Pre-existing musculoskeletal pain and its association with mortality in newly diagnosed comorbid conditions: an electronic health record cohort study

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Abstract

Objectives: Musculoskeletal pain is a common risk factor for comorbid conditions and may increase the risk of poor outcomes. The objective was to determine whether patients with pre-existing musculoskeletal pain have an increased mortality risk following a new diagnosis of a comorbid condition.

Methods: Patients aged ≥45 years with a new diagnosis of acute coronary syndrome (ACS), stroke, cancer, dementia, or pneumonia recorded in a UK electronic primary care database linked to hospital and mortality records were examined. The association of mortality with musculoskeletal pain (inflammatory conditions, osteoarthritis [OA], and regional pain) was determined.

Results: Sample size varied from 128,649 (stroke) to 406,289 (cancer) by cohort with 22-31% having pre-existing musculoskeletal conditions. In the ACS cohort, there was a higher rate of mortality for all musculoskeletal types. There were also higher unadjusted mortality rates in patients with inflammatory arthritis compared to those without musculoskeletal pain in the stroke, cancer, and dementia cohorts and for patients with OA in the stroke and cancer cohorts. Following adjustment for number of prescribed medications and age, the increased risk of

mortality remained only for patients with inflammatory arthritis in the ACS cohort (adjusted HR 1.07; 95% CI 1.03, 1.10).

Conclusion: Older adults with inflammatory arthritis and OA have increased risk of mortality when they develop a new condition, which seems to relate to prescribing of multiple medicines. Pre-existing musculoskeletal pain is an indicator of a complex patient who is at risk of poorer outcomes at the onset of new illnesses.

Keywords: musculoskeletal pain; mortality; comorbidity; epidemiology; primary care

Key messages:

- Adults with musculoskeletal pain are at increased risk of mortality from a new comorbid condition.
- Increased mortality was largely explained by them being older and being prescribed more medications.
- This study has highlighted the complexity of patients with severe musculoskeletal pain and new onset condition.

Lay summary

What does this mean for patients?

Musculoskeletal pain (pain in the joints and muscles around them) is common and those with pain often have other long-term conditions. We wanted to find out if people with musculoskeletal pain had an increased risk of earlier death following diagnosis of a new serious illness. We studied anonymised healthcare records of patients aged 45 years and over with a new diagnosis of heart attack, stroke, cancer, dementia, or pneumonia. Approximately a third of people with these new diagnoses had a musculoskeletal pain condition including inflammatory arthritis, osteoarthritis, or regional (e.g. back, knee) pain. This group had an increased risk of earlier death compared to those without existing musculoskeletal pain, with the highest risk in those with inflammatory arthritis and osteoarthritis. However, this increased risk was explained by those with musculoskeletal pain being older and on many medications. Taking multiple medicines suggests patients have more illnesses but increases possibility of being on medicines

with little benefit or that cause harm, and of not taking medicines as instructed. Doctors need to consider all of a patient's current illnesses and medicines when treating a new illness. Improving musculoskeletal pain recognition and management, and regular medicine reviews, may help improve outcomes of other illnesses.

Introduction

Musculoskeletal pain is common, with up to one in five adults consulting primary care in the UK for a painful musculoskeletal condition each year and it has a major impact on everyday activity and is a major burden on healthcare systems.(1,2) Musculoskeletal pain commonly co-exists with other conditions and may increase the risk of developing new illnesses. For example, osteoarthritis (OA) (3–5), rheumatoid arthritis (RA) (6–8) and low back pain (9,10) have been shown to be associated with an increased risk of developing heart disease and stroke. Regional pain such as back pain, psoriatic arthritis (PsA), and polymyalgia rheumatica have been linked to the onset of cancer (11–13), OA with dementia (14) and inflammatory musculoskeletal conditions with hospitalisation for community-acquired pneumonia (15). However, it is less clear whether musculoskeletal pain impacts on outcomes of these other conditions. For example, in cardiovascular disease, studies have shown increased in-hospital mortality after acute myocardial infarction, intracranial haemorrhage and ischaemic stroke in patients with RA or systemic lupus erythematosus (16), but other studies have shown no association (17,18) or even reduced mortality in patients with RA (19). Knowledge of the impact of musculoskeletal pain on the prognosis of other conditions would be important in the management of these conditions, and also the management of musculoskeletal pain. The aim of this study was

therefore to determine whether pre-existing painful musculoskeletal conditions are associated with long-term mortality in those with other newly diagnosed conditions and whether this varied by type of musculoskeletal pain. The study focused on five conditions with evidence of links to musculoskeletal pain and are amongst the most common reasons for hospitalisation globally. These index conditions were acute coronary syndrome (ACS), stroke, cancer, dementia, and community-acquired pneumonia.

Methods

Study Design and Setting

A cohort study using the UK Clinical Practice Research Datalink (CPRD) Aurum database. CPRD Aurum contains anonymised primary care electronic health records (EHR) for over 40 million patients from over 1,000 general practices using EMIS Web® software (20). These data were linked to hospital inpatient admission data from Hospital Episode Statistics (HES), and Office for National Statistics (ONS) Death Registration Data. As the study used anonymised patient electronic health records from CPRD it did not require individual participant consent. The study was approved by the CPRD Independent Scientific Advisory Committee/Research Data Governance (refs 20_000105 ACS/stroke and 20_000147 cancer [October 2020 build]; 21_000504 dementia [June 2021 build] (21); 21_000689 pneumonia [November 2021 build] (22)). The approved protocols were made available to reviewers.

Study Population

The study population consisted of patients aged 45 years or over with a first ever record of one of our index illnesses and with at least 24 months prior registration at their practice to obtain consultation records for musculoskeletal pain and covariates. For ACS and stroke we included

patients with first myocardial infarction or unstable angina, or first stroke or transient ischaemic attack in their primary care record between 2000 and 2019 and a matching hospital inpatient record with admission date within 1 month of the primary care recorded date. For cancer we included patients with a first diagnosis of breast, colon, lung, or prostate cancer in primary care between 2000 and 2019. We also included patients with a first ever recorded diagnosis of dementia in primary care between 2005 and 2019. Finally, we included patients with a first ever recorded bacterial pneumonia diagnosis in primary care, or as the reason for admission to hospital, between 2014 and 2018. Patients recorded with a pneumonia diagnosis within 2 weeks after a hospital stay were excluded to ensure pneumonia was not acquired in hospital. Patients were also excluded if they had a previous record of a viral pneumonia.

Diagnoses are recorded in UK primary care using the Read code system up to 2018 and SNOMED CT codes from 2018. Within hospital admissions, illnesses are recorded using International Classification of Diseases (ICD-10) codes. Derivation of code lists were based on those previously developed through a rigorous consensus approach in research studies by healthcare practitioners, epidemiologists and statisticians with expertise in electronic health record research at Keele University (11,23,24) and code lists based on those from external studies using electronic health records. The code lists used for each index condition can be

found at https://eprints.keele.ac.uk/id/eprint/11580/ (25). The date of first diagnosis of the index condition was defined as that patient's index date.

Outcome

The outcome was all-cause mortality. Patients were followed from their index date until the earliest of end of their registration at the practice (including death) or last date of collected data. For the ACS and stroke cohorts, those with a death record, end of registration or last data collection date before thirty days after index date were excluded. For pneumonia, as it is an acute morbidity, mortality was measured from index date for a maximum of 12 months.

Exposure

Exposure was defined as presence or absence of a painful musculoskeletal condition identified from primary care records in the 24 months prior to index date. The types of musculoskeletal pain examined were diagnosed inflammatory conditions (RA, gout, ankylosing spondylitis, giant cell arteritis, PsA); diagnosed OA; and the most common non-specific regional pains recorded in primary care (low back pain/backache, knee pain, hip pain, hand/wrist pain).

In a secondary analysis, patients with musculoskeletal pain were sub-grouped by severity and "recency" of pain as an alternative to type. Primary care EHR do not contain direct evidence of

pain severity, so we used proxy measures based on: i) a coded referral to a pain management clinic, rheumatology, orthopaedics, or physiotherapy specialists; or ii) prescription of a strong analgesic medicine (i.e. a strong opioid such as tramadol, morphine or oxycodone)(26), on the assumption a referral or stronger analgesic would normally indicate more severe pain. Current musculoskeletal pain was defined as a recorded consultation for musculoskeletal pain in the six months before index date. Patients were sub-grouped as: current and severe (recorded consultation within the six months before index date and either a referral or a prescription of strong analgesia); current and non-severe; recent (recorded consultation between six and twenty-four months before index date).

Covariates

Covariates included in the analyses for all cohorts were: age at index date, gender, geographical location, race, neighbourhood-level deprivation (Index of Multiple Deprivation, IMD), year of index consultation, recorded comorbidity in the 24 months prior to the index date (depression, anxiety or stress; diabetes; other musculoskeletal conditions), general multi-morbidity based on prescription count (number of different medications prescribed excluding analgesia) and body mass index, and smoking status recorded in the 60 months prior to the index date. Cohort-specific covariates were peripheral vascular disease and statin medicine for

ACS and stroke, chronic kidney disease for cancer, stroke for dementia, and chronic obstructive pulmonary disease (COPD), dementia, renal disease, stroke, and type of antibiotic for pneumonia.

Analysis

Binary/categorical patient characteristics were summarised as the number and percentage within each category and continuous characteristics (index year; age at index date; and number of prescriptions in the 24 months prior to the index date) were presented using median and interquartile range (IQR).

Analysis of the association of prior musculoskeletal consultation with mortality used flexible parametric survival models with 3 (ACS; stroke) or 4 (cancer; dementia; pneumonia) degrees of freedom. Each model was run with only musculoskeletal pain (categorised as none (reference), regional pain, OA, inflammatory) in the model, progressing to including all covariates. Musculoskeletal pain was included as a time-dependent effect in the fully adjusted models for cancer, dementia and pneumonia with 4 degrees of freedom for time-dependent effects. All models included robust standard errors clustered at the practice level. Adjusted hazard ratios (HR with 95% CI) are presented and, for the ACS, stroke, cancer and dementia cohorts also

determined at two, five and ten years of follow-up to assess consistency of association over time.

In the secondary analysis, associations of mortality with recency and severity of musculoskeletal pain (none; recent; current-non-severe; current-severe) were assessed.

Sensitivity Analyses

In the main analysis missing data for race, body mass index, smoking status and alcohol status was recorded as the reference category (white, normal BMI (18.0-24.9 kg/m^2), never smoked and does not drink, respectively) with sensitivity analyses also undertaken and estimates compared for: i) complete case analysis; and, ii) where missing data were coded as `missing' categories. All analyses were performed using Stata/MP 17.0 (StataCorp LLC, USA).

Results

Patient Characteristics

Baseline characteristics of each of the cohorts are shown in Table 1, and sub-grouped by type of musculoskeletal pain within each cohort in Supplementary Tables S1-5, available at *Rheumatology Advances in Practice* online. Size of population ranged from 128,649 (stroke) to 406,289 (cancer). Between 22% and 31% of patients had a consultation for one of the painful musculoskeletal conditions in the 24 months prior to the index date. Regional pain was the most common (12-17%) followed by OA (6-10%) and inflammatory arthritis (4-5%).

In all cohorts apart from dementia, those with OA (median 74-81 years) or inflammatory arthritis (75-80 years) were older than those with regional pain (69-77 years) or no musculoskeletal pain (69-77 years; Supplementary Tables S1-5). Prevalence of comorbidities and counts of prescribed medications were also generally higher for those with musculoskeletal pain compared to those without musculoskeletal pain. Those with musculoskeletal pain were more commonly ex-smokers and recorded as overweight or obese than those without musculoskeletal pain, and there were fewer men recorded with regional pain or OA in all cohorts apart from ACS (Supplementary Tables S1-5).

In the ACS cohort, there was a higher rate of mortality for all three musculoskeletal types. Patients with pre-existing inflammatory arthritis had the highest rate (92 per 1,000 person years (py), unadjusted HR vs no pre-existing musculoskeletal pain 1.51; 95% CI 1.47, 1.56), followed by OA (77/1,000py; 1,27; 1.23, 1.30). In those without musculoskeletal pain rate of mortality was 61/1,000py, and with regional pain it was 59/1000py (Table 2). There were also higher unadjusted rates of mortality in patients with pre-existing inflammatory arthritis compared to those without pre-existing musculoskeletal pain in the stroke (114 vs 95/1000py), cancer (186 vs 145/1000py), and dementia (241 vs 222/1000py) cohorts and for patients with OA in the stroke (106 vs 95/1000py) and cancer (164 vs 145/1000py) cohorts. Patients newly diagnosed with cancer with regional pain (160/1000py) had higher unadjusted rates of mortality than those with no musculoskeletal pain. There was no evidence of increased mortality in those with musculoskeletal pain in the pneumonia cohort.

Most covariates did not change the associations found in the unadjusted analyses. However, the number of prescribed medications, and to a lesser extent, age did impact on the associations and the increased risk of mortality remained only for patients with inflammatory arthritis in the ACS cohort (adjusted HR 1.07; 95% CI 1.03, 1.10) after adjusting for these covariates (Table 2). Table 3 shows the number of different medications prescribed during the

baseline period with the highest counts in those with inflammatory arthritis. Associations of musculoskeletal pain with mortality were generally consistent at 2, 5 and 10-years of follow-up.

In the secondary analysis, when assessing association of mortality with recency and severity of musculoskeletal condition, the patients with current-severe musculoskeletal pain had the highest rates of mortality for the ACS, cancer and dementia cohorts and the lowest for pneumonia (Table 4). As with the primary analysis, adjustment for number of prescribed medications had the greatest impact on observed associations and current-severe pain was only associated with an increased adjusted risk of mortality in patients with cancer (adjusted HR vs no musculoskeletal pain 1.25; 95% 1.21, 1.29)

Sensitivity Analyses

Similar estimates were obtained using the different approaches to account for missing data and did not change the study findings (data not shown).

Discussion

To our knowledge this is the first study to explore whether pre-existing musculoskeletal pain impacts on the prognosis following incident ACS, stroke, cancer, dementia or community acquired pneumonia through increased rates of mortality. This study has shown increased rates of mortality across four common chronic conditions (ACS, stroke, cancer, dementia) for people with pre-existing musculoskeletal pain. This is particularly evident for those with inflammatory arthritis. However, after adjustment for number of prescribed medications and age, the majority of these associations were not maintained. These findings persisted in the secondary analysis which focussed on the recency of consultation and severity of pain rather than the type of musculoskeletal condition.

Musculoskeletal pain is highly prevalent as evidenced by up to a third of people newly diagnosed with ACS, stroke, cancer, dementia, and pneumonia having consulted for such a problem in the previous two years. It is also disabling and can have a major impact on everyday life, reducing the ability to perform everyday tasks and impacting on sleep, mental health, and work. Musculoskeletal pain is often neglected when a patient has co-occurring conditions, and its presence may be unrecognised or inadequately addressed (27,28), with the non-musculoskeletal conditions prioritised due to a perception of greater influence on mortality,

morbidity, and healthcare use. For example, research has highlighted that people living with dementia are less likely to have recorded primary care consultation or analgesics prescription for musculoskeletal conditions compared to those without dementia.(29) Despite previously observed associations of musculoskeletal pain with onset of clinical conditions (3–12) there is little prior evidence of its impact on outcomes of these conditions. The limited number of previous studies assessing the impact of musculoskeletal conditions on mortality have given mixed findings and tended to be small and/or based outside of the UK. To our knowledge this is the first study to explore whether pre-existing musculoskeletal pain impacts on the long-term prognosis following incident ACS, stroke, cancer, dementia or community acquired pneumonia through increased rates of mortality. Studies have shown inconsistent associations of inflammatory arthritis with in-hospital mortality in patients with ACS and stroke (16–18,30). Mobility impairment was associated with mortality in pneumonia in a study in Portugal.(31) Patients with musculoskeletal pain, particularly inflammatory arthritis and OA do have an increased risk of earlier mortality. This is partly explained by being older but in addition the observed associations seemed to also be explained by increased polypharmacy in patients with musculoskeletal pain. This is consistent with our previous study looking at short term (30-day) outcomes in patients with a new ACS or stroke (32). In the current study, we found that patients

with musculoskeletal pain were being prescribed an average of 13-19 different medicines over two years. This excluded prescribed painkillers and “over the counter” medicines, so the overall number of medicines is likely to be higher. Whilst we also adjusted for specific comorbidities, this may reflect a higher multimorbidity load and increased frequency of consultation in such patients. Taking a high number of medicines has been associated with poor adherence especially when more than nine medications were prescribed and may in itself affect disease outcomes and disease progression.(33) A further concern is the possibility of inappropriate prescribing, with specific medicines increasing risk of poor outcome, for example increasing risks of falls, episodes of delirium, and hospital admissions because of adverse drug reactions. Further research is needed to understand more about the impact of multiple medications across common conditions.

Whilst this study suggests musculoskeletal pain does not directly cause poorer outcomes, it highlights that musculoskeletal pain may be an indicator that patients may be more complex, being more likely to be older and have more comorbidities and medications. There is potential for pain and restricted functioning and mobility resulting from a musculoskeletal condition to affect delivery and effectiveness of treatment and rehabilitation. Improving musculoskeletal pain recognition and management, including integration within rehabilitation, may help improve its

impact on everyday life in people across co-occurring conditions and their outcomes. Clinicians need to think about the patient as a whole when treating individual illnesses including consideration of all their illnesses and current medicines, and this study highlights the importance of regular medicine reviews.

Strengths/Limitations

The study was set in a database of routinely recorded primary care data currently including 20% of the England population, which is nationally representative and was linked to secondary care and mortality information. Recorded morbidities in UK databases such as CPRD have shown high validity (34,35).

Some patients may not have had pain at time of the onset of the new condition. Therefore, in secondary analysis we also examined those with a more recent (last six months) consultation to reflect increased likelihood of a current episode of pain. As expected, those with a more recent consultation necessitating onward referral or prescription of a strong analgesic had increased risk of mortality but again that association tended to disappear when adjusting for number of medications. Defining musculoskeletal pain by consultation to primary care suggests the musculoskeletal pain was of a severity which prompted the need to seek healthcare, however

there will be patients in the non-musculoskeletal comparison group who have musculoskeletal pain without recently seeking healthcare. This is a limitation of research using such databases and future research could evaluate impact of self-reported musculoskeletal pain on mortality. However, the subgroup of patients with musculoskeletal pain who have not consulted for two years are likely to have less severe or less chronic pain. We restricted analysis to the most common painful conditions and those previously shown to be associated with the onset of our index conditions, and also adjusted for consultation for other musculoskeletal conditions. Severity of pain is not recorded in electronic health records, and we therefore used surrogates for this, including onward referral to relevant specialists or prescription of a strong opioid analgesic (which cannot be bought over the counter). There may also be unmeasured confounding.

Conclusion

Musculoskeletal pain is common and a frequent reason for seeking health care within primary care. Older adults with inflammatory arthritis and OA often have co-existing illnesses and are on multiple medicines. As a consequence, when they have a new illness, they may be more likely to have poorer outcomes such as mortality compared to those without musculoskeletal pain.

Pre-existing musculoskeletal pain may be an indicator of a complex patient who is at risk of poorer outcomes at the onset of a new illnesses.

Acknowledgments

CPRD: This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone.

ONS Data: The interpretation and conclusions contained in this study are those of the authors alone.

ISAC reference: The study was approved by the CPRD Independent Scientific Advisory Committee (refs 20_000105; 20_000147; 21_000504; 21_000689). The approved protocols were made available to reviewers.

PPIE/Advisory group: The authors would especially like to thank the members of the Keele Research User Group for their valuable contributions to this study. We are also thankful to Keele PPIE team for their support of the public contributors. The authors would also like to thank the project advisory group for the study.

Funding statement

This project was funded by the Nuffield Foundation (OBF/43974). The Nuffield Foundation is an independent charitable trust with a mission to advance social well-being. It funds research that informs social policy, primarily in Education, Welfare, and Justice. It also funds student programmes that provide opportunities for young people to develop skills in quantitative and scientific methods. The Nuffield Foundation is the founder and co-funder of the Nuffield Council on Bioethics and the Ada Lovelace Institute. The Foundation has funded this project, but the views expressed are those of the authors and not necessarily the Foundation. Visit www.nuffieldfoundation.org

KJM, KPJ and CDM are supported by matched funding awarded to the NIHR Applied Research Collaboration West Midlands. CDM is also funded by the NIHR School for Primary Care Research.

Conflicts of Interest

The Keele School of Medicine have received funding from Bristol Myers Squibb for a non-pharmacological atrial fibrillation screening trial. The authors have no further conflicts to declare.

Data Availability Statement

Data may be obtained from a third party and are not publicly available. The data were obtained from the Clinical Practice Research Datalink. Clinical Practice Research Datalink data governance does not allow us to distribute patient data to other parties. Researchers may apply for data access at http://www.CPRD.com/.

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Table 1 - Patient Characteristics by Cohort

	ACS	Stroke	Cancer	Dementia	Pneumonia
Total, n	165,350	128,649	406,289	199,961	192,587
Type of MSK Pain, n (%)					
No MSK Pain	116,231 (70)	89,949 (70)	291,256 (72)	137,042 (69)	149,871 (78)
Regional Pain	27,344 (17)	20,799 (16)	68,339 (17)	33,783 (17)	23,352 (12)
OA	12,863 (8)	10,966 (9)	30,451 (7)	19,941 (10)	10,989 (6)
Inflammatory	8,912 (5)	6,935 (5)	16,243 (4)	9,195 (5)	8,375 (4)
Recency and severity of MSK Pain, n (%)					
No MSK Pain	116,231 (70)	89,949 (70)	291,256 (72)	137,042 (69)	149,871 (78)
Recent	29,198 (18)	23,065 (18)	66,327 (16)	38,294 (19)	25,756 (13)
Current-non-severe	10,960 (7)	8,829 (7)	25,599 (6)	14,864 (7)	8,794 (5)
Current-severe	8,961 (5)	6,806 (5)	23,107 (6)	9,761 (5)	8,166 (4)
Median follow-up, years (IQR)	4.9 (2.0, 9.3)	3.6 (1.5, 7.1)	3.3 (1.1, 7.7)	4.6 (2.5, 7.9)	4.6 (3.4, 6.0)
Median age, years (IQR)	70 (60, 79)	75 (66, 83)	70 (62, 78)	83 (77, 87)	77 (65, 86)
Males, n (%)	106,500 (64)	66,639 (52)	202,451 (50)	77,253 (39)	94,318 (49)
Smoking Status, n (%) [b]					
Current smoker	44,548 (27)	28,216 (22)	89,114 (22)	28,972 (14)	33,000 (17)
Ex-smoker	42,438 (26)	32,928 (26)	110,048 (27)	57,646 (29)	46,930 (24)
Never Smoked/not recorded	78,364 (47)	67,505 (52)	207,127 (51)	113,343 (57)	112,657 (59)
Body Mass Index, n (%) [b]					
Underweight (10.0-18.0 kg/m^2)	2,157 (1)	2,461 (2)	7,153 (2)	9,052 (5)	7,069 (4)
Normal/not recorded (18.0-<25.0 kg/m^2)	86,554 (52)	69,684 (54)	203,223 (50)	107,742 (53)	116,502 (61)
Overweight (25.0-<30.0 kg/m^2)	47,670 (29)	35,129 (27)	135,295 (33)	61,901 (31)	43,143 (22)
Obese (30.0-79.9 kg/m^2)	28,969 (18)	21,375 (17)	60,618 (15)	21,266 (11)	25,873 (13)
Index of Multiple Deprivation Quintiles, n (%) [a]					
Least deprived/not recorded	34,116 (21)	27,574 (21)	100,377 (25)	44,371 (22)	36,421 (19)
Second-least deprived	34,193 (21)	27,205 (21)	91,009 (22)	43,364 (22)	36,082 (19)
Mid deprived	32,913 (20)	26,306 (20)	80,674 (20)	39,971 (20)	37,354 (19)
Second-most deprived	32,048 (19)	24,078 (19)	70,508 (17)	37,052 (19)	38,935 (20)
Most deprived	32,080 (19)	23,486 (18)	63,721 (16)	35,203 (18)	43,795 (23)
White /not recorded race, n (%) [b]	154,740 (94)	121,323 (94)	389,089 (96)	189,647 (95)	179,253 (93)
Specific comorbid conditions, n (%) [a]					
Diabetes	30,557 (18)	23,491 (18)	43,940 (11)	33,266 (17)	21,578 (11)
Peripheral Vascular Disease	5,183 (3)	3,622 (3)	N/A	N/A	N/A
Depression, Anxiety or Stress	12,937 (8)	10,258 (8)	52,341 (13)	26,095 (13)	12,955 (7)
Other MSK consultation	46,224 (28)	36,140 (28)	24,487 (6)	61,287 (31)	42,678 (22)
Renal Disease	N/A	N/A	14,353 (4)	N/A	6,394 (3)
Stroke	N/A	N/A	N/A	15,501 (8)	5,154 (3)
COPD/asthma	N/A	N/A	N/A	N/A	27,637 (14)
Dementia	N/A	N/A	N/A	N/A	11,131 (6)
Median number of prescriptions (IQR) [a]	9 (4, 16)	11 (6, 18)	9 (5, 16)	12 (7, 19)	9 (0, 18)
Prescribed statins, n (%) [a]	61,787 (37)	47,122 (37)	N/A	N/A	N/A

Prescribed antibiotic, n (%)	N/A	N/A	N/A	N/A	20,044 (10)

Abbreviations: acute coronary syndrome (ACS); musculoskeletal (MSK); osteoarthritis (OA); interquartile range (IQR). [a] recorded in 24 months prior to index date; [b] recorded in 60 months prior to index date.

Table 2 – Association of mortality with type of musculoskeletal pain by cohort

	Rate per 1000py	Unadjusted HR (95% CI)	Adjusted [a] HR (95% CI)	Adjusted [b] HR (95% CI)	Adjusted [c] HR (95% CI)
ACS					
No MSK Pain	61 (61, 62)	1	1	1	1
Regional Pain	59 (58, 60)	0.98 (0.95, 1.00)	0.95 (0.93, 0.97)	0.81 (0.79, 0.83)	0.90 (0.88, 0.92)
OA	77 (75, 79)	1.27 (1.23, 1.30)	0.90 (0.87, 0.92)	0.98 (0.95, 1.01)	0.85 (0.83, 0.88)
Inflammatory	92 (89, 95)	1.51 (1.47, 1.56)	1.18 (1.14, 1.21)	1.12 (1.08, 1.16)	1.07 (1.03, 1.10)
Stroke					
No MSK Pain	95 (94, 96)	1	1	1	1
Regional Pain	88 (86, 90)	0.93 (0.91, 0.95)	0.92 (0.90, 0.95)	0.81 (0.79, 0.83)	0.90 (0.88, 0.92)
OA	106 (103, 109)	1.12 (1.09, 1.15)	0.90 (0.88, 0.92)	0.94 (0.91, 0.97)	0.86 (0.84, 0.89)
Inflammatory	114 (110, 118)	1.21 (1.17, 1.25)	1.08 (1.05, 1.12)	0.98 (0.95, 1.02)	1.00 (0.97, 1.04)
Cancer					
No MSK Pain	145 (144, 146)	1	1	1	1
Regional Pain	160 (158, 162)	1.09 (1.07, 1.10)	1.09 (1.07, 1.10)	0.98 (0.96, 1.00)	1.00 (0.98, 1.01)
OA	164 (161, 167)	1.10 (1.07, 1.13)	0.98 (0.95, 1.00)	0.94 (0.92, 0.97)	0.91 (0.89, 0.93)
Inflammatory	186 (182, 190)	1.24 (1.20, 1.28)	1.11 (1.07, 1.14)	1.00 (0.97, 1.03)	0.97 (0.94, 1.00)
Dementia					
No MSK Pain	222 (221, 224)	1	1	1	1
Regional Pain	218 (216, 221)	1.01 (0.99, 1.03)	1.02 (1.00, 1.04)	0.93 (0.91, 0.95)	0.95 (0.93, 0.97)
OA	216 (212, 219)	0.98 (0.95, 1.01)	0.96 (0.93, 0.99)	0.89 (0.86, 0.91)	0.92 (0.89, 0.95)
Inflammatory	241 (235, 247)	1.16 (1.11, 1.21)	1.16 (1.11, 1.21)	1.01 (0.96, 1.05)	1.01 (0.97, 1.06)
Pneumonia [d]					
No MSK Pain	127 (126, 128)	1	1	1	1
Regional Pain	105 (103, 108)	0.87 (0.85, 0.89)	0.86 (0.84, 0.88)	0.72 (0.71, 0.74)	0.86 (0.83, 0.88)
OA	107 (104, 111)	0.86 (0.83, 0.89)	0.73 (0.70, 0.75)	0.70 (0.67, 0.72)	0.75 (0.73, 0.78)
Inflammatory	125 (120, 130)	0.97 (0.93, 1.01)	0.86 (0.83, 0.90)	0.76 (0.73, 0.80)	0.83 (0.80, 0.87)

Abbreviations: acute coronary syndrome (ACS); musculoskeletal (MSK); osteoarthritis (OA); hazard ratio (HR); confidence interval (CI).

[a] adjusted for age; [b] adjusted for number of medications excluding analgesia; [c] adjusted for all covariates;

[d] mortality measured from index date to 12m.

Table 3 – Median (IQR) number of different medications prescribed at baseline excluding analgesia

Cohort	No MSK pain	Regional pain	OA	Inflammatory
ACS	8 (3, 14)	11 (6, 18)	12 (7, 20)	14 (8, 22)
Stroke	8 (4, 14)	12 (7, 18)	13 (8, 19)	14 (9, 21)
Cancer	8 (4, 14)	12 (7, 18)	14 (8, 20)	15 (10, 22)
Dementia	11 (7, 17)	14 (9, 21)	15 (9, 21)	17 (11, 24)
Pneumonia	5 (0, 15)	17 (10, 25)	18 (12, 26)	19 (13, 27)

Table 4 – Association of mortality with recency and severity of musculoskeletal pain by cohort

	Rate per 1000py	Unadjusted HR (95% CI)	Adjusted [a] HR (95% CI)
ACS			
No MSK Pain	61 (61, 62)	1	1
Recent	66 (65, 68)	1.09 (1.07, 1.12)	0.91 (0.89, 0.93)
Current-non-severe	72 (70, 74)	1.18 (1.14, 1.22)	0.91 (0.89, 0.94)
Current-severe	76 (73, 78)	1.26 (1.22, 1.30)	0.97 (0.94, 1.01)
Stroke			
No MSK Pain	95 (94, 96)	1	1
Recent	96 (94, 98)	1.01 (0.99, 1.03)	0.91 (0.89, 0.93)
Current-non-severe	101 (98, 104)	1.06 (1.03, 1.10)	0.91 (0.88, 0.93)
Current-severe	96 (93, 100)	1.02 (0.98, 1.06)	0.90 (0.87, 0.93)
Cancer			
No MSK Pain	145 (144, 146)	1	1
Recent	157 (155, 159)	1.09 (1.08, 1.11)	0.96 (0.94, 0.97)
Current-non-severe	151 (148, 153)	1.07 (1.04, 1.09)	0.96 (0.93, 0.98)
Current-severe	216 (212, 220)	1.53 (1.48, 1.58)	1.25 (1.21, 1.29)
Dementia			
No MSK Pain	222 (221, 224)	1	1
Recent	219 (217, 222)	1.02 (1.00, 1.04)	0.96 (0.94, 0.98)
Current-non-severe	222 (218, 226)	1.02 (0.98, 1.05)	0.97 (0.93, 1.00)
Current-severe	224 (219, 230)	1.07 (1.02, 1.12)	0.97 (0.92, 1.01)
Pneumonia [b]			
No MSK Pain	127 (126, 128)	1	1
Recent	111 (109, 114)	0.90 (0.88, 0.92)	0.83 (0.81, 0.85)
Current-non-severe	130 (126, 135)	1.02 (0.98, 1.06)	0.86 (0.83, 0.89)
Current-severe	85 (81, 88)	0.71 (0.67, 0.74)	0.73 (0.70, 0.77)

Abbreviations: acute coronary syndrome (ACS); musculoskeletal (MSK); hazard ratio (HR); confidence interval (CI).

[a] adjusted for all covariates; [b] mortality measured from index date to 12m.