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Risk of Comorbidities Following Physician-Diagnosed Knee or Hip Osteoarthritis: A Register-Based Cohort Study

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Objective. To estimate the risk of developing comorbidities in patients after physician-diagnosed knee or hip osteoarthritis (OA).

Methods. This was a cohort study using Swedish longitudinal health care register data; we studied residents in the Skåne region age ≥35 years on January 1, 2010 who were free from diagnosed hip or knee OA (n = 548,681). We then identified subjects with at least 1 new diagnosis of knee or hip OA (incident OA) between 2010 and 2017 (n = 50,942 considered exposed). Subjects without diagnosed OA were considered unexposed. From January 2010 both unexposed and exposed subjects were observed for the occurrence of 18 different predefined comorbidities until either relocation outside of the region, death, occurrence of the comorbidity, or December 2017, whichever came first. We calculated unadjusted hazard ratios (HRs) and adjusted HRs of comorbidities using Cox models with knee and hip OA as time-varying exposures.

Results. Subjects with incident knee or hip OA had 7% to 60% higher adjusted HRs (range 1.07–1.60) of depression, cardiovascular diseases, back pain, and osteoporosis than individuals without an OA diagnosis. An increased risk of diabetes mellitus was found only for knee OA (adjusted HR 1.19 [95% confidence interval 1.13–1.26]). For the rest of the diagnoses, we found either no increased risk or estimates with wide confidence intervals, excluding clear interpretations of the direction or size of effects.

Conclusion. Incident physician-diagnosed knee and hip OA is associated with an increased risk of depression, cardiovascular diseases, back pain, osteoporosis, and diabetes mellitus. However, the latter was only found for knee OA.

INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic conditions and ranks 12th among 359 specific diagnoses contributing the most to global disability (1). Knee and hip OA are responsible for the largest burden caused by OA (2) and are associated with substantial joint pain and reduced function and quality of life in populations worldwide (2). Historically, OA has been considered a joint-specific "wear and tear" degenerative disease; however, recent research has revealed that it is a complex disorder with multiple genetic, constitutional, and environmental risk factors (3), which may also increase the risk of other chronic conditions. In this regard, a recent systematic review reported a pooled comorbidity prevalence of 67% in people with OA; approximately 20% higher than age and sex-matched controls without OA (4).

Common comorbidities among people with OA include conditions of the cardiovascular, neurologic, endocrine, and psychological systems (4,5). Several mechanisms may explain these relations, including obesity and the often reported low-grade inflammation associated with OA, which is hypothesized to increase the risk of cardiovascular disease and diabetes mellitus (6), as well as pain and disability that may limit physical activity, influencing other risk factors for chronic conditions, e.g., further weight gain (6). Furthermore, apart from a few studies on cardiovascular diseases and diabetes mellitus (7), research on the association between OA and specific comorbidities has often been limited to cross-sectional studies (4,5,8), restricting any

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SIGNIFICANCE & INNOVATIONS

- In this longitudinal study of approximately half a million Swedish residents, we investigated the temporality between incident knee or hip osteoarthritis (OA) and comorbidity. We found that people with incident physician-diagnosed knee or hip OA are at increased risks of subsequent diagnoses of depression, cardiovascular diseases, diabetes mellitus, and back pain.
- Our results highlight the importance of considering knee and hip OA as clinically relevant and potentially modifiable risk factors in the prevention of other chronic conditions, including cardiovascular diseases, diabetes mellitus, depression, and back pain.

interpretation of the temporal or potentially causal relationship. New knowledge, taking into account the time sequence between OA and other comorbidities may be an important initial step to shed light on any temporality between OA and comorbidities. Therefore, the main aim of this explorative study was to estimate the hazard of developing a number of specific comorbidities in people with incident physician-diagnosed knee or hip OA compared to people without OA using a longitudinal study design.

MATERIALS AND METHODS

Data sources. We conducted a cohort study using data from 3 registers that comprise the entire population of Skåne, the southernmost region in Sweden, with approximately 1.23 million inhabitants (one-eighth of the Swedish population) in the year 2009. From the Swedish Population Register we retrieved data on age, sex, residential addresses, and deaths, while individual-level data on income, education, marital status, and country of birth were retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by the Swedish acronym). Last, from the Skåne Healthcare Register (SHR), we extracted information about diagnoses at any health care visit. SHR is a regional mandatory register that contains the publicly practicing physicians' diagnostic codes according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). These codes are assigned at the time of the health care visit by the physicians themselves and are automatically transferred to the register from the electronic medical records. The positive predictive value of a knee OA diagnosis in SHR has previously been reported to be 88% (9). All data from the different registers were linked through the coded personal unique identification number that is assigned to all residents in Sweden by the Swedish Tax Agency. The study was approved by the Regional Ethical Review Board in Lund, Sweden, and is reported according to the Strengthening the Reporting of Observational studies in Epidemiology guideline (10).

Study design, exposures, and outcomes. The cohort consisted of individuals age ≥35 years on January 1, 2010 who were residents in the Skåne region between January 1, 1998 and January 1, 2010. Only people with at least 1 health care visit with any diagnosis registered during this period (96% of eligible persons) were included, to minimize potential confounding due to propensity to seek care. People had to be at risk for both exposures (knee/hip OA, i.e., individuals were excluded if they had prevalent knee or hip OA) and for an outcome of interest (one of the 18 comorbidities) on January 1, 2010, and they were followed up until relocation outside of the region, death, a diagnosis of the comorbidity of interest, or December 31, 2017, whichever occurred first.

The exposure of interest was incident physician-diagnosed knee and hip OA (ICD-10 codes M17 and M16). We defined individuals as exposed if no diagnosis was recorded between January 1, 1998 and December 31, 2009 and a new diagnosis was received between January 1, 2010 and December 31, 2017 (Figure 1). Individuals with both knee and hip OA diagnoses were classified according to the first diagnostic code they received. Those with no record of either knee or hip OA diagnosis were defined as not exposed. The time from the start of follow-up to the date of the first knee or hip OA diagnosis (index date) was treated as unexposed, while the time after the OA diagnosis was treated as exposed (Figure 1).

The outcome of interest was a new diagnosis (ICD-10 code) of any of the following 18 conditions between January 1, 2010 and December 31, 2017: depression, Alzheimer's disease, other dementia, hypertension, ischemic heart diseases, heart failure,

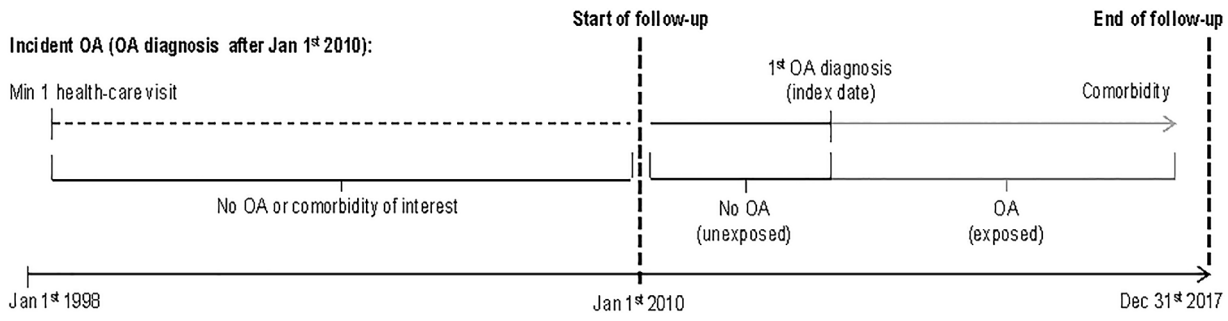

Figure 1. Study design for incident knee or hip osteoarthritis (OA). Min = minimum.

Table 1. Descriptive characteristics of the study cohort at start of follow-up (January 1, 2010)*

Characteristic (ICD-10 code)	No OA (n = 497,739)	Incident knee OA (n = 36,465)	Incident hip OA (n = 14,477)
Age at beginning of follow-up, mean ± SD years	57.3 ± 14.6	62.2 ± 12.2	65.3 ± 11.7
Women	254,593 (51)	21,553 (59)	8,306 (57)
Married†	350,172 (70)	27,955 (77)	10,937 (76)
Born in Sweden‡	422,713 (85)	31,292 (86)	12,949 (89)
Education up to 9 years§	128,738 (26)	11,364 (31)	4,745 (33)
Education, 10–12 years§	222,147 (45)	16,390 (45)	6,050 (42)
Education, 13–14 years§	59,950 (12)	3,908 (11)	1,556 (11)
Education ≥15 years§	83,620 (17)	4,590 (13)	2,065 (14)
Income in 100,000 SEK, median (interquartile range)¶	2.0 (1.3–2.7)	1.8 (1.3–2.5)	1.7 (1.3–2.5)
Alcohol-related disorders (F10)	11,694 (2)	667 (2)	322 (2)
Depression (F32.0–F33.9)	43,413 (9)	3,554 (10)	1,350 (9)
Alzheimer's disease (F00.0–F00.9, G30.0–F30.9)	2,425 (0)	91 (0)	30 (0)
Other dementia (F01.0–F03.0, G31.0–G31.1, G31.8–G32.8)	428 (0)	12 (0)	4 (0)
Hypertension (I10.0–I15.9)	99,937 (20)	10,440 (29)	4,569 (32)
Ischemic heart diseases (I20.0–I25.9)	39,246 (8)	3,491 (10)	1,733 (12)
Heart failure (I50.0–I50.9)	17,509 (4)	1,171 (3)	582 (4)
Cerebrovascular disease (I60.0–I69.8)	22,072 (4)	1,550 (4)	780 (5)
Diabetes mellitus (E10.0–E14.9)	34,616 (7)	3,054 (8)	1,255 (9)
Lung cancer (tracheal, bronchus, and lung: C33.0–C34.9)	1,206 (0)	43 (0)	33 (0)
Colorectal cancer (C18.0–C21.8)	2,906 (1)	230 (1)	111 (1)
Breast cancer, women only (C50.0–C50.9)	7,508 (3)	754 (4)	340 (4)
Prostate cancer, men only (C61)	7,634 (3)	644 (4)	351 (6)
Hip fracture (S72.0–S72.2)	7,406 (1)	327 (1)	334 (2)
Forearm fracture (S52.0–S52.9)	17,082 (3)	1,574 (4)	672 (5)
Ankle fracture (S82.3, S82.5–S82.6, S82.8)	8,370 (2)	699 (2)	307 (2)
Back pain (G54.2, G54.4, M47–M49, M49.2–M51.9, M53, M54.9, M99–M99.04, M99.1–M99.14, M99.2–M99.24, M99.3–M99.34, M99.4–M99.44, M99.5–M99.54, M99.6, M99.64, M99.7–M99.74, M99.8–M99.84)	88,552 (18)	8,827 (24)	3,672 (25)
Osteoporosis (M80.0–M82.8)	14,621 (3)	1,467 (4)	716 (5)
Chronic lower respiratory diseases (COPD, bronchitis, emphysema: J40–J44.9)	5,526 (1)	463 (1)	219 (2)

* Values are the number (%) unless indicated otherwise. Comorbidity codes are from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), at the start of follow-up as registered in the Skåne Healthcare Register during 1998–2009. COPD = chronic obstructive pulmonary disease; OA = osteoarthritis; SEK = Swedish Krona.
† Missing: n = 29.
‡ Missing: n = 44.
§ Missing: n = 3,558.
¶ Missing: n = 29.

cerebrovascular disease, diabetes mellitus, lung cancer (tracheal, bronchus, and lung), colorectal cancer, breast (in women only) and prostate cancer (in men only), fracture to the hip (neck of femur, pertrochanteric, and subtrochanteric), fracture to the forearm (radius and ulna), fracture to the ankle (lower end of tibia, and medial and lateral malleolus), back pain (neck and low back), osteoporosis, and chronic lower respiratory diseases (chronic obstructive pulmonary disease, bronchitis, and emphysema) (Table 1). These are among the most frequent conditions coexisting with OA (4,5,11), the most common cancer types (12), and the most common fractures among the elderly (13,14). In the analysis of the incidence of each comorbidity, individuals with a diagnostic code of that specific condition between January 1, 1998 and December 31, 2009 were excluded from the calculation of the hazard ratio (HR) for that comorbidity. In a sensitivity analysis, we analyzed people with prevalent OA, which was defined as having at least 1 diagnostic code for knee OA (ICD-10 code M17) or hip OA (M16) in the period between January 1, 1998 and December 31, 2009. In this case, the exposure started at the beginning of the follow-up time (January 1, 2010).

Confounders. Sex, age, alcohol-related disorders, marital status, if born in Sweden, residential area, income, education in years, and comorbidities were considered confounders, as they can potentially influence both exposure (incident OA) and outcome (incident comorbidity). For included individuals, information on income, education, marital status, and country of birth, as reported in the year 2009, was retrieved from the LISA register held by Statistics Sweden. We categorized education according to its length: <10 years, 10–12 years, 13–14 years, and ≥15 years. Marital status (married/registered partner or other) and country of birth (Sweden or outside Sweden) were binary, while income was continuous. Residential area was extracted

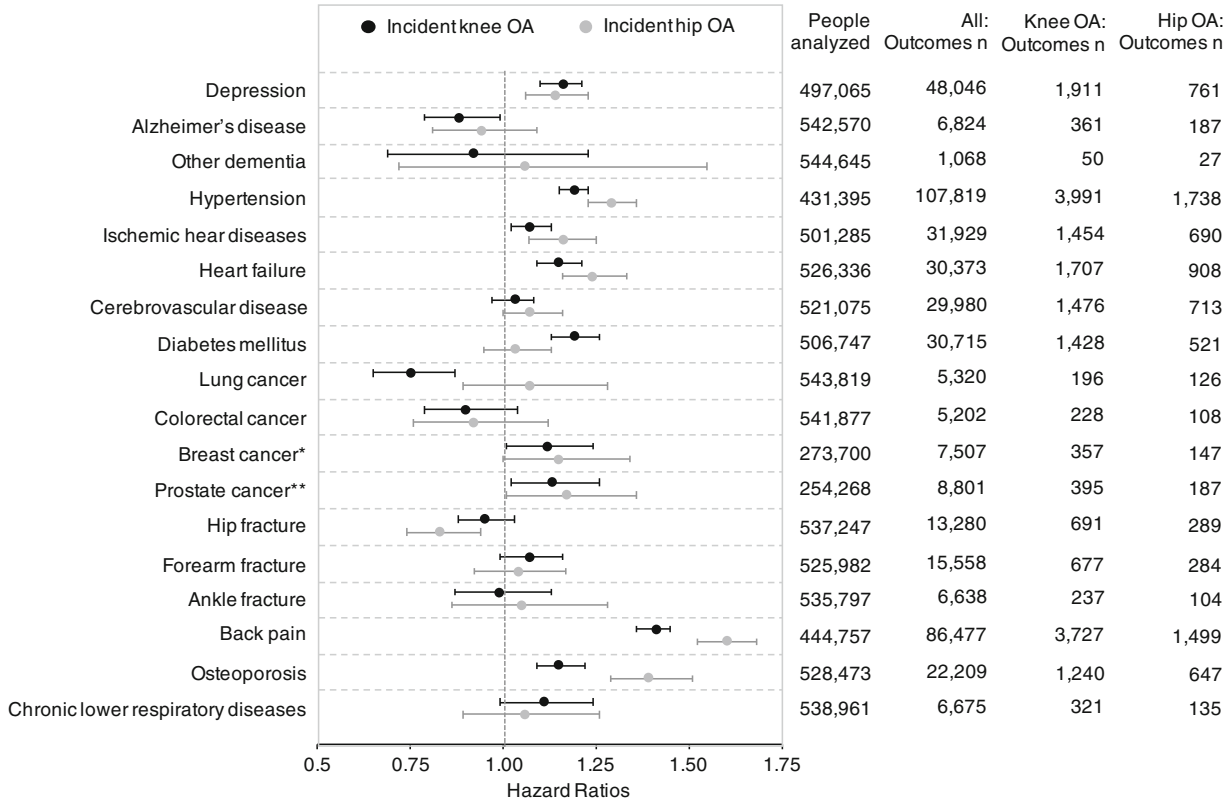

Figure 2. Adjusted hazard ratios of consultation for diseases occurring in persons with incident doctor-diagnosed knee or hip osteoarthritis (OA) compared to persons without OA. * = only women included in analysis; ** = only men included in analysis. Error bars show 95% confidence intervals. Complete crude and adjusted hazard ratios are available in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24717.

from the Swedish Population Register and was included as municipality. Information on diagnosed alcohol-related disorders (ICD-10 code F10) and all outcome conditions between January 1, 1998 and December 31, 2009 was retrieved from the SHR. Information on all covariates was collected up to the beginning of follow-up (January 1, 2010) and was not updated afterward to avoid adjusting for intermediates. Marital status and income were missing for 0.006% of all included individuals, while the country of birth was missing for 0.009% and education was missing for 0.7%. Those with missing data were a very low proportion and were thus excluded from the adjusted analyses.

Statistical analysis. Descriptive baseline data by exposure status are reported as means ± SDs, medians with interquartile ranges, or numbers with percentages as appropriate. We used the Cox proportional hazards model with calendar years as the time scale to estimate the HR of a diagnosis of each of the conditions of interest. Separate models were used for each outcome condition in which individuals diagnosed with the specific comorbidity of interest before January 1, 2010 were excluded. We adjusted all the analyses for baseline age, sex, socioeconomic status (residential area, income, and education), birth outside of Sweden, marital status, and the presence of a diagnosis of alcohol-related disorders or any of the outcome conditions (comorbidities) apart from the one analyzed. The proportional hazards assumption was evaluated using plots of Schoenfeld residuals, and no violations were detected (15). We repeated all analyses in sensitivity analyses using a stricter definition of knee and hip OA exposure (i.e., at least 2 diagnostic codes of knee or hip OA to be classified as exposed).

RESULTS

Study cohort. We included 548,681 Skåne residents with no prior records of knee or hip OA and age ≥35 years at the start of follow-up. Of these, 36,465 and 14,477 individuals were registered with at least 1 physician-recorded diagnostic code of knee or hip OA, respectively, during follow-up, i.e., considered incident OA. Those with incident OA were on average older at the start of follow-up than individuals without OA, were a higher proportion of women, and generally had a higher prevalence of comorbidities (Table 1).

Risk of comorbidities. The most common comorbidities during follow-up were depression, cardiovascular diseases, and back pain (Figure 2). In the adjusted analyses, individuals with newly diagnosed knee or hip OA had 7% to 60% higher hazards

of depression (knee OA adjusted HR 1.16 [95% confidence interval (95% CI) 1.10–1.21]; hip OA adjusted HR 1.14 [95% CI 1.06–1.23]), hypertension (knee OA adjusted HR 1.19 [95% CI 1.15–1.23]; hip OA adjusted HR 1.29 [95% CI 1.23–1.36]), ischemic heart diseases (knee OA adjusted HR 1.07 [95% CI 1.02–1.13]; hip OA adjusted HR 1.16 [95% CI 1.07–1.25]), heart failure (knee OA adjusted HR 1.15 [95% CI 1.09–1.21]; hip OA adjusted HR 1.24 [95% CI 1.16–1.33]), back pain (knee OA adjusted HR 1.41 [95% CI 1.36–1.45]; hip OA adjusted HR 1.60 [95% CI 1.52–1.68]), and osteoporosis (knee OA adjusted HR 1.15 [95% CI 1.09–1.22]; hip OA adjusted HR 1.39 [95% CI 1.29–1.51]) than individuals without an OA diagnosis (Figure 2 and Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24717). Only for knee OA, there was an association with diabetes mellitus (adjusted HR 1.19 [95% CI 1.13–1.26]), Alzheimer's disease (adjusted HR 0.88 [95% CI 0.79–0.99]), and lung cancer (adjusted HR 0.75 [95% CI 0.65–0.87]). Individuals with incident hip OA had lower hazards of hip fracture than those without OA (adjusted HR 0.83 [95% CI 0.74–0.94]), while no association was found for knee OA. For the rest of the diagnoses, we found either no association for individuals with knee or hip OA (i.e., HR estimates and their CIs close to 1.00) or estimates with wide CIs, excluding any clear interpretations of the direction or size of the effects (Figure 2).

In the sensitivity analysis for prevalent knee or hip OA, the observed associations were generally lower (i.e., HR closer to 1.00) than those observed among incident OA cases; however, for most comorbidities, the interpretations were similar (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24717). In the sensitivity analyses requiring 2 diagnostic OA codes (favoring high specificity of exposed), HRs were generally closer to 1.00 and had wider CIs than in the primary analyses (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24717). Nevertheless, the interpretation did not change for any of the comorbidities in the main analysis.

DISCUSSION

Our findings of this explorative population-based study of approximately half a million residents in Sweden show that people with physician-diagnosed OA are at increased risks of subsequent diagnoses of depression, cardiovascular diseases, diabetes mellitus, and back pain. Despite the large sample size, estimates for most other conditions were inconclusive due to wide confidence intervals.

Several studies have previously found that knee and hip OA are associated with an increased risk of cardiovascular diseases (7,16,17). Our results support these findings and add to the increasing confidence that a diagnosis of knee or hip OA is associated with a higher risk of developing cardiovascular diseases. In contrast, the association of increased risk of diabetes mellitus among individuals with knee and hip OA is less supported by our findings (18). Kendzerska et al report a larger risk of diabetes mellitus for hip OA than knee OA (18), as opposed to our study, where only knee OA was associated with diabetes mellitus. Similarly, Swain et al reported a higher risk of diabetes mellitus only in people with knee OA (17). Several factors may explain these diverse results, including difference in exposure (incident OA versus prevalent OA), difference in adjustment (we could not adjust for body mass index [BMI]), and potential residual confounders.

Other surprising findings are that people with incident knee OA appear to have a lower risk of lung cancer than people without OA. This finding might be because knee OA, to a larger extent than hip OA, is a result of a prior knee injury (19) possibly reflecting a group being physically active and in general having a healthy lifestyle. The finding is supported by 2 previous studies suggesting a reduced risk of cancer mortality in physician-diagnosed and radiographic knee OA (20,21). However, we found people with knee OA to be at higher risk of developing other types of cancer such as breast and prostate cancer but not colorectal cancer, while people with hip OA had an increased risk of developing prostate cancer only. The positive association between cancer and OA has been previously reported in other cohorts and may hypothetically be explained by the presence of low-grade inflammation in people with OA (17,22). However, the reason why only certain types of cancers appear associated with OA is not clear.

Another interesting finding is the reduced risk of consulting for Alzheimer's disease in people with knee OA. The current evidence on OA and dementia is inconsistent but appears to point toward a negative effect of OA on cognitive health (17,23,24). However, a recent meta-analysis suggested that a diagnosis of OA is associated with higher cognitive scores at baseline and with a delayed cognitive decline (25). Persons with early symptoms of dementia (on the road to later becoming diagnosed with Alzheimer's disease) may consult for their knee problems to a lesser extent than persons mentally fully alert. Thus, those with a lack of consultation do not get their incipient OA diagnosed to the same extent, leading to a biased estimate of association. Finally, people with hip OA appear to have a reduced risk of hip fracture. This finding is in line with previous literature showing no or protective association between hip OA and hip fracture (26,27).

All in all, there is evidence to suggest that the associations found in our study are biologically plausible. Low-grade inflammation, obesity, and reduced physical activity are part of the pathogenesis of OA (28) and can increase the risk of other comorbidities (6,29). Low-grade inflammation has been reported to be associated with a series of other factors, including depression symptoms (e.g., sleep problems, low energy level, and widespread pain), high BMI, insulin resistance, cancer, Alzheimer's disease, and diabetes mellitus development (30,31). Despite the fact that most of these associations have no clear directionality

and are still debated in the scientific community, the presence of low-grade inflammation may partially explain the association between OA and comorbidities (32).

Obesity has been associated with OA through several pathophysiologic pathways, including low-grade inflammation due to the production of proinflammatory cytokines by the adipose tissue (33). Furthermore, strong evidence from a meta-analysis of longitudinal studies shows the existence of a bidirectional association between obesity and depression (34). This association becomes stronger when abdominal fat rather than BMI is used to define obesity and when metabolic dysregulation (e.g., hypertension, dyslipidemia, insulin resistance) is taken into account (35,36). All the evidence appears to point toward the existence of a vicious cycle around OA, reduced physical activity, increased weight, and low-grade inflammation, which can favor the development of some of the diseases analyzed here as a result of shared pathophysiology (37,38).

Our results can have important clinical implications. On the one hand, the co-occurrence of these diseases may represent a major obstacle in the treatment of each condition separately and calls for a more comprehensive approach. On the other hand, our results highlight the importance of considering knee and hip OA as clinically relevant and potentially modifiable risk factors in the prevention of other chronic conditions, including cardiovascular diseases, diabetes mellitus, depression, and back pain. For instance, treatment strategies targeting shared disease mechanisms might be beneficial for more than a single condition. For example, lifestyle interventions aimed at modifying dietary habits while promoting increased physical activity may potentially improve OA symptoms while preventing subsequent development of other diseases (39). Identifying interventions able to improve OA symptoms and reduce the risk of developing commodities is particularly important given the fact that people with OA and other coexisting conditions report worse pain and more restricted participation in social and domestic life than individuals with OA and no comorbidities (40,41). However, to identify appropriate strategies to prevent the onset of commodities, a better understanding of the causal mechanisms by which OA may cause other conditions is needed.

This study has important limitations. First, because of the observational nature of the study, we could not determine any causal relationships between OA and comorbidities, which should be acknowledged when considering the findings. Second, we were not able to adjust for BMI, which is a major risk factor for OA, diabetes mellitus, and cardiovascular diseases, and thus lack of adjustment may have biased our estimates upward. Third, as always, there may be a certain degree of misclassification of disease in the register, which may lead to either under- or overestimation of the risk of developing comorbidities. However, the validity of the diagnostic coding in the register has been reported to be high and is expected to be largely nondifferential (9,42). Finally, we focused on the effect of incident OA and we followed up the participants for a maximum of 8 years, and thus we cannot draw conclusions on the risk of developing comorbidity in people with longer OA duration. The strengths of our study include the large population-based cohort of an entire region, which supports the generalizability of our findings to the broader population of adults having knee or hip OA, as well as our sensitivity analyses yielding similar results to the primary analyses. Nevertheless, several of the associations found have not previously been investigated and thus need to be confirmed in future studies and different countries and populations.

In conclusion, physician-diagnosed knee and hip OA seem to be associated with an increased risk of depression, cardiovascular diseases, back pain, and osteoporosis. Only knee OA seems to be associated with an increased risk of diabetes mellitus, while hip OA, in general, is associated with larger risks of most comorbidities than is knee OA. The findings highlight the fact that prevention and early and effective treatments of OA may be important to avoid the development of other chronic conditions.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Dell'Isola had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Dell'Isola, Pihl, Turkiewicz, Hughes, Zhang, Bierma-Zeinstra, Prieto-Alhambra, Englund.

Acquisition of data. Dell'Isola, Pihl, Turkiewicz, Englund.

Analysis and interpretation of data. Dell'Isola, Pihl, Turkiewicz.

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