BMJ Open

Comorbidities in people with osteoarthritis (OA): a retrospective analysis of a population-based cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033334
Article Type:	Research
Date Submitted by the Author:	31-Jul-2019
Complete List of Authors:	Marshall, Deborah; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Liu, Xiaoxiao; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Barnabe, Cheryl; University of Calgary Cumming School of Medicine, Department of Medicine; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Yee, Karen; Alberta Health Services, Research Facilitation Faris, Peter; Alberta Health Services, Research Facilitation Barber, Claire; University of Calgary Cumming School of Medicine, Department of Medicine; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Mosher, Dianne; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Noseworthy, Thomas; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Werle, Jason; University of Calgary Cumming School of Medicine, Department of Surgery Lix, Lisa; University of Manitoba, Department of Community Health Sciences
Keywords:	Osteoarthritis, Comorbidity, Depression, Hypertension < CARDIOLOGY, COPD, Administrative Health Data

Title: Comorbidities in people with osteoarthritis (OA): a retrospective analysis of a population-based cohort

Deborah A Marshall PhD [1,2 *], Xiaoxiao Liu PhD [1], Cheryl Barnabe MD MSc [1,2], Karen Yee MSc MPH [3], Peter Faris PhD [3], Claire EH Barber MD PhD [1,2], Dianne Mosher PhD [1], Tom Noseworthy[2], Jason Werle [4], Lisa M. Lix [5]

[1] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary

[2] Department of Medicine, Cumming School of Medicine, University of Calgary

[3] Research Facilitation, Alberta Health Services, Calgary

[4] Department of Surgery, Cumming School of Medicine, University of Calgary

[5] Department of Community Health Sciences, Manitoba, Winnipeg

* Correspondence: Deborah A Marshall, Cumming School of Medicine, University of Calgary. 3280 Hospital Drive NW, HRIC Building, Room 3C58, Calgary, AB. T2N 4Z6, Canada. E-mail address: damarsha@ucalgary.ca

Word Count

Abstract: 288

Body: 3,396

Number of tables: 3

Number of figures: 1

Abstract

Objectives: The purpose of this study is to estimate the prevalence of comorbidities among people with osteoarthritis (OA) using administrative health data.

Design: Retrospective cohort analysis

Setting: All residents in the province of Alberta Canada registered with the Alberta Health Care Insurance Plan (AHCIP) population registry.

Participants: 497,362 people with OA as defined by "having at least one OA-related hospitalization, or at least two OA-related physician visits or two ambulatory care visits within two years".

Primary outcome measures: We selected eight comorbidities based on literature review, clinical consultation and the availability of validated case definitions to estimate their frequencies. Sex-stratified age-standardized prevalence rates per 1,000 population of eight clinically relevant comorbidities were calculated using direct standardization with 95% confidence intervals (CIs). We applied χ^2 tests of independence with a Bonferroni correction to compare the percentage of comorbid conditions in each age group.

Results: 54.6% (n=271,794) of people meeting the OA case definition had at least one of the eight selected comorbidities. Females had a significantly higher rate of comorbidities compared to males (standardized rates ratio = 1.26, 95% CI: 1.25-1.28). Depression, chronic obstructive pulmonary disease (COPD) and hypertension were the most prevalent in both females and males after age-standardization, with 40% of all cases having any combination of these comorbidities. We observed a significant difference in the percentage of comorbidities among age groups, illustrated by the youngest age group (<45 years) having the highest percentage of cases with depression (24.6%), compared to a frequency of 16.1% in those >65 years.

Conclusions: Our findings highlight the high frequency of comorbidity in people with OA, with depression having the highest age-standardized prevalence rate. Comorbidities differentially affect females, and vary by age. These factors should inform health care programs and delivery.

Keywords: Osteoarthritis; comorbidity; depression; hypertension; COPD; administrative health data

Strengths and limitations of this study

- Strong methodological approach to identify cases of OA with a validated case definition using five linked population-based administrative databases.
- However, case identification based on administrative data may result in underreporting of cases and comorbidities.
- The age-standardized prevalence of eight comorbidities, selected on their clinical relevance and the availability of validated case definitions for administrative health data, was estimated among people with OA.
- We limited our analysis to eight comorbidities of clinical relevance.
- We stratified the analysis by sex and by age cohorts

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis, affecting 1 in 8 (13%) Canadians and representing a major cause of pain and disability in society[1,2]. OA affects people of all ages, but is more prevalent among females and older age groups[3,4]. Due to an aging population and an increase in obesity, the prevalence of OA is expected to continue to rise, predicted to affect one in four Canadians by 2040[5,6]. The high prevalence of OA in Canada has a substantial impact on quality of life and health care costs to individuals and health care systems. Quality of life was measured to be 10%-25% lower among people with OA relative to the general population[7] with an associated economic burden of $33 billion (direct and indirect costs) in Canada in 2011[3]. The annual cost per individual with OA has been estimated to be two to three times higher compared to people without OA[7], and are associated with more physician visits and hospitalizations[8].

More recently, the characterization of comorbidities among people with OA has been explored due to the potential effect of comorbidities on routine clinical practice, clinical practice guidelines, healthcare utilization and costs[9-10]. In people with OA over the age of 50 years in England, the presence of comorbidities resulted in increased physical disability compared to those without OA, with the influence of comorbidities greater than that expected for OA alone or for each comorbidity in isolation[4]. Knowledge of the prevalence of comorbidities in people with OA raises important considerations for optimal OA treatment and management, to reduce pain and physical disability, enhance the quality of life, and decrease the burden of OA. Comorbidities add complexity to the management of patients with OA to provide patient-centred care, ensure appropriate management recommendations for hhealth care programs and delivery.

The purpose of this study is to estimate the prevalence of comorbidities among people with OA in the province of Alberta, Canada, using administrative health data. This information is useful to assess the potential impact of comorbidities in clinical practice, practice guidelines and for planning health care services.

2. Materials and Methods

Data sources

We used five linked Alberta, Canada provincial administrative databases between April 1, 1994 and March 31, 2013 to identify individuals with OA who accessed health care services paid for by the provincial health care insurance plan, previously described

elsewhere in detail[6]. These databases included the Alberta Health Care Insurance Plan (AHCIP) population registry, the Discharge Abstract Database (DAD), the Physician Claims Database (claims), the Ambulatory Care Classification System (ACCS), and the National Ambulatory Care Reporting System (NACRS).

AHCIP Population Registry captures individual level demographic data on all insured persons as of the last day of each fiscal year (March 31). All Albertans who are included in the AHCIP have a unique, 9-digit personal health number, which is used when accessing health care services, and served to link datasets prior to de-identification. Members of the Armed Forces and the Royal Canadian Mounted Police, federal penitentiary inmates, and Albertans who have opted out of the AHCIP are excluded.

DAD captures admission and inpatient care data for all hospitalized patients, including diagnostic codes, interventions, patient age and sex, and administrative information. Among 25 DAD diagnostic code fields extracted from the hospital record, OA-related records were identified as those with the first 3 digits 715 or M15 to M19 based on the ninth (9) and tenth (10) revisions of the International Classification of Diseases (ICD) codes, respectively.

Claims captures OA-related physician visits, which were identified based on the aforementioned ICD codes in any of the 3 diagnostic code fields.

ACCS and NACRS contains data on hospital-based and community-based ambulatory care, including day surgery, outpatient and community-based clinics and emergency departments, and publicly funded hospital support services such as physiotherapy and occupational therapy. OA-related records were identified based on the presence of the aforementioned ICD codes in any of the 10 diagnostic code fields. NACRS was used since April 2010.

Ethics approval for this project was provided by the Conjoint Health Research Ethics Board at the University of Calgary (REB13-0100).

Patient and public involvement

No patients were involved in setting the research question, the design and conduct of the study. No patients were involved in the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants because this was admin health database analysis. We will make the publication available to the relevant patient community.

Case Definition of Osteoarthritis (OA)

OA cases were identified using a validated case definition, which was individuals with at least one OA-related hospitalization (DAD), or at least two OA-related physician visits (claims) within two years, or at least two OA-related ambulatory care visits (ACCS/NACRS) within two years, assuming none of the physicians or ambulatory care visits had occurred on the same day[11]. The algorithms have been validated[11] and applied in previous research using administrative data[5]. For our study, the OA cohort refers to those Alberta residents registered with AHCIP who have a specified OA-related diagnostic code in any diagnostic code field position. The cohort inclusion date is the earliest date of the OA-related record identified from either the Claims, DAD or ACCS/NACRS files.

Case Definitions of Comorbidities

We identified specific comorbidities to explore in this analysis based on three criteria: 1) a high frequency of reported comorbidities in the published literature on OA; 2) the availability of validated case definitions for each comorbid condition; and, 3) expert input from our clinical co-investigators. We first conducted a scoping review of the literature [12], aiming to examine the extent and range of comorbidities research among people with OA. We identified 20 studies from a range of countries (9 in North America, 8 in Europe, 1 in Asia, 1 in South American, 1 in Netherlands), using different study designs (9 cross-sectional, 5 retrospective cohort, 5 prospective cohort and 1 case control study) with a range of sample sizes (91 to 85,966,369 cases of OA). Based on the results of this review, we derived a list of comorbidities and presented it to our clinical co-investigators. On this basis, we identified 8 comorbidities to include in our analysis: hypertension, depression, COPD, diabetes, congestive heart failure (CHF), peripheral vascular disease (PVD), myocardial infarction (MI), and cerebrovascular disease (CEVD). We applied case definitions for each comorbidity to identify those present within 3 years prior to the OA diagnosis. Detailed ICD 9 and ICD 10 diagnostic codes used to identify each comorbidity are provided in Appendix 1[13–22].

Age-standardized comorbidity prevalence rate

The frequency of each comorbid condition in people meeting the case definition for OA was calculated, as was the frequency of the number of comorbidities present per individual: one comorbidity, two comorbidities, and three or more comorbidities. We stratified OA cases by sex, and by age cohorts (<35, 35-44, 45-54, 55-65, 65-74, and >=75

years). The crude rate was calculated as the number in each comorbidity group divided by the total number of OA cases. We calculated age-standardized comorbidity prevalence rates using the direct standardization method [23]. We used the 2016 Canadian population reported publicly by Statistics Canada [24] to age-standardize the estimates for females and males with 95% confidence intervals (CIs) calculated using the binomial approximation method [23]. To compare differences between females and males, standardized rate ratios (SRR) were estimated as the female age-standardized rate divided by the male age-standardized rate. We calculated 95% confidence intervals for the SRR based on the standard error for each sex, to test for a sex difference [23].

We calculated the percentage of females and males in each age group and the percentage of OA cases for each age group by sex. The percentage of comorbidities among OA population was calculated as the number of cases with specific comorbidity divided by the OA population. The percentage of comorbidities among those with comorbidities was calculated using the population with one or more of the eight comorbidities as denominator. We also calculated the frequency of common groupings of these comorbidities in people with OA.

We applied χ^2 tests of independence with a Bonferroni correction[25] to compare the percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The null hypothesis is that there is no difference in the percentage of comorbidities across age groups, which is rejected when the calculated χ^2 is greater than the critical value for a specific number of degrees of freedom and an altered significance level of 0.005 after Bonferroni correction. All analyses were conducted with R version 3.5.1 and Excel 2013.

3. Results

We identified 497,362 cases of OA, 57.9% of whom were females (Table 1). More than half of the OA cases had at least one of the eight comorbidities (54.6%, n=271,794) (Table 2). A total of 161,315 (32.4%) people with OA had one comorbidity, with 14.6% (n=72,567) having two, and 7.6% (n=37,912) having three or more of the comorbidities. Hypertension was the most frequent comorbidity (29%, n=144,453), followed by depression (19.9%, n=99,103), COPD (18.6%, n=92,273), diabetes (9.5%, n=47,102), and CHF (5.6%, n=27,905). PVD (3.0%), CEVD (1.2%) and MI (1.0%) were the least frequent comorbidities.

Table 1 Characteristics of people with OA identified in the population

Population	Age groups (years)	Female			Male			Total
		n	% by age groups	% (Female)	n	% by age groups	% (Male)	
People meeting OA case definition	<35	13,975	50.6	4.9	13,638	49.4	6.5	27,613
	35-44	25,616	52.4	8.9	23,279	47.6	11.1	48,895
	45-54	57,574	57.6	20.0	42,445	42.4	20.3	100,019
	55-64	65,528	57.1	22.8	49,329	42.9	23.6	114,857
	65-74	59,346	57.7	20.6	43,527	42.3	20.8	102,873
	75+	65,912	63.9	22.9	37,193	36.1	17.8	103,105
	Total	287,951	57.9	100.0	209,411	42.1	100.0	497,362

Note: % by age groups was calculated using total population of each specific age group (e.g. for OA <35 years, the percentage was calculated using the number of females with OA as the numerator and the total number of people with OA as the denominator (13,975 + 13,638= 27,613). % female <35 years was calculated using the number of females in the age group < 35 years as the numerator (13,975) and the number of females with OA as the denominator (287,951).

Comorbidity Patterns by Sex

A similar pattern was observed regarding the number of comorbidities (with most people with OA having one comorbidity) and the ordering of the frequency of each of the comorbidities among females and males based on age-standardized prevalence rates (Table 2). Statistically significant differences among females and males were observed by the number of comorbidities, with females having higher rates overall (SRR = 1.26, 95% CI: 1.25-1.28). The number of comorbidities was also higher for females compared to males with SRR ranging from 1.15 (95% CI: 1.11-1.18) for three or more comorbidities to 1.48 (95% CI: 1.44-1.52) for two comorbidities (Table 2).

Table 2 Frequency, percentage and age-standardized rate of comorbidities in people with OA

Comorbidity		n	% of OA cohort	% of the OA cohort with one or more of the eight comorbidities	Age standardized Rate (per 1,000 population)		
					Female (95% CI)	Male (95% CI)	SRR (95% CI)
Comorbid Conditions	Hypertension	144,453	29.0	53.1	162.2 (160.9-163.5)	146.5 (145.1-148.0)	1.11 (1.09-1.12)
	Depression	99,103	19.9	36.5	264.1 (260.9-267.3)	152.6 (149.8-155.4)	1.73 (1.69-1.77)
	Chronic obstructive pulmonary disease	92,273	18.6	33.9	195.9 (193.0-198.8)	153.6 (150.9-156.3)	1.28 (1.25-1.30)
	Diabetes	47,102	9.5	17.3	53.1 (52.0-54.2)	59.4 (58.4-60.4)	0.89 (0.87-0.92)
	Congestive heart failure	27,905	5.6	10.3	24.4 (23.9-24.9)	25.4 (24.9-26.0)	0.96 (0.93-0.99)
	Peripheral vascular disease	15,044	3.0	5.5	12.6 (12.1-13.0)	17.8 (17.2-18.3)	0.71 (0.67-0.74)
	Myocardial infarction	4,969	1.0	1.8	4.3 (4.1-4.5)	4.7 (4.4-5.0)	0.91 (0.84-0.98)

	Cerebrovascular disease	5,974	1.2	2.2	4.0 (3.8-4.2)	7.9 (7.6-8.2)	0.51 (0.48-0.54)
Number of Comorbidities	One Comorbidity	161,315	32.4	59.4	329.1 (325.7-332.4)	271.5 (268.2-274.8)	1.21 (1.19-1.23)
	Two Comorbidities	72,567	14.6	26.7	124.9 (122.8-127.1)	84.6 (82.9-86.2)	1.48 (1.44-1.52)
	Three or more Comorbidities	37,912	7.6	13.9	42.3 (41.4-43.2)	36.9 (36.2-37.7)	1.15 (1.11-1.18)
OA with Comorbidities		271,794	54.6		496.3 (492.8-499.8)	392.9 (389.4-396.4)	1.26 (1.25-1.28)
None of the 8 Comorbidities		225,568	45.4		503.7 (500.17-507.22)	607.1 (603.56-610.56)	0.83 (0.82-0.84)

Note: % of OA cohort was calculated using OA population (271,794 + 225,568 = 497,362) as denominator and the population of each comorbidity as numerator. % of the OA cohort with one or more of the eight comorbidities was calculated using population with at least one comorbidity (n= 271,794) as denominator. CI denotes Confidential Interval. SRR denotes Standardized Rate Ratio between females and males (females/males). The eight comorbidities are those with validated case definitions for administrative health data.

Depression, COPD and hypertension remained as the three most prevalent comorbidities in both females and males after age-standardization. However, the prevalence of each of these comorbidities was higher in females compared to males (Table 2Females had significantly higher prevalence rates than males for depression (SRR 1.73, 95% CI: 1.69-1.77), COPD (SRR 1.28, 95% CI: 1.25-1.30) and hypertension (SRR 1.11, 95% CI: 1.09-1.12), respectively.

The prevalence of each of these three comorbidities differed significantly in females. For example the prevalence of depression in females was 264 cases per 1,000 population, 35% higher and statistically higher than for COPD (196 cases per 1,000 population) (SRR 1.35, 95% CI 1.32-1.37). In contrast, the prevalence of these three comorbidities among males were not significantly different.

Common groupings of comorbidities in people with OA

As shown in Table 3, of the eight comorbidities in people with OA, the most frequent comorbidity was hypertension as a single comorbidity, found in 12.8% of people with OA (n=63,520). The most common grouping of two comorbidities was the coexistence of hypertension and depression (2.9%, n=14,609). The most common grouping with three comorbidities was depression, COPD and hypertension, (1.1%, n=5,262). People with OA having any combination of the top three comorbidities accounted for approximately 40% of people with OA.

Table 3 Frequency of top 10 common groupings of comorbidities

Combinations of comorbidity	n	% of OA cohort)	% of OA with comorbidities
Hypertension only	63,520	12.8	23.4
Depression only	46,226	9.3	17.0

Chronic Obstructive Pulmonary Disease only	34,464	6.9	12.7
Hypertension, Depression	14,609	2.9	5.4
Hypertension, Chronic Obstructive Pulmonary Disease	13,653	2.7	5.0
Depression, Chronic Obstructive Pulmonary Disease	13,584	2.7	5.0
Hypertension, Diabetes	11,784	2.4	4.3
Diabetes	11,054	2.2	4.1
Hypertension, Depression, Chronic Obstructive Pulmonary Disease	5,262	1.1	1.9
Hypertension, Congestive Heart Failure	3,946	0.8	1.5

Note: % of OA cohort was calculated using OA population (271,794 + 225,568 = 497,362) as denominator and the population of each comorbidity as numerator. % of OA with comorbidities was calculated using population with at least one comorbidity at the diagnosis of OA (n= 271,794) as denominator.

Comorbidity patterns by age group

As shown in Figure 1, each of the eight comorbidities, with the exception of depression, was most common in people with OA over 65 years old. Hypertension was found in 44.3% of people with OA over 65 years of age (n=91,153 cases) compared to 5.3% (n=4,040 cases) in those <44 years old. The largest number of people with OA and depression were in the 45-64 years age cohort (n=47,061 cases), with the youngest age group (<44 years) having the highest percentage of cases with depression (24.6% compared to 21.9% in the middle age group (45-64 years) and 16.1% in the older age group (>=65 years). The difference in the percentage of each of the eight comorbidities among the three age groups was statistically significant (p<0.0001).

The number of comorbidities in people with OA increased with increasing age. The percentage of people with three or more comorbidities increased significantly from 1.5% in youngest age group (<44 years), to 4.7% in the middle age group (45-64 years), and to 13% in the older age group (>=65 years) (p<0.0001).

4. Discussion

We estimated the prevalence of comorbid conditions in people with OA using provincial administrative health data. Using validated case and comorbidity definitions, we found that 54.6% of people with OA had at least one of the eight comorbidities, and 28.5% had at least two. Depression, COPD and hypertension were the three most prevalent comorbidities in both females and males after age-standardization. However, the prevalence of each of these comorbidities was significantly higher in females compared to males. People with any combination of these three comorbidities represented about 40% of the people with OA. In general, the number of comorbidities in people with OA increased with increasing age. Each of the eight comorbidities, except depression, was most common in

people with OA >= 65 years. The largest number of people with OA and depression are in the middle age group (45-64 years), with the youngest age group (<44 years) having the highest percentage of cases with depression.

The estimated prevalence of comorbidities varies among studies due to differences in case definitions, the list of included chronic conditions, data sources and study population. Our estimates of the prevalence of comorbidities in people with OA are higher than the prevalence of two or more and three or more chronic conditions among the general Canadian population (26.5% and 10.2%, respectively) as reported by Feely et al.(2017) [26], and higher than the prevalence of 12.9% (two or more chronic diseases) and 3.9% (three or more chronic diseases) reported by Roberts et al. (2015)[27]. It has been reported previously that the prevalence of one or more comorbid condition among people with musculoskeletal conditions was more than twice than those without a musculoskeletal condition but with another chronic condition[28].

We identified depression, COPD and hypertension as frequent comorbid conditions among the people with OA. This was consistent with findings reported from the Canadian Primary Care Sentinel Surveillance Network showing that the prevalence of osteoarthritis has significant association with depression, COPD and hypertension[2]. Depression is emerging as a significant comorbidity in OA. Previous findings have reported that depression was highly prevalent in people with OA[10, 29]. A systemic review of depressive symptoms in people with OA , including 49 studies worldwide and representing 15,855 individuals, reported a frequency of depression of 19.9% among people with OA[30], which was similar to our estimates.

Depressed individuals are more likely to report chronic or more severe pain, and more than half of the patients with chronic pain are depressed. People living with OA are known to have fewer social contacts, limited physical activity, increased pain and disability [31,32], worse surgical outcomes and reduced effectiveness of pain interventions [33], which are all important predictors of depression [34]. However, current clinical practice guidelines for non-surgical management of OA do not include recommendations regarding mental health management [35–38]. This emphasizes the need for treatments and management for depression to improve outcomes for people with OA[39]. It has been suggested that educating physicians about timely identification of psychological factors may be helpful to improve outcomes. In addition, self-care management could be integrated into OA management strategies as a way to reduce anxiety and depression, as well as resulting emotional and physical pain.

Guidelines suggest that OA management should also integrate pharmacotherapy carefully and be cautious about the drug interactions and adverse side effects when treating OA, depression, anxiety and pain holistically[29]. The clustering of hypertension and depression as comorbidities associated with OA is not random. Obesity, which we were unable to study using administrative data is also prevalent amongst people with OA and a risk factor for developing OA [40,41].From a clinical practice perspective, a physician has to consider the implications of prescribing non-steroidal anti-inflammatory medications for pain management, but this may worsen hypertension and have an associated increased risk of cardiovascular disease. However, without good pain management, it is difficult for patients with OA to engage in exercise programs which can help improve their muscular condition and potentially reduce obesity and hypertension. This is further complicated by the relationship of lower socioeconomic status with an increased risk of developing OA as demonstrated in the project for an Ontario Women's Health Evidence-based Report [28]

Furthermore, our analyses showed that depression not only was the most prevalent comorbidity after age-standardization in people with OA, but that rates of depression were significantly higher for females and younger people (< 44 years old). The study by Dibonaventura et al. (2011) reported that people under 65 years of age were still participating in the workforce, however OA pain resulted in significantly lower productivity and higher costs compared to those without OA pain[8]. They identified unique treatment gaps for patients younger than 60 years old because the non-operative treatment options were ineffective in long-term management of OA symptoms, but young patients were too young or maybe unwilling to undergo definitive treatment such as total joint replacement[42]. Even for those patients who undergo total joint replacement, they were more likely to be dissatisfied about the treatment than older patients, and reported poorer outcomes including residual pain and stiffness [43,44]. A survey of orthopedic surgeons found that 84% perceived a need for better treatment for younger (<60 years old) physically active OA patients, and 68.4% perceived that there is a treatment gap for these patients[42]. Due to the different presentations of comorbidities and treatment options among young and old age groups, it is imperative to examine the impact of comorbidities on management strategies in an age-stratified OA cohort.

Most clinical practice guidelines focus on single conditions[45]. Fortin et al. (2011) concluded that even though the quality of the Canadian guidelines was good, their relevance for patients with two or more chronic conditions was limited[46]. Boyd et al. (2005)

highlighted the lack of consideration of comorbidities in clinical practice guidelines may result in poor quality of care because the health care some patients received was not optimal[47]. Sharma et al., (2016) pointed out that the present literature fails to fully address the management strategies when dealing with comorbidities seen in people with OA[29]. Patient-centered care has been recommended in clinical practice guidelines with the aim of improving quality of care by focusing on the patient as a whole rather than on a single disease[48]. From a system perspective, patients with several comorbidities were also the main users of healthcare resources and services[49]. Patient-centered and coordinated care for these patients may decrease related health care use[50]. It was recommended that physicians consider these comorbidities in the management of people with OA.

A strength of our study is the large population-based number of people with OA (n=497,362) and the investigation of a group of eight comorbidities that are clinically relevant to the management of people with OA. We applied case definitions for administrative health data to identify cases of OA and each of the comorbidities. A limitation of our study is that case identification based on administrative data may result in underreporting of cases and comorbidities. The case definitions for OA in administrative data research [5] have been applied and validated with a low sensitivity of 24% and high specificity of 98%[11] Similarly, the algorithms for comorbidities may underestimate the prevalence of these comorbidities; the sensitivity for identifying depression is from 36% to 51% [18], for PVD is 39%[17] and for COPD is 53% [20] in administrative data (Appendix 1). Further, we limited our analysis to eight comorbidities of clinical relevance and for which there were case definitions in administrative data.

5. Conclusions

We found that, depression, COPD and hypertension were the three most prevalent comorbidities in people with OA, with rates significantly higher in females compared to males. Of particular note is that the largest number of people with OA and depression are in the age group between 45 and 64 years old, with the highest percentage of cases occurring in the younger age groups (<44 years). Our findings highlight the need to recognize that people with OA have high rates of comorbidities and this may affect optimal health care management of these patients.

Acknowledgements

The authors would like to acknowledge the following team members and their contributions to the study: Behnam Sharif.

Contributions

DM, PF, KY were responsible for the conception and design of the research, acquisition of the data, analysis and interpretation of data, drafting the article, and revision of the article for important intellectual content.

XL was responsible for the analysis and interpretation of data, drafting the article, and revision of the article for important intellectual content.

CB, CB, DM, TN, JW and LL were responsible for the conception and design of the research, interpreting results of the research and revision of the article for important intellectual content.

All authors approved the final version of the manuscript to be submitted.

DM (damarsha@ucalgary.ca) and XL (xiaoxili@ucalgary.ca) take responsibility for the integrity of the work as a whole.

Role of the funding source

This research was funded through a Canadian Institute for Health Research (CIHR) Operating Grant (Grant #: 126128) and the Arthur J.E. Child Chair in Rheumatology Research. There were no study sponsors and the funding agencies had no involvement in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

DM was supported by a Canada Research Chair and the Arthur J.E. Child Chair in Rheumatology Research. XL was supported by the Arthur J.E. Child Chair in Rheumatology Research, the Cumming School of Medicine Postdoctoral Scholarship and the Postdoctoral Scholarship funded by the O'Brien Institute of Public Health and the McCaig Institute for Bone and Joint Health.

Data availability

These data are not available because Alberta Health and Alberta Health Services are the custodians of the data. The authors are not authorized to share them.

Competing interests

The authors confirm that there is no financial support or other benefits from commercial sources for the work reported on in the manuscript. There are also no financial interests that the authors may have which could create a potential conflict of interest with regards to the work in the manuscript.

References

1. Leite AA, Costa AJG, Lima B de AM de, Padilha AVL, Albuquerque EC de, Marques CDL. Comorbidities in patients with osteoarthritis: frequency and impact on pain and physical function. *Rev Bras Reumatol*. 2011;51(2):118-123. doi:10.1590/S0482-50042011000200002
2. Birtwhistle R, Morkem R, Peat G, et al. Prevalence and management of osteoarthritis in primary care: an epidemiologic cohort study from the Canadian Primary Care Sentinel Surveillance Network. *C open*. 2015;3(3):E270-5. doi:10.9778/cmajo.20150018
3. Bombardier C, Hawker G, Mosher D. *The Impact of Arthritis in Canada: Today and over the next 30 Years.*; 2011.
4. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. *Ann Rheum Dis*. 2004;63(4):408-414. doi:10.1136/ARD.2003.007526
5. Kopec JA, Rahman MM, Berthelot J-M, et al. Descriptive epidemiology of osteoarthritis in British Columbia, Canada. *J Rheumatol*. 2007;34(2):386-393.
6. Marshall DA, Vanderby S, Barnabe C, et al. Estimating the Burden of Osteoarthritis to Plan for the Future. *Arthritis Care Res*. 2015;67(10):1379-1386. doi:10.1002/acr.22612
7. Tarride J-E, Haq M, O'Reilly DJ, et al. The excess burden of osteoarthritis in the province of Ontario, Canada. *Arthritis Rheum*. 2012;64(4):1153-1161. doi:10.1002/art.33467
8. Dibonaventura M dacosta, Gupta S, McDonald M, Sadosky A. Evaluating the health and economic impact of osteoarthritis pain in the workforce: results from the National Health and Wellness Survey. *BMC Musculoskelet Disord*. 2011;12:83. doi:10.1186/1471-2474-12-83
9. Rosemann T, Joos S, Szecsenyi J, Laux G, Wensing M. Health service utilization patterns of primary care patients with osteoarthritis. *BMC Health Serv Res*. 2007;7(1):169. doi:10.1186/1472-6963-7-169
10. Kim KW, Han JW, Cho HJ, et al. Association Between Comorbid Depression and Osteoarthritis Symptom Severity in Patients with Knee Osteoarthritis. *J Bone Jt Surgery-American Vol*. 2011;93(6):556-563. doi:10.2106/JBJS.I.01344
11. Lix L, Yogendran M, Mann J. *Defining and Validating Chronic Diseases: An Administrative Data Approach and Update with ICD-10-CA.*; 2008.
12. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. *Res Synth Methods*. 2014;5(4):371-385. doi:10.1002/jrsm.1123
13. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Myocardial Infarction Diagnoses in Administrative Databases: A Systematic Review. Guo Y, ed. *PLoS One*. 2014;9(3):e92286. doi:10.1371/journal.pone.0092286
14. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. *Hypertension*. 2009;54(6):1423-1428. doi:10.1161/HYPERTENSIONAHA.109.139279
15. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. *PLoS One*. 2015;10(8):e0135834. doi:10.1371/journal.pone.0135834
16. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e104519.

doi:10.1371/journal.pone.0104519

17. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *J Am Med Inform Assoc*. 2013;20(e2):e349-54. doi:10.1136/amiajnl-2013-001827

18. Townsend L, Walkup JT, Crystal S, Olfson M. A systematic review of validated methods for identifying depression using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21:163-173. doi:10.1002/pds.2310

19. Leong A, Dasgupta K, Bernatsky S, Lacaille D, Avina-Zubieta A, Rahme E. Systematic Review and Meta-Analysis of Validation Studies on a Diabetes Case Definition from Health Administrative Records. Barengo NC, ed. *PLoS One*. 2013;8(10):e75256. doi:10.1371/journal.pone.0075256

20. Smidth M, Sokolowski I, Kærsvang L, Vedsted P. Developing an algorithm to identify people with Chronic Obstructive Pulmonary Disease (COPD) using administrative data. *BMC Med Inform Decis Mak*. 2012;12(1):38. doi:10.1186/1472-6947-12-38

21. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res Clin Pract*. 2010;89(2):189-195. doi:10.1016/j.diabres.2010.03.007

22. Quan H, Sundararajan V, Halfon P, et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative. *Med Care*. 2005;43(11):1130-1139.

23. Boyle P, Parkin D. Statistical methods for registries. *Cancer Regist Princ Methods*. 1991:126-158.

24. Statistics Canada. Alberta [Province] and Canada [Country] (table). Census Profile. 2016 Census. doi:98-316-X2016001

25. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ*. 1995;310(6973):170. doi:10.1136/bmj.310.6973.170

26. Feely A, Lix LM, Reimer K. Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System. *Heal Promot chronic Dis Prev Canada Res policy Pract*. 2017;37(7):215-222. doi:10.24095/hpcdp.37.7.02

27. Roberts KC, Rao DP, Bennett TL, Loukine L, Jayaraman GC. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. *Heal Promot chronic Dis Prev Canada Res policy Pract*. 2015;35(6):87-94.

28. Hawker GA, Badley EM, Jaglal S, et al. Musculoskeletal Condtitions. In: *Project for an Ontario Women's Health Evidence-Based Report: Volume 2: Toronto*. ; 2010.

29. Sharma A, Kudesia P, Shi Q, Gandhi R. Anxiety and depression in patients with osteoarthritis: impact and management challenges. *Open access Rheumatol Res Rev*. 2016;8:103-113. doi:10.2147/OARRR.S93516

30. Stubbs B, Aluko Y, Myint PK, Smith TO. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. *Age Ageing*. 2016;45(2):228-235. doi:10.1093/ageing/afw001

31. Sale JEM, Gignac M, Hawker G. The relationship between disease symptoms, life events, coping and treatment, and depression among older adults with osteoarthritis. *J Rheumatol*. 2008;35(2):335-342.

32. Hawker GA, Gignac MAM, Badley E, et al. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res (Hoboken)*. 2011;63(10):1382-1390. doi:10.1002/acr.20298

33. Gleicher Y, Croxford R, Hochman J, Hawker G. A prospective study of mental health care for comorbid depressed mood in older adults with painful osteoarthritis. *BMC Psychiatry*. 2011;11(1):147.

doi:10.1186/1471-244X-11-147

34. Rosemann T, Backenstrass M, Joest K, Rosemann A, Szecsenyi J, Laux G. Predictors of depression in a sample of 1,021 primary care patients with osteoarthritis. *Arthritis Rheum*. 2007;57(3):415-422. doi:10.1002/art.22624

35. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthr Cartil*. 2007;15(9):981-1000. doi:10.1016/j.joca.2007.06.014

36. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthr Cartil*. 2008;16(2):137-162. doi:10.1016/j.joca.2007.12.013

37. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: Part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthr Cartil*. 2010;18(4):476-499. doi:10.1016/J.JOCA.2010.01.013

38. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartil*. 2014;22(3):363-388. doi:10.1016/j.joca.2014.01.003

39. Lin EHB, Katon W, Von Korff M, et al. Effect of Improving Depression Care on Pain and Functional Outcomes Among Older Adults With Arthritis. *JAMA*. 2003;290(18):2428. doi:10.1001/jama.290.18.2428

40. Felson DT. Weight and osteoarthritis. *J Rheumatol Suppl*. 1995;43:7-9.

41. ANDERSON JJ, FELSON DT. FACTORS ASSOCIATED WITH OSTEOARTHRITIS OF THE KNEE IN THE FIRST NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (HANES I). *Am J Epidemiol*. 1988;128(1):179-189. doi:10.1093/oxfordjournals.aje.a114939

42. Li CS, Karlsson J, Winemaker M, Sancheti P, Bhandari M. Orthopedic surgeons feel that there is a treatment gap in management of early OA: international survey. *Knee Surgery, Sport Traumatol Arthrosc*. 2014;22(2):363-378. doi:10.1007/s00167-013-2529-5

43. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KDJ. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res*. 2010;468(1):57-63. doi:10.1007/s11999-009-1119-9

44. Parvizi J, Nunley RM, Berend KR, et al. High level of residual symptoms in young patients after total knee arthroplasty. *Clin Orthop Relat Res*. 2014;472(1):133-137. doi:10.1007/s11999-013-3229-7

45. Hughes LD, Mcmurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *J Heal Soc Behav J Public Heal Med J Epidemiol Community Heal Ann Epidemiol Am J Epidemiol Age Ageing*. 2013;36(42):1-10. doi:10.1093/ageing/afs100

46. Fortin M, Contant E, Savard C, Hudon C, Poitras M-E, Almirall J. Canadian guidelines for clinical practice: an analysis of their quality and relevance to the care of adults with comorbidity. *BMC Fam Pract*. 2011;12(1):74. doi:10.1186/1471-2296-12-74

47. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases. *JAMA*. 2005;294(6):716. doi:10.1001/jama.294.6.716

48. Dawes M. Co-morbidity: we need a guideline for each patient not a guideline for each disease. *Fam Pract*. 2010;27:1-2. doi:10.1093/fampra/cmp106

49. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *Ann Fam Med*. 2012;10(2):134-141. doi:10.1370/afm.1363

50. Wolff JL, Starfield B, Anderson G. Prevalence, Expenditures, and Complications of Multiple Chronic Conditions in the Elderly. *Arch Intern Med*. 2002;162(20):2269. doi:10.1001/archinte.162.20.2269

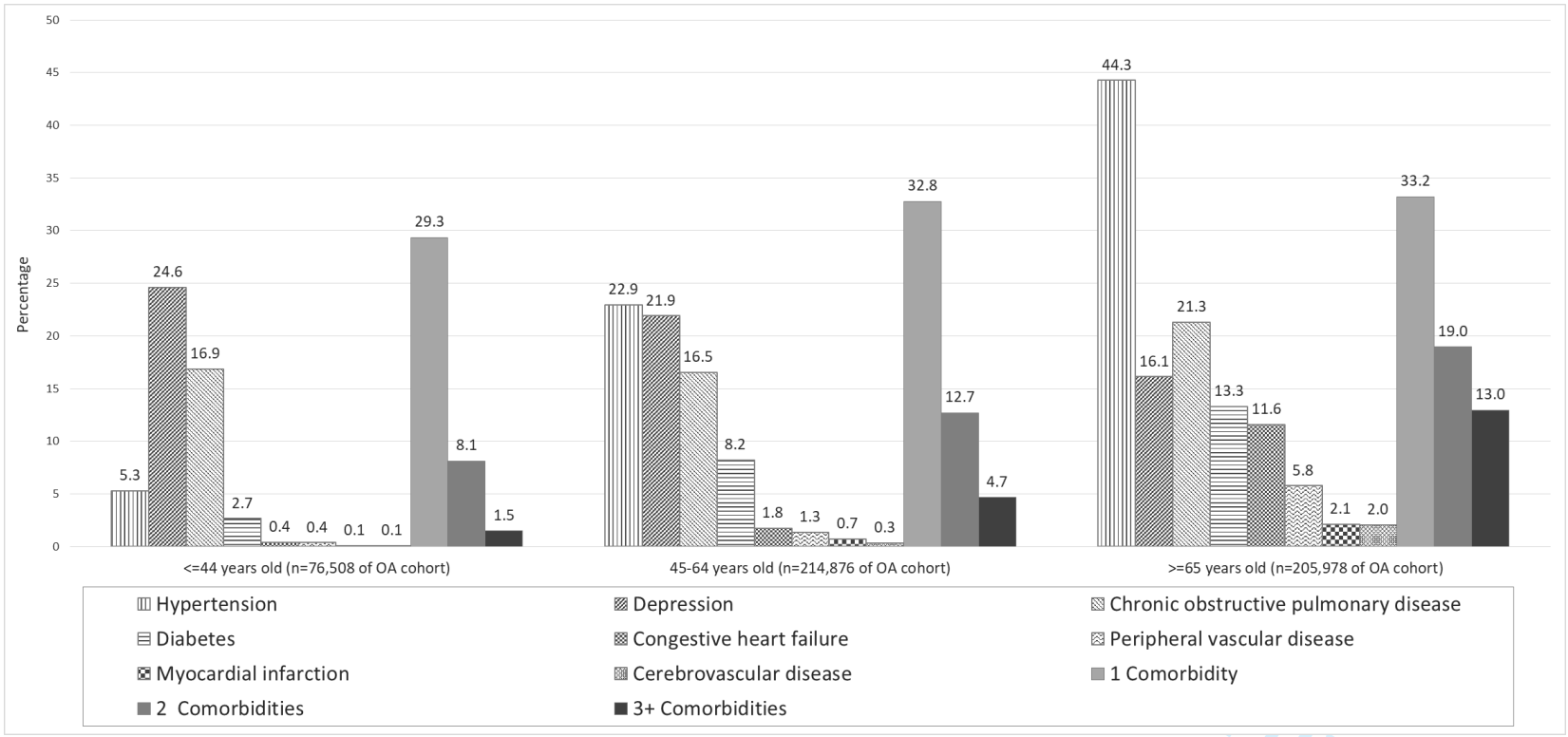

Figure 1 Percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The difference by age group was statistically significant for each comorbid conditions (p<0.0001), as was the frequency of the number of comorbidities present per individual (p<0.0001).

1 Appendix 1 Case definitions for eight comorbid conditions

	ICD9-CM Diagnosis Codes Included	ICD10-CA Diagnosis Codes Included	Exclusions	Algorithm	References
Myocardial Infarction	410	I21, I22	N/A	1 hospitalization for MI, with diagnoses codes in primary or secondary diagnosis fields.	McCormick et al., 2014[13] Quan et al., 2005[22]
Cerebrovascular Disease	3623,43301,43311,43321,43331,43381,43391,43401,43411,43491,436,430,431,435	H341, I63, I64, I61, I60, G450, G451, G452, G453, G458, G459	43300, 43310, 43320, 43330, 43380, 43390, 43400, 43410, 43490, 437, 438, I65, I66, I67, I69, G45.4	1 hospital discharge (most responsible diagnosis) for different stroke conditions	Kokotailo & Hill, 2005 McCormick et al., 2015[15]
Congestive Heart Failure	39891,40201,40211,40291,40401,40403,40411,40413,40491,40493,4254,4255,4257,4258,4259,428	I43,I50,I099,I110,I130,I132,I255,I420,I425,I426,I427,I428,I429,P290		1 hospitalization or physician claim in diagnosis field	Schultz et al., 2013 McCormick et al., 2014[16] Quan et al., 2005[22] Lee et al., 2005
Peripheral Vascular Disease	0930,4373,440,441,4431,4432,4438,4439,4471,5571,5579,V434,443	I70,I71,I731,I738,I739,I771,I790,I792,K551,K558,K559,Z958,Z959	N/A	1 hospitalization or physician claim in diagnosis field	Fan et al., 2013[17]
Chronic Obstructive Pulmonary Disease	4168,4169,490,491,492,493,494,495,496,500,501,502,503,504,505,5064,5081,5088	J40,J41,J42,J43,J44,J45,J46,J47,J60,J61,J62,J63,J64,J65,J66,J67,I278,I279,J684,J701,J703	N/A	1 hospitalization or physician claim in diagnosis field	Smidth et al. 2012[20] Quan et al., 2005[22]
Depression	2962,2963,2965,3004,309,311	F204,F313,F314,F315,F32,F33,F341,F412,F432	N/A	1 hospitalization or physician claim in diagnosis field	Townsend et al., 2012[18] Lix et al., 2006 Martens et al., 2010

Diabetes	250	E10, E11, E12, E13, E14	Physician claims with procedure code having a prefix of "X" (radiology/xray), "E" (labs) or "B" (dentist, ophthalmologist, chiropractic visits)	1 hospitalization for diabetes OR 2 physician claims in a 2-year period	Chen et al., 2010[21] Leong et al., 2013[19] Hux et al., 2002
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15	Physician claims with procedure code having a prefix of "X" (radiology/xray), "E" (labs) or "B" (dentist, ophthalmologist, chiropractic visits)	1 hospitalization for hypertension OR 2 physician claims in a 2-year period	Quan et al., 2009[14]

2

BMJ Open

Existing comorbidities in people with osteoarthritis: a retrospective analysis of a population-based cohort in Alberta, Canada

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033334.R1
Article Type:	Original research
Date Submitted by the Author:	18-Oct-2019
Complete List of Authors:	Marshall, Deborah; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Liu, Xiaoxiao; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Barnabe, Cheryl; University of Calgary Cumming School of Medicine, Department of Medicine; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Yee, Karen; Alberta Health Services, Research Facilitation Faris, Peter; Alberta Health Services, Research Facilitation Barber, Claire; University of Calgary Cumming School of Medicine, Department of Medicine; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Mosher, Dianne; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Noseworthy, Thomas; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Werle, Jason; University of Calgary Cumming School of Medicine, Department of Surgery Lix, Lisa; University of Manitoba, Department of Community Health Sciences
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research, Rheumatology
Keywords:	Osteoarthritis, Comorbidity, Depression, Hypertension < CARDIOLOGY, COPD, Administrative Health Data

Title: Existing comorbidities in people with osteoarthritis: a retrospective analysis of a population-based cohort in Alberta, Canada

Deborah A Marshall PhD [1,2 *], Xiaoxiao Liu PhD [1], Cheryl Barnabe MD MSc [1,2], Karen Yee MSc MPH [3], Peter Faris PhD [3], Claire EH Barber MD PhD [1,2], Dianne Mosher PhD [1], Tom Noseworthy[2], Jason Werle [4], Lisa M. Lix [5]

[1] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary

[2] Department of Medicine, Cumming School of Medicine, University of Calgary

[3] Research Facilitation, Alberta Health Services, Calgary

[4] Department of Surgery, Cumming School of Medicine, University of Calgary

[5] Department of Community Health Sciences, Manitoba, Winnipeg

* Correspondence: Deborah A Marshall, Cumming School of Medicine, University of Calgary. 3280 Hospital Drive NW, HRIC Building, Room 3C58, Calgary, AB. T2N 4Z6, Canada. E-mail address: damarsha@ucalgary.ca

Word Count

Abstract: 288

Body: 3,396

Number of tables: 3

Number of figures: 1

Abstract

Objectives: The purpose of this study is to estimate the prevalence of comorbidities among people with osteoarthritis (OA) using administrative health data.

Design: Retrospective cohort analysis

Setting: All residents in the province of Alberta Canada registered with the Alberta Health Care Insurance Plan (AHCIP) population registry.

Participants: 497,362 people with OA as defined by "having at least one OA-related hospitalization, or at least two OA-related physician visits or two ambulatory care visits within two years".

Primary outcome measures: We selected eight comorbidities based on literature review, clinical consultation and the availability of validated case definitions to estimate their frequencies at the time of diagnosis of OA. Sex-stratified age-standardized prevalence rates per 1,000 population of eight clinically relevant comorbidities were calculated using direct standardization with 95% confidence intervals (CIs). We applied χ^2 tests of independence with a Bonferroni correction to compare the percentage of comorbid conditions in each age group.

Results: 54.6% (n=271,794) of people meeting the OA case definition had at least one of the eight selected comorbidities. Females had a significantly higher rate of comorbidities compared to males (standardized rates ratio = 1.26, 95% CI: 1.25-1.28). Depression, chronic obstructive pulmonary disease (COPD) and hypertension were the most prevalent in both females and males after age-standardization, with 40% of all cases having any combination of these comorbidities. We observed a significant difference in the percentage of comorbidities among age groups, illustrated by the youngest age group (<45 years) having the highest percentage of cases with depression (24.6%), compared to a frequency of 16.1% in those >65 years.

Conclusions: Our findings highlight the high frequency of comorbidity in people with OA, with depression having the highest age-standardized prevalence rate. Comorbidities differentially affect females, and vary by age. These factors should inform health care programs and delivery.

Keywords: Osteoarthritis; comorbidity; depression; hypertension; COPD; administrative health data

Strengths and limitations of this study

- Strong methodological approach to identify cases of OA with a validated case definition using five linked population-based administrative databases.
- However, case identification based on administrative data may result in underreporting of cases and comorbidities.
- The age-standardized prevalence of eight comorbidities, selected on their clinical relevance and the availability of validated case definitions for administrative health data, was estimated among people with OA.
- We limited our analysis to eight comorbidities of clinical relevance.
- We stratified the analysis by sex and by age cohorts

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis, affecting 1 in 8 (13%) Canadians and representing a major cause of pain and disability in society[1,2]. OA affects people of all ages, but is more prevalent among females and older age groups[3,4]. Due to an aging population and an increase in obesity, the prevalence of OA is expected to continue to rise, predicted to affect one in four Canadians by 2040[5,6]. The high prevalence of OA in Canada has a substantial impact on quality of life and health care costs to individuals and health care systems. Quality of life was measured to be 10%-25% lower among people with OA relative to the general population[7] with an associated economic burden of $33 billion (direct and indirect costs) in Canada in 2011[3]. The annual cost per individual with OA has been estimated to be two to three times higher compared to people without OA[7], and are associated with more physician visits and hospitalizations[8].

More recently, the characterization of comorbidities among people with OA has been explored due to the potential effect of comorbidities on routine clinical practice, clinical practice guidelines, healthcare utilization and costs[9-10]. In people with OA over the age of 50 years in England, the presence of comorbidities resulted in increased physical disability compared to those without OA, with the influence of comorbidities greater than that expected for OA alone or for each comorbidity in isolation[4]. Knowledge of the prevalence of comorbidities in people with OA raises important considerations for optimal OA treatment and management, to reduce pain and physical disability, enhance the quality of life, and decrease the burden of OA. Comorbidities add complexity to the management of patients with OA to provide patient-centred care, ensure appropriate management recommendations for health care programs and delivery.

The purpose of this study is to estimate the prevalence of comorbidities among people with OA in the province of Alberta, Canada, using administrative health data. This information is useful to assess the potential impact of comorbidities in clinical practice, practice guidelines and for planning health care services.

2. Materials and Methods

Data sources

We used five linked Alberta, Canada provincial administrative databases between April 1, 1994 and March 31, 2013 to identify individuals with OA who accessed health care services paid for by the provincial health care insurance plan, previously described

elsewhere in detail[6]. These databases included the Alberta Health Care Insurance Plan (AHCIP) population registry, the Discharge Abstract Database (DAD), the Physician Claims Database (claims), the Ambulatory Care Classification System (ACCS), and the National Ambulatory Care Reporting System (NACRS).

AHCIP Population Registry captures individual level demographic data on all insured persons as of the last day of each fiscal year (March 31). All Albertans who are included in the AHCIP have a unique, 9-digit personal health number, which is used when accessing health care services, and served to link datasets prior to de-identification. Members of the Armed Forces and the Royal Canadian Mounted Police, federal penitentiary inmates, and Albertans who have opted out of the AHCIP are excluded.

DAD captures admission and inpatient care data for all hospitalized patients, including diagnostic codes, interventions, patient age and sex, and administrative information. Among 25 DAD diagnostic code fields extracted from the hospital record, OA-related records were identified as those with the first 3 digits 715 or M15 to M19 based on the ninth (9) and tenth (10) revisions of the International Classification of Diseases (ICD) codes, respectively.

Claims captures OA-related physician visits, which were identified based on the aforementioned ICD codes in any of the 3 diagnostic code fields.

ACCS and NACRS contains data on hospital-based and community-based ambulatory care, including day surgery, outpatient and community-based clinics and emergency departments, and publicly funded hospital support services such as physiotherapy and occupational therapy. OA-related records were identified based on the presence of the aforementioned ICD codes in any of the 10 diagnostic code fields. NACRS was used since April 2010.

Ethics approval for this project was provided by the Conjoint Health Research Ethics Board at the University of Calgary (REB13-0100).

Patient and public involvement

No patients were involved in setting the research question, the design and conduct of the study. No patients were involved in the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants because this was admin health database analysis. We will make the publication available to the relevant patient community.

Case Definition of Osteoarthritis (OA)

Validated case definitions have been used in previous research related to OA using administrative data[11,12]. The sensitivity of algorithms based on both physician claims and hospitalizations records within 2-5 years ranged from 24% - 46%, along with specificity and positive predictive value ranging from 92% -98%, and 39% - 54% respectively[11]. In this study, OA cases were identified as individuals with at least one OA-related hospitalization (DAD), or at least two OA-related physician visits (claims) within two years, or at least two OA-related ambulatory care visits (ACCS/NACRS) within two years, assuming none of the physicians or ambulatory care visits had occurred on the same day[11]. For our study, the OA cohort refers to those Alberta residents registered with AHCIP who have a specified OA-related diagnostic code in any diagnostic code field position. The cohort inclusion date is the earliest date of the OA-related record identified from either the Claims, DAD or ACCS/NACRS files.

Case Definitions of Comorbidities

We identified specific comorbidities to explore in this analysis based on three criteria: 1) a high frequency of reported comorbidities in the published literature on OA; 2) the availability of validated case definitions for each comorbid condition; and, 3) expert input from our clinical co-investigators. We first conducted a scoping review of the literature [13], aiming to examine the extent and range of comorbidities research among people with OA. We identified 20 studies from a range of countries (9 in North America, 8 in Europe, 1 in Asia, 1 in South American, 1 in Netherlands), using different study designs (9 cross-sectional, 5 retrospective cohort, 5 prospective cohort and 1 case control study) with a range of sample sizes (91 to 85,966,369 cases of OA). Based on the results of this review, we derived a list of comorbidities and presented it to our clinical co-investigators. On this basis, we identified 8 comorbidities to include in our analysis: hypertension, depression, COPD, diabetes, congestive heart failure (CHF), peripheral vascular disease (PVD), myocardial infarction (MI), and cerebrovascular disease (CEVD). We applied case definitions for each comorbidity to identify those present within 3 years prior to the OA diagnosis. Detailed ICD 9 and ICD 10 diagnostic codes used to identify each comorbidity are provided in Appendix 1[14–23].

Age-standardized comorbidity prevalence rate

The frequency of each comorbid condition in people meeting the case definition for OA was calculated, as was the frequency of the number of comorbidities present per individual: one comorbidity, two comorbidities, and three or more comorbidities. We stratified OA cases by sex, and by age at diagnosis (<35, 35-44, 45-54, 55-65, 65-74, and >=75 years). The crude rate was calculated as the number in each comorbidity group divided by the total number of OA cases. We calculated age-standardized comorbidity prevalence rates using the direct standardization method [24]. We used the 2016 Canadian population reported publicly by Statistics Canada [25] to age-standardize the estimates for females and males with 95% confidence intervals (CIs) calculated using the binomial approximation method [24]. To compare differences between females and males, standardized rate ratios (SRR) were estimated as the female age-standardized rate divided by the male age-standardized rate. We calculated 95% confidence intervals for the SRR based on the standard error for each sex, to test for a sex difference [24].

We calculated the percentage of females and males in each age group and the percentage of OA cases for each age group by sex. The percentage of comorbidities among OA population was calculated as the number of cases with specific comorbidity divided by the OA population. The percentage of comorbidities among those with comorbidities was calculated using the population with one or more of the eight comorbidities as denominator. We also calculated the frequency of common groupings of these comorbidities in people with OA.

We applied χ^2 tests of independence with a Bonferroni correction[26] to compare the percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The null hypothesis is that there is no difference in the percentage of comorbidities across age groups, which is rejected when the calculated χ^2 is greater than the critical value for a specific number of degrees of freedom and an altered significance level of 0.005 after Bonferroni correction. All analyses were conducted with R version 3.5.1 and Excel 2013.

3. Results

We identified 497,362 cases of OA, 57.9% of whom were females (Table 1). More than half of the OA cases had at least one of the eight comorbidities (54.6%, n=271,794) (Table 2). A total of 161,315 (32.4%) people with OA had only one comorbidity, with 14.6% (n=72,567) having two, and 7.6% (n=37,912) having three or more of the comorbidities. Hypertension was the most frequent comorbidity (29%, n=144,453),

followed by depression (19.9%, n=99,103), COPD (18.6%, n=92,273), diabetes (9.5%, n=47,102), and CHF (5.6%, n=27,905). PVD (3.0%), CEVD (1.2%) and MI (1.0%) were the least frequent comorbidities.

Table 1 Characteristics of people with OA identified in the population

Population	Age groups (years)	Female			Male			Total
		n	% by age groups	% (Female)	n	% by age groups	% (Male)	
People meeting OA case definition	<35	13,975	50.6	4.9	13,638	49.4	6.5	27,613
	35-44	25,616	52.4	8.9	23,279	47.6	11.1	48,895
	45-54	57,574	57.6	20.0	42,445	42.4	20.3	100,019
	55-64	65,528	57.1	22.8	49,329	42.9	23.6	114,857
	65-74	59,346	57.7	20.6	43,527	42.3	20.8	102,873
	75+	65,912	63.9	22.9	37,193	36.1	17.8	103,105
	Total	287,951	57.9	100.0	209,411	42.1	100.0	497,362

Note: % by age groups was calculated using total population of each specific age group (e.g. for OA <35 years, the percentage was calculated using the number of females with OA as the numerator and the total number of people with OA as the denominator (13,975 + 13,638= 27,613). % female <35 years was calculated using the number of females in the age group < 35 years as the numerator (13,975) and the number of females with OA as the denominator (287,951).

Comorbidity Patterns by Sex

A similar pattern was observed regarding the number of comorbidities (with most people with OA having one comorbidity) and the ordering of the frequency of each of the comorbidities among females and males based on age-standardized prevalence rates (Table 2). Statistically significant differences among females and males were observed by the number of comorbidities, with females having higher rates overall (SRR = 1.26, 95% CI: 1.25-1.28). The number of comorbidities was also higher for females compared to males with SRR ranging from 1.15 (95% CI: 1.11-1.18) for three or more comorbidities to 1.48 (95% CI: 1.44-1.52) for two comorbidities (Table 2).

Table 2 Frequency, percentage and age-standardized rate of comorbidities in people with OA

Comorbidity		n	% of OA cohort	% of the OA cohort with one or more of the eight comorbidities	Age standardized Rate (per 1,000 population)		
					Female (95% CI)	Male (95% CI)	SRR (95% CI)
Comorbid Conditions	Hypertension	144,453	29.0	53.1	162.2 (160.9-163.5)	146.5 (145.1-148.0)	1.11 (1.09-1.12)
	Depression	99,103	19.9	36.5	264.1 (260.9-267.3)	152.6 (149.8-155.4)	1.73 (1.69-1.77)
	Chronic obstructive pulmonary disease	92,273	18.6	33.9	195.9 (193.0-198.8)	153.6 (150.9-156.3)	1.28 (1.25-1.30)

	Diabetes	47,102	9.5	17.3	53.1 (52.0-54.2)	59.4 (58.4-60.4)	0.89 (0.87-0.92)
	Congestive heart failure	27,905	5.6	10.3	24.4 (23.9-24.9)	25.4 (24.9-26.0)	0.96 (0.93-0.99)
	Peripheral vascular disease	15,044	3.0	5.5	12.6 (12.1-13.0)	17.8 (17.2-18.3)	0.71 (0.67-0.74)
	Myocardial infarction	4,969	1.0	1.8	4.3 (4.1-4.5)	4.7 (4.4-5.0)	0.91 (0.84-0.98)
	Cerebrovascular disease	5,974	1.2	2.2	4.0 (3.8-4.2)	7.9 (7.6-8.2)	0.51 (0.48-0.54)
Number of Comorbidities	One Comorbidity	161,315	32.4	59.4	329.1 (325.7-332.4)	271.5 (268.2-274.8)	1.21 (1.19-1.23)
	Two Comorbidities	72,567	14.6	26.7	124.9 (122.8-127.1)	84.6 (82.9-86.2)	1.48 (1.44-1.52)
	Three or more Comorbidities	37,912	7.6	13.9	42.3 (41.4-43.2)	36.9 (36.2-37.7)	1.15 (1.11-1.18)
OA with Comorbidities		271,794	54.6		496.3 (492.8-499.8)	392.9 (389.4-396.4)	1.26 (1.25-1.28)
None of the 8 Comorbidities		225,568	45.4		503.7 (500.17-507.22)	607.1 (603.56-610.56)	0.83 (0.82-0.84)

Note: % of OA cohort was calculated using OA population (271,794 + 225,568 = 497,362) as denominator and the population of each comorbidity as numerator. % of the OA cohort with one or more of the eight comorbidities was calculated using population with at least one comorbidity (n= 271,794) as denominator. CI denotes Confidential Interval. SRR denotes Standardized Rate Ratio between females and males (females/males). The eight comorbidities are those with validated case definitions for administrative health data.

Depression, COPD and hypertension remained as the three most prevalent comorbidities in both females and males after age-standardization. However, the prevalence of each of these comorbidities was higher in females compared to males (Table 2Females had significantly higher prevalence rates than males for depression (SRR 1.73, 95% CI: 1.69-1.77), COPD (SRR 1.28, 95% CI: 1.25-1.30) and hypertension (SRR 1.11, 95% CI: 1.09-1.12), respectively.

The prevalence of each of these three comorbidities differed significantly in females. For example the prevalence of depression in females was 264 cases per 1,000 population, 35% higher and statistically higher than for COPD (196 cases per 1,000 population) (SRR 1.35, 95% CI 1.32-1.37). In contrast, the prevalence of these three comorbidities among males were not significantly different.

Common groupings of comorbidities in people with OA

As shown in Table 3, of the eight comorbidities in people with OA, the most frequent comorbidity was hypertension as a single comorbidity, found in 12.8% of people with OA (n=63,520). The most common grouping of two comorbidities was the coexistence of hypertension and depression (2.9%, n=14,609). The most common grouping with three comorbidities was depression, COPD and hypertension, (1.1%, n=5,262). People with OA having any combination of the top three comorbidities accounted for approximately 40% of people with OA.

Table 3 Frequency of top 10 common groupings of comorbidities

Combinations of comorbidity	n	% of OA cohort)	% of OA with comorbidities
Hypertension only	63,520	12.8	23.4
Depression only	46,226	9.3	17.0
Chronic Obstructive Pulmonary Disease only	34,464	6.9	12.7
Hypertension, Depression	14,609	2.9	5.4
Hypertension, Chronic Obstructive Pulmonary Disease	13,653	2.7	5.0
Depression, Chronic Obstructive Pulmonary Disease	13,584	2.7	5.0
Hypertension, Diabetes	11,784	2.4	4.3
Diabetes	11,054	2.2	4.1
Hypertension, Depression, Chronic Obstructive Pulmonary Disease	5,262	1.1	1.9
Hypertension, Congestive Heart Failure	3,946	0.8	1.5

Note: % of OA cohort was calculated using OA population (271,794 + 225,568 = 497,362) as denominator and the population of each comorbidity as numerator. % of OA with comorbidities was calculated using population with at least one comorbidity at the diagnosis of OA (n= 271,794) as denominator.

Comorbidity patterns by age group

As shown in Figure 1, each of the eight comorbidities, with the exception of depression, was most common in people with OA over 65 years old. Hypertension was found in 44.3% of people with OA over 65 years of age (n=91,153 cases) compared to 5.3% (n=4,040 cases) in those <44 years old. The largest number of people with OA and depression were in the 45-64 years age cohort (n=47,061 cases), with the youngest age group (<44 years) having the highest percentage of cases with depression (24.6% compared to 21.9% in the middle age group (45-64 years) and 16.1% in the older age group (>=65 years). The difference in the percentage of each of the eight comorbidities among the three age groups was statistically significant (p<0.0001). The detailed age-sex stratified crude rates per 1,000 population is provided in Appendix 1.

The number of comorbidities in people with OA increased with increasing age. The percentage of people with three or more comorbidities increased significantly from 1.5% in youngest age group (<44 years), to 4.7% in the middle age group (45-64 years), and to 13% in the older age group (>=65 years) (p<0.0001).

4. Discussion

We estimated the prevalence of comorbid conditions in people with OA using provincial administrative health data. Using validated case and comorbidity definitions, we found that 54.6% of people with OA had at least one of the eight comorbidities, and 28.5% had at least two. Depression, COPD and hypertension were the three most prevalent

comorbidities in both females and males after age-standardization. However, the prevalence of each of these comorbidities was significantly higher in females compared to males. People with any combination of these three comorbidities represented about 40% of the people with OA. In general, the number of comorbidities in people with OA increased with increasing age. Each of the eight comorbidities, except depression, was most common in people with OA >= 65 years. The largest number of people with OA and depression are in the middle age group (45-64 years), with the youngest age group (<44 years) having the highest percentage of cases with depression.

The estimated prevalence of comorbidities varies among studies due to differences in case definitions, the list of included chronic conditions, data sources and study population. We estimated that the prevalence of comorbidity among people with OA was 54.6% for one or more of the eight comorbid chronic conditions and 22.2% for two or more comorbid chronic conditions with OA. Our estimates of the prevalence of comorbidities in people with OA are higher than the prevalence of two or more and three or more chronic conditions among the general Canadian population (26.5% and 10.2%, respectively) as reported by Feely et al.(2017) [27], and higher than the prevalence of 12.9% (two or more chronic diseases) and 3.9% (three or more chronic diseases) reported by Roberts et al. (2015)[28]. In our study, among 205,978 OA cases in the age group over 65 years old, the prevalence of one or more comorbid chronic conditions was 33.2% (n=68,418) and the prevalence of two or more comorbid chronic conditions with OA was 19.0% (n=39,044). The estimated prevalence is higher than the estimates reported by Roberts et al. (2015), which showed that the prevalence of two or more chronic diseases was 31.3% and the prevalence of three or more chronic diseases was 11.3%. It has been reported previously that the prevalence of one or more comorbid condition among people with musculoskeletal conditions was more than twice than those without a musculoskeletal condition but with another chronic condition[29].

We identified depression, COPD and hypertension as frequent comorbid conditions among the people with OA. This was consistent with findings reported from the Canadian Primary Care Sentinel Surveillance Network showing that the prevalence of osteoarthritis has significant association with depression, COPD and hypertension[2,]. Depression is emerging as a significant comorbidity in OA. Previous findings have reported that depression was highly prevalent in people with OA[10, 30.] A systemic review of depressive symptoms in people with OA , including 49 studies worldwide and representing 15,855

individuals, reported a frequency of depression of 19.9% among people with OA[31], which was similar to our estimates.

Depressed individuals are more likely to report chronic or more severe pain, and more than half of the patients with chronic pain are depressed. People living with OA are known to have fewer social contacts, limited physical activity, increased pain and disability [32,33], worse surgical outcomes and reduced effectiveness of pain interventions [34], which are all important predictors of depression [35]. However, current clinical practice guidelines for non-surgical management of OA do not include recommendations regarding mental health management [36–39]. This emphasizes the need for treatments and management for depression to improve outcomes for people with OA[40]. It has been suggested that educating physicians about timely identification of psychological factors may be helpful to improve outcomes. In addition, self-care management could be integrated into OA management strategies as a way to reduce anxiety and depression, as well as resulting emotional and physical pain. Guidelines suggest that OA management should also integrate pharmacotherapy carefully and be cautious about the drug interactions and adverse side effects when treating OA, depression, anxiety and pain holistically[30]. Two or more of the comorbidities that we examined coexist in a substantial proportion of people with OA – approximately 22% in total. Obesity, which we were unable to study using administrative data is also prevalent amongst people with OA and a risk factor for developing OA[41,42]. From a clinical practice perspective, a physician has to consider the implications of prescribing non-steroidal anti-inflammatory medications for pain management, but this may worsen hypertension and have an associated increased risk of cardiovascular disease. However, without good pain management, it is difficult for patients with OA to engage in exercise programs which can help improve their muscular condition and potentially reduce obesity and hypertension. This is further complicated by the relationship of lower socioeconomic status with an increased risk of developing OA as demonstrated in the project for an Ontario Women's Health Evidence-based Report[29].

Furthermore, our analyses showed that depression not only was the most prevalent comorbidity after age-standardization in people with OA, but that rates of depression were significantly higher for females and younger people (< 44 years old). The study by Dibonaventura et al. (2011) reported that people under 65 years of age were still participating in the workforce, however OA pain resulted in significantly lower productivity and higher costs compared to those without OA pain[8]. They identified unique

treatment gaps for patients younger than 60 years old because the non-operative treatment options were ineffective in long-term management of OA symptoms, but young patients were too young or maybe unwilling to undergo definitive treatment such as total joint replacement[43]. Even for those patients who undergo total joint replacement, they were more likely to be dissatisfied about the treatment than older patients, and reported poorer outcomes including residual pain and stiffness [44,45]. A survey of orthopedic surgeons found that 84% perceived a need for better treatment for younger (<60 years old) physically active OA patients, and 68.4% perceived that there is a treatment gap for these patients[43]. Due to the different presentations of comorbidities and treatment options among young and old age groups, it is imperative to examine the impact of comorbidities on management strategies in an age-stratified OA cohort.

Most clinical practice guidelines focus on single conditions[46]. Fortin et al. (2011) concluded that even though the quality of the Canadian guidelines was good, their relevance for patients with two or more chronic conditions was limited[47]. Boyd et al. (2005) highlighted the lack of consideration of comorbidities in clinical practice guidelines may result in poor quality of care because the health care some patients received was not optimal[48]. Sharma et al., (2016) pointed out that the present literature fails to fully address the management strategies when dealing with comorbidities seen in people with OA[30]. Patient-centered care has been recommended in clinical practice guidelines with the aim of improving quality of care by focusing on the patient as a whole rather than on a single disease[49]. From a system perspective, patients with several comorbidities were also the main users of healthcare resources and services[50]. Patient-centered and coordinated care for these patients may decrease related health care use[51]. It was recommended that physicians consider these comorbidities in the management of people with OA.

A strength of our study is the large population-based number of people with OA (n=497,362) and the investigation of a group of eight comorbidities that are clinically relevant to the management of people with OA. We applied case definitions for administrative health data to identify cases of OA and each of the comorbidities at the diagnosis of OA. A limitation of our study is that case identification based on administrative data may result in underreporting of cases and comorbidities. The case definitions for OA in administrative data research [5], based on the physician claims and hospitalizations records, have been applied and validated with a sensitivity of 24%, high specificity of 98% and a positive predictive value of 54%[11]. In our study, we also included

ACCS/NACRS to mitigate the issue of underestimations[6]. Nonetheless, the estimated number of OA cases using this approach is almost certainly an underestimate. Similarly, the algorithms for comorbidities may underestimate the prevalence of these comorbidities; the sensitivity for identifying depression is from 36% to 51% [19], for PVD is 39%[18] and for COPD is 53% [21] in administrative data (Appendix 2). More importantly, the reported levels of comorbidity in patients with OA were measured at the time of OA diagnosis. New cases of comorbidity diagnosed after the OA diagnosis were not identified. Further, we limited our analysis to eight comorbidities of clinical relevance and for which there were case definitions in administrative data.

5. Conclusions

We found that, depression, COPD and hypertension were the three most prevalent comorbidities in people with OA, with rates significantly higher in females compared to males. Of particular note is that the largest number of people with OA and depression are in the age group between 45 and 64 years old, with the highest percentage of cases occurring in the younger age groups (<44 years). Our findings highlight the need to recognize that people with OA have high rates of comorbidities and this may affect optimal health care management of these patients.

Acknowledgements

The authors would like to acknowledge the following team members and their contributions to the study: Behnam Sharif.

Contributions

DM, PF, KY were responsible for the conception and design of the research, acquisition of the data, analysis and interpretation of data, drafting the article, and revision of the article for important intellectual content.

XL was responsible for the analysis and interpretation of data, drafting the article, and revision of the article for important intellectual content.

CB, CB, DM, TN, JW and LL were responsible for the conception and design of the research, interpreting results of the research and revision of the article for important intellectual content.

All authors approved the final version of the manuscript to be submitted.

DM (damarsha@ucalgary.ca) and XL (xiaoxili@ucalgary.ca) take responsibility for the integrity of the work as a whole.

Role of the funding source

This research was funded through a Canadian Institute for Health Research (CIHR) Operating Grant (Grant #: 126128) and the Arthur J.E. Child Chair in Rheumatology Research. There were no study sponsors and the funding agencies had no involvement in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

DM was supported by a Canada Research Chair and the Arthur J.E. Child Chair in Rheumatology Research. XL was supported by the Arthur J.E. Child Chair in Rheumatology Research, the Cumming School of Medicine Postdoctoral Scholarship and the Postdoctoral Scholarship funded by the O'Brien Institute of Public Health and the McCaig Institute for Bone and Joint Health.

Data availability

These data are not available because Alberta Health and Alberta Health Services are the custodians of the data. The authors are not authorized to share them.

Competing interests

The authors confirm that there is no financial support or other benefits from commercial sources for the work reported on in the manuscript. There are also no financial interests that the authors may have which could create a potential conflict of interest with regards to the work in the manuscript.

References

1. Leite AA, Costa AJG, Lima B de AM de, Padilha AVL, Albuquerque EC de, Marques CDL. Comorbidities in patients with osteoarthritis: frequency and impact on pain and physical function. *Rev Bras Reumatol*. 2011;51(2):118-123. doi:10.1590/S0482-50042011000200002
2. Birtwhistle R, Morkem R, Peat G, et al. Prevalence and management of osteoarthritis in primary care: an epidemiologic cohort study from the Canadian Primary Care Sentinel Surveillance Network. *C open*. 2015;3(3):E270-5. doi:10.9778/cmajo.20150018
3. Bombardier C, Hawker G, Mosher D. *The Impact of Arthritis in Canada: Today and over the next 30 Years.*; 2011.
4. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. *Ann Rheum Dis*. 2004;63(4):408-414. doi:10.1136/ARD.2003.007526
5. Kopec JA, Rahman MM, Berthelot J-M, et al. Descriptive epidemiology of osteoarthritis in British Columbia, Canada. *J Rheumatol*. 2007;34(2):386-393.
6. Marshall DA, Vanderby S, Barnabe C, et al. Estimating the Burden of Osteoarthritis to Plan for the Future. *Arthritis Care Res*. 2015;67(10):1379-1386. doi:10.1002/acr.22612
7. Tarride J-E, Haq M, O'Reilly DJ, et al. The excess burden of osteoarthritis in the province of Ontario, Canada. *Arthritis Rheum*. 2012;64(4):1153-1161. doi:10.1002/art.33467
8. Dibonaventura M dacosta, Gupta S, McDonald M, Sadosky A. Evaluating the health and economic impact of osteoarthritis pain in the workforce: results from the National Health and Wellness Survey. *BMC Musculoskelet Disord*. 2011;12:83. doi:10.1186/1471-2474-12-83
9. Rosemann T, Joos S, Szecsenyi J, Laux G, Wensing M. Health service utilization patterns of primary care patients with osteoarthritis. *BMC Health Serv Res*. 2007;7(1):169. doi:10.1186/1472-6963-7-169
10. Kim KW, Han JW, Cho HJ, et al. Association Between Comorbid Depression and Osteoarthritis Symptom Severity in Patients with Knee Osteoarthritis. *J Bone Jt Surgery-American Vol*. 2011;93(6):556-563. doi:10.2106/JBJS.I.01344
11. Lix L, Yogendran M, Mann J. *Defining and Validating Chronic Diseases: An Administrative Data Approach and Update with ICD-10-CA.*; 2008.
12. Kopec JA, Rahman MM, Sayre EC, et al. Trends in physician-diagnosed osteoarthritis incidence in an administrative database in British Columbia, Canada, 1996–1997 through 2003–2004. *Arthritis Rheum*. 2008;59(7):929-934. doi:10.1002/art.23827
13. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. *Res Synth Methods*. 2014;5(4):371-385. doi:10.1002/jrsm.1123
14. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Myocardial Infarction Diagnoses in Administrative Databases: A Systematic Review. Guo Y, ed. *PLoS One*. 2014;9(3):e92286. doi:10.1371/journal.pone.0092286
15. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. *Hypertension*. 2009;54(6):1423-1428. doi:10.1161/HYPERTENSIONAHA.109.139279
16. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. *PLoS One*. 2015;10(8):e0135834.

doi:10.1371/journal.pone.0135834

17. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e104519. doi:10.1371/journal.pone.0104519

18. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *J Am Med Inform Assoc*. 2013;20(e2):e349-54. doi:10.1136/amiajnl-2013-001827

19. Townsend L, Walkup JT, Crystal S, Olfson M. A systematic review of validated methods for identifying depression using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21:163-173. doi:10.1002/pds.2310

20. Leong A, Dasgupta K, Bernatsky S, Lacaille D, Avina-Zubieta A, Rahme E. Systematic Review and Meta-Analysis of Validation Studies on a Diabetes Case Definition from Health Administrative Records. Barengo NC, ed. *PLoS One*. 2013;8(10):e75256. doi:10.1371/journal.pone.0075256

21. Smidth M, Sokolowski I, Kærsvang L, Vedsted P. Developing an algorithm to identify people with Chronic Obstructive Pulmonary Disease (COPD) using administrative data. *BMC Med Inform Decis Mak*. 2012;12(1):38. doi:10.1186/1472-6947-12-38

22. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res Clin Pract*. 2010;89(2):189-195. doi:10.1016/j.diabres.2010.03.007

23. Quan H, Sundararajan V, Halfon P, et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative. *Med Care*. 2005;43(11):1130-1139.

24. Boyle P, Parkin D. Statistical methods for registries. *Cancer Regist Princ Methods*. 1991:126-158.

25. Statistics Canada. Alberta [Province] and Canada [Country] (table). Census Profile. 2016 Census. doi:98-316-X2016001

26. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ*. 1995;310(6973):170. doi:10.1136/bmj.310.6973.170

27. Feely A, Lix LM, Reimer K. Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System. *Heal Promot chronic Dis Prev Canada Res policy Pract*. 2017;37(7):215-222. doi:10.24095/hpcdp.37.7.02

28. Roberts KC, Rao DP, Bennett TL, Loukine L, Jayaraman GC. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. *Heal Promot chronic Dis Prev Canada Res policy Pract*. 2015;35(6):87-94.

29. Hawker GA, Badley EM, Jaglal S, et al. Musculoskeletal Condtitions. In: *Project for an Ontario Women's Health Evidence-Based Report: Volume 2: Toronto*. ; 2010.

30. Sharma A, Kudesia P, Shi Q, Gandhi R. Anxiety and depression in patients with osteoarthritis: impact and management challenges. *Open access Rheumatol Res Rev*. 2016;8:103-113. doi:10.2147/OARRR.S93516

31. Stubbs B, Aluko Y, Myint PK, Smith TO. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. *Age Ageing*. 2016;45(2):228-235. doi:10.1093/ageing/afw001

32. Sale JEM, Gignac M, Hawker G. The relationship between disease symptoms, life events, coping and treatment, and depression among older adults with osteoarthritis. *J Rheumatol*. 2008;35(2):335-342.

33. Hawker GA, Gignac MAM, Badley E, et al. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res (Hoboken)*. 2011;63(10):1382-1390.

doi:10.1002/acr.20298

34. Gleicher Y, Croxford R, Hochman J, Hawker G. A prospective study of mental health care for comorbid depressed mood in older adults with painful osteoarthritis. *BMC Psychiatry*. 2011;11(1):147. doi:10.1186/1471-244X-11-147

35. Rosemann T, Backenstrass M, Joest K, Rosemann A, Szecsenyi J, Laux G. Predictors of depression in a sample of 1,021 primary care patients with osteoarthritis. *Arthritis Rheum*. 2007;57(3):415-422. doi:10.1002/art.22624

36. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthr Cartil*. 2007;15(9):981-1000. doi:10.1016/j.joca.2007.06.014

37. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthr Cartil*. 2008;16(2):137-162. doi:10.1016/j.joca.2007.12.013

38. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: Part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthr Cartil*. 2010;18(4):476-499. doi:10.1016/J.JOCA.2010.01.013

39. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartil*. 2014;22(3):363-388. doi:10.1016/j.joca.2014.01.003

40. Lin EHB, Katon W, Von Korff M, et al. Effect of Improving Depression Care on Pain and Functional Outcomes Among Older Adults With Arthritis. *JAMA*. 2003;290(18):2428. doi:10.1001/jama.290.18.2428

41. Felson DT. Weight and osteoarthritis. *J Rheumatol Suppl*. 1995;43:7-9.

42. ANDERSON JJ, FELSON DT. FACTORS ASSOCIATED WITH OSTEOARTHRITIS OF THE KNEE IN THE FIRST NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (HANES I). *Am J Epidemiol*. 1988;128(1):179-189. doi:10.1093/oxfordjournals.aje.a114939

43. Li CS, Karlsson J, Winemaker M, Sancheti P, Bhandari M. Orthopedic surgeons feel that there is a treatment gap in management of early OA: international survey. *Knee Surgery, Sport Traumatol Arthrosc*. 2014;22(2):363-378. doi:10.1007/s00167-013-2529-5

44. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KDJ. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res*. 2010;468(1):57-63. doi:10.1007/s11999-009-1119-9

45. Parvizi J, Nunley RM, Berend KR, et al. High level of residual symptoms in young patients after total knee arthroplasty. *Clin Orthop Relat Res*. 2014;472(1):133-137. doi:10.1007/s11999-013-3229-7

46. Hughes LD, Mcmurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *J Heal Soc Behav J Public Heal Med J Epidemiol Community Heal Ann Epidemiol Am J Epidemiol Age Ageing*. 2013;36(42):1-10. doi:10.1093/ageing/afs100

47. Fortin M, Contant E, Savard C, Hudon C, Poitras M-E, Almirall J. Canadian guidelines for clinical practice: an analysis of their quality and relevance to the care of adults with comorbidity. *BMC Fam Pract*. 2011;12(1):74. doi:10.1186/1471-2296-12-74

48. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases. *JAMA*. 2005;294(6):716.

doi:10.1001/jama.294.6.716

49. Dawes M. Co-morbidity: we need a guideline for each patient not a guideline for each disease. *Fam Pract*. 2010;27:1-2. doi:10.1093/fampra/cmp106

50. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *Ann Fam Med*. 2012;10(2):134-141. doi:10.1370/afm.1363

51. Wolff JL, Starfield B, Anderson G. Prevalence, Expenditures, and Complications of Multiple Chronic Conditions in the Elderly. *Arch Intern Med*. 2002;162(20):2269. doi:10.1001/archinte.162.20.2269

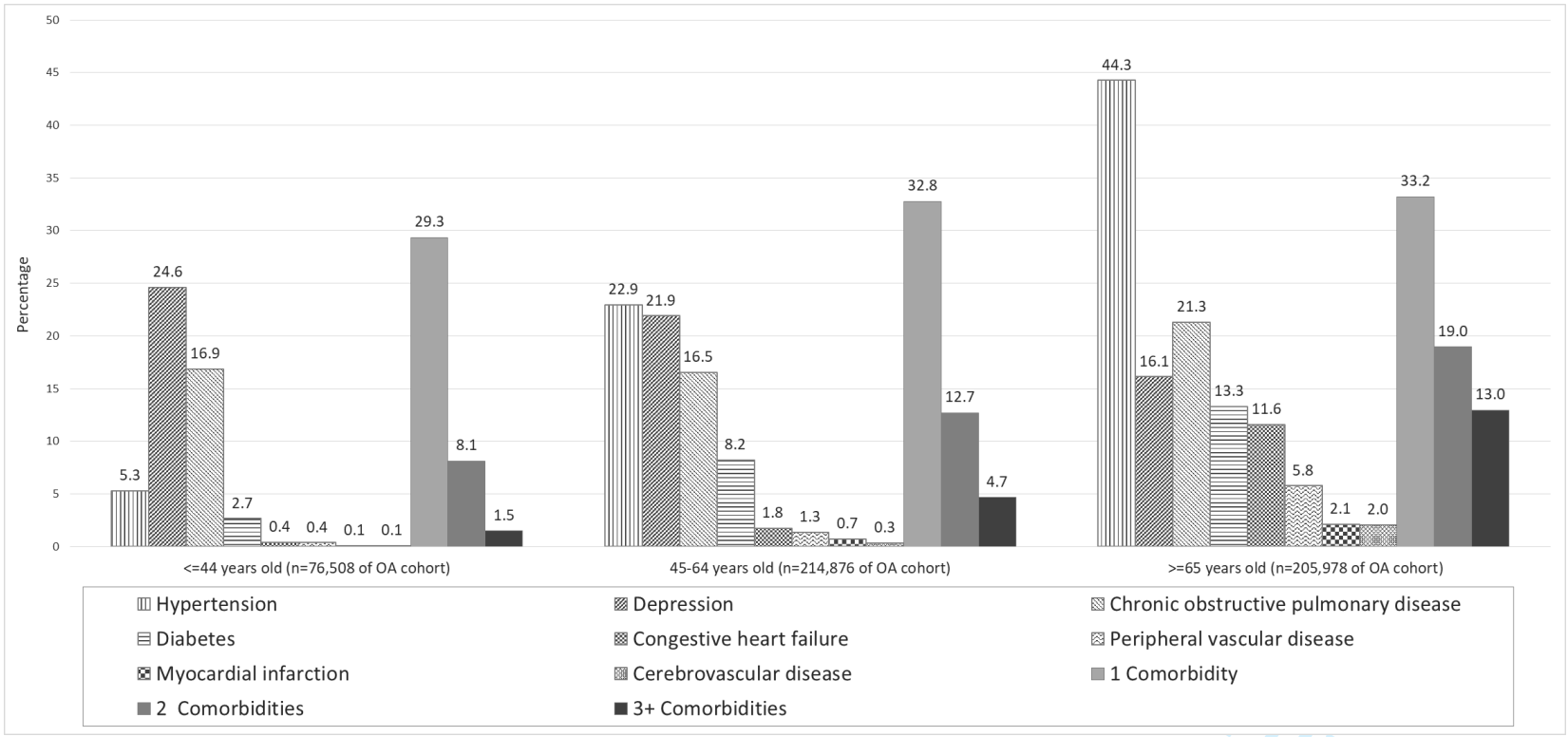

Figure 1 Percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The difference by age group was statistically significant for each comorbid conditions (p<0.0001), as was the frequency of the number of comorbidities present per individual (p<0.0001).

Appendix 1: Age-sex stratified crude rates (per 1,000 population) of comorbidities among people with OA

Age Groups	OA with Hypertension (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	2,068	1,972	39,591	36,917	52	53
45-64	28,046	21,214	123,102	91,774	228	231
>=65	57,453	33,700	125,258	80,720	459	417
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with Depression (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	12,366	6,464	39,591	36,917	312	175
45-64	32,951	14,110	123,102	91,774	268	154
>=65	23,045	10,167	125,258	80,720	184	126
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with COPD (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	7,984	4,914	39,591	36,917	202	133
45-64	22,124	13,424	123,102	91,774	180	146
>=65	24,626	19,201	125,258	80,720	197	238
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with 1 comorbidity (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	13,016	9,437	39,591	36,917	329	256
45-64	42,477	27,967	123,102	91,774	345	305
>=65	42,593	25,825	125,258	80,720	340	320
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with 2 comorbidities (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	4,268	1,956	39,591	36,917	108	53

45-64	16,975	10,324	123,102	91,774	138	112
>=65	23,879	15,165	125,258	80,720	191	188
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with 3+ comorbidities (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	757	379	39,591	36,917	19	10
45-64	5,970	4,099	123,102	91,774	48	45
>=65	15,467	11,240	125,258	80,720	123	139
Total	87,567	56,886	287,951	209,411	304	272

1 Appendix 1 Case definitions for eight comorbid conditions

	ICD9-CM Diagnosis Codes Included	ICD10-CA Diagnosis Codes Included	Exclusions	Algorithm	References
Myocardial Infarction	410	I21, I22	N/A	1 hospitalization for MI, with diagnoses codes in primary or secondary diagnosis fields.	McCormick et al., 2014[13] Quan et al., 2005[22]
Cerebrovascular Disease	3623,43301,43311,43321,43331,43381,43391,43401,43411,43491,436,430,431,435	H341, I63, I64, I61, I60, G450, G451, G452, G453, G458, G459	43300, 43310, 43320, 43330, 43380, 43390, 43400, 43410, 43490, 437, 438, I65, I66, I67, I69, G45.4	1 hospital discharge (most responsible diagnosis) for different stroke conditions	Kokotailo & Hill, 2005 McCormick et al., 2015[15]
Congestive Heart Failure	39891,40201,40211,40291,40401,40403,40411,40413,40491,40493,4254,4255,4257,4258,4259,428	I43,I50,I099,I110,I130,I132,I255,I420,I425,I426,I427,I428,I429,P290		1 hospitalization or physician claim in diagnosis field	Schultz et al., 2013 McCormick et al., 2014[16] Quan et al., 2005[22] Lee et al., 2005
Peripheral Vascular Disease	0930,4373,440,441,4431,4432,4438,4439,4471,5571,5579,V434,443	I70,I71, I731,I738,I739,I771,I790,I792,K551,K558,K559,Z958,Z959	N/A	1 hospitalization or physician claim in diagnosis field	Fan et al., 2013[17]
Chronic Obstructive Pulmonary Disease	4168,4169,490,491,492,493,494,495,496,500,501,502,503,504,505,5064,5081,5088	J40,J41,J42,J43,J44,J45,J46,J47,J60,J61,J62,J63,J64,J65,J66,J67,I278,I279,J684,J701,J703	N/A	1 hospitalization or physician claim in diagnosis field	Smidth et al. 2012[20] Quan et al., 2005[22]
Depression	2962,2963,2965,3004,309,311	F204,F313,F314,F315,F32,F33,F341,F412,F432	N/A	1 hospitalization or physician claim in diagnosis field	Townsend et al., 2012[18] Lix et al., 2006 Martens et al., 2010

Diabetes	250	E10, E11, E12, E13, E14	Physician claims with procedure code having a prefix of "X" (radiology/xray), "E" (labs) or "B" (dentist, ophthalmologist, chiropractic visits)	1 hospitalization for diabetes OR 2 physician claims in a 2-year period	Chen et al., 2010[21] Leong et al., 2013[19] Hux et al., 2002
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15	Physician claims with procedure code having a prefix of "X" (radiology/xray), "E" (labs) or "B" (dentist, ophthalmologist, chiropractic visits)	1 hospitalization for hypertension OR 2 physician claims in a 2-year period	Quan et al., 2009[14]

2

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*P5-7*
Bias	9	Describe any efforts to address potential sources of bias	P5
Study size	10	Explain how the study size was arrived at	P6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7
		(*b*) Describe any methods used to examine subgroups and interactions	P7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	The sensitivity analysis using alterative OA case definitions has been conducted previously. Please refer to Marshall et. al. (2015).
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	P7-8

		eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	P8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P8-9
		(*b*) Report category boundaries when continuous variables were categorized	P7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	The sensitivity analysis using alterative OA case definitions has been conducted previously. Please refer to Marshall et. al. (2015).
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Existing comorbidities in people with osteoarthritis: a retrospective analysis of a population-based cohort in Alberta, Canada

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033334.R2
Article Type:	Original research
Date Submitted by the Author:	31-Oct-2019
Complete List of Authors:	Marshall, Deborah; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Liu, Xiaoxiao; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Barnabe, Cheryl; University of Calgary Cumming School of Medicine, Department of Medicine; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Yee, Karen; Alberta Health Services, Research Facilitation Faris, Peter; Alberta Health Services, Research Facilitation Barber, Claire; University of Calgary Cumming School of Medicine, Department of Medicine; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Mosher, Dianne; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Noseworthy, Thomas; University of Calgary Cumming School of Medicine, Department of Community Health Sciences Werle, Jason; University of Calgary Cumming School of Medicine, Department of Surgery Lix, Lisa; University of Manitoba, Department of Community Health Sciences
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research, Rheumatology
Keywords:	Osteoarthritis, Comorbidity, Depression, Hypertension < CARDIOLOGY, COPD, Administrative Health Data

Title: Existing comorbidities in people with osteoarthritis: a retrospective analysis of a population-based cohort in Alberta, Canada

Deborah A Marshall PhD [1,2 *], Xiaoxiao Liu PhD [1], Cheryl Barnabe MD MSc [1,2], Karen Yee MSc MPH [3], Peter Faris PhD [3], Claire EH Barber MD PhD [1,2], Dianne Mosher PhD [1], Thomas Noseworthy[2], Jason Werle [4], Lisa M. Lix [5]

[1] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary

[2] Department of Medicine, Cumming School of Medicine, University of Calgary

[3] Research Facilitation, Alberta Health Services, Calgary

[4] Department of Surgery, Cumming School of Medicine, University of Calgary

[5] Department of Community Health Sciences, Manitoba, Winnipeg

* Correspondence: Deborah A Marshall, Cumming School of Medicine, University of Calgary. 3280 Hospital Drive NW, HRIC Building, Room 3C58, Calgary, AB. T2N 4Z6, Canada. E-mail address: damarsha@ucalgary.ca

Word Count

Abstract: 288

Body: 3,396

Number of tables: 3

Number of figures: 1

Abstract

Objectives: The purpose of this study is to estimate the prevalence of comorbidities among people with osteoarthritis (OA) using administrative health data.

Design: Retrospective cohort analysis

Setting: All residents in the province of Alberta Canada registered with the Alberta Health Care Insurance Plan (AHCIP) population registry.

Participants: 497,362 people with OA as defined by "having at least one OA-related hospitalization, or at least two OA-related physician visits or two ambulatory care visits within two years".

Primary outcome measures: We selected eight comorbidities based on literature review, clinical consultation and the availability of validated case definitions to estimate their frequencies at the time of diagnosis of OA. Sex-stratified age-standardized prevalence rates per 1,000 population of eight clinically relevant comorbidities were calculated using direct standardization with 95% confidence intervals (CIs). We applied χ^2 tests of independence with a Bonferroni correction to compare the percentage of comorbid conditions in each age group.

Results: 54.6% (n=271,794) of people meeting the OA case definition had at least one of the eight selected comorbidities. Females had a significantly higher rate of comorbidities compared to males (standardized rates ratio = 1.26, 95% CI: 1.25-1.28). Depression, chronic obstructive pulmonary disease (COPD) and hypertension were the most prevalent in both females and males after age-standardization, with 40% of all cases having any combination of these comorbidities. We observed a significant difference in the percentage of comorbidities among age groups, illustrated by the youngest age group (<45 years) having the highest percentage of cases with depression (24.6%), compared to a frequency of 16.1% in those >65 years.

Conclusions: Our findings highlight the high frequency of comorbidity in people with OA, with depression having the highest age-standardized prevalence rate. Comorbidities differentially affect females, and vary by age. These factors should inform health care programs and delivery.

Keywords: Osteoarthritis; comorbidity; depression; hypertension; COPD; administrative health data

Strengths and limitations of this study

- Strong methodological approach to identify cases of OA with a validated case definition using five linked population-based administrative databases.
- However, case identification based on administrative data may result in underreporting of cases and comorbidities.
- The age-standardized prevalence of eight comorbidities, selected on their clinical relevance and the availability of validated case definitions for administrative health data, was estimated among people with OA.
- We limited our analysis to eight comorbidities of clinical relevance.
- We stratified the analysis by sex and by age cohorts

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis, affecting 1 in 8 (13%) Canadians and representing a major cause of pain and disability in society[1,2]. OA affects people of all ages, but is more prevalent among females and older age groups[3,4]. Due to an aging population and an increase in obesity, the prevalence of OA is expected to continue to rise, predicted to affect one in four Canadians by 2040[5,6]. The high prevalence of OA in Canada has a substantial impact on quality of life and health care costs to individuals and health care systems. Quality of life was measured to be 10%-25% lower among people with OA relative to the general population[7] with an associated economic burden of $33 billion (direct and indirect costs) in Canada in 2011[3]. The annual cost per individual with OA has been estimated to be two to three times higher compared to people without OA[7], and are associated with more physician visits and hospitalizations[8].

More recently, the characterization of comorbidities among people with OA has been explored due to the potential effect of comorbidities on routine clinical practice, clinical practice guidelines, healthcare utilization and costs[9-10]. In people with OA over the age of 50 years in England, the presence of comorbidities resulted in increased physical disability compared to those without OA, with the influence of comorbidities greater than that expected for OA alone or for each comorbidity in isolation[4]. Knowledge of the prevalence of comorbidities in people with OA raises important considerations for optimal OA treatment and management, to reduce pain and physical disability, enhance the quality of life, and decrease the burden of OA. Comorbidities add complexity to the management of patients with OA to provide patient-centred care, ensure appropriate management recommendations for health care programs and delivery.

The purpose of this study is to estimate the prevalence of comorbidities at time of diagnosis among people with OA in the province of Alberta, Canada, using administrative health data. Our study fills the gap in knowledge regarding the patterns and burden of comorbidities in people with OA, particularly with regard to the link between OA and comorbidities associated with age. In addition, our study is unique in that we examine all of the commonly reported comorbidities simultaneously in a single study. This information is useful to consider in clinical practice guidelines and to assess the potential impact of comorbidities for clinical practice.

2. Materials and Methods

Data sources

We used five linked Alberta, Canada provincial administrative databases between April 1, 1994 and March 31, 2013 to identify individuals with OA who accessed health care services paid for by the provincial health care insurance plan, previously described elsewhere in detail[6]. These databases included the Alberta Health Care Insurance Plan (AHCIP) population registry, the Discharge Abstract Database (DAD), the Physician Claims Database (claims), the Ambulatory Care Classification System (ACCS), and the National Ambulatory Care Reporting System (NACRS).

AHCIP Population Registry captures individual level demographic data on all insured persons as of the last day of each fiscal year (March 31). All Albertans who are included in the AHCIP have a unique, 9-digit personal health number, which is used when accessing health care services, and served to link datasets prior to de-identification. Members of the Armed Forces and the Royal Canadian Mounted Police, federal penitentiary inmates, and Albertans who have opted out of the AHCIP are excluded.

DAD captures admission and inpatient care data for all hospitalized patients, including diagnostic codes, interventions, patient age and sex, and administrative information. Among 25 DAD diagnostic code fields extracted from the hospital record, OA-related records were identified as those with the first 3 digits 715 or M15 to M19 based on the ninth (9) and tenth (10) revisions of the International Classification of Diseases (ICD) codes, respectively.

Claims captures OA-related physician visits, which were identified based on the aforementioned ICD codes in any of the 3 diagnostic code fields.

ACCS and NACRS contains data on hospital-based and community-based ambulatory care, including day surgery, outpatient and community-based clinics and emergency departments, and publicly funded hospital support services such as physiotherapy and occupational therapy. OA-related records were identified based on the presence of the aforementioned ICD codes in any of the 10 diagnostic code fields. NACRS was used since April 2010.

Ethics approval for this project was provided by the Conjoint Health Research Ethics Board at the University of Calgary (REB13-0100).

Patient and public involvement

No patients were involved in setting the research question, the design and conduct of the study. No patients were involved in the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants because this was admin health database analysis. We will make the publication available to the relevant patient community.

Case Definition of Osteoarthritis (OA)

Validated case definitions have been used in previous research related to OA using administrative data[11,12]. The sensitivity of algorithms based on both physician claims and hospitalizations records within 2-5 years ranged from 24% - 46%, along with specificity and positive predictive value ranging from 92% -98%, and 39% - 54% respectively[11]. In this study, OA cases were identified as individuals with at least one OA-related hospitalization (DAD), or at least two OA-related physician visits (claims) within two years, or at least two OA-related ambulatory care visits (ACCS/NACRS) within two years, assuming none of the physicians or ambulatory care visits had occurred on the same day[11]. For our study, the OA cohort refers to those Alberta residents registered with AHCIP who have a specified OA-related diagnostic code in any diagnostic code field position. The cohort inclusion date is the earliest date of the OA-related record identified from either the Claims, DAD or ACCS/NACRS files.

Case Definitions of Comorbidities

We identified specific comorbidities to explore in this analysis based on three criteria: 1) a high frequency of reported comorbidities in the published literature on OA; 2) the availability of validated case definitions for each comorbid condition; and, 3) expert input from our clinical co-investigators. We first conducted a scoping review of the literature [13], aiming to examine the extent and range of comorbidities research among people with OA. We identified 20 studies from a range of countries (9 in North America, 8 in Europe, 1 in Asia, 1 in South American, 1 in Netherlands), using different study designs (9 cross-sectional, 5 retrospective cohort, 5 prospective cohort and 1 case control study) with a range of sample sizes (91 to 85,966,369 cases of OA). Based on the results of this review, we derived a list of comorbidities and presented it to our clinical co-investigators. On this basis, we identified 8 comorbidities to include in our analysis: hypertension, depression, COPD, diabetes, congestive heart failure (CHF), peripheral vascular disease (PVD), myocardial infarction (MI), and cerebrovascular disease (CEVD). We applied case definitions for each comorbidity to identify those present within 3 years prior to the OA

diagnosis. Detailed ICD 9 and ICD 10 diagnostic codes used to identify each comorbidity are provided in Appendix 1[14–23].

Age-standardized comorbidity prevalence rate

The frequency of each comorbid condition in people meeting the case definition for OA was calculated, as was the frequency of the number of comorbidities present per individual: one comorbidity, two comorbidities, and three or more comorbidities. We stratified OA cases by sex, and by age at diagnosis (<35, 35-44, 45-54, 55-65, 65-74, and >=75 years). The crude rate was calculated as the number in each comorbidity group divided by the total number of OA cases. We calculated age-standardized comorbidity prevalence rates using the direct standardization method [24]. We used the 2016 Canadian population reported publicly by Statistics Canada [25] to age-standardize the estimates for females and males with 95% confidence intervals (CIs) calculated using the binomial approximation method [24]. To compare differences between females and males, standardized rate ratios (SRR) were estimated as the female age-standardized rate divided by the male age-standardized rate. We calculated 95% confidence intervals for the SRR based on the standard error for each sex, to test for a sex difference [24].

We calculated the percentage of females and males in each age group and the percentage of OA cases for each age group by sex. The percentage of comorbidities among OA population was calculated as the number of cases with specific comorbidity divided by the OA population. The percentage of comorbidities among those with comorbidities was calculated using the population with one or more of the eight comorbidities as denominator. We also calculated the frequency of common groupings of these comorbidities in people with OA.

We applied χ^2 tests of independence with a Bonferroni correction[26] to compare the percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The null hypothesis is that there is no difference in the percentage of comorbidities across age groups, which is rejected when the calculated χ^2 is greater than the critical value for a specific number of degrees of freedom and an altered significance level of 0.005 after Bonferroni correction. All analyses were conducted with R version 3.5.1 and Excel 2013.

3. Results

We identified 497,362 cases of OA, 57.9% of whom were females (Table 1). More than half of the OA cases had at least one of the eight comorbidities (54.6%, n=271,794) (Table 2). A total of 161,315 (32.4%) people with OA had only one comorbidity, with 14.6% (n=72,567) having two, and 7.6% (n=37,912) having three or more of the comorbidities. Hypertension was the most frequent comorbidity (29%, n=144,453), followed by depression (19.9%, n=99,103), COPD (18.6%, n=92,273), diabetes (9.5%, n=47,102), and CHF (5.6%, n=27,905). PVD (3.0%), CEVD (1.2%) and MI (1.0%) were the least frequent comorbidities.

Table 1 Characteristics of people with OA identified in the population

Population	Age groups (years)	Female			Male			Total
		n	% by age groups	% (Female)	n	% by age groups	% (Male)	
People meeting OA case definition	<35	13,975	50.6	4.9	13,638	49.4	6.5	27,613
	35-44	25,616	52.4	8.9	23,279	47.6	11.1	48,895
	45-54	57,574	57.6	20.0	42,445	42.4	20.3	100,019
	55-64	65,528	57.1	22.8	49,329	42.9	23.6	114,857
	65-74	59,346	57.7	20.6	43,527	42.3	20.8	102,873
	75+	65,912	63.9	22.9	37,193	36.1	17.8	103,105
	Total	287,951	57.9	100.0	209,411	42.1	100.0	497,362

Note: % by age groups was calculated using total population of each specific age group (e.g. for OA <35 years, the percentage was calculated using the number of females with OA as the numerator and the total number of people with OA as the denominator (13,975 + 13,638= 27,613). % female <35 years was calculated using the number of females in the age group < 35 years as the numerator (13,975) and the number of females with OA as the denominator (287,951).

Comorbidity Patterns by Sex

A similar pattern was observed regarding the number of comorbidities (with most people with OA having one comorbidity) and the ordering of the frequency of each of the comorbidities among females and males based on age-standardized prevalence rates (Table 2). Statistically significant differences among females and males were observed by the number of comorbidities, with females having higher age-standardized rates overall (SRR = 1.26, 95% CI: 1.25-1.28). The number of comorbidities was also higher for females compared to males with SRR ranging from 1.15 (95% CI: 1.11-1.18) for three or more comorbidities to 1.48 (95% CI: 1.44-1.52) for two comorbidities (Table 2).

Table 2 Frequency, percentage and age-standardized rate of comorbidities in people with OA

Comorbidity	n	% of OA cohort	% of the OA cohort with one or more	Age standardized Rate (per 1,000 population)		
				Female (95% CI)	Male (95% CI)	SRR (95% CI)

				of the eight comorbidities			
Comorbid Conditions	Hypertension	144,453	29.0	53.1	162.2 (160.9-163.5)	146.5 (145.1-148.0)	1.11 (1.09-1.12)
	Depression	99,103	19.9	36.5	264.1 (260.9-267.3)	152.6 (149.8-155.4)	1.73 (1.69-1.77)
	Chronic obstructive pulmonary disease	92,273	18.6	33.9	195.9 (193.0-198.8)	153.6 (150.9-156.3)	1.28 (1.25-1.30)
	Diabetes	47,102	9.5	17.3	53.1 (52.0-54.2)	59.4 (58.4-60.4)	0.89 (0.87-0.92)
	Congestive heart failure	27,905	5.6	10.3	24.4 (23.9-24.9)	25.4 (24.9-26.0)	0.96 (0.93-0.99)
	Peripheral vascular disease	15,044	3.0	5.5	12.6 (12.1-13.0)	17.8 (17.2-18.3)	0.71 (0.67-0.74)
	Myocardial infarction	4,969	1.0	1.8	4.3 (4.1-4.5)	4.7 (4.4-5.0)	0.91 (0.84-0.98)
	Cerebrovascular disease	5,974	1.2	2.2	4.0 (3.8-4.2)	7.9 (7.6-8.2)	0.51 (0.48-0.54)
Number of Comorbidities	One Comorbidity	161,315	32.4	59.4	329.1 (325.7-332.4)	271.5 (268.2-274.8)	1.21 (1.19-1.23)
	Two Comorbidities	72,567	14.6	26.7	124.9 (122.8-127.1)	84.6 (82.9-86.2)	1.48 (1.44-1.52)
	Three or more Comorbidities	37,912	7.6	13.9	42.3 (41.4-43.2)	36.9 (36.2-37.7)	1.15 (1.11-1.18)
OA with Comorbidities		271,794	54.6		496.3 (492.8-499.8)	392.9 (389.4-396.4)	1.26 (1.25-1.28)
None of the 8 Comorbidities		225,568	45.4		503.7 (500.17-507.22)	607.1 (603.56-610.56)	0.83 (0.82-0.84)

Note: % of OA cohort was calculated using OA population (271,794 + 225,568 = 497,362) as denominator and the population of each comorbidity as numerator. % of the OA cohort with one or more of the eight comorbidities was calculated using population with at least one comorbidity (n= 271,794) as denominator. CI denotes Confidential Interval. SRR denotes Standardized Rate Ratio between females and males (females/males). The eight comorbidities are those with validated case definitions for administrative health data.

Depression, COPD and hypertension remained as the three most prevalent comorbidities in both females and males after age-standardization. However, the prevalence of each of these comorbidities was higher in females compared to males (Table 2Females had significantly higher prevalence rates than males for depression (SRR 1.73, 95% CI: 1.69-1.77), COPD (SRR 1.28, 95% CI: 1.25-1.30) and hypertension (SRR 1.11, 95% CI: 1.09-1.12), respectively.

The prevalence of each of these three comorbidities differed significantly in females. For example the age-standardized prevalence of depression in females was 264 cases per 1,000 population, 35% higher and statistically higher than for COPD (196 cases per 1,000 population) (SRR 1.35, 95% CI 1.32-1.37). In contrast, the prevalence of these three comorbidities among males were not significantly different.

Common groupings of comorbidities in people with OA

As shown in Table 3, of the eight comorbidities in people with OA, the most frequent comorbidity was hypertension as a single comorbidity, found in 12.8% of people with OA (n=63,520). The most common grouping of two comorbidities was the coexistence of

hypertension and depression (2.9%, n=14,609). The most common grouping with three comorbidities was depression, COPD and hypertension, (1.1%, n=5,262). People with OA having any combination of the top three comorbidities accounted for approximately 40% of people with OA.

Table 3 Frequency of top 10 common groupings of comorbidities

Combinations of comorbidity	n	% of OA cohort)	% of OA with comorbidities
Hypertension only	63,520	12.8	23.4
Depression only	46,226	9.3	17.0
Chronic Obstructive Pulmonary Disease only	34,464	6.9	12.7
Hypertension, Depression	14,609	2.9	5.4
Hypertension, Chronic Obstructive Pulmonary Disease	13,653	2.7	5.0
Depression, Chronic Obstructive Pulmonary Disease	13,584	2.7	5.0
Hypertension, Diabetes	11,784	2.4	4.3
Diabetes	11,054	2.2	4.1
Hypertension, Depression, Chronic Obstructive Pulmonary Disease	5,262	1.1	1.9
Hypertension, Congestive Heart Failure	3,946	0.8	1.5

Note: % of OA cohort was calculated using OA population (271,794 + 225,568 = 497,362) as denominator and the population of each comorbidity as numerator. % of OA with comorbidities was calculated using population with at least one comorbidity at the diagnosis of OA (n= 271,794) as denominator.

Comorbidity patterns by age group

As shown in Figure 1, each of the eight comorbidities, with the exception of depression, was most common in people with OA over 65 years old. Hypertension was found in 44.3% of people with OA over 65 years of age (n=91,153 cases) compared to 5.3% (n=4,040 cases) in those <44 years old. The largest number of people with OA and depression were in the 45-64 years age cohort (n=47,061 cases), with the youngest age group (<44 years) having the highest percentage of cases with depression (24.6% compared to 21.9% in the middle age group (45-64 years) and 16.1% in the older age group (>=65 years). The difference in the percentage of each of the eight comorbidities among the three age groups was statistically significant (p<0.0001). The detailed age-sex stratified crude rates per 1,000 population is provided in Appendix 2.

The number of comorbidities in people with OA increased with increasing age. The percentage of people with three or more comorbidities increased significantly from 1.5% in youngest age group (<44 years), to 4.7% in the middle age group (45-64 years), and to 13% in the older age group (>=65 years) (p<0.0001).

4. Discussion

We estimated the prevalence of comorbid conditions in people with OA using provincial administrative health data. Using validated case and comorbidity definitions, we found that 54.6% of people with OA had at least one of the eight comorbidities, and 22.2% had at least two. Depression, COPD and hypertension were the three most prevalent comorbidities in both females and males after age-standardization. However, the prevalence of each of these comorbidities was significantly higher in females compared to males. People with any combination of these three comorbidities represented about 40% of the people with OA. In general, the number of comorbidities in people with OA increased with increasing age. Each of the eight comorbidities, except depression, was most common in people with OA >= 65 years. The largest number of people with OA and depression are in the middle age group (45-64 years), with the youngest age group (<44 years) having the highest percentage of cases with depression.

The estimated prevalence of comorbidities varies among studies due to differences in case definitions, the list of included chronic conditions, data sources and study population. We estimated that the prevalence of comorbidity among people with OA was 54.6% for one or more of the eight comorbid chronic conditions and 22.2% for two or more comorbid chronic conditions with OA. Our estimates of the prevalence of comorbidities in people with OA are higher than the prevalence of two or more and three or more chronic conditions among the general Canadian population (26.5% and 10.2%, respectively) as reported by Feely et al.(2017) [27], and higher than the prevalence of 12.9% (two or more chronic diseases) and 3.9% (three or more chronic diseases) reported by Roberts et al. (2015)[28]. In our study, among 205,978 OA cases in the age group over 65 years old, the prevalence of one or more comorbid chronic conditions was 33.2% (n=68,418) and the prevalence of two or more comorbid chronic conditions with OA was 19.0% (n=39,044). The estimated prevalence of comorbid chronic conditions in people with OA is higher than the estimates reported by Roberts et al. (2015), which showed that the prevalence of two or more chronic diseases in the general population over 65 years old was 31.3% and the prevalence of three or more chronic diseases was 11.3%. It has been reported previously that the prevalence of one or more comorbid condition among people with musculoskeletal conditions was more than twice than those without a musculoskeletal condition but with another chronic condition[29].

We identified depression, COPD and hypertension as frequent comorbid conditions among the people with OA. This was consistent with findings reported from the Canadian Primary Care Sentinel Surveillance Network showing that the prevalence of osteoarthritis has significant association with depression, COPD and hypertension[2]. Depression is emerging as a significant comorbidity in OA. Previous findings have reported that depression was highly prevalent in people with OA[10, 30]. A systemic review of depressive symptoms in people with OA , including 49 studies worldwide and representing 15,855 individuals, reported a frequency of depression of 19.9% among people with OA[31], which was similar to our estimates.

Depressed individuals are more likely to report chronic or more severe pain, and more than half of the patients with chronic pain are depressed. People living with OA are known to have fewer social contacts, limited physical activity, increased pain and disability [32,33], worse surgical outcomes and reduced effectiveness of pain interventions [34], which are all important predictors of depression [35]. However, current clinical practice guidelines for non-surgical management of OA do not include recommendations regarding mental health management [36–39]. This emphasizes the need for treatments and management for depression to improve outcomes for people with OA[40]. It has been suggested that educating physicians about timely identification of psychological factors may be helpful to improve outcomes. In addition, self-care management could be integrated into OA management strategies as a way to reduce anxiety and depression, as well as resulting emotional and physical pain. Guidelines suggest that OA management should also integrate pharmacotherapy carefully and be cautious about the drug interactions and adverse side effects when treating OA, depression, anxiety and pain holistically[30]. Two or more of the comorbidities that we examined coexist in a substantial proportion of people with OA – approximately 22% in total. Obesity, which we were unable to study using administrative data is also prevalent amongst people with OA and a risk factor for developing OA[41,42]. From a clinical practice perspective, a physician has to consider the implications of prescribing non-steroidal anti-inflammatory medications for pain management, but this may worsen hypertension and have an associated increased risk of cardiovascular disease. However, without good pain management, it is difficult for patients with OA to engage in exercise programs which can help improve their muscular condition and potentially reduce obesity and hypertension. This is further complicated by the relationship of lower socioeconomic status with an increased risk of developing OA as demonstrated in the project for an Ontario Women's Health Evidence-based Report[29].

Furthermore, our analyses showed that depression not only was the most prevalent comorbidity after age-standardization in people with OA, but that rates of depression were significantly higher for females and younger people (< 44 years old). The study by Dibonaventura et al. (2011) reported that people under 65 years of age were still participating in the workforce, however OA pain resulted in significantly lower productivity and higher costs compared to those without OA pain[8]. They identified unique treatment gaps for patients younger than 60 years old because the non-operative treatment options were ineffective in long-term management of OA symptoms, but young patients were too young or maybe unwilling to undergo definitive treatment such as total joint replacement[43]. Even for those patients who undergo total joint replacement, they were more likely to be dissatisfied about the treatment than older patients, and reported poorer outcomes including residual pain and stiffness [44,45]. A survey of orthopedic surgeons found that 84% perceived a need for better treatment for younger (<60 years old) physically active OA patients, and 68.4% perceived that there is a treatment gap for these patients[43]. Due to the different presentations of comorbidities and treatment options among young and old age groups, it is imperative to examine the impact of comorbidities on management strategies in an age-stratified OA cohort.

Most clinical practice guidelines focus on single conditions[46]. Fortin et al. (2011) concluded that even though the quality of the Canadian guidelines was good, their relevance for patients with two or more chronic conditions was limited[47]. Boyd et al. (2005) highlighted the lack of consideration of comorbidities in clinical practice guidelines may result in poor quality of care because the health care some patients received was not optimal[48]. Sharma et al., (2016) pointed out that the present literature fails to fully address the management strategies when dealing with comorbidities seen in people with OA[30]. Patient-centered care has been recommended in clinical practice guidelines with the aim of improving quality of care by focusing on the patient as a whole rather than on a single disease[49]. From a system perspective, patients with several comorbidities were also the main users of healthcare resources and services[50]. Patient-centered and coordinated care for these patients may decrease related health care use[51]. It was recommended that physicians consider these comorbidities in the management of people with OA.

A strength of our study is the large population-based number of people with OA (n=497,362) and the investigation of a group of eight comorbidities that are clinically relevant to the management of people with OA. These eight comorbidities among people

with OA has been reported in previous studies, but only on an individual basis or in groups of a subset of these comorbidities. Our study is the first one to include all of these comorbidities, which is necessary to understand the clinical context for managing these patients. Furthermore, our analysis also delineates the patterns of occurrence and co-occurrence of these comorbidities regarding the prevalence of comorbidities that is relevant for planning and delivery of health services for this growing population of people with OA. We applied case definitions for administrative health data to identify cases of OA and each of the comorbidities at the diagnosis of OA. A limitation of our study is that case identification based on administrative data may result in underreporting of cases and comorbidities. The case definitions for OA in administrative data research [5], based on the physician claims and hospitalizations records, have been applied and validated with a sensitivity of 24%, high specificity of 98% and a positive predictive value of 54%[11]. In our study, we also included ACCS/NACRS to mitigate the issue of underestimations[6]. Nonetheless, the estimated number of OA cases using this approach is almost certainly an underestimate. Similarly, the algorithms for comorbidities may underestimate the prevalence of these comorbidities; the sensitivity for identifying depression is from 36% to 51% [19], for PVD is 39%[18] and for COPD is 53% [21] in administrative data (Appendix 2). More importantly, the reported levels of comorbidity in patients with OA were measured at the time of OA diagnosis. New cases of comorbidity diagnosed after the OA diagnosis were not identified. Further, we limited our analysis to eight comorbidities of clinical relevance and for which there were case definitions in administrative data.

5. Conclusions

We found that, depression, COPD and hypertension were the three most prevalent comorbidities in people with OA, with rates significantly higher in females compared to males. Of particular note is that the largest number of people with OA and depression are in the age group between 45 and 64 years old, with the highest percentage of cases occurring in the younger age groups (<44 years). Our findings highlight the need to recognize that people with OA have high rates of comorbidities and this may affect optimal health care management of these patients.

Acknowledgements

The authors would like to acknowledge the following team members and their contributions to the study: Behnam Sharif.

Contributions

DM, PF, KY were responsible for the conception and design of the research, acquisition of the data, analysis and interpretation of data, drafting the article, and revision of the article for important intellectual content.

XL was responsible for the analysis and interpretation of data, drafting the article, and revision of the article for important intellectual content.

CB, CB, DM, TN, JW and LL were responsible for the conception and design of the research, interpreting results of the research and revision of the article for important intellectual content.

All authors approved the final version of the manuscript to be submitted.

DM (damarsha@ucalgary.ca) and XL (xiaoxili@ucalgary.ca) take responsibility for the integrity of the work as a whole.

Role of the funding source

This research was funded through a Canadian Institute for Health Research (CIHR) Operating Grant (Grant #: 126128) and the Arthur J.E. Child Chair in Rheumatology Research. There were no study sponsors and the funding agencies had no involvement in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

DM was supported by a Canada Research Chair and the Arthur J.E. Child Chair in Rheumatology Research. XL was supported by the Arthur J.E. Child Chair in Rheumatology Research, the Cumming School of Medicine Postdoctoral Scholarship and the Postdoctoral Scholarship funded by the O'Brien Institute of Public Health and the McCaig Institute for Bone and Joint Health.

Data availability

These data are not available because Alberta Health and Alberta Health Services are the custodians of the data. The authors are not authorized to share them.

Competing interests

The authors confirm that there is no financial support or other benefits from commercial sources for the work reported on in the manuscript. There are also no financial

interests that the authors may have which could create a potential conflict of interest with regards to the work in the manuscript.

Figure 1 Percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The difference by age group was statistically significant for each comorbid conditions ($p<0.0001$), as was the frequency of the number of comorbidities present per individual ($p<0.0001$).

References

1. Leite AA, Costa AJG, Lima B de AM de, Padilha AVL, Albuquerque EC de, Marques CDL. Comorbidities in patients with osteoarthritis: frequency and impact on pain and physical function. *Rev Bras Reumatol*. 2011;51(2):118-123. doi:10.1590/S0482-50042011000200002
2. Birtwhistle R, Morkem R, Peat G, et al. Prevalence and management of osteoarthritis in primary care: an epidemiologic cohort study from the Canadian Primary Care Sentinel Surveillance Network. *C open*. 2015;3(3):E270-5. doi:10.9778/cmajo.20150018
3. Bombardier C, Hawker G, Mosher D. *The Impact of Arthritis in Canada: Today and over the next 30 Years.*; 2011.
4. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. *Ann Rheum Dis*. 2004;63(4):408-414. doi:10.1136/ARD.2003.007526
5. Kopec JA, Rahman MM, Berthelot J-M, et al. Descriptive epidemiology of osteoarthritis in British Columbia, Canada. *J Rheumatol*. 2007;34(2):386-393.
6. Marshall DA, Vanderby S, Barnabe C, et al. Estimating the Burden of Osteoarthritis to Plan for the Future. *Arthritis Care Res*. 2015;67(10):1379-1386. doi:10.1002/acr.22612
7. Tarride J-E, Haq M, O'Reilly DJ, et al. The excess burden of osteoarthritis in the province of Ontario, Canada. *Arthritis Rheum*. 2012;64(4):1153-1161. doi:10.1002/art.33467
8. Dibonaventura M dacosta, Gupta S, McDonald M, Sadosky A. Evaluating the health and economic impact of osteoarthritis pain in the workforce: results from the National Health and Wellness Survey. *BMC Musculoskelet Disord*. 2011;12:83. doi:10.1186/1471-2474-12-83
9. Rosemann T, Joos S, Szecsenyi J, Laux G, Wensing M. Health service utilization patterns of primary care patients with osteoarthritis. *BMC Health Serv Res*. 2007;7(1):169. doi:10.1186/1472-6963-7-169
10. Kim KW, Han JW, Cho HJ, et al. Association Between Comorbid Depression and Osteoarthritis Symptom Severity in Patients with Knee Osteoarthritis. *J Bone Jt Surgery-American Vol*. 2011;93(6):556-563. doi:10.2106/JBJS.I.01344
11. Lix L, Yogendran M, Mann J. *Defining and Validating Chronic Diseases: An Administrative Data Approach and Update with ICD-10-CA.*; 2008.
12. Kopec JA, Rahman MM, Sayre EC, et al. Trends in physician-diagnosed osteoarthritis incidence in an administrative database in British Columbia, Canada, 1996–1997 through 2003–2004. *Arthritis Rheum*. 2008;59(7):929-934. doi:10.1002/art.23827
13. Pham MT, Rajić A, Greig JD, Sargeant JM, Papadopoulos A, McEwen SA. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. *Res Synth Methods*. 2014;5(4):371-385. doi:10.1002/jrsm.1123
14. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Myocardial Infarction Diagnoses in Administrative Databases: A Systematic Review. Guo Y, ed. *PLoS One*. 2014;9(3):e92286. doi:10.1371/journal.pone.0092286
15. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. *Hypertension*. 2009;54(6):1423-1428. doi:10.1161/HYPERTENSIONAHA.109.139279
16. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. *PLoS One*. 2015;10(8):e0135834.

doi:10.1371/journal.pone.0135834

17. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e104519. doi:10.1371/journal.pone.0104519

18. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *J Am Med Inform Assoc*. 2013;20(e2):e349-54. doi:10.1136/amiajnl-2013-001827

19. Townsend L, Walkup JT, Crystal S, Olfson M. A systematic review of validated methods for identifying depression using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21:163-173. doi:10.1002/pds.2310

20. Leong A, Dasgupta K, Bernatsky S, Lacaille D, Avina-Zubieta A, Rahme E. Systematic Review and Meta-Analysis of Validation Studies on a Diabetes Case Definition from Health Administrative Records. Barengo NC, ed. *PLoS One*. 2013;8(10):e75256. doi:10.1371/journal.pone.0075256

21. Smidth M, Sokolowski I, Kærsvang L, Vedsted P. Developing an algorithm to identify people with Chronic Obstructive Pulmonary Disease (COPD) using administrative data. *BMC Med Inform Decis Mak*. 2012;12(1):38. doi:10.1186/1472-6947-12-38

22. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res Clin Pract*. 2010;89(2):189-195. doi:10.1016/j.diabres.2010.03.007

23. Quan H, Sundararajan V, Halfon P, et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative. *Med Care*. 2005;43(11):1130-1139.

24. Boyle P, Parkin D. Statistical methods for registries. *Cancer Regist Princ Methods*. 1991:126-158.

25. Statistics Canada. Alberta [Province] and Canada [Country] (table). Census Profile. 2016 Census. doi:98-316-X2016001

26. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ*. 1995;310(6973):170. doi:10.1136/bmj.310.6973.170

27. Feely A, Lix LM, Reimer K. Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System. *Heal Promot chronic Dis Prev Canada Res policy Pract*. 2017;37(7):215-222. doi:10.24095/hpcdp.37.7.02

28. Roberts KC, Rao DP, Bennett TL, Loukine L, Jayaraman GC. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. *Heal Promot chronic Dis Prev Canada Res policy Pract*. 2015;35(6):87-94.

29. Hawker GA, Badley EM, Jaglal S, et al. Musculoskeletal Condtitions. In: *Project for an Ontario Women's Health Evidence-Based Report: Volume 2: Toronto*. ; 2010.

30. Sharma A, Kudesia P, Shi Q, Gandhi R. Anxiety and depression in patients with osteoarthritis: impact and management challenges. *Open access Rheumatol Res Rev*. 2016;8:103-113. doi:10.2147/OARRR.S93516

31. Stubbs B, Aluko Y, Myint PK, Smith TO. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. *Age Ageing*. 2016;45(2):228-235. doi:10.1093/ageing/afw001

32. Sale JEM, Gignac M, Hawker G. The relationship between disease symptoms, life events, coping and treatment, and depression among older adults with osteoarthritis. *J Rheumatol*. 2008;35(2):335-342.

33. Hawker GA, Gignac MAM, Badley E, et al. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res (Hoboken)*. 2011;63(10):1382-1390.

doi:10.1002/acr.20298

34. Gleicher Y, Croxford R, Hochman J, Hawker G. A prospective study of mental health care for comorbid depressed mood in older adults with painful osteoarthritis. *BMC Psychiatry*. 2011;11(1):147. doi:10.1186/1471-244X-11-147

35. Rosemann T, Backenstrass M, Joest K, Rosemann A, Szecsenyi J, Laux G. Predictors of depression in a sample of 1,021 primary care patients with osteoarthritis. *Arthritis Rheum*. 2007;57(3):415-422. doi:10.1002/art.22624

36. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthr Cartil*. 2007;15(9):981-1000. doi:10.1016/j.joca.2007.06.014

37. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthr Cartil*. 2008;16(2):137-162. doi:10.1016/j.joca.2007.12.013

38. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: Part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthr Cartil*. 2010;18(4):476-499. doi:10.1016/J.JOCA.2010.01.013

39. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartil*. 2014;22(3):363-388. doi:10.1016/j.joca.2014.01.003

40. Lin EHB, Katon W, Von Korff M, et al. Effect of Improving Depression Care on Pain and Functional Outcomes Among Older Adults With Arthritis. *JAMA*. 2003;290(18):2428. doi:10.1001/jama.290.18.2428

41. Felson DT. Weight and osteoarthritis. *J Rheumatol Suppl*. 1995;43:7-9.

42. ANDERSON JJ, FELSON DT. FACTORS ASSOCIATED WITH OSTEOARTHRITIS OF THE KNEE IN THE FIRST NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (HANES I). *Am J Epidemiol*. 1988;128(1):179-189. doi:10.1093/oxfordjournals.aje.a114939

43. Li CS, Karlsson J, Winemaker M, Sancheti P, Bhandari M. Orthopedic surgeons feel that there is a treatment gap in management of early OA: international survey. *Knee Surgery, Sport Traumatol Arthrosc*. 2014;22(2):363-378. doi:10.1007/s00167-013-2529-5

44. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KDJ. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res*. 2010;468(1):57-63. doi:10.1007/s11999-009-1119-9

45. Parvizi J, Nunley RM, Berend KR, et al. High level of residual symptoms in young patients after total knee arthroplasty. *Clin Orthop Relat Res*. 2014;472(1):133-137. doi:10.1007/s11999-013-3229-7

46. Hughes LD, Mcmurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *J Heal Soc Behav J Public Heal Med J Epidemiol Community Heal Ann Epidemiol Am J Epidemiol Age Ageing*. 2013;36(42):1-10. doi:10.1093/ageing/afs100

47. Fortin M, Contant E, Savard C, Hudon C, Poitras M-E, Almirall J. Canadian guidelines for clinical practice: an analysis of their quality and relevance to the care of adults with comorbidity. *BMC Fam Pract*. 2011;12(1):74. doi:10.1186/1471-2296-12-74

48. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases. *JAMA*. 2005;294(6):716.

doi:10.1001/jama.294.6.716

49. Dawes M. Co-morbidity: we need a guideline for each patient not a guideline for each disease. *Fam Pract*. 2010;27:1-2. doi:10.1093/fampra/cmp106

50. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *Ann Fam Med*. 2012;10(2):134-141. doi:10.1370/afm.1363

51. Wolff JL, Starfield B, Anderson G. Prevalence, Expenditures, and Complications of Multiple Chronic Conditions in the Elderly. *Arch Intern Med*. 2002;162(20):2269. doi:10.1001/archinte.162.20.2269

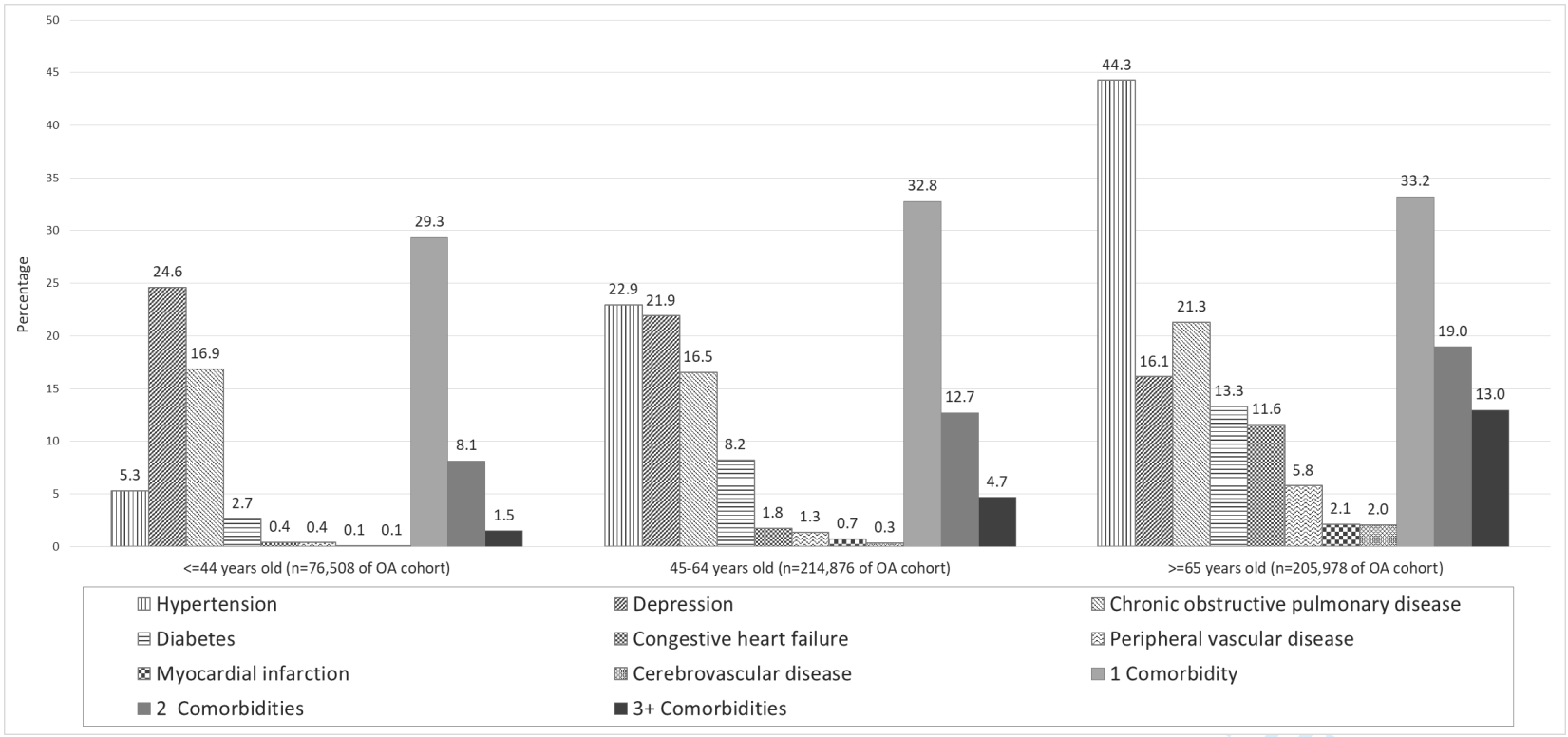

Figure 1 Percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The difference by age group was statistically significant for each comorbid conditions (p<0.0001), as was the frequency of the number of comorbidities present per individual (p<0.0001).

1 Appendix 1 Case definitions for eight comorbid conditions

	ICD9-CM Diagnosis Codes Included	ICD10-CA Diagnosis Codes Included	Exclusions	Algorithm	References
Myocardial Infarction	410	I21, I22	N/A	1 hospitalization for MI, with diagnoses codes in primary or secondary diagnosis fields.	McCormick et al., 2014[13] Quan et al., 2005[22]
Cerebrovascular Disease	3623,43301,43311,43321,43331,43381,43391,43401,43411,43491,436,430,431,435	H341, I63, I64, I61, I60, G450, G451, G452, G453, G458, G459	43300, 43310, 43320, 43330, 43380, 43390, 43400, 43410, 43490, 437, 438, I65, I66, I67, I69, G45.4	1 hospital discharge (most responsible diagnosis) for different stroke conditions	Kokotailo & Hill, 2005 McCormick et al., 2015[15]
Congestive Heart Failure	39891,40201,40211,40291,40401,40403,40411,40413,40491,40493,4254,4255,4257,4258,4259,428	I43,I50,I099,I110,I130,I132,I255,I420,I425,I426,I427,I428,I429,P290		1 hospitalization or physician claim in diagnosis field	Schultz et al., 2013 McCormick et al., 2014[16] Quan et al., 2005[22] Lee et al., 2005
Peripheral Vascular Disease	0930,4373,440,441,4431,4432,4438,4439,4471,5571,5579,V434,443	I70,I71,I731,I738,I739,I771,I790,I792,K551,K558,K559,Z958,Z959	N/A	1 hospitalization or physician claim in diagnosis field	Fan et al., 2013[17]
Chronic Obstructive Pulmonary Disease	4168,4169,490,491,492,493,494,495,496,500,501,502,503,504,505,5064,5081,5088	J40,J41,J42,J43,J44,J45,J46,J47,J60,J61,J62,J63,J64,J65,J66,J67,I278,I279,J684,J701,J703	N/A	1 hospitalization or physician claim in diagnosis field	Smidth et al. 2012[20] Quan et al., 2005[22]
Depression	2962,2963,2965,3004,309,311	F204,F313,F314,F315,F32,F33,F341,F412,F432	N/A	1 hospitalization or physician claim in diagnosis field	Townsend et al., 2012[18] Lix et al., 2006 Martens et al., 2010

Diabetes	250	E10, E11, E12, E13, E14	Physician claims with procedure code having a prefix of "X" (radiology/xray), "E" (labs) or "B" (dentist, ophthalmologist, chiropractic visits)	1 hospitalization for diabetes OR 2 physician claims in a 2-year period	Chen et al., 2010[21] Leong et al., 2013[19] Hux et al., 2002
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15	Physician claims with procedure code having a prefix of "X" (radiology/xray), "E" (labs) or "B" (dentist, ophthalmologist, chiropractic visits)	1 hospitalization for hypertension OR 2 physician claims in a 2-year period	Quan et al., 2009[14]

2

Appendix 2: Age-sex stratified crude rates (per 1,000 population) of comorbidities among people with OA

Age Groups	OA with Hypertension (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	2,068	1,972	39,591	36,917	52	53
45-64	28,046	21,214	123,102	91,774	228	231
>=65	57,453	33,700	125,258	80,720	459	417
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with Depression (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	12,366	6,464	39,591	36,917	312	175
45-64	32,951	14,110	123,102	91,774	268	154
>=65	23,045	10,167	125,258	80,720	184	126
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with COPD (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	7,984	4,914	39,591	36,917	202	133
45-64	22,124	13,424	123,102	91,774	180	146
>=65	24,626	19,201	125,258	80,720	197	238
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with 1 comorbidity (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	13,016	9,437	39,591	36,917	329	256
45-64	42,477	27,967	123,102	91,774	345	305
>=65	42,593	25,825	125,258	80,720	340	320
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with 2 comorbidities (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	4,268	1,956	39,591	36,917	108	53

45-64	16,975	10,324	123,102	91,774	138	112
>=65	23,879	15,165	125,258	80,720	191	188
Total	87,567	56,886	287,951	209,411	304	272

Age Groups	OA with 3+ comorbidities (counts)		OA population (counts)		Age-Sex Crude Rates (per 1,000 population)	
	Female	Male	Female	Male	Female	Male
<45	757	379	39,591	36,917	19	10
45-64	5,970	4,099	123,102	91,774	48	45
>=65	15,467	11,240	125,258	80,720	123	139
Total	87,567	56,886	287,951	209,411	304	272

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4
Objectives	3	State specific objectives, including any prespecified hypotheses	P4
Methods			
Study design	4	Present key elements of study design early in the paper	P5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*P5-7*
Bias	9	Describe any efforts to address potential sources of bias	P5
Study size	10	Explain how the study size was arrived at	P6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7
		(*b*) Describe any methods used to examine subgroups and interactions	P7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	The sensitivity analysis using alterative OA case definitions has been conducted previously. Please refer to Marshall et. al. (2015).
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	P7-8

		eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	P8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P8-9
		(*b*) Report category boundaries when continuous variables were categorized	P7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	The sensitivity analysis using alterative OA case definitions has been conducted previously. Please refer to Marshall et. al. (2015).
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.