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Osteoarthritis and Cartilage

Occurrence of comorbidity following osteoarthritis diagnosis: a cohort study in the Netherlands

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SUMMARY

Objective: To determine the risk of comorbidity following diagnosis of knee or hip osteoarthritis (OA).
Design: A cohort study was conducted using the Integrated Primary Care Information database, containing electronic health records of 2.5 million patients from the Netherlands. Adults at risk for OA were included. Diagnosis of knee or hip OA (=exposure) and 58 long-term comorbidities (=outcome) were defined by diagnostic codes following the International Classification of Primary Care coding system. Time between the start of follow-up and incident diagnosis of OA was defined as unexposed, and between diagnosis of OA and the end of follow-up as exposed. Age and sex adjusted hazard ratios (HRs) comparing comorbidity rates in exposed and unexposed patient time were estimated with 99.9% confidence intervals (CI).
Results: The study population consisted of 1,890,712 patients. For 30 of the 58 studied comorbidities, exposure to knee OA showed a HR larger than 1. Largest positive associations (HR with (99.9% CIs)) were found for obesity 2.55 (2.29−2.84) and fibromyalgia 2.06 (1.53−2.77). For two conditions a HR < 1 was found, other comorbidities showed no association with exposure to knee OA. For 26 comorbidities, exposure to hip OA showed a HR larger than 1. The largest were found for polymyalgia rheumatica 1.81 (1.41−2.32) and fibromyalgia 1.70 (1.10−2.63). All other comorbidities showed no associations with hip OA.
Conclusion: This study showed that many comorbidities were diagnosed more often in patients with knee or hip OA. This suggests that the management of OA should consider the risk of other long-term-conditions.

Introduction

Osteoarthritis (OA) is a chronic and burdensome disease and is one of the leading causes of disability worldwide[1]. The prevalence and associated disease burden of OA are expected to continue to rise due to the increase in obesity and the aging of the population[2].

According to Feinstein, comorbidity is defined as “any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study”[3]. Such additional conditions can adversely affect the clinical course of OA, as strong evidence was found for increased disease progression in the presence of comorbidities[4]. Furthermore, comorbidities may negatively affect the applicability of treatment options and symptom management, and may contribute to an increased risk of potentially avoidable hospitalizations in patients with OA[5–7]. These and other disadvantages of comorbidities add to the burden of OA, and emphasize the need to examine the occurrence and patterns of (chronic) comorbidity in patients with OA. Awareness of commonly

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developing comorbidities and early diagnosis of both OA and comorbidities are required to alleviate their huge burden, for example through better prevention and self-management of chronic conditions[1,8].

Previous studies have been published on comorbidity in OA. Many initially focused on cardiovascular and metabolic comorbidities, which have shown to be associated to OA in several meta-analyses[9–12]. One of the first studies investigating a wider variety of comorbidities, while also taking into account the temporality of disease onset in relation to OA, was conducted by Kadam *et al.*, in 2004[13]. The study investigated prevalence of comorbidities in OA cases compared to non-OA controls in a UK database; a study design replicated by Swain *et al.* 17 years later[14]. Another observational study on the prevalence of comorbidity prior to OA diagnosis was conducted in Canada in 2019, but this study did not compare rates between OA and non-OA patients[15].

The aim of the current study was to determine the risk of general practitioner (GP)-diagnosed comorbidity after incident knee or hip OA and to compare this with the risk of comorbidity without prior diagnosis of OA. This makes this study a validation of a recently published study of Dell'isola *et al.*, which also examined comorbidity as an outcome and used a time-varying variable for OA as exposure[16]. The present study is the first of its kind that is conducted in the Netherlands, using a large primary care database. To make a significant contribution to the growing body of knowledge on this topic, a wider range of 58 specifically pre-defined comorbidities were examined. Together with the aforementioned studies of Dell'isola *et al.* and Swain *et al.*, this study was part of a multicentre collaboration of which the details are described in a protocol paper[17].

Methods

Study source

A retrospective cohort study was conducted using data from the Integrated Primary Care Information (IPCI) database[18,19]. The IPCI database was initiated in 1992 and today contains routinely collected data from electronic health records of more than 2.5 million patients, representative of the general Dutch population. In the Netherlands, the GP acts as a gatekeeper for access to secondary care and almost all citizens are registered with one. Relevant information obtained during consultations is reported in the patients' electronic record. At every consultation, the GP also registers a symptom, complaint or diagnosis code according to the International Classification of Primary Care (ICPC) coding system[20]. Furthermore, demographic data, test results, drug prescriptions (according to the World Health Organization Anatomical Therapeutical Chemical classification), and correspondence with secondary care, such as referral and discharge letters are collected in the electronic record[21].

IPCI is a dynamic database where patients can enter the database on the date their practice started participating in IPCI, or from the date patients registered at another practice that already participated in IPCI. However, patient data only becomes available for research purposes at the IPCI start date, which is at least 1 year after registration. In this way, there is a protected window of time for the practice to complete the medical history and fill in prevalent diagnoses in the patient record, preventing researchers from counting previous conditions as incident diagnoses. Other quality rules are described in detail elsewhere[19]. The data is routinely collected per participating practice and available until the most recent data extraction date, i.e., the IPCI end date. Data availability may have ended earlier if patients died or deregistered, e.g., after moving to another district, or when their practice stopped participating in IPCI.

The scientific and ethical advisory board of the IPCI project approved the study (registration number 11/2019).

Study population

The study population consisted of patients from IPCI aged 18 years or older that were at risk for incident OA. Patients' follow-up started at the IPCI start date, but no earlier than January 1st, 2006. Follow-up ended at the IPCI end date, the patients' date of death or at December 31st, 2019, whichever came first.

Exposure & outcome

Knee and hip OA were considered the exposures in the analyses. Diagnosis of knee or hip OA was defined as the first registration of a corresponding ICPC code in the patients' record, which was L90 for knee and L89 for hip OA. The entire available look-back period in the patients' records was used to screen for the first registered code, which could maximally be from the start of IPCI in 1992 to the start of follow-up. If the first OA diagnosis was recorded prior to the start of follow-up, the patient was not considered to be at risk for OA and therefore excluded from the study population.

As this was an explorative study, the choice for comorbidities was based on criteria such as global prevalence, impact & burden of the conditions. Therefore, diseases recommended by the European League Against Rheumatism for studying comorbidity, the most prevalent and burdensome diseases according to the Global Burden of Disease study, mortality affecting diseases included in the Charlson comorbidity index, diseases from a research tool for chronic conditions in primary care, and diseases that previously showed associations with OA in comorbidity pattern studies were all considered as outcomes[22–27]. Eventually, 58 comorbidities were selected and, like OA, were defined based on their corresponding ICPC codes. The referring ICPC codes were required to have maintained a fixed and valid definition throughout the history of the IPCI database and to be disease specific. For example, diseases of the blood vessels were divided into 'peripheral vascular disease', 'thromboembolic disease' and 'coronary artery disease', all of which have different underlying disease mechanisms and risk factors. A full list of the comorbidities and their ICPC codes can be found in Supplementary Table S1.

Statistical analysis

Characteristics for non-OA, knee OA and hip OA patients were presented as means and standard deviations (SDs), medians and inter quartile ranges (IQRs) or percentages, depending on data type and distribution. Survival analyses were performed for each comorbidity separately. In each analysis, patients who were already diagnosed with the comorbidity of interest at the start of follow-up were excluded. Hip and knee OA were analyzed separately. When a patient had both a code for incident knee and hip OA during the follow up period, the code recorded first was leading for which analysis the patient was included in. Therefore, patients with both codes were only included in either the knee or the hip analysis. Exposure to incident hip or knee OA was treated as a time-varying variable: the time between the start of follow-up and first diagnosis of OA was defined as unexposed time, and from the date of OA diagnosis to the end of follow-up as exposed time. A diagnosis of the comorbidity of interest was defined as outcome event, and when the follow-up ended because of deregistration, death or the end of the study period, this was defined as no event (i.e., censoring). See Fig. 1 for a schematic overview.

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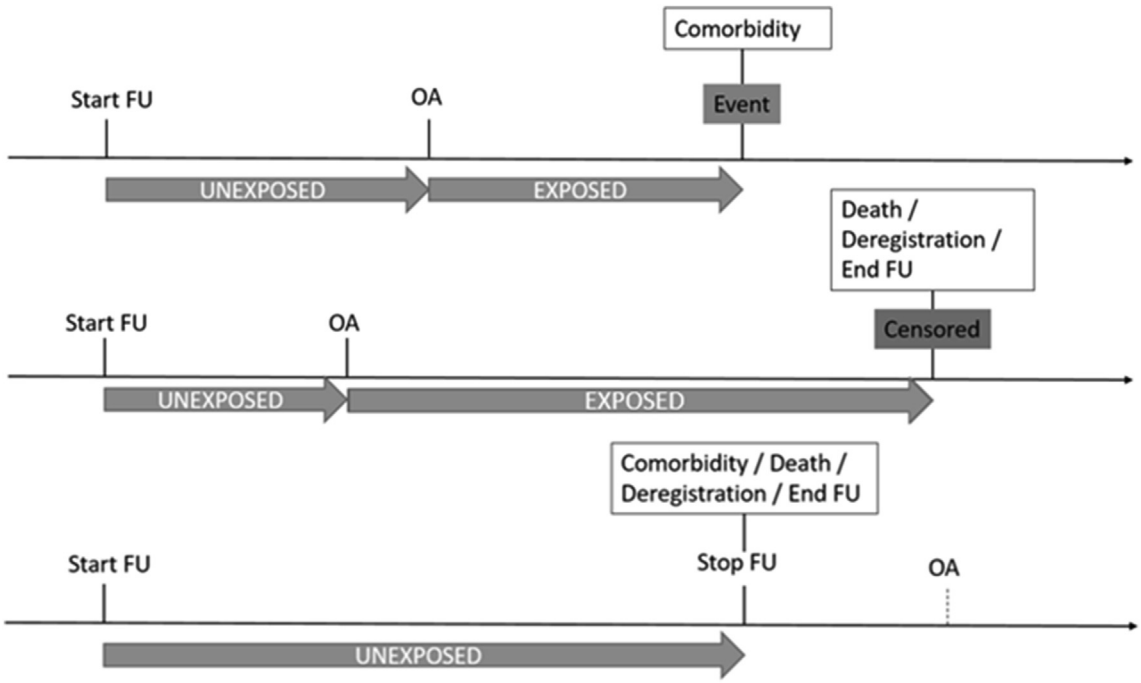

Fig. 1

Osteoarthritis and Cartilage

A schematic representation of how patients' follow-up time was allocated, including how exposure was used as a time-varying variable. The top timeline shows how the follow-up time of this patient is classified as unexposed from the start, and after the incident OA diagnosis changes exposed. Follow-up stops because this patient is diagnosed with the investigated comorbidity/outcome, which is considered an event in the survival analysis. The second timeline also represents a patient with incident OA during the follow-up. However, the follow-up time ends here due to a death, deregistration from IPCI or the end of the study period (December 31, 2019), which is included in the survival analysis as censored. Finally, the bottom timeline shows that patients sometimes do not develop OA (not at all, or not prior to being censored) and therefore only have unexposed time. Abbreviations: FU = follow-up, OA = diagnosis date of incident knee or hip OA.

Time-to-event hazard ratios (HRs) were calculated between exposed and unexposed time and were adjusted for patients' sex. In all analyses, patients' age in years was used as time scale to adjust for age while taking into account potential fluctuations in the effect of age on the development of comorbidities. HRs were displayed with 99.9% confidence intervals (CIs), corresponding to a *P*-value <0.001 that was used as the cut-off for significance to correct for multiple testing.

In addition, a secondary analysis was performed to determine the HRs for comorbidities occurring in the first year after diagnosis of OA only, to see which comorbidities were diagnosed more often shortly after incident OA (compared to >1 year after OA until end of follow-up, and to no OA). The aim of this secondary analysis was to get an impression of the double diagnoses or misclassification that potentially occurred with conditions that resemble OA. We hypothesized that 'similar to OA presenting comorbidities' with larger HRs in the year immediately after incident OA compared to in the main analysis, were likely to be registered for the same joint complaints. They may have been confused with OA, or were initially thought to be OA but the GP switched to a different working diagnosis later resulting in misclassification. Finally, an additional analysis was performed where care avoiders, defined as individuals registered in IPCI without any recorded diagnostic code of the 58 examined long-term comorbidities or OA in their entire patient records, were excluded from the study population. The main analysis for exposure to knee OA was performed on this population. The aim of this additional analysis was to get an impression of the extent to which informative presence bias may have affected the results[28]. The statistical analyses were performed using R (software version 4.0.2).

Results

The study population consisted of 1,891,066 patients, of whom 80,425 were registered with an incident OA diagnosis code (45% with 'knee OA', 28% with 'hip OA' and the remainder with 'other OA') after a median of 2.9 years of follow-up. Those with incident knee or hip OA were on average older than individuals without OA at the start of follow-up and had a higher proportion of women. See Table I for the population characteristics.

For 30 of the 58 studied comorbidities, exposure to knee OA showed a HR statistically significant larger than 1, indicating an increased risk of being diagnosed with these comorbidities after a diagnosis of knee OA. The largest positive associations (HR with (99.9% CIs)) were found for obesity 2.55 (2.29–2.84), fibromyalgia 2.06 (1.53–2.77), polymyalgia rheumatica 1.72 (1.38–2.14), drug abuse 1.53 (1.21–1.94), and rheumatoid arthritis (RA) 1.52 (1.28–1.81). For chronic obstructive pulmonary disease (COPD) 0.80 (0.70–0.91) and tobacco abuse 0.86 (0.75–0.99) there was a statistically significant negative association (HR < 1) with exposure

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	Non OA ($N = 1.810.641$)	Incident knee OA ($N = 36.194$)	Incident hip OA ($N = 22.162$)
Age at start follow-up, mean (SD)	42.8 (18.0)	63.4 (12.3)	65.3 (12.0)
Sex, percentage female	50.3	61.6	62.3
Follow-up until OA diagnosis, median (IQR)	–	2.9 (1.3–5.0)	2.8 (1.2–4.8)

Table I Osteoarthritis and Cartilage

Characteristics of the study population

to knee OA. Other conditions did not show an association with previous exposure to OA.

For 26 comorbidities, exposure to hip OA showed a statistically significant HR larger than 1. The largest positive associations were found for polymyalgia rheumatica 1.81 (1.41–2.32), fibromyalgia 1.70 (1.10–2.63), spinal disc herniation 1.64 (1.49–1.80), thromboembolic disease 1.47 (1.28–1.70) and alcohol abuse 1.44 (1.11–1.88). There were no negatively associated comorbidities as for all other comorbidities the HRs of hip OA were non-significant. The HRs with 99.9% CI of all 58 comorbidities are visualized in Figs. 2–6, grouped per area of interest.

The secondary analysis, focusing on incident comorbidity diagnosed only in the first year after OA diagnosis, showed 26 comorbidities with a positive association with knee OA. All of them were also positively associated with knee OA in the main analysis. The three largest HRs were seen in obesity with 3.16 (2.65–3.77), polymyalgia rheumatica 2.32 (1.54–3.23) and thromboembolic disease 1.98 (1.62–2.40). For hip OA, 18 positively associated comorbidities were found among which polymyalgia rheumatica 3.22 (2.22–4.65), hepatitis 2.62 (1.15–6.01) and spinal disc herniation 2.16 (1.85–2.53) showed the largest HRs. Of these 18 comorbidities, depression, hepatitis and hypertension were associated with hip OA in the secondary analysis solely and not in the main analysis.

An overview of the results of both the main- and secondary analyses, including the number included in each analysis, number of comorbidity events, HRs with CIs and *P*-values, is added in Supplementary section S2–5.

Finally, for the additional analysis to investigate informative presence bias, 308,568 individuals (16.3% of the original study population in the main analysis) were excluded. 27 of the original 30 significantly associated comorbidities were still positively associated with exposure to knee OA, and the order of associations' magnitude remained largely unchanged. The HRs were on average slightly smaller, obesity for example went from HR of 2.55 to 2.42, fibromyalgia from 2.06 to 1.96, etc., but none of the outcomes changed more than a 0.1 difference. The same 2 comorbidities (COPD and tobacco abuse) showed a significantly negative association (HR < 1).

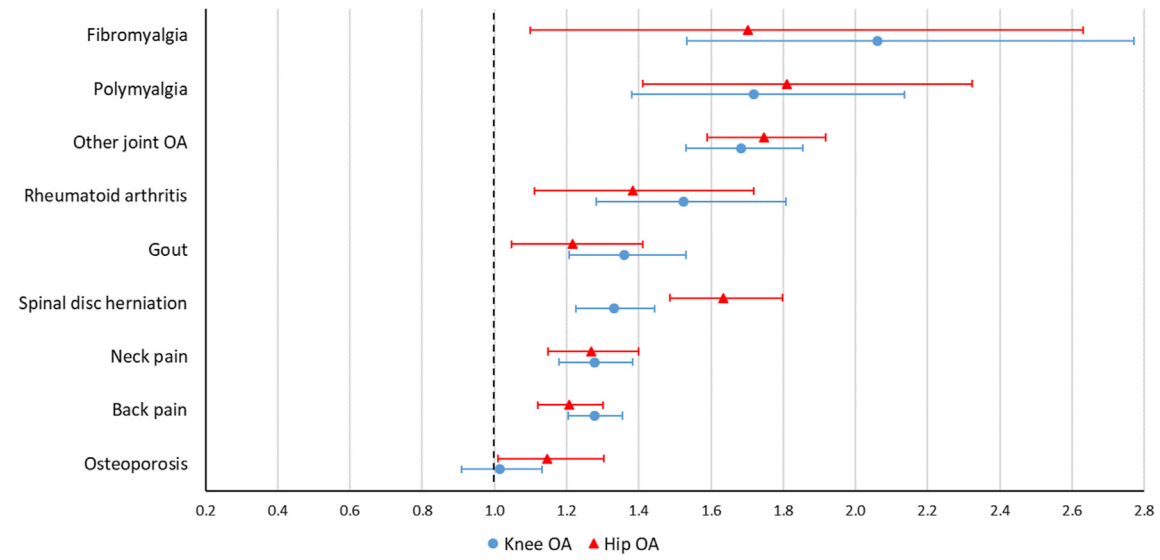

Fig. 2 Osteoarthritis and Cartilage

Hazard ratios of musculoskeletal comorbidities.

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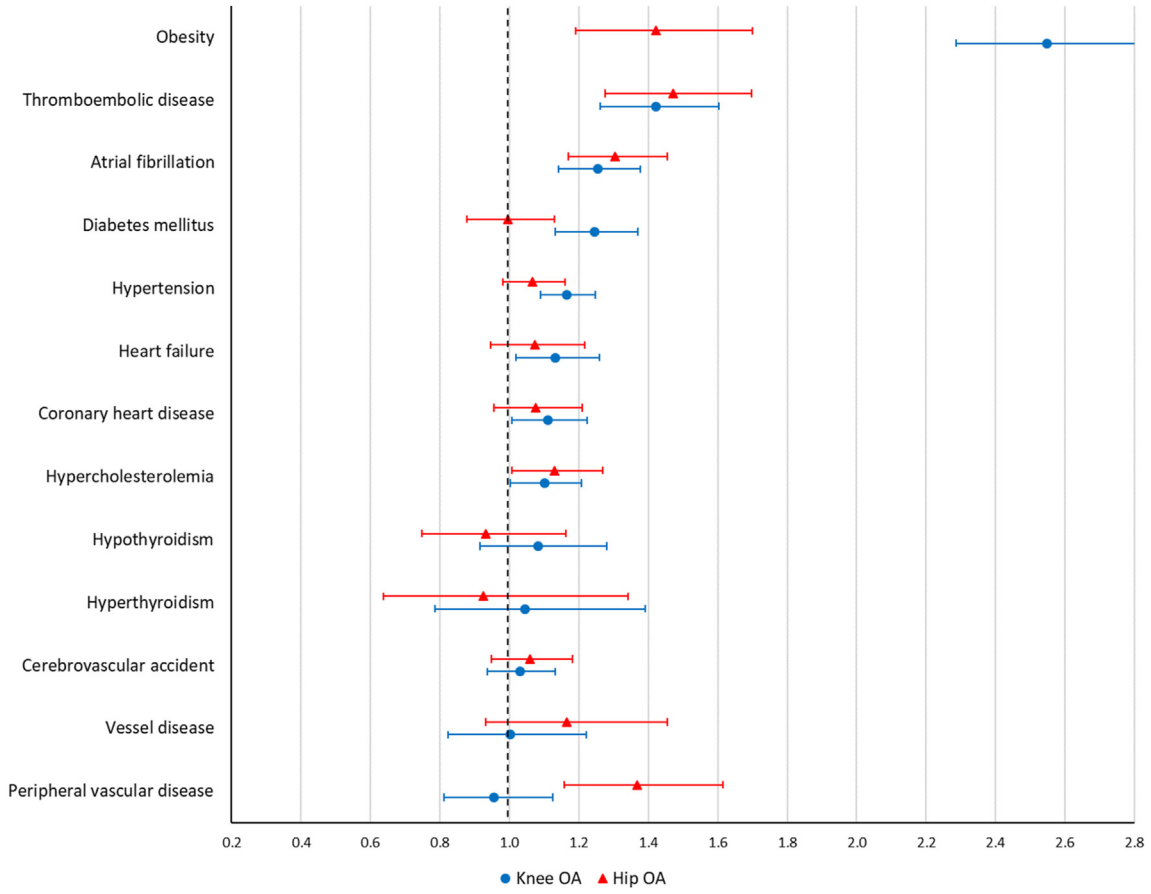

Fig. 3 Osteoarthritis and Cartilage

Hazard ratios of cardiovascular & metabolic comorbidities.

Discussion

Main findings

In this study, the risk of GP-diagnosed comorbidity following diagnosis of hip or knee OA was determined for 58 comorbidities, using a large primary care electronic health record database in the Netherlands. After a diagnosis with OA, patients had an increased risk of a subsequent diagnosis with approximately half of the comorbidities studied, compared to patients with no prior diagnosis of OA. Both knee and hip OA showed particularly strong associations with other musculoskeletal conditions, such as polymyalgia rheumatica and fibromyalgia, and with obesity, thromboembolic disease and sleeping disorders (HRs ranging between 1.42 and 2.55).

By assessing OA of the knee and hip separately, this study revealed interesting differences between site-specific OA comorbidity patterns. Within the large overlap between comorbidities associated with both knee and hip OA, some diseases were more prominently associated with one of the joints. For example, obesity had a 2.6 times higher hazard rate in patients with knee OA than in patients of the same age and sex without knee OA, representing the largest effect size found in the study, but it had a smaller association with hip OA (HR 1.4). Spinal disc herniation, on the other hand, was more prominently associated with hip OA than knee OA.

Furthermore, this study suggested that some comorbidities were exclusively associated with one of the joints only. A remarkable finding is that drug abuse was only associated with knee OA (HR 1.53), whereas alcohol abuse was only with hip OA (HR 1.44). Similarly, liver cirrhosis (HR 1.44), asthma (HR 1.34), diabetes mellitus (1.25) and depression (HR 1.23) were associated with OA of the knee but not the hip, and sinusitis (HR 1.41) and peripheral vascular disease (HR 1.37) the other way around.

Comparison to the literature

Many of these findings are in line with the literature. The association between obesity and knee OA was recently confirmed in a review focusing on differences between knee and hip OA[29]. The strong association of both knee and hip OA with other musculoskeletal diseases was also described previously[14,16,30]. In addition to the well-known relation with obesity and musculoskeletal conditions, other associations with OA were also confirmed in this study, such as: reflux disease, vertigo, asthma and depression[14,15,27,31,32]. Finally, an OA overview article in *Lancet* stated that meta-analyses show a small increased risk of developing cardiovascular disease in

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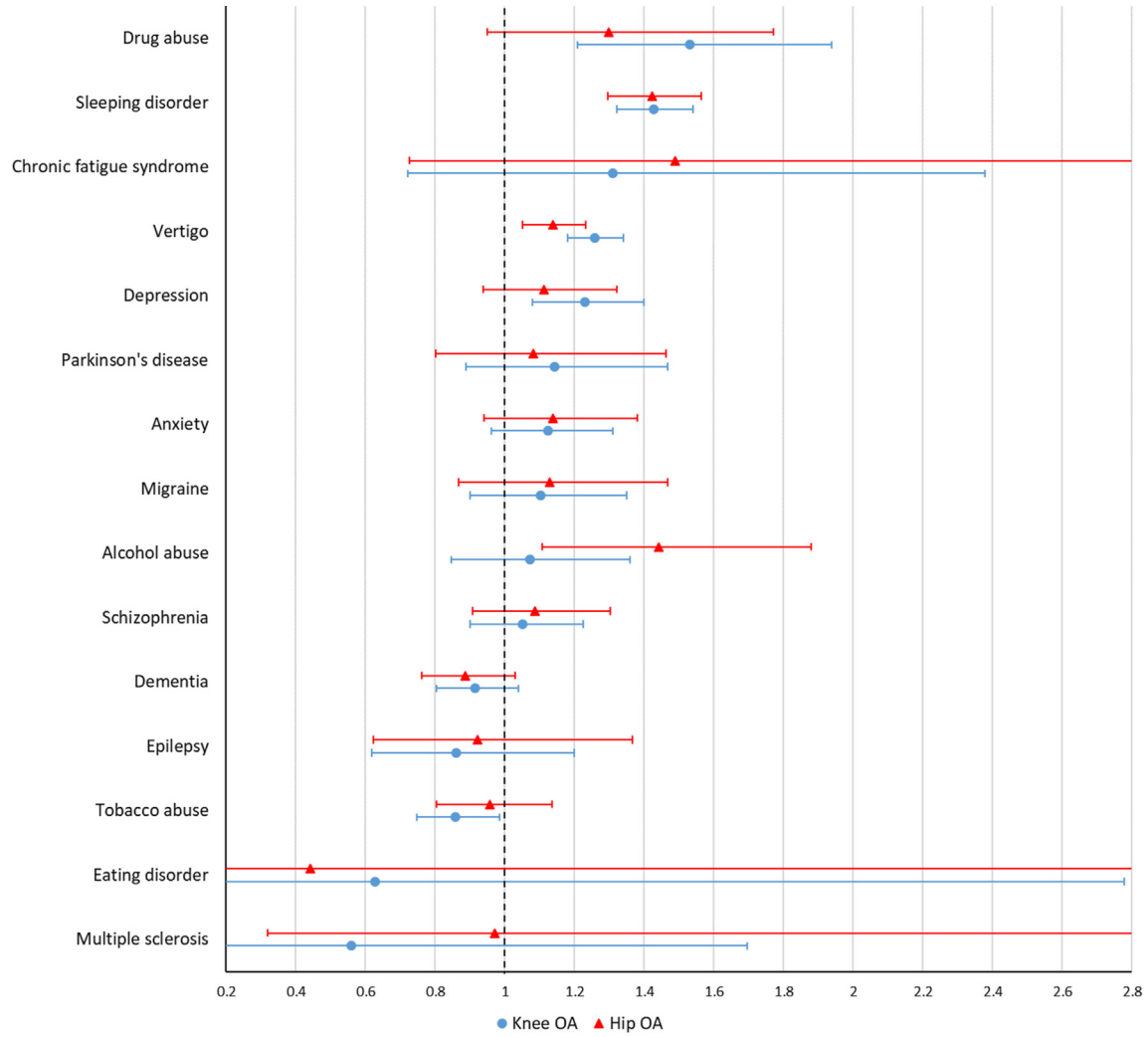

Fig. 4

Osteoarthritis and Cartilage

Hazard ratios of neurological & psychiatric comorbidities.

patients with OA compared to individuals without OA, which corresponds to the positive associations found in this study with atrial fibrillation, diabetes mellitus, hypertension and peripheral vascular disease, among others[2,9,33].

Interpretation

The association of spinal disc herniation with hip OA, which typically presents with pain in the area of the groin and lower back, might be (partly) explained by the anatomical proximity of other potentially affected structures in this area. The lower vertebrae for instance, are the most commonly affected part of the spine in spinal disc herniation, which results in (radiating) pain in the same area[34]. The probability of herniation and other painful conditions that can occur in this area, make that hip joint pain is generally perceived as more complex and is more likely to lead to referral for diagnostic radiology compared to knee pain[29]. Since the secondary analysis showed a relatively high rate of spinal disc herniation diagnoses within 1 year after diagnosis of hip OA (HR 3.11), it is plausible that this comorbidity was in part registered for the same symptoms as for which the diagnosis of hip OA was previously registered. A double registration for a single disease episode could be considered a misclassification, most probably of the first registered disease (the exposure). High HRs in the secondary analysis indicating potential misclassification of the exposure were also seen for other comorbidities that are similar presenting to OA, such as polymyalgia rheumatica, rheumatoid arthritis, and back pain. The secondary analysis thus contributes to a more cautious interpretation of the results in which misclassification might have played a role.

Finally, thromboembolic disease showed a large HR in the secondary analysis for both knee and hip OA. One possible interpretation of this finding is that swelling, redness and pain in the leg that occur in deep vein thrombosis were initially considered OA by the GP, but further investigation confirmed it was thrombosis. Another hypothesis is that OA, especially during a flair-up of pain and stiffness, could

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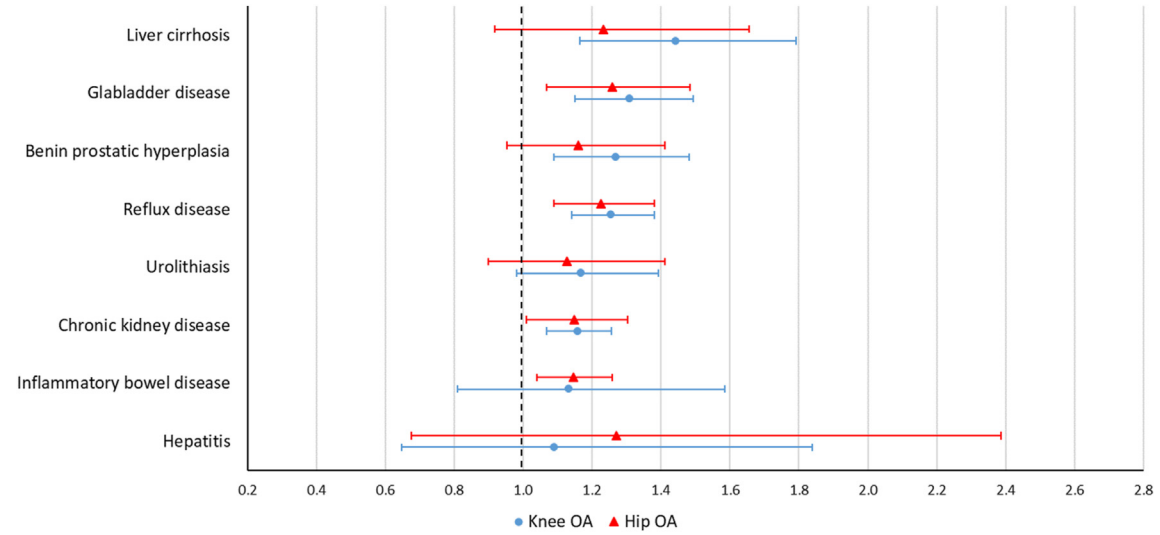

Fig. 5

Osteoarthritis and Cartilage

Hazard ratios of gastrointestinal & urology comorbidities.

cause immobilization and low-grade inflammation in the affected leg, both of which are risk factors for thromboembolic disease.

Overall, chronic low-grade inflammation might play an important role in many of the associations found. It is hypothesized that chronic conditions with inflammation may eventually lead to the spread of inflammatory mediators to arterial walls, joints and synovium. Inflammatory mediators can subsequently damage blood vessels and impede blood flow to the joint (or other organs in case of cardiovascular comorbidities)[9]. This way, diseases such as obesity and OA, or diseases with atherosclerosis as an underlying mechanism, can influence each other's development or progression through inflammatory mediators.

Limitations

The use of codified data from electronic medical records for epidemiological study purposes has several limitations. First, there is not much knowledge about the accuracy of diagnostic ICPC codes. The positive predictive value for the diagnostic code of knee OA was recently estimated to be 96.0% (95% CI 90.6–100%) in IPCI, but such information is not available for all diagnoses used[35]. However, studies in countries using similar coding systems in primary care databases, such as Read codes in the UK and ICD codes in the US, have generally shown high specificity, low to moderate sensitivity and good positive predictive values for the use of diagnostic disease codes[36–39].

In addition to that, there may be differences in the way that GPs register information and diagnostic codes. The prevalence and incidence of OA in IPCI was demonstrated to be underestimated using codified data alone, and doubled when an algorithm based on free text and patient characteristics was added[35]. Instead of using the diagnostic ICPC code for knee OA, it appeared that some GPs wrote the working diagnosis in free text or registered a symptom ICPC code (i.e., 'knee pain').

Furthermore, it was not possible to adjust for various potential confounders. After careful consideration of the available variables, it was concluded that adjusting for this would cause bias due to a data collection process in these variables that was already biased and the relatively large proportion of data missing non-randomly preventing valid data imputation. IPCI, like many other registration databases, was primarily introduced for purposes other than conducting research. Therefore, the registration and quality of information are influenced by (country-specific) common practices and financial incentives, such as agreements with health insurers[40]. This is especially evident in body mass index and smoking status, whose diagnostic codes may be a requirement to access reimbursed programs for example. Surveillance bias and the strongly related informative presence bias may also have affected the data. Patients who visit their GP very frequently, for example due to the follow-up for chronic diseases, are likely to have more diagnoses registered than patients who do not. Frequent visits may increase the possibility of expressing symptoms other than the reason for the patient's visit, and/or increase the likelihood that other symptoms will be noticed by the GP. Adjusting for the visit frequency in IPCI needs to be done with caution because it can potentially introduce new biases, especially when simply correcting for the number of visits[28]. A significant proportion of IPCI-registered adults did not visit their GP during the follow-up period: some of them may be care avoiders, but others may not have actually had any illness during that time. On the other hand, a proportion of frequent visitors may naturally have a higher proneness to develop multiple diseases, and therefore 'justifiably' received more diagnoses. An additional sensitivity analysis was performed to get an impression of the extent to which the results were influenced by informative presence bias. The results suggested that informative presence bias related to visit frequency did not substantially affect our results.

Strengths

One of the strengths of this study was the large cohort that was used from the longitudinal IPCI database. This provided sufficient power to detect even small associations and allowed methodology that could distinguish temporal comorbidity patterns in two sub-localizations of OA. Since IPCI is representative of the Dutch

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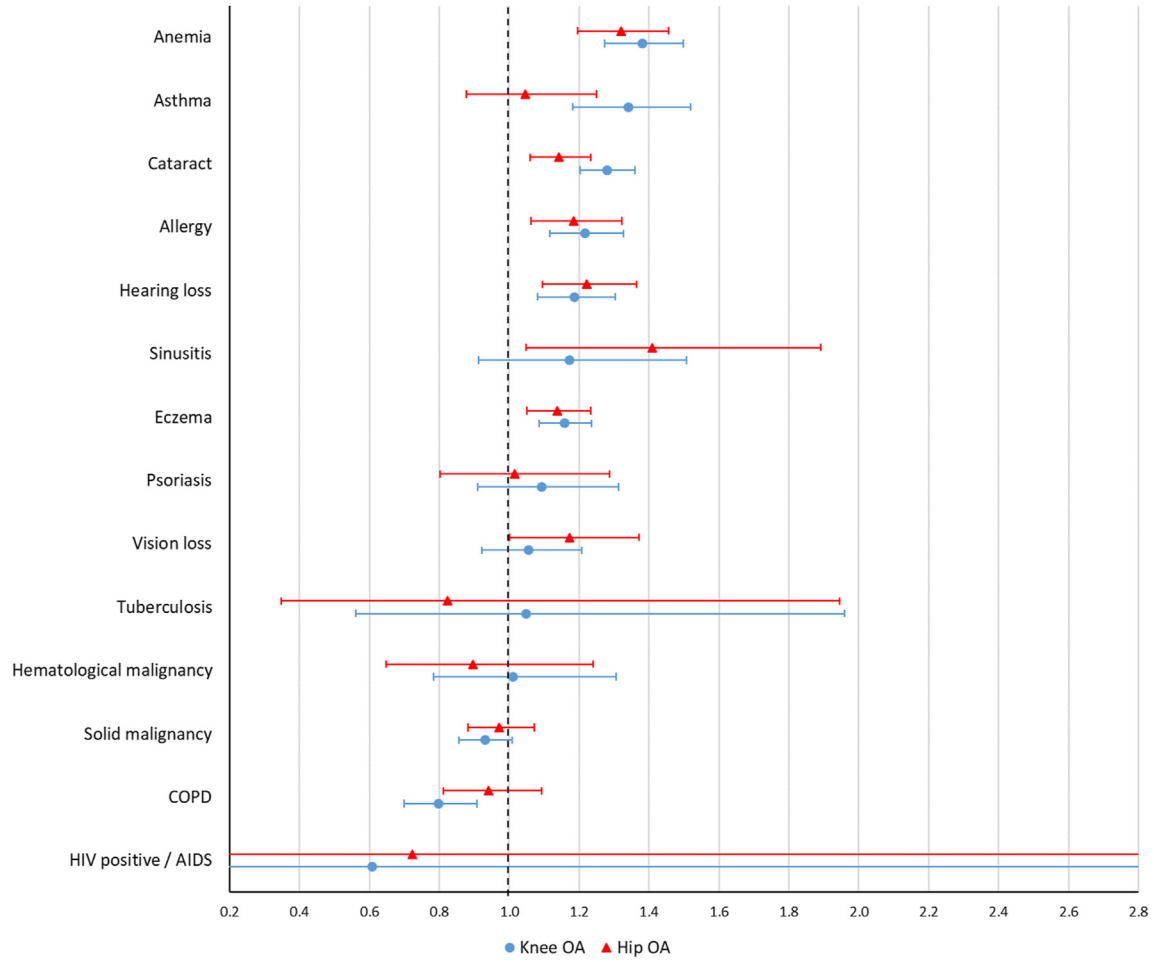

Fig. 6

Osteoarthritis and Cartilage

Hazard ratios of internal, dermatological & other comorbidities. AIDS: acquired immunodeficiency syndrome; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus.

inhabitants in terms of age, sex and living in rural/urban areas, the results are extractable. Furthermore, the Netherlands is a country where the GP has a gate keeping role: practically all inhabitants are subscribed at a general practice and referrals to secondary health care can only be arranged via the GP. Therefore, the database includes a very complete overview of patients' primary care visits and resulting diagnosis codes, but also includes information that was reported back to the GP by the medical specialist after a policlinic referral or hospitalization.

Another strength is the use of a time-varying variable for the exposure, which ensured that comorbidities diagnosed in non-exposed person time (i.e., prior to incident OA diagnosis) were appropriately included in the analysis. Without a time-varying variable, patients with incident OA diagnosed at any time point during the study period, would have had their entire follow-up time defined as 'exposed'. This would lead to bias towards a higher hazard of the exposure, because comorbidities that occurred in actual unexposed time would be included as if they took place in exposed time. Finally, this study included a wide range of comorbidities, allowing examining associations in comorbidities that have not been studied before, among which liver cirrhosis, thromboembolic disease, sinusitis, allergy and gall bladder disease. These conditions provide interesting new leads for further investigation.

Implications

This study implies that clinicians and therapists should be aware of the fact that patients with OA have a higher risk of being diagnosed with subsequent comorbidities. By improving our understanding of the temporal associations between OA and other long-term conditions, this study can support the optimization of (self-) management of OA and its associated comorbidities. Anticipating symptoms, performing routine checks for certain disease characteristics, or arranging preventive interventions are examples of practices that could be examined in future studies for their (cost) effectiveness to achieve early diagnosis and better management of comorbidities in OA. Guidelines should state the risk of highly

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associated co-morbidities and, if available, information on treatment and preventive measures that have been shown to be effective. Finally, as the associations found in this study are of explorative nature, further studies investigating the causality between OA and comorbidity are needed.

Disclaimers

There is no disclaimer.

Author contributions

SBZ, ME, DA, WZ, conceived and designed the study. MdW extracted the data. AK performed the statistical analyses and MdR and MdW supervised (and when necessary corrected) the analyses. AK, JR, MdR, MdW, JvdL, EdS, SBZ discussed the results and interpretation. AK drafted the manuscript and JR carried out the first round of revisions. All authors have read and approved the final version of the manuscript and contributed to its critical revision. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of interest

Every co-author declared their (potential) conflict of interest in the ICJME disclosure form as well as the OAC author disclosure form that were separately provided in the submission.

Role of the funding source

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Supplementary data

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