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RESEARCH ARTICLE

Musculoskeletal pain and its impact on prognosis following acute coronary syndrome or stroke: A linked electronic health record cohort study

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Abstract

Objective: Musculoskeletal painful conditions are a risk factor for cardiovascular disease (CVD), but less is known about whether musculoskeletal pain also worsens prognosis from CVD. The objective was to determine whether patients with musculoskeletal pain have poorer prognosis following acute coronary syndrome (ACS) or stroke.

Methods: The study utilised UK electronic primary care records (CPRD Aurum) with linkage to hospital and mortality records. Patients aged ≥45 years admitted to hospital with incident ACS/stroke were categorised by healthcare use for musculoskeletal pain (inflammatory conditions, osteoarthritis [OA], and regional pain) based on primary care consultations in the prior 24 months. Outcomes included mortality, length of stay, readmission and management of index condition (ACS/stroke).

Results: There were 171,670 patients with incident ACS and 138,512 with stroke; 30% consulted for musculoskeletal pain prior to ACS/stroke and these patients had more comorbidity than those without musculoskeletal pain. Rates of mortality and readmission, and length of stay were higher in those with musculoskeletal pain, particularly OA and inflammatory conditions, in ACS. Readmission was also higher for patients with musculoskeletal pain in stroke. However, increased risks associated with musculoskeletal pain did not remain after adjustment for age and polypharmacy. Inflammatory conditions were associated with increased likelihood of prescriptions for dual anti-platelets (ACS only) and anti-coagulants.

Conclusions: Patients with musculoskeletal pain have higher rates of poor outcome from ACS which relates to being older but also increased polypharmacy. The high rates of comorbidity including polypharmacy highlight the complexity of patients with musculoskeletal pain who have new onset ACS/stroke.

KEYWORDS
acute coronary syndrome, cerebrovascular accident, epidemiology, musculoskeletal pain, primary care, stroke

1 | INTRODUCTION

Musculoskeletal conditions are a common cause for primary care consultation and represent a substantial proportion of years lived with disability (GBD, 2016; Jordan et al., 2014). Each year 20% of adults consult UK primary care for a musculoskeletal condition, rising to 40% of adults aged 75 years and over (Jordan et al., 2007). Persistent pain and musculoskeletal conditions often co-exist with other morbidities, such as cardiometabolic disorders (Kadam & Croft, 2007; Violan et al., 2014). In patients with multi-morbidity, non-musculoskeletal conditions may be regarded as having greater priority by clinicians than musculoskeletal conditions (Arthritis Care, 2013; Paskins et al., 2014), potentially due to a perceived greater impact on mortality, independent living and secondary healthcare use.

Musculoskeletal conditions, including osteoarthritis (OA) (Hsu et al., 2017; Wang et al., 2016; Williams et al., 2018), inflammatory arthritis (Cox et al., 2021; Holmqvist et al., 2017; Jamnitski et al., 2013; Nikiphorou et al., 2020) and regional pain such as low back pain (Fernandez et al., 2016; Wang et al., 2020), have been shown to be associated with an increased risk of cardiovascular disease (CVD). This has been hypothesised to be for a number of reasons including common risk factors, common pathogenic mechanisms, lower levels of physical activity in patients with chronic musculoskeletal pain and prescribed analgesia (Atiquzzaman et al., 2019; Fernandes & Valdes, 2015). However, the evidence on impact of musculoskeletal painful conditions on the prognosis and care following acute cardiovascular events is limited, particularly post hospital discharge.

We hypothesised that, for patients admitted to hospital with acute coronary syndrome (ACS) or stroke, pre-existing comorbidity with a musculoskeletal condition which is typically associated with pain, would adversely impact patient outcomes. Musculoskeletal conditions may impact on the outcomes of acute cardiovascular conditions through pain, restricted functioning and mobility hindering or delaying delivery and reducing the effectiveness of appropriate treatment and rehabilitation, potentially extending time to discharge from hospital and worsening outcomes of hospitalisation. If this is the case, this would highlight the need to improve recognition of musculoskeletal problems in patients with ACS and stroke to ensure appropriate musculoskeletal pain management and rehabilitation, to improve patient outcomes. Health-system level benefits may also be seen, reducing the pressure on secondary care, particularly given the high prevalence of musculoskeletal pain in older adults.

The aims of this study were therefore to determine whether painful musculoskeletal conditions in those admitted to hospital for incident ACS or stroke were associated with poorer short-term outcomes (mortality during admission or within 30 days of discharge; longer initial admission; risk of readmission; management of index condition), and whether this varied by type of musculoskeletal pain.

2 | METHODS

2.1 | Study design and setting

This was a cohort study using electronic primary care records from the UK Clinical Practice Research Datalink (CPRD) Aurum database. CPRD Aurum has data coverage for over 40 million patients with 13 million current patients (20% of the UK population), from over 1000 general practices using EMIS Web® software (Clinical Practice Research Datalink, 2021; Wolf et al., 2019). These data were linked to hospital inpatient admission and procedures data from Hospital Episode Statistics (HES), and Office for National Statistics (ONS) Death Registration Data for information on mortality.

The study was scientifically and ethically approved by the CPRD Independent Scientific Advisory Committee (ref 20_000105).

2.2 | Study population

Patients aged 45 years or over with first ever recorded ACS/stroke between 2000 and 2019 and a matching record of ACS/stroke in the linked HES inpatient data with hospital admission date within 30 days of the primary care recorded date of ACS/stroke were included. Patients aged under 45 years were excluded due to the low incidence of ACS/stroke below this age (Bhatnagar et al., 2016). The first date satisfying criteria for entry into a cohort was defined as that patient's index date. Patients also had to have at least 24 months of prior registration at the practice so that all patients had at least 24 months prior history without an ACS/stroke and had a full baseline period for covariates.

2.3 | Index conditions

Definitions of the index conditions ACS/stroke were based on Read, SNOMED CT-UK and EMIS codes which are used to record morbidity in UK primary care, and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes for defining ACS and stroke as the primary reason for hospital admission (Marshall et al., 2022). ACS included myocardial infarction (MI) and unstable angina. Stroke included ischaemic stroke, haemorrhagic stroke, stroke where the type is not specified and transient ischaemic attack (TIA).

2.4 | Exposures

Painful musculoskeletal conditions recorded in primary care in the 24 months prior to index date were defined as: (i) the most prevalent non-specific regional pain (defined as low back pain/backache, knee pain, hip pain and hand/wrist pain); (ii) diagnosed OA; (iii) inflammatory conditions (defined as rheumatoid arthritis, gout, ankylosing spondylitis, giant cell arteritis and psoriatic arthritis). Definitions of musculoskeletal pain conditions were based on code lists used previously (Jordan et al., 2010, 2014), and confirmed or modified based on consensus of general practitioner (GP) researchers familiar with electronic health record (EHR) research (Marshall et al., 2022).

In secondary analyses we also categorised these musculoskeletal pain consulters by pain severity and recency of consultation. Referral for a musculoskeletal condition and prescriptions of strong or very strong opioid analgesia (Jordan et al., 2010) were used as markers of musculoskeletal pain severity. We categorised musculoskeletal pain according to date of primary care consultation into recent (7–24 months before the index date) and current (0–6 months before the index date). We sub-categorised those with current pain further into current-severe (if they had been referred to secondary care or they were prescribed strong/very strong opioids in the 6-month period before admission to hospital for ACS or stroke), and current-non-severe.

2.5 | Primary outcomes

Outcomes were defined as mortality during the initial admission or within 30 days of initial discharge; and, in those who survived until 30 days after initial discharge, (i) the length of hospital stay using the dates of admission and discharge from the linked admitted inpatient data; (ii) readmission to hospital within 30 days of discharge split into type of readmission (recorded as same or different reason to that of initial admission).

Management outcomes for ACS/stroke were defined in those who survived until 30 days after initial discharge as: (i) management of index condition based on procedures recorded during the initial admission by Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) codes (including percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) for ACS; and thrombolysis for stroke); and (ii) management of index condition based on prescriptions recorded in primary care in the 3 months following the index date (including angiotensin converting enzyme [ACE] inhibitors, beta-blockers, angiotensin receptor blockers, anti-coagulants, dual anti-platelet therapy for ACS; anti-platelets or anti-coagulants for stroke).

2.6 | Covariates

Covariates included 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 (including diabetes; peripheral vascular disease; depression, anxiety or stress; other musculoskeletal conditions; prescribed statins), general multimorbidity based on prescription count (number of different medications prescribed excluding analgesia) and the number of days consultations for any problem occurred in the 24 months prior to the index date, and body mass index (BMI), smoking status and alcohol status recorded in the 60 months prior to the index date. Linkage to patient neighbourhood IMD (England only) were obtained and stratified by quintile rank from least deprived to most deprived. The number of days of consultations were not included in multivariable models due to high collinearity with number of medications.

2.7 | Piloting

A pilot study was initially performed using CPRD GOLD, containing information from general practices using Vision® software database (ISAC approved ref 19_025) study (Edwards et al., 2020). Many general practices in England have switched from Vision® to EMIS Web®, hence the number of patients in GOLD has reduced considerably since 2015 (Kontopantelis et al., 2018; Wolf et al., 2019). This study included development of code lists, definitions and assessment of sample size.

2.8 | Analysis

Continuous patient characteristics (index year, age at index date and number of consultations and prescriptions in the 24 months prior to the index date) and outcomes (length of admission) were summarised using median and interquartile range (IQR) with binary/categorical characteristics and outcomes presented as the number and percentage within each category.

Risk ratios (RRs) were estimated for associations between the painful musculoskeletal conditions and the binary outcomes (mortality during admission or within 30 days of initial discharge; readmission split by ACS/stroke and different reason; management of the index condition) using robust Poisson regression (Zou, 2004). Incidence rate ratios (IRRs) were estimated for associations between consultation for the painful musculoskeletal conditions and the length of initial admission using negative binomial regression. All models included robust standard errors clustered at the practice level. Adjusted IRR (aIRR) and adjusted RR (aRR) are presented with 95% confidence intervals (CI).

The moderating effects of age, deprivation, race, geographical region and mental health (depression, anxiety or stress) on the association of the painful musculoskeletal conditions with the outcomes were examined by including interaction terms in the models. Analyses were first performed assessing associations by specific type (none; non-specific regional pain; OA; inflammatory) and then, in secondary analysis, by recency and severity of musculoskeletal pain (none; recent; current-non-severe; current-severe).

2.9 | Sensitivity analyses

All short-term outcomes were repeated for ACS conditions defined by ST-segment elevation myocardial infarction (STEMI) and non-STEMI.

Missing data for race, body mass index, smoking status and alcohol status in the main analysis was recorded as the reference category (white, normal BMI [18.0–24.9 kg/m^2], never smoked and does not drink, respectively) but sensitivity analysis was undertaken where missing data were treated in two further ways and estimates compared: (i) complete case analysis, and (ii) coded as 'missing' categories.

All analyses were performed using Stata/MP 17.0 (StataCorp LLC, USA).

3 | RESULTS

3.1 | Patient characteristics

There were 257,459 patients with ACS and 375,047 patients with stroke recorded in the primary care database (Figure 1). 171,670 (67%) patients had a primary hospital admission reason of ACS (156,046 MI; 14,670 unstable angina; 954 both) and 138,512 (37%) patients had a primary admission reason of stroke (108,472 stroke only; 30,040 TIA only) recorded in HES within 30 days of their primary care record.

Overall, 30% of patients in both the ACS and stroke cohorts had a consultation for one of the painful musculoskeletal conditions in the 24 months prior to the index date with similar proportions consulting for regional pain (17% ACS and 16% stroke), OA (8% ACS and 9% stroke) and an inflammatory condition (5% in both cohorts; Tables 1 and 2). Eighteen percentage of patients in each cohort consulted for musculoskeletal pain within 7–24 months (recent), with 7% consulting within 0–6 months (current-non-severe) and 5% within 0–6 months with a referral or prescription for strong/very strong opioids in the same period (current-severe; Tables S1 and S2).

Apart from inflammatory conditions in the stroke cohort, a higher proportion of females were observed in patients classified with musculoskeletal pain. In both cohorts, patients consulting with OA and inflammatory conditions were older and patients with a musculoskeletal condition had higher median counts of consultations and different prescribed medications, and a higher prevalence of cardiovascular risk factors including comorbid peripheral vascular disease, being overweight or obese, prescribed statins and being current alcohol drinkers than those without musculoskeletal pain consultation, with the highest proportions generally in those with inflammatory conditions (Tables 1 and 2). Stratifying by severity, those in the current-severe musculoskeletal pain group had the highest prevalence of comorbidity but had a similar median age to the other groups (Tables S1 and S2).

3.2 | Acute coronary syndrome

Slightly higher proportions of patients with inflammatory conditions or with OA died during the initial admission or within 30 days of discharge compared to those without musculoskeletal pain

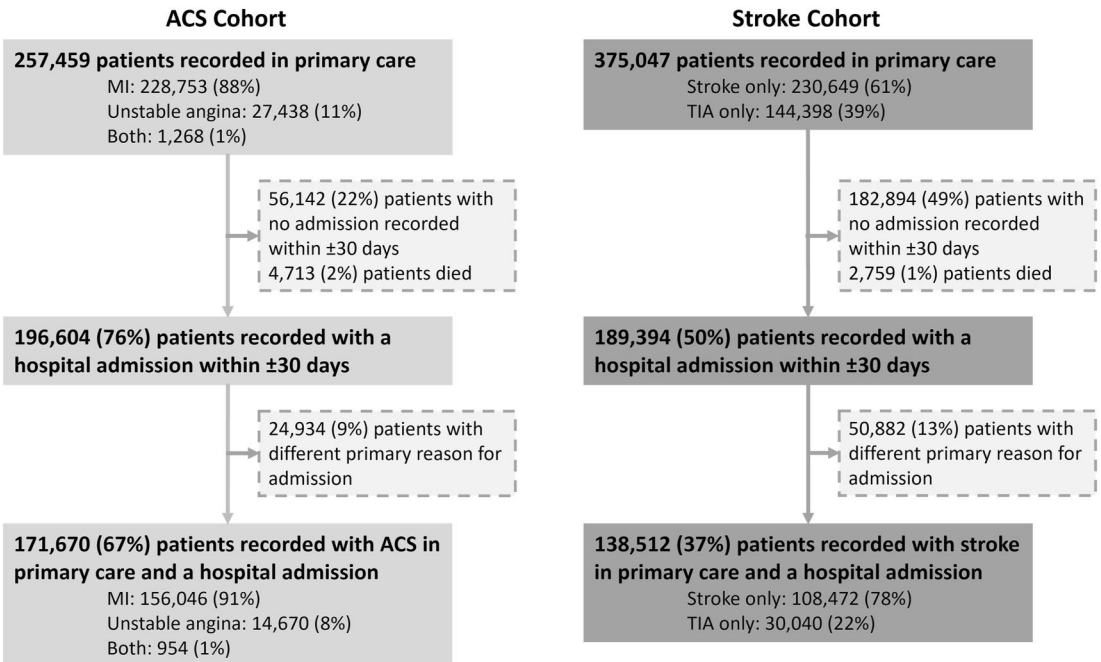

FIGURE 1 Patient flowchart. Legend: There were 257,459 patients with a record for ACS and 375,047 patients with a record for stroke in primary care. Of those, 171,670 (67%) patients in the ACS cohort and 138,512 (37%) patients in the stroke cohort met the eligibility criteria for the study with a matching primary hospital admission reason of ACS or stroke within ±30 days of their primary care record. ACS, acute coronary syndrome; MI, myocardial infarction; TIA, transient ischaemic attack.

TABLE 1 Patient characteristics of the acute coronary syndrome cohort.

		MSK pain		
	No MSK pain[a]	Regional pain	OA	Inflammatory
Total, *n* (row %)	120,681 (70)	28,253 (17)	13,422 (8)	9314 (5)
Median year of index date, (IQR)	2010 (2004, 2015)	2012 (2007, 2016)	2011 (2006, 2015)	2011 (2006, 2015)
Median age, years (IQR)	69 (59, 79)	69 (59, 79)	75 (67, 83)	75 (65, 82)
Males, *n* (%)	80,265 (67)	16,943 (60)	6782 (51)	5811 (62)
Geographical region, *n* (%)				
London	13,390 (11)	3506 (12)	1375 (10)	843 (9)
Midlands and East England	29,843 (25)	6779 (24)	3276 (24)	2417 (26)
North England	36,258 (30)	8389 (30)	4511 (34)	2699 (29)
South England	41,190 (34)	9579 (34)	4260 (32)	3355 (36)
Smoking status, *n* (%)[b]				
Current smoker	32,793 (27)	8284 (29)	2848 (21)	1952 (21)
Ex-smoker	29,384 (24)	7732 (27)	3858 (29)	2943 (32)
Never smoked/not recorded	58,504 (48)	12,237 (43)	6716 (50)	4419 (47)
Alcohol status, *n* (%)[b]				
Does not drink alcohol/not recorded	77,754 (64)	17,370 (61)	8352 (62)	5429 (58)
Currently drinks alcohol	42,927 (36)	10,883 (39)	5070 (38)	3885 (42)
Body mass index, *n* (%)[b]				
Underweight (10.0–18.0 kg/m^2)	1736 (1)	377 (1)	130 (1)	123 (1)
Normal/not recorded (18.0–<25.0 kg/m^2)	67,266 (56)	13,094 (46)	5942 (44)	4111 (44)
Overweight (25.0–<30.0 kg/m^2)	33,002 (27)	8889 (31)	4209 (31)	3075 (33)
Obese (30.0–79.9 kg/m^2)	18,677 (15)	5893 (21)	3141 (23)	2005 (22)
Index of multiple deprivation quintiles, *n* (%)				
Least deprived	24,886 (21)	5675 (20)	2725 (20)	2081 (22)
Second-least deprived	24,987 (21)	5760 (20)	2749 (20)	2036 (22)
Mid deprived	24,029 (20)	5542 (20)	2605 (19)	1971 (21)
Second-most deprived	23,463 (19)	5473 (19)	2655 (20)	1709 (18)
Most deprived	23,316 (19)	5803 (21)	2688 (20)	1517 (16)
White/not recorded race, *n* (%)[b]	113,465 (94)	25,970 (92)	12,599 (94)	8785 (94)
Median consultation count (IQR)[c]	23 (11, 41)	39 (23, 61)	42 (26, 64)	49 (30, 75)
Specific comorbid conditions, *n* (%)[c]				
Diabetes	21,010 (17)	5998 (21)	2826 (21)	2070 (22)
Peripheral vascular disease	3538 (3)	1053 (4)	485 (4)	459 (5)
Depression, anxiety or stress	7880 (7)	3235 (11)	1515 (11)	808 (9)
Other MSK consultation	24,977 (21)	12,242 (43)	6268 (47)	4449 (48)
Median number of prescriptions (IQR)[c]	8 (3, 15)	13 (7, 21)	15 (9, 23)	17 (10, 25)
Prescribed statins, *n* (%)[c]	41,662 (35)	12,224 (43)	5905 (44)	4244 (46)
Referrals[c]	11,539 (10)	8924 (32)	5461 (41)	3229 (35)
Prescribed analgesics (highest rank), *n* (%)[c]				
No prescriptions	63,166 (52)	4403 (16)	1199 (9)	1146 (12)
NSAIDs	14,031 (12)	3238 (11)	1714 (13)	896 (10)

(Continues)

TABLE 1 (Continued)

		MSK pain		
	No MSK pain[a]	Regional pain	OA	Inflammatory
Basic analgesics	7926 (7)	2608 (9)	1310 (10)	580 (6)
Weak opioids	5745 (5)	1991 (7)	994 (7)	481 (5)
Moderate opioids	12,701 (11)	6446 (23)	3168 (24)	1701 (18)
Strong/very strong opioids	17,112 (14)	9567 (34)	5037 (38)	4510 (48)

Note: Patients with missing data for region (20; 0.01%) and index of multiple deprivation (165; 0.1%) omitted; patients with missing data for race, body mass index, smoking status or alcohol status are recoded as reference categories (white; normal BMI; never smoked; does not drink alcohol).

Abbreviations: IQR, interquartile range; MSK, musculoskeletal; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis.

[a]No consultation in past 24 months for regional (lower back, knee, hip, hand/wrist) MSK pain, OA or inflammatory arthritis.

[b]Recorded in 60 months prior to index date.

[c]Recorded in 24 months prior to index date.

TABLE 2 Patient characteristics of the stroke cohort.

		MSK pain		
	No MSK pain[a]	Regional pain	OA	Inflammatory
Total, *n* (row %)	96,968 (70)	22,272 (16)	11,801 (9)	7471 (5)
Median year of index date, (IQR)	2011 (2006, 2015)	2012 (2008, 2016)	2012 (2007, 2016)	2012 (2008, 2016)
Median age, years (IQR)	75 (65, 83)	75 (65, 83)	79 (71, 85)	77 (70, 84)
Males, *n* (%)	51,345 (53)	10,425 (47)	4721 (40)	4131 (55)
Geographical region, *n* (%)				
London	11,161 (12)	2692 (12)	1202 (10)	706 (9)
Midlands and East England	23,605 (24)	5364 (24)	2871 (24)	1937 (26)
North England	27,852 (29)	6255 (28)	3635 (31)	2029 (27)
South England	34,350 (35)	7961 (36)	4093 (35)	2799 (37)
Smoking status, *n* (%)[b]				
Current smoker	21,571 (22)	5055 (23)	1987 (17)	1296 (17)
Ex-smoker	23,399 (24)	6073 (27)	3262 (28)	2444 (33)
Never smoked/not recorded	51,998 (54)	11,144 (50)	6552 (56)	3731 (50)
Alcohol status, *n* (%)[b]				
Does not drink alcohol/not recorded	62,306 (64)	13,521 (61)	7399 (63)	4329 (58)
Currently drinks alcohol	34,662 (36)	8751 (39)	4402 (37)	3142 (42)
Body mass index, *n* (%)[b]				
Underweight (10.0–18.0 kg/m^2)	2085 (2)	416 (2)	171 (1)	122 (2)
Normal/not recorded (18.0–<25.0 kg/m^2)	56,092 (58)	10,988 (49)	5581 (47)	3496 (47)
Overweight (25.0–<30.0 kg/m^2)	24,679 (25)	6573 (30)	3490 (30)	2346 (31)
Obese (30.0–79.9 kg/m^2)	14,112 (15)	4295 (19)	2559 (22)	1507 (20)
Index of multiple deprivation quintiles, *n* (%)				
Least derived	20,743 (21)	4811 (22)	2498 (21)	1743 (23)
Second-least deprived	20,400 (21)	4726 (21)	2569 (22)	1703 (23)
Mid deprived	19,755 (20)	4581 (21)	2388 (20)	1602 (21)
Second-most deprived	18,161 (19)	4154 (19)	2192 (19)	1339 (18)
Most deprived	17,909 (18)	4000 (18)	2154 (18)	1084 (15)

TABLE 2 (Continued)

		MSK pain		
	No MSK pain[a]	Regional pain	OA	Inflammatory
White/not recorded race, *n* (%)[b]	91,860 (95)	20,753 (93)	11,140 (94)	7134 (95)
Median consultation count (IQR)[c]	28 (15, 46)	43 (27, 66)	45 (29, 68)	51 (32, 77)
Specific comorbid conditions, *n* (%)[c]				
Diabetes	16,783 (17)	4534 (20)	2245 (19)	1606 (21)
Peripheral vascular disease	2586 (3)	709 (3)	383 (3)	305 (4)
Depression, anxiety or stress	6412 (7)	2613 (12)	1436 (12)	637 (9)
Other MSK consultation	20,063 (21)	9872 (44)	5370 (46)	3524 (47)
Median number of prescriptions (IQR)[c]	9 (5, 16)	14 (9, 22)	15 (10, 23)	16 (10, 24)
Prescribed statins, *n* (%)[c]	33,156 (34)	9146 (41)	4708 (40)	3160 (42)
Referrals[c]	9519 (10)	7047 (32)	4748 (40)	2593 (35)
Prescribed analgesics (highest rank), *n* (%)[c]				
No prescriptions	49,145 (51)	3135 (14)	1034 (9)	1148 (15)
NSAIDs	14,588 (15)	3251 (15)	1827 (15)	850 (11)
Basic analgesics	7297 (8)	2466 (11)	1306 (11)	586 (8)
Weak opioids	4597 (5)	1732 (8)	966 (8)	405 (5)
Moderate opioids	10,502 (11)	5308 (24)	2959 (25)	1388 (19)
Strong/very strong opioids	10,839 (11)	6380 (29)	3709 (31)	3094 (41)

Note: Patients with missing data for region (35; 0.03%) and index of multiple deprivation (138; 0.1%) omitted; patients with missing data for race, body mass index, smoking status or alcohol status are recoded as reference categories (white; normal; never smoked; does not drink alcohol).

Abbreviations: IQR, interquartile range; MSK, musculoskeletal; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis.

[a]No consultation in past 24 months for regional (lower back, knee, hip, hand/wrist) MSK pain, OA or inflammatory conditions.

[b]Recorded in 60 months prior to index date.

[c]Recorded in 24 months prior to index date.

(inflammatory 4.3%, OA 4.2%, no pain 3.7%; inflammatory unadjusted RR 1.17, 95% CI 1.06, 1.30; OA unadjusted RR 1.13, 95% CI 1.03, 1.23; Table 3).

Patients with inflammatory conditions (unadjusted IRR 1.06, 95% CI 1.04, 1.09) or OA (unadjusted IRR 1.07; 95% CI 1.04, 1.09) had slightly longer stays than those with no musculoskeletal pain.

Thirty-day readmission rates for other coded reasons than ACS were statistically significantly higher for all three pain groups compared to those without musculoskeletal pain (12%–13% vs. 10%; Table 3).

Adjusting for most of the covariates did not impact on the associations found in the unadjusted analyses. However, after adjustment for age and prescription count, having an inflammatory condition or OA were no longer independently associated with a higher risk of mortality, longer length of stay or readmission (Table 3).

Patients with musculoskeletal pain consultation had lower rates of ACE inhibitor, and higher rates of angiotensin receptor blocker and anti-coagulant prescriptions than those with no musculoskeletal pain (Table 4). Age and prescription count were again the main confounders. After adjustment for these, there was a slightly elevated likelihood of having an anti-hypertensive or dual anti-platelet medication prescribed associated with musculoskeletal pain. The strongest association was seen in patients with an inflammatory condition, with an increased likelihood of prescription of anti-coagulants (aRR 1.15; 95% CI 1.09, 1.22). A lower percentage of those with OA or inflammatory conditions had PCI than those without musculoskeletal pain.

When subgrouping musculoskeletal pain by recency and severity rather than by type, those with current-severe pain had increased rates of readmission not coded as ACS compared to those without musculoskeletal pain which remained after adjustment for covariates (RR 1.08; 95% CI 1.02, 1.14) (Table S3). Likelihood of management outcomes was not higher in patients with current-severe pain compared to those with current-non-severe pain or with recent pain (Table S4).

3.3 | Stroke

In the stroke cohort, the only unadjusted risk of worse outcome was readmission not recorded as stroke, with higher percentages in all three musculoskeletal pain groups compared to those without musculoskeletal pain (10%–11% vs. 9%). As with the outcomes for ACS, adjustment for most covariates did not explain this increased

TABLE 3 Associations of musculoskeletal pain consultation with outcomes of acute coronary syndrome and stroke.

	ACS cohort			Stroke cohort		
Mortality during admission or within 30 days of discharge	**Outcome *N* (%)**	**Univariable RR (95% CI)**	**Multivariable aRR (95% CI)**	**Outcome *N* (%)**	**Univariable RR (95% CI)**	**Multivariable aRR (95% CI)**
Total	6320 (3.7)	–	–	9863 (7.1)	–	–
No MSK pain[a]	4450 (3.7)	[Ref]	[Ref]	7019 (7.2)	[Ref]	[Ref]
Regional pain	909 (3.2)	0.87 (0.81, 0.94)	0.92 (0.85, 0.99)	1473 (6.6)	0.91 (0.86, 0.97)	0.95 (0.89, 1.00)
OA	559 (4.2)	1.13 (1.03, 1.23)	0.90 (0.83, 0.98)	835 (7.1)	0.98 (0.91, 1.05)	0.84 (0.78, 0.90)
Inflammatory conditions	402 (4.3)	1.17 (1.06, 1.30)	0.97 (0.87, 1.07)	536 (7.2)	0.99 (0.91, 1.08)	0.92 (0.85, 1.01)
Length of initial admission[b]	**Median (IQR)**	**IRR (95% CI)**	**aIRR (95% CI)**	**Median (IQR)**	**IRR (95% CI)**	**aIRR (95% CI)**
Total	5 (3, 8)	–	–	5 (2, 15)	–	–
No MSK pain[a]	5 (3, 8)	[Ref]	[Ref]	5 (2, 16)	[Ref]	[Ref]
Regional pain	4 (3, 8)	0.93 (0.91, 0.95)	0.95 (0.94, 0.97)	5 (2, 13)	0.85 (0.83, 0.87)	0.93 (0.91, 0.96)
OA	5 (3, 9)	1.07 (1.04, 1.09)	0.98 (0.96, 1.00)	5 (2, 15)	0.99 (0.96, 1.02)	0.98 (0.94, 1.01)
Inflammatory conditions	5 (3, 9)	1.06 (1.04, 1.09)	1.01 (0.98, 1.03)	5 (2, 15)	0.93 (0.89, 0.97)	0.99 (0.95, 1.04)
Readmission within 30 days of discharge: same reason[b]	***N* (%)**	**RR (95% CI)**	**aRR (95% CI)**	***N* (%)**	**RR (95% CI)**	**aRR (95% CI)**
Total	17,824 (10.6)	–	–	5804 (4.4)	–	–
No MSK pain[a]	12,408 (10.5)	[Ref]	[Ref]	4042 (4.4)	[Ref]	[Ref]
Regional pain	3026 (10.9)	1.04 (1.00, 1.08)	1.01 (0.98, 1.05)	985 (4.6)	1.06 (0.99, 1.13)	1.02 (0.95, 1.09)
OA	1437 (11.0)	1.04 (0.99, 1.10)	0.99 (0.94, 1.04)	471 (4.2)	0.96 (0.87, 1.05)	0.97 (0.88, 1.07)
Inflammatory conditions	953 (10.5)	1.00 (0.94, 1.06)	0.92 (0.87, 0.98)	306 (4.3)	0.98 (0.88, 1.10)	0.96 (0.86, 1.08)
Readmission within 30 days of discharge: different reason[b]	***N* (%)**	**RR (95% CI)**	**aRR (95% CI)**	***N* (%)**	**RR (95% CI)**	**aRR (95% CI)**
Total	18,291 (10.9)	–	–	12,903 (9.8)	–	–
No MSK pain[a]	12,032 (10.2)	[Ref]	[Ref]	8633 (9.4)	[Ref]	[Ref]
Regional pain	3451 (12.4)	1.22 (1.18, 1.26)	1.05 (1.01, 1.08)	2302 (10.8)	1.16 (1.11, 1.21)	1.03 (0.99, 1.08)
OA	1642 (12.5)	1.23 (1.17, 1.29)	0.99 (0.95, 1.04)	1167 (10.4)	1.11 (1.05, 1.18)	0.98 (0.92, 1.04)
Inflammatory conditions	1166 (12.8)	1.26 (1.19, 1.33)	0.97 (0.92, 1.03)	801 (11.3)	1.20 (1.13, 1.28)	1.01 (0.94, 1.08)

Abbreviations: ACS, acute coronary syndrome; IRR, incidence rate ratio; aIRR, adjusted incidence rate ratio; IQR, inter-quartile range; CI, confidence interval; RR, risk ratio; aRR, adjusted risk ratio; OA, osteoarthritis.

[a]No consultation in past 24 months for regional (lower back, knee, hip, hand/wrist) MSK pain, OA or inflammatory conditions.

[b]In those who survived until 30 days post-discharge.

risk however adjustment for age and prescription count of led to non-statistically significant association (Table 3). Patients with inflammatory conditions were more likely to be prescribed anti-coagulants (aRR 1.15; 95% CI 1.10, 1.21) and those with regional pain or OA were more likely to be prescribed anti-platelets compared to those without musculoskeletal pain (Table 5). Categorising by recency and severity indicated that patients with current-severe pain had higher rates of readmission for non-stroke cause but the association disappeared after adjustment, particularly for prescription count (Table S3). There was no increased likelihood of any management in patients with current-severe pain compared to the other patients with musculoskeletal pain (Table S5).

3.4 | Moderation

Inclusion of interactions in the models did not indicate there were any important moderators.

3.5 | Sensitivity analyses

Analyses restricted to STEMI and non-STEMI events had similar findings as the total ACS cohort analyses. Estimates were similar using the different approaches to accounting for missing data and did not change the study findings (data not shown).

TABLE 4 Associations of musculoskeletal pain consultation with management of acute coronary syndrome.

	Outcome *N* (%)	Univariable RR (95% CI)	Multivariable aRR (95% CI)
Anti-hypertensives			
ACE inhibitors: total	117,357 (69.8)	–	–
No MSK pain[a]	83,529 (70.7)	[Ref]	[Ref]
Regional pain	19,370 (69.8)	0.99 (0.98, 1.00)	1.02 (1.01, 1.02)
OA	8631 (65.9)	0.93 (0.92, 0.94)	1.01 (1.00, 1.03)
Inflammatory conditions	5827 (64.0)	0.91 (0.89, 0.92)	0.99 (0.97, 1.00)
Beta-blockers: total	130,010 (77.4)	–	–
No MSK pain[a]	91,523 (77.5)	[Ref]	[Ref]
Regional pain	21,689 (78.2)	1.01 (1.00, 1.02)	1.02 (1.01, 1.02)
OA	9904 (75.6)	0.98 (0.97, 0.99)	1.03 (1.02, 1.04)
Inflammatory conditions	6894 (75.8)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
Angiotensin receptor blockers: total	19,271 (11.5)	–	–
No MSK pain[a]	12,337 (10.4)	[Ref]	[Ref]
Regional pain	3616 (13.0)	1.25 (1.21, 1.29)	1.01 (0.97, 1.04)
OA	1960 (15.0)	1.43 (1.37, 1.50)	1.07 (1.02, 1.12)
Inflammatory conditions	1358 (14.9)	1.43 (1.36, 1.50)	1.05 (0.99, 1.10)
Anti-coagulants			
Total	13,850 (8.2)	–	–
No MSK pain[a]	9160 (7.8)	[Ref]	[Ref]
Regional pain	2268 (8.2)	1.05 (1.01, 1.10)	0.93 (0.89, 0.97)
OA	1307 (10.0)	1.29 (1.22, 1.36)	0.99 (0.94, 1.05)
Inflammatory conditions	1115 (12.3)	1.58 (1.49, 1.67)	1.15 (1.09, 1.22)
Dual anti-platelets			
Total	91,837 (54.7)	–	–
No MSK pain[a]	63,758 (54.0)	[Ref]	[Ref]
Regional pain	16,356 (59.0)	1.09 (1.08, 1.11)	1.04 (1.03, 1.05)
OA	6902 (52.7)	0.98 (0.96, 0.99)	1.03 (1.01, 1.05)
Inflammatory conditions	4821 (53.0)	0.98 (0.96, 1.00)	1.02 (1.00, 1.05)
Procedures			
Coronary artery bypass graft: total	1573 (0.9)	–	–
No MSK pain[a]	1141 (1.0)	[Ref]	[Ref]
Regional pain	237 (0.9)	0.88 (0.77, 1.02)	0.88 (0.77, 1.02)
OA	112 (0.9)	0.89 (0.73, 1.07)	1.05 (0.86, 1.28)
Inflammatory conditions	83 (0.9)	0.94 (0.75, 1.18)	1.07 (0.85, 1.34)
Percutaneous coronary intervention: total	32,975 (19.6)	–	–
No MSK pain[a]	23,599 (20.0)	[Ref]	[Ref]
Regional pain	5733 (20.7)	1.03 (1.01, 1.06)	1.02 (1.00, 1.05)
OA	2099 (16.0)	0.80 (0.77, 0.84)	1.01 (0.97, 1.05)
Inflammatory conditions	1544 (17.0)	0.85 (0.81, 0.89)	1.04 (0.99, 1.08)

Note: In those who survived until 30 days post-discharge.

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; OA, osteoarthritis; RR, risk ratio.

[a]No consultation in past 24 months for regional (lower back, knee, hip, hand/wrist) MSK pain, OA or inflammatory conditions.

TABLE 5 Associations of musculoskeletal pain consultation with management of stroke.

	Outcome *N* (%)	Univariable RR (95% CI)	Multivariable aRR (95% CI)
Anti-coagulants			
Total	21,134 (16.1)	—	—
No MSK pain[a]	14,301 (15.5)	[Ref]	[Ref]
Regional pain	3456 (16.3)	1.05 (1.01, 1.08)	0.96 (0.93, 0.99)
OA	1863 (16.6)	1.07 (1.03, 1.12)	0.94 (0.90, 0.98)
Inflammatory conditions	1514 (21.3)	1.37 (1.31, 1.44)	1.15 (1.10, 1.21)
Anti-platelets			
Aspirin: total	46,419 (35.3)	—	—
No MSK pain[a]	32,894 (35.7)	[Ref]	[Ref]
Regional pain	7151 (33.6)	0.94 (0.92, 0.96)	1.03 (1.01, 1.05)
OA	3998 (35.7)	1.00 (0.97, 1.03)	1.03 (1.00, 1.05)
Inflammatory conditions	2376 (33.4)	0.94 (0.91, 0.97)	0.98 (0.95, 1.02)
Clopidogrel: total	47,338 (36.0)	—	—
No MSK pain[a]	31,924 (34.7)	[Ref]	[Ref]
Regional pain	8666 (40.8)	1.18 (1.15, 1.20)	1.05 (1.03, 1.07)
OA	4118 (36.8)	1.06 (1.03, 1.09)	1.03 (1.00, 1.05)
Inflammatory conditions	2630 (37.0)	1.07 (1.03, 1.10)	0.98 (0.95, 1.01)
Dipyramidole: total	16,115 (12.2)	—	—
No MSK pain[a]	11,349 (12.3)	[Ref]	[Ref]
Regional pain	2496 (11.7)	0.95 (0.91, 0.99)	1.10 (1.05, 1.14)
OA	1445 (12.9)	1.05 (1.00, 1.10)	1.13 (1.07, 1.19)
Inflammatory conditions	825 (11.6)	0.94 (0.88, 1.01)	1.03 (0.96, 1.10)
Procedures			
Thrombolysis: total	5497 (4.2)	—	—
No MSK pain[a]	3742 (4.1)	[Ref]	[Ref]
Regional pain	1014 (4.8)	1.17 (1.09, 1.26)	1.08 (1.01, 1.16)
OA	431 (3.8)	0.95 (0.86, 1.05)	0.96 (0.87, 1.06)
Inflammatory conditions	310 (4.4)	1.07 (0.95, 1.21)	1.03 (0.91, 1.16)

Note: In those who survived until 30 days post-discharge.

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; OA, osteoarthritis; RR, risk ratio.

[a]No consultation in past 24 months for regional (lower back, knee, hip, hand/wrist) MSK pain, OA or inflammatory conditions.

4 | DISCUSSION

This study of over 300,000 patients has shown that newly diagnosed patients with ACS who have a recent history of consulting primary care for musculoskeletal pain, particularly OA or an inflammatory condition have higher rates of mortality and longer length of hospital stays, as well as increased rates of readmission within 30 days of discharge. However, musculoskeletal pain consultation was not independently associated with increased rates of patient outcomes after adjustment for age and number of different medications prescribed. These findings persisted when grouping musculoskeletal pain by recency of consultation and severity of pain rather than type of condition.

We initially hypothesised that musculoskeletal conditions may impact on the management and outcomes of acute cardiovascular conditions through the related pain and restrictions in functioning and mobility, affecting delivery and effectiveness, of appropriate treatment and rehabilitation. This would have major implications given the high prevalence of musculoskeletal pain in the general population, the high levels of disability and reduction in quality of life related to musculoskeletal pain, and that previous systematic reviews and large population cohort studies have shown that prevalent

musculoskeletal conditions including OA, inflammatory conditions and back pain increase the risk of new onset CVD (Fernandez et al., 2016; Holmqvist et al., 2017; Hsu et al., 2017; Nikiphorou et al., 2020; Wang et al., 2016, 2020; Williams et al., 2018) and cardiovascular mortality (Isogai et al., 2017; Jamnitski et al., 2013; Kang et al., 2018; Lai et al., 2020; McCoy et al., 2013). The finding that musculoskeletal pain is not independently associated with poorer outcomes in patients experiencing an ACS or stroke event is, therefore, to some extent reassuring. However, there were higher increased risks of several outcomes for people with OA or inflammatory conditions and these seemed to be explained not just by older age, but also by polypharmacy, defined as number of different medications prescribed. This highlights the complexity of patients with musculoskeletal pain with new onset ACS in that they are likely to have a high multimorbidity load. It may also reflect inappropriate prescribing and further research should tease out the reasons for the impact of polypharmacy on outcomes of ACS, particularly in patients with musculoskeletal pain. The increased prevalence of cardiovascular risk factors including comorbidities and lifestyle characteristics in these patients also highlights the need for surveillance of this group of patients presenting with new ACS or stroke. This targeted surveillance could be undertaken within specialist cardiology clinics or carried out by GPs via commissioning of a specialist primary care service, similar to other high-risk conditions such as diabetes mellitus surveillance in GP. Further research also needs to explore the impact of musculoskeletal pain on longer term outcomes including further ACS/stroke events and longer-term mortality.

The lack of independent association of musculoskeletal pain with worse short-term outcomes, particularly in stroke may also reflect better use of guideline recommended treatment. We did not observe reduced prescribing of pharmacotherapy for CVD, despite any concerns over interactions with analgesia such as non-steroidal anti-inflammatory drugs (NSAIDs). By contrast, there was a small independent association of musculoskeletal pain with some management options including receipt of beta-blockers and dual anti-platelets in ACS and anti-coagulants for those with inflammatory conditions in both patients with ACS and stroke. Whilst there was a lower rate of PCI for ACS which might have been hypothesised to be due to the potential increased risk from peri-procedural bleeding complications seen with inflammatory conditions (Martinez et al., 2020; Mohamed et al., 2021), again this appears to be related to age and polypharmacy.

Previous studies on how musculoskeletal pain affects early outcomes of CVD have generally focussed on inflammatory disease and have given mixed findings, with little prior evidence from the UK. For example, a small study from USA (231 patients) showed similar short-term outcomes and management for patients with rheumatoid arthritis after acute MI compared to patients without rheumatoid arthritis (Mccoy et al., 2013). A Japanese study also showed no increased risk of 30-day mortality following acute MI in patients with rheumatoid arthritis, nor differences in receipt of PCI, CABG or thrombolysis (Isogai et al., 2017). A study from Taiwan showed no association of in-hospital mortality or length of stay with rheumatoid arthritis in patients after a stroke (Kang et al., 2018). By contrast another large EHR-based study in Taiwan identified increased risks of in-hospital mortality after acute MI, intracranial haemorrhage and ischaemic stroke in patients with rheumatoid arthritis or systemic lupus erythematosus (Lai et al., 2020). A study from USA showed poorer functional outcome from stroke in patients with inflammatory arthritis (Nguyen-Oghalai et al., 2008). However, another study from the USA suggested reduced in-hospital mortality outcomes in patients with rheumatoid arthritis and increased receipt of thrombolysis and PCI after MI (Francis et al., 2010). These mixed findings may reflect variation in clinical care between nations and over time, and variation in study methods and outcomes. Studies in OA have been more limited (Parkinson et al., 2017), but comorbid OA has been linked to poorer cardiovascular physical symptoms (Rushton & Kadam, 2014), and in the USA, worse functional outcomes following stroke (Nguyen-Oghalai et al., 2008).

NSAIDs have been found to increase the risk of incident CVD including ACS and stroke, but as yet it is unclear if NSAIDs lead to poorer prognosis following cardiovascular events (Pirlamarla & Bond, 2016; Salvo et al., 2014). In the current study, it was not possible to account for the use of over-the-counter NSAIDs or frequency of their use, however the OA group had higher rates of prescribed NSAIDs compared to those without musculoskeletal pain and to the regional pain and inflammatory groups (data not shown). Whilst examining the impact of NSAIDs on ACS and stroke outcomes was not an objective of this study, as the OA group does not remain at increased risk of poorer prognosis after adjustment for age and polypharmacy (excluding analgesia), there is unlikely to be confounding by NSAID use.

4.1 | Strengths/limitations

The study was set in a large nationally representative database of routinely recorded primary care data linked to secondary care and mortality information, currently including 20% of the England population (Clinical Practice Research Datalink, 2021; Wolf et al., 2019). Recorded CVD in UK databases such as CPRD have shown high validity (Herrett et al., 2013; Persson et al., 2021).

A novelty of this study is its assessment of whether regional pain, OA and inflammatory musculoskeletal conditions impact on the prognosis of ACS and stroke in terms of short-term outcomes and management in patients with new onset CVD by comparison to patients without such recent musculoskeletal pain.

The definitions used may mean some patients did not have pain at time of the incident ACS/stroke; and there will be patients in the non-musculoskeletal consultation comparison group who have musculoskeletal pain without recently seeking healthcare. This lack of healthcare utilisation is a limitation of healthcare database research and future research could evaluate impact of self-reported musculoskeletal pain and functional limitations with cardiovascular outcomes. However, using a 2 year baseline period should mean the subgroup of patients in the comparison (unexposed) group with

musculoskeletal pain is small, and they are likely to have less severe or less chronic pain. Defining musculoskeletal pain as a relevant consultation in the previous 2 years suggests the musculoskeletal pain was of a severity which prompted the need to seek healthcare. We also examined those with a more recent (last 6 months) consultation to reflect increased likelihood of a current episode of pain. We did not examine all types of musculoskeletal conditions but restricted to the most common painful conditions and those previously shown to be associated with the onset of CVD and adjusted for consultation for other musculoskeletal conditions. A limitation is that severity of painful symptoms is not recorded in eHRs, and we therefore used recent musculoskeletal referral or prescription of a strong opioid analgesic (which cannot be bought over the counter) as a proxy for severity. There may also be unmeasured confounding. We restricted the population to patients with ACS or stroke who were admitted to hospital.

5 | CONCLUSION

Patients with musculoskeletal pain have increased rates of some poorer outcomes following ACS or stroke but this is likely to relate to their older age and increased morbidity burden than the musculoskeletal condition itself. This study highlights the extent and complexity of patients with new onset ACS and stroke who have musculoskeletal pain, including a higher prevalence of cardiovascular risk factors, multimorbidity and polypharmacy.

AUTHOR CONTRIBUTIONS

Dr. Mason takes responsibility for the integrity of the data extraction and the accuracy of reporting. All authors meet the ICJME authorship criteria as they substantially contributed to the study concept, design, analysis and interpretation of the data; draughted and critically revised the manuscript for important intellectual content; and have provided final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest 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/.

ETHICS STATEMENT

The study was scientifically and ethically approved by the CPRD Independent Scientific Advisory Committee (ref 20_000105).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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