**Title:** Temporal relationship between osteoarthritis and comorbidities: a combined case control and cohort study in the UK primary care setting

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**Abstract**

Objective:To determine the burden of comorbidities in osteoarthritis (OA) and their temporal relationships in the UK.

Methods:The Clinical Practice Research Datalink (CPRD) GOLD was used to identify people with incident OA andage, gender and practice matched non-OA controls from UK primary care. Controls were assigned the same index date as matched cases (date of OA diagnosis). Associations between OA and 49 individual comorbidities and multimorbidity (>2 comorbidities excluding OA) both before and after OA diagnosis were estimated, adjusting for covariates, using odds ratios (aOR) and hazard ratios (aHR) respectively.

Results: During 1997-2017, we identified 221,807 incident OA cases and 221,807 matched controls. Of 49 comorbidities examined, 38 were associated with OA both prior to, and following, the diagnosis of OA, and 2 (dementia and SLE) were associated with OA only following the diagnosis of OA. People with OA had higher risk of developing heart failure (aHR 1.63; 95% CI 1.56-1.71), dementia (aHR 1.62; 95% CI 1.56-1.68), liver diseases (aHR 1.51; 95% CI 1.37-1.67), irritable bowel syndrome (aHR 1.51; 95% CI 1.45-1.58), gastro-intestinal bleeding (aHR 1.49; 95% CI 1.39-1.59), 10 musculoskeletal conditions and 25 other conditions following OA diagnosis. The aOR for multimorbidity prior to the index date was 1.71 (95% CI 1.69-1.74), whereas the aHR for multimorbidity after the index date was 1.29 (95% CI 1.28-1.30).

Conclusions: People with OA are more likely to have other chronic conditions both before and after the OA diagnosis. Further study on shared aetiology and causality of these associations is needed.

Keyword: Osteoarthritis; comorbidity; multimorbidity; temporal association; burden

**Key messages:**

**What is already known?**

1. About 60% of people with osteoarthritis (OA) have other chronic conditions, which is 20% higher than in people without OA.
2. Current evidence on comorbidity in OA is predominantly from cross-sectional or case control studies and limited to cardiovascular and musculoskeletal diseases.

**What does this study add?**

1. 49 chronic conditions have been involved in this study and their temporal associations with OA have been examined.
2. People with OA are more likely to have multimorbidity before and after the diagnosis of OA than people without OA.
3. While musculoskeletal (MSK), gastrointestinal (GI), cardiovascular (CVD) and psychological conditions were associated with OA in both directions, dementia and SLE were only associated with OA after its diagnosis.
4. Other conditions that showed bidirectional association with OA, which have not previously been highlighted, were with anaemia, inflammatory bowel disease (IBD), benign prostatic hypertrophy (BPH), gall bladder stones, liver diseases, cancer, and hearing impairment.

**How might this impact on clinical practice or future developments?**

The temporal associations reported merit further investigation regarding causality and have important clinical implications with respect to shared risk factors and optimal management of OA and its comorbidities.

**INTRODUCTION**

Comorbidity is defined as the existence or occurrence of any additional chronic condition during the clinical course of a patient who has the index disease under study [1]. There has been growing interest in identifying comorbidities that may associate with osteoarthritis (OA), especially since the presence of additional comorbidities may escalate disease severity and healthcare utilization, and require more complex management guidelines [2]. Our recent systematic review found that 60% of people with OA had one or more other chronic conditions, which was 20% greater than in those without OA [3]. However, to date, the range of comorbidities studied is primarily limited to cardio-vascular diseases (CVD), diabetes, depression and chronic obstructive pulmonary diseases [4–6]. Furthermore, because most studies are cross-sectional and the occurrence of comorbidities after OA diagnosis has not been examined, the temporal and causal associations between them have yet to be established. With the exception shared risk factors, such as ageing and obesity, little is known about biological plausibility of concurrence of OA and associated comorbidities [7].

Multimorbidity is a rapidly evolving research area in chronic conditions and primary care, and is defined as the presence of two or more chronic conditions in the same individual [8]. To date, no studies are available on the reported associations of multimorbidity or comorbidities with OA, and many possible associated conditions have not been examined. In the United Kingdom, widespread use of electronic medical records in general practices captures research quality information on visits, diagnoses, prescribed medications, management and interventions [9]. The longitudinal nature of the recorded data allows study of information on consultations and diagnoses at multiple time points. Therefore, using data representative of the UK general population in the Clinical Practice Research Datalink (CPRD), this study aimed to examine the burden of comorbidity and multimorbidity both prior to and following the diagnosis in patients with OA compared to matched controls without OA.

**METHODS**

We used the CPRD GOLD database for both retrospective (before OA diagnosis) and prospective (after OA diagnosis) analyses. The study involved analyses of the anonymised patient level data and was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency (MHRA) Database Research (protocol 19\_030R).

**Data source**

CPRD contains primary care electronic medical records and is generalisable to the wider UK population [10]. As of 31st December 2017, CPRD contained data on ~17.5 million individuals from 736 general practices [10]. Substantial research has provided satisfactory results regarding the validity, representativeness and completeness of the CPRD [12]. More details about the database can be found at <https://cprd.com/primary-care>.

**Case definition of OA**

We used Read codes, which are a standard clinical coding system used in general practice in the UK, to identify people with a diagnosis of incident OA between 1st January 1997 and 31st December 2017. The date of the first recorded diagnosis for OA was used as the index date to separate retrospective and prospective analyses. Inclusion criteria for incident OA cases were: 1) at least one recorded physician diagnosis of OA for hip, knee, ankle/foot, wrist/hand, or recorded as ‘unspecified’; 2) aged 20 years or more at the index date; 3) having active registration for at least 36 months with the up-to-standard (UTS) practice prior to the index date; and 4) registered at a practice flagged as having acceptable data (determined by CPRD database standards).

An existing Read code list for OA ([www.keele.ac.uk/mrr](http://www.keele.ac.uk/mrr) ) was updated and adapted according to the inclusion and exclusion criteria and screened by two independent GPs before use. We used the exact list for joint in hip, knee, ankle and foot, wrist, and hand, and unspecified). The codes obtained from the given website were previously matched with ICD-10 codes (Musculoskeletal disorder chapter) [13]. Although not all OA joint codes have been validated, a recent study reported a positive predictive value of almost 80% for Read codes for hip OA in people aged 60 and over [13].

**Selection of controls**

Controls were people registered for at least 36 months with UTS practices and with no record of diagnosed OA, OA related joint pain or total joint replacement. One control was selected per OA case (i.e., 1:1 matching), matched by year of birth (+2 years), gender, year of first registration and practice. The same index date (i.e. date of first OA diagnosis) as their matched case was used.

**Definitions and extraction of comorbidities and multimorbidity**

We defined comorbidity as the recording of diagnosis of predefined chronic conditions in individuals of both groups. An extensive list of 49 chronic conditions was prepared from the Quality Outcome Framework (QOF) [15], list of the US Department of Health and Human Services Initiative on Multiple Chronic Conditions [16], and the Charlson comorbidity index [17]. The list was updated with findings from our systematic review [3] and a previous UK community-based knee pain study [3,18] by including common and important morbidities not included in the above [19,20]. We also examined the association of multimorbidity (>2 conditions other than OA) with OA before and after the diagnosis/index date.

The 49 comorbidities in our study were further categorised into eight groups, specifically: musculoskeletal (MSK), respiratory, genitourinary, neuropsychiatric, cancer, circulatory, metabolic/endocrine, and gastrointestinal (GI). In addition, nine other conditions were grouped as a ninth ‘other’ category (Supplementary Table S1.1) Wherever required, the codes were further refined after comparing with codes used by other researchers in our department and other sources [21,22]. Most of the comorbidities listed have been externally validated [12,23]. A final list of codes was shared with our GP collaborator for input and verification. Finally, the corrected codes were reviewed and agreed by the research team. A summary of the disease list with primary Read codes is given in Supplementary Table S1.1.

**Covariates**

The whole study period was divided into five observation periods (0-1 year, 0-5 years, 0-10 years, 0-15 years, and 0-20 years) before and after the index date. We extracted information on body mass index (BMI), alcohol use and smoking status at the end of each time. If information on these variables was missing in one time-period, it was imputed using the last observation carried forward from the previous time interval (i.e. assuming the value remained unchanged). However, for completely missing information we used multiple imputation with chained equations to generate five imputations per person using ‘MICE’ package in R software.

BMI (Kg/m2) was categorised as underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9) or obese (>30.0) [24]. Smoking status was categorised as ex-smoker, current smoker, or non-smoker. Alcohol use was grouped into non-user, ex-user, current user 1-9 units/week, current user >10 units/week or current user (unknown quantity).

**Statistical methods**

For the retrospective analysis, a nested matched (please see above about matching) case-control design was used. The prevalence of a specific comorbidity in OA and controls was estimated by calculating the proportions of people diagnosed with the comorbidity during the previous 1, 5, 10, 15 and 20 years (maximum) before the index date out of the total number of cases and controls. This method was used primarily to examine whether longer observational periods would give greater prevalence to assess observational bias [25] and because longer observation periods are often needed to capture the diagnosis of chronic diseases in a consultation-based database [26]. Odds ratios (OR) and 95% confidence intervals (CI) were used to estimate the associations between OA and each comorbidity. Multivariable conditional logistic regression was used to adjust for age, BMI, smoking, alcohol use, and multimorbidity at index date. Age was adjusted to account for the residual variation due to the group matching (+ 2 years). We also estimated the total number of comorbidities (none, single, two, three, and four or more comorbidities) and the OR for multimorbidity (≥2 chronic conditions) during the retrospective time periods.

In the prospective analysis a cohort study design was used. We assessed incident comorbidity at the earliest date of diagnosis after the index date. Both the OA and matched non-OA cohorts were followed up to 20 years after the index date for each specific comorbidity in people without the comorbidity studied at the index date, namely, people at risk. The follow-up period was censored at the earliest date of comorbidity diagnosis, death, transfer out or end of the study (31st Dec 2017). The Kaplan-Meir method was used to display the cumulative probability of each comorbidity in people with incident OA and matched controls. Hazard ratios (HRs) and 95% CI were calculated for each comorbidity separately Cox proportional hazards model adjusting for age, gender, BMI, smoking, alcohol use, multimorbidity count at the index date and index year. Age, BMI, smoking status, and alcohol use were included as time varying covariates. The assumption proportional hazard for each comorbidity was examined with log-log plots and Schoenfeld residual tests. We also assessed the incidence and HR of developing multimorbidity (i.e. recording of the new second condition after the index date irrespective of conditions at index date) in similar way.

Further analyses were carried out to examine the specific associations with knee, hip, wrist/hand, and ankle/foot OA. These were restricted to cases with OA at those joints and their matched controls and associations were estimated both retrospectively and prospectively using above mentioned methods.

We tested the associations with 49 comorbidities in the analyses. To address the risk of higher false discovery rate due to ‘multiple significance testing’ [27], the false discovery rate method proposed by Benjamini and Hochberg was used to calculate adjusted p values for both retrospective and prospective analyses [28]. Details of the multiple testing methods is given in supplementary file 2, page 1. The statistical analyses were performed using STATA statistical software V.15 (STATA corp, Texas) and R software V 3.5.

**Sensitivity analysis**

As a sensitivity analysis for the prospective study, we re-ran the analysis for each comorbidity restricted to people with OA and matched controls without any comorbidities on or before the index date. This study population can be defined as an ‘at risk’ group for developing any of the comorbidities of interest. For multimorbidity, the incident date was defined as the date of diagnosis of the second new chronic condition from the index date in an individual. Cox proportional hazard models were used to estimate the HR for each comorbidity adjusted for, smoking status, alcohol use and BMI.

**RESULTS**

During the period 1st January 1997 to 31st December 2017, we identified 494716 incident OA cases[29]. Of these matched controls could be found for 221,807 cases with a mean age of 61.1 years at diagnosis (standard deviation 13.2 years) with 58% being women. The mean age of control population (n=221807) was 60.9 years (standard deviation 13.3 years). Table 1 shows characteristics of OA cases and matched controls.

**Retrospective analysis**

Comorbidities prior to OA diagnosis/index date at every 5 years up to 20 years in the OA case and control groups are shown in Table 2. Within the maximum twenty-year observational period prior to the index date 53.1% cases and 41.8% controls had multimorbidity.

Of the 49 comorbidities studied, significant associations were seen with 40 comorbidities in the 20-year period (Table 2). During this period, the adjusted odds ratio (aOR) for multimorbidity prior to OA was 1.71 (95% CI 1.69-1.74). The strongest associations were seen with rheumatoid arthritis (RA) (aOR: 1.95; 95% CI 1.80-2.11), fibromyalgia (aOR: 1.89; 95% CI 1.75-2.04), polymyalgia (aOR: 1.74; 95% CI 1.62-1.87), back pain (aOR: 1.67; 95% CI 1.64-1.69), and Sjogren’s syndrome (aOR 1.67; 95% CI 1.39-2.00). (Table 2) The prevalence and aORs according to different observational periods prior to the index date, are shown in Supplementary tables S1.2 and S1.3.

Joint specific association retrospectively for each comorbidity are given in Supplementary table S1.4. For hip OA, for 20 years before the index date leading comorbidities having a positive association were back pain, and ankylosing spondylitis. Leading comorbidities associated with knee OA within 20 years of the index date were MSK conditions such as fibromyalgia, and polymyalgia. For wrist and hand OA, leading associations were seen with gout, and back pain. Comorbidities associated with ankle/foot OA within 20 years of the index date were gout, and IBS. (Table S1.4)

**Prospective analysis**

The cumulative probabilities of all comorbidities were higher in the OA group than the control group in each year of follow-up. (Table S1.5) The adjusted cumulative probabilities of having multimorbidity at 5, 15 and 20 years following the index date were 27.3%, 68.4% and 77.4% in people with incident OA and 19.5%, 42.9% and 70.7% in controls, respectively (Figure 1). The adjusted HR (aHR) for incident additional multimorbidity was 1.29 (95% CI 1.28-1.31) in OA cases compared with controls (Table 3).

Except for HIV/AIDS, psychosis, multiple sclerosis, tuberculosis, scleroderma, vision problem, schizophrenia, hypertension, and renal stones the risks of developing each of the other comorbidities were significantly higher in people with OA. (Table 3) Patients with OA were over three times more likely to develop RA (aHR 3.56; 95% CI 3.26-3.89) and 2.6 times more likely to develop fibromyalgia (aHR 2.64; 95% CI 2.41-2.89). Besides MSK conditions people with OA had higher risk compared to matched controls of developing heart failure (aHR 1.63; 95% CI 1.56-1.71), dementia (aHR 1.62; 95% CI 1.56-1.68), liver diseases (aHR 1.51; 95% CI 1.37-1.67), irritable bowel syndrome (IBS) (aHR 1.51; 95% CI 1.45-1.58), GI bleeding (aHR 1.49; 95% CI 1.39-1.59). (Table 3)

Joint specific results for each comorbidity are given in table 4. It shows that the risk of being diagnosed with other MSK conditions after OA diagnosis was higher for all the OA types. People with hip OA had higher risk of being diagnosed with anaemia and arterial/venous diseases. Whereas, among people with knee OA the leading comorbidities diagnosed prospectively were GI bleeding, and heart failure. After the diagnosis of wrist and hand OA, there were increased risk of sleep disorders and heart failure. In people with ankle/foot OA, the highest risks were for new diagnosis of dementia, and cancer. (Table 4)

A comparison of adjusted odds ratio and hazard ratio identifies that 38 conditions had significant associations both retrospectively and prospectively. (Figure 2) Dementia and SLE only had significant association prospectively and hypertension and renal stone had only significant retrospective association.

**Sensitivity analysis:**

The results from sensitivity analyses among OA patients and controls without any comorbidities at the index date showed significant prospective associations for 25 conditions. Comorbidities with the strongest prospective associations were fibromyalgia, RA, liver disease, sleep problems, and GI bleeding. The adjusted risk of developing multimorbidity was 1.34 times more (95% CI 1.28-1.41) compared to controls. For more details on sensitivity analysis refer supplementary file 2.

**DISCUSSION**

This study estimated the burden of comorbidities prior to the diagnosis of OA and the risk of developing comorbidities following the diagnosis of OA using a nationally representative large UK primary care database. The key findings are: (1) people diagnosed with OA are significantly more likely to have multimorbidity both prior and following the diagnosis of OA; (2) while MSK, GI, cardiovascular (CVD) and psychological conditions were associated with OA in both temporal directions, dementia and SLE were only associated with OA after its diagnosis; and (3) additionally, there is a bidirectional association both before and after the diagnosis of OA with anaemia, IBD, BPH, gall bladder stones, liver diseases, cancer and hearing impairment.

**Associations in both retrospective and prospective analyses**

In this study OA was found to be associated with large numbers of conditions. This is first ever study examined the association with large number of conditions in the same primary care cohort. Multimorbidity associations with OA before and after the diagnosis reveal the important role of MSK conditions. Both multimorbidity and OA have positive relationships with ageing. Multiple shared risk factors such as obesity, physical inactivity, medication use and the possible role of inflammation in multimorbidity might lead to OA and vice-versa [30,31]. Age-related changes in widespread structural components such as collagen, and reduced reparative potential with age, may also play a role in development of “degenerative diseases” in multiple tissues and systems[32].

Associations of OA with some of the identified MSK comorbidities in this study accord with previous studies [33], such as for RA [34]. The bidirectional associations with discrete chronic pain-related conditions such as fibromyalgia, back pain and IBS could result from shared non-restorative sleep and central pain sensitization, which causes reduced pain threshold and exacerbation of other causes of pain [35,36]. The association of OA with gout was stronger before the diagnosis of OA than after, and this might in part be explained by the “amplification loop” of cartilage damage enhancing urate crystal deposition and urate crystals causing cartilage damage [37]. We also found the risk of osteoporosis following diagnosis of OA was higher than the risk of OA in osteoporosis, but the evidence of their association remain speculative and controversial [38]. Care must be taken in interpreting these associations, especially where joint pain is the reason for the consultations since GP diagnoses are predominantly clinical and not pathological. Also, although characteristics of these various MSK conditions differ there is still the possibility of misdiagnosis, especially for atypical cases.

Cardiovascular diseases, such as coronary heart disease and heart failure [39], stroke [3,40], PVD [41] and diabetes [42] are well known to associate with OA. We found prospective risks of developing diabetes, PVD and heart failure were greater in OA compared to risks of developing OA in people with these conditions. This indicates possible role of obesity and hypercholesterolaemia among people with CVD causing OA and possibly the effect of NSAIDs use in people with OA for developing CVD [43]. So, screening for metabolic syndrome and CVD should be considered in people presenting with OA [44].

Even though depression and OA had a significant bidirectional association, a higher risk of depression was seen in people following the diagnosis of OA. A similar finding was seen with sleep disorders. Depression and non-restorative sleep are well recognised to associate with chronic pain experience in OA [5]. Low affect and non-restorative sleep can reduce descending pain inhibition and cause central sensitisation, and equally chronic pain and reduced participation can cause mood disturbance [45].

The risks of developing gastritis, GI bleeding, liver diseases and gall bladder stones in OA were high compared to developing OA in these conditions. GI disorders are the known comorbidities in OA resulting from NSAID usage [47]. However, recording of incident OA in people with these conditions could result from self-medication for OA pain before presenting to the general practitioner and being diagnosed with OA (i.e. protopathic bias). Interestingly, the risk of OA in liver cirrhosis is reported to be high but the reverse relationship has yet to be established [48].

Other comorbidities with significant bi-directional associations with OA were respiratory, hypothyroidism and neurological conditions such as Parkinson’s disease, epilepsy, and migraine. Thyroid disease, epilepsy, migraine, and respiratory illness may have earlier age of onset than OA, which could have led to the early recording in the database prior to OA. Also, these comorbidities could be mediated through the systemic inflammation, medication use or other comorbidities in OA. The four other conditions with bi-directional positive associations in this study were anaemia, BPH, cancer and hearing problems, which all been reported before [49,50]. Use of NSAIDs in people with OA/RA was found to reduce the haemoglobin levels in one previous study [51]. Release of inflammatory substances has been linked with sensorineural hearing loss [52], BPH [53], cataract [54] and cancer [55]. Thus, the possibility of having similar subclinical systemic inflammation from asymptomatic OA prior to clinical presentation warrants investigation.

**Association in prospective analysis only**

Dementia associated with OA only in the prospective analysis. This concurs with a recent systematic review of cross-sectional and case-control studies which reported that people with OA were 20% more likely to have dementia [56]. As dementia is predominantly an ageing problem, the association in the retrospective study may not have been significant because of the low prevalence of dementia in younger decades and difficulty in detecting OA symptoms and less consultations for OA in people dementia. However, the association with SLE could be due to misdiagnosis or miscoding of joint pain symptoms before the actual diagnosis which needs further investigation. Similar problem may exist for the associations of RA either before or after OA.

This study suggests that although structural changes of OA may appear relatively limited within the skeleton, pathologically and physiologically, its effect possibly seen in almost every organ. Thus, close observation of people with OA through annual assessment in primary care appears warranted, as recommended by NICE [57]. Concordantly, the European League Against Rheumatism (EULAR) and National Institute for Health and Care Excellence (NICE), have emphasised the importance of diagnosis and management of specific comorbidities and understanding their pattern in OA when managing people with OA [57].

**Strengths and limitations**

There are several caveats to this study. The chances of misclassification of OA because of physician diagnosis rather than full clinical and imaging assessment has been emphasised already. Nevertheless, we tried to optimise identification of symptomatic OA cases through strict inclusion and exclusion criteria using similar methodology to that of previous studies [58] and there is some reassurance that the codes for hip OA have been shown to have good validity [14]. Misclassification bias for comorbidities is also possible, though most comorbidities in the study have previously been validated [10,12]. Another important caveat is unavailability of risk factors such as diet and physical activity in the analysis, as these are not routinely recorded within CPRD. Therefore, the estimates in our study may not always relate to direct associations between OA and comorbidities and could have been mediated through other unrecorded factors as mentioned in the discussion. However, the primary aim of the study was to estimate the associations and burden of comorbidities in OA, rather than to define risk factors. The associations could to some extent be due to ascertainment bias through increased numbers of hospital or GP visits, especially for the stronger association with rheumatological conditions. Even though we have not adjusted for the count of hospitalisations, our adjusted estimated were modelled accounting for number of multimorbidity, which can be considered as a proxy indicator of healthcare visits [59]. Along with the possible Berkesonian bias a chance of collider bias due to sampling design might exist. However, we matched the controls having minimum 36 months of registration and at least one consultation for any reasons. There is also a chance of ascertainment biases due to delayed reporting of OA cases in the database than recording of date of first symptom onset. Such bias is inherent to the electronic health records, however our study population age group is quite comparable to that reported by Yu et al showing the consistency in representation of people with OA[60]. We focused more on the possible explanation of the association rather than the plausibility, which is beyond the scope of this study. Our sample size for the prospective analysis was nearly 440,000 with equal numbers of OA cases and matched controls and maximum follow-up for up to 20 years for 49 comorbidities, making this first study to provide such a clear picture of the burden of a large number of comorbidities in OA.

In conclusion, the risk of multimorbidity was higher in people with OA. MSK, GI, CVD and psychological conditions were associated with OA both before and after diagnosis. Significant associations with gall bladder stone, IBD, BPH, anaemia, hearing problems, liver disease and cancer highlight the discordant comorbidities in OA (which cannot readily be explained mechanistically). The temporal associations reported merit further investigation regarding causality and have important clinical implications with respect to optimal management of OA and its potential comorbidities. Future studies should investigate clustering of the comorbidities and shared risk factors.

**Contributor and guarantor information:** SS, WZ, CC and MD conceived and designed the study. SS and WZ acquired the data. SS performed the analysis and CC, AS and WZ supervised the statistical analysis. SS, AS, CM, CC, WZ, CFK, ME, SMA, DPA and MD interpreted the results. SS and WZ drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. WZ, CC and MD supervised the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Studies involving humans or animals:** No direct participant recruitment was done for the study. This study was approved by the independent scientific advisory committee for CPRD research (protocol reference: 19\_030 R).

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Data sharing statement:** We used anonymised data on individual patients on which the analysis, results, and conclusions reported in the paper are based. The CPRD data is not distributable under licence. However, the relevant data can be obtained directly from the agency (<https://www.cprd.com/>). The codes developed for the analysis can be available upon a valid request.

**REFERENCE**

1. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis. 1970 Dec;23(7):455–68.

2. Bähler C, Huber CA, Brüngger B, Reich O. Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study. BMC Health Serv Res. 2015;15:23.

3. Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in Osteoarthritis: A systematic review and meta-analysis of observational studies. 2019 Jun 17 [cited 2019 Jun 30]; Available from: http://doi.wiley.com/10.1002/acr.24008

4. Parkinson L, Waters DL, Franck L. Systematic review of the impact of osteoarthritis on health outcomes for comorbid disease in older people. Osteoarthritis Cartilage. 2017 Nov;25(11):1751–70.

5. Stubbs B, Aluko Y, Myint PK, Smith TO. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. Age Ageing. 2016 Mar 1;45(2):228–35.

6. Wang H, Bai J, He B, Hu X, Liu D. Osteoarthritis and the risk of cardiovascular disease: a meta-analysis of observational studies. Sci Rep [Internet]. 2016 Dec 22 [cited 2018 Feb 25];6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5177921/

7. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. J Clin Epidemiol. 2014 Mar;67(3):254–66.

8. Akker M van den, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity. Eur J Gen Pract. 1996 Jan 1;2(2):65–70.

9. Ghosh RE, Crellin E, Beatty S, Donegan K, Myles P, Williams R. How Clinical Practice Research Datalink data are used to support pharmacovigilance. Ther Adv Drug Saf. 2019 Jan;10:204209861985401.

10. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010 Jan;69(1):4–14.

11. Clinical Practice Research Datalink | CPRD [Internet]. [cited 2019 Feb 13]. Available from: https://www.cprd.com/

12. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010 Mar 1;60(572):e128–36.

13. Jordan KP, Jöud A, Bergknut C, Croft P, Edwards JJ, Peat G, et al. International comparisons of the consultation prevalence of musculoskeletal conditions using population-based healthcare data from England and Sweden. Ann Rheum Dis. 2014 Jan;73(1):212–8.

14. Ferguson RJ, Prieto-Alhambra D, Walker C, Yu D, Valderas JM, Judge A, et al. Validation of hip osteoarthritis diagnosis recording in the UK Clinical Practice Research Datalink. Pharmacoepidemiol Drug Saf [Internet]. 2018 Oct 30 [cited 2019 Feb 11]; Available from: http://doi.wiley.com/10.1002/pds.4673

15. Quality and Outcome Framework (QOF) [Internet]. [cited 2018 Mar 21]. Available from: https://digital.nhs.uk/article/8910/Quality-and-Outcome-Framework-QOF-Indicators-No-Longer-In-QOF-INLIQ-Enhanced-Services-ES-Vaccinations-and-Immunisations-V-I-and-GMS-Core-Contract-CC-extraction-specifications-business-rules-

16. Medicare C for, Baltimore MS 7500 SB, Usa M. CC\_Main [Internet]. 2017 [cited 2018 Oct 24]. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/CC\_Main.html

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987 Jan 1;40(5):373–83.

18. Sarmanova A, Fernandes GS, Richardson H, Valdes AM, Walsh DA, Zhang W, et al. Contribution of central and peripheral risk factors to prevalence, incidence and progression of knee pain: a community-based cohort study. Osteoarthritis Cartilage. 2018 Nov;26(11):1461–73.

19. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994 Nov 1;47(11):1245–51.

20. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. Am J Epidemiol. 2011 Mar 15;173(6):676–82.

21. Springate DA, Kontopantelis E, Ashcroft DM, Olier I, Parisi R, Chamapiwa E, et al. ClinicalCodes: An Online Clinical Codes Repository to Improve the Validity and Reproducibility of Research Using Electronic Medical Records. Petersen I, editor. PLoS ONE. 2014 Jun 18;9(6):e99825.

22. Payne RA, Mendonca SC, Elliott MN, Saunders CL, Edwards DA, Marshall M, et al. Development and validation of the Cambridge Multimorbidity Score. Can Med Assoc J. 2020 Feb 3;192(5):E107–14.

23. Deyo R. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992 Jun;45(6):613–9.

24. NHS. Body mass index (BMI) in UK population [Internet]. nhs.uk. 2018 [cited 2019 Jun 5]. Available from: https://www.nhs.uk/common-health-questions/lifestyle/what-is-the-body-mass-index-bmi/

25. Rassen JA, Bartels DB, Schneeweiss S, Patrick AR, Murk W. Measuring prevalence and incidence of chronic conditions in claims and electronic health record databases. Clin Epidemiol. 2018 Dec;Volume 11:1–15.

26. Chen G, Lix L, Tu K, Hemmelgarn BR, Campbell NRC, McAlister FA, et al. Influence of Using Different Databases and ‘Look Back’ Intervals to Define Comorbidity Profiles for Patients with Newly Diagnosed Hypertension: Implications for Health Services Researchers. Chamberlain AM, editor. PLOS ONE. 2016 Sep 1;11(9):e0162074.

27. Greenland S. Multiple comparisons and association selection in general epidemiology. Int J Epidemiol. 2008 Jun 1;37(3):430–4.

28. Benjamini Y, Yekutieli D. The Control of the False Discovery Rate in Multiple Testing under Dependency. Ann Stat. 2001;29(4):1165–88.

29. Swain S, Sarmanova A, Mallen C, Kuo CF, Coupland C, Doherty M, et al. Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). Osteoarthritis Cartilage. 2020 Jun;28(6):792–801.

30. Chudasama YV, Khunti KK, Zaccardi F, Rowlands AV, Yates T, Gillies CL, et al. Physical activity, multimorbidity, and life expectancy: a UK Biobank longitudinal study. BMC Med [Internet]. 2019 Dec [cited 2020 Mar 5];17(1). Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-019-1339-0

31. Friedman E.M., Christ S.L., Mroczek D.K. Inflammation Partially Mediates the Association of Multimorbidity and Functional Limitations in a National Sample of Middle-Aged and Older Adults: The MIDUS Study. J Aging Health. 2015;27(5):843–63.

32. Barnes PJ. Mechanisms of development of multimorbidity in the elderly. Eur Respir J. 2015 Mar;45(3):790–806.

33. Reeuwijk KG, de Rooij M, van Dijk GM, Veenhof C, Steultjens MP, Dekker J. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? Clin Rheumatol. 2010 Jul;29(7):739–47.

34. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013 Jan 1;21(1):16–21.

35. Kirkness CS, Yu J, Asche CV. The effect on comorbidity and pain in patients with osteoarthritis. J Pain Palliat Care Pharmacother. 2008;22(4):336–48.

36. Whitehead WE, Palsson OS, Levy RR, Feld AD, Turner M, Von Korff M. Comorbidity in Irritable Bowel Syndrome. Am J Gastroenterol. 2007 Dec;102(12):2767–76.

37. Ma CA, Leung YY. Exploring the Link between Uric Acid and Osteoarthritis. Front Med [Internet]. 2017 Dec 13 [cited 2019 Sep 25];4. Available from: http://journal.frontiersin.org/article/10.3389/fmed.2017.00225/full

38. Dequeker J, Aerssens J, Luyten FP. Osteoarthritis and osteoporosis: clinical and research evidence of inverse relationship. Aging Clin Exp Res. 2003 Oct;15(5):426–39.

39. Rahman MM, Kopec JA, Cibere J, Goldsmith CH, Anis AH. The relationship between osteoarthritis and cardiovascular disease in a population health survey: a cross-sectional study. BMJ Open. 2013;3(5):e002624.

40. Hsu P-S, Lin H-H, Li C-R, Chung W-S. Increased risk of stroke in patients with osteoarthritis: a population-based cohort study. Osteoarthritis Cartilage. 2017 Jul;25(7):1026–31.

41. Findlay DM. Vascular pathology and osteoarthritis. Rheumatology. 2007 Aug 5;46(12):1763–8.

42. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open. 2015 Jun 1;1(1):e000077.

43. McGettigan P, Henry D. Cardiovascular Risk and Inhibition of Cyclooxygenase: A Systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2. JAMA. 2006 Oct 4;296(13):1633.

44. Osteoarthritis: care and management | Guidance and guidelines | NICE [Internet]. [cited 2018 May 16]. Available from: https://www.nice.org.uk/guidance/cg177/chapter/1-recommendations

45. Parmelee PA, Tighe CA, Dautovich ND. Sleep Disturbance in Osteoarthritis: Linkages with Pain, Disability and Depressive Symptoms. Arthritis Care Res. 2015 Mar;67(3):358–65.

46. Krause AJ, Prather AA, Wager TD, Lindquist MA, Walker MP. The Pain of Sleep Loss: A Brain Characterization in Humans. J Neurosci. 2019 Mar 20;39(12):2291–300.

47. Zak M, Pasiyeshvili L. Chronic gastritis clinical features and stomach functional state during nonsteroidal anti-inflammatory drugs administration in patients with osteoarthritis. EUREKA Health Sci. 2016 Sep 30;5:17–22.

48. Arora A, Rajesh S, Bansal K, Sureka B, Patidar Y, Thapar S, et al. Cirrhosis-related musculoskeletal disease: radiological review. Br J Radiol. 2016 Oct;89(1066):20150450.

49. Zlateva G, Diazaraque R, Viala-Danten M, Niculescu L. Burden of anemia in patients with osteoarthritis and rheumatoid arthritis in French secondary care. BMC Geriatr [Internet]. 2010 Dec [cited 2019 Oct 6];10(1). Available from: https://bmcgeriatr.biomedcentral.com/articles/10.1186/1471-2318-10-59

50. Kramer SE, Kapteyn TS, Kuik DJ, Deeg DJH. The Association of Hearing Impairment and Chronic Diseases with Psychosocial Health Status in Older Age. J Aging Health. 2002 Feb;14(1):122–37.

51. Goldstein JL, Chan FKL, Lanas A, Wilcox CM, Peura D, Sands GH, et al. Haemoglobin decreases in NSAID users over time: an analysis of two large outcome trials: Haemoglobin decreases in NSAID users. Aliment Pharmacol Ther. 2011 Oct;34(7):808–16.

52. Takatsu M, Higaki M, Kinoshita H, Mizushima Y, Koizuka I. Ear involvement in patients with rheumatoid arthritis. Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc Eur Acad Otol Neurotol. 2005 Jul;26(4):755–61.

53. Chughtai B, Lee R, Te A, Kaplan S. Role of inflammation in benign prostatic hyperplasia. Rev Urol. 2011;13(3):147–50.

54. Jonas JB, Wei WB, Xu L, Wang YX. Systemic inflammation and eye diseases. The Beijing Eye Study. Liu G-S, editor. PLOS ONE. 2018 Oct 3;13(10):e0204263.

55. Ziegler J. Cancer and Arthritis Share Underlying Processes. Journal of the National Cancer Institute [Internet]. 1998;90(11). Available from: https://academic.oup.com/jnci/article-abstract/90/11/802/916061

56. Weber A, Mak S hung, Berenbaum F, Sellam J, Zheng Y-P, Han Y, et al. Association between osteoarthritis and increased risk of dementia: A systemic review and meta-analysis. Medicine (Baltimore). 2019 Mar;98(10):e14355.

57. Conaghan PG, Dickson J, Grant RL, Guideline Development Group. Care and management of osteoarthritis in adults: summary of NICE guidance. BMJ. 2008 Mar 1;336(7642):502–3.

58. Swain S, Sarmanova A, Mallen C, Kuo CF, Coupland C, Doherty M, et al. Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). Osteoarthritis Cartilage [Internet]. 2020 Mar [cited 2020 Apr 15]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1063458420309183

59. Cassell A., Edwards D., Harshfield A., Rhodes K., Brimicombe J., Payne R., et al. The epidemiology of multimorbidity in primary care: A retrospective cohort study. Br J Gen Pract. 2018;68(669):e245–51.

60. Yu D, Jordan KP, Bedson J, Englund M, Blyth F, Turkiewicz A, et al. Population trends in the incidence and initial management of osteoarthritis: age-period-cohort analysis of the Clinical Practice Research Datalink, 1992–2013. Rheumatology. 2017 Nov 1;56(11):1902–17.

**Figure Legends**

Figure 1: Cumulative probabilities of developing additional multimorbidity in cases with OA and matched non-OA controls irrespective any comorbidities at the index date

Figure 2: Comparison of adjusted Odds Ratios and adjusted Hazard Ratios for comorbidities in OA for maximum 20 years observation period (before and after index date)

Table 1 Characteristics of incident OA patients and matched controls at index date

|  |  |  |  |
| --- | --- | --- | --- |
|  | Incident OA (n=221,807)  n (%) | Controls (n=221,807)  n (%) | Unadjusted Odds Ratio# (95%CI) |
| Mean age Total (sd) | 61.05(13.17) | 60.88(13.31) |  |
| Mean age Men (sd) | 60.71(12.85) | 60.54(12.97) |  |
| Mean age Women (sd) | 61.30(13.40) | 61.12(13.55) |  |
| **Age (years)** |  |  |  |
| <40 | 12266(5.53) | 13018(5.87) | NA |
| 40-49 | 30809(13.89) | 31673(14.28) | NA |
| 50-59 | 60287(27.18) | 59606(26.87) | NA |
| 60-69 | 60442(27.25) | 59294(27.02) | NA |
| 70-79 | 40879(18.43) | 40418(18.22) | NA |
| 80-89 | 15926(7.18) | 15815(7.13) | NA |
| >90 | 1198(0.54) | 1353(0.61) | NA |
| **Gender** |  |  |  |
| Men | 93895(42.33) | 93895(42.33) | NA |
| Women | 127912(57.67) | 127912(57.67) | NA |
| **BMI (kg/m2)** |  |  |  |
| Mean BMI (sd) | 28.28(5.62) | 26.62(4.98) |  |
| <18.5 (Underweight) | 3039(1.37) | 4810 (2.17) | 0.85 (0.82-0.90)\* |
| 18.5- 24.9 (Normal) | 63547(28.65) | 86620(39.06) | Reference |
| 25.0-29.9 (Overweight) | 82734(37.30) | 83013(37.44) | 1.38 (1.36-1.40)\* |
| >30 (Obese) | 72487(32.68) | 47294(21.33) | 2.14 (2.11-2.18)\* |
| **Alcohol consumption (units/week)** |  |  |  |
| Never | 44117(19.89) | 41392(18.67) | Reference |
| Ex-drinker | 6033(2.72) | 5349(2.41) | 1.04 (1.00-1.08) |
| Current 1-9 | 77588(34.98) | 80381(36.25) | 0.89 (0.88-0.91)\* |
| Current >=10 | 43186(19.47) | 43226(19.49) | 0.92 (0.91-0.95)\* |
| Current Unknown | 50883(22.94) | 51409(23.18) | 0.92 (0.91-0.94)\* |
| **Smoking Status** |  |  |  |
| Never smoked | 117536(52.99) | 123882(55.86) | Reference |
| Ex-smoker | 62571(28.21) | 57668(26.00) | 1.15 (1.14-1.17)\* |
| Current smoker | 41700(18.80) | 40237(18.14) | 1.10 (1.08-1.12)\* |
| **Joints involved** |  |  |  |
| Hip | 25091(11.31) |  |  |
| Knee | 54841(24.72) |  |  |
| Wrist/Hand | 13255(5.97) |  |  |
| Ankle/Foot | 5311(2.39) |  |  |
| Unspecified | 158620(71.51) |  |  |

#Matched by gender, age, practice, and index date; \*p value < 0.05; NA- not applicable; BMI- body mass index; CI- confidence interval; sd- standard deviation

Table 2: Associations between OA (any joint) and comorbidities diagnosed during the period of maximum 20 years prior to the index date (Expanded version for every 5 years interval is provided in supplementary Table S1.3)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Prevalence** | | **Odds Ratio (OR)** | |
|  | **OA cases (N=209601) n(%)** | **Non-OA controls (N=208799) n(%)** | **Unadjusted OR** | **Adjusted OR#** |
| **Multimorbidity** | 117997 (53.19) | 92899 (41.88) | 1.86 (1.83-1.88)\* | 1.71(1.69-1.74)\* |
| **Musculoskeletal** |  |  |  |  |
| Ankylosing Spondylitis | 3258 (1.55) | 2158 (1.03) | 1.53 (1.45-1.62)\* | 1.53 (1.44-1.62)\* |
| Back pain | 84092 (40.12) | 61835 (29.61) | 1.70 (1.67-1.72)\* | 1.67 (1.64-1.69)\* |
| Gout | 8013 (3.82) | 4829 (2.31) | 1.69 (1.64-1.76)\* | 1.52 (1.46-1.57)\* |
| Osteoporosis | 6260 (2.98) | 4896 (2.34) | 1.27 (1.22-1.32)\* | 1.41 (1.35-1.47)\* |
| Polymyalgia | 2226 (1.06) | 1243 (0.59) | 1.80 (1.68-1.93)\* | 1.74 (1.62-1.87)\* |
| Rheumatoid Arthritis | 1956 (0.93) | 972 (0.46) | 1.97 (1.83-2.13)\* | 1.95 (1.80-2.11)\* |
| Sjogren’s syndrome | 340 (0.16) | 202 (0.09) | 1.64 (1.38-1.96)\* | 1.67 (1.39-2.00)\* |
| Systemic lupus erythematous | 122 (0.05) | 81 (0.04) | 1.49 (1.12-1.98) | 1.54 (1.15-2.07)\* |
| Fibromyalgia | 2162 (1.03) | 1073 (0.51) | 1.95 (1.81-2.10)\* | 1.89 (1.75-2.04)\* |
| Fatigue | 2453 (1.17) | 1739 (0.83) | 1.42 (1.33-1.51)\* | 1.42 (1.32-1.51)\* |
| **Respiratory** |  |  |  |  |
| Asthma | 17029 (8.12) | 12320 (5.9) | 1.41 (1.38-1.45)\* | 1.33 (1.30-1.37)\* |
| COPD | 12642 (6.05) | 9296 (4.45) | 1.40 (1.37-1.45)\* | 1.35 (1.31-1.39)\* |
| **Genito-Urinary** |  |  |  |  |
| Chronic kidney disease | 8965 (4.27) | 7527 (3.6) | 1.25 (1.20-1.29)\* | 1.12 (1.08-1.16)\* |
| Benign prostatic hypertrophy^ | 8436 (4.02) | 6365 (3.05) | 1.38 (1.32-1.43)\* | 1.38 (1.33-1.43)\* |
| Renal stone | 1923 (0.91) | 1567 (0.75) | 1.22 (1.14-1.31)\* | 1.16 (1.09-1.25)\* |
| **Neuro/Psychiatric** |  |  |  |  |
| Stroke | 16158 (7.7) | 14200 (6.8) | 1.17 (1.14-1.20)\* | 1.15 (1.11-1.19)\* |
| Dementia | 1068 (0.51) | 990 (0.47) | 1.07 (0.97-1.17) | 1.09 (0.99-1.19) |
| Epilepsy | 1376 (0.65) | 1125 (0.54) | 1.20 (1.11-1.30)\* | 1.18 (1.08-1.29)\* |
| Multiple sclerosis | 348 (0.17) | 433 (0.2) | 0.79 (0.68-0.91)\* | 0.80 (0.69-0.93)\* |
| Parkinson’s Disease | 696 (0.33) | 502 (0.24) | 1.36 (1.21-1.53)\* | 1.39 (1.23-1.57)\* |
| Migraine | 11359 (5.41) | 8489 (4.06) | 1.36 (1.32-1.39)\* | 1.37 (1.33-1.41)\* |
| Depression | 38417 (18.32) | 27362 (13.1) | 1.53 (1.50-1.56)\* | 1.49 (1.46-1.52)\* |
| Psychosis | 398 (0.19) | 419 (0.2) | 0.94 (0.82-1.08) | 0.86 (0.75-1.00) |
| Schizophrenia | 1073 (0.51) | 1034 (0.49) | 1.03 (0.95-1.12) | 0.95 (0.87-1.04) |
| **Cancer** | 8972 (4.28) | 7984 (3.8) | 1.13 (1.09-1.17)\* | 1.12 (1.09-1.16)\* |
| **Circulatory** |  |  |  |  |
| Coronary heart disease | 18302 (8.73) | 14262 (6.83) | 1.33 (1.30-1.36)\* | 1.24 (1.21-1.27)\* |
| Arterial/Venous | 1429 (0.68) | 1062 (0.51) | 1.34 (1.23-1.45)\* | 1.29 (1.19-1.41)\* |
| Heart failure | 3113 (1.48) | 1847 (0.88) | 1.72 (1.62-1.82)\* | 1.52 (1.43-1.62)\* |
| Hypertension | 53659 (25.6) | 46012 (22.03) | 1.24 (1.22-1.26)\* | 1.08 (1.06-1.10)\* |
| Peripheral vascular disease | 5539 (2.64) | 3906 (1.87) | 1.41 (1.35-1.47)\* | 1.45 (1.39-1.51)\* |
| **Metabolic/Endocrine** |  |  |  |  |
| High Cholesterol | 26558 (12.67) | 21865 (10.47) | 1.27 (1.24-1.29)\* | 1.18 (1.16-1.20)\* |
| Diabetes Mellitus | 16147 (7.7) | 12656 (6.06) | 1.31 (1.27-1.34)\* | 1.06 (1.03-1.09)\* |
| Hyperthyroid | 2047 (0.97) | 1843 (0.88) | 1.10 (1.03-1.17)\* | 1.09 (1.02-1.16)\* |
| Hypothyroidism | 12276 (5.85) | 9793 (4.69) | 1.27 (1.23-1.30)\* | 1.18 (1.15-1.22)\* |
| **Digestive** |  |  |  |  |
| Gastritis | 10527 (5.02) | 7551 (3.61) | 1.42 (1.37-1.46)\* | 1.42 (1.36-1.45)\* |
| Gastrointestinal bleed | 2253 (1.07) | 1570 (0.75) | 1.43 (1.34-1.53)\* | 1.42 (1.33-1.52)\* |
| Gall bladder stone | 9189 (4.38) | 6461 (3.09) | 1.44 (1.39-1.49)\* | 1.27 (1.22-1.31)\* |
| Inflammatory bowel disease | 8704 (4.15) | 6409 (3.06) | 1.38 (1.33-1.43)\* | 1.36 (1.32-1.41)\* |
| Liver Disease | 1029 (0.49) | 689 (0.32) | 1.47 (1.33-1.62)\* | 1.42 (1.29-1.57)\* |
| Irritable bowel syndrome | 14335 (6.83) | 10015 (4.79) | 1.47 (1.43-1.51)\* | 1.52 (1.47-1.56)\* |
| **Others** |  |  |  |  |
| HIV infection/AIDS | 19315 (9.21) | 15587 (7.46) | 1.99 (0.75-5.32) | 2.08 (0.76-5.75) |
| Hearing | 1313 (0.62) | 1136 (0.54) | 1.26 (1.24-1.29)\* | 1.26 (1.23-1.29)\* |
| Psoriasis | 4602 (2.19) | 3655 (1.75) | 1.24 (1.19-1.30)\* | 1.20 (1.14-1.25)\* |
| Scleroderma | 55 (0.02) | 54 (0.02) | 0.98 (0.67-1.43) | 0.97 (0.65-1.44) |
| Sleep Disorder | 5148 (2.45) | 3820 (1.82) | 1.43 (1.36-1.49)\* | 1.35 (1.28-1.41)\* |
| Tuberculosis | 417 (0.19) | 342 (0.16) | 1.21 (1.04-1.39) | 1.25 (1.08-1.45) |
| Anaemia | 6732 (3.21) | 5406 (2.59) | 1.25 (1.20-1.29)\* | 1.25 (1.21-1.30)\* |
| Vision problem | 12179 (5.81) | 10218 (4.89) | 1.15 (1.07-1.25) | 1.11 (1.02-1.21) |
| Cataract | 3258 (1.55) | 2158 (1.03) | 1.23 (1.19-1.27)\* | 1.21 (1.17-1.24)\* |

\*p <0.05 adjusted for multiple testing using ‘False discovery rate’; #Adjusted for age, gender, body mass index (BMI), smoking, alcohol use, multimorbidity count and index year ^Only for men; COPD- Chronic Obstructive Pulmonary Disease

Table 3*:* Hazard ratios and 95% confidence intervals for each comorbidity comparing incident OA (any joint) cases and matched controls for maximum 20 years follow up

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | OA Cases  (Incidence per  1000 p-ys) | Controls  (Incidence per 1000 p-ys) |  | Unadjusted HR  (95% CI) | Adjusted HR  (95% CI) |
| **Multimorbidity** | 77695(6.76) | 74111(5.12) |  | 1.37(1.36-1.39) | 1.29(1.28-1.30)\* |
| **Musculoskeletal** |  |  |  |  |  |
| Ankylosing Spondylitis | 218496 (0.8) | 217711 (0.48) |  | 1.63(1.49-1.77) | 1.44(1.32-1.58)\* |
| Back pain | 117392 (42.82) | 144323 (28.99) |  | 1.45(1.43-1.47) | 1.38(1.36-1.41)\* |
| Gout | 213278 (4.46) | 214843 (2.77) |  | 1.63(1.57-1.69) | 1.41(1.35-1.46)\* |
| Osteoporosis | 215723 (5.21) | 215211 (4.47) |  | 1.19(1.15-1.23) | 1.28(1.24-1.32)\* |
| Polymyalgia | 219904 (1.43) | 218863 (0.9) |  | 1.49(1.40-1.59) | 1.48(1.39-1.58)\* |
| Rheumatoid Arthritis | 219874 (1.42) | 219077 (0.36) |  | 3.82(3.50-4.17) | 3.56(3.26-3.89)\* |
| Sjogren’s Disease | 221805 (0.16) | 219902 (0.08) |  | 2.01(1.64-2.46) | 1.87(1.52-2.29)\* |
| Systemic lupus erythematous | 222027 (0.06) | 220031 (0.02) |  | 2.14(1.52-3.01) | 1.90(1.34-2.69)\* |
| Fibromyalgia | 219834 (1.28) | 218978 (0.37) |  | 3.32(3.04-3.63) | 2.64(2.41-2.89)\* |
| Fatigue | 219556 (1.54) | 218276 (1.06) |  | 1.45(1.36-1.54) | 1.30(1.22-1.38)\* |
| **Respiratory** |  |  |  |  |  |
| Asthma | 197561 (3.5) | 201834 (2.53) |  | 1.35(1.29-1.40) | 1.20(1.15-1.25)\* |
| COPD | 207583 (4.13) | 209489 (3.42) |  | 1.22(1.17-1.26) | 1.18(1.14-1.22)\* |
| **Genito-Urinary** |  |  |  |  |  |
| Chronic Kidney Disease | 212998 (1.46) | 212652 (1.26) |  | 1.17(1.15-1.19) | 1.06(1.04-1.08)\* |
| Benign prostatic hypertrophy^ | 213434 (4.01) | 213577 (3.13) |  | 1.27(1.22-1.32) | 1.27(1.22-1.32)\* |
| Renal stone | 219574 (0.74) | 217980 (0.6) |  | 1.25(1.15-1.36) | 1.10(1.01-1.19) |
| **Neuro/Psychiatric** |  |  |  |  |  |
| Stroke | 204629 (8.68) | 204936 (7.26) |  | 1.21(1.18-1.24) | 1.22(1.19-1.26)\* |
| Dementia | 221101 (4.05) | 219204 (3.18) |  | 1.36(1.32-1.42) | 1.62(1.56-1.68)\* |
| Epilepsy | 219002 (0.51) | 217678 (0.37) |  | 1.39(1.25-1.54) | 1.31(1.18-1.46)\* |
| Multiple sclerosis | 221632 (0.09) | 219473 (0.07) |  | 1.18(0.93-1.49) | 1.09(0.86-1.39) |
| Parkinson’s Disease | 221470 (0.79) | 219635 (0.58) |  | 1.41(1.29-1.53) | 1.46(1.34-1.59)\* |
| Migraine | 205856 (2.44) | 208048 (1.74) |  | 1.36(1.29-1.43) | 1.26(1.20-1.33)\* |
| Depression | 170180 (12.86) | 182837 (7.92) |  | 1.58(1.54-1.62) | 1.43(1.39-1.47)\* |
| Psychosis | 221619 (0.19) | 219562 (0.17) |  | 1.10(0.93-1.29) | 0.94(0.79-1.10) |
| Schizophrenia | 220303 (0.36) | 218301 (0.29) |  | 1.21(1.07-1.36) | 1.08(0.96-1.22) |
| **Cancer** | 212110 (9.87) | 211362 (6.72) |  | 1.50(1.47-1.54) | 1.49(1.46-1.53)\* |
| **Circulatory** |  |  |  |  |  |
| Coronary Heart Disease | 201870 (6.32) | 204490 (4.6) |  | 1.35(1.31-1.39) | 1.22(1.18-1.26)\* |
| Arterial/Venous | 220674 (1.17) | 219035 (0.84) |  | 1.43(1.33-1.53) | 1.39(1.30-1.49)\* |
| Heart failure | 219010 (2.92) | 218309 (1.69) |  | 1.74(1.66-1.83) | 1.63(1.56-1.71)\* |
| Hypertension | 161900 (23.68) | 169134 (20.58) |  | 1.13(1.11-1.15) | 1.01(0.99-1.03) |
| Peripheral vascular disease | 216126 (2.93) | 215876 (2.02) |  | 1.45(1.38-1.51) | 1.36(1.30-1.43)\* |
| **Metabolic/Endocrine** |  |  |  |  |  |
| High Cholesterol | 194351 (1.34) | 197519 (1.11) |  | 1.18(1.16-1.21) | 1.08(1.05-1.10)\* |
| Diabetes Mellitus | 204495 (11.83) | 206477 (9.05) |  | 1.33(1.30-1.36) | 1.08(1.06-1.11)\* |
| Hyperthyroid | 219061 (0.7) | 217505 (0.57) |  | 1.21(1.11-1.32) | 1.12(1.03-1.22)\* |
| Hypothyroidism | 208088 (4.59) | 209156 (3.9) |  | 1.16(1.12-1.20) | 1.06(1.02-1.09)\* |
| **Digestive** |  |  |  |  |  |
| Gastritis | 207695 (4.94) | 209676 (3.05) |  | 1.62(1.57-1.68) | 1.45(1.40-1.51)\* |
| Gastrointestinal bleed | 219414 (1.4) | 218162 (0.85) |  | 1.65(1.54-1.76) | 1.49(1.39-1.59)\* |
| Gall bladder stone | 209651 (4.0) | 211412 (2.76) |  | 1.45(1.40-1.51) | 1.23(1.18-1.28)\* |
| Inflammatory bowel Disease | 211501 (3.89) | 212175 (2.59) |  | 1.49(1.45-1.55) | 1.31(1.26-1.37)\* |
| Liver Disease | 220977 (0.65) | 219294 (0.38) |  | 1.74(1.58-1.92) | 1.51(1.37-1.67)\* |
| Irritable bowel syndrome | 222101 (3.49) | 222145 (2.45) |  | 1.50(1.44-1.56) | 1.51(1.45-1.58)\* |
| **Others** |  |  |  |  |  |
| HIV infection/AIDS | 222161 (<0.001) | 220123 (<0.001) |  | 3.79(1.23-11.65) | 2.98(0.95-9.37) |
| Hearing | 200102 (12.48) | 202329 (10.92) |  | 1.16(1.13-1.19) | 1.14(1.11-1.16)\* |
| Psoriasis | 215401 (1.3) | 214766 (1.03) |  | 1.23(1.15-1.31) | 1.14(1.06-1.21)\* |
| Scleroderma | 222097 (0.03) | 220060 (0.02) |  | 1.50(1.05-21.3) | 1.33(0.93-1.92) |
| Sleep Disorder | 216765 (3.11) | 216231 (2.06) |  | 1.49(1.43-1.56) | 1.33(1.27-1.39)\* |
| Tuberculosis | 220697 (0.1) | 218804 (0.08) |  | 1.45(1.16-1.79) | 1.36(1.09-1.69) |
| Anaemia | 214130 (5.62) | 213681 (3.62) |  | 1.57(1.52-1.62) | 1.42(1.37-1.47)\* |
| Vision problem | 220721 (7.62) | 218929 (6.89) |  | 1.12(1.03-1.21) | 1.09(1.00-1.18) |
| Cataract | 222200 (10.35) | 222215 (9.63) |  | 1.09(1.07-1.12) | 1.13(1.10-1.16)\* |

Adjusted for age, gender, body mass index (BMI), alcohol use, smoking, multimorbidity count and index year; \*p<0.05 ‘False discovery rate’ (FDR) adjusted, ^only for men

Table 4: Adjusted hazard ratio and 95% confidence interval for each comorbidity for maximum 20 years follow up, comparing incident OA cases (joint wise) and matched controls irrespective of comorbidities at the index date

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Hip**  Adjusted HR  (95% CI) | **Knee**  Adjusted HR  (95% CI) | **Wrist/Hand**  Adjusted HR  (95% CI) | **Ankle/Foot**  Adjusted HR  (95% CI) |
| **Additional multimorbidity** | 1.16(1.11-1.21)\* | 1.24(1.20-1.28)\* | 1.46(1.36-1.56)\* | 1.17(1.07-1.29)\* |
| **Musculoskeletal** |  |  |  |  |
| Ankylosing Spondylitis | 1.92(1.47-2.51)\* | 1.59(1.31-1.93)\* | 1.82(1.29-2.56)\* | 1.72(0.98-2.99) |
| Back pain | 1.36(1.29-1.43)\* | 1.41(1.36-1.46)\* | 1.30(1.21-1.39)\* | 1.38(1.24-1.53)\* |
| Gout | 1.35(1.21-1.51)\* | 1.42(1.32-1.53)\* | 1.59(1.34-1.89)\* | 1.71(1.37-2.13)\* |
| Osteoporosis | 1.28(1.17-1.40)\* | 1.37(1.28-1.46)\* | 1.45(1.27-1.66)\* | 1.22(0.98-1.52) |
| Polymyalgia | 1.42(1.18-1.69)\* | 1.38(1.20-1.58)\* | 1.67(1.27-2.20)\* | 1.43(0.90-2.27) |
| Rheumatoid Arthritis | 3.20(2.40-4.27)\* | 2.64(2.20-3.17)\* | 2.27(1.76-2.91)\* | 2.22(1.28-3.87)\* |
| Sjogren’s Disease | 0.95(0.49-1.83) | 1.61(0.99-2.58) | 1.72(0.86-3.45) | 1.72(0.34-8.63) |
| Systemic lupus erythematosus | 1.38(0.58-3.31) | 1.60(0.78-3.27) | 1.39(0.38-5.04) | - |
| Fibromyalgia | 2.32(1.69-3.19)\* | 2.32(1.88-2.86)\* | 1.68(1.24-2.28)\* | 1.68(0.93-3.05) |
| Fatigue | 1.42(1.18-1.72)\* | 1.32(1.15-1.50)\* | 1.17(0.92-1.50) | 1.10(0.74-1.64) |
| **Respiratory** |  |  |  |  |
| Asthma | 1.05(0.91-1.20) | 1.16(1.07-1.28)\* | 1.25(1.05-1.49) | 1.30(0.99-1.71) |
| COPD | 1.24(1.12-1.38)\* | 1.15(1.07-1.24)\* | 1.13(0.95-1.35) | 0.99(0.77-1.25) |
| **Genito-Urinary** |  |  |  |  |
| Chronic Kidney Disease | 1.14(1.08-1.20)\* | 1.12(1.07-1.17)\* | 1.25(1.13-1.38)\* | 1.23(1.07-1.41)\* |
| Benign prostatic hypertrophy^ | 1.27(1.14-1.42)\* | 1.42(1.32-1.53)\* | 1.22(1.01-1.47) | 1.30(1.04-1.62) |
| Renal stone | 1.29(1.01-1.65) | 1.30(1.10-1.54) | 0.99(0.69-1.41) | 1.29(0.73-2.31) |
| **Neuro/Psychiatric** |  |  |  |  |
| Stroke | 1.21(1.13-1.31)\* | 1.24(1.18-1.31)\* | 1.15(1.02-1.30) | 1.23(1.04-1.45) |
| Dementia | 1.66(1.51-1.84)\* | 1.72(1.60-1.85)\* | **1.89(1.57-2.28)\*** | **1.95(1.49-2.55)\*** |
| Epilepsy | 1.58(1.17-2.12) | 1.41(1.13-1.74) | 1.34(0.81-2.19) | 1.07(0.57-2.01) |
| Multiple sclerosis | 2.18(1.08-4.36) | 1.05(0.61-1.80) | 0.82(0.25-2.74) | 1.33(0.38-4.69) |
| Parkinson’s Disease | 1.68(1.34-2.12)\* | 1.69(1.43-1.99)\* | 1.25(0.81-1.94) | 1.83(1.04-3.20) |
| Migraine | 1.06(0.89-1.25) | 1.23(1.09-1.37)\* | 1.27(2.05-2.54) | 1.25(0.93-1.69) |
| Depression | 1.43(1.33-1.54)\* | 1.44(1.36-1.51)\* | 1.36(1.22-1.51)\* | **1.57(1.34-1.85)\*** |
| Psychosis | 0.94(0.57-1.55) | 0.99(0.68-1.43) | 1.23(0.53-2.83) | 0.78(0.25-2.44) |
| Schizophrenia | 1.26(0.87-1.84) | 0.96(0.74-1.24) | 0.77(0.42-1.42) | 0.91(0.42-1.97) |
| **Cancer** | 1.60(1.49-1.72)\* | 1.59(1.51-1.67)\* | **1.46(1.30-1.63)\*** | **1.65(1.40-1.94)\*** |
| **Circulatory** |  |  |  |  |
| Coronary Heart Disease | 1.29(1.17-1.41)\* | 1.30(1.22-1.39)\* | 1.32(1.14-1.53)\* | 1.09(0.89-1.34) |
| Arterial/Venous | 1.71(1.42-2.07)\* | 1.54(1.33-1.77)\* | 0.93(0.64-1.35) | 1.64(1.01-2.67) |
| Heart failure | 1.64(1.45-1.86)\* | 1.82(1.66-2.00)\* | **1.58(1.24-1.99)\*** | 1.36(0.97-1.90) |
| Hypertension | 1.05(0.99-1.11) | 1.04(1.01-1.08) | 1.08(0.99-1.17) | 1.01(0.91-1.13) |
| Peripheral vascular disease | 1.52(1.34-1.73)\* | 1.41(1.29-1.55)\* | **1.46(1.19-1.79)\*** | 1.42(1.05-1.93) |
| **Metabolic/Endocrine** |  |  |  |  |
| High Cholesterol | 0.97(0.91-1.04) | 1.08(1.03-1.12)\* | 1.09(0.99-1.19) | 1.16(1.01-1.33) |
| Diabetes Mellitus | 1.07(1.00-1.15) | 1.19(1.14-1.25)\* | 1.24(1.11-1.38)\* | 1.12(0.97-1.30) |
| Hyperthyroid | 1.02(0.79-1.34) | 1.04(0.86-1.27) | 1.52(1.04-2.22) | 1.07(0.62-1.86) |
| Hypothyroidism | 1.02(0.92-1.14) | 0.96(0.89-1.04) | 1.16(0.99-1.34) | 1.14(0.91-1.42) |
| **Digestive** |  |  |  |  |
| Gastritis | 1.57(1.41-1.75)\* | 1.51(1.40-1.63)\* | 1.31(1.12-1.53)\* | 1.39(1.11-1.74)\* |
| Gastrointestinal bleed | 1.62(1.34-1.96)\* | 1.97(1.71-2.26)\* | 1.28(0.94-1.74) | 1.52(1.00-2.30) |
| Gall bladder stone | 1.33(1.19-1.50)\* | 1.31(1.20-1.42)\* | **1.45(1.23-1.70)\*** | 1.13(0.88-1.46) |
| Inflammatory bowel disease | 1.41(1.25-1.59)\* | 1.41(1.29-1.53)\* | 1.33(1.12-1.58)\* | **1.62(1.26-2.08)\*** |
| Liver disease | 1.48(1.09-2.02)\* | 1.64(1.33-2.00)\* | 1.38(0.85-2.21) | 1.49(0.82-2.72) |
| Irritable bowel syndrome | 1.26(1.06-1.49)\* | 1.50(1.33-1.69)\* | **1.67(1.36-2.04)\*** | **1.50(1.09-2.09)\*** |
| **Others** |  |  |  |  |
| Hearing | 1.17(1.10-1.25)\* | 1.19(1.15-1.25)\* | 1.23(1.11-1.35)\* | 1.37(1.19-1.57)\* |
| Psoriasis | 1.09(0.89-1.33) | 1.05(0.91-1.20) | 1.12(0.85-1.47) | 0.97(0.64-1.48) |
| Scleroderma | 1.23(0.47-3.24) | 1.31(0.54-3.22) | 0.96(0.24-3.82) | - |
| Sleep Disorder | 1.35(1.19-1.54)\* | 1.39(1.27-1.52)\* | **1.66(1.35-2.03)\*** | 1.39(1.05-1.86) |
| Tuberculosis | 1.58(0.68-3.66) | 1.36(0.85-2.19) | 2.55(0.99-6.54) | 0.87(0.24-3.12) |
| Anaemia | 1.74(1.59-1.92)\* | 1.61(1.51-1.72)\* | 1.33(1.14-1.55)\* | **1.55(1.25-1.92)\*** |
| Vision problem | 1.11(0.87-1.40) | 1.09(0.93-1.29) | 1.39(0.93-2.09) | 1.37(0.76-2.48) |
| Cataract | 1.16(1.07-1.26)\* | 1.15(1.09-1.22)\* | 1.27(1.13-1.42)\* | 1.12(0.92-1.37) |

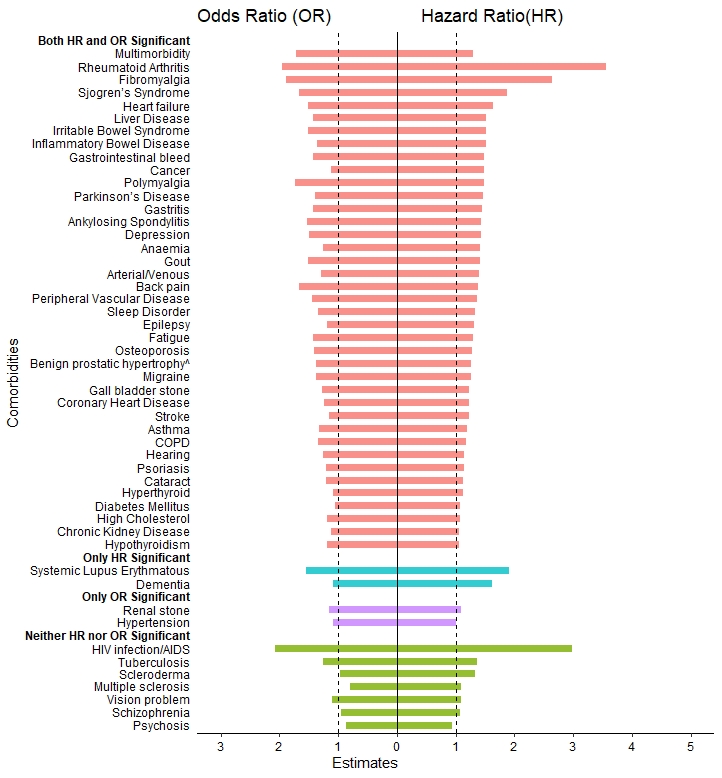
Adjusted for age, sex, BMI, alcohol use, smoking, multimorbidity count and index date; p-y person years; \*p<0.05 ‘False discovery rate’ (FDR) adjusted; COPD- Chronic Obstructive Pulmonary Disease

Figure 1: Cumulative probabilities of developing additional multimorbidity in cases with OA and matched non-OA controls irrespective any comorbidities at the index date



OA: Osteoarthritis (cases); Non-OA: Non-Osteoarthritis (controls)

Figure 2: Comparison of adjusted Odds Ratios and adjusted Hazard Ratios for comorbidities in OA for maximum 20 years observation period (before and after index date)



COPD- Chronic obstructive pulmonary diseases; HR: Hazard Ratio; OR: Odds Ratio

Red: Both HR and OR significant; Blue: Only HR significant; Purple: Only OR significant; Green: Neither HR nor OR significant. Dashed black line represents statistical significance level at OR or HR=1.

Significant means p <0.05 ‘False discovery rate’ (FDR) adjusted; ^among men.

Both the estimates were adjusted for age, sex, BMI, alcohol use, smoking, multimorbidity count, and index date.