the incidence and prevalence rates published in other joint-specific studies, these rates are lower (8,17). Thus, a longer period of record collection, such as the 18-year period I used here, will provide more accurate estimates of disease frequencies.

Apart from descriptive epidemiology, very limited data regarding changes in the incidence rates of OA over time are available. Both Canadian and international studies have shown that the projected prevalence of arthritis/ rheumatism is increasing (18,19). Other studies have shown that obesity and aging are associated with a higher risk of incident OA (15,20,21) and that obesity is increasing among Canadians (22,23). Besides age and obesity, other risk factors for OA, such as occupation and injury might influence the incidence rates over time. Thus, updated crude and age-standardized incidence rates are useful for testing the hypothesis that there will be more new OA cases over time.

Validation of OA Case Definition

The administrative definitions of OA are based on the International Classification of Disease (ICD) codes (6,24). In this study, the 9th and 10th revision of the ICD codes, ICD-9 and ICD-10, respectively, which are based on physician claim records and hospital diagnoses, were used to identify OA cases. The validity of administrative OA definitions has been assessed in previous studies against both self-reported population surveys (25) and medical records (24). Lix et al (25) validated administrative data from the province of Manitoba, using Canadian Community Health

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Survey (CCHS) data as a reference standard and Harrold et al. (24) compared administrative OA diagnosis with corresponding medical records. These studies did not recruit patients for comprehensive clinical assessments, such as joint examination, x-rays, and magnetic resonance imaging (MRI) with a view to confirming OA diagnosis; moreover they used 2-5 years of collected observation records. In order for administrative data to be appropriately utilized in OA research, it is essential to assess the validity of case definitions of OA.

Impact of OA on CVD and Diabetes

OA is a leading cause of disability among the elderly and therefore a major burden on individuals, health care systems, and social care systems; it also contributes to direct and indirect costs. Given both the higher overall life expectancy and the non-fatal nature of this condition, people with OA can live for many years in a state of disability, which increases their risk for severe co-morbid conditions. Unlike other musculoskeletal diseases such as rheumatoid arthritis, psoriatic arthritis, and lupus, co-morbidity and mortality have never been a major area of investigation for OA. However, studies suggest that OA may contribute to comorbidity such as hypertension, cardiovascular diseases, obesity, respiratory diseases, peptic ulcers, renal disease, and diabetes (26–29). These studies were, unfortunately, relatively small and either cross-sectional or case-control studies. For this reason, prospective longitudinal studies are required to investigate the true risks of developing these conditions among OA cases.

Common risk and prognostic factors for OA include age, sex, high body weight, joint injury, occupation, nutrition, and high levels of physical activity (1,6,8,30). Besides these factors, synovial inflammation can play a role in the early development of OA (13). Furthermore, muscle

weakness is a frequent symptom observed among individuals with OA (16). OA cases are less physically active compared to individuals without arthritis due to severe pain in the joints (31). Recently, OA has been recognized as a metabolic disease on the basis of data showing a higher incidence of this condition in the non-weight bearing joints of individuals who are overweight/ obese (14,15). Other studies have considered OA as a systemic disorder linked to metabolic syndromes (21,32,33). In addition, NSAIDs are commonly used drugs to treat OA-related pain, which have been found associated with an increased risk of CVD (34,35). Therefore, in this thesis, I hypothesize that OA may increase the risk of CVD and diabetes and that these associations are due, at least partially, to immobility, chronic inflammation, muscle weakness, metabolic syndromes, NSAIDs use, and other lifestyle changes attributable to OA. Given that OA is a common chronic condition among the elderly, a better understanding of its relationship to CVD and diabetes might facilitate further investigation of biological and behavioral mechanisms underlying these associations and also inform future OA management strategies.

1.2 Rationale

The primary goal of this thesis is to enhance our understanding of the relationship between OA and two severe and common chronic conditions: CVD and diabetes. A secondary goal is to update inferences regarding the descriptive epidemiology of OA, such as its incidence, prevalence, and long-term trends. This thesis addresses several important gaps in the existing knowledge based on administrative OA diagnoses.

First, I hypothesize that OA increases the risk of CVD and diabetes. Previous studies focusing on the relationship between OA and these co-morbid conditions were mostly cross-sectional and

based on small samples. To avoid problems associated with reverse causality, prospective longitudinal studies are essential. Therefore, I intended to observe prospectively the link of OA with CVD and diabetes. Second, the descriptive epidemiology of OA in most of the earlier studies was based on specific joint sites and specific case identification methods. To estimate the overall incidence and prevalence of OA at the population level, it is essential to analyze administrative health records. Third, earlier studies that generated incidence and prevalence estimates drew upon administrative health records, included insufficient length of time, and for this reason, the rates were underestimated. Fourth, with regard to observing changes in incidence rates over time, health records extending over a period of 18 years will provide more accurate results compared to those covering 13 years that have been used in previous trends analyses. Fifth, previous validation studies of administrative OA definitions did not compare cases against clinical and radiological assessments. I intend to use symptomatic, radiographic and MRI assessments, to validate administrative OA case definitions. Sixth, this thesis will contribute to the literature by providing more accurate estimates of the descriptive epidemiology of OA, which is to be achieved by using a large administrative database. The results will identify possible risks of developing CVD and diabetes among OA cases. In summary, this thesis will provide a comprehensive picture of OA in the context of an administrative database by generating the descriptive epidemiology, long-term trends, and by investigating the effect of OA on CVD and diabetes prospectively. This thesis may guide future studies aimed at investigating and explicating the causal pathways between OA and CVD, OA and diabetes, and other chronic co-morbid conditions.

1.3 Objectives

Based on the BC administrative database, my primary objectives were to investigate the impact of OA on developing CVD and diabetes prospectively. To the best of my knowledge, no prospective longitudinal studies in this area currently exist. I also intended to examine the relationship between OA and the prevalent CVD using CCHS data. Regarding other epidemiology, my intention was to provide an updated estimate of the incidence and prevalence rates, and to observe trends in overall OA in administrative health records. Additionally, I intended to conduct a validation study which involved comparing administrative OA diagnoses with a clinical and radiological based OA cohort. On the basis of physician billing claims and hospital admission records, I have defined OA to fulfill the objectives of this thesis.

My specific objectives were as follows: 1) to examine the possible association between OA and heart disease and specific cardiovascular conditions such as myocardial infarction (MI), angina, congestive heart failure (CHF), and stroke, using cross-sectional CCHS data; 2) to determine by a prospective longitudinal study whether OA increases the risk for hospitalized CVD, MI, ischemic heart disease (IHD), CHF, and stroke; 3) to estimate the risk for type 2 diabetes among OA cases by conducting a second prospective longitudinal study; 4) to obtain updated prevalence and incidence rates for OA; 5) to estimate the changes in incidence rates for OA over time; and 6) to examine the validity of administrative OA case definitions, using a clinical and radiological based cohort.

1.4 Thesis Organization

This thesis is organized in a manuscript-based style and consists of ten chapters. Thus, the content of some sections may be replicated in the Background, Methods, and Discussion chapters. Chapter 1, the introduction, includes an overview of OA epidemiology, a summary of the impact of OA on CVD and diabetes, a rationale for the study and a description of its primary objectives. Background material, along with a critical review of the literature, is presented in Chapter 2. Chapter 3 describes the data and methodology used in the study. Chapters 4 and Chapter 6 to 9, inclusive, each consist of a manuscript published in or submitted to scientific peer-reviewed journals. These chapters discuss the epidemiology of OA, validation of OA case definition, and the impact of OA on CVD and diabetes. More specifically, incidence rates for OA, based on administrative health records extending over a period of 18 years, are presented in Chapter 4. This chapter also contains the crude and age-standardized rates used to estimate trends in the incidence of OA. Estimates of the prevalence of OA are presented in Chapter 5. Chapter 6 describes the validation study of the OA case definitions. Chapter 7 presents a cross-sectional study of the relationship between OA and prevalent CVD using CCHS data. The risk for OA individuals for developing CVD and specific cardiovascular conditions as obtained from a prospective study is presented in Chapter 8. The results from a second prospective study investigating the risk of developing diabetes among individuals with OA are presented in Chapter 9. Chapter 10, the concluding chapter, synthesizes the findings from each of the above six studies and discusses the strengths, limitations, and implications of the collective work.

CHAPTER 2 BACKGROUND

2.1 Biology and Symptoms of Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease characterized by abnormalities associated with

the degradation of joints (5,36). It is further characterised by progressive biomechanical and

biochemical disorder of joint cells which leads to the gradual loss of cartilage, ulceration, bone

sclerosis and cysts, inflammation, and development of bony spurs at the margins of the joints

(37,38). "The firm and rubbery tissue that protects bone joints and allows bones to move

smoothly is called cartilage. If the cartilage breaks down or wears away, the bones rub together

and cause pain, tenderness, and stiffness" (5). The authors also suggest that OA occurs when the

repair process occurring in the joints progresses at a slower rate than the breakdown of joint

tissue, specifically, when the mechanical loads applied to the joint exceed the tolerance limits of

the joint tissue (4,5).

Although the etiology of OA is the result of abnormal biomechanical and biochemical changes to

joint cells, its symptoms include pain, tenderness, stiffness, locking, and sometimes swelling in

joints (4). Among these, the primary symptom is pain in the joint, which reduces the mobility of

patients. OA may cause a crackling noise when the affected joint is moved, and patients may

experience sudden contractions of the muscles around joints. As OA progresses, the affected

joints may appear larger and stiffer; the condition usually deteriorates with excessive or

prolonged use of the joints. In principle, any joint in the body can be affected by OA. However,

OA commonly affects the hands, feet, spine, and the large weight bearing joints, such as the hips

and knees (4,5).

2.2 Causes and Risk Factors of OA

As I discussed earlier, OA is caused by wear and tear on a joint produced by complex changes in the joint cells; aging is considered to be the most important factor of this kind of joint degradation. The symptoms of OA usually appear in middle age and are more common among women (39). Other factors that may increase the risk of OA include family history, obesity, joint injuries, lack of vitamins and minerals, poor joint alignment, muscle weakness, occupations that involve knee and hip bending, and sports that involve direct impact on the joints (1,8,39,40). Health conditions that may lead to OA include bleeding disorders around the joints, disorders that block the blood supply near the joints, and other types of inflammatory arthritis such as gout and rheumatoid arthritis (5). Although OA is often referred to as a degenerative disease, synovial inflammation also plays a role in its early development (13). Brief descriptions of each of these factors are provided below.

Age

Age is one of the most common risk factors for OA of the knee, hip, hand, and other joints (3,8,40). Studies also show a positive association between age and the progression of knee and hip OA (41,42). The exact mechanism linking aging to both the incidence and progression of OA remains unclear. However, with age individuals lose the capacity to repair joint tissue damage and become slow to adapt to other biomechanical changes. Thus, age is considered to be a proxy for the accumulation of risk factors over the years.

Sex

Higher prevalence and incidence rates of OA are found among women (6). Symptomatic hip, knee, and hand OA are all more prevalent among women than men (43–45). In a meta-analysis of population-based studies, Srikanth et al. (46) observed that sex affected both the incidence and prevalence of OA and that women, in particular, were at higher risk. Men had a lower risk for prevalent knee OA (risk ratio [RR] 0.63, 95% confidence interval [CI] 0.53-0.75) and incident knee OA (incidence rate ratio [IRR] 0.55, 95% CI 0.32-0.94). The male sex was also negatively associated with incident hip OA (IRR 0.64, 95% CI 0.48-0.86) and prevalent hand OA (RR 0.81, 95% CI 0.73-0.90). There exists no evidence that suggests why women are highly affected by OA than men. In a literature review, Hanna et al. (47) concluded that in the case of postmenopausal women, estrogen replacement therapy showed no relationship with OA incidence. In a second study involving a group of older postmenopausal women with cardiac disease, the authors found that estrogen combined with progestin therapy had no significant effect on knee pain and related disabilities compared with the placebo group (48). In the Women's Health Initiative study (49), a double-blind randomized trial involving estrogen therapy, estrogen supplementation was found to be associated with a slightly reduced rate of total joint replacement (either hip or knee) (hazard ratio [HR] 0.84, 95% CI 0.7-1.00); however, the hazard ratios proved not to be significant in separate analyses of hip and knee replacements, respectively.

Race/Ethnicity

Studies have shown that the frequency and characteristics of OA vary across racial and ethnic groups. In the Johnston County study, OA was more prevalent among black individuals

compared to white individuals (44) (black versus white radiographic knee OA was 32% versus 27% and symptomatic knee OA was 19% versus 16%). In a more recent study using the Johnston County OA project database, Kopec et al. (50) observed that African Americans had a lower rate of incident hip OA but a higher rate of progressive knee OA compared with white Americans. In the third National Health and Nutrition Examination Survey (NHANES-III), African American subjects were found to have more prevalent radiographic and symptomatic knee OA than white subjects, whereas the prevalence in white and Mexican American subjects was similar (51). Zhang et al. (52) compared Chinese individuals from Beijing with white individuals from the Framingham Study. They observed that Chinese women had more prevalent radiographic knee OA (prevalence ratio 1.5, 95% CI 1.3-1.6) and symptomatic knee OA (prevalence ratio 1.4, 95% CI 1.2-1.7) than white women; on the other hand, Chinese men had a similar overall prevalence of radiographic knee OA compared with white men. In the NHANES-I study, Nevitt et al. (53) compared hip OA among Chinese individuals and white Americans. The authors found that among Chinese subjects, hip OA was 90% lower compared to the white US subjects.

Genetic Factors

Studies have shown that genetic and environmental factors play an important role in the development of OA (54–57). A better understanding of the genetic contribution may help to detect cases at high risk for incident and progressive OA, describe specific pathways responsible for OA, and identify potential targets for treatment. In a literature review focusing on the current body of knowledge pertaining to the genetic contribution to OA, Valdes et al. (55) found that the

influence of genetic factors in radiographic knee, hip, and hand OA are 39%, 60%, and 59%

respectively, in the case of progressive knee OA.

Body Weight

Obesity has been identified as a risk factor for OA in weight-bearing joints, such as the knee. In a

Norwegian study, the authors observed that a higher body mass index (BMI) increased the risk of

knee OA and was also associated with hip OA (58). In a 2002 meta-analysis, the authors found

that those in the obese or overweight categories were 2.96 times more at risk for incident knee

OA and the over-weight group was twice as likely to develop knee OA compared with the

normal weight group (41). Thus, at the population level knee OA could be prevented to a greater

extent by reducing the mean BMI for the obese and overweight categories to normal levels. In

the Framingham study, reducing BMI by ≥ 11 lb., was associated with an approximately 50%

lower risk for developing symptomatic knee OA among women (59). The Johnston County study

findings followed this trend, indicating that the lifetime risk of symptomatic knee OA was 30%

for persons with normal BMI, 47% for overweight persons and 61% for obese persons (60).

Although the association between obesity and hip OA has never been clearly confirmed, obesity

is positively associated with both radiographic and symptomatic hand OA (61,62). These

findings highlight the role of systemic and metabolic factors in the relationship between obesity

and OA as the hands are not weight-bearing joints.

Occupation, Exercise, Sport, and Joint Injury

Repetitive joint use associated with occupation, exercise, and sports as well as joint injury due to

other reasons may increase the risk of OA. The available evidence suggests a link between

higher risk of knee OA and the specific occupation that requires excessive kneeling, squatting, lifting, climbing steps, or prolonged standing (41,63). Heavy lifting and farming are both associated with hip OA (64).

Occupations involving frequent hand use are associated with hand OA, but there is no evidence to suggest the predominant right hand is more susceptible (43). Recreational physical activities such as walking, running, and sports are part of a healthy lifestyle. Several longitudinal studies have found that recreational physical activities have no effect on the development of radiographic knee OA (65,66). However, the effects from joint injuries sustained as a result of intensive exercising or sports can contribute to the future development of OA. Some studies have found an increased risk for knee and hip OA in athletes who engage in frequent and intensive exercise and training regimens (67).

Joint injury is perhaps the most easily avoided risk factor compared with other factors such as obesity. The relationship of joint injury to subsequent OA has been studied the most with respect to the knee. In one study, self-reported knee injuries were found to be associated with approximately 4 times relative risk (RR) of knee OA (41) and in another study, the lifetime risk of symptomatic knee OA was 15% higher (60). In another study involving a large prospective cohort, the authors found that joint injuries substantially increased the risk for subsequent knee OA (RR = 5.01, 95% CI, 2.80-8.97) and hip OA (RR = 6.01, 95% CI, 1.40-25.86) (68).

Muscle Strength/Weakness

Muscle weakness is a common factor among individuals with OA. Some studies have examined the role of muscle weakness in increasing the incidence and progression of knee OA. Quadriceps muscle weakness was associated with increased risk of knee OA compared to healthy controls (16,69). Another study produced inconsistent findings with respect to the association between muscle strength and knee OA: low muscle strength was found to be associated with incident symptomatic knee OA among women, but not with incident radiographic OA (70).

Bone Mineral Density

Several population-based studies have verified an association between high bone mineral density (BMD) and higher rates of prevalent and incident knee OA (71,72). Some studies also support an association of high BMD with hand and hip OA (73,74). In their literature review, Clayton et al. (75) found an inverse relationship between osteoporosis and OA. Possible explanations for this relationship among BMD, osteoporosis, and OA include both genetic and metabolic factors (75).

Nutrition

Some epidemiologic evidence suggests that a deficiency in several dietary factors, including vitamins C, D, E, and K, constitutes a potentially modifiable risk factor for OA; other evidence, however, suggests otherwise. In one longitudinal study vitamin D intake was linked to a low OA incidence and progression (76). Vitamin C played a role in reducing the incidence of knee OA, but no association was observed with respect to OA progression (77). However, in the Framingham OA cohort study (78), vitamin C intake was found to be a significant factor in reducing the risk for cartilage loss and disease progression in individuals with OA. In the same

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study, vitamin E intake was found to be associated with a slightly lower risk of OA progression (78); however, during the randomized trials, vitamin E intake did not show any reduction in pain or cartilage loss (79,80). Vitamin K intake has been shown to reduce the incidence of knee OA (81), whereas in a 2008 randomized trial no effect of vitamin K intake was found on radiographic hand OA (82).

Chronic Inflammation

A number of studies have confirmed that synovial inflammation plays an important role in the early development of OA. Increased synovial tissue inflammation was observed in patients with early knee OA (13,83). In their systematic review, de Lange-Brokaar et al. (84) concluded that inflammation is common in OA subjects; moreover, inflammation among OA cases appears to differ both quantitatively and qualitatively from inflammation among rheumatoid arthritis cases.

Joint Alignment

Like many other potential risk factors for OA, malalignment of the joint may be either a cause or consequence of OA. In most epidemiologic studies, the researchers examine the effects of static alignment by assessing weight-bearing radiographs. A 2010 study confirms this relationship between malalignment and incident knee OA (85). In longitudinal studies, malalignment of the knee joint was also found to be an independent risk factor for the progression of knee OA (86).

2.3 OA Diagnosis

As mentioned earlier, the symptoms of OA include joint pain, tenderness, stiffness, and locking. For this reason, in epidemiological studies, OA cases are identified on the basis of these

symptoms by radiographic examination and imaging as well as self-reporting. Some degree of variation exists within each of these standard case identification strategies. Brief explanations of these diagnostic procedures are provided below.

Radiographic K-L Grade

In most joint-specific studies, OA cases were identified based on definitions involving radiographic OA or symptomatic OA (usually a combination of x-ray changes and symptoms). Diagnosis of OA cases through radiographic examination using Kellgren-Lawrence (K-L) grade (87) is a popular standard criterion for epidemiological research. Based on radiograph, OA cases may be confirmed by observing typical changes seen on x-ray plate which include joint space narrowing, subchondral sclerosis, cyst formation, and osteophytes. K-L grades for radiographic OA is a 5-point scale that includes 0-none; 1-doubtful narrowing of joint space and possible osteophyte lipping; 2-definite osteophytes and narrowing of joint space; 3-moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour; and 4-large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour (87). Based on the radiographs, cases are classified as having OA if their K-L grades are greater than or equal to 2 and are classified as severe OA if grades are 3 and 4 (87).

Imaging

Since OA is referred to as a complex disease involving degradation of joints, it is important to assess intra-articular structures of the whole joint to further understand disease pathology and progression. Recently, imaging such as magnetic resonance imaging (MRI), ultrasound, and

optical coherence tomography have enhanced OA diagnosis and management through complete picture of soft tissues. In a 2012 literature review, Braun et al. (88) concluded that since OA is a disease of the whole joint, a combination of imaging techniques may be useful to gain a clear and comprehensive picture of the disease state. Among all imaging techniques, MRI has become an increasingly popular method of identifying joint damage. MRI is a powerful tool for imaging and understanding cartilage structure, integrity, and pathology of OA (89). MRI is also regarded as an important modality for bone imaging because it can provide additional assessments of subchondral bone integrity and any abnormalities in the joint tissues (90). One of the MRI cartilage scoring techniques is usually graded on a semi-quantitative 0-4 scale based on 0-normal, 1-abnormal signal without a cartilage contour defect, 2-contour defect of 50% cartilage thickness, 3-contour defect of 50–99% cartilage thickness, and 4-100% cartilage contour defect with subjacent bone signal abnormality (91,92). Based on the MRI cartilage scores, cases are classified as having OA if the scores are greater than or equal to 2.

Self-reports

In epidemiologic studies, one of the frequently used methods of OA case identification is based on the self-report of being previously diagnosed with OA by a physician (17). Grotle et al. (93) used self-reported physician diagnosed OA from the Population Survey in Norway to estimate the prevalence and burden of OA. Ong et al. (94) used US self-report NHANES data to estimate the prevalence of OA and the relationship of OA with CVD. Using the first 3 cycles of CCHS data, Wilkins et al. (95) estimated the prevalence of OA in Canada. OA case identification through self-report has both advantages and disadvantages. Major advantages of this method are easy to implement, inexpensive, and does not require specialist for data collection. However, a

disadvantage of this method is misclassification, in the way that people are frequently unable to identify/distinguish the specific rheumatic condition that affects them.

ACR Clinical Criteria for Knee, Hip, and Hand OA

Based on the history and physical examinations, the American College of Rheumatology (ACR) clinical classification criteria for knee OA include: pain in the knee and any three of the following: 1) over 50 years of age, 2) less than 30 minutes of morning stiffness, 3) crepitus on active motion, 4) bony tenderness, 5) bony enlargement, and 6) no palpable warmth (96). Similarly, using history, physical examination, and radiographic findings, the ACR clinical classification criteria for OA in the hip includes pain in the hip and any two of the following: 1) Erythrocyte Sedimentation Rate (ESR) < 20 mm/ hour, 2) radiographic femoral or acetabular osteophytes, and 3) radiographic joint space narrowing (97). The ACR criteria for hand OA include pain, aching, or stiffness in the hand and any three of the following conditions: 1) hard tissue enlargement of two or more of the following joints: 2nd and 3rd distal interphalangeal, the 2nd and 3rd proximal inerphalangeal, and the 1st carpometacarpal joints of both hands; 2) hard tissue enlargement of 2 or more distal interphalangeal joints; 3) less than three swollen metacarpophalangeal MPC joints; 4) deformity of at least one of the joints listed in No. 1 (98).

Administrative Definition of OA

In population-based studies, OA cases are often identified by using medical administrative databases. These data usually are electronic health records, routinely collected for a long period, include all physicians' visits and hospital admission records within a healthcare system, and cover a wide geographic area such as a province of a country. These databases therefore, have

relatively complete records of all individual encounters within the healthcare system, and are promising resource for the surveillance of chronic conditions such as OA. Recently, administrative databases are frequently used for health research, in which OA cases are identified based on several definitions using the International Classification of Disease 9th revision (ICD-9) and the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) codes (6,24). The advantages of case identification procedure using administrative databases are as follows: 1) this method includes physician diagnosed cases rather than self-reported conditions, 2) it captures a large number of subjects from a population within a healthcare plan/system, 3) it is relatively easy to implement, and 4) it does not require specialists for data collection. Using administrative primary health care records of over 3 million individuals from Spain, Prieto-Alhambra et al. (99) estimated the incidence as well as determined the risk factors for hip, knee, and hand OA. Kopec et al. (6,100) used administrative health records of approximately 4 million individuals from Canada to calculate the prevalence, incidence and trends of OA. However, problems of case identification procedure using administrative databases are mainly measurement errors. Misdiagnosis or misclassification of the disease may occur in the electronic records and some cases may remain undiagnosed for long periods of time.

In this study, I have used the administrative database that was collected and maintained by the BC Ministry of Health, Canada. From the physician claim and hospital separation data, OA cases were diagnosed using both ICD-9 and ICD-10 codes. Studies have shown that estimates for OA incidence and prevalence vary due to the method of case identification used. Two case definitions were used for OA where Definition 1 required at least one visit to a health

professional or one hospital separation with the ICD-9 code 715 or the ICD-10 code from M15 to M19. Definition 2 required at least two visits to a health professional within two years (at least one day apart) or one hospital separation with the above ICD codes. Definition 2 is more specific and therefore, is expected to reduce the measurement error due to false positive cases. However, it is less sensitive and may capture only severe OA cases. This definition is more likely to miss mild OA cases and those who do not visit the physicians frequently.

The accuracy of administrative data in identifying OA cases has been validated in previous studies against both self-reported population surveys (25) and medical records (24). Lix et al. (25) validated administrative data from the province of Manitoba, Canada, comparing with CCHS data. The authors obtained a sensitivity of 42.6% and a specificity of 88.1% in two years of data for the definition of two physician claims or one hospital separation. Compared with two years of medical records, Harrold et al. (24) observed a 62% positive predictive value for administrative OA diagnosis where the prevalence was 8.7%. However, these studies covered only a few years of records and did not recruit patients for clinical assessments such as joint examination, x-rays, and MRI to identify OA.

2.4 Epidemiology

Prevalence

In general, the prevalence of OA depends on the age and sex of the population under study, the method of case identification, and the joint sites included. In epidemiologic research, there is no simple way to define the presence or absence of OA or to distinguish between incident and progressive disease. Using administrative data from BC, Canada, Kopec et al. (6) reported that

the overall prevalence rates for OA in any joint was 10.8% (8.9 % in men and 12.6% in women). These rates depend on the number of years covered by the administrative records; moreover, they were found to increase linearly between 50 and 80 years of age. The prevalence of radiographic, symptomatic (radiographic changes plus symptoms), and self-reported hip, knee, and hand OA found in international studies is reported in Table 2.1. Because of the different age cutoff points used in different studies, we cannot compare the estimates. However, the prevalence of OA was higher in the studies conducted in the USA.

Table 2.1: The prevalence (per-cent) and the 95% confidence interval of hip, knee, and hand OA collected from international studies.

Joint site	Method used	Author	Country	Age years	Prevalence overall	Prevalence women	Prevalence men
Knee	Radiograph	Jordan et al. (44)	USA	≥ 45	27.8 (26.5-29.2)	31.0 (29.2-32.8)	23.7 (22.0-25.5)
		Kang et al. (101)	China	≥ 50	15.1 (13.0-17.4)	29.6 (16.4-23.2)	10.3 (7.9-13.2)
		Shiozaki et al. (102)	Japan	54-79	21.9 (20.5-23.5)	29.7 (27.6-31.9)	10.9 (9.2-12.8)
	Symptomatic	Jordan et al. (44)	USA	≥ 45	16.4 (15.4-17.6)	18.7 (17.3-20.2)	13.5 (12.2-14.8)
		Kang et al. (101)	China	≥ 50	10.6 (8.9-12.6)	14.2 (11.4-17.4)	6.9 (5.0-9.4)
		Shiozaki et al. (102)	Japan	54-79	15.1 (13.8-16.4)	19.5 (17.7-21.5)	8.8 (7.3-10.5)
	Self-reported	Picavet et al. (103)	Netherlands	≥ 25	11.8 (11.1-12.6)	13.6 (12.1-15.1)	10.1 (8.6-11.6)
		Haq et al. (104)	Bangladesh	≥ 15	8.7 (8.0- 9.5)	10.1 (9.0-11.3)	7.4 (6.4-8.4)
Hip	Radiograph	Hirsch et al. (105)	USA	≥ 45	3.6 (2.4-5.1)	2.8 (1.6-4.7)	4.8 (2.8-7.7)
		Inoue et al. (106)	Japan	20-79	2.4 (1.5-3.7)	3.5 (2.0-5.8)	1.4 (0.6-3.0)
	Symptomatic	Quintana et al. (107)	Spain	60-89	7.4 (6.9-8.0)	8.0 (7.2-8.8)	6.7 (5.9-7.6)
	Self-reported	Picavet et al. (103)	Netherlands	≥ 25	6.7 (6.2-7.3)	9.6 (8.3-10.9)	3.9 (3.0-4.8)
Hand	Radiograph	Wilder et al. (108)	USA	40-95	41.3 (39.6-43.0)	41.1 (39.1-43.1)	41.8 (38.8-44.8)
		Haara et al. (109)	Finland	≥ 30	46.5 (44.8-48.1)	48.1 (45.9-50.3)	44.3 (41.8-46.8)
	Symptomatic	Zhang et al. (52)	USA	≥ 71	21.6 (19.2-24.2)	26.2 (22.9-29.6)	13.3 (9.8-16.7)
	Self-reported	Carmona et al. (110)	Spain	≥ 20	6.2 (5.9-6.5)	9.5 (7.9-11.3)	2.3 (1.5-3.3)

Incidence

Compared to the prevalence, there are limited published data available regarding the incidence rates of OA. Among them Felson et al. (111), Cooper et al. (112), Oliveria et al. (113), Reijman et al. (114), and Kopec et al. (6) studies used large data sets and the rates were comparable. In the Framingham OA study (111), among women age 63-91 years, the incidence rates were 2 per 100 person years for radiographic OA and approximately 1 per 100 person years for symptomatic OA. Using a population-based cohort registered in the general practice database in Bristol, UK, Cooper et al. (112) found that the incidence rate of radiographic knee OA was 2.5 per 100 person years among individuals aged 55 years or more. Reijman et al. (114) estimated that the 10-year cumulative incidence rate of radiographic hip OA was 9.3% among individual age 55 years or more, from the inhabitants in a district of Rotterdam, Netherland. Oliveria et al. (113) used data from the Fallon Community Health Plan, Massachusetts, USA and obtained incidence rates of 10, 8.8, and 24, per 1000 person years respectively, for hand, hip, and knee OA among adults age 20-89 years. From a health survey in Norway, Grotle et al. (115) estimated that the 10-year cumulative incidence of self-reported hip, knee, and hand OA were 7.3%, 5.8%, and 5.6%, respectively. All these studies were joint site specific and some of them did not include long observation periods. Additionally, these studies used different definitions of OA, were restricted to certain age groups, did not estimate the overall OA incidence, and therefore, the rates may not be representative of the general population. Using an administrative database of British Columbia (BC), Canada, Kopec et al. (6) reported that the crude incidence rates for overall OA in any joint was 11.7 per 1000 person-years in the total population (10.0 in men and 13.4 in women). The authors also showed that the incidence rates depend on the run-in period, that is, the number of years of health records used to delete the prevalent cases. This study used

9-years of data to delete the prevalent cases and for that reason it might overestimate the true incidence rates.

Incidence Trend

Given that OA is the most common form of rheumatic diseases (2), there are very limited data available regarding the changes in incidence rates of OA over time. Kopec et al. (100) estimated that the age-standardized incidence rates of physician diagnosed OA did not change in men and slightly increased among women in BC, Canada from years 1996/97 to 2003/04. The observation time was relatively short in this study to estimate trends. Studies have shown that there exists an increasing trend in overweight and obesity among Canadians (22,23). Obesity and aging are associated with a higher risk of incident OA (15,20,21). Besides the effect of age, sex, and obesity, the prevalence of other risk factors might have influenced the incidence of OA over time. Both Canadian and international studies have shown that the projected prevalence of arthritis/rheumatism is increasing (18,19). In addition, public awareness of OA may have increased recently due to new approaches of joint specific exercise and education programs (116), new drugs such as Cox-2 inhibitor for OA treatment (117), and the increased number of knee and hip replacement surgeries over the past decades (118). Therefore in the database, collected from the Canadian publicly funded health care system, I hypothesize that there will be higher physician diagnosed OA incidence over time compared to the rates obtained in the earlier studies.

2.5 Treatment and Management

Pain in the affected joints, longer pain duration, joint stiffness, and functional limitations are common problems in individuals with OA. A large number of mental health symptoms, including anxiety and depression, are also common among individuals with OA compared with non-OA individuals (119,120). Both pharmacologic and non-pharmacologic treatment choices are available for OA. Exercise and weight loss programs are considered as non-pharmacologic treatments; whereas pain relief drugs and food supplements are viewed as pharmacologic treatments; and the joint replacement surgery is a treatment option for the end stage OA (121–125). OA cannot be completely cured, and for many cases the affected joints are most likely to deteriorate over time. Studies have shown that lifestyle modification such as weight loss and exercise help to reduce joint pain and maintain overall health among OA cases (122–124). Eating a healthy and balanced diet, getting sufficient rest, applying heat and cold to the affected joints, and protecting joints from over use are also part of the non-pharmacologic lifestyle recommendations. Physical therapy can also help to improve muscle strength and motion in the stiff joints as well as balance. Among pain relief medications, acetaminophen is the most popular pharmacologic treatment for OA (122,126). For mild and moderate symptoms, acetaminophen is similar to non-steroidal anti-inflammatory drugs (NSAIDs) in terms of effectiveness; however, NSAIDs may be more effective for treating severe OA symptoms (30,126).

Opioids are also common treatment options for osteoarthritis pain. However, to prevent their abuse, it is recommended that opioids be used only if the patient does not respond to acetaminophen or NSAID therapy or is unable to tolerate them because of side effects

(122). In addition, opioids should be initially applied at a low dosage and monitored to evaluate the potential for dependence upon it. Severe OA cases might require surgery to replace damaged joints. Thus, joint replacement surgery is usually the end stage treatment and is reserved for OA cases with symptoms that do not respond to other treatments (122). An artificial joint usually lasts for 15 to 20 years. In practice, OA treatment usually begins with the safest and least expensive therapy before proceeding to the more invasive and expensive therapy.

2.6 Disease Burden and Costs

The economic costs of OA can be broken down into direct costs and indirect costs. Direct costs include charges for physician consultations, pharmacological treatments, the use of hospital resources for surgery as well as care, and the management of complications arising from OA treatment. Indirect costs include loss of work time and productivity due to pain and disability and premature mortality. In addition, the reduction in quality of life due to OA often goes unmeasured and in any case is difficult to quantify either as a disease burden or as a cost. Studies of the economic costs of OA across countries are available in the literature. Some focus on aggregate costs at the national level or the cost per capita, others on costs borne by the individual patient with OA. In their literature review, Chen et al. (127) concluded that despite the different measures used in different studies, it is clear that the costs associated with OA are very substantial and are continuing to rise. A 1997 analysis of the economic cost of musculoskeletal disorders in industrialized countries, such as Australia, Canada, France, the United Kingdom, and the United States, the authors found a rising trend of costs due to OA; the costs covered from 1.0 to 2.5% of the gross domestic product of these countries (9). The total cost of musculoskeletal disorders in Canada was $25.6 billion in 1994 Canadian dollars, where the

direct and the indirect costs were estimated at $7.5 billion and $18.1 billion, respectively (10). In

their study, Maetzel et al. (128) estimated the total cost per capita of OA to be $5,712

(Canadian), of which 80% represented direct costs. In the case of disabled OA individuals,

Gupta et al. (129) estimated the average annual cost per individual to be $12,200 (Canadian

dollars in 2002). In their literature review, Xie et al. (130) found the annual direct costs per

patient to be $9,147 in Hong Kong, $4,792 in the USA, $2,878 in Canada, $1,271 in Italy, and

$345 in France. All these amounts were in 2005 US dollars. The authors also found that 5 studies

reported indirect costs in 4 countries. The highest indirect costs were $9,847 per patient per

annum in Canada, the lowest $864 in Hong Kong. Variations in direct and indirect costs exist

due to differences in demographics and methodologies used to calculate costs. Given the heavy

and growing burden of OA, a thorough understanding of the impact of OA on other chronic

conditions, particularly CVD, diabetes, and overall mortality, is essential. A review of the impact

of OA on CVD, diabetes and mortality is provided in the following section.

2.7 Impact of OA on Chronic Comorbid Conditions

OA is a leading cause of disability worldwide and therefore a major burden on individual health

systems and social care systems. Over the past few decades the overall life expectancy has

increased and OA is considered as a non-fatal health condition. For these reasons, individuals

with OA will live for many years in a state of disability, thus may contribute to chronic comorbid

conditions. Unlike inflammatory musculoskeletal conditions such as rheumatoid arthritis,

psoriatic arthritis, or lupus, comorbidity and mortality has never been a major area of

investigation for OA. A few studies suggest that OA may contribute to CVD, diabetes, and

overall mortality. OA cases showed higher rates of comorbidity such as hypertension, CVD,

obesity, respiratory diseases, peptic ulcers, renal disease, and diabetes compared to non-OA individuals (26–29). The reasons that individuals with OA experience excess cardiovascular conditions or diabetes may include reduced physical activity due to the condition, chronic inflammation, muscle weakness, metabolic syndromes, and the use of NSAIDs. A brief literature review on the relationship between OA and CVD and diabetes is as follows.

CVD

Cardiovascular disease (CVD), such as myocardial infarction (MI), ischemic heart disease (IHD), congestive heart failure (CHF), and stroke, are the major causes of morbidity and mortality worldwide (131,132). Coronary heart disease and the related risk factors are the leading causes of morbidity and mortality in Canada (133,134). Established risk factors for CVD include demographic, clinical, social, and behavioural factors, such as age, sex, obesity, hypertension, hypercholesterolemia, income, ethnicity, exercise, smoking, and diet (131–133,135). Recently, it has become clear that systemic inflammation can promote CVD (136,137). Frailty and muscle weakness have also been reported as risk factors and comorbidities among individuals with CVD (138). Studies have shown that increased risk of both CVD and premature mortality is partly the result of physical inactivity (139,140) in those cases where immobility results from arthritis/rheumatism among the elderly (141). Although OA is the most common rheumatic disease, very little is known about the link between this condition and CVD. Furthermore, the relationship between OA and CVD has never been examined extensively in prospective longitudinal studies. However, there is evidence to suggest that individuals with OA have higher rates of CVD. Using the third US NHANES database, Singh et al. (142) found that adults with OA have a high prevalence of cardiovascular risk factors. Kadam et al. (26)

calculated the probability of developing IHD, angina, and heart failure to be 73%, 36%, and 28% higher, respectively, among OA cases compared to non-OA controls in a case-control study in England and Wales. In a 2013 cross-sectional study using US NHANES data, Ong et al. (94) calculated significantly higher odds for self-reported CVD, CHD, and angina among OA cases compared to their non OA counterparts. Although these studies focused on comorbidity among OA cases, they were either cross-sectional or case-control studies.

Diabetes

Diabetes mellitus is one of the most common chronic conditions worldwide. The global prevalence of diabetes among adults was estimated to rise from 6.4% in 2010 to 7.7% in 2030 (143). Diabetes is estimated to affect approximately 8.3% of Americans and approximately 8.8% of Canadians (144,145) and consequently a large number of patients suffer with severe organ damage/complications in the cardiovascular system, kidneys, and eyes. Diabetes is associated with age, sex, body weight, family history, ethnicity, socio-economic status, hypertension, CVD, history of gestational diabetes, physical exercise, alcohol consumption, metabolic syndrome and diet (146–148). As the prevalence of diabetes rises, there is a need to characterize determinants beyond these traditional risk factors. Studies have shown lower muscle strength among adults with type 2 diabetes (149). The increased risk of diabetes is caused in part by physical inactivity and a lower rate of diabetes was observed among physically active individuals (147,150). Although the risk of diabetes among individuals with OA has not been studied extensively in prospective studies, there is some evidence that OA is associated with diabetes or higher blood glucose. In a clinical and epidemiological survey in Italy, Cimmino et al. (151) found that fasting plasma glucose concentrations were significantly higher among OA cases compared to non-OA

controls. Among the women aged 45-64 years from a general practice in Chingford, UK, Hart et al. (152) observed that the odds ratio of raised blood glucose was 1.95 among radiographic knee OA cases compared to non-OA controls. In a cross-sectional study from Puerto Rico, Nieves-Plaza et al. (153) observed odds ratio of 2.18 between OA and diabetes where odds ratio was even higher among women. These cross-sectional studies used relatively small samples and did not adjust for all the potential confounders.

2.8 Impact of OA on Mortality

The few studies that have examined mortality among OA cases have shown that individuals with OA have increased mortality due to CVD, diabetes, dementia, and cancer compared with non-OA individuals (154,155). Nüesch et al. (154) performed a cohort study using the General Practitioners Database that was compiled in the southwest of England to examine all-cause and disease specific mortality in patients with OA of the hip and knee. After 14 years of median follow-up, they concluded that the subjects with OA had a greater rate of mortality compared with the general population and that the standard mortality ratio for CVD was 1.71 (95% CI 1.49-1.98). In a literature review on mortality among OA cases, Hochberg (155) found several studies that suggest an increased risk of death among OA cases compared with non-OA individuals (156–161). However, these studies were subject to limitations regarding subject selection, sample size, and variable selection in the multivariable analyses.

CHAPTER 3 DATA AND METHODS

3.1 The Data Source

Three different data sets were analyzed to fulfill the objectives of this study. These are: 1) BC administrative database, 2) the first three cycles of the Canadian Community Health Survey, and 3) a population-based cohort of early knee OA from the greater Vancouver area, BC. The BC health administrative database is collected and maintained by the Ministry of Health. It includes health records of all BC residents registered in the Medical Services Plan (MSP) of BC. MSP is a publicly funded plan and we have found that approximately 99% of the residents are registered in it. Both the BC Ministry of Health and the Population Data BC, who facilitate administrative data acquisition in BC, have approved access to and use of the data for this study. The database included International Classification of Disease 9th revision (ICD-9) and International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) diagnostic codes, date and type of service, birth and death dates, sex, and MSP registration start and exit dates. In addition to the hospital admission and separation dates, hospital discharge summaries included up to 25 diagnoses codes. From the administrative data, the medical records of a random sample of 640,000 individuals for the fiscal years 1991/92 through 2008/09 were analyzed. I used this random sample to calculate the incidence and prevalence of OA, to estimate the trends in OA incidence, to obtain the risk of developing CVD among OA cases, and to estimate the risk of developing diabetes among OA cases. A short description of this database is also provided in the Methods sections in Chapters 4-6, 8, and 9.

The second dataset I used was comprised of the cross-sectional CCHS cycles 1.1, 2.1, and 3.1. These datasets were used to investigate the relationship between self-reported OA and prevalent

CVD. The first 3 cycles of CCHS were conducted in years 2000/01, 2002/03, and 2004/05, respectively. Conducted and maintained by Statistics Canada, the CCHS contains nationally representative data on health determinants, health status, and health system utilization. The survey used a multistage stratified cluster probability sampling in which a dwelling was the final sampling unit. The survey sample was stratified by province/territory and urban versus rural regions within each province/territory. CCHS used three sampling frames to select the sample of households: 48-49% of the sample was selected from an area frame, 50% was selected from a list frame of telephone numbers, and 1-2% came from a Random Digit Dialing sampling frame. Sampling was designed to represent 98% of the Canadian population aged 12 years and above who lived in private dwellings in the ten provinces and the three territories (162). More detailed description of the CCHS survey design, sample frame, interviewing procedures, and sample size are given in Chapter 7.

The third dataset was a population-based cohort drawn from the greater Vancouver area. A cohort of 255 subjects, who were experiencing knee pain, was recruited through population random sampling during the period August 2002 to February 2005. The subjects met inclusion criteria if they were between 40–79 years of age and had experienced pain, aching or discomfort in or around the knee on most days of the month or at any time in the past 12 months. Subjects with inflammatory arthritis or fibromyalgia, knee arthroplasty, a history of knee surgery/ injury within the past 6 months, knee pain referred from the hip or back, or inability to undergo MRI were excluded. From the greater Vancouver telephone directory, 5,231 English-speaking persons were randomly contacted, of whom 3,269 (62.5%) agreed to participate in the study. Of the 3,269 subjects, 91.9% were ineligible due to the age restriction and other exclusion criteria. Of

the remaining 265 subjects, 10 were excluded due to missed appointments and for other reasons. The study sample recruitment procedure has been described elsewhere (163). Lastly, 255 subjects underwent comprehensive clinical assessment, self-report questions, standardized joint examination, x-rays, and MRI to identify knee OA. Since both MRI and radiograph-based diagnoses were included in the study, subjects with knee arthroplasty or a history of knee surgery/injury were excluded. Of the 255 subjects, 171 provided their written consent for data linkage. Thus, their clinical data were linked with the administrative health records for the period 1991-2004 through personal health numbers.Detailed information on this study sample is also provided in Chapter 6.

3.2 Methods and Statistical Analysis

OA Cases

In this study, two administrative case definitions were used for OA and we refer to them Definition1 and Definition 2. Definition 1 required at least one visit to a health professional or one hospital separation with the ICD-9 code 715 or the ICD-10 codes from M15 to M19. Definition 2 required at least two visits to a health professional within two years (at least one day apart) or one hospital separation with the ICD-9 code 715 or the ICD-10 code from M15 to M19. For Definition 2, the date of the second qualifying visit was used to assign the date of diagnosis. In the other chapters of the thesis, these two definitions were named as Def1 and Def2, or AOA1 and AOA2, respectively. A visit was defined as any service covered by the MSP with the exclusion of diagnostic procedures and certain other procedures, such as dialysis/transfusion, anesthesia, obstetrics, or therapeutic radiation. Visits to all types of health professionals were included. Adult OA cases age 20 years and over were included in this study. For each objective

of this thesis, specific statistical analysis was performed and a detailed description of the analytic

procedure was provided in each of the following chapters. A brief description of the overall

methods and statistical analyses are given below.

Incidence

Incidence rate was defined as the number of new cases of OA during a fiscal year (from April 1st

to March 31st) divided by the person-years at risk in that fiscal year. New cases in a fiscal year

were identified after deleting the prevalent cases, that is, persons diagnosed with OA in the

previous years. Age-sex-specific overall incidence rates were calculated using the two case

definitions discussed earlier in the year 2008/09 and expressed per 1000 person-years. For each

age-sex category, person-years at risk for a given fiscal year were calculated from the

registration records of MSP. First, I deleted the prevalent cases. Next, within each age-sex

category, we added up the number of days for which individuals were registered with the MSP.

Individuals were censored if they developed OA, died, or left the province, whichever came first.

Trends

I used the BC administrative database covering the period 1991/92-2008/09 to estimate the

trends of OA incidence rates. A 2008 study showed that in an administrative database, incidence

rate of OA depends on the number of run-in years, that is, the number of years of health records

used to delete the prevalent cases (6), and the authors recommended a longer run-in period to

control for overestimation. Since I had 18 years of data, to control for overestimation in the trend

analysis, I selected a 9-year run-in and obtained incidence rates for the period 2000/01-2008/09.

In a given age-sex category, the number of new cases were identified according to two OA

definitions, during a given one-year period; prevalent OA cases were deleted during the preceding 9-year run-in period. For example, for calculating the incidence rate in 2008/09, I excluded prevalent OA cases diagnosed between April 1999 and March 2008. The 95% confidence intervals for the incidence rates were obtained using the formula: rate ± 1.96 {rate/SQRT [new cases]}. To eliminate the effect of aging in the trends, rates were age-standardized using the direct method, in which the person-years for the fiscal year 2004/05 (obtained from the same BC random sample) were considered as the standard population. Ten-year age categories (20-29, 30-39, … , 70-79, 80+) for each sex were used in the standardization process. First, I fit linear regression models for rates on the year of diagnosis. However, statistically significant lack of fit (p-value < 0.05) was observed in these models. Therefore, Poisson regression models were fitted to estimate trends separately for each sex. Age was included in the model to obtain trends for age-adjusted rates. Finally, I obtained the annual relative change (ARC) from the estimated coefficient by using the formula as ARC = (EXP {estimated coefficient} − 1) × 100 for each case definition and sex. Along with a 9-year run-in, for the sensitivity analysis, I obtained incidence rates and ARCs for the period 2000/01-2008/09 using five years of run-in. Further detail about the incidence and trends analyses were provided in Chapter 4.

Prevalence

The point prevalence of OA in the administrative data was defined as the number of existing OA cases in the random sample at a specified time divided by the number of persons in the sample at that time. The numerator for the prevalence was the number of persons who met the definition of OA between April 1, 1991, and March 31, 2009, and were alive and registered with the MSP on

March 31, 2009. The denominator for the same was the total number in the random sample alive

and registered with the MSP on March 31, 2009. Rates were calculated for 5-year age-sex groups

and also for 10 years of age cut-off points.

Validation of Administrative OA Definitions

For validation of both administrative case definitions, I defined four reference standards: RS1,

RS2, RS3, and RS4, based on the knee, hand, and hip OA assessments. RS1 included

assessments of knee and hand OA based on the ACR clinical criteria and hip OA based on self-

reported hip pain. RS2 included assessments of knee, hand, and hip OA based on K-L grade,

ACR clinical criteria, and self-reported hip pain, respectively. RS3 included assessments of knee,

hand, and hip OA based on MRI cartilage score, ACR clinical criteria, and self-reported hip pain,

respectively. RS4 included assessments of knee, hand, and hip OA based on self-reports, ACR

clinical criteria, and self-reported hip pain, respectively. The same measurements for hand and

hip OA were consistent in the four reference standards. I calculated the sensitivity, specificity,

PPV, and NPV, for each case definition according to four reference standards. The 95%

confidence intervals (CIs) were calculated for these measures. For more detail about these

measures, please refer to Rothman et al. (164). I also calculated likelihood ratios (LR+ and LR-)

and their 95% CIs. Where LR+ = positive likelihood ratio = sensitivity/(1-specificity), and LR- =

negative likelihood ratio = (1-sensitivity)/specificity. Further description of the reference

standards and methods was given in Chapter 6.

Cross-sectional Study

To obtain the association between OA and heart disease, MI, angina, CHF, and stroke, I used the

first 3 cycles of CCHS samples. Data for the CCHS samples were collected and maintained by

the Statistics Canada. They include nationally representative data on health determinants, health

status, and health system utilization. This cross-sectional survey used a multistage stratified

cluster probability sampling in which a dwelling was the final sampling unit. The survey sample

was stratified by province/territory and urban versus rural regions within each province/territory.

Three sampling frames were used to select the sample of households: 48-49% of the sample

came from an area frame, 50% came from a list frame of telephone numbers and 1-2% came

from a Random Digit Dialing sampling frame. Selected persons were interviewed either by

telephone or face-to-face. More detailed description of the survey design, sample frame, and

interviewing procedures were provided in Chapter 7. The main independent variable in this study

was OA and the primary outcome was heart disease. Specific cardiovascular conditions such as

MI, angina, CHF, or stroke were secondary outcomes in this study. We have included

demographic, socioeconomic, and health behaviour variables to serve as control variables in

regression modeling. The socio-demographic variables were age, sex, body mass index (BMI),

education, and household income. Health behaviours included physical activity, smoking status,

fruit and vegetable consumption, and pain medication use. Chronic health conditions such as

chronic obstructive pulmonary disease (COPD), diabetes, and hypertension were included as

covariates. Detailed description of these variables and the related CCHS questions were provided

in Chapter 7.

Both bi-variable and multivariable logistic regression models were fitted to the 1:1 matched OA cases and non-OA individuals in the CCHS samples to assess the association between OA and heart disease, MI, angina, CHF, and stroke after controlling for the potential confounding variables. Initially I attempted to select 3 non-OA individuals for each OA case by matching for age, sex, and CCHS cycles. However, high prevalence of OA in the older age groups (ie., more than 40% among individuals age > 70 years have OA) was observed and therefore, it was not possible to match exactly 3 non-OA individuals in the older age groups. As part of the sensitivity analysis, all regression models were also fitted with the 1:3 approximately matched samples. Statistics Canada produced sampling weights for each of the CCHS participants. All estimates were weighted to approximate the distribution of demographic variables in the overall Canadian population. In the statistical tests, the common assumption is that data were obtained by simple random sampling and if data were collected in other procedures the traditional statistical tests become incorrect to some degree. The design effect is a concept developed for quantifying the extent to which the sampling error in a survey departs from the sampling error that can be expected under the assumption of simple random sampling. Since CCHS uses a complex sampling design, the confidence intervals of the estimates were adjusted using a design effect of 2 (162,165).

Prospective Longitudinal Study

To estimate the risks of developing CVD, OA cases and up to 3 non-OA subjects matched by age, sex, and the year of diagnoses, found in the first five years (from April 1991 to March 1996) of administrative health records were selected. For the prospective studies, I have selected OA case using Definition 2. The follow-up period started on the date when individuals met the case

definition for OA (index date) and continued until hospitalization for CVD, death, emigration, or

the end of the study period (March 31, 2009), whichever came first. Person-years at risk were

calculated for the entire follow-up period. The relative risks (RR) and 95% confidence intervals

(CI) were evaluated using the Cox proportional hazards (PH) models. The proportionality

assumptions for PH models were assessed by observing the Kaplan-Meier curves. In addition,

the proportionality tests were performed in the multivariable models and the p-values were

reported. The RRs were estimated from the Poisson regression models where proportionality

tests p-values were found to be significant. To obtain the risk of diabetes among OA cases, I

followed the same statistical procedures. In this case the 1:1 (OA versus non-OA) matched

samples were selected and the incident diabetes cases were considered as events. Further

description regarding the exposure and outcome variables and the confounders included in the

analyses were provided in Chapters 8 and 9. SAS version 9.3 (SAS Institute, Cary, NC, USA)

was used throughout the study to perform the analyses.

CHAPTER 4 INCIDENCE AND TRENDS OF OSTEOARTHRITIS[1]

4.1 Introduction

This chapter estimates the physician diagnosed incidence rates of overall OA in any joint and describes the changes in rates over time in the BC administrative database. The background of incidence and trends analyses was presented previously. In summary, OA incidence rates were estimated previously and the rates differ depending on the age and sex of the studied population, the method of case identification used, and the specificity of joint sites included (6,111–115) . All these studies are based on small samples and did not include longer observation time. Kopec et al. (100) estimated that the age-standardized incidence rates of physician diagnosed OA did not change in men and slightly increased among women in BC. This study considered relatively shorter observation time to estimate trends. Change in the prevalence of age, sex, obesity, and other risk factors of OA, new approaches of joint specific exercise and education programs (116), new drugs such as Cox-2 inhibitor for OA treatment (117), and the increased number of knee and hip replacement surgeries over the past decades (118) my hypothesis was that there will be higher physician diagnosed OA incidence over time.

The aim of this study was to estimate the annual incidence rates of OA using a large random sample drawn from BC administrative health records compiled during 1991/92-2008/09. Using the same database, we studied changes in the incidence rates of OA over time. This study also updated the results presented in earlier studies using the same database (6,100). Incidence rates

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[1] A version of this chapter has been accepted for publication in the Journal of Rheumatology. Authors include Rahman MM, Cibere J, Goldsmith CH, Anis AH, and Kopec JA. The title of the manuscript is "Osteoarthritis incidence and trend in administrative health records from British Columbia, Canada."

and trends are useful for assessing the impact of current control plans and for creating OA preventive strategies.

Section 4.2 describes the methods and statistical analysis used in this study. Results are presented in Section 4.3 and finally detailed discussion is given in Section 4.4. In the Discussion section, we compare the findings with published data and present the strengths and limitations of the study.

4.2 Methods

Database

We analyzed the medical records of a random sample of 640,000 residents from BC for the fiscal years 1991/92 through 2008/09. All visits to health professionals and hospital admissions covered by the Medical Services Plan (MSP) of BC were included in the analyses. MSP is a universal plan with first dollar coverage in which approximately 99% of BC residents are registered. Both the BC Ministry of Health and Population Data BC approved access to and use of the data for this study. The database includes International Classification of Disease 9th and 10th revision (ICD-9 and ICD-10) diagnostic codes, date and type of service, hospital admission and separation dates, birth and death dates, sex, and MSP registration start and exit dates. On the physician billing statements, only one diagnostic code is included, whereas hospital discharge summaries include up to 25 diagnostic codes. To monitor deaths of the individuals in the sample, the Ministry linked vital statistics data to billing data using personal health numbers. In our random sample, 49.1% were male, and the mean age of the entire sample on April 1, 2009 was 48.6 (standard deviation 22.7) years.

OA case definitions

Two case definitions of OA, referred to as Def1 and Def2, were used in this study. Def1 required

at least one visit to a health professional or one hospital separation with the ICD-9 code 715 or

the ICD-10 code from M15 to M19. Def2 required at least two visits to a health professional

within two years (at least one day apart) or one hospital separation with either of these ICD

codes. These codes include OA in any joint except the spine, either generalized or localized. For

Def2, the date of the second qualifying visit was used to assign the incidence date. These two

definitions were implemented previously to estimate the incidence and prevalence of OA at the

population level (6). A visit was defined as any service by a health professional covered by MSP

with the exclusion of diagnostic procedures and certain other procedures, such as

dialysis/transfusion, anesthesia, obstetrics, or therapeutic radiation.

Incidence rate

Incidence rate was defined as the number of new cases of OA during a fiscal year (from April 1st

to March 31st) divided by the person-years at risk in the same fiscal year. To calculate the overall

incidence rate for the year 2008/09, new OA cases aged 20 years and older were identified after

deleting the prevalent cases from April 1991 to March 2008 (a 17-year run-in). Age-sex-specific

incidence rates were calculated using the two case definitions discussed above and expressed per

1000 person-years.

Trend

In an administrative database, incidence rate of OA depends on the number of run-in years used

to delete the prevalent cases (6), where a longer run-in period was recommended to control

overestimation. Since we have data for 18 years, to control for overestimation in the trend

analysis, we have selected a 9-year run-in and obtained incidence rates for the period 2000/01-

2008/09. The number of new cases in a given age-sex category, were identified according to two

definitions during a given one-year period, after deleting prevalent OA cases during the

preceding 9-year run-in. For example, the incidence rate for the year 2003/04 was calculated

after deleting prevalent OA cases were diagnosed between April 1994 and March 2003. For each

age-sex category, person-years at risk for a given fiscal year were calculated from the MSP

registration records. First, we deleted the prevalent cases. Next, within each age-sex category, we

added up the number of days for which individuals were registered with the MSP. Individuals

were censored if they developed OA, died, or left the province, whichever came first.

Statistical Analysis

The 95% confidence intervals (rate $\pm$ 1.96 {rate/SQRT [new cases]}) were obtained for all

incidence rates. Rates were age-standardized using the direct method where the person-years for

the fiscal year 2004/05 were considered as the standard population. Ten-year age categories (20-

29, 30-39, … , 70-79, 80+) for each sex were used in the standardization process. Trends in

incidence were shown graphically by plotting crude and age-standardized rates against the year.

Statistically significant lack of fit (p-value < 0.05) was observed when the straight line models of

rates on the year of diagnosis were fitted. Therefore, Poisson regression models were fitted to

estimate trends separately for each sex. Age was included in the model to obtain trends for age-

adjusted rates. Finally, we calculated the annual relative change (ARC) from the estimated

coefficient as ARC = (EXP {estimated coefficient} $-$ 1) $\times$ 100 for each case definition and sex.

Along with 9 years of run-in, for the sensitivity analysis, we obtained incidence rates and ARCs

for the period 2000/01 - 2008/09 using 5 years of run-in. All analyses were performed using SAS

V.9.3 (SAS Institute, Cary, NC, USA). This study was approved by the Behavioural Research

Ethics Board of the University of British Columbia, Canada.

4.3 Results

Overall incidence rates

After deleting prevalent cases in 17 years of health records, 6,064 new OA cases were diagnosed

in the year 2008/09 using Def1. Among them 3.5% were diagnosed in the hospital and the

remaining 96.5% were diagnosed during the physician's visits. Among physicians, 84.4% were

general practitioners, 10.2% were orthopedic surgeons, and the rest were other health

professionals. The incidence rates of OA in the fiscal year 2008/09, according to two case

definitions and sex, for all ages and also for different age cut points, are shown in Table 4.1. The

overall incidence rate (95% CI) of OA in Def1 for all ages combined was 14.6 (14.0-14.8) per

1000 person-years; 12.5 (12.0-13.0) in men, and 16.3 (15.8-16.8) in women. The overall rate was

8.2 (7.9-8.4) per 1000 person-years when Def2 was used. Among persons aged 50 years or older,

the rates were 31.6 (30.6-32.5) and 17.7 (17.1-18.3) per 1000 person-years for Def1 and Def2,

respectively. The age-sex specific incidence rates for the year 2008/09 are presented in Figure

4.1. Women had higher rates than men in all age groups and the highest rates were observed in

the age group 80-89 for men and 70-79 for women.

Crude and age-standardized rates

Both crude and age-standardized incidence rates during the period 2000/01 - 2008/09 based on

the two case definitions are shown in Table 4.2 and Figure 4.2. During the observation period,

the crude rates (95% CI) based on Def1increased from 11.6 (11.2-12.0) to 14.2 (13.7-14.6) per

1000 person-years in men and from 15.4 (15.0-15.9) to 18.5 (17.9-19.0) in women. The age-

standardized rates in Def1 varied from 12.1 (11.7-12.6) to 13.2 (12.8-13.7) per 1000 person-

years in men and from 16.0 (15.5-16.5) to 17.4 (16.9-17.9) in women. Incidence rates were lower

by about 45-47% under Def2 among men and women compared to the rates obtained under

Def1, but the changes in rates over time were similar in both case definitions. Age-sex specific

crude incidence trends from 2000/01 through 2008/09 using Def1 are plotted in Figure 4.3.

Based on a 5-year run-in and Def1, crude rates rose from 13.4 (12.9-13.8) to 16.0 (15.5-16.4) per

1000 person-years among men and from 18.1 (17.6-18.6) to 21.5 (21.0-22.0) among women.

Annual Relative Change

We calculated the ARCs for both crude and age-adjusted rates from the Poisson regression

model (Table 4.2). Under Def1 and Def2 respectively, the ARC (95% CI) for crude rates were

2.8 (2.3-3.3) and 3.3 (2.6-3.9) percent for men, and 2.5 (2.1-2.9) and 2.5 (2.0-3.1) percent for

women. The age-adjusted ARCs (95% CI) were 0.6 (0.1-1.1) and 0.8 (0.2-1.4) percent under

Def1 and Def2, respectively, among men, and were not statistically significant among women.

We observed similar trends from years 2000/01 through 2008/09 in the 5-year run-in approach

(data not shown).

Table 4.1: Crude incidence rate (95% confidence interval) of osteoarthritis in the fiscal year 2008/09 per 1000 person years at different age cut points using a 17-year run-in to delete the prevalent cases.

Age years	Def1			Def2		
	Men	Women	Total	Men	Women	Total
All[*]	12.5 (12.0-13.0)	16.3 (15.8-16.8)	14.6 (14.0-14.8)	7.1 (6.8-7.4)	9.2 (8.9 -9.6)	8.2 (7.9-8.4)
≥ 20	14.9 (14.3-15.5)	19.3 (18.7-20.0)	17.1(16.7-17.5)	8.4 (7.9-8.8)	10.8 (10.3-11.2)	9.6 (9.3-9.9)
≥ 30	18.0 (17.3-18.7)	23.3 (22.6-24.1)	20.7 (20.1-21.2)	10.0 (9.5-10.5)	12.9 (12.4-13.5)	11.5 (11.1-11.8)
≥ 40	21.5 (20.7-22.4)	28.5 (27.5-29.5)	25.0 (24.3-25.6)	11.9 (11.3-12.5)	15.7 (15.1-16.4)	13.9 (13.4-14.3)
≥ 50	26.8 (25.6-28.0)	36.6 (35.2-38.0)	31.6 (30.6-32.5)	15.3 (14.4-16.1)	20.1 (19.2-21.1)	17.7 (17.1-18.3)

Def1: One visit to a health professional or one hospital diagnosis; Def2: Two visits to a health professional in two years or one hospital diagnosis.

*Osteoarthritis cases below age 20 years were deleted, but the person-years for all individuals at risk were used in the denominator.

Figure 4.1: Age-sex specific crude incidence rates and the 95% confidence intervals (error bars) of osteoarthritis in the fiscal year 2008/09 per 1000 person years using a 17-year run-in to delete the prevalent cases.
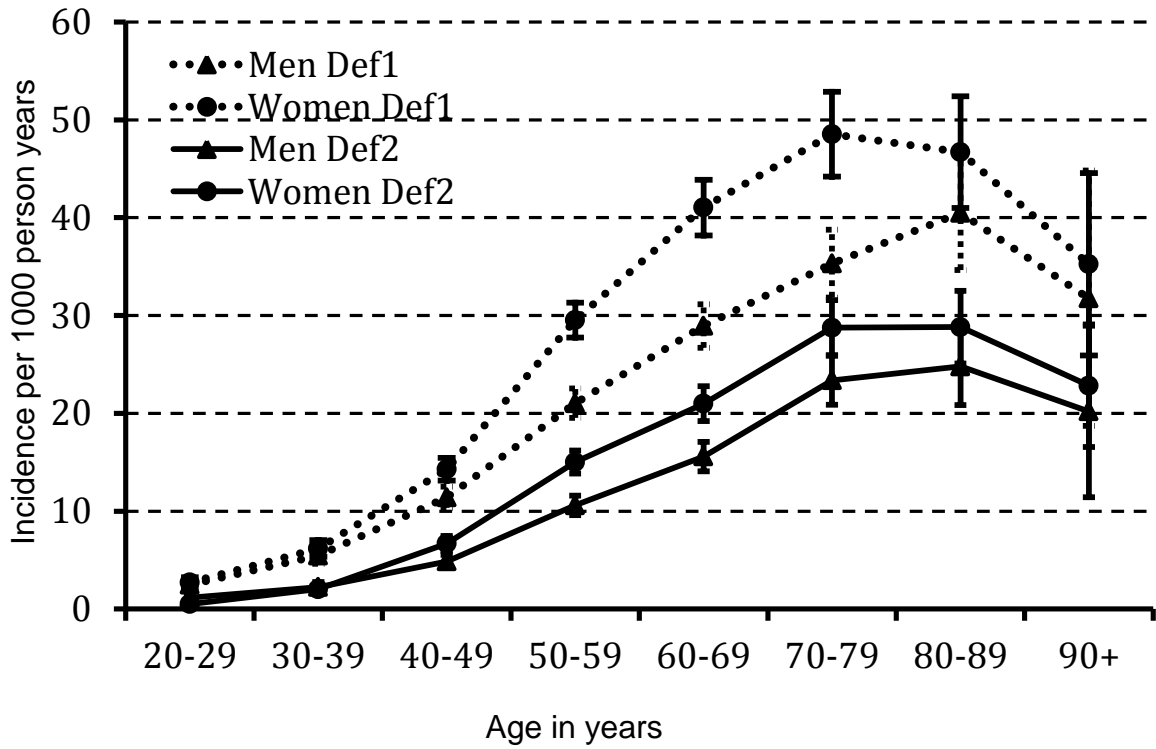
Def1: One visit to a health professional or one hospital diagnosis; Def2: Two visits to a health professional in two years or one hospital diagnosis.

Table 4.2: Crude and age-standardized incidence rates (95% confidence interval) of osteoarthritis per 1000 person years during the period 2000/01 - 2008/09 using a 9-year run-in to delete the prevalent cases.

Fiscal Year	Men Def1 Crude	Men Def1 Standardized	Men Def2 Crude	Men Def2 Standardized	Women Def1 Crude	Women Def1 Standardized	Women Def2 Crude	Women Def2 Standardized
00/01	11.8 (11.4-12.2)	12.7 (12.2-13.1)	6.3 (6.0-6.6)	6.8 (6.5-7.2)	15.7 (15.2-16.1)	17.0 (16.4-17.5)	8.5 (8.2-8.8)	9.2 (8.9-9.6)
01/02	11.6 (11.2-12.0)	12.3 (11.9-12.8)	6.1 (5.8-6.4)	6.5 (6.2-6.8)	15.7 (15.2-16.1)	16.7 (16.2-17.2)	8.8 (8.5-9.1)	9.4 (9.0-9.8)
02/03	11.7 (11.3-12.1)	12.1 (11.7-12.6)	6.2 (5.9-6.4)	6.4 (6.1-6.7)	15.4 (15.0-15.9)	16.0 (15.5-16.5)	8.5 (8.2-8.8)	8.9 (8.5-9.3)
03/04	12.5 (12.0-12.9)	12.7 (12.2-13.1)	6.6 (6.3-6.9)	6.8 (6.4-7.1)	16.9 (16.4-17.4)	17.2 (16.6-17.7)	9.3 (9.0-9.7)	9.5 (9.1-9.9)
04/05	12.6 (12.2-13.0)	12.6 (12.1-13.0)	6.7 (6.4-7.0)	6.7 (6.4-7.1)	17.3 (16.8-17.8)	17.3 (16.8-17.8)	9.7 (9.3-10.1)	9.7 (9.3-10.1)
05/06	13.6 (13.1-14.0)	13.2 (12.8-13.7)	7.1 (6.8-7.5)	6.9 (6.6-7.3)	17.8 (17.3-18.3)	17.4 (16.9-17.9)	9.7 (9.4-10.1)	9.5 (9.1-9.9)
06/07	13.5 (13.0-13.9)	12.8 (12.4-13.3)	7.5 (7.1-7.8)	7.1 (6.7-7.4)	18.1 (17.6-18.6)	17.3 (16.7-17.8)	9.8 (9.5-10.2)	9.3 (8.9-9.7)
07/08	13.9 (13.5-14.4)	12.9 (12.5-13.4)	7.4 (7.0-7.7)	6.8 (6.4-7.1)	18.1 (17.6-18.6)	16.9 (16.4-17.5)	10.2 (9.8-10.6)	9.4 (9.0-9.8)
08/09	14.2 (13.7-14.6)	12.9 (12.4-13.4)	7.9 (7.5-8.2)	7.1 (6.7-7.4)	18.5 (17.9-19.0)	16.8 (16.3-17.4)	10.2 (9.8-10.6)	9.2 (8.8-9.5)
Coefficient	0.028	0.006	0.032	0.008	0.024	0.003	0.025	0.001
(95% CI)	(0.023-0.032)	(0.001-0.011)	(0.026-0.039)	(0.002-0.014)	(0.020-0.028)	(-0.002-0.007)	(0.020-0.030)	(-0.005-0.006)
ARC (95% CI)	2.8 (2.3-3.3)	0.6 (0.1-1.1)	3.3 (2.6-3.9)	0.8 (0.2-1.4)	2.5 (2.1-2.9)	0.3 (-0.2-0.7)	2.5 (2.0-3.1)	0.1 (-0.5-0.6)

Def1: one visit to a health professional or one hospital diagnosis. Def2: two visits to a health professional in two years or one hospital diagnosis. Age-standardized rates were obtained by considering person years of the year 2004/05 as standard population.

[*]ARC: annual relative change = (EXP {coefficient} − 1) × 100 where coefficients were estimated from the Poisson regression models.

[**]Coefficients for the standardized rates were obtained from the age-adjusted Poisson regression models.

Figure 4.2: Crude and age-standardized incidence rates and the 95% confidence intervals of osteoarthritis per 1000 person years during the period 2000/01-2008/09 using a 9-year run-in to delete the prevalent cases.
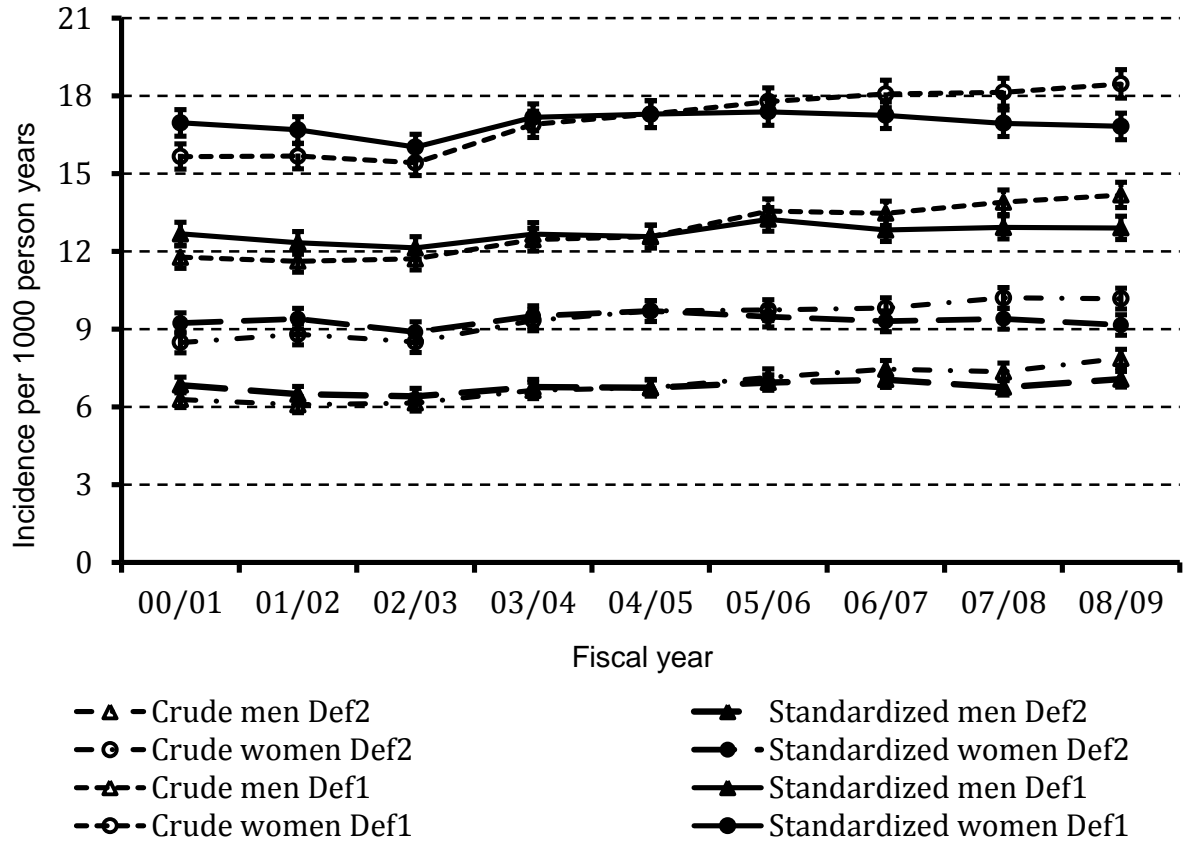
Def1: one visit to a health professional or one hospital diagnosis and Def2: two visits to a health professional in two years or one hospital diagnosis.

Figure 4.3: Age-sex specific crude incidence rates of osteoarthritis per 1000 person years during the period 2000/01-2008/09 using a 9-year run-in to delete the prevalent cases. Rates were calculated based on Def1 (one visit to a health professional or one hospital diagnosis); men on the left and women on the right.
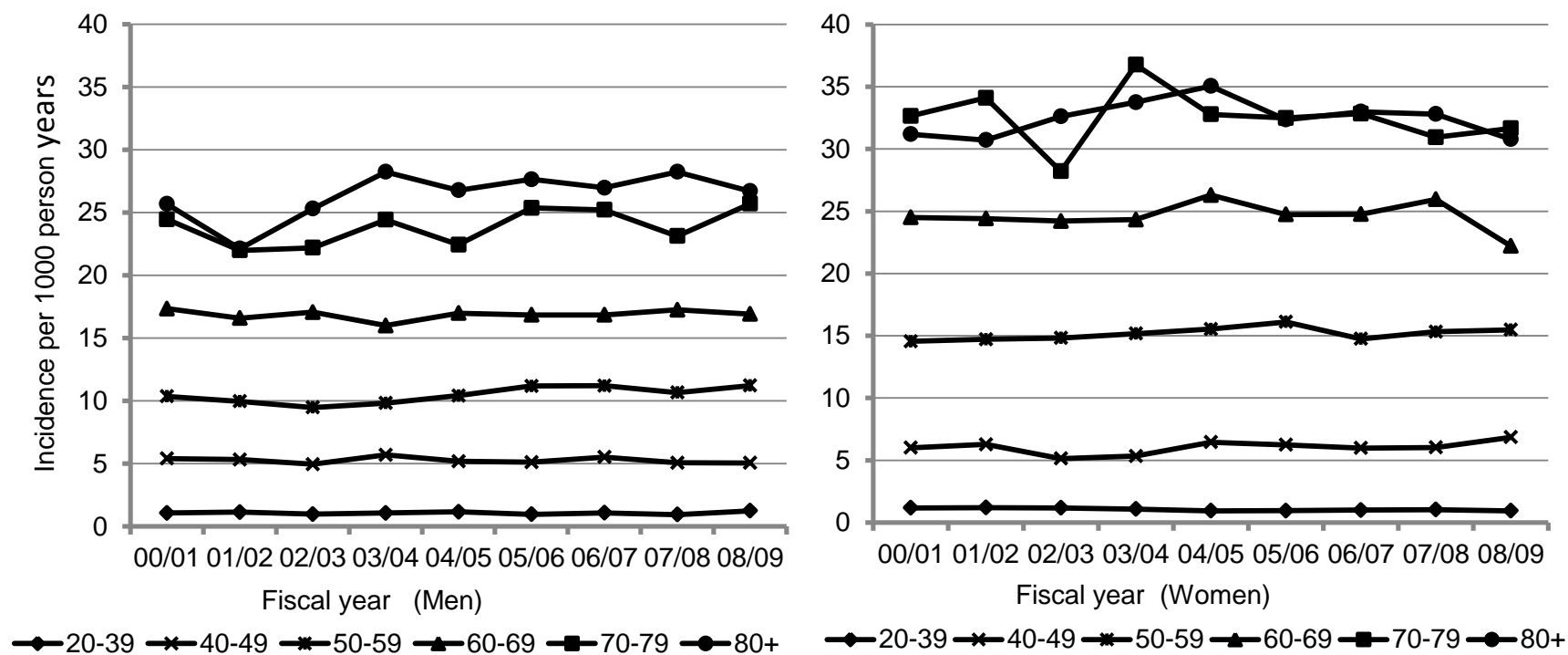
Due to low number of new OA cases, to calculate incidence rates, the first two age categories 20-29 and 30-39 were added into one age category 20-39, and the last two age categories 80-89 and 90+ were added into one age category 80+.

4.4 Discussion

In this population-based study, we estimated incidence rates and trends in the incidence of OA over time, using a large random sample drawn from administrative health records of BC, Canada. The overall incidence rate in the fiscal year 2008/09 was 14.6 per 1000 person-years in the definition that employed one visit to a physician or one hospital diagnosis. Incidence rates were lower by 44% when we used the definition of two visits to physicians within two years or one hospital diagnosis. In the trend analysis, crude rates showed a significant increase among men and women from 2000/01 to 2008/09. During this period, the age-standardized rates increased slightly for men but showed no change in the case of women.

Using the BC administrative database from April 1991 to March 2001, Kopec et al. (6) observed an overall incidence rate of 11.7 per 1000 person years according to the definition that required one physician visit or one hospital admission for OA. Our overall incidence rates are higher than these earlier results, possibly due to the differences in the observation years and the denominator used. We used exact person-years from the registration records, whereas mid-year population estimates were used in the previous denominator. Thus, this study provides more precise and updated rates. Other studies have estimated incidence rates for knee, hip, and hand OA for different age cut points. Our overall annual incidence rates using Def1 are comparable to the self-reported estimates obtained in the Grotle et al. (115) study, if the site-specific rates in the latter study were combined. Using survey data from Canada, Wilkins (95) calculated incidence rates of self-reported arthritis of 31 and 48 cases per 1000 person-years, for men and women aged 40 years or more, respectively. Our incidence rates differ slightly from those of radiographic and symptomatic knee OA estimated in the Framingham study (111), those of

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radiographic knee OA estimated in the Cooper et al. (112) study, those of self-reported arthritis obtained in the Wilkins (95) study, the rates of radiographic hip OA in the Reijman et al. (114) study, and those observed in the Oliveria et al. (113) study. These differences in rates are likely due to differences in the populations under study, the case identification used, and the joint sites considered in the definitions.

Incidence trends in our study differed from those obtained previously by Kopec et al. (100). However, the earlier study used a 5-year run-in and found an increasing trend of OA among women during the period 1996/97 - 2003/04. One possible reason for this difference could be the inclusion of health records in our study extending forward for five additional years. The sensitivity analysis with 5 years of run-in (data not shown), showed an increasing trend among women during the period 1996/97 - 2003/04. The observed trends were consistent in both 5-year and 9-year run-in approaches for the period 2000/01 - 2008/09. Thus, our study gives updated and more accurate estimates. To our knowledge, there are no other published studies that describe trends in OA derived from administrative databases using a longer observation period. Hootman et al. (31) reported an overall 1.3% increase in the prevalence of OA for the US population. Using Canadian survey data, Perruccio et al. (18) reported that the overall prevalence of self-reported arthritis/ rheumatism rose from 13.4% to 17.6% between the years 1994-2003. Our province-specific age-standardized incidence rates are not comparable with the national prevalence data. It is noteworthy that an increase in disease prevalence does not necessarily imply a simultaneous increase in incidence; nevertheless, in our study, changes in the crude incidence of OA due to population aging were in the same direction as changes in the crude prevalence of arthritis reported in earlier studies.

An important strength of our study is that it is based on a large random sample drawn from administrative health records that are representative of the entire province. All the OA cases in this study were physician-diagnosed or drawn from hospital-discharge records rather than self-reported illnesses. An additional strength is that we were able to access individual medical records over an 18-year period. However, certain limitations need to be acknowledged. Because we analyzed data from the province of BC only, the study results may not be generalizable to the entire Canadian population. Incidence rates depend on the case definition of OA (6,17), and the rates in our study were lower than those published earlier using self-reported and radiographic OA. Case definitions using ICD-9 and ICD-10 diagnostic codes represent another limitation, as both false negatives and false positives may occur due to misdiagnosis or incorrect recording on administrative forms. However, these diagnostic criteria were previously validated (25,166). Lix et al. (25) compared administrative OA diagnoses from the province of Manitoba, Canada, with the self-reported Canadian Community Health Survey data. We used data covering a period of 18 years and made every effort to minimize false positives by employing Def2. Presumably, the degree of misclassification in the administrative case definitions was fairly constant during the study period and would not affect the observed trends. Incidence rates of administrative OA are also influenced by the run-in years used to delete the prevalent cases. Therefore, a longer run-in period is recommended to control for overestimation in OA incidence rates. Our overall incidence rates for the year 2008/09 were based on a 17-year run-in time and were lower than those based on a 9-year run-in time by 12% and 10% according to Def1 and Def2, respectively. The overall rates for the year 2008/09 were also lower by 22-24% based on Def1 and a 5-year run-in time.

Among the elderly with OA and other chronic diseases, the former often receives less priority when they present themselves to a physician. The real incidence is therefore likely to be higher than that of administrative OA, but the undiagnosed proportion might be very low in health records observed for 18 years. Obesity and aging have long been recognized as two of the most important risk factors for incident OA (15,20,21). Although in Canada obesity is increasing, the obesity rate in the province of BC is significantly lower than the Canadian average (23,167); indeed, BC has experienced the smallest increase in the prevalence of obesity compared to other provinces for the period 2000 - 2011 (168). Therefore, in this province, the effect of obesity on the OA incidence rate is expected to be relatively low. Our age-standardized rates control for the effect of aging in the population. Besides age, sex, and obesity, changes in other factors such as diagnostic criteria, technology development, ICD coding, disease awareness, and access to health care system could potentially influence the incidence as well as the trends. Future studies focusing on changes to these risk factors over time may explain the pattern of OA incidence. In epidemiologic research, there is no simple way to estimate trends in OA incidence. However, such estimates are essential for policy makers and healthcare professionals to make efforts to improve the health of OA patients through detection, management, and public health programs (1,5,7,30,169). At this point, more studies are necessary using other provincial or regional data to compare and generalize these results at the national level.

In conclusion, this study has produced updated incidence rates and trends by examining administrative health records compiled over a longer period of time than heretofore, thus producing better estimates of OA incidence. Our data suggest that the incidence rate of physician

diagnosed OA in the administrative database differs due to different case definitions and the

number of observation years included. These province- specific data indicate that during the

period 2000/01 - 2008/09, the crude incidence of OA has increased among both men and women

and that the age-standardized incidence has increased only among men. However, the trend may

differ in other regions. More studies are needed to assess plausible scenarios for future OA

incidence and prevalence based on demographic trends and changes to the major risk factors.

CHAPTER 5 THE PREVALENCE OF OSTEOARTHRITIS IN BRITISH COLUMBIA, CANADA

5.1 Introduction

This chapter presents the prevalence rates of overall OA, in any joint, in the BC administrative database. The background of the prevalence of OA was presented in Chapter 2. In summary, the prevalence of OA was estimated previously. The prevalence of this condition in the general population depends on the joint sites studied, diagnostic method used, sex, age range, and the geographic region, aproximately 10 to 12 percent of the global population have OA (5–8). Using the BC administrative data, Kopec et al. (6) estimated that the overall prevalence rate of OA in any joint was 10.8% in the year of 2001 (6). Among international studies that reported the prevalence of radiographic, symptomatic, and self-reported hip, knee, and hand OA (3,8,44,45,93), the prevalence rates of OA were reported higher in the US studies.

In this chapter, we aimed to estimate the prevalence of OA using two case definitions discussed earlier. This study also updates the results presented in the previous study using the same database for a different period (6). This chapter organization is as follows. In Section 5.2, I describe the methods and statistical analyses used in this study. Results are presented in Section 5.3 and finally a detailed discussion is given in Section 5.4.

5.2 Methods

Data source

To estimate the prevalence, we used a random sample of 640,000 individuals who enrolled in the Medical Service Plan (MSP) as residents of BC, Canada, during the period April 1991 to March

2009. This administrative database includes information on date of birth, sex, physician billing

information for any health consultation, socio-economic status by area of residence, hospital

diagnoses, dates of hospital admissions, the 9th and 10th revisions of the ICD codes (ICD-9 and

ICD-10 respectively), and death records of all individuals registered in the MSP. MSP is a

publicly funded plan in which approximately 99% of BC residents are registered. The study was

approved by the Behavioral Research Ethics Board at the University of British Columbia,

Canada.

Administrative definition of OA

Administrative OA was defined in two ways using 9th and 10th revisions of the ICD codes (ICD-

9 and ICD-10 respectively): 1) at least one visit to a health professional or one hospital

admission with the ICD-9 code of 715 or the ICD-10 codes from M15 to M19 (AOA1), and 2) at

least two visits to health professionals in two years separated by at least one day or one hospital

admission with these codes (AOA2). For AOA2, the date of the second qualifying visit was used

to assign the diagnosis date.

Statistical Analysis

The point prevalence was defined as the number of OA cases in the random sample at a specified

time divided by the number of persons in the sample at that time. The numerator for prevalence

was the number of persons, within 5-year age-sex groups, who met the definition of OA between

April 1991, and March 2009, and were alive and registered with the MSP on March 31, 2009.

The denominator was the total number in the random sample within 5-year age-sex groups, who

were alive and registered with the MSP on March 31, 2009. All analyses were performed using SAS V.9.3 (SAS Institute, Cary, NC, USA).

5.3 Results

Prevalence

The point prevalence of OA in BC on March 31, 2009, for both case definitions at different age cutoff points are shown in Table 5.1. The overall prevalence of OA using AOA2 for all age groups combined was 10.8%; 9.1% in men and 12.5% in women. In AOA2, the mean age of men with OA was 66 years and the mean age of women with OA was 68 years. The overall prevalence of AOA1 was 19.6% (1.8 times the AOA2 prevalence), 16.8% in men and 22.3% in women. The prevalence of OA increased as age cut point increased and was 32.9% and 18.9% for AOA1 and AOA2 respectively, among adults age 45 years or older. In AOA1, the mean age of men and women with OA was 63 and 65 years, respectively. The age-sex specific prevalence rates are shown in Figure 5.1. In all age groups, women had higher rates than men. In the age group 45-49 years about 10% of the population had OA, and by age 70–74 years, approximately one-third of men and 40% of women had OA under case definition AOA1.

Table 5.1: The prevalence (per-cent) of osteoarthritis on March 31, 2009 at different age cut-off points based on 18 years of administrative health records drawn from British Columbia, Canada.

Age years	AOA1			AOA2		
	Men	Women	Total	Men	Women	Total
All	16.8	22.3	19.6	9.1	12.5	10.8
≥ 20	19.2	25.1	22.2	10.4	14.0	12.3
≥ 30	22.4	29.0	25.9	12.3	16.4	14.4
≥ 40	26.1	33.8	30.1	14.5	19.4	17.1
≥ 45	28.4	37.0	32.9	16.0	21.6	18.9
≥ 50	31.6	41.5	36.8	18.2	24.8	21.6

AOA1: One visit to a health professional or one hospital diagnosis; AOA2: Two visits to a health professional in two years or one hospital diagnosis.

Figure 5.1: The prevalence of osteoarthritis on March 31, 2009 obtained from British Columbia administrative health records during the period 1991-2009.
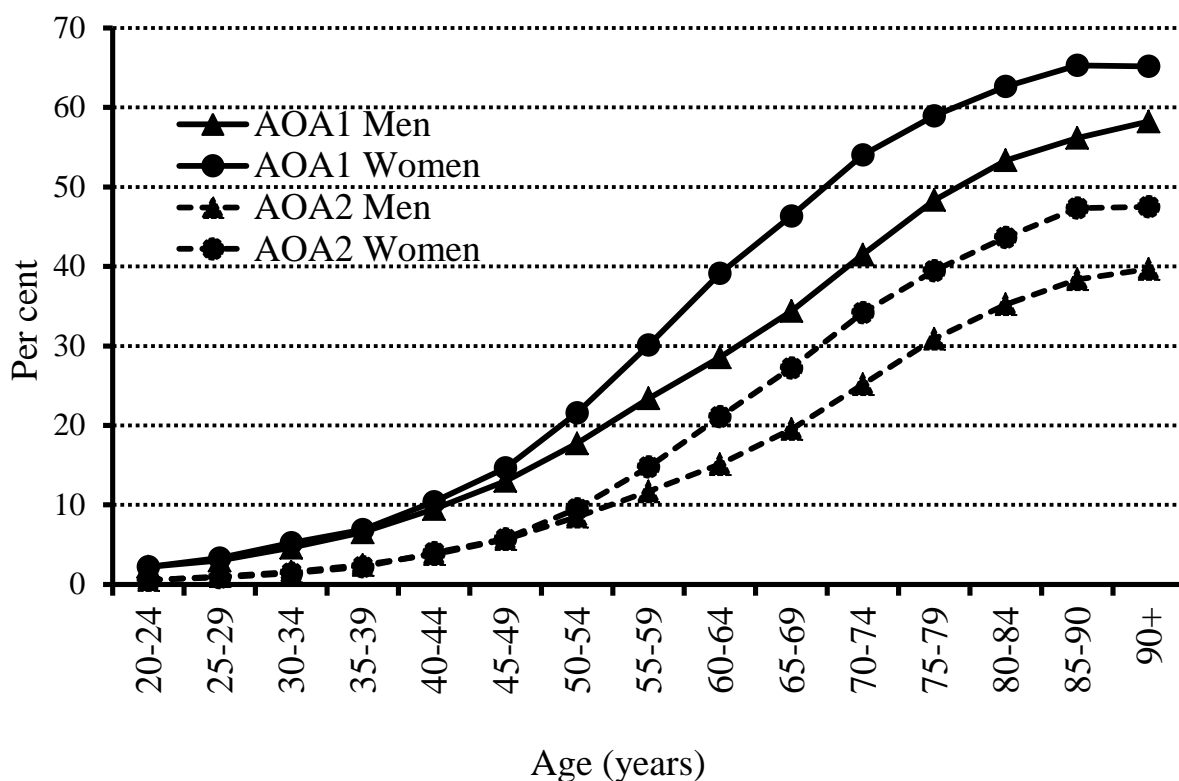
AOA1 includes at least one visit to a health professional or one hospital admission with a diagnostic code for osteoarthritis and AOA2 includes at least two visits to health professionals in two years or one hospital admission with a code for osteoarthritis.

5.4 Discussion

Based on the BC administrative health records over a period of 18 years, we have estimated the

prevalence of OA for two case definitions by age and sex. The overall prevalence of OA in the

case definition that included one physician's claim or one hospital admission was 19.6% (16.8%

in men and 22.3% in women). The observed overall prevalence was lower by 45% in the case

definition that included at least two physician's claims or one hospital admission.

In their 2007 study, Kopec et al. (6) reported that the prevalence rates of OA depend on the

number of years of health records, covered by the administrative records. As expected, compared

to the rates obtained in the earlier study based on 10 years of administrative health records (6),

we obtained approximately 82% higher rates based on 18 years of health records. From a

population survey in Norway, Grotle et al. (93) estimated that the overall prevalence of OA was

12.8%. Lawrence et al. (3) and Jordan et al. (44,45) estimated prevalence among adults aged 45

years or older. In these studies, the authors reported that the prevalence of symptomatic knee OA

was between 7-17%, hip OA was 10%, and hand OA was 11%; in which the prevalence of

radiographic OA was higher than the symptomatic OA. Our overall prevalence rates were 32.9%

and 18.9% in two case definitions among adults 45 years or older. Our estimates were slightly

different from these earlier studies due to different population and case identification methods

used. In our study, the male-to-female prevalence ratios were 0.75 and 0.73 in two case

definitions. The male-to-female prevalence ratio was 0.75 for hip OA and 0.72 for knee OA in

Jordan et al.'s (44,45) study, and 0.71 for overall OA in Grotle et al.'s (93) study.

There are limitations to the present study that should be acknowledged. Our province specific

rates may not be representative to the rates in the entire Canadian population. The case definition

using ICD-9 and ICD-10 diagnostic codes is a limitation, since both false negatives and false positives may occur due to misdiagnosis or incorrect recording in the administrative forms. Earlier studies compared administrative OA diagnoses with the self-reported OA (25) and medical records (24). Lix et al. (25) examined the administrative OA diagnosis from Manitoba, Canada, comparing with the self-reported CCHS data. The authors obtained a sensitivity of 42.6% and a specificity of 88.1% using two years of data and the case definition of at least two physician's claims or one hospital separation. Based on 2 years of administrative records, Harrold et al. (24) estimated the positive predictive value of administratively coded OA in the general population at 62%. Prevalence rates are also influenced by the number of years of health records included in the administrative data. Therefore, to control for underestimation in the prevalence a longer period of health records is recommended. We have used 18 years of data and have tried to minimize false positives by employing AOA2. Besides these limitations, an important strength of our study is that it covers a large and representative sample from BC. OA cases in this study were physician-diagnosed rather than self-reported conditions. A further strength is that we were able to observe each individual's medical records over a period of 18-year.

In conclusion, updated prevalence rates were obtained by examining administrative health records compiled over a period of 18 years. Our findings suggest that the prevalence rate of physician diagnosed OA in the administrative database differs due to different case definitions. Prevalence rates may differ across health regions. Thus rates from a different administrative database are needed to generalize these results.

CHAPTER 6 VALIDATION OF OSTEOARTHRITIS DIAGNOSIS IN THE ADMINISTRATIVE DATABASE[2]

6.1 Introduction

This chapter describes the validity of administrative OA diagnosis in any joint in the BC administrative database. Detailed background of the validation issues were presented previously in Chapter 2. In summary, administrative case definitions of OA has been validated in previous studies against self-reported population surveys (25) and against medical records (24). These studies did not recruit patients for clinical assessments such as joint examination, x-rays, and MRI to identify OA and considered 2-5 years of administrative records.

The objective of this study was to examine the validity of administrative data, including hospital separations and physician billing claims to define OA. Therefore, my primary objective was to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios of the administrative definitions of OA. The accuracy of OA case definitions was assessed using the gold standards of x-rays, MRI, self-reporting, and American College of Rheumatology (ACR) clinical criteria for OA diagnoses. Evaluating the validity of administrative data is an important step in developing chronic disease surveillance systems for OA. These data may be useful in further OA research using administrative databases.

In Section 6.2, we describe the methods and statistical analysis used in this study. Results are presented in Section 6.3 and finally a detailed discussion is given in Section 6.4. In the

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[2] A version of this chapter is under review in the Journal of Rheumatology. Authors are Rahman MM, Kopec JA, Goldsmith CH, Anis AH, and Cibere J. The title of the manuscript is "Validation of administrative case definitions for osteoarthritis using a clinical and radiological cohort".

discussion section, we compare the findings with published data and discuss the strengths and limitations of the study.

6.2 Methods

Data source

A cohort of 255 subjects with early knee OA was recruited through population random sampling from Vancouver, BC, during the period August 2002 to February 2005. The subjects met inclusion criteria if they were between 40–79 years of age and had experienced pain, aching or discomfort in or around the knee on most days of the month or at any time in the past 12 months. Subjects with inflammatory arthritis or fibromyalgia, knee arthroplasty, a history of knee surgery/ injury within the past 6 months, or knee pain referred from the hip or back, and inability to undergo MRI were excluded. From the greater Vancouver telephone directory, 5,231 English-speaking persons were randomly contacted, of whom 3,269 (62.5%) agreed to participate in the survey. Of the 3,269 subjects, 91.9% were ineligible due to the age restriction and other exclusion criteria. Of the remaining 265 subjects, 10 were excluded due to missed appointments and for other reasons. The study sample recruitment procedure has been described elsewhere (163). Lastly, 255 subjects underwent comprehensive clinical assessment, standardized joint examination, x-rays, and MRI to identify knee OA. Since both MRI and radiograph-based diagnoses were included in the study, subjects with knee arthroplasty or a history of knee surgery/injury were excluded. Of the 255 subjects, clinical data on 171 (67%) were linked with the administrative health records for the period 1991-2004 through personal health numbers, because only these subjects provided written consent to do so. Both the BC Ministry of Health and Population Data BC, the agency that facilitates administrative data acquisition in the

province, approved access to and use of the data for this study. This administrative database includes information on date of birth, sex, physician billing information for any health consultation, socio-economic status by area of residence, hospital diagnoses, dates of hospital admissions, the 9th and 10th revisions of the ICD codes (ICD-9 and ICD-10 respectively), and death records of all individuals registered in the Medical Service Plan (MSP) of BC. MSP is a publicly funded health care plan and we observed that approximately 99% of BC residents are registered. The study was approved by the Clinical Research Ethics Board at the University of British Columbia, Canada.

Administrative definition of OA

Administrative OA was defined in two ways using ICD-9 and ICD-10 codes referred to as AOA1 and AOA2. AOA1 required at least one visit to a health professional or one hospital admission with the ICD-9 code of 715 or the ICD-10 codes from M15 to M19, and AOA2 required at least two visits to health professionals in two years separated by at least one day or one hospital admission with these codes. For AOA2, the date of the second qualifying visit was used to assign the diagnosis date. These ICD codes include symptomatic and radiographic OA in any joint except the spine. The most commonly used pain medications for OA treatment are acetaminophen and non-steroidal anti-inflammatory drugs (30,126). Often these medications are available over the counter and require no prescriptions. Thus, it is not possible to include the history of pain medication use in OA case definitions.

Knee, hand and hip OA Assessment

Knee OA was assessed with a comprehensive questionnaire which included duration of knee pain, frequency of pain (number of days over the past month), and pain location using a knee diagram (170). A standardized knee examination was performed by a rheumatologist (171). The ACR clinical criteria for knee OA (96) include pain in the knee and any three of the following: 1) over 50 years of age, 2) less than 30 minutes of morning stiffness, 3) crepitus on active motion, 4) bony tenderness, 5) bony enlargement, and 6) no palpable warmth. The presence of hand OA was determined by using ACR criteria for hand OA, which included pain, aching, or stiffness in the hand and any three of the following conditions: 1) hard tissue enlargement of two or more of the following joints: 2nd and 3rd distal interphalangeal, the 2nd and 3rd proximal inerphalangeal, and the 1st carpometacarpal joints of both hands; 2) hard tissue enlargement of 2 or more distal interphalangeal joints; 3) less than three swollen metacarpophalageal joints; 4) deformity of 2 or more joints listed in (1) (98). Although ACR criteria for hip OA includes pain in the hip and any two of the following: 1) ESR < 20 mm/ hour, 2) radiographic femoral or acetabular osteophytes, and 3) radiographic joint space narrowing (97), only hip pain was assessed in our study.

Radiographic K-L grade

Knee radiography was completed within a month of the clinical assessment. Details on x-ray procedures have been described previously (163,172). X-rays were scored using the K-L 0-4 grading system (87) independently by 2 readers who were blinded to the clinical and MRI information. The intra-class correlation coefficient was 0.79 and the differences in readings were adjudicated by consensus readings by the 2 readers. Subjects were classified as having radiographic OA if their K-L grade was greater than or equal to 2.

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MRI cartilage score

MRI for the most painful knee was performed within a month of clinical assessment. Detailed information regarding how MRI was performed has been described previously (163). Briefly, six joint areas were assessed, including the medial and lateral tibial plateaux and femoral condyles, patella, and trochlear groove. Cartilage was graded on a semi-quantitative scale of 0–4 based on the following definitions: 0 = normal, 1 = abnormal signal without a cartilage contour defect, 2 = contour defect of less than 50% cartilage thickness, 3 = contour defect of 50–99% cartilage thickness, and 4 = 100% cartilage contour defect with subjacent bone signal abnormality (91,92). The MRIs were read by a single reader, who was blinded to the radiographic and clinical information. The intra-rater reliability of the cartilage readings was high, varying from 0.84 to 1.0 for different cartilage surfaces. Based on the MRI cartilage scores, subjects were classified as having knee OA if the score was greater than or equal to 2.

OA by self-report

In the baseline questionnaire, knee OA was assessed by asking two questions. 1) "Has a doctor ever told you that you have osteoarthritis (also called degenerative or wear-and-tear arthritis) in your right knee?", and 2) "Has a doctor ever told you that you have osteoarthritis (also called degenerative or wear-and-tear arthritis) in your left knee?"

Reference standard

For the cohort, knee OA was assessed based on the above four measurements. In addition, hand and hip OA were assessed using the ACR clinical criteria and the self-reported hip pain, respectively. Based on the knee, hand, and hip OA assessments, we defined four reference

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standards: RS1, RS2, RS3, and RS4. RS1 included assessments of knee and hand OA based on the ACR clinical criteria and hip OA based on self-reported hip pain. RS2 included assessments of knee, hand, and hip OA based on K-L grade, ACR clinical criteria, and self-reported hip pain, respectively. RS3 included assessments of knee, hand, and hip OA based on MRI cartilage score, ACR clinical criteria, and self-reported hip pain, respectively. RS4 included assessments of knee, hand, and hip OA based on self-reports, ACR clinical criteria, and self-reported hip pain, respectively. The same measurements for hand and hip OA were consistently included in the four reference standards.

Statistical Analysis

Baseline characteristics of the cohort were age, sex, body mass index (BMI) (kg/meter^2), hip pain, symptomatic hand OA, and pain medication used. Pain in the hip joints was assessed by the question: "In the following homunculus diagram each circle represents a joint. Please mark each joint where you have experienced pain or discomfort over the past 12 months." We counted subjects if they marked the hip joints in the homunculus diagram. These characteristics were determined separately for men and women. We calculated the sensitivity, specificity, PPV, and NPV, for each case definition according to four reference standards. The 95% confidence intervals (CIs) were calculated for these statistics. For more detail about these measures, please refer to Rothman et al. (164). In addition, we have calculated likelihood ratios (LR+ and LR-) and their 95% CIs. Where LR+ = positive likelihood ratio = sensitivity/ (1-specificity), and LR- = negative likelihood ratio = (1-sensitivity)/ specificity. All analyses were performed using SAS V.9.3 (SAS Institute, Cary, NC, USA).

6.3 Results

Characteristics of 171 subjects by sex are presented in Table 6.1. The mean age of the subjects

was 59 years, and 51% were men. The range of BMI was from 19 to 43 and men were more

overweight and obese than women (p-value = 0.02). Hip pain and hand OA were more common

in women than in men (p-value < 0.01). Statistically significant differences between men and

women were observed for the percentage diagnosed with OA by each of the four reference

standards except for RS3. Among the four different knee OA measurements, MRI detected the

highest percentages of OA (91.7% in women and 88.5% in men) and x-rays detected the lowest

percentages of OA (42.9% in women and 44.9% in men).

The validation results of two administrative OA definitions compared to the four reference

standards are presented in Table 6.2. The sensitivity of AOA1 and AOA2 varied from 47-57%

and from 21- 26%, respectively. Higher sensitivities and NPVs were observed in AOA1 for all

reference standards compared to AOA2. The highest sensitivity (95% CI) was 57% (48-66%) for

AOA1 when the reference standard included self-reported physician-diagnosed knee OA and the

lowest sensitivity (95% CI) was 21% (15-29%) for AOA2 when the reference standard included

MRI score for the knee OA. The specificity varied from 75-87% for AOA1 and from 91-100%

for AOA2. The highest specificity (95% CI) was 100% (70-100%) for AOA2 when the reference

standard included MRI of the knee OA and the lowest specificity (95% CI) was 75% (43-93%)

for AOA1 when the reference standard included MRI score for knee OA. PPVs varied from 82-

96% for AOA1 and from 85-100% for AOA2. The lowest NPV (95% CI) was 9% (5-15%) for

AOA2 when the reference standard included MRI score for knee OA and the highest NPV (95%

CI) was 45% (34-55%) for AOA1 when the reference standard included ACR criteria for knee

OA. LR+ was higher than 5 in AOA2 for the reference standards RS3 and RS4, and therefore

AOA2 may be useful in ruling in OA. On the other hand, values of LR- were between 0.5 and

0.8. Therefore, these definitions may not be very useful to ruling out OA (173).

Table 6.1: Percentage of knee, hand, and hip osteoarthritis (OA) by each reference standard, knee OA assessment, and other baseline characteristics of 171 subjects who underwent comprehensive clinical assessment for knee OA by sex.

Characteristics	Women % (n = 84)	Men % (n = 87)	p-value
Reference standards			
RS1	77.4	57.5	< 0.01
RS2	82.1	56.3	< 0.01
RS3	96.4	89.7	0.08
RS4	84.5	62.1	< 0.01
Knee OA assessment			
Clinical ACR criteria	48.8	40.2	0.26
K-L grade ≥ 2	42.9	44.9	0.79
MRI cartilage score ≥ 2	91.7	88.5	0.48
Self-report	50.0	48.3	0.82
Other characteristics			
Age in years			0.44
40-49	14.3	21.8	
50-64	51.2	46.0	
65-79	34.5	32.2	
Body Mass Index (kg/m^2)			0.02
18.5-24.9	46.3	28.7	
25.0-29.9	27.4	46.0	
30+	26.2	25.3	
Hip pain	42.9	18.4	< 0.01
Symptomatic hand OA	43.4	18.4	< 0.01

RS1, RS2, RS3, and RS4 are four reference standards based on knee, hand, and hip OA as described in the Methods section.

K-L = Kellgren-Lawrence, self-report = self-reported physician diagnosed knee OA, MRI = magnetic resonance imaging, and ACR = American College of Rheumatology.

Table 6.2: Validation results with the 95% confidence intervals of administrative definition of osteoarthritis using four reference standards that include knee, hand, and hip OA.

Reference Standard	Administrative Osteoarthritis	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	LR+ (95% CI)	LR- (95% CI)
RS1	AOA1	55 (45-64)	75 (61-85)	82 (71-89)	45 (34-55)	2.2 (1.4-3.6)	0.6 (0.5-0.8)
	AOA2	25 (17-34)	91 (80-97)	85 (68-94)	37 (29-46)	2.8 (1.2-6.9)	0.8 (0.7-0.9)
RS2	AOA1	55 (46-64)	77 (63-87)	84 (74-91)	44 (34-54)	2.4 (1.4-4.1)	0.6 (0.5-0.7)
	AOA2	26 (18-35)	94 (83-99)	91 (75-98)	36 (29-45)	4.6 (1.5-14.5)	0.8 (0.7-0.9)
RS3	AOA1	47 (39-55)	75 (43-93)	96 (88-99)	10 (5-18)	1.9 (0.7-5.0)	0.7 (0.5-1.0)
	AOA2	21 (15-29)	100 (70-100)	100 (87-100)	9 (5-15)	> 21 (21-∞)	0.8 (0.7-0.9)
RS4	AOA1	57 (48-66)	87 (73-95)	92 (83-97)	42 (33-53)	4.4 (2.0-9.3)	0.5 (0.4-0.6)
	AOA2	26(18-34)	96 (84-99)	94 (79-99)	32 (24-41)	6.5 (1.5-23.6)	0.8 (0.7-0.9)

AOA1 includes at least one visit to a health professional or one hospital admission for osteoarthritis and AOA2 includes at least two visits to health professionals in two years or one hospital admission for osteoarthritis. RS1, RS2, RS3, and RS4 are four reference standards based on knee, hand, and hip OA as described in the Methods section.

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio = sensitivity/ (1-specificity); LR-: negative likelihood ratio = (1-sensitivity)/ specificity.

6.4 Discussion

Based on the BC administrative health records, we have assessed the validity of two case definitions of OA using four reference standards. The reference standards included radiographic K-L grade, MRI cartilage scores, self-reports, and the ACR clinical criteria for the knee OA assessments, the ACR clinical criteria for the hand OA assessments, and self-reported hip pain records for the hip OA assessments. Of the two administrative definitions, AOA1 had the higher sensitivity and NPV whereas AOA2 had the higher specificity and PPV. Validity measures were similar among the four reference standards in each case definition, while both case definitions of OA yielded more than 82% PPV at about 70% prevalence.

Our validation results are comparable with those obtained in Lix et al.'s (25) study in which self-reported survey data were used as a reference standard. Using two years of data and the definition of two physician claims or one hospital separation, the authors obtained a sensitivity of 42.6% and a specificity of 88.1%. For the definition based on one physician claim, they obtained a higher sensitivity but a lower specificity, which is consistent with our results. The administrative health records may include some individuals whose OA has gone undiagnosed during the observation period. This could potentially contribute to the lower-than-expected sensitivities in both case definitions. After examining the medical history of OA cases over a period of two years, Harrold et al. (24) obtained a PPV of 62% for administrative OA diagnoses where the prevalence was 8.7%. The reason we obtained higher PPVs was that we used 13 years of administrative records and the prevalence of OA was higher in the cohort. In our cohort the majority of the subjects had pre-radiographic disease (K-L < 2); we observed that 90% of these symptomatic subjects had knee OA based on MRI cartilage assessment. In contrast to x-rays,

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MRI can detect pre-radiographic as well as radiographic OA in the knee and other joints (174,175); consequently, higher specificity and PPV were obtained when MRI knee assessment was used as the reference standard. In validation studies, PPV and NPV depend on the prevalence and severity of the disease. Thus, in addition, we have calculated positive and negative likelihood ratios, which are independent of the prevalence. On the basis of likelihood ratios, AOA2 might be useful in ruling in OA.

The limitations of the present study need to be acknowledged. First, we received written consent from 171 (67%) subjects to link their clinical data with the administrative records, which reduced the sample size. However, this reduction did not change the sample characteristics compared to those of the entire cohort (163) and therefore, no degree of generalizability was lost. Second, some of these subjects were in the early stage of OA development. The recruitment period for subjects was 2002-2005, and their administrative histories were linked from 1991 to 2004. In an ideal situation, both clinical and administrative diagnoses should have been performed in the same calendar year. However, among the elderly with OA and other chronic diseases, the former often receives lower priority when they are assessed by a physician. Therefore, the number of OA cases based on 2-3 years of administrative records is expected to be lower than the actual number of cases. To minimize the number of undiagnosed OA cases we observed the medical history of these subjects from 1991 to 2004. We did not include administrative records after the clinical assessment to reduce false positives. Third, we used hip pain as a proxy variable for hip OA in the four reference standards. Studies have shown that hip pain is considered to be the main feature of hip OA (176,177). The knee, hip, and hand are the most commonly affected joints (3,8,44,45,93) and studies have shown that individuals with OA in one joint are more likely to

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have the disease in other joints (178). By including hip OA cases according to hip pain, we

added 1-11% hip OA cases to the reference standards, which should not over-represent the actual

hip OA cases. Fourth, OA in other locations, such as the foot, elbow, jaw, and shoulder, were not

measured in the reference standards. This is unlikely to have a substantial effect on the validation

results since the prevalence rates of OA in these locations are relatively low.

The strengths of this study include the use of a representative clinical sample linked to

administrative data. Our study featured a population-based cohort that included subjects with

pre-radiographic as well as advanced radiographic knee OA. Administrative databases are

frequently used in conducting health research for OA. However, there are few validation studies

of administrative OA diagnosis. The primary objective of selecting this study cohort was to

assess MRI, x-rays, and symptomatic-based measures to detect early knee OA. In addition,

symptomatic and self-reported data were collected for hand and hip OA, which enhances the

present study. We compared two administrative OA definitions to the four reference standards.

To our knowledge, this is the first study, to compare administrative case definitions and MRI-

detected cartilage-based OA assessments. MRI is more sensitive than x-ray in detecting early

changes in the cartilage and subchondral bone composition that are characteristic of OA. It is

increasingly considered as a gold standard for OA diagnosis in clinical research (174,175).

Population-based administrative data have great potential for facilitating investigations of OA

occurrence as well as OA co-morbidity and outcome research. However, the fundamental

question to be addressed prior to using such data is, whether the data are valid for such purposes.

Our study addressed this question by comparing two case definitions with four reference

standards. The next question to be addressed is which case definition should be applied for defining OA? It is noteworthy that the observed PPV in both definitions were very high because the prevalence of OA was more than 70% based on the reference standards, whereas in the general population, the prevalence of OA is 10-20%. The sensitivity of the definition that included one physician's claim or hospital admission was 47-57%, and the specificity was 75-87%. This suggests that potential over-reporting might be a serious concern in estimating the prevalence using this definition. On the other hand, the sensitivity of the definition that included two physician's claims in two years or one hospital admission was 21-26%, and the specificity was 91-100%. This suggests that potential over-reporting might not be a concern. However, the prevalence might be under-reported using the latter definition if the true prevalence is more than 12%. In addition, the observed specificity and the PPV in the latter case definition was higher than those in the former case definition, thus producing fewer false positives cases. This definition of two physician's claims in two years or one hospital admission would therefore be more appropriate for OA epidemiology and for cohort studies assessing the effect of OA on other health conditions and overall mortality.

In conclusion, the validity of administrative OA diagnoses depends on the definitions and reference standards. On the basis of the evidence, we concluded that in descriptive epidemiology, one physician's claim or one hospital diagnosis would be appropriate for defining OA as it reduces underestimation due to false negatives. However, in the case of outcome research where avoiding false positives is critical, at least two physician claims within two years or one hospital admission should likely be applied. Despite several limitations, we have validated two administrative case definitions wherein clinical and symptomatic diagnoses of knee, hand, and

hip OA were included in the reference standards. Future validation studies, based on clinical diagnoses of all possible joints affected by OA, are needed. As the validation results may differ across administrative regions, further studies focusing on such regions are also needed to generalize our results.

CHAPTER 7 THE RELATIONSHIP BETWEEN OSTEOARTHRITIS AND CARDIOVASCULAR DISEASE: A CROSS-SECTIONAL STUDY[3]

7.1 Introduction

This chapter examines the possible association between OA and prevalent heart disease and other cardiovascular outcomes using the Canadian Community Health Survey (CCHS) data. The background of the possible link between OA and CVD was presented previously. In summary, the relationship between OA and CVD has not been studied extensively in population based studies. However, there is some evidence that OA patients have a higher rate of CVD and its risk factors than individuals without OA (26,94,142). There is also some evidence that OA patients are at an increased risk of cardiovascular mortality (154,155).

The large and nationally representative CCHS samples provide an ideal opportunity to examine the possible association between OA and heart disease and other cardiovascular outcomes. The main objective of this cross-sectional study was to examine the association between OA and CVD using the first 3 cycles of the CCHS data. More clearly, our objective was to examine the association of OA with self-reported heart disease, MI, angina, CHF, and stroke. I hypothesize that OA is associated with CVD and the association is due to or at least partially to, immobility, chronic inflammation, muscle weakness, NSAIDs use, and other lifestyle changes due to OA. Given that OA is a common condition among the elderly, a better understanding of the relationship between OA and CVD could help further investigation of potential biological and

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behavioral mechanism underlying this association and also inform future OA management strategies.

This chapter is organized as follows. Section 7.2 describes the data, methods, and statistical analysis used in this study. Results are presented in Section 7.3. Detailed discussion such as comparison of the findings with the past studies, the strengths and limitations of the study, and conclusion is given in Section 7.4.

7.2 Methodology

Data Source and Study Population

This study used data from the CCHS cycles 1.1, 2.1, and 3.1 conducted in years 2000/01, 2002/03, and 2004/05 respectively. Performed by Statistics Canada, CCHS contains nationally representative data on health determinants, health status, and health system utilization. This cross-sectional survey used a multistage stratified cluster probability sampling in which a dwelling was the final sampling unit. The survey sample was stratified by province/territory and urban versus rural regions within each province/territory. Three sampling frames were used to select the sample of households: 48-49% of the sample came from an area frame, 50% came from a list frame of telephone numbers and 1-2% came from a Random Digit Dialing sampling frame. Persons in the households selected from the telephone list frame were interviewed from centralized call centers. Those selected from the area frame were interviewed face-to-face by decentralized field interviewers. In some situations, field interviewers completed some interviews or part of an interview by telephone. Sampling was designed to represent 98% of the Canadian population aged 12 years or more who lived in private dwellings in the ten provinces

and the three territories. A detailed description of the survey design, sample frame, and

interviewing procedures has been provided elsewhere (162). In all three CCHS cycles, Statistics

Canada included the type of arthritis as a separate question in all jurisdictions. Due to very low

prevalence of OA and CVD among individuals aged 12-19 years, we decided to exclude them

from the study. The 3 cycles of CCHS used different and non-overlapping samples. There were

113,323 respondents in the 2000/2001 survey, 115,548 respondents in the 2002/03 survey, and

115,915 respondents in the 2004/05 survey, respectively, aged 20 years and older.

Concepts and Measures

OA and Cardiovascular Disease

The main independent variable in this study was OA and the primary outcome was heart disease.

Specific cardiovascular conditions such as MI, angina, CHF, or stroke were secondary outcomes

in this study. In the CCHS data, OA was assessed by asking two questions. The first question

was "Now I'd like to ask about certain chronic health conditions that have lasted 6 months or

more and have been diagnosed by a health professional. Do you have arthritis or rheumatism?"

The second question was "What type of arthritis?" and the four response options were

"Rheumatoid arthritis, osteoarthritis, other, and do not know". Since the second question is

restricted to only arthritis patients, over reporting of OA is minimized. In the sample, we

observed that out of total arthritis cases, 81% reported that they had OA. The prevalence of heart

disease were assessed by the following question "Now I'd like to ask about certain chronic

health conditions that have lasted 6 months or more and have been diagnosed by a health

professional. Do you have heart disease?" In CCHS cycles 1.1 and 2.1, persons reporting heart

disease were asked specific questions about MI, angina, CHF, and stroke: "Have you ever had a

heart attack (damage to the heart muscle)?", "Do you currently have angina (chest pain, chest tightness)?", and "Do you currently have congestive heart failure (inadequate heart-beat, fluid build-up in the lungs or legs)?". In addition, CCHS includes the question of "Do you suffer from the effects of a stroke?" These specific questions provide the data to perform disease specific analyses using each of these four health conditions as outcomes using CCHS cycles 1.1 and 2.1.

Covariates and Confounders

We have included demographic, socio-economic, and health behaviour variables to serve as control variables in regression modeling. Selection of these variables was based on previous research (133). The socio-demographic variables were age, sex, body mass index (BMI), education, and household income. Health behaviours included physical activity, smoking status, fruit and vegetable consumption, and pain medication use. Chronic health conditions such as chronic obstructive pulmonary disease (COPD), diabetes, and hypertension were included as covariates. Cigarette smoking was a derived variable which was measured using 18 different questions regarding the frequency and length of time of smoking. We categorized the smoking variable as current smoker, former smoker, and non-smoker. BMI was expressed in kg/meter^2 and was calculated from self-reported heights and weights. The classification was made based on the following four sub-groups: underweight (BMI < 18.5), normal ($18.5 \leq$ BMI < 24.9), overweight ($25.0 \leq$ BMI < 29.9), and obese (BMI $\geq$ 30.0). Physical activity was derived from the self-reported level of activity and the amount of time spent on physical activities for three months prior to the survey. These responses were categorized as being active, moderately active, or inactive. The level of education with four categories, such as less than secondary school, secondary school graduate, some post-secondary education, post-secondary graduate, and

household income level were considered as SES characteristics. Daily consumption of fruit and vegetables was expressed into three categories such as less than 3 servings per day, 4-6 servings per day, and more than 6 servings per day. Pain medication use was assessed by asking two questions: 1) "In the past month, did you take pain relievers such as aspirin or Tylenol (including arthritis medicine and anti-inflammatories)?" and 2) "In the past month, did you take codeine, Demerol or morphine?" Among all participants, BMI was missing for 13%, education status was missing for 2.5%, income was missing for 21%, and fruit & vegetable consumption was missing for 17.5% of the respondents. We imputed missing BMI values using linear regression on age and sex for complete cases, and the missing values for other categorical variables were imputed by taking the modal values after adjusting for age and sex (179).

Statistical Analysis

In this cross-sectional study, to control for age and sex in the OA and non-OA individuals in the sample, we selected 1 non-OA individual for each OA patient by matching age category, sex, and CCHS cycles. Initially we attempted to select 3 non-OA individuals for each OA case by matching for age, sex, and CCHS cycles. However, we observed high prevalence of OA in the older age groups (ie., more than 40% among individuals age > 70 years have OA) and therefore, it was not possible to match exactly 3 non-OA individuals in the older age groups. Based on 1:3 approximately matched samples we repeated the entire analyses as part of a sensitivity analysis. Frequency and percentages were calculated for all variables prior to modeling the associations between OA and CVD. Unadjusted effects of OA on CVD were calculated using logistic regression where age and sex were included in the models. Multivariable logistic regression models were used to assess the association between OA and heart disease, MI, angina, CHF, and

stroke after controlling for the potential confounding variables. All statistical analyses were performed using SAS V 9.3 (SAS Institute, Cary, NC, USA). Statistics Canada produced sampling weights for each of the study participants of CCHS. All estimates were weighted to approximate the distribution of demographic variables in the overall Canadian population. Since CCHS uses a complex sampling design, the confidence intervals of the estimates were adjusted using a design effect of 2 (162,165).

7.3 Results

The sample characteristics of the OA and non-OA respondents who were included in the analyses are presented in Table 7.1. The demographic characteristics, social status, and health conditions were compared between 40,817 OA cases and matched non-OA respondents. All these comparisons were statistically significant with p-values < 0.01. The mean age of OA cases was 66 years and 71.6 percent were women. In the 1:1 matched samples we observed that OA group were significantly more overweight and obese, had more diabetes, hypertension, and COPD, compared to non-OA respondents. The percentage of participants who reported being physically active was 16.9% in OA vs. 18.6% in non-OA and the percentage of being moderately active was similar in both groups. OA cases used more pain medications than non-OA individuals. The percentage of non-smokers was lower in the OA group. Percentages in the income, education, and fruit and vegetables categories were slightly but significantly different among OA and non-OA respondents.

Table 7.1: Sample characteristics (per-cent) of osteoarthritis (OA) and matched non-OA individuals by exposure status.

Characteristics	OA cases (n = 40,817)	1:1 matched non-OA (n=40,817)	1:3 matched non-OA (n=109,450)
Age years			
20-39	4.6	4.5	5.1
40-49	9.1	9.0	10.1
50-59	19.4	19.6	21.8
60-69	25.4	25.3	26.3
70-79	24.7	25.0	22.0
≥ 80	16.9	16.6	14.8
Women	71.6	71.6	68.2
Body Mass Index kg/m^2			
< 18.5	1.7	1.9	1.8
18.5-24.9	30.7	35.9	36.4
25-29.9	30.5	29.7	30.8
≥ 30	20.5	14.3	14.6
Missing	16.6	18.2	16.4
COPD	3.0	2.0	2.0
Diabetes	11.5	9.9	9.4
Hypertension	37.6	32.1	30.4
Physical Activity			
Active	16.9	18.6	19.0
Moderately Active	22.4	22.9	23.3
Inactive	60.6	58.5	57.7
Pain medication use	12.9	10.5	10.5
Smoking			
Currently smoke	19.7	19.0	19.8
Former smoker	49.6	46.6	47.2
Non smoker	30.7	34.4	33.0
Fruit and Vegetables serving daily			
0-3	16.1	15.6	15.3
4-6	43.1	43.7	43.6
6+	23.7	22.3	22.6
Not stated	17.1	18.5	18.5
Income			
< 29,999	32.4	29.1	27.4
30,000-49,999	21.7	20.6	20.6
50,000-79,999	17.1	16.9	17.7
$\geq 80,000$	11.8	13.3	14.4
Not stated	17.0	20.2	19.9
Education			
Less than secondary	35.4	36.4	34.6
Secondary graduate	15.4	15.9	16.2
some post-secondary	6.1	5.3	5.5
Post-secondary graduation	41.4	40.0	41.3
Not stated	1.8	2.4	2.4

The distribution of all variables listed was significantly different between OA and non-OA subjects (p-value < 0.01). COPD stands for chronic obstructive pulmonary disease.

Both unadjusted and adjusted effects of OA on the prevalence of heart disease for men, women, and total are presented in Table 7.2. In the multivariable model, those who had OA exhibited increased odds of prevalent heart disease (OR = 1.45, 95% CI 1.36, 1.54) compared to non-OA individuals after controlling for age, sex, income, education, BMI, physical activity, smoking, fruit and vegetables consumptions, pain medication use, COPD, hypertension, and diabetes. We observed a borderline significant interaction between sex and OA (p-value = 0.058) in the multivariable model and therefore we decided to perform separate analysis for men and women. ORs (95% CI) for heart disease were 1.35 (1.21, 1.50) and 1.50 (1.39, 1.64) among men and women with OA respectively. Income, education, BMI, physical activity, smoking, medication use, COPD, hypertension, and diabetes were associated with heart disease as expected.

Multivariable logistic regression models were fitted to estimate the effects of OA on the prevalence of MI, angina, CHF, and stroke for the total sample and separately for men and women and are presented in Table 7.3. OA was significantly associated with MI, angina, and CHF (OR (95% CI), 1.28 (1.15, 1.44), 1.83 (1.62, 2.06), and 1.72 (1.46, 2.01) respectively) compared with subjects without OA. In sex-specific analyses, the OR was the highest for angina (OR (95% CI), 1.76 (1.43, 2.17) and 1.85 (1.59, 2.14) for men and women respectively), followed by CHF. OA showed significantly increased OR for MI among women only but did not show a significant association with stroke. In the 1:3 matched OA vs. non-OA samples, we observed similar ORs, but with narrower CIs. OR (95% CI) of overall heart disease was 1.44 (1.36, 1.51) among men, and 1.46 (1.37, 1.56) among women in 1:3 matched samples (data not shown).

Table 7.2: Odds ratios (OR) and the 95% confidence intervals (CI) of heart disease for

osteoarthritis and non-osteoarthritis 1:1 matched samples by age and sex.

Variables	Levels	Overall OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)
Osteoarthritis Unadjusted	Yes	1.54 (1.45, 1.64)	1.47 (1.33, 1.63)	1.59 (1.47, 1.72)
Osteoarthritis Adjusted	Yes	1.45 (1.36, 1.54)	1.35 (1.21, 1.50)	1.51 (1.39, 1.64)
Age years	20-39	Reference	Reference	Reference
	40-49	2.24 (1.50, 3.33)	1.67 (0.93, 3.02)	2.62 (1.52, 4.52)
	50-59	4.28 (2.95, 6.21)	5.58 (3.27, 9.52)	3.41 (2.03, 5.72)
	60-69	7.19 (4.97, 10.41)	8.47 (4.98, 14.41)	6.09 (3.64, 10.19)
	70-79	11.87 (8.19, 17.20)	13.29 (7.79, 22.69)	10.28 (6.14, 17.21)
	≥ 80	19.33 (13.30, 28.11)	18.10 (10.51, 31.18)	18.35 (10.92, 30.82)
Income	< 30,000	Reference	Reference	Reference
	30,000-50,000	0.93 (0.85, 1.01)	0.90 (0.78, 1.04)	0.94 (0.85, 1.04)
	50,000-80,000	0.82 (0.74, 0.90)	0.89 (0.76, 1.04)	0.77 (0.68, 0.87)
	$\geq 80,000$	0.69 (0.62, 0.78)	0.65 (0.55, 0.78)	0.69 (0.59, 0.81)
Education	Elementary	Reference	Reference	Reference
	Secondary	0.87 (0.79, 0.96)	0.97 (0.81, 1.15)	0.84 (0.74, 0.94)
	Some post-secondary	0.91 (0.78, 1.06)	0.98 (0.77, 1.26)	0.88 (0.73, 1.07)
	Graduation	0.96 (0.89, 1.03)	1.05 (0.92, 1.19)	0.92 (0.83, 1.01)
Body Mass Index kg/m^2	< 18.5	1.05 (0.82, 1.35)	0.85 (0.45, 1.58)	1.06 (0.81, 1.39)
	18.5-24.9	Reference	Reference	Reference
	25-29.9	0.99 (0.92, 1.08)	1.09 (0.95, 1.24)	0.94 (0.84, 1.04)
	≥ 30	1.14 (1.03, 1.26)	1.23 (1.04, 1.45)	1.09 (0.96, 1.23)
Physical Activity	Active	Reference	Reference	Reference
	Moderate	1.11 (0.99, 1.24)	1.19 (1.01, 1.41)	1.07 (0.91, 1.25)
	Inactive	1.33 (1.21, 1.47)	1.28 (1.11, 1.48)	1.37 (1.20, 1.57)
Smoking	Non smoker	Reference	Reference	Reference
	Currently	1.16 (1.04, 1.29)	1.40 (1.16, 1.69)	1.09 (0.96, 1.25)
	Former	1.19 (1.11, 1.29)	1.39 (1.20, 1.61)	1.16 (1.06, 1.26)
Fruits and Vegetables Serving daily	0-3	Reference	Reference	Reference
	4-6	1.03 (0.96, 1.10)	1.10 (0.99, 1.23)	0.98 (0.89, 1.07)
	6+	1.15 (1.07, 1.25)	1.48 (1.31, 1.68)	1.01 (0.91, 1.11)
Pain medication use	Yes	1.13 (1.03, 1.24)	1.22 (1.04, 1.43)	1.08 (0.96, 1.21)
Hypertension	Yes	1.98 (1.86, 2.12)	1.92 (1.72, 2.14)	2.01 (1.84, 2.18)
COPD	Yes	2.79 (2.39, 3.26)	2.98 (2.35, 3.78)	2.70 (2.19, 3.31)
Diabetes	Yes	1.90 (1.75, 2.07)	1.80 (1.57, 2.06)	1.96 (1.76, 2.19)

COPD stands for chronic obstructive pulmonary disease.

Table 7.3: Adjusted and unadjusted odds ratio (OR) and the 95% confidence interval (CI) of specific cardiovascular outcomes for osteoarthritis (OA) in the age-sex matched sample.

Outcome	Model	Overall OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)
Myocardial Infraction (n=3,197)	OA Adjusted	1.28 (1.15, 1.44)	1.08 (0.91, 1.28)	1.49 (1.28, 1.75)
	OA Unadjusted	1.38 (1.23, 1.54)	1.19 (1.01, 1.40)	1.56 (1.34, 1.82)
Angina (n=3,143)	OA Adjusted	1.83 (1.62, 2.06)	1.76 (1.43, 2.17)	1.85 (1.59, 2.14)
	OA Unadjusted	1.94 (1.73, 2.18)	1.94 (1.58, 2.38)	1.94 (1.68, 2.24)
Congestive heart failure (n=1,586)	OA Adjusted	1.72 (1.46, 2.01)	1.50 (1.13, 1.97)	1.81 (1.49, 2.21)
	OA Unadjusted	1.84 (1.57, 2.15)	1.71 (1.31, 2.23)	1.91 (1.57, 2.31)
Stroke (n=1,112)	OA Adjusted	1.11 (0.95, 1.29)	1.08 (0.83, 1.40)	1.13 (0.93, 1.37)
	OA Unadjusted	1.20 (1.03, 1.39)	1.14 (0.89, 1.48)	1.23 (1.01, 1.48)

Adjusted odds ratios were obtained after controlling for age, sex, income, education, body mass index, physical activity, smoking, fruits and vegetables consumptions, pain medication use, chronic obstructive pulmonary disease, hypertension, and diabetes.

7.4 Discussion

This study sought to describe the association between OA and the prevalence of heart disease, MI, angina, CHF, and stroke using CCHS data. In this population-based study, adjusted for age, BMI, income, education, physical activity, smoking status, fruit and vegetable consumption, medication use, diabetes, hypertension, and COPD, we found statistically significant positive associations of OA with heart disease, angina, and CHF among both men and women. These associations were higher among women than among men. OA was positively associated with MI among women only and there was no significant association between OA and stroke.

There is some evidence that OA patients have higher rates of CVD and its risk factors. Singh et al. (142) found that adults with OA have a high prevalence of cardiovascular risk factors. Kadam et al. (26) observed 73%, 36%, and 28% higher odds for IHD, angina, and heart failure, respectively among OA cases compared to non-OA controls in a case-control study using the General Practitioner Database in England and Wales. In 2013, Ong et al. (94) observed significantly higher probability of self-reported CVD, CHD, and angina among OA cases compared to their non-OA counterparts in a cross-sectional study using the US National Health and Nutrition Examination Survey data. Our cross-sectional study results of statistically significant associations between OA and the prevalent heart disease, MI, angina, and CHF are consistent with the earlier findings. Similar to our study results, stroke was not associated with OA in the Ong et al.'s study (94). Our study included confounding and mediating variables such as physical activity, fruit and vegetable consumption, and pain medication use which were not adjusted for in the previous studies. In addition, our present study is generalizable to Canada because the surveys were conducted in a representative sample of the Canadian population.

Other published data have shown that OA patients had higher mortality due to CVD (154,155). Nüesch et al. (154) performed a population based cohort study to examine all-cause and disease specific mortality in patients with OA of the hip and knee, and concluded that OA patients had excess mortality compared with the general population and 71% excess standard mortality ratio of CVD. Hochberg (155) reviewed the literature on mortality in OA and found several studies suggesting an increased risk of death (156,159–161). These studies had small sample sizes and other limitations. One study recruited patients from hospitals or medical practices, one study investigated patients after total knee replacement, and not all relevant factors were adjusted for in the multivariable analyses. We observed a significant positive association between OA and the prevalence of heart disease after controlling for several covariates that were not included in previous studies of OA and mortality.

Among the covariates, BMI, income, education, physical activity, smoking status, medication use, diabetes, hypertension, and COPD were associated with heart disease, MI, angina, CHF in both men and women as expected. We observed that higher income and higher education groups had lower odds ratio providing support for previous studies showing that people with low SES are at high risk of CVD (180). The BMI was statistically significant in the multivariable models for all four health outcomes in our study, which shows agreement with previous results (181,182). The physically inactive and moderately active groups had significantly higher odds ratios than the active group in the multivariable models of heart disease and for all specific outcomes, which supports the findings of previous studies that show physical activity to be inversely associated with heart disease prevalence, controlling for covariates and confounders

(139,140). Smoking is a well-known risk factor for heart disease and we observed a significantly higher risk in current and former smokers in the multivariable models.

The present study has some limitations. The cross-sectional CCHS data prevented us from assessing the temporal exposure–outcome sequence between OA and heart disease. Until OA and CVD are measured prospectively any association suggested by cross-sectional analysis remain hypothesis-generating. However, the associations found in this study might not reflect reverse causality, because heart disease is unlikely to cause OA. A notable limitation of our study was the reliance of the survey data on self-reported risk factors and outcomes. Self-reported data tend to contain both false positive and false negative values and therefore may result in bias in the estimates. Obesity was determined from self-reported height and weight. Comparisons of measured and self-reported BMI have suggested that self-reported values may underestimate the true prevalence of obesity by 9% for men and 6% for women (183). However, this small underreporting alone would not change the OA and heart disease relationships. Missing values for BMI, education, income, and fruit & vegetable consumption were imputed. Although the imputed values may not reflect the true distribution of these variables in the sample, the effect on the results is probably small given that the relatively small percentage of missing values in our data.

The observed small differences between the unadjusted and adjusted odds ratio suggest that the confounding variables had minimal effects on the relationship between OA and CVD. In the present analysis, we were unable to study the possible mediating role of muscle weakness and chronic inflammation. Examining the effect of OA after adjusting for these factors in future

cohort studies might help elucidate the causal mechanisms for the observed associations. Other potential intermediate variables, such as physical activity and pain medication use were included in this study. However, the differences in the distribution of these variables among OA and non-OA respondents in our data were small. As a result, there was no notable difference in the odds ratios with and without these variables included in the models (data not shown). Although these data do not support the mediating role of physical activity and pain medication use in the association between OA and CVD, it is important to note that our analysis was limited by the cross-sectional nature of the data and possible errors in reporting.

The exploration of the relationship of OA with heart disease, MI, CHF, and angina remains a promising and important area of research. Since OA is a very common health condition, an association between OA and CVD would be important from a public health perspective. This study identified possible causal associations and raised further questions for subsequent research. However, the results are preliminary and therefore, conclusions should be clearly conditional on confirmation in future studies. More prospective studies are needed to understand the temporal ordering of the relationship between exposure to OA and the incidence of CVD.

In conclusion, our study findings suggest that OA may be associated with an increased risk of heart disease in a broadly representative population-based context. Our data demonstrate positive associations between OA and angina, CHF, and MI. Although these conclusions are conditional on further confirmation, there is an increased potential for more cardiovascular disease among adults with OA. This study provides a rationale for further investigation of the association

between OA and heart disease in longitudinal studies for possible biological and behavioral

mechanisms that may be responsible for this association.

CHAPTER 8 RISK OF CARDIOVASCULAR DISEASE AMONG OSTEOARTHRITIS PATIENTS: A PROSPECTIVE LONGITUDINAL STUDY [4]

8.1 Introduction

This chapter investigates the possible risk of CVD among OA cases in a prospective longitudinal study using the BC administrative database. The background of possible link between OA and CVD was presented previously. In summary, the reasons to suggest that individuals with OA may experience excess CVD events include reduced physical activity, chronic inflammation, muscle weakness, and use of NSAIDs. The relationship between OA and CVD has not been studied extensively in population based studies. However, in Chapter 7 we have observed the significantly higher odds ratio of CVD among self-reported OA cases. In addition, in the literature, there is some evidence that OA patients have higher rate of CVD and the risk factors of it compared to the individuals without OA (26,94,142). There is also some evidence that OA patients are at an increased risk of cardiovascular mortality (154,155).

Since OA may increase the risk of CVD through several mechanisms, our objective was to determine whether OA increases the risk for hospitalized CVD in a longitudinal study. We also examined the risks of MI, IHD, CHF, and stroke separately for men and women with OA. Considering that OA is a common condition among the middle age and the elderly people, a better understanding of the relationship between OA and CVD could help to extend future management strategies beyond the current focus on treating OA.

The organization of this chapter is as follows. Section 8.2 describes the data, methods, and statistical analysis used in this study. Results are presented in Section 8.3. Detailed discussion such as comparison of the findings with the past studies, the strengths and limitations of the study, and conclusion is given in Section 8.4.

8.2 Methods

Database

We used a large, random, and representative sample of all individuals registered in the Medical Service Plan as residents of British Columbia (BC), during the period April 1991 to March 2009. The sample was selected from an administrative database maintained by the BC Ministry of Health. Our sample included individual-level information on date of birth, sex, billing information for any health consultation, socio-economic status (SES) by area of residence, hospital diagnoses, dates of hospital admissions, and date and cause of death for 640,000 randomly selected residents of BC. Vital statistics death data were linked at the individual level using personal health numbers (PHN). PHNs assigned to each resident of BC were replaced by serial numbers to preserve anonymity. These serial numbers were used to track all records at the individual level and to check individuals first hospital CVD diagnoses during the study period. These records do not include data for hospital outpatients or patients treated at emergency health care units. The study was approved by the University of British Columbia Behavioral Research Ethics Board.

OA individuals

The exposure variable was the OA diagnosis by a health professional using International Classification of Disease 9th revision (ICD-9) and 10th revision (ICD-10) codes. OA patients were identified using the case definition of at least two visits to a health professional in two years separated by at least one day or one discharge from the hospital with an ICD-9 code of 715 or ICD-10 code from M15 to M19. A visit was defined as any service with the exclusion of diagnostic procedures and certain other procedures, such as dialysis/transfusion, anaesthesia, obstetrics, or therapeutic radiation. Visits to all types of health professionals were included, and the date of diagnosis was coded as the date of the second health professional visit or the date of discharge from hospital. Individuals with history of CVD prior to their OA diagnosis, based on physician's consultation or hospital admission, were excluded. All existing OA subjects aged 20 years and above in the random sample who met the above case definition from 1991 to 1996 were identified as the exposed group after deleting the prevalent CVD cases.

In the Canadian health care system, a referral from the family physician is necessary to see a specialist, such as an orthopaedic surgeon (OS). Therefore, individuals with advanced OA usually get referral to an OS for their surgical consultation. To examine the relationship between OA severity and the risk of CVD, all exposed cases were divided into three groups according to disease severity: 1) OA diagnosis only, 2) at least one OS consultation, 3) at least one total joint replacement (TJR) or revision before the baseline (March 1996). OS consultations were identified by looking at the physician specialty code in the physician's billing data as well as in the hospital records. TJR cases were identified from hospital records using procedure codes (Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP)) for hip TJR

and revision 935.x, 936.5, 936.6, 936.7, and 936.8, and for knee TJR and revision 934.0 and 934.1. These codes were explained in detail previously (184).

Non-OA individuals

From the random sample, for each OA case, up to 3 non-OA individuals were selected by matching on exact age, sex, and the year of OA diagnosis (index date). Individuals in the non-OA comparison group never had a diagnosis for OA during the entire period 1991-2009. Similar to the exposed group, the comparison group was aged 20 years and above and did not have CVD diagnoses prior to the index date.

Outcomes

Hospital admission for CVD was the primary outcome in this study. Specific CVD events such as MI, IHD other than MI, CHF, and stroke were considered as secondary outcomes. All primary and secondary CVD events were identified from the hospital discharge records based on ICD-9 codes of 410-414, 428, 430-434, 436, and 438. The corresponding ICD-10 codes are I20-I25, I50, and I60-I64. Detailed classifications of these codes according to IHD, MI, CHF, and stroke are shown in Table 8.1.

Table 8.1: International Classification of Disease 9th revision (ICD-9) and 10th revision (ICD-10) codes used to define outcomes.

Disease	ICD-9	ICD-10
Ischemic Heart Disease	410-414	I20-I25
Acute Myocardial Infarction	410	I21
Other acute forms of coronary heart disease (CHD)	411	I24
Old Myocardial Infarction	412	I22-I23
Angina Pectoris	413	I20
Other forms of chronic CHD	414	I25
Congestive Heart Failure	428	I50
Stroke	430-434, 436, and 438	I60-I64

Covariates and confounders

Common risk factors for CVD include age, sex, family history, high cholesterol, high blood pressure, diabetes, high body mass index (BMI), smoking, and diet (131,135). Other than the matched variables age and sex, the individual-level variables that were available in the database and adjusted for in the analysis, included neighbourhood SES, and health conditions known to increase risk of CVD. SES was assigned based on residential address linked to census data at the level of enumeration area (one or more adjacent blocks, up to 650 dwellings) and was grouped into 5 income groups, from 1 (lowest) to 5 (highest), based on mean household income of those residents data (185). Individuals' history of diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease (COPD) were assessed on or before the index date since March 1991. These conditions were defined by visits to health care professionals or hospital admissions with the ICD-9 codes as follows: 1) type 2 diabetes mellitus, 250; 2) hypertension, 401; 3) hyperlipidemia, 272; and 4) COPD, 490, 491, 494, and 496. Charlson co-morbidity scores (186,187) for all subjects in the study were also calculated on or before the index date. The

Charlson score contains 19 comorbidity categories and total score for each patient was calculated by adding the weights for each condition.

BMI imputation

BMI was not measured in the administrative data and therefore, we imputed BMI categories using data from the Canadian Community Health Survey (CCHS) cycles 1.1, 2.1, and 3.1. The CCHS is a large, cross-sectional, survey representative of the Canadian population, carried out by Statistics Canada. This survey contains nationally representative data on health determinants, health status, and health services utilization. A detailed description of the survey design, sample, and interviewing procedures have been found elsewhere (162). The method of imputation was designed to reproduce in our administrative dataset the associations of BMI with both OA and CVD, observed in the CCHS. Individuals with OA were identified using self-reported OA and up to 3 non-OA individuals were randomly matched to each OA subjects according to age, sex, and survey cycle. We used the CCHS question about heart disease as a proxy variable for CVD, because not all components of CVD were measured in the first three cycles. All OA and non-OA individuals were grouped according to the OA status, heart disease (yes/ no) status, sex, and 10-year age groups. For each group, we calculated the proportion of individuals in each of the four BMI (kg/m^2) categories: underweight ($<$ 18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese ($\geq$ 30.0). Finally, we imputed the same proportion of individuals in each of the BMI category from the CCHS data into our administrative data by matching on OA status, CVD status, sex, and age.

Statistical analysis

The follow-up period for analysis started on the date when individuals met the case definition for OA (index date) and continued until hospitalization for CVD, death, emigration, or the end of the study period (March 31, 2009), whichever came first. Person-years of risk were calculated for the entire follow-up period. The relative risks (RR) and the 95% confidence intervals (CI) were evaluated using the Cox proportional hazards (PH) models. The proportionality assumptions for PH models were assessed by observing the Kaplan-Meier curves of the survival function versus the survival time, and the graph of the log [-log (survival function)] versus log of survival time. In addition, the proportionality tests were performed in the multivariable models and the p-values were reported. The RRs were estimated by fitting Poisson regression models where proportionality tests p-values were significant. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used throughout the study to perform the analyses.

8.3 Results

Between April 1991 and March 1996, we documented 12,745 existing OA cases in the random sample and selected 36,886 non-OA individuals matched by age, sex, and index date. Table 8.2 shows the baseline characteristics of the study subjects according to exposure status. The mean age of OA patients was 58.2 years and 60% were women. At baseline, 11% of OA cases had COPD, 20% were hypertensive, and 5% cases had diabetes. These baseline characteristics were significantly more common in the exposed group than in the non-exposed group (p-value < 0.01). Based on 13 years of mean follow-up corresponding to 650,324 person years, we observed 7,995 new hospitalized CVD cases. Of those 2,023 were MI, 2,335 were IHD other than MI,

1,720 were CHF, and 1,917 were stroke cases. This gives the incidence rate for overall CVD of 12.3 (95% CI 12.27-12.33) per 1,000 person years.

In the multivariable Cox PH model, statistically significant interactions were observed between OA and age and OA and sex ($p < 0.01$). Separate analyses were performed using four strata: men aged < 65 years, men aged ≥ 65 years, women aged < 65 years, and women aged ≥ 65 years. We refer to these four groups as younger men, older men, younger women, and older women, respectively. None of the other variables showed statistically significant interactions with the exposure variable. The relative risk (RR) and the 95% CI of CVD from the unadjusted models and from the multivariable models according to the four subgroups are presented in Table 8.3. The proportionality test p-values were 0.41, 0.002, 0.13, 0.67, and 0.006 among younger men, older men, younger women, older women, and for total subjects, respectively. The RRs were estimated using Poisson regression models for older men as well as for total subjects. All the covariates were significant in at least one of the four age-sex strata and therefore we have included all variables in the multivariable models. In the crude analyses, individuals with OA showed a statistically significantly increased risk of CVD in all four age-sex strata. In the multivariable models, after adjusting for the history of diabetes, hypertension, hyperlipidemia, COPD, Charlson score, imputed BMI, and SES, OA was an independent predictor of CVD for older men (RR = 1.15 (95% CI 1.04-1.27)), younger women (RR = 1.26 (95% CI 1.13- 1.42)), and older women (RR = 1.17 (95% CI 1.07-1.26)), but not for younger men (RR = 1.08 (95% CI 0.96-1.17)). Hypertension, diabetes, higher Charlson comorbidity score, imputed BMI, and lower SES were associated with an increased risk of CVD.

The effects of OA on specific CVD events such as MI, IHD other than MI, CHF, and stroke are presented in Table 8.4. OA showed statistically significant RRs for IHD, CHF, MI, and stroke in the unadjusted analyses. In the adjusted models, OA showed statistically significant RRs for incident IHD in all age-sex strata except younger men. Adjusted RRs (95% CI) for IHD were 1.33 (1.11-1.62), 1.66 (1.37-2.01), and 1.45 (1.22-1.72) for OA in older men, younger women, and older women, respectively. RRs (95% CI) for CHF were 1.29 (1.00-1.68), 1.25 (1.02-1.54), and 1.20 (1.03-1.39) for OA among younger women, older men, and older women respectively. MI and stroke did not show any statistically significant association with OA in the multivariable analyses.

Among OA cases, 966 (8%) had at least one TJR or revision and 2,071 (16%) had visits to orthopaedic surgeons before the baseline. To determine whether a dose-response relationship with OA severity exists, we ran multivariable PH and Poisson regression models using OA diagnosis, visits to OS, and TJR as exposure (Table 8.5). The TJR group showed higher RR than OA diagnosis and OS consultation groups for overall CVD, IHD, and CHF. RRs (95% CI) were 1.26 (1.12-1.41), 1.44 (1.16-1.79), and 1.46 (1.16-1.83) for overall CVD, IHD, and CHF respectively in the TJR group. Men who had a TJR had RRs (95% CI) of 1.17 (0.97-1.40), 1.22 (0.89-1.67), and 1.80 (1.26-2.58) for CVD, IHD, and CHF respectively. Women who had a TJR had RRs (95% CI) of 1.31 (1.12-1.54), 1.73 (1.28-2.35), and 1.36 (1.02-1.81) for CVD, IHD, and CHF respectively. The OS consultation group showed an increased risk of IHD among women (RR (95% CI) = 1.45 (1.11-1.90)). However, the OA diagnosis group showed significantly higher RRs for CVD and IHD among both men and women.

Table 8.2: Characteristics of osteoarthritis (OA) cases and age-sex matched non-OA individuals by their exposure status at baseline.

Characteristics	Exposed (OA)	Non exposed (No-OA)
n	12,745	36,886
Age, mean (SD) years	58.2 (14.5)	57.5 (14.3)
Women	60	59
Body Mass Index kg/m^2		
< 18.5	1.6	2.3
18.5-24.9	31.9	44.3
25-29.9	32.1	36.7
≥ 30	34.4	17.7
Socio-economic status		
1 (low)	16.0	15.1
2	17.7	17.0
3	19.3	18.1
4	21.4	21.1
5 (high)	24.0	25.2
Missing	1.6	3.5
COPD	10.6	6.9
Hypertension	19.7	16.4
Hyperlipidemia	6.0	4.9
Diabetes	5.2	4.7
Charlson score, mean (SD)	0.41 (0.92)	0.35 (0.98)

The numbers are percent unless otherwise mentioned. COPD stands for chronic obstructive pulmonary disease.

Table 8.3: The relative risks (RR) and the 95% confidence intervals (CI) of cardiovascular disease for osteoarthritis (OA) cases by age and sex.

Variables	Total RR (95% CI)	Men RR (95% CI)		Women RR (95% CI)	
		Age < 65 years	Age ≥ 65 years	Age < 65 years	Age ≥ 65 years
Exposure OA					
Unadjusted	1.23 (1.17-1.29)	1.19 (1.08-1.32)	1.21 (1.10-1.33)	1.51 (1.35-1.69)	1.23 (1.14-1.33)
Adjusted	1.13 (1.07-1.18)	1.08 (0.97-1.19)	1.15 (1.04-1.27)	1.26 (1.13-1.42)	1.17 (1.07-1.26)
Body Mass Index kg/m^2					
< 18.5	1.29 (1.11-1.50)	1.04 (0.55-1.94)	1.56 (1.07-2.28)	0.95 (0.64-1.40)	1.45 (1.20-1.74)
18.5-24.9	Reference	Reference	Reference	Reference	Reference
25-29.9	1.09 (1.03-1.15)	1.33 (1.18-1.49)	1.02 (0.92-1.13)	1.26 (1.11-1.44)	0.99 (0.90-1.08)
≥ 30	1.40 (1.33-1.48)	1.93 (1.70-2.18)	1.14 (1.01-1.28)	1.88 (1.65-2.14)	1.17 (1.07-1.29)
SES					
1 (low)	1.07 (0.99-1.14)	1.09 (0.94-1.26)	1.00 (0.86-1.15)	1.20 (1.01-1.43)	1.10 (0.98-1.23)
2	1.03 (0.96-1.10)	1.00 (0.87-1.14)	1.06 (0.92-1.22)	1.19 (1.01-1.41)	0.97 (0.86-1.09)
3	1.05 (0.98-1.12)	0.97 (0.85-1.12)	1.08 (0.94-1.24)	1.14 (0.96-1.35)	1.05 (0.93-1.18)
4	1.05 (0.99-1.13)	0.87 (0.77-1.00)	1.04 (0.91-1.19)	1.29 (1.10-1.51)	1.04 (0.93-1.17)
5 (high)	Reference	Reference	Reference	Reference	Reference
COPD	1.17 (1.08-1.26)	1.23 (1.03-1.46)	1.06 (0.92-1.24)	1.31 (1.10-1.57)	1.08 (0.94-1.24)
Hypertension	1.43 (1.36-1.50)	1.93 (1.72-2.17)	1.32 (1.20-1.46)	2.23 (1.97-2.53)	1.49 (1.38-1.61)
Hyperlipidemia	1.02 (0.93-1.13)	1.26 (1.06-1.51)	0.98 (0.80-1.21)	1.27 (1.03-1.56)	0.79 (0.67-0.94)
Diabetes	1.73 (1.60-1.88)	2.05 (1.70-1.22)	1.50 (1.29-1.74)	2.30 (1.89-2.80)	1.79 (1.56-2.05)
Charlson score	1.05 (1.02-1.07)	1.15 (1.07-1.22)	1.06 (1.01-1.10)	1.14 (1.06-1.21)	1.07 (1.03-1.10)

COPD stands for chronic obstructive pulmonary disease and SES stands for socio-economic status.

Table 8.4: The relative risks (RR) and the 95% confidence intervals of specific cardiovascular

diseases for osteoarthritis cases by age and sex.

Outcome	Total RR (95% CI)	Men RR (95% CI)		Women RR (95% CI)	
		Age < 65 years	Age ≥ 65 years	Age < 65 years	Age ≥ 65 years
IHD					
Unadjusted	1.49 (1.37-1.63)	1.17 (1.00-1.37)	1.41 (1.17-1.69)	1.94 (1.61-2.34)	1.54 (1.31-1.82)
Adjusted	1.30 (1.19-1.42)	1.07 (0.91-1.25)	1.33 (1.11-1.62)	1.66 (1.37-2.01)	1.45 (1.22-1.72)
CHF					
Unadjusted	1.43 (1.29-1.58)	1.47 (1.07-2.01)	1.28 (1.05-1.56)	1.56 (1.20-2.03)	1.25 (1.08-1.43)
Adjusted	1.15 (1.04-1.28)	1.35 (0.98-1.86)	1.25 (1.02-1.54)	1.29 (1.00-1.68)	1.20 (1.03-1.39)
MI					
Unadjusted	1.20 (1.09-1.32)	1.19 (0.99-1.42)	1.12 (0.92-1.36)	1.17 (0.93-1.48)	1.14 (0.97-1.35)
Adjusted	1.02 (0.92-1.12)	1.06 (0.88-1.28)	1.11 (0.91-1.36)	0.95 (0.75-1.21)	1.06 (0.89-1.26)
Stroke					
Unadjusted	1.15 (1.04-1.27)	1.10 (0.86-1.40)	0.95 (0.78-1.17)	1.34 (1.06-1.69)	1.07 (0.92-1.24)
Adjusted	0.96 (0.87-1.06)	0.99 (0.77-1.26)	0.96 (0.78-1.17)	1.13 (0.89-1.44)	1.02 (0.87-1.19)

IHD represents ischemic heart disease other than myocardial infarction, CHF stands for

congestive heart failure, and MI stands for myocardial infarction.

Table 8.5: The relative risk (RR) and the 95% confidence intervals (CI) of cardiovascular disease for osteoarthritis (OA) according to orthopedic surgeons' (OS) consultations and total joint replacements.

Outcome	Exposure	Total RR (95% CI)	Men RR (95% CI)	Women RR (95% CI)
CVD	OA diagnosis	1.11 (1.05-1.17)	1.11 (1.02-1.20)	1.13 (1.05-1.22)
	OS consultation	1.10 (0.93-1.22)	1.06 (0.91-1.23)	1.14 (0.98-1.31)
	Total joint replacement	1.26 (1.12-1.41)	1.17 (0.97-1.40)	1.31 (1.12-1.54)
IHD	OA diagnosis	1.30 (1.18-1.43)	1.16 (1.01-1.33)	1.47 (1.28-1.69)
	OS consultation	1.25 (1.04-1.49)	1.10 (0.86-1.41)	1.45 (1.11-1.90)
	Total joint replacement	1.44 (1.16-1.79)	1.22 (0.89-1.67)	1.73 (1.28-2.35)
CHF	OA diagnosis	1.09 (0.97-1.23)	1.15 (0.94-1.41)	1.08 (0.93-1.24)
	OS consultation	1.19 (0.96-1.48)	1.40 (1.00-1.95)	1.10 (0.82-1.46)
	Total joint replacement	1.46 (1.16-1.83)	1.80 (1.26-2.58)	1.36 (1.02-1.81)

In all cases no-OA was the reference category. CVD stands for cardiovascular disease, IHD represents ischemic heart disease other than myocardial infarction, and CHF stands for congestive heart failure.

8.4 Discussion

To our knowledge, this is the first longitudinal study of the relationship between OA and incident CVD using an administrative database. In this population-based study with up to 18 years of follow-up, we observed that OA increased the risk of hospitalized CVD in both younger and older women and in older men, compared with their non-OA counterparts. The estimated increased risk of CVD was 23% among younger women, 17% among older women, and 15% among older men. Younger women with OA had a 65% increased risk of IHD and 29% increased risk of CHF. For older women and men with OA, the risks of IHD other than MI and CHF were relatively lower but were statistically significant. We also observed that women who underwent TJR had a 31% increased risk of CVD, 73% increased risk of IHD, and 36% increased risk of CHF and men who underwent TJR had an 80% increased risk of CHF. In our study, individuals with OA did not show a significant association with MI or stroke.

Evidence shows that OA patients have higher CVD rates compared to non-OA individuals. Kadam et al. (26) observed 73%, 36%, and 28% higher odds for IHD, angina, and CHF, respectively among OA cases compared to non-OA controls. In a cross-sectional study, Ong et al. (94) observed significantly higher odds for self-reported CVD, CHD, and angina among OA cases. In 2013, Rahman et al. (188) observed statistically significant associations between OA and prevalent CVD. In addition, stroke was not associated with OA in the Rahman et al.'s (188) and Ong et al.'s (94) studies. Our prospective study results are consistent with these findings.

While the primary focus of this research was to determine the risks of CVD among physician-diagnosed OA cases, some previous studies had provided evidence that mortality due to CVD

was increased in individuals with OA (154,155). In a cohort study, Nüesch et al. (154) estimated that the patients with OA had excess all-cause mortality compared with the general population and the standard mortality ratio for cardiovascular disease was 1.71 (95% CI 1.49-1.98). Hochberg (155) reviewed the literature on OA and mortality and found that several studies reported an increased risk of death among individuals with OA (156–161). However, these studies were relatively small and not all relevant factors were adjusted for in the multivariable analyses.

We analyzed a representative sample from a prospectively collected administrative database from April 1991 to March 2009. By selecting OA cases during the period 1991-1996, we ensured that both the exposed and non-exposed groups had sufficient time to develop the outcomes of interest. Inclusion of incident CVD cases as events protected the results from potential reverse causality bias. Studies have shown that the Hospital Discharge Database has a high validity (189–191), especially for cardiovascular disorders such as heart failure and IHD, for which approximately 90% of diagnoses have been demonstrated to be correct with the positive predictive values generally between 75–90% (189). The results were adjusted for age, sex, SES, BMI, and several conditions known to be associated with CVD, such as COPD, hypertension, hyperlipidemia, diabetes, and a number of severe conditions that were included in the Charlson Comorbidity Index. Finally, we were able to perform separate analyses for specific CVD events and for different severity levels of OA by age and sex.

The present study has some limitations that should be acknowledged. Our administrative database does not include information on some cardiovascular risk factors, such as smoking and

diet. However, these factors have not been shown to be related to OA and, therefore, are not expected to be confounders of the relationship. In addition, the results were adjusted for COPD which is correlated with smoking and might reduce the effect of smoking in these relationships. Some acute MI deaths occurred at home or in the hospital emergency care units were not captured in our study, however, these would not create any differential misclassification. Another limitation of this study is that we have defined OA using ICD diagnostic codes; therefore, both false negatives and false positives may occur due to misdiagnosis or incorrect recording in the administrative forms. However, these diagnostic criteria were previously validated (24,166). Harrold, et al. (24) estimated the positive predictive value of administratively coded OA in the general population at 62% when the prevalence was 8.7%. We used the case definition that required two physician's visits in two years or one hospital diagnosis, which minimized false positives in OA diagnosis. The effect of false negatives in this study will be small since we have selected non-OA individuals who never had any diagnosis for OA from 1991 to 2009 and we have deleted the prevalent CVD cases using any diagnosis either in the hospital or in the physician's visit before baseline. The misclassifications due to false positives and negatives are non-differential in this study. BMI is a confounder of the association studied and to control for confounding by BMI, we imputed BMI from the CCHS data. Although the imputed values of BMI may not reflect the true distribution in the sample, the effect on the results is probably small given that we imputed BMI by matching on age, sex, OA, and CVD status. As expected, BMI showed a positive association with CVD in the multivariable models.

The exploration of CVD risks among individuals with OA is a promising and important area of research from a public health perspective. While there is recognition of the high prevalence of

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OA among the elderly, there has been minimal work done in studying CVD outcomes among OA patients. Our work provides new information by a closer examination of cardiovascular complications among individuals with OA. Our dose-response analyses indicated that the highest relative risks were observed among those who underwent TJR, suggesting that persons with advanced stage of OA had higher risks of CVD, IHD, and CHF than those with less advanced OA. The biological explanation for the higher risk of CVD overall, and specifically IHD other than MI and CHF among individuals with OA are yet to be investigated. Although this study was not designed to explain the underlying mechanism, several possible causal paths can be hypothesized. Chronic inflammation, muscle weakness, reduced mobility, and NSAIDs use are common among individuals with OA, and are also risk factors for CVD. In the present study we were unable to adjust for these variables and therefore, these results should be interpreted with caution. It should be noted, however, that these factors are not confounders; rather, they may be considered as intermediate variables in the causal path between OA and CVD. Examining the effect of adjusting for these factors in future studies might help elucidate the causal mechanisms for the observed associations.

Despite several limitations, this large, longitudinal study has allowed us to identify statistically significant and biologically plausible relationships that provide a rationale for further biological, physiological, and epidemiological studies of cardiovascular outcomes in persons with OA. The findings suggest that OA may be associated with an increased risk of CVD in a broadly representative population-based context. Specifically, our results indicate that women with OA, irrespective of age, and older men with OA, had higher risks of CVD, especially for IHD other than MI and CHF, than age-matched men and women without OA. Further confirmation of these

findings in future studies is needed before specific recommendations for new standards of care in

OA can be offered.

CHAPTER 9 RISK OF TYPE 2 DIABETES AMONG INDIVIDUALS WITH OSTEOARTHRITIS[5]

9.1 Introduction

This chapter investigates the possible risk of type 2 diabetes among OA cases in a prospective longitudinal study using the BC administrative database. The background of the possible link between OA and diabetes was presented previously. In summary, there is some evidence that OA is associated with diabetes or increased blood glucose (151–153). These studies are cross-sectional and based on relatively small samples. There is also some evidence that OA patients are at an increased risk of mortality due to diabetes, cardiovascular disease, and cancer (154,155).

Although the causal pathways between OA and diabetes are not yet fully explained, OA may contribute to the development of type 2 diabetes through complex processes involving metabolic syndrome, muscle weakness, and physical inactivity. To avoid problems with reverse causality and unequal survival, use of incidence data is a prerequisite. To our knowledge, no prospective population based study of type 2 diabetes incidence among OA cases has been undertaken previously. Our objective therefore, was to conduct a prospective longitudinal study to determine whether OA increases the risk for diabetes. For the future management strategies beyond the current focus on treating OA and diabetes, it is crucial to investigate the nature and strength of this association.

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[5] A version of this chapter has been submitted for publication. Authors are, Rahman MM, Cibere J, Anis AH, Goldsmith CH, and Kopec JA. The title of the manuscript is "Risk of type 2 diabetes among osteoarthritis patients in a prospective longitudinal study."

The organization of this chapter is as follows. Section 9.2 describes the data, methods, and statistical analysis used in this study. Results are presented in Section 9.3. Detailed discussion such as comparison of the findings with the past studies, the strengths and limitations of the study, and conclusion is given in Section 9.4.

9.2 Methods

Administrative Data

Medical history of a large random sample (n = 640,000) drawn from approximately 4 million residents registered in the Medical Service Plan (MSP) of BC, for the period April 1991 to March 2009 were analyzed. MSP is a provincial health care plan in which approximately 99% of BC residents are registered. Both the BC Ministry of Health and the Population Data BC, who facilitates administrative data acquisition in BC, have approved access to and use of the data for this study. This administrative database contains information on date of birth, sex, billing information for any health consultation, SES by area of residence, and hospital discharge records. To monitor deaths of individuals in the sample, the Ministry linked vital statistics records to the database using personal health numbers. The database does not include records for patients treated at the emergency health care units.

Exposure and outcome

The main exposure and outcome variables of interest were the administrative diagnoses of OA and diabetes, respectively. All OA cases were identified using the case definition that include at least two visits to a health professional within two years in different days or one discharge from the hospital with an International Classification of Disease 9th revision (ICD-9) code of 715 or

International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) code of M15 to M19. These codes include symptomatic and radiographic OA in any joint except the spine. Using the same case definition as described for OA, diabetic cases were identified by looking at ICD-9 code of 250 or ICD-10 code of E10 to E14. A visit was defined as any service with the exclusion of diagnostic procedures and certain other procedures, such as dialysis/transfusion, anaesthesia, obstetrics, or therapeutic radiation. The second health professional visit or the hospital admission date was coded as the date of diagnosis. Individuals with a history of diabetes (any ICD code for diabetes mentioned above) before March 1996 (baseline) were excluded. After deleting prevalent diabetes cases, all OA cases aged 20 years and above, observed in the random sample during the period 1991-1996, were selected as the exposed group.

In the Canadian health care system, individuals with advanced stage of OA usually get referrals from their family physicians to orthopaedic surgeons (OS) for their surgical consultations. To examine the relationship between OA severity and the risk of diabetes, all exposed cases were divided into three groups according to disease severity: 1) OA diagnosis only, 2) at least one OS consultation, 3) at least one total joint replacement (TJR) or revision before the baseline. OS consultations were identified by looking at the physician specialty code in the physician's billing data as well as in the hospital records. TJR cases were identified from hospital records using procedure codes (Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures) for hip TJR and revision 935.x, 936.5, 936.6, 936.7, and 936.8, and for knee TJR and revision 934.0 and 934.1. These codes were explained in detail previously (184).

Non-exposed group

For the purpose of selecting non-exposed group, one non-OA individual was matched randomly for each OA case, based on exact age, sex, and the year of OA diagnosis (index date), from the same random sample. Individuals in the non-OA comparison group never had a diagnosis for OA during the entire period (1991-2009), were aged 20 years and above, and were not diagnosed as diabetic prior to baseline.

Covariates and confounders

The variables adjusted for in the analysis included age, sex, obesity, neighbourhood SES, and co-morbid conditions related to diabetes. SES was assigned based on residential address linked to census data at the level of enumeration area (one or more adjacent blocks, up to 650 dwellings) and was grouped into 5 approximately equal income groups, from 1 (lowest) to 5 (highest), based on mean household income of those residents data (185). Missing SES values (less than 5%) were imputed by generating random numbers from the binomial distribution. One of the most important risk factors for type 2 diabetes is obesity (146–148). We identified overweight and obese individuals using the ICD-9 code of 278. In the entire random sample, we observed that 7.1% of the individuals aged 20 years or more were coded as obese during the period 1991 - 2009. Individuals' history of hypertension, hyperlipidemia, and chronic obstructive pulmonary disease (COPD) was assessed on or before the index date. These conditions were defined by visits to health care professionals or hospital admissions on or before baseline with the ICD-9 codes as follows: 1) hypertension, 401; 2) hyperlipidemia, 272; and 3) COPD, 490, 491, 494, and 496. In addition, Charlson co-morbidity scores (186,187) were calculated on or before baseline.

The Charlson score was calculated by adding up the weights for each of 19 comorbid conditions included in the algorithm.

BMI imputation

Since body mass index (BMI) was not recorded in the administrative data, as part of sensitivity analysis, we imputed BMI categories using the Canadian Community Health Survey (CCHS) data cycles 1.1, 2.1, and 3.1. The CCHS is a large, cross-sectional, representative survey of the Canadian population, carried out by Statistics Canada. This survey contains non-overlapping nationally representative data on health determinants, health status, and health services utilization. A detailed description of the survey design, sample, and interviewing procedures may be found elsewhere (162). The method of imputation was designed to reproduce in our administrative dataset the associations of BMI with both OA and diabetes, observed in the CCHS. Individuals with OA were identified using self-reported OA and up to 3 non-OA individuals were randomly matched to each OA subjects according to age, sex, and survey cycle. All OA and non-OA individuals were grouped according to the OA status, diabetes status, sex, and 10-year age groups. For each group, we calculated the percentage of individuals in each of the four BMI categories (kg/meter^2): underweight (< 18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥ 30.0). Finally, we imputed the same percentage of individuals in each of the BMI categories from the CCHS data into our administrative data by matching on OA status, diabetes status, sex, and age.

Statistical analysis

First, we performed a cross-sectional analysis with all individuals age 20 years and above in the random sample. Using diabetes as a dependent variable, the unadjusted odds ratios (OR) and the 95% confidence intervals (CI) were calculated for OA and all other variables included in the analyses, by fitting logistic regression models. Next, in the prospective analysis, individuals were followed from the index date and continued until diabetes diagnosis, death, emigration, or the end of the study period (March 31, 2009), whichever came first. Cox proportional hazards (PH) models were fitted to estimate the relative risks (RR) and the 95% CIs. The proportionality assumptions were assessed by checking the Kaplan-Meier curves as well as the proportionality tests p-values from the multivariable PH models. The RRs were estimated by fitting Poisson regression models where the proportionality tests p-values were found to be statistically significant. All analyses were performed using SAS V.9.3 (SAS Institute, Cary, NC, USA). The study was approved by the Behavioral Research Ethics Board at the University of British Columbia, Vancouver, Canada.

9.3 Results

We observed 59,588 diabetic cases age 20 years and above in the total random sample and the crude OR (95% CI) for OA was 2.93 (2.87-2.99). All other variables included in the analysis, were significantly associated with diabetes in the cross-sectional unadjusted analysis (Table 9.1). Between April 1991 and March 1996, we documented 19,089 OA cases. The mean age of OA cases was 61.6 years and 60.4% were women. Table 9.2 shows the distribution of subjects according to exposure status (OA versus non-OA). At baseline, all variables except age and sex (matched variables) were significantly higher among the exposed group compared to the non-

exposed group (p-value < 0.05). During a 12-year mean follow-up period, corresponding to 465,399 person years, 5,231 new diabetes cases were observed. This gives an overall incidence rate (95% CI) of diabetes of 11.2 (10.90-11.50) per 1000 person years.

In the multivariable models, statistically significant interactions were observed between OA and age and OA and sex ($p < 0.05$). Therefore, separate analyses were performed using four strata: men aged 20-64 years, men aged ≥ 65 years, women aged 20-64 years, and women aged ≥ 65 years. We refer to these four groups as younger men, older men, younger women, and older women, respectively. During the follow-up, the incidence rate of diabetes was higher among men than women. Both adjusted and unadjusted RRs of diabetes according to the four subgroups are presented in Table 3. Since the proportionality test p-values were significant for older women, RRs were estimated using the Poisson regression models.

OA showed a significantly increased risk of diabetes in all groups except older men in both crude and adjusted analyses. In the multivariable models, after adjusting for SES, obesity, history of COPD, hypertension, hyperlipidemia, and the Charlson score, the RRs (95% CI) were 1.16 (1.04-1.28), 1.27 (1.15-1.41), and 1.21 (1.08-1.35), respectively, for younger men, younger women, and older women. The RR was not significant for older men (RR = 0.94 (95% CI 0.82-1.09)). Lower SES, obesity, hypertension, and hyperlipidemia were associated with an increased risk of diabetes as expected. In the models, where obesity was replaced by the imputed BMI variable, similar RRs were observed for OA (data not shown).

To check whether a dose-response relationship with disease severity exists among younger and older OA cases, we ran multivariable PH and Poisson regressions using OA diagnosis, surgical consultation, and TJR as exposure (Figure 9.1). Among OA cases, 1,811 (9.5%) had at least one TJR or revision and 3,080 (16%) had visits to orthopaedic surgeons before the baseline. Adjusted RR of diabetes was higher in the TJR group among younger OA cases (RRs (95% CI) were 1.22 (1.15-1.30), 1.15 (1.03-1.30), and 1.37 (1.14-1.63) for OA diagnosis, surgical consultation, and TJR groups, respectively). Among older OA cases (age 65 years and more) surgical consultation group showed the highest risk of diabetes (RRs (95% CI) were 1.13 (1.05-1.23), 1.30 (1.13-1.49), and 1.12 (0.96-1.31) for OA diagnosis, surgical consultation, and TJR groups, respectively).

Table 9.1: Percentage and unadjusted odds ratios (OR) of variables by diabetes mellitus (DM) status, observed in the random sample drawn from the British Columbia administrative health records, during the period 1991-2009.

Variable	No-DM (n=518,013)	DM (n= 59,588)	Unadjusted OR (95% CI)
Osteoarthritis	10.7	26.1	2.93 (2.87-2.99)
Sex (women)	51.2	48.3	0.89 (0.88-0.91)
Age (year) in 2009			
20-29	16.3	1.3	Reference
30-39	16.0	3.4	2.72 (2.50-2.96)
40-49	18.7	8.8	6.06 (5.61-6.54)
50-59	18.3	16.6	11.64 (10.80-12.54)
60-69	12.2	22.3	23.50 (21.82-25.30)
70-79	7.5	21.7	37.14 (34.48-40.00)
80+	10.8	26.0	30.99 (28.78-33.36)
Socio-economic status			
1 (low)	21.42	24.35	1.36 (1.32 -1.39)
2	21.25	22.41	1.26 (1.22 -1.29)
3	19.54	19.73	1.20 (1.17 -1.24)
4	19.05	17.8	1.11 (1.08 -1.15)
5 (high)	18.75	15.72	Reference
Obesity	6.1	16.2	3.01 (2.93-3.08)
COPD	27.2	40.3	1.81 (1.77-1.84)
Hypertension	30.8	75.2	6.82 (6.69-6.96)
Hyperlipidemia	18.4	42.6	3.29 (3.23-3.35)
Charlson score, mean (SD)	1.30 (2.10)	3.95 (3.07)	1.36 (1.36-1.37)

COPD: chronic obstructive pulmonary disease.

Table 9.2: Distribution of variables by exposure (osteoarthritis) status and unadjusted relative risks (RR) of diabetes observed in the prospective analysis.

| Variable	No-osteoarthritis (n=19,089)	Osteoarthritis (n=19,089)	Unadjusted RR (95% CI)
Diabetes	11.0	16.4	1.32 (1.25-1.39)
Sex (women)	60.4	60.4	1.01 (1.01-1.01)
Age (year)			
20-39	8.8	8.8	Reference
40-49	12.4	12.4	2.00 (1.72-2.32)
50-59	19.5	19.5	2.83 (2.47-3.25)
60-69	26.0	26.0	2.96 (2.59-3.39)
70-79	23.6	23.6	2.50 (2.17-2.87)
80+	9.8	9.8	1.76 (1.45-2.14)
Socio-economic status			
1 (low)	23.1	23.5	1.40 (1.28-1.53)
2	21.5	21.8	1.36 (1.24-1.49)
3	18.4	18.9	1.28 (1.17-1.40)
4	18.3	18.4	1.13 (1.03-1.24)
5 (high)	18.8	17.4	Reference
Obesity	5.4	11.8	2.00 (1.86-2.16)
COPD	16.0	24.4	1.28 (1.20-1.37)
Hypertension	31.5	40.2	1.92 (1.82-2.03)
Hyperlipidemia	9.3	11.4	1.44 (1.33-1.55)
Charlson score mean (SD)	0.94 (1.83)	1.07 (1.58)	1.06 (1.04-1.08)

The numbers are percent unless otherwise mentioned. OA: osteoarthritis; COPD: chronic obstructive pulmonary disease.

Table 9.3: Age-sex specific incidence rate per 1000 person years, relative risks (RR), and the

95% confidence intervals (CI) of diabetes mellitus (DM).

Variables	Men		Women	
	Age < 65 years (n = 9,086)	Age ≥ 65 years (n = 6,040)	Age < 65 years (n = 11,184)	Age ≥ 65 years (n = 11,868)
DM incidence rate (1,000)	12.5 (11.9-13.1)	13.0 (12.1-13.9)	10.2 (9.7-10.8)	10.4 (9.9-11.0)
Exposure	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
OA Unadjusted	1.32 (1.19-1.46)	0.99 (0.86-1.14)	1.53 (1.38-1.70)	1.32 (1.19-1.48)
OA Adjusted	1.16 (1.04-1.28)	0.94 (0.82-1.09)	1.27 (1.15-1.41)	1.21 (1.08-1.35)
SES				
1 (low)	1.40 (1.19-1.66)	1.18 (0.95-1.46)	1.57 (1.33-1.85)	1.16 (0.98-1.39)
2	1.27 (1.08-1.50)	1.18 (0.94-1.47)	1.53 (1.30-1.80)	1.17 (0.98-1.40)
3	1.42 (1.20-1.67)	0.91 (0.72-1.16)	1.35 (1.14-1.61)	1.18 (0.98-1.43)
4	1.07 (0.90-1.27)	1.09 (0.86-1.37)	1.12 (0.94-1.34)	1.15 (0.95-1.39)
5 (high)	Reference	Reference	Reference	Reference
Obesity	1.95 (1.70-2.24)	1.62 (1.25-2.11)	1.73 (1.54-1.95)	1.98 (1.69-2.32)
COPD	1.22 (1.06-1.41)	1.01 (0.84-1.20)	1.20 (1.05-1.36)	1.13 (0.99-1.29)
Hypertension	2.14 (1.92-2.38)	1.43 (1.24-1.65)	2.20 (1.99-2.44)	1.45 (1.30-1.63)
Hyperlipidemia	1.33 (1.16-1.53)	1.31 (1.07-1.60)	1.18 (1.02-1.36)	1.33 (1.14-1.55)
Charlson score	1.01 (0.96-1.06)	0.99 (0.95-1.03)	1.02 (0.97-1.07)	0.96 (0.93-1.00)

COPD: chronic obstructive pulmonary disease; SES: socio-economic status; OA: osteoarthritis.

Figure 9.1: Adjusted relative risk (RR) and the 95% confidence interval (CI) of diabetes according to the severity of osteoarthritis.
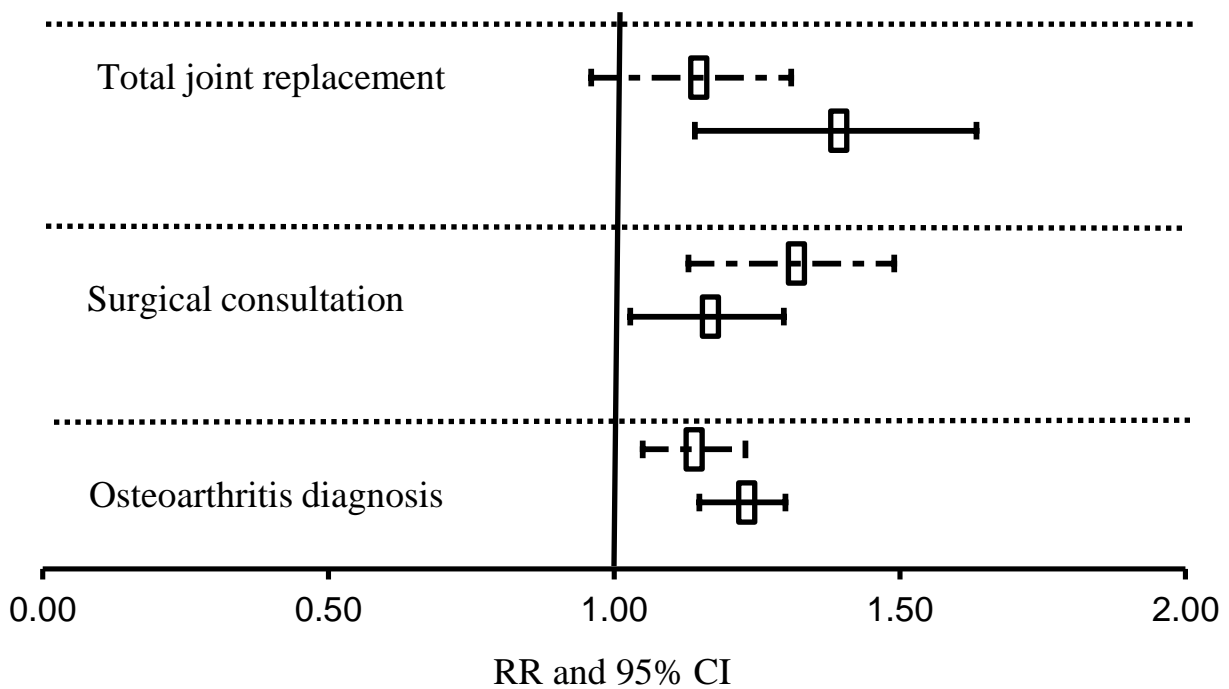
Box-plots with solid line represent cases age 20-64 years and dash line represent cases age 65 years and over. RRs were adjusted for age, sex, body mass index, socio-economic status, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, and Charlson index.

9.4 Discussion

In this population-based prospective study with a mean of 12 years of follow-up, we found that the risk of diabetes was higher in persons with OA compared to those without OA, after adjusting for confounding variables. The risk was significant in both younger and older women and in younger men, compared to their age-sex matched non-OA counterparts. We also observed that younger OA subjects who underwent TJR had a 37% increased risk of diabetes compared to non-OA individuals. Older men with OA showed no significant increased risk of diabetes.

To our knowledge, this is the first longitudinal study of the relationship between OA and incident diabetes using an administrative database. There is some evidence that OA patients have a greater probability of developing diabetes. In a clinical and epidemiological survey, Cimmino et al. (151) found that fasting glucose concentrations were significantly higher among OA cases compared to non-OA controls. Hart et al. (152) found an odds ratio of 1.95 of raised blood glucose among women with radiographic knee OA compared to non-OA women. In a cross-sectional study, Nieves-Plaza et al. (153) observed that adjusted odds ratio between OA and diabetes was 2.18, the ratio was even higher among women. The statistically significant RRs observed in our prospective study may not be comparable with the odds ratios observed in earlier studies due to the difference in the study design.

Other published data have shown that OA patients are subject to increased mortality due to diabetes (154,155). Nüesch et al. (154) performed a population-based cohort study to examine cause and disease specific mortality in patients with OA of the hip and knee. They concluded that OA patients had a 95% increased rate of mortality due to diabetes compared to the general

population. Cherhan et al. (35) obtained a crude hazard ratio of 4.99 for mortality due to diabetes among OA patients. These studies had small sample sizes, and not all the relevant factors were adjusted for in the multivariable analyses. We analyzed a representative sample drawn from a prospectively collected administrative database in which total follow-up years covered the period April 1991 to March 2009. By selecting OA cases during the years 1991 to 1996, we ensured that both the exposed and non-exposed groups had sufficient time to develop the outcomes of interest. In our study, the exclusion of prevalent diabetes cases at baseline protected the results from potential reverse causality. The results were adjusted for age, sex, SES, obesity, and several conditions known to be associated with diabetes, such as COPD, hypertension, hyperlipidemia, and a number of severe conditions listed in the Charlson Comorbidity Index. Finally, we were able to perform separate analyses for specific age and sex categories.

The population-based design and the use of long-term medical records are the strengths of this study. An additional strength is that we used a large random sample of physician-diagnosed OA cases. Therefore, our results are generalizable to the Canadian population. Nonetheless, some limitations of the present study should be acknowledged. Both false negatives and false positives may occur in the diagnostic ICD-9 codes for OA and diabetes. However, these diagnostic criteria were validated previously for diabetes (193,194) and for OA (25,166). Both Chen et al. (193) and Southern et al. (194) observed more than 70% sensitivity and positive predictive values for administrative diabetes codes. Lix et al. (25) obtained over 40% sensitivity and over 90% specificity of administrative OA diagnosis from Manitoba, Canada, compared to the self-reported CCHS data. Our case definition required two physician's visits over a two-year period

or one hospital diagnosis, effectively reduced the number of false positives. To minimize false negatives, we selected non-exposed individuals who had not been diagnosed as OA during the entire period (1991-2009); we also eliminated diabetic cases before the baseline. Another limitation is the lack of information regarding physical activity and diet. However, diet has not been shown to be related to OA; therefore, it is not expected to be a confounder of this relationship. The percentage of obese subjects in our sample was slightly lower than the BC estimate (167). Thus, for a sensitivity analysis, we imputed BMI from the CCHS data by matching randomly for age, sex, OA, and diabetes status. The RRs did not change when we replaced the obesity variable with the imputed BMI variable.

While a high prevalence of OA among the elderly has long been recognized, little work has been done to find the association between OA and diabetes. Although the biological explanation for these associations has yet to be investigated, several possible causal paths can be hypothesized, including reduced mobility, metabolic syndrome, and muscle weakness. Obesity, hypertension, hyperlipidemia, and increased blood sugar are components of metabolic syndrome, all of which are common in both diabetic and OA patients. Our results were adjusted for all these factors. In the present study, we were unable to adjust for possible confounding effects of physical activity and muscle weakness, and therefore, further studies that include these variables are recommended. It should be noted, however, that these factors may not be confounders but rather intermediate variables in the causal path between OA and diabetes.

In conclusion, this large and prospective study has identified statistically significant associations between OA and diabetes. Our study suggests that younger men and women, and older women

with OA are at higher risks for developing diabetes compared to age-sex matched non-OA adults. Future studies are needed to confirm these results and to elucidate the potential mechanisms involved.

CHAPTER 10 DISCUSSION

The primary goal of this thesis was to determine the relationship between OA and CVD and diabetes and to obtain the descriptive epidemiology of OA using a random sample drawn from the population-based administrative data, self-reported CCHS data, and a population-based cohort from BC, Canada. On the basis of administrative health records covering the 18-year period 1991-2009, the prevalence and incidence rates of OA were calculated, the trends in incidence over time were obtained, and the risks of developing CVD and diabetes were determined by two prospective longitudinal studies. Two different definitions were used to identify OA cases in physicians' billing claims and hospital records. In addition to studying OA epidemiology, I checked the validity of OA case identifications in the administrative records by comparing OA diagnoses with a symptomatic, radiographic, and MRI based cohort.

In addition to the common risk factors for CVD, systemic inflammation can increase the risk of CVD (136,137). Muscle weakness has also been reported as a risk factor among individuals with CVD (138). Studies have shown that physically inactive individuals have increased risk of CVD and premature mortality (139,140). In the development of OA, systemic inflammation plays an important role (13) and muscle weakness is a frequent symptom among individuals with OA (16). Due to pain in their joints, individuals with OA are less physically active compared to those without arthritis (31). Recently, OA has been recognized as a metabolic disease on the basis of data showing a higher incidence of this condition in the non-weight bearing joints of individuals who are overweight/ obese (14,15). Other studies have considered OA as a systemic disorder linked to metabolic syndrome (21,32,33). In addition, NSAIDs are commonly used drugs to treat OA-related pain and the use of NSAIDs is associated with an increased risk of CVD (34,35).

Thus OA may contribute to the increased risk of CVD through a number of mechanisms such as immobility and reduced physical activity, systemic inflammation, muscle weakness, metabolic syndrome, increased NSAIDs use, and other lifestyle changes attributable to OA.

Risk factors for diabetes include age, sex, body weight, family history, ethnicity, socio-economic status, hypertension, CVD, history of gestational diabetes, immobility, metabolic syndrome and diet (146–148). Studies have shown lower muscle strength among adults with type 2 diabetes compared to non-diabetic individuals (149). The risk of diabetes is increased due to physical inactivity (147,150). Therefore, a causal pathway may exist between OA and diabetes involving metabolic syndrome, muscle weakness, and physical inactivity.

The earlier studies focusing on the relationship between OA and CVD and diabetes were either cross-sectional or case-control studies, and were based on relatively small samples. Therefore, I conducted two prospective longitudinal studies to investigate the link of OA with CVD and diabetes. The descriptive epidemiology of OA in most of the earlier studies was based on specific joint sites and specific case identification methods. Previous studies that generated incidence, prevalence, and trends, from administrative health records included a shorter length of observation time. Since people with OA may not be coded as such in administrative data for many years, short observation period lead to underestimation of OA prevalence and overestimation of OA incidence (because some prevalent cases are counted as incident cases). To overcome these problems, I used the health records extending over a period of 18 years, which provided more accurate results compared to those covering 10-13 years of health records in the earlier analyses. Previous validation studies of administrative OA definitions did not compare

cases against clinical and radiological assessments. Therefore, I used symptomatic, radiographic, and MRI-based assessments to validate administrative OA case definitions. Key findings of this thesis and the comparisons with published data were presented in Chapters 4-9. A brief discussion of the findings is provided below.

10.1 Key Findings

Incidence rates of OA were calculated based on administrative health records extending over a period of 18 years. I also calculated the crude and age-standardized rates to estimate the trends in the incidence for the period 2000/01-2008/09. In the year 2008/09, the overall incidence rate of OA for all joints was 14.6 (12.7 in men and 16.5 in women) per 1000 person years in the case definition that was based on one physician's visit or one hospital diagnosis. Incidence rates were 8.2 per 1000 person years (lower by 44%) in the case of the second definition that was based on two physician's visits within two years or one hospital diagnosis. Overall incidence rates increased with age and fell after age 70 years for women and 80 years for men. In the trend analyses, crude rates rose for both men and women during the period 2000/01-2008/09, while the age-standardized rates rose slightly among men and showed no trend among women. In Chapter 4, I described these findings as well as showed the comparison of these results with the published data.

The point prevalence of OA was estimated on March 31, 2009 in BC, for both case definitions at different age cut-off points and was described in Chapter 5. The overall prevalence of OA, for all age groups combined was 10.8%; 9.1% among men and 12.5% among women in the case of the definition based on two physician's visits within two years or one hospital diagnosis; it was 1.8

times in the case of the definition based on one physician's visit or one hospital admission. Detailed comparison of these findings with the published data was provided in Chapter 5.

The goal of Chapter 6 was to obtain the validity of administrative OA case definitions comparing administrative records with symptomatic, radiographic, and MRI-based assessments. The validity was assessed against four different reference standards that included clinical and self-reported diagnoses of knee, hand, and hip OA. Among the joints, knee OA was assessed on the basis of radiographic K-L grade, MRI cartilage score, self-reported physician diagnosis, and the ACR clinical criteria. Of the two administrative case definitions, that based on at least one physician visit or one hospital admission had a higher sensitivity and NPV, whereas that based on at least two physician visits within two years or one hospital admission had a higher specificity and PPV. On the basis of the study findings, the latter definition was found to be more appropriate in defining OA when using an administrative database for analytical and outcome studies. Further description or these results and the comparison of these findings with the published data were presented in Chapter 6.

My main objective in Chapter 7 was to investigate the association between OA and the prevalent heart disease as well as other cardiovascular components such as MI, angina, CHF, and stroke. To fulfill this objective, I analyzed the first 3 cycles of the CCHS data. After adjusting for age, BMI, income, education, physical activity, smoking status, fruit and vegetable consumption, medication use, diabetes, hypertension, and COPD, I observed a statistically significant positive association between OA and heart disease. In this population-based cross-sectional study, statistically significant associations were observed between OA and angina and CHF among both

men and women in the multivariable models. The association was higher among women than among men. OA was positively associated with MI only among women, and no significant association between OA and stroke was observed. These findings provided a rationale for further investigations of the relationship between OA and cardiovascular conditions in prospective longitudinal studies. Detailed comparisons of these findings with the published data were provided in Chapter 7.

In Chapter 8, I presented the study that investigated the risk of developing CVD among OA cases based on a random sample drawn from the BC administrative health records. In this prospective longitudinal study, for which the mean follow-up period was 13 years, I observed that OA increased the risk of hospitalized CVD in both younger and older women and in older men, compared to their age-sex matched non-OA counterparts. Younger women with OA were at 65% increased risk for IHD and 29% increased risk for CHF. For older men and women with OA, the risk for IHD other than MI and CHF was lower but still statistically significant. Women who underwent TJR had a 31% increased risk of CVD, a 73% increased risk of IHD, and a 36% increased risk of CHF; men who underwent TJR had an 80% increased risk of CHF. In this study, individuals with OA showed no significant association with MI or stroke. To the best of my knowledge, this is the first prospective longitudinal study showing a relationship between OA and incident CVD that used an administrative database. A detailed comparison of these findings with the published data was presented in Chapter 8.

In my second prospective study, I investigated the risks of diabetes mellitus among individuals with OA, and this study was presented in Chapter 9. Based on the same random sample drawn

from the BC administrative database, OA cases were also found to be at increased the risk of developing diabetes in both younger and older women and in younger men, compared with age-sex matched non-OA individuals. Younger OA cases that underwent TJR, had a 37% increased risk of diabetes, compared to their matched non-OA counterparts. In this study, older men showed no significant increase in the risk of diabetes. To the best my knowledge, this is the first prospective longitudinal study of the link between OA and incident diabetes that used an administrative database. A detailed comparison of these findings with the published data was presented in Chapter 9.

10.2 Strengths of the Study

An important strength of this study is that a large random sample drawn from the BC administrative health records was analyzed. Therefore, the estimates of incidence, prevalence, and trends of OA are representative of the entire province. A second strength is that the OA cases in the administrative database were physician-diagnosed or collected from hospital-discharge records rather than self-reported conditions. A further strength lies in the use of medical records covering an 18-year period, which allows for a longer follow-up period in the prospective studies.

To estimate the risk for developing CVD and diabetes among OA cases, I used the same random sample drawn from the BC administrative health records. The strengths of these two analyses are as follows: OA cases and matched non-OA subjects were selected during the period 1991-1996, thus providing both the exposed and non-exposed groups sufficient time to develop the outcomes of interest (CVD or diabetes); inclusion of incident CVD/diabetes cases as events protected the

results from potential reverse causality bias. Studies have shown that the Hospital Discharge Database has a high validity (189–191), especially for cardiovascular disorders, such as heart failure and IHD, for which the positive predictive values have been estimated between 75–90% (189). The multivariable results were adjusted for age, sex, SES, imputed BMI, and several conditions known to be associated with CVD/diabetes, such as COPD, hypertension, hyperlipidemia, and a number of severe conditions that were included in the Charlson Comorbidity Index. Finally, separate analyses were performed for specific CVD events and for different severity levels of OA by age and sex.

To assess the relationship between OA and the prevalent CVD, I used the first 3 cycles of the nationally representative CCHS data. Hence, inferences based on CCHS data are generalizable to the entire Canadian population. In this population-based study, many possible covariates and confounding factors, such as age, BMI, income, education, physical activity, smoking status, fruit and vegetable consumption, medication use, diabetes, hypertension, and COPD were adjusted for in the multivariable analyses that were not adjusted for in the previous cross-sectional studies investigating the link between OA and prevalent CVD.

The validation study of administrative OA diagnoses has several strengths. These include, the use of a representative sample for clinical diagnoses, a population-based cohort that include subjects with pre-radiographic as well as advanced radiographic knee OA, and a comparison of two administrative OA definitions with four reference standards. To the best of my knowledge, this is the first study that compares administrative OA cases with the MRI cartilage-based OA assessments.

10.3 Limitations of the Study

Although I discussed the specific limitations of each specific components of this thesis in Chapters 4 to 9, several limitations of the overall study are discussed below. First, given that a random sample of BC administrative health records was analyzed, the results are representative of BC, and thus may not be generalizable to the entire Canadian population. Second, incidence and prevalence rates differ due to the different administrative case definitions of OA (6,17). The rates based on the two administrative definitions used in this study differed from those found in the literature that were based on self-reported, symptomatic, and radiographic OA. Third, the definition of OA based on ICD-9 and ICD-10 diagnostic codes creates a further limitation in that both false negatives and false positives may occur due to misdiagnosis or incorrect recording in the administrative forms. Lix et al. (25) validated administrative OA diagnosis comparing with the self-reported CCHS survey data. Based on two years of data and the case definition of two physician claims or one hospital separation, the authors obtained a sensitivity of 42.6% and a specificity of 88.1%. Harrold, et al. (24) used 2 years of administrative records and the estimated PPV of administratively coded OA was 62% when the prevalence was 8.7%. In my validation study, I obtained a PPV between 82 and 100% for the case definition based on two physician's visits in two years or one hospital diagnosis. Fourth, the incidence and prevalence rates for OA derived from the administrative data are also influenced by the run-in time, that is, the period during which prevalent cases are detected from the health records; a longer run-in period is recommended to have more accurate estimates of the incidence and prevalence. I used data covering a 17-year run-in period, therefore, this study produced more accurate estimates compared to those based on the earlier 10-year run-in time records (6). Fifth, the administrative database does not include information on some cardiovascular risk factors, such as smoking and

diet. However, these factors have not been shown to be related to OA and, therefore, are not

expected to be confounders of the relationships between OA and CVD and OA and diabetes. In

addition, the results were adjusted for COPD (a condition strongly associated with smoking),

which might reduce the effect of smoking in these relationships. Sixth, the administrative

database does not include patients treated in emergency care units; thus, some acute MI and

stroke deaths that occurred in the home or in hospital emergency care units, were not captured by

the study focusing on the relationship between OA and CVD. However, this should not result in

any differential misclassification in the analysis. Seventh, to control for confounding by BMI, I

imputed BMI from the CCHS data. Although the imputed values of BMI may not reflect the true

distribution in the sample, the effect on the results is probably small given that I imputed BMI by

matching on age, sex, OA, and outcomes (CVD or diabetes). Eighth, in the validation study, the

recruitment period for subjects was 2002-2005, and their administrative histories were linked

from 1991 to 2004. In an ideal situation, both clinical and administrative diagnoses should have

been performed in the same calendar year. However, among the elderly with OA and other

chronic diseases, the former often receives lower priority when they are assessed by a physician.

To minimize the number of undiagnosed OA cases I observed the medical history of these

subjects from 1991 to 2004. I did not include administrative records after the clinical assessment

to reduce false positives. Ninth, one limitation of the study based on the CCHS survey data was a

reliance on self-reported risk factors and outcomes. Self-reported data tend to contain both false

positive and false negative values. However, higher correlations were observed between the

measured and self-reported values of some of these variables. For instance, a comparison

between measured and self-reported BMI suggests that self-reported values may underestimate

the true prevalence of obesity by 9% in the case of men and 6% in the case of women (183). This underreporting has very little effect on the observed relationship between OA and heart disease.

10.4 Implications and Further Research

OA is a leading cause of disability among the elderly and the middle aged and therefore a major burden on the public health care system. Over the past several decades, overall life expectancy has increased greatly; at the same time, the non-fatal nature of this condition means that individuals will fall victim to chronic disability, making them vulnerable to other co-morbid conditions. Therefore, population-based epidemiologic data on chronic diseases, such as OA, are of critical importance to public health authorities. Although there is no cure for this condition, policy makers and healthcare professionals have made extensive efforts to improve the health of OA patients through better detection, management, and public health programs (1,5,7,30,169). This thesis describes the epidemiology of OA and estimates the risk for severe comorbidity, such as cardiovascular conditions and diabetes, among individuals with OA. Thus, as a collective work, this thesis can contribute to public health policy debates around chronic disease treatment and prevention specific to OA. The findings will be of use across several clinical disciplines, including general practice, orthopedics, rheumatology, cardiology, physical medicine and rehabilitation. They may also prove to be of use in motivating researchers conducting biological, physiological, and epidemiological studies of severe chronic conditions in persons with OA.

The epidemiologic data in Chapters 4 and 5 describe the age-sex distribution of OA cases drawn from the BC health records, the number of new cases per 1000 person-years and changes in the incidence of OA over time. These data help to understand the nature and extent of the disease in

the population, which is critical for developing prevention strategies and policies. Higher rates of incidence and prevalence were observed for both men and women compared to earlier studies based on administrative data. Thus, future studies focusing on descriptive epidemiology and drawing upon health records from different health regions would be useful for comparative purposes as well as for informing population-based health promotion and disease prevention strategies around OA.

The relationship of OA with CVD, MI, CHF, angina, and diabetes remains a promising and important area of research. Given that OA is a highly prevalent health condition, its association with CVD and diabetes is of great interest from a public health perspective in that understanding it would facilitate the formulation of policies aimed at preventing and treating these conditions. This thesis has identified possible causal associations and raised further questions for subsequent research. To the best of my knowledge, Chapters 8 and 9 present, respectively, the first prospective longitudinal studies to estimate the risk of CVD and diabetes among individuals with OA. These findings can inform additional strategies aimed at targeting both older and younger adults with OA and educating them as to its implications for cardiac management. The ultimate goal here should be to increase knowledge of the risk of both CVD and diabetes among men and women with OA and emphasize the adverse impacts of modifiable factors such as immobility, metabolic syndrome, obesity, muscle weakness, NSAIDs use, and other lifestyle changes due to OA. However, as the results are preliminary, conclusions should be conditional on confirmation by future studies. More population-based studies are needed to understand the temporal ordering of the relationship between exposure to OA and the incidence of CVD and diabetes prospectively. Prospective studies that use clinical diagnoses of these conditions include all

possible confounding factors such as BMI, and mediating variables such as drug use and physical activity are also needed. Upon confirmation these prospective longitudinal study results will provide a rationale for undertaking further biological and clinical studies of CVD risk and increased blood sugar in persons with OA.

In this thesis, OA was found not to be significantly associated with increased risk for either hospitalized MI or stroke. Developing a better understanding of the relationship between OA and MI and stroke is an important area of research. Mortality due to acute MI and stroke occurring prior to hospital admission was not included in the administrative database and obviously not in the CCHS samples. Studies that include MI and stroke-related mortality prior to hospitalization may further elucidate this relationship. Use of other sources such as data from emergency care departments may be useful for conducting this kind of research.

Administrative databases can play an important role in OA surveillance. The data therein can be used to describe demographic variations in the prevalence and incidence rates of OA, to examine trends, and to identify the groups at greater risk for the disease. These data are also useful in studying the potential disease impact on other severe comorbid conditions and mortality at the population level. Prior to using such data, it is essential to conduct validation studies aimed at examining the accuracy of administrative diagnoses. The validation study in this thesis included x-rays and MRI examinations of the knee only. Additional validation studies that include x-rays and MRI measurements for the knee as well as other joints, such as the hip, and hand, would be invaluable.

10.5 Conclusion

This thesis has provided an updated descriptive epidemiology and trends of OA by examining administrative health records that cover extended periods of time; in so doing, it has generated improved estimates of the incidence and prevalence of this condition. The validation study has suggested that the sensitivity and specificity of administrative OA diagnosis depend on the definitions and reference standards used. It has further suggested that for the purpose of defining the administrative OA, one physician's claim or one hospital admission would suffice for descriptive analyses as it reduces underestimation attributable to false negatives. In the case of outcome research, where avoiding false positives is critical, at least two physician claims within two years or one hospital admission might be a better choice. Positive associations between OA and overall heart disease, angina, CHF, and MI in the CCHS samples were observed. These findings provide a rationale for further investigations of the association between OA and CVD in prospective cohort studies. In this prospective longitudinal study, adult women and older men with OA were at higher risk for developing CVD, especially IHD and CHF, compared to their age-matched non-OA counterparts. The findings also indicate that men and women with OA are at higher risk for developing diabetes compared to their matched non-OA counterparts. Despite several limitations, this research has allowed us to identify statistically significant and biologically plausible relationships between OA and co-morbid conditions as well as to provide a rationale for further biological, physiological, and epidemiological studies of cardiovascular outcomes and diabetes in persons with OA.

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