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The Epidemiology and Risk of Developing Osteoarthritis among Albertan Farm Residents

by

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Abstract

Background

In Canada, approximately 3.9 million cases of osteoarthritis (OA) were reported in individuals aged 20 years or more, which highlights OA as a type of joint disease characterized by degeneration that significantly impacts a considerable portion of the population. According to estimates, the prevalence of OA in Canada will rise to 25% of the total population and nearly 30% of the workforce by 2040. However, certain groups may be at a higher risk for developing this condition, including farmers who engage in repetitive manual tasks and experience prolonged periods of kneeling, standing, or heavy lifting. The physical demands of farming can lead to increased strain on the joints, making farmers more susceptible to developing OA. Despite the farmers are a critical component of the Canadian economy, and their physical health is essential to maintaining productivity and economic growth, insufficient research has been conducted on OA among this particular high-risk group in Canada.

Objectives

This study aimed to estimate the risk of developing OA in individuals who are 20 years of age or older and reside on farms in Alberta and compared to non-farm rural and urban cohorts. Other objectives for this study include estimating the age-sex-specific incidence rate of OA, the lifetime risk of developing OA, and the non-injury mortality rate over 21 years.

Method

A historical cohort study was implemented, using a large sample (n = 430,293) of three cohorts: the farm, non-farm rural, and urban cases from Alberta administrative databases for the fiscal years 2000-2001 through 2020-2021. Case ascertainment for OA was defined by an algorithm that consisted of one hospital admission, two physician visits within a two-year interval, or two ambulatory care visits within two years. Using person-years (PYs) of follow-up as the denominator, crude incidence, age-sex-specific incidence, lifetime risk, and mortality rates of OA were estimated. To account for the effect of residency on the development of OA, Cox proportional hazard model was applied.

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Results

The results of this study identified 26,957 cases of OA in the farm cohort over 1,706,256 PYs of follow-up, with an overall incidence rate of 14.72 (95% CI: 14.51, 14.93) per 1000 PYs during the 21 years. The crude incidence rate of OA in the farm cohort was 10.58 (95% CI: 9.79, 11.36) per 1000 PYs in 2021. The risk of developing OA was determined 6% (95% CI: 4, 8) and 9% (95% CI: 7, 12) greater for farm and non-farm rural populations than for the urban cohort, respectively, after adjusting for age and sex. Farm residents were observed to have a higher mortality-adjusted lifetime risk of developing OA (27.7%) than their non-farm rural and urban counterparts. Non-injury mortality among farm residents with OA was found to be 13.16 (95% CI: 12.87, 13.45) per 1000 PYs.

Conclusion

This study contributes significant findings on the incidence and impact of OA among farmers in Alberta. Our findings indicate that individuals residing in rural areas, including farmers, are at a higher risk of developing OA compared to the urban group. The higher mortality-adjusted lifetime risk of developing OA among farm residents highlights the necessity of specific interventions aimed at reducing the impact of this condition in rural communities. Further research is required to identify specific occupational and lifestyle risk factors associated with OA among farmers and to develop effective strategies for prevention and management.

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Preface

This thesis is an original work by Elaheh Rahmanzadeh Koucheh under the supervision of Prof. C. Allyson Jones and Prof. Donald C. Voaklander as the committee member. The Health Research Ethics Board (HREB) of the University of Alberta granted ethics approval for this study, File No.: Pro00121377.

A version of Chapter 3 of this thesis is submitted as The Risk of Developing Osteoarthritis in Albertan Farm, Non-farm Rural, and Non-farm Urban Residents: A 21-year Retrospective Study for the Rural and Remote Health Journal. I was responsible for data analysis and manuscript writing and revision while Jones A and Voaklander D contributed to concept formation and content reviews.

No part of this thesis has been previously published. All data analyses, interpretations, manuscript compositions, and literature reviews are my original work with guidance from my supervisory committee. As the author, I take full responsibility for any error or misrepresentation in this thesis.

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Dedication

To my dearest mother and father, whose unwavering love and support have been my guiding light throughout this journey. Your sacrifices, encouragement, and words of wisdom have given me the strength and determination to pursue my dreams.

To my beloved sisters and my nieces, who have always been my confidantes and pillars of strength. Your unwavering support, patience, and understanding have helped me to stay focused and motivated, even during the toughest times.

And finally, to my loving husband, who has been my rock, my partner, and my soulmate. Your constant love, support, and belief in me have been the foundation of my success. You have stood by me through thick and thin, cheering me on every step of the way. Your presence in my life has made everything more beautiful and meaningful.

This thesis is dedicated to all of you, with all my heart and soul. Your love and support have been the bedrock of my achievements, and I could not have done it without you. Thank you for being my constant source of inspiration and for always believing in me.

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Finally, I would like to express my gratitude to Alberta Health for providing the data for the cohorts in this study, and to the School of Public Health at the University of Alberta for providing a conducive and collaborative environment for this research.

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List of Abbreviations

OA	osteoarthritis
DALYs	disability-adjusted life years
AH	Alberta Health
SES	socioeconomic status
DNA	deoxyribonucleic acid
BMLs	bone marrow lesions
CI	confidence interval
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
ISCO-88	International Standard Classification of Occupations 1988
TKR	total knee replacement
THR	total hip replacement
HR	hazard ratio
WHO	World Health Organization
BMI	body mass index
TKA	total knee arthroplasty
BMD	bone mineral density
ACL	anterior cruciate ligament
RR	relative risk
UK	United Kingdom

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YLDs	years lived with disability
GBD	Global Burden of Disease
COPD	chronic obstructive pulmonary disease
CCI	Charlson comorbidity index
ICD	International Classification of Diseases
VAS	visual analogue scale
NRS	numerical rating scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index
KOOS	Knee injury and Osteoarthritis Outcome Score
OMERACT-OARSI	Outcome Measures in Rheumatology-Osteoarthritis Research Society International
HOOS	Hip disability and Osteoarthritis Outcome Score
ICOAP	Intermittent and Constant OA Pain
AUSCAN	Australian/Canadian Osteoarthritis Hand Index
ACR	American College of Rheumatology
MCP	metacarpophalangeal
ESR	erythrocyte sedimentation rate
JSW	joint space width
KL Grade	Kellgren and Lawrence grade
JSN	joint space narrowing
MRI	magnetic resonance imaging
NSAID	non-steroidal anti-inflammatory drugs

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IPD	individual patient data
CVD	cardiovascular disease
IAA	inflammatory and autoimmune types of arthritis
CCHS	Canadian Community Health Survey
AHCIP	Alberta Health Care Insurance Plan
DAD	Discharge Abstract Database
NACRS	National Ambulatory Care Reporting System
PHN	personal health number
TVC	time-varying covariate
IRR	incidence rate ratio
KM	Kaplan Meier
BC	British Columbia
CCDSS	Canadian Chronic Disease Surveillance System
CIHI	Canadian Institute for Health Information
HIA	Health Information Act
PY	person-years

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Chapter 1. Introduction

1.1 Overview

Osteoarthritis (OA) is one of the most prevalent types of arthritis, causing significant pain and a detrimental impact on daily physical functions and quality of life, especially among the elderly[18,37–39]. According to the Global Burden of Disease Collaborative Network, an estimated 528 million (6.3%) people had OA in 2019, and the rate for disability-adjusted life years (DALYs) was 228 per 100,000 worldwide[3]. As high-income countries are facing the challenge of an aging population and growing obesity, OA prevalence is increasing among these nations[3–5,25]. In Canada, approximately 3.9 million (13.6%) people aged 20 years and above lived with diagnosed OA in 2017[6]. According to the report of the Arthritis Alliance of Canada, 25% of Canada's population and almost 30% of the workforce are estimated to have OA by 2040[7]. There are several possible risk factors for OA including age, sex, injury, and obesity[40–42]. Occupation with a heavy physical workload is another important risk factor that has been linked to OA[10,43]. Occupations that involve heavy physical workloads, including kneeling, squatting, and heavy lifting of over 25 kg, can increase the risk of developing knee OA by as much as five times[10].

Farm workers are one of the occupational groups that may be susceptible to OA due to the physical demands of their work[44]. Farming is a heterogenous occupation, with different types such as dairy, swine confinement, cattle, and crop rising, and great differences between ultramodern high technology and traditional farming[45]. Farmers are often self-employed and payment is related to output which in turn requires long hours, seven days a week. Within Alberta, farming consists of crops, livestock, and mixed farming. Crop farming has significant seasonal changes in workload, while the workload of livestock farming is generally more consistent throughout the year, with some seasonal variations during breeding or birthing seasons. Farming involves long-standing exposure to high levels of physical workload starting at a young age and continuing after regular retirement age[46]. Farm-related activities include greater strength, digging, lifting, and shoveling, compared with other types of manual labor[44,47]. As a result, farmers are at a higher risk of OA due to their heavy physical workload.

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Osteoarthritis causes a significant amount of pain and disability for patients, leading to a lower quality of life and high economic costs[8]. Because of the occupational demands of farming, focusing on OA and its risk factors among farmers and gaining an understanding of the pattern of OA incidence using health administrative data is important from a public health perspective. This can help in identifying the high-risk groups and associated risk factors, which can aid in developing targeted prevention and intervention strategies to decrease the burden of the disease.

1.2 Statement of the Problem

The 2021 Census of Agriculture data highlights the continued importance of the agriculture sector in the Canadian economy and society. Canada has a total of 189,874 farms, with 262,455 farm operators, and 242,052 paid workers[48]. Within Canada, Alberta has the second-highest number of farmers, with 118,785 individuals in the farm population[16]. Farming is widely recognized as one of the most physically demanding occupations, often involving a heavy physical workload that requires significant muscular effort and frequently combines manual labor and heavy lifting[47,49]. Advancements in farming technology have significantly increased the level of mechanization involved in agricultural production, resulting in a decrease in the amount of energy expended in farming. As a result, the nature of farm work is changing, with an increasing reliance on technology to improve productivity and reduce physical demands on workers[50]. The mechanization of farming, particularly on grain-producing farms, has led to decreased physical activity and energy expenditure among workers, potentially contributing to the risk of obesity[51–53]. This is concerning as obesity is a recognized risk factor for OA[54–56], highlighting the need for preventative measures and interventions in farming communities.

Injury is another risk factor for OA. Although mechanization and other technological advances have decreased the amount of physical labor, manual labor tasks are still common in the farm production process. Many agricultural tasks are frequently performed in unsafe environments, which can result in injuries[12,57–59]. The use of modern agricultural machinery and equipment has led to newer injuries among farmers[60]. Moreover, aged farm workers along with the lack of workforce replacements have become a severe issue, placing a greater load on those who are still employed[61]. Fatigue, poorly made tools, challenging terrain, and poor general health all increase the risk of injury[12,60,62,63].

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To our knowledge, no study has investigated the epidemiology of OA among the farm population of Alberta, although the prevalence of OA has been examined in Saskatchewan[13]. Improving our comprehension of the epidemiology of OA and its risk factors among farmers can inform policymakers and healthcare providers to enhance the health of people with OA and reduce the burden of OA through improved access to healthcare services, and public health programs.

1.3 Aim and Objectives

This thesis compares the incidence and mortality rates of OA in the Alberta farming cohort to non-farm rural and urban cohorts. Using administrative health data obtained from Alberta Health (AH) for the 21 years from the fiscal years 2000-2001 through 2020-2021, this study aims to estimate the incidence and mortality rate of OA among farm resident populations aged 20 years and older.

The specific objectives are:

1. To compare the incidence rate and hazard ratio of OA in farm residents in Alberta with the non-farm rural and urban cohorts.
2. To compare the mortality-adjusted lifetime risk of developing OA in farm residents in Alberta with the non-farm rural and urban cohorts.
3. To compare the non-injury mortality rate of OA in farm residents in Alberta with the non-farm rural and urban cohorts.

1.4 Significance

Although the relationship between occupation and OA has been the subject of some studies[64–67], very few have explored the occupational risk factors of OA among farmers[68]. Farming is one of the most common occupations involving a heavy physical workload alongside construction, firefighting, and coal mining[14]. Individuals with OA have a lower quality of life compared to the general population, with a reduction of 10 to 25 percent[1], and this contributes to an economic burden of CAD $405 billion in direct and indirect costs in Canada in 2020[7]. Farmers are at higher risk for developing OA due to occupational-related joint stress and growing obesity. There is a lack of evidence regarding OA

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occurrence in the farm population. It is, therefore, necessary to understand the incidence, all-cause mortality, and risk of developing OA among this high-risk group to develop an optimal management plan for the disease.

Different clinical studies have utilized different OA case definitions (self-reported, physician-diagnosed, radiographic, or symptomatic)[69–71]. To determine the population-level incidence of OA using administrative health data is necessary. Although a few studies used administrative health records to estimate incidence[72,73], they studied the population for a shorter period of time, which led to the overestimation of the rates[72,74]. When examining the temporal trends of chronic conditions such as OA, health data spanning 21 years will provide a more comprehensive understanding of how the disease has evolved over time, compared to data from a shorter period. To our knowledge, no studies have estimated the risk of developing OA among the Alberta farm population as compared to the non-farm rural and urban populations.

In summary, make a valuable contribution to the existing literature by providing more accurate assessments of the descriptive epidemiology of the disease and long-term trends of OA among the Albertan farm population as a cohort with a high workload using a large administrative database. This study aims to identify the potential risks of developing OA among farm residents in comparison to non-farm rural and urban cohorts. The results will also estimate the incidence and lifetime risk of developing OA and compare the mortality rates of OA cases with non-OA individuals in the farm cohort. This research could guide future studies investigating high-risk occupations for developing OA.

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Chapter 2. Literature Review

2.1 Introduction

Osteoarthritis is a prevalent chronic condition that leads to long-term disability and has substantial clinical and economic impacts[19,41,74–76]. Despite OA being capable of impacting all joints in the body, it often impacts joints that bear a significant amount of weight or pressure like hips and knees, as well as hands, feet, and the spine[77,78]. Primary symptoms include pain, functional impairment, and stiffness[79]. The incidence of OA was 8.7 per 1,000 individuals in 2016-2017 and it is anticipated to increase in Canada due to the growing prevalence of obesity and an aging population[5,80]. The burden of OA is expected to become even more significant with an economic burden[7]. Osteoarthritis significantly impairs people's quality of life, restricts their work capacity, and leads to substantial medical expenses[81]. Given the significant impact of OA on individuals and society, there is a pressing need to understand the current state of knowledge regarding this condition. This chapter will provide a comprehensive review of the epidemiology, risk factors, diagnosis, and treatment options for OA.

2.2 Osteoarthritis

As a long-term chronic disease, OA is characterized by increasing cartilage degeneration, concurrent adaptive osteogenesis, and loss of joint function (Figure 2-1)[40,82,83]. Cartilage is the rigid, elastic tissue that covers bone joints and facilitates easy bone movement. Degradation or wear of cartilage can result in bones rubbing against each other, giving rise to sensations of tenderness, pain, and stiffness[78]. Osteoarthritis can impact almost any joint, but it is more commonly observed in the hands, feet, hips, knees, and spine[84]. Recent evidence suggests that OA is not caused by the natural aging process or degenerative changes alone, but rather by the body's inability to properly repair joint tissues that have been damaged due to improper joint loading, injury, or obesity[77,78,85]. Following the initial molecular disruption of abnormal joint tissue metabolism, OA can lead to physiological and anatomical abnormalities such as cartilage degeneration, bone remodeling, osteophyte formation, joint inflammation, and decreased joint function[83].

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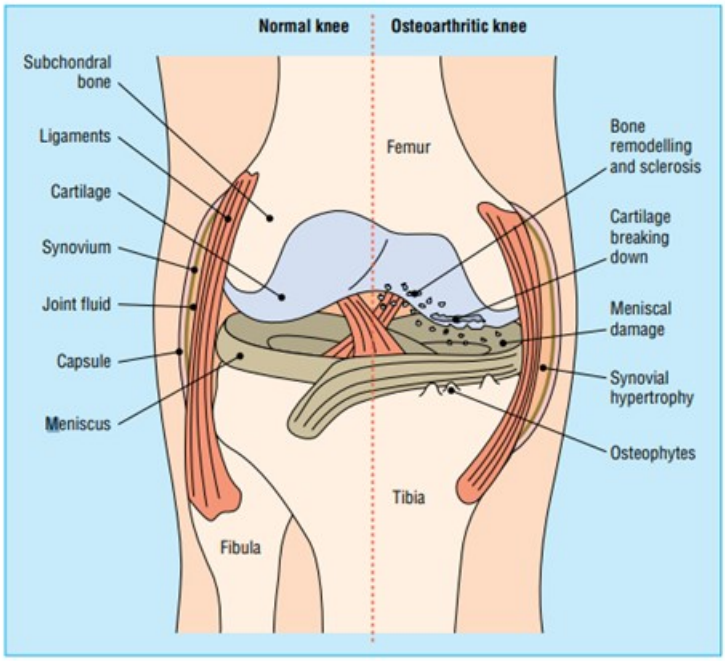

Figure 2-1 Normal versus osteoarthritic knee joint adapted from Hunter and Felson[82]

2.3 Pathology of Osteoarthritis

The pathogenesis of OA is characterized by a metabolic dynamic process that involves both the breakdown and synthesis of tissues responsible for the development of the disease. The metabolic dynamic process of OA involves both vascular and non-vascular pathology. Bones, being highly vascular structures, rely on their vasculature for growth, healing, and metabolic processes[86]. Consequently, vascular pathology may contribute to the development of OA. One possible cause of vascular pathology in OA is the intermittent reduction in blood flow through the tiny capillaries in the subchondral bone at the extremities of long bones, which can result in a corresponding decrease in interstitial fluid flow in the subchondral bone[87]. Venous blockage can restrict blood flow which can result in subchondral ischemia. Subchondral ischemia can have several effects, including impaired nutrient and gas metabolism in the articular cartilage, which can contribute to degenerative alterations in the cartilage[88]. Another cause is osteocyte apoptosis, which would lead to osteoclastic resorption of the subchondral. This process can temporarily decrease the support provided by the bone to the surrounding cartilage[89,90].

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Non-vascular pathology is also involved in the metabolic dynamic process of OA, which is characterized by the formation of new tissue in synovial joints with increased metabolic activity at multiple joint sites. This suggests the possibility of a regenerative process that follows joint degeneration. This slow repair process may be effective in many cases, resulting in a painless joint despite its structural abnormality. However, if the damage to the joint is extensive or if the repair process is inadequate, the joint may continue to remodel in an attempt to keep up with the damage. This remodeling process can eventually result in the failure of the joint, leading to symptoms such as pain and functional impairment. The smooth surface of the joint is normally covered by articular hyaline cartilage, which is responsible for providing the joint with its biomechanical properties[91]. Cartilage undergoes many transformations during OA. Initial disruption of the type II collagen framework results in an increase in cartilage volume, accompanied by an increase in water content and swelling of the proteoglycans[91]. As the disease progresses, small cracks or fibrillations develop within the cartilage, leading to ongoing protein degradation and ultimately loss of cartilage tissue[91]. In the deeper layers of the cartilage, the calcified area becomes thicker, and blood vessels and nerves penetrate the tidemark between the calcified and non-calcified cartilage, leading to neovascularization and neo-innervation of the cartilage[91]. Despite these changes, the aneural nature of articular cartilage means that pain does not typically occur until the innervated tissue is affected[92]. The stimulation of periosteal and synovial mesenchymal stem cells leads to the generation of fibrocartilage, which then undergoes endochondral ossification to form bone at the junction between cartilage and bone[93]. The formation of bony growths on the edges of joints, known as osteophytes, is a common feature of OA. Osteoarthritis causes several changes that can be observed directly within the subchondral bone, although the exact cause is unknown[91]. Bone marrow lesions (BMLs), cysts, and subchondral sclerosis are morphological changes in the subchondral bone[91].

Recent research has shown that OA involves low-grade inflammation of the synovial membrane (synovitis)[93]. It is generally accepted that OA is inflammatory, as shown by the presence of synovitis, effusion, and stiffness[94]. Others think the main cause of OA is inflammation[94,95]. According to one theory, local inflammation that results in synovitis and activates mechanoreceptors locally produces post-traumatic OA[95]. Similarly, OA is thought to be caused by low-grade systemic inflammation in metabolic syndrome, by a secretory inflammatory phenotype in old age, and by innate immunity in crystal OA[95].

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The role of mechanical factors in the development of OA has received increased attention in recent times, with a focus on the concept of a vicious cycle[96]. Meniscal tears, congenital dysplasia, malalignment, and chronic excessive loading are only a few examples of the various traumas that can cause abnormal mechanical loading[96]. The affected cartilage is destroyed, and the underlying bone may undergo remodeling, resulting in an increase in abnormal loading[96]. As a result, cartilage fragments could trigger a secondary inflammatory reaction in the synovium, which would manifest as synovitis and excessive fluid secretion[96]. This idea is mostly supported by research that has discovered links between OA risk factors, such as obesity, injury, and occupational overuse, and aberrant mechanical forces in the joint[96].

2.4 Clinical Symptoms and Signs

The main manifestations of OA are stiffness, joint pain, and reduced range of motion. Typically, middle-aged or elderly individuals only experience symptoms in one or a few joints. Osteoarthritis can also cause sequelae such as muscle weakness and impaired balance in affected patients[97]. Apart from the primary symptoms, patients with OA may also express concerns about joint deformity, locking, and swelling, without experiencing systemic symptoms such as fever or crepitus. Patients may also experience discomfort related to advancing age, and if pain persists, they may experience psychological distress related to pain[98].

2.4.1 Pain

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional encounter that is linked to real or potential tissue damage or is characterized in terms of such damage[99]. Pain is a multifaceted and individualized occurrence that is affected by biological, psychological, and societal elements, and is perceived diversely among individuals[100]. Typically, pain serves a protective function. However, when it persists beyond its warning function, as in chronic pain, it is considered maladaptive. Distinct from many other pain-related conditions, where the damage usually heals or improves, OA is a chronic condition that cannot be completely cured. As a result of its chronic nature, OA is often associated with persistent pain. Several factors can contribute to the pain experienced by individuals with OA, including both central (nervous system) and peripheral (local joint tissue)

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influences. Pain in OA is typically related to joint usage, worsens towards the end of the day, and is alleviated by rest[101].

Several qualitative research studies have explored the pain experience of individuals with OA. Hawker et al. conducted a study and identified two distinct types of pain experienced by individuals with hip and knee OA: one that was intermittent but highly intense, and another that was characterized by continuous, mild pain[101].

Although cartilage is not innervated, there are nociceptors in other structures of the joint, including the synovium, capsule, subchondral bone, and periosteum, indicating that pain in OA cannot originate from the cartilage[102]. Roughly a third of people with knee OA describe their symptoms as tingling, numbness, burning, or pins and needles, representing another variation in the quality of pain associated with OA[103]. Although there is no evidence of nerve damage in OA, the presence of different types of pain suggests that neuropathic pain might contribute to OA pain. In OA, ascending signals can be modified at the spinal cord and brain level due to biomechanical damage, soluble inflammatory mediators such as prostaglandins and cytokines, and peripheral nociceptor sensory nerves[102]. According to O'Neill and Felson, central sensitization refers to the mechanism by which activated neurons become hypersensitive to subsequent stimuli that bind to the neuron's receptor fields[104]. As a result of the increased sensitivity of the pain centers caused by persistent input and other sources of pain, even low-strength nociceptive impulses from the OA joint can cause greater pain to be perceived.

Osteoarthritis cohort studies and trials use various techniques to assess pain, including the visual analog scale (VAS), numerical rating scale (NRS), the pain subscale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[105], Knee injury and Osteoarthritis Outcome Score (KOOS)[106], Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI), Hip disability and Osteoarthritis Outcome Score (HOOS)[107], Intermittent and Constant OA Pain (ICOAP), and the Australian/Canadian Osteoarthritis Hand Index (AUSCAN)[108].

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2.4.2 Stiffness

Osteoarthritis is responsible for joint stiffness and reduced function[109]. Unlike inflammatory arthritis, stiffness caused by OA has a short duration (less than 30 minutes), often referred to as "gelling," which is a brief stiffness felt after a period of inactivity[110].

While bone density and stiffness are frequently used synonymously and apparent density is correlated with bone stiffness, it is clear that they represent separate concepts, even though one may indicate the other[111]. Calcified cartilage is one of the contributing factors to OA, as alterations to this type of cartilage can lead to joint stiffness. It is widely believed that calcified cartilage falls in between the stiffness of the thick and stiff bone located below it, and the less stiff and more flexible cartilage located above it[111].

Trabecular microfractures are also thought to contribute to stiffness in OA. Fractures in the trabeculae, along with the subsequent healing with callus formation, are believed to be responsible for subchondral bone stiffening in OA. Upon healing, the callus may undergo more extensive mineralization than regular bone. This callus formation may increase the bone volume, thereby increasing joint stiffness. Therefore, it is suggested that the interaction between these factors could lead to an increase in subchondral bone density and stiffness in OA[111].

2.4.3 Functional Impairment

Arthritis is ranked as the second primary reason for job disability, surpassed only by cardiovascular disease (CVD)[112], and it significantly affects the individual's capacity to perform job-related tasks and daily activities. Individuals with OA experience more significant limitations in their ability to participate in both work-related and everyday activities compared to those without OA. Approximately 25% of individuals with OA worldwide cannot perform their major daily activities, and 80% of them experience limitations in their mobility[113,114].

For adults with knee OA, approximately 11% of personal care tasks and 14% of daily tasks require assistance[115]. Osteoarthritis can result in disability ranging from mild to severe, with some experiencing intermittent pain and minor difficulties performing daily activities, while others experience

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chronic pain and loss of function to the extent that affected individuals may have difficulty walking or living independently. Arthritis pain is a significant obstacle to continuing physical exercise, which can be associated with the onset of frailty in older adults and can have a negative impact on mental health[116–118].

The most prevalent occupational non-fatal injuries and illnesses for farm workers, particularly those who engage in labor-intensive activities, have consistently been proven to be musculoskeletal disorders[119,120]. Musculoskeletal diseases have significant consequences for the farming community, leading to long-term disability and loss of income. This can be attributed to the unique postures and positions involved in farming, which often require long workdays with limited breaks for rest. Aging is another contributing factor to disability among farmers. Engaging in strenuous physical activity at a young age has been suggested as another contributing factor that has received some support in other studies[121]. Sprince et al. suggested that farmers who have medically diagnosed arthritis have higher odds of sustaining animal-related injuries in the future (OR: 3.0; 95% CI: 1.7, 5.2). They explained that reduced movement in the lower or upper extremities could negatively affect a farmer's ability to handle or avoid large animals[122]. The award of disability pension was higher for farmers with hip OA compared to those with physically less demanding activities in Sweden (OR: 13.8; 95% CI: 4.0, 48.1)[123].

2.5 Diagnosis

The identification of OA through clinical diagnosis is reliant on the manifestation of symptoms, and the primary objective of any intervention is to prevent or alleviate these symptoms. Typically, patients seek medical attention due to the emergence of these symptoms, rather than participating in screening or research initiatives. However, using symptoms to diagnose OA poses a challenge, as they may only present in the advanced stages of the condition, which may be irreparable. This phase can occur following a period of subclinical structural changes. As a result, detecting OA early, when intervention is more likely to be effective, may not provide significant benefits in terms of disease modification. Moreover, there are additional limitations to this approach, such as the significant variation in symptoms over time, and their susceptibility to concurrent pathology and modulation by pain pathways[98].

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Radiographic abnormalities in a joint may not always manifest as symptoms[124,125], which is why in epidemiological research, instances of OA are identified using a combination of self-reported symptoms, radiographic examination, and imaging. However, there is variation in the techniques commonly used to identify cases of OA. Below are some quick explanations about symptomatic and radiographic OA diagnosis.

2.5.1 Symptomatic Diagnosis

The prevalent indication of OA is the gradual emergence of pain in the synovial joints that may exacerbate during vigorous activity and alleviate during rest[126]. Joint inflammation and morning stiffness that persists for at least 15 minutes are also frequently indicative of OA[127]. In rare cases, severe OA can lead to joint deformity and ligament laxity[128]. The American College of Rheumatology (ACR) Criteria is the most commonly used approach for diagnosing symptomatic OA.

The ACR criteria have been created for the hand[129], knee[130] and hip[131]. The existence of subjective OA is reliant on how the patient perceives the presence of the disease. Individuals with OA who experience pain may not show any changes in radiographic exam, whereas individuals with noticeable radiographic abnormalities can experience no symptoms. The correlation between the severity of radiographic abnormalities and symptoms in individuals with OA is not very strong[132].

The diagnosis of hand OA involves the consideration of various factors, including the enlargement of hard tissue in two or more joints. These joints typically include the first carpometacarpal joint in both hands, the second and third proximal interphalangeal joints, and the second or third distal interphalangeal joints. The assessment involves the hypertrophy of hard tissue in two or more distal interphalangeal joints and the deformity of at least one joint indicated in the initial criteria. However, less than three swollen metacarpophalangeal (MCP) joints are observed in this diagnosis[129].

The ACR has developed clinical criteria for the classification of knee OA. To fulfill these criteria, patients are required to display any three of the following characteristics, in addition to knee pain: age over 50, morning stiffness that dissipates within 30 minutes at most, crepitus during movement, bony tenderness, enlarged bones, and absence of detectable warmth[130]. In the diagnosis of hip OA, patients

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are required to have hip pain and exhibit a minimum of two of the following features: radiographic joint space narrowing (JSN), radiographic femoral or acetabular osteophytes, and erythrocyte sedimentation rate (ESR) less than 20 mm/hour. These criteria have been established by the ACR to provide healthcare providers with guidelines to effectively diagnose hip OA in patients[131].

2.5.2 Radiographic Diagnosis

2.5.2.1 Radiographic K-L Grade

Despite the emergence of more sophisticated imaging techniques, radiographs remain the most convenient tool for evaluating joints affected by OA. Radiography has been traditionally utilized to examine bony changes in OA. This method provides a clear view of early disease developments. As the condition progresses, radiography is utilized to assess joint space width (JSW), which indirectly indicates the condition of the hyaline and fibrocartilage[133].

Several radiographic grading systems have been proposed for OA, but the Empire Rheumatism Council approach, initially defined by Kellgren and Lawrence over 30 years ago, has been widely adopted in most epidemiological studies[134,135].

The Empire Rheumatism Council approach rates OA at different joint sites using a radiological atlas, assigning each location to one of five grades (0-4). The increasing severity of OA is determined by the sequential appearance of osteophytes, joint space loss, sclerosis, and cysts. A KL grade of 0 indicates the absence of radiographic signs of OA, and a KL grade of 1 indicates the presence of osteophytic lipping and doubtful (JSN)[134]. Radiographic OA is assigned a KL grade of 2, indicating the presence of evident osteophytes and possible JSN on an anteroposterior weight-bearing radiograph[134]. Further disease progression is described by KL grade 3, which is defined by multiple osteophytes, definite JSN, sclerosis, and possible bony deformity. KL grade 4 indicates the most advanced disease stage, characterized by large osteophytes, marked JSN, severe sclerosis, and distinct bony deformity[134].

However, the KL grading method for radiographic OA may have two significant limitations[136]. Firstly, the descriptions of radiographic signs have been inconsistent, resulting in studies using different criteria. Secondly, the method may overemphasize the presence of osteophytes. To address these

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concerns, recent studies have examined the repeatability and clinical correlates of the individual radiographic features of this grading system. JSN, osteophytes, and the overall KL grade all demonstrate good within-observer consistency for the knee and hand, with the osteophytes, score exhibiting the strongest correlation with knee pain[137,138]. Hip joint space constriction is the most reliable and strongly associated with hip pain according to research[139]. With the availability of recent standardized radiograph atlases, it is now feasible to consistently rate these specific characteristics and extend the findings of various studies[109]

Although radiography is useful in evaluating JSW, a study conducted by Amin et al. in 2005 showed that a significant proportion of individuals experiencing symptoms have cartilage loss as detected by magnetic resonance imaging (MRI), despite the absence of JSN or evidence of disease progression on radiography. The study found that radiography had a specificity of 91% but only a sensitivity of 23% for detecting cartilage loss[140]. Given its ability to provide contrast and improve the evaluation of subchondral bone integrity and lesions, MRI is a valuable imaging modality for bone assessment.

2.5.2.2 Imaging

Due to the complexity of OA, which involves joint degeneration, a thorough evaluation of the intra-articular structures of the entire joint is critical for a better understanding of the disease's etiology and progression. In recent years, imaging techniques have significantly improved the diagnosis and management of OA by providing a comprehensive view of the soft tissues. Among these imaging modalities, MRI has become increasingly popular as a means of detecting joint deterioration.

Observing changes in the subchondral bone composition is crucial in understanding the development of OA, and MRI is an effective tool for detecting these changes. MRI can identify subchondral bone changes earlier than radiographs. Several signs of disease progression include subchondral bone attrition, subchondral cyst-like lesions, and BMLs. BMLs are lesions associated with degeneration, which are characterized by the accumulation of fluid in the bone marrow, necrosis of bone marrow tissue, fibrosis, and anomalies in the trabecular bone structure[141,142]. They are often found in conjunction with nearby cartilage degradation[143,144], and the latest research have found have linked BMLs to advancing cartilage deterioration[145–147].

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An MRI cartilage scoring technique typically involves a semi-quantitative grading system on a scale of 0 to 4. A score of 0 indicates normal cartilage, while a score of 1 indicates an abnormal signal with intact cartilage morphology. A score of 2 indicates a loss of at least 50% of the thickness of the articular cartilage surface, and a score of 3 indicates a significant loss of cartilage depth, ranging from half to almost the entire thickness of the cartilage layer. A score of 4 indicates a complete absence of cartilage in the affected area, along with an abnormality in the signal of the bone tissue just beneath the cartilage[148,149]. Cases with MRI cartilage with a value of 2 or more are categorized as having OA.

2.6 Management and Treatment

At present, there is no known cure for OA. The current treatment strategies for OA, are to alleviate symptoms, particularly reduce pain, physical disability, and handicap, and improve the function of affected joints. Surgical procedures are often an option for OA patients who fail to respond to conservative treatments[82,150]. Painkillers and dietary supplements are considered pharmacologic treatments, while weight loss programs and exercise are non-pharmacologic treatments. Arthroplasty is a therapeutic option for end-stage OA[151–154]. Guidelines recommend a care plan that focuses on individualized management and patient involvement and includes essential non-pharmacological and complementary pharmaceutical modalities[151,155].

2.6.1 Non-pharmacological Treatment

Keeping a healthy body weight, regularly engaging in physical activity, and protecting joints from harm and misuse can help to lower the chance of developing OA or delay its development[84]. While there is no cure for OA, non-pharmacological approaches, including self-management training, exercise, weight loss if overweight or obese, and walking aids, are commonly suggested and considered the first line of treatment[84,156–158].

Information regarding the treatment options, the disease, pathophysiology, etiology, and diagnostic imaging are just a few of the topics that experts and patients have agreed upon as being crucial to patients' education[159]. The implementation of self-care management can be a useful strategy in the management of OA to alleviate depression, anxiety, and physical pain.

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Over the past decade, exercise therapy is particularly effective in reducing pain and improving joint mobility[160,161]. Despite the misconception that physical activity can harm the joints, regular and appropriate exercise, including both aerobic and local strengthening exercises, is essential for the effective management of OA[93]. To improve their overall fitness, and muscle strength, and preserve joint mobility, individuals with OA are advised to continue with neuro-muscular training, strengthening, and aerobic exercise within safe limits[162]. However, implementing this therapy on a wide scale and improving long-term adherence can be challenging.

Reducing exposure to mechanical risk factors that can be modified, such as obesity, is another important therapeutic strategy. Clinical trials such as the Arthritis, Diet, and Activity Promotion, and Intensive Diet and Exercise for Arthritis have demonstrated that combining dietary weight control with exercise produces Improved outcomes about pain relief and increased functionality than either intervention alone[163,164]. The use of walking aids, splints, local heat or cold applications, and environmental modifications (such as higher toilet seats and walk-in showers instead of baths) are other ways to reduce joint stress and prevent further damage.

2.6.2 Pharmacological

The present pharmacological approach to managing OA primarily prioritizes mitigating its symptoms, especially joint stiffness and pain, given the absence of any known cure for the condition. Table 2-1 shows the most frequent drug used in OA treatment.

Table 2-1 Categories of medication for osteoarthritis (OA) treatment

Acetaminophen	NSAIDs	Opioid Analgesics	SNRIs	Injection
Acetaminophen	Celecoxib, Diclofenac, Ibuprofen, Meloxicam, Naproxen, other NSAIDs	Codeine, Tramadol, Oxycodone, Morphine, Hydromorphone, Fentanyle	Duloxetine	Intra-articular Corticosteroids & Intra-articular Hyaluronic Acid

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Acetaminophen is frequently utilized as a pharmacological treatment for OA, particularly among analgesics[152,165]. In terms of efficacy, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are very similar for mild to moderate symptoms. However, healthcare professionals need to take into account patients' reactions to paracetamol and the potential for greater toxicity when taking regular or higher doses within the recommended analgesic dosage range[166].

To manage severe symptoms of OA, NSAIDs may be more effective[40,165]. Oral NSAIDs offer analgesic, antipyretic, and anti-inflammatory effects and are efficacious in treating OA when administered at a safe dosage[167]. However, safety is a critical consideration in determining the appropriate preparation and dosage for specific patients, especially concerning gastrointestinal and cardiovascular events. A 2018 meta-analysis indicated that topical NSAIDs, along with other first-line treatments, were beneficial for pain management in OA when compared to a placebo, with (adjusted) mean effect sizes of 0.30 for pain relief and 0.35 for improving function[168]. Current studies and reports in the general population have not indicated any significant adverse effects of topical NSAIDs, such as gastrointestinal or renal events[168].

Opioids are often employed to alleviate pain caused by OA. A meta-analysis demonstrated that while tramadol or tramadol in combination with paracetamol can decrease symptoms and enhance function in individuals with OA, the benefits are modest[169]. However, healthcare professionals recommend that opioids should only be considered as a last resort if the patient does not respond to acetaminophen or NSAID therapy, or if they cannot tolerate these medications due to adverse effects to avoid their overuse[152]. A 2014 meta-analysis demonstrated that the modest average benefits of non-tramadol opioids are accompanied by significantly increased risks of side effects, particularly concerning pain outcomes (mean effect size for pain relief 0.28)[170]. While most recommendations regarding the use of opioids were unclear until 2014[157,158], recent research has indicated that prescribing these drugs to patients with OA is generally discouraged due to the limited benefits compared to the negative effects, risk of addiction, and overdose[171–174].

Duloxetine is a serotonin and norepinephrine reuptake inhibitor that possesses antidepressant, central pain inhibitory, and anxiolytic effects and is recommended for treating refractory pain[158,175].

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Two significant trials conducted in China and Japan in 2017 demonstrated that duloxetine can relieve pain and improve function[176,177]. Further studies are required to determine whether this treatment approach is especially effective in individuals with neuropathic or central pain involvement.

A meta-analysis of 27 trials showed that intra-articular corticosteroids can enhance pain reduction, and they are recommended for consideration in individuals with pain that is unresponsive to other standard analgesics[178]. However, due to the heterogeneity of the evidence, the use of hyaluronic acid in OA is still a topic of debate[179]. Individuals with hip and knee OA who have not responded to oral or topical analgesics are recommended to receive intra-articular corticosteroids[157]. A meta-analysis of individual patient data (IPD) revealed that individuals with more severe pain responded significantly better to intra-articular corticosteroid injections than those with less severe pain when compared to placebo. Furthermore, although not statistically significant, the data suggested that individuals with evidence of joint inflammation responded better to treatment than those without such indicators when compared to placebo[180]. A 2017 randomized trial has raised questions about the efficacy of intra-articular corticosteroid therapy in knee OA after finding that individuals who received 3-monthly intra-articular injections of corticosteroids had slightly greater loss of cartilage volume over two years when compared to those who received a placebo[181]. However, it is not yet known whether these small differences have any impact on clinical outcomes over the long term.

2.6.3 Surgery

Surgery is sometimes needed for severe cases of OA to replace damaged joints, but it is not a complete cure as there may still be limitations after the surgery. During the initial phases of OA, medical practitioners may contemplate joint-conserving techniques such as osteotomy or arthroscopy based on the patient's primary diagnosis[182]. Joint replacement is divided into total joint arthroplasty (TJA) and hemiarthroplasty (HA). In contrast to TJA, HA only replaces half part of the joint and is a less technically demanding procedure for the surgeon. The benefits of HA include reduced surgical trauma, less blood loss, and lower economic costs. However, it has a higher incidence of postoperative pain and can lead to further wear of the untreated acetabular cartilage. Hence, the decision to choose TJA or HA for particular patients is still a topic of debate[183,184]. In 2019-2020, over 63,000 hip replacements and 75,000 knee

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replacements were performed in Canada. There was a 2.4% increase in hip replacements and a 0.4% decrease in knee replacements compared to the previous year in Canada. Of the patients, 57.9% were female, and 43% of females receiving hip replacements were over 75 years old, while the corresponding percentage for males in the same age category was 30%. In the case of primary hip replacement, OA accounted for the most common diagnosis at a rate of 72.5%, while for primary knee replacement, OA was the most common diagnosis, accounting for 99.4%[185]. Approximately 10% of individuals who undergo hip or knee replacement surgery continue to experience discomfort in the replaced joint, according to research findings[186]. Joint replacement surgery can lead to long-term adverse effects such as infection, stiffness, functional loss resulting from scar tissue and other complications, and prosthesis-related problems[187].

2.7 Epidemiology of Osteoarthritis

The incidence of OA cannot be estimated accurately due to difficulties in defining the condition. The radiographic alterations indicate a gradual deterioration without a known starting point, and the symptoms of OA are not specific. There is limited research on the incidence of OA utilizing comprehensive datasets. However, a study conducted in Spain, which analyzed data from more than three million individuals, documented incidence rates of clinically diagnosed OA at 6.5, 2.1, and 2.4 per 1000 person-years (PYs) for knee, hip, and hand, respectively[80]. According to data obtained from healthcare databases at the provincial level in Canada, it is estimated that the occurrence rate of OA in men and women in 2003-2004 falls within the range of 6.3-12.2 and 9.3-17.4 cases per 1000 PYs, respectively[19]. The number of new cases of OA diagnosed among Canadians who are 20 years of age or older in 2016-2017 was 219,000, which corresponds to an annual incidence rate of 8.7 per 1,000 individuals[6].

The occurrence and distribution of OA can differ among countries due to a variety of factors, such as demographics, lifestyle, environment, genetics, and healthcare systems. Age is a crucial factor as the incidence of OA rises with advancing age[38,40,188]. As a result, countries with older populations may have higher incidence rates. Certain demographic factors, such as sex, ethnicity, and BMI, can also affect the incidence of OA. Lifestyle factors such as obesity and physical activity can also affect OA incidence

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rates[5]. Furthermore, environmental factors such as climate and pollution may also play a role[45], and genetic factors can contribute to an individual's predisposition to OA[189–192]. Finally, differences in healthcare systems between countries can also affect the diagnosis and treatment of OA, which in turn can affect incidence rates[193]. However, these factors are complex, and further research is necessary to gain a comprehensive understanding of differences in OA incidence between countries.

The available research is not extensive on the incidence patterns of OA, and such studies have been done only in a limited number of countries. A study conducted in the United Kingdom (UK) examined the occurrence of diagnosed OA among individuals aged 45 years or above during the period from 1997 to 2013. The study found that the incidence rate of clinical OA, adjusted for age and sex, rose from 29.2 to 40.5 per 1000 PYs between 1992 and 2013[194] A study conducted in Sweden revealed that the age-standardized hospitalization rates associated with hip and knee OA increased from 1998 to 2014[195]. In Canada, there was an increase in crude incidence rates of OA from 2000 to 2008. The incidence rate increased from 11.8 to 14.2 per 1000 PYs in men and from 15.7 to 18.5 PYs in women[73].

The prevalence of OA may fluctuate depending on several factors such as the method used to identify cases, the specific joint sites that are assessed, and the characteristics of the population under research[196]. International reports on OA prevalence suggest that an increasing number of people are being diagnosed with OA[79]. On a global scale, it is estimated that more than 7% of the world's population, which corresponds to approximately 528 million individuals, has OA[3]. The prevalence of OA is notably greater in countries with advanced market economies and aging populations, such as the United States, where it is estimated that 14% of the population has OA[3,197]. While there has been a 48% increase in the global prevalence of OA between 1990 and 2019, there are still variations in the OA prevalence rates across diverse geographical areas[3,115].

It is anticipated that the prevalence of OA will continue to increase due to various factors, including an aging population and an arise in obesity rates. In Canada, it is predicted that by 2040, approximately one in four Canadians will be affected by obesity, which could potentially contribute to a higher prevalence of OA in the future[7,72,74,198]. In Sweden, the prevalence of radiographic knee OA was 25.4% and the prevalence of symptomatic knee OA was 15.4% among individuals aged 56 to 84

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years[199]. In England, 50% of 26,000 individuals who were at least 50 years old, reported having OA in at least one of their four joints (hand, hip, foot, knee)[200]. Fransen et al. reported that rural groups in China, Bangladesh, and India had higher rates of knee pain compared to urban areas. However, in Pakistan, urban affluent people were found to be more likely to experience knee pain than urban poor people. This is likely due to the higher prevalence of obesity among wealthier citizens in Pakistan[201]. Table 2-2 describes the prevalence of OA reported in different studies.

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Table 2-2 Summary of studies on the prevalence of osteoarthritis (OA)

Study	Country	Age	Source of Database	Method of Diagnosis	OA Prevalence (%)	Limitations
Kim et al., 2014[202]	USA	>=50	Cohort Database	Radiographic	Hip: 19.6	- Unique race (Caucasian) - Long limb films
Plotnikoff et al., 2015[69]	Canada	>=18	Community Survey	Self-Reported	Overall: 14.8 Hip: 8.5 Knee: 10.5	- Self-report measures without physician verification
Quintana et al, 2008[203]	Spain	60-89	Questionnaire	Symptomatic	Hip Male: 6.7 Female: 8	- Missing data - Accessibility problems for the oldest group
Australian Bureau of Statistics., 2015[204]	Australia	>=18	Community Survey	Self-Reported	20.4	- Response bias
Kang et al., 2009[205]	China	>=50	Community Survey	Radiographic	Knee Male: 10.3 Female: 29.6	- Non-representative - Exclusion of patella-femoral joint
				Symptomatic	Knee Male: 6.9 Female: 14.2	
Picavet et al., 2003[206]	Netherland	>=25	Questionnaire	Self-Reported	Hip Male: 3.9 Female: 9.6	- Poor validity due to self-report
					Knee Male: 10.1 Female: 13.6	
Kingsbury et al., 2014[207]	UK, France, Germany, Spain, and Italy	>=65	Community Survey	Self-Reported	Hip: 30.1 Knee: 54.7 Hand: 34.7	- Poor validity of self-report - Few comorbid conditions and risk factors considered - Medication classes not reliably determined
Birtwhistle et al., 2015[198]	Canada	>=30	Canadian Primary Care Database	Administrative Data	Male: 12.4	- Misclassification errors both in the diagnosis of OA and medication prescription
					Female: 15.6	

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Calculating the incidence and prevalence rates of OA is important for assessing its burden on the population. However, there are several limitations to these measures. Osteoarthritis can be difficult to diagnose, leading to underdiagnosis and underreporting. The absence of standardized criteria for diagnosing OA and the varying criteria employed in different studies pose challenges in comparing rates across studies. The incidence and prevalence of OA may differ depending on various factors, including age, sex, race, and occupation, and incomplete data or changes in diagnostic and reporting protocols can further complicate comparisons over time. Different study designs can also lead to different incidence and prevalence rates. While these measures are valuable, it is important to take into account their limitations when interpreting the findings of research on the incidence and prevalence of OA.

2.8 Burden of Osteoarthritis

Osteoarthritis is considered the most common type of arthritis, affecting an estimated 240 million individuals worldwide. Global estimates indicate that OA symptoms affect 9.6% of men and 18.0% of women aged 60 years or older[114]. OA accounts for 2.2% of all years lived with disability (YLDs) worldwide, with 18.9 million YLDs attributed to this condition in 2019. This ranks OA as the 15th most prevalent cause of YLDs[3]. In Canada, OA affects approximately 1 in 8 people, which is equivalent to 13% of the population. It is a significant social issue as it causes pain and disabilities for those affected by the condition[2,198]. The high prevalence of OA in Canada has a considerable impact on the affected individuals, the healthcare system, and the socioeconomic costs associated with the condition[80,193].

According to the measure of Disability-Adjusted Life Years (DALYs), hip and knee OA was ranked as the 38th most severe condition globally. This highlights the significant impact that OA has on the Global Burden of Disease (GBD)[208]. The burden of OA at other sites, such as the hands and feet, which can affect dexterity, strength, and mobility, is not reflected in the GBD data as it only includes hip and knee OA. Therefore, the actual burden of OA is likely to be significantly higher, with both the prevalence and related disability being underestimated.

The economic impact of OA is substantial and can be classified into two categories: direct and indirect costs. Direct costs linked to OA include different expenditures associated with the diagnosis, treatment, and management of the condition. These expenses typically include payments for medical

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visits, pharmaceutical therapies, hospital facilities for both care and surgery, and the management of any side effects that may arise due to OA therapy. People with OA typically require more physician visits and hospitalizations than those without the condition, which contributes to the high direct costs associated with OA[209]. Studies have estimated that the annual cost per person with OA is two to three times greater compared to those without the condition[1].

Indirect costs of OA primarily stem from lost work time and unpaid informal caregiving, with approximately 40% of indirect expenses related to the latter. In the United States, the cost of absenteeism due to OA was estimated to be USD $10.3 billion[210]. Individuals with OA also experience a lower quality of life, ranging from 10% to 25% poorer than the general population[1], resulting in an economic burden of CAD $405 billion (including both direct and indirect costs) in Canada in 2011[7].

There have been various studies on the economic burden of OA in different countries. According to Chen et al., the economic burden of OA is significant and increasing[211]. In 2005, Xie et al. found that the highest direct expenditures per patient per year were in Hong Kong at USD $9,147, followed by the United States at USD $4,792, Canada at USD $2,878, Italy at USD $1,271, and France at USD $345[212]. The lowest indirect costs were found in Hong Kong at USD $864, whereas the greatest indirect costs were USD $9,847 per patient per year in Canada. It is important to note that direct and indirect costs can differ due to variations in the characteristics of the population and cost calculation methods.

Joint replacement is the most expensive treatment for OA, and the cost of knee and hip replacements was estimated to be £850 million in 2010 in the UK[211]. The increasing number of total hip and knee replacements suggests that the situation regarding OA may be worsening[213]. In conclusion, the increasing prevalence and burden of OA require a shift towards personalized patient care that considers individual needs. This can be achieved through a combination of medical and biopsychosocial approaches[214].

An increasing number of studies have focused on investigating the presence of comorbidities among individuals with OA, as this can have implications for regular clinical practice, healthcare utilization, and costs[215,216]. Comorbidities were found to have a greater impact on physical impairment

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in individuals who are 50 years old or older with OA compared to individuals without OA, with the effect of comorbidities being more significant than what would be expected from OA alone or each comorbidity individually[217]. Understanding the incidence of comorbidities among individuals with OA leads to important inquiries for the most effective management and treatment of OA to reduce pain and physical incapacity, enhance the quality of life, and lessen the impact of OA. Comorbidities can make it challenging to provide appropriate management recommendations and patient-centered care and can also have implications for healthcare programs. Therefore, understanding how OA affects other chronic conditions and total mortality is crucial, given the growing burden of OA. The following sections provide a review of the effect of OA on mortality and comorbidities.

2.9 Osteoarthritis and Mortality

Hochberg[218] conducted a review of the literature on mortality among individuals with OA. It showed a higher risk of mortality among individuals with OA than among individuals without OA[219–224]. In the study of a farm cohort in Sweden, Thelin et al identified that the farm cohort has an all-cause death hazard ratio (HR) of 0.51 (95% CI: 0.37, 0.71) with the urban group as the reference, while for non-farm rural, the HR is 0.8 (95% CI: 0.70, 0.94)[31]. Moreover, Cleveland et al. conducted a separate investigation and disclosed that the adjusted HR for mortality from any cause in individuals who had symptomatic knee OA was 1.15 (95% CI: 1.03, 1.27)[225].

The causes of death in people with OA depend on some confounding variables and are less likely to be linked to OA itself. Rather than focusing on the causal relationship, it is important to understand the overall risk of mortality in individuals with OA to better understand the burden and potential dangers associated with the condition. Some studies examining mortality among individuals with OA suggest that they have an increased risk of mortality from various causes, such as CVD, diabetes, dementia, and cancer, compared to individuals without OA. One such study, conducted by Nüesch et al., used a cohort design and the General Practitioners Database from the southwest of England to examine both disease-specific and all-cause mortality in individuals with knee or hip OA[226]. The results showed that following a 14-year median observation period, the mortality rate for CVD was 1.71 times higher than the expected rate in the general population(95% CI: 1.49, 1.98).

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2.10 Etiology of Osteoarthritis

Osteoarthritis is the result of complex changes in joint cells caused by degenerative processes that occur over time. While the exact cause of OA is still unknown, research has identified several factors that can contribute to its development and progression. Among these factors, aging is considered the most critical factor leading to OA. Occupation is recognized as another potential risk factor for OA, particularly for individuals with jobs that require repetitive joint movements, heavy lifting, and prolonged standing or kneeling. Other risk factors include obesity, genetics, joint injuries, poor diet, improper joint alignment, muscular weakness, and participation in sports that place direct stress on the joints[38,115,227,228]. Although OA is frequently described as a degenerative condition, synovial inflammation also contributes to its early onset[229]. Below are brief descriptions of the causes and risk factors that contribute to the development of OA.

2.10.1 Age

A major risk factor for OA in all joints is age[38,40,188]. However, the exact mechanisms behind the increased OA prevalence and incidence with advancing age are poorly understood. Multiple factors, including reduced joint tissue responsiveness to biomechanical stress, biological changes such as cellular senescence resulting from age-related sarcopenia, dysregulated nutrient sensing, mitochondrial dysfunction, and increased bone turnover, are likely contributing to the progression of OA[230,231]. Studies demonstrate a positive correlation between aging and the incidence of knee and hip OA[232,233]. By studying hip OA among 4 age groups including 45-54, 55-64, 65-74, and 75+ years old, the Johnston County Osteoarthritis Group found that the prevalence of radiographic hip OA was 21.2% (95% CI: 19.0, 23.6), 23.0% (95% CI: 21.1, 25.1), 31.1% (95% CI: 28.9, 33.4) and 42.9% (95% CI: 39.2, 46.7), respectively[234].

2.10.2 Sex

Sex is a significant demographic risk factor for OA, and women are more prone to the condition and experience more severe symptoms than men[41]. Research has demonstrated that women are more susceptible to developing symptomatic OA in their hands, knees, and hips than men[235–237]. There is no definitive evidence to indicate that women experience more negative effects of OA than men. Studies

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have explored the possibility of hormonal factors contributing to the development of OA, particularly in women during menopause, due to the observed rise in OA incidence among this population. Moreover, studies that have observed the effects of estrogen on OA, whether endogenous or exogenous, have been contradictory[124,238,239]. A literature review that Hanna et al. conducted, found that estrogen replacement therapy did not affect the incidence of OA in postmenopausal women[240]. Another study with older postmenopausal women with heart disease indicated that in terms of the prevalence of knee pain or related disability, the differences observed were not statistically significant between those who received estrogen combined with progestin therapy and those receiving placebo[241]

2.10.3 Race

According to research, significant disparities exist in the occurrence of osteoarthritis across diverse racial and ethnic categories[242]. Studies utilizing large databases have been carried out extensively to explore variations in OA incidence among diverse racial and ethnic categories. The National Health and Nutrition Examination Survey III (NHANES-III) data analysis found that African Americans had a greater incidence of radiographic knee OA (OR: 1.65; 95% CI: 1.17, 2.37), as well as higher symptomatic knee OA (OR: 1.52; 95% CI: 1.06, 2.19) as compared to Caucasians, whereas the prevalence in White and Mexican American individuals was comparable[243]. The study conducted in Johnston County found that the prevalence of radiographic knee OA was higher in Black individuals compared to White individuals, with 32% of Black individuals affected compared to 27% of White individuals. Similarly, Black individuals had a higher prevalence of symptomatic knee OA, with 19% affected compared to 16% of White individuals[237]. In a more recent investigation, Kopec et al. used the Johnston County Osteoarthritis Project database and findings showed that African Americans had a higher risk of experiencing progressive knee OA compared to White Americans. However, they had a lower risk of developing incident hip OA[244]. Zhang et al. compared White participants from the Framingham study with Chinese participants from Beijing. The overall prevalence of radiographic knee OA across Chinese men and White men was similar, whereas Chinese women had higher 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) as compared to White women[245]. In conclusion, the research indicates that African

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Americans exhibit inferior outcomes with osteoarthritis when compared to their white counterparts. Nevertheless, it is recommended that future studies prioritize investigating the occurrence of osteoarthritis in various racial and ethnic groups[246].

2.10.4 Occupation

Occupation may play a significant role in the development of OA, although further investigation is necessary to fully understand its impact. The relationship between occupation and OA has been the subject of several significant research[64–67]. A systematic review was carried out by Wang et al. about occupational risk factors for knee OA and identified several jobs, including farming, building, mining, carpentry, floor layering, metalworking, service work, housework, and craftsman, that were related to this condition[64]. According to the study's evidence, physically demanding occupations, such as agriculture and construction, are linked to a higher risk of knee OA due to prolonged standing, heavy lifting, kneeling, and squatting. Specifically, the study found statistically significant evidence of increased odds (1.64; 95% CI: 1.33, 2.01) of knee OA among agricultural workers, with male farmers having higher odds than female farmers. Another study conducted in Britain showed that workers aged 55 years and above who were exposed to a combination of kneeling, squatting, heavy lifting (more than 25 kg), and stair climbing had over a five-fold increased risk of developing knee OA. In contrast, those who reported regular knee flexion without lifting were only at 2.5 times greater risk[10].

In Canada, farming is still a physically demanding job despite mechanization. Farmers are required to perform more physically demanding tasks, such as lifting, digging, shoveling, and carrying heavy loads, compared to other types of manual labor[13,44,47]. Farm workers are a group of workers who are susceptible to developing OA due to the physically demanding nature of their work, as noted in previous studies[247]. Farming is a diverse occupation, with various types such as dairy, swine confinement, cattle, and crop rising, and there are significant differences between ultramodern high technology and traditional farming[45]. Farmers typically work long hours, often seven days a week, and some types of farming, such as crop rising, can experience significant seasonal changes in workload. Farming involves prolonged exposure to high levels of physical activity, often starting at a young age and

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continuing well beyond the regular retirement age[12]. This extended duration of high physical workload and standing can increase the risk of developing OA among farmers[46].

A study conducted by Voaklander et al. used probabilistic linkage between two government registries in Alberta, Canada to identify older farmers (66 years and older) and farm-related injuries for three years. The study found that farmers with injuries had 1.57 times higher odds of developing OA compared to those without injuries[248].

In a cross-sectional study of 2,473 adult residents on 1,216 farms in Saskatchewan, the prevalence of arthritis diagnosed by a physician based on self-reported data was analyzed. The study found that the prevalence of chronic arthritis diagnoses was reported by 13% of the participants, with 10% having osteoarthritis. As OA becomes more prevalent with age, it is not surprising that the farmers with arthritis in this study were older, with a mean age of 63.7 years compared to those without arthritis with a mean age of 52.9 years. Among the population with arthritis, 36% reported regular use of NSAIDs, while only 7% of those without arthritis reported the same. The findings of this study, moreover, indicated that musculoskeletal symptoms can lead to farmers taking time off work and filing for workers' compensation, which can have economic consequences. This can result in decreased productivity, even if workers do not take time off, because farmers with arthritis were less likely to engage in certain physical tasks such as combine operations and shoveling/pitchfork chores. In the context of farmers working long hours, musculoskeletal symptoms can have a substantial economic impact[13].

A study analyzed data from the Saskatchewan Farm Injury Cohort Study to investigate the prevalence and impact of MSDs on individual farms. The study examined demographic and health-related variables, farm-related injuries, and economic conditions of MSDs. The study involved 2595 farmers and investigated the links between MSDs and the amount of time spent doing farm work. The study found that 85.6% of the participants reported experiencing musculoskeletal pain in at least one body part in the past year[249]. In another study, Franklin et al. compared 8 occupational categories based on the ISCO-88 classification. According to this study, male farmers, who usually have a high physical workload, differed significantly from other work classes, with an increased likelihood for both total knee replacement (TKR) and total hip replacement (THR) for OA[15]. The result of a study in Sweden showed that OA was higher

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among farmers compared with urban controls (HR: 2.1; 95% CI: 1.4, 3.2) than non-farming rural compared with urban controls (HR: 1.1; 95% CI: 0.9, 1.4)[45]. A study of 299 ranchers and farmers from 9 counties in Montana, who provided information about their demographics, joint symptoms, arthritis history, financial status, work capacity, and reliance on others to complete their work, reported that 87.6% experienced joint pain, 47.8% reported having arthritis, and 22.4% reported having osteoarthritis.

Hand OA has been found to be related to occupations that involve extensive manual labor, although no studies have shown any evidence to suggest that the right hand (usually dominant) is more susceptible to it[235]. Research has shown that repeated motions, lifting heavy objects, working quickly, and the perceived lack of enough rest breaks are all connected with the development of OA in the hand[250,251]. A research study carried out in Saskatchewan revealed that farmers suffering from arthritis had increased risks of experiencing disabling aches, pain, and discomfort in one or both of their hands (RR: 2.65; 95% CI: 1.59, 4.41)[13]. The physical demands of farming, including repetitive use of the hands, gripping and holding heavy tools, and manual labor, can lead to degeneration of the joints typically the carpometacarpal joint in the hands, and increase the risk of developing hand OA. Exposure to vibration from operating machinery, such as tractors, can also contribute to the development of hand OA in farmers[121].

Hip OA has often linked with physically demanding work or manual activities that involve heavy loads on the hip joint[252,253]. A study evaluating occupational OA involving 84 miners and 87 other workers was conducted[254]. Of the three workers who had hip OA, all were miners. Farmers and other agricultural workers, laborers, firemen, food processing employees, female mail carriers, and female cleaners are some occupational groups that are more at risk for hip OA[49]. The physically demanding nature of farming, which involves repetitive movements, weight-bearing, and exposure to vibrations from machinery, puts farmers at a greater risk of developing hip OA[247]. The study conducted by Thelin et al. estimated the risk of hip OA in farmers by comparing the farmers radiologically diagnosed with hip OA with those who were matched for age, sex, and place of residence[121]. The pelvis and hip joint radiographs were reassessed within two years. The study found that farmers had an increased risk of hip OA with increasing years of farming, compared to controls. The OR for hip OA in farmers was 2.81 (95%

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CI: 1.31, 6.03) for 11-20 years of farming, and 7.35 (95% CI: 2.87, 18.82) for 21-30 years of farming. These results indicate a notable correlation between years of farming and the risk of hip OA.

The research outcomes indicate a correlation between knee OA and rigorous physical activity, such as the demanding tasks involved in farming[10,255]. A study comprising 518 participants diagnosed with knee OA and an equivalent number of controls matched for age and sex discovered that certain job-related tasks were linked to an elevated probability of developing knee OA. After adjusting for BMI, knee injury history, and the presence of Heberden's nodes, the study found that prolonged kneeling or squatting had an OR of 1.9 (95% CI: 1.3, 2.8), walking over 2 miles per day had an OR of 1.9 (95% CI: 1.4, 2.8), and regularly lifting weights of at least 25 kg had an OR of 1.7 (95% CI: 1.2, 2.6). The study found that the risk of developing knee OA was higher in individuals who reported prolonged kneeling or squatting in their occupation and also reported occupational lifting. This risk was further multiplied in individuals who were obese. For individuals with a BMI of over 30 kg/m^2 whose work involved kneeling or squatting for an extended period, the OR was 14.7 (95% CI: 7.2, 30.2), compared to those with a BMI less than 25 kg/m^2 who were not exposed to occupational kneeling or squatting[256].

A study investigated the relationship between knee OA and occupation in 778 subjects with X-ray-verified OA and 695 matched controls[257]. Women who worked in farming for 11-30 years had 2.1 times higher odds of developing knee OA (95% CI: 1.1, 3.9) compared to women with other physically demanding occupations. In a population-based case-referent study by Sandmark et al., 625 men and women who underwent prosthetic surgery for primary tibiofemoral OA and 548 referents were studied[11]. According to the findings, male and female farmers had respectively 3.2 (95% CI: 2, 5.2) and 2.4 (95% CI: 1.4, 4.1) times higher odds of developing knee OA compared to a randomly selected control group from the central population register in Sweden.

2.10.5 Obesity

Since 1975, there has been a threefold increase in the worldwide prevalence of obesity[258]. It has been projected that by 2025, almost half (47%) of men and over a third (36%) of women aged between 21 and 60 years in the UK will be classified as obese (BMI > 30 kg/m^2)[259]. In Canada, the prevalence of obesity is anticipated to be 326 cases per 1000 individuals in the year 2023-2024, resulting

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in a total of approximately 8.54 million individuals with obesity. The burden of obesity is projected to be higher in males, with an estimated 347 cases per 1000, compared to females with an estimated 305 cases per 1000[260]. The excess weight associated with obesity results in increased joint loading, which can lead to harmful effects on weight-bearing joints. The increase in weight can create a burden on the cartilage present in the joints which exceeds its natural capability, resulting in degenerative alterations[42,261].

Obesity has been identified as the most significant adjustable risk factor for knee OA, and both cross-sectional and longitudinal research has consistently shown a relationship between obesity, often measured by BMI, and the prevalence and incidence of knee OA[42,261]. The likelihood of needing TKA appears to increase with a higher BMI[262], however, there is not a necessarily linear relationship between BMI and OA. One study reported that overweight men had an OR of 1.7 (95% CI: 1.0, 2.6) for requiring TKA, while obese men had an OR of 5.3 (95% CI: 2.8, 10.1) for surgical intervention. A similar trend was seen with women in that overweight women had an OR of 1.6 (95% CI: 1.1, 2.2) and obese women had an OR of 4 (95% CI: 2.6, 6.1) for requiring TKA[263]. A study that investigated the association between BMI and knee and hip replacement surgery discovered highly noteworthy results. The study reported that among males, the highest OR was observed for those with a BMI ranging from 37.50 to 39.99 kg/m^2, with an OR of 9.37 (95% CI: 2.64, 33.31) for total hip replacement and an OR of 16.40 (95% CI: 5.19, 51.86) for total knee replacement. For females, the highest OR was observed for those with a BMI of 40 kg/m^2 or higher, with an OR of 4.47 (95% CI: 2.13, 9.37) for total hip replacement and an OR of 19.05 (95% CI: 9.79, 37.08) for total knee replacement[264].

2.10.6 Medical Factors

Osteoarthritis is a condition that displays heterogeneity with clear differences between its phenotypes. Due to the improved availability of advanced technologies to detect specific features of OA, there is an increasing capacity to differentiate between the potential phenotypes of OA. Phenotypes of OA can be categorized as subtypes that share distinct mechanisms of pain and pathobiology, and their consequences in terms of structure and function. Patients may be classified as belonging to one or more phenotypes simultaneously[265]. In 2014, Karsdal et al. published a review article that put forward five

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possible phenotypes of osteoarthritis. These phenotypes included genetic, auto-inflammation, hormonal, metabolic, and mechanotransduction subtypes[266].

According to studies, OA development is significantly influenced by genetics[189–192]. Studies have identified over 20 different gene polymorphisms that are associated with OA[267,268]. A twin study has revealed a correlation between genetic factors and the risk of developing radiographic hand and knee OA, particularly in women. The research indicates that the heritability of OA ranged from 39% to 65%[269]. Compared to knee OA, hand and hip OA are more likely to have a genetic predisposition[269]. It is crucial to take into account the potential likelihood of familial clustering of OA due to shared living conditions and lifestyles, which may impact the development of the condition. However, a deeper understanding of the genetic factors involved in OA can help to distinguish familial clustering from a genetic predisposition. This information can be utilized to recognize individuals who have an increased susceptibility to developing OA, better understand the underlying mechanisms that lead to OA, and potentially identify targets for treatment.

The inflammatory phenotype of OA refers to a subtype of OA in which inflammation is believed to play a more significant role in the pathogenesis of the disease. The inflammatory phenotype of OA is characterized by increased levels of inflammatory mediators such as cytokines, chemokines, and prostaglandins within the joint. These mediators can cause cartilage breakdown and bone erosion by activating catabolic enzymes and inhibiting anabolic enzymes within the joint. The inflammatory phenotype of OA is often associated with synovitis, which is inflammation of the synovial membrane that lines the joint. Synovitis can contribute to pain and stiffness in the joint by increasing the production of synovial fluid, which can cause joint swelling and inflammation. People with the inflammatory phenotype of OA may experience more severe joint pain, stiffness, and functional impairment compared to those without this subtype[265,270,271].

The hormonal dysregulation phenotype of OA refers to a subtype of OA in which hormones, particularly estrogen, have a significant impact on the progression of the disease. Estrogen, in particular, has been shown to have a protective effect on cartilage, bone, and synovial tissues. Decreased levels of estrogen, such as those that occur after menopause or as a result of surgical removal of the ovaries,

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have been linked to a higher susceptibility to developing OA. The hormonal dysregulation phenotype of OA may also involve other hormonal changes, such as alterations in the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the body's response to stress. Dysregulation of the HPA axis has been linked to changes in inflammation and pain perception, which may contribute to the progression of OA[270,272].

The metabolic phenotype of OA is characterized by the role that metabolic dysregulation plays in its development and progression. Specifically, factors such as obesity and insulin resistance are believed to contribute significantly to the pathogenesis of this type of OA. Obesity can lead to the production of inflammatory cytokines, which can contribute to the development of OA by causing cartilage breakdown and promoting synovial inflammation. Insulin resistance, which occurs when the body's cells become less responsive to insulin, can also contribute to the development of OA by promoting the accumulation of fat in the joint, increasing inflammation, and reducing the ability of chondrocytes (cartilage cells) to produce healthy cartilage. Other metabolic factors, such as dyslipidemia and high blood pressure, may also contribute to the metabolic phenotype of OA by promoting inflammation and other deleterious effects on the joint tissues[270,273].

The mechanotransduction phenotype of OA is characterized by the significant contribution of mechanical stress on joint tissues to the onset and advancement of the disease. In this subtype, mechanical loading or overloading of the joint tissues leads to an altered response of the cells in the joint, which can contribute to the breakdown of cartilage and other joint tissues. Mechanotransduction refers to the process by which cells convert mechanical signals, such as those from pressure or tension, into biochemical signals that influence cellular behavior. In the mechanotransduction phenotype of OA, altered mechanotransduction signaling within joint cells can lead to the production of catabolic enzymes that break down cartilage and other joint tissues. Factors that can contribute to the mechanotransduction phenotype of OA include abnormal joint mechanics, such as malalignment or instability, as well as repetitive or excessive loading of the joint due to activities like sports or heavy labor. People with this subtype of OA may experience joint pain and stiffness that is aggravated by mechanical stress or activity[274].

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2.10.7 Lifestyle-Related Factors

Participating in physical exercise and sports is widely recognized as a significant risk factor for the development of OA. One part of a healthy lifestyle is leisure-time physical activities such as walking, playing, and running. However, reviews have reported conflicting evidence about physical activity and OA, mainly due to inconsistencies in the measurement of physical activity[275,276]. Recreational physical activity has little impact on the development of radiographic knee OA, according to several longitudinal investigations[277,278]. A recent meta-analysis of 20 reviews and 12 original studies has indicated that common types of physical activity, such as walking, running, and select recreational sports, do not contribute to the advancement of knee OA with visible changes in the joint structure. This finding supports the safe recommendation of these activities for patients who have or are at risk of developing knee OA[279]. However, the effects of joint injury from strenuous exercise can be a contributing factor to the development of OA in the future. Several investigations have discovered a higher likelihood of hip and knee OA in athletes who participate in high-level and advanced exercise[162]. A systematic review that included 46 studies found that 31 studies reported an elevated risk of osteoarthritis, with 19 studies indicating a heightened risk in professional athletes. Regardless of the type of sport, an elevated risk of OA has been observed following sports participation (RR 1.37; 95% CI: 1.14 to 1.64; 21 studies)[275].

Nutrients can be considered another risk factor for developing OA. According to some epidemiological evidence, a lack of various dietary components, including vitamins C, D, E, and K, could increase the risk of OA, but other studies suggest the opposite. Vitamin D is the most thoroughly researched nutrient regarding OA, and research has shown that inadequate vitamin D intake may result in cartilage metabolism problems, increasing the risk of OA[280]. A longitudinal study found a correlation between vitamin D consumption and a reduced occurrence and advancement of OA. The study observed that individuals with low lumbar spine BMD at the start of the study had an increased incidence of knee radiographic OA as their vitamin D intake and serum levels decreased (pvalue< 0.03). The group with the highest dietary vitamin D intake had a lower incidence of progressive radiographic OA at 5.1% compared to 12.6% in the lowest intake group[281]. A 2008 randomized trial study demonstrated that there was no observed advantage in terms of radiographic hand OA associated with vitamin K intake. The

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randomization of vitamin K supplementation did not lead to any significant alterations in the prevalence of radiographic hand OA, joint space narrowing, or osteophytes. The odds ratios and CI for these outcomes were 1.03 (95% CI: 0.80, 1.34), 1.04 (95% CI: 0.68, 1.57), and 0.95 (95% CI: 0.64, 1.40), respectively[282], whereas in other studies consuming vitamin K is associated with a reduced risk of developing knee OA[283]. Although the occurrence of knee OA can be lowered by vitamin C consumption, there was no correlation with the progression of the disease[284]. On the other hand, the Framingham OA cohort research found that the intake of vitamins C and E played a crucial part in mitigating the chances of cartilage deterioration and the advancement of the disease in people with OA. The risk of OA progression decreased by three times in individuals who consumed vitamin C, with adjusted odds ratios of 0.3 (95% CI: 0.14, 0.8) and 0.3 (95% CI: 0.1, 0.6), respectively. There was an observed decrease in the likelihood of OA advancement associated with vitamin E intake (OR: 0.7; 95% CI: 0.3, 1.6)[285].

Smoking can also be considered another potential risk factor for developing OA. On the connection between smoking and OA, there have been conflicting reports. In certain research, smoking has been linked to a preventive effect against OA, but in other studies, smoking has been linked to a higher risk of both cartilage degradation and knee pain. A meta-analysis of 48 studies with more than 500,000 participants, showed that smoking may have a protective effect in the development of OA (OR: 0.87; 95% CI: 0.80, 0.94), particularly in case-control studies conducted in hospitals. However, the link becomes weaker in the cohort and cross-sectional research, particularly those conducted in community-based environments, implying that the connection is a false negative[232,286].

2.10.8 Sports Injuries and Physical Activity

Direct articular cartilage injury, ligament rupture, or meniscal damage are all examples of joint injuries. The connection between joint injury and OA has been extensively investigated for the knee joint in particular. Patients who have undergone knee repairs or have deficient anterior cruciate ligament (ACL) have reported altered levels of OA biomarkers in their synovial fluid[287]. The results of a systematic review indicated that in one research individuals who self-reported knee injuries had a relative risk (RR) of approximately four times higher for developing knee OA[232]. Another study reported a 15% higher

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lifetime risk of symptomatic knee OA in individuals with a history of knee injuries[30]. Gelber et.al. found that joint injuries significantly raised the chance of developing later knee and hip OA. The RR for knee OA was 5.01 (95% CI: 2.80, 8.97), and for hip OA, it was 6.01 (95% CI: 1.40, 25.86)[288]. Apart from evident injuries, repetitive microtrauma can also damage joint tissues over time.

According to the Lane et al. study, there is a greater likelihood of hip OA developing in older White women with acetabular dysplasia or a decrease in the center-edge angle. The OR for this association was found to be 3.3 (95% CI: 1.1, 10.1) and 2.8 (95% CI: 1.0, 7.9). This suggests that local anatomic anomalies may be more closely linked to hip OA than knee OA[289]. The Johnston County Osteoarthritis Project found that among men, there was a significant association between the morphology of the femoral head and the incidence of hip OA[237]. The Nottingham musculoskeletal research team identified a relationship between hip OA and the pistol-grip deformity of the hip[290]. This finding is noteworthy as it may explain the early onset of OA in a young patient who has no other apparent risk factors for the condition.

The strength of muscles has a crucial role in safeguarding the joint. Muscles with greater strength provide stability and protect weight-bearing joints from excessive loading, which in turn reduces the likelihood of damage to cartilage and joint structures. A prevalent trait among people with OA is muscle weakness. While muscle weakening and atrophy can occur due to OA resulting from disuse caused by pain avoidance, it remains uncertain whether this is a risk factor for developing OA. A study indicated that weakness in the quadriceps is Linked to a higher likelihood of developing knee osteoarthritis characterized by structural changes[291]. However, findings on the connection between muscle strength and knee OA are inconsistent across studies. A different study reported conflicting results, where low muscle strength was linked to the onset of symptomatic knee OA in women but not to the occurrence of radiographic OA[292].

Joint alignment is another essential factor to consider in relation to joint health. Dynamic alignment, which refers to changes in the knee during walking, can be relevant in comprehending the specific load effects experienced by the joint. Despite the importance of joint alignment, epidemiological studies often rely on static alignment assessed through radiographs of the entire extremity or anterior-

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posterior knee, which has some limitations. There is conflicting information about the association between misalignment and the occurrence of knee OA. Some studies have confirmed an association between misalignment and the incidence of knee OA[293,294], while the Framingham study found no effect of malalignment on the incidence of knee OA[295].

2.11 Osteoarthritis and Comorbidities

Research has recently focused on characterizing comorbidities among OA cases due to their potential impact on medical care, healthcare utilization, clinical guidelines, and costs[215,216]. This is because the presence of comorbidities can increase the burden of treatment for both patients and healthcare providers. Multiple international publications have recorded the co-occurrence of medical conditions in individuals with OA, utilizing diverse study designs and varying sample sizes[296,297]. According meta-analyses, it is indicated that the presence of one or more persistent illnesses, like CVD or diabetes, might forecast rapid deterioration or more rapid aggravation of pain[298]. In adults aged 50 or older in England who have OA, the existence of other medical conditions has been found to amplify physical disability beyond the effects of OA alone or each comorbidity in isolation[217]. This suggests that comorbidities have a greater impact on physical disability in individuals with OA than what would be expected based on their individual effects. Research conducted in Alberta, Canada has revealed that hypertension, chronic obstructive pulmonary disease (COPD), and depression are the prevalent medical conditions that coexist with OA. Roughly 50% of individuals with OA were found to have at least one of these three comorbidities[299].

To effectively treat and manage OA, it is crucial to acknowledge the frequency of coexisting medical conditions in individuals with OA. One approach to assess the burden of coexisting medical conditions in patients is through the utilization of the Charlson comorbidity index (CCI). Appendix A provides further information on the CCI.

2.12 Research Methodology

The methodology used in a research study is critical to the validity and generalizability of its findings. One important aspect of the methodology is case ascertainment, which involves identifying and

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selecting cases that meet specific inclusion criteria for the study. Accurate case ascertainment is essential to ensure that the study sample is representative of the population being studied and that the findings can be generalized to other populations. To achieve accurate case ascertainment, various methods can be employed, such as medical record review, registry-based ascertainment, self-reporting, direct observation, or surveys and questionnaires.

Self-reporting of OA by study participants is commonly used for identifying OA cases in epidemiologic studies[300]. Numerous studies have utilized self-reported physician-diagnosed OA from population surveys as a method to estimate the incidence and impact of OA. Grotle et al. is an example of such a study that relied on self-reported physician diagnoses to determine the prevalence and burden of OA in Norway[301]. In another study, the prevalence of OA and its correlation with CVD were assessed by Ong et al through the utilization of self-report data from the US NHANES[302]. Badley et al. utilized data from the Canadian population survey, specifically self-reported health professional-diagnosed arthritis, to investigate the distinctions between individuals with arthritis who are unaware of their type and those who report having OA or inflammatory and autoimmune types of arthritis (IAA)[303]. Another study estimated the frequency of OA using the Canadian Community Health Survey (CCHS)[304].

Self-reporting of OA has both advantages and disadvantages. Self-reporting is a simple and cost-effective approach. However, it can lead to misclassification, where patients may not be able to accurately recognize the specific type of rheumatic condition they are experiencing[305,306].

Health administrative data is another methodology employed in OA epidemiology studies. Health administrative data refers to health information that healthcare organizations, insurers, and governments collect for enrollment, reimbursement, and payment. These databases may include data from various healthcare settings such as hospitals, physician visits, and health insurance claims. Health administrative data use ICD codes to record information about diseases and health conditions. These codes are used to facilitate billing and reimbursement for healthcare services, as well as to generate data for research and public health purposes. However, it is important to note that ICD codes have some limitations. ICD codes may not capture the full extent of a patient's health condition, as some conditions may be underreported or not well-defined by the existing codes. Coding errors or inconsistencies can occur, which can affect the

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accuracy and reliability of the data. Finally, the use of ICD codes can result in a lack of specificity, as some codes may encompass a wide range of conditions with varying levels of severity or complexity[307]. Despite these limitations, ICD codes remain an important tool for recording and tracking health-related information, and ongoing efforts to refine and improve the coding system are underway. Appendix B provides further information on the health administrative data method.

Table 2-3 presents a comprehensive overview of the research methods utilized in studies focusing on musculoskeletal disorders among farmers.

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Table 2-3 research methods used in studies focusing on musculoskeletal disorders among farmers

Study	Country	Method	findings
Taylor-Gjevre et al., 2015[13]	Canada	Self-report	Decreased participation in a number of physical farm-related activities in farmers reporting arthritic diagnoses compared with those who did not (OA prevalence: 10%).
Rosecrance et al., 2006[308]	USA	Self-report	Farmers experienced low back pain at a much higher rate than the general working population (back pain prevalence: 36.4%).
Hawker et al., 2006[309]	Canada	Administrative Data	20.0% of framers with arthritis were willing to consider TJA.
Holmberg et al., 2004[257]	Sweden	Self-report	Women who had worked for 11–30 years in farming tended to have an increased risk of knee OA (OR: 2.1; 95% CI: 1.0, 4.5).
Johansson et al., 2018[46]	Sweden	Swedish Patient Register (administrative data)	The risk of hip arthroplasty for OA was approximately doubled (105% increase) in male farmers compared to other occupations, and 40% higher in female farmers (HR for female: 1.44; HR for male: 2.04).
Heaton et al., 2012[310]	USA	Self-report	Arthritis/rheumatism was associated with the occurrence of farm injury (OR: 1.99; 95% CI: 1.57, 2.52).
McMillan et al., 2015[249]	Canada	Self-report	The prevalence of musculoskeletal diseases was significantly related to time spent performing biomechanically demanding tasks such as heavy lifting and working with arms overhead (OR: 1.51; 95% CI: 1.13, 2.03).

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2.13 Case Ascertainment

Case ascertainment is the process of identifying and confirming cases of a particular health condition or disease within a study population. This process involves the use of various methods such as medical record reviews, self-reported data, diagnostic tests, or administrative health data to identify individuals with the condition of interest.

Medical administrative databases are commonly used in population-based studies to identify OA cases in a broad area over a long period and include physician visits and hospital admission records of the individuals. As a result, administrative databases have become a promising resource for monitoring chronic conditions like OA. The use of administrative databases in health research for identifying cases of OA has become more prevalent in recent times. The identification of OA cases is done through the use of several definitions that rely on the International Classification of Disease 9th and 10th revisions codes[74,311]. For instance, Prieto-Alhambra et al. used administrative primary healthcare records to estimate the incidence of hip, knee, and hand OA, and determine its risk factors[80]. Using administrative health data, Kopec et al. estimated the incidence, prevalence, and trends of OA in Canada[19,74]. Marshall et al. used the Alberta administrative databases to identify OA cases based on a case definition of one hospitalization or two physician or two ambulatory care visits within a two-year period[72]. Prior research has confirmed that administrative data are reliable for identifying cases of OA when compared to self-reported surveys and electronic medical records. The sensitivity and specificity of different case definitions have been estimated in Canada[312].

Using administrative health data for case ascertainment in OA research offers several advantages, such as the ability to identify cases across multiple healthcare settings and access to large sample sizes. However, it is crucial to consider the limitations of administrative health data when interpreting results. These limitations include the possibility of incomplete or inaccurate data, leading to the misclassification of cases. Therefore, it is important to carefully evaluate the quality of the administrative health data and employ appropriate statistical methods to mitigate potential bias in the results.

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Chapter 3. The Risk of Developing Osteoarthritis in Albertan Farm, Non-farm Rural, and Non-farm Urban Residents: A 21-year Retrospective Study

The format of this chapter adheres to the guidelines outlined by the Rural and Remote Health Journal.

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Original Research

The Risk of Developing Osteoarthritis in Albertan Farm, Non-farm Rural, and Non-farm Urban Residents: A 21-year Retrospective Study

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Abstract

Introduction: Due to the physically demanding nature of farming, farm residents are particularly susceptible to developing osteoarthritis (OA). However, current studies on the epidemiology of OA in Albertan farm residents are limited. The aim of this study was to determine the risk of developing OA among Albertan farm residents compared to those living in rural and urban areas.

Methods: A retrospective cohort study was performed using Alberta health administrative databases to determine the risk of developing OA among Albertan farm residents in comparison to the rural and urban residents. The study period was from the fiscal years 2000-2001 through 2020-2021 and included 3 cohorts: 143,431 farm residents, 143,431 non-farm rural residents, and 143,431 non-farm urban residents. The study identified OA cases among individuals 20 years or older using the diagnostic code for any hospital admission, two physician visits within two years, or two ambulatory care visits within two years. The study assessed the incidence rates, lifetime risk, and mortality rates. The Cox proportional hazard model was also used to examine the impact of residency status on developing OA.

Results: 26,957 OA cases were identified among 1,706,256 person-years (PYs) in the farm population. Over the 21 years, farm residents had an overall incidence rate of 15.8 (95% CI: 15.61, 15.99) per 1000 PYs. After adjusting for age and sex, farm, and non-farm rural population were respectively at a 6% (95% CI: 4%, 8%) and 9% (95% CI: 7%, 12%) greater risk of developing OA as compared to the urban cohort. The non-injury mortality rate among farm residents with OA was 13.16 (95% CI: 12.87, 13.45) per 1000 PYs which was lower than the mortality rate among both urban (14.49; 95% CI: 14.14, 14.84) and rural (17.96; 95% CI: 17.55, 18.38) residents.

Conclusions: Albertan farm and non-farm rural residents have an increased risk of developing OA as compared to the urban population. The findings also highlight that farm residents with OA had the lowest mortality rate among persons diagnosed with OA.

Keyword:

aging; agriculture; farm injury; health utilization; mortality; osteoarthritis

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Introduction

Osteoarthritis (OA) is a chronic musculoskeletal disease that causes pain, limiting function, mobility, and quality of life[1,2]. As high-income countries are facing the challenge of an aging population and growing obesity, OA prevalence is becoming a more significant problem[3–5]. In Canada, an estimated 3.9 million individuals aged 20 or older had a diagnosed case of OA in 2017, which represents 13.6% of the population[6]. It has been estimated that the prevalence of OA in Canada will rise to 25% of the total population and nearly 30% of the workforce by 2040[7]. The economic cost of OA to individuals, the healthcare system, and society is significant, as it results in lost days of work[8,9].

One of the significant risk factors for OA is heavy physical workload[10,11]. The occupation of farming in rural areas involves long-standing exposure to heavy physical workloads beginning at an early age and extending beyond the typical age of retirement[12]. The findings of a research study conducted in Saskatchewan revealed that 13% of the surveyed farm population had been diagnosed with arthritis by a physician. Among these individuals, a majority of 10% indicated that they were aware of having osteoarthritis as their arthritic condition[13]. Furthermore, a study conducted in Sweden revealed that farmers are at a greater risk of developing OA compared to their urban counterparts[14]. In another study conducted by Franklin et al., eight occupational categories were compared using the ISCO-88 (International Standard Classification of Occupations 1988) classification. It was discovered that male farmers, who typically have a high physical workload, differed significantly from other work classes, with an increased likelihood for both total hip and knee replacement for OA[15].

Alberta, a province with the second-largest number of farmers in Canada, has a farm population of 118,785 individuals[16]. The incidence of OA in this occupational group provides important information to health policymakers as this condition can have significant clinical and economic implications[1,8]. Despite the significant risk of developing OA among farm residents, limited studies have exclusively investigated this particular high-risk group. To the best of our knowledge, only one investigation has reported on the prevalence of OA among rural residents in Alberta. Marshal et al. reported that the OA prevalence rate was significantly higher among individuals residing in rural areas when compared to those residing in urban areas, although it did not focus on the farm population[17].

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Given OA currently has no known treatment, and that the susceptibility to developing OA is significantly affected by extrinsic risk factors including injury, and repetitive and excessive joint loading[18], the risk of developing OA may increase in certain occupations. The objective of this study was to estimate the OA incidence rate according to age and sex among Albertan farm residents 20 years and above using provincial administrative health records. For a more extensive comprehension of OA among farm population, we aimed to explore the temporal trends in OA between 2000-2001 and 2020-2021, the lifetime risk of developing OA, the non-injury mortality rate, and the hazards of developing OA among the farm residents as compared to non-farm rural and urban cohorts.

Methods

Study Design

This was a historical study conducted at the population level that used administrative datasets to identify OA cases over 21 years. The study population was divided into three groups: farm residents, who were considered as cases, and non-farm rural and urban residents, who were controls. The annual and overall incidence rates for all three cohorts were estimated from fiscal years 2000-2001 through 2020-2021, with three years removed to account for prevalent cases. The study also estimated the cumulative incidence rate and non-injury mortality rate for each cohort. To investigate the impact of residency status on the risk of developing OA, Cox proportional hazard regression analysis was employed.

Data Sources

Data was obtained from five health administrative databases that are provided by Alberta Health (AH) for fiscal years 1997-1998 through 2020-2021 to identify OA cases who accessed medical services funded by the provincial health coverage. Alberta has a healthcare system in that all individuals have access to physician consultations, hospital treatment, and medical care through universal coverage. Data was obtained from the Alberta Vital Statistics, Alberta Health Care Insurance Plan (AHCIP) population registry, Physician Claims Database (claims), Discharge Abstract Database (DAD), and National Ambulatory Care Reporting System (NACRS).

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AHCIP: All insured people's demographic information is recorded in the AHCIP population registry by the end of each fiscal year (March 31st). A nine-digit personal health number (PHN) is assigned to each Albertan who is enrolled in the AHCIP. This number is used to link individual healthcare encounter details of Albertan citizens and is maintained in Alberta health administrative systems. This dataset includes all eligible medical benefits recipients during the fiscal year. Members of the Royal Canadian Mounted Police, members of the Armed Forces, convicts in federal prisons, and Albertans who have not enrolled in the AHCIP are excluded.

DAD: This database is the hospital admissions which includes the demographic information of the individuals receiving treatment, date of admission and discharge, diagnosis codes, intervention codes, and hospitalized time. We collected information for all individuals receiving treatment based on OA International Classification of Diseases (ICD) codes among the 25 diagnostic fields within the DAD.

Claims: This database contains all fee-for-service billing records that physicians submit for remuneration. Physician billing statements include three diagnostic fields, and data was collected for all patients with ICD codes associated with OA across these diagnostic fields.

NACRS: This database includes outpatient medical and/or surgical services information provided by clinics, day surgery, and emergency room settings that receive public funds. Unlike the DAD database, which allows a maximum of 25 diagnostic codes, ambulatory care records are limited to 10 diagnostic codes. We collected data for every patient with ICD codes relating to OA across these 10 diagnostic code fields.

Alberta Vital Statistics: To determine the mortality status of individuals in the study population, the Alberta Vital Statistics data is linked to billing data via scrambled PHN. This data source provided access to the primary cause of death (ICD Code) and date of death as recorded on death certificates.

Study Population

The study sample comprised 430,293 individuals, consisting of farm residents from Alberta and non-farm rural and urban residents who were randomly selected. AH created a farm family cohort based on the population registry in the fiscal year 1997-1998. Through probabilistic matching with Alberta

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Agriculture and Rural Development and the Farm Fuel Tax subsidy, 143,431 farm family members of all ages with PHNs were identified. The non-farm rural cohort was generated with a random sample of 143,431 rural residents who were not in the farm cohort and have the number “0” as the second digit of their postal codes. The urban cohort was a random sample of 143,431 urban residents who were not in the farm cohort or the non-farm rural cohort and did not have “0” assigned to their postal code. We used a study-specific identifier that protects individuals' identities while allowing for unique individuals to be linked across five databases. As a closed population, no new subjects were added after the initial selection. The study population included all three cohort members who were 20 years of age and above during the fiscal years 2000-2001 through 2020-2021. Subjects left the study due to death, migration, or reaching 110 years of age; however, individuals younger than 20 years old were retained and were then included in the study population when they reached the age of 20. Prevalent cases of OA prior to April 1st, 2000 were also excluded. After applying the general inclusion and exclusion criteria, 379,784 individuals were followed up from April 1st, 2000 to March 31st, 2021 (Appendix Figure 1).

Case Ascertainment

Previous research has demonstrated that the OA incidence rates differ based on the approach employed for identifying cases. To ensure consistency, we used a validated OA case definition that has been previously employed in studies utilizing administrative data[19–21]. This case definition algorithm included at least one of the subsequent criteria: one OA-related hospitalization, two OA-related physician visits within two years, or two OA-related ambulatory care visits within two years.

Statistical Analysis

To conduct the statistical analysis, age was categorized into six groups (20-39, 40-49,50-59, 60-69, 70-79, and ≥ 80 years), and sex was categorized as male and female. Socioeconomic status was also calculated based on the Income Support Flag in the AHCIP population registry file. The mean comorbidity index was calculated for OA cases diagnosed during the observational period using the updated Romano comorbidity index that was developed for health administrative data[22–24], for 2 years prior and 5 years after the diagnostic date of OA, separately. The total score represents the probability of hospitalization and mortality.

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This study estimated the OA incidence rate for each of the three cohorts, by dividing the number of new OA cases for each age/sex group by the total person-years (PYs) at risk during the study period. PYs at risk were calculated by censoring individuals who died, moved, reached 110 years of age, received the first diagnosis of OA, had their last data collection, or had a change in residency status, whichever occurred first. To prevent overestimation of the incidence rate, data from the fiscal years 1997-1998, 1998-1999, and 1999-2000 were used for control purposes. To eliminate prevalent cases, any previous history of OA diagnosis before April 1st, 2000 was excluded. Age-specific rates were determined based on the age of the person when they became active and were stratified by sex. The risk of developing OA among farm residents relative to each of the non-farm rural and urban cohorts was estimated using the crude incidence rate ratio (IRR). The details of calculating incidence for different individuals are summarized in Appendix Figure 2 and Appendix Table 1.

This study used the Kaplan Meier (KM) method to calculate the cumulative incidence of OA considering censored data. To provide an estimated lifetime risk of OA, adjustment was made for mortality as a competing risk. The study estimated the impact of OA on the non-injury mortality rate among each cohort by calculating the ratio of overall non-injury death incident cases to the PYs of people at risk of death, separately for OA cases and non-OA cases. The "Death Code" data from the Alberta Vital Statistics file was used to exclude mortality cases that were related to injuries. The KM curve was plotted to evaluate the differences in the survival analysis of cases with OA and those without OA in different cohorts.

The Cox proportional hazards model was used to estimate the hazard ratio (HR) for OA, adjusting for age, sex, and socioeconomic status (SES) based on residency status over time. The proportionality assumption for each comorbidity was tested by examining log-log KM curves. The Cox model consisted of both time-varying covariates (TVCs) and time-invariable factors. Covariates that remained unchanged over time or changed at the same rate for all participants were sex (male or female), age-at-activation (20-39, 40-49, 50-59, 60-69, 70-79, +80), and residency status (farm, rural, and urban). TVCs that could change over time included SES (categorical). SES was calculated by dividing the number of years an individual received income support from the Alberta Government by the total years the individual was

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active in the study. Three categories for SES were generated: 0 (individuals who never received income support), 1 (individuals who received income support for less than half the time they were active in the study), and 2 (individuals who received income support for half or more than half the time they were active in the study). All statistical analyses were conducted using SAS® version 9.4 (SAS Institute Inc., Cary, NC).

Ethics Approval

The Health Research Ethics Board (HREB) of the University of Alberta granted ethics approval for this study (Pro00121377). No personal identifying information was provided to the investigators.

Results

Over the period from April 1st, 2000, to March 31st, 2021, a total of 379,784 individuals were tracked, with 41.25% of them being monitored for the entire duration of the study. Among these individuals, those who were non-farm rural residents had the lowest percentage of staying active for the entire study, with only 34.14% (Appendix Table 2). The study started with 288,291 eligible participants on April 1st, 2000, after excluding individuals under the age of 20. Among them, 51.6% (n = 148,826) were male, and the farm cohort had the highest proportion of males at 54.6% (n = 53,194). The mean age of the population was 45.1 years with a standard deviation (SD) of 16.3, and the farm residents had the highest mean age (46.7; SD: 15.9). The majority of the study population was classified as high SES (98%; n = 297,366). Table 3-1 summarizes the initial characteristics of the three cohorts based on their residency status.

At the end of the follow-up, 63.3% of individuals with OA had no comorbidities two years before their OA diagnosis. Among the farm cohort, the mean of the updated Romano comorbidity index for two years before the diagnosis of OA was 0.73 (SD: 1.48) which increased to 1.82 (SD: 2.58) in the five years following the diagnosis of OA.

The total PYs of follow-up for OA from April 1st, 2000, to March 31st, 2021, was 4,614,207. After eliminating prevalent cases in three years of health records (from April 1st, 1997, to March 31st, 2000), 67,387 individuals met the incident case criteria. Figure 3-1 shows a Venn diagram presenting the

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distribution of incident cases of OA according to the source of diagnosis. Physician claim records identified the most cases, with a case identification of 93.6%. Of those cases identified, 58.2% had health records related to OA exclusively in physician claims.

The overall crude incidence rate was 14.6 (95% confidence interval (CI): 14.49, 14.71) per 1000 PYs across all three cohorts. Farm residents had the highest incidence rate (15.8; 95% CI: 15.61, 15.99 per 1000 PYs), followed by the rural cohort (14.72; 95% CI: 14.51, 14.93 per 1000 PYs) and the urban cohort (13.25; 95% CI: 13.07, 13.42 per 1000 PYs; Table 3-2).

The overall incidence rate was substantially higher in females (16.54; 95% CI: 16.37, 16.71 per 1000 PYs) than in males (12.87; 95% CI: 12.72, 13.01 per 1000 PYs), indicating that females had 29 percent higher OA incidence compared with males. The incidence rate in the farm cohort among males (14.27; 95% CI: 14.04, 14.51 per 1000 PYs) and females (17.69; 95% CI: 17.39, 17.99 per 1000 PYs) was higher than the incidence rates in the rural and urban cohorts (Table 3-2). In all three cohorts, incidence rates were higher among females, regardless of age group. Among the three cohorts, the incidence rate of OA increased linearly with age (Appendix Figure 3). The IRR between farm and urban cohorts was 1.19 (95% CI: 1.17, 1.21) which was higher than the IRR between rural and urban cohorts (1.11; 95% CI: 1.09, 1.13). Generally, the farm-to-urban IRR was higher than the rural-to-urban IRR in both sexes (Appendix Table 3). The magnitude of the farm-to-urban IRR was higher for males than females (Figure 3-2).

OA Incidence Trends

The crude incidence rate of OA in total cohorts fluctuated from year to year ranging from 19.1 per 1000 PYs (95% CI: 18.59, 19.62) to 10.03 per 1000 PYs (95% CI: 9.56, 10.5); however, a sharp decline of crude incidence rates was seen at the fiscal year 2020-2021 for all three cohorts (Figure 3-2). The detailed annual incidence rate of OA from the fiscal year 2000-2001 to 2020-2021 is provided in Appendix Table 4. The sex-specific patterns in annual OA incidence rates were generally similar to the crude incidence rates between 2000-2001 and 2020–2021 (Figure 3-3; Appendix Figure 5 and Appendix Table 5). Throughout the study duration, in all three cohorts, females consistently had higher incidence rates compared to males.

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Mortality

After adjusting for mortality, the lifetime risk of developing OA among farm residents was 27.7% or 5.5 in 20 chances, 25.6% or 5.1 in 20 chances for rural cohorts, and 24% or 4.8 in 20 chances for the urban cohort (Appendix Figure 4). Generally, individuals with OA had higher non-injury mortality rates compared to those without OA. Among OA cases, rural residents had the highest non-injury mortality rate (17.96 per 1000 PYs; 95% CI: 17.55, 18.38), while the lowest rate was observed among farm residents (13.16 per 1000 PYs; 95% CI: 12.87, 13.45). Among non-OA individuals, rural residents had the highest non-injury mortality rate (7.83 per 1000 PYs; 95% CI: 7.66, 7.99), followed by the non-OA farm group (6.66 per 1000 PYs; 95% CI: 6.52, 6.79) and the non-OA urban group (6.16 per 1000 PYs; 95% CI: 6.03, 6.29). Overall, males had higher non-injury mortality rates than females, both among individuals with OA and non-OA individuals (Figure 3-4; Appendix Table 6 and Appendix Table 9).

Rural OA cases had the lowest survival rate during the 21-year study period (67.02%; 95% CI: 66.38, 67.65; Figure 3-5), followed by urban and farm OA groups, 72.54% (95% CI: 71.96, 73.11) and 74.38% (95% CI: 73.88, 74.88), respectively (Appendix Table 7).

Farm residents had the highest unadjusted hazards of developing OA (unadjusted HR: 1.2; 95% CI: 1.17, 1.22). After adjusting for age and sex, the farm and rural residents respectively had a 6% and 9% higher risk of developing OA as compared to the urban cohort (Table 3-3). Females across all three cohorts had a 29% higher risk of developing OA (age and residency status adjusted HR: 1.29; 95% CI: 1.27, 1.31), and the risk of developing OA increased with advancing age.

Discussion

Farm residents are at a greater risk of developing OA compared to urban residents. Although more males comprised the farming cohort, females had a high risk of developing OA. These findings are aligned with the existing literature. A previous study conducted in Saskatchewan examined the prevalence of physician-diagnosed arthritis among 2,473 individuals residing on 1,216 farms. The study found that 13% of the respondents reported chronic arthritic diagnoses, with 10% having OA. Among those who had OA, it was observed that 52.6% were female[13]. A study in Sweden found that the hazard

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of developing OA was 2.1 times (95% CI: 1.4, 3.2) greater among male farmers than the urban cohort. This could be due to the difference in the study population as the Swedish study only included males between 40-60 years of age, while we investigated both males and females aged from 20 to 110. It is anticipated that males would have a greater risk of developing OA due to their higher physical workload compared to females. The findings of our study confirm that male farm residents experienced a 29% higher risk of OA development, while female farm residents had a 14% greater risk of developing OA, in comparison with their urban counterparts. The farm cohort in the Swedish study consisted of people who owned or rented a farm and spent at least 25hr per week in farming, while in our study the farm population included all farm family members based on the probabilistic match of Alberta Agriculture and Rural Development with the Farm Fuel Tax subsidy. Another possible reason for this difference could be attributed to the types of farming practiced in these regions. Their geographic and climatic differences lead to different types of agriculture, with Sweden focusing on sustainable and efficient methods of crop production, and Alberta's emphasis on large-scale livestock farming and grain production. These varying farming practices may result in differences in physical workload, occupational exposures, and work conditions, which could impact the development of OA[14].

A study in Quebec investigated the risk of OA development among employed adults aged 25-64 by adjusting for age, smoking, and body mass index (BMI). The results showed that males with manual occupations had a 40% higher risk of primary OA development in comparison with non-manual workers (OR: 1.4; 95% CI:1.1, 1.8)[25]. These results confirm that farmers, as manual workers, are more susceptible to developing OA. However, differences in study populations, participant age distribution, and methods used to ascertain OA cases may have contributed to some of the observed variations in the results between our study and the Quebec study on male manual workers.

Our results indicate that non-farm rural residents are at higher risk of developing OA compared to urban residents. A significant portion of non-farm rural residents is farm laborers who reside in rural areas close to the farms they work on. The nature of their work involves physically demanding tasks, such as planting, harvesting, and taking care of livestock and crops. These activities can be labor-intensive, particularly during the busiest seasons, and may require manual labor for long periods. In addition, farm

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owners may assign some of the physical work to the farm laborers and spend more time on administrative and managerial duties.

Residing in rural regions in Canada can influence the identification of medical conditions as a consequence of constrained accessibility to healthcare services[26,27], lack of specialist care[28], and transportation barriers[28,29]. As a result, the hazards of developing OA among farm and non-farm rural residents might be underestimated as compared to the urban cohort.

In a study of 3,068 individuals residing in rural regions of North Carolina, Murphy et al. reported a mortality-adjusted lifetime risk of 40% for men and 47% for women with OA[30]. This is higher than the results of our study possibly because our study focused on a younger cohort of individuals aged 20 years and above, while the other study included participants aged 45 years and older. Furthermore, a key difference between the two studies could be the approach used to diagnose OA. Our study employed various sources such as physician claims, ambulatory care database, and hospitalization, while Murphy et al relied on the interview method at both baselines and follow-up to identify OA cases.

Farm residents had the lowest non-injury mortality rates among both OA and non-OA individuals, which is consistent with a farming cohort study conducted in Sweden. The Swedish study estimated that the farm cohort had lower mortality rates compared to an urban group[31]. However, the magnitude is different, which may be attributed to various factors that can influence mortality rates, such as study population, available diagnosis and treatment, and specific reporting methods, which can vary from study to study. Mortality can significantly influence the burden of disease when assessing chronic diseases. Comparing OA cases with non-OA individuals shows that in all three residential groups, OA cases have a higher mortality rate given people with OA have a higher comorbidity index, more functional limitation mobility, and higher disability-adjusted life years (DALYs)[3,32–34].

There are some limitations to this study that need to be recognized. Individuals who had OA symptoms but did not have access to healthcare services may result in underestimated OA rates. Since the diagnostic algorithm is irrespective of the physician's specialization, the accuracy of the diagnosis is questionable. To improve the precision of OA diagnosis, it is recommended that a specialist, such as a

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rheumatologist, orthopedic surgeon, occupational medicine physician, or physical medicine and rehabilitation specialist, conduct the diagnosis[35]. A further limitation of the study is the inclusion of all farm residents and their families in the farm group, which means that family members who have little involvement in farm work are also part of the study's farm cohort. Besides, the occupation and workload in rural and urban cohort did not investigate. To decrease the possibility of this selection bias, we removed anyone who moved due to the possibility of a different workload. Moreover, we lacked data on other potential risk factors such as BMI, smoking status, working hours, occupation, sports activities, and family history of OA, which may have influenced the results.

This study, however, has several notable strengths that should be considered. A significant strength of the present research was the large study population from a province with a large farming sector. The study included all farm residents from the Alberta Agriculture and Rural Development Register who matched with the Farm Fuel Tax subsidy in 1998. By including all Albertan farm residents who met the criteria, the study aimed to reduce selection bias and enhance the precision and reliability of the estimates. Another strength was the use of three administrative databases - physician claims, ambulatory care, and hospitalization records - to identify cases of OA. This method provides more accurate identification of OA cases than self-reported studies, which are prone to recall bias[36]. The use of both ICD-9 and ICD-10 codes in the administrative databases enhanced the precision of the identification process.

Conclusion

The incidence of OA increases with age and females are more susceptible to this condition. The risk of developing OA among rural residents, including both farm and non-farm populations, is higher compared to the urban population who more often have sedentary occupations. Although the differences in incidence rates are not statistically significant, it is worth noting that farmers continue working beyond retirement age and are exposed to occupational-related joint stress. It is imperative to increase awareness of the burden of OA among rural populations who may also have limited access to healthcare services. Health policymakers should consider these differences when designing programs for OA prevention, health promotion, and improving access to healthcare services in rural communities.

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Table 3-1 Baseline characteristics of the study population on April 1st, 2000

Characteristics		Total Cohort	Farm	Non-farm Rural	Non-farm Urban
		n=288291	n=97370	n=91543	n=99378
		n (%)	**n (%)**	**n (%)**	**n (%)**
Sex	**Male**	148826 (51.62)	53194 (54.63)	46218 (50.49)	49414 (49.72)
	Female	139465 (48.38)	44176 (45.37)	45325 (49.51)	49964 (50.28)
Age	**mean (SD)**	45.1 (16.3)	46.7 (15.9)	44.6 (16.8)	44.0 (16.0)
	20-39	116534 (40.42)	33536 (34.44)	39434 (43.08)	43564 (43.84)
	40-49	67828 (23.53)	22461 (23.07)	21303 (23.27)	24064 (24.21)
	50-59	47182 (16.37)	19052 (19.57)	13239 (14.46)	14891 (14.98)
	60-69	30290 (10.51)	13945 (14.32)	8227 (8.99)	8118 (8.17)
	70-79	18501 (6.42)	6686 (6.87)	6009 (6.56)	5806 (5.84)
	80+	7956 (2.76)	1690 (1.74)	3331 (3.64)	2935 (2.95)
SES	**Low SES**	5658 (1.96)	903 (0.93)	2116 (2.31)	2639 (2.66)
	High SES	282633 (98.04)	96467 (99.07)	89427 (97.69)	96739 (97.34)

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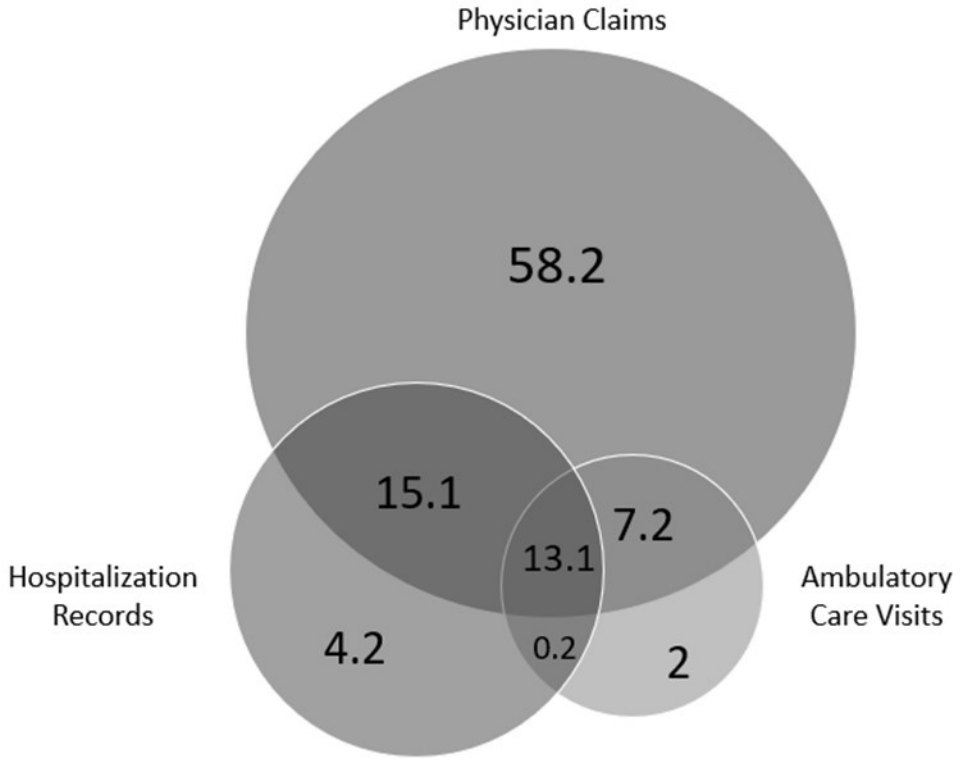

Figure 3-1 Case ascertainment from three Alberta Health (AH) data sources for osteoarthritis (OA) in Alberta, Canada from fiscal years 1997-1998 through 2020-2021 including Physician Claims, Hospitalization Records, and Ambulatory Care Visits

Table 3-2 The crude and age-sex-specific overall osteoarthritis (OA) incidence from April 1st, 2000 to March 31st, 2021

Cohort	Age Group	Total				Male				Female				Female to Male Ratio
		Person-Years	Case	Incidence (per 1000 Person-Years)	CI 95%	Person-Years	Case	Incidence (per 1000 Person-Years)	CI 95%	Person-Years	Case	Incidence (per 1000 Person-Years)	CI 95%	
Total	All	4614207	67387	14.6	(14.49, 14.71)	2430497	31270	12.87	(12.72, 13.01)	2183710	36117	16.54	(16.37, 16.71)	1.29
	20-39	2484528	11709	4.71	(4.63, 4.8)	1307604	5576	4.26	(4.15, 4.38)	1176924	6133	5.21	(5.08, 5.34)	1.22
	40-49	992695	16310	16.43	(16.18, 16.68)	516578	7541	14.6	(14.27, 14.93)	476117	8769	18.42	(18.04, 18.8)	1.26
	50-59	616656	16182	26.24	(25.84, 26.64)	327258	7412	22.65	(22.14, 23.16)	289398	8770	30.3	(29.68, 30.93)	1.34
	60-69	332825	12524	37.63	(36.98, 38.28)	183413	5996	32.69	(31.88, 33.51)	149412	6528	43.69	(42.65, 44.73)	1.34
	70-79	149820	7946	53.04	(51.9, 54.17)	79556	3743	47.05	(45.58, 48.52)	70264	4203	59.82	(58.06, 61.57)	1.27
	80<	37685	2716	72.07	(69.46, 74.68)	16090	1002	62.27	(58.54, 66.01)	21595	1714	79.37	(75.76, 82.98)	1.27
Farm	All	1706256	26957	15.8	(15.61, 15.99)	944879	13488	14.27	(14.04, 14.51)	761377	13469	17.69	(17.39, 17.99)	1.24
	20-39	848749	3637	4.29	(4.15, 4.42)	473173	1854	3.92	(3.74, 4.1)	375576	1783	4.75	(4.53, 4.97)	1.21
	40-49	361498	6092	16.85	(16.43, 17.27)	194494	2918	15	(14.46, 15.54)	167004	3174	19.01	(18.35, 19.66)	1.27
	50-59	266868	7273	27.25	(26.64, 27.87)	142126	3423	24.08	(23.29, 24.88)	124742	3850	30.86	(29.9, 31.82)	1.28
	60-69	161982	6246	38.56	(37.62, 39.5)	94174	3262	34.64	(33.47, 35.81)	67808	2984	44.01	(42.46, 45.55)	1.27
	70-79	58375	3057	52.37	(50.56, 54.18)	35866	1702	47.45	(45.25, 49.65)	22509	1355	60.2	(57.09, 63.31)	1.27
	80<	8784	652	74.23	(68.74, 79.71)	5046	329	65.2	(58.39, 72.01)	3738	323	86.41	(77.4, 95.42)	1.33
Rural	All	1295953	19075	14.72	(14.51, 14.93)	670179	8732	13.03	(12.76, 13.3)	625774	10343	16.53	(16.21, 16.84)	1.27
	20-39	724607	3816	5.27	(5.1, 5.43)	372863	1793	4.81	(4.59, 5.03)	351744	2023	5.75	(5.5, 6)	1.2
	40-49	277481	4621	16.65	(16.18, 17.13)	143615	2180	15.18	(14.55, 15.81)	133866	2441	18.23	(17.52, 18.95)	1.2
	50-59	156191	4126	26.42	(25.62, 27.21)	83512	1937	23.19	(22.17, 24.22)	72679	2189	30.12	(28.88, 31.36)	1.3
	60-69	80143	3046	38.01	(36.68, 39.33)	42937	1399	32.58	(30.9, 34.26)	37206	1647	44.27	(42.18, 46.36)	1.36
	70-79	42989	2377	55.29	(53.13, 57.45)	21199	1047	49.39	(46.47, 52.31)	21790	1330	61.04	(57.86, 64.22)	1.24
	80<	14543	1089	74.88	(70.6, 79.16)	6054	376	62.11	(56.03, 68.19)	8489	713	83.99	(78.09, 89.89)	1.35
Urban	All	1611998	21355	13.25	(13.07, 13.42)	815439	9050	11.1	(10.87, 11.33)	796559	12305	15.45	(15.18, 15.72)	1.39
	20-39	911172	4256	4.67	(4.53, 4.81)	461568	1929	4.18	(3.99, 4.37)	449604	2327	5.18	(4.97, 5.39)	1.24
	40-49	353716	5597	15.82	(15.41, 16.23)	178469	2443	13.69	(13.15, 14.23)	175247	3154	18	(17.38, 18.62)	1.31
	50-59	193597	4783	24.71	(24.01, 25.4)	101620	2052	20.19	(19.33, 21.06)	91977	2731	29.69	(28.6, 30.79)	1.47
	60-69	90700	3232	35.63	(34.43, 36.84)	46302	1335	28.83	(27.31, 30.36)	44398	1897	42.73	(40.85, 44.61)	1.48
	70-79	48456	2512	51.84	(49.87, 53.81)	22491	994	44.2	(41.51, 46.88)	25965	1518	58.46	(55.61, 61.32)	1.32
	80<	14358	975	67.91	(63.79, 72.02)	4990	297	59.52	(52.95, 66.08)	9368	678	72.37	(67.13, 77.62)	1.22

CI: confidence interval

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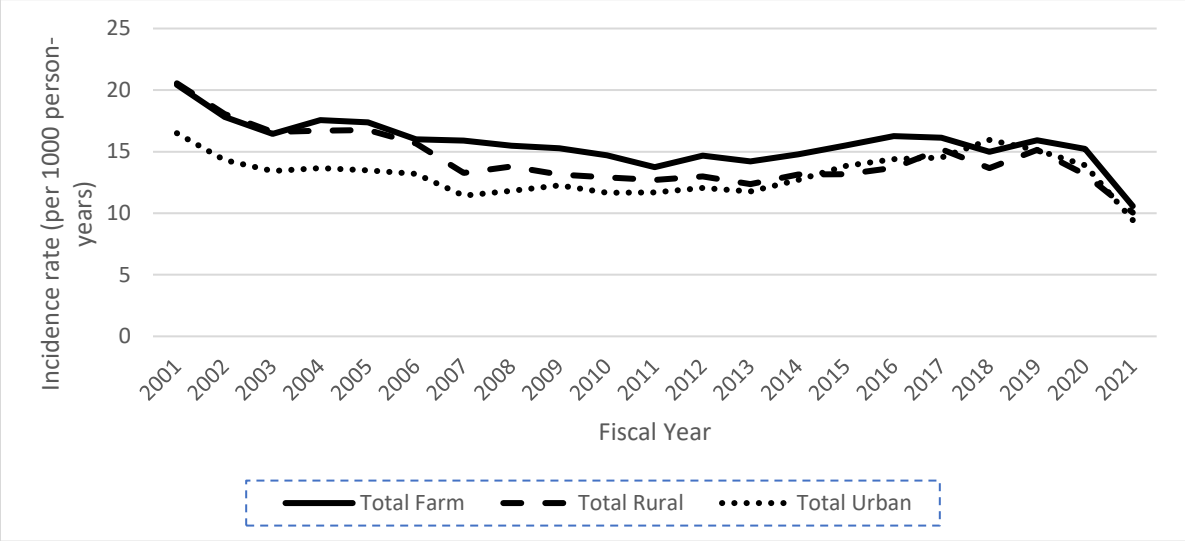

Figure 3-2 Annual incidence rate among farm, rural, and urban cohorts from the fiscal years 2000-2001 through 2020-2021

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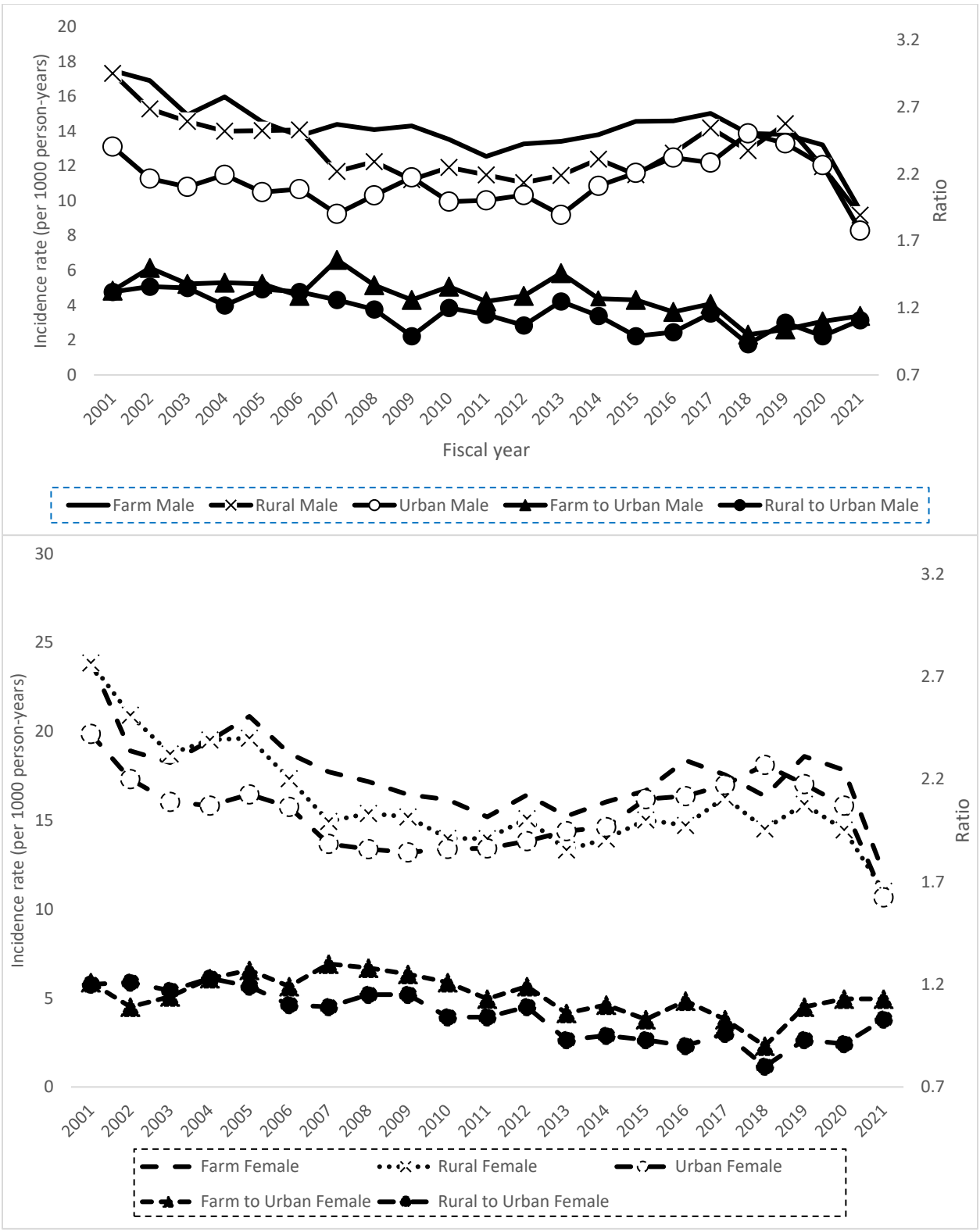

Figure 3-3 Sex-specific trends of annual incidence rate for males at the top and females at the bottom

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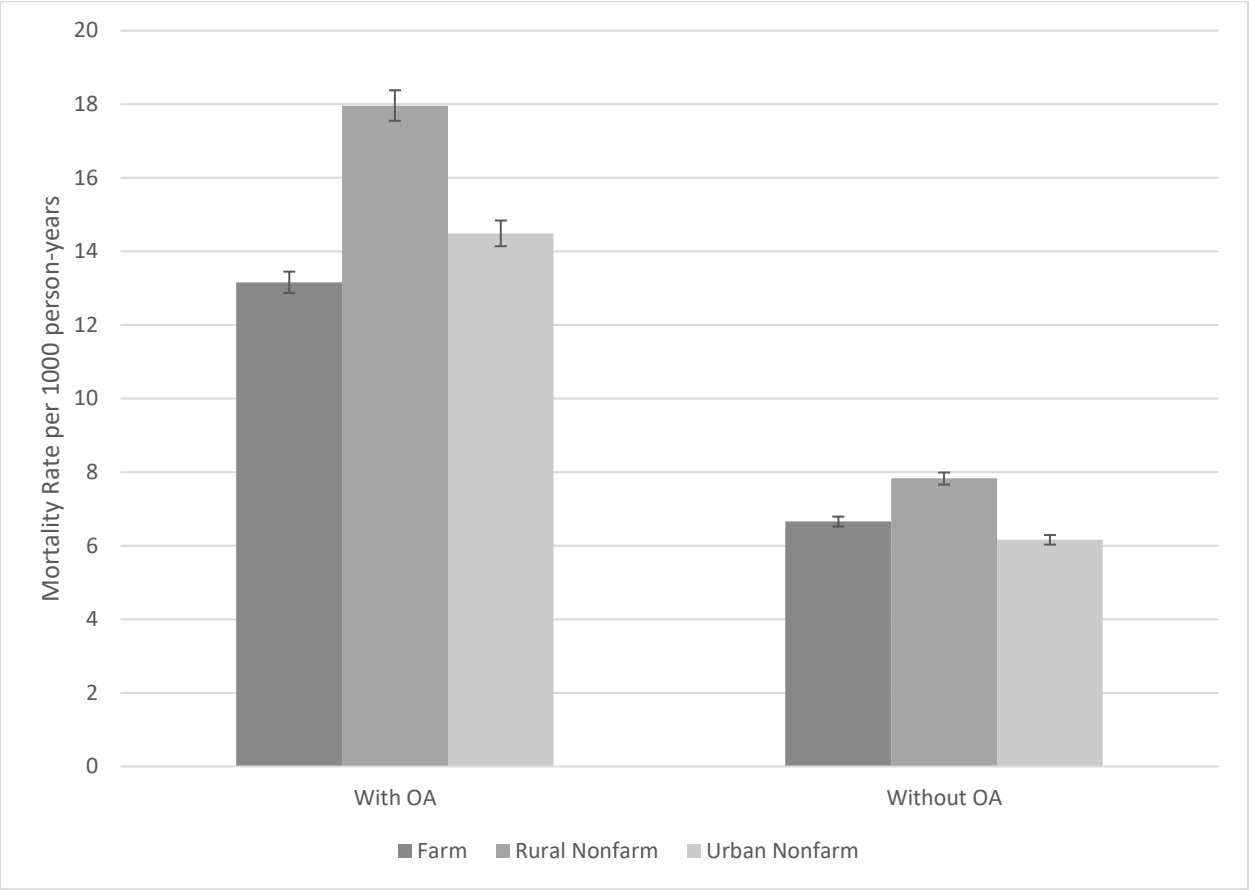

Figure 3-4 Non-injury mortality rate per 1000 person-years among osteoarthritis (OA) cases and non-OA cases in the farm, rural, and urban cohorts

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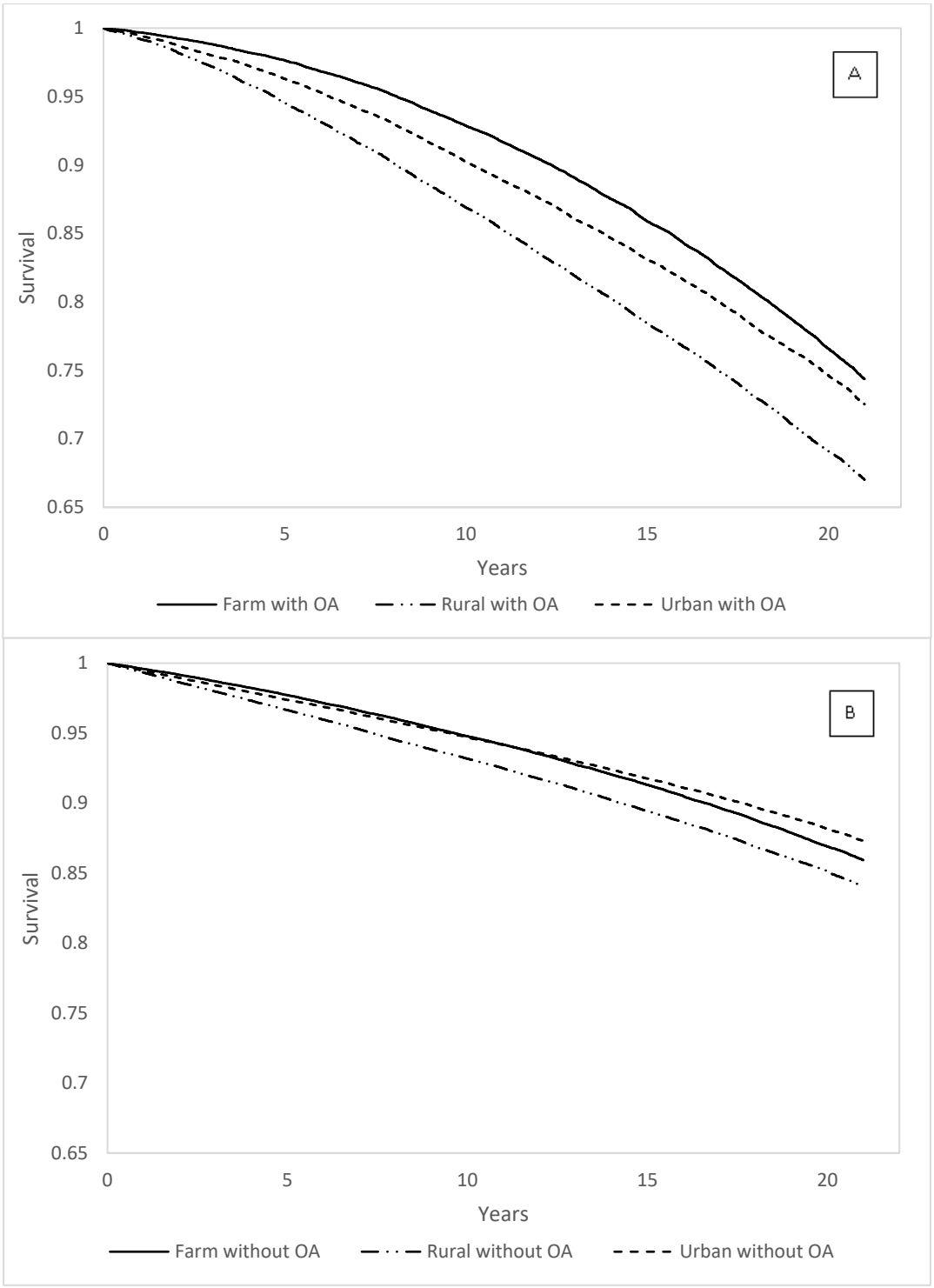

Figure 3-5 Kaplan-Meier curve for non-injury mortality rate in the farm, rural, and urban cohorts among: A) individuals with osteoarthritis (OA); B) individuals without OA

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Table 3-3 Unadjusted and adjusted hazard ratio (HR) for developing osteoarthritis (OA) based on the residency status

Category		Level	Hazard Ratio (HR)	95% CI
Unadjusted	**Residency Status Unadjusted**	**Farm**	1.2	1.17, 1.22
		Rural Non-farm	1.12	1.1, 1.14
		Urban Non-farm	Referent	Referent
Adjusted	**Residency Status Adjusted[1]**	**Farm**	1.06	1.04, 1.08
		Rural Non-farm	1.09	1.07, 1.12
		Urban Non-farm	Referent	Referent
	Sex	**Female**	1.29	1.27, 1.31
		Male	Referent	Reference
	Age at Activation Time	**20-39**	Referent	Referent
		40-49	3.38	3.3, 3.46
		50-59	5.48	5.35, 5.61
		60-69	8.08	7.88, 8.29
		70-79	11.86	11.52, 12.2
		80<	16.58	15.9, 17.3

[1] The residency status is adjusted for age and sex. However, SES is not reflected in the table as it was not statistically significant and did not survive the final modeling process.

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Chapter 4. Discussion and Conclusion

This study provides a unique contribution to the existing literature as it estimates the incidence of OA among farm residents in Alberta using administrative health data. The crude and age-sex-specific overall incidence rates for OA were calculated among farm, non-farm rural, and urban residents for the fiscal years 2000-2001 to 2020-2021. The estimates of the overall OA incidence and the annual OA incidence rate in 2020-2021 were 14.6 per 1000 person-years (95% CI: 14.49, 14.71) and 10.03 per 1000 person-years (95% CI: 9.56, 10.5), respectively. The incidence of OA is not equally distributed across different residency statuses. Farm residents exhibited the highest incidence rate, which is not unexpected, given their typical exposure to heavy workloads and higher risk of injury. There has been no prior research that has examined the incidence of OA among farm residents in Alberta. While a study conducted by Marshall et al did explore OA prevalence rates across the rural-urban continuum, they did not report on the incidence of OA[17]. The study found that the crude OA prevalence rate was higher in rural areas (150.1 per 1000 population) than in urban areas (98.9 per 1000 population), suggesting that rural residents may be at a greater risk of developing OA. This finding is consistent with our results regarding the incidence rates of OA among rural and urban residents. However, Marshall et al did not specifically investigate the incidence of OA among farm residents. A study in Saskatchewan examined the prevalence of physician-diagnosed arthritis among 2,473 adult residents who lived on 1,216 farms. According to the study, 13% of the participants had chronic arthritis diagnoses, with 10% being diagnosed with OA[13].

The trend analysis of OA incidence rates between 2000-2001 and 2020-2021 revealed a fluctuating pattern. The highest OA incidence rates were observed at the start of the study period (2000-2001 fiscal year) for all three cohorts. However, this rate was found to be overestimated due to the limited three-year run-in period (fiscal years 1997-1998 through 1999-2000). The utilization of different numbers of run-in years to exclude prevalent cases can impact the OA incidence rate in an administrative database. To control for overestimation, a longer run-in period was recommended[74]. As we have data spanning 24 years, a 3-year run-in period was chosen for the trend analysis to obtain an incidence rate at the beginning of the study. Extending the run-in period for eliminating prevalent cases has led to more

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accurate incidence rates compared to those obtained with a shorter run-in period. After 2020, there was a sharp drop in the annual incidence rate for all three cohorts, possibly due to the impact of the COVID-19 pandemic. The pandemic resulted in the diversion of many healthcare resources and staff to treat people with COVID-19, leading to a shortage of supplies and significantly reduced access to medical care[313]. This reduced access to health services, and the fear of contracting COVID-19 potentially contributed to the observed decrease in OA incidence rates.

The results of this study show that there are sex-specific variations in OA incidence rates and females consistently had a higher incidence rate of OA compared to males in the same group. This finding is supported by previous studies[18,41,234,235]. Both male and female farm residents exhibited higher OA incidence rates than their rural and urban counterparts. However, the sex-specific IRRs demonstrated that males had higher IRRs than females for both farm-to-urban and rural-to-urban, which were 11% and 10% higher than their counterparts, respectively. This higher rate may be related to the lower OA incidence rate in the urban and rural cohorts. This difference is possibly due to the fact that males in farming jobs are more exposed to physical workloads, which is a recognized risk factor for OA[14]. These findings highlight the potential impact of occupational risk factors on the development of OA and the sex-specific differences among different populations with the incidence of OA.

Mortality is an important factor to consider when assessing the burden of chronic diseases, such as OA. In this study, the rural population had a higher non-injury mortality rate (17.96 per 1000 PYs; 95% CI: 17.55, 18.38) compared to both farm and urban cohorts, regardless of OA status. Mortality rates reported in the OA cohorts were higher than those without OA regardless of the residency status. The higher mortality rate among OA cohorts may be related to several factors, including a higher comorbidity index, greater functional limitations, and general disability as reflected by greater DALY scores[3,32–34].

The unadjusted HR revealed that farm residents have the highest risk of developing OA, yet, after adjusting for age and sex, the hazard of developing OA among farm residents compared to urban residents decreased from 1.2 (95% CI: 1.17, 1.22) to 1.06 (95% CI: 1.04, 1.08). The hazard of developing OA among the rural cohort is estimated to be greater as compared to the farm cohort. This might be due to several reasons. Firstly, the rural cohort may have included some individuals with physically

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demanding occupations, such as farming, construction, or resource extraction[314]. Secondly, there is variation in age distribution within the farm and rural cohorts. Maybe, another possibility for the difference. Before adjusting for age, farm residents have a higher age distribution within the 50-69 age group, which is considered a high-risk age group for developing OA during the study [40]. An analysis of the years of active participation in the study revealed that only 34.14% of the rural population remained in the study for the entire 21-year period, while 46.85% of farm residents were active in the study for the entire duration. This difference in active participation rates could be attributed to factors such as higher mortality or immigration among rural residents. Consequently, rural residents had a lower chance of reaching the high-risk age groups for developing OA.

This study had some limitations that should be considered when interpreting the results. One limitation of our study is due to the nature of using administrative data to calculate the incidence rate. This may have resulted in an overestimation of the incidence rate, especially in the first years and overall incidence rate. Caution is needed when interpreting the incidence rate results.

There are certain limitations to this study that are intrinsic to the use of administrative databases including the possibility of diagnostic errors occurring when using administrative data. This can be due to factors such as individuals not seeking medical attention for their OA, incorrect diagnosis, and inaccurate assignment of diagnostic codes, which can lead to false negatives[74]. Conversely, a false positive is a possibility due to an inaccurate preliminary diagnosis[21]. To minimize these potential inaccuracies, we utilized a standardized algorithm for defining OA that is commonly accepted for research utilizing administrative databases. Despite these efforts, the accuracy of the OA diagnosis and coding in our database is unclear[74]. It is reasonable to assume that any potential inaccuracies in diagnosis and coding would have remained relatively random among the three cohorts and stable over the observation period, and would not have significantly skewed the patterns observed in our results.

Another limitation of our study is the potential underestimation of the number of OA cases due to the exclusion of certain groups from the population registry. Specifically, individuals such as members of the Armed Forces and the Royal Canadian Mounted Police, federal penitentiary inmates, and Albertans

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who have opted out of the AHCIP were removed from our study population. As a result, this is a very small portion of the overall population.

Lastly, the study cohorts were assembled based on their status at the beginning of this study. The farm residents and their families have been included in the farm cohort, regardless of their level of involvement in farming activities. This approach has the potential to introduce selection bias, as family members may not be involved in farm activity, and rural residents who may be involved in farming activities were not differentiated due to the lack of data for their occupation[314]. To mitigate this, we considered individuals who may have moved due to changes in workload, but there is still a possibility that some individuals may have been misclassified with an incorrect occupation status, which could contribute to selection bias. Known significant risk factors such as obesity and injury were not reported in the datasets used in the study may limit the accuracy of the estimated hazard of developing OA [248,263].

This study, however, has several notable strengths that should be considered. One notable strength of this study is the comprehensive and representative nature of the study population. Since data were obtained from a large and comprehensive population, the estimates of the incidence are representative of the rural and urban residents in a Canadian province. The sex and age strata in a specific cohort provide more understanding of how the pattern of OA changes over the course of a lifetime.

The longitudinal nature of this study is another notable strength, as it allowed for the examination of trends and changes in OA incidence over 21 years which provided sufficient time for the development of OA[315]. The duration of the follow-up and the large sample permitted a robust and stable estimate of the incidence with high precision. Overall, the use of case ascertainment used by others[19–21], and the period of observation are critical strengths of this study, which enhances the reliability and validity of our findings. To identify more cases, we employed a more comprehensive case definition, requiring at least two visits to a health professional within two years or at least two ambulatory care visits within two years, or one hospital separation. This approach allowed for the use of more resources to capture a wider range of cases.

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In conclusion, the study shows that there is a higher risk of developing OA among women, older adults, and males living in rural areas, especially those in farm communities. As a result, healthcare professionals who work in rural areas need to be aware of this increased risk and should screen these high-risk groups for OA. Additionally, future research is needed to identify specific risk factors associated with farming and rural life that contribute to the development of OA. This information can be used to develop targeted prevention and management approaches to reduce the burden of OA in these populations.

4.1 Clinical Implications

The findings of this study have significant implications for both clinical practice and health policy. The first important clinical message pertains to the burden of OA in primary care. OA is a prominent contributor to disability in middle-aged and elderly individuals, and it places a considerable burden on the public healthcare system[193]. Given that farm and non-farm rural groups often experience heavy physical workloads from a young age and continue to be exposed to such workloads even after regular retirement age[46], the burden of OA is likely to be higher than that experienced by urban residents. As Canadians living in farm and rural areas have less access to care due to geographical barriers[26,29,316], policymakers and healthcare providers should make extensive efforts to enhance the health of people with OA and reduce the burden of OA by improving diagnosis, management, and public health programs.

Policymakers and medical experts must recognize the unique needs of farm residents and develop targeted interventions that address both occupational safety and health concerns. These interventions may need to take into account the family-based nature of farming and the limited number of paid workers. By implementing effective strategies to promote the health and safety of farm residents, policymakers and healthcare professionals can help to reduce the burden of OA in this population.

Although not typically considered fatal, people with OA are at a higher risk of other comorbid conditions, and this study identified an elevated risk of mortality among individuals with OA. This finding suggests that screening people with OA for early diagnosis of linked comorbidities and associated risk factors should be considered, and the presence of known comorbidities should be taken into account in

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the management plan for people with OA. These findings have important implications for healthcare professionals in developing targeted interventions to manage risk factors for OA such as obesity. Given the unique challenges faced by rural and farm residents, such as limited access to healthcare and limited mobility, management plans for rural and farm residents with OA should focus on improving access to care, promoting healthy lifestyle changes, and providing education about the importance of early diagnosis and management of comorbidities. This may include developing community-based programs, providing telehealth services, and partnering with local resources to support rural and farm residents with OA in managing their health.

4.2 Future Research

The results of our analysis indicate that further research is necessary to obtain national estimates for the incidence of OA in the farm and rural population, using data from all provinces. Additionally, future studies should particularly focus on identifying OA cases among individuals who are not under health coverage, particularly immigrant farmers who may have limited access to healthcare or may not report OA symptoms to their physicians[317]. Clinical or population-based surveys could be conducted to capture milder cases or individuals who do not have access to the healthcare system.

The use of administrative databases can be crucial for the surveillance of OA. This data can be used to describe the epidemiology of the diseases and to identify the high-risk groups at the population level. Conducting validation studies to evaluate the precision of administrative diagnoses prior to employing administrative data is noteworthy. MRI and X-rays can both be used as the validation study.

It would be useful to investigate different types of farming and the average weekly working hours for each participant. By considering the occupation of individuals in the rural and urban cohorts and categorizing it based on physical workload, more accurate comparisons between different residency groups can be made. Furthermore, while we estimated unspecific OA among Albertan farm residents, examining joint-specific OA in detail could aid in developing effective care packages for this at-risk population.

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Appendices

Appendix A - Charlson Comorbidity Index

The CCI is a tool that uses the International Classification of Diseases (ICD) diagnosis codes from administrative data, such as hospital abstract data, to classify a patient's comorbidities. It comprises 19 comorbidity categories, each assigned a weight ranging from 1 to 6 based on the associated risk of mortality or resource utilization. The patient's total comorbidity score is calculated by adding up the weights of all comorbidity categories present, with a score of zero indicating no comorbidities identified. A higher score indicates an increased probability that the anticipated result will involve elevated usage of resources or mortality. It should be noted that the index used in research studies has evolved over time. Appendix Table A-1 shows the list of some of the significant historical changes in the CCI.

Appendix Table A-1 Historical perspectives of the Charlson comorbidity index (CCI)

Study	Year	Results
Charlson et al.,[22]	1987	19 categories of comorbidity were identified, and weights were developed for each category based on the adjusted relative risk of one-year mortality.
Deyo et al.,[318]	1992	Corresponding ICD, 9, CM diagnosis, and procedure codes for each category of the CCI were assigned. Moreover, 19 categories decreased to 17 categories by combining "leukemia" and "lymphomas" in the "any malignancy" category.
Romano et al.,[23]	1993	The list of ICD codes developed by Deyo was compared with Dartmouth, Manitoba codes
Halfon et al.,[319]	2002	The ICD, 9, CM diagnosis codes from the Deyo adaptation of the CCI were translated into ICD, 10, codes
Quan et al.,[320]	2005	A multistep process to develop ICD, 10 coding algorithms to define Charlson and Elixhauser comorbidities in administrative data was conducted and Deyo's coding algorithm was enhanced.
Li et al.,[321]	2008	The performance of the CCI and the Elixhauser Comorbidity Index using ICD, 10 coding systems were assessed and no differences were found.

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Appendix B - Health Administrative Data

A health administrative database is a desirable data source for population, based research, and surveillance. These extensive administrative health databases are increasingly being used to inform clinical practice, epidemiological research, and health policy decisions. Studying treatment of disease, actual disease patterns, disease treatments, differences in access and care quality, costs of care[322], and the efficacy of care are some fields that administrative health data used.

Alberta Health Administrative Data

One of the main aims of the health system of Canada is to provide universal coverage for inpatient and outpatient services without copayments or other patient charges via provincial health insurance. Even though there are health administrative statistics for every Canadian, the provinces are responsible for the country's health care system. Apart from federally financed hospitals, where the Canadian Institute for Health Information (CIHI) is in charge of managing the collection of hospitalization data and the distribution of data back to the provinces, therefore each province is the data custodian of its administrative data[323].

Alberta's Health Information Act (HIA) permits the disclosure of personally identifiable health information with or without the consent of an individual. An exclusive encrypted PHN will be used to link individual healthcare encounter details of Alberta citizens enrolled under the AHCIP and maintained in Alberta health administrative systems. For this study, six administrative datasets will be used for the analyses of individual encounters with the Alberta health care system.

Strengths and Limitations of the Health Administrative Data

The health administrative data is one of the largest primary care datasets which includes information on Physician claims, prescriptions, hospitalization, outpatient care, and demographic data. The database's main strengths are covering the entire population and containing longitudinal data, allowing researchers to study disease associations and outcomes. Moreover, the databases are relatively inexpensive to access and analyze and available in all provinces and territories. Even though

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administrative statistics is a reliable source of population, based data, the databases were created for administrative rather than secondary research reasons[324].

The completeness of the data on every patient with missing values for various lifestyle characteristics is one of the main drawbacks of administrative data. Information on socioeconomic data, such as occupation and employment, is generally limited. The absence of lifestyle influences is significant from the point of view of epidemiological studies. Also, it’s possible that information that is not relevant to hospital or physician compensation will not be given or documented correctly. Due to the lack of incentives for physicians to accurately code diagnoses, the accuracy of physicians' diagnosis coding can be a problem[325].

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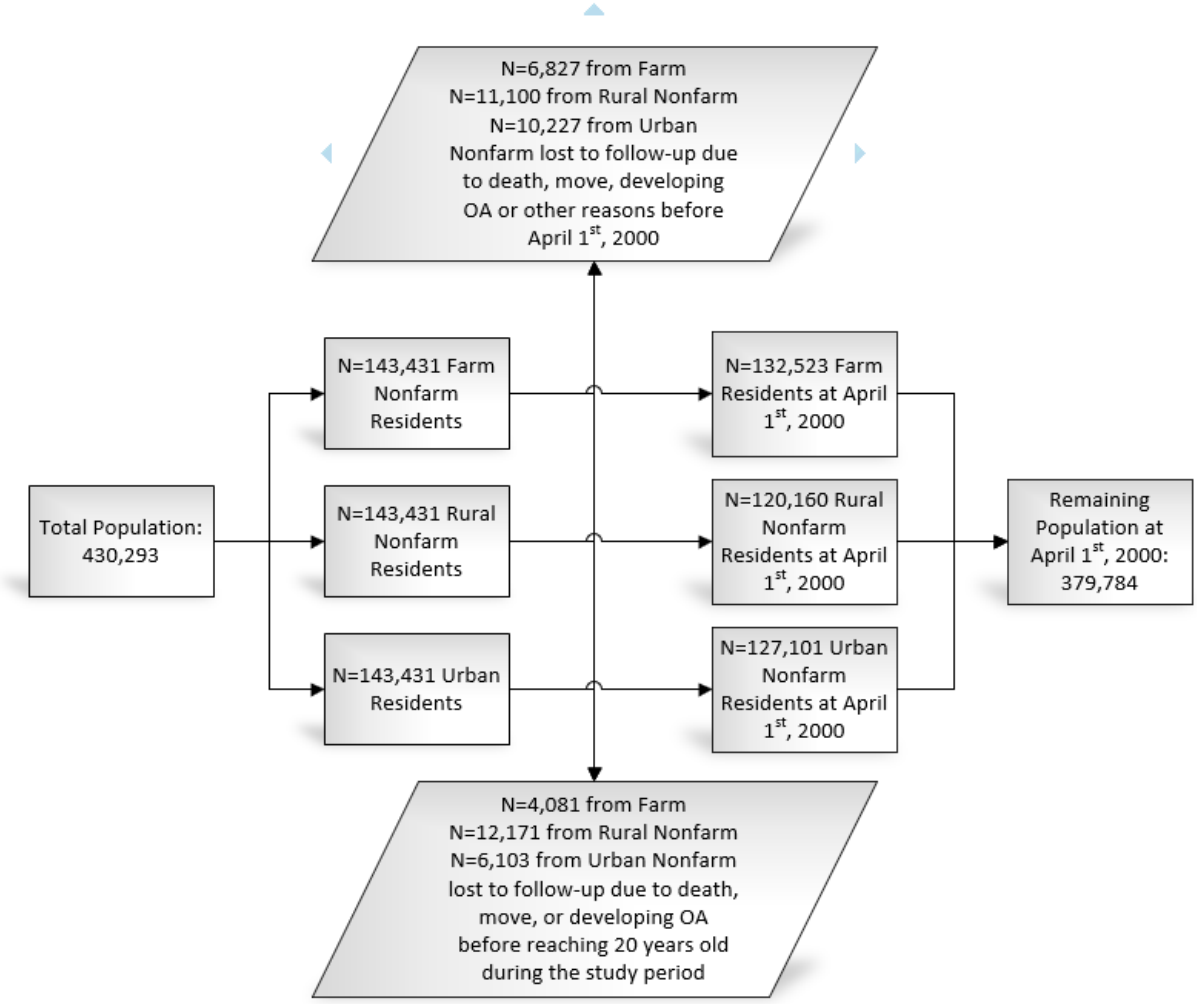
Appendix C – Tables and Figures



Appendix Figure 1 The data reduction fellow chart after applying the inclusion and exclusion criteria.

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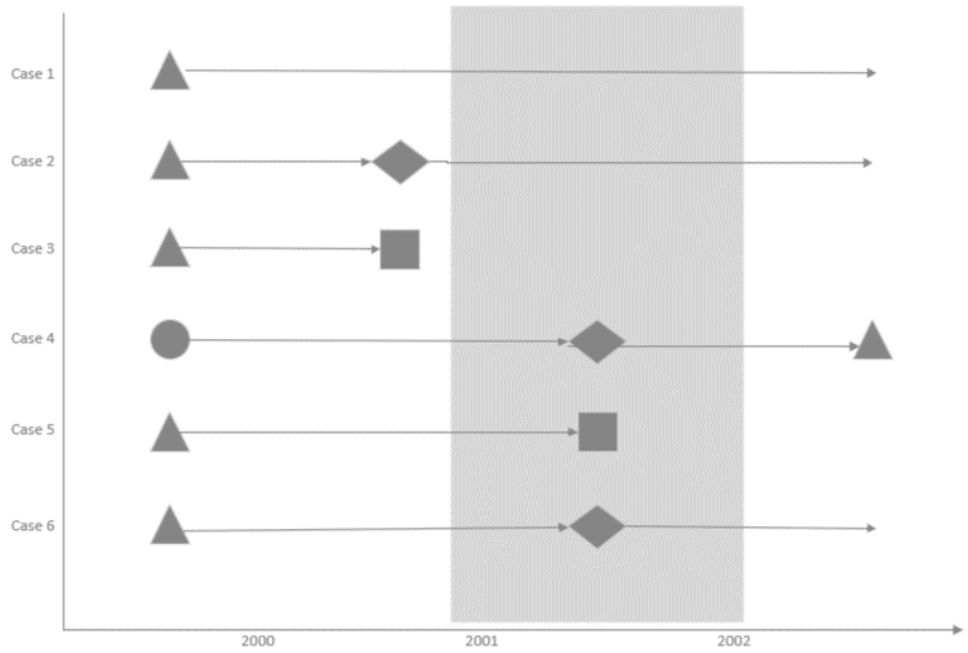

Appendix Figure 2 Selection of the study population for incidence: circle (inactive), triangle (active), diamond (diagnosis date), and square (loss to follow up because of death, move, or other reasons)

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Appendix Table 1 Selection criteria for incidence based on the dates in the datasets.

Case	Inclusion in Numerator	Inclusion in Denominator	Incidence (2001-2002)
1	No	Yes	Yes
2	No	No	No
3	No	No	No
4	No	No	No
5	No	Yes	Yes
6	Yes	Yes	Yes

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Appendix Table 2 Frequency of the population active in the study categorized on a 5-year scale

Years in Study	Total n (%)	Farm n (%)	Rural n (%)	Urban n (%)
1- 5	82282 (21.67)	22042 (16.63)	35197 (29.29)	25043 (19.7)
6- 10	53094 (13.98)	19374 (14.62)	19345 (16.1)	14375 (11.31)
11- 15	47121 (12.41)	15043 (11.35)	13428 (11.18)	18650 (14.67)
16- 20	38066 (10.02)	13982 (10.55)	11167 (9.29)	12917 (10.16)
The Whole Study	159221 (41.92)	62082 (46.85)	41023 (34.14)	56116 (44.15)

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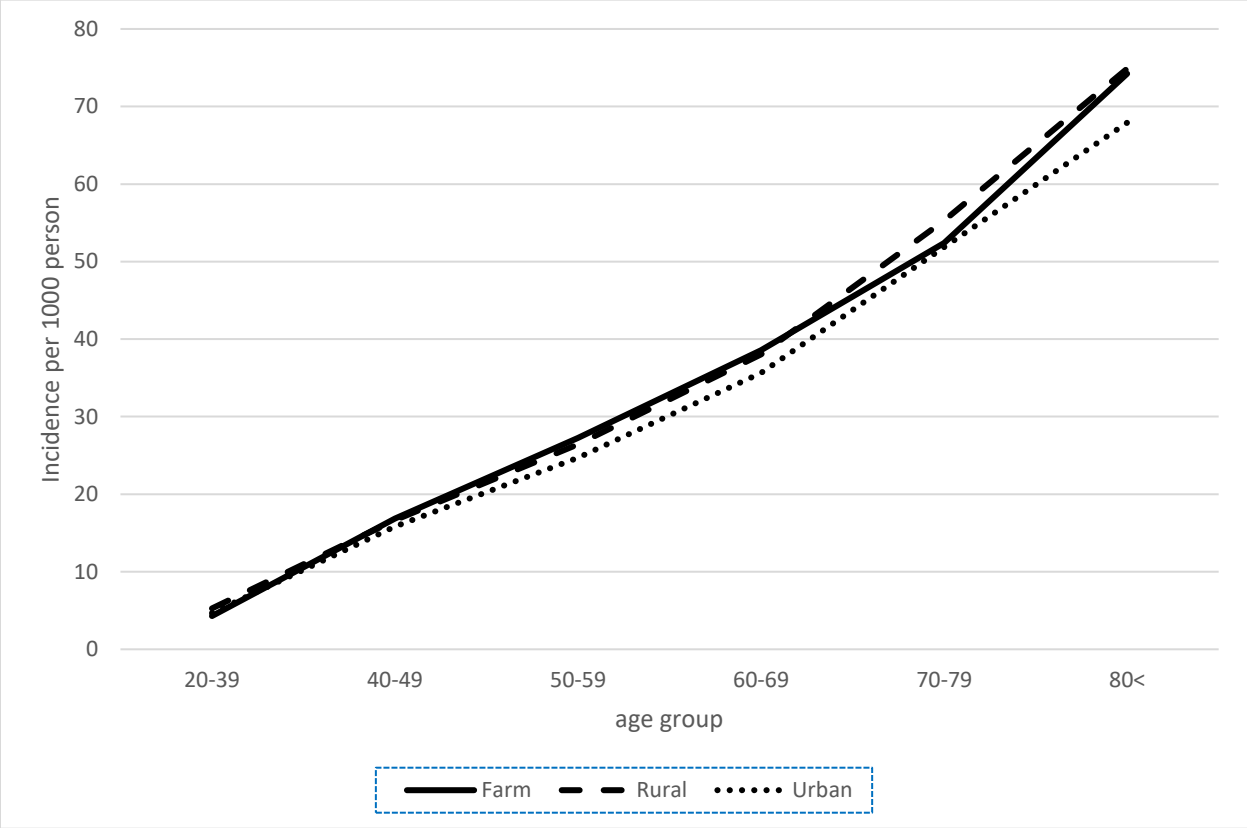

Appendix Figure 3 The age-specific overall osteoarthritis (OA) incidence from fiscal years 2000-2001 through 2020-2021 for farm, rural, and urban cohorts

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Appendix Table 3 The overall rural-to-urban and farm-to-urban Osteoarthritis (OA) Incidence Rate Ratio (IRR) from 2001 to 2021

IRR (95 % CI)						
Age	**Farm to Urban**			**Rural to Urban**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
All	1.29 (1.26-1.32)	1.14 (1.11-1.17)	1.19 (1.17-1.21)	1.17 (1.14-1.2)	1.07 (1.04-1.1)	1.11 (1.09-1.13)
20-39	0.94 (0.88-1)	0.92 (0.86-0.98)	0.92 (0.88-0.96)	1.15 (1.08-1.23)	1.11 (1.05-1.18)	1.13 (1.08-1.18)
40-49	1.1 (1.04-1.16)	1.06 (1.01-1.11)	1.07 (1.03-1.11)	1.11 (1.05-1.18)	1.01 (0.96-1.06)	1.05 (1.01-1.09)
50-59	1.19 (1.13-1.26)	1.04 (0.99-1.09)	1.1 (1.06-1.14)	1.15 (1.08-1.22)	1.01 (0.95-1.07)	1.07 (1.03-1.12)
60-69	1.2 (1.13-1.28)	1.03 (0.97-1.09)	1.08 (1.04-1.13)	1.13 (1.05-1.22)	1.04 (0.97-1.11)	1.07 (1.02-1.12)
70-79	1.07 (0.99-1.16)	1.03 (0.96-1.11)	1.01 (0.96-1.06)	1.12 (1.03-1.22)	1.04 (0.97-1.12)	1.07 (1.01-1.13)
80<	1.1 (0.94-1.29)	1.19 (1.04-1.36)	1.09 (0.99-1.2)	1.04 (0.89-1.21)	1.16 (1.04-1.29)	1.1 (1.01-1.2)
IRR: Incidence Rate Ratio, CI: Confidence Interval						

Appendix Table 4 Annual osteoarthritis (OA) incidence rate per 1000 person-years (PYs) from 2000-2001 to 2020-2021

Year	Farm			Non-farm Rural			Non-farm Urban			Total Cohort		
	Population at Risk (PYs)	OA Cases	Crude [95% CI]	Population at Risk (PYs)	OA Cases	Crude [95% CI]	Population at Risk (PYs)	OA Cases	Crude [95% CI]	Population at Risk (PYs)	OA Cases	Crude [95% CI]
2001	95169	1944	20.43 [19.53, 21.33]	84853	1744	20.55 [19.6, 21.51]	95463	1575	16.5 [15.69, 17.31]	275485	5263	19.1 [18.59, 19.62]
2002	94123	1677	17.82 [16.97, 18.66]	79455	1435	18.06 [17.13, 18.99]	91254	1305	14.3 [13.53, 15.07]	264832	4417	16.68 [16.19, 17.17]
2003	92242	1516	16.44 [15.61, 17.26]	75423	1253	16.61 [15.7, 17.53]	88394	1186	13.42 [12.66, 14.18]	256059	3955	15.45 [14.97, 15.92]
2004	90593	1591	17.56 [16.71, 18.42]	72341	1208	16.7 [15.76, 17.63]	86045	1175	13.66 [12.88, 14.43]	248979	3974	15.96 [15.47, 16.45]
2005	88967	1546	17.38 [16.52, 18.24]	69399	1163	16.76 [15.8, 17.71]	83840	1129	13.47 [12.69, 14.25]	242206	3838	15.85 [15.35, 16.34]
2006	87222	1395	15.99 [15.16, 16.83]	66894	1048	15.67 [14.73, 16.61]	81913	1081	13.2 [12.42, 13.98]	236029	3524	14.93 [14.44, 15.42]
2007	85723	1362	15.89 [15.05, 16.73]	64910	861	13.26 [12.38, 14.14]	80241	918	11.44 [10.7, 12.18]	230874	3141	13.6 [13.13, 14.08]
2008	84090	1301	15.47 [14.64, 16.31]	63007	868	13.78 [12.87, 14.69]	78448	928	11.83 [11.07, 12.59]	225545	3097	13.73 [13.25, 14.21]
2009	82460	1259	15.27 [14.43, 16.1]	61093	803	13.14 [12.24, 14.05]	76985	944	12.26 [11.48, 13.04]	220538	3006	13.63 [13.15, 14.11]
2010	81423	1197	14.7 [13.87, 15.53]	60071	776	12.92 [12.02, 13.82]	76062	887	11.66 [10.9, 12.42]	217556	2860	13.15 [12.67, 13.62]
2011	80885	1111	13.74 [12.93, 14.54]	59518	755	12.69 [11.79, 13.58]	75530	884	11.7 [10.94, 12.47]	215933	2750	12.74 [12.26, 13.21]
2012	80372	1180	14.68 [13.85, 15.51]	59008	766	12.98 [12.07, 13.89]	74969	904	12.06 [11.28, 12.84]	214349	2850	13.3 [12.81, 13.78]
2013	79447	1130	14.22 [13.4, 15.05]	58169	719	12.36 [11.46, 13.26]	74257	873	11.76 [10.98, 12.53]	211873	2722	12.85 [12.37, 13.33]
2014	78561	1162	14.79 [13.95, 15.64]	57336	753	13.13 [12.2, 14.06]	73490	934	12.71 [11.9, 13.52]	209387	2849	13.61 [13.11, 14.1]
2015	77492	1201	15.5 [14.63, 16.37]	56356	743	13.18 [12.24, 14.13]	72426	1003	13.85 [13, 14.7]	206274	2947	14.29 [13.77, 14.8]
2016	76182	1239	16.26 [15.37, 17.16]	55337	757	13.68 [12.71, 14.65]	71406	1027	14.38 [13.51, 15.26]	202925	3023	14.9 [14.37, 15.42]
2017	74643	1205	16.14 [15.24, 17.05]	54168	823	15.19 [14.16, 16.22]	70246	1021	14.53 [13.65, 15.42]	199057	3049	15.32 [14.78, 15.86]
2018	73252	1097	14.98 [14.1, 15.86]	52986	724	13.66 [12.68, 14.65]	68862	1098	15.94 [15.01, 16.88]	195100	2919	14.96 [14.42, 15.5]
2019	70476	1122	15.92 [15, 16.84]	50722	768	15.14 [14.08, 16.2]	66454	1005	15.12 [14.2, 16.05]	187652	2895	15.43 [14.87, 15.99]
2020	67693	1031	15.23 [14.31, 16.15]	48604	639	13.15 [12.13, 14.16]	64167	891	13.89 [12.98, 14.79]	180464	2561	14.19 [13.65, 14.74]
2021	65333	691	10.58 [9.79, 11.36]	46675	469	10.05 [9.14, 10.95]	62161	587	9.44 [8.68, 10.2]	174169	1747	10.03 [9.56, 10.5]
Total	1706256	26957	15.8 [15.61, 15.99]	1295953	19075	14.72 [14.51, 14.93]	1611998	21355	13.25 [13.07, 13.42]	4614207	67387	14.6 [14.49, 14.71]

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Appendix Table 5 Sex-specific annual incidence rate ratio (IRR) from fiscal years 2000-2001 through 2020-2021

IRR [95 % CI]						
Year	Farm to Urban			Rural to Urban		
	Male	Female	Total	Male	Female	Total
2001	1.33 [1.2, 1.47]	1.21 [1.11, 1.32]	1.24 [1.16, 1.33]	1.32 [1.19, 1.47]	1.2 [1.1, 1.31]	1.25 [1.17, 1.34]
2002	1.5 [1.35, 1.67]	1.09 [0.99, 1.2]	1.25 [1.16, 1.34]	1.36 [1.21, 1.53]	1.21 [1.1, 1.33]	1.26 [1.17, 1.36]
2003	1.38 [1.23, 1.55]	1.14 [1.03, 1.26]	1.23 [1.14, 1.33]	1.35 [1.19, 1.53]	1.17 [1.05, 1.3]	1.24 [1.15, 1.34]
2004	1.39 [1.24, 1.55]	1.23 [1.11, 1.36]	1.29 [1.2, 1.39]	1.22 [1.08, 1.38]	1.23 [1.11, 1.37]	1.22 [1.13, 1.32]
2005	1.38 [1.23, 1.55]	1.27 [1.15, 1.4]	1.29 [1.19, 1.39]	1.34 [1.18, 1.52]	1.19 [1.07, 1.32]	1.24 [1.14, 1.35]
2006	1.29 [1.14, 1.46]	1.19 [1.07, 1.32]	1.21 [1.12, 1.31]	1.32 [1.16, 1.5]	1.1 [0.98, 1.23]	1.19 [1.09, 1.3]
2007	1.56 [1.38, 1.77]	1.3 [1.16, 1.46]	1.39 [1.28, 1.51]	1.26 [1.09, 1.45]	1.09 [0.96, 1.23]	1.16 [1.06, 1.27]
2008	1.37 [1.21, 1.55]	1.28 [1.14, 1.44]	1.31 [1.2, 1.43]	1.19 [1.04, 1.37]	1.15 [1.02, 1.3]	1.16 [1.06, 1.27]
2009	1.26 [1.12, 1.42]	1.25 [1.11, 1.41]	1.25 [1.15, 1.36]	0.99 [0.86, 1.14]	1.15 [1.01, 1.31]	1.07 [0.97, 1.18]
2010	1.36 [1.2, 1.55]	1.21 [1.07, 1.36]	1.26 [1.16, 1.37]	1.2 [1.04, 1.38]	1.04 [0.91, 1.19]	1.11 [1.01, 1.22]
2011	1.25 [1.1, 1.42]	1.13 [1, 1.28]	1.17 [1.07, 1.28]	1.15 [1, 1.33]	1.04 [0.91, 1.19]	1.08 [0.98, 1.19]
2012	1.29 [1.14, 1.47]	1.19 [1.06, 1.34]	1.22 [1.12, 1.33]	1.07 [0.93, 1.24]	1.09 [0.96, 1.24]	1.08 [0.98, 1.19]
2013	1.46 [1.28, 1.67]	1.06 [0.94, 1.2]	1.21 [1.11, 1.32]	1.25 [1.08, 1.45]	0.93 [0.81, 1.06]	1.05 [0.95, 1.16]
2014	1.27 [1.12, 1.44]	1.1 [0.98, 1.24]	1.16 [1.06, 1.26]	1.14 [0.99, 1.31]	0.95 [0.83, 1.08]	1.03 [0.94, 1.13]
2015	1.26 [1.11, 1.42]	1.03 [0.92, 1.16]	1.12 [1.03, 1.22]	0.99 [0.86, 1.14]	0.93 [0.82, 1.06]	0.95 [0.86, 1.04]
2016	1.17 [1.04, 1.32]	1.12 [1, 1.25]	1.13 [1.04, 1.23]	1.02 [0.89, 1.17]	0.9 [0.79, 1.02]	0.95 [0.86, 1.04]
2017	1.23 [1.09, 1.39]	1.03 [0.92, 1.16]	1.11 [1.02, 1.21]	1.16 [1.01, 1.33]	0.96 [0.85, 1.09]	1.05 [0.96, 1.15]
2018	1 [0.89, 1.13]	0.9 [0.8, 1.01]	0.94 [0.86, 1.02]	0.93 [0.81, 1.07]	0.8 [0.7, 0.91]	0.86 [0.78, 0.94]
2019	1.04 [0.92, 1.18]	1.09 [0.97, 1.22]	1.05 [0.96, 1.14]	1.09 [0.95, 1.25]	0.93 [0.82, 1.06]	1 [0.91, 1.1]
2020	1.1 [0.96, 1.25]	1.13 [1, 1.28]	1.1 [1.01, 1.2]	0.99 [0.85, 1.15]	0.91 [0.79, 1.05]	0.95 [0.86, 1.05]
2021	1.14 [0.97, 1.34]	1.13 [0.97, 1.32]	1.12 [1, 1.25]	1.11 [0.93, 1.33]	1.03 [0.87, 1.22]	1.06 [0.94, 1.2]
Total	1.29 [1.26, 1.32]	1.14 [1.11, 1.17]	1.07 [1.05, 1.09]	1.17 [1.14, 1.2]	1.07 [1.04, 1.1]	1.11 [1.09, 1.13]

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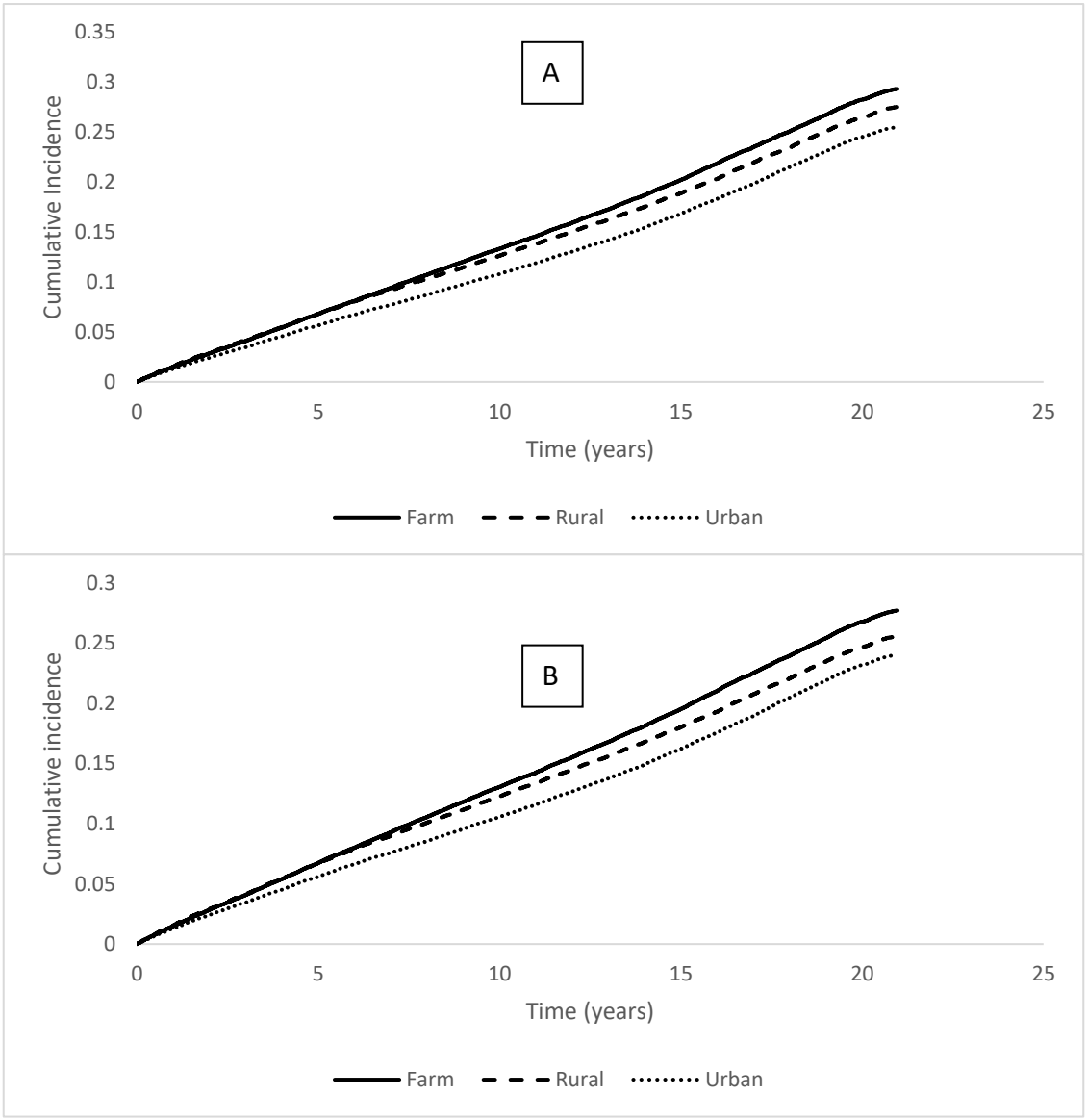

Appendix Figure 4 A) Kaplan-Meier cumulative incidence of osteoarthritis (OA) B) mortality-adjusted lifetime risk of developing OA for farm, rural, and urban cohorts

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Appendix Table 6 The crude and sex-specific non-injury mortality rate per 1000 person-years (PYs) among osteoarthritis (OA) cases and non-OA cases in the farm, rural, and urban cohorts

Non-Injury Mortality Rate per 1000 PYs (95% CI)						
Group	With OA			Without OA		
	Total	Male	Female	Total	Male	Female
Farm	13.16 (12.87, 13.45)	15.61 (15.15, 16.06)	10.81 (10.44, 11.19)	6.66 (6.52, 6.79)	7.94 (7.75, 8.13)	5.01 (4.84, 5.19)
Non-farm Rural	17.96 (17.55, 18.38)	18.59 (17.96, 19.23)	17.46 (16.91, 18.01)	7.83 (7.66, 7.99)	8.81 (8.57, 9.05)	6.75 (6.53, 6.97)
Non-farm Urban	14.49 (14.14, 14.84)	14.71 (14.16, 15.26)	14.33 (13.88, 14.79)	6.16 (6.03, 6.29)	6.65 (6.46, 6.83)	5.64 (5.46, 5.82)

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Appendix Table 7 The survival rate of the farm, rural, and urban cohorts among individuals with osteoarthritis (OA) and without OA

cohort	Having OA	Survival Distribution Function Estimate	95% CI
Farm	No	0.86	0.857, 0.862
Farm	Yes	0.744	0.739, 0.749
Non- farm Rural	No	0.841	0.837, 0.844
Non-farm Rural	Yes	0.67	0.664, 0.676
Non-farm Urban	No	0.873	0.87, 0.875
Non-farm Urban	Yes	0.725	0.719, 0.731

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Appendix Table 8 Baseline characteristics of the study population based on the residency status before removing osteoarthritis (OA) prevalent cases.

Cohort	Characteristics		Total	With OA n (%)	Without OA n (%)
Total	Total		303563	15272 (5.03)	288291 (94.97)
	Sex	Male	155378 (51.18)	6552 (4.22)	148826 (95.78)
		Female	148185 (48.82)	8720 (5.88)	139465 (94.12)
	Age	Mean (SD)	46.14 (16.75)	65.35 (14.15)	45.13 (16.25)
		20-39	117220 (38.61)	686 (0.59)	116534 (99.41)
		40-49	69364 (22.85)	1536 (2.21)	67828 (97.79)
		50-59	50028 (16.48)	2846 (5.69)	47182 (94.31)
		60-69	34022 (11.21)	3732 (10.97)	30290 (89.03)
		70-79	22490 (7.41)	3989 (17.74)	18501 (82.26)
		80+	10439 (3.44)	2483 (23.79)	7956 (76.21)
	SES	Low SES	6197 (2.04)	539 (8.7)	5658 (91.3)
		High SES	297366 (97.96)	14733 (4.95)	282633 (95.05)
Farm	Total		102724	5354 (5.21)	97370 (94.79)
	Sex	Male	55852 (54.37)	2658 (4.76)	53194 (95.24)
		Female	46872 (45.63)	2696 (5.75)	44176 (94.25)
	Age	Mean (SD)	47.68 (16.19)	64.72 (12.15)	46.74 (15.86)
		20-39	33692 (32.8)	156 (0.46)	33536 (99.54)
		40-49	22895 (22.29)	434 (1.9)	22461 (98.1)
		50-59	20178 (19.64)	1126 (5.58)	19052 (94.42)
		60-69	15589 (15.18)	1644 (10.55)	13945 (89.45)
		70-79	8115 (7.9)	1429 (17.61)	6686 (82.39)
		80+	2255 (2.2)	565 (25.06)	1690 (74.94)
	SES	Low SES	965 (0.94)	62 (6.42)	903 (93.58)
		High SES	101759 (99.06)	5292 (5.2)	96467 (94.8)
Rural	Total		97280	5737 (5.9)	91543 (94.1)
	Sex	Male	48536 (49.89)	2318 (4.78)	46218 (95.22)
		Female	48744 (50.11)	3419 (7.01)	45325 (92.99)
	Age	Mean (SD)	45.86 (17.4)	65.61 (15.32)	44.62 (16.76)
		20-39	39764 (40.88)	330 (0.83)	39434 (99.17)
		40-49	21950 (22.56)	647 (2.95)	21303 (97.05)
		50-59	14216 (14.61)	977 (6.87)	13239 (93.13)
		60-69	9430 (9.69)	1203 (12.76)	8227 (87.24)
		70-79	7448 (7.66)	1439 (19.32)	6009 (80.68)
		80+	4472 (4.6)	1141 (25.51)	3331 (74.49)
	SES	Low SES	2379 (2.45)	263 (11.06)	2116 (88.94)
		High SES	94901 (97.55)	5474 (5.77)	89427 (94.23)
Urban	Total		103559	4181 (4.04)	99378 (95.96)
	Sex	Male	50990 (49.24)	1576 (3.09)	49414 (96.91)
		Female	52569 (50.76)	2605 (4.96)	49964 (95.04)
	Age	Mean (SD)	44.89 (16.54)	65.79 (14.82)	44.01 (16.02)
		20-39	43764 (42.26)	200 (0.46)	43564 (99.54)
		40-49	24519 (23.68)	455 (1.86)	24064 (98.14)
		50-59	15634 (15.1)	743 (4.75)	14891 (95.25)
		60-69	9003 (8.69)	885 (9.83)	8118 (90.17)
		70-79	6927 (6.69)	1121 (16.18)	5806 (83.82)
		80+	3712 (3.58)	777 (20.93)	2935 (79.07)
	SES	Low SES	2853 (2.75)	214 (7.5)	2639 (92.5)
		High SES	100706 (97.25)	3967 (3.94)	96739 (96.06)

SD: Standard Deviation, SES: socioeconomic status

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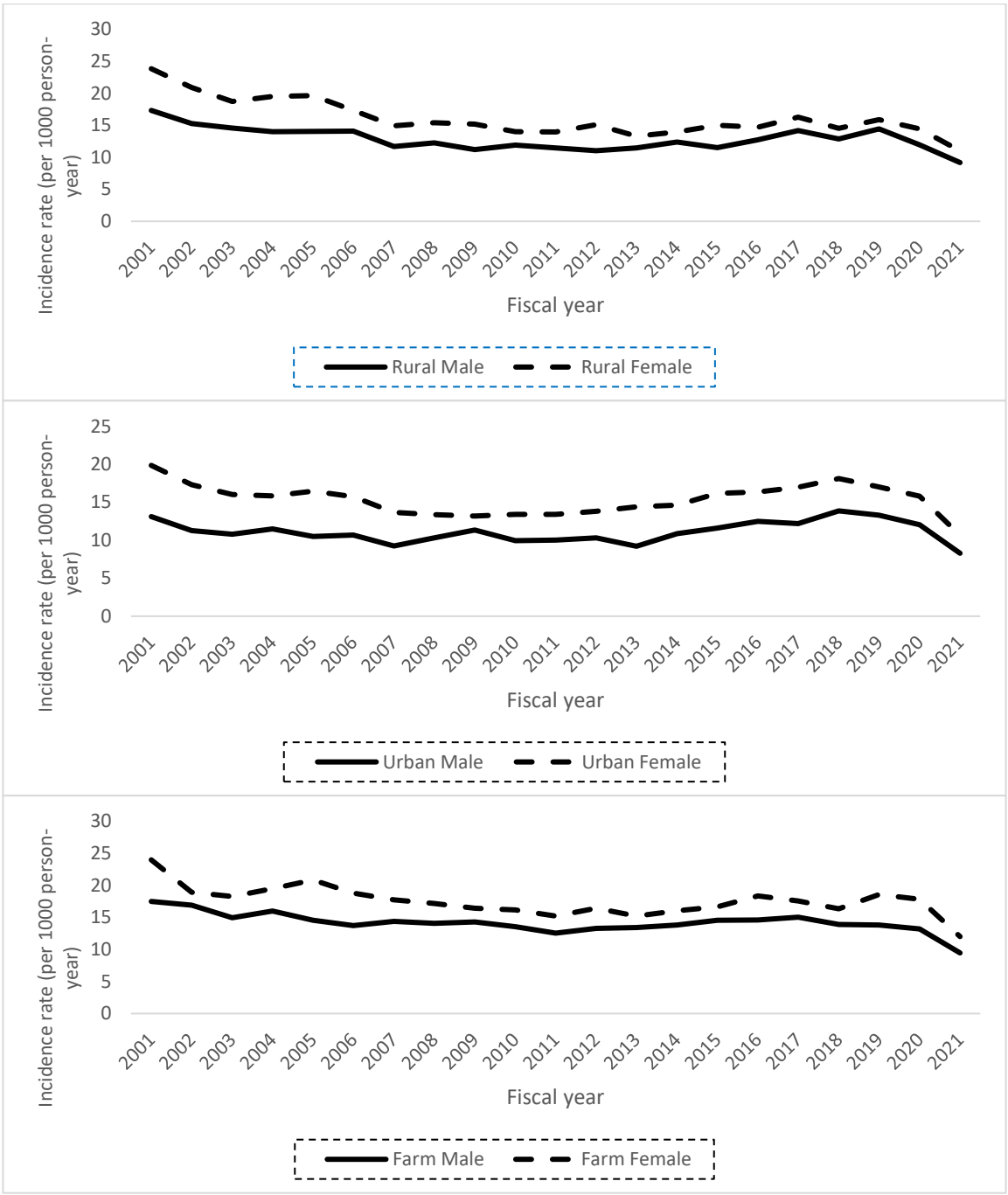

Appendix Figure 5 Sex-specific trends of annual incidence rate for each group separately

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Appendix Table 9 The crude and sex-specific all-cause mortality rate per 1000 person-years (PYs) among osteoarthritis (OA) cases and non-OA cases in the farm, rural, and urban cohorts

Mortality Rate per 1000 PYs (95% CI)						
Group	With OA			Without OA		
	Total	Male	Female	Total	Male	Female
Farm	13.51 (13.21, 13.81)	16.09 (15.63, 16.55)	11.03 (10.65, 11.4)	7.02 (6.89, 7.16)	8.45 (8.25, 8.64)	5.2 (5.02, 5.37)
Non-farm Rural	18.61 (18.19, 19.03)	19.37 (18.73, 20.01)	17.99 (17.44, 18.55)	8.43 (8.26, 8.6)	9.6 (9.35, 9.85)	7.14 (6.91, 7.36)
Non-farm Urban	14.96 (14.6, 15.32)	15.29 (14.73, 15.85)	14.73 (14.27, 15.19)	6.6 (6.47, 6.74)	7.27 (7.07, 7.46)	5.9 (5.72, 6.08)