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Investigating the association between opioid analgesics and the risk of bone fracture

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Abstract

Background

Opioids have been increasingly prescribed to people with pain; despite limited evidence to support their effectiveness and safety in the long-term. Opioids may increase the risk of bone fracture due to effects on the central nervous system (CNS) and on bone mineral density (BMD). The aim of this research was to examine the utilisation of opioids in the UK and to explore the relationship between opioids and fractures.

Methods

A systematic review was conducted to identify observational studies relating to opioids and fractures. Methodological approaches were appraised, and pooled risk estimates were synthesised by meta-analysis. People prescribed opioids were identified in the Clinical Practice Research Datalink (CPRD) and opioid prescription records were prepared to generate a time-varying measure of opioid exposure and dose. A repeat cross-sectional study and a retrospective cohort study of people prescribed opioids was conducted to describe population- and patient-level trends in opioid utilisation. Fracture events among new users of opioids were identified in the CPRD and Hospital Episode Statistics (HES) databases to estimate the incidence rate of fractures. Finally, a self-controlled case series (SCCS) study was conducted to compare the incidence of fractures during opioid exposure and non-exposure; assessing the effects of opioid duration and dose.

Results

Prior opioid-fracture association studies

A total of 26 studies were included in the systematic review; these varied by study design, population, exposure definitions and potential for confounding.

Of these, 21 studies that compared opioid use to non-use were meta-analysed; pooled hazard ratios (HRs) showed that opioids significantly increased the risk of fracture (pooled HR: 1.39; 95% confidence interval (CI): 1.20, 1.62).

Trends in opioid utilisation

1,790,046 people registered in the CPRD were prescribed opioids between 2008 and 2017. The proportion of CPRD registrants prescribed opioids increased from 14.5% to 15.9%, and the proportion of strong opioid users doubled from 3.0% to 6.6%. In 2008, strong opioid users were prescribed a median oral morphine equivalent (OMEQ) dose of 60mg/day for a median duration of 155 days, whereas weak opioid users were prescribed 18mg/day for 30 days. Of 957,664 new opioid users, most (97.5%) were initiated on weak opioids and were prescribed opioids for short durations; half discontinued opioids within 16 days. A small proportion (4.1%) of people were persistent users within one year of initiation.

Fracture incidence in people prescribed opioids

Of 539,369 new opioid users who had linkage to the HES database, 67,622 sustained ≥1 fracture. The overall rate of fracture in the cohort was 218 per 10,000 person-years; double that of the general UK population.

Risk of fracture during opioid use

67,622 people with fractures were included in the SCCS study. Opioid use was associated with a significant increase in the risk of fracture compared to non-exposure (incidence rate ratio (IRR): 3.9; 95%CI: 3.8, 4.0). The risk of fracture was greatest in the first week of use (IRR: 7.8; 95%CI: 7.4, 8.3) and declined with increasing duration of use. Re-starting opioids increased the risk

of fracture and fracture-risk was greater when the OMEQ dose was ≥50mg/day compared to when the OMEQ dose was <50mg/day.

Conclusions

Opioid prescribing has increased in the UK, and a greater proportion of people were prescribed strong opioids. Although most people are prescribed weak opioids for short durations, they remain at an increased risk of fracture; the risk is greatest during the first week of use. This research complements existing evidence to suggest a causal association between opioids and fracture. Policy makers and healthcare providers need to be aware of the potential for opioids to increase the risk of fracture, particularly at initiation.

Abstract publications and presentations resulting from this thesis:

Oral:

- The association between prescription opioid use and bone fracture: a self-controlled case series study. International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Philadelphia, PA, United States, 2019

Poster:

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- Variations in risk estimates and methodological approaches in studies exploring bone fracture associated with prescription opioid use. Poster presentation, The World Congress on Pain, Boston, MA, United States, 2018

Authorship of other publications during my PhD:

- Brooks AJ, Norman P, **Peach EJ,** Ryder A, Scott A, Narula P, Corfe BM, Rowse G, Lobo AJ. Prospective Study of Psychological Morbidity and Illness Perceptions in Young People with Inflammatory Bowel Disease. Journal of Crohn's and Colitis. 2019;13(8):1003-1011
- **Peach EJ,** Martin J. Utilising implementation intentions to promote healthy eating in adolescents. Health Psychology and Behavioral Medicine. 2017;5(1):1-13

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Abbreviations

A&E	Accident and emergency attendances
aIRR	Adjusted incidence rate ratio
APC	Admitted patient care
ATC	Anatomical Therapeutic Chemical
BMD	Bone mineral density
BNF	British National Formulary
CCG	Clinical Commissioning Group
CDSS	Computerised decision support systems
CI	Confidence interval
CNCP	Chronic non-cancer pain
CNS	Central nervous system
COX	Cyclooxygenase
CPRD	Clinical Practice Research Datalink
crd	Current registration date
DDD	Defined daily dose
DSA	Drug survival analysis
DXA	Dual-energy x-ray absorptiometry
EHR	Electronic health record
FRID	Fracture-risk increasing drug
GP	General practice
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
HPA	Hypothalamic-pituitary-adrenal axis
HR	Hazard ratio
HSCIC	The Health and Social Care Information Centre
HSE	Health Survey for England
IASP	International Association for the Study of Pain
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
INCB	International Narcotics Control Board
IQR	Interquartile range
IRR	Incidence rate ratio
ISAC	Independent Scientific Advisory Committee
lcd	Last collection date
LSOA	Lower-layer Super Output Areas
MAR	Missing at random
MCAR	Missing completely at random
MDS	Monitored dosage systems
MeSH	Medical subject heading

MNAR	Missing not at random
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
MRL	Mundipharma Research Limited
ndd	Numeric daily dose
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
OMEQ	Oral morphine equivalent
ONS	Office for National Statistics
OP	Outpatient appointments
OPCS-4	Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4th Revision
OR	Odds ratio
OTC	Over the counter
OXMIS	Oxford Medical Information Systems
PPC	Proportion of patients covered
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RECORD-PE	Reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
RR	Relative risk
RWE	Real world evidence
SCCS	Self-controlled case series
SD	Standard deviation
SNRI	Serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TCF	Treatment carried forward
textid	Text identifier
tod	Transfer out date
UK	United Kingdom
US	United States of America
uts	Up to standard
WHO	World Health Organisation

Notifications

Throughout this thesis, unless otherwise stated, all references made to opioids refer to prescribed opioids belonging to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) group N02A,[1] excluding opioids used for the treatment of opioid use disorders (ATC group N07BC). In addition, long-term opioid use refers to use of opioids for a duration of ≥3 months unless otherwise stated.

All references made to fractures throughout this thesis refer to fractures of the bone. References made to the CPRD database throughout this thesis refers to the CPRD Gold, as opposed to the CPRD Aurum database, unless otherwise stated.

All work was undertaken by myself under the guidance of my supervisors and advisors except where indicated otherwise.

Chapter 1: Introduction

1.1 Background

Chronic pain conditions are common among the UK general population, estimated to affect approximately 28 million adults,[2] which is projected to rise as the population ages.[3] Certain pain conditions, such as low back pain, are leading causes of disability,[4] and ensuring that people with pain are provided with sufficient treatment to manage their pain is essential to reduce the burden that pain has for both people and society.

Several treatments are available to help people manage pain conditions however the worldwide use of opioids in chronic pain management has risen substantially in recent decades,[5-9] despite inconclusive evidence to support their long-term effectiveness.[10-12] Observational epidemiological studies suggest that long-term opioid use is associated with an increased risk of bone fractures,[13, 14] and the incidence of fractures is also anticipated to rise given the ageing population. It is hypothesised that opioids increase the risk of fractures due to three potential mechanisms: 1) falls due to CNS effects, such as sedation and dizziness; 2) reduction in BMD due to opioid-induced osteoblast impairment and 3) reduction in BMD due to opioid-induced hypogonadism.[15] However, studies examining the association between opioids and fractures are limited by indication bias and residual confounding. Further research that overcomes some of these existing limitations is needed so that the potential for a causal relationship can be considered.

This PhD thesis outlines a programme of research that aimed to examine opioid utilisation in the UK and explore the association between opioids and the risk of bone fractures using methodology to limit the effects of bias and confounding, and overcome many limitations present in the existing evidence.

This programme of research comprises of several analyses which contributed to this overall aim, and the objectives of this research, which were to:

1. Identify, summarise and appraise existing studies that have investigated the association between opioid use and bone fracture.

2. Measure and describe population-level and patient-level opioid utilisation in a cohort of adults prescribed opioids in the UK.

3. Identify, describe and estimate the incidence of fractures in adults prescribed opioids.

4. Investigate the association between opioids and bone fractures and examine the effects of opioid duration and dose.

1.2 Structure of thesis

Figure 1-1 provides an illustration of the structure of this thesis and the remaining sections of this chapter provide an overview of the content of each of the remaining chapters presented in this thesis.

Chapter 2: Literature review

This chapter positions the role of opioid analgesics in current pain management practice, and outlines the potential safety concerns regarding the use of opioids, as well as identifying gaps in the current literature; providing the rationale for the aims and objectives of the programme of research presented in this thesis.

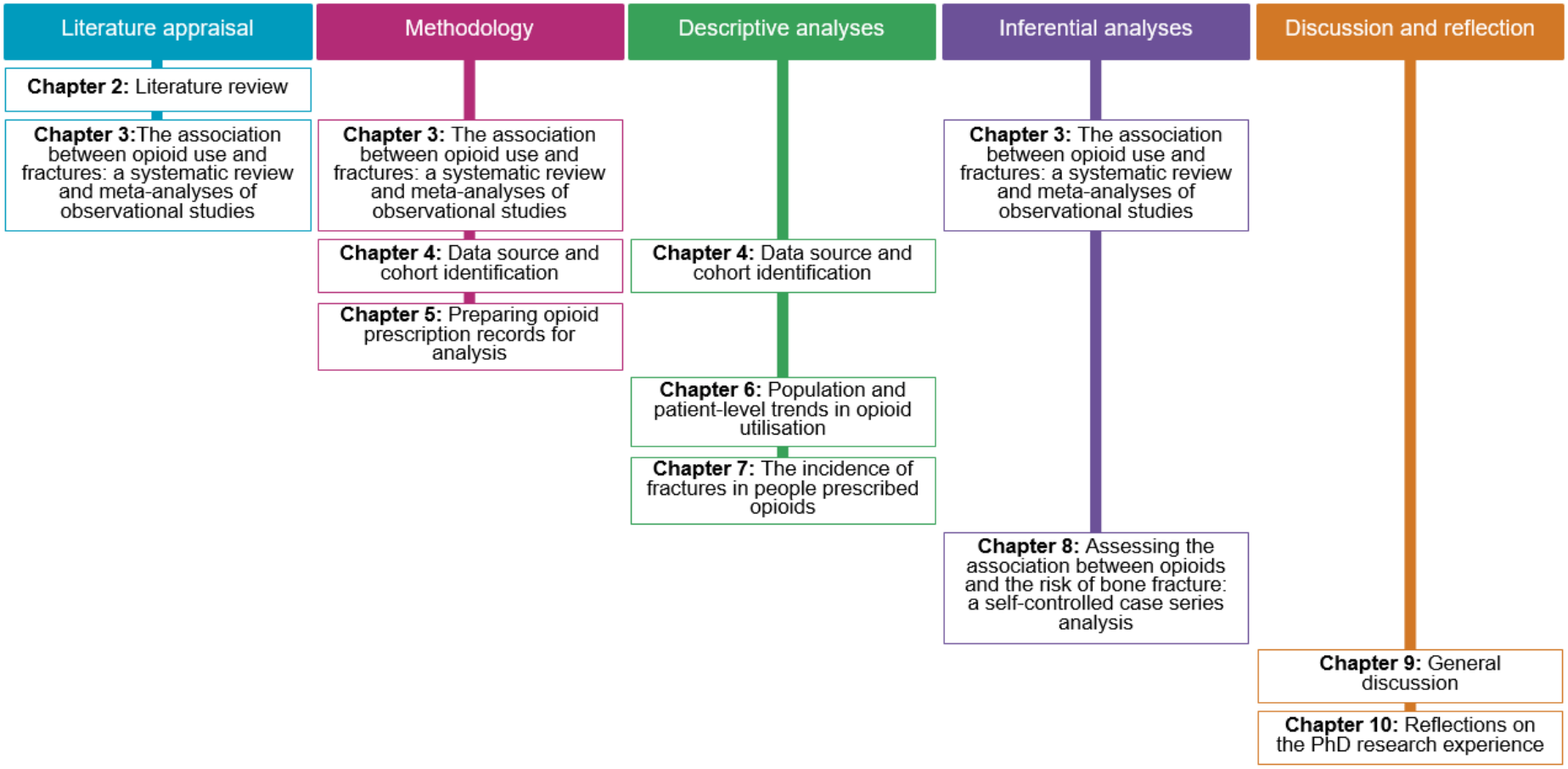


Figure 1-1. Thesis structure

Chapter 3: The association between opioid use and fractures: a systematic review and meta-analyses of observational studies

Chapter 3 contains a systematic review and meta-analyses of observational studies that assessed the association between opioid and fractures, with a focus on the methodological approaches taken by these studies; highlighting current limitations in the evidence to inform the methodological approach taken in the subsequent analyses presented in the remaining chapters of this thesis.

Chapter 4: Data source and cohort identification

Chapter 4 describes the considerations taken into account when selecting a data source and the strengths and limitations of electronic health records (EHRs) for epidemiological research, with a focus on the CPRD and the HES databases, which were selected for this programme of research. This chapter also describes the identification of a cohort of people prescribed opioids and the process of extracting their opioid prescription records for analysis.

Chapter 5: Preparing opioid prescription records for analysis

Following on from the previous chapter, Chapter 5 describes the approach to handling missing data, cleaning, restructuring and formatting the opioid prescription records so that they were ready for time-varying analyses.

Chapter 6: Population and patient-level trends in opioid utilisation

Chapter 6 outlines a population-level analysis and patient-level analysis of UK opioid prescribing; describing trends in opioid prescribing between 2008 and 2017, and patterns of opioid utilisation over patients' follow-up.

Chapter 7: The incidence of fractures in people prescribed opioids

Chapter 7 outlines the method for identifying opioid users who sustained fractures - using the CPRD and HES databases. The chapter describes the demographic characteristics of people with and without fractures and provides estimates for fracture incidence rates, which were stratified by age, sex, socioeconomic status, ethnicity, season of the year, and anatomical site. The identification of fractures occurring within this cohort provided a case-only cohort for the study reported in Chapter 8.

Chapter 8: Assessing the association between opioids and the risk of bone fracture: a self-controlled case series analysis

This chapter outlines an SCCS study that compared the incidence of fractures during periods of opioid exposure to periods of non-exposure. Exposed time was split into discrete ‘risk periods’ to assess the effects of opioid duration and dose on the risk of fractures.

Chapter 9: General discussion

This chapter provides a summary of the findings from each chapter presented in this thesis and provides an overview of the potential for chance, bias and confounding to provide alternative explanations for the findings. Additionally, a consideration of the Bradford Hill criteria for inferring causality is provided in relation to the work presented in this thesis. Finally, the chapter concludes with implications for practice and policy and directions for future research.

Chapter 10: Reflections on the PhD research experience

This final chapter provides a reflective account of some of the key areas of my development throughout the process of this PhD research programme.

Chapter 2: Literature review

2.1 Introduction

This review begins by defining different types of pain, and the current role of prescription opioids for managing pain. Potential patient safety issues regarding opioid use are discussed, with a focus on the role opioids might play in increasing the risk of bone fractures. This review highlights the significant burden of bone fractures in the UK, the multitude of factors that contribute to the risk of fractures and possible explanations for the association between opioid-use and an increased risk of fracture. Finally, methods for measuring exposure to opioids and opioid utilisation in the UK are described. The review closes with areas of research that require further investigation, which form the objectives of this PhD thesis.

2.2 Pain

The International Association for the Study of Pain (IASP) definition of pain has been commonly accepted among pain researchers and clinicians since 1973 and has been adopted by numerous organisations such as the WHO. The IASP define pain as:

'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (p.249).[16]

A recent expert commentary proposed that this definition should be updated to clarify that pain may also occur in the absence of tissue damage, adding that 'pain is a mutually recognizable somatic experience that reflects a person's apprehension of threat to their bodily or existential integrity' (p.6).[17] Taken together, the IASP definition and this contemporary definition demonstrate that pain is not only a physical experience but also embedded in the psychological and emotional experiences of people with pain.

Several types of pain exist, and these may present in isolation or together and in varying degrees of intensity. Common types of pain include: nociceptive pain, which is related to the activation of nociceptors (i.e., pain receptors); neuropathic pain, which is related to damage or disease within the somatosensory system; and inflammatory pain, which results from the release of inflammatory mediators.

In 2007, a WHO Delphi meeting of pain experts agreed that painful conditions could be classified into three broad categories: acute pain; chronic cancer pain; and chronic non-cancer pain (CNCP).[18] Since then, in 2019, an IASP task force differentiated chronic primary pain from chronic secondary pain conditions across seven distinct categories, which have been adopted by the WHO's International Classification of Diseases (ICD), version 11 (ICD-11).[19] Pain conditions, acute or chronic each have their own aetiology, duration, diagnostic criteria, and approach to management. The following sections outline the definition of acute and chronic pain conditions, and prevalence of pain conditions in the UK.

2.2.1 Acute pain

Acute pain is defined as 'the physiologic response to an experience of noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviours to avoid potential or actual tissue injury' (p.950).[20] Acute pain, therefore, is short-lived and in most cases has a known cause.

2.2.2 Chronic pain

Chronic pain is defined as the feeling of pain that lasts for a duration of more than three months or beyond the expected time period for tissue healing to have occurred.[21] In contrast to acute pain, which is transient in nature, in

chronic pain, the pain pathway continues to signal pain despite there being no apparent lasting injury.[22] The ICD-11 categories for chronic pain conditions are outlined in Table 2-1.[19]

Table 2-1. Summary of WHO classification of chronic pain conditions

Chronic pain classification	Example conditions
Chronic primary pain	Non-specific low back pain, fibromyalgia, chronic migraine, irritable bowel syndrome
Chronic secondary pain	
Chronic cancer-related pain	Tumour, metastases or treatment for these
Chronic post-surgical or post-traumatic pain	Surgery, trauma
Chronic neuropathic pain	Stroke, diabetic neuropathy
Chronic secondary headache or orofacial pain	Chronic headache, cranial neuralgias, chronic dental pain
Chronic secondary visceral pain	Ischemia, thrombosis, inflammation, traction, obstruction
Chronic secondary musculoskeletal pain	Rheumatoid arthritis, osteoarthritis, Parkinson's disease

2.2.3 Prevalence of pain

Chronic pain conditions are common among the general population, the estimated prevalence of chronic pain in European countries ranges from 12% to 30%.[23] In a Chief Medical Officer's report, moderate to severe chronic pain was estimated to affect at least 7.8 million people in the UK, and cost the National Health Service (NHS) £584 million in prescriptions for analgesics in 2008.[24] The report called for chronic pain to be considered a UK public health priority; calling for better coordination of services and routine collection of health data to understand the impact that pain has on people.

The Health Survey for England (HSE) is an annual survey of factors affecting public health which is sent out to a representative sample of the population in England.[25] Following the 2011 survey, a report was published on the findings

for self-reported chronic pain; its prevalence, severity and impact on daily living.[26] The report highlighted significant variations between age, sex, household income and deprivation on measures such as pain prevalence, severity, services, wellbeing and mental health. Women reported more chronic pain than men (37% among women and 31% among men) and respondents from the lowest household income quintile were most likely to report chronic pain than the highest income quintile (40% men and 44% women versus 24% men and 30% women respectively). Chronic pain prevalence and intensity increased with age; 39% of men and 44% of women aged 75 years and over reported pain restricting their usual activities (i.e., pain with high interference).

In 2016, a systematic review and meta-analysis of research adopting any design that reported prevalence estimates for chronic pain in the UK generated a pooled UK chronic pain prevalence estimate of 43%, equating to just under 28 million adults.[2] This estimate is slightly higher than the 31-37% prevalence figure reported by the 2011 HSE report.[26] However, both of these estimates are considerably higher than the 13% UK prevalence estimate reported by a 2006 survey of chronic pain in Europe.[23] These variations are likely to reflect differing operational definitions used for ‘chronic pain’ and peoples’ understanding of them; for example, the 2006 European survey defined chronic pain as pain for a duration of more than three months with the inclusion of additional pain intensity criteria, whereas the 2011 HSE defined chronic pain as continuous or intermittent pain experienced for more than the last three months. Despite variations in prevalence estimates, chronic and acute pain conditions affect a substantial proportion of the general UK population and this is set to rise as the population ages.[3]

2.2.4 Burden of pain

Pain conditions have a detrimental impact for people and society, affecting mental health,[27] physical function,[4] quality of life,[28] and the economy;[29-31] the 2010 WHO Global Burden of Diseases survey reported that certain chronic pain conditions, such as low back pain, are leading causes of disability worldwide.[4] Moreover, anxiety and depression were more commonly reported by people with chronic pain compared to those with no pain in the 2011 HSE.[26]

As the population ages, the rising prevalence of painful conditions will bring further challenges for the UK healthcare system due to additional economic burdens. In 2017, prescriptions for analgesics cost the NHS £509.7 million,[32] and in 1998 back pain alone was estimated to cost the UK economy a total of £140.6 million in primary care consultations.[30] Additionally, a 2016 Labour Survey reported back pain as having the highest estimated days of work lost compared to all categories of musculoskeletal illnesses caused or made worse by work,[29] concluding that back pain had the greatest economic burden compared to all other diseases studied in the UK, reflecting findings from other countries such as the Netherlands.[31] Ensuring that people with pain are provided with sufficient treatment to manage their pain is therefore essential to reduce the burden that pain has for both individuals and society.

2.3 Management of pain

There are several treatments available for people presenting to healthcare professionals with pain, these can be classified as pharmacological and non-pharmacological. The goal of pain management is to provide symptom relief and to help improve function (physical and emotional) and quality of life for people. People should be assessed based on the aetiology of their pain and

treated in accordance with their individual symptoms, taking into account the effects their pain has on physical function, psychological wellbeing and quality of life,[24] with careful consideration of potential benefits and harms of treatments.

2.3.1 Non-pharmacological pain management

Non-pharmacological treatments include therapies such as physiotherapy, cognitive-behavioural therapy, exercise, and relaxation strategies. In addition, people may undergo more invasive treatments such as nerve blocks or surgery.[33]

2.3.2 Pharmacological pain management

Pharmacological treatments can be grouped into medicine classes and subgroups within these, a summary of analgesics available for prescription in the UK is provided in Table 2-2.[33]

Simple analgesics

Paracetamol (also known as acetaminophen) is the most prominent, and commonly used drug within this group. Paracetamol is an antipyretic and also has a slight anti-inflammatory action; despite being commonly used as an analgesic, the mechanism of action remains unclear.[34] However, there is little evidence to support the use of paracetamol in people with chronic pain conditions such as osteoarthritis,[35] and acute or chronic low back pain.[36]

Table 2-2. Summary of analgesic drugs

Analgesic drug class	Example drugs
Simple analgesics	Paracetamol
NSAIDs	Ibuprofen, naproxen, diclofenac, celecoxib, mefenamic acid, etoricoxib, indomethacin, aspirin
Anti-epileptics	Pregabalin, gabapentin
Antidepressants	Amitriptyline, duloxetine
Compound analgesics*	Co-codamol (codeine and paracetamol), co-dydramol (dihydrocodeine and paracetamol), co-codaprin (codeine and aspirin)
Weak opioids	Codeine, dihydrocodeine
Strong opioids	Morphine, buprenorphine, fentanyl, methadone, oxycodone, tapentadol, tramadol

Notes: NSAIDs, non-steroidal anti-inflammatory drugs. *Compound analgesics are usually a combination of paracetamol or an NSAID with a weak opioid.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase (COX) enzyme which reduces inflammation and modulates central and peripheral nociception.[37] However, there is little evidence to support or refute their effectiveness for managing chronic neuropathic pain conditions,[38] and NSAIDs have only been found to be slightly more effective than placebo when used to manage chronic low back pain.[39]

Anti-epileptics

Gabapentin and pregabalin are anti-epileptic drugs that are licensed for managing neuropathic pain, epilepsy and generalised anxiety disorder (pregabalin only) in the UK. National Institute for Health and Care Excellence (NICE) clinical guidelines recommend that gabapentin or pregabalin (as well as antidepressants such as duloxetine or amitriptyline) are used as first-line treatments for neuropathic pain.[40]

Antidepressants

Serotonin and noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) such as duloxetine and amitriptyline, respectively, each show some clinical benefit in people with neuropathic pain conditions.[41, 42] However, evidence for the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in treating neuropathic pain is limited,[42] therefore, NICE recommend duloxetine or amitriptyline (or an anti-epileptic) as first-line treatments for the management of neuropathic pain.[40]

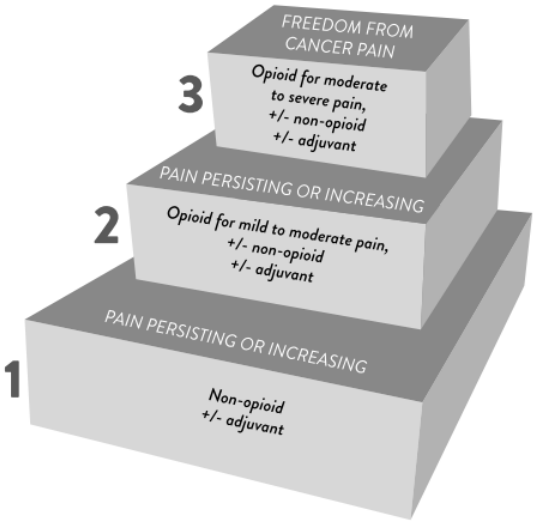
Opioids

Opioids are synthetic or naturally occurring substances that produce effects similar to morphine. These are distinct to 'opiates' which include only naturally occurring substances derived from the opium poppy. Opioids produce analgesic effects primarily through activation of opioid receptors (i.e., μ, κ and δ receptors) that are located within the CNS and peripheral tissues. Activation of opioid receptors inhibits the transmission of pain neurotransmitters and facilitates the release of other neurotransmitters such as dopamine, which can have euphoric effects.[43] Opioids can be classified as weak or strong based on their affinity for the μ receptor. Weak opioids include codeine, dihydrocodeine and meptazinol, and strong opioids include all other opioid drugs.[44]

In the UK, low strength weak opioid analgesics are available over the counter (OTC) in the form of compound analgesics, examples include co-codamol and co-dydramol; individual forms of opioids or compound analgesics containing higher strength opioids must be obtained via prescription. The Misuse of Drugs Regulations 2001 details the legislative requirements for the supply, possession, prescribing and record keeping of controlled drugs;[45] opioids fall

under different schedules within these regulations and therefore have varying requirements to ensure they are appropriately managed and used safely. In addition to a variety of formulations and strengths, opioids can be prescribed at varying doses and may be used by people in different ways such as continually, intermittently, short-term or long-term.

The WHO have advised that 'opioid analgesics are essential for the adequate treatment of moderate to severe cancer pain',[46] and several opioids are included in the 2017 release of the WHO Model list of essential medicines for pain and palliative care.[47] The place of opioids within treatment strategies for cancer pain are represented in the WHO's three-step analgesic ladder (Figure 2-1). Since its introduction, this approach to pain management has also been adopted for CNCP conditions,[48] and the role of opioids in chronic pain management has become commonplace in the UK, and globally.



Notes: Figure obtained from WHO;[46] step 1 (mild pain) includes non-opioids and adjuvants; step 2 (moderate pain) adds opioids; step 3 (severe pain) adds more potent opioids.

Figure 2-1. The WHO three-step analgesic ladder

2.4 Effectiveness of opioids

The effectiveness of opioids for managing CNCP conditions has been assessed in several clinical trials and summarised in several Cochrane reviews. However, few studies have systematically investigated the effectiveness of opioids to provide clinically significant pain relief or improved functional ability in the long-term. A Cochrane review by Noble *et al.* (2010), summarised 26 randomised controlled trials (RCTs), case series studies, and uncontrolled extensions to RCTs that assessed the effectiveness of long-term opioid use to reduce CNCP and improve quality of life in the long-term (defined as ≥6 months).[12] Noble *et al.* defined long-term opioid use as opioids taken at any dose for at least six months. Although a clinically significant reduction in pain scores were reported, these varied between individual opioid drugs, formulations and between individual studies. The quality of these studies was considered to be low due to a high risk of bias; consequently, the reviewers concluded that these studies provided weak evidence for the effectiveness of opioids beyond a duration of six months. This is partly because the open-label extension studies had a high risk of selection bias, and publication biases were found to be present. Furthermore, there was insufficient evidence to demonstrate clinically meaningful improvements in quality of life measures for physical function and psychological wellbeing due to a low number of studies reporting such outcomes and variability in how these were assessed. Most studies conducted to date have only compared opioids to placebo rather than comparing opioids to the best available treatment.

In another Cochrane review, Chaparro *et al.* (2014) summarised RCTs that compared opioids to placebo and alternative treatments such as NSAIDs in people with chronic low back pain.[10] Very few studies compared opioids to

alternative treatments which meant that no meta-analysis could be performed. Furthermore, the two studies that did compare to alternative treatments did not exceed a treatment duration of 15 weeks. The reviewers recommended taking extreme caution when initiating opioids for managing chronic low back pain due to uncertainties regarding long-term effectiveness and safety.

The effectiveness of opioids for pain management has also been assessed using pragmatic RCT methodology. Krebs *et al.* (2018),[11] using a pragmatic RCT design, compared the effectiveness and safety of opioids, with that of non-opioid analgesics, over a 12-month period. Outcomes included pain-related function, pain intensity and the occurrence of adverse effects. Similar to the Cochrane reviews, Krebs *et al.* showed little evidence for the effectiveness of opioids; people taking opioid analgesics showed no clinically significant improvement for pain intensity nor physical function over the 12 month study period. Moreover, people taking opioids were more likely to discontinue their treatment, discontinuation was 19% for opioids and 8% for non-opioids, and significantly more adverse effects were reported among people prescribed opioids (0.9 point difference on scores from a medication-related symptom checklist, which ranged from 0 to 19 where high scores referred to more adverse effects). The study by Krebs *et al.* provided a longer duration of follow-up than traditional RCTs and used a study population that was more generalisable to real-world opioid users. The maximum dose was limited to an OMEQ dose ≤100mg per day and therefore may have potentially under-estimated the occurrence of adverse events that are dose dependent. Additionally, because the study duration was 12 months, longer term adverse outcomes that occur beyond 12 months could not be assessed.

2.5 Safety of opioids

RCTs have shown that opioids are not well tolerated by many people when initiated; 22.9% (95%CI: 15.3, 32.8%) of people who commence oral opioids discontinue them usually within the first six months due to adverse effects.[12] Common side effects include: constipation, nausea, dyspepsia, headache, fatigue, and urinary complications; most of these subside over time.[12]

Although RCTs are the gold-standard of study designs for establishing a cause-effect relationship between exposure and outcome, RCTs and pragmatic RCTs are limited by short trial durations in selected patient populations. Observational studies therefore, at present, remain more informative when making inferences about the long-term safety of prescription opioids, as well as being potentially more informative due to the inclusion of a more generalisable study population than typically recruited into an RCT.

A systematic review by Chou *et al.* (2015), reported evidence for the effectiveness and harms of opioid therapy for chronic pain,[49] summarising RCTs and observational studies published between January 2008 and August 2014. An objective of the review was to assess the risk of various harms in people prescribed opioids versus placebo or no opioids. The study selection criteria specified that eligible studies included adults with chronic pain who were prescribed opioids for a duration of more than three months, or were prescribed long-acting opioids. From an initial 4,209 studies, 19 studies reported harms in users of opioids who had chronic pain, these studies are summarised in Table 2-3.

Table 2-3. Summary of studies reporting harms associated with long-term opioid use

Outcome	Studies	Comparison	Adjusted risk estimates
Abuse and addiction	1 cohort[50]	Use vs. non- use	OMEQ 1-36mg/day: OR: 14.9 ;95%CI: 10.4, 21.5
			OMEQ ≥120mg/day: OR: 122.5; 95%CI: 72.8, 206.0
	10 uncontrolled[51-61]	No comparison	No comparison
Overdose	1 cohort[62]	Recent use vs. non-use	Any overdose: HR: 5.2; 95%CI: 2.1, 12.5
			Serious overdose: HR: 8.4; 95%CI: 2.5, 28.0
		OMEQ ≥20mg/day vs. OMEQ 1-19mg/day	Any overdose: ORs ranged from 1.44 to 8.87 depending on OMEQ dose
			Serious overdose: ORs ranged from 1.19 to 11.18 depending on dose
	1 nested case-control[63]	OMEQ ≥20mg/day vs. OMEQ 1-19mg/day	Overdose death: ORs ranged from 1.32 to 2.88 depending on dose
Fractures	1 cohort[14]	Current use vs. current non-use	HR: 1.28; 95%CI: 0.99, 1.64
	1 nested case-control[13]	Current use vs. non-use	OR: 1.27; 95%CI: 1.21, 1.33
Myocardial infarction	1 cohort[64]	Opioid use on ≥180 days over 3.5 years vs. non-use	IRR: 2.66; 95%CI: 2.30, 3.08
	1 case-control[65]	Current use vs. non-use	OR: 1.28; 95%CI: 1.19, 1.37
Testosterone deficiency	1 cross-sectional[66]	Long-term use vs. non-use	OR: 1.45; 95%CI: 1.12, 1.87
Motor vehicle accidents	1 case-control[67]	OMEQ ≥20mg/day vs. OMEQ 1-19mg/day	ORs ranged from 1.21 to 1.42 depending on OMEQ dose

Notes: OMEQ, oral morphine equivalent; OR, odds ratio; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; Table adapted from Chou *et al.* (2015).[49]

Due to the small number of studies identified for each outcome, meta-analyses were not performed and therefore no summary estimates were reported; additionally, publication bias was not explored. The review by Chou *et al.* has some further limitations; studies of tramadol, weak opioids, and people with acute pain conditions were excluded from the review and some studies were excluded if it could not be ascertained whether their study populations had chronic pain or had received opioids for ≥3 months. As a consequence, fewer studies will have been identified in this review due to the strict study selection criteria employed. The results from this review may therefore not relate to opioid users in general, such as those prescribed weaker opioids or those prescribed opioids in the short-term for acute pain conditions.

Despite these limitations, long-term opioid use is associated with increased risk of overdose, opioid abuse, fractures, myocardial infarction, motor vehicle accidents, and markers of sexual dysfunction. These outcomes, particularly with regard to an association with fractures (whereby the evidence in the review by Chou *et al.* is sparse and inconsistent), warrants further investigation.

2.6 Fractures

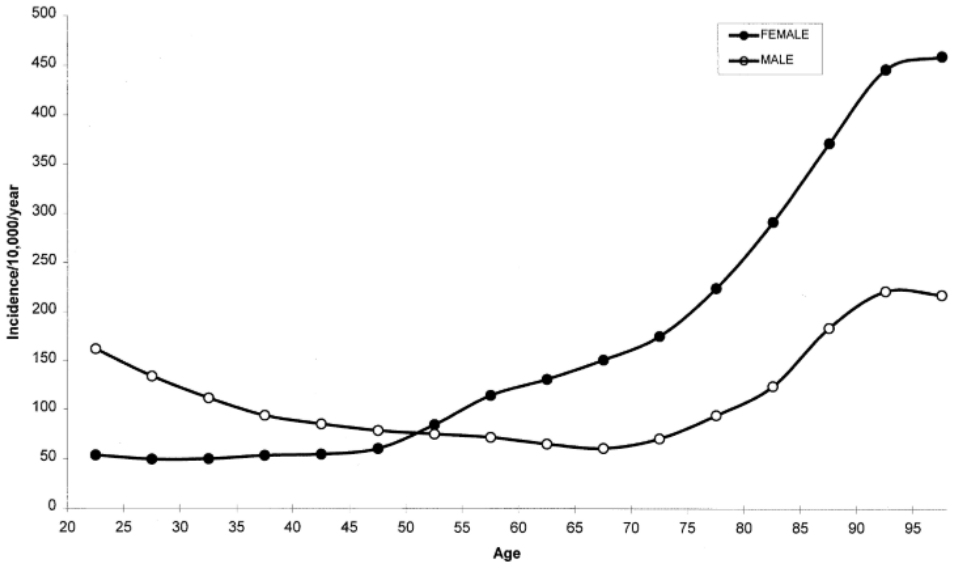
A bone fracture refers to a fissure within the bone or when a bone is broken. A fracture can occur due to high or repeated physical forces or weakening of the bone structure. Falls and accidents are common causes of fractures, however, bone diseases such as osteoporosis, characterised by low BMD, make people more susceptible to fractures than those without low BMD. Fragility fractures are fractures that result from forces that would not ordinarily result in fracture; people with osteoporosis are more likely to experience

fragility fractures, due to their less dense and more fragile bones. Fragility fractures occur most commonly in the spine, shoulder, forearm, wrist and hip.[68]

2.6.1 Incidence of fractures

Fractures are a global public health concern. It is estimated that there are approximately 8.9 million osteoporotic fractures worldwide each year.[69] Furthermore, in the year 2000, the greatest number of osteoporotic fractures occurred in Europe (34.8%).[69] In the UK, a retrospective cohort study using data from the CPRD (formally known as the General Practice Research Database - GPRD) from 1988 to 1998 estimated that the lifetime risk of any fracture was 53.2% among females and 20.7% among males aged ≥50 years.[70] A sharp increase in the incidence of fracture was observed in females aged ≥50 years (Figure 2-2). The study identified first fractures only (i.e., the first code for fracture recorded during follow-up), and may therefore have under-estimated the incidence of fractures. In addition to age and sex differences, the UK incidence of fracture also varies according to anatomical site,[70] geographical location,[71] ethnicity,[71] and level of social deprivation.[71]

The UK population is ageing and the Office for National Statistics (ONS) projections estimate that by 2037, 24% of the UK population will be over the age of 65 years.[72] Therefore, as the population ages it is anticipated that the incidence of fractures will increase.



Notes: Figure obtained from Van Staa *et al.* (2001).[70]

Figure 2-2. Age and sex specific incidence of fractures, 1988 to 1998

2.6.2 Burden of fractures

Fractures pose a considerable burden for individuals and society, due to immediate complications, longer-term declines in health, increasing care needs and decreasing quality of life. Hip fractures alone account for an average loss of 2.7% of healthy life expectancy.[73]

Klop *et al.* (2017),[74] conducted a retrospective cohort study comparing mortality rates among the English general population with rates for people who experienced a fracture. They found that people with a prior fracture had a 3.2-fold increase in the risk of death in the year following their fracture; this risk increased with age and was greater among males. Additionally, a meta-analysis exploring the magnitude of excess mortality risk in people aged ≥50 years following hip fractures showed that the three-month period following a fracture was associated with the greatest risk for all-cause mortality in both females (HR: 5.75; 95%CI: 4.94, 6.69) and males (HR:7.95; 95%CI: 6.13, 10.30).[75]

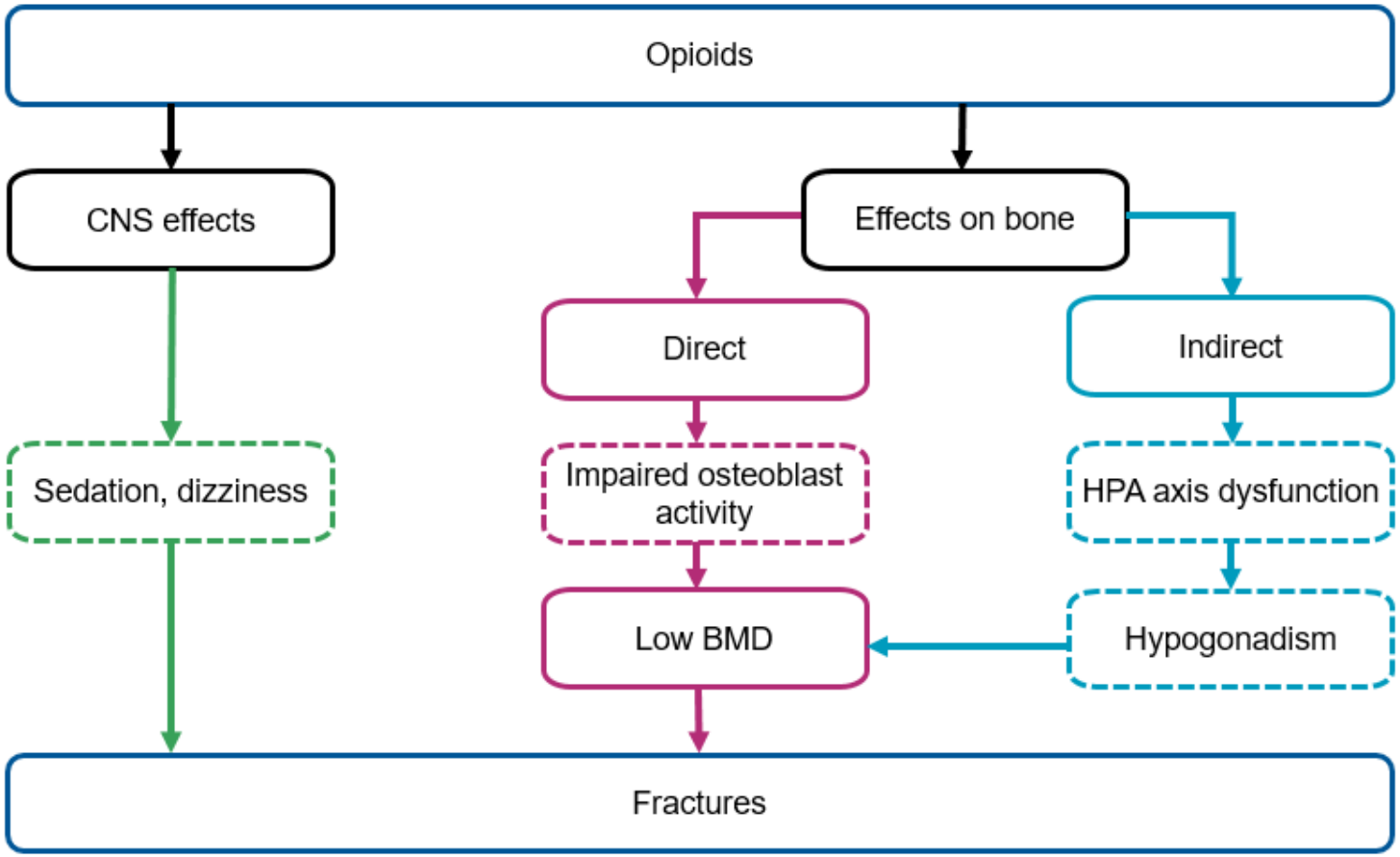
In 2017, fragility fractures in the UK were associated with a healthcare cost of £4.5 billion, and this figure is predicted to rise to £5.9 billion by 2030.[76] Given the increasing burden of fractures for people, healthcare providers and the UK economy, the identification of modifiable risk factors is an important area of research.

2.6.3 Opioids and fractures

As reported by Chou *et al's* systematic review,[49] evidence from observational studies suggests use of opioids is associated with an increased risk of fracture. There are three hypothesised mechanisms used to explain this association: 1) falls due to CNS effects, such as sedation and dizziness; 2) reduction in BMD due to opioid-induced osteoblast impairment and 3) reduction in BMD due to opioid-induced hypogonadism (Figure 2-3).[15]

The CNS side-effects of opioid analgesics are well established, and these mainly occur at initiation of opioid therapy or following a significant dose increase. Symptoms include dizziness, confusion and sedation. These effects usually resolve after a few days of use once a degree of tolerance has developed.

Contrary to CNS effects, changes in BMD occur over prolonged periods. Bone matter is repeatedly resorbed into the body by osteoclasts, and re-formed by osteoblasts. This balanced remodelling process is essential to maintain BMD, and as a consequence bone strength. An imbalance towards resorption decreases BMD and can result in bone diseases such as osteoporosis.[77] Opioids have been found to affect osteoblast *in-vitro* activity using human cells and may therefore lead to a reduction in BMD by causing an imbalance



Notes: CNS, central nervous system; BMD, bone mineral density; HPA, hypothalamic-pituitary-adrenal axis; figure adapted from Coluzzi *et al.* (2015).[15]

Figure 2-3. Hypothesised mechanism to explain the association between opioids and increased risk of fracture

in bone remodelling processes.[78] Additionally, indirect endocrine effects of opioids, specifically on sex hormones, have been observed in both males and females across several studies,[79] which may also result in a reduction in BMD. Studies of people with opioid use disorder support these hypotheses, finding that people receiving methadone maintenance therapy had low BMD.[80, 81]

The systematic review by Chou *et al.* included just two studies that investigated the association between opioids and fractures, one nested case-control study and one cohort study. The nested case-control study by Lin *et al.* (2013) was conducted within a retrospective cohort of opioid users and compared those with a fracture to those without a fracture; these controls were matched based on age, sex, index date, and registered GP.[13] Odds ratios (ORs) were adjusted for potential confounding factors relating to lifestyle, comorbidities, other medication, and pain condition.Current opioid use (i.e., use ≤30 days prior to fracture) increased the risk of fracture compared to non-use, (i.e., no opioid use prior to fracture or >365 days before fracture) (OR: 1.27; 95%CI: 1.21, 1.33). Relative to non-use, the greatest effect was observed in current opioid users with just one opioid prescription prior to their fracture (OR: 2.70; 95%CI: 2.34, 3.13), no significant increase in fracture-risk was reported for people with >20 prescriptions prior to fracture. These findings lend support towards CNS effects rather than direct and indirect effects on BMD.

The cohort study by Saunders *et al.* (2010) examined fracture-risk in elderly people who were chronic users of opioids (defined as ≥3 opioid prescriptions within 90 days).[14] Compared with persons not currently using opioids, opioid use was associated with a non-significant increase in fracture risk (HR: 1.28;

95%CI: 0.99, 1.64), however, OMEQ doses >50 mg/day were associated with a significant two-fold increase in fracture risk (HR: 2.00; 95%CI: 1.24, 3.24). A key strength of this study is that confounding by indication was limited by comparing unexposed and exposed groups who had each been diagnosed with chronic pain and had been prescribed opioids, meaning that they were better matched on their pain condition and severity of pain. Additionally, exposure was treated as a time-dependent variable and therefore took account of changes in opioid use over time, reducing exposure misclassification bias. One potential reason for the non-significant finding is that people were only followed after their initial 90 days of chronic opioid use, once eligibility was established. This may have introduced survivor bias, whereby people likely to fracture would have had the fracture before follow-up started. Indeed, based on the findings from Lin *et al.*,[13] fractures were most likely to occur in those people who received just one opioid prescription. Despite these limitations, the study by Saunders *et al*. demonstrated a dose-dependent relationship between opioids and fracture which lends further support towards a causal association, according to the Bradford Hill criteria, which outlines conditions for determining causation.[82]

An earlier meta-analysis reported by Takkouche *et al.* (2007) identified six studies relating to opioids and fractures,[83] all of which were not included by Chou *et al*. in their systematic review. This discrepancy is likely due to the specificity of the study selection criteria employed by Chou *et al.* in their review. The random effects meta-analysis by Takkouche *et al.* estimated a pooled relative risk (RR) of 1.38 (95%CI: 1.15, 1.66) in opioid users compared to non-users, which is similar to Lin *et al*'s case-control study,[13] and greater than Saunders *et al's* cohort study.[14] A summary of the pooled studies from Takkouche *et al's* meta-analysis is provided in Table 2-4.

Further to these studies, a recent prospective cohort study,[84] followed pre-menopausal women for five years through the menopause, and assessed the effects of various analgesics, including opioid analgesics, on BMD. People were categorised as exposed to opioids based on interviewer-administered questionnaires at baseline, and were censored if they deviated from their initial treatment group during follow-up. A greater decline in hip BMD was observed in opioid users relative to paracetamol users by the fifth year (-1.07% vs. -0.61% change respectively). One notable limitation of the study was that reliable medication exposure data were not available which may have led to misclassification bias. The authors recommended that further research was needed to assess BMD decline over a longer duration of follow-up, which may provide more insight into the potential for opioids to increase the risk of fracture over the long-term.

2.6.4 Other risk factors

There are a multitude of reasons for experiencing a bone fracture, which may include genetic, lifestyle and clinical factors; and these may increase fracture-risk by increasing the risk of falls or by lowering BMD. These risk factors can be broadly categorised into medication-related and non-medication-related factors (Table 2-5). Although this PhD research focuses on medication-related factors, specifically opioids, the consideration of the effects of other medicines and non-medication-related factors is important to address potential confounding in the studies presented in this thesis.

Table 2-4. Summary of opioid-fracture association studies reported in Takkouche *et al's* (2007) meta-analysis

First author, year	Study design, Sample size	Population	Comparison	Fracture site	Results	Conclusions
French, 2005[85]	Case-control Cases: 2,212 Controls: 4,424	People admitted to hospital with ≥1 prior prescription	None - descriptive analysis only	Hip	16.0% of cases prescribed opioid; 9.5% of those admitted for MI, and 14.4% for pneumonia	No specific conclusion relating to the association between opioids and fracture
Jensen, 1991[86]	Case-control Cases: 200 Controls: 200	People aged >59 years admitted to hospital	No opioid use	Hip	OR 1.00 (95%CI: 0.50, 1.98)	No significant increase in the risk of hip fracture in those taking opioids in the 14-day period prior to fracture, compared to non-users
Guo, 1998[87]	Prospective cohort 1,608	Elderly (≥75 years) community residents	No opioid use	Hip	HR 1.79 (95%CI: 1.05, 3.05)	Opioid use increased the risk of hip fracture by 80% when compared to non-users
Ensrud, 2003[88]	Prospective cohort 8,127	Women aged ≥65 years	Non-use of CNS-active medicines	Non-vertebral	HR 1.40 (95%CI: 1.06, 1.83)	Rates of non-spine fracture during periods of opioid use increased by 40% compared to non-users of CNS-active medicines
Shorr, 1992[89]	Case-control Cases: 4,500 Controls: 24,041	People aged ≥65 years	No opioid use	Hip	RR 1.6 (95%CI: 1.4, 1.9)	Codeine and propoxyphene users had a 60% increase in risk of hip fracture compared to non-users
Card, 2004[90]	Retrospective cohort 16,550	People with a diagnosis of IBD	No opioid use	Hip	HR 1.67 (95%CI: 1.12, 2.48)	Regular opioid use (>1 prescription per year) increased the risk of hip fracture by 67% compared to non-users

Notes: OR, odds ratio; CI, confidence interval; RR, relative risk; HR, hazard ratio; IBD, inflammatory bowel disease

Table 2-5. Summary of risk factors for fracture

Non-medication related	Medication-related
Demographic e.g., age, sex, ethnicity, socioeconomic status	Psychoactive medicines
Lifestyle e.g., smoking, alcohol consumption, calcium intake, serum vitamin D concentration, physical activity	Cardiovascular medicines
Previous falls or fractures	Glucocorticoids
Comorbidities e.g., osteoporosis, Parkinson's disease	

2.6.4.1 Non-medication-related factors

Demographic factors

Older age increases the risk of fractures,[70, 71] due to natural physiological changes as a result of decreased muscle mass, a reduction in physical activity, cognitive decline and comorbidity associated with chronic illnesses. As people age, their BMD decreases because of increased resorption of calcium and decreased deposition. Females are more likely to sustain fractures than are males, particularly after the menopause due to a decline in oestrogen levels which lowers BMD. However, differences between males and females in fracture incidence may also be accounted for by differences in lifestyle, comorbidities and falls risk.[91]

The incidence of fractures in the UK also varies considerably according to ethnic origin. The lowest rates of fracture are observed among black males and black females; incidence rates for fragility fracture were found to be 4.7 times greater in white women than in black women.[71] Additionally, low socioeconomic status (measured by the Index of Multiple Deprivation (IMD);[92] a measure of relative deprivation) is associated with an increased risk of hip fracture; 30% (RR: 1.3; 95%CI: 1.21, 1.41) higher for people with low socioeconomic status (IMD category 5) compared to people with high

socioeconomic status (IMD category 1).[71] This disparity might be explained by poorer health as a consequence of low income and inadequate social support. The same study also found that the incidence of fragility fractures varied according to geographical location in the UK, with higher rates of fracture in the South West, Northern Ireland and Scotland; the incidence of fragility fractures in women aged over 50 years in Scotland was 46% higher than in London.[71]

Lifestyle and behavioural factors

Smoking may increase the risk of fractures due to diminished BMD because of the effects of nicotine. Smoking carries a moderate and dose dependent risk for low BMD when comparing current smokers and never smokers, after adjusting for differences in physical activity and weight.[93] Additionally, moderate to heavy alcohol consumption has also been associated with the risk of fractures due to an increased risk of falling and potential effects of alcohol on BMD.[94, 95] Low dietary calcium intake is also associated with an increased risk of fractures, however this effect is moderated by serum vitamin D concentrations.[96] Several observational studies and RCTs have also shown that physical activity is associated with improved muscle strength and a reduction in the risk of falls and fractures.[97]

Previous falls or fracture

A recent population-based cohort study from Reykjavik, Iceland found that the risk of fracture is increased following an initial fracture. For all prior fractures combined, the RR of any subsequent fracture is 2.2 times greater than the population-risk of fracture (95%CI: 1.9, 2.6).[98] This is consistent with an earlier meta-analysis which showed that the RR of having a hip fracture or a vertebral fracture was twice as high for people with prior history of most types

of fracture, compared to those without a prior fracture.[99] Moreover, the risk of an incident fracture is increased in those with a prior fall, compared to those without a prior fall (HR: 1.69; 95%CI: 1.49, 1.90).[100]

Comorbidities

Comorbidities have also been associated with an increased risk of fractures. A large, multinational, prospective cohort study investigated the effect of comorbidities on fracture risk among 52,960 women participating in the Global Longitudinal Study of Osteoporosis in Women. Participants completed baseline questionnaires regarding co-morbidities and history of fractures. Participants were followed-up annually to identify any incident clinical fractures. All comorbidities were significantly associated with an increased risk of fracture, and conditions that contributed most to fracture prediction were: Parkinson's disease, multiple sclerosis, chronic obstructive pulmonary disease, osteoarthritis, and heart disease.[101] The study did not investigate the potential interaction between comorbidities and medicines used and therefore these associations could be attributed to the medicines taken rather than the conditions themselves.

2.6.4.2 Medication-related factors

Elderly people tend to be prescribed more medicines than younger people; a report from the 2016 HSE found that 19% of young adults (aged 16 to 24 years) reported taking one or more medicines in the last week, whereas this figure was 90% for respondents aged ≥75 years.[102] As people age, they develop altered mechanisms for absorbing and metabolising drugs which can increase the potential for medicines to affect the risk of falls and fractures. The following sections outline some of the main groups of medicines that have been associated with an increased risk of fracture.

Psychoactive medicines

Psychoactive medicines act on the CNS and elicit effects on cognitive processes either therapeutically or as an adverse effect; many studies have reported an increased risk of falls and fractures in people taking these medicines.[83] Psychoactive medicines include the following classes of medicines: antidepressants, opioids, antipsychotics, benzodiazepines, benzodiazepine-related drugs, antiepileptic drugs, anti-Parkinson's medicines and anticholinesterases. Takkouche *et al.* (2007) carried out a random effects meta-analysis of 98 observational studies that reported the RR of fracture in people exposed to several classes of psychoactive medicines.[83] The pooled RR for fracture in people exposed to any psychotropic medicine, compared to those not exposed was 1.48 (95%CI: 1.41, 1.59; n=10). Additional subgroup analyses, by medication class, were carried out and all classes except for hypnotics were found to significantly increase the risk of fracture (Table 2-6).

Table 2-6. Pooled RRs (95%CIs) of fracture and use of various psychotropic medication classes, relative to non-use

Medication class	Number of studies	Pooled RR (95%CI)
Antidepressants	16	1.60 (1.38, 1.86)
Antipsychotics	12	1.59 (1.27, 1.98)
Barbiturate antiepileptic drugs	5	2.17 (1.35, 3.50)
Benzodiazepines	23	1.34 (1.24, 1.45)
Hypnotics	13	1.15 (0.94, 1.39)
Non-barbiturate antiepileptic drugs	13	1.54 (1.24, 1.93)
Opioids	6	1.38 (1.15, 1.66)

Notes: RR, relative risk; CI, confidence interval

High heterogeneity (I^2=0.89) was observed among studies of hypnotics, and after stratifying by study design, a significant positive association was observed for hospital-based case-control studies (pooled RR: 1.53; 95%CI:

1.45, 1.61; n=5). The authors noted that all included studies were susceptible to residual confounding and that potential publication bias was present. However in their sensitivity analyses the results of the meta-analysis for antidepressant medications was robust to this potential publication bias.

Cardiovascular medication

A retrospective, nationwide, cohort study of Danish people aged ≥65 years found that cardiovascular drugs, specifically furosemide (IRR: 1.74; 95%CI: 1.61, 1.89), thiazides (IRR: 1.41; 95%CI: 1.04, 1.16) and digoxin (IRR: 1.18; 95%CI: 1.02, 1.37) were associated with an increased incidence of fragility fractures, compared to people not exposed to these medicines.[103] The association was found to be greatest in the first two weeks from treatment initiation, suggesting that these cardiovascular medicines were likely to increase the risk of falls rather than affecting BMD over extended use.

Corticosteroids and glucocorticoids

Another group of medicines associated with fractures are corticosteroids and glucocorticoids.[90, 104] These are medicines often used to treat inflammatory conditions and can help to improve associated pain. A meta-analysis of 66 studies on BMD outcomes and 23 studies on fracture outcomes found that using daily corticosteroids at doses of more than prednisolone 5mg per day (or equivalent) reduced BMD and increased the risk of fracture during treatment.[105] Additionally, corticosteroid use was found to contribute to fracture-risk in people with inflammatory bowel disease (IBD) in both the short- and long-term.[90] Glucocorticoids were also found to increase the risk of fracture in people with rheumatoid arthritis during periods of use compared to never use (HR: 1.43; 95%CI: 1.21, 1.68), and the effect was found to be

dependent upon the daily dose, duration of treatment and recency of initiation.[104]

2.6.5 Prevention of medication-related fractures

As a large proportion of fractures are attributable to falls, and risk factors are common between falls and fractures,[106] fall prevention strategies can also be viewed as fracture prevention strategies. The WHO's 2007 global report on falls prevention in older age recommends conducting medication reviews and reducing polypharmacy in older people to reduce falls risk.[107] Additionally, several pharmacological agents that increase BMD by decreasing bone resorption or by directly affecting bone remodelling are available to reduce the risk of fracture in people with low BMD; including bisphosphonates, calcitonin, selective oestrogen receptor modulators, oestrogen, calcium and vitamin D, and parathyroid hormone.

Risk assessment tools are available for use in the UK that support healthcare professionals to identify people with an increased risk of fracture so that they can be invited for a fracture-review.[108, 109] These reviews provide the opportunity for healthcare professionals to review medication regimes and inform people about strategies that can help to reduce fracture-risk. Such strategies may include holding the handrail on stairs, identifying trip hazards, taking regular exercise, ensuring sufficient intake of dietary calcium and exposure to sunlight (for the synthesis of vitamin D).

As established in section 2.6.3, opioid analgesics are associated with an increased risk of fracture, and this may be a potential modifiable risk factor for fracture that can be addressed during fracture-review. Importantly, the proportion of people prescribed opioid analgesics in the UK has risen over the

past two decades,[5, 110, 111] which combined with an ageing population, may further increase the incidence of fractures. The following section will outline commonly used measures to describe opioid utilisation and will describe changes in opioid utilisation globally, and in the UK, over recent decades.

2.7 Opioid utilisation

2.7.1 Measuring opioid utilisation

Opioid utilisation studies use varying measures to describe population-level and patient-level trends in opioid utilisation, below is an overview of utilisation measures that are frequently used to describe opioid use in studies examining utilisation patterns.

Defined daily doses and OMEQ dose

Opioid consumption can be measured in units referred to by the WHO as defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.[1] At a population level, DDDs have been shown to have limitations in determining opioid consumption, such as not reflecting daily use for some clinical indications where doses may differ to those used for the main indication, for example, the DDD of morphine is based upon its use in cancer pain rather than for CNCP conditions.[112] Using the DDD in opioid utilisation research can be problematic when investigating opioid utilisation in specific populations or individual people as the pain conditions for which opioids are used and severity of pain may vary. These factors, in addition to the age, weight and clinical characteristics (e.g., renal function) of people may influence their recommended daily dose of an opioid. Consequently, the DDD may not accurately reflect the prescribed daily dose.

Clinical equianalgesic ratios can be used to convert opioid doses across drugs and formulations to a total OMEQ dose. Equianalgesic ratios represent the analgesic potency of an opioid drug-formulation combination relative to oral morphine; there remains to be a consensus on the clinical equianalgesic ratios used in clinical practice and research. The OMEQ dose is calculated by multiplying the dose (mg) of a specific opioid formulation by its respective equianalgesic ratio. Using OMEQs in addition to DDDs facilitates comparison between users of all opioids, particularly for strong and weak opioids, and avoids assumptions regarding clinical indication.[113]

Chronic or long-term use

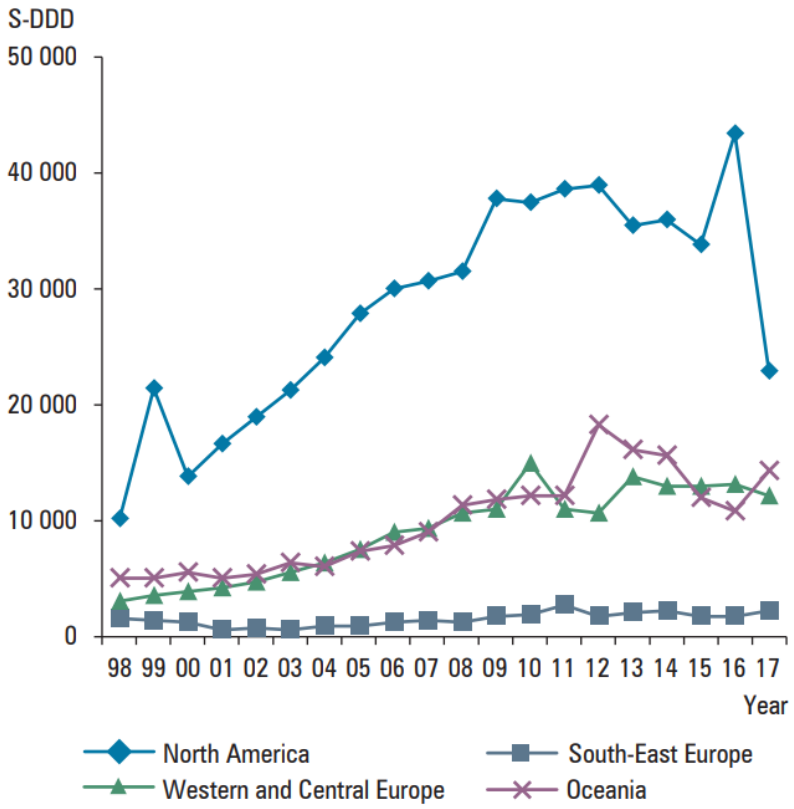
Various methods have been used in health record data and administrative claims databases to classify people based on their opioid utilisation. Long-term use of opioids refers to the duration of treatment, and in observational opioid utilisation research, long-term use is commonly set at three or more prescriptions for opioids within the first 90 days of an episode of treatment.[14, 62, 114] Defining and measuring patient-level utilisation in this way does not take into account adherence to treatment or variations in the dose prescribed.

Persistence

Definitions of persistence combines measures of opioid dose, duration of use, frequency of supplies and the distribution of prescriptions over time, to describe opioid utilisation. Measures of persistence provide more complete estimates of opioid-taking behaviour.[115] Currently, there are no studies in a UK population that have described opioid utilisation in terms of persistency.

2.7.2 Global trends

The use of opioids has increased over the last two decades in countries such as the United States of America (US), Canada, Australia, Norway and the UK.[5-9] Observational studies of opioid utilisation have used large datasets of health records, employing epidemiological study designs to characterise trends in prescribing. Concerns regarding these trends were raised following a sharp increase in the amount of opioids consumed in the US, as a result of a number of influences such as drug marketing, loose regulatory requirements, and improvements in the management of cancer pain.[48, 116, 117] International Narcotics Control Board (INCB) statistics show that North American countries have the highest opioid consumption globally; more than treble that of Europe, however from 2016 opioid consumption has declined in North American countries as shown in Figure 2-4.[118]



Notes: S-DDD, defined daily doses for statistical purposes; figure obtained from INCB (2018).[118]

Figure 2-4. Consumption of opioids for pain management in regions with the highest consumption

2.7.3 UK prescribing trends

A UK cross-sectional study of strong opioid prescribing between 2000 and 2010 showed an overall increase in the utilisation of strong opioids; demonstrating a 466.2% increase in the number of strong opioid users during the study period.[5] In addition, 83.9% of users were found to not have a diagnosis of cancer, thereby meaning that the majority of the study population were non-cancer users. Both DDDs and OMEQs were used to measure opioid consumption, showing that in the UK, the majority of both cancer and non-cancer patients were prescribed a low daily OMEQ dose (≤50 mg/day).

A similar trend was observed in Bedson *et al's* (2016) retrospective observational study of UK people prescribed opioids in the long-term for musculoskeletal conditions between 2002 and 2013.[110] Long-term opioid use was defined as three or more opioid prescriptions within a 90-day period following opioid-initiation.

The incidence of long-term prescribing increased by 38% between 2002 and 2009 but decreased slightly from 2011 onwards. There was an increase in the prescribing of long-acting opioid formulations for people who had taken opioids for >2 years over the study period (3.5% in 2004; 22.6% in 2013). Additionally, there was an increase in the proportion of long-acting formulations initiated early on in treatment (i.e., within 90 days of opioid initiation) (2.3% in 2002; 9.9% in 2013).

These observed trends are supported by UK population-level data of dispensed prescriptions. The Health and Social Care Information Centre (HSCIC), now NHS Digital, reported an increase between 2005 and 2015 for

prescription items dispensed for strong opioids such as oxycodone, morphine and buprenorphine (10.5%, 9.2% and 8.9% increase respectively).[119]

Further to this, a recently published report by Public Health England examined trends in the use of dependence forming medicines using the CPRD database; opioid analgesics was one of the drug classes studied. The report found that, in 2014, 34% of people were continuously prescribed opioids for a duration >30 days, equating to 1.8% of the CPRD population.[120] The definition of 'continuous prescribing' permitted a 35-day gap between prescriptions, and therefore some of these longer-term continuous opioid users may have actually been intermittent users of opioids. Additionally, the authors of the report acknowledged the need for further research that examines trends in opioid utilisation with a consideration of the OMEQ doses prescribed, and that patient-level studies of opioid utilisation are needed to further understand the individual characteristics of people prescribed opioids and duration of opioid use.

2.7.3.1 Patient-level trends

There have been few patient-level studies of opioid utilisation in the UK, [5, 110, 121-124] with the majority being cross-sectional in design, and just one longitudinal study.[123] This retrospective cohort study followed new users of opioids with a diagnosis of CNCP between 2006 and 2011 and found that most people (89.5%) were initiated on weak opioids and that the mean duration of opioid use was less than six months. These findings suggest that in the UK, opioids are typically used at low OMEQ doses and for short durations. However, due to the paucity of evidence, more longitudinal studies of patient-level opioid utilisation are needed.

2.8 Research aims and objectives

Further information is needed on the utilisation of opioids in the UK, particularly longitudinal patient-level trends and descriptions of opioid persistency. Moreover, there is currently no consensus to conclude whether opioids increase the risk of fracture over prolonged exposure or in the short-term, and confounding is a concern in existing studies. Further investigation is required to examine the effect of duration of opioid use on fracture-risk whilst providing better control for potential confounding. Therefore, this PhD thesis sought to measure and describe opioid utilisation in the UK, and to investigate the effects of opioid use on the risk of bone fractures. The objectives included:

1. To identify, summarise and appraise existing studies that have investigated the association between opioid use and bone fracture.

2. To measure and describe population-level and patient-level opioid utilisation in a cohort of adults prescribed opioids in the UK.

3. To identify, describe and estimate the incidence of fractures in adults prescribed opioids.

4. To investigate the association between opioids and bone fractures and examine the effects of opioid duration and dose.

Chapter 3: The association between opioid use and fractures: a systematic review and meta-analyses of observational studies

3.1 Abstract

Background

Opioids have been associated with an increased risk of fracture across several observational studies, but methodological approaches are inconsistent. This review aimed to summarise the methodological approaches of these studies and synthesise the risk of fracture by meta-analysis.

Methods

The MEDLINE, EMBASE and CINAHL PLUS databases were searched using keywords and medical subject headings (MeSH) relating to opioids, fractures, and observational designs. Included studies reported risk estimates for fractures in adults exposed to opioids. Data relating to study objectives, population, design, exposure definition, comparator and risk estimates with 95%CIs were extracted for each study. Risk of bias was assessed using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool. Pooled HRs and ORs for fractures, comparing opioid use and non-use were synthesised by random-effects meta-analyses. Heterogeneity was explored using the I^2 statistic and subgroup analyses.

Results

The 26 included studies varied by study design, population, exposure definitions and potential confounding. Of the 21 studies that compared opioid use to non-use, pooled HRs from cohort studies showed a significantly increased risk of unspecified fractures (pooled HR: 1.39; 95%CI: 1.20, 1.62; n=7) and hip fractures (pooled HR: 1.57; 95%CI: 1.18, 2.09; n=8). Similarly, case-control and nested case-control studies also found a significantly increased risk of unspecified fractures (pooled OR: 2.16; 95%CI: 1.18, 3.98;

n=3) and hip fractures (pooled OR: 1.48; 95%CI: 1.26, 1.72; n=6) related to opioid use.

Conclusions

Opioid use is associated with an increased risk of fracture compared to non-use. Current evidence is limited due to potential confounding and inadequate modelling of opioid exposure.

3.2 Introduction

Existing RCTs have been unable to demonstrate the long-term safety of prescription opioids. Despite trials providing the gold-standard of study designs in terms of proving a cause-effect relationship, their utility for assessing long-term safety is limited because of short trial durations, selected patient populations and treatment changes. Accordingly, observational studies are relied upon to make inferences about the long-term safety of prescription opioids. Evidence from observational studies suggests an association between opioids and fractures.[13, 14] Moreover, several systematic reviews have reported an association between opioids and an increased risk of fracture,[49, 83, 125-128] however, just two of these have provided summary estimates for the association,[127, 128] and the methodological approaches between these studies have been inconsistent.

Teng *et al*. (2015) reported a systematic review and meta-analysis of eight cohort studies that were published up to 2014, which found a significant positive association between opioid use and bone fracture (pooled RR: 1.88; 95%CI: 1.51, 2.34).[127] However, Teng *et al*'s review only included cohort studies, and operational definitions for opioid exposure were not reported.

Ping *et al.* (2015) published a systematic review and meta-analysis of ten observational studies that were published up to June 2015; [128] and found that opioid users had a significantly increased risk of hip fracture (pooled RR: 1.54; 95%CI: 1.34, 1.77) compared with non-users, albeit with a lower RR. Ping *et al.* (2015) only included studies reporting hip fracture outcomes, this has important limitations as fracture site may elucidate whether people taking opioids are more prone to fall-related or osteoporotic-related fractures,[129] and indicate where future intervention can be made by healthcare professionals.

Differences between studies combined by meta-analytic techniques need to be investigated to provide confidence in summary risk estimates.[130] The aforementioned meta-analyses reported high levels of heterogeneity when combining studies and did not explore important methodological differences between their included studies. Consequently, there is a lack of understanding of how methodological approaches, such as definitions used to classify opioid exposure may bias the interpretation of summary risk estimates. Without this knowledge, the risk of fracture attributed to opioids may be under- or over-estimated due to systematic differences between studies. Currently, no systematic review and meta-analysis has included all available observational studies reporting the relationship between opioids and fractures to any anatomical site, nor has there been a full summary and appraisal of the methods adopted by such studies. Therefore, a meta-analysis that presents risk estimates with a thorough consideration of demographic and methodological heterogeneity is required.

3.3 Aims and objectives

The aim of this review was to summarise the risk estimates and critically appraise the methodology of observational studies reporting the risk of fracture associated with opioid use. The objectives included:

1. To identify all available observational studies investigating fracture outcomes associated with opioid use.

2. To summarise and critique the methodological approaches adopted by the identified observational studies.

3. To summarise the risk estimates reported by the identified studies - comparing opioid use to non-use, and where possible, perform a meta-

analysis to provide a precise risk estimate for opioid-related fractures, accounting for important differences between studies by subgroup analyses.

3.4 Methods

The protocol for this systematic review was registered in the PROSPERO database (CRD42018083354) (see Appendix A),[131] and was written in accordance with PRISMA-P guidelines.[132] The report of this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[133, 134]

3.4.1 Search strategy

An electronic database search was conducted by applying structured search strategies in MEDLINE (from 1946 to 16th March 2018; Appendix B), EMBASE (from 1974 to 16th March 2018; Appendix C) and CINAHL Plus (from 1937 to 16th March 2018; Appendix D). The search strategies included keywords and MeSH terms relating to prescription opioids, fracture, and analytic observational study designs, citations were limited to published full-text original articles and research letters, published in English language and conducted in humans. A medical research librarian (Isla Kuhn, IK) checked each search strategy to ensure appropriate sensitivity and specificity prior to retrieving citations from each database. The reference lists for each full-text article meeting the inclusion and exclusion criteria were hand-searched to identify any further potentially relevant citations.

3.4.2 Inclusion and exclusion criteria

Studies were included if they met the following inclusion criteria: (1) published full-text observational studies or open-label extension studies; (2) participants aged ≥18 years; and (3) reported either an OR, RR, IRR or HR and corresponding 95%CIs for the association between exposure to prescription opioids and fracture. Studies were excluded if: (1) the study population was exclusive to pregnant women, people undergoing palliative care or end of life care, or those with an opioid use disorder; or (2) reported an effect estimate for exposure to opioid substitution therapy or illicit opioids (Table 3-1).

Table 3-1. Inclusion and exclusion criteria for study eligibility

Category	Inclusion criteria	Exclusion criteria
Population	Adults (aged ≥18 years)	People aged <18 years; pregnant women. People with: cancer; receiving treatment for an opioid use disorder; or undergoing end of life care
Exposure	Prescription opioid analgesics included in section N02A of the WHO ATC[(1)]	Opioid substitution therapy; illicit opioids e.g., heroin use or opioids obtained illegally
Outcome	Studies reporting a risk estimate (OR, RR, IRR or HR) for fracture	Studies that do not report one of these risk estimates for this outcome
Types of studies	Published observational studies or open-label extension studies	Any other study design
Type of publication	Published full-text original articles and letters reporting original research	Conference proceedings, abstracts, commentaries, letters not reporting original research, editorials analysis, reviews, clinical guidelines
Limitations	English language, human studies	Non-English language, animal studies

3.4.3 Study selection

All identified citations were exported from the databases and collated in EndNote X7 (Thomson Reuters, Philadelphia, 2013) where duplicate citations

were identified and removed. Titles and abstracts underwent a preliminary screen by two independent reviewers (Emily Peach, EP and Andrew Cooper, AC) using the reviewer screening guideline to ensure consistency in the screening process (Appendix E). Decisions made by each reviewer for each citation were recorded in Microsoft Excel; agreement between the two reviewers at this stage was assessed by calculating a Cohen's kappa coefficient using a statistical program - Stata/MP 15 (StataCorp, Texas, 2017); a coefficient of 0.61 or above indicates substantial agreement between the reviewers' decisions.[135]

Eligible studies identified from the preliminary screen then underwent full-text review; full-text articles were retrieved and assessed for eligibility by each reviewer (EP and AC) in accordance with the inclusion and exclusion criteria. Any disagreements that arose between the two reviewers during study selection were resolved through discussion, or with a third reviewer (Roger Knaggs, RK) when this was necessary.

3.4.4 Data extraction

Data were extracted from the included full-text articles by two independent reviewers (EP and AC), including: first author; year of publication; publication title; study objective; country of study population; age, sex and specified pain condition (if relevant) of study participants; study design; comparison group; duration of follow-up; definition of opioid exposure; definition of fracture cases; method of statistical analysis; covariates adjusted for in the analysis; OR, RR, IRR, or HR reported and corresponding 95%CIs; results of any subgroup analyses. Any disagreements that arose between the two reviewers during data extraction were resolved through discussion, or with a third reviewer (RK) when this was necessary.

3.4.5 Risk of bias assessment

The ROBINS-I tool was used to assess bias due to confounding, selection of participants, classification of intervention, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result.[136] The ROBINS-I was selected over other available quality assessment tools due to its comprehensive assessment of quality relating to non-randomised studies.

Each included study was independently assessed by two reviewers (EP and AC) using a ROBINS-I assessment form (Appendix F) which was developed from the standardised ROBINS-I guideline to record reviewers' judgements for each domain of bias. The judgements for each of these seven domains of bias were combined into one overall rating for risk of bias, ranging between five categories: no information; critical; serious; moderate; and low risk of bias. Any disagreements were resolved through discussion, or with a third reviewer (RK).

3.4.6 Data synthesis and statistical analysis

All eligible articles were included in the narrative summary, regardless of their overall judgement for risk of bias. Studies reporting risk estimates for fracture with use of prescription opioids compared to non-use were included in the meta-analyses to ensure that results for the same comparisons were synthesised. Where multiple articles reported data from the same study cohort the most recent publication was selected to be included in the meta-analyses, providing this was of equal or greater statistical power (i.e., larger sample size or number of cases) than the earlier study.

For the primary meta-analyses, results from studies of the same design (i.e., cohort vs. case-control, and nested-case control) reporting the same risk estimates (i.e., HR vs. OR) for fractures of an unspecified anatomical site were combined. In a secondary meta-analysis, studies of the same design, reporting the same risk estimates for fractures of the hip were combined.

A random-effects model using the generic inverse variance method was used to generate a pooled risk estimate from fully-adjusted ORs, RRs, IRRs, HRs and their corresponding 95%CIs. As the risk of fracture in each group is considered rare (<20%), ORs were considered to approximate RRs so that these risk estimates could be combined.[137]

Statistical heterogeneity was assessed using I^2 tests, a value between 50% and 75% was taken to indicate moderate between-study variation, and I^2 values over 75% indicated high levels of heterogeneity.[130] Any moderate or high between-study heterogeneity was explored using subgroup analyses; grouping studies by methodological and demographic characteristics. Methodological subgroups included: definition of exposure (i.e., recent use vs. ever use vs. regular use vs. time-varying use) and study objective (i.e., primary vs. exploratory). Primary objectives are those that are primarily aimed to assess the relationship between opioid use and fracture; exploratory objectives refer to studies that did not specify this as the primary research aim. Demographic subgroup analyses included: age (i.e., any age vs. aged ≥60 years); sex (i.e., both sexes vs. women only vs. men only); and region of study (i.e., Europe vs. North America).

Cumulative meta-analyses were performed to assess changes in the pooled risk estimates over time by adding studies to the model (by year of

publication) to enable identification of influential studies. Sensitivity analyses were performed to: (1) assess the effect of removing influential studies and (2) assess the effect of removing studies with a critical risk of bias. Publication bias was assessed by visual inspection of funnel plots and calculation of Egger's test for asymmetry.[138]

All statistical analyses were carried out using the statistical software - Stata/MP 15 (StataCorp, Texas, USA). All p-values <0.05 were considered statistically significant.

3.5 Results

3.5.1 Selection of studies

Overall, 13,404 citations were identified from the electronic database searches. After removing duplicate citations using the EndNote 'Find Duplicates' function, 10,722 citations remained. Of those, 10,662 citations were excluded following the preliminary screening of titles and abstracts (Figure 3-1), and a total of 60 eligible articles were identified. There was substantial agreement (99.75%) between the two reviewers at the title and abstract screening stage, with a Cohen's kappa of 0.71 (95%CI: 0.60, 0.80). An additional 12 articles were identified from hand-searching the reference lists of the 60 eligible articles. In total, 72 articles were selected for full-text review, and of these, 46 articles were excluded for the reasons listed in Figure 3-1,[139-184] and 26 articles were included in the narrative review.[13, 14, 86-90, 185-203]

Of the 26 included articles, two studies reported data from the same study cohorts as other more recently published articles, and were excluded from the meta-analyses.[195, 200] In addition, three studies that did not compare opioid

use to non-use were excluded,[189, 190, 192] 21 studies were included for the meta-analyses.[13, 14, 86-90, 185-188, 191, 193, 194, 196-199, 201-203]

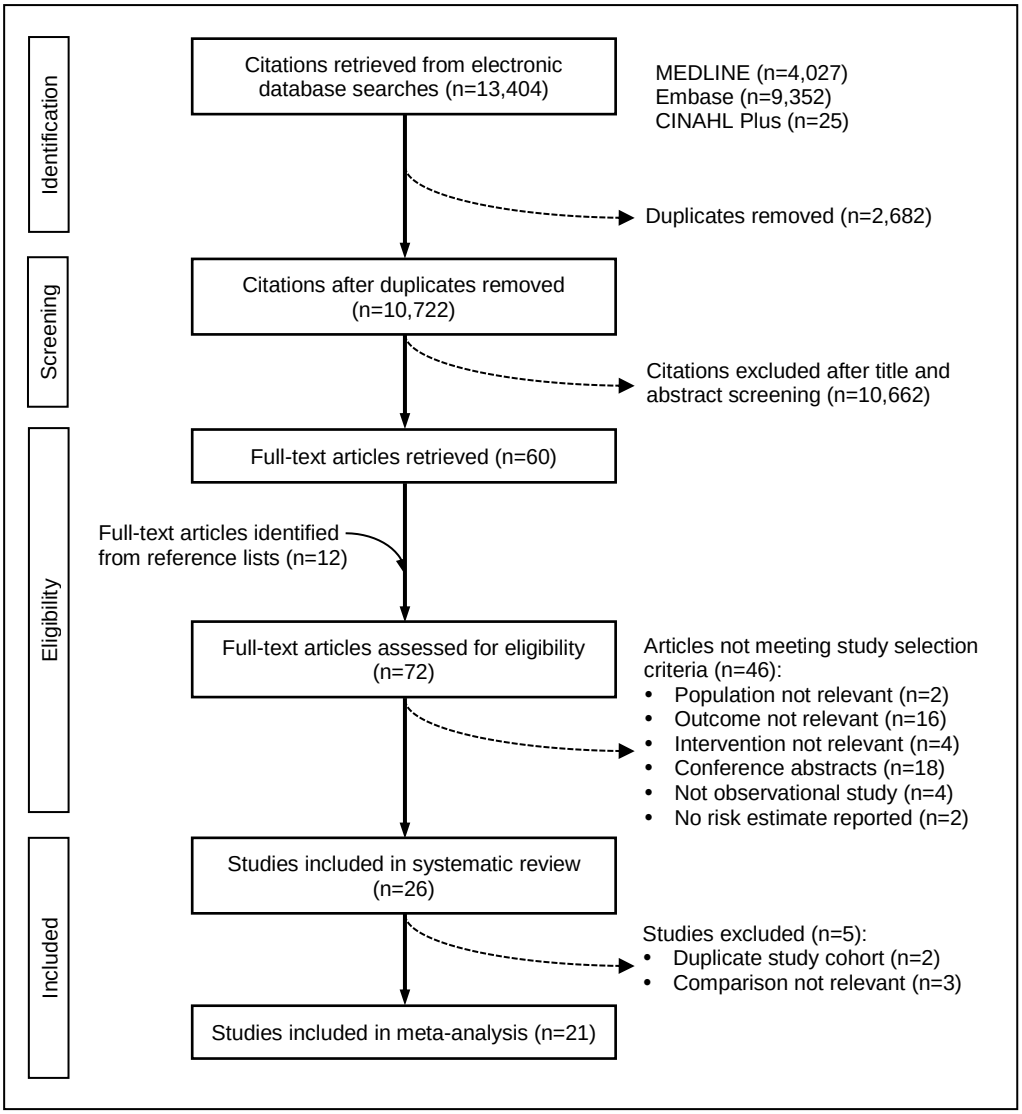


Figure 3-1. Selection of included studies

3.5.2 Characteristics of the included studies

Study design

All included studies were published between 1991 and 2018, and study durations ranged between nine months and 14 years. Ten studies reported a primary objective to assess the relationship between exposure to opioids and risk of fracture (Appendix G);[13, 14, 89, 192, 193, 196-198, 200, 202] and the remaining 16

studies did not specify this as the primary objective for their study (Appendix H). A variety of observational study designs were identified from the 26 included studies, consisting of case-control (n=5),[86, 89, 193, 194, 203] nested case-control (n=3),[13, 191, 202] case-crossover (n=1),[195] prospective cohort (n=7),[87, 88, 185, 188, 196, 197, 199] and retrospective cohort studies (n=10).[14, 90, 186, 187, 189, 190, 192, 198, 200, 201] Characteristics of the included studies are shown in Table 3-2 and Table 3-3.

All included studies made between-participant comparisons, with the exception of one case-crossover study that used participants' own unexposed time to make within-participant comparisons.[195] Of the 25 studies that made between-participant comparisons, 22 studies compared opioid users to non-users,[13, 14, 86-90, 185-188, 191, 193, 194, 196-203] two studies compared opioid users to NSAID users,[189, 192] and one study compared hydrocodone users to users of all other opioids.[190]

Study population

Half of the studies were conducted in North America (n=13),[14, 88, 89, 188-190, 192, 196-198, 200-202] and the rest in Europe (n=10),[13, 86, 87, 90, 185-187, 191, 199, 203] Australia (n=2),[194, 195] and Latin America (n=1).[193] Of the 26 included studies, 16 studies restricted their study population to adults aged ≥60 years.[14, 86-89, 187, 188, 191-199] The majority of studies included both males and females, except for three studies that included only males,[196, 200, 203] and three studies that included only females.[88, 185, 199]

Table 3-2. Characteristics of case-control, nested case-control and case-crossover studies

First author, publication year	Country, duration	Primary objective*	Sample size	Age, sex, diagnosis	Fracture sites	Fracture identification	ROBINS-I rating
Case-control studies							
Machado-Duque, 2017[193]	Colombia, 1yr	✓	Cases: 287 Controls: 574	Age >65yrs Males & females	Hip	ICD codes	Critical
Leach, 2017[194]	Australia, 4yrs	×	Cases: 8,828 Controls: 35,310	Age >65yrs Males & females	Hip	ICD codes	Critical
Abrahamsen, 2009[203]	Denmark, 1yr	×	Cases: 15,716 Controls: 47,149	Age ≥50yrs Males	Any, Hip, Spine	ICD codes	Critical
Shorr, 1992[89]	Canada, 8yrs	✓	Cases: 4,500 Controls: 24,041	Age ≥65yrs Males & females	Hip	ICD codes	Critical
Jensen, 1991[86]	Denmark, 9 months	×	Cases: 200 Controls: 200	Age ≥60yrs Males & females	Hip	ICD codes	Critical
Nested case-control studies							
Acurcio, 2016[202]	Canada, 5yrs	✓	Cases: 1,723 Controls: 8,046	Age ≥20yrs Males & females Rheumatoid arthritis	Non-vertebral	ICD codes Procedure codes Billing codes	Critical
Snacken, 2015[191]	Belgium, 7.5yrs	×	Cases: 101 Controls: 101	Age >70yrs Males & females Diabetes	Any	Medical chart review	Critical
Li, 2013[13]	United Kingdom, 18yrs	✓	Cases: 21,739 Controls: 85,326	Age 18-80yrs Males & females	Hip, Humerus Wrist	Read codes	Serious
Case-crossover studies							
Leach, 2015[195]	Australia, 3yrs	×	Cases: 8,828	Age >65yrs Males & females	Hip	ICD codes	Critical

Notes: ROBINS-I, Risk of Bias in Non-randomised Studies of Interventions; ICD, International Classification of Diseases
*Primary objective refers to whether a study's primary aim was to test for an association between prescription opioids and fracture

Table 3-3. Characteristics of prospective and retrospective cohort studies

First author, publication year	Country, duration	Primary objective*	Sample size	Age, sex, diagnosis	Fracture sites	Fracture identification	ROBINS-I rating
Prospective cohort studies							
Krebs, 2016[196]	United States, 9yrs	✓	2,902	Age ≥65yrs Males Persistent pain	Any Hip	Patient/carer report	Serious
Vestergaard, 2012[185]	Denmark, 10yrs	×	2,016	Age 45-58yrs Females	Any	Patient/carer report	Serious
Dobnig, 2007[199]	Austria, 2yrs	×	1,664	Age >70yrs Females Nursing home resident	Non-vertebral Hip	Patient/carer report	Serious
Spector, 2007[188]	United States, 1yr	×	2,711	Age ≥65yrs Males & females Nursing home resident	Any	Patient/carer report	Serious
Kamal-Bahl, 2006[197]	United States, 1.5yrs	✓	362,503	Age ≥65yrs Males & females	Hip	ICD codes	Serious
Ensrud, 2003[88]	United States, 9yrs	×	8,127	Age ≥65yrs Females	Non-vertebral Hip	Patient/carer report	Serious
Guo, 1998[87]	Sweden, 6yrs	×	1,608	Age ≥75yrs Males & females	Hip	ICD codes	Serious
Retrospective cohort studies							
Grewal, 2018[198]	Canada, 5yrs	✓	13,012	Age ≥65yrs Males & females Peripheral vertigo	Any	ICD codes	Critical
Tolppanen, 2016[186]	Finland, 7yrs	×	67,072	Age ≥34yrs Males & females Alzheimer's disease	Hip	ICD codes	Critical
Bethel, 2016[201]	United States, 10yrs	×	22,516	Adults Males & females Spinal cord injury	Any, Hip, Femur, Tibia/fibula	ICD codes	Serious

Notes: footnote on next page

Table 3 3. Characteristics of prospective and retrospective cohort studies [continued]

First author, publication year	Country, duration	Primary objective*	Sample size	Age, sex, diagnosis	Fracture sites	Fracture identification	ROBINS-I rating
Thorell, 2014[187]	Sweden, 1yr	×	38,407	Age ≥75yrs Males & females	Hip	ICD codes	Serious
Carbone, 2013[200]	United States, 5yrs	✓	7,447	Adults Males Spinal cord injury	Lower limb	ICD codes	Serious
Miller, 2011[192]	United States, 7yrs	✓	17,310	Age ≥65yrs Males & females Arthritis	Composite: hip/ humerus/ ulna/ wrist	ICD codes Procedure codes Billing codes	Serious
Solomon, 2010a[190]	United States, 6yrs	×	12,840	Adults Males & females Arthritis	Composite: hip/ pelvis/ wrist/ humerus	ICD codes Procedure codes Billing codes	Serious
Solomon, 2010b[189]	United States, 9yrs	×	31,375	Adults Males & females Non-cancer pain	Composite: hip/ pelvis/ wrist/ humerus	ICD codes Procedure codes Billing codes	Serious
Saunders, 2010[14]	United States, 5yrs	✓	2,341	Age ≥60yrs Males & females CNCP	Non-vertebral	ICD codes	Serious
Card, 2004[90]	United Kingdom, 14yrs	×	16,550	Adults Males & females IBD	Hip	Read codes OXMIS codes	Serious

Notes: ROBINS-I, Risk of Bias in Non-Randomised Studies of Interventions; ICD, International Classification of Diseases; CNCP, chronic non-cancer pain; IBD, inflammatory bowel disease; OXMIS, Oxford Medical Information Systems.
*Primary objective refers to whether a study's primary aim was to test for an association between prescription opioids and fracture

Identification of fractures

Hip fractures were the most frequently reported outcome of interest; 16 studies reported risk estimates for hip fractures.[13, 86-90, 186, 187, 193-197, 199, 201, 203] Eleven studies reported risk estimates for fractures of unspecified anatomical sites,[14, 88, 185, 188, 191, 196, 198, 199, 201-203] and four studies reported risk estimates for a composite of fracture sites,[13, 189, 190, 192] including fractures of the hip/pelvis, humerus/ulna and wrist; sites typically associated with fragility fracture.[204] Additional fracture sites with reported risk estimates included: humerus,[13] wrist,[13] and other lower limb sites.[200, 201]

In 14 studies, fractures were identified by ICD codes,[14, 86, 87, 89, 186, 187, 193-195, 197, 198, 200, 201, 203], and four studies used ICD codes in combination with procedure codes and billing codes.[189, 190, 192, 202] Two UK studies used Read and Oxford Medical Information Systems (OXMIS) codes,[13, 90] one study reviewed medical charts,[191] and five prospective studies used patient or carer reports to identify fractures.[88, 185, 188, 196, 199]

Definition of opioid exposure

The included studies used different operational definitions in terms of time-period and duration of exposure assessment, intensity, and frequency of use in order to measure the presence of an opioid prescription or opioid utilisation. Furthermore, this information came from a variety of sources: pharmacy records, prescribing records, healthcare claims, medical charts and patient/carer reports. For studies that employed more than one definition of exposure, only the definition used in their primary analyses are reported.

Table 3-4. Exposure definitions and data sources used by case-control, nested case-control and case-crossover studies

First author, year	Measure of utilisation	Data source	Time-point before fracture	Intensity
Recent use				
Acurcio, 2016[202]	Reimbursed	Regié de l'assurance maladie du Québec (RAMQ)	≤30 days	-
Jensen, 1991[86]	Administered	Patient report	≤14 days	-
Leach, 2015[195]	Reimbursed	Australian Government Department of Veterans' Affairs	≤14 days	-
Leach, 2017[194]	Reimbursed	Australian Government Department of Veterans' Affairs	≤14 days	-
Li, 2013[13]	Prescribed	CPRD	≤30 days	-
Machado-Duque, 2017[193]	Dispensed	Audifarma S.A.	≤30 days	-
Shorr, 1992[89]	Dispensed	Hospital pharmacy records	≤30 days	-
Ever use				
Abrahamsen, 2009[203]	Dispensed	Danish National Prescriptions Database	≤5 years	≥60 DDDs
Snacken, 2015[191]	Administered	Medical chart	Any, before or after fracture	-

Notes: CPRD, Clinical Practice Research Datalink; DDD, Defined Daily Dose

Of the nine case-control, nested case-control and case-crossover studies, four studies defined exposure as presence of an opioid within 30 days prior to fracture;[13, 89, 193, 202] three studies as presence of an opioid within 14 days prior to fracture;[86, 194, 195] one study as more than 60 DDDs of opioid prescriptions dispensed over the 5-year period prior to fracture;[203] and one nested case-control study as any record during follow-up, before or after fracture (Table 3-4).[191]

Of the 17 prospective and retrospective cohort studies, seven studies defined exposure as ever use of an opioid during or before follow-up;[87, 185-188, 199, 200] one study as regular opioid use, defined as more than one prescription in each year of follow-up;[90] three studies as continuous prescription coverage

for each day of follow-up, from initiation to 7-15 days after the final available dose;[189, 190, 192] and six studies as time-varying opioid use, determined by exposure status at specified intervals during follow-up (Table 3-5).[14, 88, 196-198, 201]

3.5.3 Risk of bias

Most studies (n=16) were rated as having a 'serious' risk of bias; the remaining ten studies were rated as having a 'critical' risk of bias (see Table 3-2 and Table 3-3). Potential for confounding was particularly prominent across studies that made between-participant comparisons. Measurement of potential confounding factors varied substantially across studies; the most commonly measured confounders were age, sex, comorbidities, use of other medication and prior fracture (Figure 3-2). In addition to potential for confounding, most did not report sufficient detail regarding how missing data were handled, which may have introduced further bias.

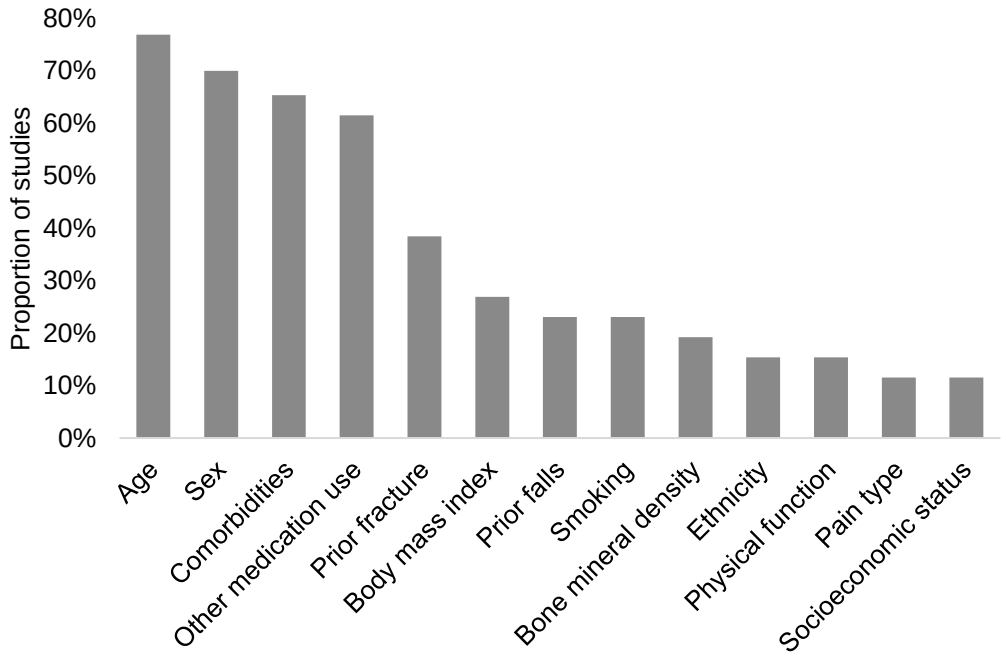


Figure 3-2. Potential confounding factors commonly reported by the included studies

Table 3-5. Exposure definitions and data sources used by prospective and retrospective cohort studies

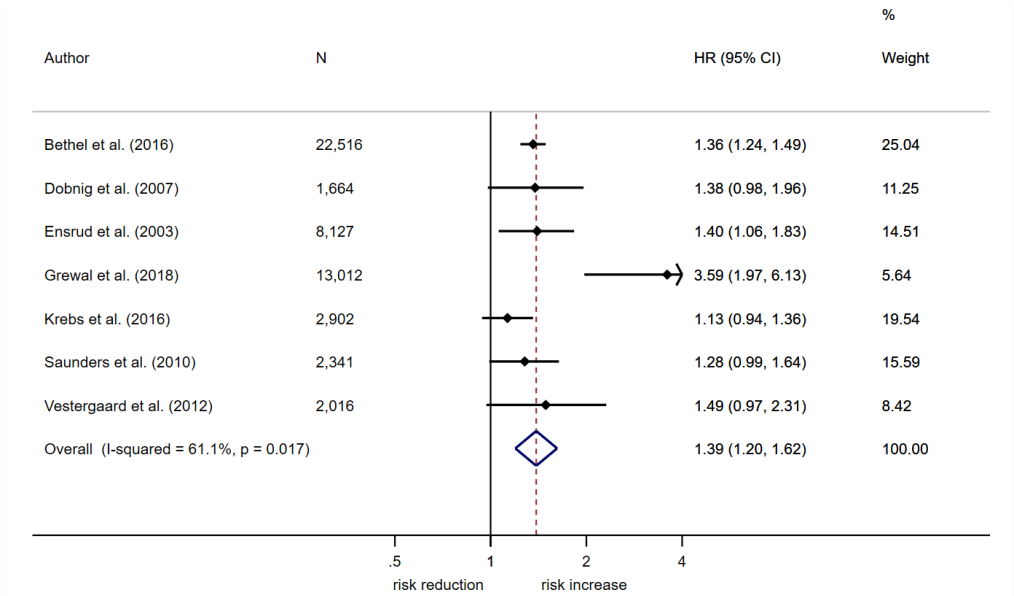
First author, year	Measure of utilisation	Data source	Period of exposure ascertainment	Length of assessment	Time-varying interval
Ever use					
Carbone, 2013[200]	Dispensed	VA Pharmacy Benefits Management Group Prescription Database	Follow-up	≤5 years	-
Dobnig, 2007[199]	Administered	Medical chart	At cohort entry	1 day	-
Guo, 1998[87]	Administered	Patient or carer report	Prior to cohort entry	≤14 days	-
Spector, 2007[188]	Administered	Medical chart	Follow-up	1 year	-
Thorell, 2014[187]	Dispensed	Apotekt AB	Follow-up	1 year	-
Tolppanen, 2016[186]	Reimbursed	Finnish National Prescription Register	Prior to cohort entry	≤5 yrs	-
Vestergaard, 2012[185]	Administered	Patient report	At any follow-up visit	10 years	-
Continuous or regular use					
Card, 2004[90]	Prescribed	CPRD	Follow-up (1-year intervals)	3.7 years*	-
Miller, 2011[192]	Dispensed	Pharmacy records	Follow-up	≤7 years	-
Solomon, 2010a[190]	Dispensed	Pharmacy records	Follow-up	137 days*	-
Solomon, 2010b[189]	Dispensed	Pharmacy records	Follow-up	≤30 & ≤180 days	-
Time-varying use					
Bethel, 2016[201]	Dispensed	VA Pharmacy Benefits Management Group Prescription Database	Follow-up	6.2 years*	3 months
Ensrud, 2003[88]	Administered	Patient report	Prior to each follow-up visit	≤14 days	1 year
Grewal, 2018[198]	Reimbursed	Ontorio Drug Benefit Database	Follow-up	≤90 days	1 day
Kamal-Bahl, 2006[197]	Reimbursed	MarketScan Medicare Supplemental and Coordination of Benefits Database	Prior to each fracture event	≤14 days	Variable
Krebs, 2016[196]	Administered	Patient report	At each follow-up visit	9.1 years*	3 years
Saunders, 2010[14]	Dispensed	Group Health Cooperative	Follow-up (3-month intervals)	2.7 years*	1 month

Notes: * mean/median follow-up duration; CPRD, Clinical Practice Research Datalink

3.5.4 Risk of fracture associated with opioids

Risk of fracture to unspecified sites

Of the 21 studies that compared opioid users to non-users, seven cohort studies reported HRs for the risk of fracture in unspecified anatomical sites.[14, 88, 185, 196, 198, 199, 201] The pooled results of these seven studies showed a significantly increased risk of an unspecified fracture in users of opioids (pooled HR: 1.39; 95%CI: 1.20, 1.62) with moderate heterogeneity (I^2: 61.1%; p=0.017) (Figure 3-3). Additionally, one cohort study reported a significantly increased risk of an unspecified fracture, comparing opioid users to non-users. (OR: 1.52; 95%CI: 1.03, 2.24).[188] Three case-control and nested case-control studies reported significant ORs;[191, 202, 203] suggesting an increased risk between unspecified fractures and opioid use (pooled OR: 2.16; 95%CI: 1.18, 3.98) with high heterogeneity (I^2: 95.9%; p<0.001) (Figure 3-4).



Notes: The small black diamonds and horizontal lines correspond to studies' risk estimates and 95%CIs. The blue diamond represents the pooled risk estimate and 95%CIs. The solid vertical line resembles no effect and the red, dashed vertical line represents the pooled risk estimate.

Figure 3-3. Pooled HRs for fracture to unspecified anatomical sites, comparing opioid users to non-users in seven cohort studies

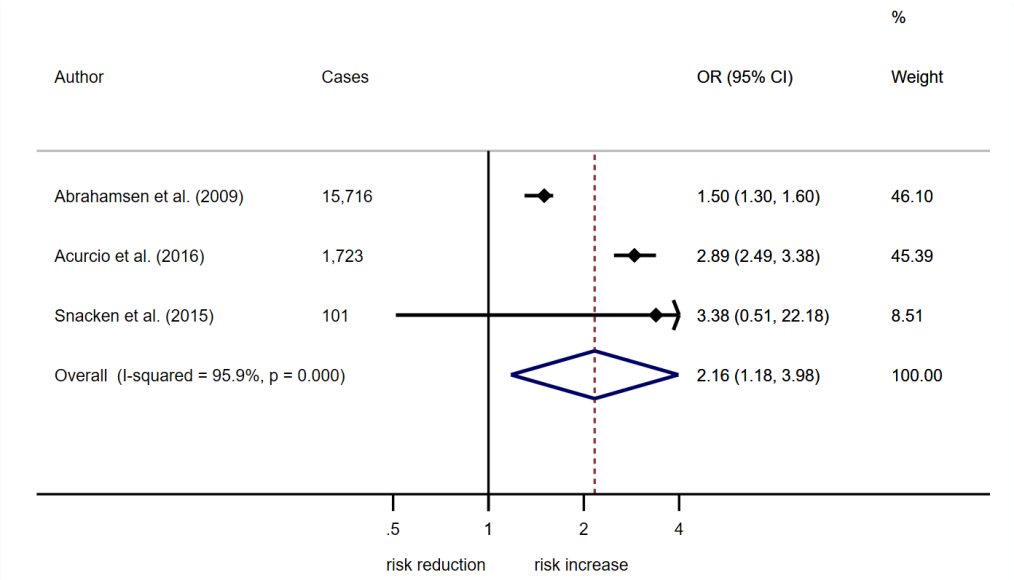


Figure 3-4. Pooled ORs for fracture to unspecified anatomical sites, comparing opioid users to non-users in one case-control study and two nested case-control studies

Risk of hip fracture

The pooled HRs of eight cohort studies demonstrated a significantly increased risk of hip fracture, comparing opioid use to non-use (pooled HR: 1.57; 95%CI: 1.18, 2.09) with high heterogeneity (I^2: 93.0%; p<0.001) (Figure 3-5).[87, 88, 90, 186, 196, 197, 199, 201] Another cohort study reported a significantly increased risk of hip fracture in opioid use (OR: 1.56; 95%CI: 1.34, 1.82).[187]

The pooled results from six case-control and nested case-control studies also demonstrated a significantly increased risk of hip fracture in opioid use compared to non-use (pooled OR: 1.48; 95%CI: 1.26, 1.72) with high heterogeneity (I^2: 82.3%; p<0.001) (Figure 3-6).[13, 86, 89, 193, 194, 203] One case-crossover study, which made within-person comparisons, also reported a significantly increased risk of hip fracture; comparing opioid use in the 14-day period prior to fracture, to opioid use during a control period (OR: 1.62; 95%CI: 1.42, 1.84).[195]

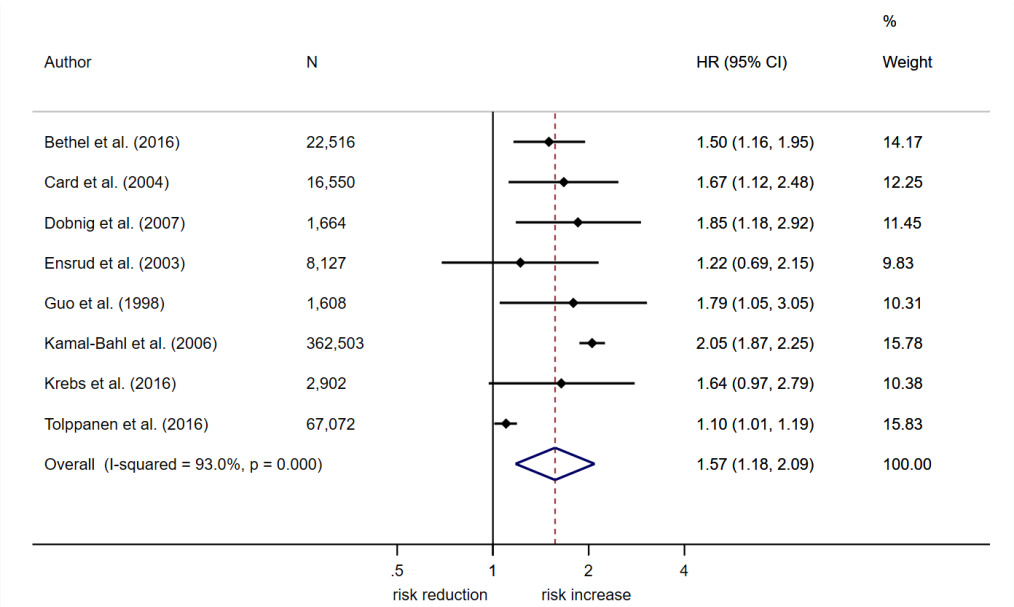


Figure 3-5. Pooled HRs for hip fracture, comparing opioid users to non-users in eight cohort studies

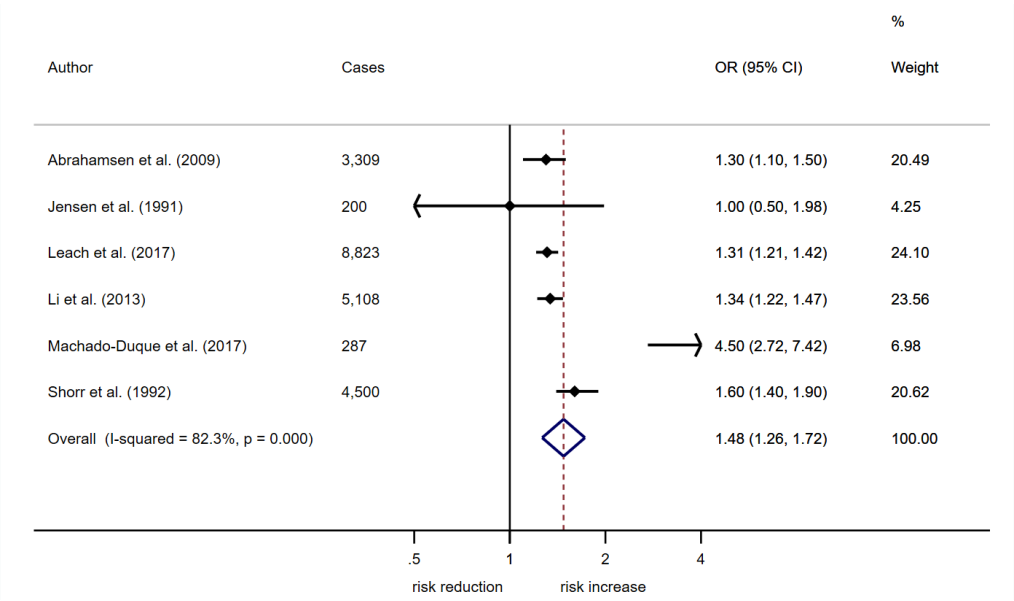


Figure 3-6. Pooled ORs for hip fracture, comparing opioid users to non-users in five case-control studies and one nested case-control study

Risk of fracture in other anatomical sites

Four studies reported risk estimates for fragility-related fractures, of these, Li *et al*. (2013) reported a significant increase in fracture-risk, comparing opioid use to non-use (OR: 1.27; 95%CI: 1.21, 1.33).[13] Two studies compared the incidence of fragility-related fractures in opioid users against NSAID users, both studies found a significantly increased risk of fracture in opioid users

(HR: 4.9; 95%CI: 3.5, 6.9, and HR: 4.47; 95%CI: 3.12, 6.41).[189, 192] Solomon *et al.* (2010) compared the risk of fragility-related fractures across different opioid drugs, finding that propoxyphene (IRR: 0.58; 95%CI: 0.49, 0.69) and tramadol (IRR: 0.32; 95%CI: 0.25, 0.40) demonstrated a lower risk of fragility-related fracture, when compared to hydrocodone use.[190] Risk estimates for fractures to other anatomical sites and composites of fracture-sites included: humerus (OR: 1.38; 95%CI: 1.26, 1.52);[13] wrist (OR: 1.14; 95%CI: 1.07, 1.23);[13] lower limb (HR: 1.82 95%CI: 1.59, 2.09);[200] femur (HR: 1.50; 95%CI: 1.19, 1.88);[201] and tibia/fibula (HR: 1.28; 95%CI: 1.06, 1.54).[201]

3.5.5 Effects of opioid duration and dose

A dose effect was found across some studies that compared people using different opioid doses to people not using opioids. Kamal-Bahl *et al.* (2006) reported a prospective cohort study and found a significant increase in the risk of hip fracture, comparing people using high propoxyphene doses (>260 mg/day; HR: 2.05; 95%CI: 1.85, 2.29) and low opioid doses (≤260 mg/day; HR: 1.45; 95%CI: 1.26, 1.67) to people not using opioids.[197] Saunders *et al.* (2010) reported a significant increase in the risk of fracture, comparing people using OMEQ doses of ≥50 mg/day (HR: 2.00; 95%CI: 1.24, 3.24) and OMEQ doses <20mg/day (HR: 1.20; 95%CI: 0.92, 1.56) to people not using opioids.[14]

In addition, Miller *et al.* (2011), reported a significantly increased risk of fragility-fracture, comparing people using high (>225mg codeine equivalent dose/day) opioid doses (HR: 5.1; 95%CI: 3.7, 7.2) and low (<75mg codeine equivalent dose/day) opioid doses (HR: 2.2; 95%CI: 0.9, 5.2) to people who used NSAIDs.[192] Similarly, Shorr *et al.* (1992) reported a greater risk of hip fracture in people using high (≥30mg) opioid doses (RR: 1.6; 95%CI: 1.2, 2.3)

and low (<30mg) opioid doses (RR: 1.5; 95%CI: 1.1, 2.1) to people not using opioids.[89]

Arcurcio *et al.* (2016) reported an increased risk of non-vertebral fracture in current opioid users prescribed one to seven days' supply ≤1 year prior to fracture compared to people not using opioids (OR: 16.87; 95%CI: 11.94, 23.84), this risk estimate declined as the duration of opioid use increased (8-20 days OR: 6.31; 95%CI: 4.22-9.43, and 21-155 days OR: 1.75; 95%CI: 1.31, 2.33).[202] In addition, Carbone *et al.* (2013) also reported a decline in the strength of the association between opioids and fractures over time, as the duration of opioid use increased.[200] Li *et al.* (2013) also reported that fracture-risk was at its greatest in current opioid users with one prescription prior to fracture, compared to non-use (1 prescription OR: 2.7; 95%CI: 2.34, 3.13, and 21-50 prescriptions OR: 1.06; 95%CI: 0.98, 1.15).[13]

3.5.6 Subgroup analyses

Subgroup analyses were conducted to explore methodological and demographic heterogeneity between cohort studies that reported unspecified fractures (Appendix I) and hip fractures (Appendix J), and between case-control and nested case-control studies that reported risk estimates for hip fractures (Appendix K). As only three case-control and nested case-control studies reported ORs for fractures of unspecified sites, an exploration of heterogeneity by subgroup analyses was not feasible.

Studies with a primary objective to investigate the association between opioids and fractures reported a higher risk of fracture than studies with exploratory objectives, this finding was consistent across fracture sites and study designs. Additionally, studies with a population aged ≥60 years reported

a higher risk of fracture than studies including people of any adult age, this finding was consistent across fracture sites and study designs. The results of all subgroup analyses are presented in Table 3-6.

3.5.7 Sensitivity analyses

Cumulative meta-analyses of studies reporting the risk of fractures to an unspecified site showed that the HRs reported by cohort studies, and ORs reported by case-control and nested case-control studies consistently demonstrated a positive association between opioids and fractures from the first study in 2003 to the most recent study, published in 2018 (Appendix L).

The cumulative meta-analysis of HRs for hip fractures reported by cohort studies showed a continued significant positive relationship from the first study in 1998 until the most recent study, published in 2016. The cumulative meta-analysis of ORs for hip fracture reported by case-control and nested case-control studies showed that the pooled OR became significant with addition of a third study,[203] published in 2009, from there on the OR remained significant and relatively stable (Appendix M). No influential studies were identified from the cumulative meta-analysis, therefore no studies were removed from the primary meta-analyses.

Table 3-6. Subgroup analyses

Factor	Subgroup	N	Risk estimate (95%CI)	I^2 (p value)
Cohort studies: Unspecified fractures				
Objective	Primary	3	1.58 (1.00, 2.48)	86.1% (p=0.001)
	Exploratory	4	1.37 (1.26, 1.49)	0.0% (p=0.979)
Exposure	Ever	2	1.42 (1.08, 1.86)	0.0% (p=0.787)
	Time-varying	5	1.40 (1.16, 1.69)	73.6% (p=0.004)
Age	Over 60 years	5	1.45 (1.08, 1.86)	73.2% (p=0.005)
	Any	2	1.37 (1.25, 1.49)	0.0% (p=0.687)
Sex	Mixed	3	1.63 (1.14, 2.32)	82.4% (p=0.003)
	Female only	3	1.41 (1.16, 1.71)	0.0% (p=0.961)
Continent	Europe	2	1.42 (1.08, 1.86)	0.0% (p=0.787)
	North America	5	1.40 (1.16, 1.69)	73.6% (p=0.004)
Cohort studies: Hip fractures				
Objective	Primary	6	2.04 (1.86, 2.23)	0.0% (p=0.415)
	Exploratory	2	1.44 (1.14, 1.80)	67.0% (p=0.010)
Exposure	Ever	3	1.45 (0.97, 2.18)	74.4% (p=0.020)
	Time-varying	4	1.69 (1.32, 2.16)	62.8% (p=0.045)
Age	Over 60 years	5	2.00 (1.83, 2.18)	0.0% (p=0.406)
	Any	3	1.34 (1.02, 1.78)	76.6% (p=0.014)
Sex	Mixed	5	1.57 (1.09, 2.26)	95.9% (p<0.001)
	Female only	2	1.56 (1.04, 2.33)	20.7% (p=0.262)
Continent	Europe	4	1.49 (1.07, 2.08)	73.7% (p=0.010)
	North America	4	1.69 (1.32, 2.16)	62.8% (p=0.045)
Case-control studies: Hip fractures				
Objective	Primary	3	1.89 (1.32, 2.70)	91.6% (p<0.001)
	Exploratory	3	1.30 (1.22, 1.40)	0.0% (p=0.746)
Age	Over 60 years	4	1.71 (1.23, 2.38)	89.0% (p<0.001)
	Any	2	1.33 (1.23, 1.44)	0.0% (p=0.743)

Notes: Insufficient number of case-control studies for subgroup analyses for unspecified fracture, and for exposure, sex and continent subgroups for hip fracture.

A sensitivity analysis compared pooled risk estimates before and after excluding studies with a critical risk of bias. For cohort studies reporting HRs for unspecified fractures, just one study with a 'critical' risk of bias was removed,[198] the restricted pooled HR continued to demonstrate a similarly increased risk of fracture in opioid use (pooled HR: 1.32; 95%CI: 1.23, 1.42; I^2: 0.0%; p=0.590) when compared to the primary meta-analysis (pooled HR: 1.39; 95%CI: 1.20, 1.62; I^2: 61.1%; p=0.017). For cohort studies reporting HRs for hip fractures, one study of 'critical' risk of bias was removed,[186] the restricted pooled HR showed a greater increased risk of fracture in opioid users (pooled HR: 1.77; 95%CI: 1.53, 2.05; I^2: 31.3%; p=0.189) than the primary meta-analysis (pooled HR: 1.57; 95%CI: 1.18, 2.09; I^2: 93.0%; p<0.001). All but one of the case-control and nested case-control studies were of 'critical' risk of bias,[13] and therefore no sensitivity analysis was possible for studies employing these designs.

Publication bias

After visual inspection of funnel plots for cohort studies (Figure 3-7) and case-control and nested case-control studies (Figure 3-8) that reported the risk of unspecified fractures, there was no evidence of publication bias. This was confirmed by Egger's test for asymmetry for cohort studies (p=0.946), and case-control and nested case-control studies (p=0.705).

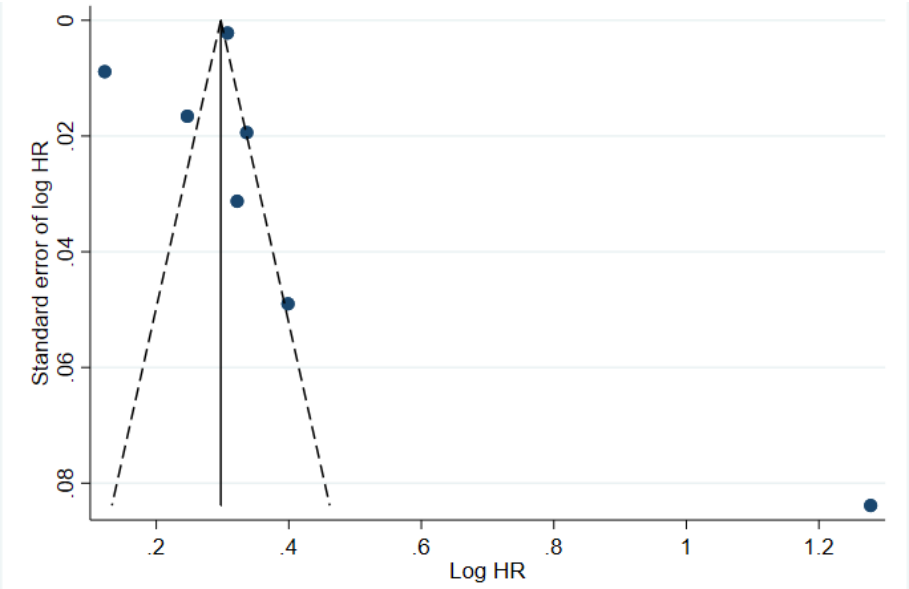


Figure 3-7. Funnel plot for cohort studies reporting HRs for unspecified fractures

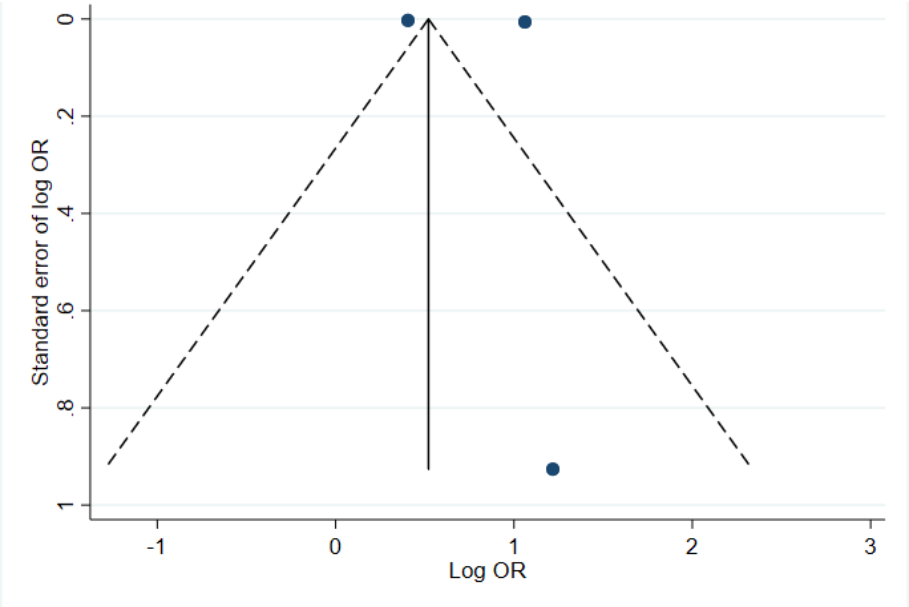


Figure 3-8. Funnel plot for case-control and nested case-control studies reporting ORs for unspecified fractures

Similarly, visual inspection of funnel plots for cohort studies (Figure 3-9) reporting HRs, and case-control and nested case-control studies reporting ORs (Figure 3-10) for hip fracture showed no evidence of publication bias. Again, these findings were confirmed by Egger's test for asymmetry for cohort studies (p=0.806), and case-control and nested case-control studies (p=0.237).

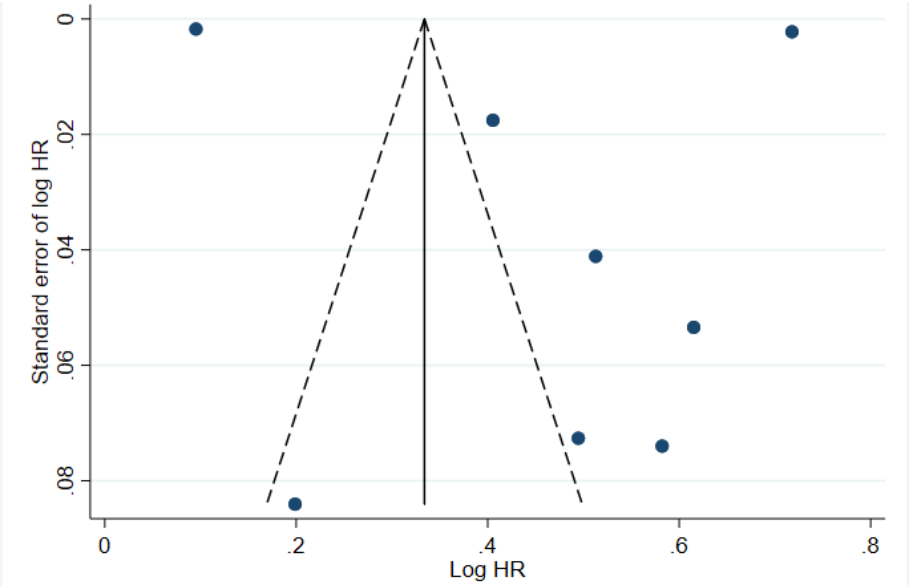


Figure 3-9. Funnel plot for cohort studies reporting HRs for hip fractures

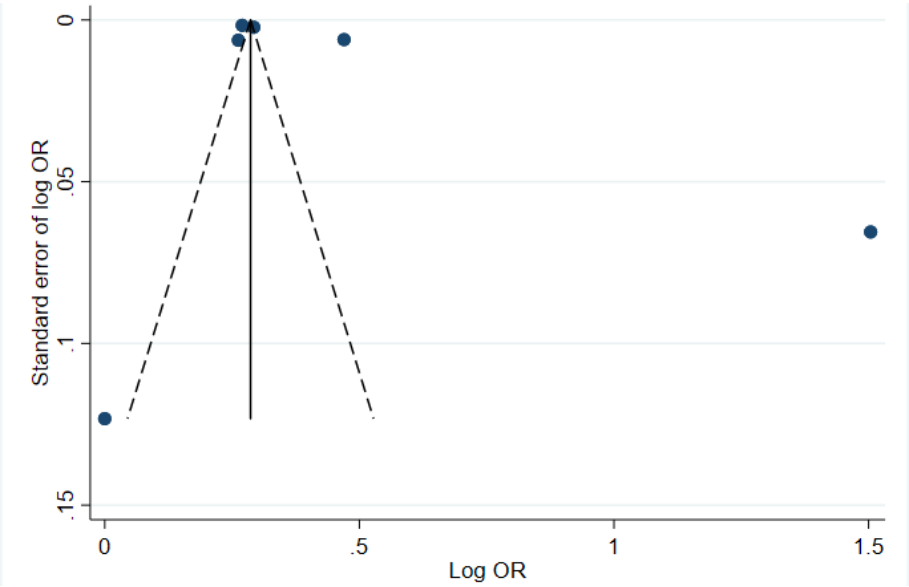


Figure 3-10. Funnel plot for case-control and nested case-control studies reporting ORs for hip fractures

3.6 Discussion

This systematic review and meta-analyses included a total of >795,000 individuals from 21 studies and provided a comprehensive assessment of the association between opioid use and fractures. Overall, the use of opioids is associated with a significantly increased risk of fracture compared to non-use. Included cohort studies show that, at any time-point following opioid initiation,

users of opioids have a 57% increased risk of hip fracture and a 39% increased risk of non-specific fractures. The findings of this review are consistent with, and provides a similar estimate for the magnitude of effect, to previous meta-analyses of cohort-only studies,[127] and of studies reporting hip-only fractures.[128] In addition, this review has found evidence to support that shorter durations of opioid use,[13, 200, 202] and higher daily doses,[14, 89, 192, 197] are associated with a further elevated risk of fracture.

Although heterogeneity was considerable, there was consistency in the direction and magnitude of effect across studies, supporting the finding that opioids are associated with an increased risk of fracture. It is noteworthy that findings from the cumulative meta-analyses showed that a significantly increased risk of fracture associated with opioid use has been consistently reported across studies published over three decades, providing further consistency of this effect.

The findings of this review support the hypothesis that opioids may have acute effects on the CNS, resulting in increased susceptibility to fall-related injuries.[15] These effects reduce in the initial days/weeks of treatment once a tolerance has been developed. Although previous literature has also suggested that opioids may increase the risk of fracture over periods of sustained use, resulting from an accumulative detrimental impact on BMD, [80, 81, 205] this review did not identify any studies to directly support this opioid-induced osteoporotic effect.

Considerable heterogeneity was identified among studies included in the meta-analyses. The subgroup analyses, by study objective, exposure definition, age and sex of participants, and region of study suggest that each

of these factors had a degree of influence on study heterogeneity. In addition, the various definitions of opioid exposure may have introduced potential non-differential misclassification of exposure, which may have biased risk estimates toward the null, thereby potentially under-estimating the effect of opioids on the risk of fracture.[206]

A variety of data sources were used across the included studies to assess opioid exposure and these provided differing measures of utilisation: prescribed, dispensed, administered or reimbursed opioid prescriptions. Further to this, exposure definitions varied across studies, three common exposure definitions were identified among cohort studies: ‘ever use’, ‘continuous/regular use’ and ‘time-varying use’; and two common definitions among case-control studies: ‘recent use’ and ‘ever use’. The period, length, intensity and interval of exposure assessment also varied between these definitions.

In addition, residual confounding and approaches to dealing with missing data are potential sources of bias across most of the included studies. Unmeasured confounders, as well as variation in the adjustment of models might have affected the results of individual studies, thereby potentially biasing the pooled risk estimates. Additionally, comparisons made between users of opioids and non-users of opioids may have led to confounding by indication, whereby an individual’s medical condition is associated with both use of opioids and fractures.[206]

3.6.1 Strengths and limitations

The strengths of this review and meta-analyses are that, firstly, a comprehensive search of the literature was performed, resulting in a greater

number of included studies than the previous systematic reviews and meta-analyses reporting on this topic. Secondly, the risk of bias was assessed using a recently developed, comprehensive risk of bias assessment tool,[136] thereby allowing for identification of biases present in the current literature. Thirdly, this review provided a comprehensive summary of the methodologies employed in the current literature. Providing an overview of how such studies have been conducted has allowed for an extensive exploration of heterogeneity in these meta-analyses, which has not been performed in previous meta-analyses.[127, 128]

This systematic review and meta-analyses have several limitations to consider. The search strategy was limited to English language articles which may have excluded studies published in other languages, resulting in potential language bias.[207] Publication bias is a possible weakness of systematic reviews and meta-analytic approaches,[208] however, no evidence for publication bias was apparent. Significant heterogeneity was observed across studies when combining risk estimates, and although possible sources of heterogeneity were explored in subgroup analyses, this was not removed and could have been due to other, unmeasured factors differing between studies. The presence of heterogeneity reflects the methodological and demographic inconsistency observed between studies, and suggests that the direction and magnitude of the effect of opioids on fractures may differ to the reported pooled estimate, depending on the methodological and demographic features of a given study. Most of the included studies provided only fully-adjusted risk estimates with adjustment for a multitude of covariates; studies may not have accounted for, nor appropriately adjusted for, important factors – this may have led to an unknown level of confounding in the overall estimate of effect. Finally, there were insufficient data available in the included studies to

discriminate between different opioid drugs, formulations, doses, and durations meaning that further analyses, including dose-response analysis, were not feasible.

3.6.2 Recommendations for future research

Studies should clearly report covariates included in statistical models and provide unadjusted, minimally adjusted (age and sex) and fully adjusted risk estimates to allow for direct comparison to other studies. Furthermore, researchers should adhere to the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE) to provide transparency in their methodological approaches, such as those taken to address missing data.[209]

Future research needs to provide an appropriate method for measuring exposure to opioids that allows for the assessment of the effects of time-varying opioid use on the risk of fracture. Additionally, subsequent research should implement alternative, within-person study designs, such as the SCCS design,[210, 211] which allow for time-varying exposures whilst controlling for unmeasured time-invariant confounding.

Advancing methods for exposure classification and reduction of residual confounding will allow for further investigation of the hypothesised CNS effects and osteoporotic effects of opioids, accounting for factors such as opioid dose, duration of exposure, and timing of fractures in relation to opioid use. Such research will identify specific factors that can elevate the risk of an opioid-related fracture, providing healthcare professionals with the information they require to minimise this potential risk to people.

3.7 Conclusions

This systematic review and meta-analyses have provided a comprehensive overview and summary of studies that have reported on the association between opioids and fractures. The current evidence from these observational studies consistently show a significantly increased risk of fracture associated with use of prescription opioids. Additionally, the evidence suggests that this may be due to initial CNS effects of opioids. The findings from this review provides important insights as to where healthcare professionals may be able to minimise the risk of opioid-related fractures. However, there are considerable methodological and demographic differences between these studies and important limitations are present in the existing evidence, such as potential for exposure misclassification, confounding by indication and unmeasured confounding, particularly in studies that have made between-person comparisons.

Chapter 4: Data source and cohort identification

4.1 Introduction

An appropriate data source was needed to identify a cohort of adults prescribed opioids and to provide information regarding these people, their prescriptions, and their clinical diagnoses so that the relationship between opioid use and bone fractures could be investigated. Furthermore, this data source needed to contain research-quality records for a sufficient number of people to represent the population of interest i.e., adults prescribed opioids in the UK, for the management of pain.

4.2 Aims and objectives

This chapter outlines the selection of a data source, the identification of a study cohort, and the extraction of study variables for this research. The objectives were:

1. To describe the data sources used in this research and outline the strengths and limitations of these.

2. To identify a cohort that represents the population of interest.

3. To define and extract study variables that relate to the demographic and clinical characteristics of the study cohort.

4. To describe characteristics of the study cohort and their prescription records.

4.3 Data sources

The primary data source selected for this research was the CPRD, an EHR database that covers a selection of people in the UK. The subsequent sections discuss the strengths and limitations of using EHRs for

pharmacoepidemiological research, and will describe the CPRD, linked datasets and rationale for selecting these for this research.

4.3.1 Electronic health records

Many healthcare providers, across primary, secondary and social care services use electronic methods for recording and retaining patient health information, in the form of EHRs. These EHRs can be transferred, anonymised and collated in large databases, and there are now several large EHR databases available in the UK that contain both drug exposure and clinical outcome data which can be used for research purposes (Table 2-2).[212]

Table 4-1. EHR databases available in the UK

Data Source	Country	Start date
The Electronic Data Research and Innovation Service	Scotland	1981
CPRD	UK	1987
QResearch	UK	1989
Medicines Monitoring Unit Scotland	Scotland	1990
The Health Improvement Network	UK	2002
Hospital Treatment Insights	UK	2010
Secure Anonymised Information Linkage	Wales	2007
ResearchOne	England	2013

4.3.2 Strengths and limitations of the EHR databases

The use of EHR databases for pharmacoepidemiological research has important strengths and limitations.

Strengths of EHR databases

EHRs contain routinely collected data about individual people; procedures are present for assuring the data contained within EHR databases are of

research-quality. This is a pertinent advantage for pharmacoepidemiological research since classification of exposure and outcome need to be as accurate as possible to avoid misclassification of exposure and outcome, which may result in regression dilution bias and less precise risk estimates, respectively.[213]

EHR databases usually contain data for many thousands of people over long durations of follow-up, allowing researchers to detect outcomes that may occur several years after initial drug exposure. Prospective methods for obtaining longitudinal patient data take many years to gather and are comparatively very expensive. The availability of EHR databases enables longitudinal patient data to be collated retrospectively, saving on both time and cost.

The real-world activities of clinicians and patients are recorded in EHRs, thereby allowing researchers to study changes in drug exposure and clinical outcomes over time. The use of EHRs in health-research, within a well-defined population, can bring greater external validity than RCTs offer, the latter of which generally include a restricted study population that do not represent the more complex patients who receive treatment in real-world clinical practice e.g., those with multiple comorbidities. Additionally, the large size of EHR databases means that they often cover a large and representative proportion of the target population.

EHR databases use coding systems to signify events in patients' medical histories. Most databases employ standardised coding systems, which enables researchers to systematically identify events of interest, such as when medicines are prescribed, or when a specific diagnosis is recorded.

Some large EHR databases offer linkage to other databases containing different but complementary health information, for example, linkage between primary care data from the CPRD and secondary care data from hospital records databases. The benefit of linkage is that it allows people to be followed more comprehensively over time, where the exposure or event of interest may occur in either or both information sources. The ability to link primary and secondary care data was a requirement for this research since, routine opioid prescriptions can be identified in primary care EHRs whereas bone fractures can be identified in primary care and/or secondary care EHRs.

Limitations of EHR databases

Often in observational pharmacoepidemiological research, groups of people are compared according to exposure to a certain medicine of interest, these groups are not randomised to their treatment and therefore systematic differences exist because of the presence or absence of an indication for the treatment if it affects the probability of the outcome, known as confounding by indication. A limitation of EHR databases is that they currently do not offer enough data to allow researchers to control for all potentially confounding factors when comparing groups. The result is that residual confounding may be present between groups, resulting in a biased risk estimate.

Classification of exposure to a medicine of interest is usually carried out using code lists for medicinal products; dates of prescriptions are then extracted and used to build a longitudinal measure of exposure from EHR databases. Records of prescriptions do not reflect whether the person received or used the medication, which can lead to some misclassification of exposure. Additionally, EHR databases do not contain data regarding OTC or non-NHS purchased medicines. Alternative data sources for classifying exposure to

medicinal products include patient medication diaries and interviews, as well as electronic medication administration devices. However, these prospective methods take a long time to gather data for a sufficient duration of follow-up, are limited by recall bias, and cost substantially more than the use of retrospective, routinely collected data.

4.3.3 The Clinical Practice Research Datalink

The CPRD is one of the world's largest EHR databases,[214] containing the anonymised records of people who are registered with a UK GP (using Vision® software) that have agreed to provide data to the CPRD on a regular basis. GP services are free at the point of access and are the initial point of care for non-urgent healthcare in the UK. GP services include prescribing, clinical testing, ongoing disease monitoring, diagnosis and treatment of illnesses and referrals to secondary care and specialist services.

As of July 2017, the CPRD contained data deemed acceptable for research for over 14.9 million UK people from 718 GPs.[215] The CPRD patients are generally representative of the UK population in terms of age, sex and ethnicity.[214]

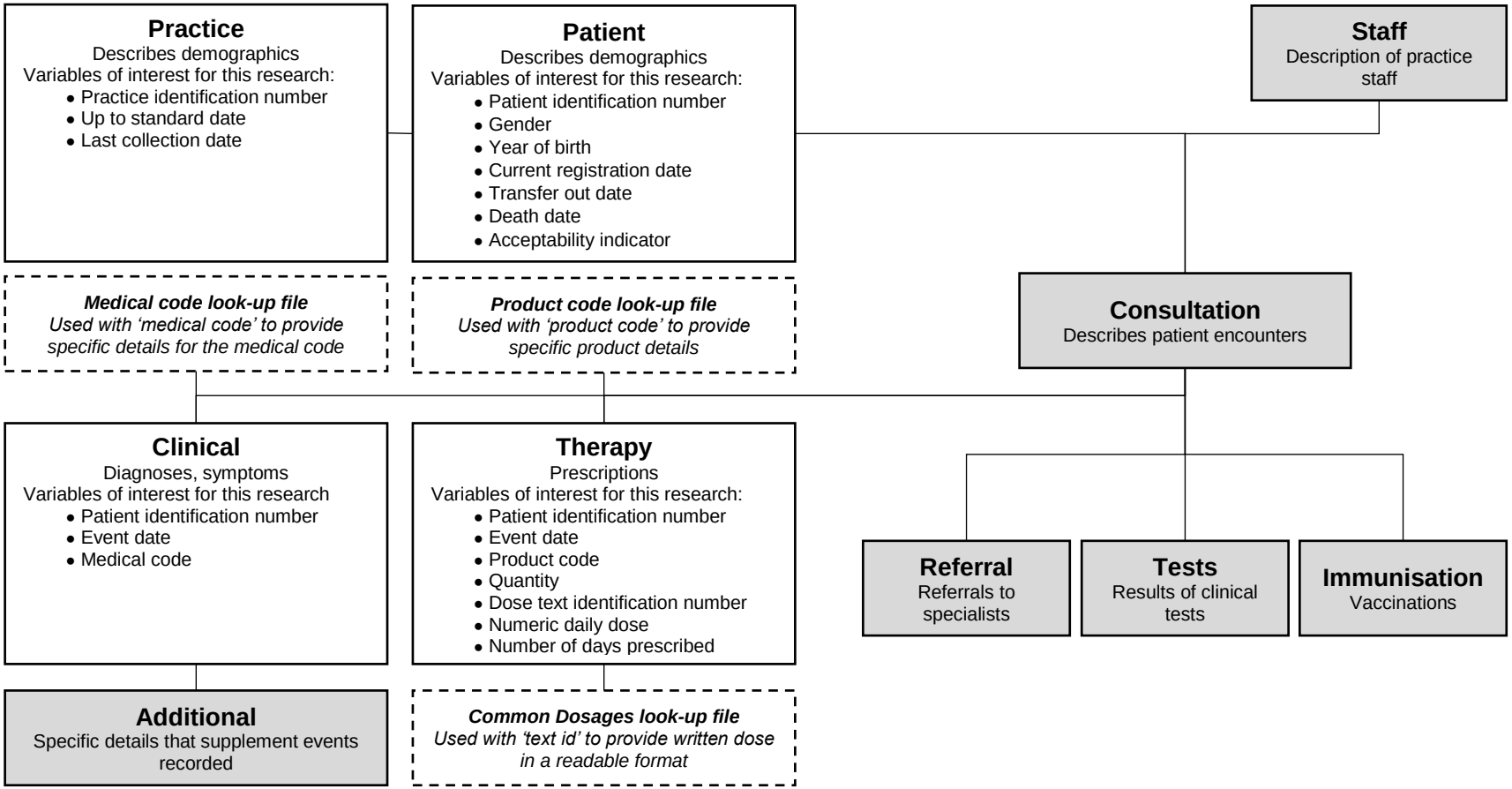
Database structure

Details of GP services are recorded in the patients' EHRs, and details of secondary care services are, theoretically, retrospectively added to patients' EHRs by GP staff from communications and discharge documentation sent from secondary care service providers. Data within EHRs are captured in two main formats: free-text data, which are freely typed records of events, and codes, which can be either a medical or product code that correspond to the

event recorded; only coded data are available for research using the standard CPRD data source.[214]

The data from the EHR for each CPRD patient is organised into nine files (Figure 4-1), the data contained within each file has an event date and can be traced to each person using a unique patient identification number. Each CPRD patient has a CPRD practice registration date, and (if applicable) a transfer out date and death date, which allows researchers to identify the date that a person enters and exits a study. In some instances, CPRD practices may cease to provide data to the CPRD, in which case a last collection date is recorded for these practices and can be used to generate an exit date for their registered patients.

To ensure data is of research quality there are two measures of data quality: (1) the practice up-to-standard date and (2) patient data acceptability.[214] A practice is deemed to be 'up-to-standard' if they provide continuous research-quality data with no meaningful gaps and if they record an expected number of patient deaths, based on their practice size. Patient data is deemed as acceptable if, following a series of checks regarding registration status, date-recording and the validity of age and gender; patients have continuous follow-up and well recorded data.



Notes: Figure adapted from Herrett *et al*. (2015);[214] shaded boxes represent files that have not been used for this research; boxes with a dashed outline refer to look-up files that have provided supplementary data.

Figure 4-1. Illustration of CPRD data structure

Data access

To gain access to data from the CPRD, researchers must purchase and agree to a full CPRD licence agreement, and submit a study protocol to, and gain approval from, the CPRD's Independent Scientific Advisory Committee (ISAC) in order to disseminate any findings.

4.3.3.1 Data linkage

A subgroup of English CPRD practices have consented to patient-level linkage with supplementary data sources using an anonymous patient identification number. The addition of linked data to the CPRD data has been shown to improve the detection of study outcomes, such as acute myocardial infarction, which can improve the internal validity of EHR research.[216] Data sources linked to the CPRD include: HES (hospital records), ONS (death registration), IMD and Townsend scores (deprivation data), National Cancer Registration and Analysis Service (cancer data), and Mental Health Dataset (mental health data);[217] the linked data sources that were selected for this research, and rationale for doing so, are listed in Table 4-2. These datasets can be linked on request, via a trusted third party, to CPRD records for people registered in CPRD practices that have consented to linkage; a patient-level record of consent is available in a linkage eligibility look-up file provided by the CPRD.

Hospital Episode Statistics

The HES datasets are used for the reimbursement of hospitals for their activity across all NHS Clinical Commissioning Groups (CCGs) within England. HES comprise of three separate datasets: admitted patient care (APC), outpatient appointments (OP), and accident and emergency attendances (A&E), each containing individual-level patient records. Data is

included for NHS patients, private patients, and patients residing outside of England, for NHS secondary care services provided in England. Data include: clinical diagnoses and operations, patient demographics, administrative dates, methods of admission and discharge, and geographical information such as where the person was treated.[218] The HES dataset undergoes automatic data cleaning to resolve common data quality issues and to derive additional data to supplement the HES dataset. The HES datasets use the WHO's ICD codes to record diagnosis information,[219] and Office of Population, Censuses and Surveys Classification of Interventions and Procedures (OPCS) codes are used to record details of any procedures or interventions performed.[220]

Table 4-2. Linked data sources to be used in this research

Data Source	Description	Rationale	Start date
Hospital Episode Statistics			
Admitted Patient Care (HES APC)	Episodes that require a person to be admitted to hospital as an inpatient	Detection of fractures, where a person is admitted to hospital as an inpatient	April 1997
Outpatient (HES OP)	Episodes refer to a single appointment for a consultant clinic, where a person is not admitted as a hospital inpatient	Detection of fractures, where a person attends an outpatient appointment	April 2003
Deprivation and rural urban classification			
IMD	Measure of relative deprivation and rural urban classification at a patient and practice level	Ascertain patients' relative deprivation	2015*

Notes: * The IMD dataset is not a longitudinal dataset and has no 'start date'. Instead, 2015 relates to the version used.

Index of Multiple Deprivation (LSOA level)

The IMD is the official measure of relative deprivation for small areas in England and was selected to indicate the socioeconomic status of people in

this research.[92] These 34,753 small areas are referred to as LSOAs (Lower-layer Super Output Areas) and each contains 1,000 to 3,000 people.

On request, the CPRD maps patients' home postcodes to the 2015 English IMD to obtain the IMD quintile for the LSOA covering the patients' home postcodes. The IMD combines measures of: income deprivation; employment deprivation; education, skills and training deprivation; health deprivation and disability; crime; barriers to housing and services; and living environment deprivation.[92]

4.3.3.2 Strengths and limitations of the CPRD

The strengths and limitations that are specific to the CPRD and linked datasets are outlined below.

Strengths of the CPRD

The CPRD is one of the largest UK EHR data sources and provides a long-established history of use for pharmacoepidemiological studies. People in the UK can only register with one GP at a time, this means that the majority of prescriptions that a person receives are accounted for during their follow-up time within a CPRD practice, and are therefore captured within the CPRD database.

Data from the CPRD covers, and is generally representative of the UK. Linkage to HES data is for English practices only, and therefore studies requiring linkage will represent an English population only. The CPRD contains data from practices using Vision® software which, in 2016, represented 9% of practices in England.[221] A second CPRD dataset was introduced in October 2017 called CPRD Aurum. Aurum contains data from a

selection of UK GPs using EMIS Web® software (this software was used by 56% of English practices in 2016),[221] and contained data for 19 million people (as of September 2018).[222] Due to the novelty of this data source, access to CPRD Aurum was not possible at the time of undertaking this research.

The standard CPRD database contains data in the format of product codes and clinical codes, therefore the detection of prescriptions or medical conditions relies heavily on valid code lists and good coding processes. Primary care clinicians may not routinely capture some data, and coding practices may be affected by incentives such as the Quality and Outcomes Framework or locally commissioned services. Inconsistencies in data-entry within and between practices may affect the validity of code lists. Code lists need to be generated with clinicians and/or those experienced in data entry in healthcare to ensure that code lists are both sensitive and specific for their purpose, and undergo validation testing.

The CPRD contains records of prescriptions generated by the CPRD practice but does not indicate whether a prescription was dispensed nor whether it was taken by or administered to a person. Furthermore, it is unknown whether the person used the medication as directed on the prescription. As such, assumptions have to be made by researchers using CPRD data in terms of their trust of data pertaining to prescriptions dispensed and used i.e., exactly as directed by the clinician.

Finally, the CPRD contains limited or no information on certain lifestyle factors such as diet and physical activity, and may be opportunistically recorded for factors such as weight and smoking status. Additionally, there may be systematic bias in which people have certain details recorded, for example,

Bhaskaran *et al.* (2013) showed that the completeness of body mass index recording varies over calendar time, age and sex for people registered in the CPRD.[223] Limited records for such factors result in residual confounding when making comparisons between people who differ in respect to potentially confounding factors such as these.

4.4 Study design, population and data extraction

4.4.1 ISAC approval

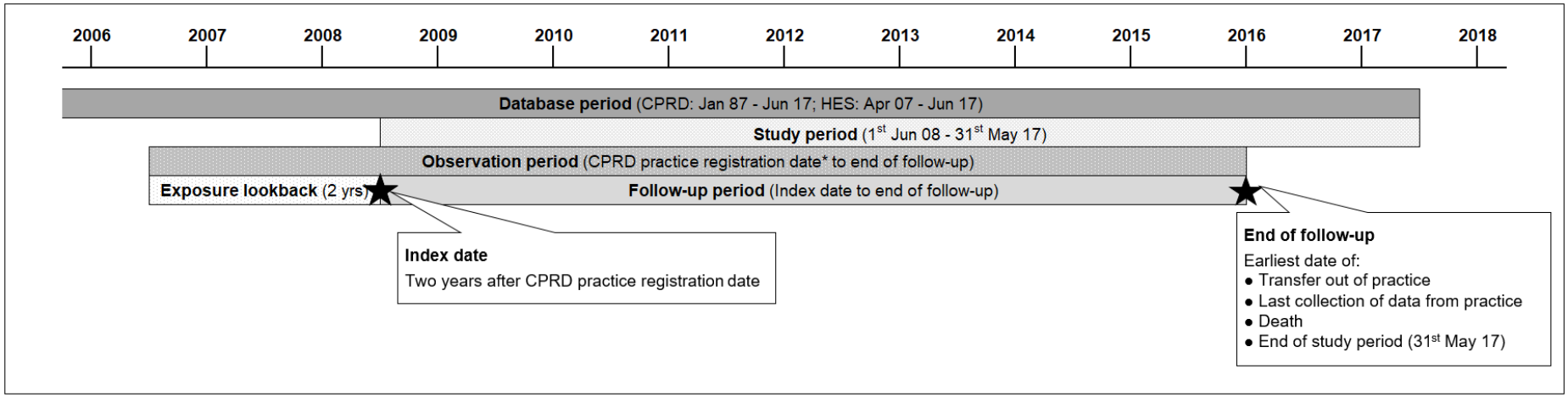
A study protocol outlining the research presented in the following chapters of this thesis was approved by the CPRD ISAC (protocol 18_282R) on 21st January 2019, the approval notification is provided in Appendix N. Additionally, linked data from the HES and LSOA IMD was supplied by the CPRD after making a linkage request for the study cohorts outlined in Chapter 7 and Chapter 8.

4.4.2 Study design

A retrospective open cohort of adults prescribed opioids was followed over a nine-year study period starting on 1st June 2008 and ending 31st May 2017. This study period was selected due to the availability of data for opioid prescriptions and for the diagnosis of fractures, and to ensure that each person had sufficient data available to determine whether they were an existing or a new user of prescribed opioids. The focus of this chapter is to describe the process for selecting this overall study cohort, extracting the study variables, and characterising the cohort. The subsequent chapters in this thesis outline the specific cohorts and methods used for each analysis.

4.4.2.1 Defining study time-periods

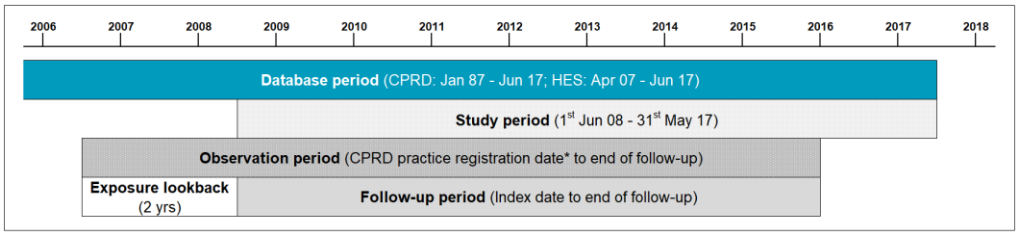
The first step when identifying the study cohort was to define the database period, length of lookback period, study period, patient observation period, and follow-up period. These periods are illustrated in Figure 4-2 and described in the following sections.



Notes: Observation starts from the latest of: (1) CPRD practice registration date or (2) CPRD practice 'up to standard' date or (3) 1st June 2006

Figure 4-2. Illustration of periods and dates relevant to the study design

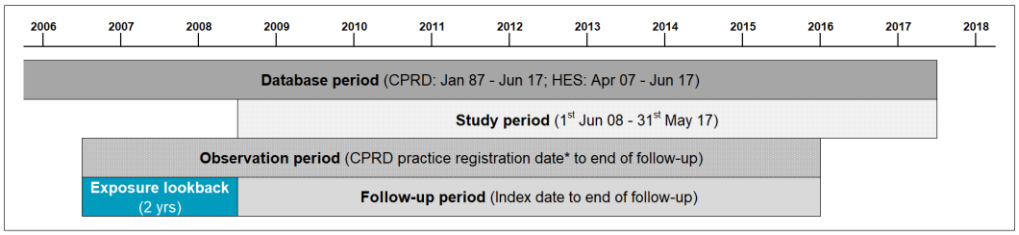
Database period



The database period refers to the period of time that data was available from the relevant data sources. This study used the July 2017 release of CPRD data which included primary care data recorded from CPRD-registered practices from January 1987 to 31st May 2017,[1] this was considered the CPRD database period.

For Chapters 7 and 8, patient-level data from the CPRD was linked to the 16th release of the HES which covered a period starting on 1st April 2007 and ending on 30th June 2017[2]. The HES database period ran from 1st April 2007 to 31st May 2017.

Lookback period



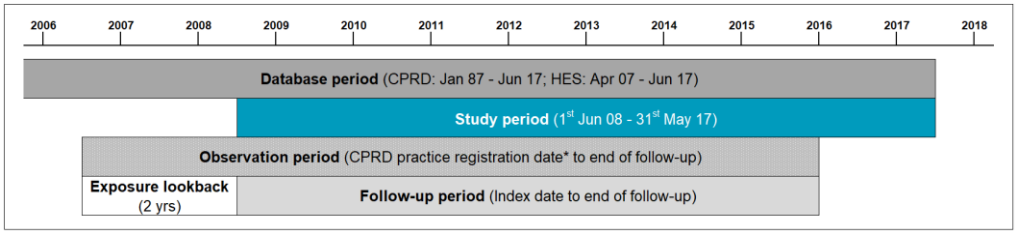
The lookback period refers to the period of time prior to the start of a person's follow-up that was used to ascertain baseline patient information. Lookback periods are often used in pharmacoepidemiological research to identify people

[1] Most CPRD practices had a recorded 'last collection date' during June 2017, therefore the July 2017 release of the CPRD was considered to cover most practices until 31st May 2017.
[2] Originally, all three HES datasets were to be used to identify fracture events; the database period and study period were based upon the availability of these datasets. Subsequently, due to a change in CPRD-licensing arrangements, only HES APC and OP were used for the research presented in this thesis.

without recent history of exposure to a drug or outcome of interest.[224] The chosen length of a lookback period depends on a number of factors, such as how frequently the medicine of interest is used, the number of visits a person makes to a health care provider, whether multiple codes are entered but relate to the same event, the length of the database period and the typical length of patient observation within the data source. Although there is no gold standard for selecting the duration of a lookback period, the longer the lookback period is the less the potential for misclassification when identifying new users of medication.[225] A two-year opioid lookback period was selected to avoid misclassifying prevalent opioid users as incident opioid users (i.e., new users), this length allowed for a relatively conservative lookback period whilst retaining as much follow-up time as possible.

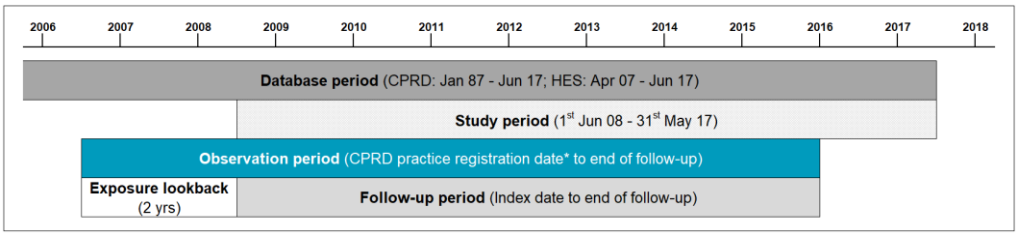
Additionally, in Chapters 7 and 8, a fracture lookback period of six months was used to ensure that fractures occurring before patient follow-up were not misclassified as new fractures. This is because multiple codes may be entered on separate dates but relate to just one fracture event. A six-month fracture lookback period was selected based on the approach taken in a prior CPRD study that examined incident fractures, which used a six-month lookback to define new fracture events.[226] However, it is acknowledged that there is potential for misclassification of prevalent fractures as incident if there are multiple records relating to the same fracture event.

Study period



The study period refers to the time period whereby a person can enter and exit the cohort. A study period of 1st June 2008 to 31st May 2017 was selected for all research chapters included in this thesis; this was so that all the available data from the selected data sources could be utilised whilst allowing for a two-year opioid lookback period within the CPRD, and a six-month fracture lookback period within both the CPRD and HES databases.

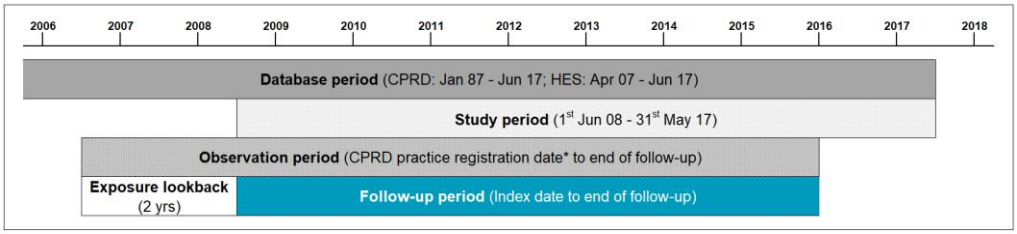
Observation period



People were observed from the latest of: (1) their CPRD practice 'current registration date' (crd), (2) their CPRD practice 'up to standard' (uts) date or (3) 1st June 2006.[3] Observation of people continued from the start of their observation period until they were censored from the study cohort, the reasons for this are outlined in the following section.

[3] 1st June 2006 was selected as the earliest possible observation start date, this was to allow for a two-year opioid lookback period prior to the start of the study period (1st June 2008)

Follow-up period



People were eligible to enter the study cohort two years after their observation period began, this served as the index date. The two-year period between the observation start date and the start of follow-up period served as the two-year opioid lookback period.

People were censored from the cohort at the earliest of the following dates:

1. The date the person discontinued their registration with their GP, indicated by the 'transfer out date' (tod) variable from the Patient file in the CPRD.

2. The date the patient's GP ceased to contribute data to the CPRD, indicated by the 'last collection date' (lcd) variable from the Practice file in the CPRD.

3. The date the person died, if this was during the study period, indicated by the 'death date' (deathdate) variable from the Patient file in the CPRD.

4. 31st May 2017 if the person reached the end of the study period.

4.4.2.2 Study medication

The British National Formulary (BNF) chapter field of the CPRD product code look-up file was searched for the terms 'opioid' and 'analgesic' to identify all product codes for opioid-containing products. The product name and drug substance fields were manually checked against the inclusion criteria below for each product code. This was to ensure that the resulting opioid product

code list (Appendix O) related to opioid analgesics and compound opioid analgesics used primarily for the self-management of pain in primary care.

Products were included in the opioid code list if they met all the following criteria:

1. They contained an opioid drug.

2. The ‘product’ field within the CPRD product code look-up file detailed the drug substance and strength or, for branded products, if this information could be found in the BNF.[44]

3. They were not an injectable formulation as these formulations are typically administered by healthcare professionals and not self-managed.

4. They were not a generic or branded version of 2mg, 4mg or 8mg buprenorphine sub-lingual tablets nor a generic or branded version of methadone oral solution. These products are used for people with opioid use disorders rather than pain management.

5. They were not the fentanyl iontophoretic transdermal system as this is for use within secondary care.

4.4.2.3 Study cohort selection

People were included if they met all of the following eligibility criteria:

1. Aged ≥18 years on their index date.

2. Prescribed an eligible opioid product (see section 4.4.2.2) with a corresponding prescription date that fell within the patient’s follow-up period.

3. Two or more years of ‘up-to-standard’ CPRD practice registration prior to their index date.

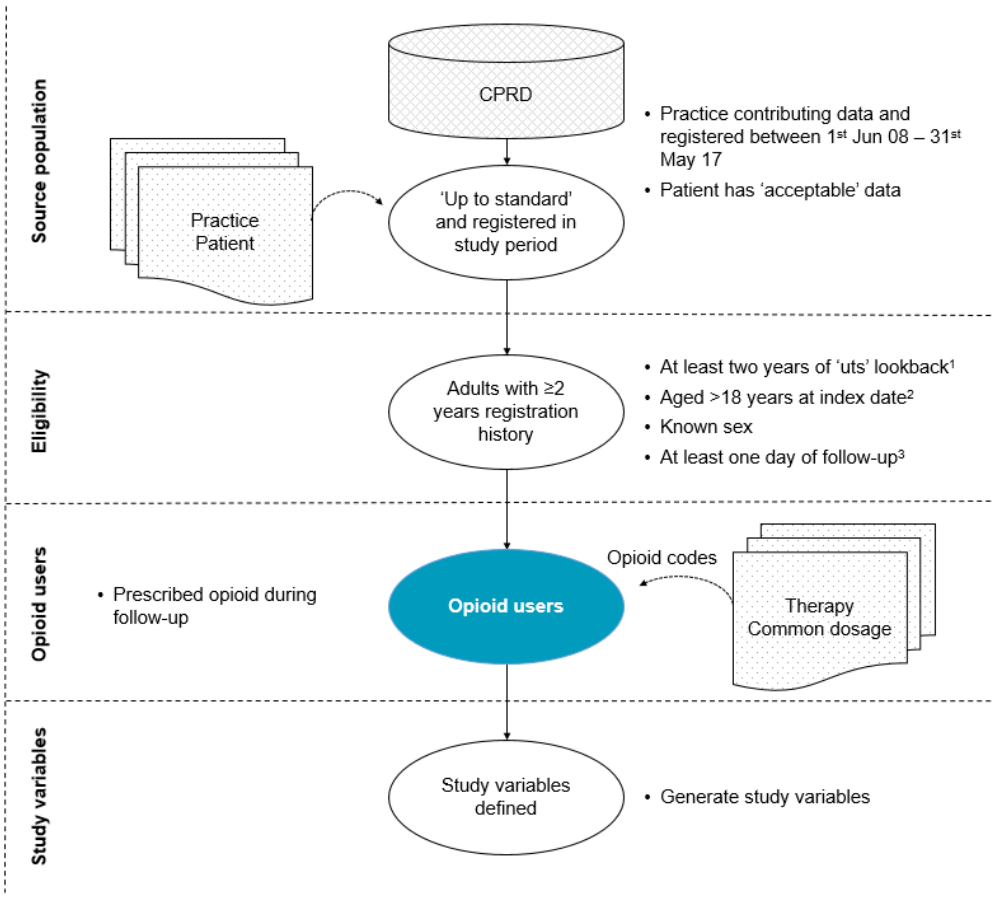
4. ‘Acceptable’ standard data – determined by the CPRD ‘accept’ indicator within the CPRD Patient file.

5. Sex recorded as male or female within the CPRD Patient file.

6. At least one day of follow-up. Follow-up duration was calculated by subtracting the end of follow-up date from the index date (dates defined in section 4.4).

4.4.3 Data extraction and study variables

The CPRD dataset was available in a flat file format for all people across 718 practice files. To identify eligible people and extract their data, the CPRD .txt formatted files were imported into Stata/MP 15 for each of the nine file types illustrated in Figure 4-1. Date variables were converted from string formats into Stata-format dates (i.e., number of days from 1960). The process for identifying the cohort and extracting data from the CPRD is outlined in the following sections and is illustrated in Figure 4-3, a summary of the study variables is provided in Table 4-3.



Notes: CPRD, Clinical Practice Research Datalink; lcd, last collection date; uts, up to standard; crd, current registration date.
[1] Lookback start = the latest of: 1st June 2006, 'crd', or 'uts', lookback ends two years after the lookback start date.
[2] Index date = lookback start + two years.
[3] End of follow-up = the earliest of: transfer out of practice (tod), practice last collection date (lcd), date of death, or 31st May 2017.

Figure 4-3. Process for cohort selection and data extraction

Table 4-3. Study variables following extraction and generation

Study variable	Description
Patient demographics	
Age	Age at index date
Sex	CPRD recorded sex
Observation start date	Latest of: (1) current registration date (2) practice 'up to standard' date (3) 1st June 2006
Index date	Date of cohort entry and start of follow-up – calculated by adding two years to the observation start date
End of follow-up date	Earliest of: (1) date of death (2) practice last collection date (3) transfer out date (4) 31st May 2017
End of follow-up reason	Reason for censorship, corresponds to date selected for end of follow-up
Follow-up duration	Number of days follow-up – calculated by subtracting index date from end of follow-up date
New opioid user	Indicates whether a person was classified as a new user of opioids (no opioid prescription during two-year exposure lookback period)
Prescriptions	
Event date	Date associated with the prescription, as entered by the prescriber
Product code	Unique CPRD code for the product prescribed
Quantity	Total quantity entered by the prescriber
Text identifier	Identifier that allows free-text prescription directions to be retrieved
Numeric daily dose	Numeric daily dose prescribed for the prescription. Derived using a CPRD algorithm on common dosages
Days supplied	Number of treatment days prescribed (entered by the prescriber)
Dose duration	Number of treatment days prescribed (obtained from the common dosages look-up file, and based on numeric daily dose)

Identifying the CPRD source population

The source population consisted of people with acceptable data who were registered with a practice that contributed 'up-to-standard' data between 1st June 2008 and 31st May 2017. Practice 'up to standard' dates were extracted from the CPRD Practice file and patient current registration dates and acceptability indicators were extracted from the CPRD Patient file.

Identifying eligible people

People from the source population were then checked for eligibility based on the criteria in section 4.4.2.3. An observation start date was generated for each patient, this was the latest of their (1) current registration date, (2) practice 'up to standard' date or (3) 1st June 2006. Each person was also given an index date that was two years after their observation start date. People were excluded if their index date occurred after 31st May 2017. Age at the index date was generated for each person using the year of birth variable from the CPRD Patient file. People aged <18 years on their index date were excluded from the cohort. Each patient's recorded sex was extracted from the CPRD Patient file; any people with missing, unknown or indeterminate sex status were excluded.

An end of follow-up date was assigned for each patient, which was the earliest of: (1) date of death (extracted from the CPRD Patient file), (2) practice last collection date (extracted from the CPRD Practice file), (3) transfer out date (extracted from the CPRD Patient file), or (4) 31st May 2017. Additionally, each person was assigned with a reason for end of follow-up which corresponded to which of these four dates was used. Duration of follow-up was calculated for each person by subtracting the index date from the end of follow-up date;

people with a follow-up duration of less than one day were excluded from the cohort.

Identifying eligible people prescribed opioids

Eligible people were assessed for the presence of an opioid prescription during their follow-up period. All prescription records with event dates during each eligible patient's observation period were extracted from the CPRD Therapy file. This data was then merged with the opioid product code list (Appendix O) to identify people prescribed an opioid. Prescription records were supplemented with dose duration data from the common dosages look-up file using the text identifier (textid) provided in the CPRD Therapy file. People with no prescription for an opioid during their follow-up period were excluded from the cohort. A 'new user' variable was generated to indicate whether a person was a new user of opioids on their index date, these were people that had a record of an opioid prescription during their follow-up period but had no record of an opioid prescription in their two-year opioid lookback period. People with a record of an opioid prescription in both their follow-up period and their two-year opioid lookback period were classified as prevalent opioid users.

Each subsequent analysis chapter has used a sub-cohort from this overall cohort and these study variables have been used to generate variables specific to each analysis, these are described in the methods sections of the relevant chapters. Additionally, Chapters 7 and 8 have utilised HES data; a description of the linkage process and data extracted are provided in those chapters.

4.4.4 Data analysis

The annual incidence of entrants to the study cohort was calculated by dividing the number of people entering the study in each study-year by the number of active CPRD registrants that became eligible in each study-year. The study population was described using descriptive statistics and presented in tables and figures. Missing data for variables relating to opioid prescription records were presented as a total number and a proportion of total opioid prescription records.

Study variables with a high proportion of missing data were manually inspected using a subsample of prescription records from one CPRD practice chosen at random in order to further understand the nature of the missing data i.e., missing: completely at random (MCAR), at random (MAR), or not at random (MNAR), so that a suitable approach to dealing with this missing data could be selected. All data management processes and statistical analyses were carried out using the statistical software - Stata/MP 15 (StataCorp, Texas, USA).

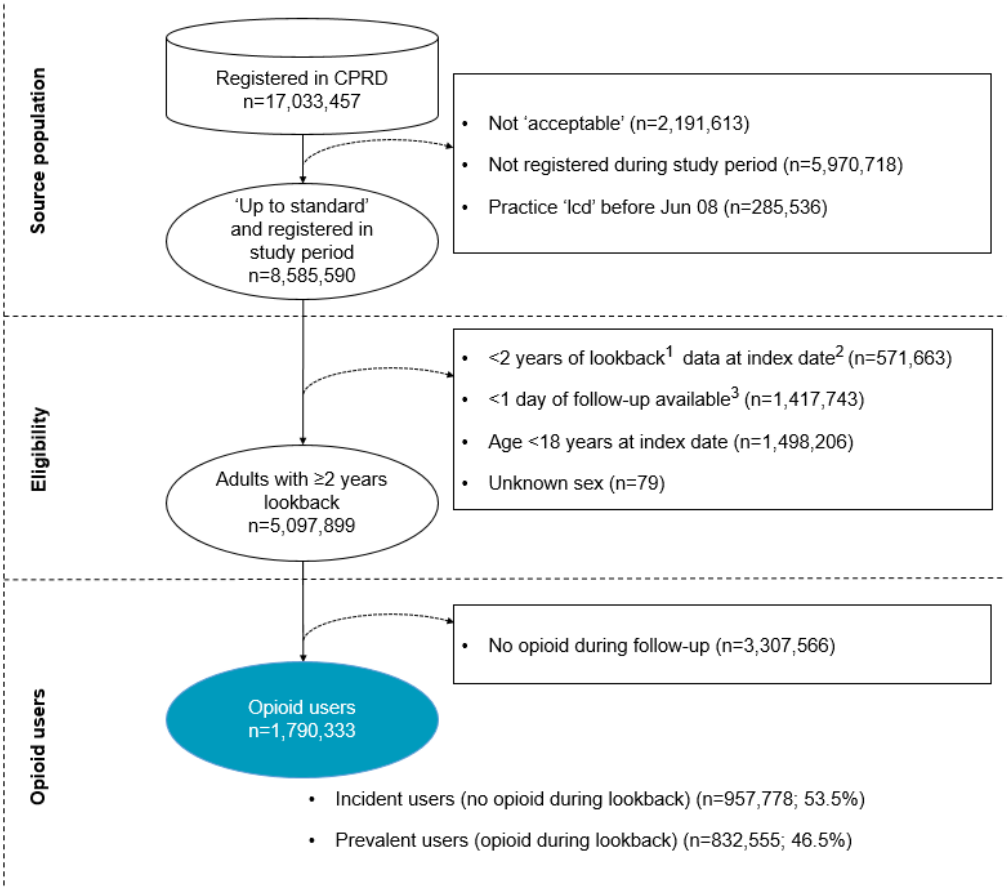
4.5 Results

4.5.1 Selection of study cohort

A total of 17,033,457 people from 718 practices contributed data to the July 2017 release of the CPRD. Of these, 8,585,590 people (50.4%) had acceptable data[4] and were registered with a CPRD practice that contributed 'up to standard' data during the study period, this comprised the source population. Of the source population, 5,097,899 people met the study cohort selection criteria (section 4.4.2.3) and were eligible for inclusion. Of these,

[4] Acceptability of a patient's data indicated by the CPRD, which is based on the registration status, recording of events, and validity of age and gender.

1,790,333 (35.1%) eligible people had a record of at least one opioid prescription during their follow-up period and were included in the study cohort. After assessing for the presence of an opioid prescription during the two-year exposure lookback period, 957,778 (53.5%) people were classified as incident (new users) of opioids, and 832,555 (46.5%) people as prevalent users (Figure 4-4).



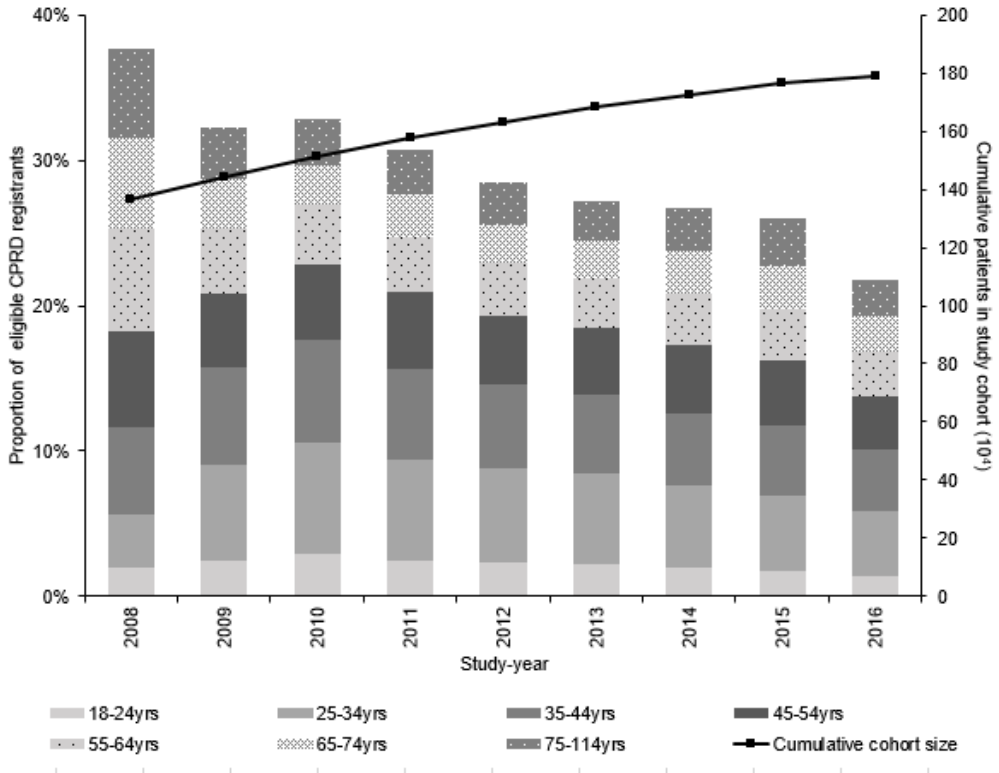
Notes: CPRD, Clinical Practice Research Datalink; lcd, last collection date; uts, up to standard; crd, current registration date.

[1] Lookback start = the latest of: 1st June 2006, 'crd', or 'uts', lookback ends two years after the lookback start date.
[2] Index date = lookback start + two years.
[3] End of follow-up = the earliest of: transfer out of practice (tod), practice last collection date (lcd), date of death, or 31st May 2017.

Figure 4-4. Selection of study cohort

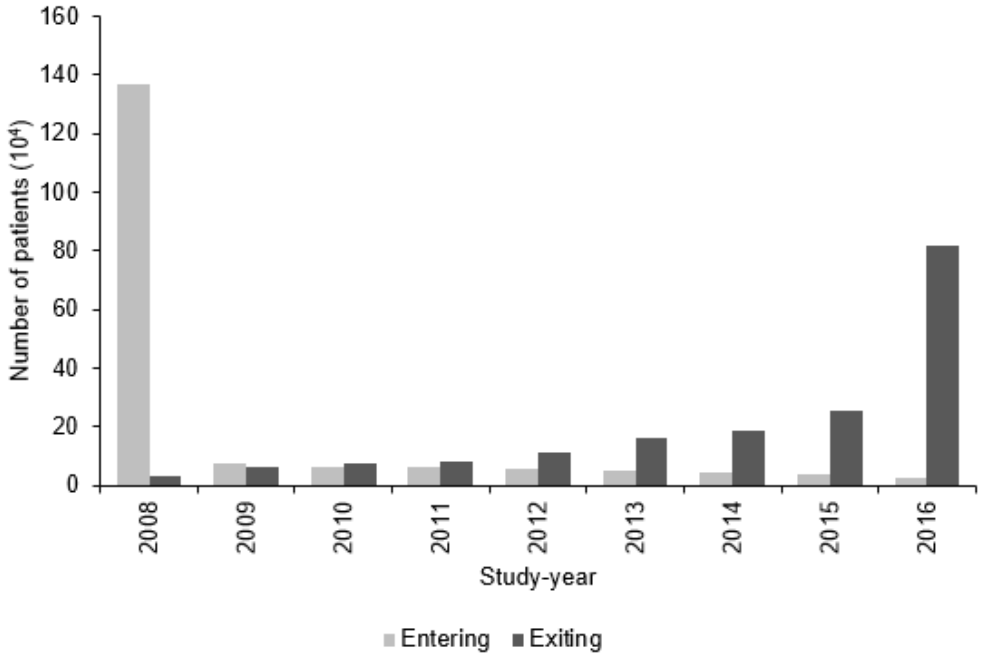
The proportion of eligible people entering the study cohort declined over the study period, from 37.6% in 2008-09 to 21.8% in 2016-17 (Figure 4-5). As

expected, most people entered the study cohort in 2008-09, the first study-year, and exited the study in 2016-17, the final study-year (Figure 4-6). Reasons for exiting the study were: last collection of data from the practice (41.0%), person reaching the end of the study period (34.9%), person left their GP (16.9%), and death (7.3%). The study cohort contributed a total of 10,471,832 person-years of follow-up time during the study period and the median follow-up duration was 6.4 years (interquartile range (IQR): 3.4, 8.9 years).



Notes: Study-years run from 1st June to 31st May, and are labelled by the commencing year i.e., 2008 refers to the study year running from 1st June 2008 to 31st May 2009.

Figure 4-5. People entering study cohort each year by age



Notes: Study-years run from 1st June to 31st May, and are labelled by the commencing year i.e., 2008 refers to the study year running from 1st June 2008 to 31st May 2009.

Figure 4-6. People entering and exiting the study population each study year

4.5.2 Patient demographics

The mean age at entry into the study cohort was 53.0 years (standard deviation (SD) 18.5) and 57.9% of people in the cohort were female (n=1,037,076). Compared to the 5,097,899 eligible people in the CPRD, the study cohort contained a higher proportion of females and were, on average, six years older; the proportion of females among eligible people was 50.9% and the mean age when people became eligible for inclusion was 47.0 years (SD: 18.4).

4.5.3 Opioid prescription records

The CPRD Therapy file contained 27,266,882 records of opioid prescriptions for the 1,790,333 people in the study cohort. Of these, 79.2% of records (n=21,585,611) were for people who were prevalent opioid users at cohort entry, and 20.8% of records (n=5,681,271) were for incident opioid users.

The CPRD Therapy files were merged with the opioid product code list (Appendix O) and the common dosage look-up file to extract study variables relating to the opioid prescription records. All data were present for the date of prescription and the product supplied except for a small proportion of missing data for the recorded opioid quantity (0.02%). A high proportion of data relating to daily doses (35.4%) and duration of supply (days supplied: 98.4%; dose duration: 31.8%) were missing (Table 4-4). Daily doses can be used alongside quantities to calculate the duration of supply, therefore, further investigation was required to develop an approach to handling missing dose information.

Table 4-4. Study variables extracted for opioid prescription records

Study variable	Definition	Missing data	
		(n)	(%)
Event date	Date associated with the prescription, as entered by the prescriber	0	0.00%
Product code	Unique CPRD code for the product prescribed	0	0.00%
Quantity	Total quantity entered by the prescriber	6,058	0.02%
Text identifier	Identifier that allows free-text prescription directions to be retrieved	8,658,332	31.75%
Numeric daily dose	Numeric daily dose prescribed for the prescription. Derived using a CPRD algorithm on common dosages	9,654,371	35.41%
Days supplied	Number of treatment days prescribed (entered by the prescriber)	26,825,249	98.38%
Dose duration	Number of treatment days prescribed (obtained from the common dosages look-up file, and based on numeric daily dose)	8,658,332	31.75%

Inspection of missing dose data

Due to the high proportion of missing data for the numeric daily dose (ndd) variable, a subsample of prescription records were inspected to further understand the nature of the missing data. The textid values for 31,226

prescription records of 3,198 people from one CPRD practice were merged with the common dosages look-up file, to obtain the free-text dose instructions and the corresponding ndd assigned by the CPRD during their data preparation process. A total of 637 unique free-text dose instructions were manually inspected and categorised as unambiguous, ambiguous, unknown or missing (see Table 4-5 for definitions); 19.4% of prescription records had unambiguous doses, 40.3% were ambiguous, 37.2% were missing, and 3.0% were unknown (Table 4-5). Additionally, the proportion of prescriptions with a dose in each of these categories varied across opioid drug (Figure 4-7) and formulation (Figure 4-8), suggesting that data for the ndd variable were MNAR.

Table 4-5. Inspection of dose instructions in a sample of opioid prescription records (n= 31,226)

Category	Definition	Example	Proportion of records	
			(n)	(%)
Unambiguous	Dose is clearly translated into an ndd	Take one twice a day (ndd=2)	6,063	19.42%
Ambiguous	Assumes half the maximum dose to translate into an ndd	Take 1-2 twice a day (ndd=2)	12,598	40.34%
Unknown	Cannot be translated into an ndd	Take when required (ndd=0)	947	3.03%
Missing	Text identifier not listed as a common dose and cannot be interpreted as text data	Missing (ndd=0)	11,618	37.21%

Notes: ndd, numeric daily dose

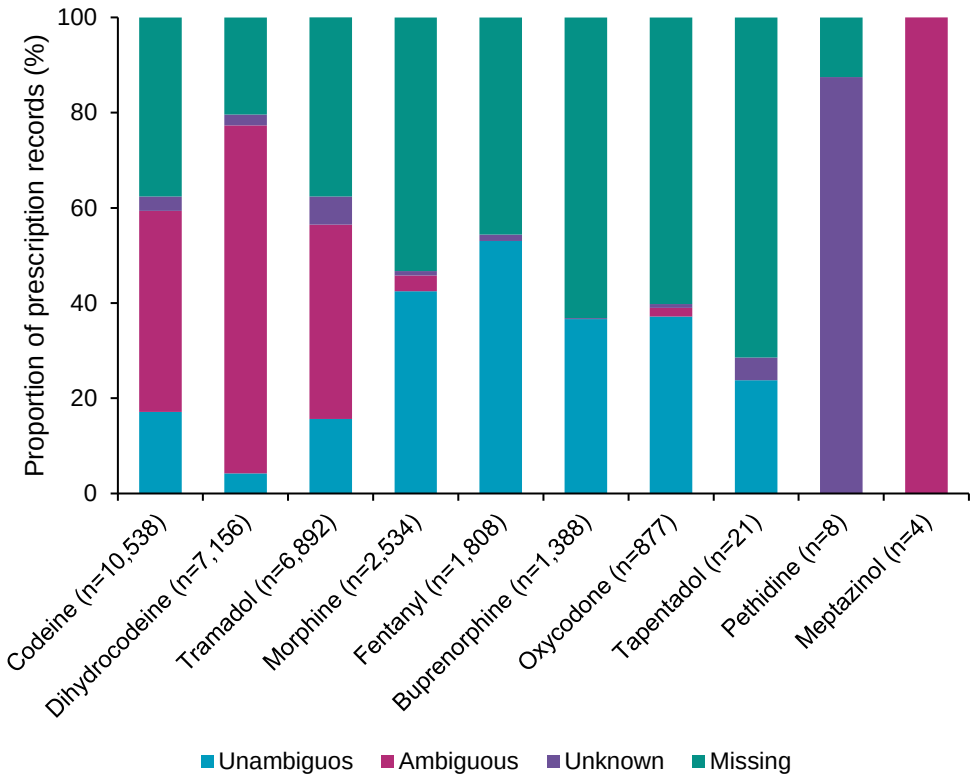
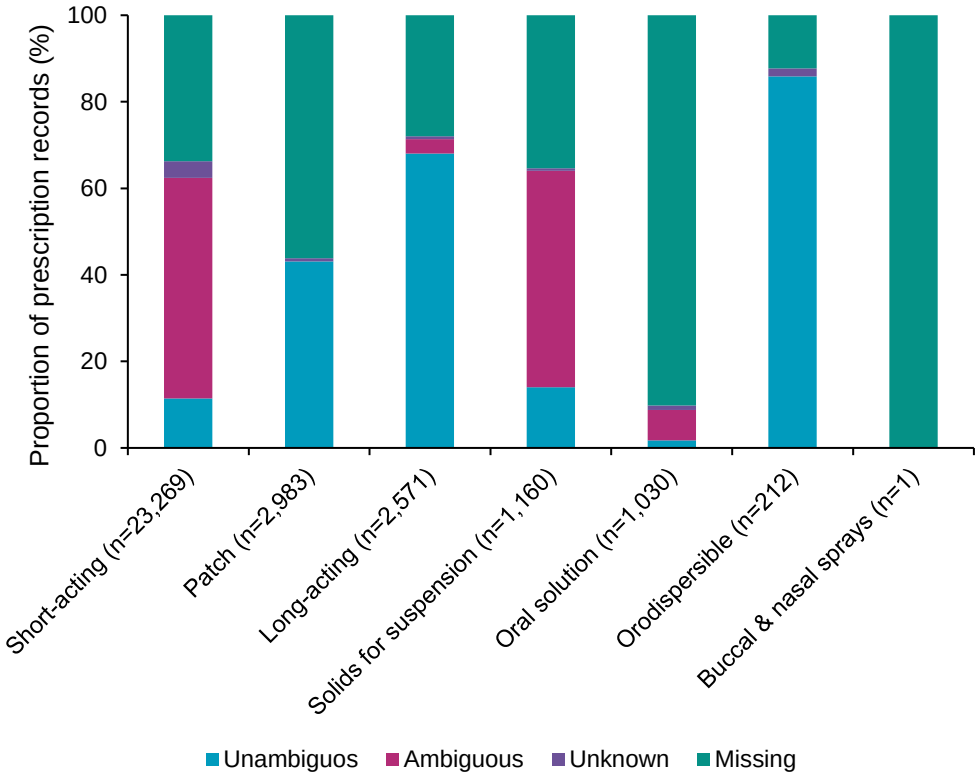


Figure 4-7. Proportion of opioid prescription records with a daily dose that is unambiguous, ambiguous, unknown or missing, by opioid drug



Notes: Short-acting and long-acting formulations refer to solid, oral formulations

Figure 4-8. Proportion of opioid prescription records with a daily dose that is unambiguous, ambiguous, unknown or missing, by formulation

4.6 Discussion

This chapter has outlined the important role of large EHR databases when conducting pharmacoepidemiological research which, whilst having several limitations, offers many important advantages over other data sources. These include retrospective access to exposure and clinical data which negates the need for lengthy and costly prospective approaches to data collection. Furthermore, the data contained within EHR databases are routinely captured by general practitioners and reflects real-world prescribing practices, meaning that the findings from the analyses presented in the subsequent chapters are likely to be generalisable to real-world opioid users; at least those in the UK. The data within the CPRD and HES is systematically recorded so that code lists can be used to identify relevant records, thereby allowing easy sharing of methods between researchers and facilitates replication of studies. Additionally, the selection of the CPRD as a data source provides a representative sample of the general UK population and has the added benefit of linkage to the HES. These advantages mean that the CPRD and HES provide high-quality data that is well suited to real-world research purposes.

The selection of a study period from 1st June 2008 to 31st May 2017 provides a total duration of nine years for the study. This study period comes after a change in UK controlled drugs prescribing legislation that legalised computer-generated prescriptions for controlled drugs, whereas, prior to 2005, prescriptions for controlled drugs needed to be hand-written. Although hand-written prescriptions should have been manually recorded in EHRs, there is potential that some opioid prescribing prior to 2005 would not have been captured in all EHRs and would therefore have been missing from the CPRD. As the study period for the current analyses started in 2008, the potential for exposure misclassification arising from this would not need to be considered

as a factor in the interpretation of the study findings. Additionally, this study period has allowed for the full use of the HES APC and OP datasets.

Linkage to the HES allows for a more accurate ascertainment of the incidence of fracture events and the date of their occurrence, this reduces the likelihood of under-estimating the incidence rate of fractures within the cohort. Additionally, the use of more accurately dated fracture events reduces the possibility of detecting a reverse-causal relationship when estimating the risk of fracture associated with use of opioids. A reverse-causal relationship would arise when fractures cause the opioid to be prescribed, rather than the opioid causing the fracture; having accurate dates for prescriptions and fracture events has ensured that a temporal order of events was established, preventing this potential limitation.

The study population of people prescribed at least one opioid during follow-up, consisted of a higher proportion of females and were older than CPRD registrants not prescribed an opioid during follow-up; the mean age at the index date was 53.0 years (SD: 18.5) and 57.9% of the cohort were female. These findings are similar to those of a study using the French Claims database. In that study, Chenaf *et al.* (2019) showed that people prescribed opioids between 2004-2017 had a mean age of 51.5 years (SD: 19.4), and 57.0% were female.[227] Additionally, a Danish study by Svendsen *et al.* (2012) that included people prescribed opioids in 2005 also reported a higher proportion of females (56.2%), as well as a similar mean age (52.9 years; SD: 18.8) for non-persistent users of opioids (forming 89.4% of their cohort).[113] Higher rates of opioid use in females, compared to males, has also been reported in studies of strong-opioid utilisation and long-term opioid use in the UK.[5, 110] Taken together, these studies support those of a meta-analysis of

studies reporting chronic pain prevalence in the UK - the prevalence of chronic pain was consistently greater in females and increased steadily with age.[2]

A total of 27,266,882 records of opioid prescriptions were extracted for the study cohort, missing data was minimal for the prescription date, product and quantity prescribed. However, there was a high proportion of missing data for the ndd and duration of supply, which were MNAR. This posed a challenge for measuring exposure to opioids over time, Chapter 5 outlines the options available to handle the missing prescription data and describes the application and extension of a novel algorithm to prepare CPRD prescription records for analysis.

4.6.1 Strengths and limitations

The identified study cohort consisted of 1,790,333 people with 10,471,832 person-years of follow-up time; and the median duration of follow-up was 6.4 years, thereby providing a sufficient length of follow-up to investigate the effects of both short and long-term use of opioids on the risk of bone fracture. Additionally, each person included was required to have a two-year opioid lookback period which enabled the assessment of opioid exposure prior to their index date. This ability to distinguish between new users of opioids and prevalent users was particularly important for the analyses presented in Chapter 6 and 8 so that the duration of opioid exposure could be established.

There are several opioid preparations that are available for people to purchase OTC; some people may also be supplied with opioids in secondary care. Additionally, people may obtain prescription opioids without a prescription, such as opioids prescribed for their friends or family.

Consequently, the CPRD may not capture all instances where a person is exposed to prescription opioids.

In this research the presence of an opioid prescription is assumed to mean that a person had the opioid dispensed and used it according to the dose instructions on the prescription. However, it is acknowledged that not all people will have had their medication dispensed, nor will they have taken them as directed by their prescribing clinician. Additionally, this research classified incident opioid users as those who did not have a record of an opioid prescription during their two-year opioid lookback period. It is acknowledged that it cannot be definitively claimed that all people classed as incident users were naïve to opioids upon cohort entry. However, this would not be anticipated to have a great impact on the interpretation of the study findings, particularly when investigating acute effects of opioid exposure on risk of bone fracture.

One main limitation when using routinely collected data for research purposes is that not all potentially confounding factors are measured with precision, or even measured, thereby meaning that residual confounding will persist. Confounding is a factor which needs to be considered in all observational research studies, as highlighted in Chapter 3. The subsequent analysis in Chapter 8 minimises the impact of unmeasured confounders by adopting a within participants design, a more detailed explanation of which is provided in Chapter 8.

4.7 Conclusions

The CPRD provides high quality research data with linkage to the HES and is well suited for pharmacoepidemiological research. A large cohort of adult

users of prescription opioids was identified from the CPRD with a considerable duration of follow-up available. The male-female ratio and mean age of the study cohort reflects previous reports from the UK and other European countries examining opioid utilisation, which provides some assurance that this cohort reflects the population of interest. The identified study cohort has formed the basis for all of the cohorts studied in the subsequent chapters of this thesis, each chapter provides a detailed explanation of the selection of the cohort from this main study cohort.

Study variables were extracted and generated from the CPRD data; opioid prescription records had no or very low levels of missing data for prescription date, product and quantity prescribed. High levels of missing data were found for the daily dose and duration of prescriptions, and after further investigation of these found them to be MNAR. Chapter 5 details the approach taken to handle these missing data to prepare opioid prescription records for further analyses.

Chapter 5: Preparing opioid prescription records for analysis

5.1 Introduction

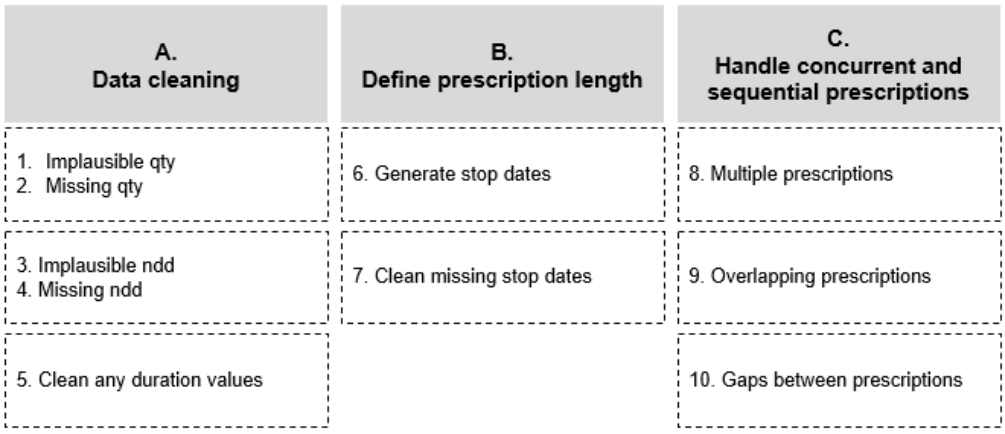
The analyses presented in the previous chapter showed that the opioid prescription records for the study cohort had a high level of missing data for the dose and duration prescribed, which were MNAR. The ndd assigned to each prescription record was a particularly important variable as it was used alongside the quantity prescribed in order to calculate the duration of the prescription, if the duration was not recorded elsewhere. There are a number of general approaches to analysis in the presence of missing data, these are summarised in Table 5-1.

Table 5-1. Approaches to analysis in the presence of missing data

Method	Description	Considerations
Complete case analysis	People with any missing data are excluded from the analysis.	People with complete data may be inherently different to those with missing data. This could considerably reduce the size of the study cohort and lead to a loss of power and precision.
Mean/median substitution	Population mean/median value is substituted for a missing value.	When the proportion of missing data is high, this method can reduce the spread of the data (the variance).
Missing indicator	A dummy variable is used to indicate a missing value; there is no substitution of missing values.	Can result in residual confounding for non-randomised studies, regardless of whether data is MCAR or MAR.[228]
Last observation carried forward	Substituting the missing value with a previously recorded value.	Some people may not have a previous observation to carry forward; previous values may not reflect the 'true value'.
Multiple imputation	A range of values from across the distribution of a variable is used to substitute missing values. This is repeated to generate multiple, complete datasets. Analyses are carried out on each dataset and the results combined.	Requires that data are MCAR or MAR. The use of this method in data that are MNAR may lead to misleading results.[229]

Notes: MCAR, missing completely at random (no difference between missing and observed values); MAR, missing at random (differences between missing and observed values that can be attributed to a measurable variable); MNAR, missing not at random.

In addition to handling missing values, the prescription records required preparation that included cleaning, restructuring and formatting the data ready for analysis. Methods for preparing prescription data are often poorly reported in pharmacoepidemiological studies and approaches vary depending on the specific database used, as different databases contain varying types and formats of data, and the nature of any missing data will be different. In 2018, Pye *et al.* published their 'DrugPrep' algorithm for preparing longitudinal CPRD prescription records for analysis, resulting in a binary indicator (currently exposed or unexposed) for medication exposure status, which varies over patient follow-up time.[230] This algorithm sets out a series of ten decision nodes, from cleaning the data (including handling missing data), to defining prescription lengths, and to handling concurrent and sequential prescriptions (Figure 5-1). At each node there are different decisions that can be made regarding data preparation, each introducing their own assumptions.



Notes: Adapted from Pye *et al.* (2018);[230] qty, quantity supplied; ndd, numeric daily dose.

Figure 5-1. DrugPrep algorithm decision nodes

The effect of assumptions made at each decision node in the DrugPrep algorithm was investigated by comparing two datasets that were prepared using different decisions at each node. It was found that both datasets

resulted in similar risk estimates when estimating the association between oral hypoglycaemic drugs and glucocorticoids on cardiovascular events. However, assumptions regarding prescription length had a greater influence on the results than other assumptions. The findings reported by Pye *at al.* highlight the importance of clearly reporting prescription preparation methods and the careful consideration required when making assumptions throughout the drug preparation process; the DrugPrep algorithm facilitates systematic decision making and the reporting of this process. Currently, the DrugPrep algorithm does not include preparation of a current dose variable, an extension of the algorithm was needed to describe and examine the effects of opioid dose in the analyses presented in subsequent chapters. To achieve the objectives of this research, a time-varying indicator for opioid exposure status and daily OMEQ dose was required, therefore an adapted and extended version of the DrugPrep was needed.

5.2 Aims and objectives

The aim of this chapter was to apply the DrugPrep algorithm when preparing the opioid prescription records of the study cohort, and to extend the algorithm to include the generation of a daily OMEQ dose variable. Specifically, the objectives of this chapter were:

1. To apply the DrugPrep algorithm and generate a time-varying indicator of current opioid exposure or non-exposure for the study cohort.

2. To extend the DrugPrep algorithm and generate a time-varying indicator of current daily OMEQ dose for the study cohort.

5.3 Method

All records for opioid prescriptions with a prescription date (eventdate) during the follow-up period for each person in the study cohort was extracted as detailed in Chapter 4. Prior to applying the DrugPrep algorithm, an opioid product look-up file was developed so that prescribed opioid products could be readily categorised during prescription preparation.

5.3.1 Developing an opioid product look-up file

The opioid product code list (Appendix O) was developed into an opioid product look-up file (Appendix P). For each opioid product code, the product name, strength, drug substance, formulation and route of administration variables were obtained from the CPRD product code look-up file and were manually screened and categorised to generate the variables listed in Table 5-2.

Table 5-2. Variables contained in opioid product look-up file

Study variable	Description	Categories (if applicable)	
Opioid	The opioid drug contained in the product	1=alfentanil 2=buprenorphine 3=codeine 4=dextromoramide 5=dextropropoxyphene 6=diamorphine 7=dihydrocodeine 8=dipipanone 9=ethylmorphine 10=fentanyl 11=hydromorphone 12=levorphanol	13=meptazinol 14=methadone 15=morphine 16=omnopon 17=oxycodone 18=papaveretum 19=pentazocine 20=pethidine 21=phenazocine 22=tapentadol 23=tramadol
Form	The formulation of the product	1=long-acting oral solids 2=short-acting oral solids 3=transdermal patches 4=oral solutions 5=solids/semi-solids for oral suspension* 6=orodispersibles** 7=buccal and nasal sprays 8=suppositories	
Product code	The code that corresponds to the product supplied		
Days per patch (applies to transdermal patches only)	Number of days a patch is intended to be worn, according to the manufacturer's instructions		
Strength/unit	The strength (in milligrams (mg)) of the product per unit prescribed e.g., mg per 1 tablet; mg per 1 millilitre (ml); mg per patch		
Equianalgesic ratio	Each combination of opioid and form was ascribed with an equianalgesic ratio from Table 5-3		
OMEQ/unit	The strength per unit, expressed as milligrams of the OMEQ dose. Calculated by multiplying the strength/unit by equianalgesic ratio		

Notes: *includes effervescent, soluble or dispersible tablets, and granules or suspension; **includes orodispersible, sublingual or buccal tablets, or lozenges and lollipops

The resulting opioid product look-up file contained 23 different opioid drugs across nine different formulations, each with an assigned OMEQ dose per unit prescribed (Table 5-3). The opioid product look-up file was merged with the study cohort's prescription records to create a dataset containing variables ready for preparation using the DrugPrep algorithm. Table 5-4 provides descriptions and examples of the variables used in the prescription preparation process.

Table 5-3. Equianalgesic ratios to calculate OMEQ doses

Opioid, (source)	Form*	Equianalgesic ratio
Alfentanil,[231]	SPR	30.00
Buprenorphine,[112]	TD	110.00
	OD	50.00
Codeine,[112]		0.15
Dextromoramide,[232]		2.00
Dextropropoxyphene,[112]		0.15
Diamorphine**		1.00
Dihydrocodeine,[112]		0.13
Dipipanone,[233]		0.50
Fentanyl,[112, 234]	TD	100.00
	OD	50.00
	SPR	160.00
Hydromorphone,[112]		6.00
Methadone,[235]		3.00
Meptazinol,[233]		0.03
Morphine,[112]		1.00
Oxycodone,[112]		1.50
Pentazocine,[234]		0.37
Pethidine,[112]		0.10
Tapentadol,[235]		0.40
Tramadol,[112]		0.20

Notes: *form refers to an oral preparation unless otherwise stated; SPR, sprays (buccal and nasal); TD, transdermal patch; OD, orodispersible; **diamorphine is rarely prescribed as an oral formulation, a specialist pain management pharmacist (RK) advised that oral diamorphine and morphine are equivalent.

Table 5-4. Study variables used during prescription preparation

Study variable	Description	Example*
Patient ID	Patient identification number	123001
End of follow-up	Date the person was censored	30Jul2014**
Event date	Date the opioid was prescribed	01Aug2009**
Product code	Code that corresponds to the product prescribed	7107
Opioid	Opioid drug contained in the product prescribed	10
Form	Formulation of the product prescribed	3
Quantity	Quantity prescribed	5
Numeric daily dose	Prescribed dose - number of units per day	0.33
Days supplied	Number of treatment days prescribed (entered by prescriber)	15
Dose duration	Number of treatment days prescribed (obtained from the common dosages look-up file)	15
Days per patch	Number of days that each patch is intended to be worn	3
Strength/unit	The amount (mg) of the opioid per unit prescribed	3.6
Equianalgesic ratio	Equianalgesic ratio as per Table 5-3	100
OMEQ/unit	The strength per unit, expressed as OMEQ (mg)	360

Notes: *The example refers to a prescription for Durogesic DTrans 50micrograms/hour transdermal patches; **dates are displayed in a readable format, however they are recorded as the number of days elapsed since 1st Jan 1960; OMEQ, oral morphine equivalent

5.3.2 Preparing opioid prescription records for analysis

An overview of the applied DrugPrep data preparation process and the decisions made at each stage are illustrated in Figure 5-2. The following sections provide detail on how the data were handled at each stage in the process.

		Setting values	Generating variables	Identifying records	Imputing values	Removing records
A. Data cleaning	**Quantity and dose**	Minimum and maximum values for quantity and daily dose		Missing and implausible quantities	Missing and implausible quantities via a series of steps	People with any missing or implausible quantities
				Missing and implausible doses	Missing and implausible doses via a series of steps	People with any missing or implausible doses
B. Define prescription length	**Duration and stop date**	Maximum value for duration	Duration based on quantity and daily dose, and stop date based on start date and duration	Records with multiple durations	Replace with mean of durations if ≤30days difference (those >30 days set to missing)	
				Missing and implausible durations	Missing and implausible durations via a series of steps	
C. Handle concurrent and sequential prescriptions	**Overlaps between identical products**			Records for the same product with identical start date	Replace duration with the sum of durations	Excess records
				Records with overlapping days	Start and stop dates, and durations for overlapping days that were moved to gaps and end of records	Overlapping days that extend beyond end of follow-up
	Gaps between identical products	Permissible gap		Records for the same product that have a permissible gap	Stop date and duration extended to close the gap	
D. Calculate daily OMEQ dose	**OMEQ dose/day**	Equianalgesic ratio for each opioid formulation	OMEQ dose/day for each record			
	Total OMEQ dose/day		Opioid exposure status for each record	Overlapping records for different products	OMEQ dose/day with the sum dose for overlapping days	Join records for any opioid into single exposed periods and drop excess records

Notes: Adapted from Pye *et al.* (2018);[230] OMEQ, oral morphine equivalent

Figure 5-2. Overview of prescription preparation process

5.3.2.1 Quantity and daily dose

Setting minimum and maximum values

The setting of plausible values for quantities and daily doses was needed in order to identify and appropriately manage anomalous values. This was an important step in the process since extreme and possibly erroneous values could have resulted in misclassification of exposure, and potentially biased the results presented in subsequent chapters of this thesis.

In an example of the application of the DrugPrep algorithm, Pye *et al.* (2018) used the BNF to guide decisions about which daily doses and quantities for oral hypoglycaemic and oral glucocorticoid drugs qualified as plausible.[44, 230] In their example, Pye *et al.* studied much smaller groups of drugs with clearer clinical guidelines on dosing, compared to opioid analgesics. Instead, to determine plausible quantity and dose values, the opioid prescription records for the study cohort were grouped by opioid drug and formulation to obtain descriptive statistics for the prescribed quantities and ndds. The 1st and 99th percentiles for quantity and ndd values were used to determine the minimum and maximum plausible values respectively. When necessary, these values were adjusted to clinically plausible values with advice from a specialist pain management pharmacist (RK). These adjustments took typical doses, pack sizes, and common durations of supply, based on clinical experience, into consideration.

Identifying implausible values

A dummy variable (1=yes, 0=no) was generated to indicate whether a prescription record had a quantity that exceeded the minimum or maximum plausible quantity recorded for that opioid drug-formulation combination. This process was repeated for ndd values.

Imputing missing and implausible values

Missing values and implausible values were treated in the same way at this stage of the data management process. As such, records that exceeded the plausible values were replaced as missing values for both the quantity and ndd variables. Imputation was performed for missing values in a series of steps:

1. The value (quantity and/or daily dose) was replaced with the value recorded for a subsequent prescription for the same product[5], for the same person. If there was no subsequent prescription for the product, or if the value for the subsequent prescription was missing or implausible, step 2 was followed.

2. The value was replaced with the value recorded for the previous prescription for the same product, for the same person. If there was no previous prescription for the product, or if the value for the previous prescription was missing or implausible, step 3 was followed.

3. The value was replaced with the median value for the individual person, taken from all plausible values recorded for their prescriptions for the same product. If there were no other prescriptions for the product, or if the values recorded for all other prescriptions were also missing or implausible, step 4 was followed.

4. The value was replaced with the population-median value, taken from all plausible values recorded for all prescriptions for the same product, across all people in the study cohort. If there were no other prescriptions for the product, or if the values recorded on all other prescriptions were also

[5] Records with matching product codes were considered as records for the same product.

missing or implausible, these records were removed, as detailed in the following section.

Removing records with incomplete data

Any person that had a missing or implausible quantity or ndd value (after the imputation stage) was excluded from the cohort; all records of their prescriptions were dropped from the dataset.

5.3.2.2 Durations and stop dates

Generating a duration

A duration (in days) was calculated for each opioid prescription record by dividing the quantity by the ndd value (Equation 5-1).

Equation 5-1. Calculation of prescription duration

$$Calculated\ duration = \frac{quantity}{numeric\ daily\ dose}$$

Setting a maximum duration

A maximum plausible duration was set using the median, 1st percentile and 99th percentile of the calculated duration values recorded across all opioid prescription records, in addition to clinical experience of opioid prescribing and common prescription durations.

Identifying missing, implausible or multiple durations

The following three duration variables were available in the dataset:

1. Days supplied: number of treatment days prescribed as entered by prescriber; obtained from the CPRD Therapy file.

2. Dose duration: based on the daily dose; obtained from the common dosages look-up file.

3. Calculated duration: calculated by dividing the quantity supplied by the ndd for each prescription (calculated as outlined in Equation 5-1).

Duration values were considered implausible if they exceeded the maximum duration, in which case they were replaced as missing values. In some instances, prescription records had more than one duration value recorded. A dummy variable was used to indicate the presence of multiple duration values so that one single duration value could be assigned to these prescription records. The following section explains the process for assigning one duration in the presence of multiple recorded durations, and for imputing missing durations.

Imputing multiple durations and missing durations

A ‘new duration’ variable was generated which took the duration value from records with one plausible duration. Records with more than one duration value had their ‘new duration’ ascribed with the mean of all duration values for that record, providing these values were ≤30 days apart. If multiple duration values were present but >30 days apart, the prescription record was considered to have a missing ‘new duration’. Prescription records with a missing ‘new duration’ had this imputed in two steps:

1. The ‘new duration’ was replaced using the median duration for the individual patient, taken from all of their prescriptions for the same product. If there were no other prescriptions for the product, or if the durations recorded on all other prescriptions were also missing, step 2 was followed.

2. The ‘new duration’ was replaced using the population-median duration, taken from all prescriptions for the same product, across the entire study cohort.

Generating a stop date

A stop date was required to identify periods of exposure and non-exposure to opioids; the ‘new duration’ was used to generate a stop date for each prescription record. Stop dates were generated by adding the ‘new duration’ to the start date (Equation 5-2). Records with a stop date that extended beyond the patient’s end of follow-up date had their duration shortened to result in a stop date that matched the patient’s end of follow-up date.

Equation 5-2. Calculation of prescription stop date

$$Stop\ date = start\ date + new\ duration\ (days)$$

5.3.2.3 Overlapping exposure periods

A dummy variable was generated to identify records for identical products that had the same start date, for the same patient; these duplicate records were combined into one period of exposure. A second dummy variable was generated to identify records for identical products for the same person that overlapped with each other; the overlapping periods were moved to gaps in exposure to remove overlaps. The following sections describe these two steps in more detail.

Duplicate prescription records

More than one prescription may be generated by a prescriber on the same day for the same product for the following reasons:

1. Public holidays: practices sometimes provide multiple supplies on the same date to reduce workload during these busy periods and to account for practice closure.

2. Patient holidays: people may request additional supplies in advance to cover the duration of a holiday.

3. Monitored dosage systems (MDS): practices sometimes provide community pharmacies with multiple 7-day duration prescriptions on the same date so that community pharmacies can be remunerated by the NHS for the additional work involved in supplying people with a weekly MDS.

For each person, prescription records were flagged as duplicates if they had the same start date and were for the same product code. Prescription records flagged as duplicated had their durations combined by totalling the durations for the multiple records and replacing the original duration with the summed duration. Of the records combined, just one record with the summed duration was kept; excess records were dropped from the analysis. This process resulted in one single period of exposure containing the combined duration of its constituent records; a stop date for this period was recalculated using the summed duration[6]. Records with a stop date that extended beyond the person's end of follow-up date had their duration shortened to result in a stop date that matched the patient's end of follow-up date.

[6] 6,289 duplicated records had numeric daily doses that were not identical to one another; the combined record was assigned with the greatest numeric daily dose of its constituent records.

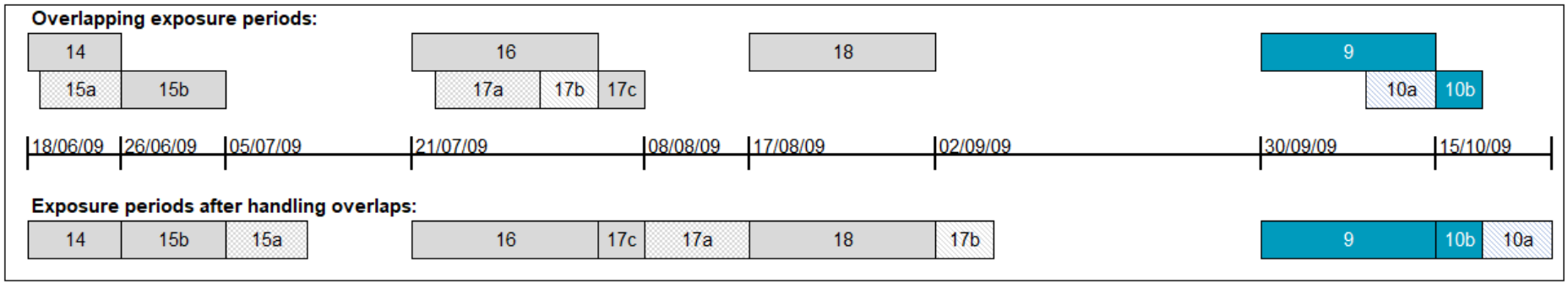
Overlapping exposure periods

Exposure periods may overlap; when the start date of a period occurs before the end date of a previous period. As different opioid products can be used concurrently, overlapping periods for different products may indicate simultaneous use and were retained in the dataset. Overlapping periods for the same product, on the other hand, were more likely to be early supplies that prevented a gap between one prescription and the next; overlaps for identical products were handled using the following process:

1. Overlapping periods were identified by comparing the start date (i.e., event date) and stop dates of neighbouring prescriptions for the same product, for the same person. Periods were flagged as containing an overlap if the start date occurred before the stop date of a previous period (i.e., a prescription with an earlier start date).

2. Overlapping periods were split into: (1) days overlapping with the previous period, and (2) days with no overlap. Overlapping days were moved to a later gap in exposure, however, if the gap was too short to incorporate all overlapping days, the remaining days of overlap were moved to the next available gap (illustrated in Figure 5-3).

3. Some of the moved periods had start and stop dates that extended beyond the person's end of follow-up date. Periods with a start date after the end of follow-up were dropped; those with a stop date after the end of follow up were shortened to result in a stop date that matched the person's end of follow-up date.



Notes: Exposure periods are numbered and overlaps divided into parts a, b or c. Periods coloured grey refer to periods of exposure to codeine, and blue refers to morphine. Periods of exposure to codeine (14 & 15 and 16 & 17) overlapped, 15 was split into parts 15a (days overlap with period 14) and 15b (no days overlap with period 14). Part 15a was carried forward to the next available gap. Periods 16 and 17 overlap, 17 was split into parts 17a, 17b and 17c. Part 17a was carried forward to the first available gap; which was too short to accommodate all days for periods 17a and 17b, therefore, 17b was carried forward to a subsequent gap, after period 18. Periods of exposure to morphine (9 & 10) overlapped, 10 was split into parts 10a and 10b; part 10a was carried forward to the next available gap.

Figure 5-3. Illustration of overlapping exposure periods

5.3.2.4 Gaps between exposure periods

The durations and stop dates of exposure periods were extended to bridge small gaps when these occurred between periods for the same product. These permissible gaps were filled to allow for irregularities in prescribing dates,[236] and to avoid misclassifying exposed days as unexposed.[237] The maximum length of the permissible gaps was set to 15 days based on prior opioid research,[192] and clinical experience (of RK and EP) of opioid prescribing and utilisation.

Identifying exposure periods with a permissible gap

The length of the gaps between exposure periods for the same product, for the same patient, were calculated as detailed in Equation 5-3. Periods that had a gap-length of ≤15 days were flagged as having a permissible gap.

Equation 5-3. Calculating gap-length between periods of exposure

$$Gap\ length = start\ date\ of\ subsequent\ period - end\ date\ of\ current\ period$$

Combining records that have a permissible gap

Exposure periods flagged as having a permissible gap had their duration extended by adding the length of the gap (i.e., ≤15 days) to the existing duration, the stop date was replaced to reflect the new duration.

5.3.2.5 Exposure status and OMEQ dose

Calculating OMEQ dose per day

Each exposure period was assigned with a dose in the form of OMEQ dose per day. The OMEQ/day was obtained by: (1) merging the dataset with the opioid lookup file to obtain the OMEQ per unit for each product code (see Appendix P) and (2) calculating the OMEQ/day using Equation 5-4.

Equation 5-4. Calculating OMEQ/day

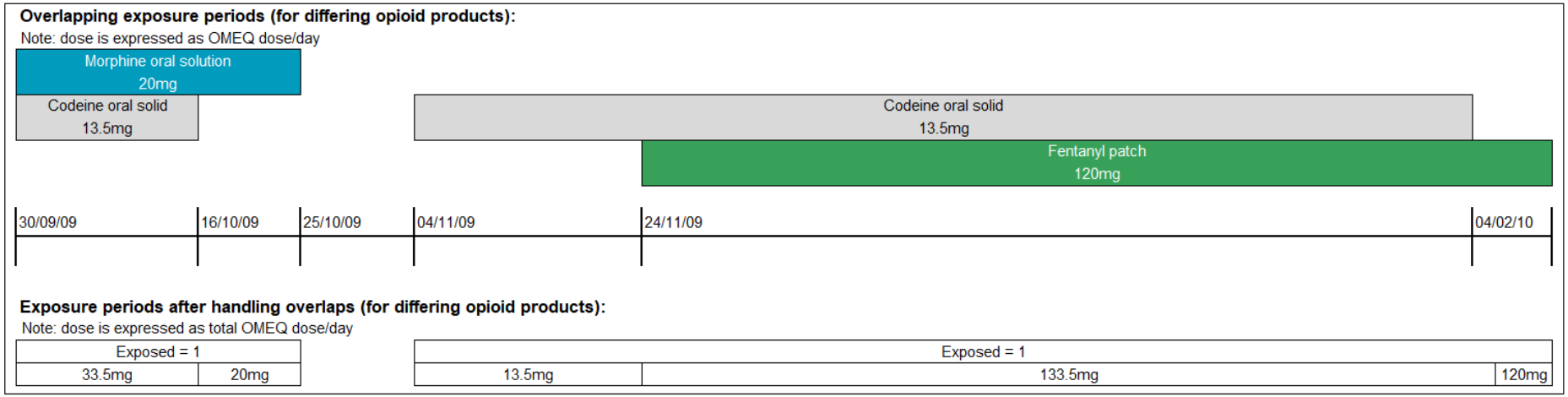
$$OMEQ/day = numeric\ daily\ dose \times OMEQ\ per\ unit$$

The following steps outline the generation of a total OMEQ dose per day, and a binary indicator for opioid exposure, which accounts for concurrent use of differing opioid products. This next stage resulted in the loss of data regarding the specific opioid drug prescribed, therefore a dataset was set aside for some of the analyses reported in Chapter 6 so that data regarding the opioid drug prescribed could be analysed.

Calculating total OMEQ dose per day

In section 5.3.2.3, the method for handling overlapping periods of exposure to the same product was outlined. Following this process, there remained periods of exposure to differing opioid products that overlapped with one another; it is clinically feasible that people used different opioid products concurrently, and therefore, the OMEQ dose/day for differing products was summed for days of overlap.

Overlapping products were identified by comparing the start and end dates (as outlined in section 5.3.2.3), the periods were split into one-day periods. One-day periods with the same start date, for the same person were combined by summing the OMEQ dose/day and dropping the surplus periods for that start date. This process resulted in periods of exposure (to any opioid) that did not overlap, each of which was assigned with a total OMEQ dose per day (total OMEQ/day), as illustrated in Figure 5-4.



Notes: OMEQ, oral morphine equivalent

Figure 5-4. Illustration of overlapping exposure periods for different opioid products

Generating an exposure status

During the previous step, variables relating to the specific opioid prescribed were removed so that a total OMEQ dose per day could be generated. A dummy variable was generated to indicate exposure to any opioid (1=exposed) for all periods at this stage; unexposed time was added at a later stage, the process for which is detailed in Chapter 8.

5.3.3 Data analysis

Descriptive statistics were used to calculate the proportion of each opioid drug prescribed, using the total number of opioid prescription records as the denominator. The proportion of prescription records for each opioid drug-formulation combination was calculated by dividing the number of prescription records for each opioid drug-formulation category by the total number of prescription records within each opioid drug category. The proportion of missing ndd values for each opioid drug-formulation category was calculated by dividing the number of records with a missing daily dose value within each opioid drug-formulation category by the total number of prescription records within the corresponding opioid drug-formulation category. The number of prescription records and people processed at each stage of the prescription preparation process was presented as numbers and proportions.

Where the spread of data was inspected for decisions regarding the plausibility of values and imputation, the distribution of values was initially inspected to determine whether a mean (with SD) or median (with IQR) was an appropriate statistic to guide decisions. All data management processes and statistical analyses were carried out using the statistical software - Stata/MP 15 (StataCorp, Texas, USA).

5.4 Results

27,266,882 opioid prescription records were extracted from the CPRD Therapy files for the cohort of 1,790,333 opioid users. Most prescription records were for weak opioid drugs; 49.5% of prescriptions were for codeine, 18.6% were for tramadol, and 14.0% for dihydrocodeine. Morphine (7.7%), buprenorphine (3.8%), oxycodone (3.2%) and fentanyl (2.6%) accounted for the majority of strong opioids prescribed (Table 5-5).

5.4.1 Quantity and daily dose

The minimum and maximum plausible values for each opioid drug-formulation category ranged between 1 to 2,000 units. The proportion of missing ndd values ranged between 2.3% to 100.0% depending on the combination of opioid drug and formulation prescribed (Table 5-5).

Imputing missing or implausible quantities

Quantities were identified as implausible if they were less than the minimum plausible quantities or more than the maximum plausible quantities listed in Table 5-5. In total, 11,618 (0.04%) prescription records contained implausible quantities and 6,058 (0.02%) records were missing quantity values. Following the imputation process outlined in section 5.3.2.1, five prescription records remained implausible or missing (Figure 5-5) and were dropped during the next step.

Table 5-5. Minimum and maximum values for quantity, numeric daily dose and duration, by opioid drug and formulation

Drug (*n*, %*)	SA	LA	TD	SOL	EFF	OD	SPR	Prescription records		Numeric daily dose			Quantity	
								(*n*)	(%**)	Missing***	Min	Max	Min	Max
Codeine	✓							12,647,831	93.66%	31.18%	0.5	48	1	600
13,504,574 (49.53%)					✓			849,758	6.29%	22.32%	1.0	12	7	500
				✓				6,985	0.05%	72.71%	4.0	60	100	1,500
Tramadol	✓							4,131,963	81.44%	49.19%	0.5	48	1	600
5,073,367 (18.61%)		✓						916,669	18.07%	19.27%	0.5	9	1	480
					✓			19,031	0.38%	52.16%	0.5	8	20	224
						✓		5,578	0.11%	70.15%	0.5	8	14	600
				✓				126	0.00%	90.48%	-	-	10	60
Dihydrocodeine	✓							3,555,375	93.10%	26.80%	0.5	12	1	500
3,818,698 (14.00%)		✓						260,141	6.81%	19.45%	0.5	6	1	448
				✓				3,169	0.08%	60.43%	5.0	120	50	1,350
					✓			13	0.00%	38.46%	7.0	8	12	120
Morphine		✓						1,222,113	58.47%	27.90%	0.5	24	1	720
2,090,320 (7.67%)				✓				726,600	34.76%	82.00%	0.5	90	10	2,000
	✓							134,166	6.42%	63.51%	0.5	12	1	500
					✓			7,441	0.36%	33.22%	0.5	8	14	120

Notes: footnote on next page

Table 5-5. Minimum and maximum values for quantity, numeric daily dose and duration, by opioid drug and formulation [continued]

Drug (*n*, %*)	SA	LA	TD	SOL	EFF	OD	SPR	Prescription records (*n*)	Prescription records (%**)	Numeric daily dose Missing***	Numeric daily dose Min	Numeric daily dose Max	Quantity Min	Quantity Max
Buprenorphine 1,035,454 (3.80%)			✓					949,278	91.68%	54.39%	0.1	0.7	1	24
						✓		86,176	8.32%	48.57%	0.5	10.0	1	448
Oxycodone 876,881 (3.22%)		✓						558,435	63.68%	22.86%	0.5	12.0	1	500
	✓							249,225	28.42%	57.23%	0.5	16.0	1	448
				✓				69,221	7.89%	86.89%	1.3	80.0	10	2,000
Fentanyl 719,136 (2.64%)			✓					697,284	96.96%	41.34%	0.1	0.7	1	40
						✓		21,546	3.00%	80.71%	0.5	12.0	3	180
							✓	306	0.04%	95.10%	4.0	6.0	6	80
Meptazinol 46,719 (0.17%)	✓							46,719	100.00%	33.76%	1.0	12.0	4	224
Pethidine 32,029 (0.12%)	✓							32,029	100.00%	69.56%	1.0	9.0	1	336
Tapentadol 30,662 (0.11%)		✓						24,063	78.48%	25.48%	1.0	10.0	10	150
	✓							6,539	21.33%	53.10%	1.0	8.0	14	224
				✓				60	0.20%	81.67%	10.0	10.0	100	200
Dipipanone 12,820 (0.05%)	✓							12,820	100.00%	41.29%	1.0	8.0	1	336
Methadone 12,382 (0.05%)	✓							12,382	100.00%	70.88%	1.0	20.0	1	340

Notes: footnote on next page

Table 5-5. Minimum and maximum values for quantity, numeric daily dose and duration, by opioid drug and formulation [continued]

Drug (*n*, %*)	SA	LA	TD	SOL	EFF	OD	SPR	Prescription records		Numeric daily dose			Quantity	
								(*n*)	(%**)	Missing***	Min	Max	Min	Max
Hydromorphone		✓						5,664	64.52%	29.03%	1.0	6.0	14	168
8,778 (0.03%)	✓							3,114	35.48%	74.04%	2.0	6.0	14	168
Pentazocine	✓							3,510	100.00%	35.81%	1.0	8.0	20	112
3,510 (0.01%)														
Alfentanil							✓	870	100.00%	100.00%	0.1	1.1	5	120
870 (0.00%)														
Diamorphine	✓							343	90.74%	58.60%	15.0	15.0	1	500
378 (0.00%)				✓				35	9.26%	97.14%	2.0	6.0	1	200
Dextropropoxyphene	✓							267	99.63%	2.25%	4.0	8.0	100	100
268 (0.00%)				✓				1	0.37%	100.00%	6.0	6.0	50	50
Dextromoramide	✓							36	100.00%	97.22%	1.0	1.0	5	70
36 (0.00%)														

Notes: *prescription records for each opioid, as a proportion of all opioid prescription records; ** as a proportion of the total prescription records within each opioid drug category; ***as a proportion of prescription records within each opioid drug-formulation category; SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray.

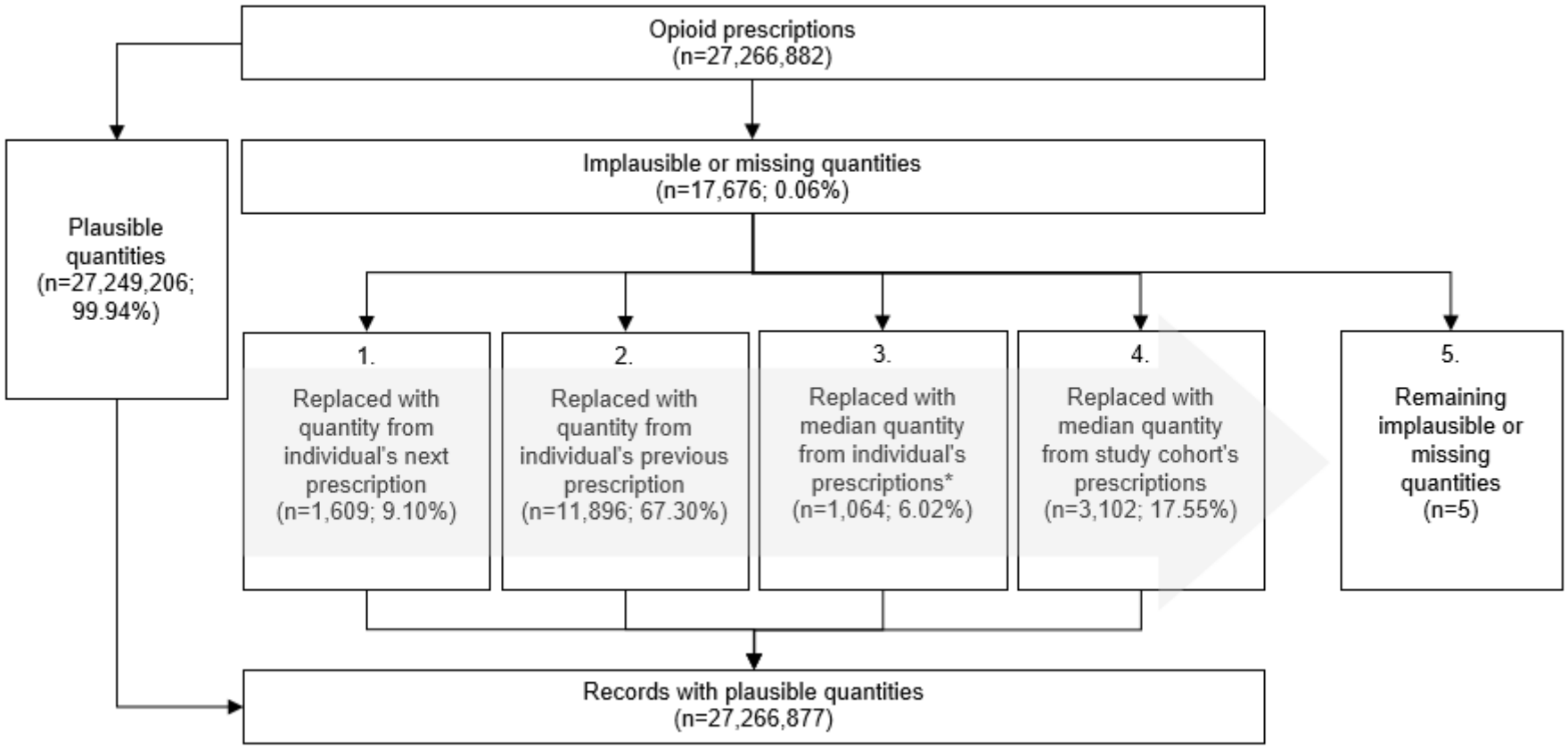


Figure 5-5. Imputing implausible or missing quantities

Imputing missing or implausible doses

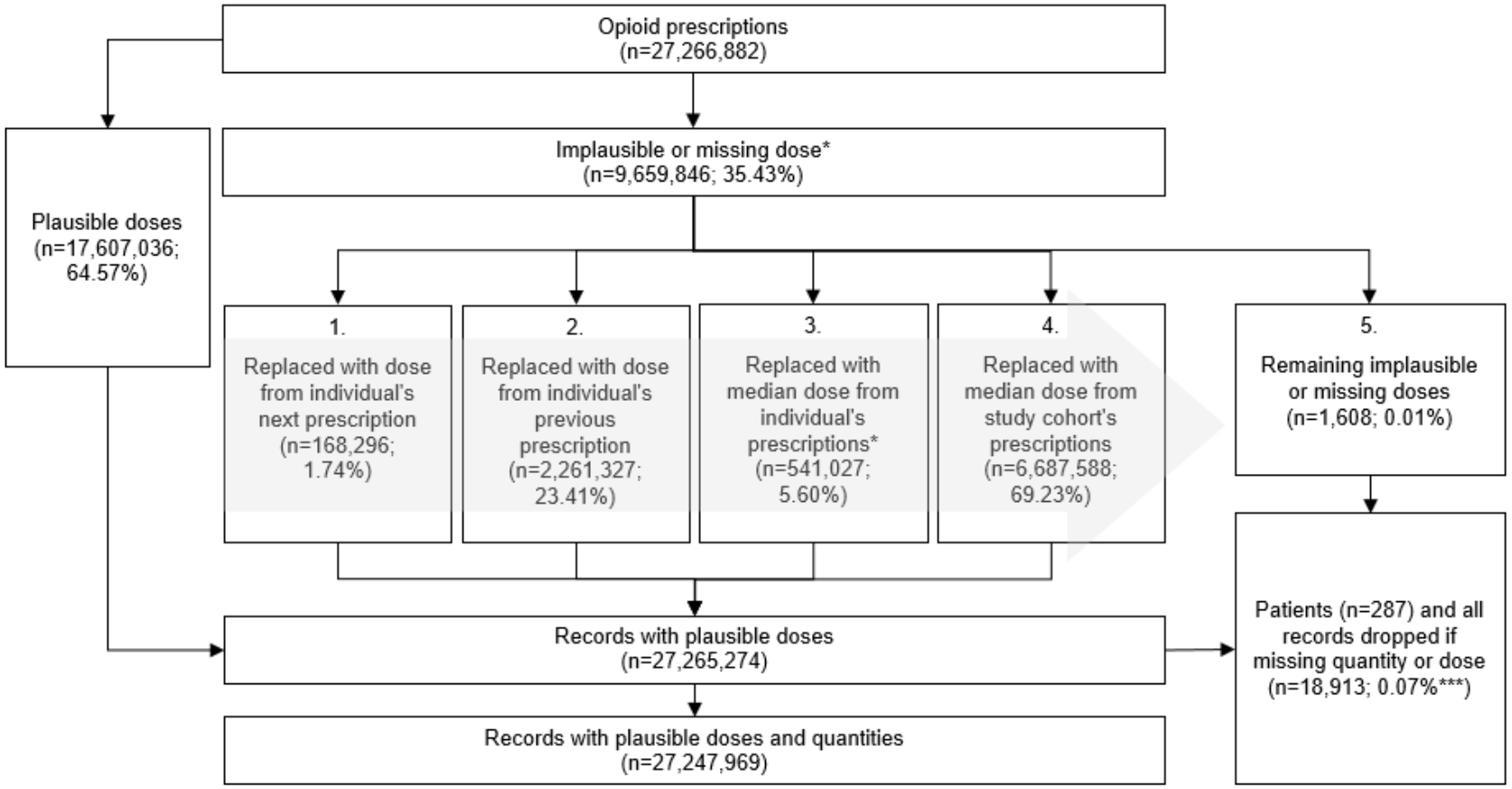
Numeric daily doses were identified as implausible if they were less than the minimum plausible daily doses or more than the maximum plausible daily doses listed in Table 5-5. In total, 5,589 (0.02%) prescription records contained implausible daily doses and 9,654,371 (35.4%) prescription records were missing daily doses. These implausible and missing daily doses were replaced using the method outlined in section 5.3.2.1. Following this process, 1,608 (0.01%) prescription records from 287 people were considered to have missing daily doses. These 287 people and their opioid prescription records (n=18,913) were dropped and excluded from subsequent analyses (Figure 5-6).

5.4.2 Durations and stop dates

Implausible durations

A 90-day maximum duration was chosen based on the spread of calculated duration values across all opioid prescriptions (median=16 days; 1st percentile=3 days, 99th percentile=60 days) and by clinical experience (EP and RK) of opioid prescribing. In total, 67,745 (0.25%) duration values exceeded 90 days and were considered missing[7].

[7] Some prescription records contained more than one duration value, this relates to the proportion of duration values that were missing, and not the proportion of prescription records with missing duration values.



Notes: *dose refers to the numeric daily dose variable; **this step applies when a quantity replaced by an individual's previous or next prescription continues to be implausible; ***proportion of all opioid prescription records.

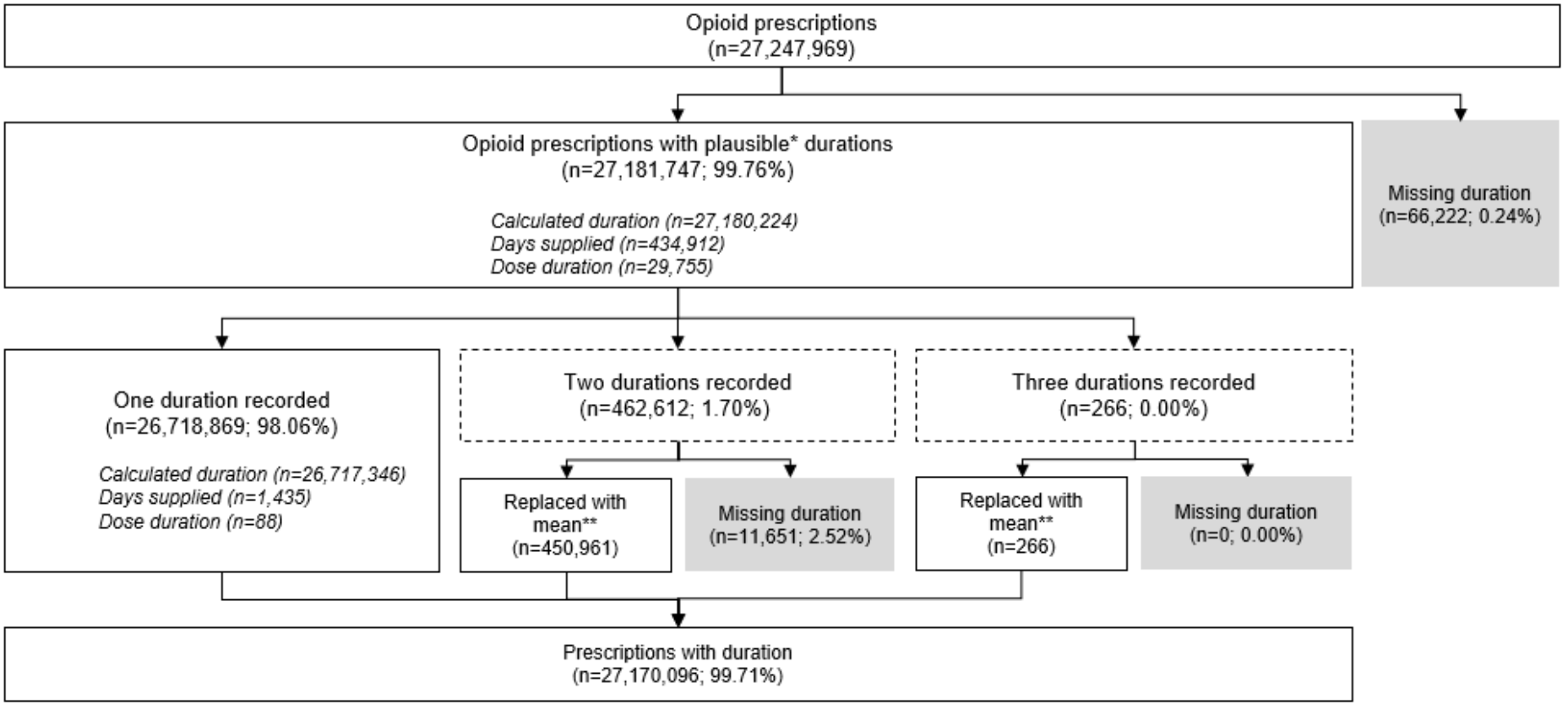
Figure 5-6. Imputing implausible or missing numeric daily doses

Prescription records with multiple durations

In total, 27,181,747 (99.8%) prescription records contained plausible durations, of which 98.1% had one recorded duration, 1.7% had two durations, and <0.01% had three durations recorded. Durations were replaced with the mean in 450,961 prescription records that had values ≤30days apart. Following this process, 99.7% of records contained one plausible duration and a total of 77,873 (0.3%) records had missing duration values (Figure 5-7).

Imputing missing durations and generating a stop date

Of the 77,873 prescription records with missing durations, 79.0% (n=61,540) had these replaced using the patient-median duration for their prescriptions for the exact same product; the remaining 21.0% of records (n=16,333) had no durations available to calculate a patient-median duration and were replaced with the population-median duration for the product. Following this process, all 27,247,969 prescription records had a stop date generated using their event date and duration (as detailed in section 5.3.2.2).



Notes: *durations considered plausible if ≤90 days; **replaced with mean if ≤30 days between values

Figure 5-7. Handling multiple duration values

5.4.3 Overlapping exposure periods

Duplicate prescription records

489,895 (1.8%) records were identified as duplicate records. Of these, 207,148 had their duration and stop date extended, and 282,747 periods were dropped[8]. Following this process, 26,965,222 exposure periods remained.

Overlapping exposure periods

6,227,144 (23.1%) exposure periods were identified as containing days of exposure that overlapped with other periods for the same product, for the same person. Overlapping periods were split into parts and moved to gaps in exposure. Following this process, there were 40,419,693 periods of exposure, with no overlaps between periods for the same product; 2,169,239 of these periods were dropped because their start date occurred after the person's end of follow-up date; 38,250,454 exposure periods remained.

5.4.4 Gaps between exposure periods

Of the 38,250,454 exposure periods, 26,643,497 (69.7%) had a permissible gap (≤15 days) and their durations and stop dates were extended by ≤15 days to close the gap between exposure periods.

5.4.5 Exposure status and OMEQ dose

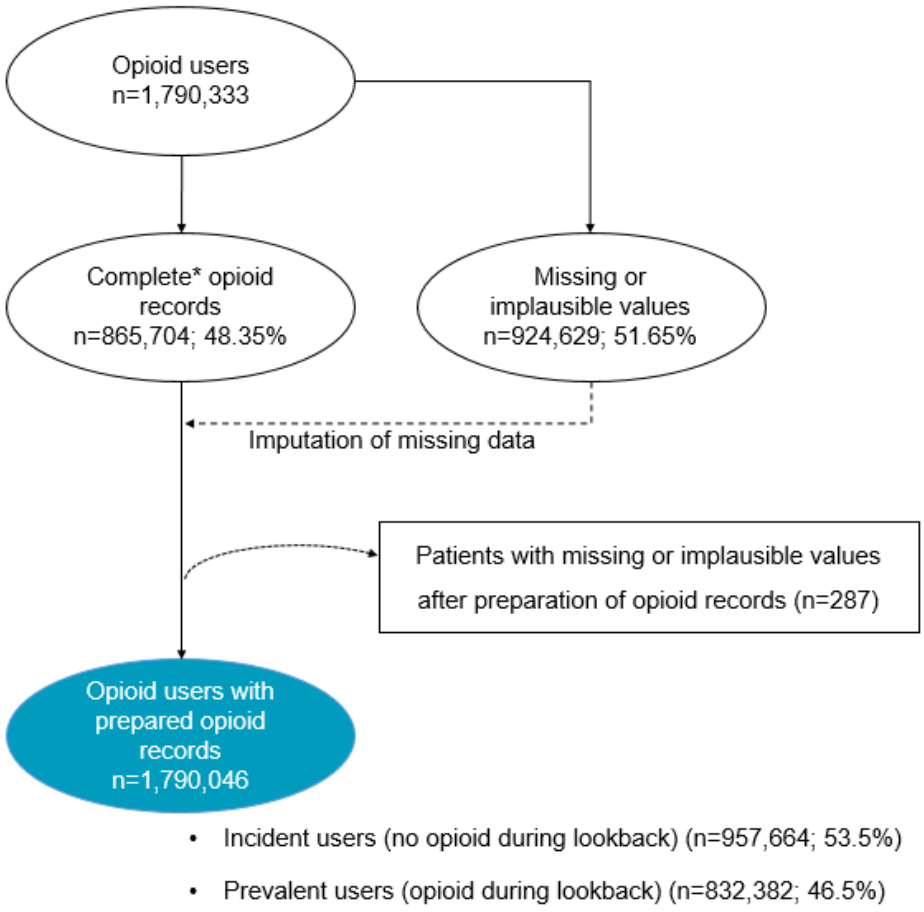
An OMEQ dose per day was calculated for each period as outlined in section 5.3.2.4 and this dataset, which contained 38,250,454 periods that specified the opioid drug prescribed, was set aside to describe the utilisation of opioids (Chapter 6). A copy of this dataset was processed (as detailed in section

[8] In some cases a period overlapped with more than one period, therefore more periods were dropped than extended.

5.3.2.3) to combine periods of exposure to differing products; an indicator of opioid exposure was generated, and a total OMEQ dose/day was generated for overlapping periods, this resulted in a second dataset used for analyses in Chapters 6 and 8.

5.4.6 Study cohort

Following the preparation of prescriptions for the original study cohort of 1,790,333 people, 287 people were dropped due to missing prescription data that could not be imputed; 1,790,046 people remained in the final cohort, 53.5% were incident and 46.5% were prevalent opioid users (Figure 5-8).



Notes: *People with no missing or implausible quantity, dose, duration values, and one stop date available, for all opioid records

Figure 5-8. Study cohort after preparation of opioid prescriptions

5.5 Discussion

This chapter has outlined the process used for preparing the prescription records that were extracted for the 1,790,333 people in the study cohort. After this process, 1,790,046 people, with complete (or imputed) prescription records, remained in the cohort. Two datasets were produced for the analyses presented in Chapter 6 and Chapter 8: one contained the opioid products prescribed and the other contained opioid exposure status and the total OMEQ dose per day.

The approach described in this chapter has applied and extended Pye *et al's* (2018) DrugPrep algorithm,[230] to prepare prescription records for opioid analgesics, and to generate a measure of daily OMEQ dose. The analysis of missing opioid prescription record values presented in Chapter 4 showed that there was a high level of missing data for both dose and duration variables, and that these data were MNAR. The approach taken to impute these missing data has taken account of this and has used a stepwise combination of approaches to imputation; using the person's next prescription, previous prescription, patient-median and population-median of values from records for the same opioid product.

A previous study has shown that CPRD prescription data, prepared according to the DrugPrep algorithm, provide reasonable estimates of exposure status when compared to self-reported use of glucocorticoid drugs in 78 people.[238] The study compared current glucocorticoid exposure based on prepared CPRD prescription data and 24 hour recall diaries of people, for a given day during follow-up. The CPRD data correctly classified 67 (86%) people as exposed/unexposed to glucocorticoids. When using the CPRD prescription data to estimate the current dose for glucocorticoid users, there was a mean

difference of 3.2mg (SD: 4.2mg) between self-reported dose and the CPRD-estimates. The findings support the use of the DrugPrep algorithm to prepare prescription data. However, it is noted that each study using the algorithm will vary in their decisions and assumptions made throughout the preparation process. Additionally, the medication class under investigation and the setting in which cohorts are identified will also affect the degree of exposure misclassification present.

5.5.1 Strengths and limitations

An important strength of this work is that missing prescription data were handled using a systematic approach and that records were handled so that duplicate prescriptions, gaps and overlaps were accounted for. In doing so, this chapter has made some assumptions regarding daily doses; each of which may have led to some degree of exposure or dose misclassification. Firstly, duplicate exposure periods were combined and where the dose differed; the combined period took the greatest dose value, which may have resulted in an overestimation of the daily opioid dose. The number of instances where this occurred was small and is therefore not expected to influence the results in subsequent analyses. Secondly, overlapping periods were moved to gaps; where the dose differed between overlapping periods it was assumed that the earliest prescription was finished first, this may have introduced a delay in dose changes. Thirdly, permissible gaps (<15days) were filled at the dose recorded for the prescription record immediately prior to the gap. Finally, it was assumed that overlapping opioid products that differed to one another were taken concurrently, this may have over-estimated the total OMEQ dose/day if these products were not used together on overlapping days.

It is acknowledged that the total OMEQ dose/day variable may not accurately reflect the actual daily OMEQ dose prescribed to a person on a day-to-day basis, and that people may also deviate from the prescribed daily dose given the nature of painful conditions and variability in symptoms over time.

5.6 Conclusions

The application of the DrugPrep algorithm provided a systematic approach to imputing prescription data that was implausible or MNAR. Additionally, periods of exposure were prepared to provide a time-varying measure of opioid exposure, handling gaps and overlaps between prescriptions. Finally, the extension of the DrugPrep algorithm to generate a daily OMEQ dose has provided a time-varying measure of the intensity of opioid exposure. The datasets generated from the prescription preparation process were used to: describe longitudinal exposure to opioids (Chapter 6) and to investigate the effect of opioid exposure on the risk of bone fracture, taking into account OMEQ dose and proximity to opioid initiation (Chapter 8).

Chapter 6: Population and patient-level trends in opioid utilisation

6.1 Abstract

Background

Observational studies from several countries suggests an increase in opioid utilisation but few studies have examined within-patient utilisation over time. The aims of this study were to: describe opioid utilisation in the UK between 2008 and 2017, and to describe opioid utilisation from initiation to discontinuation among new opioid users.

Methods

This was a retrospective cohort study and repeat cross-sectional study of people prescribed opioids between June 2008 and May 2017. Prescriptions for opioids were split by study-year; utilisation measures included: number of users, opioid drugs prescribed, annual days covered and daily dose. Prescriptions for new users were split by patient-year, starting from opioid initiation. Utilisation measures included: time to first gap and to discontinuation; opioid drugs prescribed; days covered per patient-year; daily dose and persistency.

Results

The proportion of registrants prescribed opioids increased from 14.5% to 15.9% between 2008 and 2017, and the proportion of strong opioid users rose from 3.0 to 6.6%. In 2008, strong opioid users were covered for a median duration of 155 days per year (IQR: 28, 340 days) whereas weak opioid users were covered for 30 days per year (IQR: 15, 110 days). The median daily OMEQ dose for strong opioid users remained stable at 60mg (IQR: 29, 115mg) whereas it increased from 18mg (IQR: 8, 27mg) to 25mg (IQR: 10, 27mg) for weak opioid users. Patient-level analyses of new opioid users showed that 97.5% were initiated on weak opioids and half were prescribed

opioids for ≤16 days (95%CI: 16, 16 days); 2.5% were initiated on strong opioids and half were prescribed opioids for ≤40 days (95%CI: 36, 43 days). 95.9% of new users were not persistent users in their first patient-year, and <2.0% became persistent users.

Conclusions

Using data from the CPRD collected between 2008 and 2017, this study demonstrates that the proportion of strong opioid users has doubled. Additionally, strong opioid users were prescribed opioids for longer durations than those prescribed weak opioids. The impact of dose and duration on patient safety warrants further investigation.

6.2 Introduction

Cross-sectional and longitudinal opioid utilisation studies from the US,[9, 239, 240] Canada,[6] Australia,[8] and several European countries,[7, 227, 241] including the UK,[5, 110, 111, 124, 242, 243] have shown a substantial increase in opioid utilisation. In the UK, opioid prescribing has increased over the past two decades. Curtis *et al.* (2018), using NHS prescribing data for England, reported a 34% increase in the number of opioid prescriptions issued between 1998 and 2016.[111] Moreover, after correcting for oral morphine equivalency, this increase was reported to be 127%, showing that opioids were being prescribed at higher OMEQ doses. These findings are consistent with an earlier study of UK opioid utilisation by Zin *et al.* (2010). In their study, Zin *et al.* used UK prescribing data from the CPRD database and showed a 466% increase in the number of strong opioid users between 2000 and 2010.[5] However, the study was restricted to commonly prescribed strong opioids, and therefore did not describe utilisation of opioids considered to be weak (i.e., codeine, dihydrocodeine and tramadol).

In another UK study, Bedson *et al.* (2016) investigated opioid prescribing in people with musculoskeletal conditions and found that the incidence of long-term opioid prescribing among these people increased by 38% between 2002 and 2009.[110] However, the study only included people that had a record of a musculoskeletal condition in close proximity to their initial opioid prescription, and further restricted their cohort to those receiving at least three opioid prescriptions within a 90-day period from the date of opioid initiation. The study conducted by Bedson *et al.* therefore did not describe trends in opioid utilisation for people that may use opioids in the short-term or intermittently following their initial prescription.

These existing UK studies have reported trends in opioid utilisation over time on a population-level (i.e., over study-years), however these have not provided a description of changes in daily OMEQ doses and annual days covered per person, taking concurrent use of different opioid products into account. Providing a better measure of daily OMEQ doses would provide a better understanding of opioid utilisation in the UK, and among new users of opioids.

One retrospective cohort study has described treatment patterns among 46,043 people who initiated opioids in the UK between 2008 and 2012. The study found that 89.5% of new opioid users were initiated on weak opioids, and that the duration of continuous opioid treatment was <6 months.[123] The study censored people at the end of a period of continuous opioid use, defined by a period of non-exposure to opioids for >30 days, therefore the study did not examine intermittent opioid exposure, which may have under-estimated the duration of opioid treatment. Another limitation was that no cross-sectional description of opioid treatment patterns was provided, which would have enabled a better understanding of changes in opioid utilisation over patient follow-up. Moreover, the study used a one-year exposure lookback period to identify new users of opioids, the length of this period may have increased the potential for misclassification of prevalent users as new users, meaning that the study findings might not generally represent new users of opioids.

More research is needed to enable a better understanding of changes in opioid utilisation at an individual patient-level, especially regarding daily OMEQ dose, duration of use and persistency, from the date of first opioid prescription to end of follow-up (i.e., patient-years).[113] It remains unclear how

long people remain on continuous or intermittent opioid treatment, how prescribing frequency and doses change over time within people and what proportion of people become persistent users of opioids.

6.3 Aims and objectives

Given the weaknesses and evidence gaps in the literature to-date, the aim of this chapter was to describe population-level and patient-level trends in opioid utilisation over a long duration of follow-up (i.e., between 2008 and 2017). The objectives of this chapter were to:

1. Describe the process for managing opioid prescription records to enable the generation of annual measures of opioid utilisation for population- and patient-level analyses.

2. Describe population-level opioid utilisation between 2008 and 2017.

3. Describe patient-level opioid utilisation for a subgroup of incident opioid users, from the date of first opioid prescription to end of follow-up.

6.4 Method

6.4.1 Study design

This was a retrospective cohort study and repeat cross-sectional study of people prescribed opioids between June 2008 and May 2017.

6.4.2 Data source

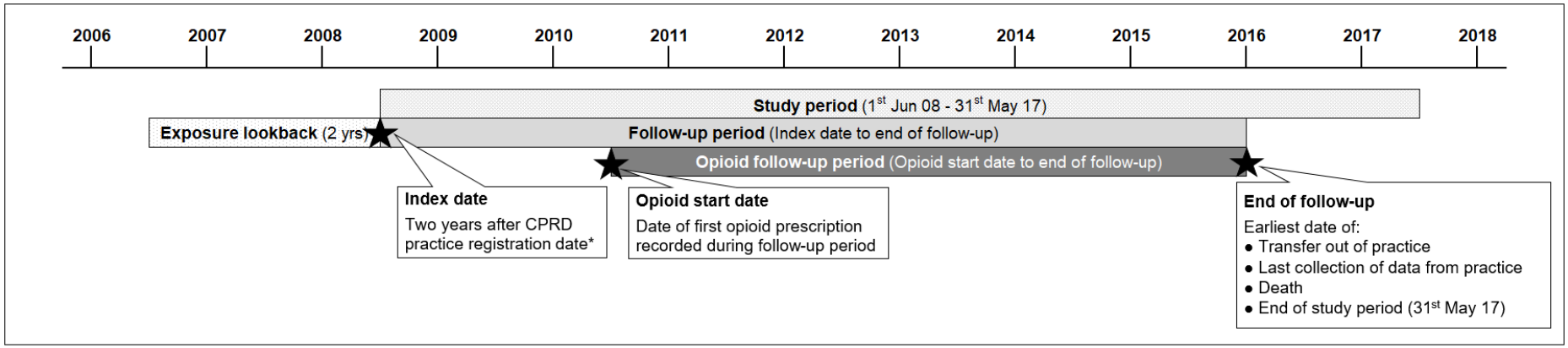
In the previous chapter (Chapter 5), prescription records were extracted from the CPRD database and prepared for analysis using an adapted version of the DrugPrep algorithm.[230] The original extraction of prescription records and

the two datasets generated, as explained in Chapter 5, were used for this study.

6.4.3 Cohort identification

All prevalent and incident opioid users with complete (or imputed) opioid prescription data, as described in Chapter 5, were included in the population-level analysis. Only incident opioid users were included in the patient-level analysis; prevalent users were excluded so that every person could be followed from the date they initiated opioids.

In the population- and patient-level analyses, people were followed from the date of their first record of an opioid prescription (opioid start date) until their end of follow-up date, this period is referred to as the ‘opioid follow-up period’ (Figure 6-1).



Notes: *the latest of: (1) CPRD practice registration date, (2) CPRD practice 'up to standard' date or (3) 1st June 2006.

Figure 6-1. Illustration of opioid follow-up period

6.4.4 Study variables

Chapter 5 described the process for preparing the opioid prescription records into periods of exposure to opioids. Two datasets were generated, one contained data regarding the opioid drug that people were prescribed, and the other contained an OMEQ/day that was calculated by combining opioid products prescribed concurrently. Additionally, the original extraction of opioid prescription records[9], prior to the prescription preparation process, was used for some outcome measures. The key variables used in the analyses of these three datasets are detailed in Table 6-1, Table 6-2 and Table 6-3.

Table 6-1. Dataset I: Unprepared opioid prescription records

Study variable	Description	Example
Patient ID	Patient identification number	123001
Opioid start date	Start date of the first opioid prescription recorded during a patient's follow-up	01Aug2008*
End of follow-up	Date the person was censored	30Jul2014*
Event date	Date associated with the prescription, as entered by the prescriber	01Aug2009*
Opioid	Opioid drug contained in the product prescribed	10
Weak** opioid	Dummy variable to indicate whether opioid prescribed was weak (=1) or strong (=0)	0
New user	Dummy variable to indicate whether person was an incident (=1) or prevalent (=0) user of opioids on their index date	1

Notes: *dates are displayed in a readable format, however they recorded as the number of days elapsed since 1st Jan 1960; **weak opioid refers to codeine, dihydrocodeine and tramadol, strong opioids are any other opioid drug.

[9] For people included in the cohort of 1,790,046 people with complete (or imputed data).

Table 6-2. Dataset II: Prepared opioid exposure period, including opioid drug

Study variable	Description	Example
Patient ID	Patient identification number	123001
Opioid start date	Start date of the first opioid prescription recorded during a patient's follow-up	01Aug2008*
End of follow-up	Date the person was censored	30Jul2014*
Start date	Date that an opioid exposure period began	01Aug2009*
Stop date	Date that an opioid exposure period ended i.e., the first day not covered by the exposure period	31Aug2009*
Opioid	Opioid drug contained in the product prescribed	10
Duration	Number of treatment days covered by an exposure period	30
OMEQ/day	The OMEQ dose per day (mg)	120
Weak** opioid	Dummy variable to indicate whether opioid prescribed was weak (=1) or strong (=0)	0
New user	Dummy variable to indicate whether person was an incident (=1) or prevalent (=0) user of opioids on their index date	1

Notes: *dates are displayed in a readable format, however they recorded as the number of days elapsed since 1st Jan 1960; **weak opioid refers to codeine, dihydrocodeine and tramadol, strong opioids are any other opioid drug; OMEQ, oral morphine equivalent; mg, milligrams.

Table 6-3. Dataset III: Prepared opioid exposure periods, including combined OMEQ/day

Study variable	Description	Example
Patient ID	Patient identification number	123001
Opioid start date	Start date of the first opioid prescription recorded during a patient's follow-up	01Aug2008*
End of follow-up	Date the person was censored	30Jul2014*
Start date	Date that an opioid exposure period began	01Aug2009*
Stop date	Date that an opioid exposure period ended i.e., the first day not covered by the exposure period	31Aug2009*
Duration	Number of treatment days covered by an exposure period	30
Combined OMEQ/day	The OMEQ dose per day (mg), where more than one opioid product covered a given day the OMEQ reflects the combined OMEQ across all opioid products	120
New user	Dummy variable to indicate whether person was an incident (=1) or prevalent (=0) user of opioids on their index date	1

Notes: *dates are displayed in a readable format, however they recorded as the number of days elapsed since 1st Jan 1960; OMEQ, oral morphine equivalent; mg, milligrams

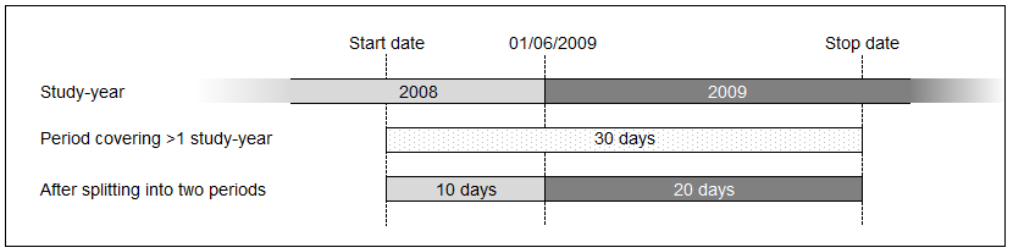
6.4.5 Preparing prescription data for analysis

6.4.5.1 Population-level analyses

The unprepared prescription records (Dataset I) were split into separate parts so that there were nine datasets, each corresponding to a study-year. For example, the dataset for study-year 2008 contained prescriptions with an event date between 1st June 2008 and 31st May 2009. Prescriptions for opioid drugs that were not commonly prescribed[10] were grouped together as 'other' opioids. There remained 8 categories for opioid drugs (buprenorphine, codeine, dihydrocodeine, fentanyl, morphine, oxycodone, tramadol, and other opioids).

The prepared opioid exposure periods, with opioid drug (Dataset II) were also split so that there were nine datasets corresponding to each study-year. Exposure periods that started in one study-year and ended in another study-year were split so that they ended at the end of the study-year and a new period started on the following day, at the start of the next study-year; durations, start dates and stop dates were updated for these split periods (Figure 6-2). Periods of exposure to opioid drugs that were not commonly prescribed were grouped together as 'other' opioids. The prepared opioid exposure periods, with combined OMEQ/day (Dataset III) were also split by study-year as illustrated in Figure 6-2.

[10] Alfentanil, dextromoramide, dextropropoxyphene, diamorphine, dipipanone, ethylmorphine, hydromorphone, levorphanol, meptazinol, methadone, omnopon, papaveretum, pentazocine, pethidine, phenazocine, tapentadol.



Notes: Original 30-day exposure period covered study-years 2008 and 2009. This was split into two periods covering 10 days and 20 days, each within one study-year only.

Figure 6-2. Illustration of handling exposure periods that cover >1 study-year

6.4.5.2 Patient-level analyses

For all three datasets the new user variable was used to identify incident users, all prescription records and exposure periods for prevalent opioid users were dropped from the datasets and analyses.

The unprepared prescription records (Dataset I) were split into nine datasets, each corresponding to a patient-year. The start and end date for each patient-year was generated for each person based on their opioid start date (Table 6-4). Prescription records for opioid drugs not commonly prescribed were grouped together as ‘other’ opioids.

The prepared opioid exposure periods, with opioid drug (Dataset II) were also split so that there were nine datasets corresponding to each patient-year. Periods that covered >1 patient-year were handled as illustrated in Figure 6-2. Periods of exposure to opioid drugs that were not commonly prescribed were grouped together as ‘other’ opioids. The prepared opioid exposure periods, with combined OMEQ/day (Dataset III) were also split by patient-year as illustrated in Figure 6-2.

Table 6-4. Definition of start and end dates for each patient-year

Year	Start date	End date
1	Opioid start date	Opioid start date + 365.25 days
2	Opioid start date + 365.25 days	Opioid start date + (2*365.25 days)
3	Opioid start date + (2*365.25 days)	Opioid start date + (3*365.25 days)
4	Opioid start date + (3*365.25 days)	Opioid start date + (4*365.25 days)
5	Opioid start date + (4*365.25 days)	Opioid start date + (5*365.25 days)
6	Opioid start date + (5*365.25 days)	Opioid start date + (6*365.25 days)
7	Opioid start date + (6*365.25 days)	Opioid start date + (7*365.25 days)
8	Opioid start date + (7*365.25 days)	Opioid start date + (8*365.25 days)
9	Opioid start date + (8*365.25 days)	Opioid start date + (9*365.25 days)

Notes: Opioid start date is the event date of the first opioid prescription record for a person during their follow-up period.

6.4.6 Outcome measures

The following outcome measures were generated using the study variables available in each dataset, these are presented separately for the population-level and patient-level analyses.

6.4.6.1 Population-level outcome measures

Proportion of people with opioid coverage

The number of people who had ≥1 day of opioid prescription coverage[11] in a given study-year was calculated and presented as the proportion of eligible CPRD registrants[12] with opioid coverage. This outcome measure was used to account for attrition of CPRD practices and registrants in the later years of the study period, this was due to GPs changing their clinical system software, meaning their data was no longer compatible with the CPRD. The proportion

[11] Prescription coverage refers to when a given time-point or time-period lies within the start and stop dates of ≥1 opioid exposure period.
[12] People aged ≥18 years with acceptable data that were registered during the study period, with >1 day follow-up, known sex and ≥2 years lookback available.

of eligible CPRD registrants with opioid prescription coverage in a given study-year was calculated using Equation 6-1:

Equation 6-1. Calculation of proportion of CPRD registrants with opioid coverage

$$Proportion\ of\ covered\ registrants = \frac{Number\ of\ people\ with\ opioid\ coverage}{Number\ of\ active\ \&\ eligible\ CPRD\ registrants}$$

Proportions of opioid drugs prescribed

People covered by opioids in a given study-year were categorised as being exposed to: (1) strong opioids only, (2) weak opioids only, or (3) both weak and strong opioids. The proportion of people in each of these categories was calculated by dividing the number of people in each category by the number of people covered by any opioid in the given study-year.

The proportion of covered days for weak opioids, strong opioids and individual opioid drugs were calculated by summing the number of days with opioid prescription coverage for the specific opioid/group of opioids across the cohort for a given study-year, and dividing this by the sum of days with any opioid prescription coverage in that study-year (Equation 6-2).

Equation 6-2. Calculation of proportion of covered days for a specific opioid drug/group of opioids

$$Proportion\ of\ covered\ days = \frac{\sum days\ covered\ with\ opioid\ drug/group\ of\ opioids}{\sum days\ covered\ with\ any\ opioid}$$

The proportion of prescriptions with an ‘event date’ in a given study-year was also used to compare the proportion of weak opioids, strong opioid and individual opioid drugs prescribed. This was calculated by summing the number of prescriptions for the specific opioid drug/group of opioids in a given

study-year and dividing this by the sum of prescriptions for any opioid drug prescribed in that study-year (Equation 6-3).

Equation 6-3. Calculation of proportion of prescriptions for a specific opioid drug/group of opioids

$$Proportion\ of\ prescriptions = \frac{\sum prescriptions\ for\ opioid\ drug/group\ of\ opioids}{\sum prescriptions\ for\ any\ opioid}$$

Median annual days covered

The median number of days that a person was covered by opioids over a given study-year was calculated by summing the number of days covered by any opioid for each person within the given study-year. The median (and IQR) was then calculated using the number of days covered for every person covered by an opioid in the given study-year.

Median OMEQ/day

The daily dose (expressed as OMEQ/day) for each period of opioid exposure was multiplied by the duration for each period of opioid exposure and these values were summed across the study-year for each person to generate the annual OMEQ dose per person. The annual OMEQ dose was then divided by the number of days covered within the study-year, resulting in a mean OMEQ/day for each person (Equation 6-4, where *n* refers to the number of exposure periods in the given study-year).

Equation 6-4. Calculation of the mean OMEQ/day per person

$$Mean\ OMEQ\ dose = \frac{\sum^{n} (OMEQ/day \times duration)}{\sum days\ covered}$$

The median (and IQR) was then calculated from each person's mean OMEQ/day providing they were covered by an opioid in the given study-year.

6.4.6.2 Patient-level outcome measures

Proportion of people with opioid coverage

Two measures were used to present the proportion of people exposed to opioids at any given time-point during follow-up:

1. Time to first treatment break: Based on standard drug survival analysis (DSA) methods,[244] people were followed from opioid initiation until their first gap (>120 days) in opioid exposure. People were censored at the earliest of their end of follow-up date or the day immediately following exposure, at their first treatment break. The proportion covered included only continuous users of opioids.

2. Time to final treatment break: Based on the proportion of people covered (PPC) method,[245] people were followed from opioid initiation until their final treatment break (>120 days). People re-entered the cohort if they re-started opioids after a treatment break. People were censored at the earliest of their end of follow-up date or the day immediately following their final day of opioid exposure, at their final treatment break. The proportion covered could be intermittent as well as continuous users of opioids.

The start and stop dates of opioid exposure periods were used to identify a treatment break. A treatment break was defined as >120 days between the stop date of the previous exposure period and the start date of the subsequent period. In a US opioid utilisation study, Marin *et al.* (2011) defined discontinuation of opioids as a 182-day gap in exposure,[246] and a prior analgesic utilisation study by Gore *et al.* (2011) defined discontinuation as a 60-day gap.[247] This study used a definition of a 120-day gap in exposure, and sensitivity analysis were conducted for alternative gap-lengths.

Proportions of opioid drugs prescribed

People covered by an opioid were categorised as being either: (1) exposed to strong opioids only, (2) exposed to weak opioids only, or (3) exposed to both weak and strong opioids. The proportion of people in each of these categories were calculated by dividing the number of people in each category by the number of people covered by any opioid in the given patient-year. The proportion of covered days/prescriptions for a specific opioid drug/group of opioids was calculated for each patient-year in the same way as described in Equation 6-2 and Equation 6-3.

Median annual days covered

This was the median number of days that a person was covered by opioids over a given patient-year, calculated from the sum of days that each person was covered by any opioid within a given patient-year.

Median OMEQ/day per patient

This was the median daily dose (OMEQ/day) that a person was prescribed over a given patient-year, calculated as detailed in Equation 6-4.

Persistent opioid use

Each person was classified as: not persistent, wide persistent, intermediate persistent or strict persistent in their first year of opioid use (Table 6-5).These definitions were based upon: (1) the total OMEQ per year, (2) the total DDDs per year, (3) the total prescriptions per year and (4) the number of quarters (3-month periods) with a prescription, as proposed by Svendsen *et al.* (2012).[113] The annual DDD was calculated by taking the daily dose (mg/day, prior to conversion to OMEQ), multiplying this by the opioid-specific DDD conversion factor defined by the WHO and summing the DDD/day for the patient-year.[1]

Each person was classified according to these definitions for their subsequent years of follow-up (i.e., patient-years), and the proportion of people remaining in their initial persistence category was reported.

Table 6-5. Definitions of persistent opioid use within one patient-year (365 days)

Persistence category	Amount of opioid	Number of prescriptions	Number of quarters*	Clinical scenario
Not persistent	≤180 DDD or ≤4,500mg OMEQ	-	-	Use less than half of the year
Wide	>180 DDD or >4,500mg OMEQ	-	≥3 quarters	Use at least half of the year
Intermediate	>365 DDD or >9,000mg OMEQ	-	All 4 quarters	Use every day of the year
Strict	>730 DDD or >18,000mg OMEQ	≥10 prescriptions	All 4 quarters	Continuous therapeutic use

Notes: Adapted from Svendsen *et al.* (2012);[113] DDD, defined daily dose; OMEQ, oral morphine equivalent; * quarters refer to 3-month periods starting from the opioid initiation date.

6.4.7 Data analysis

Data were prepared and analysed separately for the population-level and patient-level analyses. Descriptive statistics were used to describe the outcome measures as frequencies, proportions (percent, %), medians and IQR; the median was selected as the most appropriate measure after plotting the distribution of values for the outcome measures.

Results were stratified into subgroups of weak and strong opioids when reporting the proportions of opioid drugs prescribed since proportions differed substantially between weak and strong opioids. When reporting the median days covered and median OMEQ/day, people were grouped by whether they were a user of weak opioids alone, strong opioids alone, or a combination of weak and strong opioids, within each study- or patient-year, as appropriate.

For the patient-year analyses, both the DSA and PPC methods were used for estimating the time covered by opioids, Kaplan-Meier survival curves were generated, depicting the proportion of people exposed to opioids at any given point in time. People were stratified into initiators of weak opioids and strong opioids. People initiated on both weak and strong opioids were classed as initiators of strong opioids. Sensitivity analyses were conducted to study the impact of the defined length of a treatment break; Kaplan-Meier curves were generated for gap-lengths that were greater than 60, 90, 120 and 180 days.

All data management processes and statistical analyses were carried out using the statistical software - Stata/MP 15 (StataCorp, Texas, USA).

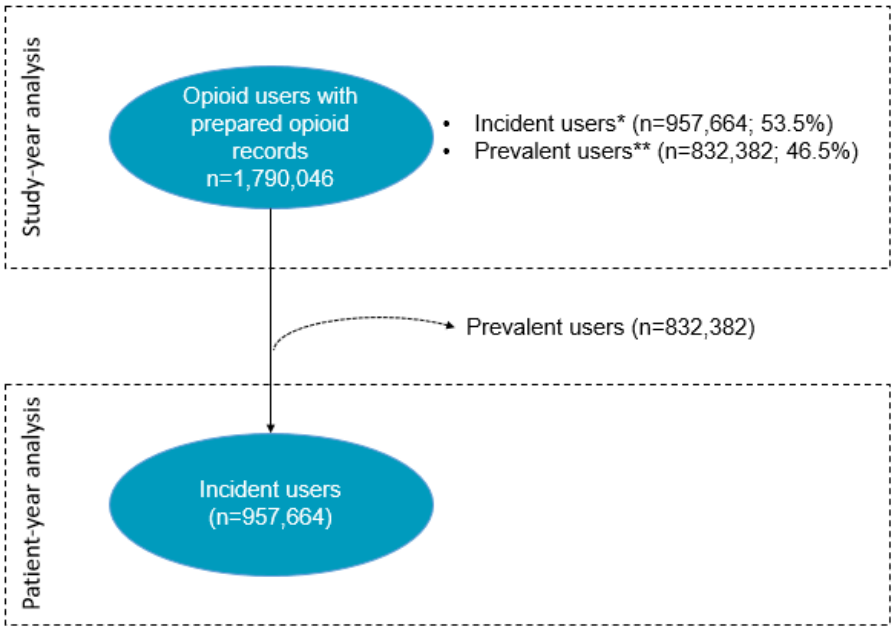
6.5 Results

6.5.1 Study cohort

1,790,046 people (957,664 incident and 832,382 prevalent users of opioids) were identified in Chapter 5 as having complete (or imputed) opioid prescription records, which were prepared for analyses. These 1,790,046 people were included in the population-level analyses (Figure 6-3).

6.5.2 Population-level utilisation

The following results are presented by study-years, which start on 1st June and end on 31st May, for example, the study-year 2008 refers to the period starting on 1st June 2008 and ending on 31st May 2009.



Notes: *people with no record of an opioid prescription during 2-year lookback period; **people with ≥1 record of an opioid prescription during 2-year lookback period.

Figure 6-3. Cohort identification

6.5.2.1 Proportion of people with opioid coverage

Between study-years from 2008 to 2016, the proportion of CPRD registrants with any opioid prescribed increased from 14.5% to 15.9% (Figure 6-4). The number of people decreased over the study-years, this was anticipated due to attrition of people from the CPRD dataset in the later years of the study period. The proportion of prevalent opioid users steadily increased over the study period, from 69.9% to 87.0%.

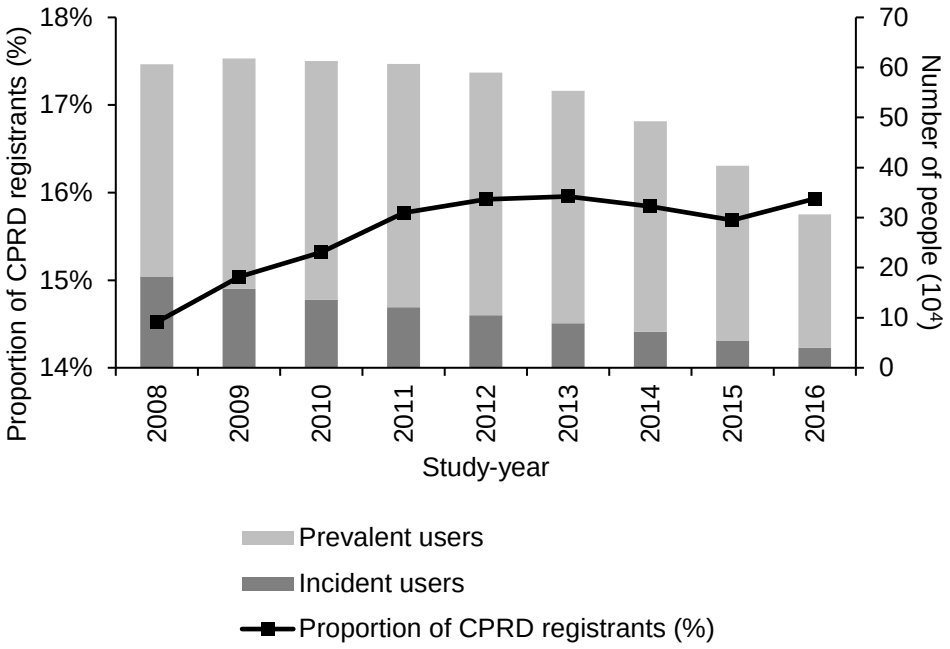
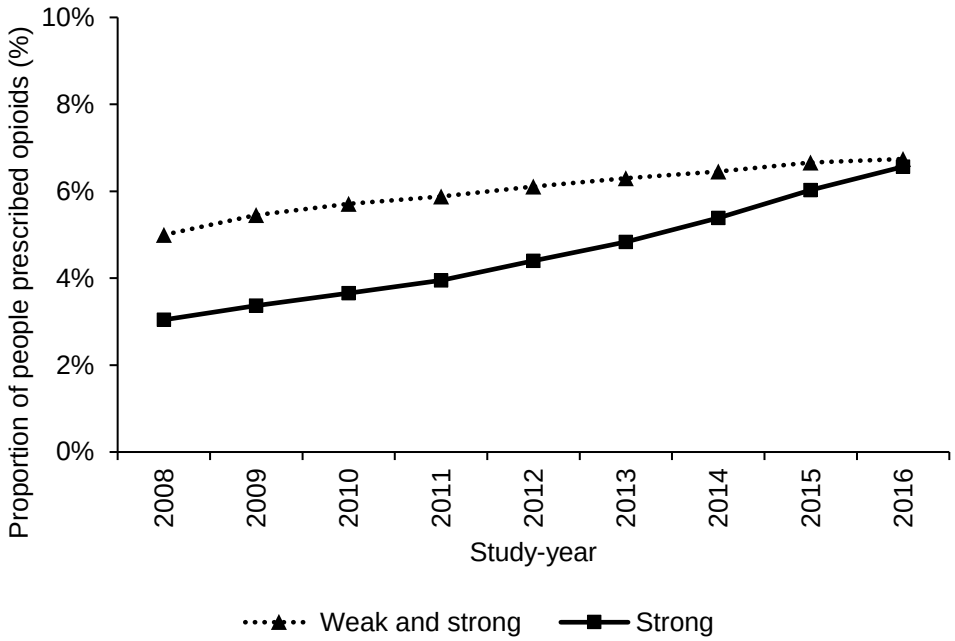


Figure 6-4. Proportion of people with opioid coverage, by study-year

6.5.2.2 Proportions of opioid drugs prescribed

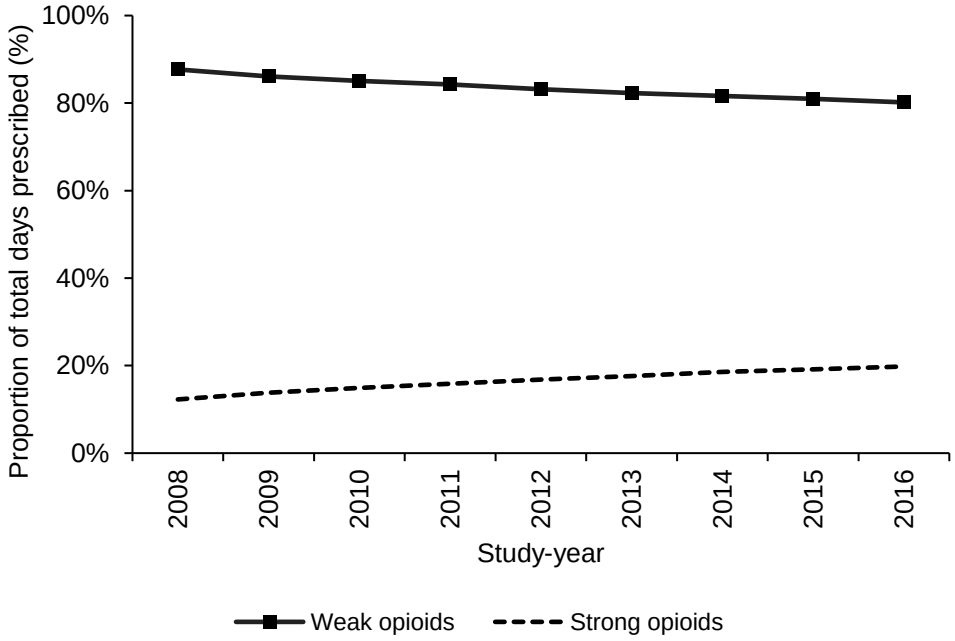
The majority of people were prescribed weak opioids alone in each study-year (92.0% in 2008 and 86.7% in 2016), however, the proportion of people prescribed strong opioids during a given study-year increased over the study period, rising from 3.0 to 6.6% of opioid users. The proportion of people prescribed weak and strong opioids within the same study-year increased from 5.0% to 6.7% of opioid users (Figure 6-5).

The proportion of days covered by strong opioid drugs increased over the study period, from 12.3% to 19.8%; whereas, the proportion for weak opioids declined (Figure 6-6).



Notes: Strong, people prescribed strong opioids only within the study-year; Weak and strong, people prescribed both weak and strong opioids within the same study-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug.

Figure 6-5. Proportion of people prescribed strong, or both weak and strong opioids



Notes: Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug. When the proportions of weak and strong opioids are combined the total comes to >100%, this is because some days are covered by both a weak and strong opioid and are therefore counted twice.

Figure 6-6. Proportion of weak and strong opioids prescribed

Of the weak opioids prescribed, codeine contributed to the greatest proportion of days covered by any opioid, accounting for 49.4% of days covered by any opioid in 2008. The proportion of days covered with codeine declined between 2008 and 2013, from 49.4% to 47.3% of covered days, whereas the proportion of days covered with tramadol increased from 19.6% to 21.9% of covered days. However, from 2013 the proportion of days covered with tramadol declined from 21.9% to 19.7% of covered days, and codeine increased from 47.3% to 49.3% of covered days. The proportion of days covered with dihydrocodeine steadily declined over the entire study period. The proportion of prescriptions measure provided very similar results to days covered (Figure 6-7).

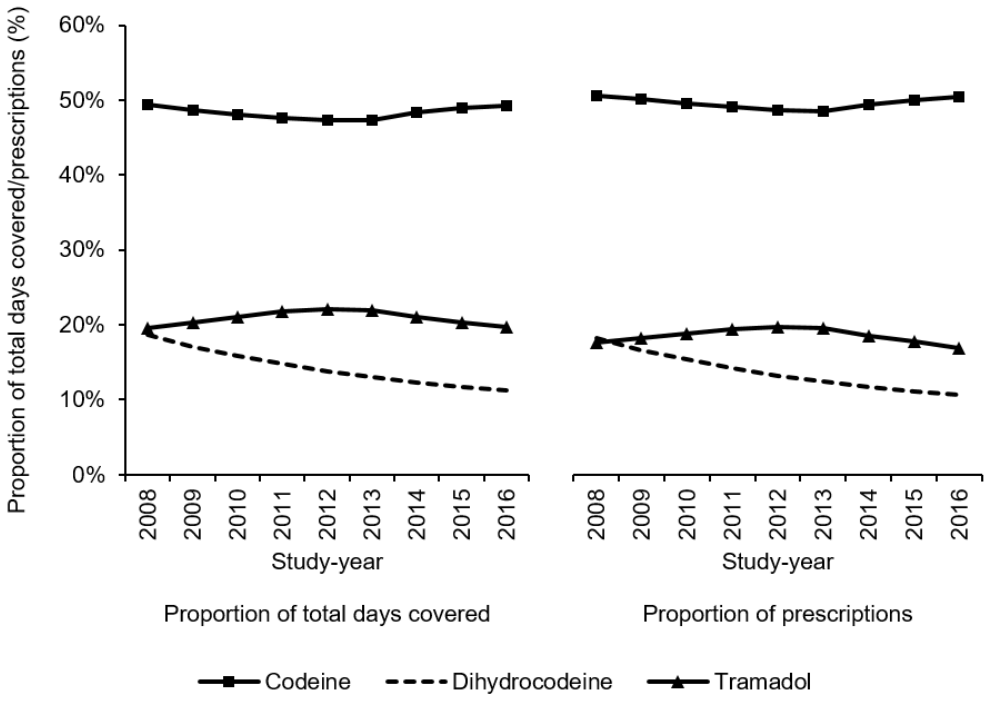
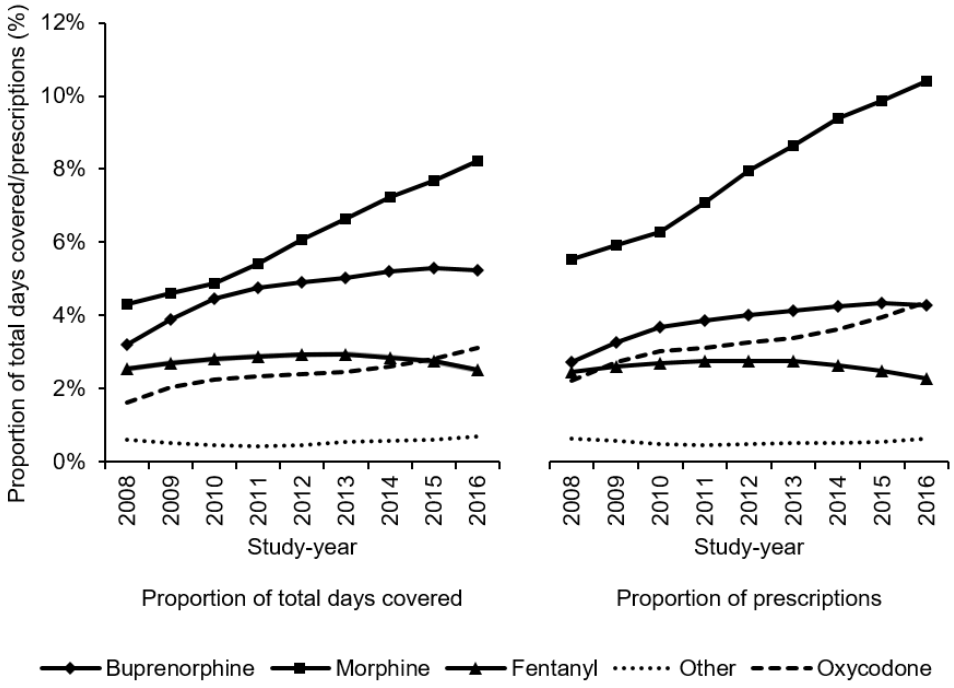


Figure 6-7. Proportion of weak opioid drugs prescribed

Of the strong opioids prescribed, morphine contributed to the greatest proportion of days covered by any opioid. Additionally, the proportion of days covered by morphine increased over the study period, from 4.3% to 8.2% of

covered days. The proportion of days covered by buprenorphine increased from 3.2% to 5.2% of covered days, and the days covered by oxycodone increased from 1.6% to 3.1% of covered days. Days covered by fentanyl and opioids within the 'other' category remained relatively stable throughout the study period (Figure 6-8)



Notes: 'Other' refers to: alfentanil, dextromoramide, dextropropoxyphene, diamorphine, dipipanone, ethylmorphine, hydromorphone, levorphanol, meptazinol, methadone, omnopon, papaveretum, pentazocine, pethidine, phenazocine, tapentadol

Figure 6-8. Proportion of strong opioid drugs prescribed

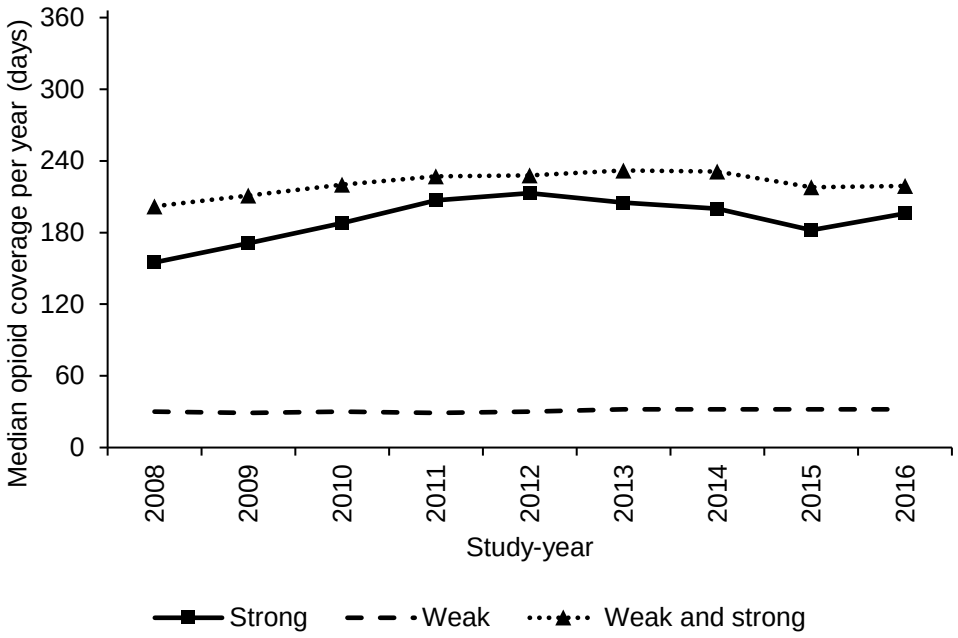
The proportion of prescriptions measure was greater for morphine and oxycodone, and smaller for buprenorphine, when compared to the proportion of days covered measure. After inspecting the median prescription length of each opioid drug, it was apparent that this difference was likely due to variations in the duration of prescriptions of each opioid (see Appendix Q).

6.5.2.3 Median annual days covered

The median annual days covered was greater for people prescribed strong opioids or a combination of weak and strong opioids. People prescribed weak opioids in 2008 (n=557,431; 92.0%) were covered for a median duration of 30 days (IQR: 15, 110 days) and this remained relatively stable over the study period. People prescribed strong opioids in 2008 (n=18,435; 3.0%) were covered for a median duration of 155 days (IQR: 28, 340 days), this peaked at 213 days (IQR: 35, 365 days) in 2012 and dropped to 196 days (IQR: 34, 364 days) in 2016. People prescribed both weak and strong opioids in 2008 (n=30,291; 5.0%) were covered for a median duration of 202 days (IQR: 85, 327 days) and this increased slightly to 219 days (IQR: 86, 355 days) in 2016 (Figure 6-9).

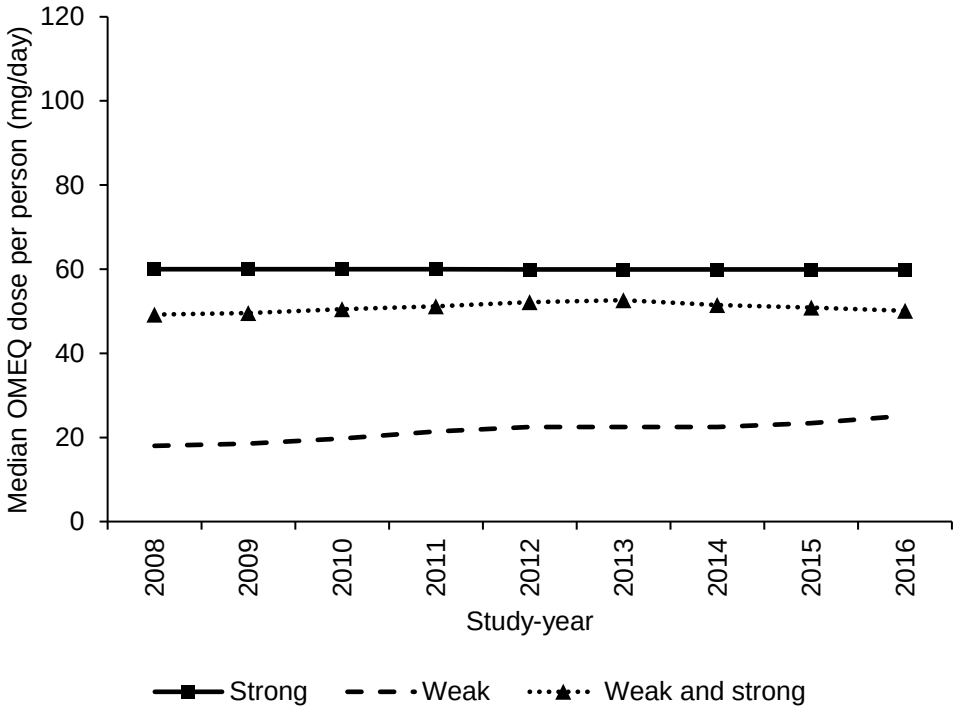
6.5.2.4 Median OMEQ/day

The median OMEQ/day prescribed to people using strong opioids was 60.0mg (IQR: 29.1, 114.6mg), and 49.3mg (IQR: 30.5, 79.4mg) for people prescribed both weak and strong opioids in the same study-year; these doses remained stable throughout the study period. The median OMEQ/day for people prescribed weak opioids increased from 18.0mg (IQR: 7.8, 27mg) to 25.1mg (IQR: 10.4, 27.0mg) over the study period (Figure 6-10).



Notes: Strong, people prescribed strong opioids only within the study-year; Weak, people prescribed weak opioids only within the study year; Weak and strong, people prescribed both weak and strong opioids within the same study-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug.

Figure 6-9. Median days of opioid coverage per person, per study-year



Notes: Strong, people prescribed strong opioids only within the study-year; Weak, people prescribed weak opioids only within the study year; Weak and strong, people prescribed both weak and strong opioids within the same study-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug. OMEQ, oral morphine equivalent.

Figure 6-10. Median OMEQ/day per person

The range of daily OMEQ doses for people prescribed strong or a combination of weak and strong opioids was large, with some people reaching OMEQ doses up to 3,058mg/day. Those prescribed weak opioids alone did not exceed OMEQ doses of 500mg/day (Table 6-6).

6.5.3 Patient-level utilisation

The following results are presented by patient-years, the start and end dates for each patient-year was generated for each person and was based on their opioid start date as detailed in Table 6-4. A total of 957,664 people, who were incident users of opioids on their index date, were included in the patient-level analyses.

6.5.3.1 Proportion of people with opioid coverage

All 957,664 people had a record of at least ≥1 day of opioid exposure at the start of the first patient-year. Of these, 933,660 people (97.5%) were initiated on weak opioids and the remaining 24,004 people (2.5%) were initiated on strong opioids.

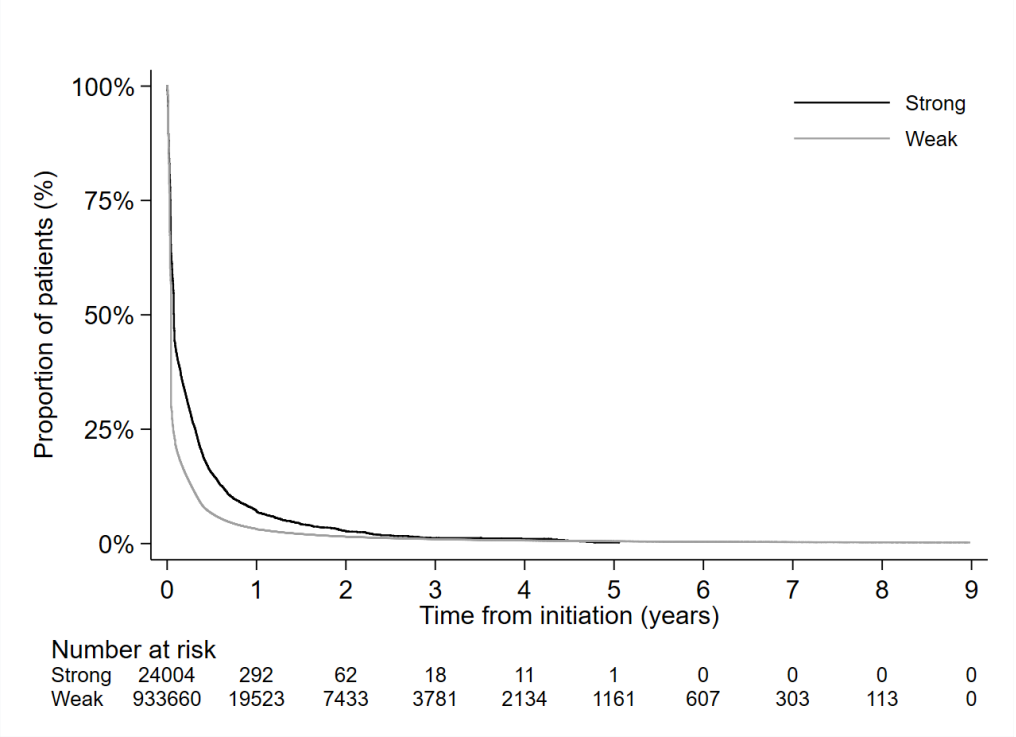
Time from initiation to first treatment break

People initiated on strong opioids experienced their first treatment break later than those initiated on weak opioids. The median time to first break for people initiating strong opioids was 28 days (95%CI: 27, 28 days), and 16 days (95%CI: 16, 16 days) for those initiated on weak opioids. Of the people initiating strong opioids, 75% were continuously exposed to opioids, without a break for ≤115 days (95%CI: 110, 119 days) after initiation, whilst 75% of people initiating weak opioids were continuously exposed for ≤25 days (95%CI: 25, 25 days) after opioid initiation (Figure 6-11).

Table 6-6. Median (IQR) and maximum recorded daily OMEQ doses (mg) per person prescribed weak, strong or a combination of weak and strong opioids in each study-year

	Weak		Strong		Weak & strong	
Study-year	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
2008	18.0mg (7.8, 27.0mg)	0.6, 440.0mg	60.0mg (29.1, 114.6mg)	3.0, 1,536.8mg	49.3mg (30.5, 79.4mg)	2.8, 2,282.8mg
2009	18.5mg (7.8, 27.0mg)	0.6, 277.4mg	60.0mg (28.7, 107.0mg)	2.0, 1,634.5mg	49.6mg (30.6, 79.9mg)	2.9, 2,248.8mg
2010	19.7mg (7.8, 27.0mg)	1.0, 395.6mg	60.0mg (28.8, 106.3mg)	3.0, 1,670.5mg	50.5mg (30.9, 81.2mg)	2.9, 2,101.6mg
2011	21.4mg (8.0, 27.0mg)	1.1, 240.0mg	60.0mg (28.8, 104.2mg)	2.5, 2,115.3mg	51.2mg (31.2, 82.0mg)	2.9, 1,118.0mg
2012	22.5mg (9.0, 27.1mg)	1.1, 480.0mg	60.0mg (28.8, 100.2mg)	2.5, 1,814.3mg	52.2mg (31.7, 82.4mg)	2.7, 2,826.5mg
2013	22.5mg (9.6, 27.0mg)	1.1, 319.8mg	59.9mg (28.8, 100.0mg)	1.9, 2,161.5mg	52.6mg (31.8, 83.8mg)	2.8, 3,058.2mg
2014	22.5mg (9.6, 27.0mg)	0.6, 261.0mg	59.9mg (28.8, 100.0mg)	4.0, 2,108.4mg	51.5mg (31.2, 82.3mg)	3.4, 2,869.4mg
2015	23.4mg (9.6, 27.0mg)	1.1, 260.0mg	59.9mg (28.8, 100.0mg)	3.8, 1,762.2mg	50.9mg (30.9, 82.3mg)	2.6, 2,907.0mg
2016	25.1mg (10.4, 27.0mg)	1.1, 240.0mg	59.9mg (28.8, 100.0mg)	3.8, 2,047.9mg	50.1mg (30.8, 81.1mg)	2.9, 1,155.4mg

Notes: Strong, people prescribed strong opioids only within the study-year; Weak, people prescribed weak opioids only within the study year; Weak & strong, people prescribed both weak and strong opioids within the same study-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug; IQR, interquartile range.

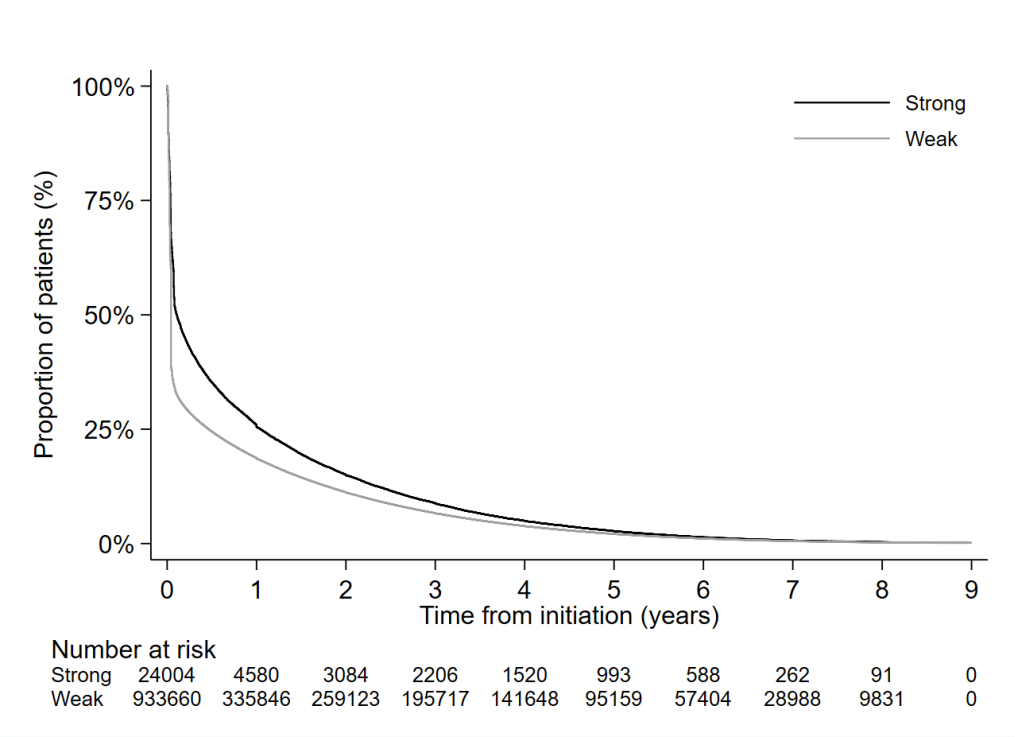


Notes: Opioid initiation refers to the first day of opioid exposure recorded during a patient's follow-up period. Strong, people prescribed a strong opioid on their first day of opioid exposure; weak, people prescribed a weak opioid (exclusively) on their first day of opioid exposure.

Figure 6-11. Proportion of people continuously exposed to opioids from initiation to their first treatment break (>120 days)

Time from initiation to final treatment break

The median duration of continuous or intermittent (i.e., with gaps) opioid treatment was 40 days (95%CI: 36, 43 days) for people initiated on strong opioids, and 16 days (95%CI: 16, 16 days) for initiators of weak opioids. Of the people initiated on strong opioids, 25% continued to be intermittently or continuously exposed to opioids one year after opioid initiation; 25% were exposed >382 days (95%CI: 365, 400 days) after initial exposure, whereas, 25% of people initiated on weak opioids were exposed for >170 days (95%CI: 168, 172 days) (Figure 6-12).



Notes: Opioid initiation refers to the first day of opioid exposure recorded during a patient's follow-up period. Strong, people prescribed a strong opioid on their first day of opioid exposure; weak, people prescribed a weak opioid (exclusively) on their first day of opioid exposure.

Figure 6-12. Proportion of people intermittently or continuously exposed to opioids from initiation to their final treatment break (>120 days)

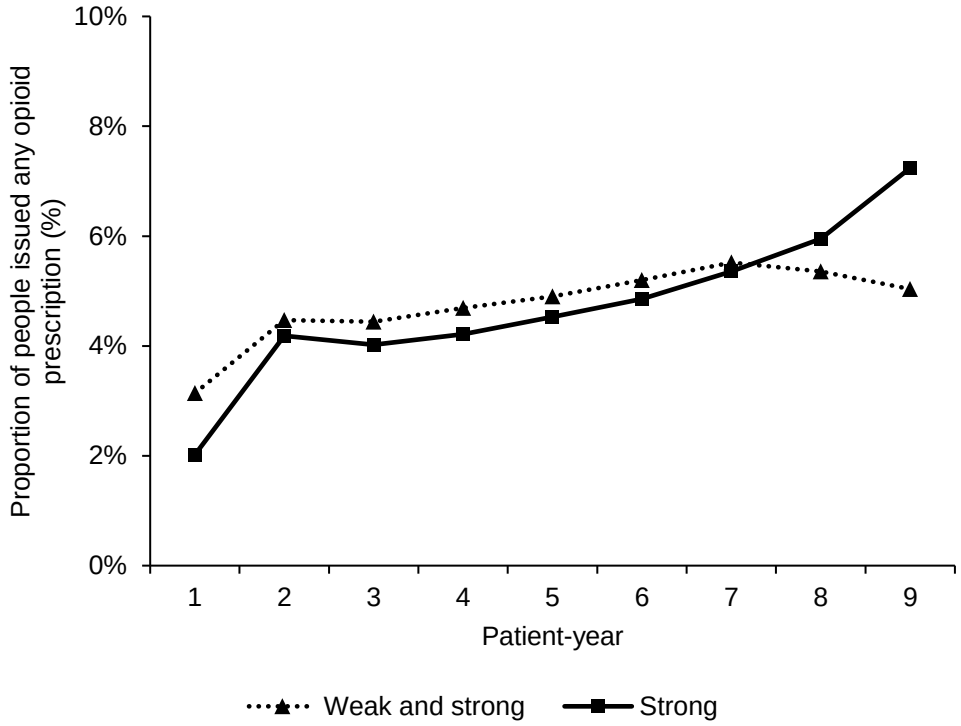
Sensitivity analyses

The length of the gap used to define a break in treatment affected the proportion of people covered with an opioid at a given time-point, for people initiated on weak and those initiated on strong opioids; the longer the gap, the longer the time on treatment. The results of these analyses, including Kaplan-Meier survival graphs, are shown in Appendix R.

6.5.3.2 Proportions of opioid drugs prescribed

The majority of people were prescribed weak opioids alone in each patient-year, however, the proportion of people prescribed strong opioids increased from 2.0% of people prescribed opioids in their first patient-year to 7.2% of those prescribed opioids in their ninth patient-year. The proportion of people prescribed both weak and strong opioids increased from 3.1% to 5.0% of

people prescribed opioids in their first and ninth patient-years, respectively (Figure 6-13).

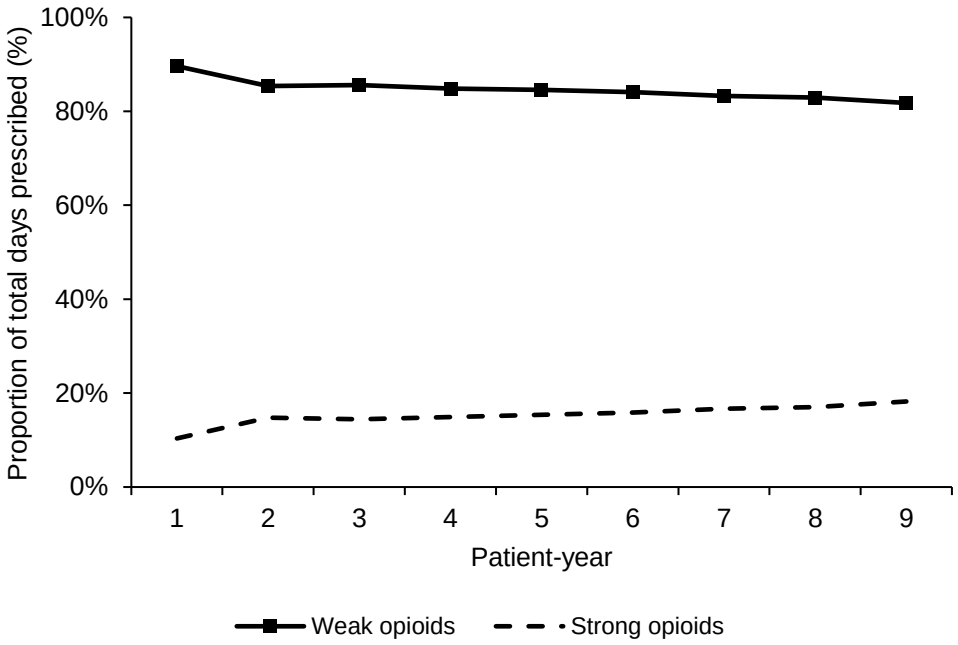


Notes: Strong, people prescribed strong opioids only within the study-year; Weak and strong, people prescribed both weak and strong opioids within the same study-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug.

Figure 6-13. Proportion of people prescribed strong, or weak and strong opioids

The proportion of days covered by strong opioid drugs increased by 76.0% over patient follow-up (from 10.3% to 18.2%) whereas the proportion for weak opioids declined (Figure 6-14).

Of the weak opioids prescribed, codeine contributed to the greatest proportion of days covered by any opioid across all patient-years. The proportion of days covered with codeine declined between the first and second patient-years (from 62.6% to 55.8% of covered days) whereas the proportion of days



Notes: Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug. When the proportions of weak and strong opioids are combined the total comes to >100%, this is because some days are covered by both a weak and strong opioid and are therefore counted twice.

Figure 6-14. Proportion of weak and strong opioids prescribed

covered with tramadol increased (from 14.8% to 19.5% of covered days). The proportion of days covered with dihydrocodeine steadily declined from 12.0% to 9.2% of covered days over patient follow-up (Figure 6-15). The proportion of prescriptions measure demonstrated similar results to the proportion of covered days measure.

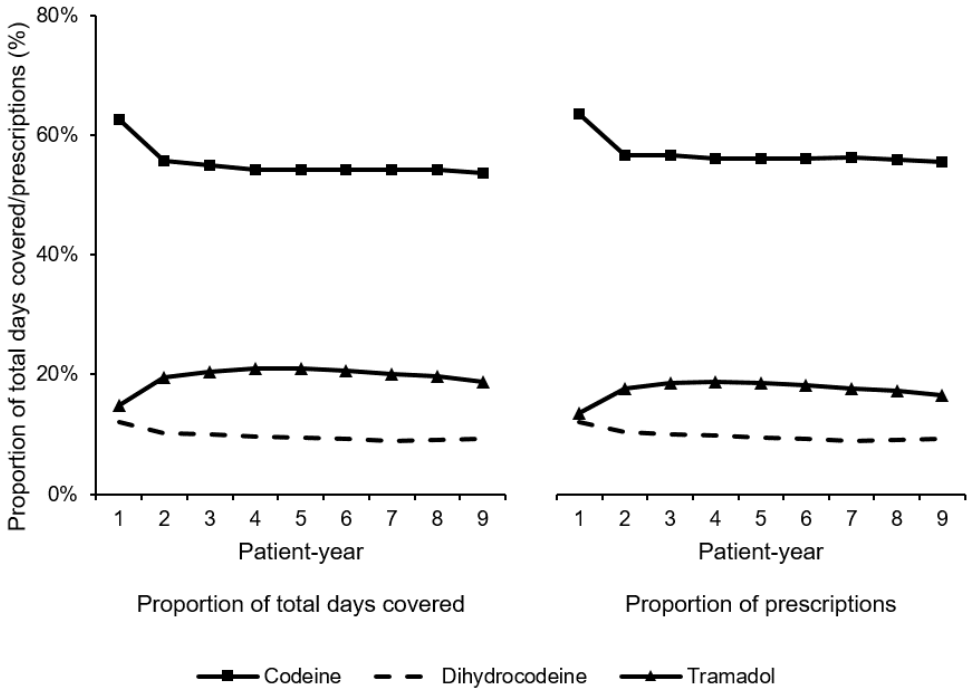
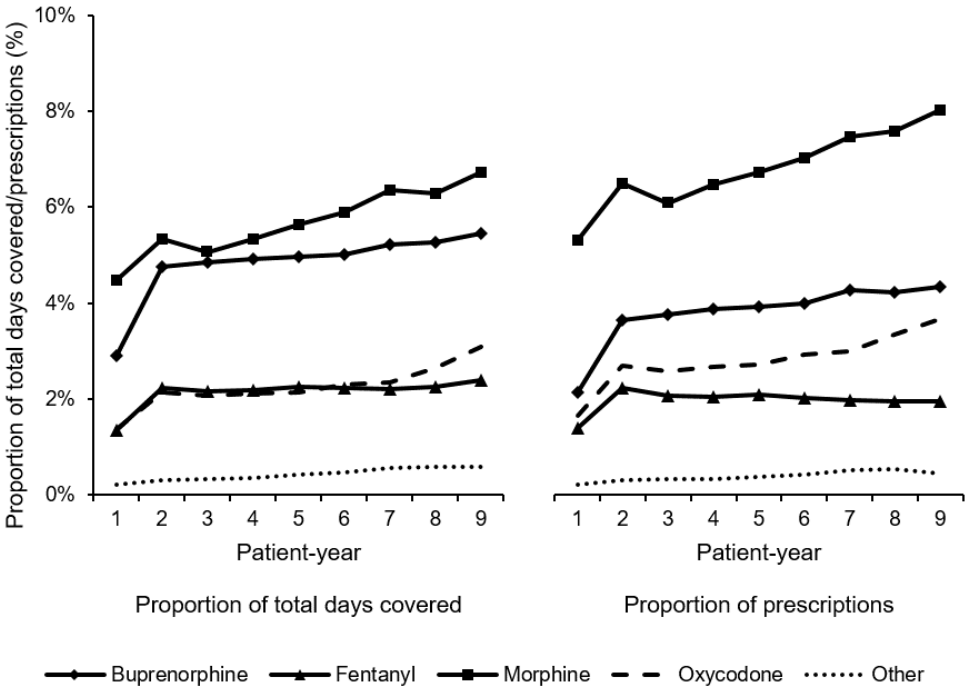


Figure 6-15. Proportion of weak opioid drugs prescribed

Of the strong opioids prescribed, morphine contributed to the greatest proportion of days covered by any opioid; 4.5%-6.7% of covered days across the patient-years. The proportion of days covered by morphine, buprenorphine, oxycodone and fentanyl increased sharply for people prescribed opioids in their second patient-year; the greatest increase was observed for buprenorphine, which increased between the first and second patient-years, from 2.9% to 4.7% of covered days. The proportion of days covered by morphine, buprenorphine and oxycodone continued to increase over the remaining patient-years (Figure 6-16).

Similar to the population-level analysis, the proportion of prescriptions measure provided greater proportions for morphine and oxycodone, and smaller proportions for buprenorphine, when compared to the proportion of days covered measure.



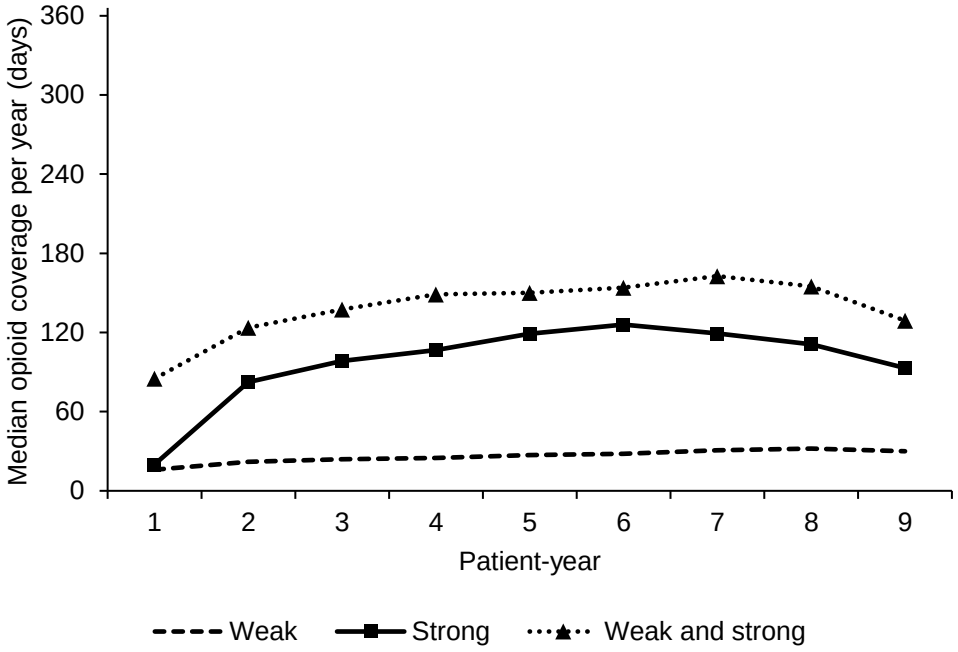
Notes: 'other' refers to: alfentanil, dextromoramide, dextropropoxyphene, diamorphine, dipipanone, ethylmorphine, hydromorphone, levorphanol, meptazinol, methadone, omnopon, papaveretum, pentazocine, pethidine, phenazocine, tapentadol

Figure 6-16. Proportion of strong opioid drugs prescribed

6.5.3.3 Median annual days covered

The median annual days covered with opioids increased over follow-up and was greater for people prescribed strong opioids or a combination of weak and strong opioids, compared to those prescribed weak opioids alone. People prescribed weak opioids in their first patient-year (n=908,257; 94.8%) were covered for a median of 16 days (IQR: 10, 28 days), and those prescribed weak opioids in their ninth patient-year (n=10,746; 87.7%) were covered for a median of 30 days (IQR: 15, 86 days). People prescribed strong opioids in their first patient-year (n=19,336; 2.0%) were covered for a median of 20 days (IQR: 7, 59 days), and those prescribed strong opioids in their ninth patient-year (n=887; 7.2%) were covered for a median of 93 days (IQR: 28, 195 days). People prescribed weak and strong opioids within the same patient-year were covered for the greatest number of days in a year, 85 days (IQR:

42, 177 days) for people prescribed them in their first patient-year (n=30,071; 3.1%), and 129 days (IQR: 57, 220 days) for people prescribed them in the ninth patient-year (n=617; 5.0%) (Figure 6-17).



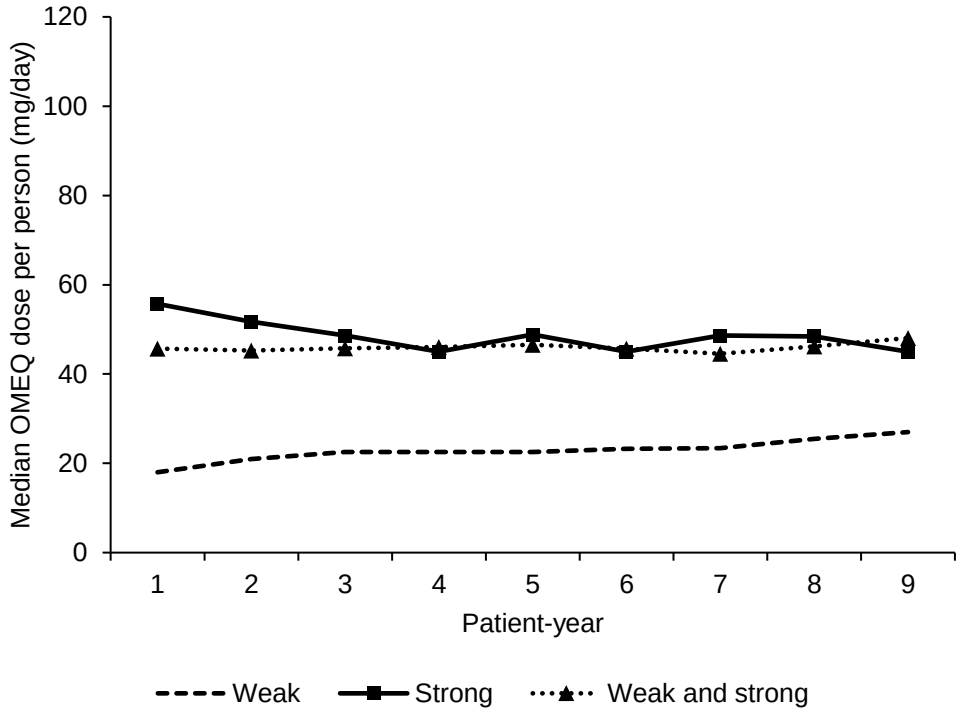
Notes: Strong, people prescribed strong opioids only within the patient-year; Weak, people prescribed weak opioids only within the patient-year; Weak and strong, people prescribed both weak and strong opioids within the same patient-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug.

Figure 6-17. Median days of opioid coverage per person, per study-year

6.5.3.4 Median OMEQ/day

The median daily OMEQ dose for people prescribed weak opioids increased over follow-up, rising from 18.0mg (IQR: 7.8, 27.0mg) in the first patient-year (n=908,257; 94.8%), to 27mg (IQR: 10.4, 27.1mg) for people prescribed them in their ninth patient-year (n=10,746; 87.7%). People prescribed strong opioids in their first or second patient-year were prescribed greater daily OMEQ doses than those who had them prescribed in later patient-years. The median OMEQ/day decreased from 55.7mg (IQR: 28, 100mg) in the first patient-year (n=19,336; 2.0%) to 48.6mg (IQR: 26.4, 100mg) for those who had them

prescribed in the third patient-year (n=6,449; 4.0%); the daily OMEQ dose remained stable from the third patient-year. The median OMEQ/day for people prescribed both weak and strong opioids in their first patient-year (n=30,071; 3.1%), increased slightly but remained similar for those who had them prescribed in any patient-year (45.7mg to 48.1mg) (Figure 6-18).



Notes: Strong, people prescribed strong opioids only within the patient-year; Weak, people prescribed weak opioids only within the patient-year; Weak and strong, people prescribed both weak and strong opioids within the same patient-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug. OMEQ, oral morphine equivalent.

Figure 6-18. Median OMEQ/day per person

Across groups of weak and strong opioid users, the cohort of 957,664 incident opioid users did not exceed a daily OMEQ dose of 1,700mg/day in any patient-year. People prescribed weak opioids were prescribed a maximum daily OMEQ dose of 299.8mg/day, whereas people prescribed strong opioids were prescribed daily OMEQ doses of up to 1,678.0mg/day (Table 6-7).

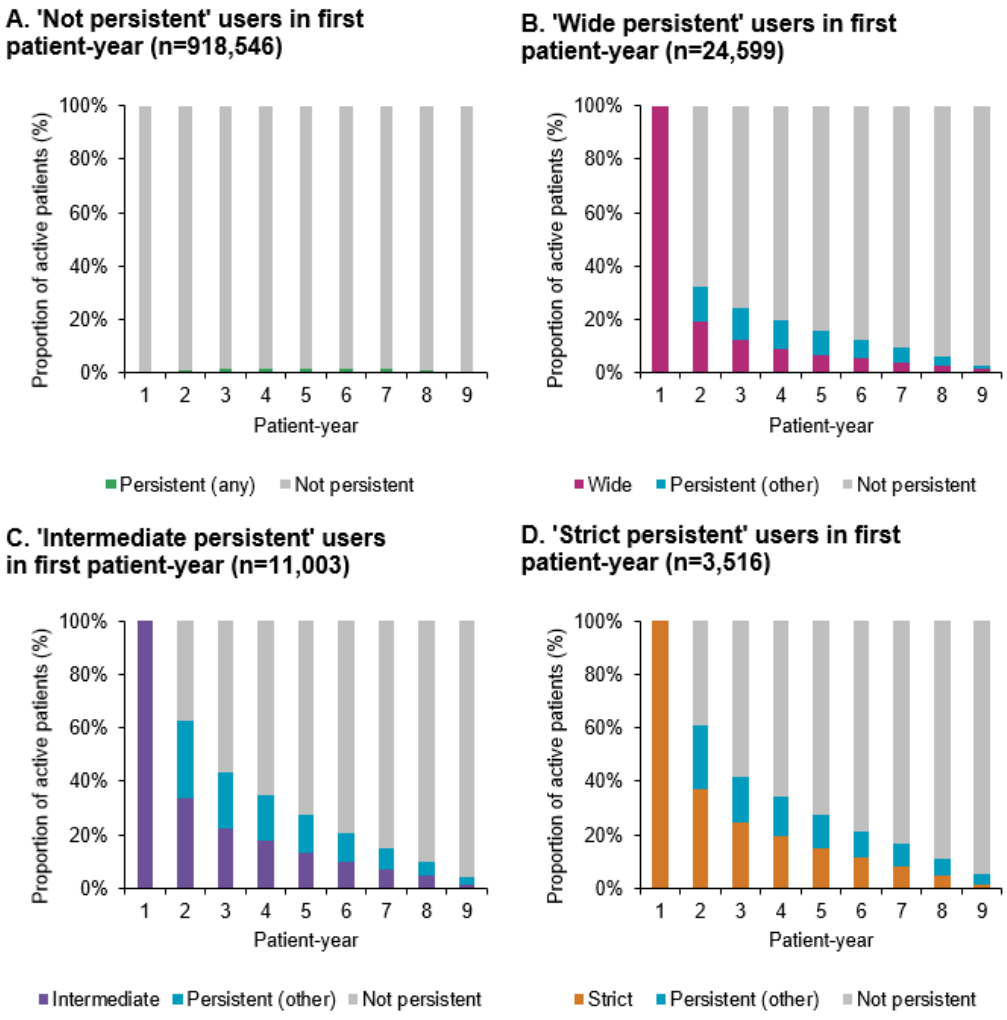
6.5.3.5 Persistent opioid use

Of the 957,664 incident opioid users, most (n=918,546; 95.9%) did not meet any of the three definitions for persistent opioid use in their first patient-year, and <2.0% became persistent users during any year of follow-up. Of those defined as persistent users in their first patient-year, 5.0% of people meeting the ‘strict persistent’ definition continued to meet this definition in their ninth patient-year (Figure 6-19). The numbers of active and censored people in each patient-year and proportion of people meeting each persistence definition are available in Appendix S.

Table 6-7. Median (IQR) and maximum recorded daily OMEQ doses (mg) per person prescribed weak, strong or a combination of weak and strong opioids in each patient-year

	Weak		Strong		Weak & strong	
Patient-year	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
1	18.0mg (7.8, 27.0mg)	1.2, 285.0mg	55.7mg (28.8, 100.0mg)	2.0, 1,000.0mg	45.7mg (28.8, 71.1mg)	3.6, 831.4mg
2	20.9mg (8.6, 27.0mg)	1.2, 252.0mg	51.7mg (26.4, 100.0mg)	3.0, 1,678.0mg	45.2mg (28.2, 71.9mg)	2.5, 657.0mg
3	22.5mg (9.0, 27.0mg)	1.2, 240.0mg	48.6mg (26.4, 100.0mg)	5.0, 1,146.7mg	45.8mg (28.5, 71.5mg)	3.0, 560.7mg
4	22.5mg (9.6, 27.0mg)	1.2, 213.5mg	45.0mg (26.4, 100.0mg)	2.5, 1,003.1mg	46.0mg (29.2, 72.1mg)	3.6, 836.6mg
5	22.5mg (9.6, 27.0mg)	1.2, 227.0mg	48.8mg (26.4, 100.0mg)	5.0, 1,156.6mg	46.6mg (29.0, 71.4mg)	5.1, 534.8mg
6	23.3mg (9.6, 27.0mg)	1.1, 299.8mg	45.0mg (26.4, 98.8mg)	5.6, 1,462.5mg	45.7mg (29.2, 72.5mg)	4.8, 629.0mg
7	23.4mg (9.6, 27.0mg)	1.3, 177.0mg	48.6mg (26.4, 100.0mg)	3.8, 841.4mg	44.5mg (29.1, 72.2mg)	7.5, 673.3mg
8	25.5mg (9.7, 27.0mg)	1.3, 160.0mg	48.4mg (26.4, 100.0mg)	3.8, 587.0mg	46.2mg (29.7, 75.0mg)	3.9, 542.4mg
9	27.0mg (10.4, 27.0mg)	1.3, 177.0mg	45.0mg (26.4, 96.7mg)	3.8, 495.2mg	48.1mg (29.1, 74.9mg)	8.4, 360.4mg

Notes: Strong, people prescribed strong opioids only within the patient-year; Weak, people prescribed weak opioids only within the patient-year; Weak & strong, people prescribed both weak and strong opioids within the same patient-year. Weak opioid drugs include: codeine, dihydrocodeine and tramadol; strong opioid drugs include any other opioid drug; IQR, interquartile range.



Notes: Wide persistent, >180DDD or >4,500mg OMEQ in ≥3 quarters/year; intermediate persistent, >365DDD or >9,000mg OMEQ in 4 quarters/year; strict persistent, >730DDD or 18,000mg OMEQ and ≥10 prescriptions in 4 quarters/year; not persistent, not meeting any definition for persistence.

Figure 6-19. Proportion of active patients meeting definitions for persistent opioid use

6.6 Discussion

This chapter demonstrates that the proportion of CPRD registrants prescribed an opioid increased between 2008 and 2017 and that the proportion of strong opioid users more than doubled over the same period. Compared with people who were prescribed weak opioids, those prescribed strong opioids were covered for over five times the number of days in a given year as well as being prescribed greater daily OMEQ doses. Additionally, the daily OMEQ doses prescribed to users of weak opioids increased over the study period.

This is the largest UK study that has examined opioid utilisation at a patient-level and demonstrates that the majority of people were initiated on weak opioids and were prescribed opioids for <30 days. After accounting for intermittent use, the median duration of opioid treatment was twice as long for people initiated on strong opioids in comparison to initiators of weak opioids. The proportion of strong opioid users and annual days covered increased over patient-years. Daily OMEQ doses for weak opioid users increased over patient-years, whereas doses for strong opioid users declined. A small proportion of people were identified as being persistent opioid users (i.e., continuous opioid coverage for at least half of the year) in their first year of opioid use. Of those who were persistent users in their first patient-year, the likelihood of remaining persistent decreased over follow-up.

6.6.1 Population-level utilisation

Consistent with previous studies of opioid utilisation among people in the UK,[5, 110, 111, 124, 242, 243] the results presented in this chapter showed an increase in opioid utilisation over time, with the proportion of CPRD registrants prescribed an opioid at least once increasing from 14.5% to 15.9% between 2008 and 2017. A recent National Institute for Health Research (NIHR) commissioned study by Farias *et al.* (2017) reported that the proportion of people prescribed opioids doubled between 2000 and 2012 (rising from 2.6% to 5.0% of the CPRD base population[13]).[242] This increase is considerably different to that reported in these analyses. This discrepancy is likely due to differences in the denominator populations used. In the study by Farias *et al.*, all active and inactive CPRD registrants defined their denominator population, which would have under-estimated the proportion of people prescribed

[13] The base population refers to all people within the CPRD that have research-quality data.

opioids. The denominator population used in the analyses presented in this chapter included only active and eligible CPRD registrants, thereby giving a more realistic reflection of the proportion of registrants that had the potential to be prescribed an opioid during the study period. Recently, the report by Farias *et al.* was updated; describing continuous opioid prescribing that exceeded six months and 12 months.[120] The updated report showed that, the proportion of people who exceeded a six-month prescribing period increased from 6% to 8% of opioids users between 2001 and 2014; and increased 2% to 4% for periods >12 months. The update of the report complements previous studies and the findings of this chapter, which show an increase in opioid utilisation over time in the UK.

This study showed that the majority of people prescribed opioids were prescribed weak opioids (>85% of people in any study-year), and that codeine accounted for nearly half of all days covered by any opioid. In addition, tramadol prescribing declined from 2013 onwards, around the time of the reclassification of tramadol to a schedule three controlled drug in the UK, that is – June 2014.[248] This finding is consistent with a previous tramadol utilisation study that reported a decline in the number of DDDs of tramadol prescribed per 1,000 UK inhabitants after reclassification.[249]

Although most people were prescribed weak opioids, the proportion of people prescribed strong opioids alone more than doubled over the study period, rising from 3.0 to 6.6% of opioid users. These findings are consistent with an earlier study of strong opioid utilisation,[5] which reported a 466.2% rise in the number of strong opioid users between 2000 and 2010. Similarly, Foy *et al.* (2016), reported a six-fold increase in strong opioid prescribing and a two-fold increase in weak opioid prescribing between 2005 and 2012 in their cross-

sectional, longitudinal analysis of prescribing within the Leeds and Bradford area in the UK.[243] The study by Foy *et al.* also reported that the proportion of strong opioid users increased from 4.0% to 13.7% between 2005 and 2012. In accordance with these findings, the results presented in this chapter showed an increase in strong opioid users from 8.0% to 12.7%, when combined with people prescribed both weak and strong opioids within the same study-year. It is well documented that there is a great deal of geographical variation in opioid prescribing throughout the UK,[111, 250] and therefore it is likely that differences in the proportions reported in this chapter and by Foy *et al.* may be due to differences in the study populations analysed; Foy *et al*. covered a specific region of the UK, whereas this study covered a broader geographical area. A study of opioid utilisation in Scotland similarly found that strong opioid prescribing doubled between 2003 and 2012.[251]

The rise in strong opioid prescribing was reflected by an increase in the proportion of covered days for morphine, buprenorphine and oxycodone products. A recent population-level analysis of opioid prescribing by Curtis *et al.* (2018) used UK NHS prescribing data to study trends in opioid prescribing between 1998 and 2018.[111] Curtis *et al.* found that morphine, fentanyl, oxycodone and buprenorphine made up more of the total OMEQ prescribed than any other opioids, consistent with our finding that these drugs are the most common strong opioids prescribed in the UK. Additionally, Zin *et al.* (2014) found that morphine was the most frequently prescribed strong opioid and that oxycodone showed the greatest increase in prescriptions during 2000 to 2010. Complementary to these findings, the results from the study presented in this chapter shows that the rise in oxycodone prescribing has plateaued in more recent years and that since 2010, there has been a sharp increase in morphine prescribing.

A previous UK study examining the annual days of supply of strong opioids reported the mean annual days' supply per person (with non-cancer pain) to be 148.4 days in 2010, having increased 50.5% between 2000 and 2010.[5] Consistent with this study, the results showed that, in 2008, strong opioid users were covered for a median of 155 days (IQR: 28, 340 days), and that people prescribed a combination of weak and strong opioids were covered for 202 days (IQR: 85, 327 days). The figure reported in this chapter is slightly larger than that reported by Zin *et al.*, however, it is possible that this is due to differences in methods for preparing the prescription data and the inclusion of prescription data for weak opioids. The present study accounted for duplicates, gaps, overlaps and concurrently used opioids when calculating the annual days of opioid coverage per person whereas such methods were not used by Zin *et al*. Nevertheless, these findings are similar to the previous literature and provide assurance of the consistency of these findings.

The analysis of daily dose in this chapter showed that strong opioid users were prescribed greater daily doses than weak opioid users, and that although daily OMEQ doses for strong opioid users remained stable, average doses for weak opioid users increased over the study period. The median daily OMEQ dose for strong opioid users was 60.0mg (IQR: 29.1, 114.6mg), and 49.3mg (IQR: 30.5, 79.4mg) in people prescribed both weak and strong opioids. Additionally, the median daily OMEQ dose prescribed to weak opioid users increased from 18.0mg (IQR: 7.8, 27mg) to 25.1mg (IQR: 10.4, 27.0mg) between 2008 and 2017. A previous UK study reported that between 2000 and 2010 the mean daily OMEQ dose for strong opioid users with non-cancer pain was 86.0mg (±8.7mg/day),[5] which is slightly higher than the results presented in this chapter. It is likely that this difference is due to the reporting of mean and median estimates; the examination of doses presented in this

chapter showed that some people exceeded daily OMEQ doses of 3,000mg/day, and therefore the median was found to be more representative of the 'average' strong opioid user. Another study reported that daily opioid doses remained stable between 2000 and 2012,[242] however, only the five most common opioid products prescribed were analysed and presented as the number of tablets taken daily, therefore, the findings could not be compared to the more comprehensive analyses presented in this chapter. The present study converted daily doses from across all opioids to daily OMEQ doses using equianalgesic ratios to allow for comparison across opioid drugs and formulations, the benefit of this approach means that the findings from this study can be readily compared to other studies of opioid utilisation.

6.6.2 Patient-level utilisation

Contrary to the population-level analysis, there are few studies that have examined opioid utilisation on a patient-level, and therefore very few that can be used to compare the findings from this study. The patient-level analyses showed that most new users of opioids were initiated on weak opioids (98.5%) and that just 2.5% were initiated on a strong opioid. This is inconsistent with a previous study by Chevalier *et al.* (2014), who reported that 89.5% of new adult users of opioids were initiated on weak opioids, and 10.5% were initiated on strong opioids.[123] This discrepancy is likely to be due to the definitions used to identify 'new opioid users'; a one-year exposure lookback period was used by Chevalier *et al.* to assess for a prior opioid prescription whereas the study presented in this chapter used a two-year exposure lookback period. A shorter lookback duration would have misclassified prevalent users as new users leading to the greater proportion of people initiating strong opioids reported by Chevalier *et al*. The longer lookback period used to identify the new opioid users examined in this chapter reduced the possibility of

misclassification of new users, which explains the greater proportion of people found to initiate weak opioids.

People initiated on strong opioids were prescribed opioids for longer than people initiated on weak opioids; the median duration of continuous or intermittent opioid use was 40 days (95%CI: 36, 43 days) for people initiated on strong opioids, and 16 days (95%CI: 16, 16 days) for initiators of weak opioids. These findings are supported by Chevalier *et al*. (2014),[123] who reported that most people prescribed opioids took them for less than six months.

Opioids Aware is a prescribing resource funded by Public Health England which recommends that an opioid trial with a duration of no longer than 7-14 days is carried out when people are initiated on strong opioids.[252] The objective of this trial is to assess effectiveness and potential adverse effects. The findings from this chapter shows that most people are initiated on opioids for the short-term, with the median duration of the first continuous period of opioid use being 28 days (95%CI: 27, 28 days) for initiators of strong opioids, and 16 days (95%CI: 16, 16 days) for initiators of weak opioids. These findings therefore suggest that, based on the *Opioids Aware* recommendations,[252] people initiated on strong opioids may have been prescribed too many days' supply at first prescription. It is important to bear in mind however that the definition of a new opioid user in the analyses presented in this chapter was based on a two-year exposure lookback period, and that some people may not have been truly 'opioid naïve' when prescribed their first CPRD-recorded opioid.

Most people were prescribed weak opioids, however, compared to the first patient-year, those prescribed opioids in their second patient-year were twice as likely to be prescribed strong opioids. This may reflect a switch to stronger opioids in people where weak opioids did not provide adequate pain relief, or additionally, this may reflect people becoming tolerant to the effects of weak opioids after continued use. The sharp rise in strong opioid prescribing was reflected by a sharp increase in the proportion of days covered by morphine, buprenorphine, oxycodone and fentanyl products in the second patient-year.

The results of the dose analysis showed that daily OMEQ doses for weak opioid users increased over the duration of follow-up. This is consistent with the results from the population-level analysis, which showed that daily doses for weak opioids increased over the study period. On the other hand, the median daily OMEQ dose for strong opioid users declined over the first three years of patient follow-up. This trend is consistent with the findings reported by Chevalier *et al.*,[123] who, using data from the CPRD, found that the mean OMEQ dose for initiators of strong opioids was lower than the starting dose. One possible explanation for this finding is that people initiated on strong opioids and people prescribed strong opioids in their early years of opioid use may have been prescribed them for conditions such as cancer pain, post-operative pain and end-of-life pain, whereas people prescribed strong opioids later in their follow-up may have been prescribed them for other, perhaps more chronic conditions. The *Opioids Aware* prescribing resource suggests that OMEQ doses >120mg/day are unlikely to benefit pain reduction or improve function for people,[252] the findings from this patient-level analysis show that the majority of people prescribed opioids, irrespective of the duration of use, do not exceed this recommended maximum dose. However, when inspecting the maximum recorded doses for people in both the patient-

year and study-year analyses it was found that a small minority of people were prescribed doses that far exceeded this threshold, particularly in the study-year analysis, which included prevalent users of opioids.

The median annual days covered was ≤20 days for any given year of follow-up in people prescribed weak opioids. People prescribed strong opioids were covered for a median duration of ≤93 days for any given year of follow-up. This is consistent with the findings presented in this chapter, showing that only a small proportion of new opioid users demonstrated persistent use; 4.1% of people met any of the three definitions for persistent opioid use by the end of their first patient-year. Furthermore, of those who were persistent users in their first patient-year, the likelihood of remaining persistent declined over follow-up. Svendsen *et al.* (2011) described persistency of opioid use in a Norwegian population using a prescription database,[113] reporting that 10.6% of people met any of these three definitions of persistency. This proportion is much higher than the findings from the present study, it is likely that this is due to differences in study populations and differences in whether the data were examined over study-years or patient-years. The study by Svendsen *et al.* included opioid prescriptions for incident and prevalent opioid users, analysing data by study-year whereas the present study included incident users only and analysed opioid use by patient-year. Additionally, Svendsen *et al.* found that 70% of all non-persistent opioid users in their cohort were new users of opioids, and that just 5–9% of the people meeting the definitions for persistent opioid use were new users, suggesting that the inclusion of prevalent opioid users would have increased the proportion of persistent users considerably.

6.6.3 Strengths and limitations

This study has a number of strengths and complements previous UK opioid utilisation studies by providing a patient-level analysis of opioid utilisation reporting the number of opioid users, daily dose, duration of opioid use, and persistency.[5, 110, 111, 124, 242, 243] The use of routinely collected EHRs provided a large study population of both prevalent and incident opioid users with a long duration of follow-up in order to examine real-world opioid prescribing over a nine year study period. This cohort, unlike those examined in most opioid utilisation studies to-date,[5, 110] included people with and without a cancer diagnosis and therefore represented all people prescribed opioids. Additionally, the CPRD prescription data were prepared using a systematic approach to dealing with missing data as well as accounting for gaps and overlaps based on a novel prescription preparation algorithm (as described in Chapter 5). The adoption of this prescription preparation method allowed an OMEQ dose to be calculated for each person on any given day of opioid use that accounted for concurrent use of opioid products.

This study also, uniquely, reported the proportion of opioid drugs prescribed using the duration of prescription coverage rather than number of prescription items, meaning that the proportions of opioid drugs reported were not influenced by differences in prescription lengths for different opioid products. Another strength of this study is that the PPC method was combined with standard drug survival analysis methods to estimate both duration of an initial course of opioid use, and also the duration of opioid use that is either continuous or intermittent.

There are also several limitations of this study which warrant consideration. There was the potential to over-estimate the number of individuals prescribed

an opioid due to the anonymised nature of the CPRD prescription data; people might have been counted more than once in a year if they moved to another CPRD practice and assigned with a new patient identifier. It is expected that the frequency at which this occurred was minimal, and would therefore have had little impact on the findings. Also, it cannot be guaranteed that people had their prescriptions dispensed nor that they took their opioid as indicated by the prescriber; prescribed opioids may not have been used continuously as assumed, and instead used intermittently for longer durations or, on the other hand, opioids may have been used more frequently than prescribed and for shorter durations. In addition, people may have stopped their opioid and disposed of unrequired medication, or they may have obtained more opioids via pharmacy purchases, secondary care, friends/family or illegitimate means. For these reasons, exposure misclassification bias may have been introduced; unpredictably impacting on the study outcomes.

The findings from this study would ideally be complemented by linked prescription data from secondary care and data regarding pain conditions. This study did not describe nor analyse prescription data based on the pain condition for which people were prescribed their opioid. This was due to the nature of the CPRD database meaning that a diagnosis could not be linked to opioid prescriptions. Previous studies have shown that recording of pain conditions is very poor within the CPRD database; finding that just 15.6% of opioid prescriptions could be linked to a general diagnosis of ‘pain’ which would not have been informative for this study.[242] Additionally, as there were no data available for secondary care prescribing it may have been possible that people had actually initiated opioids in hospital, however no hospital prescribing data were available to determine whether this was the case.

Therefore, this study may have under-estimated the proportion of people prescribed opioids as well as potentially overestimating the proportion of people initiated on strong opioids. Finally, in the patient-level analysis the time to first or final break in treatment was based on a pre-defined duration of non-exposure to opioids (i.e., a gap). Sensitivity analyses showed that the gap-length affected the estimated time on treatment. However, this study used a gap-length within those reported by previous studies reporting the duration of opioid,[246] and analgesic use.[247]

6.7 Conclusions

This study showed that most people are initiated on weak opioids, are prescribed OMEQ doses that are <120mg/day, and use opioids for short durations, which is consistent with UK prescribing recommendations. However, this study also showed that opioid utilisation increased between 2008 and 2017, and that the proportion of strong opioid users more than doubled. It was also found that people who continue to use opioids beyond their first year are more likely to be prescribed strong opioids which are used for longer durations and at greater daily doses than weak opioids.

Chapter 7: The incidence of fractures in people prescribed opioids

7.1 Abstract

Background

Fractures affect a substantial proportion of the UK population and risk factors such as medicine use can increase the risk of fracture. The aim of this study was to identify and describe fractures in people prescribed opioids, and to calculate the incidence rate of fractures in this cohort.

Methods

This was a retrospective cohort study of new opioid users who were prescribed opioids between June 2008 and May 2017. Incident fractures during follow-up were identified in the CPRD and HES databases. Characteristics of people with and without a fracture were described. The incidence rate of fracture was calculated by dividing the number of people with fractures by the total fracture-free follow-up time, fracture rates were stratified by age, sex, socioeconomic status, ethnicity, fracture site and season of year.

Results

87,454 incident fractures were identified, 67,622 of which were first fractures. Of the 67,622 people with fractures, the mean age at baseline was 56 years, and 58.7% were female. The overall rate of fracture was 218 per 10,000 person-years. Fracture rates varied considerably by age and sex and was greatest among females aged ≥50 years (323 per 10,000 person-years). Fracture rates increased with increasing deprivation, particularly in younger males who had an IRR of 1.2 in IMD level 5 (most deprived), compared to IMD level 1 (least deprived). Fracture rates were greatest among white females aged ≥50 years and were 3.1 times greater than the rate among black females aged ≥50 years. Additionally, fracture rates were greatest in the winter months

for males aged ≥50 years, whereas the rate of fracture was highest in the summer and winter months for females aged ≥50 years.

Conclusions

The incidence of fractures in this cohort of new opioid users was nearly double that reported for the general UK population, implying that opioid users are more prone to fractures. People with fractures tended to be older and female, which is consistent with trends observed in the general UK population. Further research is needed that assesses the potential contribution of opioids to this higher rate of fracture.

7.2 Introduction

Fractures impose a considerable and increasing burden on people and healthcare systems. A retrospective cohort study using data from the CPRD estimated that the lifetime risk of any fracture was 53.2% among females and 20.7% among males aged ≥50 years residing in England and Wales.[70] Moreover, another retrospective cohort study demonstrated that, compared to the general population, English people experiencing a fracture had a 3.2-fold increase in the risk of mortality in the year following their fracture; this risk of mortality increased with age.[74]

The UK population is ageing and the ONS projections estimate that by 2037 24.0% of the UK population will be aged ≥65 years.[72] Consequently, the prevalence of conditions associated with ageing such as osteoporosis will increase, leading to an increase in the incidence of fragility fractures and subsequent increase healthcare expenditure. In 2017, fragility fractures were associated with a healthcare cost of £4.5 billion, which is expected to rise to £5.9 billion, by 2030.[76] Given the increasing burden of fractures for people, healthcare providers as well as the UK economy, the identification of modifiable risk factors is an important area of research.

Observational studies have demonstrated a significant positive association between use of opioids and an increased risk of bone fractures.[13, 87-90, 186-190, 192-195, 197-203] However, the ability to make causal inferences from these studies has been limited by potential for confounding. Most of these studies identified fractures from codes entered in hospital and GP records. The only UK opioid-fracture association study conducted to date identified fractures from GP records alone, thereby likely under-estimating the incidence of fractures among UK opioid users. Identifying fractures from both primary and secondary

care data sources will provide more accurate incidence rates for fracture risk among opioid users. Additionally, use of hospital records may provide more accurate dates for fracture events, thereby providing greater certainty about the temporal order of opioid exposure and fracture outcomes.

7.3 Aims and objectives

The aims of this chapter were to identify and describe the incidence of new fractures (i.e., incident fractures) among people initiating prescription opioids between 1st June 2008 and 31st May 2017. The objectives for this study were to:

1. Identify incident fractures among new opioid users in the CPRD and HES databases.

2. Describe the demographic characteristics of people with and without fractures.

3. Estimate the incidence rate of fractures among new opioid users and examine variations in fracture rates by age, sex, fracture site, socioeconomic status, ethnicity and season of year.

7.4 Method

7.4.1 Study design

This was a retrospective cohort study of people initiating[14] prescribed opioids between 1st June 2008 and 31st May 2017.

[14] New users of opioids were defined as people with no opioid prescription during their two-year exposure lookback period

7.4.2 Data source

A list of people who were incident opioid users was merged with the CPRD linkage eligibility file to identify people eligible for linkage to HES and IMD data sources. Records of fractures were extracted from the CPRD Clinical file and linked with data from the HES and IMD databases; section 7.4.4 outlines the method used to identify incident fractures in these data sources.

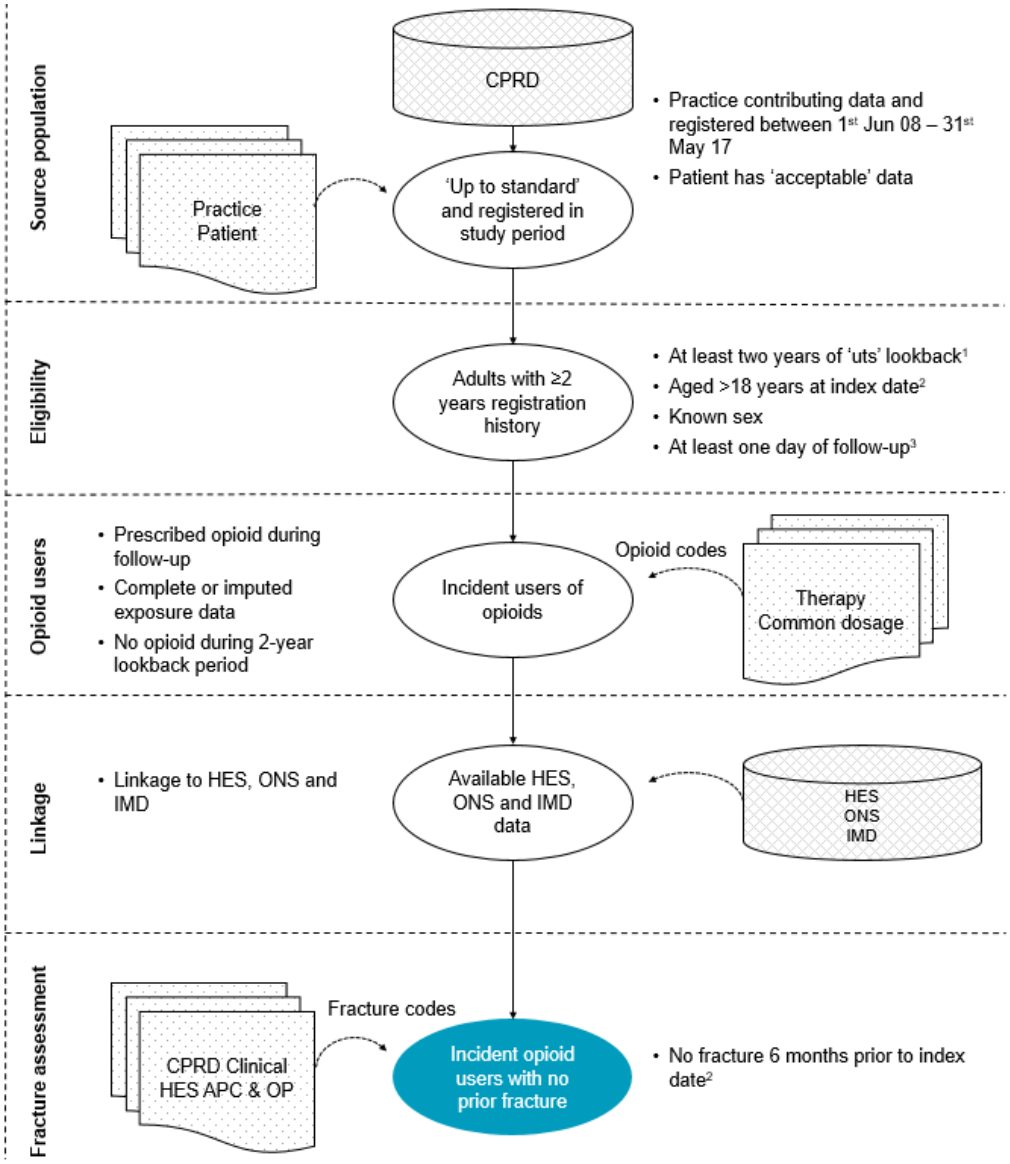
People were classified as having osteoporosis (ever vs. never) based on the presence of an osteoporosis 'medcode' in the CPRD Clinical file. An ever vs. never approach was used because people may only undergo a dual-energy x-ray absorptiometry (DXA) scan to assess for osteoporosis subsequent to a fracture event, once osteoporosis is suspected, a diagnosis recorded after a fracture was therefore considered to indicate likely osteoporosis prior to a fracture. It is therefore acknowledged that osteoporosis detection may be biased by the occurrence of a fracture. The osteoporosis code list (Appendix T) was based on previously published osteoporosis code lists,[253-256] and searching the CPRD medical code browser for 'osteoporosis'; the final list was checked by a clinician (Fiona Pearce, FP).

Other medicines may increase the likelihood of fracture, particularly psychoactive medicines, cardiovascular medicines and glucocorticoids.[83, 90, 103, 104] A list of product codes was generated in collaboration with a pharmacist (RK) to identify prescriptions recorded in patients' CPRD Therapy files for potential fracture-risk increasing drugs (FRIDs) (Appendix U). People were classified as having received a FRID based on the presence of a prescription for a FRID, with a prescription 'eventdate' during follow-up.

The ethnicity of each person was obtained from both the CPRD and HES databases using the approach adopted by Mathur *et al.* (2014) (Appendix V).[257] Ethnicity was categorised using five categories: white, mixed, Asian or Asian British, Black or black British and other. People with missing ethnicity data were coded as having an unknown ethnicity.

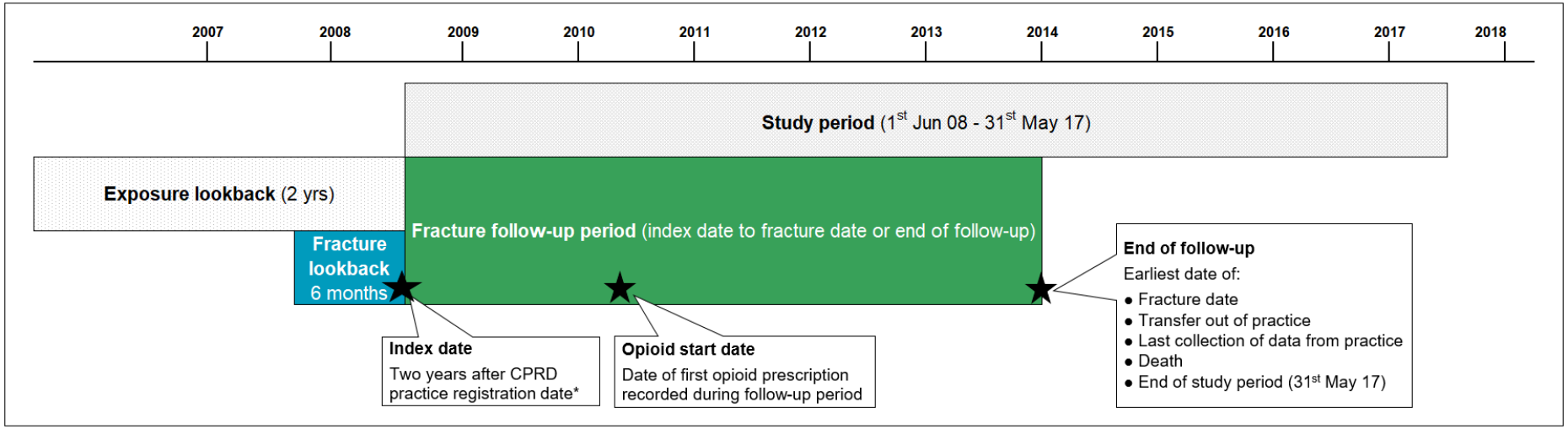
7.4.3 Cohort identification

All new opioid users with complete (or imputed) opioid prescription data (identified in Chapter 5) who were eligible for linkage to the HES and IMD were included. People were excluded if they had a record of a fracture in the six-month period prior to their index date (Figure 7-1). This six-month fracture lookback period was used to ensure that fractures occurring before follow-up were not misclassified as incident fractures. This is because multiple codes may have been entered on separate dates despite relating to just one fracture event. The six-month fracture lookback period was selected based on advice from clinicians regarding fracture-healing times, and the approach taken in a prior CPRD study that identified and characterised incident fractures.[226] People were followed from their index date until the earliest of: (1) date of first fracture or (2) end of follow-up date (see Figure 7-2). The reason for following people from their index date rather than opioid start date was to identify fracture cases for a subsequent opioid-fracture association study (outlined in Chapter 8 of this thesis), so that attributable risk could be estimated relating to this source population.



Notes: CPRD, Clinical Practice Research Datalink; lcd, last collection date; uts, up to standard; crd, current registration date.
[1] Lookback start = the latest of: 1st June 2006, 'crd', or 'uts', lookback ends two years after the lookback start date.
[2] Index date = lookback start + two years.
[3] End of follow-up = the earliest of: transfer out of practice (tod), practice last collection date (lcd), date of death, or 31st May 2017.

Figure 7-1. Selection of study cohort



Notes: *Index date is two years after the latest of: (1) CPRD practice registration date, (2) CPRD practice 'up to standard' date or (3) 1st June 2006. The fracture lookback period is indicated by the blue box and was six months in length.

Figure 7-2. Illustration of fracture follow-up period

7.4.4 Identification of fractures

7.4.4.1 Generating fracture code lists

Three code lists were generated to identify fractures in the data sources: 'medcodes' for the CPRD database and ICD as well as OPCS codes for the HES database. These code lists were generated for the CPRD and HES data sources and were checked by coding specialists (Robina Okes-Voysey, ROV and Kathryn Liddiard, KL) working in primary and secondary care settings, respectively. The following sections outline the process for generating these code lists.

The CPRD

'Medcodes' are the codes assigned to clinical events in the CPRD and are based on Read codes. The CPRD has a medical browser which can be used to 'translate' between 'medcodes' and Read codes. 'Medcodes' and Read codes relating to fractures were identified from existing literature after searching for CPRD studies reporting fracture outcomes.[258-260] Additionally, the CPRD medical browser was searched for the keyword 'fracture'; all 'medcodes' and Read codes were extracted and combined with the existing codes to identify any codes recorded in the CPRD and not present in the published code lists. This combined list of codes was manually checked by inspecting the Read terms and descriptions assigned to the Read codes and 'medcodes'; assessing them for relevance to fractures or fracture procedures. Each code was also assigned with a category relating to the anatomical site of fracture, where this was unspecified or unclear the site was categorised as 'unspecified'. The final 'medcode' list (see Appendix W) was reviewed by a clinical pharmacist specialising in clinical system coding (ROV) to ensure all

codes were captured, relevant and appropriately categorised by anatomical site.

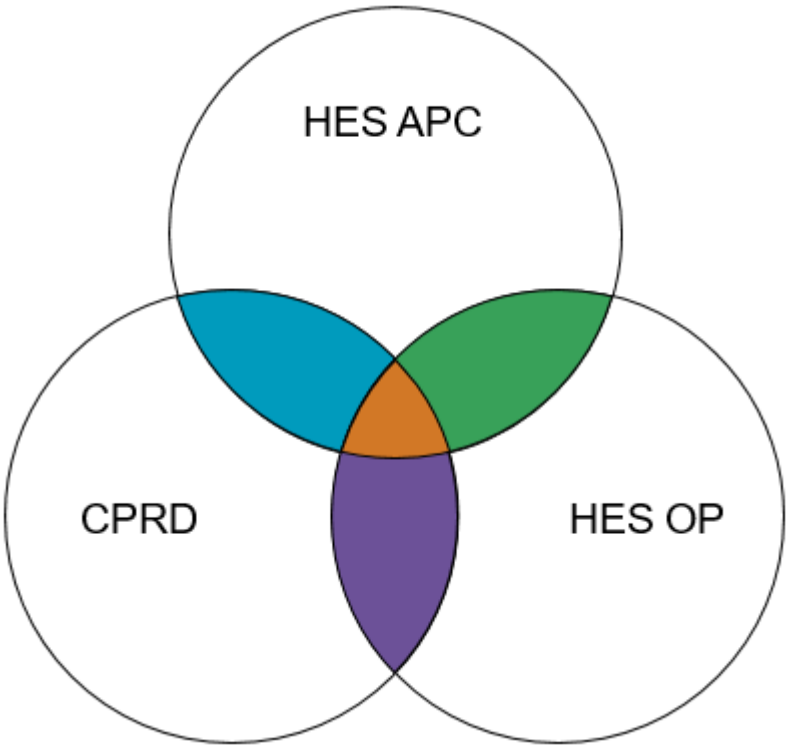
HES APC and OP

The WHO's ICD codes are used to record diagnoses and NHS Digital's OPCS codes are used to record operations and procedures in the HES APC and OP databases. The 10th version of the ICD code list (ICD-10) and 4th version of the OPCS code list (OPCS-4) were used to identify codes relating to fracture diagnoses and procedures.[261, 262] The generated code list was referenced against codes reported by existing studies that identified fractures using any version of ICD codes, these studies were identified in the systematic review reported in Chapter 3 of this thesis. The description for each code was manually checked for relevance to fractures and categorised by anatomical site. The final ICD-10 and OPCS-4 code lists (see Appendix X and Appendix Y) were subsequently reviewed by an NHS hospital informatics manager (KL) to ensure all codes were captured, relevant and appropriately categorised by anatomical site.

7.4.4.2 Identifying incident fractures

People with a record of a fracture during follow-up were identified in each of the three data sources (illustrated in Figure 7-3) and merged into one file. In cases where a person had more than one record of a fracture, the earliest record was considered the first fracture. Subsequent fractures were assumed to be incident if they occurred in a different anatomical site, or were recorded >6 months after a preceding fracture to the same site. People with multiple records for fractures to different anatomical sites that were recorded on the same date were reclassified as having one fracture to 'multiple' sites on that date. People with a record of fracture in the six-month fracture-lookback

period were excluded from the analysis. Additionally, any people that had a record of a fracture with a missing date in any of the data sources were also excluded.



Notes: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; APC, Admitted Patient Care; OP, Outpatients. Fracture events may be recorded in more than one data source, denoted by the coloured sections.

Figure 7-3. Illustration of fracture records identified across the data sources

7.4.5 Data analysis

Demographic characteristics of people during their fracture follow-up period were reported as frequencies, proportions and mean/medians (after visually inspecting the spread of data). Where people had more than one fracture recorded, the date of their first fracture during follow-up was used to calculate incidence rates. Therefore, follow-up for these people was curtailed on the date of their first fracture. Subsequent fractures (i.e., beyond follow-up) were described separately.

Incidence rates were calculated to provide the number of fractures per year of patient follow-up. The numerator was the number of people with a fracture during follow-up and the denominator was the total fracture-free follow-up time for all people in the cohort (Equation 7-1). The fracture-free follow-up time was calculated as the number of days from the index date to the earliest of: (1) the date of first fracture, or (2) end of follow-up date. Incidence rates were reported in units of 10,000 person-years and were stratified into subgroups by age (<50 years, ≥50 years), sex (female, male), fracture site, socioeconomic status (IMD quintiles), ethnicity (white, black, Asian, mixed, other, unknown) and season (spring, summer, autumn, winter).

Equation 7-1. Calculation of incidence rate for fractures

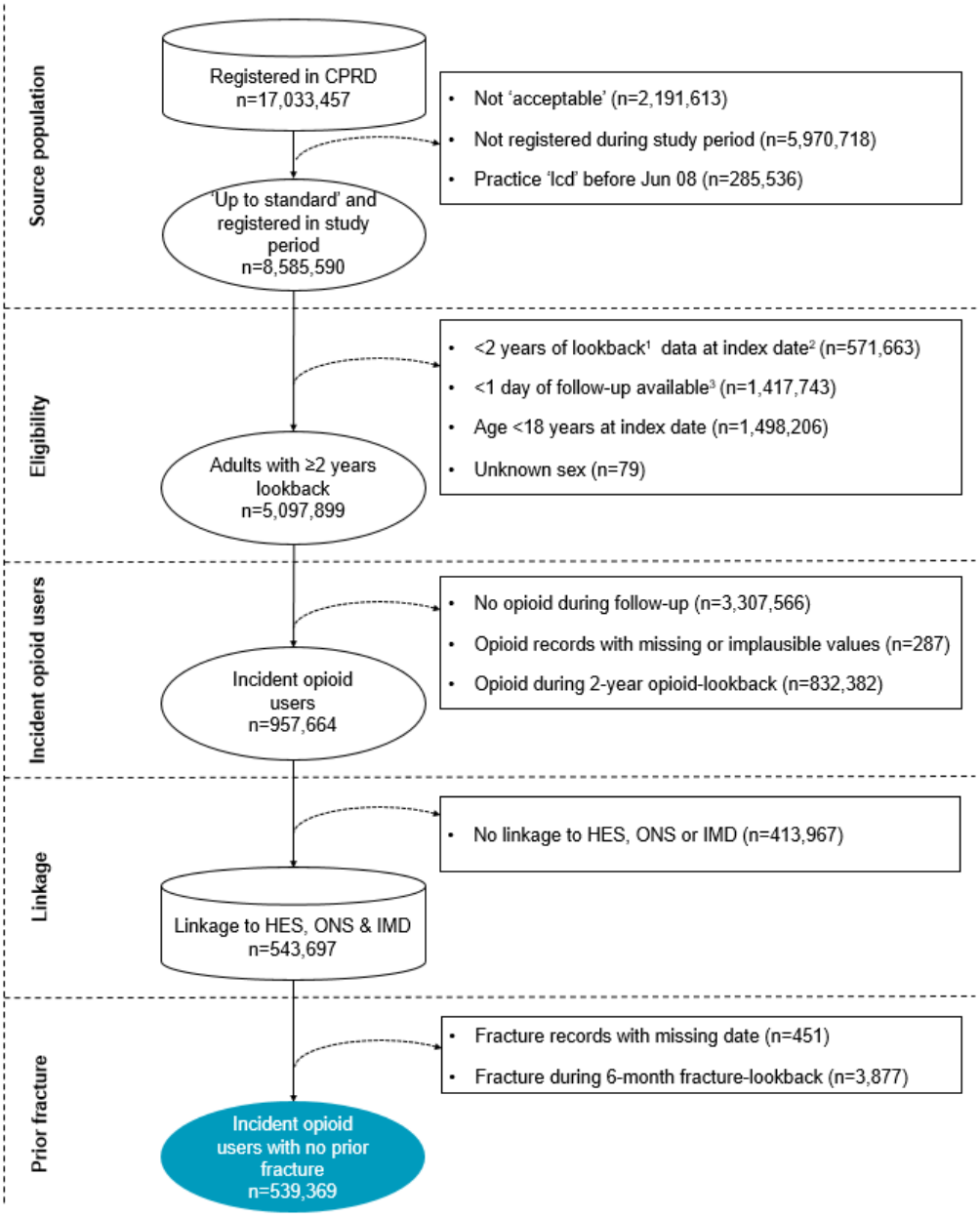
$$Fracture\ incidence\ rate = \frac{Number\ of\ patients\ with\ a\ fracture}{Total\ 'fracture\ free'follow\ up\ time}$$

All data management processes and statistical analyses were carried out using the statistical software - Stata/MP 15 (StataCorp, Texas, USA).

7.5 Results

7.5.1 Study cohort

In total, 957,664 incident opioid users were identified. Of these, 543,697 people (56.8% of the 957,664) were eligible for linkage to HES, ONS and IMD. Of these, 451 people were excluded because they had fracture records with missing event dates, and a further 3,877 people were excluded because they had a fracture recorded six-months prior to their index date. In total, 539,369 people were included in the cohort for this study (Figure 7-4). Of the 539,369 people, 298,578 (55.4%) were female and the mean baseline age was 51.8 years (SD: 18.1).



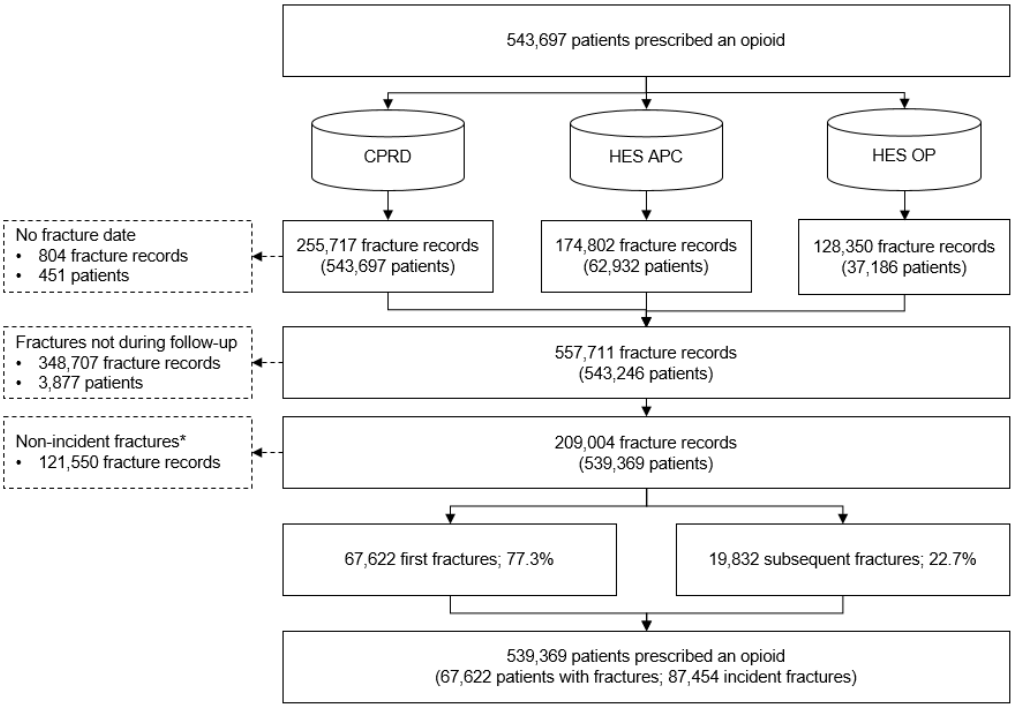
CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics; IMD, Index of Multiple Deprivation; lcd, last collection date; uts, up to standard; crd, current registration date.

[1] Lookback start = the latest of: 1st June 2006, 'crd', or 'uts', lookback ends two years after the lookback start date.
[2] Index date = lookback start + two years.
[3] End of follow-up = the earliest of: transfer out of practice (tod), practice last collection date (lcd), date of death, or 31st May 2017.

Figure 7-4. Identification of study cohort

7.5.2 Fracture identification

67,622 people were identified as having at least one incident fracture recorded in the CPRD, HES APC or HES OP datasets during their follow-up period. Among these 67,622 people, a total of 87,454 incident fractures were identified, of which 22.7% were subsequent fractures (i.e., not the first incident fracture recorded for a person during follow-up) (Figure 7-5). Of the 87,454 incident fractures that were identified, 42,021 (48.1%) were identified in the HES and 45,433 (51.9%) were identified in the CPRD.



Notes: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; EPC, Admitted Patient Care; OP, Outpatients; *non-incident fractures were defined as fracture codes recorded for the same anatomical site as a preceding fracture that was recorded ≤6 months before.

Figure 7-5. Identification of incident fractures among opioid user cohort

7.5.3 Patient characteristics

The final study cohort comprised of 539,369 people, of which 67,622 sustained ≥1 fracture during follow-up. The cohort contributed a total of 3,106,768 person-years of follow-up time - the median duration of follow-up was 6.1 years (IQR: 3.8, 8.0). A total of 240,791 (44.6%) of the study cohort were male and contributed a duration of 1,397,067 person-years of follow-up; 27,945 (11.6%) males sustained a fracture during their follow-up time. A total of 298,578 (55.4%) of the study cohort comprised of females with a total follow-up duration of 1,709,701 person-years; 39,677 (13.3%) females sustained a fracture.

People experiencing a fracture were, on average, five years older on their index date compared with people without fractures and had a mean age of 56.1 years (SD: 19.6). A higher proportion of people with fracture were female (58.7%), compared with those without fracture (54.9% female), and were from the least deprived IMD levels (IMD level 1: 23.2%; IMD level 2: 22.0%), compared to people without fracture (IMD level 1: 22.2%; IMD level 2: 21.7%). People with fractures were more likely to be of white ethnicity (93.1%) than those without fractures (85.2%).

A greater proportion of people with fractures had a diagnosis of osteoporosis recorded at any time-point in their CPRD Clinical file; 12.9% of people with a fracture had a code for osteoporosis whereas 2.6% of people without a fracture had an osteoporosis code. A smaller proportion of people with a fracture (62.8%) were exposed to any FRID (excluding opioids) during their follow-up compared with people without a fracture (71.1%) (Table 7-1).

Table 7-1. Characteristics of opioid users with and without fractures

Characteristic	People without fracture (n=471,747)			People with fracture (n=67,622)		
	Mean (SD)	N	%	Mean (SD)	N	%
Age at index (years)	51.20 (17.79)			56.13 (19.59)		
Sex (female)		258,901	54.88%		39,677	58.67%
IMD quintile:						
1 (least deprived)		104,475	22.15%		15,663	23.16%
2		102,586	21.74%		14,903	22.04%
3		97,452	20.66%		13,934	20.61%
4		89,006	18.87%		12,235	18.09%
5 (most deprived)		77,925	16.52%		10,852	16.05%
Missing		303	0.06%		35	0.05%
Ethnicity:						
White		401,709	85.15%		62,983	93.14%
Asian/Asian British		16,309	3.46%		1,137	1.68%
Black/black British		10,150	2.15%		569	0.84%
Other		5,877	1.25%		447	0.66%
Mixed		2,696	0.57%		226	0.33%
Unknown		35,006	7.42%		2,260	3.34%
Osteoporosis*		12,084	2.56%		8,715	12.89%
FRID		335,209	71.06%		42,463	62.79%

Notes: FRID, fracture-risk increasing drug; IMD, Index of Multiple Deprivation; *has a record of osteoporosis ever in their CPRD Clinical file (i.e., before or after fracture)

7.5.4 Fracture incidence

7.5.4.1 Age, sex and fracture site

The incidence of fracture among the entire cohort of opioid users was 217.7 per 10,000 person-years (95%CI: 216.0, 219.3). Fractures most commonly occurred in people aged ≥50 years (61.7% of people with a fracture were aged ≥50 years), and fracture incidence increased substantially with age for females from approximately the age of 50 years. In contrast, the rate of

fractures showed a bimodal distribution in males, with peaks at ages 18-24 years and increasing from the age of 65 years (Figure 7-6).

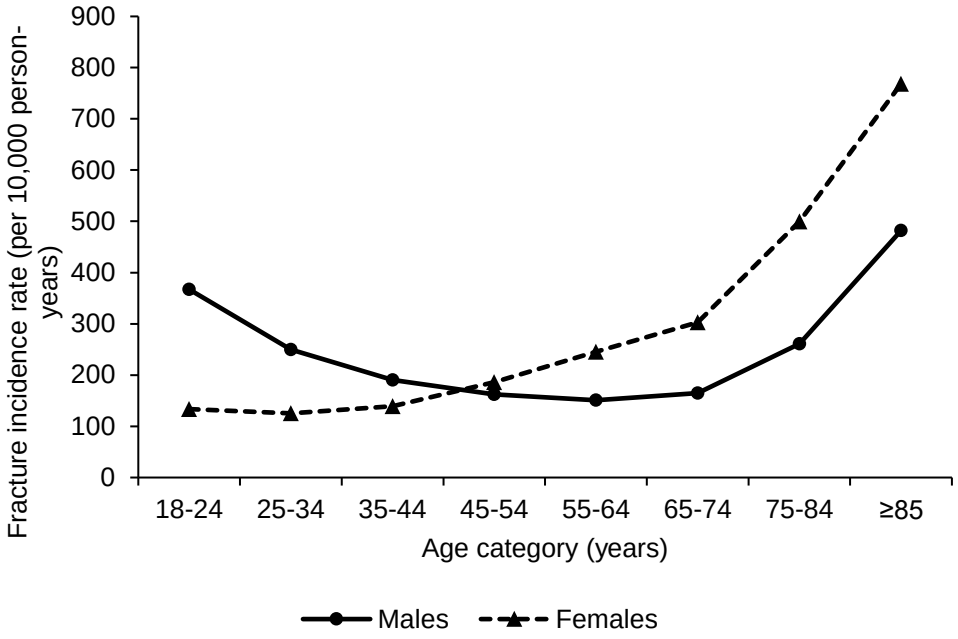


Figure 7-6. Fracture incidence (per 10,000 person-years), by age and sex

After stratifying by age and sex, the incidence rate for males aged <50 years was 222.5 per 10,000 person-years (95%CI: 218.8, 226.2), whereas this was 140.6 per 10,000 (95%CI: 138.1, 143.1) for females aged <50 years (Table 7-2). Comparing males and females aged ≥50 years; females had a substantially greater rate of fracture, the rate of fracture was 181.8 per 10,000 person-years in males (95%CI: 178.8, 184.8), and 322.9 per 10,000 person-years (95%CI: 319.1, 326.7) in females (Table 7-3). There was considerable heterogeneity between rates of fractures to each anatomical site by age and sex; in particular, females aged ≥50 years had over double the rate of fracture to the hip compared with males aged ≥50 years (49.2 and 24.2 per 10,000 person-years, respectively) (Table 7-3). The rate of hip fractures among females aged <50 years was much lower at 1.1 per 10,000 person-years compared with females aged ≥50 years (Table 7-2).

Table 7-2. Fracture incidence by anatomical site among opioid users aged <50 years

Fracture site	Males		Females		Both	
	N	Rate	N	Rate	N	Rate
Any	13,920	222.49	11,970	140.56	25,890	175.26
Fragility*	3,292	55.61	3,004	36.65	6,296	44.60
Chest	774	13.26	440	5.43	1,214	8.71
Head and neck	1,425	24.33	825	10.16	2,250	16.10
Hip	112	1.92	85	1.05	197	1.42
Leg, ankle and foot	2,863	48.50	3,213	39.17	6,076	43.08
Multiple sites	630	10.80	283	3.49	913	6.55
Shoulder and arm	2,193	37.27	2,289	28.01	4,482	31.89
Spine/back/pelvis	243	4.17	227	2.80	470	3.38
Unspecified	2,811	47.55	2,999	36.55	5,810	41.16
Wrist and hand	2,869	48.63	1,609	19.75	4,478	31.88

Notes: Rate is expressed in fractures per 10,000 person-years; *fragility is a composite of fractures to the hip, spine, rib, humerus, radius/ulna, or pelvis.[71]

Table 7-3. Fracture incidence by anatomical site among opioid users aged ≥50 years

Fracture site	Males		Females		Both	
	N	Rate	N	Rate	N	Rate
Any	14,025	181.81	27,707	322.88	41,732	256.10
Fragility*	6,661	89.40	13,814	170.73	20,475	131.74
Chest	1,316	18.14	1,306	17.05	2,622	17.58
Head and neck	785	10.85	774	10.13	1,559	10.48
Hip	1,761	24.22	3,810	49.17	5,571	37.09
Leg, ankle and foot	2,015	27.71	4,423	56.97	6,438	42.82
Multiple sites	780	10.78	1,400	18.27	2,180	14.63
Shoulder and arm	2,569	35.20	6,634	84.67	9,203	60.81
Spine/back/pelvis	1,048	14.46	2,169	28.19	3,217	21.53
Unspecified	2,423	33.20	4,577	58.77	7,000	46.40
Wrist and hand	1,328	18.32	2,614	33.95	3,942	26.37

Notes: Rate is expressed in fractures per 10,000 person-years; *fragility is a composite of fractures to the hip, spine, rib, humerus, radius/ulna, or pelvis.[71]

In Figure 7-7 and Figure 7-8, the variability between fracture rates to different fracture sites is shown for males and females aged 18-50 years and those aged ≥50 years. The rate of fractures to sites associated with fragility were much greater in females aged ≥50 years, and this is evident by the individual rates for fracture to the hip, shoulder and arm, and the spine, lower back and pelvis.

7.5.4.2 Socioeconomic status

The rate of fracture increased with increasing levels of deprivation among men, particularly for men aged <50 years, who had an IRR of 1.2 (95%CI: 1.1, 1.3) in IMD level 5 (most deprived) compared to IMD level 1 (least deprived). Fracture rates in women were least affected by level of deprivation (Table 7-4 and Table 7-5).

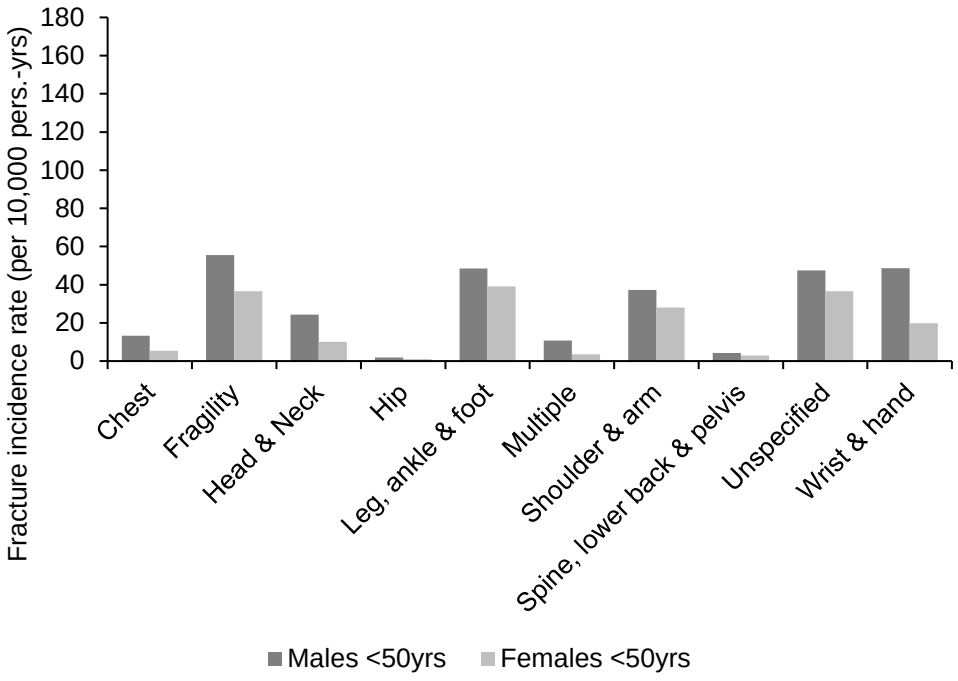


Figure 7-7. Incidence of fracture by site in males and females aged <50 years on date of first fracture (n=25,890)

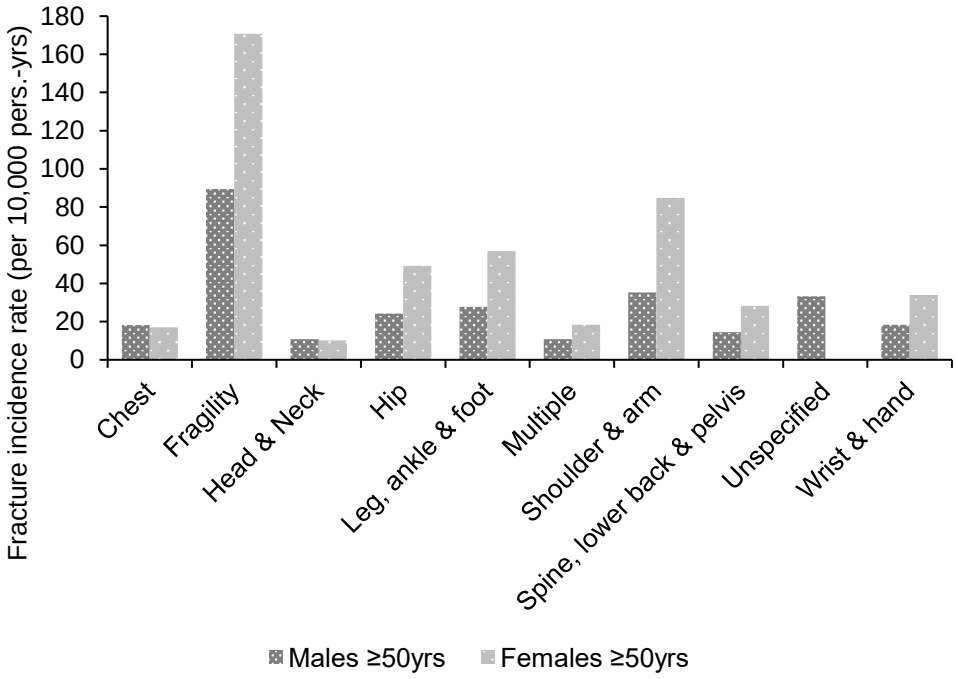


Figure 7-8. Incidence of fracture by site in males and females aged ≥50 years on date of first fracture (n=41,732)

Table 7-4. Fracture incidence by IMD quintile among opioid users aged <50 years

IMD quintile	Males			Females		
	N	Rate per 10,000 person-years	IRR (95%CI)	N	Rate per 10,000 person-years	IRR (95%CI)
1 (least deprived)	2,635	209.89	-	2,455	138.47	-
2	2,586	212.66	1.01 (0.96,1.07)	2,405	142.53	1.03 (0.97,1.09)
3	2,648	213.76	1.02 (0.96,1.08)	2,353	140.04	1.01 (0.96,1.07)
4	2,856	222.70	1.06 (1.01,1.12)	2,372	138.12	0.99 (0.94,1.06)
5 (most deprived)	3,186	252.85	1.21 (1.14,1.27)	2,376	143.75	1.04 (0.98,1.10)

Notes: IRR: incidence rate ratio; CI, confidence interval

Table 7-5. Fracture incidence by IMD quintile among opioid users aged ≥50 years

IMD quintile	Males			Females		
	N	Rate per 10,000 person-years	IRR (95%CI)	N	Rate per 10,000 person-years	IRR (95%CI)
1 (least deprived)	3,462	176.09	-	7,111	324.39	-
2	3,228	178.58	1.01 (0.97,1.06)	6,684	326.84	1.00 (0.97,1.04)
3	2,953	179.59	1.02 (0.97,1.07)	5,980	323.76	1.00 (0.96,1.03)
4	2,449	187.32	1.06 (1.01,1.12)	4,558	312.55	0.96 (0.93,1.00)
5 (most deprived)	1,931	195.91	1.11 (1.05,1.18)	3,359	325.02	1.00 (0.96,1.04)

Notes: IRR: incidence rate ratio; CI, confidence interval

7.5.4.3 Ethnicity

The rate of fracture varied considerably between ethnicities (Table 7-6 and Table 7-7). The highest rate of fracture was observed among white individuals across all ages and sexes. Among males and females aged <50 years, the lowest fracture-rate was observed among Asian and Asian British individuals, whereas among males and females aged ≥50 years the lowest rates were observed among black or black British individuals. The most pronounced difference was observed in females aged ≥50 years, where the rate of fracture among white females was 3.1 times greater than that of black and black British females (white IR: 343.2; black and black British IR: 111.7).

Table 7-6. Fracture incidence by ethnicity among opioid users aged <50 years

Ethnicity	Males		Females		Both	
	N	Rate	N	Rate	N	Rate
White	12,241	255.27	10,961	152.38	23,202	193.53
Asian/Asian British	336	122.51	285	73.06	621	93.47
Black/black British	199	132.89	200	76.31	399	96.88
Other	134	154.27	105	81.85	239	111.09
Mixed	79	183.13	76	102.76	155	132.36
Unknown	931	102.62	343	73.27	1,274	92.63

Notes: Rate is expressed in fractures per 10,000 person-years

Table 7-7. Fracture incidence by ethnicity among opioid users aged ≥50 years

Ethnicity	Males		Females		Both	
	N	Rate	N	Rate	N	Rate
White	13,378	192.11	26,403	343.20	39,781	271.42
Asian/Asian British	210	135.39	306	193.35	516	164.66
Black/black British	65	83.54	105	111.74	170	98.96
Other	68	110.61	140	193.72	208	155.52
Mixed	26	134.77	45	201.96	71	170.78
Unknown	278	63.65	708	130.83	986	100.82

Notes: Rate is expressed in fractures per 10,000 person-years

7.5.4.4 Season

More fractures occurred during summer months (June, July and August) for males and females aged <50 years compared to other seasons of the year (summer IR: 66.2 and 39.9 per 10,000 person-years, respectively) (Table 7-8). The rate of fracture was greatest in the winter months for males aged ≥50 years (winter IR: 50.6 per 10,000 person-years) whereas the rate of fracture was equally high in the summer and winter months for females aged ≥50 years (summer IR: 92.2 and winter IR: 91.3 per 10,000 person-years) (Table 7-9).

Table 7-8. Fracture incidence by season of year among opioid users aged <50 years

Season of year	Males			Females		
	N	Rate	Rate change*	N	Rate	Rate change*
Spring	3,391	57.19	-	2,812	34.30	-
Summer	3,926	66.20	15.75%	3,275	39.94	16.44%
Autumn	3,459	58.39	2.10%	2,975	36.30	5.83%
Winter	3,144	53.14	-7.08%	2,908	35.49	3.47%

Notes: Rate is expressed in fractures per 10,000 person-years; *relative to rate of fractures during spring

Table 7-9. Fracture incidence by season of year among opioid users aged ≥50 years

Season of year	Males			Females		
	N	Rate	Rate change*	N	Rate	Rate change*
Spring	3,354	45.71	-	6,549	83.31	-
Summer	3,508	47.89	4.77%	7,251	92.21	10.68%
Autumn	3,451	47.08	3.00%	6,729	85.77	2.95%
Winter	3,712	50.58	10.65%	7,178	91.30	9.59%

Notes: Rate is expressed in fractures per 10,000 person-years; *relative to rate of fractures during spring

After comparing the rate of fractures during summer months to spring-time months (March, April and May), the rate of fracture showed the greatest increase in males and females aged <50 years (15.8% and 16.4% respectively), and also increased in males and females aged ≥50 years (4.8% and 10.7% respectively). Compared to spring-time fractures, the rate of fractures in autumnal months (September, October, and November) increased slightly in all ages and sexes, ranging from a 2.1% to 5.8% increase. Males and females aged ≥50 years demonstrated a considerably greater increase in the rate of fractures in winter months (December, January, February) compared with the rate of fractures in spring (10.7% and 9.6% respectively). Females aged <50 years also showed an increase in fractures during winter (3.5% increase). Conversely, the rate of fractures declined in winter months in males aged <50 years (7.1% decline) (Figure 7-9).

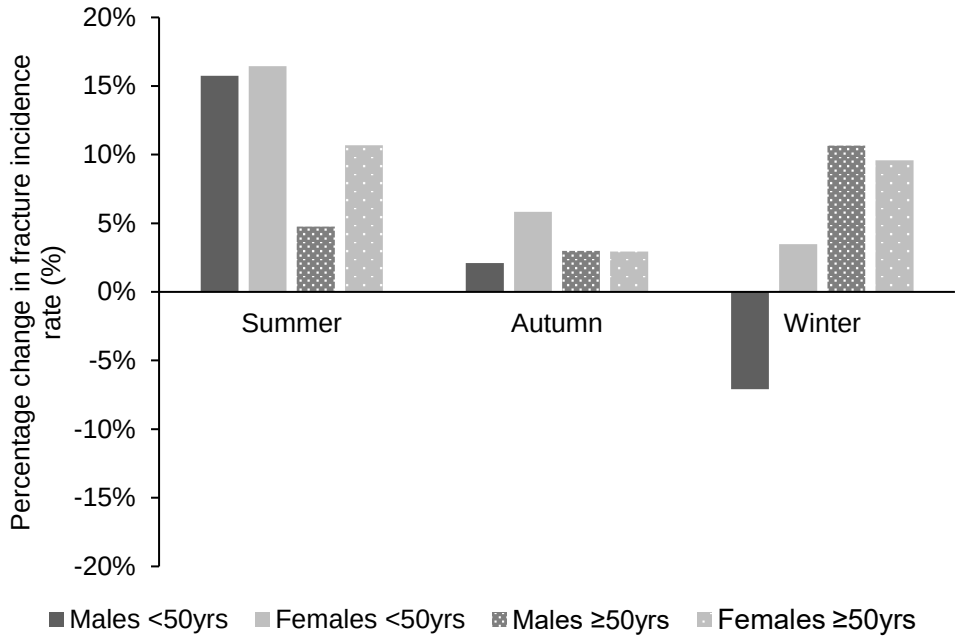


Figure 7-9. Percentage change in seasonal fracture incidence (per 10,000 person-years), relative to rate of fractures in spring

7.5.4.5 Subsequent fractures

Of the 67,622 people who sustained a fracture, 14,015 (20.7%) experienced a subsequent fracture (i.e., a fracture of a different site to the prior fracture or >6 months after a prior fracture). The number of incident fractures per person ranged from 1 to 14 fractures and <1% of people with fractures sustained ≥4 subsequent fractures (Figure 7-10).

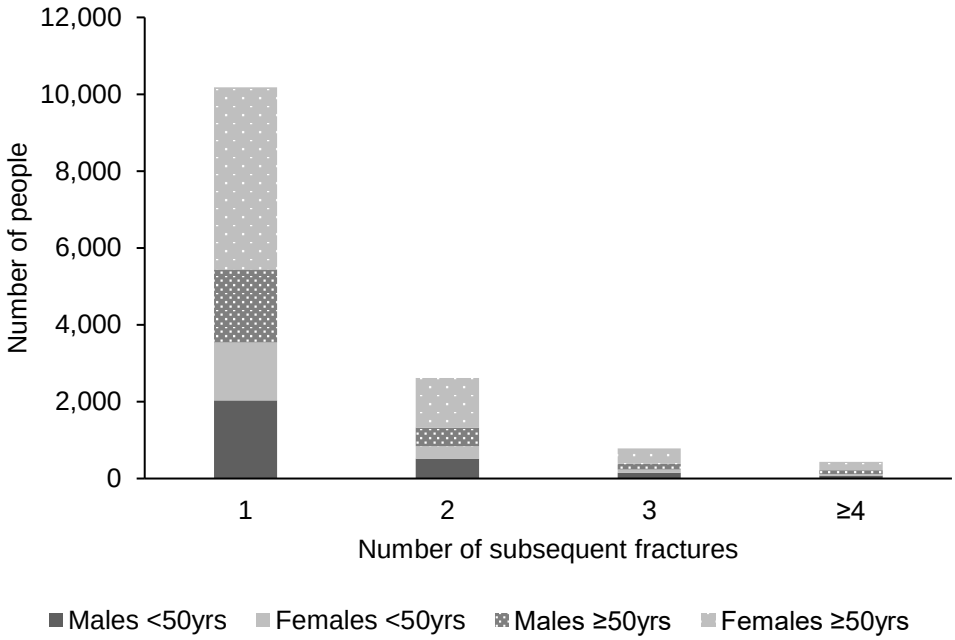


Figure 7-10. Number of subsequent fractures per person with >1 fracture, by age and sex (n=14,015)

The greatest proportion of people experiencing subsequent fractures were female (61.5%) and had a higher mean age (58 years) compared with people sustaining only one fracture (57.9% female; mean age 56 years). The proportion of people within each IMD level were similar across the two groups, as were the proportion exposed to other FRIDs, and the proportion of people within each ethnic category. Nearly twice the proportion of people with a subsequent fracture had a record of osteoporosis present when compared with people who experienced one fracture (20.9% and 10.8% respectively) (Table 7-10).

Table 7-10. Comparison of people experiencing one fracture against those with subsequent fractures

Characteristic	People with one fracture (n=53,607)			People with subsequent fractures (n=14,015)		
	Mean (SD)	N	%	Mean (SD)	N	%
Age at index (years)	55.54 (19.45)			58.39 (19.95)		
Sex (female)		31,061	57.94%		8,616	61.48%
IMD quintile:						
1 (least deprived)		12,374	23.08%		3,289	23.47%
2		11,850	22.11%		3,053	21.78%
3		11,017	20.55%		2,917	20.81%
4		9,731	18.15%		2,504	17.87%
5 (most deprived)		8,609	16.06%		2,243	16.00%
Missing		26	0.05%		9	0.06%
Ethnicity:						
White		49,584	92.50%		13,399	95.60%
Asian/Asian British		950	1.77%		187	1.33%
Black/black British		483	0.90%		86	0.61%
Other		375	0.70%		72	0.51%
Mixed		175	0.33%		51	0.36%
Unknown		2,040	3.81%		220	1.57%
Osteoporosis*		5,782	10.79%		2,933	20.93%
FRID		33,750	62.96%		8,713	62.17%

Notes: FRID, fracture-risk increasing drug; IMD, Index of Multiple Deprivation; *has a record of osteoporosis ever in their CPRD Clinical file (i.e., before or after fracture)

7.6 Discussion

In this retrospective cohort study of over 500,000 people prescribed opioids between June 2008 and May 2017, 67,622 people sustained ≥1 fracture during their follow-up period. Overall, the rate of first fractures was 217.7 per 10,000 person-years of follow-up. Additional stratification of the cohort demonstrated substantial differences in fracture incidence by age, sex, fracture site, socioeconomic status, ethnicity and season of year.

7.6.1 Comparison with general UK population

In the UK, the rate of fracture between 1988 and 2012 among females aged ≥50 years was 155.4 per 10,000 person-years, whereas the incidence rate for males aged ≥50 years was substantially lower (71.8 per 10,000 person-years).[71] The results presented in this chapter also showed that females aged ≥50 years had a higher rate of fracture (322.9 per 10,000 person-years) compared with males aged ≥50 years (181.8 per 10,000 person-years). Additionally, the rate of fracture in males showed a bimodal distribution which has been reported by previous UK studies.[70, 71]

Age- and sex-specific fracture rates were described across fracture sites, and it was found that these differed by age and sex. Most notably, females aged ≥50 years had the highest incidence of hip fractures and fractures to the shoulder and upper arm, which has also been reported in the general UK population.[71] Similarly, the results presented in this chapter also showed a significant variation in the rate of fracture among men when comparing the rate of fracture in the most deprived IMD quintile with the least deprived. This trend was not observed in females and this too has been reported in the general UK population.[71]

It was also observed that there was considerable variability in fracture rates by ethnicity, the rate of fracture was 3.1 times greater in white females aged ≥50 years when compared with those of black or black British ethnicity. These findings are consistent with differences in fracture rates that have been reported previously,[71] and might be explained by ethnic differences in bone microarchitecture. A study comparing the bones of African-American and Caucasian individuals found that African-Americans had larger and denser

bones that were more resilient to fractures when compared with Caucasians.[263]

A relationship between fractures and season was also observed in this cohort; a greater incidence of fractures in females ≥50 years in the winter months was found, which is consistent with previous studies.[264-266] However, these studies did not report a peak in fractures during summer months. The differences in fracture rates across seasons might suggest that weather conditions i.e., snow and ice, may increase the risk of falls and thereby fractures,[264] and may also suggest that people are more mobile or partake in riskier activities during the summer months.

Despite similarities to previous epidemiological studies of fractures, the rate of fracture in this chapter's cohort was approximately double that of the general UK population. This is likely due to inherent differences between this population of opioid users and the general UK population, such as more comorbidities, polypharmacy and inactivity, all of which affect fracture-risk.[83, 97, 101]

7.6.2 Comparison with other opioid-user populations

Previous studies examining the association between opioid-use and fractures were identified and summarised in Chapter 3 of this thesis. A small selection of these studies reported fracture incidence rates among their opioid user study populations. However, there was considerable heterogeneity between studies in terms of the population under investigation and the incidence rates reported. Miller *et al.* (2011) investigated the incidence of fractures in a US-based cohort of new opioid users who were aged ≥65 years and had a diagnosis of rheumatoid arthritis or osteoarthritis, and reported a rate of 1,200

fractures per 10,000 person-years.[192] Additionally, Solomon *et al*. (2010) studied a similar US population of elderly new opioid users with arthritic conditions and reported a rate of 1,010 fractures per 10,000 person-years.[189] The rates reported in these studies are substantially higher than the rate reported in this chapter, which is likely due to inherent differences in the study populations analysed. Although opioid use was a similar criterion, the populations studied by Miller *et al.* and by Solomon *et al.* contained a considerably higher proportion of females (>80%) and had mean ages of approximately 80 years whereas the cohort from this study was 55% female and had a mean age of 52 years. Fracture studies have consistently shown that females aged ≥50 years have a much greater risk of fracture and therefore it is unsurprising that studies such as those reported by Miller *et al.* and Solomon *et al.*, which have predominantly female, elderly cohorts, report much higher rates of fracture.[70, 71]

In a matched-cohort study of hip fractures, Tolppanen *et al.* (2016) reported a rate of 112 hip fractures per 10,000 person-years among Finnish residents without Alzheimer's disease, or prior fracture who were prescribed opioids.[186] The rate of hip fracture calculated in the study presented in this chapter was approximately 37 per 10,000 person-years, which is much lower than the rate reported by Tolppanen *et al*. The population studied by Tolpannen *et al.* also had a higher mean age (80 years) than the present study, which as with the aforementioned studies, may explain this discrepancy in rates. Similarly, another US study by Saunders *et al.* (2010) analysed any fracture among chronic users of opioids, aged >60 years and reported a rate of 611.80 fractures per 10,000 person-years.[14] It is unsurprising that a higher fracture rate was detected in the population studied by Saunders *et al.* because the present study was not limited to chronic opioid users nor the elderly.

7.6.3 Strengths and limitations

This is the first UK study to report the incidence rates of fracture in a cohort of people who have been prescribed opioids, and has uniquely shown that fractures occur at double the rate of the general UK population. This information is essential to contextualise the risk of fracture in opioid users and will inform the analyses carried out in the next chapter of this thesis.

Key strengths of this study include that fractures were identified using primary and secondary care data sources along with code lists that were produced in collaboration with primary and secondary care coding specialists; this approach identified more cases of fracture than using data from the CPRD alone and consequently this study is unlikely to have under-estimated the rate of fractures in this cohort.

A potential limitation of this study is that no information was obtained on the indication for opioid prescription and therefore the underlying medical conditions present in the cohort are unknown. Additionally, the proportion of people identified as having osteoporosis was determined by the presence of an osteoporosis code in patients' CPRD clinical files at any time-point. Assessment and diagnosis of osteoporosis might be more likely to occur following a suspected fragility fracture and therefore might have resulted in differential misclassification of osteoporosis among fracture cases and non-cases in this cohort. This may in-part explain why there was a considerable difference between the proportion of people with osteoporosis among fracture cases.

Identifying incident fractures across multiple data sources relied upon an operational definition for what constituted an incident fracture. This study

defined these using the same definition as a prior CPRD study of fractures - fractures occurring in a different site or >6 months after a prior incident fracture.[267] This definition could have potentially under- or over-estimated the incidence of fracture in the cohort. However, for this reason, first fractures were analysed and described separately to subsequent fractures. Furthermore, when stratifying fracture rates by anatomical site there may have been an under-estimation of fractures that are less likely to be detected and thus recorded, such as vertebral fractures.[268]

The CPRD and HES data sources do not contain the reason for fractures occurring and therefore it was not possible to distinguish between low and high trauma fractures. Instead, a composite of sites that are associated with fragility was used to categorise fractures as fragility fractures.[71] Therefore this study assumed that fractures to these sites were due to fragility and fractures to other sites were not, this may have over-estimated the incidence of fragility fractures in this cohort.

This study described the incidence of fracture in people prescribed opioids between June 2008 and May 2017, however, fractures identified in this cohort may have occurred prior to opioid initiation. The greater fracture rate observed in this cohort, when compared to the general UK population is therefore likely due to a multitude of underlying factors that differentiate people included in this cohort from the general population e.g., opioid use, indication for opioid use, underlying comorbidities and frailty.

7.7 Conclusions

This study demonstrates that people prescribed opioids are particularly susceptible to fractures; the rate of fractures among people prescribed opioids

was double that reported for the general UK population. Fracture rates were found to vary considerably by age, sex, fracture site, socioeconomic status, ethnicity and season. The following chapter of this thesis builds on this study by assessing the association between the risk of fracture during periods of opioid use and non-use among people with fracture that were identified in the work presented in this chapter.

Chapter 8: Assessing the association between opioids and the risk of bone fracture: a self-controlled case series analysis

8.1 Abstract

Background

Existing observational studies have reported an increased risk of fractures among people prescribed opioids. However, causal inferences regarding this association are limited by the high potential for confounding. The aims of this study were to: a) minimise the potential for confounding of the opioid-fracture risk association by using a within-participant study design whereby the comparison is made between exposed and unexposed periods, and b) investigate the effects of the duration and dose of opioid exposure on the risk of fracture, also utilising the within-participant study design.

Methods

An SCCS study of people who initiated opioids and experienced an incident fracture between June 2008 and May 2017 was used. People were followed from their CPRD registration date to end of follow-up, regardless of when their fracture occurred. IRRs (and 95%CIs) for fracture during periods of opioid exposure and non-exposure were calculated using conditional Poisson regression adjusted for time-varying age and season. The effects of duration and dose were explored by comparing IRRs for 'risk periods', stratified by daily OMEQ dose.

Results

In total, 67,622 people sustained 87,454 incident fractures. Opioid use was associated with an increase in fracture-risk, compared to baseline (unexposed) periods (IRR: 3.9; 95%CI: 3.8, 4.0). Fracture-risk was greatest in the first week of opioid use (IRR: 7.8; 95%CI: 7.4, 8.3) and declined with increasing duration of use. Re-starting opioids after a gap in exposure increased fracture-risk (IRR: 5.1; 95%CI: 4.8, 5.3), and was greater when the

OMEQ dose was ≥50mg/day (Day 1-7 IRR: 6.1; 95%CI: 5.6, 6.6) compared to when the OMEQ dose was <50mg/day (Day 1-7 IRR: 4.7; 95%CI: 4.5, 5.0).

Conclusions

Periods of opioid use were associated with a 4-fold increase in fracture-risk, and an 8-fold increase in fracture-risk during the first week of opioid use; this risk decreased with longer durations of opioid use, thereby suggesting that the association is likely a function of the effects of opioids on the CNS (i.e., dizziness and sedation). People prescribed opioids should be informed of this elevated risk of fracture early in the treatment pathway and advised to be particularly vigilant when starting or re-starting on opioid medicines.

8.2 Introduction

Observational studies have demonstrated a significant positive association between the use of opioids and an increased risk of fracture.[13, 87-90, 186-190, 192-195, 197-203] However, the ability to draw causal inferences from these studies is limited by the high potential for confounding, especially with regard to the high risk for substantial confounding by indication. This chapter builds on the previous chapter of this thesis by examining the association between opioid use and non-use in the people who were identified as experiencing incident fractures during follow-up.

All but one of the opioid-fracture association studies identified in Chapter 3 of this thesis used methods to statistically match opioid users to non-users to make between-participant comparisons in fracture-risk possible. The aim of matching is to increase the comparability between groups so that any observed differences are more likely to be attributable to the treatment as opposed to other differences between groups which may confound the exposure-outcome association. Matching is typically done using statistical methods, however, an *a priori* understanding of which factors differ between the groups and their causal pathway is critical. Even with an in-depth understanding, if data on these factors are not available for the analysis then any estimation of the exposure-outcome association is likely to be confounded. Retrospective studies that use routinely collected data can be limited by which factors were recorded and the quality of the data. Consequently, it is rare that there are sufficient data for a ‘perfect match’, the result of which is a high risk of estimating a biased exposure-outcome risk estimate.

8.3 Aims and objectives

The aim of this chapter was to examine the risk of fracture when using opioids among new opioid users with ≥1 incident fracture between 1st June 2008 and 31st May 2017. The objectives for this study were to:

1. Describe the process for handling data for these people to generate 'risk periods' and to adjust for time-varying covariates.

2. Estimate the risk of fracture during opioid use, and during specific 'risk periods', compared to periods of non-use.

3. Assess the effect of opioid dose on the risk of fracture.

4. Explore potential cumulative effects of opioid use on fracture-risk by sequentially comparing unexposed periods throughout follow-up.

5. Calculate measures of attributable risk for the source cohort (new users of opioids studied in Chapter 7 of this thesis).

8.4 Method

8.4.1 Study design

This was an SCCS study of people initiating[15] prescribed opioids between 1st June 2008 and 31st May 2017 and who had ≥1 incident fracture recorded during their follow-up.

Currently, there are no SCCS studies that have examined the association between opioids and fractures. Moreover, previous studies are highly likely to

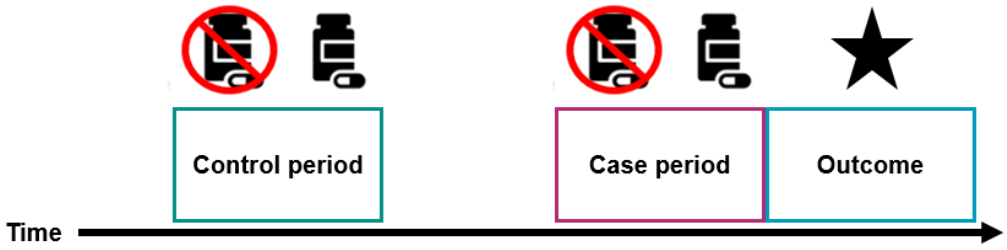
[15] New users of opioids were defined as people with no opioid prescription during their two-year exposure lookback period

suffer from inadequate matching of people and inadequate statistical adjustment due to unknown, unmeasured or poorly measured confounders.

Self-controlled methods

One alternative to address potential confounding is to use a self-controlled study design, where participants act as their own control; comparing outcomes at an unexposed time period to a period of exposure. The advantage is that all factors remaining constant within a person, including those that are unknown or unmeasured, are inherently controlled-for by-design.

There are two main types of self-controlled study designs, case-crossover and SCCS. Case-crossover studies may be considered analogous to case-control studies. In case-control studies, cases (i.e., people with an outcome of interest) are identified and compared to matched people without the outcome (i.e., controls). Whereas, in a case-crossover study, the presence of exposure is assessed during a case period (i.e., immediately before the outcome) and the rate of the outcome during the case period is compared to the rate of the outcome during a control period (i.e., an earlier period) for each individual; these case and control time-periods are therefore selected in relation to the date of outcome (Figure 8-1).

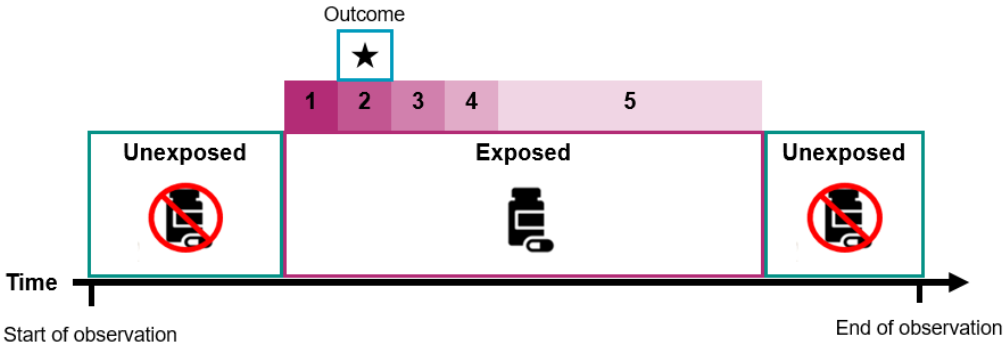


Notes: Exposure status is assessed in the case and control period, both of which precede the outcome of interest.

Figure 8-1. Illustration of case-crossover design

A limitation with the case-crossover design is that the selection of case and control periods is anchored on the date that the outcome of interest occurred. Case-crossover studies are therefore sensitive to the choice of the duration and proximity of these periods to the date that the outcome occurred. Another limitation is that people are censored at the occurrence of the outcome, this makes the design susceptible to exposure trend bias; whereby the exposure is increasingly used by the source population over follow-up which biases risk estimates towards higher values.[269] This may be problematic when studying opioids because, as shown in Chapter 6 of this thesis, the frequency and intensity of prescribing increases over the duration of patient follow-up.

SCCS studies are another self-controlled design and, unlike the case-crossover design, are analogous to a cohort study. Rather than defining specific time-periods for comparison, this design includes all follow-up time in the analysis and therefore observation is not related to, nor censored at, the outcome of interest; making this design less susceptible to exposure trend bias (Figure 8-2).[270] Moreover, the inclusion of all follow-up time permits the inclusion of an exposure measure that is time-varying - this is of particular importance as opioid use and dose can be transient or intermittent.



Notes: Exposed time can be split into discrete 'risk periods' that relate to the duration of exposure, these are denoted by boxes 1-5.

Figure 8-2. Illustration of self-controlled case series design

The SCCS method has been used in previous pharmacoepidemiological studies to explore risk of fracture associated with other medicines such as thiazolidinediones,[267] and TCAs and SSRIs.[271] Additionally, the effects of opioids on other outcomes of interest, such as road traffic accidents, have also been studied using SCCS methodology.[272] The SCCS study design was therefore considered appropriate and well suited to the study of opioids and the risk of fracture. However, prior to designing this study there were assumptions to consider;[273] Peterson *et al.* (2016) have proposed solutions to instances where SCCS assumptions may be violated,[211] and a summary of the assumptions and design considerations is provided in Table 8-1.

Table 8-1. Assumptions of the self-controlled case series method

Assumption	Description	Design consideration	Solution
Events arise independently within individuals or, if non-recurrent, are uncommon	The SCCS likelihood is derived under the assumption that, where outcomes may be repeated for an individual, these arise according to a Poisson distribution. Accordingly, the first event should not influence the occurrence of a subsequent event.[274]	This assumption is violated for recurrent fractures because the risk of subsequent fractures increases after the first fracture,[98] therefore events are not independent.	Conduct sensitivity analysis whereby only first fractures are studied, as fractures are suitably rare in the population under investigation*.[211, 274]
Occurrence of an event does not influence the subsequent period of observation	If the event increases the probability of death then it is likely that observation of an individual may cease as a result of the event occurring.	The risk of mortality increases following fracture,[74, 204] therefore this assumption is violated.	Conduct sensitivity analysis whereby people who died in close proximity to the fracture are excluded.[211, 275]
Occurrence of an event does not influence subsequent exposures	Some outcomes may temporarily increase or decrease the probability of exposure, which may result in a reverse-causal relationship or may bias risk estimates towards the null, respectively.	Following a fracture, people are more likely to be prescribed opioid analgesics,[276] which violates this assumption.	Introduce a pre-exposure period, whereby any fracture occurring within a defined time-period prior to the initiation of an opioid is removed from the calculation of the baseline incidence rate.[272]
Exposures do not influence the ascertainment of events	The ascertainment of an event should not depend on an instance of exposure.	This study utilised the CPRD and HES for records of fractures and opioid prescriptions, which are recorded independently of each other in most cases.	

Notes: SCCS, self-controlled case series; CPRD, the Clinical Practice Research Datalink; HES, Hospital Episode Statistics

*Suitably rare was determined by calculating the probability of the event occurring during the median observation period, and the estimated bias was half of this probability. The probability of a fracture during the median observation was 0.15 based on an incidence rate of 217.7 per 10,000 person-years and median follow-up of 7.1 years. The estimated bias is 0.08 meaning that a relative incidence of 2.0 could be estimated at 2.2.[273]

8.4.2 Data source

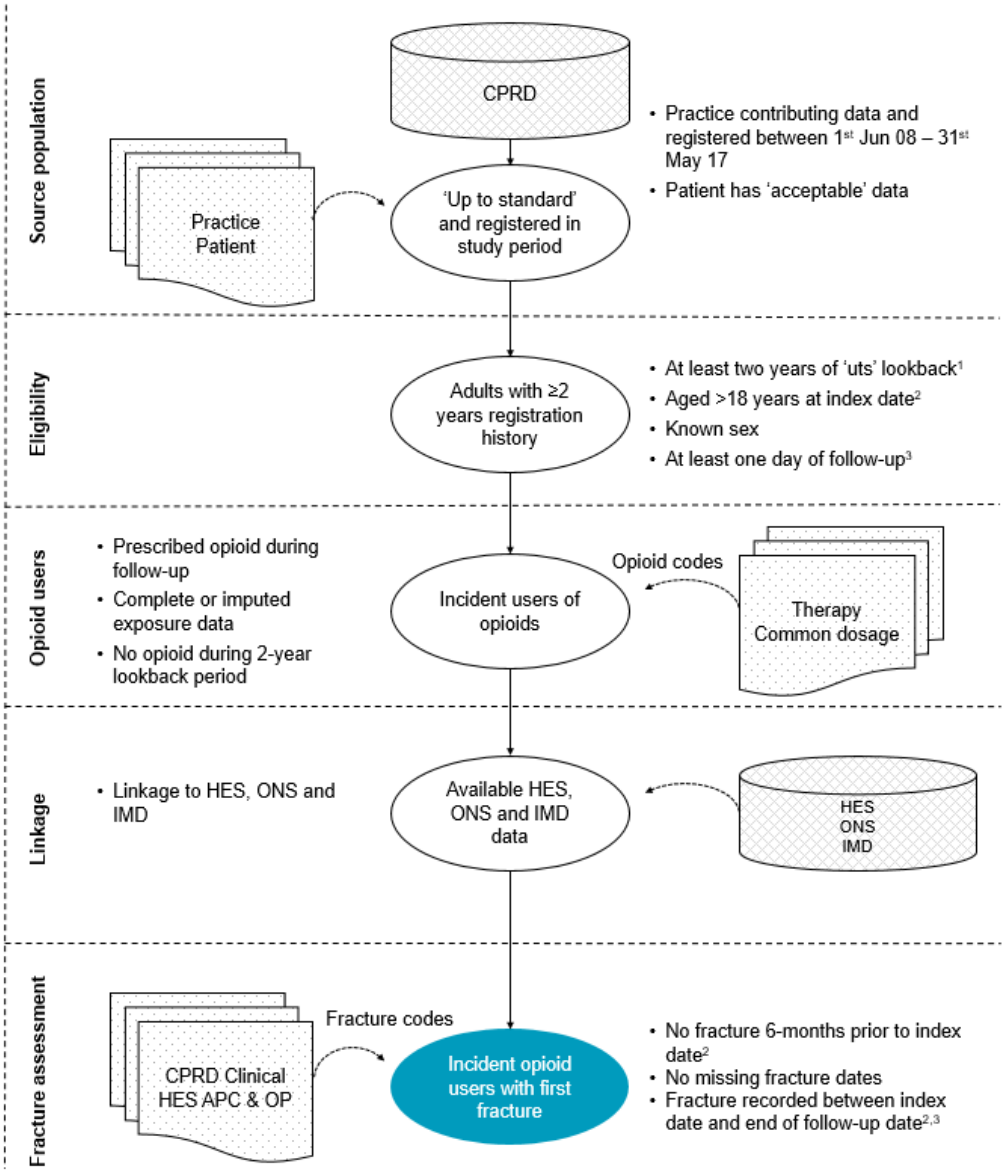
Opioid prescription records were obtained from the CPRD and prepared as outlined in Chapter 5 of this thesis. Demographic information regarding age and sex were extracted from the CPRD 'Patient' file and records of prescriptions for FRIDs were also extracted from the CPRD (outlined in Chapter 7 of this thesis). Fracture events (detailing the site of fracture and date of fracture) were extracted from the CPRD and HES APC and OP data sources, incident fractures were identified using the process described in Chapter 7 of this thesis.

8.4.3 Cohort identification

New opioid users with complete (or imputed) opioid prescription data eligible for linkage to the HES and IMD with a record of ≥1 incident fracture during follow-up were eligible for study inclusion. People were excluded if they had a record of a fracture with a missing date or if they had a record of a fracture within the six-month fracture lookback period prior to their index date (Figure 8-3).

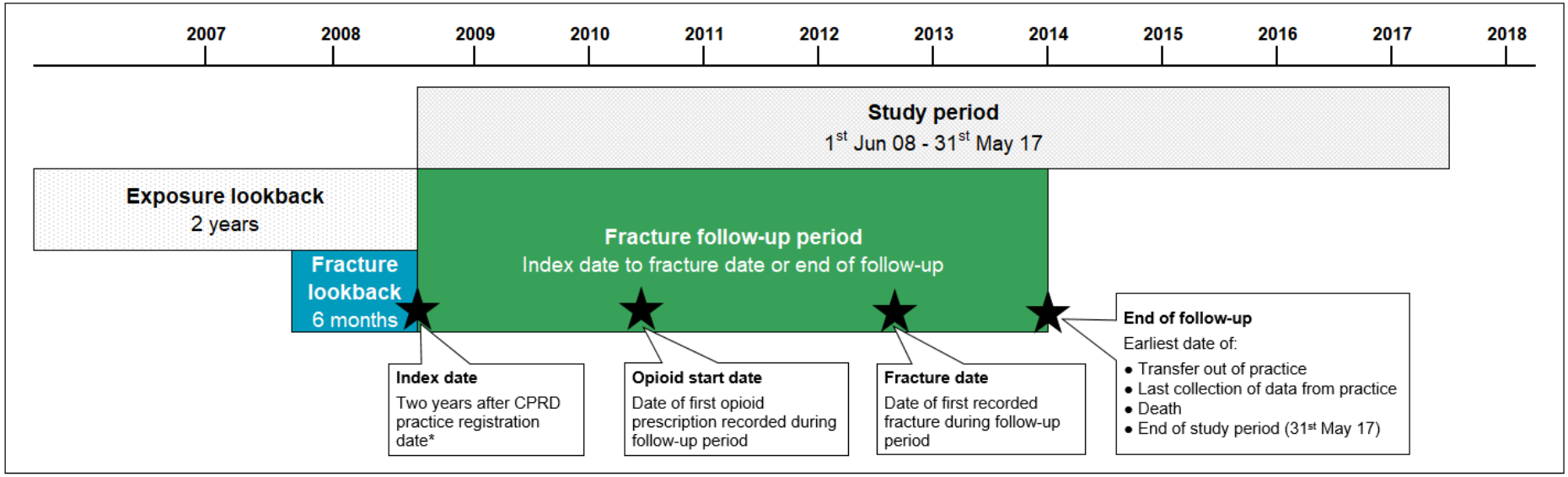
People were followed from their index date[16] until the end of follow-up date; these dates were independent of the opioid start date and fracture dates, as illustrated in Figure 8-4.

[16] Index date was defined as two years after the latest of: (1) CPRD practice registration date, (2) CPRD practice 'up to standard' date or (3) 1st June 2006.



Notes: CPRD, Clinical Practice Research Datalink; lcd, last collection date; uts, up to standard; crd, current registration date.
[1] Lookback start = the latest of: 1st June 2006, 'crd', or 'uts', lookback ends two years after the lookback start date.
[2] Index date = lookback start + two years.
[3] End of follow-up = the earliest of: transfer out of practice (tod), practice last collection date (lcd), date of death, or 31st May 2017.

Figure 8-3. Selection of fracture cases for study cohort



Notes: *Index date is two years after the latest of: (1) CPRD practice registration date, (2) CPRD practice 'up to standard' date or (3) 1st June 2006. The blue box refers to the fracture lookback period which had a duration of six months.

Figure 8-4. Illustration of self-controlled case series study follow-up

8.4.4 Data preparation and risk periods

Prepared opioid prescription records (Dataset III that was generated in Chapter 5 of this thesis) were obtained for the study cohort and merged with other datasets containing patient demographic details. A summary of the study variables is provided in Table 8-2.

Table 8-2. Summary of study variables

Study variable	Description	Example
Patient ID	Patient identification number	123001
Sex	Sex (male, female)	female
Index age	Age (years) on index date	57
Index date	Defined as two years after the latest of: (1) CPRD practice registration date, (2) CPRD practice 'up to standard' date or (3) 1st June 2006	01Jun2006*
Opioid start date	Start date of the first opioid prescription recorded during a patient's follow-up	01Aug2008*
End of follow-up	Date the person was censored	30Jul2014*
Start date	Date that an opioid exposure period began	01Aug2009*
Stop date	Date that an opioid exposure period ended i.e., the first day not covered by the exposure period	31Aug2009*
Duration	Number of treatment days covered by an exposure period	30
Combined OMEQ/day	The OMEQ dose per day (mg/day), where more than one opioid product covered a given day the OMEQ reflects the combined OMEQ across all opioid products	120
Exposure status	Indicator for current exposure to opioids (1=yes, 0=no)	1

Notes: *Dates are displayed in a readable format, however they recorded as the number of days elapsed since 1st Jan 1960; OMEQ, oral morphine equivalent; mg, milligrams.

8.4.4.1 Exposed and unexposed periods

The dataset comprised of multiple rows per patient, where each row referred to periods of opioid exposure with a total OMEQ/day for each period. Unexposed periods were added by adding additional rows with an exposure status value of 0, these had start and stop dates that covered follow-up time:

(1) from the index date until the opioid start date, (2) between exposed periods, and (3) from the final exposed day to the end of follow-up date (Figure 8-5).

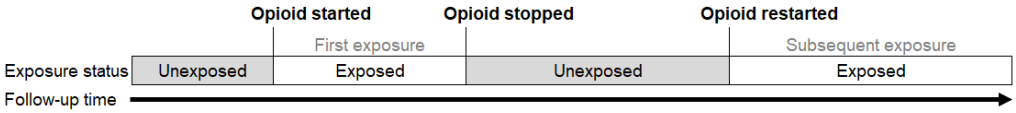


Figure 8-5. Illustration of division of follow-up time into periods of opioid exposure and non-exposure

8.4.4.2 Risk periods

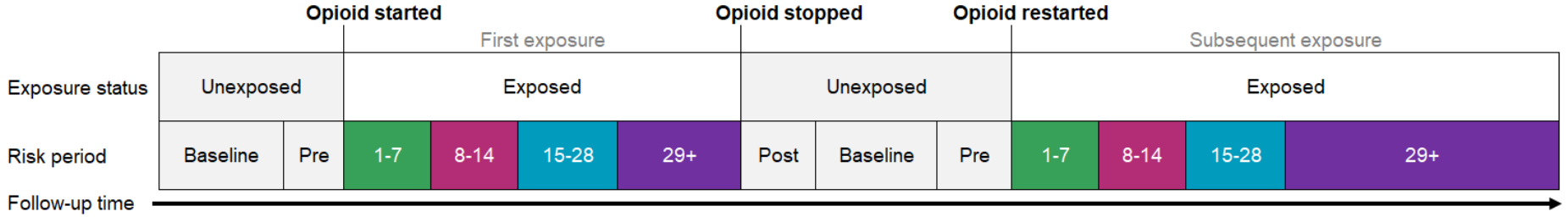
Periods of exposure and non-exposure to opioids were split into discrete 'risk periods' for the first period of exposure to opioids, and any subsequent periods of exposure. The purpose for these risk periods and the duration of these are outlined below and are illustrated in Figure 8-6.

Baseline (unexposed)

The baseline risk period was defined as any follow-up time without exposure to an opioid prescription; excluding a pre-exposure risk period and a post-exposure risk period, which were introduced to avoid biases that might have arisen due to event-dependent exposure (as summarised in Table 8-1) and any residual drug effects.

Pre-exposure (unexposed)

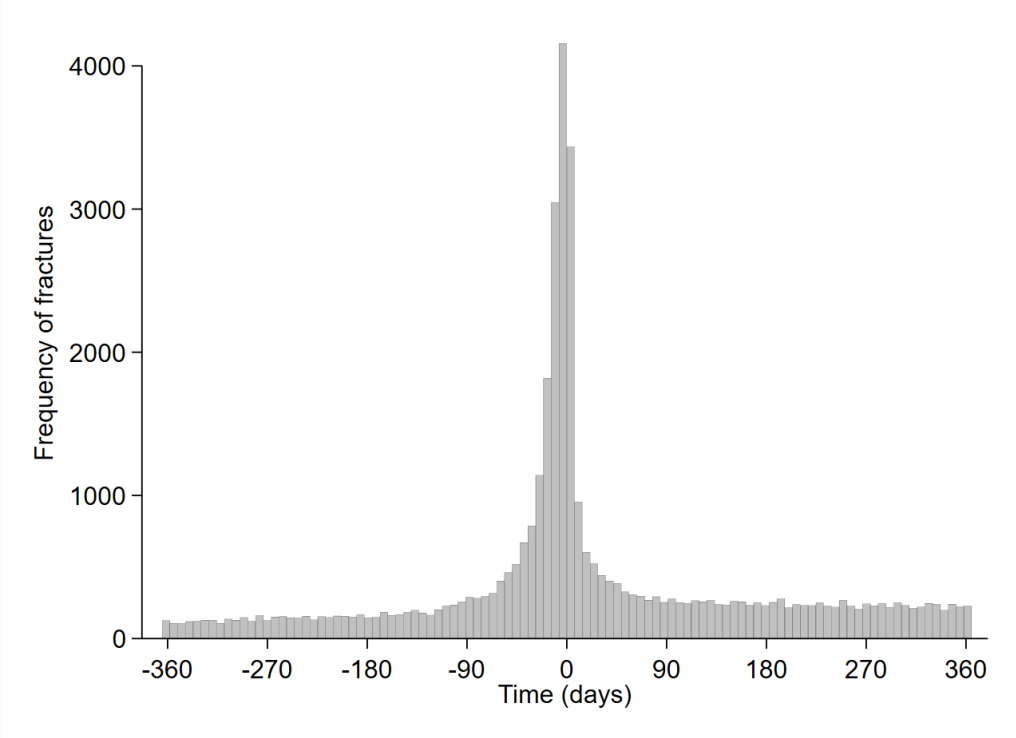
The pre-exposure risk period was used to remove fracture events occurring within a defined time period prior to opioid initiation, which would otherwise have been included in the baseline incidence rate for fracture, and would have under-estimated the risk of fracture during exposed periods. To select the most appropriate length of the pre-exposure risk period the proximity of



Notes: Pre, pre-exposure risk period; post, post-exposure risk period; 1-7, days 1 to 7 from opioid start date; 8-14, days 8 to 14 from opioid start date; 15-28, days 15 to 28 from opioid start date; 29+, day 29 from opioid start date ending on the stop date of a continuous period of exposure; subsequent exposure refers to any further periods of exposure to opioids beyond the first continuous period of exposure.

Figure 8-6. Division of exposed and unexposed follow-up time into risk periods

fracture dates to opioid start dates were inspected visually using a histogram, which indicated that 90 days was an appropriate duration (Figure 8-7). A sharp rise in fractures immediately prior to opioid initiation was observed, indicating that event-dependent exposures were present and that there was a clear need for a pre-exposure risk period.



Notes: Time-point 0 indicates that the date of fracture and opioid start date were the same. A positive value indicates that a fracture occurred after opioid initiation, and a negative value indicates that a fracture occurred before opioid initiation.

Figure 8-7. Proximity of fracture dates to opioid start dates

Post-exposure (unexposed)

This period was added to remove fractures that occurred immediately following exposure to opioids; to account for any residual effects from opioid exposure. The length of this period was 28 days, based on pharmacological advice from a pharmacist (RK) regarding the half-life of the various opioid drugs included in the analyses.

Exposed risk periods

The exposed risk period was any time exposed to opioids and refers to the combination of each of the following exposed risk periods.

First exposure: Days 1-7, Days 8-14, Days 15-28 and Days 29+ (exposed)

Days 1 to 7 referred to the first week of opioid exposure, starting one day after the opioid start date (rather than on the opioid start date), due to the possibility that opioids could be initiated because of a fracture (as shown in Figure 8-7) and to ensure that a temporal order between exposure and outcome was established.

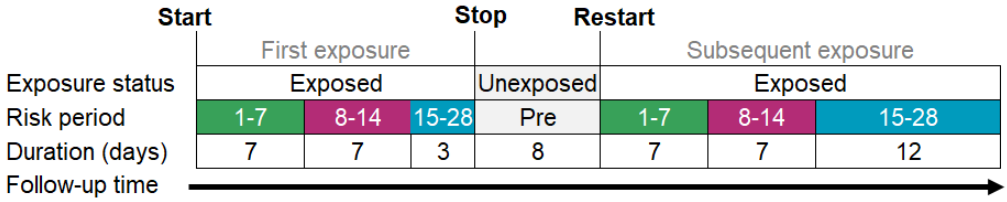
Following the first week of opioid use, a further two risk periods were defined: days 8 to 14 (7 days in duration), and days 15-28 (14 days in duration). Following the first four weeks of use, any remaining exposed days were defined as 'Days 29+' (variable duration); starting from day 29 of a continuous period of opioid use and ending when there was a gap in exposure.

Subsequent exposures: Days 1-7, Days 8-14, Days 15-28 and Days 29+ (exposed)

If, following a gap in exposure, opioids were re-started then all exposed time for these subsequent exposed periods were defined as 'subsequent exposure' and were split into the same risk periods used for the first exposure: days 1-7, 8-14, 15-28, and 29+.

8.4.4.3 Curtailment of risk periods

Where the stop date of an unexposed or exposed period occurred part-way through the duration of any risk period, the following period of exposure or non-exposure and corresponding risk period took priority (Figure 8-8).



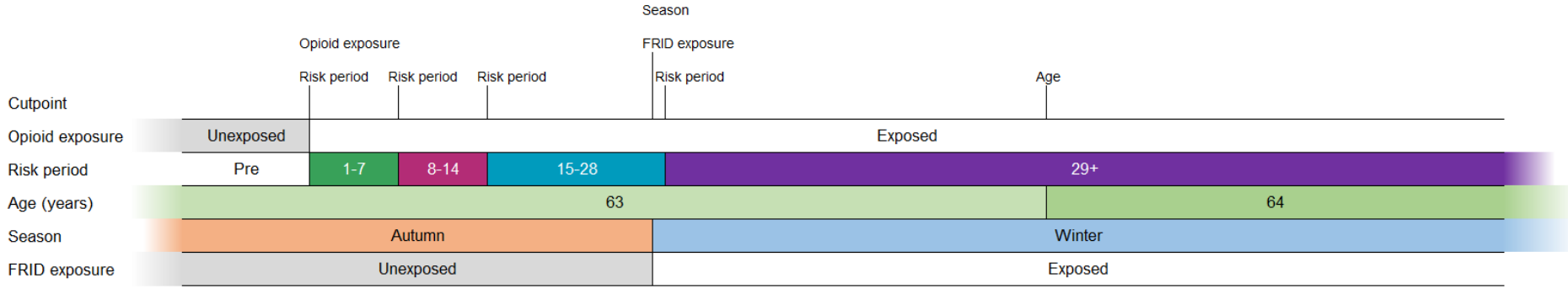
Notes: In this example the risk period 'Day 15-28' for the first exposed period, which is ordinarily 14 days in duration, was curtailed at three days due to the stop date of the period of exposure. An eight-day gap followed which was too short to incorporate a 28-day post-exposure period, baseline period and 90-day pre-exposure period; therefore the pre-exposure period took priority and was curtailed at eight days due to the re-start of an opioid.

Figure 8-8. Illustration of curtailment of risk periods

8.4.4.4 Time-varying covariates

The SCCS design inherently controls for all time-invariant confounding, however, within-person factors that vary over time may confound the relationship between opioids and fracture, and needed to be controlled for. Following a consideration of time-variable factors that were controlled for in previous opioid-fracture association studies (see Chapter 3), and of factors that were found to affect fracture rates (see Chapter 7); age, season and exposure to FRIDs were included as covariates in this analysis, providing they significantly improved the model fit (measured by the likelihood ratio test). Follow-up time for each person was further split so that each risk period had distinct levels for each covariate over time, as illustrated in Figure 8-9.

Periods of exposed and unexposed time were split into yearly periods with age increasing in one-year increments, and into 3-monthly intervals corresponding to spring, summer, autumn and winter. As exposure to other FRIDs may vary over time too, a binary indicator was generated (1=yes, 0=no) to indicate whether each person had a prescription for a FRID that had an 'eventdate' occurring in each 3-month interval.



Notes: FRIDs, fracture-risk increasing drugs. Each cutpoint represents a new row of data whereby the start and stop date, duration and level of factors that have changed are updated accordingly. In this example, the factors that have changed level are noted above the corresponding cutpoint.

Figure 8-9. Splitting follow-up time into discrete periods to account for changes in levels across multiple factors

Opioid dose, expressed as OMEQ dose per day (OMEQ/day), was already present in the dataset and was generated as part of the prescription preparation process described in Chapter 5. The opioid prescription records therefore already contained a variable for the daily OMEQ dose and were split at dates where the daily OMEQ dose changed, which therefore allowed for a time-varying measure of opioid dose.

8.4.5 Data analysis

Crude IRRs, adjusted IRRs (aIRRs) and 95%CIs, comparing the risk of fracture during exposed risk periods with the baseline risk period, were estimated using fixed-effects Poisson regression conditioned on the individual. Model fit was assessed using the likelihood ratio test. The results were stratified by sex and, to investigate possible dose effects; risk periods were stratified by OMEQ dose (<50mg/day, ≥50mg/day).

To test for potential cumulative effects, all baseline risk periods were categorised by the year of follow-up they occurred in. These one-year bands of baseline risk were then compared to the first baseline risk period using conditional Poisson regression to estimate IRRs and 95%CIs.

Measures of attribution were calculated to contextualise the results for future risk communication. The attributable fraction (AF) was calculated to provide the proportion of events arising during a specified risk period that may be attributed to opioid exposure using Equation 8-1, where ρ denotes the IRR for fracture during a specified risk period.

Equation 8-1. Calculation of attributable fraction (AF)

$$AF = \frac{\rho - 1}{\rho}$$

The population attributable fraction (PAF) was calculated to ascertain the proportion of fractures occurring within the source cohort that were attributed to opioid exposure using Equation 8-2, where n denotes the total number of events in the SCCS cohort and n_1 denotes the number of events in each specific risk period.

Equation 8-2. Calculation of population attributable fraction (PAF)

$$PAF = \frac{\rho_{-1}}{\rho} \times \frac{n_1}{n}$$

Finally, the attributable risk (AR) was calculated to provide the probability that an individual from the source cohort (i.e., a new opioid user) would experience a fracture due to opioid exposure using Equation 8-3, where E is the number of people prescribed opioids in the source cohort. The reciprocal of the AR was also calculated to give the number needed to harm (NNH) for the specified risk period (Equation 8-4).

Equation 8-3. Calculation of attributable risk (AR)

$$AR = \frac{\rho_{-1}}{\rho} + \frac{n_1}{E}$$

Equation 8-4. Calculation of number needed to harm (NNH)

$$NNH = \frac{1}{AR}$$

Sample size and power

The signed root likelihood ratio formula, proposed by Musonda *et al.* (2006),[277] was used to estimate the sample size required. In total, it was estimated that 26,953 fracture cases with a median observation period of 7.1 years was needed to detect an IRR of 1.2 for fracture within the first 28 days after initiation of an opioid, with 95% power and a 5% significance level. Additionally, to detect the same effect, with the same parameters over one year (as opposed to 28 days) would require 2,445 fracture cases.

Sensitivity analyses

A number of sensitivity analyses were carried out to assess the effect of the violation of the assumptions that were outlined in Table 8-1. Firstly, people who died within 90 days of their first fracture were removed from the analysis; this was to test the sensitivity of the results to the potential for fractures to influence the duration of observation. Secondly, as a fracture increases the risk of subsequent fractures, the analyses were carried out for first fractures only to test the sensitivity of the results to events that are not independent of each other. Finally, a complete case analysis was performed to assess for potential bias arising from the imputation of exposure data that was outlined in Chapter 5 of this thesis.

All data management processes and statistical analyses were carried out using the statistical software - Stata/MP 15 (StataCorp, Texas, USA).

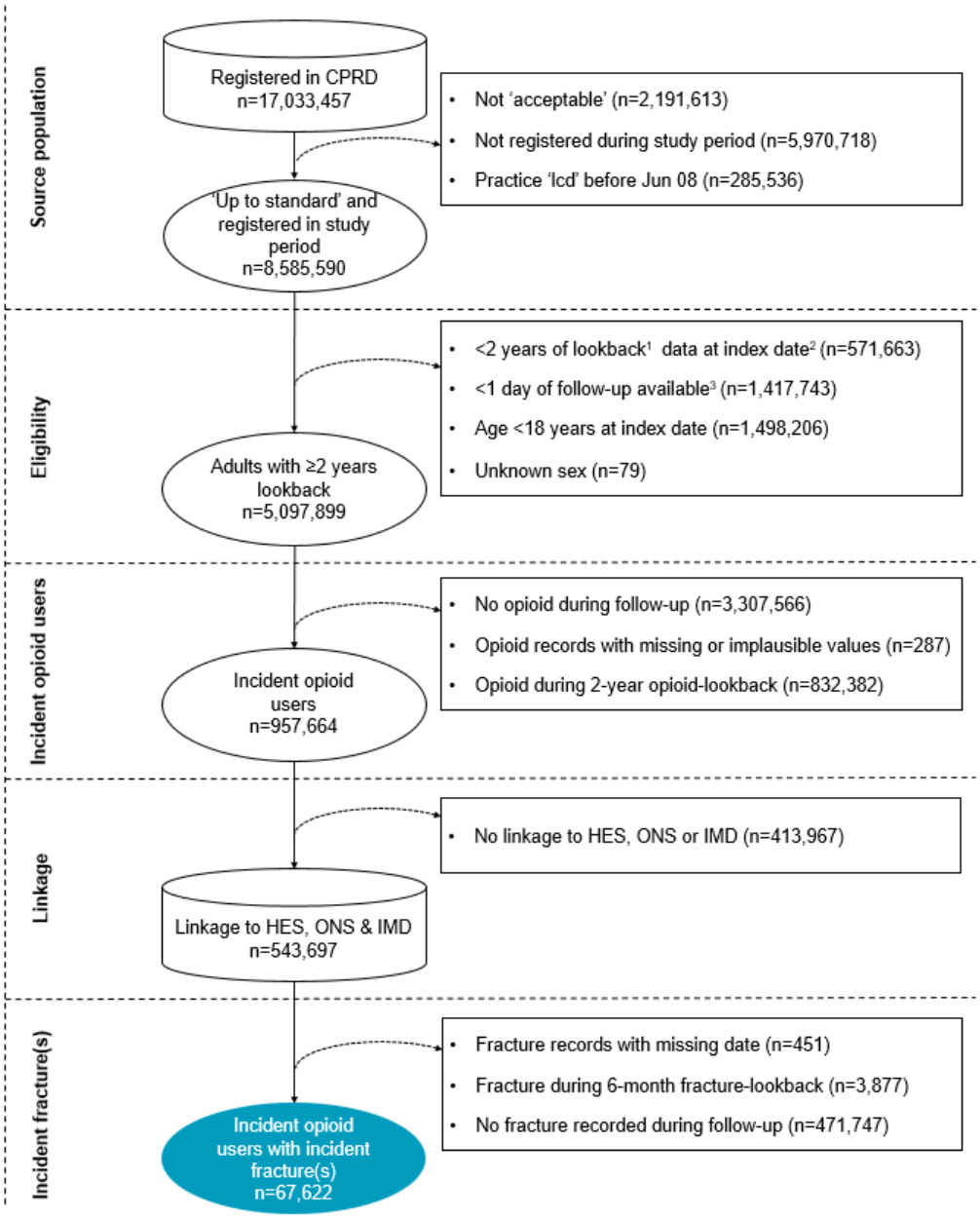
8.5 Results

8.5.1 Study cohort

67,622 new users of opioids, sustaining a total of 87,454 fractures during follow-up, and including 452,347 person-years of follow-up (median follow-up of 7.1 years), were identified in Chapter 7. These 67,622 people were included in the cohort for this study. The 471,747 people without a fracture or with a fracture in the 6-month fracture lookback period (n=3,877), as well as those missing fracture dates (n=451), were excluded (Figure 8-10). This sample size was therefore large enough to have sufficient power to detect an IRR of 1.2 within a 28-day or 365-day period.

8.5.2 Patient characteristics

The characteristics of the study cohort were presented in Chapter 7. In brief, 58.7% were female and the mean age was 56 years; the median duration of follow-up per person was 7.1 years (IQR: 5.3, 8.1 years). Most people were of white ethnicity (93.1%) and a greater proportion were from the most affluent areas as opposed to the most deprived (23.2% from IMD level 1, 16.1% from IMD level 5). Over one-tenth of the cohort had a diagnosis of osteoporosis (12.9%) and over half (62.8%) were prescribed ≥1 FRID (excluding opioids) during follow-up (Table 8-3).



Notes: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics; IMD, Index of Multiple Deprivation; lcd, last collection date; uts, up to standard; crd, current registration date.

[1] Lookback start = the latest of: 1st June 2006, 'crd', or 'uts', lookback ends two years after the lookback start date.
[2] Index date = lookback start + two years.
[3] End of follow-up = the earliest of: transfer out of practice (tod), practice last collection date (lcd), date of death, or 31st May 2017.

Figure 8-10. Identification of fracture cases for study cohort

Table 8-3. Characteristics of opioid users with ≥1 incident fractures

Characteristic	Mean (SD) or Median (IQR)	N	%
Follow-up (median, years)	7.12 (5.30, 8.71)		
Age at index (mean, years)	56.13 (19.59)		
Sex (female)		39,677	58.67%
IMD quintile:			
1 (least deprived)		15,663	23.16%
2		14,903	22.04%
3		13,934	20.61%
4		12,235	18.09%
5 (most deprived)		10,852	16.05%
Missing		35	0.05%
Ethnicity:			
White		62,983	93.14%
Asian or Asian British		1,137	1.68%
Black or black British		569	0.84%
Other ethnic groups		447	0.66%
Mixed		226	0.33%
Unknown ethnicity		2,260	3.34%
Osteoporosis*		8,715	12.89%
FRID during follow-up		42,463	62.79%

Notes: FRID, fracture-risk increasing drug; IMD, Index of Multiple Deprivation; *has a record of osteoporosis ever in their CPRD Clinical file (i.e., before or after fracture)

8.5.3 Risk of fracture

The likelihood ratio test (LRT) indicated that age was best fitted as a categorical rather than linear variable ($p<0.001$), which reflects the non-linear relationship between age and fracture rates presented in Chapter 7 of this thesis. Additionally, the LRT indicated that the inclusion of age and season as covariates significantly improved the model fit ($p<0.001$), however, the LRT did suggest that the inclusion of exposure to FRIDs did not significantly improve the model fit ($p=0.543$) and therefore FRIDs were omitted from the adjusted analyses presented in this chapter. Consequently, the final adjusted model included age and season as time-varying covariates.

The crude IRR for fracture during the exposed risk period, relative to the baseline (unexposed) risk period, was 4.2 (95%CI: 4.1, 4.3). After adjusting for age in one-year increments and season in 3-monthly intervals, the aIRR for risk of fracture was 3.9 (95%CI: 3.8, 4.0) during the exposed period, compared to the baseline (unexposed) risk period.

8.5.3.1 Duration of use

After splitting exposed time into risk periods, the risk of fracture in days 1-7 of the first exposure period was greatest (aIRR: 7.8; 95%CI: 7.4, 8.3) and steadily decreased over the first exposure period to 1.7 (95%CI: 1.5, 2.0) on days 29 onwards. The aIRR for fracture in the first 28 days in subsequent periods of exposure was lower than the first exposure period. A similar, decreasing risk of fracture with increasing duration of use was observed, until day 29 onwards for subsequent exposure, which was greater than the first exposure (Table 8-4 and Figure 8-11).

Table 8-4. IRRs for fracture during periods of exposure to opioids

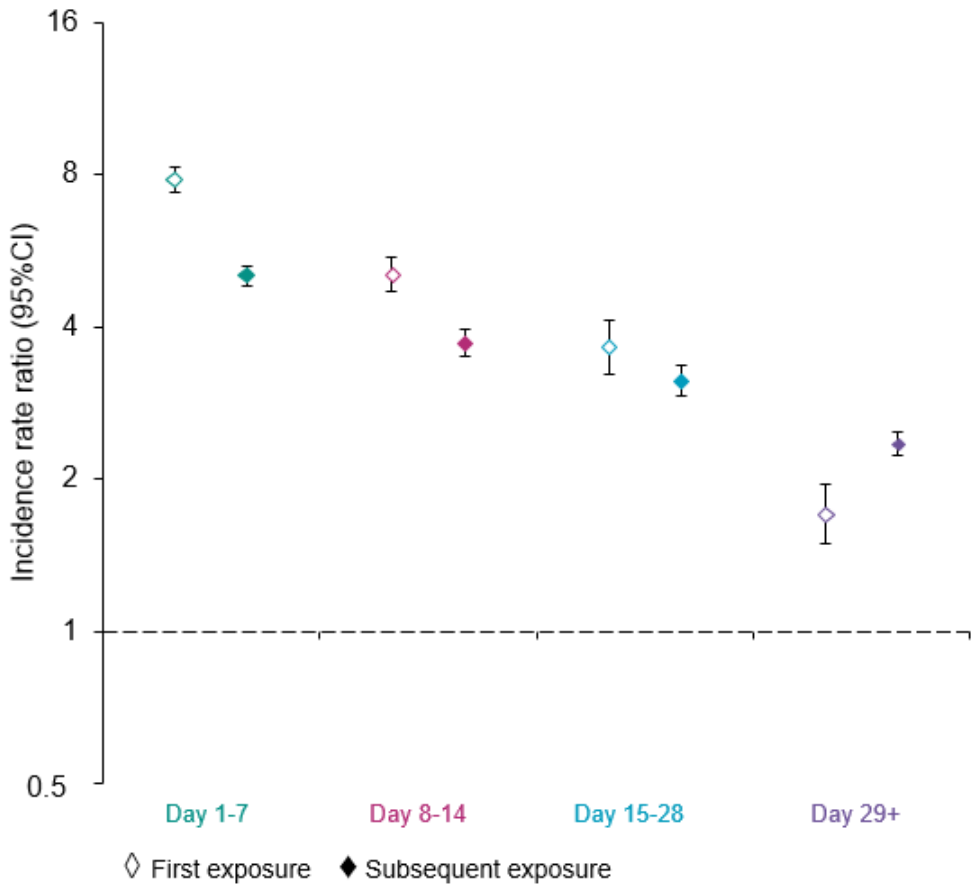
Risk period*	Fractures (*n*)	Follow-up (person-years)	Crude IRR (95%CI)	aIRR** (95%CI)
Baseline	49,473	377,665	Baseline	Baseline
Pre-exposure	26,853	42,779	5.63 (5.54, 5.72)	5.49 (5.40, 5.58)
Post-exposure	2,626	9,044	2.37 (2.28, 2.47)	2.31 (2.22, 2.40)
First exposure				
Days 1-7	1,327	1,196	7.74 (7.32, 8.17)	7.81 (7.40, 8.25)
Days 8-14	592	828	5.03 (4.64, 5.46)	5.08 (4.68, 5.51)
Days 15-28	256	484	3.65 (3.22, 4.13)	3.65 (3.23, 4.13)
Days 29+	257	1,047	1.77 (1.55, 2.03)	1.71 (1.49, 1.95)
Subsequent exposures				
Days 1-7	2,080	4,248	5.45 (5.20, 5.71)	5.05 (4.83, 5.29)
Days 8-14	1,114	3,175	4.02 (3.78, 4.27)	3.72 (3.50, 3.96)
Days 15-28	823	2,788	3.42 (3.18, 3.67)	3.12 (2.91, 3.36)
Days 29+	2,053	9,093	2.69 (2.55, 2.84)	2.35 (2.22, 2.48)

Notes: IRR, incidence rate ratio; CI, confidence interval.

* Risk periods:

- Baseline, periods when not exposed to opioids (excluding 90-day pre-exposure period and 28-day post-exposure period).
- Pre-exposure, 90-days prior to and including the first day of starting or re-starting an opioid.
- Post-exposure, 28 days after stopping an opioid
- First exposure, first period of exposure to opioids, split into days 1-7, 8-14, 15-28 and 29+.
- Subsequent exposures, periods of opioid exposure following a gap in exposure from the first exposure period, split into days 1-7, 8-14, 15-28 and 29+.

**adjusted for 1-year increments in age, 3-monthly intervals for season.



Notes: IRRs (and 95%CIs) plotted on logarithmic scale.

Figure 8-11. Adjusted IRRs and 95%CIs for fracture during first and subsequent periods of opioid exposure relative to the rate of fracture in the baseline (unexposed) risk period

When stratifying by sex, age-bands needed to be increased to three-year increments in age rather than one-year increments, due to the smaller sample size in the strata. Following adjustment for 3-yearly age increments and 3-monthly intervals for season, the trends in aIRRs for fracture across exposed risk periods was similar in males and females. Males demonstrated slightly higher aIRRs for fracture in each strata of exposed period when compared to females, however, this difference was only significant for days 1-7 and 15-28 of subsequent exposure periods (Table 8-5 and Figure 8-12).

Table 8-5. Adjusted IRRs for fracture during exposure to opioids, stratified by sex

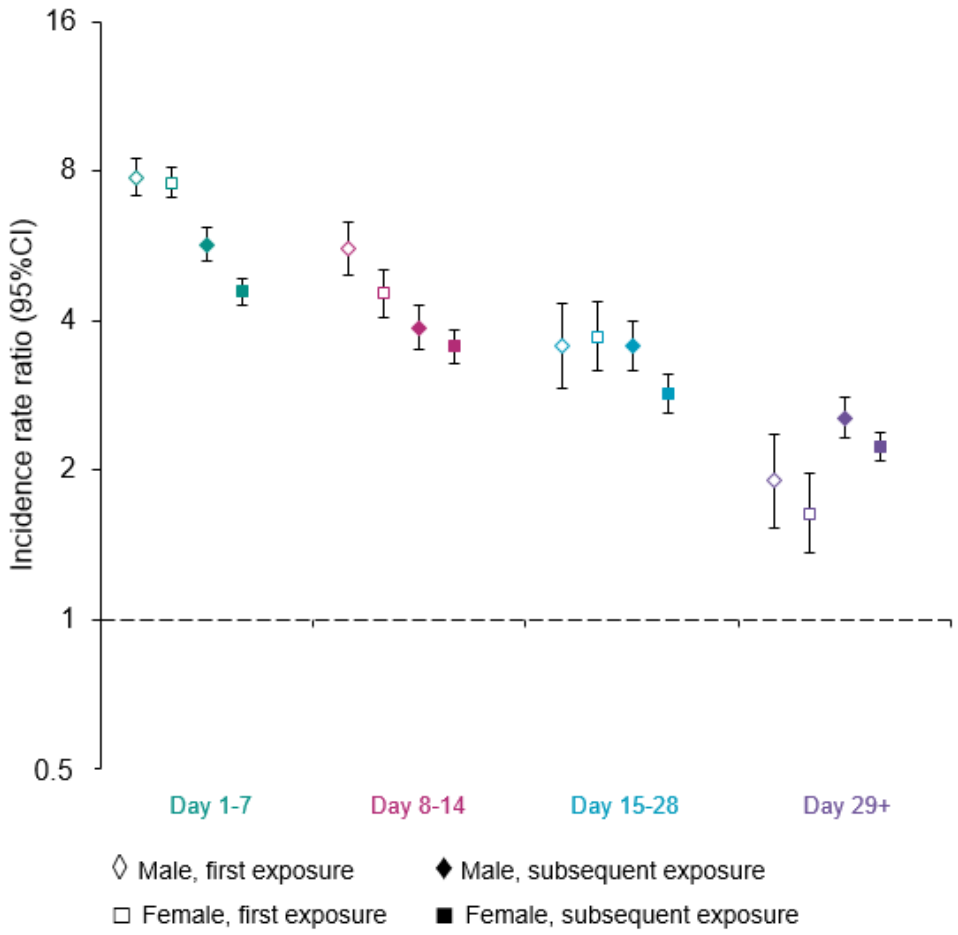
			Males (n=27,945)	Females (n=39,677)
Risk period*	Fractures (*n*)	Follow-up (person-years)	aIRR** (95%CI)	aIRR** (95%CI)
Baseline	49,473	377,665	Baseline	Baseline
Pre-exposure	26,853	42,779	6.13 (5.96, 6.31)	4.62 (4.51, 4.73)
Post-exposure	2,626	9,044	2.30 (2.15, 2.45)	2.20 (2.09, 2.31)
First exposure				
Days 1-7	1,327	1,196	7.77 (7.12, 8.48)	7.58 (7.05, 8.14)
Days 8-14	592	828	5.60 (4.95, 6.33)	4.53 (4.05, 5.07)
Days 15-28	256	484	3.56 (2.92, 4.34)	3.71 (3.16, 4.35)
Days 29+	257	1,047	1.90 (1.53, 2.36)	1.64 (1.36, 1.96)
Subsequent exposures				
Days 1-7	2,080	4,248	5.68 (5.26, 6.14)	4.58 (4.31, 4.86)
Days 8-14	1,114	3,175	3.87 (3.48, 4.29)	3.55 (3.28, 3.84)
Days 15-28	823	2,788	3.56 (3.16, 4.00)	2.85 (2.59, 3.12)
Days 29+	2,053	9,093	2.54 (2.31, 2.79)	2.23 (2.08, 2.39)

Notes: IRR, incidence rate ratio; CI, confidence interval.

* Risk periods:

- Baseline, periods when not exposed to opioids (excluding 90-day pre-exposure period and 28-day post-exposure period).
- Pre-exposure, 90-days prior to and including the first day of starting or re-starting an opioid.
- Post-exposure, 28 days after stopping an opioid
- First exposure, first period of exposure to opioids, split into days 1-7, 8-14, 15-28 and 29+.
- Subsequent exposures, periods of opioid exposure following a gap in exposure from the first exposure period, split into days 1-7, 8-14, 15-28 and 29+.

**adjusted for 3-year increments in age, 3-monthly intervals for season.



Notes: IRRs (and 95%CIs) plotted on logarithmic scale.

Figure 8-12. Adjusted IRRs and 95%CIs for fracture during first and subsequent periods of opioid exposure relative to the rate of fracture in the baseline (unexposed) risk period, stratified by sex

8.5.3.2 Dose effects

To investigate the effect of dose, risk periods were stratified into periods of low (<50mg/day) and high (≥50mg/day) daily OMEQ doses. A dose-dependent effect was observed in subsequent exposure risk periods, with a greater risk of fracture in the initial days following the re-start of an opioid when the daily OMEQ dose was ≥50mg/day (Day 1-7 aIRR: 6.1; 95%CI: 5.6, 6.6) compared to when the OMEQ dose was <50mg/day (Day 1-7 aIRR: 4.7; 95%CI: 4.5, 5.0). This trend was not observed in the first period of exposure (Table 8-6 and Figure 8-13).

Table 8-6. Adjusted IRRs for fracture during exposure to opioids, stratified by OMEQ dose per day

			OMEQ <50mg/day	OMEQ ≥50mg/day
Risk period*	**Fractures (*n*)**	**Follow-up (person-years)**	**aIRR** (95%CI)**	**aIRR** (95%CI)**
Baseline	49,473	377,665	Baseline	Baseline
First exposure				
Days 1-7	1,327	1,196	7.75(7.31, 8.22)	8.33 (7.09, 9.78)
Days 8-14	592	828	4.92(4.51, 5.36)	6.56 (5.23, 8.22)
Days 15-28	256	484	3.76(3.30, 4.28)	2.86 (1.91, 4.28)
Day 29+	257	1,047	1.78(1.55, 2.06)	1.19 (0.77, 1.85)
Subsequent exposures				
Days 1-7	2,080	4,248	4.71(4.46, 4.98)	6.06 (5.60, 6.56)
Days 8-14	1,114	3,175	3.53(3.29, 3.79)	4.38 (3.91, 4.90)
Days 15-28	823	2,788	2.99(2.75, 3.25)	3.59 (3.15, 4.10)
Day 29+	2,053	9,093	2.28(2.15, 2.43)	2.62 (2.37, 2.91)

Notes: OMEQ, oral morphine equivalent; mg, milligrams; IRR: incidence rate ratio; CI, confidence interval.

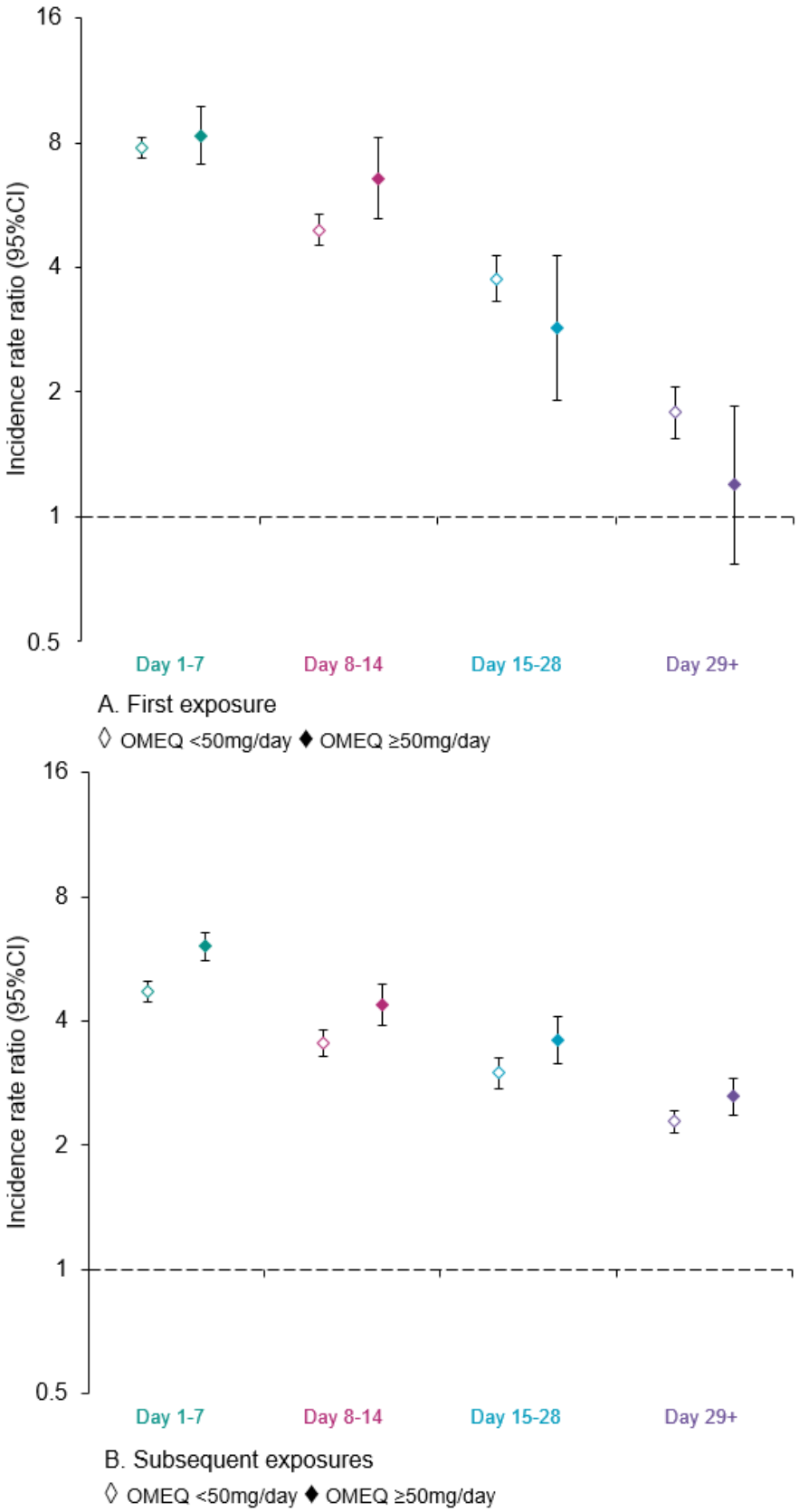
* Risk periods:

- Baseline, periods when not exposed to opioids (excluding 90-day pre-exposure period and 28-day post-exposure period).
- First exposure, first period of exposure to opioids, split into days 1-7, 8-14, 15-28 and 29+.
- Subsequent exposures, periods of opioid exposure following a gap in exposure from the first exposure period, split into days 1-7, 8-14, 15-28 and 29+.

**adjusted for 1-year increments in age, 3-monthly intervals for season.

8.5.3.3 Cumulative effects

Comparison of baseline risk periods across each year of follow-up showed no increasing trend when inspecting the aIRRs for fracture over unexposed periods throughout follow-up (Table 8-7 and Figure 8-14).



Notes: IRRs (and 95%CIs) plotted on logarithmic scale; OMEQ, oral morphine equivalent.

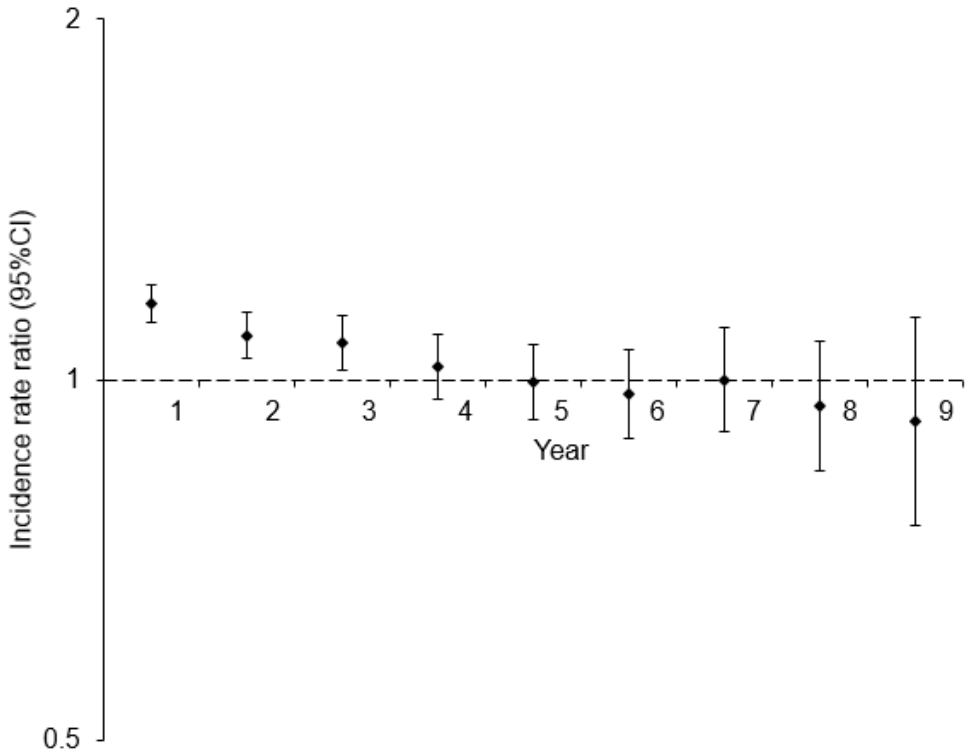
Figure 8-13. Adjusted IRRs and 95%CIs for fracture during first and subsequent periods of opioid exposure relative to the rate of fracture in the baseline (unexposed) risk period, stratified by OMEQ dose per day

Table 8-7. Adjusted IRRs for fracture during baseline (unexposed) risk periods, by year

Baseline risk period	Fractures (*n*)	Follow-up (person-years)	aIRR* (95%CI)
First baseline risk period	20,245	175,082	Baseline
Year 1 baseline risk	7,607	47,851	1.16 (1.12, 1.20)
Year 2 baseline risk	6,207	42,685	1.09 (1.04, 1.14)
Year 3 baseline risk	5,021	35,337	1.07 (1.02, 1.13)
Year 4 baseline risk	3,792	27,891	1.03 (0.96, 1.09)
Year 5 baseline risk	2,789	20,853	1.00 (0.93, 1.07)
Year 6 baseline risk	1,907	14,251	0.97 (0.89, 1.06)
Year 7 baseline risk	1,214	8,623	1.00 (0.91, 1.11)
Year 8 baseline risk	554	4,087	0.95 (0.84, 1.08)
Year 9 baseline risk	137	1,005	0.92 (0.76, 1.13)

Notes: IRR, incidence rate ratio; CI, confidence interval.

*adjusted for 1-year increments in age, 3-monthly intervals for season.



Notes: IRRs (and 95%CIs) plotted on logarithmic scale.

Figure 8-14. Adjusted IRRs and 95%CIs for fracture during baseline risk periods within each year of follow-up, relative to the first baseline risk period

8.5.3.4 Sensitivity analyses

Three sensitivity analyses were carried out to assess the sensitivity of the results to: (1) event-dependent observation; (2) non-random occurrence of events and (3) imputation of exposure data. The results from these sensitivity analyses did not considerably differ to the results presented in the primary analyses (Appendix Z).

8.5.3.5 Attributable risk

Measures of attribution were estimated for the SCCS cohort (n=67,622) and for the source population for this cohort (n=539,369). This study found that 7.3% (95%CI: 7.2, 7.3%) of fractures that occurred in the 539,369 people who were newly prescribed opioids between June 2008 and May 2017 could be attributable to opioid exposure – equating to 11.8 (95%CI: 11.6, 11.9) fractures that occurred in every 1,000 of these people. The number needed to harm (i.e., the number of people needed to be exposed to opioids for one opioid-induced fracture to occur) was 85.1 (95%CI: 85.9, 84.3) (Table 8-8).

Table 8-8. Measures of risk attribution

Risk period*	Fractures (*n*)	Follow-up (py)	aIRR** (95%CI)	Attributable fraction (%) (95%CI)	Population attributable fraction (%) (95%CI)	Attributable risk (fractures per 1,000) (95%CI)	Number needed to harm (95%CI)
Baseline	49,473	377,665					
Exposed	**8,502**	**22,859**	**3.93 (3.82, 4.04)**	**74.55 (73.82, 75.25)**	**7.25 (7.18, 7.32)**	**11.75 (11.64, 11.86)**	**85.09 (85.94, 84.31)**
First exposure							
Days 1-7	1,327	1,196	7.81 (7.40, 8.25)	87.20 (86.49, 87.88)	1.32 (1.31, 1.33)	2.15 (2.13, 2.16)	466.11 (469.97, 462.52)
Days 8-14	592	828	5.08 (4.68, 5.51)	80.32 (78.63, 81.85)	0.54 (0.53, 0.55)	0.88 (0.86, 0.90)	1134.35 (1158.68, 1113.11)
Days 15-28	256	484	3.65 (3.23, 4.13)	72.61 (69.04, 75.79)	0.21 (0.20, 0.22)	0.34 (0.33, 0.36)	2901.53 (3051.71, 2780.04)
Days 29+	257	1,047	1.71 (1.49, 1.95)	41.37 (32.89, 48.72)	0.12 (0.10, 0.14)	0.20 (0.16, 0.23)	5073.32 (3681.80, 4307.88)
Subsequent exposures							
Days 1-7	2,080	4,248	5.05 (4.83, 5.29)	80.21 (79.30, 81.10)	1.91 (1.89, 1.93)	3.09 (3.06, 3.13)	323.28 (327.02, 319.76)
Days 8-14	1,114	3,175	3.72 (3.50, 3.96)	73.14 (71.43, 74.75)	0.93 (0.91, 0.95)	1.51 (1.48, 1.54)	662.01 (677.84, 647.75)
Days 15-28	823	2,788	3.12 (2.91, 3.36)	68.00 (65.64, 70.24)	0.64 (0.62, 0.66)	1.04 (1.00, 1.07)	963.83 (998.49, 933.07)
Days 29+	2,053	9,093	2.35 (2.22, 2.48)	57.39 (54.95, 59.68)	1.35 (1.29, 1.40)	2.18 (2.09, 2.27)	457.78 (478.07, 440.24)

Notes: py, person-years; aIRR, adjusted incidence rate ratio.

* Risk periods:

- Baseline, periods when not exposed to opioids (excluding 90-day pre-exposure period and 28-day post-exposure period).
- Exposed, a combination of all exposed risk periods.
- First exposure, first period of exposure to opioids, split into days 1-7, 8-14, 15-28 and 29+.
- Subsequent exposures, periods following a gap in exposure from the first exposure period, split into days 1-7, 8-14, 15-28 and 29+.

**adjusted for 1-year increments in age, 3-monthly intervals for season.

8.6 Discussion

This is the first SCCS study to examine the association between opioids and the risk of bone fracture, which controls for time-invariant confounding by-design. The findings from this study suggest that the risk of fracture is increased 4-fold during opioid-use, compared to periods of non-use. Furthermore, the risk of fracture was greatest in the first seven days after opioid initiation, and was increased 8-fold during this time period, compared to periods of non-use. It was also found that, during subsequent periods of exposure, the risk of fracture was greater when OMEQ doses were ≥50mg/day (Day 1-7 IRR: 6.1; 95%CI: 5.6, 6.6) compared to when OMEQ doses were <50mg/day (Day 1-7 IRR: 4.7; 95%CI: 4.5, 5.0). The findings show that there is both a duration- and dose-dependent relationship between opioids and fractures; whereby the rate of fracture increases with higher opioid doses, and decreases with longer durations of exposure, thereby supporting the hypothesis that acute CNS effects of opioids (and resulting dizziness and falls) increase the risk of fracture.[15]

However, there also appeared to be a higher risk of fracture in the longer-term; from days 29 onwards of subsequent exposure risk periods. Tentatively, this finding might suggest the potential for cumulative deleterious effects on BMD. This was further explored by comparing the baseline risk periods within each year of follow-up, with the first baseline risk period. However, the findings showed no significant difference or trend in baseline IRRs over time, thereby suggesting that opioids do not have residual effects on fracture-risk that endure, post-exposure.

Existing UK studies of the association between opioids and fractures are scarce, only one UK study has aimed to examine this association. In their

nested case-control study, Li *et al.* (2013) compared fracture-risk in opioid users and non-users and found that current opioid use (i.e., use ≤30 days prior to fracture) was associated with a 27% increase in the risk of fragility fracture.[13] Additionally, they also found that the risk of fracture was greatest with initial opioid exposure, finding a 2.7-fold increase in fracture-risk in people with only one opioid prescription, which decreased with an increasing number of prescriptions. Similar trends were also reported in studies conducted outside of the UK.[200, 202] The study presented in this chapter found a greater risk of fracture in the first week of opioid use compared to later periods, which is consistent with the literature.

Previous studies have also observed a dose-dependent relationship between opioids and fractures.[14, 89, 192, 197] A US retrospective cohort study by Saunders *et al.* (2010) found that people prescribed OMEQ doses of ≥50 mg/day had a higher risk of fracture (HR: 2.0; 95%CI: 1.2, 3.2) than those prescribed OMEQ doses <20mg/day (HR: 1.2; 95%CI: 0.9, 1.6), compared to people who were not using opioids.[14] The study presented in this chapter also found a greater risk of fracture with higher daily doses, although not in the first period of opioid exposure. Very few people were initiated on OMEQ doses ≥50mg/day in the initial weeks of opioid use, which may explain the absence of a significant dose-relationship in the first exposure risk periods.

Only one other study has used a self-controlled design to examine the association between opioids and fractures;[195] this study, by Leach *et al.* (2015), used a case-crossover design to study the association between a range of psychoactive medicines (including opioids) and hip fractures in people aged ≥65 years. The case window was the 14 days prior to fracture and the control window was between 45 and 58 days prior to fracture. Leach

et al. found that there was significantly more opioid use in the 14-day period prior to fracture than during the control window (OR: 1.6; 95%CI: 1.4, 1.8). The study did not explore duration or dose effects and people were not classified as new or prevalent users of opioids. The study presented in this chapter builds on this work by using the case series approach which allowed duration and dose effects to be investigated.

8.6.1 Strengths and limitations

Existing opioid-fracture association studies are susceptible to time-varying and time-invariant confounding as well confounding by indication, which makes it difficult to establish whether the relationship might be one of cause and effect. This study has overcome many of the limitations of prior studies by adopting a self-controlled design which circumvents issues of time-invariant confounding and limits potential confounding by indication because people act as their own controls. An additional strength of this study was that a systematic approach was taken to measuring opioid exposure and identifying fracture cases and therefore there was a lower chance of misclassification of both exposure and outcome than in previous studies. Another strength of this study was that all fracture cases were identified from a defined source population of new users of opioids, which allowed attributable risk to be estimated. This is particularly important as it enabled for the contextualisation of risk so that implications for public health can be considered in absolute terms.

There are several limitations in this present study which need to be considered. Pain indication is poorly reported in the CPRD database,[242] and it may be that the indication for the initiation of opioid analgesics increased the risk of fracture rather than effects of the opioids themselves, which would

have introduced a degree of confounding by indication. Stratification of the results by pain indication would be advisable in future studies to assess the potential impact of indication bias; providing that the indication for initiating opioids is well recorded. Moreover, factors that vary over time are not inherently controlled for when using self-controlled methods but were instead included as time-varying covariates in regression models. Although important factors were included in the model, it is possible that some residual time-variant confounding remained, such as variations over time in physical activity, alcohol intake, smoking status, muscle mass, BMI and pain severity, which were not well recorded at regular intervals in the CPRD or HES databases.

An important consideration when interpreting these results is that the assumptions underlying the self-controlled case series study design are violated when examining opioid exposure with fracture-risk.[211] However, measures were taken at the design stage to minimise these, and additional sensitivity analyses were undertaken to identify the possible impact that these violations would have had on the results. Sensitivity analyses were conducted where: (1) people who died in close proximity to the outcome of interest were excluded to assess the impact of event-dependent observation; (2) first fractures were studied to assess the impact of potential non-random events; and (3) people with imputed exposure data were excluded to assess the impact of the exposure imputation process outlined in Chapter 5. The results of these sensitivity analyses did not substantially differ to results from the primary analyses, thereby suggesting the study findings were not biased by these factors. In addition to sensitivity analyses, the potential impact of event-dependent exposure was removed at the design stage by introducing a pre-exposure risk period, as conducted by previous SCCS studies.[272] Fractures

occurring in the 90-day pre-exposure period were removed from the baseline incidence rate, which counteracted the effect of event-dependent exposures that would have biased exposed IRRs towards the null.[278] Additionally, fractures occurring on the first day of opioid exposure were incorporated into the pre-exposure risk period incidence, which eliminated the introduction of protopathic bias. However, as a result of this decision, the risk of fracture on 'day 0' (i.e., the first day of opioid exposure) was not estimated and this is expected to have resulted in an under-estimation of the initial risk of fracture associated with opioids.

Identifying incident fractures across multiple data sources relied upon an operational definition for what constituted an incident fracture. This study defined these using the same definition as a prior CPRD study of fractures - fractures occurring in a different site or >6 months after a prior incident fracture.[267] This definition could have potentially under- or over-estimated the incidence of fracture in the source cohort (i.e., new users of opioids) and biased estimates for attributable risk. However, the sensitivity analysis showed that studying first fractures only did not impact on the study findings and therefore potential misclassification of incident fractures is unlikely to impact on the findings.

The target population for this study were people who were naïve to prescription opioid analgesics. It is however acknowledged that operationally defining new-use using a two-year exposure lookback window does not guarantee these people were naïve to opioids. Furthermore, as this was a new-user cohort, the findings from this study cannot be generalised to prevalent opioid users. There is also potential for misclassification of exposure as it was assumed that people had their opioid prescriptions dispensed and

that they took them as indicated by the prescriber. People may have stopped their opioids, taken them differently to the directions on the prescription, or obtained more opioids via pharmacy purchases, secondary care, friends/family or illegitimate means, which would not have been recorded in the CPRD database.

Finally, comparison of baseline risk at yearly intervals throughout follow-up showed no evidence of a cumulative increase in fracture-risk when not exposed to opioids, after adjusting for time-variable age effects and season. However, this approach did not take cumulative dose into account and future work is needed to investigate potential cumulative effects of opioids on fracture-risk. One methodological approach outlined by Schuemie *et al*. (2016) provides an extension to the SCCS method that enables cumulative exposures to be investigated.[279] The application of this method would advance the use of the SCCS design in this area as well as pharmacoepidemiological research in general.

8.7 Conclusions

This study found that exposure to opioid analgesics is associated with a 4-fold increase in the risk of fractures, rising to an 8-fold increase during the first week of opioid exposure. Decreasing fracture-risk with longer durations of opioid use, and greater fracture-risk in those who re-started opioids at higher OMEQ doses, suggests this is primarily due to the acute CNS effects of opioids.

The findings from this study suggest that a considerable number of fractures could be prevented by the early introduction of tailored fracture interventions

in new users of opioids. Further work is needed to investigate the potential cumulative effects of opioids on BMD.

Chapter 9: General Discussion

9.1 Introduction

The aims of this thesis were to describe the utilisation of opioids in the UK and to examine the association between the use of opioids and the risk of bone fracture. This discussion chapter provides an overview of the key findings from the studies presented in this thesis and a discussion regarding the interpretation of these findings, with a consideration of the key epidemiological concepts of chance, bias and confounding. Finally, the implications of these findings for practice and policy are discussed and recommendations for future research to advance this work are proposed.

9.2 Summary of main findings

Chapter 3: The association between opioid use and fractures: a systematic review and meta-analyses of observational studies

Previously published systematic reviews have reported an association between opioids and an increased risk of fracture,[49, 83, 125-128] however, no systematic reviews included all relevant observational studies nor has there been a full summary and appraisal of the methods adopted by these studies. The reason for conducting this review was to inform the design of the pharmacoepidemiological study assessing the association between opioid use and fractures presented in this thesis, so that the limitations of the previous literature could be addressed and minimised. This review has some key advantages over previous reviews in this area, these being: 1) a comprehensive search of the literature was performed, resulting in inclusion of a substantially greater number of studies, 2) risk of bias was assessed using a recently developed, comprehensive risk of bias (ROBINS-I) assessment tool,[136] and 3) a comprehensive summary of the methodologies employed in

the current literature allowed for an extensive exploration of heterogeneity in the meta-analyses, which had been established previously.

Three electronic databases were searched, 10,722 titles and abstracts were screened, and 26 articles were included in the systematic review. The systematic review highlighted some important limitations of the methodological approaches adopted by the included studies. Firstly, studies varied in how they defined opioid exposure; some using time-varying and time-invariant measures, which introduced a degree of misclassification bias. Secondly, most studies did not account for all known confounders and/or included poorly measured confounders which resulted in a high potential for residual confounding.

The meta-analyses included a total of >795,000 individuals from 21 studies that compared opioid use to non-use. Overall, the meta-analyses of cohort studies showed that, at any time-point following opioid initiation, users of opioids had a 57% increased risk of hip fracture (pooled HR: 1.57; 95%CI: 1.18, 2.09; n=8) and a 39% increased risk of non-specific fractures (pooled HR: 1.39; 95%CI: 1.20, 1.62; n=7) compared with non-users. The meta-analyses of case-control and nested case-control studies also found a significantly increased risk of unspecified fractures (pooled OR: 2.16; 95%CI: 1.18, 3.98; n=3) and hip fractures (pooled OR: 1.48; 95%CI: 1.26, 1.72; n=6) related to opioid use. One of the main limitations of the meta-analysis was that heterogeneity was considerable and although this was comprehensively examined in subgroup analyses, it was not possible to explain this with the available data. Nevertheless, there was consistency in the direction and magnitude of risk estimates across studies, which supports the hypothesis of

a positive association between opioid use and risk of fracture, compared to non-use.

Chapter 4: Data source and cohort identification

The CPRD and linked HES databases were selected as the main data sources for the analyses presented in this thesis. The aim of this chapter was to outline the considerations made when selecting these data sources and to identify and describe the main study cohort. The CPRD database was selected because it is one of the world's largest EHR databases that is of research quality and broadly represents the UK population. Additionally, the CPRD database provides linkage to other databases, such as HES and IMD which meant that the key study variables (i.e., prescription and fracture records) were available for the analysis chapters of this thesis. To ultimately study the association between opioid use and fractures, a retrospective cohort of adults prescribed opioids was identified in the CPRD database. A nine-year study period was selected due to the length of data collection in each database, and to allow for a two-year lookback period to determine whether people were new or prevalent users of opioids.

A total of 1,790,333 people were included in the cohort; 53.5% were new users and 46.5% were prevalent users of opioids. These people had 27,266,882 records of opioid prescriptions that were extracted from the CPRD database, however, it was found that a high proportion of data relating to daily doses (35.4%) were missing. The proportion of missing doses varied across opioid drug and formulation; suggesting that the dose data were MNAR; posing a challenge for generating a measure of opioid exposure over time. Overcoming this challenge was a key priority for the subsequent analyses

because the systematic review reported in Chapter 3 highlighted exposure misclassification as one of the main limitations of the existing literature.

Chapter 5: Preparing opioid prescription records for analysis

Following on from the previous chapter, an approach to handling missing data for the extracted opioid prescription records was needed. In addition to handling missing data, the prescription records required preparation for analysis; including cleaning, restructuring and formatting of the data. Methods for preparing prescription data are often poorly reported in pharmacoepidemiological studies and approaches vary depending on the specific database used. This chapter outlined the application and extension of a recently published framework – the 'DrugPrep' algorithm,[230] to impute missing prescription data and to prepare the extracted opioid prescription records for time-varying analyses which included a measure of daily OMEQ dose.

Of the 27,266,882 opioid prescription records, 0.1% had implausible or missing quantities, and 35.4% had implausible or missing doses. These records had their quantity or dose replaced by the first available value identified in the following order: 1) value recorded for a subsequent prescription for the same product, for the same patient; or 2) value recorded for a previous prescription for the same product, for the same patient; or 3) patient's median value from all plausible values recorded for the same product, for the same patient; or 4) population's median value from all plausible values recorded for the same product. Subsequently, these prescription records underwent the following processes: 1) generation of a stop date, 2) handling overlapping records, 3) combination of records into one

continuous period of exposure where gaps were permissible, and 4) generation of OMEQ dose (mg/day).

The prescription preparation resulted in two datasets ready for analysis; one detailing the opioid products prescribed and their respective start and stop dates and one detailing start and stop dates for exposure to any opioid with a total OMEQ dose (mg/day) for each period of exposure. This is the first study to apply this prescription preparation framework in the context of opioid research. The application of the DrugPrep algorithm provided a systematic approach to imputing and handling prescription data; a key strength was the extension of the algorithm to generate a daily OMEQ dose, which provided a time-varying measure of the dose as well as exposure. The generation of these datasets was fundamental to the descriptive and inferential analyses presented in Chapters 6 and 8 of this thesis, respectively.

Chapter 6: Population and patient-level trends in opioid utilisation

The generation of datasets detailing the day-to-day opioid exposure status, and OMEQ dose for people identified as either new or prevalent opioid users provided the opportunity to describe UK opioid utilisation on both a population- and patient-level. This is the largest UK study to examine patient-level opioid utilisation and to describe opioid persistency over time.

The population-level analysis showed an increase in opioid utilisation over time, increasing from 14.5% to 15.9% of CPRD registrants. Despite most people being prescribed weak opioids (>85% of people in any study-year), the proportion of people prescribed strong opioids more than doubled over the study period, rising from 3.0 to 6.6% of all opioid users. Compared with people who were prescribed weak opioids, those prescribed strong opioids were

covered for over five times the number of days in any given year and were prescribed greater daily OMEQ doses. In 2008, strong opioid users had a median duration of 155 days of opioids prescribed (IQR: 28, 340 days), whereas weak opioid users had a median duration of only 30 days of opioids prescribed (IQR: 15, 110 days). Although the median OMEQ dose remained relatively stable at 60.0mg/day (IQR: 29.1, 114.6mg/day) for strong opioid users, the median OMEQ dose for weak opioid users increased from 18.0mg/day (IQR: 7.8, 27.0mg/day) to 25.1mg/day (IQR: 10.4, 27.0mg/day) between 2008 and 2017.

The patient-level analyses showed that most new users of opioids were initiated on weak opioids (97.5%). The very small proportion (2.5%) of people initiated on strong opioids were prescribed opioids for longer durations than those initiated on weak opioids; the median duration of continuous or intermittent opioid use was 40 days (95%CI: 36, 43 days) for initiators of strong opioids, whereas this is 16 days (95%CI: 16, 16 days) for initiators of weak opioids. Although most people were prescribed weak opioids for short durations, those prescribed opioids in their second patient-year were twice as likely to be prescribed strong opioids compared with those prescribed opioids in their first patient-year. Only a small proportion of new opioid users demonstrated persistent use; 4.1% of people met any of the three definitions for persistent opioid use by the end of their first patient-year; and of those who were persistent users in their first patient-year, the likelihood of remaining a persistent user declined over follow-up.

The results from this chapter suggest that most people are initiated on weak opioids, are prescribed OMEQ doses that are <120mg/day, and have them prescribed for short durations. However, opioid utilisation increased between

2008 and 2017, and the proportion of people using strong opioids, which are typically prescribed at greater OMEQ doses than weak opioids, more than doubled.

Chapter 7: The incidence of fractures in people prescribed opioids

The aim of this chapter was to identify and describe fractures in a cohort of new opioid users so that the association between opioids and fractures could be examined in Chapter 8. Of the 957,664 new users of opioids studied in Chapter 6, 539,369 had linkage to the HES and IMD databases, and met the cohort inclusion criteria. Fracture events were identified in the CPRD and HES databases using code lists that were generated for the purpose of this study.

Of the 539,369 new opioid users eligible for this study, 67,622 were identified as having ≥1 fracture, with a total of 87,454 incident fractures being identified. People experiencing a fracture were, on average, five years older on their index date compared with people who did not experience a fracture, and a higher proportion of people with fractures were female (58.7%), compared with those without fractures (54.9% female). People with fractures were more likely to be of white ethnicity (93.1%) than those without fractures (85.2%) and a slightly higher proportion of people with fractures were from areas of low deprivation (IMD level 1: 23.2%; IMD level 2: 22.0%), compared with people without fracture (IMD level 1: 22.2%; IMD level 2: 21.7%). People with fracture were more likely to have a recorded diagnosis for osteoporosis; 12.9% of people with a fracture had a code for osteoporosis whereas 2.6% of people without a fracture had an osteoporosis code. However it was not possible to ascertain exactly when people had low BMD and whether the increased proportion of osteoporosis was influenced by DXA scans prompted by a fracture.

The incidence of fracture among the entire cohort of opioid users was 217.7 per 10,000 person-years (95%CI: 216.0, 219.3). Additional stratification of the cohort demonstrated substantial differences in fracture incidence rates by age, sex, fracture site, socioeconomic status and ethnicity, which is consistent with trends observed in the general UK population.[70, 71] The rate of fracture was greatest among females aged ≥50 years (322.9 per 10,000 person-years) and there was considerable heterogeneity between rates of fractures to each anatomical site by age and sex; females aged ≥50 years had over double the rate of fracture to the hip compared with males aged ≥50 years (49.2 and 24.2 per 10,000 person-years, respectively). Fracture rates increased with increasing deprivation, particularly in younger males who had an IRR of 1.2 in IMD level 5 (most deprived), compared to IMD level 1 (least deprived). The highest rate of fractures was observed among white individuals across all ages and sexes. The most pronounced difference was observed in females aged ≥50 years, where the rate of fracture among white females was 3.1 times greater than that of black and black British females (white IR: 343.2; black and black British IR: 111.7). Additionally, more fractures occurred during summer months (June, July and August) for males and females aged <50 years compared with other seasons of the year (summer IR: 66.2 and 39.9 per 10,000 person-years, respectively). The rate of fracture was greatest in the winter months for males aged ≥50 years (winter IR: 50.6 per 10,000 person-years) whereas the rate of fracture was equally high in the summer and winter months for females aged ≥50 years (summer IR: 92.2 and winter IR: 91.3 per 10,000 person-years).

This is the first UK study to report the incidence rates for fracture in a cohort of people who have been prescribed opioids and demonstrates that people prescribed opioids are particularly susceptible to fractures; the rate of fracture

among people prescribed opioids was double that reported for the general UK population.[70, 71] The identification of all fractures occurring within this cohort provided a case-only cohort for the SCCS study reported in Chapter 8, and importantly, identification of all fracture events within this cohort allowed for estimation of attributable risk among new opioid users.

Chapter 8: Assessing the association between opioids and the risk of bone fracture: a self-controlled case series analysis

This chapter built on earlier chapters of this thesis, firstly by using a study design that has not been used previously to examine the relationship between opioids and fractures; the SCCS study design overcomes some of the key limitations found in the existing literature which were identified and summarised in Chapter 3 of this thesis. Additionally, in Chapter 4, a cohort of opioid users was identified, and in Chapter 5 the opioid prescription records for these people were prepared for time-varying analyses. In Chapter 6, this cohort was split into new and prevalent users so that utilisation could be described; new users formed the cohort for Chapter 7. In Chapter 7, the identified new users of opioids were linked to the HES database, and after applying exclusion criteria, the source cohort was formed. Incident fractures were identified and described in the new opioid user cohort and these people formed the case-only cohort for the SCCS study presented in this chapter.

The 67,622 people with ≥1 incident fracture were observed from their index date (anchored on their CPRD registration date) to end of follow-up, regardless of when their fracture occurred. Incidence rates for fractures during periods of opioid exposure and non-exposure were compared; splitting exposed time into discrete ‘risk periods’ to assess the effect of duration of opioid use on fracture-risk. To minimise the effect of protopathic bias, a pre-

exposure period was introduced to remove fracture-related opioid exposure from the baseline (unexposed) incidence rate; a post-exposure period was also introduced to remove residual effects of opioids from the baseline risk. Additionally, risk periods were stratified by low (<50mg/day) and high (≥50mg/day) OMEQ doses to assess dose effects.

Opioid use was associated with an increase in the risk of fracture, compared to baseline (unexposed) periods (IRR: 3.9; 95%CI: 3.8, 4.0). Fracture-risk was greatest in the first week of opioid use (IRR: 7.8; 95%CI: 7.4, 8.3) and declined with increasing duration of use. Re-starting opioids after a gap in exposure increased fracture-risk (IRR: 5.1; 95%CI: 4.8, 5.3), and was greater when the OMEQ dose was ≥50mg/day (Day 1-7 IRR: 6.1; 95%CI: 5.6, 6.6) compared to when the OMEQ dose was <50mg/day (Day 1-7 IRR: 4.7; 95%CI: 4.5, 5.0). Estimation of attributable risk demonstrated that 11.8 fractures that occurred in every 1,000 people from the source cohort of new users of opioids, were attributable to opioid exposure. The number needed to harm (i.e., the number of people needed to be exposed to opioids for one opioid-induced fracture to occur) was 85. The findings suggest that opioids increase the risk of fracture 8-fold during the first week of opioid use, which is likely due to acute CNS effects. This study has important implications for public health policy and indicates where fracture interventions can be made to reduce the risk of opioid-related fractures.

9.3 The role of chance, bias and confounding

The findings from this PhD research suggest that opioids increase the risk of fracture, particularly in close proximity to the initiation or re-initiation of opioids. This section outlines the role of chance, bias and confounding in the interpretation of these findings.

9.3.1 Chance

The cohort of people studied in this thesis came from a study population (i.e., CPRD registrants) that was selected to represent a target population (i.e., people using opioids). Estimating the effect of opioids on the risk of fracture from a sample of the study population is likely to have introduced a degree of random error, whereby the effect estimate varies from one sample to another. To reduce the impact of random error on the findings from this research, a large sample size was drawn from the study population and p-values were estimated - a value ≤0.05 was considered statistically significant. Additionally, 95%CIs were provided with effect estimates, which provided the range of values that the true effect estimate would be expected to take in 95 of 100 replications.

9.3.2 Bias

Selection bias

As discussed above, this thesis studied samples of people taken from a study population, which was selected to best represent the population of interest – opioid users. The CPRD database was selected as the data source for sampling these people due to the representativeness of CPRD patients to the general UK population in terms of age, sex, ethnicity and BMI.[214] However it is acknowledged that GPs providing data to the CPRD, and healthcare providers that work in these practices may not represent UK GPs and their opioid prescribing behaviour. Therefore, there is the potential for sampling bias to have affected the external validity of, in particular, the findings presented in Chapter 6. Despite this potential bias, the findings reflect UK population trends in opioid utilisation that have been reported by Curtis *et al*. (2018),[111] who used prescribing data for all GPs in England; sampling bias is

therefore not expected to have had a considerable impact on the findings reported in this thesis.

Publication bias

Selection bias may have also been present in the form of publication bias in the meta-analyses presented in Chapter 3. It is widely known that journals are more likely to accept and publish studies that demonstrate significant findings with greater effect estimates than similar, unpublished studies;[280] this results in meta-analyses with summary estimates that are biased away from the null. The presence of publication bias was assessed by visually inspecting funnel plots and Egger's test for asymmetry.[138] No evidence was found to suggest that publication bias was present and therefore it is unlikely the findings from the meta-analyses can be explained by this.

Matching bias

Matching bias occurs when people are matched on confounding and non-confounding factors, which results in overmatching and attenuation of risk estimates. The adoption of the SCCS study design circumvented matching bias as the SCCS approach negates the need for matching.

Missing information bias

This is a form of bias that is common to retrospective studies, where only people with complete data are included in the final model when estimating effect estimates.[206] People with complete data may be intrinsically different to those with missing data; this was observed in Chapter 4 when examining missing opioid prescription data for daily doses that showed dose information was MNAR. The work outlined in Chapter 5 of this thesis sought to limit the potential for missing information to bias the results of the subsequent

analyses by taking a systematic approach to imputing the missing opioid prescription data, which allowed people with complete or missing (and therefore imputed) data to be included in the analyses.

Retention bias

People were censored if they transferred out of their GP during follow-up. This may have introduced some retention bias as people who left their GP may have been demographically different to those who did not. The presence of retention bias would affect the external validity of the results presented in this thesis, therefore, the findings may not apply to all people who are prescribed opioid analgesics.

Detection bias

Vertebral fractures are less likely to be detected than fractures to other sites,[281] and therefore might not have been well recorded in patients' EHRs. This might have resulted in an under-estimation of the incidence of fracture in opioid users, and may have led to the inclusion of fewer cases in the SCCS study resulting in less statistical power. Nevertheless, after calculating the target sample size, the number of cases identified was sufficient for detecting a significant effect and therefore detection bias is unlikely to have impacted on the findings from the SCCS study.

Misclassification bias

In Chapter 3 it was demonstrated that several cohort studies adopted definitions for exposure using the treatment carried forward (TCF) approach (equivalent to intention to treat analyses in RCTs).[87, 185-188, 199, 200] The TCF approach, whereby people are classified as users or non-users of opioids on or before their index date is carried forward throughout their follow-up and can

introduce substantial misclassification bias, particularly for long periods of follow-up.[282] In the research presented in this thesis, a time-varying measure of exposure (equivalent to the 'per protocol' analyses in RCTs) was generated to limit misclassification bias. The time-varying approach allows exposure to be followed regardless of stopping, re-starting, switching and adding further treatments, which provides a 'real-world' measure of patients' exposure to medicines.

Despite using a time-varying measure of exposure, misclassification bias may still have been introduced due to the nature of the data source used. Exposure to opioids was determined by the presence of an opioid prescription in the CPRD database and the length of exposure was determined by the prescribed dose and quantity in most circumstances. Measuring exposure based on prescription information does not provide a guarantee that a person had their medicines dispensed by a pharmacy, nor that they took their medication at the prescribed dose for the assumed duration, if at all. Additionally, people may have obtained supplies of opioids that were not recorded in the CPRD database (e.g., from hospitals, OTC purchases, or obtaining from family or friends) which would have misclassified exposed time as unexposed time. It is expected that, given the non-differential nature of misclassification of exposed and unexposed time, that effect estimates would be attenuated – leading to an under-estimate of IRRs presented in the SCCS study.[283]

Protopathic bias

Protopathic bias can occur when an exposure is influenced by the outcome.[284] This was a concern in the SCCS study presented in Chapter 8 because it is common for people with a fracture to experience pain and

require analgesics such as opioids.[276] To limit the attenuating effects of protopathic bias in the SCCS study, a pre-exposure risk period was introduced to remove fractures ≤90 days before opioids were started or re-started.

Chronology bias

One potential source of bias is chronology bias, where the timing of initiation of exposure and outcome events overlap, this can mask a temporal association and limits causal inferences that can be made from the study findings. This study adopted a new-user design to avoid such bias,[285] using a conservative definition to define people as new users of opioids (i.e., two years prior to non-exposure). Additionally, fractures occurring on the same day as an opioid was started or re-started were included in the pre-exposure risk period of the SCCS study, which limited any temporal ambiguity.

9.3.3 Confounding

Confounding occurs when a risk factor (i.e., a confounder) is independently associated with an exposure and outcome, and is not on the causal pathway between the exposure and outcome. Confounding can be reduced in observational studies at the design stage by ensuring that known confounders are adequately measured and that people are matched or randomised based on these, or are adjusted for in statistical models. Nevertheless, confounders which remain unknown, and therefore likely unmeasured, cannot be excluded as an explanation for findings. It was therefore important to consider confounding during the design stage of the SCCS study. The SCCS design controls for all time-invariant confounders, therefore, only time-varying confounders needed to be measured and adjusted for in the analyses. A key importance of this method is that it is almost possible to completely exclude

confounding as an explanation for the observed associations even if the confounders were not measured, were poorly measured or remain unknown.

Time-varying confounding

Retrospective studies that use routinely collected data can be problematic when it comes to confounding because in most cases the data used were not collected for the specific purpose of the study. Therefore, confounders may not be measured, or may have a high degree of missing data, which may not be at random. Additionally, there may not be regular recording of these confounders in the data source which means that the level for these confounding factors is not updated over time.

The final model used for the SCCS study included adjustment for time-varying age and season of year, which had affected incidence rates for fracture in Chapter 7; time-varying exposure to FRIDs did not significantly improve model fit and was therefore was not included in the final model. Despite the inclusion of these factors, the SCCS remained susceptible to residual confounding because time-varying confounders were either absent from the data sources or not recorded frequently enough to provide a time-varying measure from which to adjust in the analyses. Examples of such time-varying confounders include: smoking status,[93] alcohol consumption,[94, 95] low dietary calcium intake and serum vitamin D concentration,[96] physical activity and muscle mass,[97] and comorbidities.[101] However, some of these factors, such as muscle mass and comorbidities,[286, 287] are associated with ageing, and therefore may have been partially controlled for when adjusting for changes in age.

Confounding by indication

Confounding by indication (also known as indication bias) occurs when the exposure is indicated for a condition that is related to the outcome of interest. Comparing users of opioids with non-users is therefore likely to introduce confounding by indication, because people prescribed opioids may have a greater risk of fracture due to the underlying indication for their opioids. The SCCS study design was selected to limit confounding by indication; making within-participant comparisons rather than between-participant comparisons. However, the indication for opioids may have changed throughout a patient's follow-up period; potentially introducing confounding by indication by comparing periods of exposure and non-exposure, and levels of OMEQ dose, that had differing indications which may have had variable effects on the risk of fracture. For this reason, confounding by indication cannot be completely ruled out as a potential source of bias in the SCCS study. If indication bias was present, this would unpredictably affect the association between opioids and fractures either towards or away from the null.

One alternative approach to the SCCS design would have been to adopt an active comparator new-user design,[282] however, there was no well-matched active comparator to opioid analgesics to select for comparison. Previous studies have attempted this by comparing opioids with NSAIDs but this may not be considered suitable as they are likely to be indicated for different pain conditions or levels of pain.[189, 192]

9.4 Causal inference

Given that chance, bias and confounding all have a variable role in the interpretation of associations between exposure and outcome the question arises as to what extent the evidence suggests causation. In 1965, Sir Austin

Bradford Hill outlined nine aspects of association (termed the Bradford Hill criteria) to be considered when interpreting a relationship as causal, these criteria serve as a guide to causal inference but do not provide indisputable evidence for causality.[82] This section will outline these nine criteria in relation to the work presented in this thesis.

9.4.1 Strength

The strength of the relationship between exposure and outcome is more likely to suggest causality if it is strong.[288] This is because other factors would need to have stronger relationships with the outcome than the exposure and therefore it is less likely to be possible with strong exposure-outcome relationships than weak relationships. The IRRs reported in the SCCS were relatively large (aIRRs ranged between 1.7 and 7.8 for exposed risk periods) and therefore the strength of the association, particularly in the early weeks of opioid use, is less likely to be explained by residual confounding or biases and is suggestive of a causal relationship.

9.4.2 Consistency

If a relationship is causal, it is expected that replications of studies examining the relationship will report a similar effect across different study populations and at different time-points, unless it is anticipated that some populations will demonstrate a different response to an exposure than others.[288] In Chapter 3, it was illustrated that although existing studies examining the relationship between opioids and fractures adopted differing methodological approaches and studied a variety of patient populations, most studies demonstrated a significant positive association between opioid use and fractures. Additionally, there was no evidence of publication bias among the meta-analysed studies, which may have provided an alternative explanation for consistent findings.

9.4.3 Specificity

This criterion suggests that the exposure should be limited to the outcome of interest, and no other outcome. Opioids have been associated with adverse outcomes other than fractures,[49] and therefore this relationship does not fulfil this criteria. However, this is regarded as the weakest criterion within the Bradford Hill criteria and is usually omitted because many exposures are causally associated with multiple and varied outcomes (e.g., smoking is associated with a multitude of cancers and cardiovascular disease among many other conditions).[288]

9.4.4 Temporality

The establishment of a chronological order whereby exposure precedes outcome is the only criterion from the Bradford Hill criteria that is regarded as necessary for making causal inferences. In prospective studies it is often easier to establish a temporal relationship between exposure and outcome compared to retrospective designs. This is because, in retrospective studies, records of start and stop dates for exposure and the timing of an event may be inaccurately recorded or difficult to ascertain from the available data.[288]

Considered definitions were developed for identifying incident fractures and for determining when opioids were initiated by a person. However, there is the chance that opioid exposure was misclassified as people may have had their prescription dispensed, or started taking their opioid at a later date than the prescription start date suggested. Additionally, fractures may have occurred earlier than the date recorded either due to administrative reasons or a delay in fracture diagnosis following the event itself. For these reasons, although a temporal order was established between exposure and outcome, misclassification of these may have introduced a degree of uncertainty about

their true chronological order, which could have introduced protopathic bias. However, because a 90-day pre-exposure period was introduced to the SCCS study, this is unlikely to impact on the study findings. One alternative approach to overcome this uncertainty would be to conduct a large prospective cohort study that measures exposure to opioids and assesses the occurrences of fractures over a long period of follow-up. However, this approach would be unfeasible in terms of time and cost.

9.4.5 Biologic gradient

As the amount of exposure increases it is expected that the risk of the disease will also increase. However, dose may not have a linear effect in some cases and an outcome may only occur once a threshold level of exposure is reached.[288] The relative incidence of fracture was higher for high OMEQ dose exposed periods than low OMEQ dose exposed periods (≥50mg/day day 1-7 aIRR: 6.1; <50mg/day day 1-7 aIRR: 4.7), which suggests there was a biologic gradient present between opioids and the risk of fracture.

9.4.6 Plausibility

Although not essential for establishing causality, causal inference can be supported by coherence with existing biological knowledge underpinning the association under investigation.[288] The pharmacodynamic effects of opioids in relation to CNS effects are well documented as common side-effects in medical reference texts such as the BNF,[44] and hypotheses based on pharmacological knowledge of opioids have been purported to explain the association between opioids and fractures, on a biological level.[15] The finding that opioids increase the risk of fracture during exposed periods, and that this risk is increased in close proximity to the initiation of an opioid or the re-

initiation of an opioid concurs with existing knowledge and provides a coherent explanation for the association between opioids and fractures.

9.4.7 Coherence

The observed association should not seriously contradict existing known facts regarding the natural history of the outcome of interest, this criterion is closely related to the criterion of plausibility. The association found between opioids and fractures does not contradict existing evidence and concurs with existing hypotheses.[15]

9.4.8 Experiment

In some cases experimental evidence may be appropriate to ascertain support for a causal hypothesis, and provides strong evidence for causation. However, for this programme of research, and in many other cases, conducting such experiments on patients in a trial setting would be considered unethical and so it is often unfeasible to fulfil this criterion.[288]

9.4.9 Analogy

If an exposure-outcome relationship is similar to that under investigation then it may provide support for a causal relationship.[288] This can be a difficult criterion to demonstrate, nevertheless, opioids have been associated with an increased risk of motor vehicle accidents,[272] whereby the risk of the event decreases with increasing duration of exposure; providing an analogous example of an association between opioids and an alternative adverse outcome.

9.5 Implications for practice and policy

The findings of this thesis imply that opioid prescribing, particularly strong opioid prescribing, has increased over recent years and that people prescribed opioids are more susceptible to fractures than the general UK population. A key objective of this thesis was to examine when fractures occur in relation to opioid exposure and the finding that the risk of fracture increases with closer proximity to opioid initiation and re-initiation, and that high OMEQ doses (≥50mg/day) further increase this risk, provide the opportunity for intervention. The consensus of evidence from studies summarised in Chapter 3 and the SCCS study reported in Chapter 8 is that opioids increase the risk of fracture primarily due to acute CNS effects. Therefore it is recommended that practice and policy focus on fracture prevention in new users of opioids and those re-starting opioids after a break in use.

There are a number of established falls and fracture prevention recommendations that can be applied to reduce the risk of opioid-related fracture. The WHO's 2007 global report on falls prevention in older age recommends conducting medication reviews and reducing polypharmacy in older people to reduce the risk of falling.[107] However, given that the risk of fracture is particularly raised at the point of opioid initiation, intervention is required at the point of prescribing or dispensing. In 2017, Public Health England, in collaboration with the National Falls Prevention Coordination Group, published a consensus statement to support commissioning for the prevention of falls and fracture.[289] One of the recommendations provided in the consensus statement was to evaluate and monitor fracture-risk using robust and meaningful data. EHRs provide data for people to be electronically screened for fracture-risk using available fracture-risk assessment algorithms such as FRAX and QFracture;[108, 109] it is recommended that people deemed

to be at high risk of fractures receive a comprehensive risk assessment by a trained healthcare professional.

Computerised decision support systems (CDSSs) are information systems designed to improve clinical decision making and can be designed to provide automated recommendations based on patients' EHR data at the point of clinical decision making.[290] CDSSs can be used to target prescribing behaviour across a variety of clinical circumstances such as disease monitoring, preventative prescribing, and to highlight specific safety information. CDSSs can provide targeted information by using algorithms to display an alert only when data from patients' EHRs, or clinician data-entry match a specific set of criteria.[291] A systematic review of CDSS intervention studies demonstrated that CDSSs were effective when safety messages were displayed automatically after a drug had been selected in the EHR: examples of safety alerts included drug interactions, contraindications, cautions, or advice on medicines usage.[292] Development of CDSSs that provide tailored alerts to prescribers about fracture-risk at the point of prescribing a new opioid prescription might provide one strategy to reduce the risk of fracture in these people.

Additionally, community pharmacists are ideally placed to provide advice regarding medicines to people at the point of dispensing. This could simply be to warn people of potential dizziness when starting opioids, when there is a dose increase, or if the pharmacist has observed a gap in supplies which might indicate a person is re-starting opioids. Some people are unable to visit community pharmacies due to a range of accessibility issues and therefore these people may not receive any intervention. Housebound people often have their medicines delivered to their home and one solution could be to

phone these people prior to the delivery of their medicines or to provide an advice-slip regarding falls prevention.[293]

There are a multitude of organisations available in the UK that can provide the opportunity to disseminate information regarding opioids and the risk of fracture to healthcare professionals, including the Centre for Pharmacy Postgraduate Education (CPPE), the Royal Pharmaceutical Society (RPS), the Royal College of General Practitioners (RCGP), and the Medicines and Healthcare products Regulatory Agency (MHRA). In order for interventions to be made on a national level, policy makers would need to ensure healthcare professionals are provided with the information, capacity and remuneration for providing suitable evidence-based interventions. One example of such a service is the New Medicines Service (NMS) which was introduced in 2011 among English community pharmacies. As part of the NMS, community pharmacists are provided with remuneration for providing people with medicines advice when starting a new medicine and following-up with people two and four weeks after starting their new medicine. The aim of the service is to ensure that medicines are used safely and to best effect, and it is suggested, as a consequence of this research, that opioids could potentially be added to this service.

Communicating relative risks to people should be supported by absolute risk to contextualise the magnitude of risk.[294] One approach to communicating risk to the public is to display expected frequencies using icon arrays.[295] Figure 9-1 provides an illustrated example for communicating the risk of fracture using an icon array based on fracture incidence rates reported in Chapter 7 and measures of attribution presented in Chapter 8. Illustrations

such as this could aid healthcare professionals in communicating the risk of fracture to people prescribed opioids.

Notes: Of 100 people who are new opioid users and observed for 10 years, 22 people (black icons) will have a fracture and 2 (blue icons) of those 22 people will have a fracture that is attributable to opioids. Based on a fracture incidence rate of 217.7 per 10,000 person-years and population attributable fraction of 7.2% for any period of opioid exposure.

Figure 9-1. Fractures in 100 people prescribed opioids observed for 10 years

9.6 Future research

The work presented in this PhD thesis included the development a time-varying measure of opioid exposure that can be applied to other opioid research. In the area of opioid safety research, opioids have been associated with an increased risk of myocardial infarction,[64, 65] and the approach taken in this thesis could be applied to examine this outcome. This work could be supplemented by a validation study, comparing day-to-day exposure generated using the EHR data with self-reported opioid use, similar to a study examining exposure misclassification in people prescribed glucocorticoids.[238] This further work would provide information regarding the validity of this approach in specific relation to opioid analgesics.

SCCS studies have been rarely conducted in pharmacoepidemiological research that utilises EHR databases.[296] However, the application of self-

controlled designs, such as the SCCS approach, in pharmacoepidemiological research is increasing.[297] Furthermore, recent extensions to the SCCS study design allows questions that were previously unsuitable to address using the SCCS approach, to be studied using extended designs. One recent development by Schuemie *et al.* (2016) extends the SCCS method so that the effects of cumulative exposures can be investigated.[279] Currently, no study has applied this method to answer a clinical question; future research that applies the method by Schuemie *et al.* would provide further understanding of the association between opioids and the potential for cumulative effects on the risk of fracture, and would advance pharmacoepidemiological research methods by providing an applied example for other researchers.

9.7 Conclusion

The research presented in this thesis has shown that people prescribed opioids are particularly susceptible to fractures and that periods of opioid exposure are associated with an increased risk of fracture, especially during the first weeks of opioid use, or following a break in opioids. Additionally, it was observed that greater OMEQ doses further increased the risk of fractures. The evidence provided in this thesis supports the findings of prior research and supports the hypothesis that opioids increase the risk of fractures due to acute CNS effects. No evidence was found to support the hypothesis that opioids have long-term, cumulative effects on BMD and further research is needed to assess the cumulative effects of opioids on the risk of fracture. This research has important implications for patient safety and it is recommended, given the consensus in evidence regarding the relationship between opioids and fractures, that healthcare providers advise people regarding the risk of fracture at the point of prescribing and dispensing opioids for the first time to a patient, or following a break in supplies.

Chapter 10: Reflections on the PhD research experience

10.1 Introduction

Many lessons have been learned throughout my postgraduate research. These experiences have all, in their own way, positively impacted on my knowledge and skill-set as a researcher. Here I outline a few reflections on some of the key areas of my development.

10.2 Areas of development

10.2.1 Data access, management and analysis

Prior to embarking on my PhD research, I worked with live EHR data; identifying people at high-risk of medicine-related adverse effects, conducting audits and developing safety alerts for GP clinical systems. Despite this experience, I had a lot to learn about EHRs in the context of large datasets; the University of Nottingham department for Epidemiology and Public Health offered courses which were tremendously helpful early on in my PhD. I now understand more about data management methods and the importance of generating systematic and annotated code for statistical programs.

As part of the process for gaining authorisation to use and access linked data from the CPRD, I submitted an ISAC protocol. Developing and writing this protocol showed me the importance of clearly thinking through any study before embarking on any data management or analysis. I also learned that sometimes there can be unexpected delays in research that require pragmatism and good communication to navigate successfully.

10.2.2 Project management

I have been very fortunate to have the opportunity to work with a number of supervisors and advisors during my PhD research. Changes in academic

supervisors and industry advisors occurred during this three-year period and this required me to be proactive in building new relationships and managing a changing advisory team, whilst remaining on-target with my research plan. To ensure that this PhD research was completed within my target deadline I needed to not only organise my own time but the time of others too – with all agreeing on timelines during meetings and adhering to them. This required forward-thinking and good communication as well as passion and enthusiasm to keep the momentum going. The experience of managing my PhD-research team has enhanced my skills in both project management and leadership, and has also given me the confidence to strive to become an independent researcher in the future.

10.2.3 Academic writing

Over the course of my PhD I have improved my academic writing style so that I convey sometimes complex information succinctly, and with as much clarity as possible. I have also developed a robust approach to version control of large documents and managing the review process, which at times has required the involvement of several contributors across different teams and organisations. I am currently in the process of writing two papers relating to this PhD research, these skills will be immensely beneficial during the submission and peer-review process for these future publications.

10.2.4 Collaboration

Finally, my PhD research has been a collaborative effort; jointly funded by the University of Nottingham and Mundipharma Research Ltd (MRL). The experience of collaborating with MRL, and having the opportunity to fulfil a three-month internship within their Drug Safety and Pharmacovigilance team, provided insight into the applications of real world evidence (RWE) beyond

academia. Moving forward, I have an appreciation of the importance for commercial and academic collaborations and the benefits this can bring when considering the impact and application of research findings.

Outside of my PhD-research team, I have collaborated with other individuals when specialist advice on certain topics was sought. My experience of reaching out to both academic and non-academic professionals has been a pleasure, and has taught me the value of discussing research with others and asking for, as well as offering, advice.

Through collaborations I have worked with many individuals from a variety of backgrounds, each of them offering unique perspectives. Working alongside others during my PhD has challenged my thinking and has highlighted the importance of keeping an open mind to alternative perspectives when looking for new solutions to existing problems.

11: References

1. World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Available from: https://www.whocc.no/filearchive/publications/2017_guidelines_web.pdf [Accessed 2017 Mar 14].

2. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open*. 2016;6(6):e010364.

3. Office for National Statistics (ONS). National Population Projections: 2014-based Statistical Bulletin. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections [Accessed 2017 Jan 30].

4. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C*, et al.* The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(6):968-74.

5. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain*. 2014;18(9):1343-51.

6. Fischer B, Jones W, Rehm J. Trends and changes in prescription opioid analgesic dispensing in Canada 2005–2012: an update with a focus on recent interventions. *BMC Health Serv Res*. 2014;14(1):90.

7. Fredheim OM, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway. *Eur J Pain*. 2010;14(3):289-94.

8. Leong M, Murnion B, Haber P. Examination of opioid prescribing in Australia from 1992 to 2007. *Intern Med J*. 2009;39(10):676-81.

9. Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD*, et al.* Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf*. 2009;18(12):1166-75.

10. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. *Spine (Phila Pa 1976)*. 2014;39(7):556-63.

11. Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The space randomized clinical trial. *JAMA*. 2018;319(9):872-82.

12. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C*, et al.* Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010(1):Cd006605.

13. Li L, Setoguchi S, Cabral H, Jick S. Opioid Use for Noncancer Pain and Risk of Fracture in Adults: A Nested Case-Control Study Using the General Practice Research Database. *Am J Epidemiol*. 2013;178(5):559-69.

14. Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB*, et al.* Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med*. 2010;25(4):310-5.

15. Coluzzi F, Pergolizzi J, Raffa RB, Mattia C. The unsolved case of “bone-impairing analgesics”: the endocrine effects of opioids on bone metabolism. *Ther Clin Risk Manag*. 2015;11:515-23.

16. International Association for the Study of Pain (IASP). Pain terms: a list with definitions and notes on usage. *Pain*. 1979;6(3):249.

17. Cohen M, Quintner J, van Rysewyk S. Reconsidering the International Association for the Study of Pain definition of pain. *Pain Rep*. 2018;3(2):e634-e.

18. Kumar N. WHO normative guidelines on pain management. Available from: https://www.who.int/medicines/areas/quality_safety/delphi_study_pain_%20guidelines.pdf [Accessed 2019 Oct 9].

19. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R*, et al.* Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. 2019;160(1):19-27.

20. Kent ML, Tighe PJ, Belfer I, Brennan TJ, Bruehl S, Brummett CM*, et al.* The ACTTION-APS-AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions. *Pain Med*. 2017;18(5):947-58.

21. Merskey H, Bogduk N. Classification of chronic pain descriptions of chronic pain syndromes and definitions of pain terms (2nd edition). Available from: https://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf [Accessed 2017 Jun 6].

22. International Association for the Study of Pain (IASP). Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Available from: http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf [Accessed 2017 Mar 15].

23. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10(4):287-333.

24. Donaldson LJ. Pain: breaking through the barrier. 150 years of the Annual Report of the Chief Medical Officer: on the state of the public health. Available from: https://www.pelvicpain.org.uk/uploads/documents/Pain%20call%20for%20network%20of%20clinics-%20DH_096233.pdf [Accessed 2017 Jan 11].

25. Health and Social Care Information Centre (HSCIC). Health survey for England. Available from: http://content.digital.nhs.uk/catalogue/PUB09300 [Accessed 2017 May 2].

26. Bridges S. Chronic pain. Available from: https://catalogue.ic.nhs.uk/publications/public-health/surveys/heal-surv-eng-2011/HSE2011-Ch9-Chronic-Pain.pdf [Accessed 2017 Jan 12].

27. Magni G, Marchetti M, Moreschi C, Merskey H, Luchini SR. Chronic musculoskeletal pain and depressive symptoms in the National Health and Nutrition Examination. I. Epidemiologic follow-up study. *Pain*. 1993;53(2):163-8.

28. Becker N, Bondegaard Thomsen A, Olsen AK, Sjogren P, Bech P, Eriksen J. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. *Pain*. 1997;73(3):393-400.

29. Health and Safety Executive (HSE). Labour Force Survey. Available from: http://www.hse.gov.uk/statistics/lfs/lfsilltyp.xlsx [Accessed 2017 Jan 30].

30. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain*. 2000;84(1):95-103.

31. van Tulder MW, Koes BW, Bouter LM. A cost-of-illness study of back pain in The Netherlands. *Pain*. 1995;62(2):233-40.

32. National Health Service (NHS) Digital. Prescription Cost Analysis - England. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018 [Accessed 2019 Sept 8].

33. British Medical Association. Chronic pain: supporting safer prescribing of analgesics. Available from: https://www.bma.org.uk/-/media/files/pdfs/collective%20voice/policy%20research/public%20and%20population%20health/analgesics-chronic-pain.pdf?la=en [Accessed 2017 May 2].

34. Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2011(9):Cd008659.

35. Ennis ZN, Dideriksen D, Vaegter HB, Handberg G, Pottegard A. Acetaminophen for Chronic Pain: A Systematic Review on Efficacy. *Basic Clin Pharmacol Toxicol*. 2016;118(3):184-9.

36. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. *Cochrane Database Syst Rev*. 2016(6):Cd012230.

37. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature*. 2001;413(6852):203-10.

38. Moore RA, Chi CC, Wiffen PJ, Derry S, Rice AS. Oral nonsteroidal anti-inflammatory drugs for neuropathic pain. *Cochrane Database Syst Rev*. 2015(10):Cd010902.

39. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev*. 2016;2:Cd012087.

40. National Institute for Health and Care Excellence (NICE). Neuropathic pain in adults: pharmacological management in non-specialist settings. Clinical guideline 173. Available from: https://www.nice.org.uk/guidance/cg173 [Accessed 2019 Jul 19].

41. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015(7):Cd008242.

42. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*. 2007(4):Cd005454.

43. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain physician*. 2008;11(2 Suppl):S133-53.

44. Joint Formulary Committee. British National Formulary (BNF). Available from: http://www.medicinescomplete.com [Accessed 2017 Feb 7].

45. Department of Health. The Misuse of Drugs Regulations. Available from: http://www.legislation.gov.uk/uksi/2001/3998/pdfs/uksi_20013998_en.pdf [Accessed 2017 Feb 8].

46. World Health Organization (WHO). WHO Guidelines Approved by the Guidelines Review Committee. [Accessed 2019 Sept 9].

47. World Health Organization (WHO). WHO model list of essential medicines: 20th list. Available from: https://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1 [Accessed 28 Jun 2019].

48. Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. *Br Med J (Clin Res Ed)*. 2016;352:i20.

49. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I*, et al.* The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4):276-86.

50. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain*. 2014;30(7):557-64.

51. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug Alcohol Depend*. 2009;104(1-2):34-42.

52. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS*, et al.* Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*. 2010;105(10):1776-82.

53. Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement noncompliance. *J Pain Symptom Manage*. 2008;36(4):383-95.

54. Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Med*. 2003;4(4):340-51.

55. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain*. 2007;8(7):573-82.

56. Hojsted J, Nielsen PR, Guldstrand SK, Frich L, Sjogren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain*. 2010;14(10):1014-20.

57. Portenoy RK, Farrar JT, Backonja MM, Cleeland CS, Yang K, Friedman M*, et al.* Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain*. 2007;23(4):287-99.

58. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med*. 2002;17(3):173-9.

59. Saffier K, Colombo C, Brown D, Mundt MP, Fleming MF. Addiction Severity Index in a chronic pain sample receiving opioid therapy. *J Subst Abuse Treat*. 2007;33(3):303-11.

60. Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag*. 2010;6(6):385-95.

61. Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF*, et al.* Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? *Clin J Pain*. 2009;25(3):193-8.

62. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD*, et al.* Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85-92.

63. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171(7):686-91.

64. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. *Pharmacoepidemiol Drug Saf*. 2011;20(7):754-62.

65. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *J Intern Med*. 2013;273(5):511-26.

66. Deyo RA, Smith DH, Johnson ES, Tillotson CJ, Donovan M, Yang X*, et al.* Prescription opioids for back pain and use of medications for erectile dysfunction. *Spine (Phila Pa 1976)*. 2013;38(11):909-15.

67. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med*. 2013;173(3):196-201.

68. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporos Int*. 2001;12(5):417-27.

69. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006;17(12):1726-33.

70. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. *Bone*. 2001;29(6):517-22.

71. Curtis EM, van der Velde R, Moon RJ, van den Bergh JP, Geusens P, de Vries F*, et al.* Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. *Bone*. 2016;87:19-26.

72. Office for National Statistics (ONS). Overview of the UK population. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/november2018#the-uk-population-is-ageing [Accessed 2019 Jul 10].

73. Papadimitriou N, Tsilidis KK, Orfanos P, Benetou V, Ntzani EE, Soerjomataram I*, et al.* Burden of hip fracture using disability-adjusted life-years: a pooled analysis of prospective cohorts in the CHANCES consortium. *Lancet Public Health*. 2017;2(5):e239-e46.

74. Klop C, van Staa TP, Cooper C, Harvey NC, de Vries F. The epidemiology of mortality after fracture in England: variation by age, sex, time, geographic location and ethnicity. *Osteoporos Int*. 2017;28(1):161-8.

75. Haentjens P, Magaziner J, Colón-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B*, et al.* Meta-analysis: excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010;152(6):380-90.

76. International Osteoporosis Foundation (IOF). Broken Bones, Broken Lives: A roadmap to solve the fragility fracture crisis in the United Kingdom. Available from: http://share.iofbonehealth.org/EU-6-Material/Reports/IOF_report_UK.pdf [Accessed 2019 Jul 10].

77. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest*. 2005;115(12):3318-25.

78. Perez-Castrillon JL, Olmos JM, Gomez JJ, Barrallo A, Riancho JA, Perera L*, et al.* Expression of opioid receptors in osteoblast-like MG-63 cells, and effects of different opioid agonists on alkaline phosphatase and osteocalcin secretion by these cells. *Neuroendocrinology*. 2000;72(3):187-94.

79. Katz N, Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain*. 2009;25(2):170-5.

80. Kim TW, Alford DP, Malabanan A, Holick MF, Samet JH. Low bone density in patients receiving methadone maintenance treatment. *Drug Alcohol Depend*. 2006;85(3):258-62.

81. Pedrazzoni M, Vescovi PP, Maninetti L, Michelini M, Zaniboni G, Pioli G*, et al.* Effects of chronic heroin abuse on bone and mineral metabolism. *Acta Endocrinol (Copenh)*. 1993;129(1):42-5.

82. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med*. 1965;58(5):295-300.

83. Takkouche B, Montes-Martínez A, Gill SS, Etminan M. Psychotropic Medications and the Risk of Fracture. *Drug Saf*. 2007;30(2):171-84.

84. Yoshida K, Yu Z, Greendale GA, Ruppert K, Lian Y, Tedeschi SK*, et al.* Effects of analgesics on bone mineral density: A longitudinal analysis of the prospective SWAN cohort with three-group matching weights. *Pharmacoepidemiol Drug Saf*. 2018;27(2):182-90.

85. French DD, Campbell R, Spehar A, Cunningham F, Foulis P. Outpatient medications and hip fractures in the US: a national veterans study. *Drugs Aging*. 2005;22(10):877-85.

86. Jensen J, Nielsen LH, Lyhne N, Hallas J, Brosen K, Gram LF. Drugs and femoral neck fracture: A case-control study. *J Intern Med*. 1991;229(1):29-33.

87. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. *Am J Epidemiol*. 1998;148(9):887-92.

88. Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A*, et al.* Central nervous system active medications and risk for fractures in older women. *Arch Intern Med*. 2003;163(8):949-57.

89. Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. *J Gerontol*. 1992;47(4):M111-5.

90. Card T, West J, Hubbard R, Logan RFA. Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: A population based cohort study. *Gut*. 2004;53(2):251-5.

91. Campbell AJ, Spears GF, Borrie MJ. Examination by logistic regression modelling of the variables which increase the relative risk of elderly women falling compared to elderly men. *J Clin Epidemiol*. 1990;43(12):1415-20.

92. Department for Communities and Local Government. The English Index of Multiple Deprivation (IMD) 2015 – Guidance. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/464430/English_Index_of_Multiple_Deprivation_2015_-_Guidance.pdf [Accessed 2019 May 7].

93. Gerdhem P, Obrant KJ. Effects of cigarette-smoking on bone mass as assessed by dual-energy X-ray absorptiometry and ultrasound. *Osteoporos Int*. 2002;13(12):932-6.

94. Felson DT, Kiel DP, Anderson JJ, Kannel WB. Alcohol consumption and hip fractures: the Framingham Study. *Am J Epidemiol*. 1988;128(5):1102-10.

95. Sheppard MC, Holder R, Franklyn JA. Levothyroxine treatment and occurrence of fracture of the hip. *Arch Intern Med*. 2002;162(3):338-43.

96. Kim KM, Choi SH, Lim S, Moon JH, Kim JH, Kim SW*, et al.* Interactions Between Dietary Calcium Intake and Bone Mineral Density or Bone Geometry in a Low Calcium Intake Population (KNHANES IV 2008–2010). *J Clin Endocrinol Metab*. 2014;99(7):2409-17.

97. Karlsson MK, Nordqvist A, Karlsson C. Physical activity, muscle function, falls and fractures. *Food Nutr Res*. 2008; 52(1). Available from: https://www.ncbi.nlm.nih.gov/pubmed/19158939. [Accessed 2019 Sept 10].

98. Johansson H, Siggeirsdottir K, Harvey NC, Oden A, Gudnason V, McCloskey E*, et al.* Imminent risk of fracture after fracture. *Osteoporos Int*. 2017;28(3):775-80.

99. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15(4):721-39.

100. Harvey NC, Odén A, Orwoll E, Lapidus J, Kwok T, Karlsson MK*, et al.* Falls Predict Fractures Independently of FRAX Probability: A Meta-Analysis of the Osteoporotic Fractures in Men (MrOS) Study. *J Bone Miner Res*. 2018;33(3):510-6.

101. Dennison EM, Compston JE, Flahive J, Siris ES, Gehlbach SH, Adachi JD*, et al.* Effect of co-morbidities on fracture risk: findings from the Global Longitudinal Study of Osteoporosis in Women (GLOW). *Bone*. 2012;50(6):1288-93.

102. National Health Service (NHS) Digital. Health Survey for England 2016 - Prescribed medicines. Available from: http://healthsurvey.hscic.gov.uk/media/63790/HSE2016-pres-med.pdf [Accessed 2019 Sept 8].

103. Torstensson M, Hansen AH, Leth-Moller K, Jorgensen TS, Sahlberg M, Andersson C*, et al.* Danish register-based study on the association between specific cardiovascular drugs and fragility fractures. *BMJ Open*. 2015;5(12):e009522.

104. Robinson DE, van Staa TP, Dennison EM, Cooper C, Dixon WG. The limitations of using simple definitions of glucocorticoid exposure to predict fracture risk: A cohort study. *Bone*. 2018;117:83-90.

105. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int*. 2002;13(10):777-87.

106. Grisso JA, Kelsey JL, Strom BL, Ghiu GY, Maislin G, O'Brien LA*, et al.* Risk Factors for Falls as a Cause of Hip Fracture in Women. *N Engl J Med*. 1991;324(19):1326-31.

107. World Health Organization (WHO). WHO global report on falls prevention in older age. Available from: https://www.who.int/ageing/publications/Falls_prevention7March.pdf?ua=1 [Accessed 2019 Sept 5].

108. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ*. 2012;344:e3427.

109. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19(4):385-97.

110. Bedson J, Chen Y, Hayward RA, Ashworth J, Walters K, Dunn KM*, et al.* Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. *Pain*. 2016;157(7):1525-31.

111. Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. *The Lancet Psychiatry*. 2018.

112. Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliat Med*. 2011;25(7):725-32.

113. Svendsen K, Skurtveit S, Romundstad P, Borchgrevink PC, Fredheim OM. Differential patterns of opioid use: defining persistent opioid use in a prescription database. *Eur J Pain*. 2012;16(3):359-69.

114. Halbert BT, Davis RB, Wee CC. Disproportionate longer-term opioid use among U.S. adults with mood disorders. *Pain*. 2016;157(11):2452-7.

115. Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. *Clin Ther*. 2006;28(9):1411-24.

116. Stannard C. Opioids in the UK: what's the problem? *BMJ*. 2013;347:f5108.

117. Weisberg DF, Becker WC, Fiellin DA, Stannard C. Prescription opioid misuse in the United States and the United Kingdom: cautionary lessons. *Int J Drug Policy*. 2014;25(6):1124-30.

118. International narcotics control board. Narcotic Drugs Technical Report: Estimated World Requirements for 2019. Available from: https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2018/INCB-Narcotics_Drugs_Technical_Publication_2018.pdf [Accessed 2019 Sept 9].

119. Health and Social Care Information Centre (HSCIC). Prescriptions Dispensed in the Community: England 2005-15. Available from: http://content.digital.nhs.uk/catalogue/PUB20664/pres-disp-com-eng-2005-15-rep.pdf [Accessed 2017 Jan 17].

120. Sehmi R, Nguyen A, Mcmanus S, Smith N. Trends in long-term prescribing of dependence forming medicines. London: PHRC/NatCen; 2019.

121. Ashworth J, Green DJ, Dunn KM, Jordan KP. Opioid use among low back pain patients in primary care: Is opioid prescription associated with disability at 6-month follow-up? *Pain*. 2013;154(7):1038-44.

122. Bedson J, Belcher J, Martino OI, Ndlovu M, Rathod T, Walters K*, et al.* The effectiveness of national guidance in changing analgesic prescribing in primary care from 2002 to 2009: an observational database study. *Eur J Pain*. 2013;17(3):434-43.

123. Chevalier P, Smulders M, Chavoshi S, Sostek M, LoCasale R. A description of clinical characteristics and treatment patterns observed within prescribed opioid users in Germany and the UK. *Pain Manag*. 2014;4(4):267-76.

124. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain*. 2015;19(1):59-66.

125. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P*, et al.* Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-30.

126. Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik JG*, et al.* The effectiveness and risks of long-term opioid treatment of chronic pain. Available from: https://www.ncbi.nlm.nih.gov/books/NBK258809/ [Accessed 2018 Apr 20].

127. Teng Z, Zhu Y, Wu F, Zhu Y, Zhang X, Zhang C*, et al.* Opioids Contribute to Fracture Risk: A Meta-Analysis of 8 Cohort Studies. *PLoS One*. 2015;10(6):e0128232.

128. Ping F, Wang Y, Wang J, Chen J, Zhang W, Zhi H*, et al.* Opioids increase hip fracture risk: a meta-analysis. *J Bone Miner Metab*. 2017;35(3):289-97.

129. Warriner AH, Patkar NM, Curtis JR, Delzell E, Gary L, Kilgore M*, et al.* Which fractures are most attributable to osteoporosis? *J Clin Epidemiol*. 2011;64(1):46-53.

130. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.

131. Peach E, Otete H, Chen L-C, Cooper A, Knaggs R. Prescription opioids and adverse outcomes: a protocol for a systematic review and meta-analysis of observational studies; CRD42018083354. Available from: www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018083354 [Accessed 2019 Feb 2].

132. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M*, et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.

133. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-12.

134. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D*, et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-12.

135. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med*. 2005;37(5):360-3.

136. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M*, et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.

137. Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? *BMJ*. 1998;316(7136):989-91.

138. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-34.

139. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with the use of morphine and opiates. *J Intern Med*. 2006;260(1):76-87.

140. Stockl KM, Le L, Zhang S, Harada AS. Clinical and economic outcomes associated with potentially inappropriate prescribing in the elderly. *Am J Manag Care*. 2010;16(1):e1-10.

141. Soderberg Lofdal K, Moller J, Laflamme L. Risk of fall injuries with concomitant use of codeine and CYP2D6 inhibitors. *Basic Clin Pharmacol Toxicol*. 2014;115:85-6.

142. Söderberg KC, Laflamme L, Möller J, Söderberg KC, Laflamme L, Möller J. Newly initiated opioid treatment and the risk of fall-related injuries. A nationwide, register-based, case-crossover study in Sweden. *CNS Drugs*. 2013;27(2):155-61.

143. Sjöberg C, Bladh L, Klintberg L, Mellström D, Ohlsson C, Wallerstedt SM. Treatment with fall-risk-increasing and fracture-preventing drugs before and after a hip fracture: an observational study. *Drugs Aging*. 2010;27(8):653-61.

144. Shirley M, Johnson EF, Piecre JR. Fall-related injury in the hospital related to narcotic use but not age. *J Am Geriatr Soc*. 2012;60:S103.

145. Shirley M, Johnson E, Kang H, Pierce J. Fall-related injury in the hospital. *J Hosp Med*. 2012;7:S48-S9.

146. Schink T, Jobski K, Schmedt N, Kollhorst B, Garbe E. Antidepressants and the risk of hip fractures. *31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management*; Boston MA, United States. Pharmacoepidemiology and Drug Safety: John Wiley and Sons Ltd; 2015. p. 554.

147. Salahuddin F, Gilani O, Fang M, Altman R, Mirza F. Increased incidence of bone fractures in elderly osteoarthritic patients with persistent opioid use. *2016 Annual Meeting of the American Society for Bone and Mineral Research*; Atlanta, Georgia, United States. Journal of Bone and Mineral Research: John Wiley and Sons Inc.; 2017.

148. Ryg J, Abrahamsen B, Brixen K, Masud T, Frost M. Osteoarthritis and falls in men aged 60-74 years. *2011 European Congress on Osteoporosis and Osteoarthritis*; Valencia, Spain. Osteoporosis International: Springer London; 2011. p. S263.

149. Rolita L, Spegman A, Tang X, Cronstein BN. Greater Number of Narcotic Analgesic Prescriptions for Osteoarthritis Is Associated with Falls and Fractures in Elderly Adults. *J Am Geriatr Soc*. 2013;61(3):335-40.

150. Reece AS. Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine. *J Subst Abuse Treat*. 2009;37(3):256-65.

151. Perreault S, Dragomir A, Blais L, Moride Y, Rossignol M, Ste-Marie LG*, et al.* Population-based study of the effectiveness of bone-specific drugs in reducing the risk of osteoporotic fracture. *Pharmacoepidemiol Drug Saf*. 2008;17(3):248-59.

152. Parekh N, Ali K, Stevenson JM, Davies JG, Schiff R, Harchowal J*, et al.* Incidence and cost of medication-related harm in older adults following hospital discharge in the UK: Results from the PRIME study. *13th International Congress of the European Union Geriatric Medicine Society*; Nice, France. European Geriatric Medicine: Elsevier Masson SAS; 2017. p. S39.

153. Ozen G, Pedro S, Wolfe F, Michaud K. Medications associated with osteoporotic fracture risk in patients with rheumatoid arthritis. *2017 American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting*; San Diego, CA, United States. Arthritis & rheumatology (Hoboken, N.J.): John Wiley and Sons Inc.; 2017. p. 69.

154. Nurminen J, Puustinen J, Piirtola M, Vahlberg T, Lyles A, Kivelä S-L. Opioids, antiepileptic and anticholinergic drugs and the risk of fractures in patients 65 years of age and older: a prospective population-based study. *Age Ageing*. 2013;42(3):318-24.

155. Minkowitz HS, Gruschkus SK, Shah M, Raju A. Adverse drug events among patients receiving postsurgical opioids in a large health system: Risk factors and outcomes. *Am J Health Syst Pharm*. 2014;71(18):1556-65.

156. Marcum Z, Larson E, Walker R, Golchin N, Rosenberg D, Crane P*, et al.* Initiation of medications acting on the central nervous system (CNS) and fall-related injuries. *Pharmacoepidemiol Drug Saf*. 2017;26:170.

157. Makris UE, Pugh M, Alvarez CA, Mortensen EM. Exposure to high risk medications is associated with worse outcomes in older veterans with chronic pain. *2015 Annual Scientific Meeting of the American Geriatrics Society*; National Harbor, MD United States. Journal of the American Geriatrics Society: Blackwell Publishing Inc.; 2015. p. S71.

158. Mak J, Baguley IJ. Relationship between hip fracture subtypes and analgesia use. *J Am Geriatr Soc*. 2007;55(4):626-7.

159. Lord SR, Menz HB, Tiedemann A. A physiological profile approach to falls risk assessment and prevention. *Phys Ther*. 2003;83(3):237-52.

160. Lee RH, Sloane R, Colon-Emeric C. Factors associated with increased bone fracture risk among older male veterans with type 2 diabetes mellitus. *76th Scientific Sessions of the American Diabetes Association*; New Orleans, Louisiana, United States. Diabetes: American Diabetes Association; 2016. p. A362-A3.

161. Leach MJ, Pratt NL, Roughead EE. Medicine use and the risk of hip fracture in the elderly: A case-crossover study. *Pharmacoepidemiol Drug Saf*. 2014;23:180-1.

162. Leach MJ, Pratt NL, Roughead EE. Medicine Use among Older Australians Before and After Hip Fracture. *JPPR*. 2013;43(4):265-8.

163. Le B, Waller J, Radhakrishnan R, Oh SJ, Bethel M, Rice C*, et al.* Risk factors for incident fractures in patients with systemic lupus erythematosus on dialysis. *2016 American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting*; Washington, D.C, United States. Arthritis & rheumatology (Hoboken, N.J.): John Wiley and Sons Inc.; 2016. p. 1512.

164. Kuschel BM, Laflamme L, Moller J. The risk of fall injury in relation to commonly prescribed medications among older people-a Swedish case-control study. *Eur J Public Health*. 2015;25(3):527-32.

165. Krebs EE, Paudel M, Taylor BC, Bauer D, Fink HA, Lane NE*, et al.* Association of opioid use with falls and fractures among older men with musculoskeletal pain. *37th Annual Meeting of the Society of General Internal Medicine*; San Diego, CA United States. Journal of General Internal Medicine: Springer New York; 2014. p. S34-S5.

166. Hirst A, Knight C, Hirst M, Dunlop W, Akehurst R. Tramadol and the risk of fracture in an elderly female population: a cost utility assessment with comparison to transdermal buprenorphine. *Eur J Health Econ*. 2016;17(2):217-27.

167. Gilmore TM, Alexander BH, Mueller BA, Rivara FP. Occupational injuries and medication use. *Am J Ind Med*. 1996;30(2):234-9.

168. Fernandez Villaseca S, Garcia-Cabrera L, Valdez Disla L, Alvarez-Nebreda ML, Sanchez-Castellano C, Cruz-Jentoft AJ. Treatment with fall-risk-increasing drugs and fracture-prevention drugs in elderly patients admitted with a hip fracture. Specific focus on recurrent fallers. *Eur Geriatr Med*. 2014;5:S167.

169. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC*, et al.* Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc*. 2002;50(10):1629-37.

170. Ekholm O, Kurita GP, Hojsted J, Juel K, Sjogren P. Chronic pain, opioid prescriptions, and mortality in Denmark: A population-based cohort study. *Pain*. 2014;155(12):2486-90.

171. Ebly EM, Hogan DB, Fung TS. Potential adverse outcomes of psychotropic and narcotic drug use in Canadian seniors. *J Clin Epidemiol*. 1997;50(7):857-63.

172. Ducharme MM, Boothby LA. Analysis of adverse drug reactions for preventability. *Int J Clin Pract*. 2007;61(1):157-61.

173. Daniell HW. Opioid osteoporosis. *Arch Intern Med*. 2004;164(3):338.

174. Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. *Drugs Aging*. 1998;12(1):43-53.

175. Cowan DT, Allan L, Griffiths P. A pilot study into the problematic use of opioid analgesics in chronic non-cancer pain patients. *Int J Nurs Stud*. 2002;39(1):59-69.

176. Coplan PM, Sessler NE, Harikrishnan V, Singh R, Perkel C. Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analgesics in the National Poison Data System. *Postgrad Med*. 2017;129(1):55-61.

177. Buckeridge D, Huang A, Hanley J, Kelome A, Reidel K, Verma A*, et al.* Risk of injury associated with opioid use in older adults. *J Am Geriatr Soc*. 2010;58(9):1664-70.

178. Bonafede M, Shi N, Barron R, Li X, Crittenden DB, Chandler D. Predicting imminent risk for fracture in patients with osteoporosis using commercially insured claims data. *2015 Annual Meeting of the American Society for Bone and Mineral Research*; Seattle, Washington, United States. Journal of Bone and Mineral Research: John Wiley and Sons Inc.; 2015.

179. Bohnert ASB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA*, et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-21.

180. Benard-Laribiere A, Noize P, Pambrun E, Bazin F, Verdoux H, Tournier M*, et al.* Comorbidities and concurrent medications increasing the risk of adverse drug reactions: prevalence in French benzodiazepine users. *Eur J Clin Pharmacol*. 2016;72(7):869-76.

181. Aung KK, Turner BJ, Pugh MJ. Outcomes associated with exposure to high risk medications in elderly with chronic pain. *35th Annual Meeting of the Society of General Internal Medicine*; Orlando, FL United States. Journal of General Internal Medicine: Springer New York; 2012. p. S257.

182. Aparasu RR, Chatterjee S. Use of narcotic analgesics associated with increased falls and fractures in elderly patients with osteoarthritis. *Evid Based Med*. 2014;19(1):37-8.

183. Allolio B. Risk factors for hip fracture not related to bone mass and their therapeutic implications. *Osteoporos Int*. 1999;9(8):S9-S16.

184. Acurcio FA, Moura CS, Bernatsky S, Bessette L, Rahme E. Opioids use and risk of fractures in rheumatoid arthritis patients: Results of a Canadian epidemiological study. *2015 Annual European Congress of Rheumatology of the European League Against Rheumatism*; Rome Italy. Annals of the Rheumatic Diseases: BMJ Publishing Group; 2015. p. 781.

185. Vestergaard P, Hermann P, Jensen JEB, Eiken P, Mosekilde L. Effects of paracetamol, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, and opioids on bone mineral density and risk of fracture: Results of the Danish Osteoporosis Prevention Study (DOPS). *Osteoporos Int*. 2012;23(4):1255-65.

186. Tolppanen A-M, Taipale H, Tanskanen A, Tiihonen J, Hartikainen S. Comparison of predictors of hip fracture and mortality after hip fracture in community-dwellers with and without Alzheimer's disease - exposure-matched cohort study. *BMC Geriatr*. 2016;16:204.

187. Thorell K, Ranstad K, Midlov P, Borgquist L, Halling A. Is use of fall risk-increasing drugs in an elderly population associated with an increased risk of hip fracture, after adjustment for multimorbidity level: a cohort study. *BMC Geriatr*. 2014;14:131.

188. Spector W, Shaffer T, Potter DEB, Correa-de-Araujo R, Limcangco MR. Risk factors associated with the occurrence of fractures in U.S. nursing homes: resident and facility characteristics and prescription medications. *J Am Geriatr Soc*. 2007;55(3):327-33.

189. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170(22):1968-78.

190. Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J*, et al.* The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med*. 2010;170(22):1979-86.

191. Snacken M, Crenier L, Fery F, Praet JP, Pepersack T. Correlates of fractures in elderly, diabetic outpatients. *Acta Clin Belg*. 2015;70(5):321-4.

192. Miller M, Stürmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc*. 2011;59(3):430-8.

193. Machado-Duque ME, Castano-Montoya JP, Medina-Morales DA, Castro-Rodriguez A, Gonzalez-Montoya A, Machado-Alba JE. Association between the use of benzodiazepines and opioids with the risk of falls and hip fractures in older adults. *Int Psychogeriatr*. 2017:1-6.

194. Leach MJ, Pratt NL, Roughead EE. Risk of Hip Fracture in Older People Using Selective Serotonin Reuptake Inhibitors and Other Psychoactive Medicines Concurrently: A Matched Case-Control Study in Australia. *Drugs Real World Outcomes*. 2017;4(2):87-96.

195. Leach MJ, Pratt NL, Roughead EE. Psychoactive medicine use and the risk of hip fracture in older people: A case-crossover study. *Pharmacoepidemiol Drug Saf*. 2015;24(6):576-82.

196. Krebs E, Paudel M, Taylor B, Bauer D, Fink H, Lane N*, et al.* Association of Opioids with Falls, Fractures, and Physical Performance among Older Men with Persistent Musculoskeletal Pain. *J Gen Intern Med*. 2016;31(5):463-9.

197. Kamal-Bahl SJ, Stuart BC, Beers MH. Propoxyphene use and risk for hip fractures in older adults. *Am J Geriatr Pharmacother*. 2006;4(3):219-26.

198. Grewal K, Austin PC, Kapral MK, Lu H, Atzema CL. The impact of opioid medications on subsequent fractures in discharged emergency department patients with peripheral vertigo. *CJEM*. 2018;20(1):28-35.

199. Dobnig H, Piswanger-Solkner JC, Obermayer-Pietsch B, Tiran A, Strele A, Maier E*, et al.* Hip and nonvertebral fracture prediction in nursing home patients: Role of bone ultrasound and bone marker measurements. *J Clin Endocrinol Metab*. 2007;92(5):1678-86.

200. Carbone LD, Chin AS, Lee TA, Burns SP, Svircevs JN, Hoenig HM*, et al.* The association of opioid use with incident lower extremity fractures in spinal cord injury. *J Spinal Cord Med*. 2013;36(2):91-6.

201. Bethel M, Weaver FM, Bailey L, Miskevics S, Svircev JN, Burns SP*, et al.* Risk factors for osteoporotic fractures in persons with spinal cord injuries and disorders. *Osteoporos Int*. 2016;27(10):3011-21.

202. Acurcio FA, Moura CS, Bernatsky S, Bessette L, Rahme E. Opioid Use and Risk of Nonvertebral Fractures in Adults with Rheumatoid Arthritis: A Nested Case-Control Study Using Administrative Databases. *Arthritis Rheumatol*. 2016;68(1):83-91.

203. Abrahamsen B, Brixen K. Mapping the prescriptiome to fractures in men-a national analysis of prescription history and fracture risk. *Osteoporos Int*. 2009;20(4):585-97.

204. Ravindrarajah R, Hazra NC, Charlton J, Jackson SHD, Dregan A, Gulliford MC. Incidence and mortality of fractures by frailty level over 80 years of age: cohort study using UK electronic health records. *BMJ Open*. 2018;8(1):e018836.

205. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*. 2002;3(5):377-84.

206. Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health*. 2004;58(8):635.

207. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet*. 1997;350(9074):326-9.

208. Egger M, Smith GD. Bias in location and selection of studies. *BMJ*. 1998;316(7124):61.

209. Langan SM, Schmidt SAJ, Wing K, Ehrenstein V, Nicholls SG, Filion KB*, et al.* The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*. 2018;363:k3532.

210. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006;25(10):1768-97.

211. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ*. 2016;354.

212. Pacurariu A, Plueschke K, McGettigan P, Morales DR, Slattery J, Vogl D*, et al.* Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation. *BMJ Open*. 2018;8(9):e023090.

213. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *BMJ*. 2010;340:c2289.

214. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T*, et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-36.

215. Medicines and Healthcare products Regulatory Agency. Release Notes - CPRD GOLD July 2017. London: MHRA; 2017.

216. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T*, et al.* Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ*. 2013;346:f2350.

217. Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. *Eur J Epidemiol*. 2019;34(1):91-9.

218. National Health Service (NHS) Digital. Hospital Episode Statistics (HES). Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics [Accessed 2019 May 7].

219. National Health Service (NHS) Digital. National Clinical Coding Standards ICD-10 Available from: https://hscic.kahootz.com/gf2.ti/f/762498/46448165.2/PDF/-/National_Coding_Standards_ICD10_reference_book_2019.pdf [Accessed 2019 May 7].

220. National Health Service (NHS) Digital. National Clinical Coding Standards OPCS-4. Available from: https://hscic.kahootz.com/gf2.ti/f/762498/48443045.1/PDF/-/NCCSOPCS420196.pdf [Accessed 2019 May 7].

221. Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. *BMJ Open*. 2018;8(2):e020738.

222. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J*, et al.* Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol*. 2019; dyz034. Available from: https://doi.org/10.1093/ije/dyz034.

223. Bhaskaran K, Forbes HJ, Douglas I, Leon DA, Smeeth L. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). *BMJ Open*. 2013;3(9):e003389.

224. Riis AH, Johansen MB, Jacobsen JB, Brookhart MA, Sturmer T, Stovring H. Short look-back periods in pharmacoepidemiologic studies of new users of antibiotics and asthma medications introduce severe misclassification. *Pharmacoepidemiol Drug Saf*. 2015;24(5):478-85.

225. Czwikla J, Jobski K, Schink T. The impact of the lookback period and definition of confirmatory events on the identification of incident cancer cases in administrative data. *BMC Med Res Methodol*. 2017;17:122.

226. Baker R, Tata LJ, Kendrick D, Orton E. Identification of incident poisoning, fracture and burn events using linked primary care, secondary care and mortality data from England: implications for research and surveillance. *Inj Prev*. 2016;22(1):59-67.

227. Chenaf C, Kabore JL, Delorme J, Pereira B, Mulliez A, Zenut M*, et al.* Prescription opioid analgesic use in France: Trends and impact on morbidity-mortality. *Eur J Pain*. 2019;23(1):124-34.

228. Groenwold RHH, White IR, Donders ART, Carpenter JR, Altman DG, Moons KGM. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. *Can Med Assoc J*. 2012;184(11):1265-9.

229. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG*, et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.

230. Pye SR, Sheppard T, Joseph RM, Lunt M, Girard N, Haas JS*, et al.* Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. *Pharmacoepidemiol Drug Saf*. 2018;27(7):781-8.

231. National Health Service (NHS) Scotland. Scottish Palliative Care Guidelines. Available from: https://www.palliativecareguidelines.scot.nhs.uk/guidelines/medicine-information-sheets/alfentanil.aspx [Accessed 2019 May 5].

232. Keats AS, Telford J, Kurosu Y. Studies of analgesic drugs: III. Dextromoramide and a comparison of methods of estimating pain relief in man. *J Pharmacol Exp Ther*. 1960;130(2):212.

233. National Health Service (NHS) Wales. Opiate Conversion Doses. Available from: https://www.wales.nhs.uk/sites3/Documents/814/OpiateConversionDoses%5BFinal%5DNov2010.pdf [Accessed 2019 May 5].

234. Centers for Medicare & Medicaid Services. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors. Available from: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf [Accessed 2019 May 5].

235. Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R*, et al.* Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;10:Cd012509.

236. Gardarsdottir H, Souverein PC, Egberts TC, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *J Clin Epidemiol*. 2010;63(4):422-7.

237. Pazzagli L, Linder M, Zhang M, Vago E, Stang P, Myers D*, et al.* Methods for time-varying exposure related problems in pharmacoepidemiology: An overview. *Pharmacoepidemiol Drug Saf*. 2018;27(2):148-60.

238. Joseph RM, Staa TP, Lunt M, Abrahamowicz M, Dixon WG. Exposure measurement error when assessing current glucocorticoid use using UK primary care electronic prescription data. *Pharmacoepidemiol Drug Saf*. 2019;28(2):179-86.

239. Von Korff M, Saunders K, Thomas Ray G, Boudreau D, Campbell C, Merrill J*, et al.* De facto long-term opioid therapy for noncancer pain. *Clin J Pain*. 2008;24(6):521-7.

240. Braden JB, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. *J Pain*. 2008;9(11):1026-35.

241. Birke H, Kurita GP, Sjogren P, Hojsted J, Simonsen MK, Juel K*, et al.* Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: trends from 2000 to 2013. *Acta Anaesthesiol Scand*. 2016;60(5):623-33.

242. Farias JC, Porter L, McManus S, Strang J, Hickman M, Reed K*, et al.* Prescribing patterns in dependence forming medicines. London: NatCen; 2017.

243. Foy R, Leaman B, McCrorie C, Petty D, House A, Bennett M*, et al.* Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. *BMJ Open*. 2016;6(5):e010276.

244. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care*. 2005;11(7):449-57.

245. Rasmussen L, Pratt N, Hansen MR, Hallas J, Pottegård A. Using the "proportion of patients covered" and the Kaplan-Meier survival analysis to describe treatment persistence. *Pharmacoepidemiol Drug Saf*. 2018;27(8):867-71.

246. Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med*. 2011;26(12):1450-7.

247. Gore M, Sadosky A, Leslie D, Tai KS, Seleznick M. Patterns of therapy switching, augmentation, and discontinuation after initiation of treatment with select medications in patients with osteoarthritis. *Clin Ther*. 2011;33(12):1914-31.

248. Advisory Council on the Misuse of Drugs. Advisory council on the misuse of drugs consideration of tramadol. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/144116/advice-tramadol.pdf [Accessed 2019 Jun 12].

249. Chen T-C, Chen L-C, Knaggs RD. A 15-year overview of increasing tramadol utilisation and associated mortality and the impact of tramadol classification in the United Kingdom. *Pharmacoepidemiol Drug Saf*. 2018;27(5):487-94.

250. Chen T-C, Chen L-C, Kerry M, Knaggs RD. Prescription opioids: Regional variation and socioeconomic status - evidence from primary care in England. *Int J Drug Policy*. 2019;64:87-94.

251. Torrance N, Mansoor R, Wang H, Gilbert S, Macfarlane GJ, Serpell M*, et al.* Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study. *Br J Anaesth*. 2018;120(6):1345-55.

252. The Royal College of Anaesthetists. Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. Available from: https://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware [Accessed 2019 Jun 21].

253. Doran T, Kontopantelis E, Valderas JM, Campbell S, Roland M, Salisbury C*, et al.* Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. *BMJ*. 2011;342:d3590.

254. Kontopantelis E, Springate DA, Reeves D, Ashcroft DM, Rutter M, Buchan I*, et al.* Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia*. 2015;58(3):505-18.

255. National Health Service (NHS) Digital. Quality and Outcomes Framework (QOF) business rules v 38 2017-2018 October code release. Available from: https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/quality-and-outcomes-framework-qof/quality-and-outcome-framework-qof-business-rules/quality-and-outcomes-framework-qof-business-rules-v-38-2017-2018-october-code-release [Accessed 2019 Sept 11].

256. O'Connell NE, Smith KJ, Peterson MD, Ryan N, Liverani S, Anokye N*, et al.* Incidence of osteoarthritis, osteoporosis and inflammatory musculoskeletal diseases in adults with cerebral palsy: A population-based cohort study. *Bone*. 2019;125:30-5.

257. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E*, et al.* Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)*. 2014;36(4):684-92.

258. Paskins Z, Whittle R, Abdul Sultan A, Muller S, Blagojevic-Bucknall M, Helliwell T*, et al.* Risk of fragility fracture among patients with late-onset psoriasis: a UK population-based study. *Osteoporos Int*. 2018;29(7):1659-64.

259. Ogdie A, Harter L, Shin D, Baker J, Takeshita J, Choi HK*, et al.* The risk of fracture among patients with psoriatic arthritis and psoriasis: a population-based study. *Ann Rheum Dis*. 2017;76(5):882.

260. Judge A, Javaid MK, Leal J, Hawley S, Drew S, Sheard S*, et al.* Health Services and Delivery Research. Southampton: NIHR Journals Library; 2016.

261. National Health Service (NHS) Digital. OPCS-4 eVersion Book. Available from: https://isd.digital.nhs.uk/trud3/user/guest/group/0/pack/37 [Accessed 2019 Sept 11].

262. World Health Organization (WHO). International Classification for Diseases Available from: https://icd.who.int/browse10/2016/en [Accessed 2017 Sept 23].

263. Putman MS, Yu EW, Lee H, Neer RM, Schindler E, Taylor AP*, et al.* Differences in skeletal microarchitecture and strength in African-American and white women. *J Bone Miner Res*. 2013;28(10):2177-85.

264. Bulajic-Kopjar M. Seasonal variations in incidence of fractures among elderly people. *Inj Prev*. 2000;6(1):16-9.

265. Crawford JR, Parker MJ. Seasonal variation of proximal femoral fractures in the United Kingdom. *Injury*. 2003;34(3):223-5.

266. Hayashi S, Noda T, Kubo S, Myojin T, Nishioka Y, Higashino T*, et al.* Variation in fracture risk by season and weather: A comprehensive analysis across age and fracture site using a National Database of Health Insurance Claims in Japan. *Bone*. 2018;120:512-8.

267. Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. *PLoS Med*. 2009;6(9):e1000154.

268. Fink HA, Milavetz DL, Palermo L, Nevitt MC, Cauley JA, Genant HK*, et al.* What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? *J Bone Miner Res*. 2005;20(7):1216-22.

269. Hallas J, Pottegård A. Use of self-controlled designs in pharmacoepidemiology. *J Intern Med*. 2014;275(6):581-9.

270. Maclure M, Fireman B, Nelson JC, Hua W, Shoaibi A, Paredes A*, et al.* When should case-only designs be used for safety monitoring of medical products? *Pharmacoepidemiol Drug Saf*. 2012;21 Suppl 1:50-61.

271. Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. *Am J Epidemiol*. 2003;158(1):77-84.

272. Gibson JE, Hubbard RB, Smith CJP, Tata LJ, Britton JR, Fogarty AW. Use of Self-controlled Analytical Techniques to Assess the Association Between Use of Prescription Medications and the Risk of Motor Vehicle Crashes. *Am J Epidemiol*. 2009;169(6):761-8.

273. Farrington P, Whitaker H, Ghebremichael-Weldeselassie Y. Self-controlled case series studies : a modelling guide with R. London: CRC Press; 2018.

274. Whitaker HJ, Ghebremichael-Weldeselassie Y. Self-Controlled Case Series Methodology. *Annual Review of Statistics and Its Application*. 2019;6(1):241-61.

275. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. *Clin Infect Dis*. 2014;58(11):1497-503.

276. Simoni AH, Nikolajsen L, Olesen AE, Christiansen CF, Pedersen AB. Opioid use after hip fracture surgery: A Danish nationwide cohort study from 2005 to 2015. *Eur J Pain*. 2019;23(7):1309-17.

277. Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. *Stat Med*. 2006;25(15):2618-31.

278. Whitaker HJ, Ghebremichael-Weldeselassie Y, Douglas IJ, Smeeth L, Farrington CP. Investigating the assumptions of the self-controlled case series method. *Stat Med*. 2018;37(4):643-58.

279. Schuemie MJ, Trifirò G, Coloma PM, Ryan PB, Madigan D. Detecting adverse drug reactions following long-term exposure in longitudinal observational data: The exposure-adjusted self-controlled case series. *Stat Methods Med Res*. 2016;25(6):2577-92.

280. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ*, et al.* Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess*. 2010;14(8):1-193.

281. Delmas PD, van de Langerijt L, Watts NB, Eastell R, Genant H, Grauer A*, et al.* Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. *J Bone Miner Res*. 2005;20(4):557-63.

282. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep*. 2015;2(4):221-8.

283. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol*. 1977;105(5):488-95.

284. Gerhard T. Bias: Considerations for research practice. *Am J Health Syst Pharm*. 2008;65(22):2159-68.

285. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-20.

286. Curtis E, Litwic A, Cooper C, Dennison E. Determinants of Muscle and Bone Aging. *J Cell Physiol*. 2015;230(11):2618-25.

287. Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. *Eur Respir J*. 2014;44(4):1055-68.

288. Gordis L. Epidemiology. 5th ed. Philadelphia: Elsevier/Saunders; 2014.

289. Public Health England with the National Falls Prevention Coordination Group. Falls and fracture consensus statement. Available from: https://www.england.nhs.uk/south/wp-content/uploads/sites/6/2017/03/falls-fracture.pdf [Accessed 2019 Sept 5].

290. Duerden M, Millson D, Avery A, Smart S. The quality of GP prescribing. London: The King's Fund; 2011.

291. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J*, et al.* Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA*. 2005;293(10):1223-38.

292. Pearson SA, Moxey A, Robertson J, Hains I, Williamson M, Reeve J*, et al.* Do computerised clinical decision support systems for prescribing change practice? A systematic review of the literature (1990-2007). *BMC Health Serv Res*. 2009;9:154.

293. Chartered Society of Physiotherapy. Get up and go: a guide to staying steady. Available from: https://www.csp.org.uk/system/files/get_up_and_go_0.pdf [Accessed 2019 Oct 18].

294. Freeman ALJ, Spiegelhalter DJ. Communicating health risks in science publications: time for everyone to take responsibility. *BMC Med*. 2018;16(1):207.

295. Spiegelhalter DJ. The art of statistics. UK: Penguin; 2019.

296. Gault N, Castaneda-Sanabria J, Guillo S, Foulon S, Tubach F. Underuse of self-controlled designs in pharmacoepidemiology in electronic healthcare databases: a systematic review. *Pharmacoepidemiol Drug Saf*. 2016;25(4):372-7.

297. Gault N, Castaneda-Sanabria J, De Rycke Y, Guillo S, Foulon S, Tubach F. Self-controlled designs in pharmacoepidemiology involving electronic healthcare databases: a systematic review. *BMC Med Res Methodol*. 2017;17(1):25.

298. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L*, et al.* Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004–2014. *BMJ Open*. 2017;7(2):e014444.

12: Appendices

Appendix A. PROSPERO registered systematic review protocol

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Prescription opioids and adverse outcomes: a protocol for a systematic review and meta-analysis of observational studies

Emily Peach, Li-Chia Chen, Andrew Cooper, Harmony Otete, Roger Knaggs

Citation

Emily Peach, Li-Chia Chen, Andrew Cooper, Harmony Otete, Roger Knaggs. Prescription opioids and adverse outcomes: a protocol for a systematic review and meta-analysis of observational studies. PROSPERO 2018 CRD42018083354 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018083354

Review question

1) To what extent does the use of prescription opioids affect the risk of the following adverse outcomes in adults?

a) Bone fractures
b) Motor vehicle accidents
c) Myocardial infarction
d) Unintentional overdose

2) Which epidemiological methods have been used to identify these outcomes and assess their association with the use of prescription opioids?

Searches

Electronic databases:
MEDLINE (via Ovid) 1946- 17th October 2017
Embase (via Ovid) 1947- 17th October 2017
CINAHL Plus with Full-Text (EBSCO) 1937- 17th October 2017

Hand searching reference lists of retrieved relevant citations

Limited to English language, human studies.

Types of study to be included

Inclusion: published observational studies or open-label extension studies

Exclusion: any other study design.

Condition or domain being studied

The use of prescription opioids in adults.

Participants/population

Inclusion: adults (aged 18 years or over).

Exclusion: children and adolescents (aged under 18 years); pregnant women; patients with cancer, undergoing palliative care or end of life care, or receiving treatment for an opioid use disorder.

Intervention(s), exposure(s)

Appendix A. PROSPERO registered systematic review protocol [continued]

Inclusion: prescription opioid analgesics included in section N02A of the WHO Anatomical Therapeutic Classification (ATC) Index

Exclusion: opioid substitution therapy; illicit opioids e.g. heroin use or opioids obtained illegally

Comparator(s)/control

Not applicable.

Context

Primary outcome(s)

Bone fractures, motor vehicle accidents, myocardial infarction and unintentional overdose in adults taking prescription opioids.

The definition and measurement of these outcomes can vary substantially between observational studies. The secondary outcome of this review will, in part, provide a summary of the outcome definitions and measurement methods employed by the included studies.

Timing and effect measures

The effect measure will be reported as a hazard ratio, rate ratio, odds ratio or risk ratio. The outcome will occur at any length of time after exposure to prescription opioids.

Secondary outcome(s)

The epidemiological methods employed by the included studies will be summarised and critiqued. This will include a comparison of exposure and outcome definitions, and their measurement; control for potential confounding variables and statistical approaches.

Timing and effect measures

Data extraction (selection and coding)

Selection of studies: All identified citations will be collated and uploaded into EndNote X7 and duplicates removed. Titles and abstracts will undergo a preliminary screen by two independent reviewers using the inclusion/exclusion criteria to identify potentially relevant articles. These decisions will be recorded in Microsoft Excel and agreement between the two reviewers at this stage will be reported by Cohen's kappa coefficient, a coefficient of 0.6 or above will indicate moderate agreement between the reviewers decisions. Selected full-text articles will be retrieved and assessed for eligibility by each reviewer in accordance with the inclusion/exclusion criteria.

Data extraction: The data from included studies will be extracted using a piloted standardised data extraction form. Data will be extracted by two independent reviewers and will include details about each included study. Examples of details to be extracted are the study design, data source, population, methodology, statistical analysis, and results and risk estimates reported. Corresponding authors of studies with missing or ambiguous data will be contacted to provide any missing or additional data.

Any disagreements that arise between the reviewers at any stage during the study selection and data extraction process will be resolved through discussion, or with a third reviewer where necessary.

Risk of bias (quality) assessment

Each included study will be assessed for risk of bias by two independent reviewers. The ROBINS-I tool will be used to assess the risk of bias for included observational studies. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Appendix A. PROSPERO registered systematic review protocol [continued]

The results of the critical appraisal will be incorporated into the discussion of the findings provided and in a summary table. Data synthesis and, where possible, meta-analysis will be undertaken for all studies, regardless of the rating of their methodological quality. A sensitivity analysis will be performed to assess the impact of removing poor quality studies from the meta-analysis.

Strategy for data synthesis

The findings from all included studies will be presented in tables and figures in addition to a narrative summary. These will be grouped by each adverse outcome under investigation and sectioned into methodological approaches and study risk estimates (presented as either hazards ratio, rate ratio, odds ratio or risk ratio) with detail of comparison group.

Where possible, for each adverse outcome, the reported effect estimates and 95% confidence intervals for the proportion of opioid users and non-users experiencing the outcome will be pooled using a random-effects meta-analytic approach. Heterogeneity between studies will be assessed statistically using I^2 tests, a value of 50% will indicate moderate heterogeneity which will be explored by performing subgroup analyses. Study quality will be assessed in a sensitivity analysis. Risk estimates will be compared for differences in (but not limited to) study country, pain condition and opioid drug using stratified meta-analysis.

Publication bias will be assessed visually by generating funnel plots. Three review authors will examine these and the conclusions will be reported. All statistical analyses will be performed using STATA/MP 15 (StataCorp, Texas, 2017).

Analysis of subgroups or subsets

Where reported, results from stratification and subgroup analyses (e.g. by dose, duration of use and cumulative use) will be extracted and summarised to provide a summary risk estimate.

Contact details for further information

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Organisational affiliation of the review

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Mundipharma Research Ltd

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Dr Harmony Otete. University of Nottingham
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Anticipated or actual start date

17 October 2017

Anticipated completion date

01 January 2019

Funding sources/sponsors

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Conflicts of interest

Dr Andrew Cooper is an employee of Mundipharma Research Ltd

Appendix A. PROSPERO registered systematic review protocol [continued]

Language

(there is not an English language summary)

Country

England

Stage of review

Review_Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Analgesics, Opioid; Humans; Prescriptions

Date of registration in PROSPERO

19 March 2018

Date of publication of this version

19 March 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

19 March 2018

Appendix B. Database search strategies in Ovid Medline

Ovid MEDLINE(R) 1946 to March Week 2 2018		
#	Search terms	Citations
1	opioid.ti,ab. or exp Analgesics, Opioid/ or Analgesics, Opioid/ae [Adverse Effects]	131027
2	narcotic.ti,ab. or exp Narcotics/	115966
3	(opiate* or opioid* or narcotic*).ti,ab.	92877
4	(alfentanil or alphaprodine or bezitramide or buprenorphine or butorphanol or carfentanil or codeine or deltorphin or dextromoramide or dextropropoxyphene or dezocine or diamorphine or dichloralphenazone or dihydrocodeine or dihydromorphine or dipipanone or ethoheptazine or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or hydromorphone or ketobemidone or levorphanol or lofentanil or meptazinol or methadone or methadyl or morphine or nalbuphine or nicomorphine or opium or oxycodone or oxymorphone or papaveretum or pentazocine or pethidine or phenazocine or phenoperidine or pholcodine or pirinitramide or piritramide or promedol or remifenta* or sufentanil or tapentadol or tilidine or tramadol or meperidine or hydrocodone or propoxyphene or prodine or carfentanyl or dermenkephalin or acetylmethadol or trimeperidine).ti,ab.	91247
5	or/1-4	174186
6	exp Patient Harm/	102
7	harm*.ti,ab.	114269
8	exp Long Term Adverse Effects/ or exp "Drug-Related Side Effects and Adverse Reactions"/	104678
9	(adverse event* or adverse effect* or adverse reaction* or adverse drug reaction* or adverse outcome*).ti,ab.	260706
10	exp Fractures, Bone/	167112
11	(fracture* or break or broken).ti,ab.	239191
12	exp "Wounds and Injuries"/	826984
13	exp Epidemiologic Studies/ or exp Case-Control Studies/ or exp Observation/ or observation*.ti,ab.	2651358
14	observational studies.ti,ab. or exp Observational Study/	62188
15	exp Cohort Studies/ or cohort*.ti,ab. or exp Prospective Studies/ or prospective*.ti,ab.	1986411
16	exp Retrospective Studies/ or retrospective*.ti,ab.	776260
17	(quasi-randomi$ed controlled trial* or quasi randomi$ed controlled trial* or non-randomi$ed controlled trial* or non randomi$ed controlled trial* or prospective cohort or retrospective cohort or historically controlled trial* or nested case-control or nested case control or cross-sectional study or cross sectional study or case report or case series or open-label extension or open label extension or open-label trial extension or open label trial extension).ti,ab.	432239
18	(controlled before and after stud*).ti,ab.	565
19	(before and after comparison*).ti,ab.	274
20	exp Longitudinal Studies/ or longitudinal*.ti,ab.	227303
21	exp Case-Control Studies/ or case control*.ti,ab. or case-control*.ti,ab.	922738
22	or/13-21	3258834
23	or/6-12	1367187
24	5 and 22 and 23	4497
25	exp animals/ not (exp human/ and exp animals/)	4431776
26	24 not 25	4369
27	limit 26 to english language	4027

Appendix C. Database search strategies in Embase

Embase 1974 to 2018 March 16		
#	Search terms	Citations
1	exp *opiate/	24079
2	exp *narcotic agent/	115129
3	(opiate* or opioid* or narcotic*).ti,ab.	137360
4	(alfentanil or alphaprodine or bezitramide or buprenorphine or butorphanol or carfentanil or codeine or deltorphin or dextromoramide or dextropropoxyphene or dezocine or diamorphine or dichloralphenazone or dihydrocodeine or dihydromorphine or dipipanone or ethoheptazine or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or hydromorphone or ketobemidone or levorphanol or lofentanil or meptazinol or methadone or methadyl or morphine or nalbuphine or nicomorphine or opium or oxycodone or oxymorphone or papaveretum or pentazocine or pethidine or phenazocine or phenoperidine or pholcodine or pirinitramide or piritramide or promedol or remifenta* or sufentanil or tapentadol or tilidine or tramadol or meperidine or hydrocodone or propoxyphene or prodine or carfentanyl or dermenkephalin or acetylmethadol or trimeperidine).ti,ab.	133846
5	or/1-4	257153
6	exp *patient harm/	165
7	harm*.ti,ab.	177386
8	exp *adverse drug reaction/	172264
9	exp *adverse outcome/	4242
10	(adverse event* or adverse effect* or adverse reaction* or adverse drug reaction* or adverse outcome*).ti,ab.	466063
11	exp *side effect/	62331
12	(side effect* or side-effect*).ti,ab.	314803
13	exp *fracture/	150660
14	(fracture* or break or broken).ti,ab.	337509
15	exp *accidental injury/ or exp *injury/	969616
16	exp *epidemiology/	343182
17	exp *epidemiological data/ or exp *epidemiological monitoring/	320525
18	exp *case control study/	6540
19	exp *observation/ or exp *prospective study/ or exp *observational study/	20364
20	exp *cohort analysis/ or exp *follow up/	47641
21	exp *retrospective study/	11449
22	(observation* or cohort* or retrospective or prospective).ti,ab.	2542419
23	(quasi-randomi$ed controlled trial* or quasi randomi$ed controlled trial* or non-randomi$ed controlled trial* or non randomi$ed controlled trial* or prospective cohort or retrospective cohort or historically controlled trial* or nested case-control or nested case control or cross-sectional study or cross sectional study or case report or case series or open label extension or open-label extension or open label trial extension or open-label trial extension).ti,ab.	722958
24	(controlled before and after stud*).ti,ab.	730
25	exp *longitudinal study/	5463
26	(before and after comparison*).ti,ab.	429
27	(longitudinal or case control or case-control).ti,ab.	394250
28	or/16-27	3625125
29	or/6-15	2167197
30	5 and 28 and 29	10418
31	exp animal/ not (human/ and exp animal/)	4809838
32	30 not 31	10139
33	limit 32 to english language	9352

Appendix D. Database search strategies in CINAHL Plus

CINAHL Plus with Full Text (EBSCO)		
#	Search terms	Citations
1	(MH "Analgesics, Opioid+") OR (MH "Narcotics+")	36246
2	(AB narcotic* OR opioid* OR opiate*) OR (TI narcotic* OR opioid* OR opiate*)	29454
3	(AB "alfentanil" OR "alphaprodine" OR "bezitramide" OR "buprenorphine" OR " butorphanol" OR "carfentanil" OR "codeine" OR "deltorphin" OR "dextromoramide" OR "dextropropoxyphene" OR "dezocine" OR "diamorphine" OR "dichloralphenazone" OR "dihydrocodeine" OR "dihydromorphine" OR "dipipanone" OR "ethoheptazine" OR "ethylketocyclazocine" OR "ethylmorphine" OR "etorphine" OR "fentanyl" OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR "meptazinol" OR "methadone" OR "methadyl" OR "morphine" OR "nalbuphine" OR "nicomorphine" OR "opium" OR "oxycodone" OR "oxymorphone" OR "papaveretum" OR "pentazocine" OR "pethidine" OR "phenazocine" OR "phenoperidine" OR "pholcodine" OR "pirinitramide" OR "piritramide" OR "promedol" OR "remifenta*" OR "sufentanil" OR "tapentadol" OR "tilidine" OR "tramadol" OR "meperidine" OR "hydrocodone" OR "propoxyphene" OR "prodine" OR "carfentanyl" OR "dermenkephalin" OR "acetylmethadol" OR "trimeperidine") OR (TI "alfentanil" OR "alphaprodine" OR "bezitramide" OR "buprenorphine" OR " butorphanol" OR "carfentanil" OR "codeine" OR "deltorphin" OR "dextromoramide" OR "dextropropoxyphene" OR "dezocine" OR "diamorphine" OR "dichloralphenazone" OR "dihydrocodeine" OR "dihydromorphine" OR "dipipanone" OR "ethoheptazine" OR "ethylketocyclazocine" OR "ethylmorphine" OR "etorphine" OR "fentanyl" OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR "meptazinol" OR "methadone" OR "methadyl" OR "morphine" OR "nalbuphine" OR "nicomorphine" OR "opium" OR "oxycodone" OR "oxymorphone" OR "papaveretum" OR "pentazocine" OR "pethidine" OR "phenazocine" OR "phenoperidine" OR "pholcodine" OR "pirinitramide" OR "piritramide" OR "promedol" OR "remifenta*" OR "sufentanil" OR "tapentadol" OR "tilidine" OR "tramadol" OR "meperidine" OR "hydrocodone" OR "propoxyphene" OR "prodine" OR "carfentanyl" OR "dermenkephalin" OR "acetylmethadol" OR "trimeperidine")	25197
4	(AB harm*) OR (TI harm*)	36371
5	(AB harm* OR adverse event* OR adverse effect* OR adverse reaction* OR adverse drug reaction*) OR (TI harm* OR adverse event* OR adverse effect* OR adverse reaction* OR adverse drug reaction*)	428841
6	(MH "Adverse Health Care Event+") OR (MH "Adverse Drug Event+")	49673
7	(AB side effect* OR side-effect*) OR (TI side effect* OR side-effect*)	30131
8	(MH "Fractures+")	44023
9	(AB fracture* OR break OR broken) OR (TI fracture* OR break OR broken)	61080
10	(MH "Epidemiology+") OR (MH "Epidemiological Research+")	546096
11	(MH "Case Control Studies+") OR (MH "Matched Case Control") OR (MH "Population-Based Case Control")	64569
12	(MH "Nonexperimental Studies+") OR (MH "Prospective Studies+") OR (MH "Concurrent Prospective Studies") OR (MH "Cross Sectional Studies") OR (MH "Observational Methods+") OR (MH "Participant Observation") OR (MH "Nonconcurrent Prospective Studies") OR (MH "Historically Controlled Study") OR (MH "Controlled Before-After Studies") OR (MH "Quasi-Experimental Studies+") OR (MH "Comparative Studies") OR (MH "Interrupted Time Series Analysis")	688956
13	(MH "Retrospective Design") OR (MH "Retrospective Panel Studies")	184559
14	(AB observation* OR cohort* OR retrospective OR quasi-randomi$ed controlled trial* OR quasi randomi$ed controlled trial* OR non-randomi$ed controlled trial* OR non randomi$ed controlled trial* OR prospective cohort OR retrospective cohort OR historically controlled trial* OR nested case-control OR nested case control OR cross-sectional study OR cross sectional study OR case report OR case series OR prospective OR open label extension OR open-label extension OR open label trial extension OR open--label trial extension) OR (TI observation* OR cohort* OR retrospective OR quasi-randomi$ed controlled trial* OR quasi randomi$ed controlled trial* OR non-randomi$ed controlled trial* OR non randomi$ed controlled trial* OR prospective cohort OR retrospective cohort OR historically controlled trial* OR nested case-control OR nested case control OR cross-sectional study OR cross sectional study OR case report OR case series OR prospective OR open label extension OR open-label extension OR open label trial extension OR open--label trial extension)	846103
15	(AB longitudinal) OR (TI longitudinal)	59515
16	S1 OR S2 OR S3	50203
17	S4 OR S5 OR S6 OR S7 OR S8 OR S9	536556
18	S10 OR S11 OR S12 OR S13 OR S14 OR S15	1367668
19	S16 AND S17 AND S18 (Limiters - English Language; Human)	25

Appendix E. Reviewer guidelines for title and abstract screening

Reviewer guidelines for screening citations for eligibility

All citations are listed in the Excel spreadsheet - 180320_Screening_Fracture_only_AC

Refer to **Table 1** for the study inclusion/exclusion criteria

Title screening

Read the title and determine if the citation is relevant to the review and whether to *reject* if:

1. The title is too unclear to assess eligibility
2. The title does not wholly or partially reflect the inclusion criteria
3. The title meets any of the exclusion criteria

Abstract screening

Read the abstracts for citations that have not been rejected after title screening and determine whether to *accept* if:

1. The abstract meets all inclusion criteria
2. The abstract partially meets the inclusion criteria but there is insufficient information in the abstract to meet all inclusion criteria
3. There is no abstract present

Note: If the abstract meets any of the exclusion criteria this must be rejected

Indicate the decision to accept or reject each citation in column E

Note: indicate any duplicate citations or comments in column G

1

Appendix E. Reviewer guidelines for title and abstract screening [continued]

Table 1. Inclusion and exclusion criteria for eligibility

Criteria	Inclusion	Exclusion
Population	Adults (aged ≥18 years)	Patients aged <18 years; pregnant women Patients with: cancer; receiving treatment for an opioid use disorder; or undergoing end of life care
Intervention	Prescription opioid analgesics included in section N02A of the WHO ATC	Opioid substitution therapy; illicit opioids e.g. heroin use or opioids obtained illegally
Outcome	Studies reporting a risk estimate (OR, RR, IRR, HR) for bone fracture	Studies that do not report one of these risk estimates for this outcome
Types of studies	Published observational studies or open-label extension studies	Any other study design
Type of publication	Published full-text original articles and letters reporting original research	Conference proceedings, abstracts, commentaries, letters not reporting original research, editorials analysis, reviews, clinical guidelines
Limitations	English language, human studies	Non-English language, animal studies

Appendix F. ROBINS-I quality assessment form

Reviewer: Date: Author(s), year:

Specify the review question

Participants	Adults (aged 18 years or over) Exclusion: children and adolescents (aged under 18 years); pregnant women; patients with cancer, undergoing palliative care or end of life care or receiving treatment for an opioid use disorder.
Experimental intervention	Prescription opioid analgesics Exclusion: opioid substitution therapy; illicit opioids e.g. heroin use or opioids obtained illegally
Comparator	Any
Outcomes	Bone fracture

Specify a target randomized trial specific to the study

Design	Individually randomized / Cluster randomized / Matched (e.g. cross-over)
Participants	
Experimental intervention	
Comparator	

Is your aim for this study…?

☐ to assess the effect of *assignment to* intervention
☐ to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify the numerical result being assessed

Confounding domains	Measured variable(s)	Controlling unnecessary?	Measured validly and reliably?
Age			
Alcohol use			
Body mass index			
Bone mineral density			
Comorbidity			
Sex			
Smoking			
Socioeconomic status			
Other medication use (antidepressants, benzodiazepines, bisphosphonates, diuretics, steroids, vitamin D)			

Additional co-interventions	Controlling unnecessary?	Favours experimental or comparator?

1

Appendix F. ROBINS-I quality assessment form [continued]

1. Confounding	Y/PY	N/PN	NI
1.1 Is there potential for confounding of the effect of intervention in this study?		No further questions	
1.2 Was the analysis based on splitting participants' follow up time according to intervention received?	Q1.3	Q1.4-1.6	
1.3 Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Q1.7-1.8	Q1.4-1.6	
1.4 Did the authors use an appropriate analysis method that controlled for all the important confounding domains?			
1.5 **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?			
1.6 Did the authors control for any post-intervention variables that could have been affected by the intervention?			
1.7 Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?			
1.8 **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?			

2. Selection of participants	Y/PY	N/PN	NI
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?		Q2.4	
2.2 **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?			
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?			
2.4 Do start of follow-up and start of intervention coincide for most participants?			
2.5 **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?			

3. Classification of interventions	Y/PY	N/PN	NI
3.1 Were intervention groups clearly defined?			
3.2 Was the information used to define intervention groups recorded at the start of the intervention?			
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?			

4. Deviations from intended interventions	Y/PY	N/PN	NI
If your aim for this study is to assess the effect of assignment to intervention, answer Q4.1 and 4.2			
4.1 Were there deviations from the intended intervention beyond what would be expected in usual practice?			
4.2 **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?			
If your aim for this study is to assess the effect of starting and adhering to intervention, answer Q4.3 to 4.6			
4.3 Were important co-interventions balanced across intervention groups?			
4.4 Was the intervention implemented successfully for most participants?			
4.5 Did study participants adhere to the assigned intervention regimen?			
4.6 **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?			

2

Appendix F. ROBINS-I quality assessment form [continued]

5. Missing data	Y/PY	N/PN	NI
5.1 Were outcome data available for all, or nearly all, participants?			
5.2 Were participants excluded due to missing data on intervention status?			
5.3 Were participants excluded due to missing data on other variables needed for the analysis?			
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?			
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?			

6. Measurement of outcomes	Y/PY	N/PN	NI
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?			
6.2 Were outcome assessors aware of the intervention received by study participants?			
6.3 Were the methods of outcome assessment comparable across intervention groups?			
6.4 Were any systematic errors in measurement of the outcome related to intervention received?			

7. Selection of the reported result	Y/PY	N/PN	NI
Is the reported effect estimate likely to be selected, on the basis of the results, from...			
7.1 ... multiple outcome *measurements* within the outcome domain?			
7.2 ... multiple *analyses* of the intervention-outcome relationship?			
7.3 ... different *subgroups*?			

Overall bias	Judgement
Overall risk of bias judgement:	
1. **Confounding**	
2. **Selection of participants**	
3. **Classification of interventions**	
4. **Deviations from intended interventions**	
5. **Missing data**	
6. **Measurement of outcomes**	
7. **Selection of the reported result**	

3

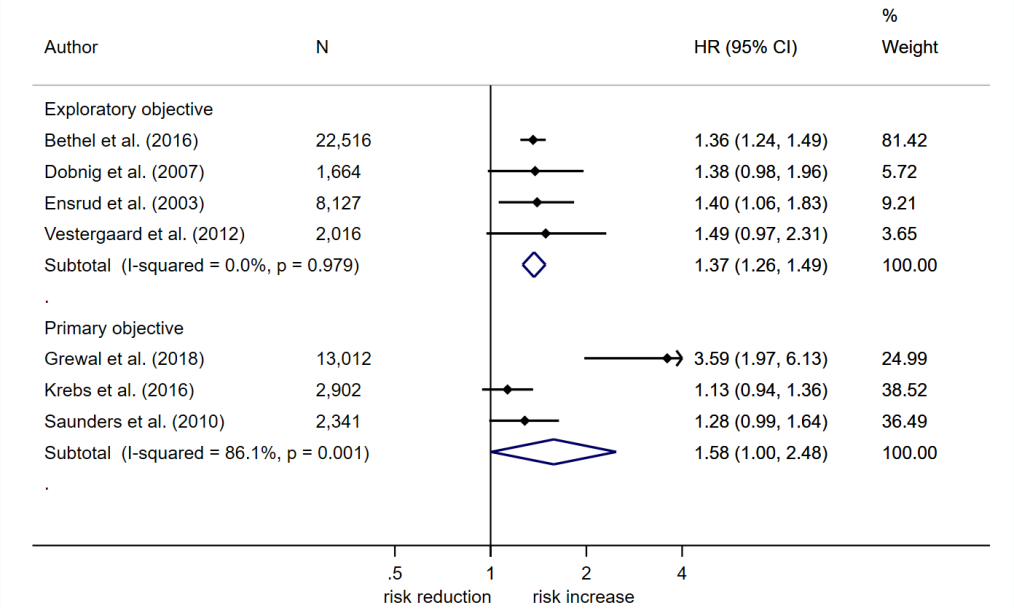
Appendix G. Objectives specific to studying the association between opioid use and fracture

First author	Study objective
Acurcio[202]	Assess whether opioids increase the risk of non-vertebral fracture in adults with rheumatoid arthritis
Carbone[200]	Assess the effect of opioid use compared to non-use on number of fractures in people with spinal cord injury
Grewal[198]	To examine the risk of fracture in discharged patients with peripheral vertigo who were being prescribed opioids at the same time
Kamal-Bahl[197]	Examine risk of fracture associated with propoxyphene use in older adults
Krebs[196]	Investigate longitudinal association between opioid use and falls/fractures and physical performance in older men with persistent musculoskeletal pain
Li[13]	Evaluate the association between opioid use and risk of fracture, particularly extensive use and the hypogonadism mechanism
Machado-Duque[193]	Determine the association between use of opioids and benzodiazepines and the risk of falls with hip fracture in people aged over 65 years in Colombia
Miller[192]	Examine whether the risk of hip fracture among incident users of opioids varies by duration of opioid action (long-acting versus short-acting)
Saunders[14]	To assess whether risk of fracture increases with opioid dose among older people initiating sustained use of opioids for CNCP.
Shorr[89]	To investigate whether use of codeine and propoxyphene increases the risk of hip fracture in non-hospitalised elderly people

Appendix H. Objectives not specific to studying the association between opioid use and fracture

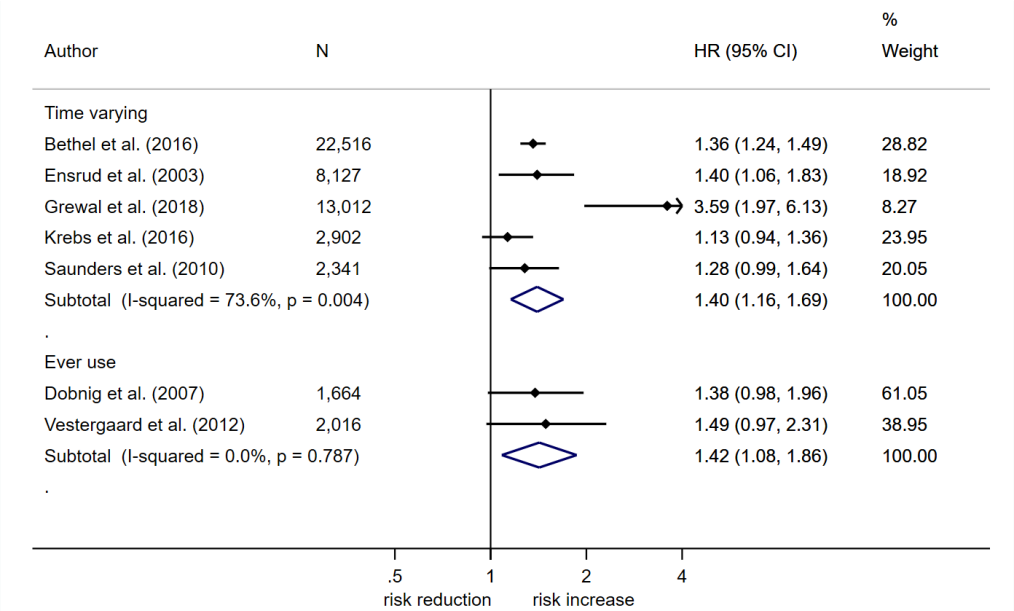
First author	Study objective
Abrahamsen[203]	To study the impact of drugs on fracture burden in men
Bethel[201]	To identify risk factors for incident osteoporotic fracture in persons with a spinal cord injury that can easily be determined at the point of care
Card[90]	Assess current cumulative use of corticosteroids and risk of hip fracture in people with IBD
Dobnig[199]	Investigate whether bone ultrasound measurements and or markers of bone turnover help predict hip or non-vertebral fracture
Ensrud[88]	Investigate the association between current use of four CNS-active medication classes and non-vertebral fractures in older women
Guo[87]	Investigate risk factors for hip fracture, examining especially cognitive function and drug use in a geographically defined cohort aged ≥75
Jensen[86]	Investigate the relationship between drugs and hip fractures
Leach[195]	Assess the association between psychoactive medication and hip fracture in the elderly
Leach[194]	To assess the risk of hip fracture in older people as a result of concurrent SSRI and other psychoactive medicine use
Snacken[191]	To assess whether risk of hip and/or wrist fracture is increased by strict glycaemic control in older diabetic patients and to explore other potential risk factors
Solomon(a)[190]	Compare the safety of NSAIDs, coxibs and opioids
Solomon(b)[189]	Compare the safety of opioids commonly used for CNCP
Spector[188]	Investigate the effect of nursing home resident characteristics and prescription medication use on the occurrence of fractures
Thorell[187]	Explore the association of fall risk increasing drugs in combination with multi-morbidity with hip fracture in people aged 75 and over
Tolppanen[186]	Compare predictors of hip fractures and mortality after hip fracture in persons with and without Alzheimer's disease
Vestergaard[185]	Study the effects of paracetamol, NSAIDs, aspirin and opioids on BMD and risk of fractures

Appendix I. Forest plots of subgroup analyses of cohort studies reporting HRs for fractures of unspecified anatomical sites in opioid use



Note: Studies were coded as having a 'primary objective' if their primary objective was to investigate the association between opioid use and fractures.

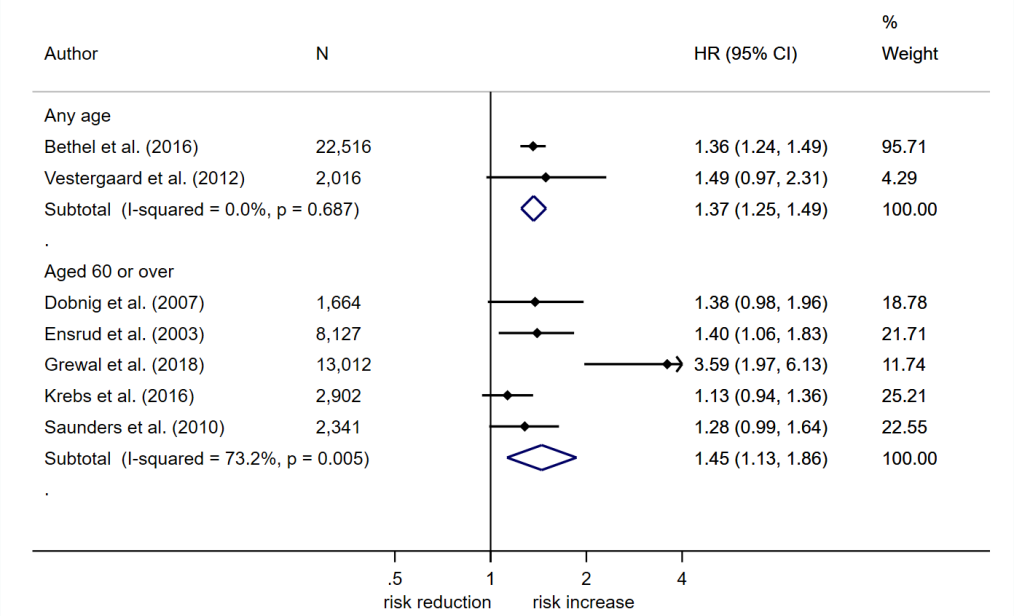
Forest plot of cohort studies grouped by study objective



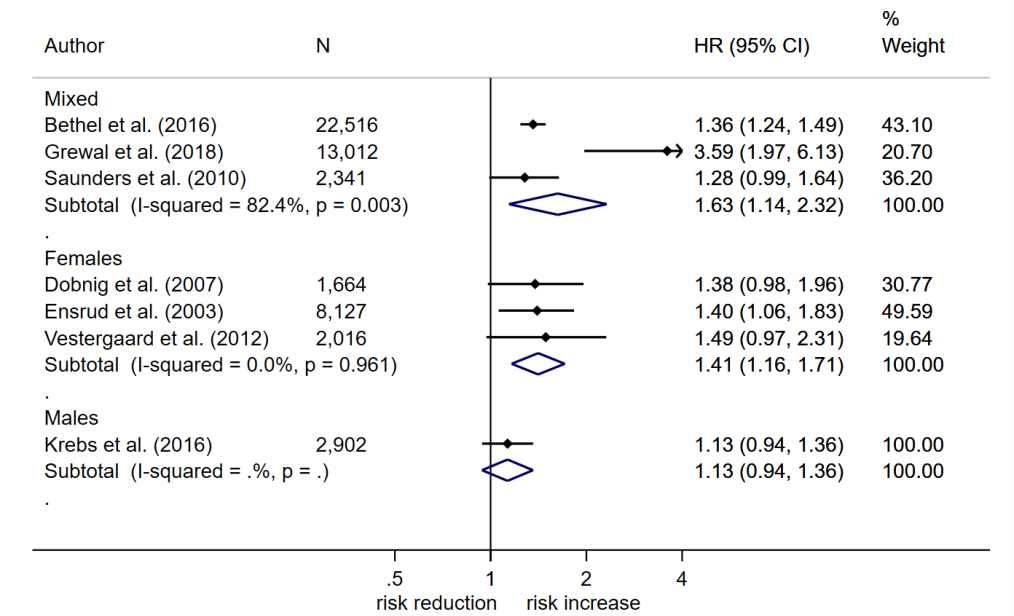
Note: Definitions for opioid exposure are outlined in Table 3-5.

Forest plot of cohort studies grouped by definition of opioid exposure

Appendix I. Forest plots of subgroup analyses of cohort studies reporting HRs for fractures of unspecified anatomical sites in opioid use [continued]

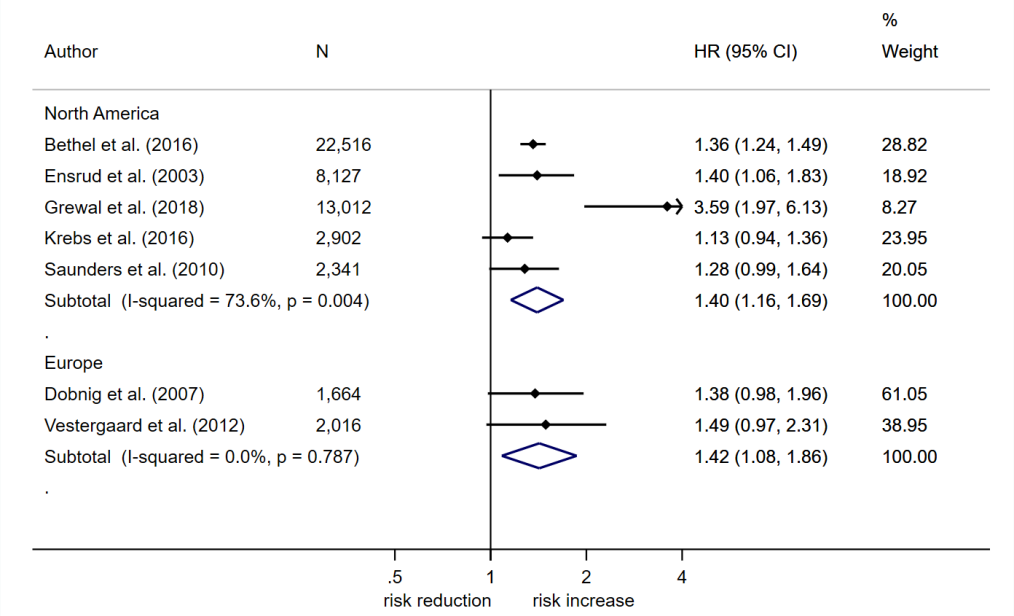


Forest plot of cohort studies grouped by age (years) of inclusion for study population



Forest plot of cohort studies grouped by sex of study population

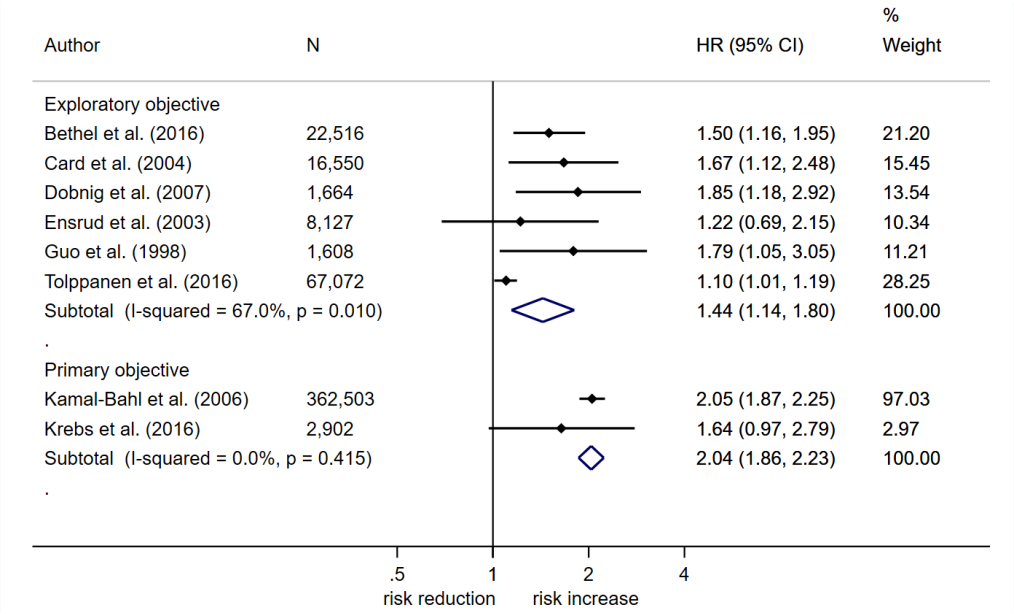
Appendix I. Forest plots of subgroup analyses of cohort studies reporting HRs for fractures of unspecified anatomical sites in opioid use [continued]



Note: North American countries included Canada and the United States of America; European countries included Austria and Denmark

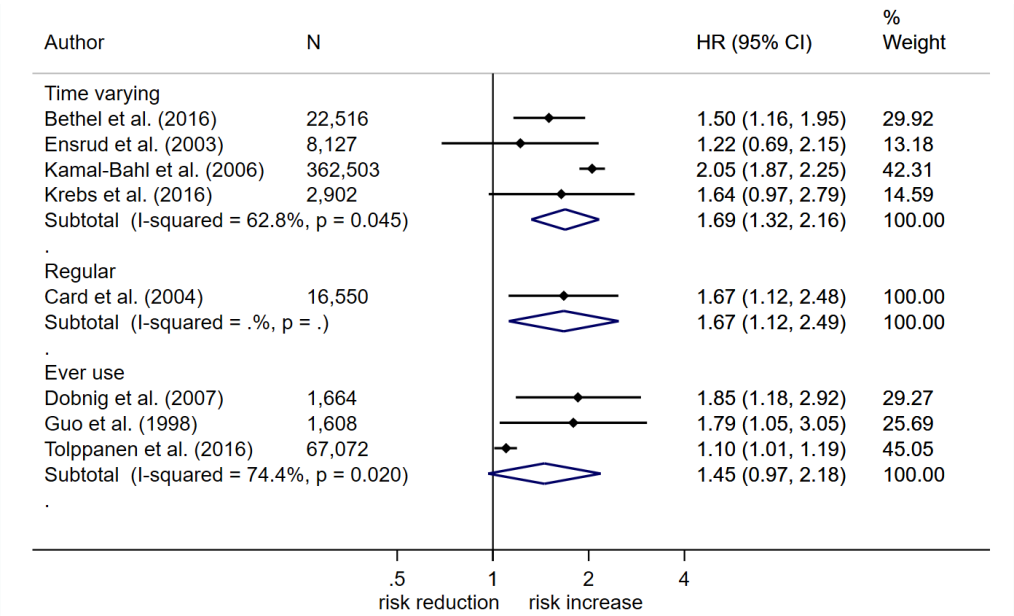
Forest plot of cohort studies grouped by geographical location of study population

Appendix J. Forest plots of subgroup analyses of cohort studies reporting HRs ratios for hip fractures in opioid use



Note: Studies were coded as having a 'primary objective' if their primary objective was to investigate the association between opioid use and fractures.

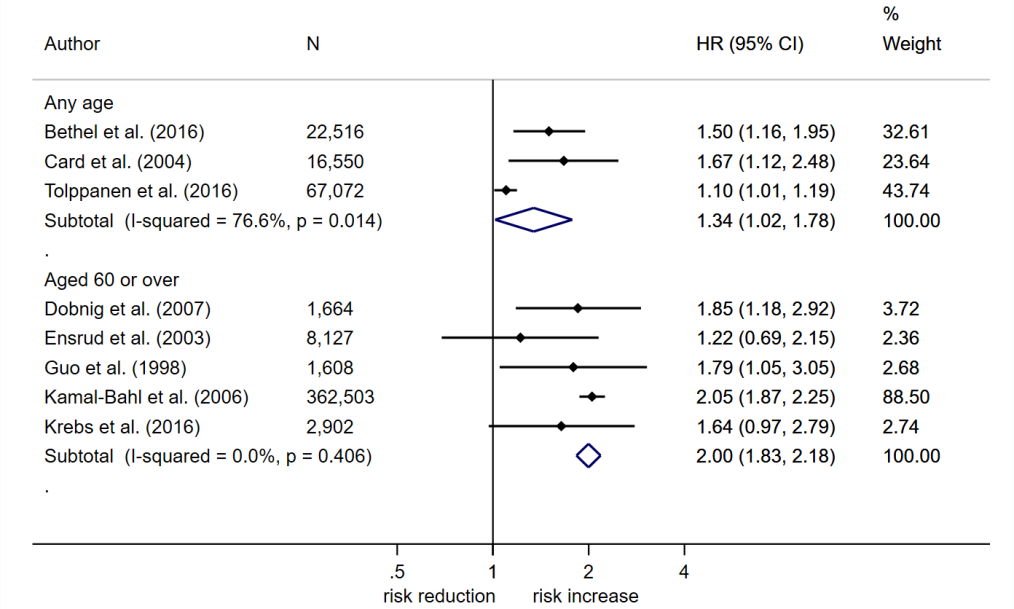
Forest plot of cohort studies grouped by study objective



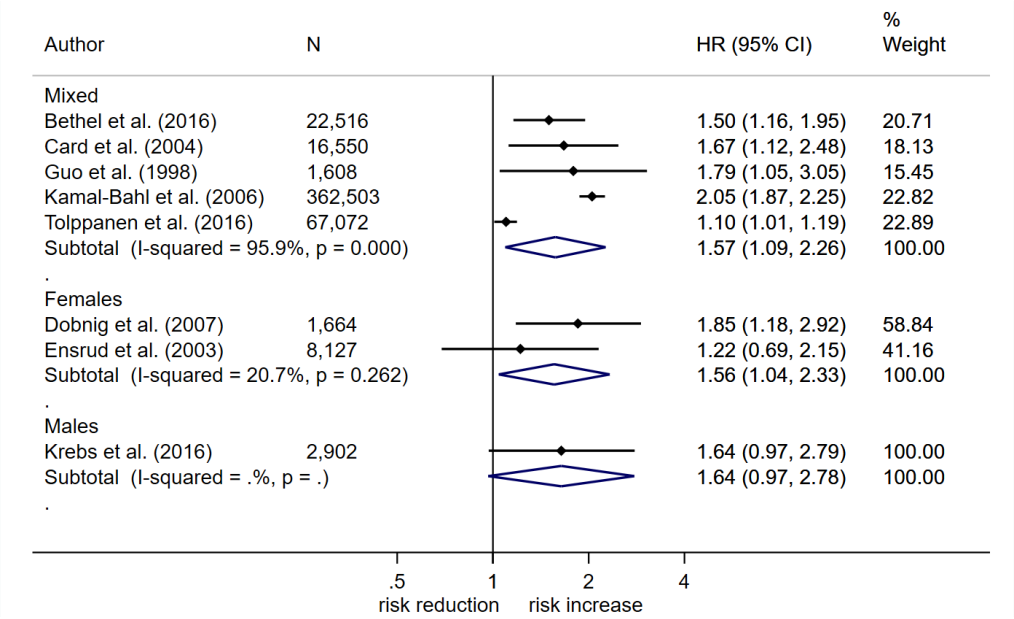
Note: Definitions for opioid exposure are outlined in Table 3-5.

Forest plot of cohort studies grouped by definition of opioid exposure

Appendix J. Forest plots of subgroup analyses of cohort studies reporting HRs ratios for hip fractures in opioid use [continued]

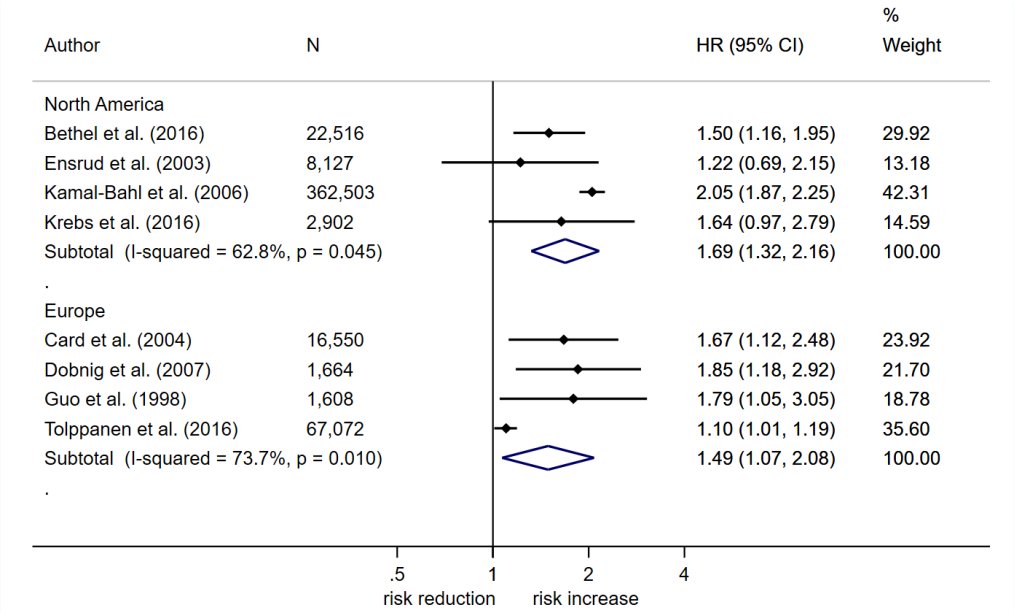


Forest plot of cohort studies grouped by age (years) of inclusion for study population.



Forest plot of cohort studies grouped by sex of study population.

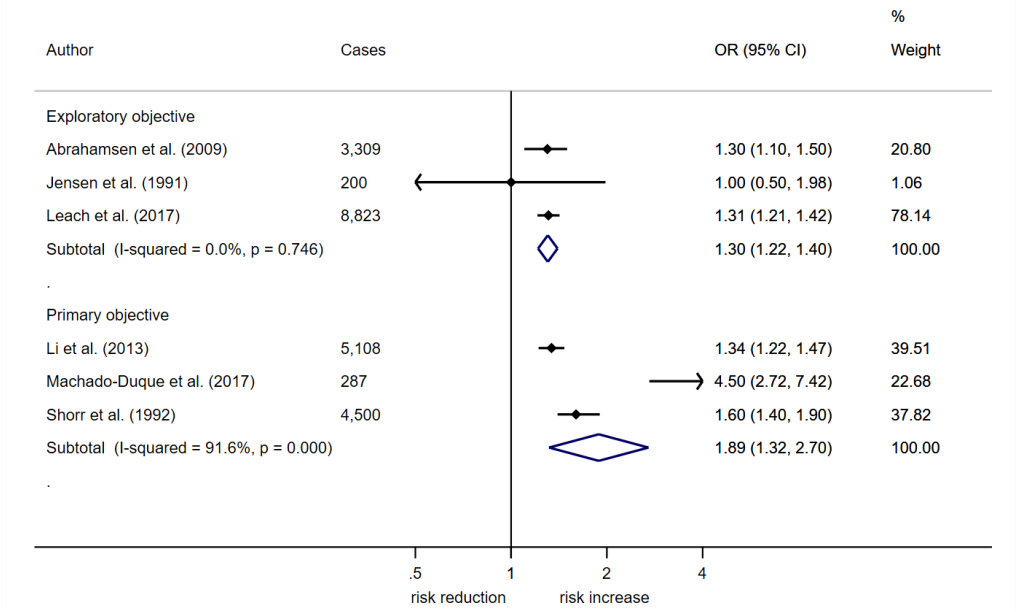
Appendix J. Forest plots of subgroup analyses of cohort studies reporting HRs ratios for hip fractures in opioid use [continued]



Note: North American countries included Canada and the United States of America; European countries included United Kingdom, Austria, Sweden and Finland

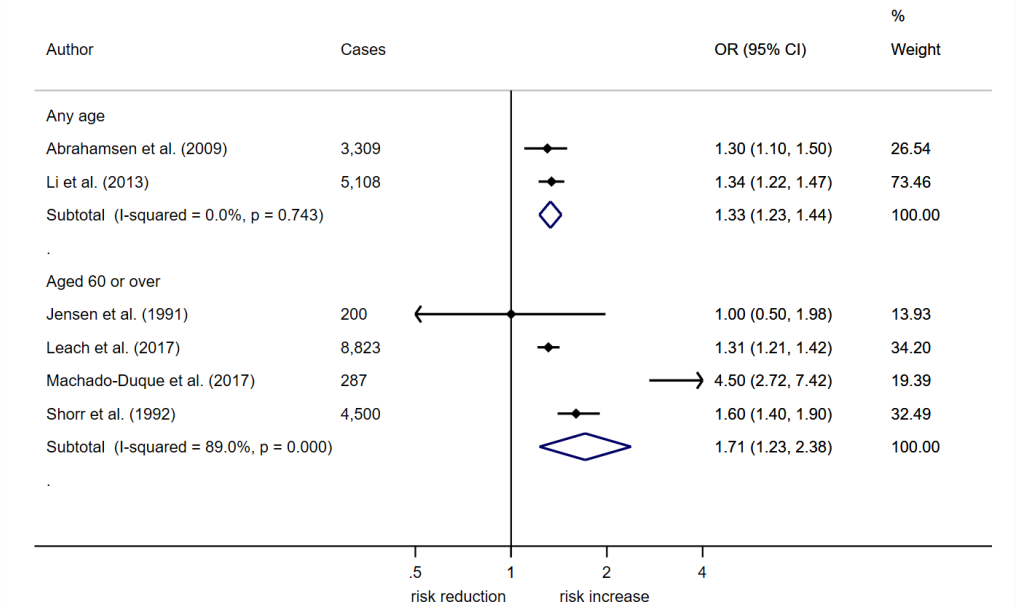
Forest plot of cohort studies grouped by geographical location of study population

Appendix K. Forest plots of subgroup analyses of case-control and nested case-control studies reporting ORs for hip fractures in opioid use



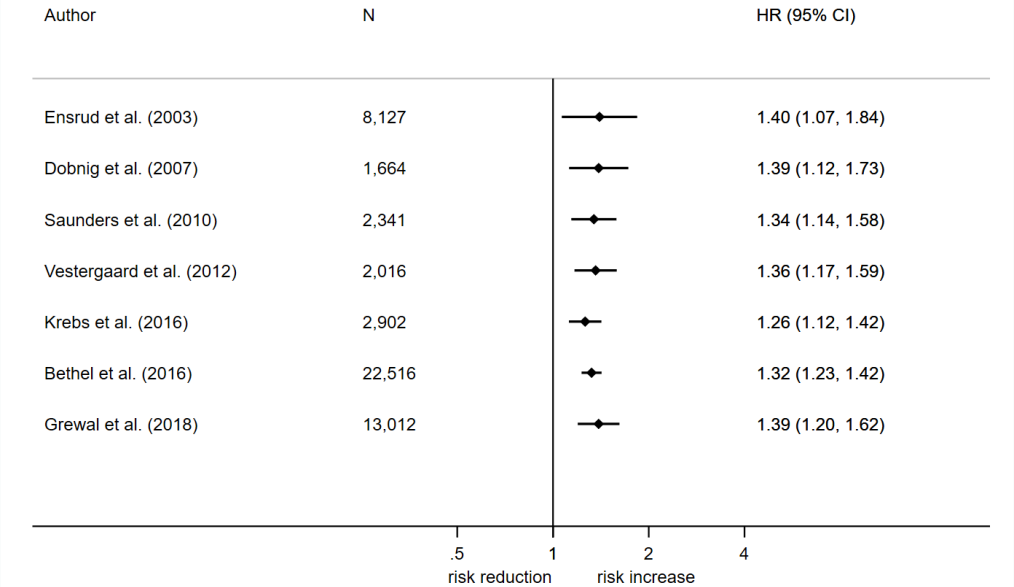
Note: studies were coded as having a ‘primary objective’ if their primary objective was to investigate the association between opioid use and fractures.

Forest plot of case-control and nested case-control studies grouped by study objective

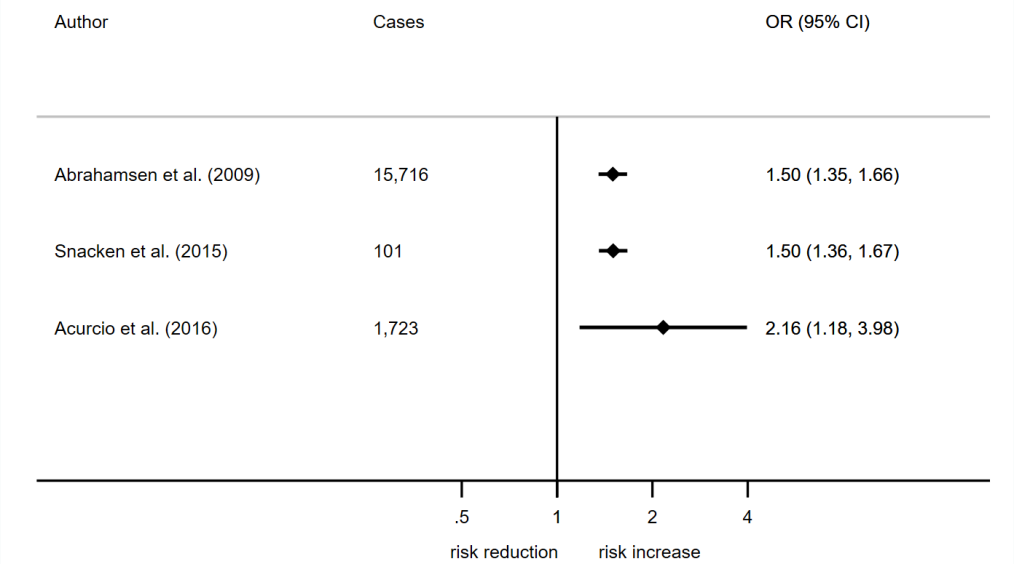


Forest plot of case-control and nested case-control studies grouped by age (years) of inclusion for study population

Appendix L. Cumulative meta-analyses of studies reporting risk estimates for fractures of an unspecified anatomical site in opioid use

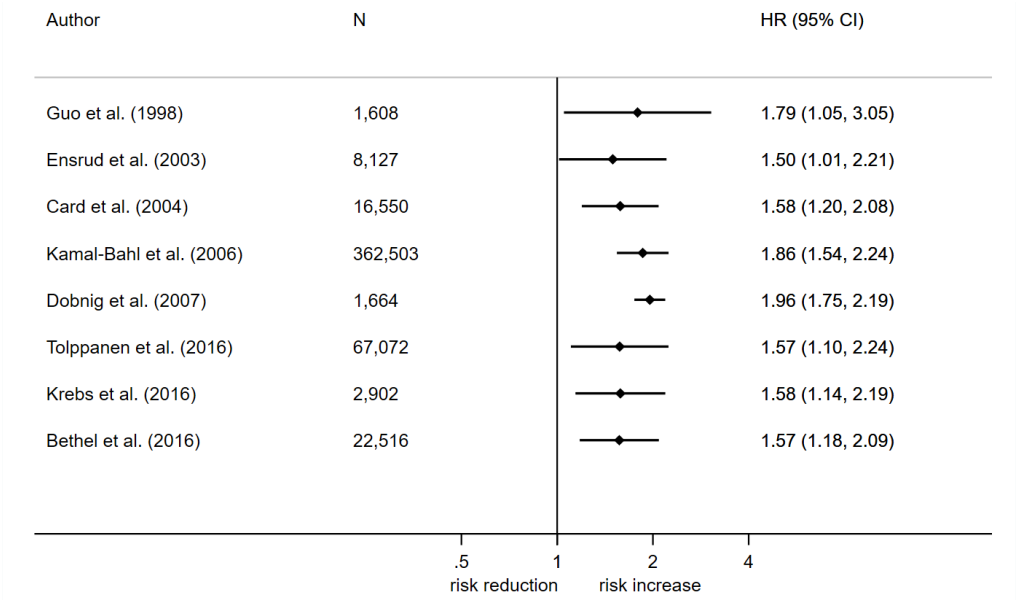


Forest plot of cohort studies reporting HRs for risk of fractures of an unspecified site, by study publication year

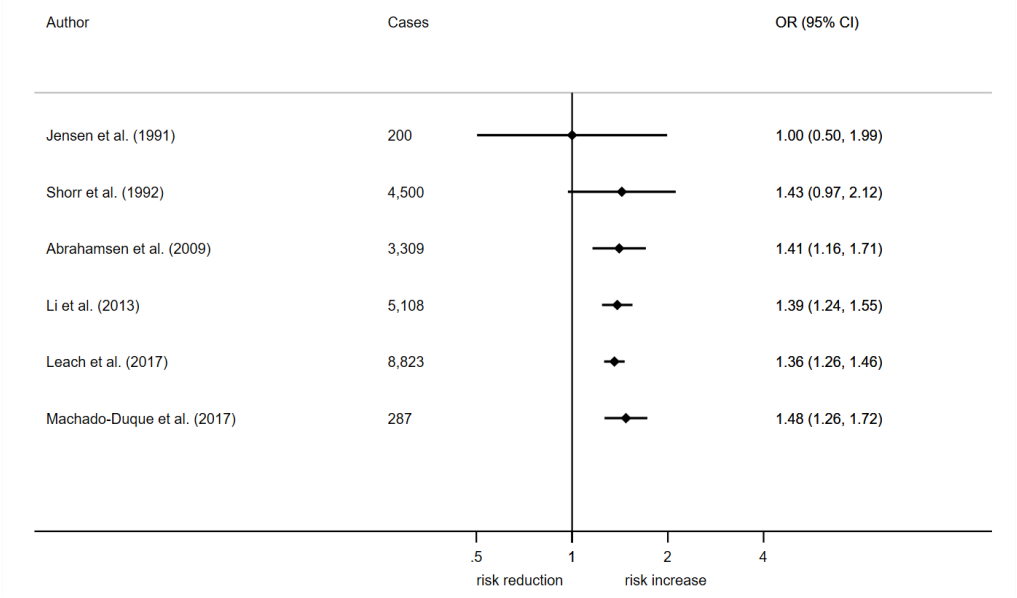


Forest plot of case-control and nested case-control studies reporting ORs for risk of fractures of an unspecified site, by study publication year

Appendix M. Cumulative meta-analyses of studies reporting risk estimates for hip fractures in opioid use



Forest plot of cohort studies reporting HRs for risk of hip fractures, by study publication year



Forest plot of case-control and nested case-control studies reporting ORs for risk of hip fractures, by study publication year

Appendix N. ISAC protocol approval notification

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL			***by e-mail***
PROTOCOL NO:	18_282R		
PROTOCOL TITLE:	The association between prescription opioids and risk of bone fracture: a self-controlled case series study using the Clinical Practice Research Datalink		
APPLICANT:	Dr Roger Knaggs University of Nottingham roger.knaggs@nottingham.ac.uk		
APPROVED ☒	**APPROVED WITH COMMENTS (resubmission not required)** ☐	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐
INSTRUCTIONS: ***Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.*** **REVIEWER COMMENTS:** **APPLICANT FEEDBACK:**			
DATE OF ISAC FEEDBACK:	21/01/19		
DATE OF APPLICANT FEEDBACK:			

For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.

Guidance on resubmitting applications, or making amendments to approved protocols, can be found on the CPRD website at https://cprd.com/research-applications.

Appendix O. Opioid product codes

Drug	Code	Product name
Alfentanil	37251	Alfentanil 0.1% nasal spray
Alfentanil	56581	Alfentanil 5mg/5ml buccal spray
Buprenorphine	66689	Butec 5micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)
Buprenorphine	68479	Bupeaze 70micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)
Buprenorphine	13300	BuTrans 20micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
Buprenorphine	56671	BuTrans 5micrograms/hour transdermal patches (Waymade Healthcare Plc)
Buprenorphine	68241	Reletrans 10micrograms/hour transdermal patches (Sandoz Ltd)
Buprenorphine	68743	Bupeaze 35micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)
Buprenorphine	66280	BuTrans 15micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
Buprenorphine	67356	Transtec 70micrograms/hour transdermal patches (Lexon (UK) Ltd)
Buprenorphine	59473	Hapoctasin 52.5micrograms/hour transdermal patches (Actavis UK Ltd)
Buprenorphine	69315	Butec 15micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)
Buprenorphine	60053	Tephine 200microgram sublingual tablets (Sandoz Ltd)
Buprenorphine	68196	Reletrans 15micrograms/hour transdermal patches (Sandoz Ltd)
Buprenorphine	68402	Panitaz 5micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)
Buprenorphine	68172	Reletrans 20micrograms/hour transdermal patches (Sandoz Ltd)
Buprenorphine	68890	Sevodyne 5micrograms/hour transdermal patches (Aspire Pharma Ltd)
Buprenorphine	69243	Bupeaze 52.5micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)
Buprenorphine	5936	Transtec 35micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
Buprenorphine	68888	Sevodyne 20micrograms/hour transdermal patches (Aspire Pharma Ltd)
Buprenorphine	61100	Tephine 400microgram sublingual tablets (Sandoz Ltd)
Buprenorphine	64155	Buprenorphine 400microgram sublingual tablets sugar free (Teva UK Ltd)
Buprenorphine	59392	Hapoctasin 70micrograms/hour transdermal patches (Actavis UK Ltd)
Buprenorphine	10205	BuTrans 10micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
Buprenorphine	7555	BuTrans 5micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
Buprenorphine	59618	Transtec 35micrograms/hour transdermal patches (Mawdsley-Brooks & Company Ltd)
Buprenorphine	54806	Transtec 52.5micrograms/hour transdermal patches (DE Pharmaceuticals)
Buprenorphine	69942	Buprenorphine 400microgram sublingual tablets sugar free (Phoenix Healthcare Distribution Ltd)
Buprenorphine	396	Buprenorphine 200microgram sublingual tablets sugar free
Buprenorphine	68848	Buplast 52.5micrograms/hour transdermal patches (Mylan Ltd)
Buprenorphine	68167	Reletrans 5micrograms/hour transdermal patches (Sandoz Ltd)
Buprenorphine	6917	Buprenorphine 52.5micrograms/hour transdermal patches
Buprenorphine	8017	Temgesic 400microgram sublingual tablets (Indivior UK Ltd)
Buprenorphine	6040	Transtec 52.5micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
Buprenorphine	67901	Transtec 52.5micrograms/hour transdermal patches (Lexon (UK) Ltd)
Buprenorphine	11584	Buprenorphine 70micrograms/hour transdermal patches
Buprenorphine	68472	Prenotrix 52.5micrograms/hour transdermal patches (Genesis Pharmaceuticals Ltd)
Buprenorphine	7238	Buprenorphine 20micrograms/hour transdermal patches
Buprenorphine	66470	Butec 10micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)
Buprenorphine	62675	Buprenorphine 200microgram sublingual tablets sugar free (A A H Pharmaceuticals Ltd)
Buprenorphine	7334	Buprenorphine 5micrograms/hour transdermal patches
Buprenorphine	58766	BuTrans 10micrograms/hour transdermal patches (Waymade Healthcare Plc)
Buprenorphine	68559	Panitaz 10micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)
Buprenorphine	66695	Butec 20micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)
Buprenorphine	67018	Buprenorphine 35micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
Buprenorphine	60170	Hapoctasin 35micrograms/hour transdermal patches (Actavis UK Ltd)
Buprenorphine	60943	Transtec 35micrograms/hour transdermal patches (Sigma Pharmaceuticals Plc)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Buprenorphine	3064	Buprenorphine 400microgram sublingual tablets sugar free
Buprenorphine	6181	Transtec 70micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)
Buprenorphine	13031	Subutex 0.4mg sublingual tablets (Indivior UK Ltd)
Buprenorphine	6879	Buprenorphine 35micrograms/hour transdermal patches
Buprenorphine	69795	Prenotrix 35micrograms/hour transdermal patches (Genesis Pharmaceuticals Ltd)
Buprenorphine	68889	Sevodyne 10micrograms/hour transdermal patches (Aspire Pharma Ltd)
Buprenorphine	69254	Buplast 35micrograms/hour transdermal patches (Mylan Ltd)
Buprenorphine	3522	Temgesic 200microgram sublingual tablets (Indivior UK Ltd)
Buprenorphine	66463	Buprenorphine 15micrograms/hour transdermal patches
Buprenorphine	59146	BuTrans 20micrograms/hour transdermal patches (Waymade Healthcare Plc)
Buprenorphine	7236	Buprenorphine 10micrograms/hour transdermal patches
Codeine	56461	Co-codamol 30mg/500mg tablets (Kent Pharmaceuticals Ltd)
Codeine	64108	Codeine 15mg tablets (Crescent Pharma Ltd)
Codeine	58828	Generic Migraleve tablets
Codeine	42792	Codeine 15mg/5ml Oral solution (Actavis UK Ltd)
Codeine	16039	Solpadeine Capsule (GlaxoSmithKline Consumer Healthcare)
Codeine	57865	Co-codamol 30mg/500mg caplets (Actavis UK Ltd)
Codeine	11554	Ibuprofen 200mg / Codeine 12.8mg tablets
Codeine	23952	Panadeine Effervescent tablet (Sanofi-Synthelabo Ltd)
Codeine	34667	Co-codamol 30mg/500mg tablets (A A H Pharmaceuticals Ltd)
Codeine	31577	Co-codamol 30mg/500mg capsules (A A H Pharmaceuticals Ltd)
Codeine	44159	Solpadeine Max soluble tablets (Omega Pharma Ltd)
Codeine	56006	Co-codamol 8mg/500mg tablets (Bristol Laboratories Ltd)
Codeine	46906	Co-codamol 8mg+500mg Effervescent tablet (Numark Management Ltd)
Codeine	27785	Co-codamol 30mg/500mg tablets (Zentiva)
Codeine	41214	Codeine 15mg/5ml Oral solution (Thornton & Ross Ltd)
Codeine	60958	Codeine 15mg tablets (DE Pharmaceuticals)
Codeine	28784	Codeine phosphate 8mg with aspirin 400mg tablets
Codeine	57381	Codeine 60mg tablets (Teva UK Ltd)
Codeine	61091	Codeine 60mg tablets (Waymade Healthcare Plc)
Codeine	29342	Co-codamol 8mg+500mg Tablet (M & A Pharmachem Ltd)
Codeine	656	Tylex 30mg/500mg capsules (UCB Pharma Ltd)
Codeine	27784	Co-codamol 8mg/500mg tablets (Actavis UK Ltd)
Codeine	11325	Paracetamol 500mg with codeine phosphate 30 mg tablet
Codeine	60489	Codeine 30mg suppositories
Codeine	3724	Migraleve Yellow tablets (McNeil Products Ltd)
Codeine	14785	Paracetamol500mg with codeine phosphate 15mg tablet
Codeine	43550	Codeine 15mg tablets (Ranbaxy (UK) Ltd)
Codeine	625	Co-codamol 8mg/500mg capsules
Codeine	11009	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg tablet
Codeine	41535	Codeine 30mg tablets (Teva UK Ltd)
Codeine	34172	Codeine 15mg/5ml Oral solution (William Ransom)
Codeine	34552	Codeine 30mg tablets (Actavis UK Ltd)
Codeine	34840	Co-codamol 30mg/500mg tablets (Almus Pharmaceuticals Ltd)
Codeine	55309	Codeine 15mg tablets (Phoenix Healthcare Distribution Ltd)
Codeine	59986	Co-codamol 30mg/500mg tablets (M & A Pharmachem Ltd)
Codeine	51084	Co-codamol 30mg/500mg capsules (AMCo)
Codeine	14912	Codeine phosphate 8mg with Paracetamol 500mg capsules

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Codeine	63900	Co-codamol 8mg/500mg tablets (DE Pharmaceuticals)
Codeine	59442	Co-codamol 30mg/500mg caplets (Phoenix Healthcare Distribution Ltd)
Codeine	46633	Co-codamol 8mg/500mg capsules (A A H Pharmaceuticals Ltd)
Codeine	53600	Codeine 60mg tablets (Alliance Healthcare (Distribution) Ltd)
Codeine	34152	Codeine 15mg/5ml Oral solution (Celltech Pharma Europe Ltd)
Codeine	64387	Co-codamol 30mg/500mg tablets (DE Pharmaceuticals)
Codeine	1640	Kapake 30mg/500mg tablets (Galen Ltd)
Codeine	17158	Panadeine forte Tablet (Sanofi-Synthelabo Ltd)
Codeine	158	Codeine 30mg tablets
Codeine	53679	Co-codamol 30mg/500mg effervescent tablets (A A H Pharmaceuticals Ltd)
Codeine	56817	Codeine 15mg tablets (Almus Pharmaceuticals Ltd)
Codeine	2047	Co-codaprin 8mg with 400mg tablets
Codeine	767	Solpadol 30mg/500mg capsules (Sanofi)
Codeine	67751	Codeine 30mg tablets (Almus Pharmaceuticals Ltd)
Codeine	50659	Codeine 60mg tablets (A A H Pharmaceuticals Ltd)
Codeine	11807	Paracetamol 500mg with codeine 12.8mg tablet
Codeine	46729	Co-codamol 15mg/500mg capsules
Codeine	52966	Generic Solpadeine Plus tablets
Codeine	40663	Co-codamol 30mg/500mg effervescent tablets (Actavis UK Ltd)
Codeine	30123	Panadol Ultra 12.8mg/500mg tablets (GlaxoSmithKline Consumer Healthcare)
Codeine	68252	Co-codamol 30mg/500mg tablets (Bristol Laboratories Ltd)
Codeine	7072	Co-codamol 15mg/500mg tablets
Codeine	48311	Co-codamol 30mg/500mg caplets (Kent Pharmaceuticals Ltd)
Codeine	9432	Aspirin 500mg / Codeine 8mg soluble tablets
Codeine	64545	Co-codamol 8mg/500mg tablets (Aspar Pharmaceuticals Ltd)
Codeine	31700	Codeine 15mg tablets (Actavis UK Ltd)
Codeine	65118	Codeine 30mg tablets (Crescent Pharma Ltd)
Codeine	50468	Codeine 15mg tablets (Alliance Healthcare (Distribution) Ltd)
Codeine	52929	Codeine 15mg tablets (Sigma Pharmaceuticals Plc)
Codeine	63551	Co-codamol 8mg/500mg effervescent tablets (Vantage)
Codeine	11250	Migraleve - 2 8mg+500mg Tablet (Pfizer Consumer Healthcare Ltd)
Codeine	67753	Co-codamol 8mg/500mg tablets (Wockhardt UK Ltd)
Codeine	39340	Co-codamol 8mg/500mg caplets (Vantage)
Codeine	34815	Co-codamol 8mg/500mg tablets (Kent Pharmaceuticals Ltd)
Codeine	47003	Codeine 60mg tablets (Ranbaxy (UK) Ltd)
Codeine	52888	Codeine 15mg tablets (Kent Pharmaceuticals Ltd)
Codeine	51644	Codeine 30mg tablets (Bristol Laboratories Ltd)
Codeine	14964	Solpadeine Plus soluble tablets (Omega Pharma Ltd)
Codeine	58501	Co-codamol 30mg/500mg caplets (AM Distributions (Yorkshire) Ltd)
Codeine	4671	Codeine phosphate 30mg with Paracetamol 500mg capsules
Codeine	810	Co-codamol 30mg/500mg effervescent tablets
Codeine	34437	Codeine 15mg/5ml Oral solution (Nucare Plc)
Codeine	33643	Co-codamol 8mg+500mg Tablet (Family Health)
Codeine	17926	Aspirin 400mg with Codeine 8mg tablets
Codeine	53617	Ibuprofen and codeine 200mg+12.8mg Tablet (Almus Pharmaceuticals Ltd)
Codeine	25109	Veganin tablets (Omega Pharma Ltd)
Codeine	3435	Tylex 30mg/500mg effervescent tablets (UCB Pharma Ltd)
Codeine	59479	Co-codamol 30mg/500mg capsules (Actavis UK Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Codeine	47081	Paracetamol 500mg with codeine phosphate 12.8mg & caffeine 30mg effervescent tablet
Codeine	41275	Co-codamol 8mg+500mg Tablet (Nucare Plc)
Codeine	31871	Paracetamol 450mg with codeine phosphate 8.1mg tablet
Codeine	33679	Co-codamol 8mg/500mg tablets (Zentiva)
Codeine	63658	Co-codaprin 400/8 Tablet (Hillcross Pharmaceuticals Ltd)
Codeine	68861	Codeine 25mg/5ml oral solution (DE Pharmaceuticals)
Codeine	67106	Co-codamol 30mg/500mg caplets (Wockhardt UK Ltd)
Codeine	66115	Codeine 60mg tablets (Kent Pharmaceuticals Ltd)
Codeine	57929	Co-codamol 8mg/500mg capsules (Waymade Healthcare Plc)
Codeine	50421	Codeine phosphate 15mg Tablet (Celltech Pharma Europe Ltd)
Codeine	21703	Paracetamol 1000mg with codeine phosphate 60mg effervescent powder sugar free
Codeine	3185	Paracetamol 500mg with codeine phosphate 30mg capsule
Codeine	53287	Co-codamol 30mg/500mg effervescent tablets (Alliance Healthcare (Distribution) Ltd)
Codeine	9462	Paracetamol 500mg with codeine phosphate 8mg effervescent tablet
Codeine	68509	Codeine phosphate 30mg Tablet (Celltech Pharma Europe Ltd)
Codeine	25529	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg tablet
Codeine	48775	Co-codamol 30mg/500mg caplets (AMCo)
Codeine	64726	Co-codamol 15mg/500mg tablets (Galen Ltd)
Codeine	38085	Paracetamol 500mg with codeine phosphate 10mg capsule
Codeine	7542	Codeine phosphate 8mg with paracetamol 500mg tablets
Codeine	11665	Zapain 30mg/500mg tablets (AMCo)
Codeine	46511	Co-codamol 15mg/500mg effervescent tablets sugar free
Codeine	55044	Co-codamol 30mg/500mg caplets (Waymade Healthcare Plc)
Codeine	34968	Co-codamol 8mg/500mg tablets (Teva UK Ltd)
Codeine	39461	Solpadeine Migraine Ibuprofen & Codeine tablets (Omega Pharma Ltd)
Codeine	57752	Codeine 10mg/5ml oral solution
Codeine	539	Codeine 60mg tablets
Codeine	24125	Codeine 15mg/5ml Oral solution (Approved Prescription Services Ltd)
Codeine	53702	Co-codamol 30mg/500mg tablets (Actavis UK Ltd)
Codeine	31943	Codeine 30mg tablets (IVAX Pharmaceuticals UK Ltd)
Codeine	34789	Codeine 30mg tablets (Kent Pharmaceuticals Ltd)
Codeine	61647	Co-codamol 15mg/500mg tablets (Alliance Healthcare (Distribution) Ltd)
Codeine	17563	Solpadeine Max 12.8mg/500mg tablets (Omega Pharma Ltd)
Codeine	1616	Migraleve Pink tablets (McNeil Products Ltd)
Codeine	9516	Kapake 30mg/500mg capsules (Galen Ltd)
Codeine	800	Co-codamol 30mg/500mg capsules
Codeine	68538	Codeine 30mg/5ml oral solution
Codeine	16467	Codeine phosphate 30mg with paracetamol 500mg effervescent tablets
Codeine	25514	Paracetamol 500mg with codeine phosphate 10mg tablet
Codeine	4805	Codeine phosphate 15mg/5ml diabetic oral solution
Codeine	66904	Co-codamol 8mg/500mg caplets (Wockhardt UK Ltd)
Codeine	46987	Co-codamol 15mg+500mg Tablet (Hillcross Pharmaceuticals Ltd)
Codeine	66602	Generic Solpadeine Max soluble tablets sugar free
Codeine	57	Co-codamol 8mg/500mg effervescent tablets
Codeine	51937	Codeine 15mg tablets (Bristol Laboratories Ltd)
Codeine	57353	Co-codamol 30mg/500mg caplets (DE Pharmaceuticals)
Codeine	65314	Co-codamol 8mg/500mg caplets (Actavis UK Ltd)
Codeine	15831	Codeine phosphate 30mg with paracetamol 500mg effervescent powder sugar free

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Codeine	66352	Co-codamol 8mg/500mg caplets (Kent Pharmaceuticals Ltd)
Codeine	47952	Codeine phosphate 30mg Tablet (Wockhardt UK Ltd)
Codeine	46898	Codipar 15mg/500mg capsules (AMCo)
Codeine	66893	Codeine 15mg tablets (Mawdsley-Brooks & Company Ltd)
Codeine	34497	Co-codamol 8mg+500mg Tablet (Berk Pharmaceuticals Ltd)
Codeine	47508	Codipar 15mg/500mg effervescent tablets (AMCo)
Codeine	64752	Codeine 30mg tablets (Sigma Pharmaceuticals Plc)
Codeine	2794	Co-codamol 30mg/500mg tablets (Wockhardt UK Ltd)
Codeine	3713	Medocodene Tablet (Manufacturer unknown)
Codeine	213	Codeine 25mg/5ml oral solution
Codeine	9460	Paracetamol 500mg with codeine phosphate 8mg capsule
Codeine	65269	Codeine 60mg tablets (DE Pharmaceuticals)
Codeine	19	Co-codamol 8mg/500mg tablets
Codeine	15779	Codeine 8mg with aspirin 500mg soluble tablets
Codeine	69576	Codeine 10mg/5ml oral suspension
Codeine	56559	Codeine 30mg tablets (Phoenix Healthcare Distribution Ltd)
Codeine	32692	Co-codamol 8mg/500mg effervescent tablets (A A H Pharmaceuticals Ltd)
Codeine	34383	Codeine 30mg tablets (A A H Pharmaceuticals Ltd)
Codeine	8329	Solpadeine Tablet (GlaxoSmithKline Consumer Healthcare)
Codeine	31155	Parake Tablet (Galen Ltd)
Codeine	40385	Co-codamol 8mg/500mg effervescent tablets (Almus Pharmaceuticals Ltd)
Codeine	7518	Aspirin 400mg with Codeine 8mg dispersible tablets
Codeine	34845	Co-codamol 30mg/500mg effervescent tablets (Zentiva)
Codeine	1527	Migraleve tablets (McNeil Products Ltd)
Codeine	41259	Co-codamol 30mg/500mg effervescent tablets (Teva UK Ltd)
Codeine	59131	Co-codamol 8mg/500mg capsules (Bayer Plc)
Codeine	18221	Codeine phosphate 15mg with paracetamol 500mg tablets
Codeine	52889	Codeine 25mg/5ml oral solution (A A H Pharmaceuticals Ltd)
Codeine	43244	Co-codamol 30mg+500mg Effervescent tablet (Hillcross Pharmaceuticals Ltd)
Codeine	38088	Paracetamol 500mg with codeine phosphate 30 mg tablet
Codeine	57900	Co-codamol 30mg/500mg caplets (A A H Pharmaceuticals Ltd)
Codeine	56565	Co-codamol 15mg/500mg tablets (A A H Pharmaceuticals Ltd)
Codeine	10602	Paracodol 8mg/500mg effervescent tablets (Bayer Plc)
Codeine	41276	Co-codamol 8mg/500mg tablets (Almus Pharmaceuticals Ltd)
Codeine	51327	Codeine 30mg tablets (Alliance Healthcare (Distribution) Ltd)
Codeine	57839	Co-codamol 15mg/500mg tablets (Waymade Healthcare Plc)
Codeine	20127	Codeine phosphate 8mg with aspirin 400mg with caffeine dispersible tablets
Codeine	69066	Codeine 5mg/5ml oral suspension
Codeine	51819	Co-codamol 8mg/500mg capsules (Phoenix Healthcare Distribution Ltd)
Codeine	58288	Co-codamol 30mg/500mg capsules (DE Pharmaceuticals)
Codeine	62228	Codeine 30mg tablets (DE Pharmaceuticals)
Codeine	21880	Zapain 30mg/500mg capsules (AMCo)
Codeine	48004	Codeine 30mg tablets (Ranbaxy (UK) Ltd)
Codeine	2917	Paracetamol 500mg with codeine phosphate 30 mg tablet
Codeine	56340	Co-codamol 30mg/500mg caplets (J M McGill Ltd)
Codeine	65806	Co-codamol 8mg/500mg tablets (Alliance Healthcare (Distribution) Ltd)
Codeine	16818	Paracetamol 500mg with codeine phosphate 30mg effervescent powder sugar free
Codeine	35792	Codeine 25mg/5ml oral solution (Thornton & Ross Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Codeine	4369	Galcodine 3mg/5ml Oral solution (Thornton & Ross Ltd)
Codeine	9457	Paracetamol 500mg with codeine phosphate 8mg tablet
Codeine	14676	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg effervescent tablet
Codeine	63683	Aspirin with codeine Dispersible tablet (Actavis UK Ltd)
Codeine	36608	Co-codamol Effervescent tablet (A A H Pharmaceuticals Ltd)
Codeine	44210	Kapake 15mg/500mg tablets (Galen Ltd)
Codeine	29488	Co-codamol 8mg/500mg effervescent tablets (Zentiva)
Codeine	66538	Co-codamol 8mg/500mg capsules (Alliance Healthcare (Distribution) Ltd)
Codeine	66553	Co-codamol 30mg/500mg effervescent tablets (AMCo)
Codeine	55465	Co-codamol 30mg/500mg capsules (Sigma Pharmaceuticals Plc)
Codeine	58855	Co-codamol 30mg/500mg capsules (Waymade Healthcare Plc)
Codeine	56266	Co-codamol 30mg/500mg tablets (Alliance Healthcare (Distribution) Ltd)
Codeine	43414	Co-codamol 8mg/500mg effervescent tablets (Bayer Plc)
Codeine	96	Co-codamol 30mg/500mg tablets
Codeine	12709	Ibuprofen and codeine 200mg + 12.5mg Tablet
Codeine	57487	Codeine 30mg tablets (Waymade Healthcare Plc)
Codeine	3156	Solpadol 30mg/500mg caplets (Sanofi)
Codeine	57097	Co-codamol 30mg/500mg capsules (Alliance Healthcare (Distribution) Ltd)
Codeine	41416	Codeine 60mg tablets (Wockhardt UK Ltd)
Codeine	6886	Codeine phosphate 30mg with paracetamol 500mg tablets
Codeine	48153	Codeine 60mg tablets (Actavis UK Ltd)
Codeine	47919	Codeine phosphate 15mg Tablet (Wockhardt UK Ltd)
Codeine	9742	Solpadeine Soluble tablet (GlaxoSmithKline Consumer Healthcare)
Codeine	2846	Paracetamol 500mg with codeine phosphate 30mg effervescent tablet
Codeine	40662	Co-codamol 8mg/500mg effervescent tablets (Actavis UK Ltd)
Codeine	10176	Codipar 15mg/500mg tablets (AMCo)
Codeine	41682	Co-codamol 30mg+500mg Effervescent tablet (Roche Consumer Health)
Codeine	8246	Codeine phosphate 8mg with paracetamol 500mg effervescent tablets
Codeine	34229	Co-codamol 8mg+500mg Dispersible tablet (Rhone-Poulenc Rorer Ltd)
Codeine	69304	Co-codamol 15mg/500mg tablets (Actavis UK Ltd)
Codeine	22764	Panadeine Tablet (GlaxoSmithKline UK Ltd)
Codeine	59705	Co-codamol 8mg/500mg capsules (DE Pharmaceuticals)
Codeine	44924	Co-codamol 30mg/500mg tablets (Teva UK Ltd)
Codeine	52085	Co-codamol 30mg/500mg effervescent tablets (Zanza Laboratories Ltd)
Codeine	65245	Codeine 30mg tablets (Mawdsley-Brooks & Company Ltd)
Codeine	20565	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg capsule
Codeine	60517	Co-codamol 30mg/500mg effervescent tablets (Almus Pharmaceuticals Ltd)
Codeine	8335	Paracodol 8mg/500mg capsules (Bayer Plc)
Codeine	56549	Co-codamol 8mg/500mg effervescent tablets (Waymade Healthcare Plc)
Codeine	382	Codeine 15mg tablets
Codeine	56171	Co-codamol 30mg/500mg capsules (Kent Pharmaceuticals Ltd)
Codeine	34176	Codeine 15mg/5ml Oral solution (Rusco Ltd)
Codeine	34444	Codeine 15mg tablets (Wockhardt UK Ltd)
Codeine	10226	Solpadeine Plus tablets (Omega Pharma Ltd)
Codeine	31452	Codeine 30mg tablets (Wockhardt UK Ltd)
Codeine	21673	Paracetamol 500mg with codeine phosphate 8mg & caffeine 30mg effervescent tablet
Codeine	65904	Co-codamol 8mg/500mg capsules (Sigma Pharmaceuticals Plc)
Codeine	37904	Co-codamol 12.8mg/500mg tablets

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Codeine	51381	Generic Solpadeine Plus capsules
Codeine	23420	Codeine phosphate 60mg with paracetamol 1000mg effervescent powder sugar free
Codeine	13893	Nurofen Plus tablets (Reckitt Benckiser Healthcare (UK) Ltd)
Codeine	16096	Codeine 6.75mg/5ml oral solution
Codeine	58636	Co-codamol 8mg/500mg effervescent tablets (Teva UK Ltd)
Codeine	56205	Boots Paracetamol and Codeine Extra capsules (The Boots Company Plc)
Codeine	34518	Co-codamol 8mg/500mg tablets (A A H Pharmaceuticals Ltd)
Codeine	34348	Codeine 15mg tablets (A A H Pharmaceuticals Ltd)
Codeine	10178	Solpadeine Plus capsules (Omega Pharma Ltd)
Codeine	2211	Solpadol 30mg/500mg effervescent tablets (Sanofi)
Codeine	41599	Codeine 15mg tablets (Teva UK Ltd)
Codeine	36993	Co-codamol 30mg/500mg capsules (Teva UK Ltd)
Codeine	60640	Codeine 15mg tablets (Waymade Healthcare Plc)
Codeine	53999	Codeine phosphate 60mg Tablet (Wockhardt UK Ltd)
Codeine	65092	Co-codamol 30mg/500mg caplets (Mawdsley-Brooks & Company Ltd)
Codeine	69285	Boots Ibuprofen and Codeine 200mg/12.8mg tablets (The Boots Company Plc)
Codeine	34865	Co-codamol 8mg+500mg Tablet (C P Pharmaceuticals Ltd)
Codeine	57465	Co-codamol 8mg/500mg caplets (DE Pharmaceuticals)
Codeine	38363	Codeine phosphate 12.8mg with paracetamol 500mg tablets
Codeine	21251	Ultramol Soluble tablets (Zentiva)
Codeine	60040	Generic Migraleve Pink tablets
Codeine	47847	Co-codamol 30mg/500mg capsules (Zentiva)
Codeine Phosphate/Papaverine Hydrochloride/Morphine Hydrochloride	19764	Papaveretum 10mg tablet
Codeine Phosphate/Papaverine Hydrochloride/Morphine Hydrochloride	19317	Omnopon 10mg Tablet (Roche Products Ltd)
Dextromoramide	4236	Palfium 5mg tablets (Roche Products Ltd)
Dextromoramide	39419	Palfium 5mg Tablet (IDIS World Medicines)
Dextromoramide	3990	Dextromoramide 5mg tablets
Dextropropoxyphene	28253	Co-proxamol 32.5/325 Oral suspension (Rosemont Pharmaceuticals Ltd)
Dextropropoxyphene	18482	Paracetamol 325mg with dextropropoxyphene 32.5mg tablet
Dextropropoxyphene	12076	Dextropropoxyphene 60mg capsules
Dextropropoxyphene	45231	Co-proxamol 32.5mg+325mg Tablet (Regent Laboratories Ltd)
Dextropropoxyphene	2462	Cosalgesic Tablet (Actavis UK Ltd)
Dextropropoxyphene	43536	Co-proxamol 32.5/325 Tablet (Numark Management Ltd)
Dextropropoxyphene	34546	Co-proxamol 32.5mg+325mg Tablet (Neo Laboratories Ltd)
Dextropropoxyphene	33995	Co-proxamol 32.5/325 Tablet (Berk Pharmaceuticals Ltd)
Dextropropoxyphene	34554	Co-proxamol 32.5/325 Tablet (C P Pharmaceuticals Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Dextropropoxyphene	483	Co-proxamol (dextropropoxyphene and paracetamol) 32.5mg with 325mg/5ml oral suspension sugar free
Dextropropoxyphene	34397	Co-proxamol 32.5mg+325mg Tablet (M & A Pharmachem Ltd)
Dextropropoxyphene	45276	Co-proxamol 32.5mg+325mg Tablet (Sigma Pharmaceuticals Plc)
Dextropropoxyphene	30966	Co-proxamol 32.5/325 Tablet (Dista Products Ltd)
Dextropropoxyphene	1762	Dextropropoxyphene HCl with paracetamol 32.5mg with 325mg tablets
Dextropropoxyphene	25979	Doloxene 60mg Capsule (Eli Lilly and Company Ltd)
Dextropropoxyphene	4607	Co-proxamol 32.5/325 Tablet (Dista Products Ltd)
Diamorphine	30761	Diamorphine 10mg/5ml Oral solution (Manufacturer unknown)
Diamorphine	58279	Diamorphine 10mg tablets (A A H Pharmaceuticals Ltd)
Diamorphine	13420	Diamorphine 15mg/5ml Oral solution (Manufacturer unknown)
Diamorphine	31033	Diamorphine hydrochloride 3mg/5ml oral solution
Diamorphine	28711	Diamorphine hydrochloride bpc 1973 3mg/5ml oral solution
Diamorphine	18792	Diamorphine 10mg tablets
Diamorphine	9945	Diamorphine 10mg Tablet (Aurum Pharmaceuticals Ltd)
Diamorphine	15339	Diamorphine 10mg/5ml oral solution
Diamorphine	7114	Diamorphine 3mg/5ml oral solution
Diamorphine	8735	Diamorphine 5mg/5ml Oral solution (Manufacturer unknown)
Diamorphine	8866	Diamorphine 10mg Tablet (Manufacturer unknown)
Diamorphine	31960	Diamorphine 15mg/5ml oral solution
Diamorphine	58499	Diamorphine 3mg/5ml oral solution
Diamorphine	29500	Diamorphine 5mg/5ml oral solution
Dihydrocodeine	38970	DF 118 Forte 40mg tablets (Martindale Pharmaceuticals Ltd)
Dihydrocodeine	33340	Co-dydramol 10mg+500mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
Dihydrocodeine	65689	Dihydrocodeine 30mg/5ml oral solution
Dihydrocodeine	40159	Dihydrocodeine 10mg/5ml oral solution (Martindale Pharmaceuticals Ltd)
Dihydrocodeine	64074	Co-dydramol 10mg/500mg tablets (DE Pharmaceuticals)
Dihydrocodeine	55530	Co-dydramol 10mg/500mg tablets (Phoenix Healthcare Distribution Ltd)
Dihydrocodeine	34579	Dihydrocodeine 30mg tablets (Actavis UK Ltd)
Dihydrocodeine	65035	Co-dydramol 10mg/500mg tablets (Almus Pharmaceuticals Ltd)
Dihydrocodeine	64368	Paracetamol 500mg / Dihydrocodeine 30mg tablets (Icarus Pharmaceuticals Ltd)
Dihydrocodeine	59989	Dihydrocodeine 30mg tablets (Ranbaxy (UK) Ltd)
Dihydrocodeine	47071	Co-dydramol (dihydrocodeine and paracetamol) 10mg with 500mg/5ml oral suspension
Dihydrocodeine	34440	Dihydrocodeine 30mg tablets (A A H Pharmaceuticals Ltd)
Dihydrocodeine	33654	Dihydrocodeine 30mg tablets (Wockhardt UK Ltd)
Dihydrocodeine	3698	Df118 40mg Tablet (Martindale Pharmaceuticals Ltd)
Dihydrocodeine	34008	Dihydrocodeine 30mg tablets (IVAX Pharmaceuticals UK Ltd)
Dihydrocodeine	21113	Dihydrocodeine with paracetamol forte 30mg with 500mg effervescent tablets
Dihydrocodeine	48133	Dihydrocodeine 30mg tablets (Almus Pharmaceuticals Ltd)
Dihydrocodeine	28780	Co-dydramol 10mg/500mg tablets (A A H Pharmaceuticals Ltd)
Dihydrocodeine	58848	Dypracet 30mg/500mg tablets (Auden McKenzie (Pharma Division) Ltd)
Dihydrocodeine	9785	Remedeine 30mg+500mg Tablet (Napp Pharmaceuticals Ltd)
Dihydrocodeine	43441	Co-dydramol 10mg+500mg Tablet (Celltech Pharma Europe Ltd)
Dihydrocodeine	62635	Co-dydramol 10mg/500mg tablets (Alliance Healthcare (Distribution) Ltd)
Dihydrocodeine	9313	Dihydrocodeine 90mg modified-release tablets

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Dihydrocodeine	30165	Co-dydramol (dihydrocodeine and paracetamol) 7.46mg with 500mg tablets
Dihydrocodeine	54713	Dypracet 20mg/500mg tablets (Auden McKenzie (Pharma Division) Ltd)
Dihydrocodeine	10023	Dihydrocodeine with paracetamol 20mg+500mg tablets
Dihydrocodeine	57197	Co-dydramol 10mg/500mg tablets (Waymade Healthcare Plc)
Dihydrocodeine	14688	Paracetamol 500mg with dihydrocodeine 10mg tablet
Dihydrocodeine	191	Dihydrocodeine 10mg/5ml oral solution
Dihydrocodeine	2555	Dihydrocodeine with paracetamol 10mg+500mg tablets
Dihydrocodeine	38950	Remedeine Forte tablets (Crescent Pharma Ltd)
Dihydrocodeine	19206	Paracetamol 500mg / Dihydrocodeine 7.46mg tablets
Dihydrocodeine	4950	Dihydrocodeine with paracetamol 30mg+500mg tablets
Dihydrocodeine	4823	Dihydrocodeine 40mg tablets
Dihydrocodeine	53	Dihydrocodeine 30mg tablets
Dihydrocodeine	9855	Paracetamol 500mg / Dihydrocodeine 20mg tablets
Dihydrocodeine	28598	Paracetamol with dihydrocodeine 500mg +10mg/5ml suspension sugar free
Dihydrocodeine	59978	Dihydrocodeine 30mg tablets (Waymade Healthcare Plc)
Dihydrocodeine	6234	Dihydrocodeine 120mg modified-release tablets
Dihydrocodeine	9275	DHC Continus 120mg tablets (Napp Pharmaceuticals Ltd)
Dihydrocodeine	9562	Remedeine 30mg+500mg Effervescent tablet (Napp Pharmaceuticals Ltd)
Dihydrocodeine	38430	Co-dydramol 10mg+500mg Tablet (Merck Generics (UK) Ltd)
Dihydrocodeine	7063	Co-dydramol 10mg/500mg/5ml oral suspension
Dihydrocodeine	38521	Dihydrocodeine 30mg tablets (Teva UK Ltd)
Dihydrocodeine	66121	Dihydrocodeine 10mg/5ml oral suspension
Dihydrocodeine	61372	Co-dydramol 10mg/500mg tablets (Kent Pharmaceuticals Ltd)
Dihydrocodeine	55425	Dihydrocodeine 10mg tablets
Dihydrocodeine	7469	Df118 10mg/5ml Oral solution (Martindale Pharmaceuticals Ltd)
Dihydrocodeine	34730	Dihydrocodeine 30mg Tablet (Berk Pharmaceuticals Ltd)
Dihydrocodeine	4556	Paramol tablets (SSL International Plc)
Dihydrocodeine	11	Co-dydramol 10mg/500mg tablets
Dihydrocodeine	34939	Co-dydramol 10mg+500mg Tablet (Duncan Flockhart Ltd)
Dihydrocodeine	2041	Dihydrocodeine 60mg modified-release tablets
Dihydrocodeine	34662	Dihydrocodeine 30mg tablets (Mylan Ltd)
Dihydrocodeine	8456	DHC Continus 60mg tablets (Napp Pharmaceuticals Ltd)
Dihydrocodeine	9163	Remedeine 20mg+500mg Effervescent tablet (Napp Pharmaceuticals Ltd)
Dihydrocodeine	32926	Co-dydramol 10mg/500mg tablets (Actavis UK Ltd)
Dihydrocodeine	64079	Dihydrocodeine 10mg/5ml oral solution (Waymade Healthcare Plc)
Dihydrocodeine	34737	Co-dydramol 10mg/500mg tablets (Teva UK Ltd)
Dihydrocodeine	17917	Dihydrocodeine with paracetamol 20mg with 500mg effervescent tablets
Dihydrocodeine	34920	Co-dydramol 10mg+500mg Tablet (Berk Pharmaceuticals Ltd)
Dihydrocodeine	5955	Paracetamol 500mg / Dihydrocodeine 30mg tablets
Dihydrocodeine	39558	Dihydrocodeine 30mg tablets (Zentiva)
Dihydrocodeine	40422	Co-dydramol 10mg/500mg tablets (Zentiva)
Dihydrocodeine	54354	Dihydrocodeine 30mg tablets (Kent Pharmaceuticals Ltd)
Dihydrocodeine	9209	DHC Continus 90mg tablets (Napp Pharmaceuticals Ltd)
Dihydrocodeine	36019	Co-dydramol 10mg+500mg Tablet (M & A Pharmachem Ltd)
Dihydrocodeine	10122	Dihydrocodeine 10mg with paracetamol 500mg/5ml oral suspension sugar free
Dihydrocodeine	42208	Df118 30mg Tablet (Martindale Pharmaceuticals Ltd)
Dihydrocodeine	2040	Remedeine tablets (Crescent Pharma Ltd)
Dihydrocodeine	30295	Dihydrocodeine with paracetamol 7.46mg+500mg tablets

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Dihydrocodeine	15198	Co-dydramol 10mg+500mg Tablet (C P Pharmaceuticals Ltd)
Dihydrocodeine	33743	Dihydrocodeine with paracetamol 7.46mg with 500mg effervescent tablets
Dihydrocodeine	61698	Co-dydramol 10mg/500mg/5ml oral solution
Dihydrocodeine	50532	Dihydrocodeine 30mg tablets (Bristol Laboratories Ltd)
Dihydrocodeine	53079	Co-dydramol 10mg/500mg tablets (Sigma Pharmaceuticals Plc)
Dihydrocodeine	67779	Co-dydramol 10mg/500mg tablets (Wockhardt UK Ltd)
Dipipanone	9001	Diconal tablets (Amdipharm Plc)
Dipipanone	12020	Dipipanone 10mg / Cyclizine 30mg tablets
Dipipanone	38301	Cyclizine 30mg with dipipanone 10mg tablets
Ethylmorphine	34073	Collins 1.5mg/5ml elixir (Collins Elixir Co)
Fentanyl	47759	Fentanyl 400micrograms/dose nasal spray
Fentanyl	38351	Matrifen 75micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	40576	Fentanyl 400microgram buccal tablets sugar free
Fentanyl	48571	Durogesic DTrans 50micrograms transdermal patches (Waymade Healthcare Plc)
Fentanyl	45549	Victanyl 25micrograms/hour transdermal patches (Actavis UK Ltd)
Fentanyl	36040	Matrifen 100micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	60477	Fentanyl 25micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
Fentanyl	63340	Fentanyl 133microgram sublingual tablets sugar free
Fentanyl	40098	Fentanyl 400microgram sublingual tablets sugar free
Fentanyl	42591	Osmanil 25micrograms/hour transdermal patches (Zentiva)
Fentanyl	41161	Osmach 75micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	59482	Fentanyl 37.5microgram/hour transdermal patches
Fentanyl	37719	Fentalis Reservoir 100micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	38031	Mezolar Matrix 25micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	60766	Fentanyl 25micrograms/hour transdermal patches (Waymade Healthcare Plc)
Fentanyl	5657	Durogesic 75micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	39469	Fentanyl 100microgram sublingual tablets sugar free
Fentanyl	11982	Durogesic DTrans 12micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	46657	Fencino 75micrograms/hour transdermal patches (Ethypharm UK Ltd)
Fentanyl	39723	Fentanyl 100microgram buccal tablets sugar free
Fentanyl	4691	Fentanyl 100micrograms/hour transdermal patches
Fentanyl	31053	Tilofyl 25micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
Fentanyl	67474	Opiodur 50micrograms/hour transdermal patches (Pfizer Ltd)
Fentanyl	44837	Victanyl 50micrograms/hour transdermal patches (Actavis UK Ltd)
Fentanyl	46733	Fencino 25micrograms/hour transdermal patches (Ethypharm UK Ltd)
Fentanyl	22066	Tilofyl 50micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
Fentanyl	59057	Fentanyl 400microgram buccal films sugar free
Fentanyl	16618	Tilofyl 75micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
Fentanyl	748	Durogesic 25micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	7082	Durogesic DTrans 25micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	45598	Instanyl 50micrograms/dose nasal spray (Takeda UK Ltd)
Fentanyl	67830	Fentanyl 12micrograms/hour transdermal patches (DE Pharmaceuticals)
Fentanyl	5651	Fentanyl 400microgram lozenges
Fentanyl	59443	Fentanyl 200microgram buccal films sugar free
Fentanyl	67258	Durogesic DTrans 25micrograms transdermal patches (Waymade Healthcare Plc)
Fentanyl	50929	Durogesic DTrans 12micrograms transdermal patches (Mawdsley-Brooks & Company Ltd)
Fentanyl	38553	Mezolar Matrix 100micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	67425	Yemex 25micrograms/hour transdermal patches (Sandoz Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Fentanyl	39180	Mezolar Matrix 50micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	39518	Abstral 100microgram sublingual tablets (Kyowa Kirin Ltd)
Fentanyl	46354	PecFent 400micrograms/dose nasal spray (Kyowa Kirin Ltd)
Fentanyl	61708	Recivit 267microgram sublingual tablets (Grunenthal Ltd)
Fentanyl	11843	Fentanyl 200microgram lozenges
Fentanyl	46658	Fencino 100micrograms/hour transdermal patches (Ethypharm UK Ltd)
Fentanyl	68209	Mylafent 100micrograms/hour transdermal patches (Mylan Ltd)
Fentanyl	42399	Fentanyl 800microgram sublingual tablets sugar free
Fentanyl	757	Fentanyl 50micrograms/hour transdermal patches
Fentanyl	28189	Tilofyl 100micrograms/hour transdermal patches (Tillomed Laboratories Ltd)
Fentanyl	42021	Victanyl 100micrograms/hour transdermal patches (Actavis UK Ltd)
Fentanyl	39799	Abstral 800microgram sublingual tablets (Kyowa Kirin Ltd)
Fentanyl	43617	Instanyl 200micrograms/dose nasal spray (Takeda UK Ltd)
Fentanyl	39756	Abstral 200microgram sublingual tablets (Kyowa Kirin Ltd)
Fentanyl	26021	Actiq 1.6mg lozenges with integral oromucosal applicator (Teva UK Ltd)
Fentanyl	45439	PecFent 100micrograms/dose nasal spray (Kyowa Kirin Ltd)
Fentanyl	55752	Fentanyl 100micrograms/hour transdermal patches (Phoenix Healthcare Distribution Ltd)
Fentanyl	35968	Matrifen 25micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	45092	Fentanyl 200micrograms/dose nasal spray
Fentanyl	41135	Fentanyl 50micrograms/dose nasal spray
Fentanyl	42538	Fentanyl 600microgram buccal tablets sugar free
Fentanyl	42576	Victanyl 75micrograms/hour transdermal patches (Actavis UK Ltd)
Fentanyl	26908	Actiq 800microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
Fentanyl	43152	Osmanil 50micrograms/hour transdermal patches (Zentiva)
Fentanyl	40018	Fentanyl 200microgram buccal tablets sugar free
Fentanyl	37960	Osmach 50micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	29577	Actiq 1.2mg lozenges with integral oromucosal applicator (Teva UK Ltd)
Fentanyl	45460	Osmanil 100micrograms/hour transdermal patches (Zentiva)
Fentanyl	13076	Actiq 200microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
Fentanyl	67766	Fentanyl 75micrograms/hour transdermal patches (Phoenix Healthcare Distribution Ltd)
Fentanyl	10922	Durogesic 100micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	37779	Fentalis Reservoir 25micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	65437	Fentanyl 100micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
Fentanyl	39590	Fentanyl 200microgram sublingual tablets sugar free
Fentanyl	37923	Fentalis Reservoir 50micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	37928	Matrifen 12micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	65168	Mylafent 12micrograms/hour transdermal patches (Mylan Ltd)
Fentanyl	14900	Durogesic DTrans 100micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	36211	Matrifen 50micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	69023	Yemex 100micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	61156	Fentanyl 12micrograms/hour transdermal patches (Waymade Healthcare Plc)
Fentanyl	65646	Fentanyl 267microgram sublingual tablets sugar free
Fentanyl	39987	Abstral 400microgram sublingual tablets (Kyowa Kirin Ltd)
Fentanyl	50671	Fentanyl 12micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
Fentanyl	43089	Instanyl 100micrograms/dose nasal spray (Takeda UK Ltd)
Fentanyl	42590	Osmanil 75micrograms/hour transdermal patches (Zentiva)
Fentanyl	56670	Fentanyl 25micrograms/hour transdermal patches (Sigma Pharmaceuticals Plc)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Fentanyl	15337	Fentanyl 1.2mg lozenges
Fentanyl	45894	Fentanyl 100micrograms/dose nasal spray
Fentanyl	41286	Abstral 300microgram sublingual tablets (Kyowa Kirin Ltd)
Fentanyl	51235	Fentanyl 25micrograms/hour transdermal patches (Phoenix Healthcare Distribution Ltd)
Fentanyl	7107	Durogesic DTrans 50micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	37954	Mezolar Matrix 12micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	46560	Fencino 50micrograms/hour transdermal patches (Ethypharm UK Ltd)
Fentanyl	65359	Mylafent 50micrograms/hour transdermal patches (Mylan Ltd)
Fentanyl	44487	Osmanil 12micrograms/hour transdermal patches (Zentiva)
Fentanyl	38365	Fentalis Reservoir 75micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	18174	Actiq 400microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
Fentanyl	41348	Fentanyl 600microgram sublingual tablets sugar free
Fentanyl	46555	Fentanyl 800microgram buccal tablets sugar free
Fentanyl	47413	Fentanyl 75micrograms/hr Transdermal patch (Sandoz Ltd)
Fentanyl	63139	Fentanyl 12micrograms/hour transdermal patches (Phoenix Healthcare Distribution Ltd)
Fentanyl	5048	Durogesic 50micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	6298	Fentanyl 75micrograms/hour transdermal patches
Fentanyl	25199	Actiq 600microgram lozenges with integral oromucosal applicator (Teva UK Ltd)
Fentanyl	46559	Fencino 12micrograms/hour transdermal patches (Ethypharm UK Ltd)
Fentanyl	40957	Effentora 800microgram buccal tablets (Teva UK Ltd)
Fentanyl	39929	Effentora 200microgram buccal tablets (Teva UK Ltd)
Fentanyl	40508	Abstral 600microgram sublingual tablets (Kyowa Kirin Ltd)
Fentanyl	61305	Mylafent 75micrograms/hour transdermal patches (Mylan Ltd)
Fentanyl	620	Fentanyl 25micrograms/hour transdermal patches
Fentanyl	7397	Durogesic DTrans 75micrograms transdermal patches (Janssen-Cilag Ltd)
Fentanyl	39251	Osmach 25micrograms/hour transdermal patches (Teva UK Ltd)
Fentanyl	61086	Opiodur 12micrograms/hour transdermal patches (Pfizer Ltd)
Fentanyl	39084	Osmach 100micrograms/hour transdermal patches (Ratiopharm UK Ltd)
Fentanyl	7126	Fentanyl 12micrograms/hour transdermal patches
Fentanyl	40434	Effentora 600microgram buccal tablets (Teva UK Ltd)
Fentanyl	40128	Effentora 400microgram buccal tablets (Teva UK Ltd)
Fentanyl	38326	Mezolar Matrix 75micrograms/hour transdermal patches (Sandoz Ltd)
Fentanyl	54979	Fentanyl 50micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)
Fentanyl	24986	Fentanyl 1.6mg lozenges
Fentanyl	40940	Fentanyl 300microgram sublingual tablets sugar free
Fentanyl	59490	Mezolar Matrix 37.5microgram/hour transdermal patches (Sandoz Ltd)
Fentanyl	5696	Fentanyl 600microgram lozenges
Fentanyl	5697	Fentanyl 800microgram lozenges
Fentanyl	39746	Effentora 100microgram buccal tablets (Teva UK Ltd)
Hydromorphone	21285	Palladone SR 24mg capsules (Napp Pharmaceuticals Ltd)
Hydromorphone	19954	Palladone SR 16mg capsules (Napp Pharmaceuticals Ltd)
Hydromorphone	15792	Hydromorphone 2mg modified-release capsules
Hydromorphone	5138	Hydromorphone 1.3mg capsules
Hydromorphone	19972	Hydromorphone 16mg modified-release capsules
Hydromorphone	9330	Palladone 2.6mg capsules (Napp Pharmaceuticals Ltd)
Hydromorphone	9331	Palladone SR 4mg capsules (Napp Pharmaceuticals Ltd)
Hydromorphone	9615	Palladone 1.3mg capsules (Napp Pharmaceuticals Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Hydromorphone	9332	Palladone SR 2mg capsules (Napp Pharmaceuticals Ltd)
Hydromorphone	15798	Hydromorphone 8mg modified-release capsules
Hydromorphone	21275	Palladone SR 8mg capsules (Napp Pharmaceuticals Ltd)
Hydromorphone	9325	Hydromorphone 4mg modified-release capsules
Hydromorphone	5137	Hydromorphone 2.6mg capsules
Hydromorphone	24736	Hydromorphone 24mg modified-release capsules
Levorphanol	20039	Dromoran roche 1.5mg Tablet (Roche Products Ltd)
Levorphanol	30633	Levorphanol 1.5mg Tablet
Meptazinol	3239	Meptazinol 200mg tablets
Meptazinol	39842	Meptid 200mg tablets (Almirall Ltd)
Meptazinol	8447	Meptid 200mg Tablet (Shire Pharmaceuticals Ltd)
Methadone	5322	Physeptone 5mg tablets (Martindale Pharmaceuticals Ltd)
Methadone	6441	Methadone 5mg tablets
Methadone	64463	Methadone 30mg capsules
Methadone	59295	Methadone 100mg capsules
Methadone	60944	Methadone 5mg capsules
Morphine	10239	MXL 150mg capsules (Napp Pharmaceuticals Ltd)
Morphine	6366	Sevredol 50mg tablets (Napp Pharmaceuticals Ltd)
Morphine	9137	Morphine 20mg tablets
Morphine	9557	Morphine 15mg modified-release tablets
Morphine	63593	Morphine sulfate 10mg/5ml oral solution (Actavis UK Ltd)
Morphine	9672	Morphine 100mg modified-release granules sachets sugar free
Morphine	3919	Sevredol 10mg tablets (Napp Pharmaceuticals Ltd)
Morphine	9381	MXL 90mg capsules (Napp Pharmaceuticals Ltd)
Morphine	22690	Morphine sulphate 24 120mg Modified-release capsule
Morphine	14050	Morphine sulphate 12 100mg Modified-release capsule
Morphine	9342	MXL 60mg capsules (Napp Pharmaceuticals Ltd)
Morphine	22756	Filnarine SR 30mg tablets (Teva UK Ltd)
Morphine	495	MST Continus 10mg tablets (Napp Pharmaceuticals Ltd)
Morphine	1503	Oramorph 10mg/5ml oral solution (Boehringer Ingelheim Ltd)
Morphine	60518	Morphine sulfate 500micrograms/5ml oral solution
Morphine	7875	Morphine 30mg modified-release tablets
Morphine	655	Morphine sulfate 10mg/5ml oral solution unit dose vials sugar free
Morphine	16273	Oramorph sr 30mg Tablet (Boehringer Ingelheim Ltd)
Morphine	15815	Morphine 50mg tablets
Morphine	8039	MST Continus 200mg tablets (Napp Pharmaceuticals Ltd)
Morphine	43652	Morphine 100mg modified-release capsules
Morphine	18166	Morphine sulphate 12 200mg Modified-release capsule
Morphine	17893	Oramorph sr 60mg Tablet (Boehringer Ingelheim Ltd)
Morphine	5991	MST Continus 100mg tablets (Napp Pharmaceuticals Ltd)
Morphine	5652	Morphine sulphate 12 50mg Modified-release capsule
Morphine	19477	Morphgesic SR 100mg tablets (AMCo)
Morphine	4266	Morphine 10mg tablets
Morphine	5681	Morphine 10mg modified-release tablets
Morphine	47867	Morphine 150mg modified-release capsules
Morphine	2957	MST Continus 30mg tablets (Napp Pharmaceuticals Ltd)
Morphine	8876	Oramorph 20mg/ml concentrated oral solution (Boehringer Ingelheim Ltd)
Morphine	29020	Morphine 200mg modified-release granules sachets sugar free

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Morphine	6269	Morphine sulfate 20mg/ml oral solution sugar free
Morphine	13117	Zomorph 30mg modified-release capsules (Ethypharm UK Ltd)
Morphine	26284	Filnarine SR 100mg tablets (Teva UK Ltd)
Morphine	14156	Morphine sulfate 30mg/5ml oral solution unit dose vials sugar free
Morphine	9602	Morphine 5mg modified-release tablets
Morphine	11698	Morphine sulphate 24 30mg Modified-release capsule
Morphine	64417	Morphine sulfate 2mg/5ml oral solution
Morphine	12591	Morphine 60mg modified-release granules sachets sugar free
Morphine	5563	Morphine sulphate 12 20mg Modified-release capsule
Morphine	10631	Morphine 10mg/ml Tincture
Morphine	15781	Morphine sulphate 24 90mg Modified-release capsule
Morphine	19092	Morcap sr 50mg Modified-release capsule (Faulding Pharmaceuticals (Dbl))
Morphine	9371	MXL 120mg capsules (Napp Pharmaceuticals Ltd)
Morphine	23060	MST Continus Suspension 200mg granules sachets (Napp Pharmaceuticals Ltd)
Morphine	60950	Morphine sulfate 5mg/5ml oral solution
Morphine	9337	MXL 30mg capsules (Napp Pharmaceuticals Ltd)
Morphine	58879	Morphine hydrochloride 10mg/5ml oral solution
Morphine	17943	Sevredol 20mg/ml concentrated oral solution (Napp Pharmaceuticals Ltd)
Morphine	53639	Morphine 10mg modified-release tablets (Sigma Pharmaceuticals Plc)
Morphine	9484	Morphine sulphate 24 60mg Modified-release capsule
Morphine	11838	Morphine 200mg modified-release tablets
Morphine	18700	SRM-RHOTARD 30mg Modified-release tablet (Pharmacia Ltd)
Morphine	15950	Zomorph 200mg modified-release capsules (Ethypharm UK Ltd)
Morphine	19449	Morphgesic SR 30mg tablets (AMCo)
Morphine	9960	Morphine sulphate 12 60mg Modified-release capsule
Morphine	23063	Morphine 1mg/5ml / Peppermint oil 1.5microlitres/5ml oral solution
Morphine	47985	M-eslon 10mg Capsule (Trinity Pharmaceuticals Ltd)
Morphine	30252	Morphine 8.4mg/ml elixir
Morphine	61423	Morphine 30mg modified-release tablets (Sigma Pharmaceuticals Plc)
Morphine	12604	MST Continus Suspension 100mg granules sachets (Napp Pharmaceuticals Ltd)
Morphine	22024	Rhotard Morphine SR 10mg tablets (Sovereign Medical Ltd)
Morphine	47154	Filnarine SR 200mg tablets (Teva UK Ltd)
Morphine	14226	Morphine 30mg modified-release granules sachets sugar free
Morphine	47753	Morphine 90mg modified-release capsules
Morphine	2997	Oramorph sr 10mg Tablet (Boehringer Ingelheim Ltd)
Morphine	6232	Sevredol 20mg tablets (Napp Pharmaceuticals Ltd)
Morphine	56788	Morphine sulfate 10mg/5ml oral solution (A A H Pharmaceuticals Ltd)
Morphine	45736	Morphine 60mg modified-release capsules
Morphine	607	MST Continus Suspension 20mg granules sachets (Napp Pharmaceuticals Ltd)
Morphine	6736	Morphine 20mg modified-release granules sachets sugar free
Morphine	12889	Oramorph 100mg/5ml oral solution unit dose vials (Boehringer Ingelheim Ltd)
Morphine	5714	MST Continus 15mg tablets (Napp Pharmaceuticals Ltd)
Morphine	5555	Sevredol 10mg/5ml oral solution (Napp Pharmaceuticals Ltd)
Morphine	27058	Filnarine SR 60mg tablets (Teva UK Ltd)
Morphine	19471	Morphgesic SR 60mg tablets (AMCo)
Morphine	4280	MST Continus 5mg tablets (Napp Pharmaceuticals Ltd)
Morphine	5840	Morphine sulfate 10mg/5ml oral solution
Morphine	4476	MST Continus Suspension 60mg granules sachets (Napp Pharmaceuticals Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Morphine	18656	SRM-RHOTARD 10mg Modified-release tablet (Pharmacia Ltd)
Morphine	17936	MXL 200mg capsules (Napp Pharmaceuticals Ltd)
Morphine	42380	Morphine sulphate 10mg Modified-release capsule
Morphine	13711	Morcap sr 20mg Modified-release capsule (Faulding Pharmaceuticals (Dbl))
Morphine	43657	Morphine 200mg modified-release capsules
Morphine	18881	Morphgesic SR 10mg tablets (AMCo)
Morphine	18801	Morcap SR 100mg capsules (Hospira UK Ltd)
Morphine	4477	MST Continus 60mg tablets (Napp Pharmaceuticals Ltd)
Morphine	6002	Morphine 10mg modified-release capsules
Morphine	4693	Oramorph 10mg/5ml oral solution unit dose vials (Boehringer Ingelheim Ltd)
Morphine	9183	Morphine 100mg modified-release tablets
Morphine	68712	Morphine hydrochloride 100mg/5ml oral solution
Morphine	19291	Morphine sulfate 100mg/5ml oral solution unit dose vials sugar free
Morphine	8822	Morphine 60mg modified-release tablets
Morphine	18734	Oramorph sr 100mg Tablet (Boehringer Ingelheim Ltd)
Morphine	13995	Morphine sulphate 24 200mg Modified-release capsule
Morphine	11342	Oramorph 30mg/5ml oral solution unit dose vials (Boehringer Ingelheim Ltd)
Morphine	13997	Morphine sulphate 100mg Modified-release capsule
Morphine	15964	Zomorph 60mg modified-release capsules (Ethypharm UK Ltd)
Morphine	34477	Morphine sulfate 10mg/5ml oral solution (Martindale Pharmaceuticals Ltd)
Morphine	59584	Morphine sulfate 10mg/5ml oral solution (Alliance Healthcare (Distribution) Ltd)
Morphine	22026	Rhotard Morphine SR 30mg tablets (Sovereign Medical Ltd)
Morphine	13114	Zomorph 10mg modified-release capsules (Ethypharm UK Ltd)
Morphine	47949	Morphine 120mg modified-release capsules
Morphine	53273	Morphine hydrochloride 10mg/5ml oral solution (Special Order)
Morphine	24453	Morcap sr 100mg Modified-release capsule (Faulding Pharmaceuticals (Dbl))
Morphine	7197	Morphine sulphate 12 30mg Modified-release capsule
Morphine	40563	Morphine 30mg modified-release capsules
Morphine	27749	Morphine sulphate 24 150mg Modified-release capsule
Morphine	26283	Filnarine SR 10mg tablets (Teva UK Ltd)
Morphine	12900	MST Continus Suspension 30mg granules sachets (Napp Pharmaceuticals Ltd)
Morphine	14063	Zomorph 100mg modified-release capsules (Ethypharm UK Ltd)
Oxycodone	6609	Oxycodone 5mg/5ml oral solution sugar free
Oxycodone	53116	Longtec 20mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	58853	Lynlor 10mg capsules (Actavis UK Ltd)
Oxycodone	57033	Oxylan 10mg modified-release tablets (Actavis UK Ltd)
Oxycodone	5585	Oxycodone 10mg capsules
Oxycodone	46187	Oxycodone 120mg modified-release tablets
Oxycodone	9874	OxyNorm liquid 5mg/5ml oral solution (Napp Pharmaceuticals Ltd)
Oxycodone	49940	OxyNorm 5mg capsules (Lexon (UK) Ltd)
Oxycodone	64164	Reltebon 15mg modified-release tablets (Actavis UK Ltd)
Oxycodone	49742	OxyContin 5mg modified-release tablets (DE Pharmaceuticals)
Oxycodone	5843	Oxycodone 10mg modified-release tablets
Oxycodone	52216	Longtec 5mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	50733	OxyContin 10mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
Oxycodone	39475	Oxycodone 10mg / Naloxone 5mg modified-release tablets
Oxycodone	5599	OxyContin 10mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	64965	Oxycodone 5mg/5ml oral solution sugar free (Wockhardt UK Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Oxycodone	64552	Longtec 60mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	52220	Longtec 40mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	51384	OxyNorm 20mg capsules (DE Pharmaceuticals)
Oxycodone	39478	Targinact 20mg/10mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	9973	OxyNorm 10mg capsules (Napp Pharmaceuticals Ltd)
Oxycodone	40616	Oxycodone 5mg / Naloxone 2.5mg modified-release tablets
Oxycodone	61836	Reltebon 20mg modified-release tablets (Actavis UK Ltd)
Oxycodone	69559	Shortec liquid 5mg/5ml oral solution (Qdem Pharmaceuticals Ltd)
Oxycodone	40961	Targinact 40mg/20mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	60158	Shortec 20mg capsules (Qdem Pharmaceuticals Ltd)
Oxycodone	7406	OxyNorm 10mg/ml concentrate oral solution (Napp Pharmaceuticals Ltd)
Oxycodone	65932	Abtard 40mg modified-release tablets (Ethypharm UK Ltd)
Oxycodone	61935	Reltebon 10mg modified-release tablets (Actavis UK Ltd)
Oxycodone	45745	OxyContin 30mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	65392	Abtard 20mg modified-release tablets (Ethypharm UK Ltd)
Oxycodone	59865	Shortec 10mg capsules (Qdem Pharmaceuticals Ltd)
Oxycodone	63714	Reltebon 60mg modified-release tablets (Actavis UK Ltd)
Oxycodone	7389	OxyContin 20mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	54694	Longtec 80mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	61779	Reltebon 40mg modified-release tablets (Actavis UK Ltd)
Oxycodone	51896	OxyContin 80mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
Oxycodone	7167	OxyContin 5mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	45929	Oxycodone 60mg modified-release tablets
Oxycodone	11405	Oxycodone 10mg/ml oral solution sugar free
Oxycodone	63332	Reltebon 30mg modified-release tablets (Actavis UK Ltd)
Oxycodone	69474	Oxycodone 5mg/5ml oral solution sugar free (DE Pharmaceuticals)
Oxycodone	45790	Oxycodone 15mg modified-release tablets
Oxycodone	52217	Longtec 10mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	66606	Oxeltra 10mg modified-release tablets (Wockhardt UK Ltd)
Oxycodone	58217	Lynlor 5mg capsules (Actavis UK Ltd)
Oxycodone	6769	Oxycodone 5mg modified-release tablets
Oxycodone	66298	Abtard 10mg modified-release tablets (Ethypharm UK Ltd)
Oxycodone	6708	Oxycodone 40mg modified-release tablets
Oxycodone	10021	OxyContin 80mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	45827	Oxycodone 30mg modified-release tablets
Oxycodone	51789	OxyNorm 10mg capsules (Waymade Healthcare Plc)
Oxycodone	58039	Oxycodone 5mg/5ml oral solution
Oxycodone	56665	Oxylan 10mg modified-release tablets (Chanelle Medical UK Ltd)
Oxycodone	45830	OxyContin 120mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	64807	Longtec 120mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	60196	Oxylan 40mg modified-release tablets (Chanelle Medical UK Ltd)
Oxycodone	64333	Longtec 30mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	6608	Oxycodone 20mg modified-release tablets
Oxycodone	67446	Abtard 60mg modified-release tablets (Ethypharm UK Ltd)
Oxycodone	45788	OxyContin 15mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	61936	Reltebon 5mg modified-release tablets (Actavis UK Ltd)
Oxycodone	66837	Abtard 15mg modified-release tablets (Ethypharm UK Ltd)
Oxycodone	66760	Abtard 5mg modified-release tablets (Ethypharm UK Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Oxycodone	66616	OxyContin 5mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
Oxycodone	53113	OxyContin 10mg modified-release tablets (DE Pharmaceuticals)
Oxycodone	57052	Oxylan 20mg modified-release tablets (Actavis UK Ltd)
Oxycodone	39477	Targinact 10mg/5mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	39498	Oxycodone 20mg / Naloxone 10mg modified-release tablets
Oxycodone	68797	Oxeltra 20mg modified-release tablets (Wockhardt UK Ltd)
Oxycodone	40645	Targinact 5mg/2.5mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	50095	OxyNorm 5mg capsules (DE Pharmaceuticals)
Oxycodone	52809	OxyContin 10mg modified-release tablets (Lexon (UK) Ltd)
Oxycodone	60146	Shortec 5mg capsules (Qdem Pharmaceuticals Ltd)
Oxycodone	9927	OxyContin 40mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	6557	OxyNorm 5mg capsules (Napp Pharmaceuticals Ltd)
Oxycodone	58493	Oxylan 20mg modified-release tablets (Chanelle Medical UK Ltd)
Oxycodone	66619	OxyContin 20mg modified-release tablets (Waymade Healthcare Plc)
Oxycodone	65390	Abtard 30mg modified-release tablets (Ethypharm UK Ltd)
Oxycodone	58114	Lynlor 20mg capsules (Actavis UK Ltd)
Oxycodone	7372	OxyNorm 20mg capsules (Napp Pharmaceuticals Ltd)
Oxycodone	7275	Oxycodone 20mg capsules
Oxycodone	64150	Oxylan 5mg modified-release tablets (Chanelle Medical UK Ltd)
Oxycodone	52592	OxyNorm 10mg capsules (DE Pharmaceuticals)
Oxycodone	45766	OxyContin 60mg modified-release tablets (Napp Pharmaceuticals Ltd)
Oxycodone	49787	OxyContin 20mg modified-release tablets (Lexon (UK) Ltd)
Oxycodone	65933	Abtard 80mg modified-release tablets (Ethypharm UK Ltd)
Oxycodone	64426	Longtec 15mg modified-release tablets (Qdem Pharmaceuticals Ltd)
Oxycodone	6790	Oxycodone 5mg capsules
Oxycodone	62322	Reltebon 80mg modified-release tablets (Actavis UK Ltd)
Oxycodone	6948	Oxycodone 80mg modified-release tablets
Oxycodone	40785	Oxycodone 40mg / Naloxone 20mg modified-release tablets
Oxycodone	63198	OxyContin 40mg modified-release tablets (DE Pharmaceuticals)
Papaveretum	18261	Aspirin 500mg with Papaveretum 7.71mg dispersible tablets
Pentazocine	8375	Fortral 25mg tablets (Zentiva)
Pentazocine	328	Pentazocine 50mg capsules
Pentazocine	36472	Paracetamol 500 mg+ pentazocine 15mg tablet
Pentazocine	2367	Pentazocine 25mg tablets
Pentazocine	10769	Fortral 50mg Capsule (Sanofi-Synthelabo Ltd)
Pentazocine	7450	Pentazocine 15mg with paracetamol 500mg tablet
Pethidine	40239	Pethidine 50mg tablets (Martindale Pharmaceuticals Ltd)
Pethidine	17386	Pethidine 50mg Tablet (Roche Products Ltd)
Pethidine	2450	Pethidine 50mg tablets
Pethidine	38103	Pethidine 25mg Tablet (Roche Products Ltd)
Pethidine	31935	Pethidine 50mg Tablet (Roche Products Ltd)
Pethidine	57027	Pethidine 50mg tablets (A A H Pharmaceuticals Ltd)
Pethidine	56022	Pethidine 50mg Capsule (Martindale Pharmaceuticals Ltd)
Pethidine	234	Pethidine 25mg tablet
Pethidine	54790	Pethidine 50mg tablets (Teva UK Ltd)
Pethidine	58737	Pethidine 50mg tablets (Alliance Healthcare (Distribution) Ltd)
Pethidine	38013	Pethidine 50mg capsules
Phenazocine	17167	Narphen 5mg Tablet (Smith & Nephew Healthcare Ltd)

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Phenazocine	14394	Phenazocine hydrobromide 5mg tablet
Tapentadol	45811	Tapentadol 50mg tablets
Tapentadol	60759	Tapentadol 20mg/ml oral solution sugar free
Tapentadol	45800	Tapentadol 200mg modified-release tablets
Tapentadol	46461	Tapentadol 75mg tablets
Tapentadol	46159	Palexia SR 150mg tablets (Grunenthal Ltd)
Tapentadol	61764	Palexia 20mg/ml oral solution (Grunenthal Ltd)
Tapentadol	45936	Palexia 50mg tablets (Grunenthal Ltd)
Tapentadol	45982	Palexia SR 50mg tablets (Grunenthal Ltd)
Tapentadol	46021	Tapentadol 50mg modified-release tablets
Tapentadol	47460	Palexia SR 250mg tablets (Grunenthal Ltd)
Tapentadol	46022	Palexia 75mg tablets (Grunenthal Ltd)
Tapentadol	46018	Tapentadol 100mg modified-release tablets
Tapentadol	46019	Tapentadol 150mg modified-release tablets
Tapentadol	46659	Palexia SR 200mg tablets (Grunenthal Ltd)
Tapentadol	47399	Tapentadol 250mg modified-release tablets
Tapentadol	46020	Palexia SR 100mg tablets (Grunenthal Ltd)
Tramadol	21797	Zamadol SR 200mg capsules (Meda Pharmaceuticals Ltd)
Tramadol	49324	Marol 100mg modified-release tablets (Teva UK Ltd)
Tramadol	64731	Tramadol 100mg modified-release capsules (Icarus Pharmaceuticals Ltd)
Tramadol	46643	Zeridame SR 150mg tablets (Actavis UK Ltd)
Tramadol	60751	Tilodol SR 200mg tablets (Sandoz Ltd)
Tramadol	63898	Tramadol 50mg modified-release capsules (J M McGill Ltd)
Tramadol	39798	Nobligan retard 100mg tablets (Grunenthal Ltd)
Tramadol	36697	Mabron 200mg modified-release tablets (Morningside Healthcare Ltd)
Tramadol	68427	Tramadol 50mg modified-release capsules (CST Pharma Ltd)
Tramadol	9389	Zamadol SR 50mg capsules (Meda Pharmaceuticals Ltd)
Tramadol	46587	Tramadol 100mg/ml oral drops
Tramadol	67197	Tramadol 50mg capsules (DE Pharmaceuticals)
Tramadol	43198	Tramadol sr 50mg Capsule (Hillcross Pharmaceuticals Ltd)
Tramadol	36949	Tramquel SR 50mg capsules (Beechmere Pharmaceuticals Ltd)
Tramadol	35651	Tradorec XL 200mg tablets (Endo Ventures Ltd)
Tramadol	8416	Tramadol 12 Modified-release tablet
Tramadol	42280	Tramadol 37.5mg / Paracetamol 325mg effervescent tablets sugar free
Tramadol	61610	Tramadol 50mg capsules (Morningside Healthcare Ltd)
Tramadol	687	Tramacet 37.5mg/325mg tablets (Grunenthal Ltd)
Tramadol	11746	Tramadol 300mg modified-release tablets
Tramadol	34065	Tramadol sr 150mg Modified-release tablet (Winthrop Pharmaceuticals Ltd)
Tramadol	68210	Tramadol 100mg modified-release tablets (Elite Pharma (Surrey) Ltd)
Tramadol	36873	Zydol SR 50mg tablets (Grunenthal Ltd)
Tramadol	23981	Zamadol SR 150mg capsules (Meda Pharmaceuticals Ltd)
Tramadol	38956	Tramquel SR 200mg capsules (Beechmere Pharmaceuticals Ltd)
Tramadol	52977	Tramadol 100mg modified-release capsules (A A H Pharmaceuticals Ltd)
Tramadol	34570	Tramadol 50mg capsules (Teva UK Ltd)
Tramadol	31107	Dromadol XL 150mg tablets (IVAX Pharmaceuticals UK Ltd)
Tramadol	21947	Zydol XL 150mg tablets (Grunenthal Ltd)
Tramadol	65266	Tramadol 50mg capsules (Kent Pharmaceuticals Ltd)
Tramadol	86	Tramadol 50mg capsules

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Tramadol	6558	Tramadol 37.5mg / Paracetamol 325mg tablets
Tramadol	40883	Maxitram SR 150mg capsules (Chiesi Ltd)
Tramadol	58316	Tramadol 50mg modified-release capsules (DE Pharmaceuticals)
Tramadol	67744	Zydol 50mg capsules (Lexon (UK) Ltd)
Tramadol	11734	Tramadol 50mg orodispersible tablets sugar free
Tramadol	39750	Marol 150mg modified-release tablets (Morningside Healthcare Ltd)
Tramadol	54023	Tramadol 50mg modified-release capsules (A A H Pharmaceuticals Ltd)
Tramadol	64871	Maneo 100mg modified-release tablets (Mylan Ltd)
Tramadol	5257	Tramadol 12 Modified-release tablet
Tramadol	20310	Zamadol Melt 50mg tablets (Meda Pharmaceuticals Ltd)
Tramadol	56491	Zamadol SR 200mg capsules (Lexon (UK) Ltd)
Tramadol	4115	Tramadol 100mg modified-release tablets
Tramadol	21397	Zydol XL 400mg tablets (Grunenthal Ltd)
Tramadol	40058	Tramulief SR 100mg tablets (AMCo)
Tramadol	40249	Maxitram SR 100mg capsules (Chiesi Ltd)
Tramadol	62778	Tramacet 37.5mg/325mg tablets (Waymade Healthcare Plc)
Tramadol	31105	Dromadol XL 200mg tablets (IVAX Pharmaceuticals UK Ltd)
Tramadol	36732	Tramadol 50mg modified-release tablets
Tramadol	40926	Larapam SR 150mg tablets (Sandoz Ltd)
Tramadol	42798	Tramadol 150mg modified-release tablets (A A H Pharmaceuticals Ltd)
Tramadol	11748	Tramadol 400mg modified-release tablets
Tramadol	66729	Tilodol SR 100mg tablets (Sandoz Ltd)
Tramadol	34639	Tramadol 50mg capsules (Genus Pharmaceuticals Ltd)
Tramadol	3378	Tramadol 50mg soluble tablets sugar free
Tramadol	65954	Tramadol 50mg modified-release capsules (Cubic Pharmaceuticals Ltd)
Tramadol	66299	Maneo 200mg modified-release tablets (Mylan Ltd)
Tramadol	67310	Zydol SR 200mg tablets (Mawdsley-Brooks & Company Ltd)
Tramadol	32450	Zamadol 24hr 400mg modified-release tablets (Meda Pharmaceuticals Ltd)
Tramadol	46279	Tramadol 200mg modified-release capsules (A A H Pharmaceuticals Ltd)
Tramadol	34260	Tramadol sr 100mg Modified-release tablet (Winthrop Pharmaceuticals Ltd)
Tramadol	28728	Zamadol 24hr 300mg modified-release tablets (Meda Pharmaceuticals Ltd)
Tramadol	9396	Zamadol SR 100mg capsules (Meda Pharmaceuticals Ltd)
Tramadol	26336	Dromadol XL 300mg tablets (IVAX Pharmaceuticals UK Ltd)
Tramadol	40060	Tramulief SR 200mg tablets (AMCo)
Tramadol	27591	Zamadol 24hr 150mg modified-release tablets (Meda Pharmaceuticals Ltd)
Tramadol	29860	Tramadol 50mg capsules (IVAX Pharmaceuticals UK Ltd)
Tramadol	4999	Tramadol 24 Modified-release tablet
Tramadol	58129	Zeridame SR 100mg tablets (Actavis UK Ltd)
Tramadol	23625	Dromadol SR 150mg tablets (Teva UK Ltd)
Tramadol	37021	Tramadol 200mg modified-release tablets
Tramadol	34521	Tramadol 50mg capsules (A A H Pharmaceuticals Ltd)
Tramadol	21777	Dromadol SR 200mg tablets (Teva UK Ltd)
Tramadol	16395	Zydol XL 200mg tablets (Grunenthal Ltd)
Tramadol	37831	Mabron 100mg modified-release tablets (Morningside Healthcare Ltd)
Tramadol	67323	Zydol SR 150mg tablets (Waymade Healthcare Plc)
Tramadol	32165	Tramadol 50mg Capsule (Generics (UK) Ltd)
Tramadol	61775	Tramadol 50mg capsules (Sigma Pharmaceuticals Plc)
Tramadol	37020	Tramadol 150mg modified-release tablets

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Tramadol	38196	Larapam SR 200mg tablets (Sandoz Ltd)
Tramadol	6215	Tramadol 200mg modified-release capsules
Tramadol	26986	Zamadol 24hr 200mg modified-release tablets (Meda Pharmaceuticals Ltd)
Tramadol	5028	Tramadol 24 Modified-release tablet
Tramadol	11101	Zydol 50mg soluble tablets (Grunenthal Ltd)
Tramadol	49323	Marol 150mg modified-release tablets (Teva UK Ltd)
Tramadol	64459	Tramadol 37.5mg / Paracetamol 325mg tablets (A A H Pharmaceuticals Ltd)
Tramadol	35438	Tramquel SR 100mg capsules (Beechmere Pharmaceuticals Ltd)
Tramadol	19993	Dromadol SR 100mg tablets (Teva UK Ltd)
Tramadol	41976	Tramadol 100mg modified-release tablets (A A H Pharmaceuticals Ltd)
Tramadol	40254	Maxitram SR 50mg capsules (Chiesi Ltd)
Tramadol	52605	Tramadol 50mg capsules (Accord Healthcare Ltd)
Tramadol	52495	Tramadol 50mg capsules (Bristol Laboratories Ltd)
Tramadol	39709	Marol 200mg modified-release tablets (Morningside Healthcare Ltd)
Tramadol	35656	Tradorec XL 100mg tablets (Endo Ventures Ltd)
Tramadol	34281	Tramadol sr 200mg Modified-release tablet (Winthrop Pharmaceuticals Ltd)
Tramadol	35806	Larapam SR 100mg tablets (Sandoz Ltd)
Tramadol	61272	Tramadol 50mg capsules (Phoenix Healthcare Distribution Ltd)
Tramadol	44371	Mabron 150mg modified-release tablets (Morningside Healthcare Ltd)
Tramadol	48090	Tramadol 200mg modified-release tablets (A A H Pharmaceuticals Ltd)
Tramadol	37867	Tramadol (roi) Tablet
Tramadol	16076	Paracetamol 325mg with tramadol 37.5 mg tablet
Tramadol	69894	Zeridame SR 200mg tablets (Actavis UK Ltd)
Tramadol	14490	Tramake 50mg capsules (Galen Ltd)
Tramadol	40805	Tramquel SR 150mg capsules (Beechmere Pharmaceuticals Ltd)
Tramadol	16271	Zydol XL 300mg tablets (Grunenthal Ltd)
Tramadol	47854	Tramadol (roi) Tablet
Tramadol	34808	Tramadol 50mg capsules (PLIVA Pharma Ltd)
Tramadol	5169	Zydol SR 200mg tablets (Grunenthal Ltd)
Tramadol	34422	Tramadol 50mg capsules (Actavis UK Ltd)
Tramadol	38528	Tramadol 50mg Capsule (Tillomed Laboratories Ltd)
Tramadol	3644	Zydol SR 100mg tablets (Grunenthal Ltd)
Tramadol	43513	Tramadol 50mg capsules (Zentiva)
Tramadol	60121	Tramadol 50mg modified-release capsules (Waymade Healthcare Plc)
Tramadol	39811	Maxitram SR 200mg capsules (Chiesi Ltd)
Tramadol	6153	Zydol SR 150mg tablets (Grunenthal Ltd)
Tramadol	4834	Tramadol 150mg modified-release capsules
Tramadol	36035	Tradorec XL 300mg tablets (Endo Ventures Ltd)
Tramadol	42332	Tramacet 37.5mg/325mg effervescent tablets (Grunenthal Ltd)
Tramadol	187	Zydol 50mg capsules (Grunenthal Ltd)
Tramadol	50947	Tramadol 100mg modified-release capsules (Alliance Healthcare (Distribution) Ltd)
Tramadol	4114	Tramadol 100mg modified-release capsules
Tramadol	68833	Tramadol 100mg modified-release capsules (DE Pharmaceuticals)
Tramadol	50862	Marol 200mg modified-release tablets (Teva UK Ltd)
Tramadol	39505	Marol 100mg modified-release tablets (Morningside Healthcare Ltd)
Tramadol	701	Tramadol 50mg modified-release capsules
Tramadol	63047	Tramadol 100mg modified-release capsules (Waymade Healthcare Plc)
Tramadol	35347	Tramadol 24 Modified-release tablet

Appendix O. Opioid product codes [continued]

Drug	Code	Product name
Tramadol	40061	Tramulief SR 150mg tablets (AMCo)
Tramadol	13813	Zamadol 50mg capsules (Meda Pharmaceuticals Ltd)
Tramadol	31734	Dromadol XL 400mg tablets (IVAX Pharmaceuticals UK Ltd)
Tramadol	40166	Tramadol 50mg capsules (Niche Generics Ltd)
Tramadol	64496	Tramadol 100mg modified-release capsules (Ennogen Healthcare Ltd)
Tramadol	40718	Tramadol 50mg capsules (Almus Pharmaceuticals Ltd)
Tramadol	67161	Tramadol 150mg modified-release capsules (A A H Pharmaceuticals Ltd)

Appendix P. Opioid product look-up

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
alfentanil				
SPR	37251		1.00	30.00
	56581		1.00	30.00
buprenorphine				
TD	68479	4	6.72	739.20
	69795	3	2.52	277.20
	66463	7	2.52	277.20
	68196	7	2.52	277.20
	7555	7	0.84	92.40
	68241	7	1.68	184.80
	7236	7	1.68	184.80
	59146	7	3.36	369.60
	69254	4	3.36	369.60
	66695	7	3.36	369.60
	59473	3	3.78	415.80
	7334	7	0.84	92.40
	6181	4	6.72	739.20
	11584	4	6.72	739.20
	68402	7	0.84	92.40
	68889	7	1.68	184.80
	13300	7	3.36	369.60
	59618	4	3.36	369.60
	60943	4	3.36	369.60
	68167	7	0.84	92.40
	6040	4	5.04	554.40
	59392	3	5.04	554.40
	67356	4	6.72	739.20
	68848	4	5.04	554.40
	6917	4	5.04	554.40
	66470	7	1.68	184.80
	7238	7	3.36	369.60
	68888	7	3.36	369.60
	68472	3	3.78	415.80
	6879	4	3.36	369.60
	60170	3	2.52	277.20
	68559	7	1.68	184.80
	58766	7	1.68	184.80
	66689	7	0.84	92.40
	69315	7	2.52	277.20
	5936	4	3.36	369.60
	54806	4	5.04	554.40
	56671	7	0.84	92.40
	67901	4	5.04	554.40
	68172	7	3.36	369.60

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
buprenorphine				
TD	68890	7	0.84	92.40
	68743	4	3.36	369.60
	66280	7	2.52	277.20
	67018	4	3.36	369.60
	69243	4	5.04	554.40
	10205	7	1.68	184.80
OD	62675		0.20	10.00
	3064		0.40	20.00
	69942		0.20	10.00
	64155		0.40	20.00
	396		0.40	20.00
	3522		0.20	10.00
	60053		0.40	20.00
	61100		0.40	20.00
	8017		0.20	10.00
	13031		0.40	20.00
codeine				
SA	31452		30.00	4.50
	10176		15.00	2.25
	43550		15.00	2.25
	57865		30.00	4.50
	53600		60.00	9.00
	64752		30.00	4.50
	52888		15.00	2.25
	34497		8.00	1.20
	57381		60.00	9.00
	44924		30.00	4.50
	800		30.00	4.50
	59705		8.00	1.20
	51084		30.00	4.50
	34789		30.00	4.50
	11807		12.80	1.92
	56559		30.00	4.50
	58288		30.00	4.50
	7072		15.00	2.25
	57487		30.00	4.50
	41535		30.00	4.50
	11325		30.00	4.50
	58828		8.00	1.20
	13893		12.80	1.92
	47847		30.00	4.50
	60040		8.00	1.20
	51381		8.00	1.20

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit	Form	Product code	Days/TD	Strength/unit	OMEQ/unit
codeine					**codeine**				
SA	61091		60.00	9.00	SA	47003		60.00	9.00
	10178		8.00	1.20		38363		12.80	1.92
	56205		8.00	1.20		67751		30.00	4.50
	48153		60.00	9.00		57839		15.00	2.25
	34552		30.00	4.50		25529		8.00	1.20
	57929		8.00	1.20		6886		30.00	4.50
	39340		8.00	1.20		64387		30.00	4.50
	37904		12.80	1.92		61647		15.00	2.25
	55465		30.00	4.50		34815		8.00	1.20
	56006		8.00	1.20		3724		8.00	1.20
	46729		15.00	2.25		41275		8.00	1.20
	25109		8.00	1.20		46987		15.00	2.25
	68509		30.00	4.50		48311		30.00	4.50
	47919		15.00	2.25		51644		30.00	4.50
	96		30.00	4.50		41276		8.00	1.20
	9516		30.00	4.50		59442		30.00	4.50
	27784		8.00	1.20		51819		8.00	1.20
	34840		30.00	4.50		20565		8.00	1.20
	17563		12.80	1.92		36993		30.00	4.50
	51937		15.00	2.25		28784		8.00	1.20
	65245		30.00	4.50		31871		8.10	1.22
	2917		30.00	4.50		31577		30.00	4.50
	69285		12.80	1.92		17158		15.00	2.25
	65118		30.00	4.50		30123		12.80	1.92
	50468		15.00	2.25		56461		30.00	4.50
	38088		30.00	4.50		158		30.00	4.50
	59131		8.00	1.20		59986		30.00	4.50
	1527		8.00	1.20		2794		30.00	4.50
	57465		8.00	1.20		34348		15.00	2.25
	33643		8.00	1.20		66352		8.00	1.20
	11250		8.00	1.20		3156		30.00	4.50
	39461		12.80	1.92		65806		8.00	1.20
	34444		15.00	2.25		11665		30.00	4.50
	656		30.00	4.50		41416		60.00	9.00
	46898		15.00	2.25		59479		30.00	4.50
	60640		15.00	2.25		65092		30.00	4.50
	34667		30.00	4.50		58501		30.00	4.50
	65904		8.00	1.20		48004		30.00	4.50
	1616		8.00	1.20		57900		30.00	4.50
	8329		8.00	1.20		9460		8.00	1.20
	65314		8.00	1.20		56340		30.00	4.50
	11009		8.00	1.20		55044		30.00	4.50
	58855		30.00	4.50		56266		30.00	4.50

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit	Form	Product code	Days/TD	Strength/unit	OMEQ/unit
codeine					**codeine**				
SA	53702		30.00	4.50	SA	48775		30.00	4.50
	7542		8.00	1.20		44210		15.00	2.25
	34383		30.00	4.50		50421		15.00	2.25
	63658		8.00	1.20		64545		8.00	1.20
	53999		60.00	9.00		67106		30.00	4.50
	66904		8.00	1.20		50659		60.00	9.00
	56817		15.00	2.25		56565		15.00	2.25
	11554		12.80	1.92		767		30.00	4.50
	1640		30.00	4.50		53617		12.80	1.92
	31155		8.00	1.20		34865		8.00	1.20
	34968		8.00	1.20		8335		8.00	1.20
	66115		60.00	9.00		29342		8.00	1.20
	31700		15.00	2.25		2047		8.00	1.20
	62228		30.00	4.50		38085		10.00	1.50
	3713		8.00	1.20		382		15.00	2.25
	9457		8.00	1.20		4671		30.00	4.50
	69304		15.00	2.25		17926		8.00	1.20
	57353		30.00	4.50		56171		30.00	4.50
	16039		8.00	1.20		25514		10.00	1.50
	31943		30.00	4.50		51327		30.00	4.50
	66893		15.00	2.25		65269		60.00	9.00
	66538		8.00	1.20		57097		30.00	4.50
	68252		30.00	4.50		34518		8.00	1.20
	19		8.00	1.20		60958		15.00	2.25
	625		8.00	1.20		63900		8.00	1.20
	14785		15.00	2.25		14912		8.00	1.20
	3185		30.00	4.50		22764		8.00	1.20
	67753		8.00	1.20	SOL	34172		3.00	0.45
	33679		8.00	1.20		4805		3.00	0.45
	52929		15.00	2.25		34152		3.00	0.45
	47952		30.00	4.50		16096		1.35	0.20
	539		60.00	9.00		42792		3.00	0.45
	27785		30.00	4.50		35792		5.00	0.75
	55309		15.00	2.25		24125		3.00	0.45
	64726		15.00	2.25		34437		3.00	0.45
	12709		12.50	1.88		213		5.00	0.75
	52966		8.00	1.20		4369		0.60	0.09
	18221		15.00	2.25		68538		6.00	0.90
	10226		8.00	1.20		68861		5.00	0.75
	21880		30.00	4.50		52889		5.00	0.75
	41599		15.00	2.25		34176		3.00	0.45
	64108		15.00	2.25		57752		2.00	0.30
	46633		8.00	1.20		41214		3.00	0.45

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
diamorphine				
SOL	15339		2.00	2.00
	31960		3.00	3.00
	31033		0.60	0.60
dihydrocodeine				
LA	9209		90.00	11.70
	2041		60.00	7.80
	6234		120.00	15.60
	9275		120.00	15.60
	8456		60.00	7.80
	9313		90.00	11.70
SA	55425		10.00	1.30
	19206		7.46	0.97
	57197		10.00	1.30
	39558		30.00	3.90
	9855		20.00	2.60
	34737		10.00	1.30
	32926		10.00	1.30
	38970		40.00	5.20
	43441		10.00	1.30
	11		10.00	1.30
	38430		10.00	1.30
	34440		30.00	3.90
	53		30.00	3.90
	33654		30.00	3.90
	53079		10.00	1.30
	10023		20.00	2.60
	4823		40.00	5.20
	28780		10.00	1.30
	59989		30.00	3.90
	30295		7.46	0.97
	14688		10.00	1.30
	34730		30.00	3.90
	4556		7.46	0.97
	30165		7.46	0.97
	50532		30.00	3.90
	34008		30.00	3.90
	40422		10.00	1.30
	34920		10.00	1.30
	4950		30.00	3.90
	64074		10.00	1.30
	61372		10.00	1.30
	58848		30.00	3.90
	48133		30.00	3.90

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
dihydrocodeine				
SA	15198		10.00	1.30
	67779		10.00	1.30
	62635		10.00	1.30
	3698		40.00	5.20
	54354		30.00	3.90
	5955		30.00	3.90
	64368		30.00	3.90
	38521		30.00	3.90
	34579		30.00	3.90
	55530		10.00	1.30
	2555		10.00	1.30
	42208		30.00	3.90
	38950		30.00	3.90
	2040		20.00	2.60
	65035		10.00	1.30
	34662		30.00	3.90
	36019		10.00	1.30
	59978		30.00	3.90
	54713		20.00	2.60
	34939		10.00	1.30
	9785		30.00	3.90
SOL	40159		2.00	0.26
	191		2.00	0.26
	47071		2.00	0.26
	61698		2.00	0.26
	33340		2.00	0.26
	28598		2.00	0.26
	64079		2.00	0.26
	66121		2.00	0.26
	10122		2.00	0.26
	7063		2.00	0.26
	7469		2.00	0.26
	65689		6.00	0.78
EFF	21113		30.00	3.90
	9562		30.00	3.90
	17917		20.00	2.60
	33743		7.46	0.97
	9163		20.00	2.60
dipipanone				
SA	12020		10.00	5.00
	38301		10.00	5.00
	9001		10.00	5.00

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
codeine				
SOL	69576		2.00	0.30
	69066		1.00	0.15
EFF	21673		8.00	1.20
	9742		8.00	1.20
	43244		30.00	4.50
	810		30.00	4.50
	10602		8.00	1.20
	34229		8.00	1.20
	14964		8.00	1.20
	23420		60.00	9.00
	44159		30.00	4.50
	53679		30.00	4.50
	3435		30.00	4.50
	58636		8.00	1.20
	41682		30.00	4.50
	2846		30.00	4.50
	16818		30.00	4.50
	40662		8.00	1.20
	53287		30.00	4.50
	23952		8.00	1.20
	46906		8.00	1.20
	63551		8.00	1.20
	32692		8.00	1.20
	36608		30.00	4.50
	40385		8.00	1.20
	66553		30.00	4.50
	7518		8.00	1.20
	29488		8.00	1.20
	21251		8.00	1.20
	47081		12.80	1.92
	14676		8.00	1.20
	15779		8.00	1.20
	41259		30.00	4.50
	66602		12.80	1.92
	56549		8.00	1.20
	52085		30.00	4.50
	60517		30.00	4.50
	2211		30.00	4.50
	57		8.00	1.20
	46511		15.00	2.25
	34845		30.00	4.50
	63683		8.00	1.20
	9432		8.00	1.20

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
codeine				
EFF	16467		30.00	4.50
	40663		30.00	4.50
	15831		30.00	4.50
	20127		8.00	1.20
	43414		8.00	1.20
	8246		8.00	1.20
	21703		60.00	9.00
	47508		15.00	2.25
	9462		8.00	1.20
SUP	60489		30.00	
dextromoramide				
SA	4236		5.00	
	3990		5.00	
	39419		5.00	
dextropropoxyphene				
SA	43536		32.50	4.88
	30966		32.50	4.88
	12076		60.00	9.00
	45276		32.50	4.88
	2462		32.50	4.88
	25979		60.00	9.00
	45231		32.50	4.88
	34397		32.50	4.88
	34554		32.50	4.88
	1762		32.50	4.88
	18482		32.50	4.88
	34546		32.50	4.88
	4607		32.50	4.88
	33995		32.50	4.88
SOL	28253		0.65	0.10
	483		6.50	0.98
diamorphine				
SA	58279		10.00	10.00
	9945		10.00	10.00
	18792		10.00	10.00
	8866		10.00	10.00
SOL	58499		0.60	0.60
	8735		1.00	1.00
	7114		0.60	0.60
	30761		2.00	2.00
	13420		3.00	3.00
	28711		0.60	0.60
	29500		1.00	1.00

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
ethylmorphine				
SOL	34073		0.30	
fentanyl				
TD	51235	3	1.80	180.00
	38365	3	5.40	540.00
	42591	3	1.80	180.00
	39180	3	3.60	360.00
	42590	3	5.40	540.00
	11982	3	0.86	86.40
	39084	3	7.20	720.00
	5048	3	3.60	360.00
	10922	3	7.20	720.00
	50929	3	0.86	86.40
	45460	3	7.20	720.00
	6298	3	5.40	540.00
	46560	3	3.60	360.00
	36040	3	7.20	720.00
	54979	3	3.60	360.00
	748	3	1.80	180.00
	47413	3	5.40	540.00
	56670	3	1.80	180.00
	41161	3	5.40	540.00
	61156	3	0.86	86.40
	37719	3	7.20	720.00
	61305	3	5.40	540.00
	67766	3	5.40	540.00
	37954	3	0.86	86.40
	35968	3	1.80	180.00
	39251	3	1.80	180.00
	59482	3	2.70	270.00
	37928	3	0.86	86.40
	67425	3	1.80	180.00
	38031	3	1.80	180.00
	38553	3	7.20	720.00
	46733	3	1.80	180.00
	44487	3	0.86	86.40
	46658	3	7.20	720.00
	36211	3	3.60	360.00
	67830	3	0.86	86.40
	7126	3	0.86	86.40
	42021	3	7.20	720.00
	37779	3	1.80	180.00
	45549	3	1.80	180.00
	7082	3	1.80	180.00

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
fentanyl				
TD	7107	3	3.60	360.00
	55752	3	7.20	720.00
	46657	3	5.40	540.00
	37923	3	3.60	360.00
	69023	3	7.20	720.00
	65437	3	7.20	720.00
	63139	3	0.86	86.40
	43152	3	3.60	360.00
	50671	3	0.86	86.40
	28189	3	7.20	720.00
	67474	3	3.60	360.00
	59490	3	2.70	270.00
	60766	3	1.80	180.00
	5657	3	5.40	540.00
	46559	3	0.86	86.40
	67258	3	1.80	180.00
	68209	3	7.20	720.00
	620	3	1.80	180.00
	61086	3	0.86	86.40
	38351	3	5.40	540.00
	65359	3	3.60	360.00
	14900	3	7.20	720.00
	7397	3	5.40	540.00
	37960	3	3.60	360.00
	22066	3	3.60	360.00
	38326	3	5.40	540.00
	757	3	3.60	360.00
	42576	3	5.40	540.00
	44837	3	3.60	360.00
	16618	3	5.40	540.00
	48571	3	3.60	360.00
	4691	3	7.20	720.00
	60477	3	1.80	180.00
	65168	3	0.86	86.40
	31053	3	1.80	180.00
OD	24986		0.60	30.00
	39469		0.30	15.00
	46555		0.40	20.00
	40018		0.60	30.00
	25199		0.60	30.00
	40508		0.60	30.00
	39590		0.40	20.00
	39723		0.40	20.00

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
fentanyl				
OD	40098		0.40	20.00
	59443		0.40	20.00
	61708		0.10	5.00
	41348		0.20	10.00
	40940		0.10	5.00
	39746		0.80	40.00
	29577		0.40	20.00
	42399		0.40	20.00
	40576		0.10	5.00
	18174		0.60	30.00
	65646		0.40	20.00
	42538		0.10	5.00
	40434		0.40	20.00
	39929		0.60	30.00
	39756		0.30	15.00
	59057		0.60	30.00
	41286		0.80	40.00
	26908		0.20	10.00
	13076		0.40	20.00
	39799		0.20	10.00
	5697		0.80	40.00
	11843		0.80	40.00
	63340		0.20	10.00
	39987		0.80	40.00
	39518		0.27	13.35
	15337		0.20	10.00
	5651		0.13	6.65
	40128		0.20	10.00
	26021		0.80	40.00
	5696		0.27	13.35
	40957		0.20	10.00
SPR	43089		0.10	16.00
	45894		0.10	16.00
	45092		0.20	32.00
	45439		0.40	64.00
	46354		0.05	8.00
	47759		0.10	16.00
	43617		0.05	8.00
	41135		0.20	32.00
	45598		0.10	16.00
hydromorphone				
LA	24736		24.00	144.00
	21285		24.00	144.00
hydromorphone				
LA	15798		8.00	48.00
	9332		2.00	12.00
	9331		4.00	24.00
	9325		4.00	24.00
	19972		16.00	96.00
	15792		2.00	12.00
	19954		16.00	96.00
	21275		8.00	48.00
SA	5137		2.60	15.60
	9615		1.30	7.80
	9330		2.60	15.60
	5138		1.30	7.80
levorphanol				
SA	30633		1.50	16.50
	20039		1.50	16.50
meptazinol				
SA	3239		200.00	6.00
	39842		200.00	6.00
	8447		200.00	6.00
methadone				
SA	6441		5.00	15.00
	59295		100.00	300.00
	64463		30.00	90.00
	5322		5.00	15.00
	60944		5.00	15.00
morphine				
LA	61423		30.00	30.00
	47867		150.00	150.00
	5681		10.00	10.00
	17893		60.00	60.00
	9484		60.00	60.00
	9960		60.00	60.00
	13117		30.00	30.00
	5652		50.00	50.00
	43657		200.00	200.00
	7197		30.00	30.00
	13711		20.00	20.00
	26284		100.00	100.00
	15950		200.00	200.00
	19092		50.00	50.00
	18656		10.00	10.00
	5991		100.00	100.00
	42380		10.00	10.00

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
morphine				
LA	18166		200.00	200.00
	13995		200.00	200.00
	2957		30.00	30.00
	18734		100.00	100.00
	19449		30.00	30.00
	8822		60.00	60.00
	53639		10.00	10.00
	45736		60.00	60.00
	18801		100.00	100.00
	4280		5.00	5.00
	19471		60.00	60.00
	4477		60.00	60.00
	27058		60.00	60.00
	22024		10.00	10.00
	24453		100.00	100.00
	9557		15.00	15.00
	8039		200.00	200.00
	18881		10.00	10.00
	16273		30.00	30.00
	13114		10.00	10.00
	7875		30.00	30.00
	22690		120.00	120.00
	11838		200.00	200.00
	22756		30.00	30.00
	26283		10.00	10.00
	13997		100.00	100.00
	9381		90.00	90.00
	47949		120.00	120.00
	43652		100.00	100.00
	15964		60.00	60.00
	47753		90.00	90.00
	17936		200.00	200.00
	10239		150.00	150.00
	2997		10.00	10.00
	18700		30.00	30.00
	15781		90.00	90.00
	11698		30.00	30.00
	9371		120.00	120.00
	9183		100.00	100.00
	27749		150.00	150.00
	5714		15.00	15.00
	9337		30.00	30.00
	5563		20.00	20.00

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
morphine				
LA	6002		10.00	10.00
	495		10.00	10.00
	47154		200.00	200.00
	40563		30.00	30.00
	9602		5.00	5.00
	47985		10.00	10.00
	14063		100.00	100.00
	19477		100.00	100.00
	9342		60.00	60.00
	22026		30.00	30.00
	14050		100.00	100.00
SA	6366		50.00	50.00
	15815		50.00	50.00
	3919		10.00	10.00
	4266		10.00	10.00
	6232		20.00	20.00
	9137		20.00	20.00
SOL	23063		0.20	0.20
	34477		2.00	2.00
	53273		2.00	2.00
	10631		10.00	10.00
	60950		1.00	1.00
	11342		6.00	6.00
	30252		8.40	8.40
	8876		20.00	20.00
	63593		2.00	2.00
	17943		20.00	20.00
	5555		2.00	2.00
	56788		2.00	2.00
	68712		20.00	20.00
	64417		0.40	0.40
	12889		20.00	20.00
	5840		2.00	2.00
	19291		20.00	20.00
	1503		5.00	5.00
	58879		2.00	2.00
	60518		100.00	100.00
	59584		2.00	2.00
	14156		0.10	0.10
	4693		2.00	2.00
	6269		20.00	20.00
	655		2.00	2.00
EFF	23060		200.00	200.00

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
morphine				
EFF	607		20.00	20.00
	4476		60.00	60.00
	12604		100.00	100.00
	29020		200.00	200.00
	12900		30.00	30.00
	12591		60.00	60.00
	14226		30.00	30.00
	9672		100.00	100.00
	6736		20.00	20.00
omnopon				
SA	19317		10.00	
	19764		10.00	
oxycodone				
LA	58493		20.00	30.00
	40645		5.00	7.50
	61836		20.00	30.00
	63332		30.00	45.00
	39498		20.00	30.00
	45788		15.00	22.50
	67446		60.00	90.00
	54694		80.00	120.00
	65392		20.00	30.00
	53113		10.00	15.00
	7167		5.00	7.50
	6708		40.00	60.00
	10021		80.00	120.00
	64807		120.00	180.00
	7389		20.00	30.00
	50733		10.00	15.00
	49742		5.00	7.50
	52217		10.00	15.00
	64426		15.00	22.50
	9927		40.00	60.00
	52220		40.00	60.00
	66298		10.00	15.00
	66616		5.00	7.50
	5843		10.00	15.00
	56665		10.00	15.00
	45830		120.00	180.00
	45766		60.00	90.00
	64164		15.00	22.50
	63714		60.00	90.00
	6948		80.00	120.00

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
oxycodone				
LA	6769		5.00	7.50
	49787		20.00	30.00
	45790		15.00	22.50
	40961		40.00	60.00
	61936		5.00	7.50
	52216		5.00	7.50
	57033		10.00	15.00
	66760		5.00	7.50
	65932		40.00	60.00
	65933		80.00	120.00
	39475		10.00	15.00
	64150		5.00	7.50
	45745		30.00	45.00
	40616		5.00	7.50
	5599		10.00	15.00
	45827		30.00	45.00
	66837		15.00	22.50
	66619		20.00	30.00
	46187		120.00	180.00
	64552		60.00	90.00
	66606		10.00	15.00
	63198		40.00	60.00
	61935		10.00	15.00
	68797		20.00	30.00
	39477		10.00	15.00
	65390		30.00	45.00
	39478		20.00	30.00
	60196		40.00	60.00
	51896		80.00	120.00
	61779		40.00	60.00
	62322		80.00	120.00
	6608		20.00	30.00
	45929		60.00	90.00
	40785		40.00	60.00
	52809		10.00	15.00
	57052		20.00	30.00
	64333		30.00	45.00
	53116		20.00	30.00
SA	51384		20.00	30.00
	7275		20.00	30.00
	60146		5.00	7.50
	51789		10.00	15.00
	50095		5.00	7.50

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit	Form	Product code	Days/TD	Strength/unit	OMEQ/unit
tramadol					**tramadol**				
LA	50947		100.00	20.00	LA	26336		300.00	60.00
	37020		150.00	30.00		48090		200.00	40.00
	46279		200.00	40.00		16271		300.00	60.00
	42798		150.00	30.00		40058		100.00	20.00
	46643		150.00	30.00		40805		150.00	30.00
	32450		400.00	80.00		35656		100.00	20.00
	68833		100.00	20.00		11746		300.00	60.00
	39505		100.00	20.00		4114		100.00	20.00
	40254		50.00	10.00		66729		100.00	20.00
	40926		150.00	30.00		21947		150.00	30.00
	23981		150.00	30.00		38956		200.00	40.00
	49323		150.00	30.00		8416		200.00	40.00
	21777		200.00	40.00		40061		150.00	30.00
	56491		200.00	40.00		68210		100.00	20.00
	44371		150.00	30.00		58129		100.00	20.00
	66299		200.00	40.00		37831		100.00	20.00
	36035		300.00	60.00		6153		150.00	30.00
	40060		200.00	40.00		50862		200.00	40.00
	43198		50.00	10.00		36732		50.00	10.00
	36873		50.00	10.00		39811		200.00	40.00
	58316		50.00	10.00		63047		100.00	20.00
	11748		400.00	80.00		35651		200.00	40.00
	26986		200.00	40.00		28728		300.00	60.00
	60121		50.00	10.00		4999		150.00	30.00
	64496		100.00	20.00		31105		200.00	40.00
	49324		100.00	20.00		60751		200.00	40.00
	41976		100.00	20.00		5257		150.00	30.00
	40249		100.00	20.00		34065		150.00	30.00
	31107		150.00	30.00		39709		200.00	40.00
	34260		100.00	20.00		23625		150.00	30.00
	21797		200.00	40.00		35347		100.00	20.00
	64731		100.00	20.00	SA	43513		50.00	10.00
	37021		200.00	40.00		34808		50.00	10.00
	4834		150.00	30.00		187		50.00	10.00
	4115		100.00	20.00		29860		50.00	10.00
	63898		50.00	10.00		65266		50.00	10.00
	701		50.00	10.00		37867		100.00	20.00
	3644		100.00	20.00		61610		50.00	10.00
	39798		100.00	20.00		13813		50.00	10.00
	9389		50.00	10.00		14490		50.00	10.00
	36949		50.00	10.00		40718		50.00	10.00
	31734		400.00	80.00		38528		50.00	10.00
	39750		150.00	30.00		61272		50.00	10.00

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
oxycodone				
SA	52592		10.00	15.00
	49940		5.00	7.50
	6557		5.00	7.50
	59865		10.00	15.00
	6790		5.00	7.50
	60158		20.00	30.00
	58853		10.00	15.00
	7372		20.00	30.00
	5585		10.00	15.00
	58114		20.00	30.00
	58217		5.00	7.50
	9973		10.00	15.00
SOL	64965		1.00	1.50
	7406		10.00	15.00
	69474		1.00	1.50
	69559		1.00	1.50
	6609		1.00	1.50
	58039		1.00	1.50
	9874		1.00	1.50
	11405		10.00	15.00
papaveretum				
EFF	18261		7.71	
pentazocine				
SA	36472		15.00	5.55
	10769		50.00	18.50
	7450		15.00	5.55
	2367		25.00	9.25
	8375		25.00	9.25
	328		50.00	18.50
pethidine				
SA	40239		50.00	5.00
	17386		50.00	5.00
	57027		50.00	5.00
	38013		50.00	5.00
	56022		50.00	5.00
	54790		50.00	5.00
	234		25.00	2.50
	58737		50.00	5.00
	38103		25.00	2.50
	2450		50.00	5.00
	31935		50.00	5.00

Form	Product code	Days/TD	Strength/unit	OMEQ/unit
phenazocine				
SA	17167		5.00	
	14394		5.00	
tapentadol				
LA	46020		100.00	40.00
	46659		200.00	80.00
	47399		250.00	100.00
	47460		250.00	100.00
	45982		50.00	20.00
	46019		150.00	60.00
	45800		200.00	80.00
	46021		50.00	20.00
	46018		100.00	40.00
	46159		150.00	60.00
SA	46461		75.00	30.00
	45936		50.00	20.00
	46022		75.00	30.00
	45811		50.00	20.00
SOL	61764		20.00	8.00
	60759		20.00	8.00
tramadol				
LA	67310		200.00	40.00
	69894		200.00	40.00
	35806		100.00	20.00
	40883		150.00	30.00
	19993		100.00	20.00
	67323		150.00	30.00
	54023		50.00	10.00
	9396		100.00	20.00
	36697		200.00	40.00
	6215		200.00	40.00
	68427		50.00	10.00
	34281		200.00	40.00
	35438		100.00	20.00
	27591		150.00	30.00
	38196		200.00	40.00
	67161		150.00	30.00
	52977		100.00	20.00
	64871		100.00	20.00
	65954		50.00	10.00
	5028		200.00	40.00
	16395		200.00	40.00
	21397		400.00	80.00
	5169		200.00	40.00

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix P. Opioid product look-up [continued]

Form	Product code	Days/TD	Strength/unit	OMEQ/unit	Form	Product code	Days/TD	Strength/unit	OMEQ/unit
tramadol									
SA	64459		37.50	7.50					
	52605		50.00	10.00					
	34422		50.00	10.00					
	6558		37.50	7.50					
	34570		50.00	10.00					
	34639		50.00	10.00					
	67744		50.00	10.00					
	52495		50.00	10.00					
	62778		37.50	7.50					
	86		50.00	10.00					
	687		37.50	7.50					
	61775		50.00	10.00					
	47854		50.00	10.00					
	16076		37.50	7.50					
	40166		50.00	10.00					
	34521		50.00	10.00					
	32165		50.00	10.00					
	67197		50.00	10.00					
SOL	46587		100.00	20.00					
EFF	3378		50.00	10.00					
	42280		37.50	7.50					
	42332		37.50	7.50					
	11101		50.00	10.00					
OD	11734		50.00	10.00					
	20310		50.00	10.00					

Notes: SA, short-acting oral solid; LA, long-acting oral solid; TD, transdermal patch; SOL, oral solution; EFF, solids and semi-solids for oral suspension; OD, orodispersible; SPR, buccal and nasal spray; SUP, suppository

Appendix Q. Median duration (days) of prescriptions, by opioid drug

Opioid drug	Median (IQR) prescription duration* (days)
Buprenorphine	27 days (IQR: 27, 27 days)
Codeine	16 days (IQR: 12, 16 days)
Dihydrocodeine	16 days (IQR: 12, 25 days)
Fentanyl	30 days (IQR: 15, 30 days)
Morphine	25 days (IQR: 10, 30 days)
Oxycodone	28 days (IQR: 14, 28 days)
Tramadol	16 days (IQR: 12, 30 days)
Other	18 days (IQR: 9, 28 days)

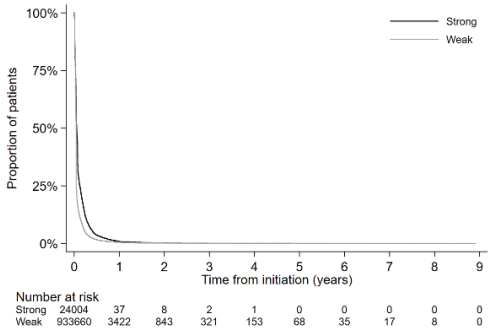
Notes: *this is the calculated duration, obtained by dividing the quantity supplied by the numeric daily dose; IQR, interquartile range.

Appendix R. Sensitivity analysis of the definition used for a break in opioid exposure

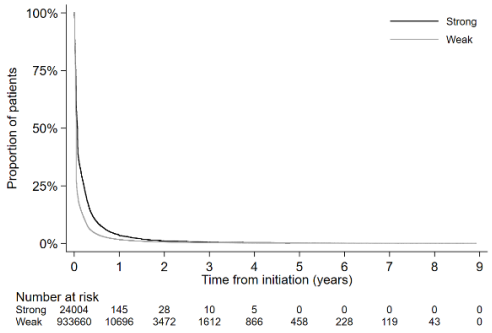
Table 1. Time to first treatment break and final treatment break for 50% and 25% of people initiated on opioids, split by those initiated on weak and strong opioids.

Gap length (days)	Opioid at initiation	Time to first break (days) (95%CI)		Time to final break (days) (95%CI)	
		50%	25%	50%	25%
60	Strong	20 (20-21)	45 (43-48)	27 (27-27)	181 (173-190)
	Weak	16 (16-16)	16 (16-16)	16 (16-16)	77 (76-78)
90	Strong	27 (25-27)	78 (76-82)	29 (28-30)	286 (272-298)
	Weak	16 (16-16)	20 (20-20)	16 (16-16)	121 (119-122)
120	Strong	28 (27-28)	115 (110-119)	40 (36-43)	382 (365-400)
	Weak	16 (16-16)	25 (25-25)	16 (16-16)	170 (168-172)
180	Strong	36 (33-39)	192 (186-199)	79 (73-86)	585 (563-610)
	Weak	16 (16-16)	43 (42-43)	16 (16-16)	277 (275-280)

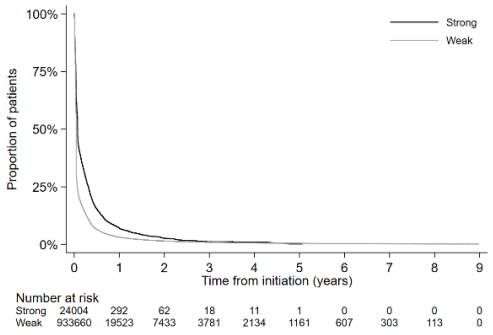
A. 60-day gap



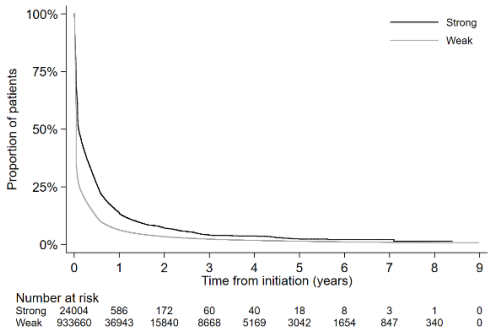
B. 90-day gap



C. 120-day gap



D. 180-day gap

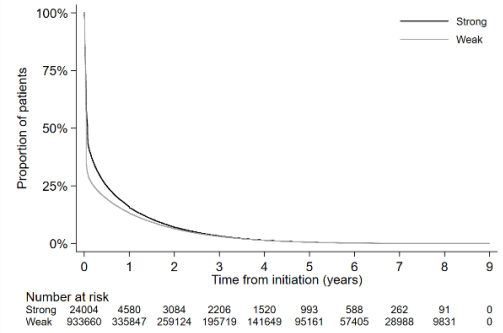


Notes: Treatment break defined as a gap of 60 days (A), 90 days (B), 120 days (C) and 180 days (D).

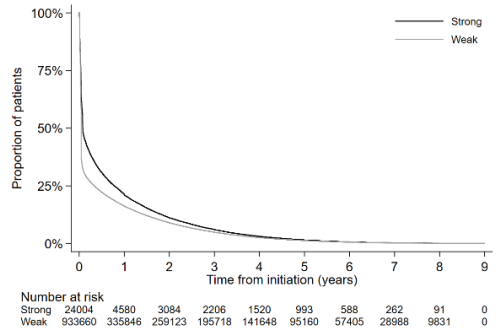
Figure 1. Proportion of people continuously exposed to opioids from initiation to their first break in opioid exposure.

Appendix R. Sensitivity analysis of the definition used for a break in opioid exposure [continued]

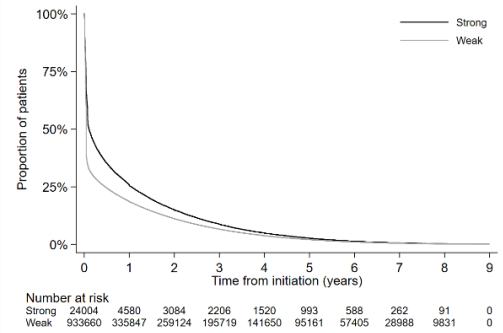
A. 60-day gap



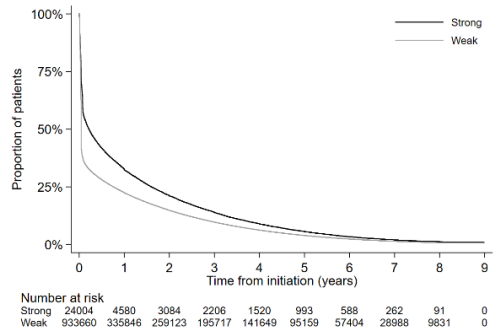
B. 90-day gap



C. 120-day gap



D. 180-day gap



Notes: Treatment break defined as a gap of 60 days (A), 90 days (B), 120 days (C) and 180 days (D).

Figure 2. Proportion of people intermittently or continuously exposed to opioids from initiation to their final break in opioid exposure.

Appendix S. People meeting definitions for persistent opioid-use in their first patient-year and the proportion of active patients that continue to meet that definition each year of follow-up

Year	Not persistent			Wide			Intermediate			Strict		
1	**918,546**	**95.9%**		**24,599**	**2.6%**		**11,003**	**1.1%**		**3,516**	**0.4%**	
	Active	900,754		Active	24,301		Active	10,961		Active	3,507	
Year 2	Persistent (any)	1.1%	Censored 17,792	**Wide**	**19.0%**	Censored 298	**Intermediate**	**33.7%**	Censored 42	**Strict**	**36.9%**	Censored 9
	Not persistent	**98.9%**		Persistent (other)	13.1%		Persistent (other)	28.7%		Persistent (other)	24.2%	
				Not persistent	67.8%		Not persistent	37.6%		Not persistent	38.9%	
	Active	861,567		Active	22,933		Active	10,551		Active	3,254	
Year 3	Persistent (any)	1.5%	Censored 39,187	**Wide**	**12.3%**	Censored 1,368	**Intermediate**	**22.5%**	Censored 410	**Strict**	**24.6%**	Censored 253
	Not persistent	**98.5%**		Persistent (other)	11.9%		Persistent (other)	21.1%		Persistent (other)	16.8%	
				Not persistent	75.8%		Not persistent	56.5%		Not persistent	58.6%	
	Active	809,645		Active	21,257		Active	9,836		Active	2,900	
Year 4	Persistent (any)	1.7%	Censored 51,922	**Wide**	**9.2%**	Censored 1,676	**Intermediate**	**17.7%**	Censored 715	**Strict**	**19.6%**	Censored 354
	Not persistent	**98.3%**		Persistent (other)	10.4%		Persistent (other)	17.3%		Persistent (other)	14.6%	
				Not persistent	80.4%		Not persistent	64.9%		Not persistent	65.8%	
	Active	752,489		Active	19,408		Active	9,054		Active	2,567	
Year 5	Persistent (any)	1.7%	Censored 57,156	**Wide**	**6.9%**	Censored 1,849	**Intermediate**	**13.0%**	Censored 782	**Strict**	**15.2%**	Censored 333
	Not persistent	**98.3%**		Persistent (other)	8.9%		Persistent (other)	14.5%		Persistent (other)	12.2%	
				Not persistent	84.2%		Not persistent	72.5%		Not persistent	72.6%	
	Active	681,836		Active	17,334		Active	8,098		Active	2,213	
Year 6	Persistent (any)	1.6%	Censored 70,653	**Wide**	**5.3%**	Censored 2,074	**Intermediate**	**10.0%**	Censored 956	**Strict**	**11.4%**	Censored 354
	Not persistent	**98.4%**		Persistent (other)	7.2%		Persistent (other)	10.5%		Persistent (other)	10.0%	
				Not persistent	87.4%		Not persistent	79.5%		Not persistent	78.6%	
	Active	594,501		Active	14,883		Active	6,954		Active	1,842	
Year 7	Persistent (any)	1.3%	Censored 87,335	**Wide**	**3.8%**	Censored 2,451	**Intermediate**	**6.9%**	Censored 1,144	**Strict**	**7.9%**	Censored 371
	Not persistent	**98.7%**		Persistent (other)	5.6%		Persistent (other)	8.3%		Persistent (other)	8.8%	
				Not persistent	90.5%		Not persistent	84.8%		Not persistent	83.3%	
	Active	486,199		Active	12,009		Active	5,634		Active	1,459	
Year 8	Persistent (any)	1.0%	Censored 108,302	**Wide**	**2.7%**	Censored 2,874	**Intermediate**	**4.6%**	Censored 1,320	**Strict**	**5.0%**	Censored 383
	Not persistent	**99.0%**		Persistent (other)	3.6%		Persistent (other)	5.5%		Persistent (other)	5.8%	
				Not persistent	93.7%		Not persistent	90.0%		Not persistent	89.6%	
	Active	363,244		Active	8,890		Active	4,239		Active	1,030	
Year 9	Persistent (any)	0.4%	Censored 122,955	**Wide**	**1.4%**	Censored 3,119	**Intermediate**	**1.3%**	Censored 1,395	**Strict**	**1.5%**	Censored 429
	Not persistent	**99.6%**		Persistent (other)	1.1%		Persistent (other)	2.7%		Persistent (other)	3.6%	
				Not persistent	97.5%		Not persistent	95.9%		Not persistent	95.0%	

Notes: Wide persistent, >180DDD or >4,500mg OMEQ in ≥3 quarters/year; intermediate persistent, >365DDD or >9,000mg OMEQ in 4 quarters/year; strict persistent, >730DDD or 18,000mg OMEQ and ≥10 prescriptions in 4 quarters/year; not persistent, not meeting any definition for persistence

Appendix T. Medcodes to identify people with osteoporosis in the CPRD

Medcode	Read code	Description
51891	585O.00	Quantitative ultrasound scan of heel - result osteoporotic
13987	58E4.00	Forearm DXA scan result osteoporotic
37972	58E8.00	Heel DXA scan T score
46510	58EA.00	Heel DXA scan result osteoporotic
40904	58EE.00	Hip DXA scan T score
42354	58EG.00	Hip DXA scan result osteoporotic
11581	58EK.00	Lumbar spine DXA scan T score
39217	58EM.00	Lumbar DXA scan result osteoporotic
97266	58ES.00	Femoral neck DEXA scan T score
96342	58EV.00	Femoral neck DEXA scan result osteoporotic
37646	66a2.00	Osteoporosis treatment started
34129	66a4.00	Osteoporosis treatment changed
48962	66a5.00	Osteoporosis - no treatment
70233	66aA.00	Osteoporosis - treatment response
98189	66aB.00	Osteoporosis - no treatment response
110401	8B31E00	Osteoporosis medication compliance review
101068	8B6b.00	Osteoporosis medication prophylaxis
98760	9kj0.00	Bone sparing drug treatment offered for osteoporosis - ESA
277	N330.00	Osteoporosis
14967	N330000	Osteoporosis; unspecified
16307	N330100	Senile osteoporosis
9700	N330200	Postmenopausal osteoporosis
40428	N330300	Idiopathic osteoporosis
62702	N330400	Disuse osteoporosis
24093	N330500	Drug-induced osteoporosis
70349	N330600	Postoophorectomy osteoporosis
93655	N330700	Postsurgical malabsorption osteoporosis
54232	N330800	Localized osteoporosis - Lequesne
60433	N330900	Osteoporosis in multiple myelomatosis
31580	N330A00	Osteoporosis in endocrine disorders
3346	N330B00	Vertebral osteoporosis
16857	N330C00	Osteoporosis localized to spine
25650	N330D00	Osteoporosis due to corticosteroids
34798	N330z00	Osteoporosis NOS
44386	N331.14	Osteoporotic vertebral collapse
39334	N331200	Postoophorectomy osteoporosis with pathological fracture
33526	N331300	Osteoporosis of disuse with pathological fracture
68019	N331400	Postsurgical malabsorption osteoporosis with path fracture
46894	N331500	Drug-induced osteoporosis with pathological fracture
27597	N331600	Idiopathic osteoporosis with pathological fracture
17377	N331800	Osteoporosis + pathological fracture lumbar vertebrae
12673	N331900	Osteoporosis + pathological fracture thoracic vertebrae
48772	N331A00	Osteoporosis + pathological fracture cervical vertebrae
38395	N331B00	Postmenopausal osteoporosis with pathological fracture
45736	N331H00	Collapse of cervical vertebra due to osteoporosis
5841	N331J00	Collapse of lumbar vertebra due to osteoporosis
19048	N331K00	Collapse of thoracic vertebra due to osteoporosis
4013	N331L00	Collapse of vertebra due to osteoporosis NOS
11503	N331M00	Fragility fracture due to unspecified osteoporosis
93705	N331M11	Minimal trauma fracture due to unspecified osteoporosis
36432	N374600	Osteoporotic kyphosis

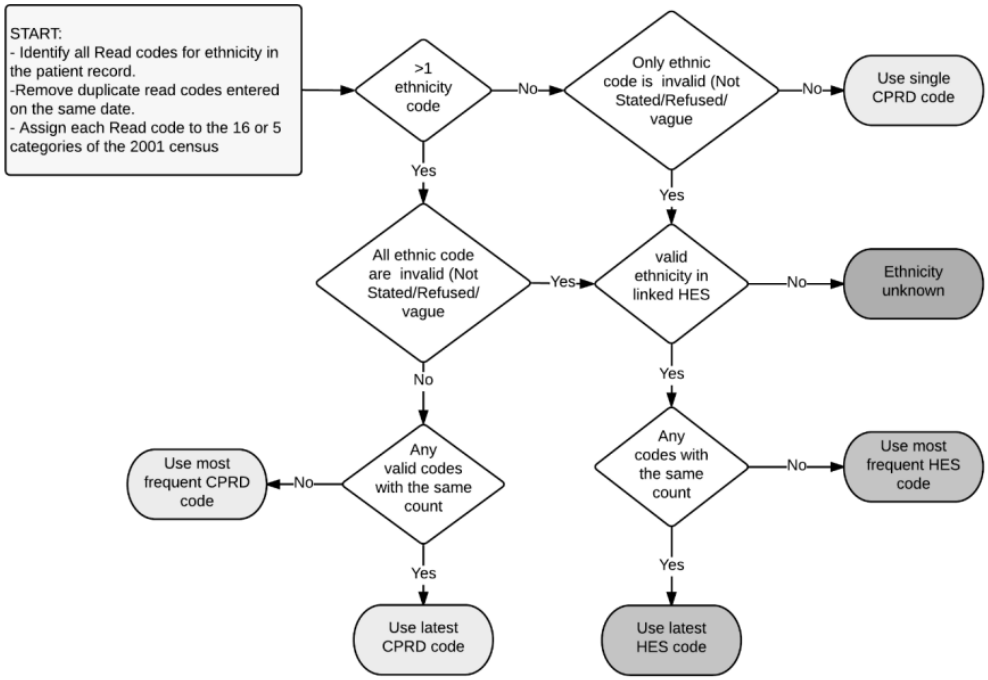
Appendix T. Medcodes to identify people with osteoporosis in the CPRD [continued]

Medcode	Read code	Description
57301	NyuB000	[X]Other osteoporosis with pathological fracture
41755	NyuB100	[X]Other osteoporosis
102730	NyuB200	[X]Osteoporosis in other disorders classified elsewhere
18825	NyuB800	[X]Unspecified osteoporosis with pathological fracture

Appendix U. Fracture-risk increasing drugs

Psychoactive				
agomelatine	co-beneldopa	levetiracetam	pericyazine	sertraline
alprazolam	co-careldopa	levopromazine	perphenazine	sodium oxybate
amantadine	diazepam	lithium	phenelzine	sodium valproate
amisulpiride	dosulepin	lofepramine	phenobarbital	sulpiride
amitriptyline	doxepin	loprazolam	phenytoin	temazepam
apomorphine	duloxetine	lorazepam	pimozide	thiopental
aripiprazole	entacapone	lorazepam	pramipexole	tigabine
asenapine	escitalopram	lormetazepam	pregabalin	tolcapone
benperidol	eslicarbazepine	melatonin	primidone	topiramate
bromocriptine	ethosuximide	meprobamate	prochlorperazine	tranylcypromine
buspirone	fluoxetine	mianserin	procyclidine	trazodone
cabergoline	flupentixol	mirtazapine	promazine	trifluoperazine
carbamazepine	flupentixol	moclobemide	promethazine	trihexyphenidyl
chloral hydrate	fluphenazine	nitrazepam	quetiapine	trimipramine
chlordiazepoxide	flurazepam	nortriptyline	rasagiline	valproic acid
chlorpromazine	fluvoxamine	olanzapine	reboxetine	venlafaxine
citalopram	gabapentin	orphenadrine	retigabine	vigabatrin
clobazam	haloperidol	oxycarbazepine	risperidone	zaleplon
clomipramine	imipramine	paliperidone	ropinerole	zolpidem
clomthiazole	isocerboxazid	paroxetine	rotigotine	zonisamide
clonazepam	lacosamide	perampanel	rufinamide	zopiclone
clozapine	lamotrigine	pergolide	selegiline	zuclopentixol
Cardiovascular				
acebutolol	cilazapril	frusene	metoprolol	riociguat
aliskiren	clonidine	furosemide	minoxidil	sildenafil
ambrisentan	co-amilofrise	hydralazine	moexipril	sodium nitroprusside
amiloride	co-amilozide	iloprost	moxonidine	sotalol
atenolol	co-flumactone	imidapril	nadolol	spironolactone
azilsartan	co-triamterzide	indapamide	nebivolol	tadalafil
bendroflumethiazide	cyclopenthiazide	indoramin	olmesartan	telmisartan
bisoprolol	digoxin	irbesartan	oxprenolol	terazosin
bosentan	doxazosin	labetalol	perindopril	timolol
bumetanide	enalapril	lasilactone	phenoxybenzamine	torasemide
candesartan	eplerenone	lisinopril	phentolamine	trandolapril
captopril	eprosartan	losartan	prazosin	triamterene
carbedilol	esmolol	macitentan	propanolol	valsartan
celiprolol	flecainide	methyldopa	quinapril	xipamide
chlortalidone	fosinopril	metolazone	ramipril	
Steroids/glucocorticoids				
betamethasone	dexamethasone	methylprednisolone	prednisone	
deflazacort	hydrocortisone	prednisolone		

Appendix V. Approach to extracting ethnicity data



Notes: Figure obtained from Mathur *et al.* (2017).[298]

Appendix W. Medcodes to identify fractures in the CPRD

Medcode	Read code	Description	Site
5929	S2...11	Arm fracture	Arm
1179	S28..11	Ill-defined fracture of arm	Arm
2660	S28z.00	Ill-defined fractures of upper limb NOS	Arm
49267	S28..00	Ill-defined fractures of upper limb	Arm
47478	S280.00	Closed ill-defined fractures of upper limb	Arm
66853	S281.00	Open ill-defined fractures of upper limb	Arm
31708	S29..11	Multiple fractures of arm	Arm
95633	S294000	Cl fractures involving multiple regions of both upper limbs	Arm
92830	SR12000	Closed fractures involving multiple regions of one upp limb	Arm
11004	S120900	Closed fracture multiple ribs	Chest
16494	S120100	Closed fracture of one rib	Chest
7831	S120000	Closed fracture of rib, unspecified	Chest
35849	S112.00	Closed fracture of thoracic spine with spinal cord lesion	Chest
280	S120.00	Closed fracture rib	Chest
3983	S122.00	Closed fracture sternum	Chest
27404	S102.00	Closed fracture thoracic vertebra	Chest
41138	S102z00	Closed fracture thoracic vertebra not otherwise specified	Chest
39816	S102000	Closed fracture thoracic vertebra, burst	Chest
99516	S102500	Closed fracture thoracic vertebra, posterior arch	Chest
64872	S102300	Closed fracture thoracic vertebra, spinous process	Chest
96659	S102200	Closed fracture thoracic vertebra, spondylolysis	Chest
48886	S102400	Closed fracture thoracic vertebra, transverse process	Chest
28524	S102100	Closed fracture thoracic vertebra, wedge	Chest
35260	S150000	Closed multiple fractures of thoracic spine	Chest
15837	N331011	Collapse of thoracic vertebra	Chest
9319	N331F00	Collapse of thoracic vertebra	Chest
19048	N331K00	Collapse of thoracic vertebra due to osteoporosis	Chest
9688	S127.00	Fracture of rib	Chest
11969	S128.00	Fracture of sternum	Chest
5381	S15..00	Fracture of thoracic vertebra	Chest
11277	S150.00	Multiple fractures of thoracic spine	Chest
17107	S29..12	Multiple rib fractures	Chest
11770	S102y00	Other specified closed fracture thoracic vertebra	Chest
11378	S12z.11	Rib fracture NOS	Chest
30616	N331000	Pathological fracture of thoracic vertebra	Chest
63253	S103.00	Open fracture thoracic vertebra	Chest
62047	S103100	Open fracture thoracic vertebra, wedge	Chest
101318	S103500	Open fracture thoracic vertebra, posterior arch	Chest
40533	S120200	Closed fracture of two ribs	Chest
56384	S120300	Closed fracture of three ribs	Chest
34197	S120400	Closed fracture of four ribs	Chest
55424	S120500	Closed fracture of five ribs	Chest
65484	S120600	Closed fracture of six ribs	Chest
90494	S120700	Closed fracture of seven ribs	Chest
68652	S120800	Closed fracture of eight or more ribs	Chest
8968	S120A00	Cough fracture	Chest
28244	S120z00	Closed fracture of rib(s) NOS	Chest
48224	S121.00	Open fracture rib	Chest

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
73613	S121000	Open fracture of rib, unspecified	Chest
44826	S121200	Open fracture of two ribs	Chest
73956	S121700	Open fracture of seven ribs	Chest
71452	S121900	Open fracture multiple ribs	Chest
101560	S121z00	Open fracture of rib(s) NOS	Chest
63982	S123.00	Open fracture sternum	Chest
10696	S127000	Multiple fractures of ribs	Chest
28538	S127100	Cough fracture of ribs	Chest
27818	S12z.12	Sternum fracture NOS	Chest
66322	S150100	Open multiple fracture of thoracic spine	Chest
68899	S29..13	Multiple fractures of sternum	Chest
65155	S4J0000	Closed fracture-dislocation of sternum	Chest
94236	S4J1000	Open fracture-dislocation of sternum	Chest
24615	S4J1200	Open fracture-dislocation sterno-clavicular joint, anterior	Chest
62631	S4J2000	Closed fracture-subluxation of sternum	Chest
94593	S4J3000	Open fracture-subluxation of sternum	Chest
58190	S12X000	Closed fracture of bony thorax part unspecified	Chest
95839	S12y000	Closed fracture of other parts of bony thorax	Chest
4310	S352300	Closed fracture cuboid	Foot
3937	S352700	Closed fracture metatarsal	Foot
8276	S350.00	Closed fracture of calcaneus	Foot
4306	S360.00	Closed fracture of one or more phalanges of foot	Foot
11453	7K1LB00	Closed reduction of fracture of hallux	Foot
7339	7K1LA00	Closed reduction of fracture of toe	Foot
6062	S356.00	Fracture of metatarsal bone	Foot
2672	S36..00	Fracture of one or more phalanges of foot	Foot
7159	S363.00	Fracture of other toe	Foot
2442	S355.00	Fracture of talus	Foot
169	S35..11	Metatarsal bone fracture	Foot
9174	S3x4.00	Multiple fractures of foot	Foot
31847	S362100	Open fracture of great toe	Foot
15166	S350.12	Os calcis fracture	Foot
1873	S36..11	Toe fracture	Foot
38433	7K1L900	Closed reduction of fracture of metatarsus	Foot
2710	S35..12	Tarsal bone fracture	Foot
8263	S350.11	Heel bone fracture	Foot
57924	S350000	Closed fracture calcaneus, extra-articular	Foot
34723	S350100	Closed fracture calcaneus, intra-articular	Foot
43378	S351.00	Open fracture of calcaneus	Foot
70226	S351100	Open fractures calcaneus, intra-articular	Foot
15927	S352.00	Closed fracture of other tarsal and metatarsal bones	Foot
1700	S352.11	March fracture	Foot
20253	S352000	Closed fracture of tarsal bone, unspecified	Foot
15079	S352100	Closed fracture of talus	Foot
30611	S352111	Closed fracture of astragalus	Foot
11635	S352200	Closed fracture navicular	Foot
34954	S352400	Closed fracture medial cuneiform	Foot
58065	S352500	Closed fracture intermediate cuneiform	Foot

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
49847	S352600	Closed fracture lateral cuneiform	Foot
37450	S352800	Closed fracture talus, head	Foot
46955	S352900	Closed fracture talus, neck	Foot
45664	S352A00	Closed fracture talus, body	Foot
24620	S352B00	Closed fracture metatarsal base	Foot
27567	S352C00	Closed fracture metatarsal shaft	Foot
29748	S352D00	Closed fracture metatarsal neck	Foot
35077	S352E00	Closed fracture metatarsal head	Foot
28371	S352F00	Closed fracture metatarsal, multiple	Foot
64378	S352G00	Closed tarsal fractures, multiple	Foot
36304	S352H00	Closed fracture of cuneiforms	Foot
28875	S352J00	Closed fracture of base of fifth metatarsal	Foot
43153	S352z00	Closed fracture of one or more tarsal + metatarsal bones NOS	Foot
67007	S353.00	Open fracture of other tarsal and metatarsal bones	Foot
100196	S353000	Open fracture of tarsal bone, unspecified	Foot
39758	S353100	Open fracture of talus	Foot
40992	S353200	Open fracture navicular	Foot
49821	S353300	Open fracture cuboid	Foot
66231	S353400	Open fracture medial cuneiform	Foot
97211	S353500	Open fracture intermediate cuneiform	Foot
108242	S353600	Open fracture lateral cuneiform	Foot
55939	S353700	Open fracture metatarsal	Foot
109115	S353800	Open fracture talus, head	Foot
93536	S353900	Open fracture talus, neck	Foot
97386	S353A00	Open fracture talus, body	Foot
72586	S353B00	Open fracture metatarsal base	Foot
64545	S353C00	Open fracture metatarsal shaft	Foot
97803	S353D00	Open fracture metatarsal neck	Foot
105612	S353E00	Open fracture metatarsal head	Foot
66099	S353F00	Open fracture metatarsal, multiple	Foot
40658	S353H00	Open fracture cuneiforms	Foot
67239	S353J00	Open fracture of base of fifth metatarsal	Foot
48925	S353z00	Open fracture of tarsal and metatarsal bones NOS	Foot
25073	S360000	Closed fracture proximal phalanx, toe	Foot
29804	S360100	Closed fracture middle phalanx, toe	Foot
28251	S360200	Closed fracture distal phalanx, toe	Foot
53905	S360300	Closed fracture multiple phalanges, toe	Foot
37865	S361.00	Open fracture of one or more phalanges of foot	Foot
50517	S361000	Open fracture proximal phalanx, toe	Foot
69728	S361100	Open fracture middle phalanx, toe	Foot
51213	S361200	Open fracture distal phalanx, toe	Foot
61556	S361300	Open fracture multiple phalanges, toe	Foot
28604	S362000	Closed fracture of great toe	Foot
44628	S4H0.00	Closed fracture-dislocation foot	Foot
56599	S4H0000	Closed fracture-dislocation, subtalar joint	Foot
71132	S4H0100	Closed fracture-dislocation, midtarsal joint	Foot
67849	S4H0200	Closed fracture-dislocation, tarsometatarsal joint	Foot
28800	S4H0400	Closed fracture-dislocation, IPJ, single toe	Foot

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
92268	S4H0600	Closed fracture-dislocation, IPJ, multiple toes	Foot
52340	S4H1.00	Open fracture-dislocation, foot	Foot
40445	S4H1000	Open fracture-dislocation, subtalar joint	Foot
108596	S4H1100	Open fracture-dislocation, midtarsal joint	Foot
92043	S4H1200	Open fracture-dislocation, tarsometatarsal joint	Foot
39893	S4H1300	Open fracture-dislocation, metatarsophalangeal joint, single	Foot
42902	S4H1400	Open fracture-dislocation, IPJ, single toe	Foot
106875	S4H1600	Open fracture-dislocation, IPJ, multiple toes	Foot
44673	S4H2.00	Closed fracture-subluxation, foot	Foot
72071	S4H2000	Closed fracture-subluxation, subtalar joint	Foot
65028	S4H2100	Closed fracture-subluxation, midtarsal joint	Foot
73703	S4H2200	Closed fracture-subluxation, tarsometatarsal joint	Foot
95728	S4H2400	Closed fracture-subluxation, IPJ, single toe	Foot
72822	S4H2600	Closed fracture-subluxation, IPJ, multiple toes	Foot
93650	S4H3.00	Open fracture-subluxation, foot	Foot
65895	S4H3300	Open fracture-subluxation, metatarsophalangeal joint, single	Foot
68514	S4H3400	Open fracture-subluxation, IPJ, single toe	Foot
52977	Syu5400	[X]Fracture of forearm, unspecified	Forearm
102916	Syu5300	[X]Fracture of other parts of forearm	Forearm
19058	S234D00	Closed fracture distal radius, extra-articular, other type	Forearm
44844	S234C00	Closed fracture distal radius, intra-articular, die-punch	Forearm
28293	S234E00	Closed fracture distal radius, intra-articular, other type	Forearm
40476	S234500	Closed fracture distal ulna, unspecified	Forearm
27591	S234z00	Closed fracture of forearm, lower end, NOS	Forearm
18389	S234000	Closed fracture of forearm, lower end, unspecified	Forearm
50654	S23x000	Closed fracture of forearm, unspecified	Forearm
43570	S230.00	Closed fracture of proximal radius and ulna	Forearm
34371	S230400	Closed fracture of proximal ulna, comminuted	Forearm
17952	S23x100	Closed fracture of radius (alone), unspecified	Forearm
18299	S234.00	Closed fracture of radius and ulna, lower end	Forearm
36328	S23xz00	Closed fracture of radius and ulna, NOS	Forearm
26324	S232.00	Closed fracture of radius and ulna, shaft	Forearm
33808	S232z00	Closed fracture of radius and ulna, shaft, NOS	Forearm
15764	S23x.00	Closed fracture of radius and ulna, unspecified part	Forearm
51364	S232000	Closed fracture of radius, shaft, unspecified	Forearm
1742	S234200	Closed fracture of the distal radius, unspecified	Forearm
34426	S230500	Closed fracture of the proximal ulna	Forearm
42864	S232100	Closed fracture of the radial shaft	Forearm
4359	S23x300	Closed fracture of the radius and ulna	Forearm
44790	S232200	Closed fracture of the ulnar shaft	Forearm
24621	S23x200	Closed fracture of ulna (alone), unspecified	Forearm
9538	S230100	Closed fracture olecranon, extra-articular	Forearm
28708	S234600	Closed fracture radius and ulna, distal	Forearm
35031	S232300	Closed fracture radius and ulna, middle	Forearm
44538	S230A00	Closed fracture radius and ulna, proximal	Forearm
7009	S230600	Closed fracture radius, head	Forearm
7660	S230700	Closed fracture radius, neck	Forearm
17922	S4C0000	Closed fracture-dislocation distal radio-ulnar joint	Forearm

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
40268	S234800	Closed Galeazzi fracture	Forearm
7034	7K1LE00	Closed reduction of fracture of elbow	Forearm
6213	S23C.00	Fracture of lower end of both ulna and radius	Forearm
199	S23B.00	Fracture of lower end of radius	Forearm
6825	S23..00	Fracture of radius and ulna	Forearm
909	S23z.00	Fracture of radius and ulna, NOS	Forearm
137	S23x111	Fracture of radius NOS	Forearm
7988	S239.00	Fracture of shaft of radius	Forearm
8382	S238.00	Fracture of shaft of ulna	Forearm
10149	S23A.00	Fracture of shafts of both ulna and radius	Forearm
1073	S23x211	Fracture of ulna NOS	Forearm
2303	S237.00	Fracture of upper end of radius	Forearm
6942	7K1LL00	Closed reduction of fracture of radius and or ulna	Forearm
10640	S23..11	Forearm fracture	Forearm
33933	S230000	Closed fracture of proximal forearm, unspecified part	Forearm
17822	S230200	Closed fracture of ulna, coronoid	Forearm
2662	S230300	Closed Monteggia's fracture	Forearm
34370	S230800	Closed fracture proximal radius, comminuted	Forearm
33883	S230900	Closed fracture of the proximal radius	Forearm
12063	S230B00	Closed fracture olecranon, intra-articular	Forearm
42957	S230z00	Closed fracture of proximal forearm not otherwise specified	Forearm
45695	S231.00	Open fracture of proximal radius and ulna	Forearm
50223	S231000	Open fracture of proximal forearm, unspecified	Forearm
29152	S231100	Open fracture olecranon, extra-articular	Forearm
52614	S231200	Open fracture of ulna, coronoid	Forearm
10246	S231300	Open Monteggia's fracture	Forearm
61374	S231500	Open fracture of the proximal ulna	Forearm
7636	S231600	Open fracture radial head	Forearm
34737	S231700	Open fracture radial neck	Forearm
72408	S231800	Open fracture proximal radius, comminuted	Forearm
63948	S231900	Open fracture of the proximal radius	Forearm
37875	S231A00	Open fracture radius and ulna, proximal	Forearm
8410	S231B00	Open fracture olecranon, intra-articular	Forearm
55201	S231z00	Open fracture of forearm, upper end, NOS	Forearm
3748	S233.00	Open fracture of radius and ulna, shaft	Forearm
60518	S233000	Open fracture of radius, shaft, unspecified	Forearm
66233	S233100	Open fracture of the radial shaft	Forearm
70503	S233200	Open fracture of the ulnar shaft	Forearm
48245	S233300	Open fracture radius and ulna, middle	Forearm
27784	S233z00	Open fracture of radius and ulna, shaft, NOS	Forearm
23987	S234211	Dupuytren's fracture, radius - closed	Forearm
9165	S234300	Closed fracture of ulna, styloid process	Forearm
42076	S234400	Closed fracture of ulna, lower epiphysis	Forearm
102302	S234G00	Greenstick fracture of distal radius	Forearm
27590	S235.00	Open fracture of radius and ulna, lower end	Forearm
60630	S235000	Open fracture of forearm, lower end, unspecified	Forearm
44924	S235200	Open fracture of the distal radius, unspecified	Forearm
105278	S235211	Dupuytren's fracture, radius - open	Forearm

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
11262	S235300	Open fracture of ulna, styloid process	Forearm
96691	S235400	Open fracture of ulna, lower epiphysis	Forearm
49796	S235500	Open fracture distal ulna - other	Forearm
38398	S235600	Open fracture radius and ulna, distal	Forearm
30418	S235800	Open Galeazzi fracture	Forearm
104070	S235C00	Open fracture distal radius, intra-articular, die-punch	Forearm
53698	S235D00	Open fracture distal radius, extra-articular other type	Forearm
63588	S235E00	Open fracture distal radius, intra-articular other type	Forearm
66774	S235z00	Open fracture of forearm, lower end, NOS	Forearm
54780	S23y.00	Open fracture of radius and ulna, unspecified part	Forearm
70590	S23y000	Open fracture of forearm, unspecified	Forearm
34367	S23y100	Open fracture of radius (alone), unspecified	Forearm
28741	S23y200	Open fracture of ulna (alone), unspecified	Forearm
8704	S23y300	Open fracture of the radius and ulna	Forearm
65301	S23yz00	Open fracture of radius and ulna, NOS	Forearm
8915	S293.00	Multiple fractures of forearm	Forearm
4225	S024000	Closed fracture maxilla	Head
417	S020.00	Closed fracture nose	Head
2251	S024100	Closed fracture zygoma	Head
26130	7K1LD00	Closed reduction of fracture of nasal bone	Head
27287	S02x000	Fracture of alveolus, closed	Head
2461	S01..00	Fracture of base of skull	Head
33593	S01z.00	Fracture of base of skull NOS	Head
9103	S02..00	Fracture of face bones	Head
16890	S022.12	Fracture of lower jaw, closed	Head
14878	S024.00	Fracture of malar or maxillary bones, closed	Head
11161	S028300	Fracture of mandible	Head
2642	S022.00	Fracture of mandible, closed	Head
36268	S022z00	Fracture of mandible, closed, NOS	Head
5280	S028000	Fracture of nasal bones	Head
4978	S02x100	Fracture of orbit NOS, closed	Head
20515	S028100	Fracture of orbital floor	Head
721	S0...00	Fracture of skull	Head
17455	S02z.11	Jaw fracture NOS	Head
44949	S02B.00	Le Fort II fracture maxilla	Head
39859	S04..12	Multiple skull fractures	Head
9736	S01..15	Occiput bone fracture	Head
3408	S021.00	Open fracture nose	Head
3095	7J03100	Reduction of fracture of nasal bones NEC other	Head
4465	7J03200	Reduction of fracture of zygomatic bones	Head
57328	S03z.00	Skull fracture NOS	Head
10736	7206100	Open reduction of fracture of orbit	Head
5972	7206200	Removal of fixation from fracture of orbit	Head
20445	7206400	Open reduction of fracture of orbit and internal fixation	Head
39071	7206700	Packing of maxilla to correct blow-out fracture of orbit	Head
89101	7206800	Internal fixation of fracture of orbit	Head
30186	7403600	Outfracture of turbinates of nose	Head
89236	7403900	Surgical outfracture of turbinate of nose	Head

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
34632	7J02200	Elevation of depressed fracture of cranium	Head
53575	7J02300	Repair of fracture of cranium NEC	Head
15800	7J03.00	Reduction of fracture of facial bone	Head
25173	7J03000	Reduction of fracture of nasoethmoid complex of bones	Head
43730	7J03300	Reduction of closed fracture of orbit bone	Head
63064	7J03y00	Other specified reduction of fracture of facial bone	Head
28621	7J03z00	Reduction of fracture of facial bone NOS	Head
6994	7J12.00	Reduction of fracture of mandible	Head
17443	7J12.11	Reduction of fracture of jaw NEC	Head
60254	7J12000	Reduction of fracture of alveolus of mandible	Head
28926	7J12100	Open reduction of fracture of mandible NEC	Head
11342	7J12200	Closed reduction of fracture of mandible NEC	Head
27361	7J12y00	Other specified reduction of fracture of mandible	Head
37297	7J12z00	Reduction of fracture of mandible NOS	Head
22780	7J13.00	Reduction of fracture of maxilla	Head
30288	7J13000	Reduction of fracture of alveolus of maxilla	Head
51392	7J13100	Open reduction of fracture of maxilla NEC	Head
35889	7J13200	Closed reduction of fracture of maxilla NEC	Head
25312	7J13300	Reduction of blowout fracture of orbital floor	Head
4350	7J13400	Reduction of Le Fort 1 fracture of maxilla	Head
51147	7J13500	Reduction of Le Fort 2 fracture of maxilla	Head
60412	7J13600	Reduction of Le Fort 3 fracture of maxilla	Head
88784	7J13y00	Other specified reduction of fracture of maxilla	Head
69319	7J13z00	Reduction of fracture of maxilla NOS	Head
17138	7J17700	Traction for fracture of jaw	Head
47842	S000.00	Closed fracture vault of skull without intracranial injury	Head
27657	S001.00	Closed fracture vault of skull with intracranial injury	Head
57246	S002.00	Open fracture vault of skull without intracranial injury	Head
51299	S003.00	Open fracture vault of skull with intracranial injury	Head
59798	S01..11	Anterior fossa fracture	Head
30707	S01..12	Ethmoid sinus fracture	Head
41675	S01..13	Frontal sinus fracture	Head
24135	S01..14	Middle fossa fracture	Head
37609	S01..16	Orbital roof fracture	Head
61757	S01..17	Posterior fossa fracture	Head
37686	S01..18	Sphenoid bone fracture	Head
5567	S01..19	Temporal bone fracture	Head
62977	S010.00	Closed fracture base of skull without intracranial injury	Head
63679	S011.00	Closed fracture base of skull with intracranial injury	Head
69737	S012.00	Open fracture base skull without mention intracranial injury	Head
97064	S013.00	Open fracture base of skull with intracranial injury	Head
9771	S020.11	Closed fracture nasal bone	Head
37192	S021.11	Open fracture nasal bone	Head
29091	S022000	Closed fracture mandible (site unspecified)	Head
12179	S022100	Closed fracture of mandible, condylar process	Head
41730	S022200	Closed fracture of mandible, subcondylar	Head
59341	S022300	Closed fracture of mandible, coronoid process	Head
28913	S022400	Closed fracture of mandible, ramus, unspecified	Head

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
41707	S022500	Closed fracture of mandible, angle of jaw	Head
71583	S022600	Closed fracture of mandible, symphysis of body	Head
57190	S022700	Closed fracture of mandible, alveolar border of body	Head
59006	S022800	Closed fracture of mandible, body, other and unspecified	Head
37904	S022x00	Closed fracture of mandible, multiple sites	Head
70673	S023000	Open fracture mandible (site unspecified)	Head
60633	S023100	Open fracture of mandible, condylar process	Head
99549	S023200	Open fracture of mandible, subcondylar	Head
68660	S023400	Open fracture of mandible, ramus, unspecified	Head
55955	S023500	Open fracture of mandible, angle of jaw	Head
104931	S023600	Open fracture of mandible, symphysis of body	Head
106283	S023700	Open fracture of mandible, alveolar border of body	Head
60260	S023800	Open fracture of mandible, body, other and unspecified	Head
54553	S023x00	Open fracture of mandible, multiple sites	Head
32011	S025000	Open fracture maxilla	Head
12462	S025100	Open fracture zygoma	Head
24790	S026.00	Closed orbital blow-out fracture	Head
33459	S027.00	Open orbital blow-out fracture	Head
44343	S02A.00	Le Fort I fracture maxilla	Head
68981	S02C.00	Le Fort III fracture maxilla	Head
29119	S02x.00	Closed fracture other facial bone	Head
59233	S02y.00	Open fracture other facial bone	Head
61388	S03..00	Other and unqualified skull fractures	Head
57644	S030.00	Closed fracture of skull NOS without intracranial injury	Head
27492	S031.00	Closed fracture of skull NOS with intracranial injury	Head
67603	S033.00	Open fracture of skull NOS with intracranial injury	Head
23780	S03z.11	Depressed skull fracture NOS	Head
46142	S04..00	Multiple fractures involving skull or face with other bones	Head
31797	S04..11	Multiple face fractures	Head
33515	S044.00	Multiple fractures involving skull and facial bones	Head
50247	S04z.00	Multiple fractures involving skull/face with other bones NOS	Head
53670	7K1J011	Cl red intracaps frac neck femur fix-Garden cannulated screw	Hip
40999	7K1J012	Cl red intracaps fract neck femur fix - Smith-Petersen nail	Hip
36391	S300400	Closed fracture head of femur	hip
19387	S302011	Closed fracture of femur, greater trochanter	Hip
8648	S302400	Closed fracture of femur, intertrochanteric	Hip
48337	S302012	Closed fracture of femur, lesser trochanter	Hip
68229	S300y11	Closed fracture of femur, subcapital	Hip
45779	S300A00	Closed fracture of femur, upper epiphysis	Hip
18273	S30y.00	Closed fracture of neck of femur NOS	Hip
5301	S302.00	Closed fracture of proximal femur, pertrochanteric	Hip
24276	S30w.00	Closed fracture of unspecified proximal femur	Hip
52194	S300300	Closed fracture proximal femur, basicervical	Hip
45141	S302100	Closed fracture proximal femur, intertrochanteric, two part	Hip
65690	S300200	Closed fracture proximal femur, midcervical section	Hip
49209	S300y00	Closed fracture proximal femur, other transcervical	Hip
34351	S300600	Closed fracture proximal femur, subcapital, Garden grade I	Hip
33957	S300700	Closed fracture proximal femur, subcapital, Garden grade II	Hip

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
36599	S300800	Closed fracture proximal femur, subcapital, Garden grade III	Hip
34078	S300900	Closed fracture proximal femur, subcapital, Garden grade IV	Hip
38489	S300.00	Closed fracture proximal femur, transcervical	Hip
62966	S300z00	Closed fracture proximal femur, transcervical, NOS	Hip
69919	S300100	Closed fracture proximal femur, transepiphyseal	Hip
51861	S300311	Closed fracture, base of neck of femur	Hip
6660	7K1L400	Closed reduction of fracture of hip	Hip
39322	7K1Jd00	Closed reduction of intracapsular # NOF internal fixat DHS	Hip
44735	S302z00	Cls # of proximal femur, pertrochanteric section, NOS	Hip
39984	S300000	Cls # prox femur, intracapsular section, unspecified	Hip
17019	S300500	Cls # prox femur, subcapital, Garden grade unspec.	Hip
51216	S302300	Cls # proximal femur, intertrochanteric, comminuted	Hip
19117	S302000	Cls # proximal femur, trochanteric section, unspecified	Hip
57514	7K1J013	Cls red+int fxn prox femoral #+Richard's cannulat hip screw	Hip
8719	7K1J000	Cls red+int fxn proximal femoral #+screw/nail device alone	Hip
9792	7K1D01E	DHS - Dynamic hip screw primary fixation of neck of femur	Hip
12544	7K1D01F	Dynamic hip screw primary fixation of neck of femur	Hip
2225	S30..00	Fracture of neck of femur	Hip
1994	S30..11	Hip fracture	Hip
10570	S30y.11	Hip fracture NOS	Hip
67633	S303000	Open # of proximal femur, trochanteric section, unspecified	Hip
100771	S301311	Open fracture base of neck of femur	Hip
39396	S303400	Open fracture of femur, intertrochanteric	Hip
73234	S301y11	Open fracture of femur, subcapital	Hip
96518	S301A00	Open fracture of femur, upper epiphysis	Hip
38054	S30z.00	Open fracture of neck of femur NOS	Hip
61733	S303.00	Open fracture of proximal femur, pertrochanteric	Hip
70479	S303z00	Open fracture of proximal femur, pertrochanteric, NOS	Hip
58642	S30x.00	Open fracture of unspecified proximal femur	Hip
97971	S303300	Open fracture proximal femur, intertrochanteric, comminuted	Hip
101567	S303100	Open fracture proximal femur, intertrochanteric, two part	Hip
68668	S301y00	Open fracture proximal femur, other transcervical	Hip
73981	S301.00	Open fracture proximal femur, transcervical	Hip
72138	S301100	Open fracture proximal femur, transepiphyseal	Hip
60885	S301600	Open fracture proximal femur,subcapital, Garden grade I	Hip
67394	S301700	Open fracture proximal femur,subcapital, Garden grade II	Hip
23803	S301800	Open fracture proximal femur,subcapital, Garden grade III	Hip
51999	S301900	Open fracture proximal femur,subcapital, Garden grade IV	Hip
38878	S301500	Open fracture proximal femur,subcapital, Garden grade unspec	Hip
50727	S301000	Opn # proximal femur, intracapsular section, unspecified	Hip
28965	S304.00	Pertrochanteric fracture	Hip
54819	7K1JC00	Prim cls rd+int fxn prox fem #+screw/nail+intramdulry device	Hip
97337	7K1D013	Prim op red # nck femur & op fix - Deyerle multiple hip pin	Hip
52395	7K1D012	Prim op red # nck femur & op fix- Charnley compression screw	Hip
57889	7K1D01D	Prim op red # nck femur & op fix- Zickel intramed nail plate	Hip
105803	7K1DE00	Prim op red frac neck fem op fix us prox fem nail antirotatn	Hip

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
56568	7K1D017	Prim open red # neck femur & op fix - McLaughlin nail plate	Hip
58817	7K1D011	Prim open reduct # neck femur & op fix - Blount nail plate	Hip
94714	7K1D014	Prim open reduct # neck femur & op fix - Holt nail	Hip
105352	7K1D015	Prim open reduct # neck femur & op fix - Jewett nail plate	Hip
46258	7K1D018	Prim open reduct # neck femur & op fix - Neufield nail plate	Hip
65536	7K1D019	Prim open reduct # neck femur & op fix - Pugh nail plate	Hip
24493	7K1D01A	Prim open reduct # neck femur & op fix - Richards screw	Hip
57884	7K1D01B	Prim open reduct # neck femur & op fix - Ross Brown nail	Hip
55386	7K1JB00	Primary cls red+int fxn prox fem #+screw/nail device alone	Hip
46959	7K1JD00	Primary cls red+int fxn prox fem #+screw/nail+plate device	Hip
102313	7K1K500	Primary cls reduction+external fixation proximal femoral #	Hip
70018	7K1K300	Primary external fixation(without reduction) prox femoral #	Hip
35004	7K1J500	Primary int fxn(no red) prox fem #+screw/nail device alone	Hip
38856	7K1J700	Primary int fxn(no red) prox fem #+screw/nail+plate device	Hip
44594	7K1J600	Primary int fxn(no red) prox fem #+scrw/nail+intramed device	Hip
41888	7K1G200	Primary open reduction+external fixation of femoral fracture	Hip
34764	7K1D700	Prmy open red+int fxn prox fem #+screw/nail+intramed device	Hip
33624	7K1D600	Prmy open red+int fxn prox femoral #+screw/nail device alone	Hip
5742	7K1D000	Prmy open red+int fxn prox femoral #+screw/nail+plate device	Hip
72525	S130000	Closed fracture acetabulum, anterior lip alone	Hip
94649	S130100	Closed fracture acetabulum, posterior lip alone	Hip
73479	S130200	Closed fracture acetabulum, anterior column	Hip
57923	S130300	Closed fracture acetabulum, posterior column	Hip
69418	S130400	Closed fracture acetabulum, floor	Hip
98267	S130600	Closed fracture acetabulum, double column unspecified	Hip
59904	S130y00	Other specified closed fracture acetabulum	Hip
45527	S130z00	Closed fracture acetabulum NOS	Hip
53566	S131.00	Open fracture acetabulum	Hip
62562	S131y00	Other specified open fracture acetabulum	Hip
64777	S131z00	Open fracture acetabulum NOS	Hip
73210	S301400	Open fracture head, femur	Hip
96644	S303011	Open fracture of femur, greater trochanter	Hip
40267	S4E0.00	Closed fracture-dislocation, hip joint	Hip
58720	S4E1.00	Open fracture-dislocation, hip joint	Hip
93374	S4E2.00	Closed fracture-subluxation, hip joint	Hip
8891	S3...00	Fracture of lower limb	Leg
2603	S3...11	Leg fracture	Leg
55077	7K1LC00	Closed reduction of fracture of lower limb	Leg
40368	S370.00	Closed fracture of lower limb, level unspecified	Leg
44245	S371.00	Open fracture of lower limb, level unspecified	Leg
45517	S3x..00	Other, multiple and ill-defined fractures of lower limb	Leg
37291	S3x0.00	Other, multiple and ill-defined closed fractures lower limb	Leg
69917	S3x1.00	Other, multiple and ill-defined open fractures of lower limb	Leg
103049	SR15000	Cl fractures involving multiple regions upper with lower lmb	Leg
109439	SyuL400	[X]Sequelae of other fractures of lower limb	Leg

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
1591	S130.00	Closed fracture acetabulum	Lower back and pelvis
3888	S104.00	Closed fracture lumbar vertebra	Lower back and pelvis
42968	S104000	Closed fracture lumbar vertebra, burst	Lower back and pelvis
95842	S104500	Closed fracture lumbar vertebra, posterior arch	Lower back and pelvis
35096	S104300	Closed fracture lumbar vertebra, spinous process	Lower back and pelvis
61150	S104200	Closed fracture lumbar vertebra, spondylolysis	Lower back and pelvis
29089	S104400	Closed fracture lumbar vertebra, transverse process	Lower back and pelvis
95585	S104600	Closed fracture lumbar vertebra, tricolumnar	Lower back and pelvis
8266	S104100	Closed fracture lumbar vertebra, wedge	Lower back and pelvis
44059	S114.00	Closed fracture of lumbar spine with spinal cord lesion	Lower back and pelvis
28375	S13y.00	Closed fracture of pelvis NOS	Lower back and pelvis
27854	S134600	Closed fracture pelvis, iliac wing	Lower back and pelvis
34708	S134100	Closed fracture pelvis, ischium	Lower back and pelvis
6667	S132100	Closed fracture pelvis, multiple pubic rami - stable	Lower back and pelvis
7004	S132000	Closed fracture pelvis, single pubic ramus	Lower back and pelvis
5302	S132.00	Closed fracture pubis	Lower back and pelvis
28702	S132z00	Closed fracture pubis NOS	Lower back and pelvis
34910	S4J0100	Closed fracture-dislocation of pelvis	Lower back and pelvis
34212	S4J2100	Closed fracture-subluxation of pelvis	Lower back and pelvis
23686	N331111	Collapse of lumbar vertebra	Lower back and pelvis
11543	N331G00	Collapse of lumbar vertebra	Lower back and pelvis
5841	N331J00	Collapse of lumbar vertebra due to osteoporosis	Lower back and pelvis
9072	S10B400	Fracture of acetabulum	Lower back and pelvis
835	S10B200	Fracture of coccyx	Lower back and pelvis
12406	S10B.00	Fracture of lumbar spine and pelvis	Lower back and pelvis
10990	S10B000	Fracture of lumbar vertebra	Lower back and pelvis
2328	S10B500	Fracture of pubis	Lower back and pelvis
738	S13..00	Fracture or disruption of pelvis	Lower back and pelvis
45934	SR11.00	Fractures involving thorax with lower back and pelvis	Lower back and pelvis
8613	S10B600	Multiple fractures of lumbar spine and pelvis	Lower back and pelvis
64139	S13z.00	Open fracture of pelvis NOS	Lower back and pelvis
33961	S134.00	Other or multiple closed fracture of pelvis	Lower back and pelvis
11639	S134z00	Other or multiple closed fracture of pelvis NOS	Lower back and pelvis
30352	N331100	Pathological fracture of lumbar vertebra	Lower back and pelvis
42780	S105.00	Open fracture lumbar vertebra	Lower back and pelvis
73601	S105000	Open fracture lumbar vertebra, burst	Lower back and pelvis
65302	S105100	Open fracture lumbar vertebra, wedge	Lower back and pelvis
105695	S105400	Open fracture lumbar vertebra, transverse process	Lower back and pelvis
15877	S106.00	Closed fracture sacrum	Lower back and pelvis
72404	S106000	Closed compression fracture sacrum	Lower back and pelvis
72600	S106100	Closed vertical fracture of sacrum	Lower back and pelvis
66434	S107.00	Open fracture sacrum	Lower back and pelvis
105935	S107000	Open compression fracture sacrum	Lower back and pelvis
97354	S107100	Open vertical fracture of sacrum	Lower back and pelvis
14834	S108.00	Closed fracture pelvis, coccyx	Lower back and pelvis
55280	S109.00	Open fracture pelvis, coccyx	Lower back and pelvis
94189	S115.00	Open fracture of lumbar spine with spinal cord lesion	Lower back and pelvis
57444	S116.00	Closed fracture of sacrum with spinal cord lesion	Lower back and pelvis

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
99376	S116z00	Closed fracture of sacrum with spinal cord lesion NOS	Lower back and pelvis
96473	S117.00	Open fracture of sacrum with spinal cord lesion	Lower back and pelvis
94584	S117300	Open fracture of sacrum with other spinal cord injury	Lower back and pelvis
51018	S118.00	Closed fracture of coccyx with spinal cord lesion	Lower back and pelvis
101517	S118z00	Closed fracture of coccyx with spinal cord lesion NOS	Lower back and pelvis
46592	S132200	Closed fracture pelvis, multiple pubic rami - unstable	Lower back and pelvis
38895	S132y00	Other specified closed fracture pubis	Lower back and pelvis
50749	S133.00	Open fracture of pubis	Lower back and pelvis
34685	S133000	Open fracture pelvis, single pubic ramus	Lower back and pelvis
51038	S133100	Open fracture pelvis, multiple pubic rami - stable	Lower back and pelvis
101447	S133200	Open fracture pelvis, multiple pubic rami - unstable	Lower back and pelvis
94127	S133y00	Other specified open fracture of pubis	Lower back and pelvis
70674	S133z00	Open fracture of pubis NOS	Lower back and pelvis
40643	S134000	Closed fracture of ilium, unspecified	Lower back and pelvis
41698	S134300	Closed fracture pelvis, ischial tuberosity	Lower back and pelvis
28234	S134400	Closed fracture pelvis, anterior superior iliac spine	Lower back and pelvis
40587	S134500	Closed fracture pelvis, anterior inferior iliac spine	Lower back and pelvis
52470	S134700	Closed vertical fracture of ilium	Lower back and pelvis
34195	S134800	Closed fracture dislocation of sacro-iliac joint	Lower back and pelvis
65084	S135.00	Other or multiple open fracture of pelvis	Lower back and pelvis
96984	S135000	Open fracture of ilium, unspecified	Lower back and pelvis
108000	S135100	Open fracture pelvis, ischium	Lower back and pelvis
68763	S135300	Open fracture pelvis, ischial tuberosity	Lower back and pelvis
43448	S135400	Open fracture pelvis, anterior superior iliac spine	Lower back and pelvis
67669	S135600	Open fracture pelvis, iliac wing	Lower back and pelvis
94655	S135800	Open fracture dislocation of sacro-iliac joint	Lower back and pelvis
99203	S135y00	Other open fracture of pelvis	Lower back and pelvis
35018	S135z00	Other/multiple open fracture of pelvis NOS	Lower back and pelvis
45011	S4J1100	Open fracture-dislocation of pelvis	Lower back and pelvis
65297	S4J3100	Open fracture-subluxation of pelvis	Lower back and pelvis
7317	S344.00	Closed fracture ankle, bimalleolar	Lower leg and ankle
7340	S342.00	Closed fracture ankle, lateral malleolus	Lower leg and ankle
4737	S34x.00	Closed fracture ankle, unspecified	Lower leg and ankle
27719	S334.00	Closed fracture distal tibia	Lower leg and ankle
34151	S334000	Closed fracture distal tibia, extra-articular	Lower leg and ankle
6839	S339000	Closed fracture of distal fibula	Lower leg and ankle
4304	S33x100	Closed fracture of fibula, unspecified part, NOS	Lower leg and ankle
44830	S330.00	Closed fracture of tibia and fibula, proximal	Lower leg and ankle
4572	S33x200	Closed fracture of tibia and fibula, unspecified part	Lower leg and ankle
971	S33x000	Closed fracture of tibia, unspecified part, NOS	Lower leg and ankle
29121	S332.00	Closed fracture of tibia/fibula, shaft	Lower leg and ankle
41287	S320400	Closed fracture patella, comminuted (stellate)	Lower leg and ankle
33656	S330100	Closed fracture proximal fibula	Lower leg and ankle
18840	S330300	Closed fracture proximal tibia, medial condyle (plateau)	Lower leg and ankle
28426	S332100	Closed fracture shaft of fibula	Lower leg and ankle
40653	S4F0.00	Closed fracture-dislocation, knee joint	Lower leg and ankle
33666	S4F2.00	Closed fracture-subluxation, knee joint	Lower leg and ankle
6106	7K1L800	Closed reduction of fracture of ankle	Lower leg and ankle

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
8800	7K1L600	Closed reduction of fracture of knee	Lower leg and ankle
5886	7K1L700	Closed reduction of fracture of tibia and or fibula	Lower leg and ankle
325	S34..00	Fracture of ankle	Lower leg and ankle
9212	S34z.00	Fracture of ankle, NOS	Lower leg and ankle
806	S339.00	Fracture of fibula alone	Lower leg and ankle
6731	S349.00	Fracture of lateral malleolus	Lower leg and ankle
10007	S338.00	Fracture of lower end of tibia	Lower leg and ankle
845	S35..00	Fracture of one or more tarsal and metatarsal bones	Lower leg and ankle
235	S32..00	Fracture of patella	Lower leg and ankle
35011	S32z.00	Fracture of patella, NOS	Lower leg and ankle
7723	S337.00	Fracture of shaft of tibia	Lower leg and ankle
2630	S33..00	Fracture of tibia and fibula	Lower leg and ankle
6917	S336.00	Fracture of upper end of tibia	Lower leg and ankle
29911	S4F..00	Fracture-dislocation or subluxation knee	Lower leg and ankle
9348	S3x3.00	Multiple fractures of lower leg	Lower leg and ankle
18584	S345.00	Open fracture ankle, bimalleolar	Lower leg and ankle
12369	S339100	Open fracture of distal fibula	Lower leg and ankle
62787	S33yz00	Open fracture of tibia and fibula, unspecified part, NOS	Lower leg and ankle
29164	S33y000	Open fracture of tibia, unspecified part, NOS	Lower leg and ankle
14746	S3xz.00	Other, multiple and ill-defined fractures of lower limb NOS	Lower leg and ankle
2250	S344.12	Pott's fracture - ankle	Lower leg and ankle
7930	7K1F500	Primary open reduction fracture patella fixat tension band	Lower leg and ankle
33393	S320.00	Closed fracture of the patella	Lower leg and ankle
49526	S320000	Closed fracture patella, transverse	Lower leg and ankle
50549	S320100	Closed fracture patella, proximal pole	Lower leg and ankle
44329	S320200	Closed fracture patella, distal pole	Lower leg and ankle
54660	S320300	Closed fracture patella, vertical	Lower leg and ankle
28273	S321.00	Open fracture of the patella	Lower leg and ankle
50227	S321000	Open fracture patella, transverse	Lower leg and ankle
100159	S321100	Open fracture patella, proximal pole	Lower leg and ankle
33475	S321200	Open fracture patella, distal pole	Lower leg and ankle
50254	S321400	Open fracture patella, comminuted (stellate)	Lower leg and ankle
28550	S330000	Closed fracture of the proximal tibia	Lower leg and ankle
53951	S330011	Closed fracture of tibial condyles	Lower leg and ankle
22761	S330012	Closed fracture of tibial tuberosity	Lower leg and ankle
54280	S330200	Closed fracture of tibia and fibula, proximal	Lower leg and ankle
22370	S330400	Closed fracture proximal tibia, lateral condyle (plateau)	Lower leg and ankle
40164	S330500	Closed fracture proximal tibia, bicondylar	Lower leg and ankle
33768	S330600	Closed fracture spine, tibia	Lower leg and ankle
38733	S330700	Closed fracture tubercle, tibia	Lower leg and ankle
52499	S330800	Closed fracture fibula, head	Lower leg and ankle
52322	S330900	Closed fracture fibula, neck	Lower leg and ankle
42978	S330z00	Closed fracture of tibia and fibula, proximal NOS	Lower leg and ankle
40069	S331.00	Open fracture of tibia and fibula, proximal	Lower leg and ankle
33706	S331000	Open fracture of the proximal tibia	Lower leg and ankle
93029	S331011	Open fracture of tibial condyles	Lower leg and ankle
49801	S331012	Open fracture of tibial tuberosity	Lower leg and ankle
33457	S331100	Open fracture proximal fibula	Lower leg and ankle

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
54145	S331200	Open fracture of tibia and fibula, proximal	Lower leg and ankle
44276	S331300	Open fracture proximal tibia, medial condyle (plateau)	Lower leg and ankle
44786	S331400	Open fracture proximal tibia, lateral condyle (plateau)	Lower leg and ankle
63633	S331600	Open fracture spine, tibia	Lower leg and ankle
49798	S331700	Open fracture tubercle, tibia	Lower leg and ankle
99027	S331800	Open fracture fibula, head	Lower leg and ankle
99161	S331900	Open fracture fibula, neck	Lower leg and ankle
101840	S331A00	Open fracture tibial plateau	Lower leg and ankle
57439	S331z00	Open fracture of tibia and fibula, proximal NOS	Lower leg and ankle
34021	S332000	Closed fracture shaft of tibia	Lower leg and ankle
33520	S332200	Closed fracture of tibia and fibula, shaft	Lower leg and ankle
55464	S332z00	Closed fracture of tibia and fibula, shaft, NOS	Lower leg and ankle
28068	S333.00	Open fracture of tibia/fibula, shaft	Lower leg and ankle
28118	S333000	Open fracture shaft of tibia	Lower leg and ankle
51938	S333100	Open fracture shaft of fibula	Lower leg and ankle
20678	S333200	Open fracture of tibia and fibula, shaft	Lower leg and ankle
28198	S333z00	Open fracture of tibia and fibula, shaft, NOS	Lower leg and ankle
8465	S334100	Closed fracture distal tibia, intra-articular	Lower leg and ankle
27992	S335.00	Open fracture distal tibia	Lower leg and ankle
27721	S335000	Open fracture distal tibia, extra-articular	Lower leg and ankle
65228	S335100	Open fracture distal tibia, intra-articular	Lower leg and ankle
100640	S33B.00	Open fracture of distal tibia and fibula	Lower leg and ankle
100202	S33C.00	Closed fracture of distal tibia and fibula	Lower leg and ankle
29109	S33x.00	Closed fracture of tibia and fibula, unspecified part, NOS	Lower leg and ankle
35253	S33x.11	Lower leg fracture NOS	Lower leg and ankle
41971	S33xz00	Closed fracture of tibia and fibula, unspecified part, NOS	Lower leg and ankle
28233	S33y.00	Open fracture of tibia and fibula, unspecified part, NOS	Lower leg and ankle
28352	S33y100	Open fracture of fibula, unspecified part, NOS	Lower leg and ankle
29084	S33y200	Open fracture of tibia and fibula, unspecified part	Lower leg and ankle
6286	S340.00	Closed fracture ankle, medial malleolus	Lower leg and ankle
33974	S341.00	Open fracture ankle, medial malleolus	Lower leg and ankle
7135	S342000	Closed fracture ankle, lateral malleolus, low	Lower leg and ankle
35620	S342100	Closed fracture ankle, lateral malleolus, high	Lower leg and ankle
18388	S343.00	Open fracture ankle, lateral malleolus	Lower leg and ankle
43566	S343000	Open fracture ankle, lateral malleolus, low	Lower leg and ankle
73105	S343100	Open fracture ankle, lateral malleolus, high	Lower leg and ankle
14826	S344.11	Dupuytren's fracture, fibula	Lower leg and ankle
42969	S344000	Closed fracture ankle, bimalleolar, low fibular fracture	Lower leg and ankle
52371	S344100	Closed fracture ankle, bimalleolar, high fibular fracture	Lower leg and ankle
66808	S345000	Open fracture ankle, bimalleolar, low fibular fracture	Lower leg and ankle
105816	S345100	Open fracture ankle, bimalleolar, high fibular fracture	Lower leg and ankle
10009	S346.00	Closed fracture ankle, trimalleolar	Lower leg and ankle
56525	S346000	Closed fracture ankle, trimalleolar, low fibular fracture	Lower leg and ankle
52346	S346100	Closed fracture ankle, trimalleolar, high fibular fracture	Lower leg and ankle
9917	S347.00	Open fracture ankle, trimalleolar	Lower leg and ankle
47828	S347000	Open fracture ankle, trimalleolar, low fibular fracture	Lower leg and ankle
105819	S347100	Open fracture ankle, trimalleolar, high fibular fracture	Lower leg and ankle
38765	S34y.00	Open fracture ankle, unspecified	Lower leg and ankle

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
28731	S4F1.00	Open fracture-dislocation, knee joint	Lower leg and ankle
57196	S4F3.00	Open fracture-subluxation, knee joint	Lower leg and ankle
29981	S4F4.00	Closed fracture-dislocation, patello-femoral joint	Lower leg and ankle
60669	S4F5.00	Open fracture-dislocation, patello-femoral joint	Lower leg and ankle
40650	S4F6.00	Closed fracture-subluxation, patello-femoral joint	Lower leg and ankle
38943	S4F7.00	Open fracture-subluxation, patello-femoral joint	Lower leg and ankle
34302	S4G0.00	Closed fracture-dislocation, ankle joint	Lower leg and ankle
56927	S4G1.00	Open fracture-dislocation, ankle joint	Lower leg and ankle
59411	S4G2.00	Closed fracture-subluxation, ankle joint	Lower leg and ankle
28070	S4G3.00	Open fracture-subluxation, ankle joint	Lower leg and ankle
33918	SC0X.00	Sequelae of other fracture of thorax and pelvis	Multiple
73786	SR10000	Closed fractures involving head with neck	Multiple
57223	SR16000	Closed fracture inv thorax wth low back and pelvis and limbs	Multiple
50270	SR1z.00	Multiple fractures, unspecified	Multiple
73336	SR1z000	[X]Closed multiple fractures unspecified	Multiple
96460	SR1z100	[X]Open multiple fractures unspecified	Multiple
11296	S100.00	Closed fracture of cervical spine	Neck
52300	S110.00	Closed fracture of cervical spine with cord lesion	Neck
17008	N331E00	Collapse of cervical vertebra	Neck
45736	N331H00	Collapse of cervical vertebra due to osteoporosis	Neck
28133	S10A000	Fracture of first cervical vertebra	Neck
3288	S10A.00	Fracture of neck	Neck
34403	S10A100	Fracture of second cervical vertebra	Neck
19189	S10A200	Multiple fractures of cervical spine	Neck
48772	N331A00	Osteoporosis + pathological fracture cervical vertebrae	Neck
37945	N331C00	Pathological fracture of cervical vertebra	Neck
15613	S100000	Closed fracture of unspecified cervical vertebra	Neck
5445	S100100	Closed fracture atlas	Neck
42561	S100111	C1 vertebra closed fracture - no spinal cord lesion	Neck
16277	S100200	Closed fracture axis	Neck
33967	S100211	C2 vertebra closed fracture without spinal cord lesion	Neck
60593	S100300	Closed fracture of third cervical vertebra	Neck
52699	S100311	C3 vertebra closed fracture without spinal cord lesion	Neck
41548	S100400	Closed fracture of fourth cervical vertebra	Neck
67358	S100411	C4 vertebra closed fracture without spinal cord lesion	Neck
27575	S100500	Closed fracture of fifth cervical vertebra	Neck
34873	S100511	C5 vertebra closed fracture without spinal cord lesion	Neck
27654	S100600	Closed fracture of sixth cervical vertebra	Neck
33503	S100611	C6 vertebra closed fracture without spinal cord lesion	Neck
24672	S100700	Closed fracture of seventh cervical vertebra	Neck
38053	S100711	C7 vertebra closed fracture without spinal cord lesion	Neck
98393	S100800	Closed fracture atlas, isolated arch or articular process	Neck
69974	S100900	Closed fracture atlas, comminuted	Neck
39887	S100A00	Closed fracture axis, odontoid process	Neck
105702	S100B00	Closed fracture axis, spondylolysis	Neck
42149	S100C00	Closed fracture axis, spinous process	Neck
94292	S100D00	Closed fracture axis, transverse process	Neck
95006	S100E00	Closed fracture axis, posterior arch	Neck

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
67973	S100G00	Closed fracture cervical vertebra, burst	Neck
53337	S100H00	Closed fracture cervical vertebra, wedge	Neck
95620	S100J00	Closed fracture cervical vertebra, spondylolysis	Neck
54299	S100K00	Closed fracture cervical vertebra, spinous process	Neck
64297	S100L00	Closed fracture cervical vertebra, transverse process	Neck
95513	S100M00	Closed fracture cervical vertebra, posterior arch	Neck
55346	S100x00	Multiple closed fractures of cervical vertebrae	Neck
41930	S100z00	Closed fracture of cervical spine not otherwise specified	Neck
55627	S101.00	Open fracture of cervical spine	Neck
101574	S101000	Open fracture of unspecified cervical vertebra	Neck
69645	S101100	Open fracture atlas	Neck
69098	S101111	C1 vertebra open fracture without spinal cord lesion	Neck
53976	S101200	Open fracture axis	Neck
97120	S101211	C2 vertebra open fracture without spinal cord lesion	Neck
60382	S101311	C3 vertebra open fracture without spinal cord lesion	Neck
24671	S101500	Open fracture of fifth cervical vertebra	Neck
99151	S101511	C5 vertebra open fracture without spinal cord lesion	Neck
65300	S101600	Open fracture of sixth cervical vertebra	Neck
62719	S101611	C6 vertebra open fracture without spinal cord lesion	Neck
59996	S101711	C7 vertebra open fracture without spinal cord lesion	Neck
110732	S101900	Open fracture atlas, comminuted	Neck
94844	S101A00	Open fracture axis, odontoid process	Neck
72617	S101x00	Multiple open fractures of cervical vertebrae	Neck
40078	S125100	Closed fracture of hyoid bone	Neck
96643	S126100	Open fracture of hyoid bone	Neck
52457	Syu4300	[X]Fracture of other parts of shoulder and upper arm	Shoulder and upper arm
53866	Syu4400	[X]Fracture of shoulder and upper arm, unspecified	Shoulder and upper arm
29899	S200300	Closed fracture clavicle, lateral end	Shoulder and upper arm
6893	S224100	Closed fracture distal humerus, supracondylar	Shoulder and upper arm
33749	S200.00	Closed fracture of clavicle	Shoulder and upper arm
52083	S224500	Closed fracture of distal humerus, trochlea	Shoulder and upper arm
33720	S224000	Closed fracture of elbow, unspecified part	Shoulder and upper arm
19186	S222000	Closed fracture of humerus NOS	Shoulder and upper arm
27886	S222100	Closed fracture of humerus, shaft	Shoulder and upper arm
36464	S222.00	Closed fracture of humerus, shaft or unspecified part	Shoulder and upper arm
61378	S222z00	Closed fracture of humerus, shaft or unspecified part NOS	Shoulder and upper arm
52406	S220500	Closed fracture of humerus, upper epiphysis	Shoulder and upper arm
38353	S220z00	Closed fracture of proximal humerus not otherwise specified	Shoulder and upper arm
33489	S220200	Closed fracture of proximal humerus, anatomical neck	Shoulder and upper arm
44721	S220000	Closed fracture of proximal humerus, unspecified part	Shoulder and upper arm
15376	S224.00	Closed fracture of the distal humerus	Shoulder and upper arm
11222	S220.00	Closed fracture of the proximal humerus	Shoulder and upper arm
29137	S220700	Closed fracture proximal humerus, four part	Shoulder and upper arm
11044	S220300	Closed fracture proximal humerus, greater tuberosity	Shoulder and upper arm
28739	S220400	Closed fracture proximal humerus, head	Shoulder and upper arm
11313	S220100	Closed fracture proximal humerus, neck	Shoulder and upper arm
40330	S220600	Closed fracture proximal humerus, three part	Shoulder and upper arm
16389	S210100	Closed fracture scapula, acromion	Shoulder and upper arm

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
4029	S210300	Closed fracture scapula, glenoid	Shoulder and upper arm
8348	S4A0.00	Closed fracture-dislocation shoulder	Shoulder and upper arm
44652	S4C2000	Closed fracture-subluxation, distal radio-ulnar jt	Shoulder and upper arm
7428	7K1LG00	Closed reduction of fracture of shoulder	Shoulder and upper arm
4211	S20..11	Collar bone fracture	Shoulder and upper arm
1250	S224.11	Elbow fracture - closed	Shoulder and upper arm
483	S20..00	Fracture of clavicle	Shoulder and upper arm
517	S22..00	Fracture of humerus	Shoulder and upper arm
10382	S22z.00	Fracture of humerus NOS	Shoulder and upper arm
1548	S228.00	Fracture of lower end of humerus	Shoulder and upper arm
1177	S21..00	Fracture of scapula	Shoulder and upper arm
30659	S227.00	Fracture of shaft of humerus	Shoulder and upper arm
2101	S226.00	Fracture of upper end of humerus	Shoulder and upper arm
6195	S2...00	Fracture of upper limb	Shoulder and upper arm
5345	S4A..00	Fracture-dislocation or subluxation shoulder	Shoulder and upper arm
16944	S292.00	Multiple fractures of clavicle, scapula and humerus	Shoulder and upper arm
6379	7K1LF00	Closed reduction of fracture of humerus	Shoulder and upper arm
38131	7K1LN00	Closed reduction of fracture of upper limb	Shoulder and upper arm
44715	S200000	Closed fracture of clavicle, unspecified part	Shoulder and upper arm
44711	S200100	Closed fracture clavicle, medial end	Shoulder and upper arm
28307	S200200	Closed fracture clavicle, shaft	Shoulder and upper arm
28179	S200z00	Closed fracture of clavicle NOS	Shoulder and upper arm
61812	S201.00	Open fracture of clavicle	Shoulder and upper arm
70864	S201000	Open fracture of clavicle, unspecified part	Shoulder and upper arm
100040	S201100	Open fracture clavicle, medial end	Shoulder and upper arm
17956	S201200	Open fracture clavicle, shaft	Shoulder and upper arm
68556	S201300	Open fracture clavicle, lateral end	Shoulder and upper arm
94460	S201z00	Open fracture of clavicle NOS	Shoulder and upper arm
10735	S21..11	Shoulder blade fracture	Shoulder and upper arm
27620	S210.00	Closed fracture of scapula	Shoulder and upper arm
38028	S210000	Closed fracture of scapula, unspecified part	Shoulder and upper arm
34907	S210200	Closed fracture scapula, coracoid	Shoulder and upper arm
5344	S210400	Closed fracture scapula, blade	Shoulder and upper arm
48859	S210500	Closed fracture scapula, spine	Shoulder and upper arm
36332	S210600	Closed fracture scapula, neck	Shoulder and upper arm
57592	S210z00	Closed fracture of scapula NOS	Shoulder and upper arm
35386	S211.00	Open fracture of scapula	Shoulder and upper arm
73768	S211000	Open fracture of scapula, unspecified part	Shoulder and upper arm
55687	S211100	Open fracture scapula, acromion	Shoulder and upper arm
64021	S211200	Open fracture scapula, coracoid	Shoulder and upper arm
60108	S211300	Open fracture scapula, glenoid	Shoulder and upper arm
73109	S211400	Open fracture scapula, blade	Shoulder and upper arm
71953	S211600	Open fracture scapula, neck	Shoulder and upper arm
94435	S211z00	Open fracture of scapula NOS	Shoulder and upper arm
9420	S221.00	Open fracture of the proximal humerus	Shoulder and upper arm
10622	S221.11	Shoulder fracture - open	Shoulder and upper arm
53688	S221000	Open fracture of proximal humerus, unspecified part	Shoulder and upper arm
53622	S221100	Open fracture proximal humerus, neck	Shoulder and upper arm

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
71207	S221200	Open fracture of proximal humerus, anatomical neck	Shoulder and upper arm
48239	S221300	Open fracture proximal humerus, greater tuberosity	Shoulder and upper arm
70486	S221400	Open fracture proximal humerus, head	Shoulder and upper arm
59943	S221500	Open fracture of humerus, upper epiphysis	Shoulder and upper arm
70604	S221600	Open fracture proximal humerus, three part	Shoulder and upper arm
70653	S221700	Open fracture proximal humerus, four part	Shoulder and upper arm
45275	S221z00	Open fracture of proximal humerus not otherwise specified	Shoulder and upper arm
33680	S223.00	Open fracture of humerus, shaft or unspecified part	Shoulder and upper arm
48961	S223000	Open fracture of humerus NOS	Shoulder and upper arm
40358	S223100	Open fracture of humerus, shaft	Shoulder and upper arm
73426	S223z00	Open fracture of humerus, shaft or unspecified part NOS	Shoulder and upper arm
18394	S224200	Closed fracture distal humerus, lateral condyle	Shoulder and upper arm
40367	S224300	Closed fracture distal humerus, medial condyle	Shoulder and upper arm
32348	S224400	Closed fracture of distal humerus, condyle(s) unspecified	Shoulder and upper arm
8661	S224600	Closed fracture distal humerus, lateral epicondyle	Shoulder and upper arm
28724	S224700	Closed fracture distal humerus, medial epicondyle	Shoulder and upper arm
28393	S224800	Closed fracture distal humerus, capitellum	Shoulder and upper arm
53677	S224900	Closed fracture distal humerus, bicondylar (T-Y fracture)	Shoulder and upper arm
62833	S224x00	Closed fracture of distal humerus, multiple	Shoulder and upper arm
33540	S224z00	Closed fracture of distal humerus, not otherwise specified	Shoulder and upper arm
34172	S225.00	Open fracture of the distal humerus	Shoulder and upper arm
7754	S225.11	Elbow fracture - open	Shoulder and upper arm
44142	S225000	Open fracture of elbow, unspecified part	Shoulder and upper arm
31760	S225100	Open fracture distal humerus, supracondylar	Shoulder and upper arm
60163	S225200	Open fracture distal humerus, lateral condyle	Shoulder and upper arm
69312	S225300	Open fracture distal humerus, medial condyle	Shoulder and upper arm
86803	S225400	Open fracture of distal humerus, condyle(s) unspecified	Shoulder and upper arm
63899	S225500	Open fracture of distal humerus, trochlea	Shoulder and upper arm
48217	S225600	Open fracture distal humerus, lateral epicondyle	Shoulder and upper arm
16866	S225700	Open fracture distal humerus, medial epicondyle	Shoulder and upper arm
32646	S225800	Open fracture distal humerus, capitellum	Shoulder and upper arm
97820	S225900	Open fracture distal humerus, bicondylar (T-Y fracture)	Shoulder and upper arm
99325	S225x00	Open fracture of distal humerus, multiple	Shoulder and upper arm
47839	S225z00	Open fracture of distal humerus, not otherwise specified	Shoulder and upper arm
40976	S292000	Closed multiple fractures of clavicle, scapula and humerus	Shoulder and upper arm
66237	S292100	Open multiple fractures of clavicle, scapula and humerus	Shoulder and upper arm
33704	S4A0000	Closed fracture-dislocation shoulder joint	Shoulder and upper arm
27718	S4A0100	Closed fracture-dislocation acromio-clavicular joint	Shoulder and upper arm
64229	S4A1.00	Open fracture-dislocation shoulder	Shoulder and upper arm
102965	S4A1000	Open fracture-dislocation shoulder joint	Shoulder and upper arm
50573	S4A1100	Open fracture-dislocation acromio-clavicular joint	Shoulder and upper arm
35789	S4A2.00	Closed fracture-subluxation shoulder	Shoulder and upper arm
60580	S4A2000	Closed fracture-subluxation shoulder joint	Shoulder and upper arm
24534	S4A2100	Closed fracture-subluxation acromio-clavicular joint	Shoulder and upper arm
111060	S4A3.00	Open fracture-subluxation shoulder	Shoulder and upper arm
60828	S4A3100	Open fracture-subluxation acromio-clavicular joint	Shoulder and upper arm
33687	S4B0.00	Closed fracture-dislocation elbow	Shoulder and upper arm
9468	S4B0000	Closed fracture-dislocation elbow joint	Shoulder and upper arm

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
62960	S4B0100	Closed fracture-dislocation superior radio-ulnar joint	Shoulder and upper arm
43972	S4B1.00	Open fracture-dislocation elbow	Shoulder and upper arm
54149	S4B1000	Open fracture-dislocation elbow joint	Shoulder and upper arm
104355	S4B1100	Open fracture-dislocation superior radio-ulnar joint	Shoulder and upper arm
58752	S4B2.00	Closed fracture-subluxation elbow	Shoulder and upper arm
67036	S4B2000	Closed fracture-subluxation elbow joint	Shoulder and upper arm
104356	S4B2100	Closed fracture-subluxation superior radio-ulnar joint	Shoulder and upper arm
85491	S4B3.00	Open fracture-subluxation elbow	Shoulder and upper arm
97352	Syu4200	[X]Multiple fractures of clavicle, scapula and humerus	Shoulder and upper arm
73900	Nyu6700	[X]Collapsed vertebra in diseases classified elsewhere	Spine
90472	7J41500	Balloon kyphoplasty of fracture of spine	Spine
30956	S11x.00	Closed fracture of spine with spinal cord lesion unspecified	Spine
3573	S10x.00	Closed fracture of spine, unspecified,	Spine
73611	S112z00	Closed fracture of thoracic spine with cord lesion NOS	Spine
95529	S114100	Closed spinal fracture with complete lumbar cord lesion	Spine
49567	S114000	Closed spinal fracture with unspecified lumbar cord lesion	Spine
31545	S112700	Cls spinal fracture with complete thorac cord lesion, T7-12	Spine
102043	S112A00	Cls spinal fracture with posterior thorac cord lesion, T7-12	Spine
43091	S112600	Cls spinal fracture with unspec thoracic cord lesion, T7-12	Spine
108484	S112000	Cls spinal fracture with unspec thoracic cord lesion,T1-6	Spine
48958	S112100	Cls spinal fracture wth complete thoracic cord lesion,T1-6	Spine
28575	N331.11	Collapse of spine NOS	Spine
4013	N331L00	Collapse of vertebra due to osteoporosis NOS	Spine
2793	N331.12	Collapse of vertebra NOS	Spine
38728	N331D00	Collapsed vertebra NOS	Spine
31933	7J41.00	Decompression of fracture of spine	Spine
16895	N1y1.00	Fatigue fracture of vertebra	Spine
34850	7J43100	Fixation of fracture of spine using Harrington rod	Spine
32063	S11..00	Fracture of spine with spinal cord lesion	Spine
55195	S11z.00	Fracture of spine with spinal cord lesion NOS	Spine
8255	S10..00	Fracture of spine without mention of spinal cord injury	Spine
34166	S10z.00	Fracture of spine without mention of spinal cord lesion NOS	Spine
30058	S10..11	Fracture of transverse process spine - no spinal cord lesion	Spine
43786	S11..12	Fracture of vertebra with spinal cord lesion	Spine
4409	S10..12	Fracture of vertebra without spinal cord lesion vert	Spine
19235	14G8.00	H/O: vertebral fracture	Spine
43600	7J42400	Halo skull traction for fracture of spine	Spine
17377	N331800	Osteoporosis + pathological fracture lumbar vertebrae	Spine
12673	N331900	Osteoporosis + pathological fracture thoracic vertebrae	Spine
44386	N331.14	Osteoporotic vertebral collapse	Spine
106504	7J41000	Complex decompression of fracture of spine	Spine
68811	7J41100	Anterior decompression of fracture of spine	Spine
98016	7J41200	Posterior decompression of fracture of spine	Spine
88269	7J41300	Vertebroplasty of fracture of spine	Spine
91658	7J41400	Posterior decompression of fracture of spine NEC	Spine
65606	7J41y00	Other specified decompression of fracture of spine	Spine
45410	7J41z00	Decompression of fracture of spine NOS	Spine
20744	7J42.00	Other reduction of fracture of spine	Spine

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
48159	7J42.11	Other reduction of fracture of spine and stabilisation	Spine
49564	7J42000	Open reduction of fracture of spine & excis facet of spine	Spine
34634	7J42100	Open reduction of fracture of spine NEC	Spine
49529	7J42200	Manipulative reduction of fracture of spine	Spine
63452	7J42300	Spinal extension traction for fracture of spine	Spine
15622	7J42500	Spinal traction for fracture of spine NEC	Spine
51521	7J42600	Primary bedrest stabilisation of spinal fracture	Spine
46171	7J42700	Primary collar stabilisation of spinal fracture	Spine
71006	7J42900	Primary cast stabilisation of spinal fracture	Spine
98165	7J42B00	Primary other external stabilisation of spinal fracture	Spine
100161	7J42C00	Revision to bedrest stabilisation of spinal fracture	Spine
58589	7J42D00	Revision to collar stabilisation of spinal fracture	Spine
94374	7J42G00	Revision to external fixation stabilisation spinal fracture	Spine
110247	7J42J00	Primary closed reduction spinal fracture alone	Spine
104803	7J42L00	Primary cls reduction spinal fracture+bedrest stabilisation	Spine
61389	7J42M00	Primary cls reduc spinal fracture+skull traction stabilisatn	Spine
93752	7J42y00	Other specified other reduction of fracture of spine	Spine
92356	7J42z00	Other reduction of fracture of spine NOS	Spine
20598	7J43.00	Fixation of fracture of spine	Spine
62489	7J43.11	Internal fixation of fracture of spine	Spine
28966	7J43000	Primary open reduc spinal fracture+internal fix+plate	Spine
63980	7J43200	Fixation of fracture of spine and skull traction HFQ	Spine
63954	7J43211	Barr skull traction for fracture of spine	Spine
64388	7J43300	Primary open reduc spinal fracture+internal fix+wire	Spine
61491	7J43400	Primary open reduc spinal fracture+internal fix+rod system	Spine
91649	7J43700	Primary open reduc spinal fracture+other internal fix	Spine
67910	7J43900	Rvsn open reduc spinal fracture+internal fix+plate	Spine
98056	7J43A00	Rvsn open reduc spinal fracture+internal fix+rod system	Spine
63218	7J43C00	Rvsn open reduc spinal fracture+internal fix+internl fixator	Spine
103434	7J43E00	Removal of fracture fixation device from spine	Spine
73344	7J43y00	Other specified fixation of fracture of spine	Spine
60352	7J43z00	Fixation of fracture of spine NOS	Spine
66164	S10y.00	Open fracture of spine, unspecified,	Spine
62337	S110000	Cls spinal fracture with unspec cervical cord lesion, C1-4	Spine
109377	S110100	Cls spinal fracture with complete cervcl cord lesion, C1-4	Spine
72711	S110600	Cls spinal fracture with unspec cervical cord lesion, C5-7	Spine
102735	S110700	Cls spinal fracture with complete cervcl cord lesion, C5-7	Spine
96514	S110800	Cls spinal fracture with anterior cervcl cord lesion, C5-7	Spine
73416	S110z00	Closed fracture of cervical spine with cord lesion NOS	Spine
69432	S111.00	Open fracture of cervical spine with spinal cord lesion	Spine
60615	S113.00	Open fracture of thoracic spine with spinal cord lesion	Spine
101299	S113000	Opn spinal fracture with unspec thoracic cord lesion, T1-6	Spine
104755	S113A00	Opn spinal fracture with posterior thorac cord lesion, T7-12	Spine
73788	S114500	Closed spinal fracture with cauda equina lesion	Spine
38355	S312500	Closed fracture distal femur, lateral condyle	Thigh
5332	S312300	Closed fracture distal femur, supracondylar	Thigh
53279	S312000	Closed fracture of distal femur, unspecified	Thigh
6320	S312100	Closed fracture of femoral condyle, unspecified	Thigh

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
22329	S312.11	Closed fracture of femur, distal end	Thigh
21922	S312200	Closed fracture of femur, lower epiphysis	Thigh
6868	S310.00	Closed fracture of femur, shaft or unspecified part	Thigh
37662	S310000	Closed fracture of femur, unspecified part	Thigh
29145	S302200	Closed fracture proximal femur, subtrochanteric	Thigh
18962	7K1L500	Closed reduction of fracture of femur	Thigh
520	S31z.00	Fracture of femur, NOS	Thigh
8589	S315.00	Fracture of lower end of femur	Thigh
8646	S314.00	Fracture of shaft of femur	Thigh
21773	S3x2.00	Multiple fractures of femur	Thigh
42972	S311.00	Open fracture of femur, shaft or unspecified part	Thigh
8040	S31..00	Other fracture of femur	Thigh
8243	S305.00	Subtrochanteric fracture	Thigh
12791	S310011	Thigh fracture NOS	Thigh
71282	S303200	Open fracture proximal femur, subtrochanteric	Thigh
20893	S310012	Upper leg fracture NOS	Thigh
24674	S310100	Closed fracture shaft of femur	Thigh
52318	S310z00	Closed fracture of shaft or unspecified part, NOS	Thigh
34106	S311000	Open fracture of femur, unspecified part	Thigh
10095	S311100	Open fracture shaft of femur	Thigh
94360	S311z00	Open fracture of femur, shaft or unspecified part, NOS	Thigh
28954	S312.00	Closed fracture distal femur	Thigh
45562	S312400	Closed fracture distal femur, medial condyle	Thigh
54242	S312600	Closed fracture distal femur, bicondylar (T-Y fracture)	Thigh
55327	S312x00	Closed fracture distal femur, comminuted/intra-articular	Thigh
61802	S312z00	Closed fracture of distal femur not otherwise specified	Thigh
51170	S313.00	Open fracture distal femur	Thigh
32866	S313.11	Open fracture of femur, distal end	Thigh
45529	S313000	Open fracture distal femur, unspecified	Thigh
49595	S313100	Open fracture of femoral condyle, unspecified	Thigh
48142	S313200	Open fracture of femur, lower epiphysis	Thigh
42805	S313300	Open fracture distal femur, supracondylar	Thigh
67294	S313400	Open fracture distal femur, medial condyle	Thigh
34738	S313500	Open fracture distal femur, lateral condyle	Thigh
73208	S313x00	Open fracture distal femur, comminuted/intra-articular	Thigh
88737	S313z00	Open fracture of distal femur not otherwise specified	Thigh
27989	SC3D400	Sequelae of fracture of femur	Thigh
10252	S1...00	Fracture of neck and trunk	Unspecified
57301	NyuB000	[X]Other osteoporosis with pathological fracture	Unspecified
18825	NyuB800	[X]Unspecified osteoporosis with pathological fracture	Unspecified
37310	S3z0.00	Closed fracture of bones, unspecified	Unspecified
46894	N331500	Drug-induced osteoporosis with pathological fracture	Unspecified
358	S3z..11	Fracture NOS	Unspecified
54834	N331700	Fracture of bone in neoplastic disease	Unspecified
29162	S3zz.00	Fracture of bones NOS	Unspecified
2470	S3z..00	Fracture of unspecified bones	Unspecified
16769	TC7..00	Fracture, cause unspecified	Unspecified
93497	N331N00	Fragility fracture	Unspecified

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
11503	N331M00	Fragility fracture due to unspecified osteoporosis	Unspecified
455	S3z0000	Greenstick fracture	Unspecified
27597	N331600	Idiopathic osteoporosis with pathological fracture	Unspecified
2887	7K1L100	Manipulation of fracture of bone NEC	Unspecified
93981	N331N11	Minimal trauma fracture	Unspecified
93705	N331M11	Minimal trauma fracture due to unspecified osteoporosis	Unspecified
4629	7K1L.00	Other closed reduction of fracture of bone	Unspecified
5526	N331.00	Pathological fracture	Unspecified
38395	N331B00	Postmenopausal osteoporosis with pathological fracture	Unspecified
4115	7K1D100	Prim open reduct fract long bone & fixation rigid	Unspecified
4763	7K1D400	Prim open reduction fragment of bone & fixation using	Unspecified
11872	7K1LV00	Primary closed reduction of fracture alone	Unspecified
7672	7K1D.00	Primary open reduction fracture bone & intramedull fixation	Unspecified
22393	7K1JH00	Primary wire fixation of fracture	Unspecified
23971	7K1D800	Prmy open reduction #+locked reamed intramedullary nail fxtn	Unspecified
17508	7K1E000	Prmy open reduction of #+internal fixation with plate NEC	Unspecified
33711	7K1E800	Prmy open reduction of #+internal fixation with screw(s)	Unspecified
29582	7K1D511	K wiring of fracture	Unspecified
34277	7K1Dy00	Prim open reduction fracture bone & intramedullary fixatn OS	Unspecified
36698	7K1Dz00	Prim open reduction fracture bone & intramedull fixation NOS	Unspecified
36449	7K1Ez00	Prim open reduction fracture bone & extramedull fixation NOS	Unspecified
30429	7K1F.00	Primary open reduction of intraarticular fracture of bone	Unspecified
45394	7K1F300	Primary intraarticular fixation intraartic fracture bone NEC	Unspecified
97111	7K1F400	Prim extraarticular reduction intraartic fracture bone NEC	Unspecified
53348	7K1Fy00	Primary open reduction of intraarticular fracture bone OS	Unspecified
50460	7K1Fz00	Primary open reduction of intraarticular fracture bone NOS	Unspecified
4528	7K1G.00	Other primary open reduction of fracture of bone	Unspecified
49870	7K1G000	Prmy open reduction of fracture and skeletal traction	Unspecified
34396	7K1G100	Prmy open reduction of fracture and external fixation	Unspecified
40321	7K1G300	Primary open reduction of fracture alone	Unspecified
33602	7K1G400	Primary open reduction of fracture and cast immobilisation	Unspecified
63085	7K1G500	Primary open reduction of fracture and functional bracing	Unspecified
91919	7K1G600	Primary open reduction of fracture and skin traction	Unspecified
21942	7K1Gy11	Primary open reduction of bone fracture & external fixation	Unspecified
16141	7K1Gz00	Other primary open reduction of fracture of bone NOS	Unspecified
9727	7K1H.00	Secondary open reduction of fracture of bone	Unspecified
54959	7K1H.11	Revision to open reduction of fracture of bone	Unspecified
55447	7K1H200	Secondary open reduction of intraarticular fracture of bone	Unspecified
68992	7K1H400	Secondary open reduct fracture bone & external fixation HFQ	Unspecified
57626	7K1H900	Revision to open reduction of fracture alone	Unspecified
108001	7K1HD00	Revision to open reduction of fracture and skeletal traction	Unspecified
59716	7K1HE00	Revision to open reduction of fracture and external fixation	Unspecified
28081	7K1Hy00	Other specified secondary open reduction of fracture of bone	Unspecified
62029	7K1Hz00	Secondary open reduction of fracture of bone NOS	Unspecified
6248	7K1J.00	Closed (or no) reduction of fracture and internal fixation	Unspecified

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
12823	7K1J300	Closed reduction fracture small bone & fixation using screw	Unspecified
30748	7K1JJ00	Revision to wire fixation of fracture	Unspecified
34355	7K1JK00	Primary closed reduction of fracture and wire fixation	Unspecified
44899	7K1JL00	Revision to closed reduction of fracture and wire fixation	Unspecified
42186	7K1Jy00	Closed reduction of bone fracture and internal fixation OS	Unspecified
36497	7K1Jz00	Closed reduction of bone fracture and internal fixation NOS	Unspecified
24715	7K1K.00	Closed (or no) reduction of fracture and external fixation	Unspecified
64862	7K1K000	Closed reduction fracture bone and fixation to skeleton HFQ	Unspecified
38868	7K1K200	Remanipulation of fracture of bone and external fixation HFQ	Unspecified
69702	7K1K700	Primary functional bracing of fracture	Unspecified
11333	7K1K800	Primary external fixation of fracture	Unspecified
99994	7K1K900	Other primary external immobilisation of fracture	Unspecified
96903	7K1KA00	Revision to functional bracing of fracture	Unspecified
12165	7K1KB00	Revision to external fixation of fracture	Unspecified
110066	7K1KC00	Other revision to external immobilisation of fracture	Unspecified
29103	7K1KE00	Primary closed reduction of fracture and external fixation	Unspecified
10102	7K1Ky00	Closed reduction of bone fracture and external fixation OS	Unspecified
64222	7K1Kz00	Closed reduction of bone fracture and external fixation NOS	Unspecified
55308	7K1L011	Manipulation of fracture and skeletal traction NEC	Unspecified
104067	7K1L211	Remanipulation of fracture and skeletal traction NEC	Unspecified
30213	7K1L300	Remanipulation of fracture of bone NEC	Unspecified
57893	7K1LT00	Primary closed reduction of fracture and cast immobilisation	Unspecified
36893	7K1LW00	Primary closed reduction of fracture and skin traction	Unspecified
35052	7K1LX00	Revision to closed reduction of fracture alone	Unspecified
48219	7K1LZ00	Primary skin traction of fracture	Unspecified
24809	7K1La00	Revision to skin traction of fracture	Unspecified
41760	7K1Lb00	Primary cast immobilisation of fracture	Unspecified
46862	7K1Lc00	Revision to cast immobilisation of fracture	Unspecified
38472	7K1Ld00	Primary arthroscopic reduction of fracture	Unspecified
32012	7K1Le00	Primary arthroscopic reduction and fixation of fracture	Unspecified
35742	7K1Lf00	Revision to arthroscopic reduction of fracture	Unspecified
34743	7K1Lg00	Revision to arthroscopic reduction and fixation of fracture	Unspecified
70919	7K1Ly00	Other specified other closed reduction of fracture of bone	Unspecified
15085	7K1Lz00	Other closed reduction of fracture of bone NOS	Unspecified
73812	7K1N900	Primary skeletal traction of fracture	Unspecified
4641	7K1T100	Debridement of open fracture	Unspecified
102254	7K1Y.00	Second closed reduction fracture bone and internal fixation	Unspecified
104066	7K1Y100	Remanip fracture long bone and rigid internal fixation NEC	Unspecified
107718	7K1Yy00	OS second closed reduct fracture bone and internal fixation	Unspecified
24611	7K6F200	Primary open reduction of fracture dislocation of joint NEC	Unspecified
55930	7K6FE00	Primary open reduction of fracture dislocation alone	Unspecified
22144	7K6GN00	Closed reduction fracture disloc joint & internal fixation	Unspecified
61653	7K6GX00	Primary closed reduction of fracture dislocation alone	Unspecified
54198	7K6H200	Secondary open reduction fracture dislocation of joint NEC	Unspecified
35866	7K6H400	Revision to closed reduction of fracture dislocation alone	Unspecified
69362	7K6H411	Remanipulation of fracture dislocation alone	Unspecified
36783	7K6H700	Secondary open reduction fracture disloc joint & fixation	Unspecified
99297	7K6HX00	Revision to open reduction fracture dislocation alone	Unspecified

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
85656	7K6Hh00	Sec open red fracture dislocat joint and intern fixation NEC	Unspecified
10737	82...11	Closed reduction of fracture	Unspecified
95674	N1y2.00	Pars interarticularis stress fracture	Unspecified
100677	N331.13	Sponanteous fracture	Unspecified
39334	N331200	Postoophorectomy osteoporosis with pathological fracture	Unspecified
33526	N331300	Osteoporosis of disuse with pathological fracture	Unspecified
68019	N331400	Postsurgical malabsorption osteoporosis with path fracture	Unspecified
29332	N331y00	Other specified pathological fracture	Unspecified
62343	N331z00	Pathological fracture NOS	Unspecified
10008	N338.00	Malunion and nonunion of fracture	Unspecified
4849	N338000	Malunion of fracture	Unspecified
12879	N338100	Pseudoarthrosis - fracture nonunion	Unspecified
5312	N338111	Nonunion of fracture	Unspecified
50250	N338200	Hypertrophic non-union of fracture	Unspecified
42069	N338300	Atrophic non-union of fracture	Unspecified
57377	N338400	Angular mal-union of fracture	Unspecified
65470	N338500	Rotational mal-union of fracture	Unspecified
9676	N338600	Delayed union of fracture	Unspecified
3809	S00..11	Frontal bone fracture	Unspecified
8573	S00..12	Parietal bone fracture	Unspecified
60608	S140.00	Closed fracture of ill-defined bone of trunk	Unspecified
953	S3z1.00	Open fracture of bones, unspecified	Unspecified
3025	S3z2.00	Stress fracture	Unspecified
868	S4...13	Fracture dislocations and fracture subluxations	Unspecified
40752	S4J..00	Other fracture-dislocation or subluxation	Unspecified
34993	S4J0.00	Other closed fracture-dislocation	Unspecified
38590	S4J1.00	Other open fracture-dislocation	Unspecified
71622	S4J2.00	Other closed fracture-subluxation	Unspecified
111125	S4J3.00	Other open fracture-subluxation	Unspecified
44916	SC0z.11	Delayed union of fracture	Unspecified
69786	Zw02400	[Q] Stress fracture	Unspecified
111268	Zw02D00	[Q] Open fracture grade 1	Unspecified
95619	Zw02E00	[Q] Open fracture grade 2	Unspecified
53068	Syu6500	[X]Fracture of other & unspecified parts of wrist and hand	Wrist and hand
50053	S234A00	Closd dorsal Barton's fracture	Wrist and hand
10033	S234F00	Closed Barton's fracture	Wrist and hand
343	S234100	Closed Colles' fracture	Wrist and hand
107741	S234A12	Closed dorsal Barton fracture-subluxation	Wrist and hand
57736	S234A11	Closed dorsal Barton's fracture-dislocation	Wrist and hand
17606	S240700	Closed fracture capitate	Wrist and hand
27881	S250600	Closed fracture finger metacarpal	Wrist and hand
33905	S250200	Closed fracture finger metacarpal base	Wrist and hand
6392	S250.00	Closed fracture of metacarpal bone(s)	Wrist and hand
8302	S260.00	Closed fracture of one or more phalanges of hand	Wrist and hand
6168	S240100	Closed fracture of the scaphoid	Wrist and hand
6915	S234B00	Closed fracture radial styloid	Wrist and hand
26045	S240500	Closed fracture trapezium	Wrist and hand
17921	S4C2.00	Closed fracture-subluxation of the wrist	Wrist and hand

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
50148	S4C2100	Closed fracture-subluxation radiocarpal joint	Wrist and hand
6069	7K1LH00	Closed reduction of fracture of finger	Wrist and hand
2862	S234700	Closed Smith's fracture	Wrist and hand
65636	S234912	Closed volar Barton fracture-subluxation	Wrist and hand
11066	S234900	Closed volar Barton's fracture	Wrist and hand
53689	S234911	Closed volar Barton's fracture-dislocation	Wrist and hand
5260	S26..11	Finger fracture	Wrist and hand
8056	S242.00	Fracture at wrist and hand level	Wrist and hand
12516	S2B..00	Fracture of bone of hand	Wrist and hand
22375	S24..00	Fracture of carpal bone	Wrist and hand
7564	S242100	Fracture of first metacarpal bone	Wrist and hand
2888	S25..00	Fracture of metacarpal bone	Wrist and hand
6299	S263.00	Fracture of other finger	Wrist and hand
993	S242200	Fracture of other metacarpal bone	Wrist and hand
553	S242000	Fracture of scaphoid	Wrist and hand
7500	S262.00	Fracture of thumb	Wrist and hand
18614	S4C..00	Fracture-dislocation or subluxation of wrist	Wrist and hand
10250	S4D..00	Fracture-dislocation/subluxation finger/thumb	Wrist and hand
2643	S25..11	Hand fracture - metacarpal bone	Wrist and hand
4725	S242300	Multiple fractures of metacarpal bones	Wrist and hand
6074	S235100	Open Colles' fracture	Wrist and hand
36556	S261000	Open fracture of phalanx or phalanges, unspecified	Wrist and hand
6380	S235B00	Open fracture radial styloid	Wrist and hand
203	S234.11	Wrist fracture - closed	Wrist and hand
8885	7K1LJ00	Closed reduction of fracture of thumb	Wrist and hand
35530	7K1LK00	Closed reduction of fracture of metacarpus	Wrist and hand
5951	7K1LM00	Closed reduction of fracture of wrist	Wrist and hand
52389	S234111	Smith's fracture - closed	Wrist and hand
10022	S235.11	Wrist fracture - open	Wrist and hand
98681	S235111	Smith's fracture - open	Wrist and hand
34730	S235700	Open Smith's fracture	Wrist and hand
61675	S235900	Open volar Barton's fracture	Wrist and hand
111858	S235A00	Open dorsal Barton's fracture	Wrist and hand
18301	S235F00	Open Barton's fracture	Wrist and hand
10167	S24..11	Hand fracture - carpal bone	Wrist and hand
15666	S240.00	Closed fracture of carpal bone	Wrist and hand
57979	S240000	Closed fracture of carpal bone, unspecified	Wrist and hand
10357	S240200	Closed fracture lunate	Wrist and hand
28413	S240300	Closed fracture triquetral	Wrist and hand
5354	S240400	Closed fracture pisiform	Wrist and hand
35837	S240600	Closed fracture trapezoid	Wrist and hand
31999	S240800	Closed fracture hamate	Wrist and hand
39458	S240900	Closed fracture hamate, hook	Wrist and hand
16985	S240A00	Closed fracture scaphoid, proximal pole	Wrist and hand
19403	S240B00	Closed fracture scaphoid, waist, transverse	Wrist and hand
47837	S240C00	Closed fracture scaphoid, waist, oblique	Wrist and hand
44712	S240D00	Closed fracture scaphoid, waist, comminuted	Wrist and hand
28425	S240E00	Closed fracture scaphoid, tuberosity	Wrist and hand

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
73165	S240F00	Closed fracture carpal bones, multiple	Wrist and hand
56886	S240y00	Closed fracture of other carpal bone	Wrist and hand
33929	S240z00	Closed fracture of carpal bone NOS	Wrist and hand
65141	S241.00	Open fracture of carpal bone	Wrist and hand
68085	S241000	Open fracture of carpal bone, unspecified	Wrist and hand
17286	S241100	Open fracture of the scaphoid	Wrist and hand
68765	S241200	Open fracture lunate	Wrist and hand
51666	S241300	Open fracture triquetral	Wrist and hand
44156	S241400	Open fracture pisiform	Wrist and hand
56311	S241500	Open fracture trapezium	Wrist and hand
98933	S241600	Open fracture trapezoid	Wrist and hand
64725	S241700	Open fracture capitate	Wrist and hand
69213	S241800	Open fracture hamate	Wrist and hand
110906	S241900	Open fracture hamate, hook	Wrist and hand
55814	S241A00	Open fracture scaphoid, proximal pole	Wrist and hand
73824	S241B00	Open fracture scaphoid, waist, transverse	Wrist and hand
59985	S241C00	Open fracture scaphoid, waist, oblique	Wrist and hand
64575	S241D00	Open fracture scaphoid, waist, comminuted	Wrist and hand
49588	S241E00	Open fracture scaphoid, tuberosity	Wrist and hand
102013	S241z00	Open fracture of carpal bone NOS	Wrist and hand
31525	S250000	Closed fracture of metacarpal bone (s), site unspecified	Wrist and hand
25519	S250300	Closed fracture finger metacarpal shaft	Wrist and hand
12546	S250400	Closed fracture finger metacarpal neck	Wrist and hand
24598	S250500	Closed fracture finger metacarpal head	Wrist and hand
52895	S250700	Closed fracture finger metacarpal, multiple	Wrist and hand
25811	S250800	Closed fracture of thumb metacarpal	Wrist and hand
50634	S250A00	Closed fracture thumb metacarpal shaft	Wrist and hand
49598	S250B00	Closed fracture thumb metacarpal neck	Wrist and hand
53650	S250C00	Closed fracture thumb metacarpal head	Wrist and hand
21175	S250x00	Closed fractures of multiple sites of unspecified metacarpus	Wrist and hand
6881	S250z00	Closed fracture of metacarpal bone(s) NOS	Wrist and hand
29111	S251.00	Open fracture of metacarpal bone(s)	Wrist and hand
62853	S251000	Open fracture of metacarpal bone(s), site unspecified	Wrist and hand
73150	S251200	Open fracture finger metacarpal base	Wrist and hand
52305	S251300	Open fracture finger metacarpal shaft	Wrist and hand
52588	S251400	Open fracture finger metacarpal neck	Wrist and hand
53693	S251500	Open fracture finger metacarpal head	Wrist and hand
40361	S251600	Open fracture finger metacarpal	Wrist and hand
72407	S251700	Open fracture finger metacarpal, multiple	Wrist and hand
60765	S251800	Open fracture of thumb metacarpal	Wrist and hand
98867	S251A00	Open fracture thumb metacarpal shaft	Wrist and hand
102225	S251C00	Open fracture thumb metacarpal head	Wrist and hand
94393	S251x00	Open fractures of multiple sites of unspecified metacarpus	Wrist and hand
47847	S251z00	Open fracture of metacarpal bone(s) NOS	Wrist and hand
7531	S252.00	Closed fracture sesamoid bone of hand	Wrist and hand
52067	S253.00	Open fracture sesamoid bone of hand	Wrist and hand
482	S26..12	Thumb fracture excluding base	Wrist and hand
34058	S260000	Closed fracture of phalanx or phalanges, unspecified	Wrist and hand

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
33582	S260300	Closed fracture thumb proximal phalanx	Wrist and hand
33678	S260400	Closed fracture thumb proximal phalanx, base	Wrist and hand
43681	S260500	Closed fracture thumb proximal phalanx, shaft	Wrist and hand
64027	S260600	Closed fracture thumb proximal phalanx, neck	Wrist and hand
33651	S260700	Closed fracture thumb proximal phalanx, head	Wrist and hand
28249	S260800	Closed fracture thumb distal phalanx	Wrist and hand
34080	S260900	Closed fracture thumb distal phalanx, base	Wrist and hand
62808	S260A00	Closed fracture thumb distal phalanx, shaft	Wrist and hand
42139	S260B00	Closed fracture thumb distal phalanx, tuft	Wrist and hand
61181	S260C00	Closed fracture thumb distal phalanx, mallet	Wrist and hand
24516	S260D00	Closed fracture finger proximal phalanx	Wrist and hand
27699	S260E00	Closed fracture finger proximal phalanx, base	Wrist and hand
18338	S260F00	Closed fracture finger proximal phalanx, shaft	Wrist and hand
33679	S260G00	Closed fracture finger proximal phalanx, neck	Wrist and hand
44943	S260H00	Closed fracture finger proximal phalanx, head	Wrist and hand
44737	S260J00	Closed fracture finger proximal phalanx, multiple	Wrist and hand
33616	S260K00	Closed fracture finger middle phalanx	Wrist and hand
33598	S260L00	Closed fracture finger middle phalanx, base	Wrist and hand
33757	S260M00	Closed fracture finger middle phalanx, shaft	Wrist and hand
34356	S260N00	Closed fracture finger middle phalanx, neck	Wrist and hand
34307	S260P00	Closed fracture finger middle phalanx, head	Wrist and hand
67097	S260Q00	Closed fracture finger middle phalanx, multiple	Wrist and hand
29117	S260R00	Closed fracture finger distal phalanx	Wrist and hand
27643	S260S00	Closed fracture finger distal phalanx, base	Wrist and hand
33695	S260T00	Closed fracture finger distal phalanx, shaft	Wrist and hand
33845	S260U00	Closed fracture finger distal phalanx, tuft	Wrist and hand
52398	S260V00	Closed fracture finger distal phalanx, mallet	Wrist and hand
45094	S260W00	Closed fracture finger distal phalanx, multiple	Wrist and hand
45374	S260x00	Closed fractures of phalanx or phalanges, multiple sites	Wrist and hand
40535	S260z00	Closed fracture of one or more phalanges of hand NOS	Wrist and hand
18336	S261.00	Open fracture of one or more phalanges of hand	Wrist and hand
61279	S261300	Open fracture thumb proximal phalanx	Wrist and hand
94031	S261400	Open fracture thumb proximal phalanx, base	Wrist and hand
94416	S261500	Open fracture thumb proximal phalanx, shaft	Wrist and hand
99397	S261600	Open fracture thumb proximal phalanx, neck	Wrist and hand
101316	S261700	Open fracture thumb proximal phalanx, head	Wrist and hand
37986	S261800	Open fracture thumb distal phalanx	Wrist and hand
65731	S261900	Open fracture thumb distal phalanx, base	Wrist and hand
65715	S261A00	Open fracture thumb distal phalanx, shaft	Wrist and hand
53593	S261B00	Open fracture thumb distal phalanx, tuft	Wrist and hand
103416	S261C00	Open fracture thumb distal phalanx, mallet	Wrist and hand
33684	S261D00	Open fracture finger proximal phalanx	Wrist and hand
44700	S261E00	Open fracture finger proximal phalanx, base	Wrist and hand
62334	S261F00	Open fracture finger proximal phalanx, shaft	Wrist and hand
64113	S261G00	Open fracture finger proximal phalanx, neck	Wrist and hand
61529	S261H00	Open fracture finger proximal phalanx, head	Wrist and hand
69729	S261J00	Open fracture finger proximal phalanx, multiple	Wrist and hand
40304	S261K00	Open fracture finger middle phalanx	Wrist and hand

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
67718	S261L00	Open fracture finger middle phalanx, base	Wrist and hand
33866	S261M00	Open fracture finger middle phalanx, shaft	Wrist and hand
69363	S261N00	Open fracture finger middle phalanx, neck	Wrist and hand
99459	S261P00	Open fracture finger middle phalanx, head	Wrist and hand
28197	S261R00	Open fracture finger distal phalanx	Wrist and hand
48837	S261S00	Open fracture finger distal phalanx, base	Wrist and hand
52333	S261T00	Open fracture finger distal phalanx, shaft	Wrist and hand
51700	S261U00	Open fracture finger distal phalanx, tuft	Wrist and hand
102046	S261V00	Open fracture finger distal phalanx, mallet	Wrist and hand
54123	S261W00	Open fracture finger distal phalanx, multiple	Wrist and hand
67011	S261x00	Open fracture of phalanx or phalanges, multiple sites	Wrist and hand
50781	S261z00	Open fracture of one or more phalanges of hand NOS	Wrist and hand
8199	S264.00	Multiple fractures of fingers	Wrist and hand
33908	S27..00	Multiple fractures of hand bones	Wrist and hand
44431	S270.00	Closed multiple fractures of hand bones	Wrist and hand
33990	S271.00	Open multiple fractures of hand bones	Wrist and hand
53923	S27z.00	Multiple fractures of hand bones NOS	Wrist and hand
34429	S4C0.00	Closed fracture dislocation of wrist	Wrist and hand
38408	S4C0100	Closed fracture-dislocation radiocarpal joint	Wrist and hand
67584	S4C0200	Closed fracture-dislocation mid carpal	Wrist and hand
27783	S4C0300	Closed fracture-dislocation, carpometacarpal joint	Wrist and hand
64435	S4C0400	Closed fracture-dislocation lunate (volar)	Wrist and hand
96136	S4C0500	Closed fracture-dislocation peri-lunate (dorsal)	Wrist and hand
55212	S4C0600	Closed fracture-dislocation peri-lunate trans-scaphoid	Wrist and hand
42844	S4C1.00	Open fracture dislocation wrist	Wrist and hand
9261	S4C1000	Open fracture-dislocation, distal radio-ulnar joint	Wrist and hand
49256	S4C1100	Open fracture-dislocation radiocarpal joint	Wrist and hand
97476	S4C1300	Open fracture-dislocation carpometacarpal joint	Wrist and hand
63292	S4C1600	Open fracture-dislocation peri-lunate trans-scaphoid	Wrist and hand
103524	S4C2200	Closed fracture-subluxation mid carpal	Wrist and hand
68595	S4C2300	Closed fracture-subluxation, carpometacarpal joint	Wrist and hand
55412	S4C2400	Closed fracture-subluxation lunate (volar)	Wrist and hand
63712	S4C2600	Closed fracture-subluxation peri-lunate trans-scaphoid	Wrist and hand
100350	S4C2y00	Closed fracture-subluxation other carpal	Wrist and hand
59219	S4C3.00	Open fracture-subluxation of the wrist	Wrist and hand
60343	S4C3000	Open fracture-subluxation, distal radio-ulnar joint	Wrist and hand
46798	S4C3100	Open fracture-subluxation radiocarpal joint	Wrist and hand
94661	S4C3300	Open fracture-subluxation, carpometacarpal joint	Wrist and hand
68262	S4C3600	Open fracture-subluxation peri-lunate trans-scaphoid	Wrist and hand
35198	S4D0.00	Closed fracture-dislocation digit	Wrist and hand
42990	S4D0000	Closed fracture-dislocation digit, unspecified	Wrist and hand
25445	S4D0100	Closed fracture-dislocation, metacarpophalangeal joint	Wrist and hand
39708	S4D0200	Closed fracture-dislocation IPJ, unspecified	Wrist and hand
33985	S4D0300	Closed fracture-dislocation, distal interphalangeal joint	Wrist and hand
19375	S4D0400	Closed fracture-dislocation, proximal interphalangeal joint	Wrist and hand
10462	S4D0500	Closed fracture-dislocation, interphalangeal joint thumb	Wrist and hand
63049	S4D0600	Closed fracture-dislocation multiple digits	Wrist and hand
18841	S4D1.00	Open fracture-dislocation digit	Wrist and hand

Appendix W. Medcodes to identify fractures in the CPRD [continued]

Medcode	Read code	Description	Site
65848	S4D1000	Open fracture-dislocation digit, unspecified	Wrist and hand
61858	S4D1100	Open fracture-dislocation, metacarpophalangeal joint	Wrist and hand
94265	S4D1200	Open fracture-dislocation IPJ, unspecified	Wrist and hand
43423	S4D1300	Open fracture-dislocation, distal interphalangeal joint	Wrist and hand
37582	S4D1400	Open fracture-dislocation, proximal interphalangeal joint	Wrist and hand
45690	S4D1500	Open fracture-dislocation, interphalangeal joint thumb	Wrist and hand
96998	S4D1600	Open fracture-dislocation multiple digits	Wrist and hand
48874	S4D2.00	Closed fracture-subluxation digit	Wrist and hand
41558	S4D2000	Closed fracture-subluxation digit, unspecified	Wrist and hand
36527	S4D2100	Closed fracture-subluxation, metacarpophalangeal joint	Wrist and hand
60487	S4D2200	Closed fracture-subluxation IPJ, unspecified	Wrist and hand
55356	S4D2300	Closed fracture-subluxation, distal interphalangeal joint	Wrist and hand
40817	S4D2400	Closed fracture-subluxation, proximal interphalangeal joint	Wrist and hand
63071	S4D2500	Closed fracture-subluxation, interphalangeal joint thumb	Wrist and hand
104015	S4D2600	Closed fracture-subluxation multiple digits	Wrist and hand
73986	S4D3.00	Open fracture-subluxation digit	Wrist and hand
66544	S4D3100	Open fracture-subluxation, metacarpophalangeal joint	Wrist and hand
51946	S4D3300	Open fracture-subluxation, distal interphalangeal joint	Wrist and hand
65494	S4D3400	Open fracture-subluxation, proximal interphalangeal joint	Wrist and hand
92349	S4D3500	Open fracture-subluxation, interphalangeal joint thumb	Wrist and hand
96438	S4D3600	Open fracture-subluxation multiple digits	Wrist and hand

Appendix X. ICD-10 codes to identify fractures in HES APC and OP data sources

ICD-10 code	Description	Site
T02	**Fractures involving multiple body regions**	**Multiple**
T02.0	Fractures involving head with neck	Multiple
T02.1	Fractures involving thorax with lower back and pelvis	Multiple
T02.2	Fractures involving multiple regions of one upper limb	Arm
T02.3	Fractures involving multiple regions of one lower limb	Lower leg and ankle
T02.4	Fractures involving multiple regions of both upper limbs	Arm
T02.5	Fractures involving multiple regions of both lower limbs	Lower leg and ankle
T02.6	Fractures involving multiple regions of upper limb(s) with lower limb(s)	Multiple
T02.7	Fractures involving thorax with lower back and pelvis with limb(s)	Multiple
T02.8	Fractures involving other combinations of body regions	Multiple
T02.9	Multiple fractures, unspecified	Multiple
T08	**Fracture of spine, level unspecified**	**Spine**
T10	**Fracture of upper limb, level unspecified**	**Upper limb**
T12	**Fracture of lower limb, level unspecified**	**Lower limb**
T14.2	Fracture of unspecified body region	Unspecified
S02	**Fracture of skull and facial bones**	**Head**
S02.0	Fracture of vault of skull	Head
S02.1	Fracture of base of skull	Head
S02.2	Fracture of nasal bones	Head
S02.3	Fracture of orbital floor	Head
S02.4	Fracture of malar and maxillary bones	Head
S02.5	Fracture of tooth	Head
S02.6	Fracture of mandible	Head
S02.7	Multiple fractures involving skull and facial bones	Head
S02.8	Fractures of other skull and facial bones	Head
S02.9	Fracture of skull and facial bones, part unspecified	Head
S12	**Fracture of neck**	**Neck**
S12.0	Fracture of first cervical vertebra	Neck
S12.1	Fracture of second cervical vertebra	Neck
S12.2	Fracture of other specified cervical vertebra	Neck
S12.7	Multiple fractures of cervical spine	Neck
S12.8	Fracture of other parts of neck	Neck
S12.9	Fracture of neck, part unspecified	Neck
S22	**Fracture of rib(s), sternum and thoracic spine**	**Chest**
S22.0	Fracture of thoracic vertebra	Chest
S22.1	Multiple fractures of thoracic spine	Chest
S22.2	Fracture of sternum	Chest
S22.3	Fracture of rib	Chest
S22.4	Multiple fractures of ribs	Chest
S22.5	Flail chest	Chest
S22.8	Fracture of other parts of bony thorax	Chest
S22.9	Fracture of bony thorax, part unspecified	Chest
S32	**Fracture of lumbar spine and pelvis**	**Lower back and pelvis**
S32.0	Fracture of lumbar vertebra	Lower back and pelvis
S32.1	Fracture of sacrum	Lower back and pelvis
S32.2	Fracture of coccyx	Lower back and pelvis
S32.3	Fracture of ilium	Lower back and pelvis
S32.4	Fracture of acetabulum	Lower back and pelvis

Appendix X. ICD-10 codes to identify fractures in HES APC and OP data sources [continued]

ICD-10 code	Description	Site
S32.5	Fracture of pubis	Lower back and pelvis
S32.7	Multiple fractures of lumbar spine and pelvis	Lower back and pelvis
S32.8	Fracture of other and unspecified parts of lumbar spine and pelvis	Lower back and pelvis
S42	**Fracture of shoulder and upper arm**	**Shoulder and upper arm**
S42.0	Fracture of clavicle	Shoulder and upper arm
S42.1	Fracture of scapula	Shoulder and upper arm
S42.2	Fracture of upper end of humerus	Shoulder and upper arm
S42.3	Fracture of shaft of humerus	Shoulder and upper arm
S42.4	Fracture of lower end of humerus	Shoulder and upper arm
S42.7	Multiple fractures of clavicle, scapula and humerus	Shoulder and upper arm
S42.8	Fracture of other parts of shoulder and upper arm	Shoulder and upper arm
S42.9	Fracture of shoulder girdle, part unspecified	Shoulder and upper arm
S52	**Fracture of forearm**	**Forearm**
S52.0	Fracture of upper end of ulna	Forearm
S52.1	Fracture of upper end of radius	Forearm
S52.2	Fracture of shaft of ulna	Forearm
S52.3	Fracture of shaft of radius	Forearm
S52.4	Fracture of shafts of both ulna and radius	Forearm
S52.5	Fracture of lower end of radius	Forearm
S52.6	Fracture of lower end of both ulna and radius	Forearm
S52.7	Multiple fractures of forearm	Forearm
S52.8	Fracture of other parts of forearm	Forearm
S52.9	Fracture of forearm, part unspecified	Forearm
S62	**Fracture of wrist and hand level**	**Wrist and hand**
S62.0	Fracture of navicular [scaphoid] bone of hand	Wrist and hand
S62.1	Fracture of other carpal bone(s)	Wrist and hand
S62.2	Fracture of first metacarpal bone	Wrist and hand
S62.3	Fracture of other metacarpal bone	Wrist and hand
S62.4	Multiple fractures of metacarpal bones	Wrist and hand
S62.5	Fracture of thumb	Wrist and hand
S62.6	Fracture of other finger	Wrist and hand
S62.7	Multiple fractures of fingers	Wrist and hand
S62.8	Fracture of other and unspecified parts of wrist and hand	Wrist and hand
S72	**Fracture of femur**	**Thigh and hip**
S72.0	Fracture of neck of femur	Hip
S72.1	Pertrochanteric fracture	Hip
S72.2	Subtrochanteric fracture	Hip
S72.3	Fracture of shaft of femur	Thigh
S72.4	Fracture of lower end of femur	Thigh
S72.7	Multiple fractures of femur	Thigh and hip
S72.8	Fractures of other parts of femur	Thigh and hip
S72.9	Fracture of femur, part unspecified	Thigh and hip
S82	**Fracture of lower leg, including ankle**	**Lower leg and ankle**
S82.0	Fracture of patella	Lower leg and ankle
S82.1	Fracture of upper end of tibia	Lower leg and ankle
S82.2	Fracture of shaft of tibia	Lower leg and ankle
S82.3	Fracture of lower end of tibia	Lower leg and ankle
S82.4	Fracture of fibula alone	Lower leg and ankle

Appendix X. ICD-10 codes to identify fractures in HES APC and OP data sources [continued]

ICD-10 code	Description	Site
S82.5	Fracture of medial malleolus	Lower leg and ankle
S82.6	Fracture of lateral malleolus	Lower leg and ankle
S82.7	Multiple fractures of lower leg	Lower leg and ankle
S82.8	Fractures of other parts of lower leg	Lower leg and ankle
S82.9	Fracture of lower leg, part unspecified	Lower leg and ankle
S92	**Fracture of foot, except ankle**	**Foot**
S92.0	Fracture of calcaneus	Foot
S92.1	Fracture of talus	Foot
S92.2	Fracture of other tarsal bone(s)	Foot
S92.3	Fracture of metatarsal bone	Foot
S92.4	Fracture of great toe	Foot
S92.5	Fracture of other toe	Foot
S92.7	Multiple fractures of foot	Foot
S92.9	Fracture of foot, unspecified	Foot

Appendix Y. OPCS-4 codes to identify fractures in HES APC and OP data sources

OPCS-4 code	Description	Site
V08	**Reduction of fracture of maxilla**	**Head**
V08.1	Reduction of fracture of alveolus of maxilla	Head
V08.2	Open reduction of fracture of maxilla NEC	Head
V08.3	Closed reduction of fracture of maxilla NEC	Head
V08.8	Other specified	Head
V08.9	Unspecified	Head
V09	**Reduction of fracture of other bone of face**	**Head**
V09.1	Reduction of fracture of nasoethmoid complex of bones	Head
V09.2	Reduction of fracture of nasal bone NEC	Head
V09.3	Reduction of fracture of zygomatic complex of bones	Head
V09.8	Other specified	Head
V09.9	Unspecified	Head
V11	**Fixation of bone of face**	**Head**
V11.1	Intermaxillary fixation of maxilla	Head
V11.2	Internal fixation of maxilla NEC	Head
V11.3	Extraoral fixation of maxilla	Head
V11.4	Fixation of maxilla NEC	Head
V11.5	Removal of fixation from bone of face	Head
V11.8	Other specified	Head
V11.9	Unspecified	Head
V15	**Reduction of fracture of mandible**	**Head**
V15.1	Reduction of fracture of alveolus of mandible	Head
V15.2	Open reduction of fracture of mandible NEC	Head
V15.3	Closed reduction of fracture of mandible NEC	Head
V15.8	Other specified	Head
V15.9	Unspecified	Head
V17	**Fixation of mandible**	**Head**
V17.1	Intermaxillary fixation of mandible	Head
V17.2	Internal fixation of mandible NEC	Head
V17.3	Extraoral fixation of mandible	Head
V17.4	Removal of fixation from mandible	Head
V17.8	Other specified	Head
V17.9	Unspecified	Head
V44	**Decompression of fracture of spine**	**Spine**
V44.1	Complex decompression of fracture of spine	Spine
V44.2	Anterior decompression of fracture of spine	Spine
V44.3	Posterior decompression of fracture of spine NEC	Spine
V44.4	Vertebroplasty of fracture of spine	Spine
V44.5	Balloon kyphoplasty of fracture of spine	Spine
V44.8	Other specified	Spine
V44.9	Unspecified	Spine
V45	**Other reduction of fracture of spine**	**Spine**
V45.1	Open reduction of fracture of spine and excision of facet of spine	Spine
V45.2	Open reduction of fracture of spine NEC	Spine
V45.3	Manipulative reduction of fracture of spine	Spine
V45.8	Other specified	Spine
V45.9	Unspecified	Spine
V46	**Fixation of fracture of spine**	**Spine**

Appendix Y. OPCS-4 codes to identify fractures in HES APC and OP data sources [continued]

OPCS-4 code	Description	Site
V46.1	Fixation of fracture of spine using plate	Spine
V46.2	Fixation of fracture of spine using Harrington rod	Spine
V46.3	Fixation of fracture of spine using wire	Spine
V46.4	Fixation of fracture of spine and skull traction HFQ	Spine
V46.5	Removal of fixation device from spine	Spine
V46.8	Other specified	Spine
V46.9	Unspecified	Spine
W19	**Primary open reduction of fracture of bone and intramedullary fixation**	**Unspecified**
W19.1	Primary open reduction of fracture of neck of femur and open fixation using pin and plate	Unspecified
W19.2	Primary open reduction of fracture of long bone and fixation using rigid nail NEC	Unspecified
W19.3	Primary open reduction of fracture of long bone and fixation using flexible nail	Unspecified
W19.4	Primary open reduction of fracture of small bone and fixation using screw	Unspecified
W19.5	Primary open reduction of fragment of bone and fixation using screw	Unspecified
W19.6	Primary open reduction of fragment of bone and fixation using wire system	Unspecified
W19.8	Other specified	Unspecified
W19.9	Unspecified	Unspecified
W20	**Primary open reduction of fracture of bone and extramedullary fixation**	**Unspecified**
W20.1	Primary open reduction of fracture of long bone and extramedullary fixation using plate NEC	Unspecified
W20.2	Primary open reduction of fracture of long bone and extramedullary fixation using cerclage	Unspecified
W20.3	Primary open reduction of fracture of long bone and extramedullary fixation using suture	Unspecified
W20.4	Primary open reduction of fracture of long bone and complex extramedullary fixation NEC	Unspecified
W20.5	Primary open reduction of fracture of ankle and extramedullary fixation NEC	Unspecified
W20.6	Wiring of sternum	Unspecified
W20.8	Other specified	Unspecified
W20.9	Unspecified	Unspecified
W21	**Primary open reduction of intra-articular fracture of bone**	**Unspecified**
W21.1	Primary reduction of intra-articular fracture of bone using arthrotomy as approach	Unspecified
W21.2	Primary excision of intra-articular fragment of intra-articular fracture of bone	Unspecified
W21.3	Primary fixation of fragment of chondral cartilage of intra-articular fracture of bone	Unspecified
W21.4	Primary intra-articular fixation of intra-articular fracture of bone NEC	Unspecified
W21.5	Primary extra-articular reduction of intra-articular fracture of bone	Unspecified
W21.8	Other specified	Unspecified
W21.9	Unspecified	Unspecified
W22	**Other primary open reduction of fracture of bone**	**Unspecified**
W22.1	Primary open reduction of fracture of bone and skeletal traction HFQ	Unspecified
W22.2	Primary open reduction of fracture of bone and external fixation HFQ	Unspecified
W22.8	Other specified	Unspecified
W22.9	Unspecified	Unspecified
W23	**Secondary open reduction of fracture of bone**	**Unspecified**
W23.1	Secondary open reduction of fracture of bone and intramedullary fixation HFQ	Unspecified
W23.2	Secondary open reduction of fracture of bone and extramedullary fixation HFQ	Unspecified
W23.3	Secondary open reduction of intra-articular fracture of bone	Unspecified
W23.4	Secondary open reduction of fracture of bone and skeletal traction HFQ	Unspecified
W23.5	Secondary open reduction of fracture of bone and external fixation HFQ	Unspecified
W23.6	Secondary open reduction of fracture of bone and internal fixation HFQ	Unspecified
W23.8	Other specified	Unspecified

Appendix Y. OPCS-4 codes to identify fractures in HES APC and OP data sources [continued]

OPCS-4 code	Description	Site
W23.9	Unspecified	Unspecified
W24	**Closed reduction of fracture of bone and internal fixation**	**Unspecified**
W24.1	Closed reduction of intracapsular fracture of neck of femur and fixation using nail or screw	Unspecified
W24.2	Closed reduction of fracture of long bone and rigid internal fixation NEC	Unspecified
W24.3	Closed reduction of fracture of long bone and flexible internal fixation HFQ	Unspecified
W24.4	Closed reduction of fracture of small bone and fixation using screw	Unspecified
W24.5	Closed reduction of fragment of bone and fixation using screw	Unspecified
W24.6	Closed reduction of fracture of bone and fixation using nail or screw	Unspecified
W24.8	Other specified	Unspecified
W24.9	Unspecified	Unspecified
W25	**Closed reduction of fracture of bone and external fixation**	**Unspecified**
W25.1	Closed reduction of fracture of bone and fixation to skeleton HFQ	Unspecified
W25.2	Closed reduction of fracture of bone and fixation using functional bracing system	Unspecified
W25.3	Remanipulation of fracture of bone and external fixation HFQ	Unspecified
W25.8	Other specified	Unspecified
W25.9	Unspecified	Unspecified
W26	**Other closed reduction of fracture of bone**	**Unspecified**
W26.1	Manipulation of fracture of bone and skeletal traction NEC	Unspecified
W26.2	Manipulation of fracture of bone NEC	Unspecified
W26.3	Remanipulation of fracture of bone and skeletal traction NEC	Unspecified
W26.4	Remanipulation of fracture of bone NEC	Unspecified
W26.8	Other specified	Unspecified
W26.9	Unspecified	Unspecified
W27	**Fixation of epiphysis**	**Unspecified**
W27.1	Permanent cross union epiphysiodesis	Unspecified
W27.2	Epiphysioplasty	Unspecified
W27.3	Insertion of staple into epiphysis	Unspecified
W27.4	Removal of staple from epiphysis	Unspecified
W27.5	Temporary fixation of epiphysis	Unspecified
W27.8	Other specified	Unspecified
W27.9	Unspecified	Unspecified
W28	**Other internal fixation of bone**	**Unspecified**
W28.1	Application of internal fixation to bone NEC	Unspecified
W28.2	Adjustment to internal fixation of bone NEC	Unspecified
W28.3	Removal of internal fixation from bone NEC	Unspecified
W28.4	Insertion of intramedullary fixation and cementing of bone	Unspecified
W28.8	Other specified	Unspecified
W28.9	Unspecified	Unspecified
W29	**Skeletal traction of bone**	**Unspecified**
W29.1	Application of skeletal traction to bone NEC	Unspecified
W29.2	Adjustment to skeletal traction of bone	Unspecified
W29.3	Removal of skeletal traction from bone	Unspecified
W29.8	Other specified	Unspecified
W29.9	Unspecified	Unspecified
W30	**Other external fixation of bone**	**Unspecified**
W30.1	Application of external fixation to bone NEC	Unspecified
W30.2	Adjustment to external fixation of bone NEC	Unspecified

Appendix Y. OPCS-4 codes to identify fractures in HES APC and OP data sources [continued]

OPCS-4 code	Description	Site
W30.3	Removal of external fixation from bone NEC	Unspecified
W30.4	Application of external ring fixation to bone NEC	Unspecified
W30.8	Other specified	Unspecified
W30.9	Unspecified	Unspecified
W65.1	Primary open reduction of fracture dislocation of joint and skeletal traction HFQ	Unspecified
W65.3	Primary open reduction of fracture dislocation of joint NEC	Unspecified
W65.4	Primary open reduction of fracture dislocation of joint and internal fixation NEC	Unspecified
W65.5	Primary open reduction of fracture dislocation of joint and combined internal and external fixation	Unspecified
W66.1	Primary closed reduction of fracture dislocation of joint and skeletal traction HFQ	Unspecified
W66.3	Primary manipulative closed reduction of fracture dislocation of joint NEC	Unspecified
W66.4	Primary closed reduction of fracture dislocation of joint and internal fixation	Unspecified
W67.1	Secondary open reduction of fracture dislocation of joint and skeletal traction HFQ	Unspecified
W67.3	Secondary open reduction of fracture dislocation of joint NEC	Unspecified
W67.5	Remanipulation of fracture dislocation of joint	Unspecified
W67.7	Secondary open reduction of fracture dislocation of joint and internal fixation NEC	Unspecified
X48	**Immobilisation using plaster cast**	**Unspecified**
X48.1	Application of plaster cast	Unspecified
X48.2	Change of plaster cast	Unspecified
X48.3	Removal of plaster cast	Unspecified
X48.8	Other specified	Unspecified
X48.9	Unspecified	Unspecified
X49	**Other external support of limb**	**Unspecified**
X49.1	Application of splint NEC	Unspecified
X49.2	Change of splint NEC	Unspecified
X49.3	Removal of splint NEC	Unspecified
X49.4	Skin traction	Unspecified
X49.5	Application of sling NEC	Unspecified
X49.6	Application of elastic support bandage NEC	Unspecified
X49.7	Application of gauze support bandage NEC	Unspecified
X49.8	Other specified	Unspecified
X49.9	Unspecified	Unspecified

Appendix Z. Sensitivity analyses: IRRs for fractures during periods of exposure to opioids

Risk period	Primary		Sensitivity analyses* 1		2		3	
	aIRR** (95%CI)		aIRR** (95%CI)		aIRR** (95%CI)		aIRR** (95%CI)	
Baseline	Baseline		Baseline		Baseline		Baseline	
Pre-exposure	5.49	(5.40, 5.58)	5.53	(5.44, 5.62)	5.81	(5.71, 5.92)	5.68	(5.55, 5.82)
Post-exposure	2.31	(2.22, 2.40)	2.25	(2.16, 2.34)	2.27	(2.17, 2.38)	2.26	(2.13, 2.40)
First exposure								
Days 1-7	7.81	(7.40, 8.25)	7.73	(7.31, 8.17)	7.74	(7.28, 8.24)	7.95	(7.37, 8.57)
Days 8-14	5.08	(4.68, 5.51)	5.08	(4.68, 5.51)	4.90	(4.46, 5.37)	4.96	(4.43, 5.56)
Days 15-28	3.65	(3.23, 4.13)	3.60	(3.17, 4.08)	3.61	(3.13, 4.16)	3.39	(2.82, 4.07)
Days 29+	1.71	(1.49, 1.95)	1.70	(1.48, 1.95)	1.72	(1.46, 2.02)	1.65	(1.34, 2.04)
Subsequent exposures								
Days 1-7	5.05	(4.83, 5.29)	4.80	(4.58, 5.04)	5.13	(4.86, 5.42)	4.74	(4.32, 5.20)
Days 8-14	3.72	(3.50, 3.96)	3.56	(3.34, 3.79)	3.75	(3.49, 4.04)	3.04	(2.66, 3.47)
Days 15-28	3.12	(2.91, 3.36)	3.04	(2.82, 3.27)	3.06	(2.80, 3.34)	3.04	(2.61, 3.53)
Days 29+	2.35	(2.22, 2.48)	2.29	(2.17, 2.42)	2.23	(2.09, 2.39)	1.98	(1.75, 2.23)

Notes: OMEQ, oral morphine equivalent; mg, milligrams; IRR: incidence rate ratio; CI, confidence interval
*Sensitivity analyses: (1) excluding people who died ≤90 days after first fracture; (2) outcome defined as first fractures only; (3) excluding people who had dose or duration data imputed i.e., complete-case analysis; **adjusted for 1-year increments in age, 3-monthly intervals for season