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ORIGINAL RESEARCH

Hospital-Treated Infections and 15-year Incidence of Musculoskeletal Disorders: A Large Population-Based Cohort Study

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Background: Basic science evidence reveals interactions between the immune and bone systems. However, population studies linking infectious diseases and musculoskeletal (MSK) disorders are limited and inconsistent. We aimed to examine the risk of six main MSK disorders (osteoarthritis, rheumatoid arthritis, osteoporosis, gout, low back pain, and neck pain) following hospital-treated infections in a large cohort with long follow-up periods.

Methods: We analysed data from 502,409 UK Biobank participants. Participants free of specific MSK disorders at baseline were included in each analysis. Hospital-treated infections before baseline were identified using national inpatient data, while incident MSK outcomes were ascertained from inpatient records, primary care, and death registers. Participants with prior infections were propensity score matched (1:5) with those without. Hazard ratios (HRs) and absolute rate differences (ARDs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. To assess potential reverse causality due to delayed diagnosis of preexisting illness, analyses were repeated excluding MSK disorder cases that occurred within the first 5 and 10 years post-baseline.

Results: A hospital-treated infection was associated with increased risks of all six MSK disorders, with particularly strong associations for osteoporosis (HR, 1.55 [1.48–1.63]; ARD, 1.48 [95% CI 1.29–1.68] per 1000 person-years) and rheumatoid arthritis (HR, 1.53 [1.41–1.65]; ARD, 0.58 [0.46–0.71] per 1000 person-years), while other disorders showed HRs of 1.28–1.32. Bacterial and viral infections showed similar associations, with MSK infections (generally stronger risk) and other locations both linked to increased risks. Associations remained significant even for incident cases that occurred more than 10 years post-baseline.

Conclusion: Hospital-treated infections are associated with long-term MSK disorder risks, regardless of pathogen type or disorder nature (inflammatory or degenerative). Long-term monitoring and care for MSK health in patients with prior hospital-treated infections are recommended.

Plain Language Summary: Recent studies have revealed intimate interactions between immune and bone cells. However, population studies on the link between infection and musculoskeletal (MSK) disorders are limited. In this large-scale study with balanced covariates and over 15 years of follow-up, we found that people who had hospital-treated infections had a higher risk of developing MSK conditions, including those related to bone metabolism (osteoporosis), inflammation (eg, rheumatoid arthritis, gout), and degenerative processes (eg, osteoarthritis). This increased risk was not specific to a particular infection and grew with more

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frequent and severe infections, suggesting a systemic rather than pathogen-specific effect. The risk persists beyond 10 years, highlighting the need for long-term MSK care for individuals with a history of severe infections.

Keywords: infectious disease, osteoarthritis, rheumatoid arthritis, osteoporosis, gout, low back pain

Introduction

According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021, approximately 1.69 billion people worldwide live with musculoskeletal (MSK) disorders, including osteoarthritis, rheumatoid arthritis, osteoporosis, gout, low back pain, and neck pain, resulting in an estimated 119,000 deaths and 162 million disability-adjusted life years per annum.[1] Understanding the aetiology of MSK disorders to identify prevention strategies is an urgent public health priority. Recent advances in osteoimmunology highlight the shared microenvironment, signalling molecules, and intimate interactions between the immune and bone systems.[2] For example, both immune cells and osteoclasts are derived from hematopoietic stem cells;[3] cytokines regulate the differentiation of osteoclasts and osteoblasts, influencing bone turnover;[2] immune cells and cytokines also act on nociceptor neurons, increasing MSK pain.[4]

Chronic inflammatory conditions, characterized by excessive and persistent immune activation without a clear external cause, have been linked to MSK disorders. For example, asthma and atopic dermatitis are associated with increased risks of osteoporosis,[5] rheumatoid arthritis,[6] and osteoarthritis.[7] Similarly, inflammatory bowel disease[8–10] and chronic obstructive pulmonary disease[11,12] are associated with higher risks of osteoporosis and rheumatoid arthritis. These findings underscore the role of immune system dysregulation and a pro-inflammatory milieu in the development of MSK disorders. In contrast, external infectious pathogens, another key stimulus for immune activation and inflammation, have been less studied in their relation to MSK disorders. This is crucial because infections can often be prevented through vaccination, improved hygiene, and sanitation. Therefore, if infections are proven to be common triggers for a range of MSK disorders, they could emerge as a promising modifiable risk factor. The most studied pathogen for MSK health is SARS-CoV-2, which has been associated with bone loss,[13] osteoarthritis,[14] rheumatoid arthritis,[15,16] and low back pain.[17] However, evidence for other infections is limited and inconsistent. For instance, non-COVID respiratory infections show varying associations with rheumatoid arthritis,[18–20] while gastroenteritis is linked to increased osteoporosis risk[21] but decreased rheumatoid arthritis risk.[18] These studies are limited by self-reported infection data,[18] case-control or ecological designs prone to confounding,[18–20] and a narrow focus on single infections or outcomes.[18–21] To reveal unknown pathogen-MSK disorder associations, compare relative risks across pathogens, and highlight the broader benefits of infection prevention, a comprehensive assessment of the full array of infections and their long-term impacts on various MSK disorders is needed.

In this large-scale study, we systematically assessed the risk of six major MSK disorders associated with a spectrum of hospital-treated infections, categorized by pathogen and location infected. We also examined the dose-response relationship and the short-term and long-term risks between infection and MSK disorder risk.

Materials and Methods

Data Source

Between 2006 and 2010, UK Biobank (UKB) sent study invitations to 9.2 million adults aged 40–69 years who were registered with the UK's National Health Service (NHS) and lived near one of 22 assessment centres across England, Scotland, and Wales.[22] The UKB cohort was formed by ~500,000 participants (5.5% participation rate) who consented and attended the baseline assessment at an assessment centre. At baseline, participants completed a self-administered touchscreen questionnaire covering sociodemographic and lifestyle factors, a nurse-led verbal interview for medical history, and physical measurements. Participants' health conditions are captured through linkage to various national databases, including hospital inpatient admissions (data available from 1997 in England, 1998 in Wales, and 1981 in Scotland), death and cancer registrations, and primary care records (available for 45% of UKB participants).

Our research uses data exclusively from UK Biobank, which operates under a comprehensive ethical framework approved by the North West Multi-Centre Research Ethics Committee (MREC). This approval exempts researchers who access UK Biobank data through the approved application process from obtaining separate institutional ethical clearance. All UK Biobank participants provided written informed consent (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics).

Our study (Application 105435) was reviewed and approved through UK Biobank's standard application process, which includes an assessment of the research proposal's scientific merit and ethical considerations.

Study Population

The study was based on the latest UK Biobank data release, which included 502,409 participants. For the analysis of each MSK outcome, participants with a diagnosis of the respective outcome at baseline were excluded, based on self-reported medical history or linked health records prior to baseline. The number of exclusions for each outcome was as follows: osteoarthritis (n=65,428), osteoporosis (n=10,365), low back pain (n=52,314), neck pain (n=22,411), gout (n=10,494), and rheumatoid arthritis (n=7149). See eFigure 1 for a detailed overview of the study design.

Exposures and Outcomes

The primary exposure was any hospital-treated infection, defined as having at least one infection diagnosis in the hospital inpatient records before baseline. We captured infection diagnoses using the International Classification of Diseases, Tenth Revision (ICD-10), and Ninth Revision (ICD-9) codes from the list developed by Sipilä et al (eTable 1).[23] Secondary exposures further classified infections based on causative pathogens (bacterial and viral) and infection sites (musculoskeletal, lower respiratory tract, urinary tract, and gastrointestinal). For all exposures, exposed individuals were compared to those without any hospital-treated infections. Hospital-treated infections identified using ICD codes from administrative databases (eg, Medicaid, Veterans Affairs) have shown high validity for identifying severe infections, with overall positive predictive values (PPVs) ranging from 80% to 90%.[24,25]

We selected six MSK disorders as outcomes, which have been included in the GBD:[1,26] osteoarthritis, rheumatoid arthritis, osteoporosis, gout, low back pain, and neck pain. Incident cases were identified using the earliest diagnosis across primary care records, hospital inpatient records, and death registries. eTable 2 provides the code list for the predefined outcomes. Evidence supports the validity of using administrative data diagnoses to identify MSK outcomes. The PPV for rheumatoid arthritis ranges from 38.7% to 77.1%,[27] for gout 86%,[28] and for osteoarthritis 82–100%.[29] Chronic back and neck pain diagnoses show sensitivity and specificity above 70%.[30]

We also included ultraviolet radiation (UV)-related skin conditions as a negative control outcome, comprising sunburn (ICD-10 L55), photodermatitis (L56), and actinic keratosis (L57).[31] These diagnoses were obtained from the same data source as MSK outcomes. This outcome has a well-defined external cause (UV exposure) that is unrelated to infection. Therefore, no significant association with infection is expected. Any observed association would likely indicate the presence of bias.

Covariates

We studied covariates related to infection and musculoskeletal health, including age, sex, Townsend deprivation index, education, ethnicity, body mass index (BMI), alcohol consumption, smoking status, physical activity level, and disease history before baseline (cancer, chronic kidney disease, ischaemic heart disease, depression, anxiety or stress disorder, diabetes, hypertension, and peripheral vascular disease). Detailed definitions and classifications for these covariates are provided in eTable 3.

Statistical Analyses

The proportion of missing data for each covariate in the exposed and non-exposed groups is provided in eTable 4. Under the missing at random assumption, multiple imputation with chained equations was used to impute missing covariates

and create five imputed datasets. The imputation model included a binary variable for history of any hospital-treated infection and all covariates.

In each imputed dataset, we first excluded individuals with the outcome diagnosis at baseline, and then performed propensity score matching (1:5 matching) to balance covariates between exposed and unexposed groups, using a caliper width of 0.2 times the standard deviation of the propensity score. Propensity scores were calculated using a logistic regression model that included all covariates, which adjusted for confounding from all of these covariates.

For each outcome, we randomly selected one imputed dataset matched on the primary exposure, calculated summary statistics of baseline covariates and the maximum standardized mean difference (SMD) across the five imputed datasets, and plotted Kaplan-Meier curves to assess the difference in cumulative incidence of the outcome between individuals with and without hospital-treated infections. The incidence rate for each outcome was calculated as incident cases per total person-years during follow-up.

In the primary analysis, we used Cox proportional hazards models to compute hazard ratios (HRs) for the associations of primary and secondary exposures with six incident MSK disorders. Individuals were followed from baseline until the diagnosis of the outcome, death, or the censoring date of hospital inpatient records (October 31, 2022, for England; August 31, 2022, for Scotland; and May 31, 2022, for Wales), whichever came first. The results across all five imputed datasets were pooled using Rubin's rules. Absolute rate differences (ARDs) were calculated as $I_0 \times (HR - 1)$, where I_0 is the incidence in individuals without hospital-treated infections.

We evaluated the dose-response relationships between infection burden and infection severity with MSK disorders. Infection burden, measured as the number of infection-related hospital admissions before baseline, was categorized into no hospital-treated infections (reference), 1, 2, or ≥3 episodes, with risk estimates calculated relative to the reference. Infection severity was assessed by the length of hospital stay for the earliest infection episode, classified as same-day discharge, 1–3 days, or ≥4 days, again using those with no hospital-treated infections as the reference. To examine whether associations differ by length of follow-up and address reverse causality, we stratified the population by follow-up time: <5, 5 to <10, and ≥10 years. By restricting the analysis to participants with follow-up periods of 5 to <10 years and ≥10 years, we inherently omitted incident MSK disorder cases occurring within the first 5 and 10 years, respectively.

Six sensitivity analyses were conducted. First, to assess the association between hospital-treated infections and less severe MSK disorders, we restricted the analyses to UKB participants with available primary care data and captured outcomes based only on primary care diagnoses. Primary care data were available only until 31 May 2016 (England, data provider TPP), 31 May 2017 (England, data provider Vision), 31 March 2017 (Scotland), and 31 August 2017 (Wales). Second, individuals who were not infected at baseline but became infected during the follow-up were censored. Third, we accounted for the competing risk of non-MSK disorder-related death using the Fine-Gray subdistribution hazard model. Fourth, we restricted analyses to those without any of the six MSK disorders at baseline. Fifth, we additionally included history of chronic inflammatory diseases that may increase MSK disorder risks, including asthma, atopic dermatitis, inflammatory bowel disease, and chronic obstructive pulmonary disease, in the propensity score models. Sixth, for dose-response analysis, we estimated propensity scores for each dose category using inverse probability of treatment weighting (IPTW).[32]

Secondary and sensitivity analyses were conducted in one randomly selected dataset from the five imputed datasets.

Results

At baseline, individuals with hospital-treated infections were comparable in age and sex to those without, but they had lower socioeconomic status, higher BMI, were more likely to smoke, more physically inactive, and had more medical conditions (Table 1). After matching, the covariates for those exposed and unexposed to hospital-treated infections were well-balanced for all outcomes, with SMDs below 0.10 for all characteristics across all imputed datasets (Table 1 and eTable 5).

The cumulative incidence of all outcomes was higher for individuals with previous hospital-treated infections compared to those without (Figure 1). This trend was observed both in the main analysis, when outcomes were captured

Table 1 Baseline Characteristics of Individuals with and without Hospital-Treated Infection Before and After Propensity-Score Matching

Characteristics[a]	Before Matching		SMD	After Matching[b]		SMD[c]
	No Infection	Any Infection		No Infection	Any Infection	
N	456207	46152		182091	37797	
Age (mean (SD))	57.01 (8.08)	57.36 (8.29)	0.04	56.37 (8.27)	56.54 (8.39)	0.01
Sex (%)						
Male	207303 (45.4)	21762 (47.2)	0.03	86696 (47.6)	18270 (48.3)	<0.01
Female	248904 (54.6)	24390 (52.8)	0.03	95395 (52.4)	19527 (51.7)	<0.01
Townsend deprivation index quintile (%)						
1 (Least deprived)	92804 (20.3)	7674 (16.6)	0.10	31180 (17.1)	6464 (17.1)	<0.01
2	92335 (20.2)	8138 (17.6)	0.07	33489 (18.4)	6767 (17.9)	<0.01
3	91927 (20.2)	8534 (18.5)	0.04	34235 (18.8)	7003 (18.5)	<0.01
4	90968 (19.9)	9484 (20.5)	0.02	37020 (20.3)	7726 (20.4)	<0.01
5 (Most deprived)	88173 (19.3)	12322 (26.7)	0.18	46167 (25.4)	9837 (26.0)	<0.01
Education (%)						
Primary	76299 (16.7)	11009 (23.9)	0.18	37028 (20.3)	8030 (21.2)	<0.01
Secondary	102618 (22.5)	10075 (21.8)	0.02	40266 (22.1)	8429 (22.3)	0.01
Post-secondary non-tertiary	55003 (12.1)	5354 (11.6)	0.01	20270 (11.1)	4347 (11.5)	<0.01
Tertiary	222287 (48.7)	19714 (42.7)	0.12	84527 (46.4)	16991 (45.0)	0.01
Ethnic group (%)						
White	431937 (94.7)	43183 (93.6)	0.05	170425 (93.6)	35224 (93.2)	<0.01
Other ethnic groups	24270 (5.3)	2969 (6.4)	0.05	11666 (6.4)	2573 (6.8)	<0.01
BMI (%)						
Normal	152926 (33.5)	12911 (28.0)	0.12	55531 (30.5)	11447 (30.3)	<0.01
Overweight	194867 (42.7)	18483 (40.0)	0.05	74998 (41.2)	15349 (40.6)	<0.01
Obese	108414 (23.8)	14758 (32.0)	0.18	51562 (28.3)	11001 (29.1)	<0.01
Alcohol intake (%)						
≤ 4 times per week	362087 (79.4)	38266 (82.9)	0.09	151792 (83.4)	31119 (82.3)	<0.01
Daily or almost daily	94120 (20.6)	7886 (17.1)	0.09	30299 (16.6)	6678 (17.7)	0.01
Smoking (%)						
Never	252711 (55.4)	22271 (48.3)	0.14	91110 (50.0)	18512 (49.0)	<0.01
Previous	156932 (34.4)	17127 (37.1)	0.06	65179 (35.8)	13695 (36.2)	<0.01
Current	46564 (10.2)	6754 (14.6)	0.13	25802 (14.2)	5590 (14.8)	<0.01
Physical activity (%)						
Low	84008 (18.4)	10341 (22.4)	0.10	37151 (20.4)	8155 (21.6)	0.01
Moderate	185936 (40.8)	17836 (38.6)	0.04	71394 (39.2)	14735 (39.0)	<0.01
High	186263 (40.8)	17975 (38.9)	0.04	73546 (40.4)	14907 (39.4)	0.01
Medical history (%)						
Anxiety or stress disorder	24129 (5.3)	3329 (7.2)	0.08	11184 (6.1)	2571 (6.8)	<0.01
Cancer	41034 (9.0)	6765 (14.7)	0.18	24392 (13.4)	5370 (14.2)	<0.01
Chronic kidney disease	4804 (1.1)	1251 (2.7)	0.12	3177 (1.7)	910 (2.4)	<0.01
Ischaemic heart disease	16065 (3.5)	3906 (8.5)	0.21	10696 (5.9)	2850 (7.5)	<0.01
Depression	36328 (8.0)	5782 (12.5)	0.15	19388 (10.6)	4377 (11.6)	<0.01
Diabetes	11528 (2.5)	3494 (7.6)	0.23	8519 (4.7)	2579 (6.8)	<0.01
Hypertension	118445 (26.0)	16089 (34.9)	0.19	54983 (30.2)	12195 (32.3)	<0.01
Peripheral vascular disease	4528 (1.0)	1090 (2.4)	0.11	2705 (1.5)	768 (2.0)	<0.01

Notes: [a]The baseline characteristics before matching were calculated based on a dataset randomly selected from five imputed datasets. Since we excluded people with a history of each study outcome at baseline, individuals included in the post-matching dataset vary by outcome. Here, we show the baseline characteristics based on the dataset (randomly selected from five imputed datasets) used for one of the six outcomes, osteoarthritis. Baseline characteristics based on datasets for other outcomes are provided in eTable 5. [b]Unexposed individuals matched 5:1 to those exposed. Some exposed individuals might have fewer than five matches, if there were not enough unexposed individuals with propensity scores fall within the caliper range. We performed matching without replacement. [c]The largest SMD across all the imputed datasets.

Abbreviations: N, number of participants; SD, Standard deviation; SMD, standardized mean difference; BMI, body mass index.

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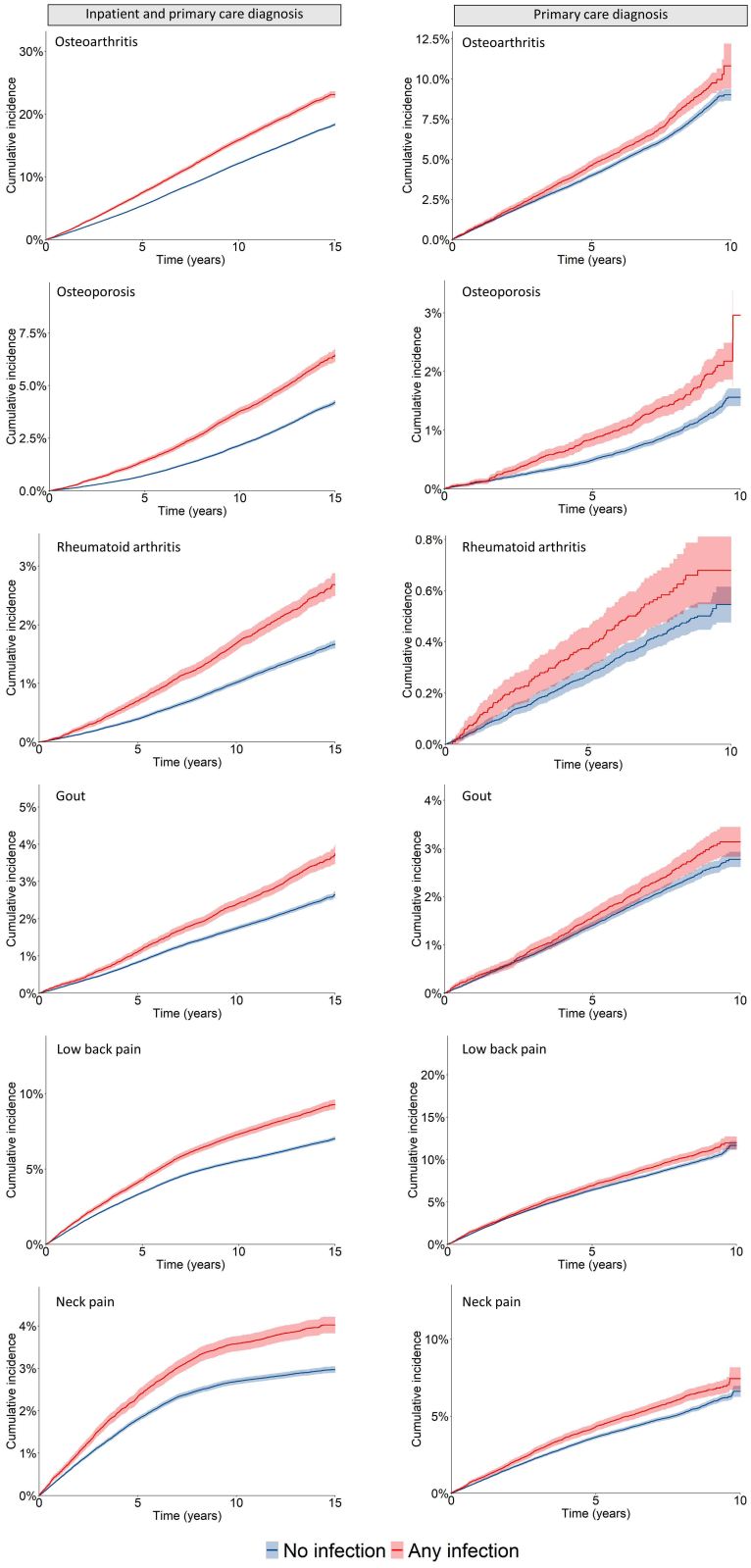

Figure 1 Kaplan-Meier cumulative incidence plots for all outcomes. Shaded areas indicate 95% confidence intervals.

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from all sources (hospital inpatient, death, and primary care records); as well as when outcomes were captured exclusively in primary care, which may indicate milder cases or earlier presentations of the conditions. For the main analysis, the 15-year cumulative incidence and its difference between individuals with and without infection were particularly high for osteoarthritis (23.10% [95% CI, 22.59–23.60%] vs 18.37% [95% CI, 18.14–18.60%]), low back pain (9.28% [95% CI, 8.95–9.60%] vs 7.01% [95% CI, 6.88–7.15%]), and osteoporosis (6.43% [95% CI, 6.13–6.74%] vs 4.19% [95% CI, 4.08–4.31%]). As expected for a negative control outcome, the cumulative incidence of UV-related skin conditions was similar between the two groups (eFigure 2).

Compared with no history of infection, a history of any hospital-treated infection was associated with an increased risk of all six MSK disorders, with the highest risks observed for osteoporosis (HR 1.55 [95% CI, 1.48–1.63]; ARD 1.48 [95% CI, 1.29–1.68] per 1000 person-years), rheumatoid arthritis (HR 1.53 [95% CI, 1.41–1.65]; ARD 0.58 [95% CI, 0.46–0.71] per 1000 person-years), and gout (HR 1.32 [95% CI, 1.24–1.40]; ARD 0.56 [95% CI, 0.42–0.71] per 1000 person-years) (Table 2). No significant association was found with UV-related skin conditions (HR 1.02 [95% CI, 0.97–1.09]; ARD 0.06 [95% CI, −0.08–0.20] per 1000 person-years) (eTable 6).

Associations with bacterial and viral infections were of comparable strength across all outcomes (Figure 2). Compared to other infection locations, MSK infections had the strongest associations with osteoarthritis (HR 1.93 [95% CI, 1.55–2.42]), osteoporosis (HR 2.14 [95% CI, 1.59–2.88]), and especially rheumatoid arthritis (HR 2.73 [95% CI, 1.84–4.05]). However, it showed no significant association with gout (HR 1.27 [95% CI, 0.83–1.95]). Among non-MSK infections, the strongest associations were with lower respiratory tract (HR 2.11 [95% CI, 1.88–2.36]) and gastrointestinal infections (HR 1.88 [95% CI, 1.60–2.20]) for osteoporosis. When unexposed individuals were censored at the time of their first hospital-treated infection during follow-up, slightly larger effect sizes were observed (eTable 7). The Fine-Gray models accounting for the competing risks of non-MSK death, analyses excluding patients with a history of any outcomes at baseline, and analyses adjusted for history of chronic inflammatory diseases, showed results broadly similar to the main analyses (eTable 7).

For all six outcomes, there was a dose-response association between infection burden and risk, particularly for gout, osteoporosis, and rheumatoid arthritis. Compared with no infection-related admissions, HRs for these conditions were below 1.5 for one admission and above 2 for three or more admissions (Figure 3A). A similar dose-response relationship pattern was observed for infection severity, with HRs increasing from 1.16 (gout), 1.42 (osteoporosis), and 1.52 (rheumatoid arthritis) for same-day discharge to above 1.75 for hospital stays exceeding three days (Figure 3B).

A history of any hospital-treated infection showed the greatest short-term risk for osteoporosis (HR 1.97 [95% CI, 1.79–2.16] within the first 5 years after baseline), with risk remaining significant beyond 10 years (Figure 4). Osteoarthritis and rheumatoid arthritis also had the highest risk during the first 5 years, which attenuated but remained stable with longer follow-up. In contrast, the risk for gout, low back pain, and neck pain increased over time: for gout, the HR rose from 1.34 (within the first 5 years) to 1.52 (more than 10 years after baseline), and for neck pain, it increased from 1.30 to 1.61.

Table 2 Association Between Any Hospital-Treated Infection and Subsequent Risk of Six Musculoskeletal Disorders

Outcomes	No Infection			Any Infection			HR (95% CI)	ARD (95% CI) per 1000 Person-years
	No. of Participants	No. of Events	IR per 1000 Person-years	No. of Participants	No. of Events	IR per 1000 Person-years		
Osteoarthritis	182091	29507	13.29	37797	7673	17.50	1.29 (1.25–1.32)	3.81 (3.33–4.30)
Osteoporosis	212830	7456	2.69	44512	2377	4.23	1.55 (1.48–1.63)	1.48 (1.29–1.68)
Rheumatoid arthritis	214575	3090	1.10	44907	1014	1.77	1.53 (1.41–1.65)	0.58 (0.46–0.71)
Gout	213927	4929	1.76	44783	1411	2.48	1.32 (1.24–1.40)	0.56 (0.42–0.71)
Low back pain	190642	12278	5.07	39816	3339	6.86	1.28 (1.23–1.34)	1.43 (1.17–1.70)
Neck pain	207190	5905	2.20	43417	1642	3.02	1.30 (1.23–1.37)	0.66 (0.50–0.82)

Notes: IRs were calculated from one randomly selected imputed dataset. HR and CI were estimated by pooling results from all five imputed datasets. The median follow-up time for all outcomes in both the any infection and no infection groups ranged from 13.1 to 13.6 years, with a maximum follow-up time of 16.6 years for all groups.
Abbreviations: IR, incidence rate; HR, hazard ratio; ARD, absolute rate differences; CI, confidence interval.

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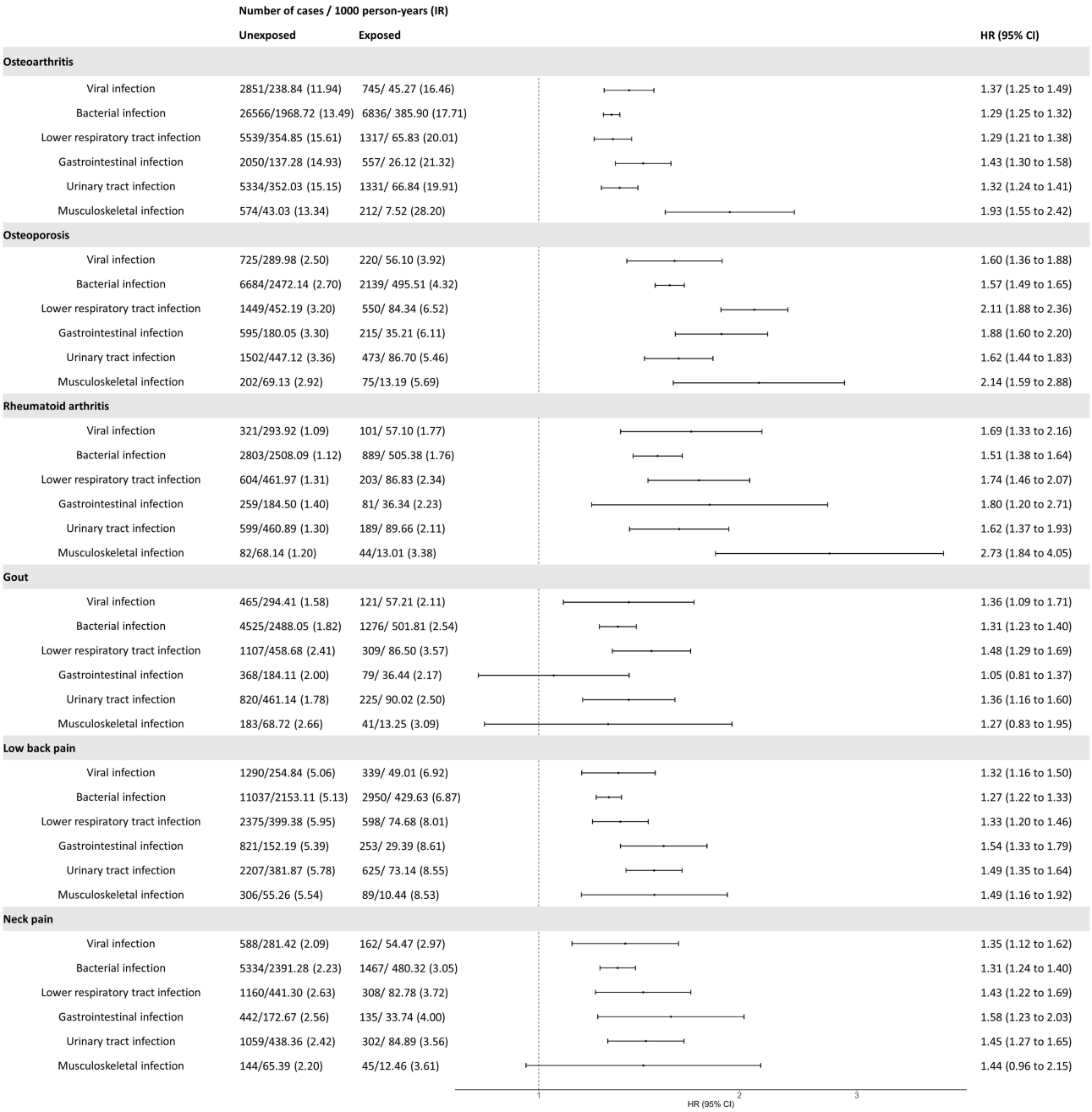

Figure 2 Association between specific types of hospital-treated infection and risk of musculoskeletal disorders. IRs were calculated from one randomly selected imputed dataset. HRs and CIs were estimated by pooling results from all five imputed datasets. Some infections, such as parasitic and fungal infections, as well as unspecified infections, are included in "any infection" but were not analysed separately due to their rarity.
Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence interval.

Discussion

We assessed the associations between various hospital-treated infections and the risk of six MSK disorders over 15 years of follow-up. Infections were associated with a 1.28 to 1.55-fold increased risk of all six MSK disorders, with the highest risks for osteoporosis and rheumatoid arthritis. These risks remained significant after 10 years of follow-up. Compared with infections at other sites, MSK infections were associated with the highest risk for osteoarthritis, osteoporosis, and rheumatoid arthritis. Associations were similar for bacterial and viral infections and showed little specificity by infection

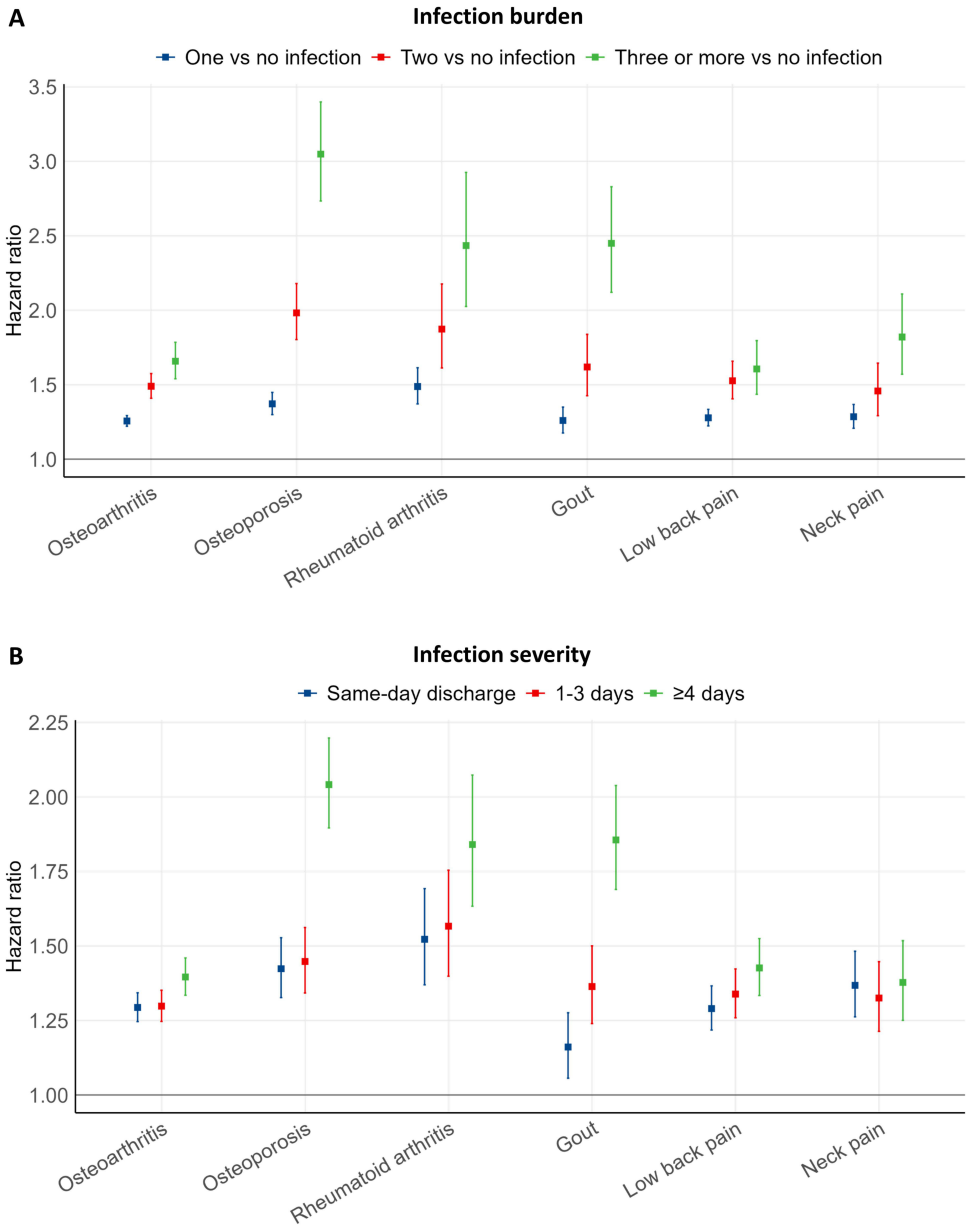

Figure 3 Dose-response associations of infection burden and infection severity with musculoskeletal disorder outcomes. Error bars are 95% confidence intervals. The risk of musculoskeletal disorders was compared between participants with no hospital-treated infections and those with 1, 2, or ≥3 episodes of infection-related hospital admissions before baseline (**A**). The risk of musculoskeletal disorders was compared between participants with no hospital-treated infections and those whose earliest infection-related hospital admission resulted in same-day discharge, a stay of 1–3 days, or a stay of ≥4 days (**B**).

type. A dose-response relationship was observed between multiple episodes of hospital-treated infections and increased MSK disorder risk.

For any hospital-treated infection, the strongest association was observed for osteoporosis, with elevated risk not limited to MSK infections but also other sites. This finding aligns with previous research showing that hepatitis B virus (HBV),[33] hepatitis C virus (HCV),[34] and Helicobacter pylori[21] infections increase osteoporosis risk. Invading pathogens such as bacteria and viruses can colonize bone, leading to bone loss;[35] cytokines such as RANKL, IL-6, and IL-1β also upregulate osteoclast activity and inhibit osteoblast activity.[2] The highest risk observed immediately after infection may be due to reverse causality, as patients with low bone mineral density have a higher risk of infections such as pneumonia, urinary tract infection, and sepsis.[36] Also, a lower respiratory tract infection or urinary tract infection can precipitate a fall

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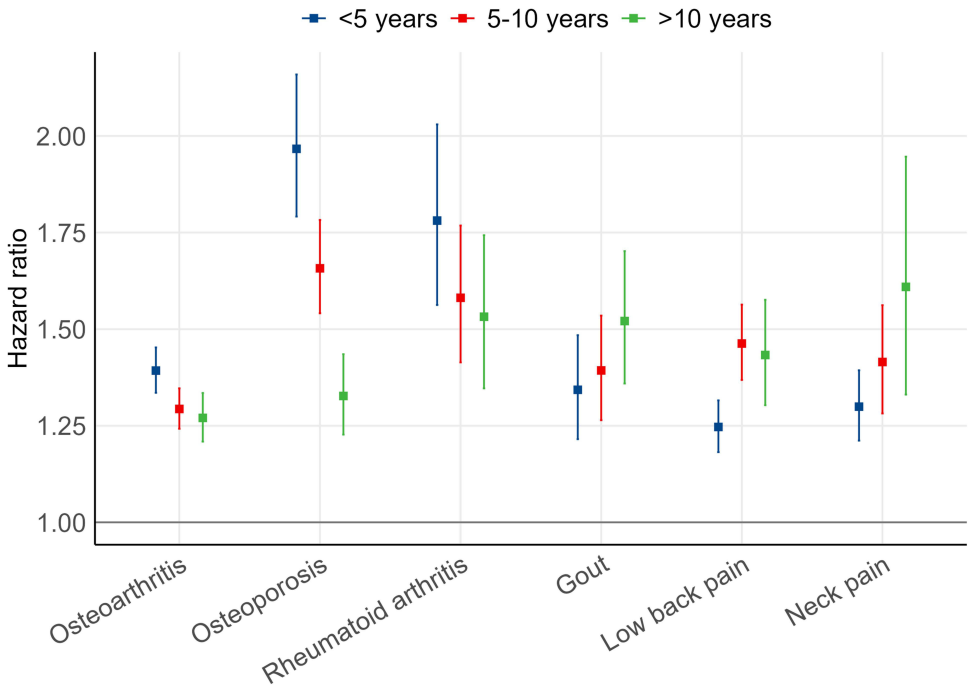

Figure 4 Association between any hospital-treated infection and musculoskeletal disorder outcomes over years. Error bars are 95% confidence intervals. The risks of musculoskeletal disorders for different follow-up periods were estimated by restricting the analysis to participants with follow-up periods of <5 years, 5 to <10 years, and ≥10 years, with the latter two groups inherently omitting incident MSK disorder cases occurring within the first 5 and 10 years after baseline, respectively.

and fracture,[37,38] increasing the likelihood of seeing an orthogeriatrician and receiving an osteoporosis diagnosis.[39] However, the association remained significant beyond 10 years of follow-up, and previous studies have shown that hospital-treated Human papillomavirus (HPV) infection[40] and herpes zoster[41] increase osteoporosis risk over similar (>10 years) periods, suggesting a bidirectional relationship.

For rheumatoid arthritis, the highest risk was observed within the first 5 years of follow-up, remaining stable thereafter. This finding aligns with a Danish study, which reported the highest risk within the first month of any hospital-treated infection (HR = 6.45), decreasing to 2.08 within the second to twelfth months, and stabilizing at around 1.5 for more than 10 years of follow-up.[42] A case-control study on periodontitis and rheumatoid arthritis showed a similar pattern, with the highest risk within the first year and stabilization thereafter.[43] Acute autoimmune diagnoses following infections may be due to increased cross-reactivity between foreign pathogens and self-antigens shortly after infection,[44] as seen with SARS-CoV-2.[45] Alternatively, reverse causality may also be a factor, with evidence showing autoimmune diseases increase SARS-CoV-2 infection risk.[46] Mendelian randomization analyses indicate seropositive rheumatoid arthritis increases the risk of periodontitis, with no significant causal relationship in the reverse direction.[47] However, the long-term association suggests lasting sequelae of infections. For example, cytokines produced by lymphocytes in response to pathogens can activate additional lymphocytes,[48] perpetuating inflammation independently of specific antigens and ultimately leading to autoimmune pathology.

We extend previous findings that showed an increased risk of osteoarthritis following SARS-CoV-2 infection to a broader range of infections.[14] In the SARS-CoV-2 study, osteoarthritis risk decreased from the first to the third year of follow-up but remained significant,[14] aligning with the temporal risk pattern observed in our study. Traditionally, osteoarthritis has been considered a "wear and tear" disease primarily driven by non-inflammatory causes, such as abnormal joint loading. However, both the SARS-CoV-2 study and our findings highlight the role of infection in osteoarthritis development. This is further supported by studies detecting cytokines in the synovial fluid, cartilage, and synovium of osteoarthritis patients, which are absent in healthy controls.[49]

For osteoporosis, rheumatoid arthritis, and osteoarthritis, our findings suggest that both local and systemic inflammation contribute to their development. This is supported by the strongest associations observed for MSK infections, yet infections across different anatomical sites also showed consistent significant associations, with overlapping confidence intervals indicating similar effect sizes. This aligns with previous literature showing an increased risk of MSK disorders following infection with various pathogens (eg, SARS-CoV-2, HBV, HCV, HPV, and periodontitis) and with our observed dose-response relationship between infection burden, as a proxy for inflammation level, and MSK disorder risk. A previous Swedish study assessing the association between self-reported infections and rheumatoid arthritis risk found no significant association for respiratory infections, and gastrointestinal and urinary tract infections were associated with a lower risk.[18] This suggests that a significant increase in MSK disorder risk may require infections severe enough to necessitate hospitalization.

This study is the first to find a significant association between infection and increased risk of gout. Unlike other MSK disorders, gout risk was linked to respiratory and urinary tract infections, not MSK infections. This suggests a unique underlying mechanism: rather than being driven by post-infectious joint damage, infection may indirectly increase the risk of gout by exacerbating the inflammatory response to monosodium urate crystals.[50] Respiratory and urinary tract infections may also elevate the risk of other potential gout risk factors such as metabolic changes and renal disease.[51–53] Therefore, the time interval from infection to gout clinical manifestation could be lengthy, consistent with the observed higher risk in longer follow-up periods.

Our findings indicate that low back pain and neck pain are significant post-acute sequelae for various infections, not just SARS-CoV-2.[17] These pains are multifactorial; prior research has linked infections to major causes of pain like ankylosing spondylitis[42,54–57] and myopathy.[58,59] Notably, studies found higher bacterial infection rates in degenerated discs,[60] estimated at over 40%,[61] compared to non-degenerated discs. Observational studies and randomized controlled trials also reported benefits from antibiotic treatment for discogenic pain.[61] We observed similar associations between MSK and non-MSK infections with pain, aligning with evidence that bacteria from non-MSK infections could contribute to disc degeneration via haematogenous spread.[62] This also suggests that pain may not require a localized infection, as inflammatory factors like cytokines can circulate and sensitize peripheral and central nociceptors, exacerbating and prolonging pain.[4]

Our study, encompassing over 900 types of infections and approximately 500,000 participants, represents the largest and most comprehensive examination of the association between infection and MSK disorders to date. The extended follow-up period minimized the potential for reverse causation. However, there are limitations to consider. Firstly, we are unable to disentangle the potential effect of drugs. For example, antibiotics have been associated with autoimmunity and painful neuropathy,[63,64] and antiretroviral therapy accelerates bone loss.[65] However, treatments may also reduce inflammation and lower MSK risk, making the direction of bias unclear. Secondly, there might be missed MSK disorders cases, particularly for conditions (eg, osteoporosis and pain) that are frequently underdiagnosed.[66] This could lead to non-differential misclassification, biasing estimates toward the null. Thirdly, it remains unclear whether the association can be generalized to mild infections that do not require hospitalization.

Conclusions

Severe infections are associated with an increased long-term risk of major MSK disorders. This connection is not notably specific to the type of pathogen or anatomical location infected, although the local MSK infections appear to present the highest risk. These findings suggest that the systemic inflammation triggered by infections could be the key mechanism leading to MSK disorders. For individuals recovering from severe infections, particularly recurrent or prolonged episodes, clinicians may consider monitoring musculoskeletal health in routine care, such as early screening for osteoporosis, rheumatoid arthritis, and osteoarthritis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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