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# BMJ Open

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

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3 **1 Title: Comorbidities in people with osteoarthritis (OA): a retrospective analysis of a**  
4 **2 population-based cohort**  
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3 31 **Abstract**  
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5 32 **Objectives:** The purpose of this study is to estimate the prevalence of comorbidities among people  
6 33 with osteoarthritis (OA) using administrative health data.

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8 34 **Design:** Retrospective cohort analysis  
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10 35 **Setting:** All residents in the province of Alberta Canada registered with the Alberta Health Care  
11 36 Insurance Plan (AHCIP) population registry.

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13 37 **Participants:** 497,362 people with OA as defined by “having at least one OA-related hospitalization,  
14 38 or at least two OA-related physician visits or two ambulatory care visits within two years”.

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16 39 **Primary outcome measures:** We selected eight comorbidities based on literature review, clinical  
17 40 consultation and the availability of validated case definitions to estimate their frequencies. Sex-  
18 41 stratified age-standardized prevalence rates per 1,000 population of eight clinically relevant  
19 42 comorbidities were calculated using direct standardization with 95% confidence intervals (CIs). We  
20 43 applied  $\chi^2$  tests of independence with a Bonferroni correction to compare the percentage of  
21 44 comorbid conditions in each age group.

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23  
24 45 **Results:** 54.6% (n=271,794) of people meeting the OA case definition had at least one of the eight  
25 46 selected comorbidities. Females had a significantly higher rate of comorbidities compared to males  
26 47 (standardized rates ratio = 1.26, 95% CI: 1.25-1.28). Depression, chronic obstructive pulmonary  
27 48 disease (COPD) and hypertension were the most prevalent in both females and males after age-  
28 49 standardization, with 40% of all cases having any combination of these comorbidities. We observed  
29 50 a significant difference in the percentage of comorbidities among age groups, illustrated by the  
30 51 youngest age group (<45 years) having the highest percentage of cases with depression (24.6%),  
31 52 compared to a frequency of 16.1% in those >65 years.

32  
33 53 **Conclusions:** Our findings highlight the high frequency of comorbidity in people with OA, with  
34 54 depression having the highest age-standardized prevalence rate. Comorbidities differentially affect  
35 55 females, and vary by age. These factors should inform health care programs and delivery.

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37 56  
38 57 **Keywords:** Osteoarthritis; comorbidity; depression; hypertension; COPD; administrative health  
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3 61 Strengths and limitations of this study  
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- 5 62 • Strong methodological approach to identify cases of OA with a validated case  
6 63 definition using five linked population-based administrative databases.  
7 64 • However, case identification based on administrative data may result in  
8 65 underreporting of cases and comorbidities.  
9 66 • The age-standardized prevalence of eight comorbidities, selected on their clinical  
10 67 relevance and the availability of validated case definitions for administrative health  
11 68 data, was estimated among people with OA.  
12 69 • We limited our analysis to eight comorbidities of clinical relevance.  
13 70 • We stratified the analysis by sex and by age cohorts  
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## 71 **1. Introduction**

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

83 More recently, the characterization of comorbidities among people with OA has been  
84 explored due to the potential effect of comorbidities on routine clinical practice, clinical  
85 practice guidelines, healthcare utilization and costs<sup>9-10</sup>. In people with OA over the age of  
86 50 years in England, the presence of comorbidities resulted in increased physical disability  
87 compared to those without OA, with the influence of comorbidities greater than that  
88 expected for OA alone or for each comorbidity in isolation<sup>4</sup>. Knowledge of the prevalence  
89 of comorbidities in people with OA raises important considerations for optimal OA  
90 treatment and management, to reduce pain and physical disability, enhance the quality of  
91 life, and decrease the burden of OA. Comorbidities add complexity to the management of  
92 patients with OA to provide patient-centred care, ensure appropriate management  
93 recommendations for health care programs and delivery.

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

## 98 **2. Materials and Methods**

### 99 *Data sources*

100 We used five linked Alberta, Canada provincial administrative databases between April  
101 1, 1994 and March 31, 2013 to identify individuals with OA who accessed health care  
102 services paid for by the provincial health care insurance plan, previously described

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3 103 elsewhere in detail<sup>6</sup>. These databases included the Alberta Health Care Insurance Plan  
4 104 (AHCIP) population registry, the Discharge Abstract Database (DAD), the Physician  
5 105 Claims Database (claims), the Ambulatory Care Classification System (ACCS), and the  
6 106 National Ambulatory Care Reporting System (NACRS).  
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10 107 AHCIP Population Registry captures individual level demographic data on all insured  
11 108 persons as of the last day of each fiscal year (March 31). All Albertans who are included in  
12 109 the AHCIP have a unique, 9-digit personal health number, which is used when accessing  
13 110 health care services, and served to link datasets prior to de-identification. Members of the  
14 111 Armed Forces and the Royal Canadian Mounted Police, federal penitentiary inmates, and  
15 112 Albertans who have opted out of the AHCIP are excluded.  
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21 113 DAD captures admission and inpatient care data for all hospitalized patients, including  
22 114 diagnostic codes, interventions, patient age and sex, and administrative information.  
23 115 Among 25 DAD diagnostic code fields extracted from the hospital record, OA-related  
24 116 records were identified as those with the first 3 digits 715 or M15 to M19 based on the  
25 117 ninth (9) and tenth (10) revisions of the International Classification of Diseases (ICD)  
26 118 codes, respectively.  
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32 119 Claims captures OA-related physician visits, which were identified based on the  
33 120 aforementioned ICD codes in any of the 3 diagnostic code fields.  
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36 121 ACCS and NACRS contains data on hospital-based and community-based ambulatory  
37 122 care, including day surgery, outpatient and community-based clinics and emergency  
38 123 departments, and publicly funded hospital support services such as physiotherapy and  
39 124 occupational therapy. OA-related records were identified based on the presence of the  
40 125 aforementioned ICD codes in any of the 10 diagnostic code fields. NACRS was used since  
41 126 April 2010.  
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47 127 Ethics approval for this project was provided by the Conjoint Health Research Ethics  
48 128 Board at the University of Calgary (REB13-0100).  
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### 50 129 *Patient and public involvement*

51 130 No patients were involved in setting the research question, the design and conduct of  
52 131 the study. No patients were involved in the interpretation or writing up of results. There are  
53 132 no plans to disseminate the results of the research to study participants because this was  
54 133 admin health database analysis. We will make the publication available to the relevant  
55 134 patient community.  
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### 135 *Case Definition of Osteoarthritis (OA)*

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

### 145 *Case Definitions of Comorbidities*

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

### 162 *Age-standardized comorbidity prevalence rate*

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



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3 167 years). The crude rate was calculated as the number in each comorbidity group divided by  
4 168 the total number of OA cases. We calculated age-standardized comorbidity prevalence rates  
5 169 using the direct standardization method<sup>23</sup>. We used the 2016 Canadian population reported  
6 170 publicly by Statistics Canada<sup>24</sup> to age-standardize the estimates for females and males with  
7 171 95% confidence intervals (CIs) calculated using the binomial approximation method<sup>23</sup>. To  
8 172 compare differences between females and males, standardized rate ratios (SRR) were  
9 173 estimated as the female age-standardized rate divided by the male age-standardized rate.  
10 174 We calculated 95% confidence intervals for the SRR based on the standard error for each  
11 175 sex, to test for a sex difference<sup>23</sup>.

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19 176 We calculated the percentage of females and males in each age group and the  
20 177 percentage of OA cases for each age group by sex. The percentage of comorbidities among  
21 178 OA population was calculated as the number of cases with specific comorbidity divided by  
22 179 the OA population. The percentage of comorbidities among those with comorbidities was  
23 180 calculated using the population with one or more of the eight comorbidities as denominator.  
24 181 We also calculated the frequency of common groupings of these comorbidities in people  
25 182 with OA.

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32 183 We applied  $\chi^2$  tests of independence with a Bonferroni correction<sup>25</sup> to compare the  
33 184 percentage of specific comorbid conditions among the population with OA in each age  
34 185 group (<45, 45-64, and  $\geq$ 65 years). The null hypothesis is that there is no difference in the  
35 186 percentage of comorbidities across age groups, which is rejected when the calculated  $\chi^2$  is  
36 187 greater than the critical value for a specific number of degrees of freedom and an altered  
37 188 significance level of 0.005 after Bonferroni correction. All analyses were conducted with R  
38 189 version 3.5.1 and Excel 2013.

### 3. Results

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46 191 We identified 497,362 cases of OA, 57.9% of whom were females (Table 1). More  
47 192 than half of the OA cases had at least one of the eight comorbidities (54.6%, n=271,794)  
48 193 (Table 2). A total of 161,315 (32.4%) people with OA had one comorbidity, with 14.6%  
49 194 (n=72,567) having two, and 7.6% (n=37,912) having three or more of the comorbidities.  
50 195 Hypertension was the most frequent comorbidity (29%, n=144,453), followed by  
51 196 depression (19.9%, n=99,103), COPD (18.6%, n=92,273), diabetes (9.5%, n=47,102), and  
52 197 CHF (5.6%, n=27,905). PVD (3.0%), CEVD (1.2%) and MI (1.0%) were the least frequent  
53 198 comorbidities.  
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199 **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
	<b>Total</b>	<b>287,951</b>	<b>57.9</b>	<b>100.0</b>	<b>209,411</b>	<b>42.1</b>	<b>100.0</b>	<b>497,362</b>

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).

200 *Comorbidity Patterns by Sex*

201 A similar pattern was observed regarding the number of comorbidities (with most  
 202 people with OA having one comorbidity) and the ordering of the frequency of each of the  
 203 comorbidities among females and males based on age-standardized prevalence rates (Table  
 204 2). Statistically significant differences among females and males were observed by the  
 205 number of comorbidities, with females having higher rates overall (SRR = 1.26, 95% CI:  
 206 1.25-1.28). The number of comorbidities was also higher for females compared to males  
 207 with SRR ranging from 1.15 (95% CI: 1.11-1.18) for three or more comorbidities to 1.48  
 208 (95% CI: 1.44-1.52) for two comorbidities (Table 2).

209 **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)
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)
<b>Number of Comorbidities</b>	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)
<b>OA with Comorbidities</b>		271,794	54.6		496.3 (492.8-499.8)	392.9 (389.4-396.4)	1.26 (1.25-1.28)
<b>None of the 8 Comorbidities</b>		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.

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

216 The prevalence of each of these three comorbidities differed significantly in females.  
 217 For example the prevalence of depression in females was 264 cases per 1,000 population,  
 218 35% higher and statistically higher than for COPD (196 cases per 1,000 population) (SRR  
 219 1.35, 95% CI 1.32-1.37). In contrast, the prevalence of these three comorbidities among  
 220 males were not significantly different.

### 221 *Common groupings of comorbidities in people with OA*

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

229 **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.

### 230 *Comorbidity patterns by age group*

231 As shown in Figure 1, each of the eight comorbidities, with the exception of  
 232 depression, was most common in people with OA over 65 years old. Hypertension was  
 233 found in 44.3% of people with OA over 65 years of age (n=91,153 cases) compared to  
 234 5.3% (n=4,040 cases) in those <44 years old. The largest number of people with OA and  
 235 depression were in the 45-64 years age cohort (n=47,061 cases), with the youngest age  
 236 group (<44 years) having the highest percentage of cases with depression (24.6% compared  
 237 to 21.9% in the middle age group (45-64 years) and 16.1% in the older age group (>=65  
 238 years). The difference in the percentage of each of the eight comorbidities among the three  
 239 age groups was statistically significant (p<0.0001).

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

### 244 **4. Discussion**

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

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3 254 people with OA  $\geq$  65 years. The largest number of people with OA and depression are in  
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5 255 the middle age group (45-64 years), with the youngest age group (<44 years) having the  
6  
7 256 highest percentage of cases with depression.

8  
9 257 The estimated prevalence of comorbidities varies among studies due to differences in  
10  
11 258 case definitions, the list of included chronic conditions, data sources and study population.  
12  
13 259 Our estimates of the prevalence of comorbidities in people with OA are higher than the  
14  
15 260 prevalence of two or more and three or more chronic conditions among the general  
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17 261 Canadian population (26.5% and 10.2%, respectively) as reported by Feely et al.(2017)<sup>26</sup>,  
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19 262 and higher than the prevalence of 12.9% (two or more chronic diseases) and 3.9% (three or  
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21 263 more chronic diseases) reported by Roberts et al. (2015)<sup>27</sup>. It has been reported previously  
22  
23 264 that the prevalence of one or more comorbid condition among people with musculoskeletal  
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25 265 conditions was more than twice than those without a musculoskeletal condition but with  
26  
27 266 another chronic condition<sup>28</sup>.

28  
29 267 We identified depression, COPD and hypertension as frequent comorbid conditions  
30  
31 268 among the people with OA. This was consistent with findings reported from the Canadian  
32  
33 269 Primary Care Sentinel Surveillance Network showing that the prevalence of osteoarthritis  
34  
35 270 has significant association with depression, COPD and hypertension<sup>2</sup>. Depression is  
36  
37 271 emerging as a significant comorbidity in OA. Previous findings have reported that  
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39 272 depression was highly prevalent in people with OA<sup>10,29</sup>. A systemic review of depressive  
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41 273 symptoms in people with OA , including 49 studies worldwide and representing 15,855  
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43 274 individuals, reported a frequency of depression of 19.9% among people with OA<sup>30</sup>, which  
44  
45 275 was similar to our estimates.

46  
47 276 Depressed individuals are more likely to report chronic or more severe pain, and more  
48  
49 277 than half of the patients with chronic pain are depressed. People living with OA are known  
50  
51 278 to have fewer social contacts, limited physical activity, increased pain and disability<sup>31,32</sup>,  
52  
53 279 worse surgical outcomes and reduced effectiveness of pain interventions<sup>33</sup>, which are all  
54  
55 280 important predictors of depression<sup>34</sup>. However, current clinical practice guidelines for non-  
56  
57 281 surgical management of OA do not include recommendations regarding mental health  
58  
59 282 management<sup>35-38</sup>. This emphasizes the need for treatments and management for depression  
60  
283 to improve outcomes for people with OA<sup>39</sup>. It has been suggested that educating physicians  
284  
285 about timely identification of psychological factors may be helpful to improve outcomes. In  
286  
287 addition, self-care management could be integrated into OA management strategies as a  
288  
289 way to reduce anxiety and depression, as well as resulting emotional and physical pain.

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3 287 Guidelines suggest that OA management should also integrate pharmacotherapy carefully  
4  
5 288 and be cautious about the drug interactions and adverse side effects when treating OA,  
6  
7 289 depression, anxiety and pain holistically<sup>29</sup>. The clustering of hypertension and depression as  
8  
9 290 comorbidities associated with OA is not random. Obesity, which we were unable to study  
10  
11 291 using administrative data is also prevalent amongst people with OA and a risk factor for  
12  
13 292 developing OA <sup>40,41</sup>. From a clinical practice perspective, a physician has to consider the  
14  
15 293 implications of prescribing non-steroidal anti-inflammatory medications for pain  
16  
17 294 management, but this may worsen hypertension and have an associated increased risk of  
18  
19 295 cardiovascular disease. However, without good pain management, it is difficult for patients  
20  
21 296 with OA to engage in exercise programs which can help improve their muscular condition  
22  
23 297 and potentially reduce obesity and hypertension. This is further complicated by the  
24  
25 298 relationship of lower socioeconomic status with an increased risk of developing OA as  
26  
27 299 demonstrated in the project for an Ontario Women's Health Evidence-based Report <sup>28</sup>

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300 Furthermore, our analyses showed that depression not only was the most prevalent  
301  
302 comorbidity after age-standardization in people with OA, but that rates of depression were  
303  
304 significantly higher for females and younger people (< 44 years old). The study by  
305  
306 Dibonaventura et al. (2011) reported that people under 65 years of age were still  
307  
308 participating in the workforce, however OA pain resulted in significantly lower  
309  
310 productivity and higher costs compared to those without OA pain<sup>8</sup>. They identified unique  
311  
312 treatment gaps for patients younger than 60 years old because the non-operative treatment  
313  
314 options were ineffective in long-term management of OA symptoms, but young patients  
315  
316 were too young or maybe unwilling to undergo definitive treatment such as total joint  
317  
318 replacement<sup>42</sup>. Even for those patients who undergo total joint replacement, they were more  
319  
320 likely to be dissatisfied about the treatment than older patients, and reported poorer  
321  
322 outcomes including residual pain and stiffness <sup>43,44</sup>. A survey of orthopedic surgeons found  
323  
324 that 84% perceived a need for better treatment for younger (<60 years old) physically active  
325  
326 OA patients, and 68.4% perceived that there is a treatment gap for these patients<sup>42</sup>. Due to  
327  
328 the different presentations of comorbidities and treatment options among young and old age  
329  
330 groups, it is imperative to examine the impact of comorbidities on management strategies in  
331  
332 an age-stratified OA cohort.

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

1  
2  
3 320 highlighted the lack of consideration of comorbidities in clinical practice guidelines may  
4  
5 321 result in poor quality of care because the health care some patients received was not  
6  
7 322 optimal<sup>47</sup>. Sharma et al., (2016) pointed out that the present literature fails to fully address  
8  
9 323 the management strategies when dealing with comorbidities seen in people with OA<sup>29</sup>.  
10 324 Patient-centered care has been recommended in clinical practice guidelines with the aim of  
11  
12 325 improving quality of care by focusing on the patient as a whole rather than on a single  
13  
14 326 disease<sup>48</sup>. From a system perspective, patients with several comorbidities were also the  
15  
16 327 main users of healthcare resources and services<sup>49</sup>. Patient-centered and coordinated care for  
17  
18 328 these patients may decrease related health care use<sup>50</sup>. It was recommended that physicians  
19  
20 329 consider these comorbidities in the management of people with OA.

21 330 A strength of our study is the large population-based number of people with OA  
22  
23 331 (n=497,362) and the investigation of a group of eight comorbidities that are clinically  
24  
25 332 relevant to the management of people with OA. We applied case definitions for  
26  
27 333 administrative health data to identify cases of OA and each of the comorbidities. A  
28  
29 334 limitation of our study is that case identification based on administrative data may result in  
30  
31 335 underreporting of cases and comorbidities. The case definitions for OA in administrative  
32  
33 336 data research<sup>5</sup> have been applied and validated with a low sensitivity of 24% and high  
34  
35 337 specificity of 98%<sup>11</sup>. Similarly, the algorithms for comorbidities may underestimate the  
36  
37 338 prevalence of these comorbidities; the sensitivity for identifying depression is from 36% to  
38  
39 339 51%<sup>18</sup>, for PVD is 39%<sup>17</sup> and for COPD is 53%<sup>20</sup> in administrative data (Appendix 1).  
40  
41 340 Further, we limited our analysis to eight comorbidities of clinical relevance and for which  
42  
43 341 there were case definitions in administrative data.

## 42 342 **5. Conclusions**

44 343 We found that, depression, COPD and hypertension were the three most prevalent  
45  
46 344 comorbidities in people with OA, with rates significantly higher in females compared to  
47  
48 345 males. Of particular note is that the largest number of people with OA and depression are in  
49  
50 346 the age group between 45 and 64 years old, with the highest percentage of cases occurring  
51  
52 347 in the younger age groups (<44 years). Our findings highlight the need to recognize that  
53  
54 348 people with OA have high rates of comorbidities and this may affect optimal health care  
55  
56 349 management of these patients.

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1  
2  
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4  
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### 6 7 353 **Contributions**

8  
9 354 DM, PF, KY were responsible for the conception and design of the research,  
10  
11 355 acquisition of the data, analysis and interpretation of data, drafting the article, and revision  
12  
13 356 of the article for important intellectual content.

14  
15 357 XL was responsible for the analysis and interpretation of data, drafting the article, and  
16  
17 358 revision of the article for important intellectual content.

18  
19 359 CB, CB, DM, TN, JW and LL were responsible for the conception and design of the  
20  
21 360 research, interpreting results of the research and revision of the article for important  
22  
23 361 intellectual content.

24  
25 362 All authors approved the final version of the manuscript to be submitted.

26  
27 363 DM (damarsha@ucalgary.ca) and XL (xiaoxili@ucalgary.ca) take responsibility for  
28  
29 364 the integrity of the work as a whole.

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41 370 manuscript; or in the decision to submit the manuscript for publication.

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### 52 53 376 **Data availability**

54  
55 377 These data are not available because Alberta Health and Alberta Health Services are  
56  
57 378 the custodians of the data. The authors are not authorized to share them.

### 58 59 379 **Competing interests**



1  
2  
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5 381 commercial sources for the work reported on in the manuscript. There are also no financial  
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9 383 regards to the work in the manuscript.  
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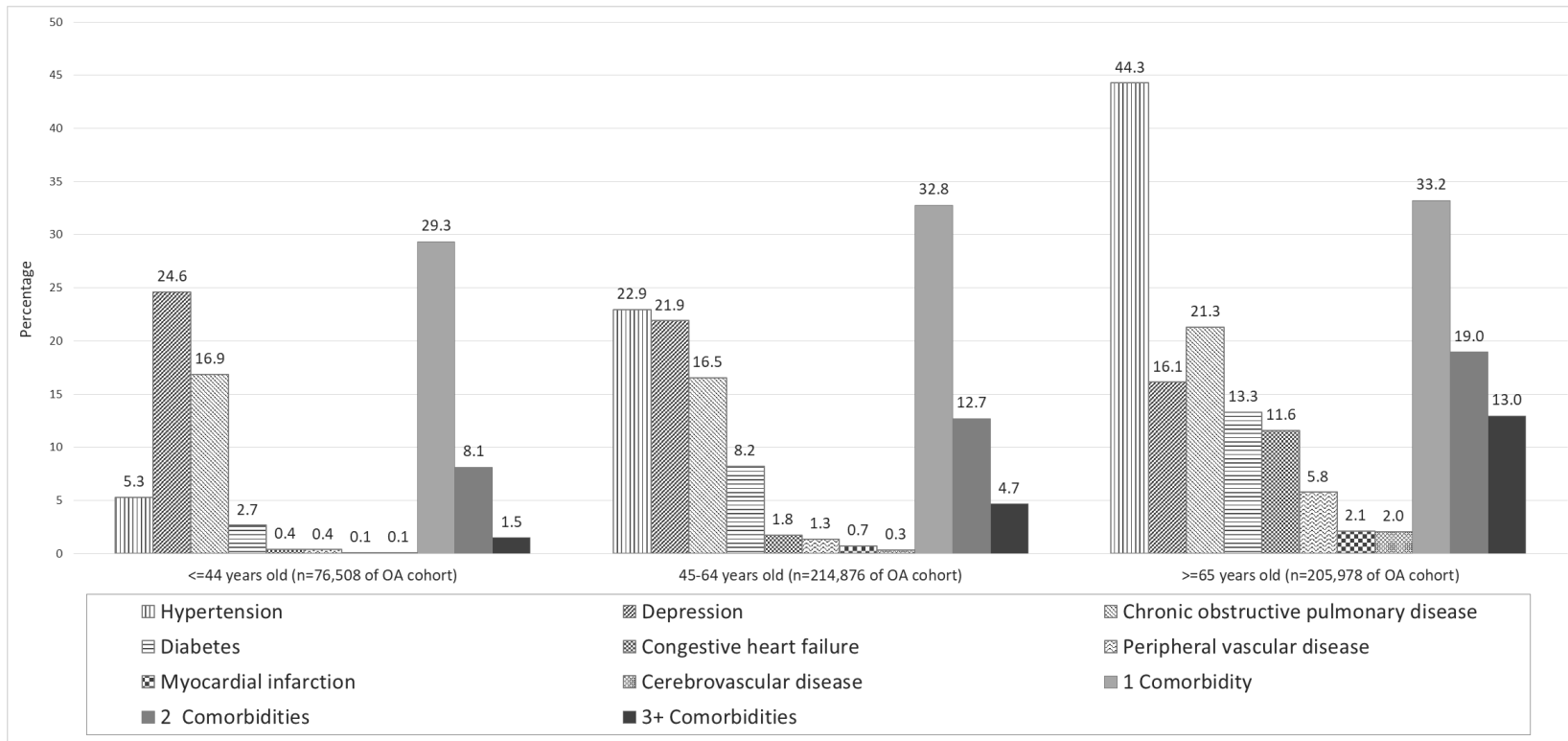


Figure 1 Percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The difference by age group was statistically significant for each comorbid conditions (p<0.0001), as was the frequency of the number of comorbidities present per individual (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
<b>Myocardial Infarction</b>	410	I21, I22	N/A	1 hospitalization for MI, with diagnoses codes in primary or secondary diagnosis fields.	McCormick et al., 2014 <sup>13</sup> Quan et al., 2005 <sup>22</sup>
<b>Cerebrovascular Disease</b>	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 <sup>15</sup>
<b>Congestive Heart Failure</b>	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 <sup>16</sup> Quan et al., 2005 <sup>22</sup> Lee et al., 2005
<b>Peripheral Vascular Disease</b>	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 <sup>17</sup>
<b>Chronic Obstructive Pulmonary Disease</b>	4168,4169,490,491,492,493,494,495,496,500,501,502,503,504,505,506,5081,5088	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 <sup>20</sup> Quan et al., 2005 <sup>22</sup>
<b>Depression</b>	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 <sup>18</sup> Lix et al., 2006 Martens et al., 2010

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

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# BMJ Open

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

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3 **1 Title: Existing comorbidities in people with osteoarthritis: a retrospective analysis of a**  
4 **2 population-based cohort in Alberta, Canada**

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3 31 **Abstract**  
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5 32 **Objectives:** The purpose of this study is to estimate the prevalence of comorbidities among people  
6 33 with osteoarthritis (OA) using administrative health data.

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8 34 **Design:** Retrospective cohort analysis  
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10 35 **Setting:** All residents in the province of Alberta Canada registered with the Alberta Health Care  
11 36 Insurance Plan (AHCIP) population registry.

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13 37 **Participants:** 497,362 people with OA as defined by “having at least one OA-related hospitalization,  
14 38 or at least two OA-related physician visits or two ambulatory care visits within two years”.

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16 39 **Primary outcome measures:** We selected eight comorbidities based on literature review, clinical  
17 40 consultation and the availability of validated case definitions to estimate their frequencies at the  
18 41 time of diagnosis of OA. Sex-stratified age-standardized prevalence rates per 1,000 population of  
19 42 eight clinically relevant comorbidities were calculated using direct standardization with 95%  
20 43 confidence intervals (CIs). We applied  $\chi^2$  tests of independence with a Bonferroni correction to  
21 44 compare the percentage of comorbid conditions in each age group.

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24 45 **Results:** 54.6% (n=271,794) of people meeting the OA case definition had at least one of the eight  
25 46 selected comorbidities. Females had a significantly higher rate of comorbidities compared to males  
26 47 (standardized rates ratio = 1.26, 95% CI: 1.25-1.28). Depression, chronic obstructive pulmonary  
27 48 disease (COPD) and hypertension were the most prevalent in both females and males after age-  
28 49 standardization, with 40% of all cases having any combination of these comorbidities. We observed  
29 50 a significant difference in the percentage of comorbidities among age groups, illustrated by the  
30 51 youngest age group (<45 years) having the highest percentage of cases with depression (24.6%),  
31 52 compared to a frequency of 16.1% in those >65 years.

32  
33 53 **Conclusions:** Our findings highlight the high frequency of comorbidity in people with OA, with  
34 54 depression having the highest age-standardized prevalence rate. Comorbidities differentially affect  
35 55 females, and vary by age. These factors should inform health care programs and delivery.

36  
37 56  
38 57 **Keywords:** Osteoarthritis; comorbidity; depression; hypertension; COPD; administrative health  
39 58 data  
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3 61 Strengths and limitations of this study  
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- 5 62 • Strong methodological approach to identify cases of OA with a validated case  
6 63 definition using five linked population-based administrative databases.  
7 64 • However, case identification based on administrative data may result in  
8 65 underreporting of cases and comorbidities.  
9 66 • The age-standardized prevalence of eight comorbidities, selected on their clinical  
10 67 relevance and the availability of validated case definitions for administrative health  
11 68 data, was estimated among people with OA.  
12 69 • We limited our analysis to eight comorbidities of clinical relevance.  
13 70 • We stratified the analysis by sex and by age cohorts  
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## 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<sup>1,2</sup>. OA affects people of all ages, but is more prevalent among females and older age groups<sup>3,4</sup>. 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<sup>5,6</sup>. 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<sup>7</sup> with an associated economic burden of \$33 billion (direct and indirect costs) in Canada in 2011<sup>3</sup>. The annual cost per individual with OA has been estimated to be two to three times higher compared to people without OA<sup>7</sup>, and are associated with more physician visits and hospitalizations<sup>8</sup>.

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<sup>9-10</sup>. 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<sup>4</sup>. 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

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3 103 elsewhere in detail<sup>6</sup>. These databases included the Alberta Health Care Insurance Plan  
4 104 (AHCIP) population registry, the Discharge Abstract Database (DAD), the Physician  
5 105 Claims Database (claims), the Ambulatory Care Classification System (ACCS), and the  
6 106 National Ambulatory Care Reporting System (NACRS).  
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10 107 AHCIP Population Registry captures individual level demographic data on all insured  
11 108 persons as of the last day of each fiscal year (March 31). All Albertans who are included in  
12 109 the AHCIP have a unique, 9-digit personal health number, which is used when accessing  
13 110 health care services, and served to link datasets prior to de-identification. Members of the  
14 111 Armed Forces and the Royal Canadian Mounted Police, federal penitentiary inmates, and  
15 112 Albertans who have opted out of the AHCIP are excluded.  
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21 113 DAD captures admission and inpatient care data for all hospitalized patients, including  
22 114 diagnostic codes, interventions, patient age and sex, and administrative information.  
23 115 Among 25 DAD diagnostic code fields extracted from the hospital record, OA-related  
24 116 records were identified as those with the first 3 digits 715 or M15 to M19 based on the  
25 117 ninth (9) and tenth (10) revisions of the International Classification of Diseases (ICD)  
26 118 codes, respectively.  
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32 119 Claims captures OA-related physician visits, which were identified based on the  
33 120 aforementioned ICD codes in any of the 3 diagnostic code fields.  
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36 121 ACCS and NACRS contains data on hospital-based and community-based ambulatory  
37 122 care, including day surgery, outpatient and community-based clinics and emergency  
38 123 departments, and publicly funded hospital support services such as physiotherapy and  
39 124 occupational therapy. OA-related records were identified based on the presence of the  
40 125 aforementioned ICD codes in any of the 10 diagnostic code fields. NACRS was used since  
41 126 April 2010.  
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47 127 Ethics approval for this project was provided by the Conjoint Health Research Ethics  
48 128 Board at the University of Calgary (REB13-0100).  
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### 50 129 *Patient and public involvement*

51 130 No patients were involved in setting the research question, the design and conduct of  
52 131 the study. No patients were involved in the interpretation or writing up of results. There are  
53 132 no plans to disseminate the results of the research to study participants because this was  
54 133 admin health database analysis. We will make the publication available to the relevant  
55 134 patient community.  
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### 135 *Case Definition of Osteoarthritis (OA)*

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

### 148 *Case Definitions of Comorbidities*

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

### 165 *Age-standardized comorbidity prevalence rate*

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3 166 The frequency of each comorbid condition in people meeting the case definition for  
4 167 OA was calculated, as was the frequency of the number of comorbidities present per  
5 168 individual: one comorbidity, two comorbidities, and three or more comorbidities. We  
6 169 stratified OA cases by sex, and by age at diagnosis (<35, 35-44, 45-54, 55-65, 65-74, and  
7 170  $\geq 75$  years). The crude rate was calculated as the number in each comorbidity group  
8 171 divided by the total number of OA cases. We calculated age-standardized comorbidity  
9 172 prevalence rates using the direct standardization method<sup>24</sup>. We used the 2016 Canadian  
10 173 population reported publicly by Statistics Canada<sup>25</sup> to age-standardize the estimates for  
11 174 females and males with 95% confidence intervals (CIs) calculated using the binomial  
12 175 approximation method<sup>24</sup>. To compare differences between females and males, standardized  
13 176 rate ratios (SRR) were estimated as the female age-standardized rate divided by the male  
14 177 age-standardized rate. We calculated 95% confidence intervals for the SRR based on the  
15 178 standard error for each sex, to test for a sex difference<sup>24</sup>.

16 179 We calculated the percentage of females and males in each age group and the  
17 180 percentage of OA cases for each age group by sex. The percentage of comorbidities among  
18 181 OA population was calculated as the number of cases with specific comorbidity divided by  
19 182 the OA population. The percentage of comorbidities among those with comorbidities was  
20 183 calculated using the population with one or more of the eight comorbidities as denominator.  
21 184 We also calculated the frequency of common groupings of these comorbidities in people  
22 185 with OA.

23 186 We applied  $\chi^2$  tests of independence with a Bonferroni correction<sup>26</sup> to compare the  
24 187 percentage of specific comorbid conditions among the population with OA in each age  
25 188 group (<45, 45-64, and  $\geq 65$  years). The null hypothesis is that there is no difference in the  
26 189 percentage of comorbidities across age groups, which is rejected when the calculated  $\chi^2$  is  
27 190 greater than the critical value for a specific number of degrees of freedom and an altered  
28 191 significance level of 0.005 after Bonferroni correction. All analyses were conducted with R  
29 192 version 3.5.1 and Excel 2013.

### 30 193 **3. Results**

31 194 We identified 497,362 cases of OA, 57.9% of whom were females (Table 1). More  
32 195 than half of the OA cases had at least one of the eight comorbidities (54.6%, n=271,794)  
33 196 (Table 2). A total of 161,315 (32.4%) people with OA had only one comorbidity, with  
34 197 14.6% (n=72,567) having two, and 7.6% (n=37,912) having three or more of the  
35 198 comorbidities. Hypertension was the most frequent comorbidity (29%, n=144,453),



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

202 **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
	<b>Total</b>	<b>287,951</b>	<b>57.9</b>	<b>100.0</b>	<b>209,411</b>	<b>42.1</b>	<b>100.0</b>	<b>497,362</b>

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).

### 203 *Comorbidity Patterns by Sex*

204 A similar pattern was observed regarding the number of comorbidities (with most  
 205 people with OA having one comorbidity) and the ordering of the frequency of each of the  
 206 comorbidities among females and males based on age-standardized prevalence rates (Table  
 207 2). Statistically significant differences among females and males were observed by the  
 208 number of comorbidities, with females having higher rates overall (SRR = 1.26, 95% CI:  
 209 1.25-1.28). The number of comorbidities was also higher for females compared to males  
 210 with SRR ranging from 1.15 (95% CI: 1.11-1.18) for three or more comorbidities to 1.48  
 211 (95% CI: 1.44-1.52) for two comorbidities (Table 2).

212 **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)
<b>Number of Comorbidities</b>	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)
<b>OA with Comorbidities</b>		271,794	54.6		496.3 (492.8-499.8)	392.9 (389.4-396.4)	1.26 (1.25-1.28)
<b>None of the 8 Comorbidities</b>		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.

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

219 The prevalence of each of these three comorbidities differed significantly in females.  
 220 For example the prevalence of depression in females was 264 cases per 1,000 population,  
 221 35% higher and statistically higher than for COPD (196 cases per 1,000 population) (SRR  
 222 1.35, 95% CI 1.32-1.37). In contrast, the prevalence of these three comorbidities among  
 223 males were not significantly different.

#### 224 *Common groupings of comorbidities in people with OA*

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

#### 232 **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.

### 233 *Comorbidity patterns by age group*

234 As shown in Figure 1, each of the eight comorbidities, with the exception of  
 235 depression, was most common in people with OA over 65 years old. Hypertension was  
 236 found in 44.3% of people with OA over 65 years of age (n=91,153 cases) compared to  
 237 5.3% (n=4,040 cases) in those <44 years old. The largest number of people with OA and  
 238 depression were in the 45-64 years age cohort (n=47,061 cases), with the youngest age  
 239 group (<44 years) having the highest percentage of cases with depression (24.6% compared  
 240 to 21.9% in the middle age group (45-64 years) and 16.1% in the older age group (>=65  
 241 years). The difference in the percentage of each of the eight comorbidities among the three  
 242 age groups was statistically significant (p<0.0001). The detailed age-sex stratified crude  
 243 rates per 1,000 population is provided in Appendix 1.

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

### 248 **4. Discussion**

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

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3 253 comorbidities in both females and males after age-standardization. However, the prevalence  
4 of each of these comorbidities was significantly higher in females compared to males.  
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6 255 People with any combination of these three comorbidities represented about 40% of the  
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8 256 people with OA. In general, the number of comorbidities in people with OA increased with  
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10 257 increasing age. Each of the eight comorbidities, except depression, was most common in  
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12 258 people with OA  $\geq$  65 years. The largest number of people with OA and depression are in  
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14 259 the middle age group (45-64 years), with the youngest age group (<44 years) having the  
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16 260 highest percentage of cases with depression.

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18 261 The estimated prevalence of comorbidities varies among studies due to differences in  
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20 262 case definitions, the list of included chronic conditions, data sources and study population.  
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22 263 We estimated that the prevalence of comorbidity among people with OA was 54.6% for one  
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24 264 or more of the eight comorbid chronic conditions and 22.2% for two or more comorbid  
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26 265 chronic conditions with OA. Our estimates of the prevalence of comorbidities in people  
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28 266 with OA are higher than the prevalence of two or more and three or more chronic  
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30 267 conditions among the general Canadian population (26.5% and 10.2%, respectively) as  
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32 268 reported by Feely et al.(2017)<sup>27</sup>, and higher than the prevalence of 12.9% (two or more  
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34 269 chronic diseases) and 3.9% (three or more chronic diseases) reported by Roberts et al.  
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36 270 (2015)<sup>28</sup>. In our study, among 205,978 OA cases in the age group over 65 years old, the  
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38 271 prevalence of one or more comorbid chronic conditions was 33.2% (n=68,418) and the  
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40 272 prevalence of two or more comorbid chronic conditions with OA was 19.0% (n=39,044).  
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42 273 The estimated prevalence is higher than the estimates reported by Roberts et al. (2015),  
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44 274 which showed that the prevalence of two or more chronic diseases was 31.3% and the  
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46 275 prevalence of three or more chronic diseases was 11.3%. It has been reported previously  
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48 276 that the prevalence of one or more comorbid condition among people with musculoskeletal  
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50 277 conditions was more than twice than those without a musculoskeletal condition but with  
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52 278 another chronic condition<sup>29</sup>.

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54 279 We identified depression, COPD and hypertension as frequent comorbid conditions  
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56 280 among the people with OA. This was consistent with findings reported from the Canadian  
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58 281 Primary Care Sentinel Surveillance Network showing that the prevalence of osteoarthritis  
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60 282 has significant association with depression, COPD and hypertension<sup>2</sup>. Depression is  
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284 283 emerging as a significant comorbidity in OA. Previous findings have reported that  
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286 284 depression was highly prevalent in people with OA<sup>10,30</sup>. A systemic review of depressive  
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288 285 symptoms in people with OA , including 49 studies worldwide and representing 15,855

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3 286 individuals, reported a frequency of depression of 19.9% among people with OA<sup>31</sup>, which  
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5 287 was similar to our estimates.  
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7 288 Depressed individuals are more likely to report chronic or more severe pain, and more  
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9 289 than half of the patients with chronic pain are depressed. People living with OA are known  
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11 290 to have fewer social contacts, limited physical activity, increased pain and disability<sup>32,33</sup>,  
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13 291 worse surgical outcomes and reduced effectiveness of pain interventions<sup>34</sup>, which are all  
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15 292 important predictors of depression<sup>35</sup>. However, current clinical practice guidelines for non-  
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17 293 surgical management of OA do not include recommendations regarding mental health  
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19 294 management<sup>36-39</sup>. This emphasizes the need for treatments and management for depression  
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21 295 to improve outcomes for people with OA<sup>40</sup>. It has been suggested that educating physicians  
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23 296 about timely identification of psychological factors may be helpful to improve outcomes. In  
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25 297 addition, self-care management could be integrated into OA management strategies as a  
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27 298 way to reduce anxiety and depression, as well as resulting emotional and physical pain.  
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29 299 Guidelines suggest that OA management should also integrate pharmacotherapy carefully  
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31 300 and be cautious about the drug interactions and adverse side effects when treating OA,  
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33 301 depression, anxiety and pain holistically<sup>30</sup>. Two or more of the comorbidities that we  
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35 302 examined coexist in a substantial proportion of people with OA – approximately 22% in  
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37 303 total. Obesity, which we were unable to study using administrative data is also prevalent  
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39 304 amongst people with OA and a risk factor for developing OA<sup>41,42</sup>. From a clinical practice  
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41 305 perspective, a physician has to consider the implications of prescribing non-steroidal anti-  
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43 306 inflammatory medications for pain management, but this may worsen hypertension and  
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45 307 have an associated increased risk of cardiovascular disease. However, without good pain  
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47 308 management, it is difficult for patients with OA to engage in exercise programs which can  
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49 309 help improve their muscular condition and potentially reduce obesity and hypertension.  
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51 310 This is further complicated by the relationship of lower socioeconomic status with an  
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53 311 increased risk of developing OA as demonstrated in the project for an Ontario Women's  
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55 312 Health Evidence-based Report<sup>29</sup>.

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57 313 Furthermore, our analyses showed that depression not only was the most prevalent  
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59 314 comorbidity after age-standardization in people with OA, but that rates of depression were  
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315 significantly higher for females and younger people (< 44 years old). The study by  
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317 Dibonaventura et al. (2011) reported that people under 65 years of age were still  
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productivity and higher costs compared to those without OA pain<sup>8</sup>. They identified unique

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3 319 treatment gaps for patients younger than 60 years old because the non-operative treatment  
4 320 options were ineffective in long-term management of OA symptoms, but young patients  
5 321 were too young or maybe unwilling to undergo definitive treatment such as total joint  
6 322 replacement<sup>43</sup>. Even for those patients who undergo total joint replacement, they were more  
7 323 likely to be dissatisfied about the treatment than older patients, and reported poorer  
8 324 outcomes including residual pain and stiffness<sup>44,45</sup>. A survey of orthopedic surgeons found  
9 325 that 84% perceived a need for better treatment for younger (<60 years old) physically active  
10 326 OA patients, and 68.4% perceived that there is a treatment gap for these patients<sup>43</sup>. Due to  
11 327 the different presentations of comorbidities and treatment options among young and old age  
12 328 groups, it is imperative to examine the impact of comorbidities on management strategies in  
13 329 an age-stratified OA cohort.

14  
15 330 Most clinical practice guidelines focus on single conditions<sup>46</sup>. Fortin et al. (2011)  
16 331 concluded that even though the quality of the Canadian guidelines was good, their  
17 332 relevance for patients with two or more chronic conditions was limited<sup>47</sup>. Boyd et al. (2005)  
18 333 highlighted the lack of consideration of comorbidities in clinical practice guidelines may  
19 334 result in poor quality of care because the health care some patients received was not  
20 335 optimal<sup>48</sup>. Sharma et al., (2016) pointed out that the present literature fails to fully address  
21 336 the management strategies when dealing with comorbidities seen in people with OA<sup>30</sup>.  
22 337 Patient-centered care has been recommended in clinical practice guidelines with the aim of  
23 338 improving quality of care by focusing on the patient as a whole rather than on a single  
24 339 disease<sup>49</sup>. From a system perspective, patients with several comorbidities were also the  
25 340 main users of healthcare resources and services<sup>50</sup>. Patient-centered and coordinated care for  
26 341 these patients may decrease related health care use<sup>51</sup>. It was recommended that physicians  
27 342 consider these comorbidities in the management of people with OA.

28 343 A strength of our study is the large population-based number of people with OA  
29 344 (n=497,362) and the investigation of a group of eight comorbidities that are clinically  
30 345 relevant to the management of people with OA. We applied case definitions for  
31 346 administrative health data to identify cases of OA and each of the comorbidities at the  
32 347 diagnosis of OA. A limitation of our study is that case identification based on  
33 348 administrative data may result in underreporting of cases and comorbidities. The case  
34 349 definitions for OA in administrative data research<sup>5</sup>, based on the physician claims and  
35 350 hospitalizations records, have been applied and validated with a sensitivity of 24%, high  
36 351 specificity of 98% and a positive predictive value of 54%<sup>11</sup>. In our study, we also included

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3 352 ACCS/NACRS to mitigate the issue of underestimations<sup>6</sup>. Nonetheless, the estimated  
4 353 number of OA cases using this approach is almost certainly an underestimate. Similarly, the  
5 354 algorithms for comorbidities may underestimate the prevalence of these comorbidities; the  
6 355 sensitivity for identifying depression is from 36% to 51%<sup>19</sup>, for PVD is 39%<sup>18</sup> and for  
7 356 COPD is 53%<sup>21</sup> in administrative data (Appendix 2). More importantly, the reported levels  
8 357 of comorbidity in patients with OA were measured at the time of OA diagnosis. New cases  
9 358 of comorbidity diagnosed after the OA diagnosis were not identified. Further, we limited  
10 359 our analysis to eight comorbidities of clinical relevance and for which there were case  
11 360 definitions in administrative data.

## 19 361 **5. Conclusions**

21 362 We found that, depression, COPD and hypertension were the three most prevalent  
22 363 comorbidities in people with OA, with rates significantly higher in females compared to  
23 364 males. Of particular note is that the largest number of people with OA and depression are in  
24 365 the age group between 45 and 64 years old, with the highest percentage of cases occurring  
25 366 in the younger age groups (<44 years). Our findings highlight the need to recognize that  
26 367 people with OA have high rates of comorbidities and this may affect optimal health care  
27 368 management of these patients.

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## 40 372 **Contributions**

42 373 DM, PF, KY were responsible for the conception and design of the research,  
43 374 acquisition of the data, analysis and interpretation of data, drafting the article, and revision  
44 375 of the article for important intellectual content.

48 376 XL was responsible for the analysis and interpretation of data, drafting the article, and  
49 377 revision of the article for important intellectual content.

52 378 CB, CB, DM, TN, JW and LL were responsible for the conception and design of the  
53 379 research, interpreting results of the research and revision of the article for important  
54 380 intellectual content.

58 381 All authors approved the final version of the manuscript to be submitted.

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2  
3 382 DM (damarsha@ucalgary.ca) and XL (xiaoxili@ucalgary.ca) take responsibility for  
4 383 the integrity of the work as a whole.

6  
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20  
21 395 **Data availability**

22  
23 396 These data are not available because Alberta Health and Alberta Health Services are  
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25  
26 398 **Competing interests**

27  
28 399 The authors confirm that there is no financial support or other benefits from  
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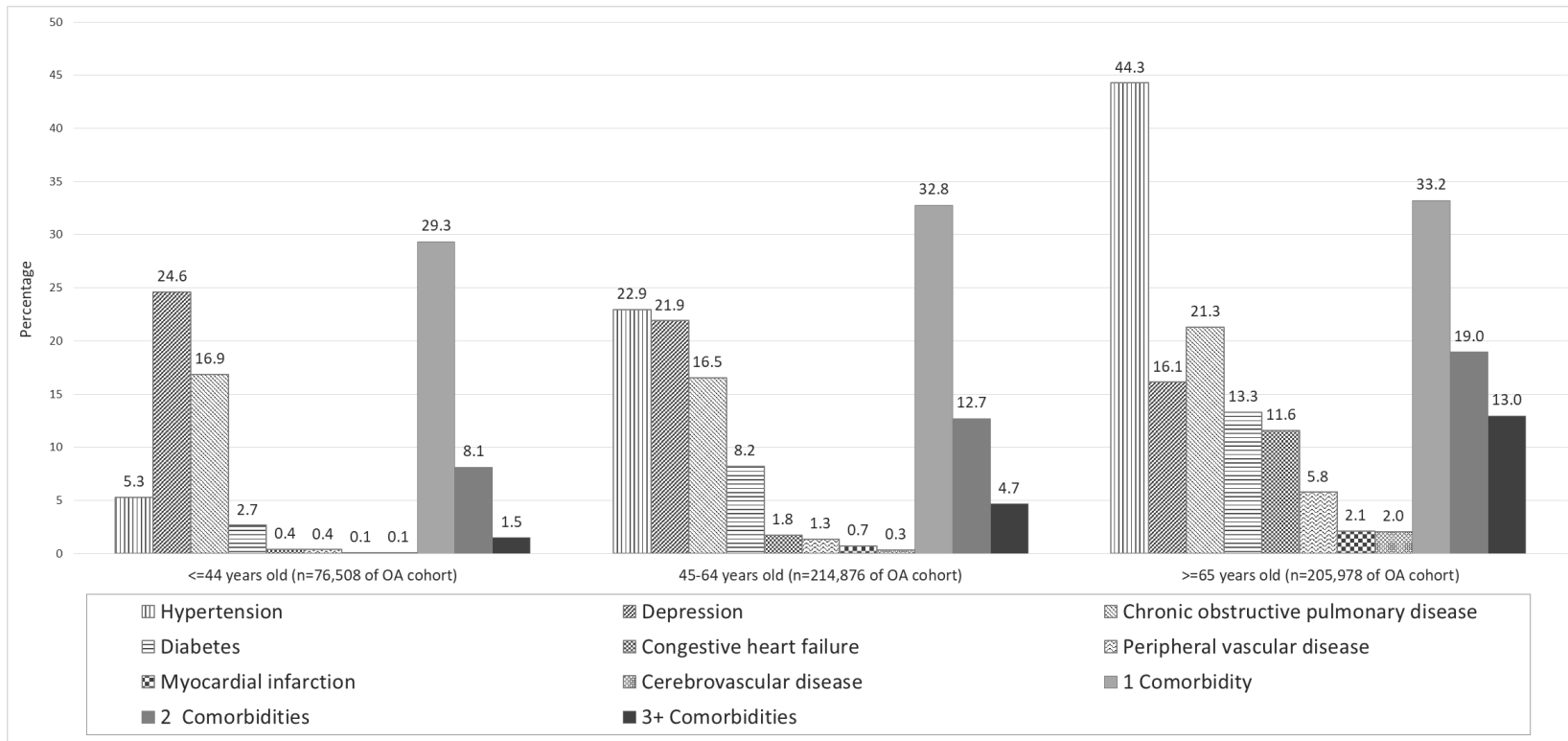


Figure 1 Percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The difference by age group was statistically significant for each comorbid conditions (p<0.0001), as was the frequency of the number of comorbidities present per individual (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
<b>Total</b>	<b>87,567</b>	<b>56,886</b>	<b>287,951</b>	<b>209,411</b>	<b>304</b>	<b>272</b>

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
<b>Total</b>	<b>87,567</b>	<b>56,886</b>	<b>287,951</b>	<b>209,411</b>	<b>304</b>	<b>272</b>

## 1 Appendix 1 Case definitions for eight comorbid conditions

	ICD9-CM Diagnosis Codes Included	ICD10-CA Diagnosis Codes Included	Exclusions	Algorithm	References
<b>Myocardial Infarction</b>	410	I21, I22	N/A	1 hospitalization for MI, with diagnoses codes in primary or secondary diagnosis fields.	McCormick et al., 2014 <sup>13</sup> Quan et al., 2005 <sup>22</sup>
<b>Cerebrovascular Disease</b>	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 <sup>15</sup>
<b>Congestive Heart Failure</b>	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 <sup>16</sup> Quan et al., 2005 <sup>22</sup> Lee et al., 2005
<b>Peripheral Vascular Disease</b>	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 <sup>17</sup>
<b>Chronic Obstructive Pulmonary Disease</b>	4168,4169,490,491,492,493,494,495,496,500,501,502,503,504,505,506,5081,5088	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 <sup>20</sup> Quan et al., 2005 <sup>22</sup>
<b>Depression</b>	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 <sup>18</sup> Lix et al., 2006 Martens et al., 2010



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

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Pages
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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 alternative OA case definitions has been conducted previously. Please refer to Marshall et. al. (2015).
<b>Results</b>			
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 alternative OA case definitions has been conducted previously. Please refer to Marshall et al. (2015).
<b>Discussion</b>			
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
<b>Other information</b>			
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

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

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# BMJ Open

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Health services research, Rheumatology
Keywords:	Osteoarthritis, Comorbidity, Depression, Hypertension < CARDIOLOGY, COPD, Administrative Health Data

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Manuscripts

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3 **1 Title: Existing comorbidities in people with osteoarthritis: a retrospective analysis of a**  
4 **2 population-based cohort in Alberta, Canada**

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6 3 Deborah A Marshall PhD <sup>1,2</sup>\*, Xiaoxiao Liu PhD <sup>1</sup>, Cheryl Barnabe MD MSc <sup>1,2</sup>, Karen Yee MSc  
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3 31 **Abstract**  
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5 32 **Objectives:** The purpose of this study is to estimate the prevalence of comorbidities among people  
6 33 with osteoarthritis (OA) using administrative health data.

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8 34 **Design:** Retrospective cohort analysis  
9

10 35 **Setting:** All residents in the province of Alberta Canada registered with the Alberta Health Care  
11 36 Insurance Plan (AHCIP) population registry.

12  
13 37 **Participants:** 497,362 people with OA as defined by “having at least one OA-related hospitalization,  
14 38 or at least two OA-related physician visits or two ambulatory care visits within two years”.

15  
16 39 **Primary outcome measures:** We selected eight comorbidities based on literature review, clinical  
17 40 consultation and the availability of validated case definitions to estimate their frequencies at the  
18 41 time of diagnosis of OA. Sex-stratified age-standardized prevalence rates per 1,000 population of  
19 42 eight clinically relevant comorbidities were calculated using direct standardization with 95%  
20 43 confidence intervals (CIs). We applied  $\chi^2$  tests of independence with a Bonferroni correction to  
21 44 compare the percentage of comorbid conditions in each age group.

22  
23  
24 45 **Results:** 54.6% (n=271,794) of people meeting the OA case definition had at least one of the eight  
25 46 selected comorbidities. Females had a significantly higher rate of comorbidities compared to males  
26 47 (standardized rates ratio = 1.26, 95% CI: 1.25-1.28). Depression, chronic obstructive pulmonary  
27 48 disease (COPD) and hypertension were the most prevalent in both females and males after age-  
28 49 standardization, with 40% of all cases having any combination of these comorbidities. We observed  
29 50 a significant difference in the percentage of comorbidities among age groups, illustrated by the  
30 51 youngest age group (<45 years) having the highest percentage of cases with depression (24.6%),  
31 52 compared to a frequency of 16.1% in those >65 years.

32  
33 53 **Conclusions:** Our findings highlight the high frequency of comorbidity in people with OA, with  
34 54 depression having the highest age-standardized prevalence rate. Comorbidities differentially affect  
35 55 females, and vary by age. These factors should inform health care programs and delivery.

36  
37 56  
38 57 **Keywords:** Osteoarthritis; comorbidity; depression; hypertension; COPD; administrative health  
39 58 data  
40 59  
41 60

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2  
3 61 Strengths and limitations of this study  
4

- 5 62 • Strong methodological approach to identify cases of OA with a validated case  
6 63 definition using five linked population-based administrative databases.  
7 64 • However, case identification based on administrative data may result in  
8 65 underreporting of cases and comorbidities.  
9 66 • The age-standardized prevalence of eight comorbidities, selected on their clinical  
10 67 relevance and the availability of validated case definitions for administrative health  
11 68 data, was estimated among people with OA.  
12 69 • We limited our analysis to eight comorbidities of clinical relevance.  
13 70 • We stratified the analysis by sex and by age cohorts  
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For peer review only



## 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<sup>1,2</sup>. OA affects people of all ages, but is more prevalent among females and older age groups<sup>3,4</sup>. 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<sup>5,6</sup>. 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<sup>7</sup> with an associated economic burden of \$33 billion (direct and indirect costs) in Canada in 2011<sup>3</sup>. The annual cost per individual with OA has been estimated to be two to three times higher compared to people without OA<sup>7</sup>, and are associated with more physician visits and hospitalizations<sup>8</sup>.

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<sup>9-10</sup>. 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<sup>4</sup>. 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

### 103 *Data sources*

104 We used five linked Alberta, Canada provincial administrative databases between April  
105 1, 1994 and March 31, 2013 to identify individuals with OA who accessed health care  
106 services paid for by the provincial health care insurance plan, previously described  
107 elsewhere in detail<sup>6</sup>. These databases included the Alberta Health Care Insurance Plan  
108 (AHCIP) population registry, the Discharge Abstract Database (DAD), the Physician  
109 Claims Database (claims), the Ambulatory Care Classification System (ACCS), and the  
110 National Ambulatory Care Reporting System (NACRS).

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

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

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

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

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

### 133 *Patient and public involvement*

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2  
3 134 No patients were involved in setting the research question, the design and conduct of  
4  
5 135 the study. No patients were involved in the interpretation or writing up of results. There are  
6  
7 136 no plans to disseminate the results of the research to study participants because this was  
8  
9 137 admin health database analysis. We will make the publication available to the relevant  
10  
11 138 patient community.

### 12 139 *Case Definition of Osteoarthritis (OA)*

14  
15 140 Validated case definitions have been used in previous research related to OA using  
16  
17 141 administrative data<sup>11,12</sup>. The sensitivity of algorithms based on both physician claims and  
18  
19 142 hospitalizations records within 2-5 years ranged from 24% - 46%, along with specificity  
20  
21 143 and positive predictive value ranging from 92% -98%, and 39% - 54% respectively<sup>11</sup>. In  
22  
23 144 this study, OA cases were identified as individuals with at least one OA-related  
24  
25 145 hospitalization (DAD), or at least two OA-related physician visits (claims) within two  
26  
27 146 years, or at least two OA-related ambulatory care visits (ACCS/NACRS) within two years,  
28  
29 147 assuming none of the physicians or ambulatory care visits had occurred on the same day<sup>11</sup>.  
30  
31 148 For our study, the OA cohort refers to those Alberta residents registered with AHCIP who  
32  
33 149 have a specified OA-related diagnostic code in any diagnostic code field position. The  
34  
35 150 cohort inclusion date is the earliest date of the OA-related record identified from either the  
36  
37 151 Claims, DAD or ACCS/NACRS files.

### 38 152 *Case Definitions of Comorbidities*

39  
40 153 We identified specific comorbidities to explore in this analysis based on three criteria:  
41  
42 154 1) a high frequency of reported comorbidities in the published literature on OA; 2) the  
43  
44 155 availability of validated case definitions for each comorbid condition; and, 3) expert input  
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46 156 from our clinical co-investigators. We first conducted a scoping review of the literature<sup>13</sup>,  
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48 157 aiming to examine the extent and range of comorbidities research among people with OA.  
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50 158 We identified 20 studies from a range of countries (9 in North America, 8 in Europe, 1 in  
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52 159 Asia, 1 in South American, 1 in Netherlands), using different study designs (9 cross-  
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54 160 sectional, 5 retrospective cohort, 5 prospective cohort and 1 case control study) with a  
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56 161 range of sample sizes (91 to 85,966,369 cases of OA). Based on the results of this review,  
57  
58 162 we derived a list of comorbidities and presented it to our clinical co-investigators. On this  
59  
60 163 basis, we identified 8 comorbidities to include in our analysis: hypertension, depression,  
164  
165 164 COPD, diabetes, congestive heart failure (CHF), peripheral vascular disease (PVD),  
166  
167 165 myocardial infarction (MI), and cerebrovascular disease (CEVD). We applied case  
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169 166 definitions for each comorbidity to identify those present within 3 years prior to the OA

1  
2  
3 167 diagnosis. Detailed ICD 9 and ICD 10 diagnostic codes used to identify each comorbidity  
4  
5 168 are provided in Appendix 1<sup>14-23</sup>.

### 7 169 *Age-standardized comorbidity prevalence rate*

9 170 The frequency of each comorbid condition in people meeting the case definition for  
11 171 OA was calculated, as was the frequency of the number of comorbidities present per  
12  
13 172 individual: one comorbidity, two comorbidities, and three or more comorbidities. We  
14  
15 173 stratified OA cases by sex, and by age at diagnosis (<35, 35-44, 45-54, 55-65, 65-74, and  
16  
17 174 >=75 years). The crude rate was calculated as the number in each comorbidity group  
18  
19 175 divided by the total number of OA cases. We calculated age-standardized comorbidity  
20  
21 176 prevalence rates using the direct standardization method<sup>24</sup>. We used the 2016 Canadian  
22  
23 177 population reported publicly by Statistics Canada<sup>25</sup> to age-standardize the estimates for  
24  
25 178 females and males with 95% confidence intervals (CIs) calculated using the binomial  
26  
27 179 approximation method<sup>24</sup>. To compare differences between females and males, standardized  
28  
29 180 rate ratios (SRR) were estimated as the female age-standardized rate divided by the male  
30  
31 181 age-standardized rate. We calculated 95% confidence intervals for the SRR based on the  
32  
33 182 standard error for each sex, to test for a sex difference<sup>24</sup>.

34 183 We calculated the percentage of females and males in each age group and the  
35  
36 184 percentage of OA cases for each age group by sex. The percentage of comorbidities among  
37  
38 185 OA population was calculated as the number of cases with specific comorbidity divided by  
39  
40 186 the OA population. The percentage of comorbidities among those with comorbidities was  
41  
42 187 calculated using the population with one or more of the eight comorbidities as denominator.  
43  
44 188 We also calculated the frequency of common groupings of these comorbidities in people  
45  
46 189 with OA.

47 190 We applied  $\chi^2$  tests of independence with a Bonferroni correction<sup>26</sup> to compare the  
48  
49 191 percentage of specific comorbid conditions among the population with OA in each age  
50  
51 192 group (<45, 45-64, and >=65 years). The null hypothesis is that there is no difference in the  
52  
53 193 percentage of comorbidities across age groups, which is rejected when the calculated  $\chi^2$  is  
54  
55 194 greater than the critical value for a specific number of degrees of freedom and an altered  
56  
57 195 significance level of 0.005 after Bonferroni correction. All analyses were conducted with R  
58  
59 196 version 3.5.1 and Excel 2013.

## 57 197 **3. Results**

198 We identified 497,362 cases of OA, 57.9% of whom were females (Table 1). More  
 199 than half of the OA cases had at least one of the eight comorbidities (54.6%, n=271,794)  
 200 (Table 2). A total of 161,315 (32.4%) people with OA had only one comorbidity, with  
 201 14.6% (n=72,567) having two, and 7.6% (n=37,912) having three or more of the  
 202 comorbidities. Hypertension was the most frequent comorbidity (29%, n=144,453),  
 203 followed by depression (19.9%, n=99,103), COPD (18.6%, n=92,273), diabetes (9.5%,  
 204 n=47,102), and CHF (5.6%, n=27,905). PVD (3.0%), CEVD (1.2%) and MI (1.0%) were  
 205 the least frequent comorbidities.

206 **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
	<b>Total</b>	<b>287,951</b>	<b>57.9</b>	<b>100.0</b>	<b>209,411</b>	<b>42.1</b>	<b>100.0</b>	<b>497,362</b>

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).

207 *Comorbidity Patterns by Sex*

208 A similar pattern was observed regarding the number of comorbidities (with most  
 209 people with OA having one comorbidity) and the ordering of the frequency of each of the  
 210 comorbidities among females and males based on age-standardized prevalence rates (Table  
 211 2). Statistically significant differences among females and males were observed by the  
 212 number of comorbidities, with females having higher age-standardized rates overall (SRR =  
 213 1.26, 95% CI: 1.25-1.28). The number of comorbidities was also higher for females  
 214 compared to males with SRR ranging from 1.15 (95% CI: 1.11-1.18) for three or more  
 215 comorbidities to 1.48 (95% CI: 1.44-1.52) for two comorbidities (Table 2).

216 **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			
<b>Comorbid Conditions</b>	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)
<b>Number of Comorbidities</b>	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)
<b>OA with Comorbidities</b>		271,794	54.6		496.3 (492.8-499.8)	392.9 (389.4-396.4)	1.26 (1.25-1.28)
<b>None of the 8 Comorbidities</b>		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.

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

223 The prevalence of each of these three comorbidities differed significantly in females.  
 224 For example the age-standardized prevalence of depression in females was 264 cases per  
 225 1,000 population, 35% higher and statistically higher than for COPD (196 cases per 1,000  
 226 population) (SRR 1.35, 95% CI 1.32-1.37). In contrast, the prevalence of these three  
 227 comorbidities among males were not significantly different.

### 228 *Common groupings of comorbidities in people with OA*

229 As shown in Table 3, of the eight comorbidities in people with OA, the most frequent  
 230 comorbidity was hypertension as a single comorbidity, found in 12.8% of people with OA  
 231 (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  $\geq$  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)<sup>27</sup>, 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)<sup>28</sup>. 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<sup>29</sup>.



1  
2  
3 284 We identified depression, COPD and hypertension as frequent comorbid conditions  
4  
5 285 among the people with OA. This was consistent with findings reported from the Canadian  
6  
7 286 Primary Care Sentinel Surveillance Network showing that the prevalence of osteoarthritis  
8  
9 287 has significant association with depression, COPD and hypertension<sup>2</sup>. Depression is  
10  
11 288 emerging as a significant comorbidity in OA. Previous findings have reported that  
12  
13 289 depression was highly prevalent in people with OA<sup>10,30</sup>. A systemic review of depressive  
14  
15 290 symptoms in people with OA , including 49 studies worldwide and representing 15,855  
16  
17 291 individuals, reported a frequency of depression of 19.9% among people with OA<sup>31</sup>, which  
18  
19 292 was similar to our estimates.

20  
21 293 Depressed individuals are more likely to report chronic or more severe pain, and more  
22  
23 294 than half of the patients with chronic pain are depressed. People living with OA are known  
24  
25 295 to have fewer social contacts, limited physical activity, increased pain and disability<sup>32,33</sup>,  
26  
27 296 worse surgical outcomes and reduced effectiveness of pain interventions<sup>34</sup>, which are all  
28  
29 297 important predictors of depression<sup>35</sup>. However, current clinical practice guidelines for non-  
30  
31 298 surgical management of OA do not include recommendations regarding mental health  
32  
33 299 management<sup>36-39</sup>. This emphasizes the need for treatments and management for depression  
34  
35 300 to improve outcomes for people with OA<sup>40</sup>. It has been suggested that educating physicians  
36  
37 301 about timely identification of psychological factors may be helpful to improve outcomes. In  
38  
39 302 addition, self-care management could be integrated into OA management strategies as a  
40  
41 303 way to reduce anxiety and depression, as well as resulting emotional and physical pain.  
42  
43 304 Guidelines suggest that OA management should also integrate pharmacotherapy carefully  
44  
45 305 and be cautious about the drug interactions and adverse side effects when treating OA,  
46  
47 306 depression, anxiety and pain holistically<sup>30</sup>. Two or more of the comorbidities that we  
48  
49 307 examined coexist in a substantial proportion of people with OA – approximately 22% in  
50  
51 308 total. Obesity, which we were unable to study using administrative data is also prevalent  
52  
53 309 amongst people with OA and a risk factor for developing OA<sup>41,42</sup>. From a clinical practice  
54  
55 310 perspective, a physician has to consider the implications of prescribing non-steroidal anti-  
56  
57 311 inflammatory medications for pain management, but this may worsen hypertension and  
58  
59 312 have an associated increased risk of cardiovascular disease. However, without good pain  
60  
313 management, it is difficult for patients with OA to engage in exercise programs which can  
314 help improve their muscular condition and potentially reduce obesity and hypertension.  
315 This is further complicated by the relationship of lower socioeconomic status with an  
316 increased risk of developing OA as demonstrated in the project for an Ontario Women's  
317 Health Evidence-based Report<sup>29</sup>.

1  
2  
3 318 Furthermore, our analyses showed that depression not only was the most prevalent  
4 319 comorbidity after age-standardization in people with OA, but that rates of depression were  
5 320 significantly higher for females and younger people (< 44 years old). The study by  
6 321 Dibonaventura et al. (2011) reported that people under 65 years of age were still  
7 322 participating in the workforce, however OA pain resulted in significantly lower  
8 323 productivity and higher costs compared to those without OA pain<sup>8</sup>. They identified unique  
9 324 treatment gaps for patients younger than 60 years old because the non-operative treatment  
10 325 options were ineffective in long-term management of OA symptoms, but young patients  
11 326 were too young or maybe unwilling to undergo definitive treatment such as total joint  
12 327 replacement<sup>43</sup>. Even for those patients who undergo total joint replacement, they were more  
13 328 likely to be dissatisfied about the treatment than older patients, and reported poorer  
14 329 outcomes including residual pain and stiffness<sup>44,45</sup>. A survey of orthopedic surgeons found  
15 330 that 84% perceived a need for better treatment for younger (<60 years old) physically active  
16 331 OA patients, and 68.4% perceived that there is a treatment gap for these patients<sup>43</sup>. Due to  
17 332 the different presentations of comorbidities and treatment options among young and old age  
18 333 groups, it is imperative to examine the impact of comorbidities on management strategies in  
19 334 an age-stratified OA cohort.

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21  
22 335 Most clinical practice guidelines focus on single conditions<sup>46</sup>. Fortin et al. (2011)  
23 336 concluded that even though the quality of the Canadian guidelines was good, their  
24 337 relevance for patients with two or more chronic conditions was limited<sup>47</sup>. Boyd et al. (2005)  
25 338 highlighted the lack of consideration of comorbidities in clinical practice guidelines may  
26 339 result in poor quality of care because the health care some patients received was not  
27 340 optimal<sup>48</sup>. Sharma et al., (2016) pointed out that the present literature fails to fully address  
28 341 the management strategies when dealing with comorbidities seen in people with OA<sup>30</sup>.  
29 342 Patient-centered care has been recommended in clinical practice guidelines with the aim of  
30 343 improving quality of care by focusing on the patient as a whole rather than on a single  
31 344 disease<sup>49</sup>. From a system perspective, patients with several comorbidities were also the  
32 345 main users of healthcare resources and services<sup>50</sup>. Patient-centered and coordinated care for  
33 346 these patients may decrease related health care use<sup>51</sup>. It was recommended that physicians  
34 347 consider these comorbidities in the management of people with OA.

35 348 A strength of our study is the large population-based number of people with OA  
36 349 (n=497,362) and the investigation of a group of eight comorbidities that are clinically  
37 350 relevant to the management of people with OA. These eight comorbidities among people

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3 351 with OA has been reported in previous studies, but only on an individual basis or in groups  
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5 352 of a subset of these comorbidities. Our study is the first one to include all of these  
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7 353 comorbidities, which is necessary to understand the clinical context for managing these  
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9 354 patients. Furthermore, our analysis also delineates the patterns of occurrence and co-  
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11 355 occurrence of these comorbidities regarding the prevalence of comorbidities that is relevant  
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13 356 for planning and delivery of health services for this growing population of people with OA.  
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15 357 We applied case definitions for administrative health data to identify cases of OA and each  
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17 358 of the comorbidities at the diagnosis of OA. A limitation of our study is that case  
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19 359 identification based on administrative data may result in underreporting of cases and  
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21 360 comorbidities. The case definitions for OA in administrative data research <sup>5</sup>, based on the  
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23 361 physician claims and hospitalizations records, have been applied and validated with a  
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25 362 sensitivity of 24%, high specificity of 98% and a positive predictive value of 54%<sup>11</sup>. In our  
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27 363 study, we also included ACCS/NACRS to mitigate the issue of underestimations<sup>6</sup>.  
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29 364 Nonetheless, the estimated number of OA cases using this approach is almost certainly an  
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31 365 underestimate. Similarly, the algorithms for comorbidities may underestimate the  
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33 366 prevalence of these comorbidities; the sensitivity for identifying depression is from 36% to  
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35 367 51% <sup>19</sup>, for PVD is 39%<sup>18</sup> and for COPD is 53% <sup>21</sup> in administrative data (Appendix 2).  
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37 368 More importantly, the reported levels of comorbidity in patients with OA were measured at  
38  
39 369 the time of OA diagnosis. New cases of comorbidity diagnosed after the OA diagnosis were  
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41 370 not identified. Further, we limited our analysis to eight comorbidities of clinical relevance  
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43 371 and for which there were case definitions in administrative data.

## 40 372 **5. Conclusions**

41  
42 373 We found that, depression, COPD and hypertension were the three most prevalent  
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44 374 comorbidities in people with OA, with rates significantly higher in females compared to  
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46 375 males. Of particular note is that the largest number of people with OA and depression are in  
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48 376 the age group between 45 and 64 years old, with the highest percentage of cases occurring  
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50 377 in the younger age groups (<44 years). Our findings highlight the need to recognize that  
51  
52 378 people with OA have high rates of comorbidities and this may affect optimal health care  
53  
54 379 management of these patients.

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55  
56  
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### 383 **Contributions**

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

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

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

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

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

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### 406 **Data availability**

407 These data are not available because Alberta Health and Alberta Health Services are  
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### 409 **Competing interests**

410 The authors confirm that there is no financial support or other benefits from  
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3 412 interests that the authors may have which could create a potential conflict of interest with  
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5 413 regards to the work in the manuscript.  
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9 415 Figure 1 Percentage of specific comorbid conditions among the population with OA in each  
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11 416 age group (<45, 45-64, and >=65 years). The difference by age group was statistically  
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13 417 significant for each comorbid conditions ( $p<0.0001$ ), as was the frequency of the number of  
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15 418 comorbidities present per individual ( $p<0.0001$ ).  
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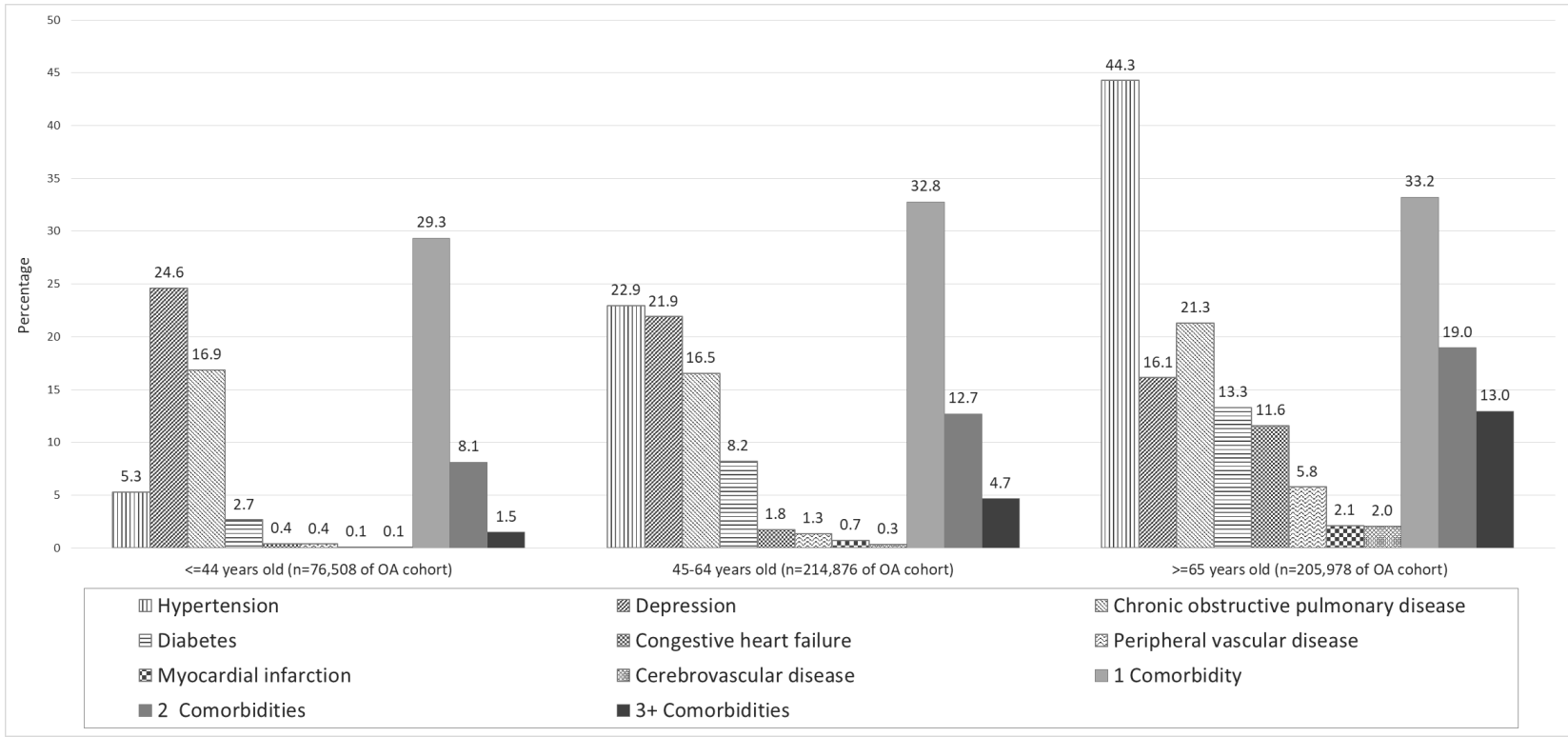


Figure 1 Percentage of specific comorbid conditions among the population with OA in each age group (<45, 45-64, and >=65 years). The difference by age group was statistically significant for each comorbid conditions (p<0.0001), as was the frequency of the number of comorbidities present per individual (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
<b>Myocardial Infarction</b>	410	I21, I22	N/A	1 hospitalization for MI, with diagnoses codes in primary or secondary diagnosis fields.	McCormick et al., 2014 <sup>13</sup> Quan et al., 2005 <sup>22</sup>
<b>Cerebrovascular Disease</b>	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 <sup>15</sup>
<b>Congestive Heart Failure</b>	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 <sup>16</sup> Quan et al., 2005 <sup>22</sup> Lee et al., 2005
<b>Peripheral Vascular Disease</b>	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 <sup>17</sup>
<b>Chronic Obstructive Pulmonary Disease</b>	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 <sup>20</sup> Quan et al., 2005 <sup>22</sup>
<b>Depression</b>	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 <sup>18</sup> Lix et al., 2006 Martens et al., 2010

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<b>Diabetes</b>	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 <sup>21</sup> Leong et al., 2013 <sup>19</sup> Hux et al., 2002
<b>Hypertension</b>	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 <sup>14</sup>

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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
<b>Total</b>	<b>87,567</b>	<b>56,886</b>	<b>287,951</b>	<b>209,411</b>	<b>304</b>	<b>272</b>

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
<b>Total</b>	<b>87,567</b>	<b>56,886</b>	<b>287,951</b>	<b>209,411</b>	<b>304</b>	<b>272</b>

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

	Item No	Recommendation	Pages
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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 alternative OA case definitions has been conducted previously. Please refer to Marshall et. al. (2015).
<b>Results</b>			
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 alternative OA case definitions has been conducted previously. Please refer to Marshall et al. (2015).
<b>Discussion</b>			
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
<b>Other information</b>			
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



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2 <http://www.annals.org/>, and *Epidemiology* at <http://www.epidem.com/>). Information on the STROBE Initiative is  
3 available at [www.strobe-statement.org](http://www.strobe-statement.org).  
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