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Estimating the direct healthcare utilization and cost of musculoskeletal pain among people with comorbidity: a retrospective electronic health record study

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ABSTRACT

Objective: To investigate the impact of pre-existing painful musculoskeletal conditions on healthcare utilization and costs among patients with five common conditions: acute coronary syndrome (ACS), stroke, cancer, dementia and pneumonia.

Methods: Using primary and secondary care services data from electronic health records, a negative binomial regression model was used to compare resource use while a two-part model was used to compare costs across the five conditions, between those with and without a pre-existing musculoskeletal pain.

Results: The study included 760,792 patients (144,870 with ACS, 121,208 with stroke, 231,702 with cancer, 134,638 with dementia, and 128,374 with pneumonia) in the complete case analysis. Pre-existing musculoskeletal pain had an incident rate ratio of above one for most healthcare resources over the follow-up period and an adjusted additional mean cumulative total healthcare costs per patient of £674.59 (95%CI 570.30 to 778.87) for ACS; £613.34 (95%CI 496.87 to 729.82) for stroke; £459.26 (95%CI 376.60 to 541.91) for cancer; and £766.23 (95%CI 655.06 to 877.39) for dementia over five years after diagnosis; and £200.85 (95%CI 104.16 to 297.55) for pneumonia over one year after diagnosis compared to those without musculoskeletal pain.

Conclusion: This study highlights that individuals with painful musculoskeletal conditions have higher healthcare utilizsation and costs than those without painful musculoskeletal conditions. Given the high occurrence of musculoskeletal pain in patients with other conditions, effective management strategies are needed to reduce the burden on healthcare resources.

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Cost; pain; musculoskeletal; comorbidity

Introduction

Musculoskeletal conditions comprise a variety of ailments affecting the joints (e.g. osteoarthritis), bones, muscles and multiple body areas or systems (e.g. regional or inflammatory diseases). A rising obesity rate, increasingly sedentary lifestyles, and an ageing world population are among the factors contributing to a rise in the prevalence of musculoskeletal conditions[1–4]. In the UK, around 23.4 million workdays were lost in 2022 due to musculoskeletal pain and morbidity[5], costing the economy an estimated £3 billion in one year if a median wage of £640 per week[6] and a 5-workday per week were assumed. Musculoskeletal conditions are usually characterized by persistent pain[4], and musculoskeletal pain has been estimated to affect between 13.5% and 47% of the general population[7]. Many people with painful musculoskeletal conditions have other multiple long-term health problems[8–10] (also known as multimorbidity). For instance, up to one in three people with coronary heart disease live with a painful musculoskeletal condition[8]. Other common pairings of comorbidities with musculoskeletal conditions include cancer[11], and dementia[12,13].

Despite evidence[14] that painful musculoskeletal conditions, such as low back pain, are the 'main contributor to the overall burden of musculoskeletal conditions', there is a lack of studies that have estimated the additional healthcare cost of having musculoskeletal pain with other conditions. The issue is whether having such pain substantially increases the costs of health service utilization in comorbid conditions. Indeed, acute cardiovascular disease (acute coronary syndrome (ACS) and stroke), the most common forms of cancer

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(breast, prostate, lung, colorectal), dementia, and community-acquired pneumonia are among the most common reasons for hospitalization in the National Health Service (NHS) and therefore of high priority[15].

Our aim was to estimate the impact of pre-existing musculoskeletal conditions on healthcare utilization and costs in patients with five index conditions: acute coronary syndrome (ACS), stroke, cancer, dementia and pneumonia. We compared the healthcare service use and costs among patients with and without a pre-existing painful musculoskeletal condition among these five index conditions. Our findings will help to shed light on the healthcare costs associated with musculoskeletal conditions in patients with multimorbidity, which has important implications for healthcare resource allocation and management of these complex patients.

Methods

Data sources

Clinical Practice Research Datalink (CPRD) Aurum and Hospital Episode Statistics (HES) data were used in this observational study; CPRD Aurum includes practices that use the EMIS Web® software and captures high-quality data from over 40 million patients in over 1000 general practices, with 13 million current patients (20% of the UK population)[16,17]. HES dataset obtained in this study contained hospital inpatient admissions, for most patients attending secondary care services within the NHS in England[18]. The study was approved by the CPRD Independent Scientific Advisory Committee/Research Data Governance process (refs: 20_000105 ACS and stroke and 20_000147 cancer [October 2020 build], 21_000504 dementia [June 2021 build][19], 21_000689 pneumonia [November 2021 build][20])

Study population

Five index conditions (ACS, stroke, cancer, dementia and pneumonia) that were associated with musculoskeletal pain and are the most common reasons for hospitalization worldwide were chosen to be examined in this study. Patients aged 45 years or over with first primary care recorded ACS (myocardial infarction or unstable angina), stroke (including transient ischaemic attack), cancer (breast, colon, lung, or prostate; selected as the most common forms in the general population), or dementia and with at least 24 months before they registered at their practice were included. Patients with ACS and stroke needed to have a matching record in the linked hospital inpatient data with an admission date within one month of the first primary care recorded to date. For the pneumonia cohort, we included patients with a first recorded bacterial pneumonia diagnosis in primary care or as the reason for hospital admission but excluded those with a recorded pneumonia diagnosis within two weeks of a hospital stay to ensure that it was not hospital-acquired pneumonia. The periods for deriving the population were 2000–2019 (ACS, stroke, and cancer), 2005–2019 (dementia) and 2014–2018 (pneumonia). The different search dates for dementia and pneumonia were due to the introduction of the Quality and Outcomes Framework and an increase in dementia recording, while the feasibility study of pneumonia suggested that the sample size from 2014–2018 would be big enough. The index date was defined as the date of entry into the studied population. The follow-up period of ACS, stroke, cancer, and dementia was five years after the index date, while the follow-up period of pneumonia was one year after the index date. This is because of the acute but often self-limiting nature of pneumonia which means that a one-year follow-up is sufficiently long enough to capture the impact of musculoskeletal conditions on service utilization among patients with pneumonia.

The Read code system up to 2018 and SNOMED CT codes from 2018 captured the diagnoses, symptoms, and processes of care (for example, referrals, tests) in the UK primary care setting, while International Classification of Diseases (ICD-10) codes captured the illnesses within hospital admissions. Index conditions that consisted of the derivation of appropriate Read and ICD-10 code lists were defined based on a rigorous consensus approach in previous research studies[21].

Exposure

Primary care records were used to identify painful musculoskeletal conditions 24 months before the index date. The types of musculoskeletal pain that were examined in the study included: (1) the most common non-specific regional pain disorders (low back pain/backache, knee pain, hip pain, hand/wrist pain); (2) diagnosed osteoarthritis; and (3) diagnosed inflammatory musculoskeletal condition such as rheumatoid arthritis, gout, ankylosing spondylitis, giant cell arteritis, psoriatic arthritis (inflammatory conditions). Overall musculoskeletal pain was defined when any of the three musculoskeletal (pain) disorders: (1) non-specific pain disorders, (2) osteoarthritis; and (3) inflammatory musculoskeletal conditions were present, and no musculoskeletal pain when none of them were present.

Covariates

Covariates that were selected a priori as expected confounders of the association of musculoskeletal pain and healthcare resource and cost within each index condition and adjusted for in the analyzes included age at index date, sex, ethnicity, geographical region, neighbourhood deprivation (i.e. Index of Multiple Deprivation), index year, body mass index, smoking and alcohol status. We also adjusted for other musculoskeletal conditions and for comorbidities and prescribed preventative medicine specific to each index disease, where comorbidity was identified from a relevant primary care record 24 months before the diagnosis of the index condition. Specifically, mental health (depression, anxiety, stress) and diabetes were used to adjust for all five index conditions; peripheral vascular disease and statin medicine for heart attacks and strokes; chronic kidney disease for cancer; stroke in people living with dementia; and chronic obstructive pulmonary disease, dementia, renal disease, stroke, and type of antibiotic for pneumonia. Other musculoskeletal conditions refer to musculoskeletal conditions other than diagnosed osteoarthritis, diagnosed inflammatory conditions and the most common non-specific regional pain disorders (low back pain/backache, knee pain, hip pain, hand/wrist pain) which defined our exposure. Therefore, these included the less common diagnoses and less common regional pain (such as shoulder pain and elbow pain) defined by consensus of electronic health record researchers and general practitioners and with code lists based on those used in previous studies within Keele University[21].

Valuation of costs

Healthcare service use and costs of primary and secondary healthcare services over the follow-up period of each index condition were categorized as: (1) primary care prescriptions, (2) primary care consultations, and (3) hospital admissions.

The estimated unit cost of prescriptions was available within the CPRD Aurum. The unit cost of primary care consultations was obtained primarily from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2020 compendium[22] (Supplementary Table A1). There were a few assumptions made regarding the unit cost of primary care consultations. First, all consultations were assumed to last for 50 min, 9.22 min and 4 min for home, surgery and phone consultations respectively based on the average time reported in the PSSRU[23,24]. Second, staff below NHS Agenda for Change (AfC) pay band four were assumed to work 1618 h per year like those in band four[23].

The unit cost of hospital admission was obtained from the NHS Reference Cost 2019/20 based on the clinic specialty, inpatient length of stay (short-stay or long-stay) and type of admission (elective or non-elective) after generating the Health Resource Group (HRG) codes from the HRG4 + 2021/22 Reference Cost Grouper at the Full Consultant Episode (FCE) level[25,26]. Hospital admission costs were analyzed at the episode level by aggregating the FCE costs within episodes to generate total mean costs for one inpatient episode. Patients who died were assumed to incur zero service utilization and costs for the remaining follow-up period. All costs were adjusted to 2020/21 prices using the NHS Cost Inflation Index (NHSCII)[27].

Statistical analysis

The characteristics of patients with no musculoskeletal pain and those with a painful musculoskeletal condition for each index condition were summarized using mean and standard deviations for continuous variables and percentages for categorical variables.

Resource use was summarized using negative binomial regression model while differences in resource use were explored using incident rate ratio (IRR) computed from the same model, where a utilization IRR of one suggests no difference, a utilization IRR of less than one suggests lower resource use in the musculoskeletal pain group relative to the no musculoskeletal pain and an IRR of more than one suggests higher resource use among those with than those without musculoskeletal pain.

For each index condition, the mean cost of each resource category (i.e. prescriptions, consultations and hospital admissions) was computed using a two-part model to account for the skewed nature of the cost distribution due to the presence of a large number of patients with no or low costs and very few patients with extremely high costs. This model consisted of two stages, first a logistic regression where the dependent variable (total cost) indicated the presence of no costs (yes versus no); and second, a gamma distribution and log-link function for costs among patients with positive values.

The aforementioned models were adjusted for the baseline cost and baseline count of each respective resource category when estimating the mean cost and mean resource use respectively, and for the covariates described above. Baseline was defined as the year before the index date. A Yeo-Johnson transformation was performed on the baseline cost and count of each resource category before adjustment due to the presence of many zeros. The total mean cost was computed from the sum of the adjusted mean cost of prescriptions, consultations, and hospital admissions so no standard errors or confidence intervals. The mean cumulative total cost was then computed using the summation of these adjusted mean total costs since the index date.

Due to the large dataset available for analysis, only patients with complete data, including those who died, across resource categories over one year of follow-up were included in the pneumonia cohort, and five years of follow-up from the index date in ACS, stroke, cancer and dementia cohorts. All statistical analyzes were conducted using R version 4.2[28].

Results

Study population

There was complete data in 144,870 out of 171,670 (84%) ACS patients, 121,208 out of 138,512 (88%) stroke patients, 231,702 out of 406,289 (57%) cancer patients, 134,638 out of 199,961 (67%) patients with dementia, and 128,374 out of 192,587 (67%) pneumonia patients. The baseline characteristics of each cohort are summarized in Supplementary Table A2.

Healthcare utilization

Among the conditions (i.e. ACS, stroke, cancer and dementia) that were followed up over five years, the adjusted mean number of prescriptions increased over time while the consumption of primary care consultation and hospital admissions decreased over time (Supplementary Tables A3–A6). For example, those with ACS and no musculoskeletal pain had an adjusted mean number of 19.57 (SE 0.41) prescriptions in the first year and this increased to 26.03 (SE 0.81) number of prescriptions in the fifth year (Supplementary Table A3). Those with musculoskeletal pain conditions had

16.40 (SE 0.35) number of prescriptions in the first year and 27.66 (SE 0.89) number of prescriptions in the fifth year. Patients with ACS and no musculoskeletal pain had 1.16 (SE 0.02) consultations in the first year and this decreased to 0.69 (SE 0.02) consultations in the fifth year. Those with ACS and musculoskeletal pain had 1.33 (SE 0.03) consultations in the first year and 0.89 (SE 0.03) consultations in the fifth year. Patients with ACS and no musculoskeletal pain had 3.26 (SE 0.03) hospital admissions in the first year and this decreased to 0.03 (SE 0.003) consultations in the fifth year. Those with ACS and musculoskeletal pain had 3.29 (SE 0.03) consultations in the first year and 0.04 (SE 0.003) consultations in the fifth year.

The adjusted mean difference in the number of prescriptions between those with and without musculoskeletal pain increased over the 5-year follow-up, while the adjusted mean difference of consultations and hospital admissions increased and peaked around the third or fourth year among those with ACS, stroke, cancer and dementia. For example, even though those with ACS and musculoskeletal pain had a lower adjusted mean number of prescriptions than those with ACS and no musculoskeletal pain in the first year (difference: −3.16 95%CI −3.62 to −2.69; IRR: 0.84 95%CI 0.82 to 0.86), this reversed to 1.67 (95%CI 0.61 to 2.72; IRR 1.06 95%CI 1.03 to 1.10) by the fifth year (Supplementary Table A3). Those with ACS and musculoskeletal pain had a consistently higher adjusted mean number of consultations than those with ACS and no musculoskeletal pain from the first year (difference: 0.17 95%CI 0.14 to 0.20; IRR: 1.14 95%CI 1.12 to 1.17) to the third year (difference: 0.22 95%CI 0.18 to 0.25; IRR 1.30 95%CI 1.26 to 1.34). Similarly, those with ACS and musculoskeletal pain had a consistently higher adjusted mean number of hospital admissions than those with ACS and no musculoskeletal pain from the first year (difference: 0.04 95%CI 0.002 to 0.074; IRR: 1.01 95%CI 1.00 to 1.02) to the fourth year (difference: 0.11 95%CI 0.08 to 0.14; IRR 1.16 95%CI 1.12 to 1.19).

The adjusted mean number of prescriptions, consultations and hospital admissions for patients with pneumonia and no musculoskeletal pain was 47.85 (SE 1.18), 2.85 (SE 0.07) and 3.08 (SE 0.04) respectively (Supplementary Table A7) over one year of follow-up. Those with pneumonia and musculoskeletal pain had an adjusted mean number of 57.13 (SE 1.42) prescriptions, 3.41 (SE 0.08) consultations and 3.11 (SE 0.05) hospital admissions. Those with pneumonia and musculoskeletal pain had higher adjusted mean number of prescriptions (difference: 9.43 95%CI 8.13 to 10.74; IRR: 1.20 95%CI 1.18 to 1.22), consultations (difference: 0.56 95%CI 0.48 to 0.63; IRR: 1.20 95%CI 1.18 to 1.22), and hospital admissions (difference: 0.04 95%CI −0.002 to 0.081; IRR: 1.01 95%CI 1.00 to 1.02) than those with pneumonia but no musculoskeletal pain.

Healthcare costs of prescriptions, consultations, and hospital admissions

Supplementary Tables A8–A11 show the adjusted mean cost of each resource category incurred by patients with ACS, stroke, cancer, dementia and pneumonia over their respective follow-up period. The adjusted mean cost of prescriptions, consultations and hospital admissions decreased over the follow-up period. For example, the adjusted mean cost of prescriptions, consultations and hospital admissions among those with ACS and no musculoskeletal pain were £417.99 (SE 2.70, £162.52 (SE 1.93), and £6218.08 (SE 19.07) respectively in the first year and these adjusted mean costs decreased to £211.21 (SE 2.53), £56.73 (SE 1.39), and £52.56 (SE 1.74) in the fifth year (Supplementary Table A8).

The adjusted mean cost difference of prescriptions between those with and without musculoskeletal pain conditions increased over the follow-up period while the adjusted mean cost difference of consultations and hospital admissions between those with musculoskeletal pain conditions and those without musculoskeletal pain conditions peaked during the fourth year for those with ACS, stroke, cancer and dementia. For example, ACS patients with musculoskeletal pain had a lower adjusted mean cost of prescription than those without musculoskeletal pain (-£17.77 95% −26.98 to −8.55) during the first year but those with musculoskeletal pain had a higher adjusted mean cost than those without musculoskeletal pain (£24.64 95% 15.23 to 34.04) in the fifth year. The adjusted mean cost difference of consultation between ACS patients with and without musculoskeletal pain was £6.98 (95% 1.77 to 12.19) in the first year and peaked during the fourth year (£15.46 95% 11.30 to 19.61). Likewise, the adjusted mean cost difference of hospital admission between ACS patients with and without musculoskeletal pain was £62.24 (95% −7.78 to 132.26) in the first year and peaked during the fourth year (£180.70 95% 139.31 to 222.09).

The adjusted mean cost of hospital admissions decreased drastically after the fourth year of diagnosis among patients with ACS, stroke, cancer and dementia as there were more patients who did not have hospital admissions in the fifth year and among those who had hospital admissions, the cost of hospital admissions was much lower than the previous years. For example, the number of ACS patients who incurred an unadjusted hospital admission cost of more than £1000 was 130,864 among 136,506 patients (96%) who incurred a hospital admission cost in the first year after diagnosis compared to 1953 patients with an unadjusted hospital admission cost of more than £1000 among 3723 patients (52%) who incurred a hospital admission cost in the fifth year after diagnosis.

Among those with pneumonia, the adjusted mean cost of prescriptions, consultations and hospital admissions among those without musculoskeletal pain were £466.77 (SE 5.32), £287.73 (SE 2.58) and £6195.76 (SE 26.58) respectively. The adjusted mean cost of prescriptions, consultations and hospital admissions among pneumonia patients with musculoskeletal pain were £498.22 (SE 7.33), £307.35 (SE 3.29) and £6345.55 (SE 40.35) respectively. Pneumonia patients with musculoskeletal pain had a higher adjusted mean cost of prescriptions (£31.47 95%CI 14.17 to 48.77), consultations (£19.56 95%CI 11.94 to 27.17) and hospital admissions (£149.25 95%CI 53.54 to 244.97) than those without musculoskeletal pain.

Cumulative total costs

The adjusted mean cumulative total cost over the follow-up period for each medical condition was plotted according to their musculoskeletal pain condition in Figure 1 and presented in Supplementary Tables A8–A12. The adjusted additional mean cumulative total healthcare costs per patient among those with musculoskeletal pain compared to patients without musculoskeletal pain was £674.59 (95%CI 570.30 to 778.87) for ACS; £613.34 (95%CI 496.87 to 729.82) for stroke; £459.26 (95%CI 376.60 to 541.91) for cancer; and £766.23 (95%CI 655.06 to 877.39) for dementia over five years after diagnosis; and £200.85 (95%CI 104.16 to 297.55) for pneumonia over one year after diagnosis. In general, those with no musculoskeletal pain had lower mean cumulative total cost than those with musculoskeletal pain over the follow-up period. Among the musculoskeletal pain conditions, those with inflammatory musculoskeletal conditions incurred the highest mean cumulative total cost than the other musculoskeletal pain conditions such as regional pain and osteoarthritis for patients with ACS, stroke, dementia and pneumonia over the follow-up period. Among patients with cancer, those with osteoarthritis incurred the highest cost among the musculoskeletal pain conditions over the follow-up period.

Discussion

The study aimed to estimate the impact of pre-existing musculoskeletal conditions on healthcare utilization and costs in patients with five index conditions: acute coronary syndrome (ACS), stroke, cancer, dementia, and pneumonia. By comparing healthcare service use and costs between patients with and without a pre-existing painful musculoskeletal condition among these five index conditions, the study provides valuable insights into the healthcare costs associated with musculoskeletal conditions in patients with multimorbidity. Our data suggests that having a painful musculoskeletal condition increases the direct healthcare utilization and cost among patients with a new diagnosis of five common yet impactful illnesses. Those with inflammatory musculoskeletal conditions generally incurred the highest costs. The main cost driver for each comorbidity was hospital admission at the time of diagnosis or soon after diagnosis. Patients with each index condition had the highest healthcare costs during the first year of diagnosis. The decreasing costs over time after diagnosis could be due to the first-year cost of high initial/early hospitalization rate and/or expensive procedures. This decreasing trend has also been observed in other cost-of-illness studies that involve ACS, stroke, cancer, dementia and pneumonia[29–33].

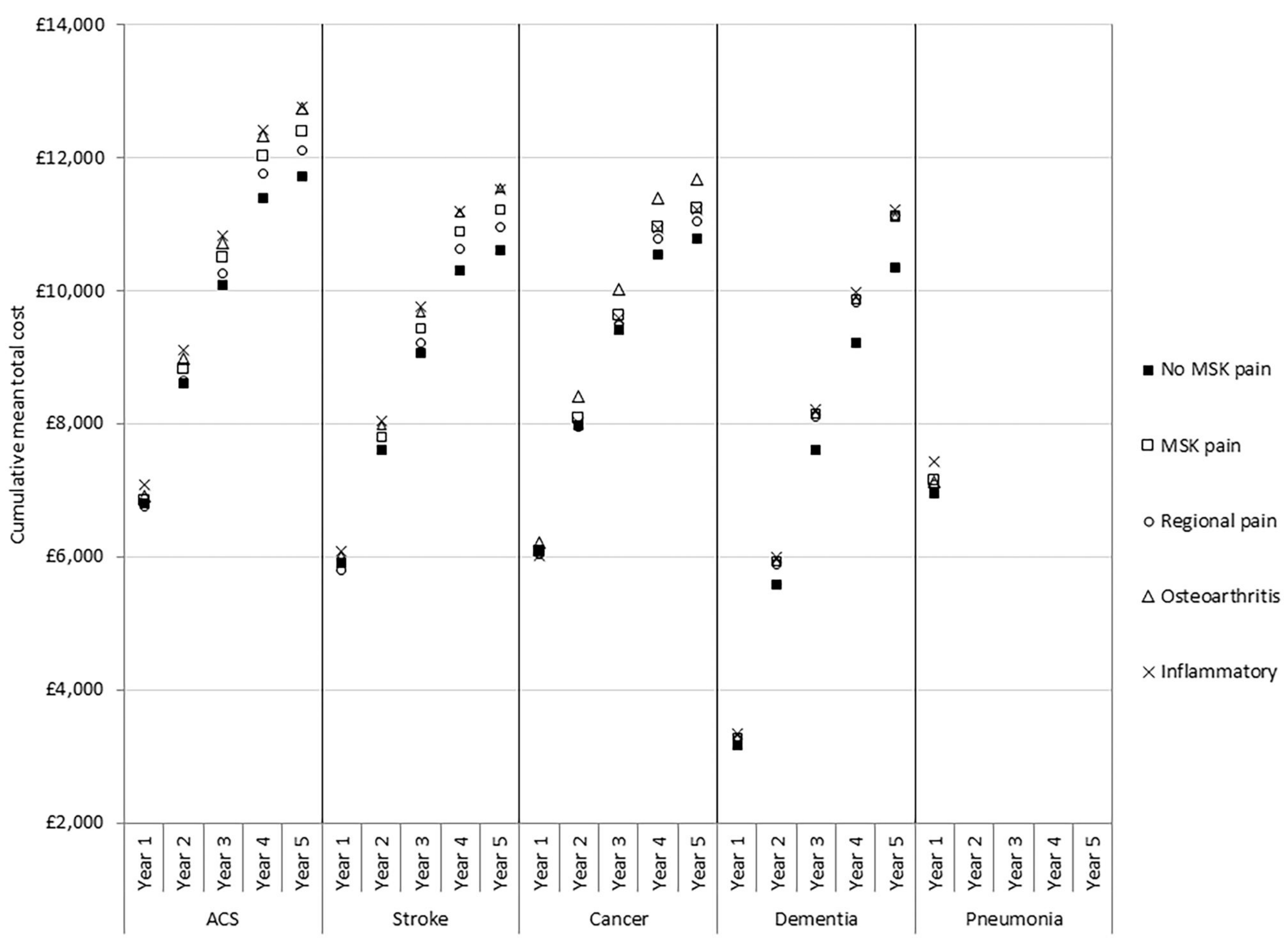

Figure 1. Adjusted mean cumulative total cost over the follow-up period for each medical condition by their musculoskeletal pain condition.
Abbreviations. ACS, acute coronary syndrome; MSK, musculoskeletal. Participants in the pneumonia dataset was followed up for only one year. MSK pain is when any of the three musculoskeletal (pain) disorders: (1) non-specific pain disorders, (2) osteoarthritis; and (3) inflammatory musculoskeletal conditions were present, and no MSK pain when none of them were present.

One of the strengths of the study is that it used a large, retrospective database study design, which allowed for the analysis of a vast amount of data from the Clinical Practice Research Datalink and linked inpatient data in England. Additionally, the study used two-part modelling, which allowed for the comparison of costs across the five multimorbidity domains. And to our knowledge, there is only one previous study that aimed to estimate the cost related to chronic pain and multimorbidity but no results have yet been published[34]. Studies were found to have investigated the cost-of-illness of musculoskeletal pain but they did not specifically examine the effect of other health conditions on the cost of musculoskeletal pain[35,36], neither did they compare the costs among the different musculoskeletal pain conditions (i.e. regional pain, osteoarthritis, and inflammatory condition) Hence, this is the first study that estimates the direct healthcare cost of painful musculoskeletal conditions among patients with other morbidities, namely ACS, stroke, cancer, dementia and pneumonia.

This study is not without its limitations. First, the cost of social care services, outpatient and emergency visits were not included in this study, and this underestimates the direct healthcare costs in this study. Second, the cases (those with a painful musculoskeletal condition) and controls (those without painful musculoskeletal condition) had different baseline characteristics as this study did not use matching but we have adjusted for baseline characteristics in all of our models including baseline costs. This is also the reason for not presenting the unadjusted estimates as it would show a biased effect size[37]. Health resource consumption was assumed to be similar within each musculoskeletal pain condition and we did not investigate the differences between sites of pain. Similarly, we did not investigate the health resource consumption of different combinations of musculoskeletal pain conditions, or presence of more than one index condition. Last, we did not investigate the specific factors contributing to the observed trend in the fourth year where costs seemed to peak, and a longer-term study would be needed to determine if the fourth year was a true clinically important cornerstone.

Future research should prioritise investigating the impact of specific types and site of pain of musculoskeletal conditions on healthcare utilization and costs from broader perspectives that capture outpatient costs and indirect costs associated with lost productivity, as well as the impact of disease progression and treatment interventions on these outcomes. Additionally, further research could explore potential interventions to reduce healthcare utilization and costs in patients with multimorbidity and musculoskeletal conditions, such as tailored exercise programs or multidisciplinary care approaches. Ultimately, such research can help to optimize healthcare resource allocation and improve outcomes for patients with these complex conditions.

Conclusions

In conclusion, this study showed that those with a painful musculoskeletal condition among people with five common comorbid conditions have a higher utilization rate and cost of healthcare services than those without pain. In general, those with inflammatory conditions incurred the highest adjusted mean cost followed by osteoarthritis and regional pain. The high healthcare utilization and costs associated with painful musculoskeletal conditions in patients with multimorbidity suggest a need for effective management strategies to reduce the burden on healthcare resources, as well as a focus on preventative measures and early intervention to address these conditions. Additionally, these findings highlight the importance of integrated care approaches that take into account the complexity of multimorbidity and the interplay between different conditions to ensure optimal patient outcomes.

Transparency

Declaration of funding

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-founder 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 of the Foundation. Visit www.nuffieldfoundation.org. KJM, KPJ and CDM are also 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.

Declaration of financial/other relationships

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Author contributions

All authors contributed to the study's conception and design. Data collection was performed by KJM and JB. Data analysis was performed by MEP. The first draft of the manuscript was written by MEP, MM, KPJ and FA. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Clinical Practice Research Datalink (CPRD) Data: 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. Office of National Statistics (ONS) Data: The interpretation and conclusions contained in this study are those of the authors alone. Hospital Episode Statistics (HES) Data/ONS Data: Copyright © 2020, re-used with the permission of The Health & Social Care Information Centre. All rights reserved. OPCS: The OPCS Classification of Interventions and Procedures, codes, terms and text is Crown copyright (2016) published by Health and Social Care Information Centre, also known as NHS Digital and licensed under the Open Government Licence available at www.nationalarchives.gov.uk/doc/open-government-licence/open-government-licence.htm.

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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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