LONDON'S GLOBAL UNIVERSITY

Improving physical healthcare for people who use heroin and crack cocaine

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Degree: PhD Epidemiology and Public Health

Date submitted: 10 January 2022

Date revision submitted: 10 March 2022

Declaration: I, Dan Lewer confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Funding: I am funded by a National Institute of Health Research (NIHR) Doctoral Research Fellowship (DRF-2018-11-ST2-016). This document presents independent research funded by the NIHR. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Word count excluding references: 47,141

1 Abstract

Background: People who use heroin and crack cocaine today are older than in the past. The main causes of illness and death are shifting from infections and drug poisoning (the main health issues in this population in the 1980s and 1990s) to respiratory, cardiovascular, and other non-communicable diseases. Qualitative research has identified barriers to treatment of these conditions. However, research remains focused on preventing crime, drug overdoses, and transmission of blood-borne viruses. This thesis aims to understand the physical health needs of this population, with a focus on people using heroin and crack cocaine in England, and provide recommendations for more accessible healthcare.

Methods: The thesis includes: (a) literature reviews relating to frequency of healthcare utilisation, access to healthcare for physical health problems, and interventions that aim to improve physical healthcare; (b) a qualitative study of clinicians working in community drug and alcohol services to understand how they perceive their role in physical healthcare; (c) a study of causes of death among people who use illicit opioids; (d) a case study of the burden and treatment of chronic obstructive pulmonary disease (COPD) among people who use illicit opioids.

Results: The literature reviews found limited research into access to physical healthcare for people who use illicit drugs, or the effectiveness of interventions that aim to improve healthcare for this population. Existing studies focused on cancer screening participation in the United States, finding that illicit drug use was associated with lower uptake. The qualitative study found that clinicians working in community drug and alcohol services in the UK often take a 'health advocate' approach to help their clients get appointments with GPs and other health services. However, participants reported limited success, and many referrals end in non-attendance. Although participants said they were often the first point of contact for a wide range of health problems, they did not have the resources to respond to these needs and felt isolated from other health services. The study of mortality found that illicit opioid use was associated with greater risk of all causes of death, including respiratory diseases, cancers, cardiovascular diseases, infections, liver disease, and accidents. While the highest relative mortality risks were associated with drug poisoning and viral hepatitis, more excess deaths were caused by physical non-communicable diseases. At a population level, the increasing average age of people using drugs explains an increase in deaths due to non-communicable diseases, but not the recent increase in drug-related deaths. The case study of COPD found that a history of illicit opioids was associated with more severe disease at diagnosis, approximately double the risk of adverse outcomes such as acute exacerbations, but similar probability of treatments such as COPD-specific medications, immunisation against respiratory infections, and smoking cessation support.

Conclusion: The health needs of people who use heroin and crack cocaine are shifting toward physical non-communicable diseases. Services that support people who use heroin and crack cocaine are not equipped for this. The case study of COPD suggests that COPD-related inequalities are likely to be driven by exposures before diagnosis and later diagnosis, rather than access to care after diagnosis. This shows the need for more accessible primary care for this population and investment in primary prevention such as smoking cessation.

2 Acknowledgements

Many thanks to everyone who has helped me with this research.

I was supervised by Andrew Hayward at UCL, Kate Morley at King's College London and RAND Europe, Rob Aldridge and UCL, and Paula Zaninotto at UCL.

Martin McCusker at the Lambeth Service User Council provided guidance and organised Patient and Public Involvement workshops.

The CALIBER team at UCL including Arturo Gonzalez-Izquierdo, Muhammad Qummer Ul Arfeen, and Natalie Fitzpatrick helped me design the studies using data from the Clinical Practice Research Datalink and provided technical support.

Staff at the NIHR Maudsley Biomedical Research Centre including Megan Pritchard and Amelia Jewell helped me design studies using data from the CRIS resource, extracted data, and provided technical support.

Magdalena Harris at the London School of Hygiene and Tropical Medicine provided guidance, particularly refining the research questions and my approach to Patient and Public Involvement.

Irene Petersen at UCL provided feedback on Chapter 9 and Chapter 11 and discussed my approach to handling missing data.

John Hurst at UCL and Royal Free London NHS Foundation Trust, Caroline Jolley at King's College London and King's College Hospital NHS Foundation Trust, and Jennifer Quint at Imperial College London and Royal Brompton and Imperial College London NHS Foundation Trusts discussed the respiratory health needs of people who use heroin and crack cocaine. These discussions particularly informed Chapter 11.

Dinah Logan and Ben Watson at the Avon & Wiltshire Mental Health Partnership NHS Trust reviewed a list of medicines to confirm that they are used for opioid agonist therapy, as described in Chapter 9.

Eva Emanuel and Sara Croxford at Public Health England (Blood Safety, Hepatitis, Sexually Transmitted Infections and HIV Division) provided data from the Unlinked Anonymous Monitoring Survey of People Who Inject Drugs. These data are used in Chapter 5.

Tommy Brothers at UCL and Dalhousie University provided feedback on Chapter 5.

Participants in the qualitative study reported in Chapter 8 freely provided their time.

3 Impact statement

The purpose of this research is to improve physical healthcare for people who use heroin and crack cocaine. This may happen through 4 routes:

(1) Informing national policy and clinical guidance. The recent 'Black Review' of drug markets and drug treatment services recommended restructure and more funding for services that support people who use heroin and crack cocaine. I hope my work will inform this programme of investment. In particular, my work shows that services supporting this population need to work in closer partnership with primary care and other NHS services to provide more accessible healthcare.

(2) Building understanding of the health of people who use heroin and crack cocaine. My work highlights inequalities in long-term physical health problems between people who use heroin and crack cocaine and the general population. It also shows the importance of ageing due to a cohort of people who started using these drugs in the 1990s, and the resulting changing health needs. I have presented this work in non-academic forums including the Public Health England Conference, the Drug Research Network Scotland, the Royal College of Psychiatrists in Scotland Addictions Faculty Conference, and at local NHS trusts. I hope my work will help people working in this sector to understand the health needs of people who use heroin and crack cocaine, and the increasing importance of preventing and treating non-communicable diseases.

(3) Providing foundational resources for other researchers. As part of this thesis, I developed methods for studying people who use illicit opioids in electronic health records. These methods are publicly available and I hope they will help other researchers study the health of people who use illicit opioids. I am aware of 2 other researchers who are currently using these resources. One is studying suicide in relation to opioid agonist therapy (with results now published in the journal Lancet Psychiatry[1]) and the other is studying the incidence of injecting-related bacterial and fungal infections.

(4) New projects that have been informed by this work. Discussions in my Patient and Public Involvement group focused on experiences of healthcare. Participants said that hospital discharge can be a difficult time. Discharge in unfamiliar neighbourhoods with reduced opioid tolerance can lead to unsafe drug use. I set up a project together with Public Health England (now the Office for Health Improvement and Disparities at the Department of Health and Social Care) to investigate this issue and have written a report in the journal PLoS Medicine.[2] I hope this work will prompt the development of better guidelines for the care of hospital patients who use illicit opioids. It has also informed a successful programme grant application that aims to improve the timeliness of opioid agonist therapy in hospitals, which is often delayed to concerns about medicine safety, funded by National Institute for Health Research (called Improving Hospital Opiate Substitution Therapy; iHOST).

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5 Introduction

5.1 Summary

This introductory chapter explains why physical health and healthcare are important issues among people who use heroin and crack cocaine in England. It discusses the demographic and health profile of this group, particularly that the average age is increasing and the most important health conditions are shifting from infections and drug overdoses to long-term conditions such as cardiovascular and respiratory diseases. It then explains that evidence for effective healthcare interventions in this population has not kept up with this shift in health needs, and how my research addresses this gap.

5.2 Why does this research focus on people who use heroin and crack cocaine?

Key points

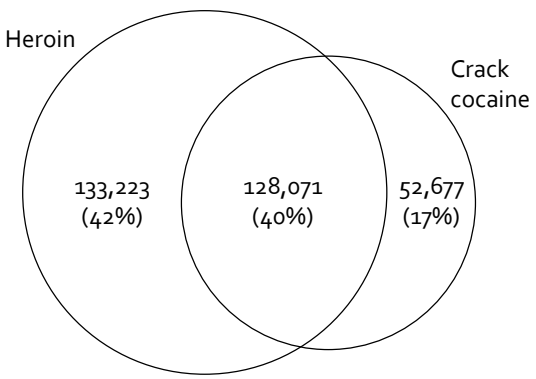
- Heroin and crack cocaine are closely associated with social deprivation
- Use of heroin and crack cocaine is typically regular and long-term
- People who use heroin and crack cocaine have high mortality rates but poor healthcare access

People use many different psychoactive drugs, some illegally produced and others pharmaceutically produced and "diverted" for non-medical uses. Focusing on a group defined by use of specific drugs might seem reductive.

Heroin and crack cocaine are the drugs most closely associated with social marginalisation and poor healthcare access in the UK. A lot of other drugs are more widely used. The illicit drugs that most people have tried are cannabis, powder cocaine, amphetamines, and ecstasy, in that order.[3] The distribution of frequency and duration of use is much wider for these drugs, and people who use them are more likely to use them occasionally, or stop as they get older. In part, this may be due to the lower propensity for these drugs to produce dependent behaviour than for heroin and crack cocaine.[4] In contrast, heroin and crack cocaine are often used regularly and for many years.[5,6] This regular and longer-term use is reflected in the value of illegal drugs markets. Consumer spending on heroin is estimated at £3.8bn per year in the UK, with a further £1.3bn on crack cocaine, compared to £2.4bn on cannabis and £40m on ecstasy.[7]

There is a large crossover between people who use heroin and those who use crack cocaine. Only 1-in-6 of those who use either drug use crack cocaine but not heroin (Figure 1). Many people mix the drugs together in a 'snowball' or 'speedball'.

Figure 1: Venn diagram of the number people who use heroin and crack cocaine in England, based on capture-recapture estimates from 2016/17



Data source: Liverpool John Moores University[8]

The population that uses these drugs has unique features and health needs that I will outline in this chapter. People who use heroin and crack cocaine are older on average than people who use other drugs, mainly because the duration of use is longer. The age of people who died after taking ecstasy, for example, is 25 (based on linear interpolation of the number of deaths within age-groups, 2015-2019, reported by the UK Office for National Statistics[9]), compared to 44 for heroin. Another important feature of this population is that experiences of social exclusion and trauma are very common. Estimates of the prevalence of childhood maltreatment among people who are dependent on opioids range from 16% to 43%.[10] Among participants in the Unlinked Anonymous Monitoring Survey of People Who Inject Drugs 2019, the largest cross-sectional survey of this population in the UK, 42% reported homelessness in the past year, and 66% reported ever being in prison.[11]

These are powerful determinants of health. As well as the immediate risks of drug use, many people who use heroin and crack cocaine have experienced assault and injury while homeless or in prison. Access to food and cooking facilities is sometimes limited. Stigma and discrimination in health services are sometimes reported.[12,13] As a result, the probability of death during 1 year of life in this population is up to 15 times that of people of the same age and sex in the general population.[14,15]

5.3 Population size and history

Key points

- The number of people who use heroin and crack cocaine increased in the 1980s and 1990s
- The average age of this population has increased, driven by a cohort of people who started using drugs in the 1990s
- Most people who use heroin and crack cocaine today have done so for more than 10 years
- Today, approximately 1% of people aged 15-64 use heroin or crack cocaine

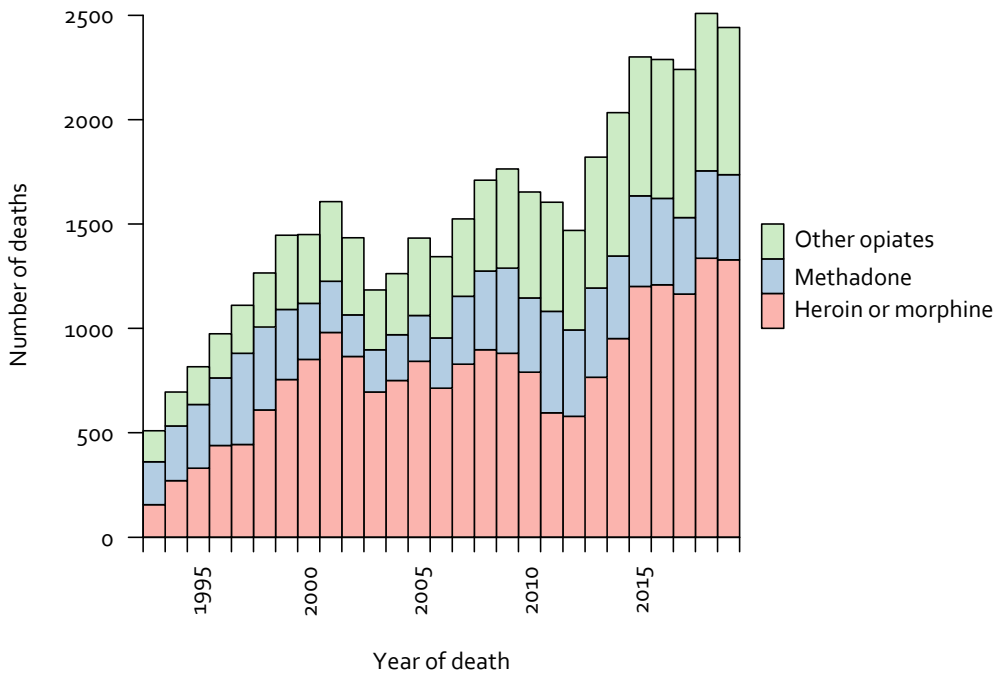
5.3.1 Heroin in the 1970s and early 1980s

Heroin was not widely used in the UK before the 1970s, and users were mainly affluent people living in London and using pharmaceutically produced morphine.[16] A new supply of 'brown heroin' (a less refined powder version of the drug) from the Middle East in the late 1970s made heroin more affordable and coincided with an increase in the number of users during the 1980s.[17] People who started using heroin in the 80s were mainly in their late teens and early 20s and were mostly unemployed.[18]

5.3.2 A growing population in the 1980s and 1990s

The reasons for increasing use of heroin are not certain, and may relate to (a) supply factors, i.e. an increasing availability of drugs; (b) economic factors such as unemployment, which was high in the UK in the early 1990s; and (c) policy factors, with some arguing that the Misuse of Drugs Act 1971 created incentives for criminal suppliers to expand illicit drug markets.[19] In 1993, 151 people died after using heroin or morphine in England and Wales; by 2000 this number had grown more than 5-fold to 851 (Figure 2).[9] After a plateau between 2000 and 2011, opiate-related deaths again increased from 2011. The drivers of this second period of increasing deaths are the subject of current inquiries,[7,20] and are likely to relate to an increasing risk of fatal overdose rather than another increase in the size of the population. Possible reasons for the increasing risk include reducing accessibility of opioid agonist therapies and a shorter duration of treatment, increasing age of people who use drugs, and increasing purity and availability of drugs. The contribution of the increasing age of the population to the rate drug-related deaths is investigated in Chapter 10.

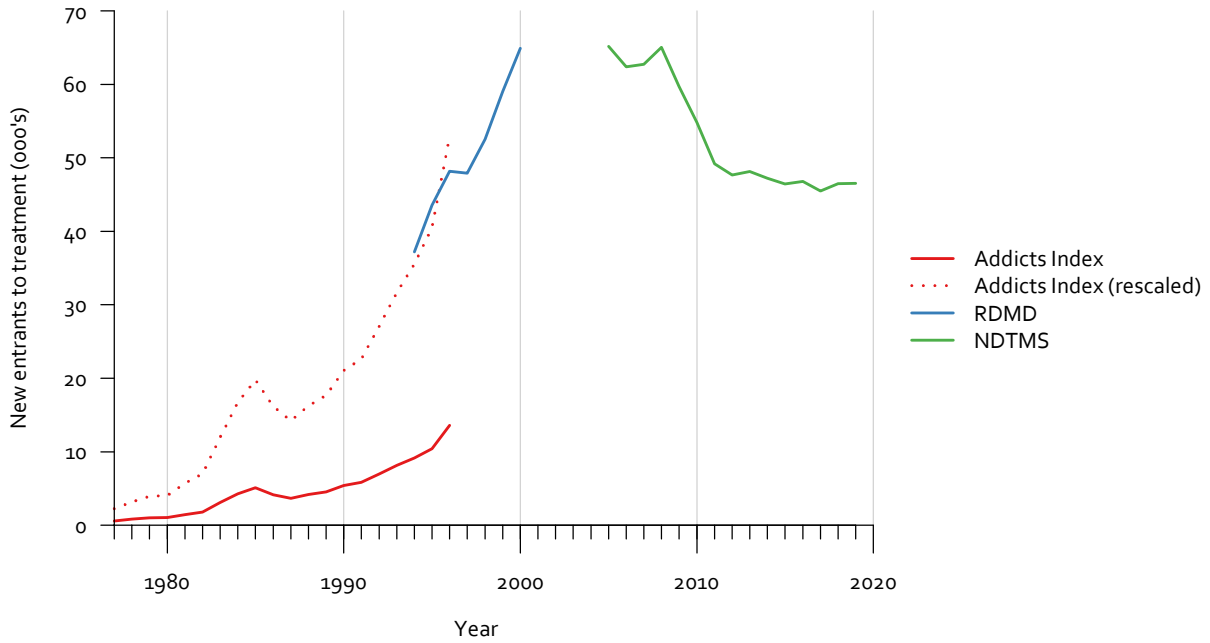
Figure 2: drug-related deaths where an opioid was mentioned on the death certificate, England and Wales, 1993-2019



Data source: Office for National Statistics[9]

The number of people entering treatment for opioid dependence also grew substantially during the 1990s, although changes to the treatment system mean that numbers are difficult to compare across a long period of time (Figure 3). The cohort that started using heroin and crack cocaine in the 1990s still makes up many of the people who use these drugs, and explains some of the trends in the age and health of this population that we will now consider.

Figure 3: Entrants to treatment for opioid dependence in England

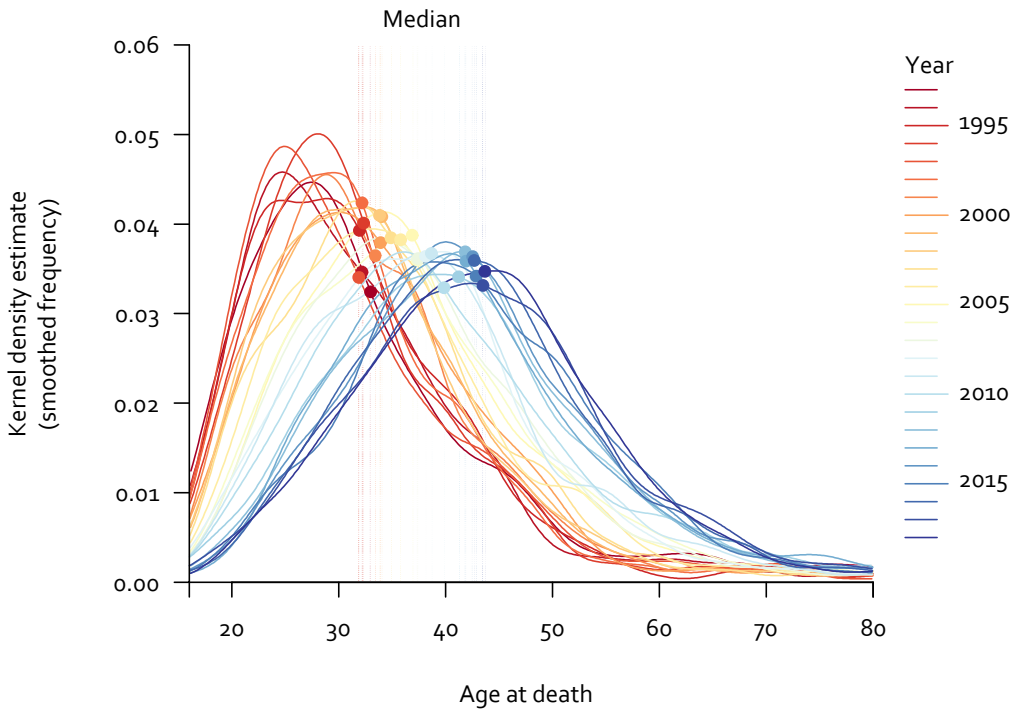


Data sources and notes: 'Addicts Index' shows the number of individuals starting treatment for heroin dependence for the first time.[21] The Regional Drug Misuse Database (RDMD)[22] and National Drug Treatment Monitoring System (NDTMS)[23] record the number of 'new presentations' to treatment (rather than individuals). I have rescaled the Addicts Index using the ratio of the RDMD:Addicts Index during the cross-over in data (1993-1996), to provide better comparability (though the figure is intended to show time trends rather than comparable values).

5.3.3 Increasing average age of people who use heroin and crack cocaine

Professionals working in drug and alcohol services often refer to an 'ageing cohort' of people who use heroin and crack cocaine.[24] This trend is clear in management data reported by community drug and alcohol services, which show that the average age of people in treatment for opiates or crack cocaine increased from 33 in 2006-07 to 42 in 2019-20.[23] Similarly, the average age of death among people who died due to an opioid overdose has increased in parallel, from 34 in 2000 to 44 in 2018 (Figure 4).

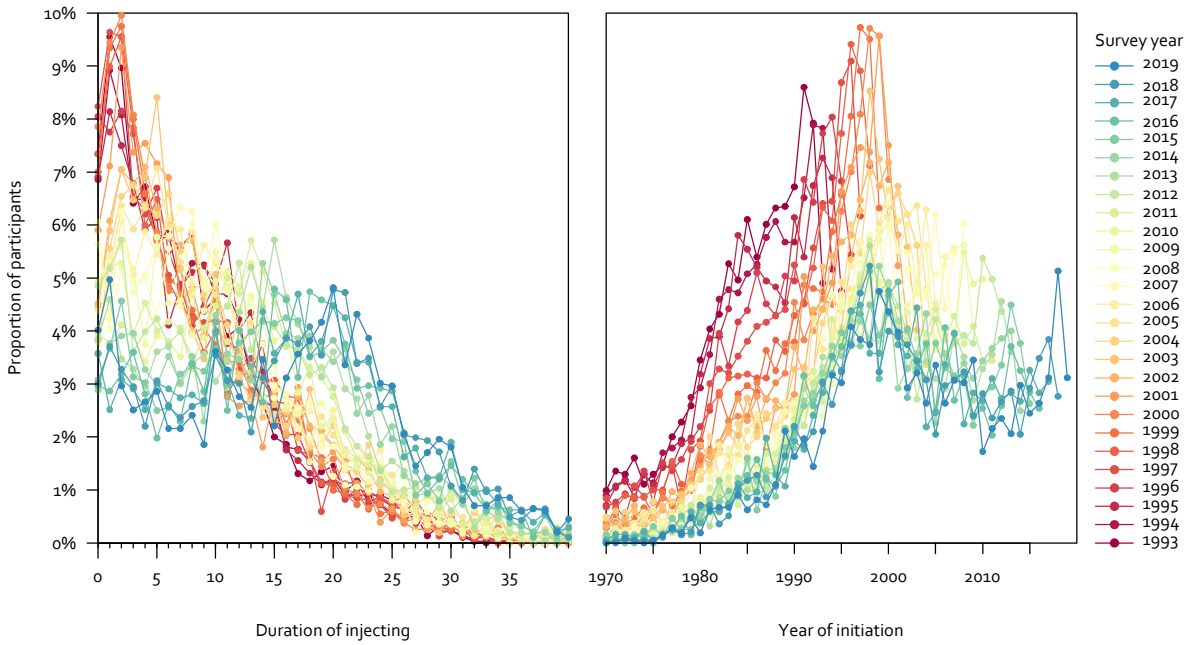
Figure 4: Histograms of age at death for people who died due to drug poisoning, where an opioid was mentioned on the death certificate, by year, 1993-2018, England and Wales



Data source: Office for National Statistics[25]

The Unlinked Anonymous Monitoring Survey of People Who Inject Drugs[26] (UAM) can help us understand demographic changes in this population over time. UAM is an annual cross-sectional survey of people who inject drugs in the UK, set up to monitor the prevalence of blood-borne viral infections. It has run since the early 1990s, recruiting participants through treatment services, needle exchanges, and other outreach centres. Participants report their age and how long they have been injecting. The '90s cohort' can be seen in the right panel of Figure 5. In each survey year, the biggest number of participants said they started injecting in the mid-90s. As this cohort ages, the typical duration of drug use in the cohort increases, and in 2019 the median duration of injecting was 16 years (IQR 8-23 years).

Figure 5: Histograms of injecting duration and year of initiation among participants in the Unlinked Anonymous Monitoring Survey of People who Inject Drugs, stratified by survey year



Data source: UAM (original analysis conducted as part of my role at Public Health England)

Although there are various sources that suggest an increasing average age of the population, all of these sources are likely to have selection biases. People starting treatment and those participating in UAM surveys may be more likely to engage with services. It is possible that services have become less accessible to younger clients over time, and there may be an "invisible" population of younger people using drugs.

5.3.4 Number of people who use heroin and crack cocaine today

It is difficult to estimate the precise number of people who use heroin and crack cocaine. Some surveys of the general population ask about illicit drug use. For example, 0.6% of participants in the Crime Survey for England and Wales 2017/18 said they have used heroin in their lifetime, and 0.8% said they have used crack cocaine; while past-month use was 0.1% for both drugs.[27] The Adult Psychiatric Morbidity Survey 2014 similarly found 1.0% reported lifetime use of heroin, and 1.1% crack cocaine, and past-year use was 0.2% for both drugs.[3] However, these surveys use samples of adults living in private households and are likely to exclude many people who use heroin and crack cocaine, who may be homeless, living in temporary accommodation or an institution, or less likely to participate for other reasons. In addition, self-report surveys may have social desirability bias in which participants do not want to say that they have used heroin and crack cocaine.

Therefore, some researchers have used different methods to estimate the size of this population. One method is 'capture-recapture', which analyses the overlap between different population registers, and then uses assumptions about the independence of these registers to estimate the number of unobserved individuals. One study used individual-level linkage between databases from the police, drug treatment, probation, and prisons, and estimated that 314,000 people used opiates or crack

cocaine in England in 2016/17, or 0.9% of 15-64 year-olds.[28] These estimates have been created for a number of years and suggest only minor changes in the population size since 2011/12.[29] Another method uses the number of drug-related deaths reported by the Office for National Statistics, and then uses mortality rates in cohorts of people who use drugs to estimate the size of the population from which the deaths arose. One study used this method and estimated that there were 283,000 people dependent on opioids in England in 2008/09, or 0.8% of 15-64 year-olds.[30] In 2017/18 there were 144,288 adults in treatment for heroin and/or crack cocaine,[31] which implies that about half of the population is currently enrolled in treatment.

Both estimates are substantially higher than estimates from surveys of the general population, suggesting that the traditional surveys are unlikely to include many people who use heroin and crack cocaine.

5.3.5 Long duration of drug use

People often use heroin and crack cocaine for many years. Cohort studies with long follow-up[6,32] show that people sometimes continue using heroin for decades. This long duration of use is an important feature of the population today, and many people started using drugs a long time ago. Among those in treatment for heroin dependence in 2019/20, 69% first used heroin prior to 2000.[23]

5.4 A shift health in health needs toward long-term conditions

Key points

- The risk of death among people who use heroin and crack cocaine is many times higher than people of the same age in the general population
- In the 1980s and 90s, the most common causes of death were HIV/AIDS and drug overdoses
- More recent studies show that long-term conditions now cause the most excess deaths
- There are many studies that aim to prevent or treat infections and drug overdoses, and little research into preventing and treating long-term conditions in this population

5.4.1 People who use heroin and crack cocaine have an extremely high all-cause mortality rate

There are many studies of all-cause mortality among people who use illicit opioids. International systematic reviews of people who are dependent on opioids[14,33] and people who inject drugs[15] have found mortality risk of 10-15 times the general population, with higher rates associated with male sex, drug injection, HIV positive status, and being out-of-treatment (i.e. not taking prescribed methadone or buprenorphine). This increased risk of death has been observed for many years. For example, in a study of 128 people attending a heroin clinic in London in 1969, 43 had died by 1991, compared to an expected 4 deaths among 128 people of the same age in the general population (i.e. a standardised mortality ratio of 11).[6]

The high mortality rate among people who use heroin and crack cocaine is a result of multiple risk factors. The most well-known risks are fatal drug overdoses, the chronic toxicity of drugs such as the cardiotoxic effect of crack cocaine, the risk of blood-borne virus transmission via shared injecting equipment, and serious bacterial infections originating at injecting-site wounds. But many people who use heroin and crack cocaine have other risk factors that cause age-related diseases, including tobacco smoking, which is nearly universal and causes lung and vascular diseases;[34] smoking of heroin and crack cocaine, which damage and irritate lungs;[35] alcohol use, which is an independent risk factor for cirrhosis and liver cancer but also multiplies the risk associated with hepatitis virus infections, and is associated with cardiomyopathy, dementia and congestive heart failure;[36] poor nutrition; head injuries and hypoxic brain injury after opioid overdoses, which contribute to cognitive impairment and frailty; and the high prevalence of mental health problems that increase the risk of suicide.[37]

5.4.2 Shift in causes of death from infections and drug poisoning to non-communicable diseases

There are fewer studies of cause-specific mortality. Studies in the 1980s and 1990s show that the majority of deaths among people who used illicit opiates were caused by drug poisoning[6,32] or AIDS.[38] In contrast, data from cohort studies in the UK in the 2000's and 2010's show that a much bigger proportion of deaths was due to non-communicable diseases.[39,40]

This shift may be due to the increasing average age of the population. In studies of mortality that include participants with a range of ages, drug poisoning accounts for a larger proportion of deaths among younger participants. For example, in a cohort study of people who use illicit opioids in Australia, drug overdoses accounted for 64% of deaths in people aged under 25, compared to 24% for people aged over 45.[41] In this study, the risk of death due to liver disease, cardiovascular disease and cancer all increased substantially with age (as expected, given the association between these diseases and age in the general population), while risk of overdose did not increase. Similarly, data from Scotland shows that 58% of deaths among people prescribed methadone aged under 35 are 'drug-related', compared to 11% among those aged over 55,[42] leading the authors to argue that "a cultural shift is needed in treatment services because degenerative non-drug-related-deaths predominate as methadone clients age."

The changing causes of death over time may also relate to improving treatment for HIV and hepatitis C, and increased availability of interventions that reduce risk of overdose such as opioid agonist therapy and naloxone.

5.4.3 Studies of morbidity are focused on HIV and hepatitis C infections

Studies of physical morbidity among people who use heroin and crack cocaine have focused almost exclusively on blood-borne viral infections. A systematic review in 2011 found 127 studies of viral hepatitis prevalence among people who inject drugs,[43] and a systematic review in 2008 found 168 studies of HIV prevalence among people who inject drugs.[44] UAM is the main source of seroprevalence data in England. 57% of participants in 2018 had hepatitis C antibodies (i.e. 57% had been exposed to the virus in the past); 1.2% had HIV antibodies (a low prevalence among people who inject drugs compared to most other countries[44]); and 9.1% had hepatitis B antibodies (of which most would probably have cleared the virus).[45]

There are few studies of other diseases. A small group of studies have measured prevalence of COPD among people in treatment for opioid dependence in the UK, typically finding prevalence of 30%-40%.[46–49] This prevalence is extremely high, and treatment for COPD in this population is the subject of Chapter 11.

Some data linkage studies use hospital admissions as a proxy for morbidity. These studies show a wide range of physical health problems. For example, studies of people who have had an episode of opioid agonist therapy in Scotland[50] and Australia[51] both found that only 1-in-7 admissions was directly related to illicit drug use (such as withdrawal or overdose), with the rest caused by a wide range of physical and mental health problems.

5.4.4 There is a discrepancy between the increasing importance of long-term conditions and the continued research focus on preventing and treating infections and overdoses

There are now effective treatments and preventative strategies for opioid overdoses and blood-borne viral infections.

Systematic reviews of RCTs have shown that opioid agonist therapy (methadone or buprenorphine) reduces the risk of opioid overdose. Another systematic review identified 27 studies of psychosocial interventions that complement opioid agonist therapy.[52]

Several observational studies show that community-distributed naloxone can reduce the risk of death after an overdose[53] (RCTs of this intervention are unethical due to the obvious benefit of providing naloxone when someone has had an overdose).

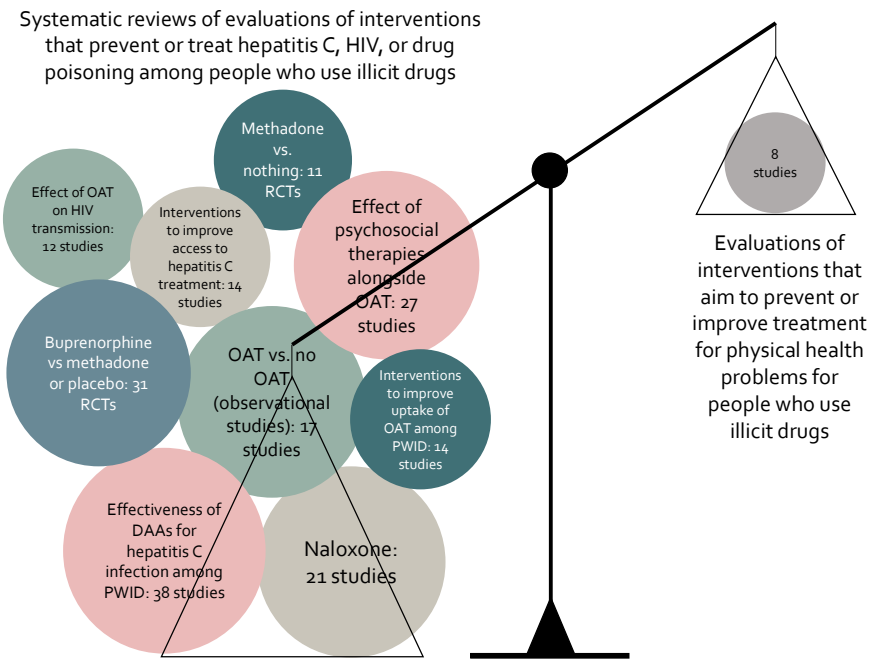
At least 13 systematic reviews have investigated the effectiveness of needle and syringe programmes, with outcomes focused on HIV transmission, hepatitis C transmission, and injecting risk behaviours.[54]

There are also many evaluations of interventions that aim to improve access to treatment for HIV and hepatitis C. For example, a systematic review identified 14 studies of interventions that improve testing, linkage to care, and treatment uptake for hepatitis C infection among people who inject drugs.[55]

In contrast, few studies evaluate interventions that aim to improve treatment for long-term conditions in this population. Chapter 7 is a scoping review of such studies, and concludes that there is very limited research, and existing studies tend to focus on a model of integrated primary care and drug treatment that was established in the US around 2000-2010.

Research into health interventions therefore no longer matches the needs of this population (Figure 6) and appears focused on a narrow set of 'drug-related' health outcomes. There is a need to develop and evaluate interventions that prevent and improve access to treatment for long-term physical health problems among people who use heroin and crack cocaine.

Figure 6: Evidence for interventions that prevent or treat blood-borne viral infections or overdoses among people who use drugs, vs. interventions that prevent or improve physical health care for people who use drugs



OAT = opioid agonist therapy. DAA = direct acting antivirals. PWID = people who inject drugs. RCT = randomised controlled trial. Sources: Naloxone[53]; Methadone vs. nothing[56]; Interventions to improve access to hepatitis C treatment[55]; OAT vs. no OAT (observational studies)[57]; Effectiveness of DAAs for hepatitis C infection among PWID[58]; Buprenorphine vs. methadone or placebo[59]; Effect of psychosocial therapies alongside OAT[52]; Interventions to improve uptake of OAT among PWID[60]; Effect of OAT on HIV transmission[61].

5.5 Barriers to healthcare

Key points

- There is a body of qualitative research into the experience of healthcare for people who use heroin and crack cocaine
- Both patients and staff report substantial barriers to healthcare, related to stigma, bureaucracy, and basic priorities that compete with health

Although there are few quantitative studies investigating access to general healthcare for people who use illicit drugs, there are qualitative studies that document this population's experiences of healthcare. Some include accounts from people who use drugs, and others include accounts from healthcare staff. While patients and staff have different perspectives, there are common themes.

People who use drugs report: (a) stigmatising attitudes among healthcare staff, including the perception that they are seeking prescriptions for non-medical purposes;[12,62–67] (b) barriers to attending appointments, such as transport costs, inflexible timeslots, housing problems, and competing priorities such as finding enough food or money for the day;[12,63,64,68–71] (c) that healthcare staff deprioritise physical health problems in relation to drug dependence, or attribute symptoms to drug use rather than doing a thorough investigation (sometimes called 'diagnostic overshadowing');[12,63,67,69,72] and (d) delaying help-seeking due to normalisation of pain, fear of stigma in services, and concern about inadequate opioid agonist therapy and pain control when admitted to hospital.[73]

Health professionals report: (a) insufficient training and skills to address the needs of people who use drugs;[13,64,69,74] (b) insufficient resources to provide adequate care for a patient group with high needs;[67,70,71,74] and (c) mistrust of people who use drugs, including that patients may be 'drug-seeking', and that they mistrust reports of pain.[66,67,69]

These barriers mean that people who use heroin and crack cocaine often do not seek help until they are very unwell. This was an important message from my Patient and Public Involvement work, and in the accounts of staff of community drug and alcohol services in my qualitative study reported in Chapter 8).

5.6 Research questions and thesis structure

This research aims to improve our understanding of the physical health needs of people who use heroin and crack cocaine, and provide priorities for improving access to physical healthcare.

The research questions are:

RQ1. How do people who use heroin and crack cocaine use health services?

RQ2. What approaches to improving physical healthcare for people who use heroin and crack cocaine have already been developed?

RQ3. What are the main causes of death among people who use heroin and crack cocaine and how have they changed over time?

RQ4. Do people who use heroin and crack cocaine experience inequality in treatment for chronic conditions?

The thesis includes the following chapters:

Chapter 6 is a systematic review of the frequency of healthcare utilisation among people who use illicit drugs (addressing RQ1).

Chapter 7 is a scoping review of research into access to routine physical healthcare and evaluations of interventions that aim to improve physical healthcare for people who use illicit drugs (addressing RQ2).

Chapter 8 is a qualitative study of the experiences of clinical staff working at community drug and alcohol services in the UK (addressing RQ1 and RQ2).

Chapter 9 explains the development of 3 new cohorts of people who use illicit opioids in England, using electronic health records.

Chapter 10 describes mortality rates and causes of death in the 3 cohorts developed in Chapter 9 (addressing RQ3).

Chapter 11 is a case study of healthcare for chronic obstructive pulmonary disease among people who use illicit opioids, using an epidemiological analysis of the cohorts developed in chapter 9 (addressing RQ4).

Chapter 12 is a conclusion, summarising my contributions to this field and the implications for policy and practice.

5.7 Patient and public involvement

My research plan was informed by three workshops with people who use heroin and crack cocaine. These workshops were organised by the service user council at South London and Maudsley NHS Foundation Trust (SLaM) and the charity Pathway. Each workshop had 3-5 participants and lasted 1-2 hours. The outcome of these workshops was a focus on access to care for long-term physical health problems, as participants felt this issue was more important than my earlier focus on treatment for bacterial infections. I discussed my early findings at 2 similar workshops of people who use heroin and crack cocaine at SLaM. Participants helped me interpret selection biases in my cohort studies by discussing which individuals might not be identified by GPs, and highlighted the importance of unplanned hospital admissions in the management of long-term conditions. My approach to patient and public involvement was disrupted by the COVID-19 pandemic, as it was not possible to meet participants face-to-face. I therefore had several one-to-one phone calls with two individual participants, who provided feedback during the later stages of my studies. One of these participants was particularly interested in my related study of fatal opioid poisonings after hospital discharge and co-authored this study. My thesis is profoundly different as a result of patient and public involvement. Specifically, I have changed the overall focus of the thesis, dropped some elements (particularly a planned study of 'pathways' or 'modalities' of care), adding other elements (particularly the case study of treatment for chronic obstructive pulmonary disease, because participants often discussed poor access to care for respiratory symptoms), and initiated new projects beyond my PhD. I expected the process would involve detailed feedback on a study's aims, design, and results. In fact it involved a series of discussions with varying focuses. While these discussions did not always answer the questions I prepared, they gave me an understanding of the priorities of people who use heroin and crack cocaine and changed the direction of my research.

6 Frequency of healthcare utilisation by adults who use illicit drugs: a systematic review and meta-analysis

6.1 Summary

Background: Use of illicit drugs is associated with high need for health services, but research into the frequency of healthcare utilisation in this population has not been reviewed.

Methods: Systematic search of MEDLINE, EMBASE and PsychINFO for observational studies published between 1 January 2000 and 3 December 2018. Key inclusion criteria were (a) participants used heroin, powder cocaine, crack cocaine, methamphetamine, amphetamine, ecstasy/3,4-methylenedioxymethamphetamine (MDMA), cannabis, hallucinogens or novel psychoactive substances; have a diagnosis of 'substance use disorder'; or use drug treatment services; (b) participants were recruited from community settings; and (c) studies reported the cumulative incidence (risk) or rate of care episodes in at least one of 3 settings: primary care, hospital admissions (in-patient) and A&E.

Results: 98 studies were included, 82 (84)% from North America and Australia. Most studies focused on people using heroin, methamphetamine or crack cocaine, or who had a diagnosis of drug dependence. We were able to conduct a meta-analysis of rates across 25 studies reporting A&E episodes and 25 reporting hospital admissions, finding pooled rates of 151 (95% CI 114–201) and 41 (95% CI 30–57) per 100 person-years, respectively; on average 4.8 and 7.1 times more often than the general population. Heterogeneity was very high and was not explained by drugs used, country of study, recruitment setting or demographic characteristics. Predictors of healthcare utilisation were consistent across studies and included unstable housing, drug injection and mental health problems. Opioid agonist therapy was consistently associated with reduced A&E presentation and hospital admission. There was minimal research on healthcare utilisation by people using ecstasy/MDMA, powder cocaine, hallucinogens or novel psychoactive substances.

Conclusion: People who use illicit drugs are admitted to A&E or hospital several times more often than the general population. However, there is little research into engagement with primary care, or whether high rates of healthcare utilisation are explained by morbidity or other types of need.

This systematic review has been published in the journal Addiction.[75]

6.2 Background

Key points

- Perceptions of healthcare use among people who use illicit drugs may be inaccurate
- Many studies recruit participants from healthcare settings are these are likely to be biased. Studies that use community-based recruitment can give a more representative insight into healthcare use
- Many cohort studies have reported healthcare use by people who use illicit drugs but these have not been reviewed

Some types of healthcare are obviously associated with drug use. If an ambulance is called to help someone in respiratory depression after taking heroin, or someone needs antibiotics after an injecting site gets infected, then the fact that person uses drugs is evident. It may be less obvious that a patient admitted to hospital because they have inflamed airways and are feeling breathless is someone who uses drugs. It is easy to associate people who use drugs with certain health problems, especially drug overdoses and infections.

Another reason why there may be biased perceptions of healthcare in this population is that healthcare staff encounter an unusual subgroup, particularly those who attend hospital frequently. Surveys of people who frequently attend A&E have found that illicit drug use is common.[76–78] This supports a belief that people who use drugs are reliant on A&E for healthcare, and attend A&E often. I recently contributed to research into hospital readmission for patients experiencing homelessness;[79] a population that overlaps with people who use heroin and crack cocaine. The study found high rates of emergency readmission. Someone with experience of homelessness who co-authored this study said: “a hospital represents a building with indoor comforts and facilities like heat, light and hot water and crucially, a place populated by people who are perceived to have a duty to play nicely. Perhaps this cohort of ‘regulars’ is partly responsible for the medical profession’s distaste of us as a whole.”

A third reason for inaccurate perceptions of healthcare utilisation in this population is that staff are most likely to remember patients who are obviously intoxicated or behaving in ‘challenging’ ways.

For these reasons, population-based studies of healthcare utilisation are useful. Studies that recruit a sample of people who use illicit drugs from the community (rather than from healthcare settings), and then determine their healthcare utilisation can capture individuals who engage with healthcare less often. Although many such studies have been done, to my knowledge they have not been reviewed or summarised.

I led a systematic review of population-based cohort and cross-sectional studies that report all-cause healthcare utilisation by people who use illicit drugs, aiming to (a) describe the frequency of A&E visits, hospital admissions and GP utilisation, and calculate pooled averages; (b) compare the frequency of healthcare utilisation to the general population; and (c) summarise evidence on the predictors and causes of healthcare utilisation. The study was done with a team of researchers, whose contributions are listed in the published article.

6.3 Methods

6.3.1 Search strategy

We conducted a systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[80] A protocol for this review has been registered with PROSPERO (identifier: CRD42017076525; available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=76525). We searched Medline, PsychINFO and EMBASE from 1 January 2000 to 27 September 2017 (updated on 3 December 2018) using keywords and MeSH terms related to illicit drugs, health service utilisation and observational study designs. Example search terms for MEDLINE are shown in Table 1, with search terms for other databases listed at https://www.crd.york.ac.uk/PROSPEROFILES/76525_STRATEGY_20180226.pdf. We also included studies from a manual search of references of all included studies.

Table 1: Search terms for MEDLINE via the Ovid interface

Concept	Terms
Illicit drugs	addict*.mp, (chemical adj2 dependenc*).mp, (substance adj2 misuse*).mp, (substance adj2 abus*).mp, "substance use".mp, (drug adj1 user*).mp, (drug adj2 abus*).mp, (drug adj2 dependen*).mp, (inject* adj2 drug*).mp, heroin.mp, opiate*.mp, cocaine.mp, crack.mp, amphetamine.mp, methamphetamine.mp, benzodiazepine.mp, mdma.mp, ecstasy.mp, cannabis.mp, Substance-Related Disorders/, Amphetamine-Related Disorders/, Cocaine-Related Disorders/, Heroin Dependence/, Substance Abuse, Intravenous/, Cannabis/, Marijuana abuse/, Heroin/, Crack Cocaine/, Cocaine/, Methamphetamine/, Amphetamine/, Benzodiazepines/
Health service utilisation	"healthcare use".mp, "healthcare usage".mp, "care use".mp, "care usage".mp, "service use".mp, "service usage".mp, (hospital* adj3 rate*).mp, (hospital* adj3 incidence).mp, (hospital* adj3 prevalence).mp, ("use of" adj2 primary).mp, ("use of" adj2 secondary).mp, ("use of" adj2 emergency).mp, ("use of" adj2 service*).mp, ("use of" adj2 healthcare).mp, ("use of" adj2 care).mp, (utili* adj2 primary).mp, (utili* adj2 secondary).mp, (utili* adj2 emergency).mp, (utili* adj2 service*).mp, (utili* adj2 healthcare).mp, (utili* adj2 care).mp, (visits adj2 primary).mp, (visits adj2 secondary).mp, (visits adj2 emergency).mp, (visits adj2 service*).mp, (visits adj2 healthcare).mp, (visits adj2 care).mp, Health Resources/, Health Expenditures/, Primary Health Care/, Secondary Care/
Observational study designs	Epidemiologic studies/, cohort studies/, (cohort adj1 stud*).tw, (cohort adj1 analy*).tw, ("follow up" adj1 stud*).tw, (observational adj1 stud*).tw, Longitudinal.tw, Retrospective.tw, "cross-sectional".tw, Cross-sectional studies/, "Surveys and Questionnaires"/, linkage.tw, survey.tw

6.3.2 Study inclusion and exclusion criteria

Inclusion criteria were: (a) cohort or cross-sectional studies; (b) 75% or more of participants recently used illicit drugs, defined as heroin, powder cocaine, crack cocaine, methamphetamine, amphetamine, ecstasy/4-methylenedioxymethamphetamine (MDMA), cannabis, hallucinogens or novel psychoactive substances; (c) studies reported the rate or cumulative incidence of A&E visits, hospital admissions, or primary care visits; (d) studies were published in English. Exclusion criteria were: (a) participants were recruited from acute healthcare services (such as A&E); (b) participants were recruited on the basis of having an acute disease (such as hepatitis A); (c) the study was primarily of pregnant people; (d) more than 25% of participants were aged under 18; (e) the study included fewer than 30 participants or less than 30 days of observation per participant.

6.3.3 Screening and data extraction

2 authors independently screened titles and abstracts using Rayyan,[81] with agreement of 94% (Cohen's Kappa 0.58). We accessed full texts and one author used a piloted data extraction tool to record the study design, year, location, recruitment setting (drug treatment services, community or healthcare), participant demographics, predominant drugs used, and denominator and numerator for primary outcomes. Where predictors of healthcare use and cause-specific healthcare use were reported, we marked the study for narrative synthesis. A second author checked that all data was accurate. Any conflicts not resolved by discussion were referred to a third author for a final decision.

6.3.4 Study quality assessment

Methodological quality was assessed using a modified Newcastle-Ottowa scale[82] that included recruitment bias, non-response, ascertainment of illicit drug use, ascertainment of health-care utilization, adequacy of follow-up (for cohort studies), selection of comparison groups (for relative measures) and adjustment (for relative measures). The system for scoring studies and determining whether studies have a 'high risk' of bias is available here: https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fadd.14892&file=ADD14892-sup-0001-supplementary_information.pdf.

6.3.5 Analysis

I first did a narrative review in which I described predictors of healthcare utilisation and causes of healthcare utilisation by disease.

I then did a quantitative analysis, starting by displaying rates and cumulative incidences of A&E episodes and hospital admissions using forest plots. To provide informal comparisons with the general population, I used published frequencies of healthcare utilisation in the US, Canada, Australia and the UK,[83–85] for the general population group with the most similar age- and sex-profile as the study population.

I used random effects meta-analysis to report the average frequency of healthcare utilisation across study populations, limited to results from high-income countries and excluding studies of subgroups likely to have unusual healthcare utilisation (such as people living with HIV and prisoners). I anticipated that the strongest determinants of heterogeneity would be the predominant drug and the country where the study was conducted and therefore stratified results by these variables. As an exploratory analysis of further sources of heterogeneity (not pre-specified), I included each of the following variables in the meta-analysis equation as a moderator:[86] recruitment setting (healthcare, drug treatment services, community or prison), country, study design, study era (1990-1999, 2000-2009, 2010-2018), risk-of-bias score (low or high), age (average age under or over 30) and sex (greater or less than 60% male), using a threshold of $p<0.05$ to identify significant moderators.

All analysis was conducted using R version 3.5.1.

6.4 Results

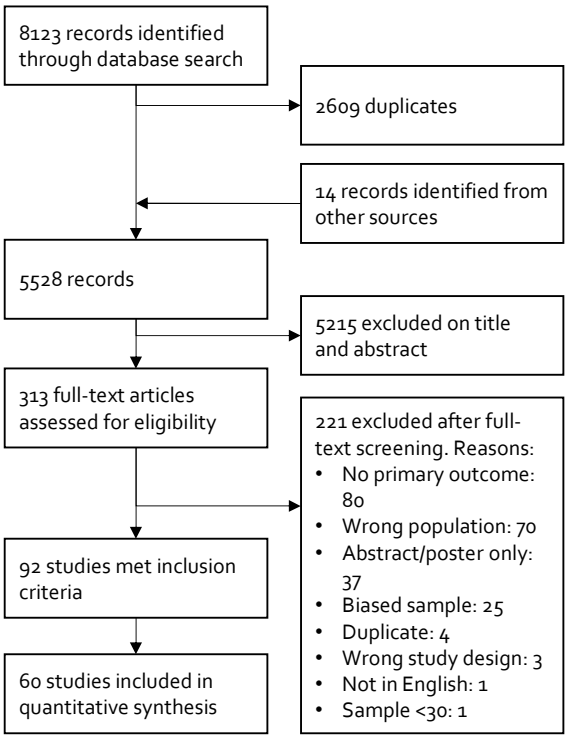
The search identified 5,528 studies after deduplication, of which 313 were selected for full-text review. 92 were included in narrative review and 60 in quantitative analysis. Figure 7 is a flow-chart of included studies. Some studies included multiple groups from distinct regions or with distinct drug use patterns, while some studies duplicated results. I identified 98 unique populations with 204 relevant data points. The full dataset is available at https://github.com/danlewer/thesis/blob/main/sys_rvw_public_data.csv.

Of the 98 study populations: 53 were in the United States; 16 in Australia; 13 in Canada; 3 in Ireland; 2 each in Taiwan, Italy, New Zealand, UK, Vietnam; and 1 each in Denmark, Finland and Norway.

Although the search strategy included people using a wide range of illicit drugs, studies focused on people who used drugs associated with dependence. The largest group was people prescribed opioid agonist therapies (31 populations), mostly recruited from drug treatment services. The next was people who inject drugs (29 populations), mostly recruited from community settings. 8 studies focused on cannabis users, 7 focused on stimulant users (where injecting was not specified) and 5 focused on opiate users (where injecting was not specified). No studies recruited participants who predominantly used MDMA/ecstasy, powder cocaine, novel psychoactive substances or hallucinogens such as LSD and psilocybin.

A mean of 68% (sd. 12%) of participants were male and the mean of average ages (reported in some studies as means and in others as medians) was 36.7 (sd. 6.0).

Figure 7: Flow-chart of included studies



6.4.1 Study quality

58/204 (28%) data points had high risk of bias. The main risk was lack of information on non-response. Table 2 summarises results from the quality assessment.

Table 2: Results of quality assessment

	Data points	High risk	Proportion high risk
Recruitment bias	204	28	14%
Non-response	204	121	59%
Ascertainment of illicit drug use	204	43	21%
Ascertainment of healthcare utilisation	204	44	22%
Adequacy of follow-up	82	21	26%
Selection of comparison group	47	4	9%
Adjustment for confounders	47	4	9%
Global assessment	204	58	28%

6.4.2 Narrative review

Frequencies of all outcomes were high and heterogeneous. The rate of A&E visits ranged from 19[87] to 1,061[88] per 100 person-years. The proportion of participants visiting A&E in the past 12 months ranged from 10%[89] to 72%.[90] Studies including relative measures showed frequency of A&E utilisation of 3 to 10 times that of comparison groups not using illicit drugs.[91–94] Exceptions were a study in rural Taiwan, showing that people who inject heroin had a similar rate of A&E presentation as the general population,[95] and a study of older people who use cannabis in the United States showing similar odds of A&E presentation as those who do not use cannabis.[96]

The rate of inpatient episodes ranged from 8[97] to 852[91] per 100 person-years. The proportion of participants who were hospitalised in the past 12 months ranged from 8%[98] to 41%.[99] Studies including relative measures showed frequency of hospital admission of 2-8 times that of comparison groups not using illicit drugs.[91–93,100–103] Again, studies of people who inject drugs in rural Taiwan and older people who use cannabis in the United States were exceptions, showing similar frequencies of hospital admission to the general population.[95,104]

There were fewer studies of primary care utilisation. 10 studies reported rates, ranging from 231[105] to 2,087[100] episodes per 100 person-years. The proportion of participants visiting primary care in the past 12 months ranged from 38%[106] to 90%.[107] 3 studies found higher frequency than the general population: a study of insurance data in Canada found people with diagnoses of 'substance abuse' had 4.2 times more primary care visits than those without this diagnosis;[100] a study of patients at a specialist primary care clinic in Ireland that found that those with methadone prescriptions had 4.2 times the odds of a primary care consultation during 6 months, excluding visits for 'drug-related problems';[108] and a study of people in drug treatment in Australia that found those primarily in treatment for opioids had a median of 12 primary care visits in the past year, compared to 7 for those in treatment for alcohol.[107]

Studies comparing the frequency of healthcare utilisation between care settings showed that primary care episodes are more frequent than A&E or inpatient episodes.[109–113]

A&E presentation was consistently associated with regular or recent injecting,[114–117] sex work,[114,118] diagnosed Hepatitis C,[119] diagnosed HIV,[93,99,116,120,121] female sex,[99,109,122–125] homelessness or unstable housing,[88,115,116,122,126] crack cocaine or stimulant use,[116,122,123] alcohol use,[124,127,128] polydrug use,[129,130] and mental health problems.[99,100,124]

Hospital admission was associated with similar factors: regular or recent injecting,[115–117,131,132] diagnosed Hepatitis C,[50,119] diagnosed HIV,[98,116,131–133] low CD4 count among HIV positive participants,[134] female sex,[50,101,102,109,131,132,134] homelessness or unstable housing,[115,131] alcohol use,[50] polydrug use,[129] and mental health problems.[93,100]

One study (the Melbourne Injecting Drug User Cohort Study) reported similar associations with primary care utilisation: regular injecting, homelessness, cocaine injection and unstable income.[135,136]

Opioid agonist therapy was consistently associated with lower frequency of A&E presentation and hospital admission[89,99,105,113,117,119,133,137–142] than comparison groups of untreated opiate users. Among people on opioid agonist therapy, consistent medication was associated with a lower rate of

A&E utilisation.[138,139,143] Some studies looked at different types of treatment. For example, one study found that take-home methadone was associated with lower risk of hospital admission.[144] No studies looked at the effect of treatment for dependence on drugs other than opioids.

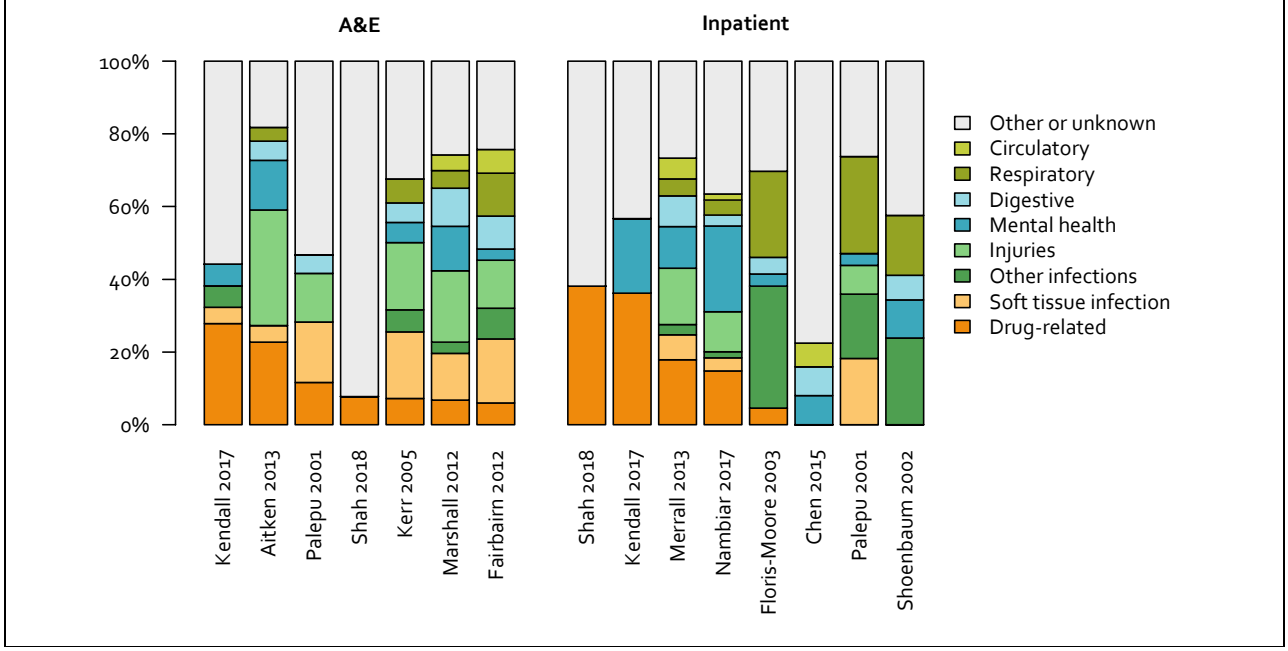
Some studies reported non-significant associations with these factors, but none found associations in the opposite direction.

Although some studies show that mental or physical morbidity is associated with increased healthcare utilisation, no studies attempted to show whether increased frequency of healthcare utilisation among people who use illicit drugs was explained by morbidity or other indicators of need for services.

6.4.3 Causes of healthcare utilisation

Studies with cause-specific data showed that a minority of A&E visits and inpatient episodes relate to the direct effects of illicit drugs, such as withdrawal, overdose and intoxication (Figure 8). Infections and particularly skin and soft tissue infections were common causes of A&E and inpatient episodes in study populations in Canada, Norway and Taiwan.[88,93,95,105,114,116,120,131] All infections and particularly pneumonias were important causes of healthcare utilisation in HIV positive opiate users.[132,134] Infections were less important causes of healthcare utilisation in studies in Australia.[51,145] Traumas, injuries and mental health problems were important causes of A&E utilisation and hospital admission in all studies.[50,51,95,114,116,145]

Figure 8: Causes of A&E visits and hospital admission (inpatient)

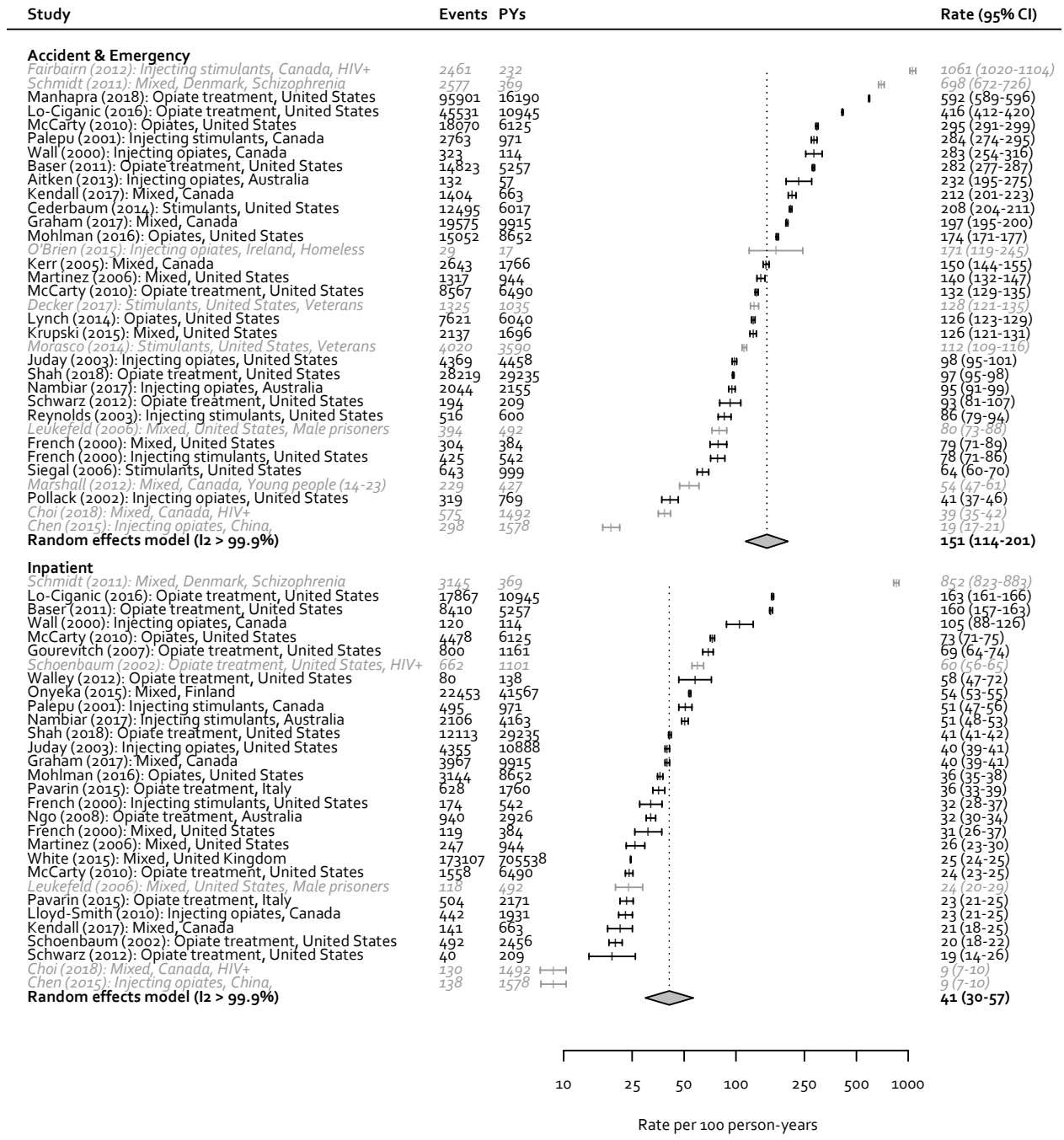


6.4.4 Quantitative results

I conducted meta-analysis of healthcare utilisation rates (25 studies reporting A&E episodes and 25 reporting hospital admission) and 12-month cumulative incidence (11 studies reporting A&E episodes and 11 reporting hospital admission). 12 months was the most common period examined in the literature. While we collected data from studies of other periods, I did not analyse these data because the periods varied too widely. I was unable to determine the consistency of the definition of primary care visits across studies and therefore did not attempt quantitative analysis. I restricted analysis to populations who primarily use heroin, crack cocaine or methamphetamine or have a diagnosis of 'substance abuse disorder' or drug dependence, since there were few studies of people who use cannabis or have other patterns of use.

A&E frequencies are shown in Figure 9 and Figure 10. An average of 29% (95% CI 24%-35%) of participants visited A&E over a 12-month period. The pooled rate was 151 visits per 100 person-years (95% CI 114-201). There was high heterogeneity, with I^2 approaching 100% for both analyses. 32 study populations were matched with published rates for groups of a similar age and sex in the general population. A&E presentation ranged from 0.9 to 24.7 times the general population (mean 4.8). Stratified meta-analysis by predominant drug and country did not show significant differences to the overall pooled estimate (results are shown in the published article[75]) and the exploratory meta-regression found no significant moderators.

Figure 9: Forest plot of rates of A&E and inpatient utilisation

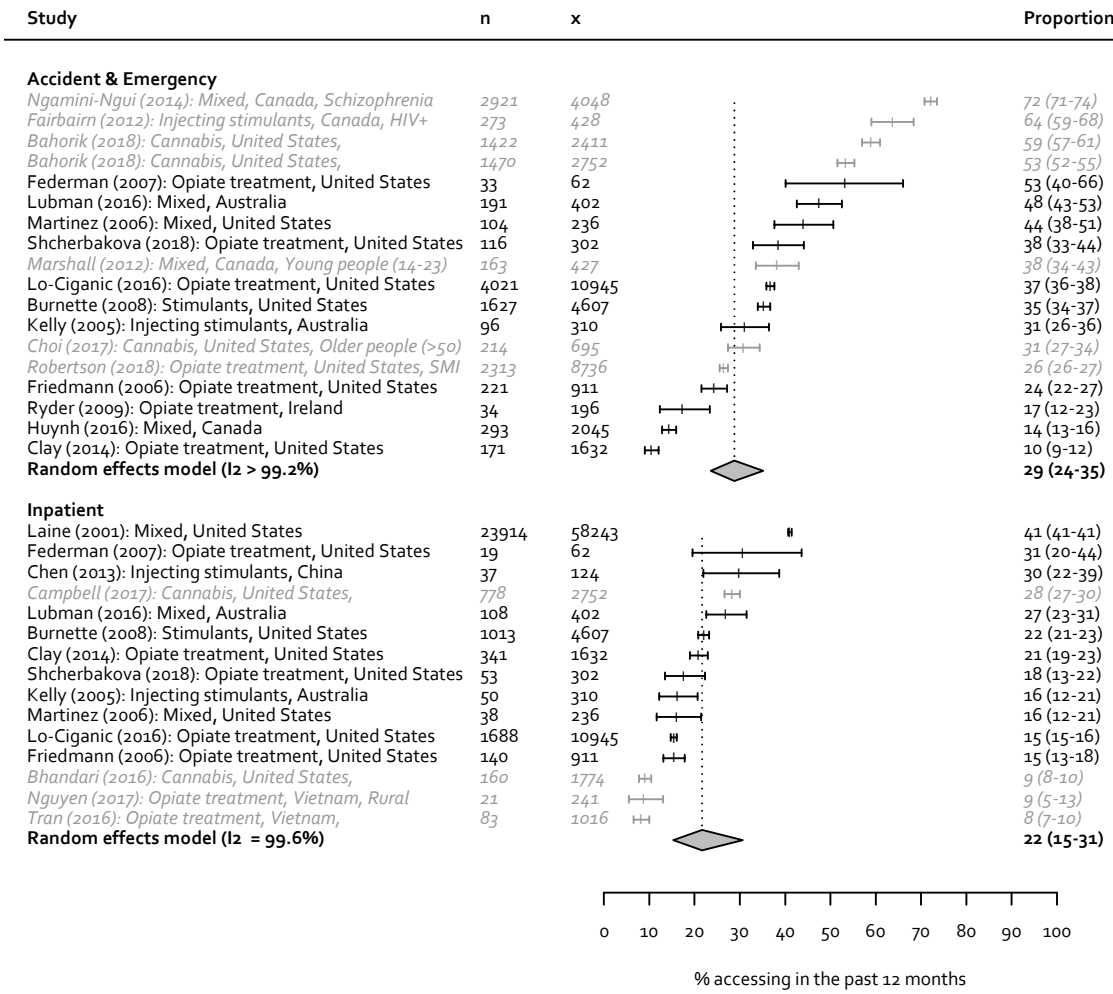


Studies in grey and italics are excluded from meta-analysis because they are in middle-income countries, use drugs that were excluded from meta-analysis (such as cannabis) or are otherwise unusual populations (such as people in prison).

Hospital admission rates and cumulative incidences are shown in Figure 9 and Figure 10. An average of 22% (95% CI 15%-31%) of participants were hospitalised over a 12-month period. The pooled rate was 41 episodes per 100 person-years (95% CI 30-57). There was high heterogeneity, with I^2 approaching 100% for both analyses. 27 study populations were matched with published rates for comparable groups in the general population. Hospital admission rates ranged from 1.9 to

35.5 times the general population (mean 7.1). As with the A&E results, stratified meta-analysis by predominant drug and country did not show significant differences to the overall pooled estimate, and the exploratory meta-regression found no significant moderators.

Figure 10: Forest plot of cumulative incidence (risk) of A&E and inpatient utilisation



SMI = severe mental illness

Studies in grey and italics are excluded from meta-analysis because they are in low- or middle-income countries, use drugs that were excluded from meta-analysis (such as cannabis) or are otherwise unusual populations (such as people in prison).

6.5 Discussion

Key findings

A large number of studies have reported the frequency of healthcare utilisation among people who use illicit drugs. These studies cover diverse populations and health systems, and rates of healthcare vary widely, but in almost all studies exceed rates in the general population. Predictors of more frequent healthcare utilisation were consistent across studies and included unstable housing, drug injection and mental health problems. Opioid agonist therapy was consistently associated with lower frequency of A&E episodes and hospital admission. There was limited research into primary care utilisation by people using any type of illicit drugs.

6.5.1 Strengths and limitations

Most studies in the past have described patients in healthcare services to show the proportion that use drugs, rather than using population-based approaches. This has led in particular to a focus on A&E and frequent healthcare users. To broaden this focus, I synthesized observational studies that often report healthcare utilisation as a secondary outcome. The strength of this approach is that it has shown the wide variation in utilisation of acute hospital services, and in some settings primary care may be attended more frequently.

There were 3 key limitations in the evidence:

First, half the studies in the review (43/92) rely on linked electronic healthcare records, which may have inaccuracies in diagnostic coding. For example, there is evidence that drug-related events such as overdoses are under-recorded in A&E data and may be given other diagnostic codes.[146,147] This could contribute to the small proportion of healthcare episodes that are 'drug-related' in our results. In addition, few studies include data from the recent period when synthetic opioids such as fentanyl became more common in North American illicit drug markets. Opioid-related overdoses in the United States have increased during this period,[148] and the proportion of healthcare episodes that are drug-related may have increased.

Second, the quality assessment identified non-response as the most common problem. This usually resulted from recruitment relying on volunteers or convenience samples, where non-response cannot be measured, rather than systematically or randomly inviting participants from a sample frame. Difficulty constructing sample frames may also account for the relative lack of studies of people using some illicit drugs, such as powder cocaine, although this may also be due to less severe health outcomes in these groups.

Third, none of the studies included in this review looked at whether higher morbidity explained higher rates of healthcare use, so we were not able to discuss the appropriateness of health service use. This is a central limitation of analysis of healthcare utilisation: without the context of health needs, it is unclear whether differences in utilisation reflect need or access. Health needs are diverse and adjusting healthcare utilisation using a composite measure of morbidity such as the Charlson Index[149] is unlikely to show whether differences in utilisation are explained by need. Chapter 11 is a

case study of people with incident COPD, a group with some definable health needs, to investigate whether illicit opioid use is associated with healthcare access.

The review also had 3 key methodological limitations:

First, we only included English-language studies, which may partially explain the large proportion of studies from English-speaking countries—although the English-language restriction only excluded 179/5528 search results (3%).

Second, given the heterogeneity of results, meta-analysis is only intended to provide an average across studies, rather than a meaningful estimate of healthcare utilisation for any specific population.

Third, I defined healthcare utilisation using simple rates and proportions. While this enabled a traditional systematic review, it meant that the results provide limited insight into the appropriateness or equity of the high rates of healthcare utilisation among people who use illicit drugs.

Fourth, the review focuses on 3 mainstream healthcare settings (primary care, A&E and in-patient hospital care), and did not consider other potential sources of health care such as community drug treatment services, which sometimes provide a wider set of interventions. Future research should consider the full range of healthcare provision for people who use drugs, including opportunities for integration between drug treatment and mainstream health services.

6.5.2 Interpretation and relevance for policy, practice, and research

The high rates of healthcare utilisation among people who use illicit drugs in part reflects the higher prevalence of many health problems. Studies in this review focused on people who use drugs such as heroin, crack cocaine, and methamphetamine, and this population has high health needs. However, high healthcare utilisation is difficult to interpret further. There are perceptions that high rates of healthcare among people with mental health and drug-related problems may relate to a group of "frequent users" who visit hospital regularly for non-urgent problems or because they are "drug seeking" (i.e. seeking prescriptions for non-medical purposes).[150] In the context of the health needs of the population, the rates of healthcare utilisation may either be higher or lower than expected, and the results in this study do not provide insight into healthcare access.

The results show extremely heterogenous frequencies of healthcare utilisation. Effectively all of the variation across studies was attributable to differences between populations rather than within-study error (reflected in the I^2 statistics of almost 100%). Despite consistent predictors of healthcare utilisation within studies, I was not able to explain the variation between studies by the predominant drugs used by study participants, the country of the study or any other study-level variables that we extracted. Results varied widely even within countries and populations with apparently similar drug use. For example, in the United States, the rate of hospital admission of people in opioid agonist therapy ranged from 51 to 592 per 100 person-years.[113,137–139,151–153] The extent of heterogeneity may suggest that social and healthcare contexts can substantially affect healthcare utilisation. The heterogeneity also highlights the difficulty of generalising results from single studies of healthcare utilisation.

The consistent predictors of healthcare utilisation reflect previously observed risk factors for poor health among people who use drugs. It is not surprising that poor health is associated with

healthcare use, though this may suggest that patterns of healthcare in this population relate at least in part to need rather than other factors such as "drug seeking". The high hospital utilisation is likely to reflect poor health and a need for more accessible primary care, though this review does not provide evidence for models of care that might work.

The review identified 3 main gaps in the evidence that may inform priorities for future research. First, 84% of study populations were from the United States, Canada or Australia. We did not identify any studies from low-income countries. Second, there were few studies with primary care data, even though existing studies suggest people who use illicit drugs visit primary care more often than acute healthcare settings,[109–113] contrary to the stereotype of reliance on A&E. Third, almost all studies were of people who use heroin, crack cocaine or methamphetamine, or have a diagnosis of drug dependence. There were only 8 studies of people who use cannabis and none of people using MDMA/ecstasy, powder cocaine, hallucinogens, novel psychoactive substances or other drugs.

6.5.3 Conclusion

People who use drugs such as heroin and crack cocaine have high rates of emergency healthcare. However, there is little research into engagement with primary care, or whether high rates of healthcare utilisation are explained by morbidity or other types of need.

Linking statement

This chapter has reviewed literature on healthcare utilisation among people who use illicit drugs. The results show that healthcare utilisation is high but this needs to be considered in the context of the population's health needs. In the next chapter, I will review research into healthcare access for people who use illicit drugs, and interventions that have tried to improve healthcare for this patient group.

7 Research into access to routine physical healthcare and interventions to improve physical healthcare for people who use illicit drugs: a scoping review

7.1 Summary

Background: Research into health interventions for people who use illicit drugs has focused on 'drug-related' problems such as overdoses and infections. There appears to be less research into healthcare for long-term physical health problems. This scoping review aims to map research in this field.

Methods: I searched MEDLINE on 18 September 2019, including studies of adults who use illicit drugs and focus on two areas: (a) access to treatment for non-communicable diseases, defined as diabetes, cardiovascular diseases, respiratory disease, cancer, or liver disease; and (b) interventions that improve access to treatment for non-communicable diseases. I extracted the main findings from relevant studies and summarised common themes.

Results: 26 studies were included. 15/26 studied the first area and assessed access to healthcare for people who use illicit drugs, with most (8/15) focusing on uptake of cancer screening. Most of these studies found lower uptake among people who use illicit drugs than the general population. 5/15 studies looked at treatment after a diagnosis of cardiovascular disease or diabetes, finding lower access among participants who use illicit drugs. 2/15 studies looked at mortality after a cancer diagnosis, both finding higher mortality rates among participants who use illicit drugs after adjusting for clinical characteristics at baseline. 11/26 studied the second area and evaluated interventions that aimed to improve healthcare for people who use illicit drugs, with most (7/11) evaluating integrated primary care and drug treatment services. These studies had varied results, for example observational studies showed that integrated care was associated with reduced hospital visits and increased drug abstinence, but did not find evidence of an association with health outcomes, while a randomised control trial found that integrated care had no effect on drug abstinence or healthcare costs. 3/11 studies reported piloting of spirometry in community drug and alcohol services in the UK. These found high prevalence of chronic obstructive pulmonary disease and suggested that spirometry-based screening is acceptable to patients in these settings. Most studies (16/26) were from North America, and most samples were of people with generic diagnoses such as 'substance use disorder' (which may include people who use alcohol) and did not report the drugs used by participants.

Conclusion: In contrast to the extensive research into healthcare for people with severe mental health problems such as schizophrenia, there is limited research into healthcare for people who use illicit drugs. Existing research suggests that access to physical healthcare is likely to be worse that for the general population, though effective interventions to improve healthcare for this population have not yet been identified.

7.2 Background

Key points

- Research into health interventions for people who use illicit drugs has focused on 'drug-related' problems such as overdoses and infections
- There appears to be less research into the healthcare for long-term physical health problems
- A 'scoping review' maps a body of research and identifies gaps

A large body of research has investigated health interventions that aim to improve the health of people who use illicit drugs, although this research has focused on specific health problems. There are systematic reviews of evaluations of interventions that prevent Hepatitis C infection,[154] improve access to Hepatitis C treatment,[55] prevent overdose through community-distributed naloxone,[53,155] and use opioid agonist therapy to reduce criminal activity and improve health.[56] There is less attention on the healthcare for long-term physical health problems such as cardiovascular and respiratory diseases. This chapter is a 'scoping review' that summarises research undertaken in these areas.

A scoping review "aims [to map] key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge".[156] The process is designed to understand what research has been conducted, drawing on research of varying methods and differing populations or exposure/outcome definitions. Traditional systematic reviews rely on consistency in these definitions across studies and are not always suited to summarising a more diverse body of evidence. I chose this approach because I wanted to understand existing research rather than synthesise comparable studies.

The research questions are:

- What research has been undertaken into access to routine physical healthcare for people who use drugs?
- What research has been undertaken into interventions that improve physical healthcare for people who use drugs?

To help focus a literature search, the review focuses on 5 long-term conditions: diabetes, cardiovascular diseases, respiratory diseases, cancer, and liver disease. The first 4 are often considered the 'big 4' non-communicable diseases in the general population,[157] while liver disease causes a large number of deaths among people who use drugs (see chapter 10). Populations will not be limited to people who use heroin and crack cocaine, as different drugs are associated with similar problems in other countries (such as methamphetamine in the United States and Australia). The approach will draw on existing reviews of physical healthcare for people with severe mental illnesses.[158,159]

7.3 Methods

7.3.1 Population, Concept, Context

Traditional systematic review often use a 'Population, Intervention, Comparison, Outcome' framework, which has been developed into a 'Population, Concept, Context' (PCC) framework to guide scoping reviews.[160] A PCC framework for this review is given in Table 3.

Table 3: Parameters for a scoping review into the literature studying physical healthcare for people who use drugs

	Question 1: What research has been undertaken access to routine physical healthcare for people who use drugs?	Question 2: What research has been undertaken into interventions that improve physical healthcare for people who use drugs?
Population	*People who use illicit drugs* Adults who use heroin, crack cocaine, or methamphetamine, or inject drugs, or have a diagnosis of 'drug dependence' or 'substance use disorder'.	
Concept	*Secondary prevention or treatment of non-communicable diseases* Provision of evidence-based case-finding, screening or treatment for diabetes, cardiovascular diseases, respiratory disease, cancer, or liver disease, or interventions that aim improve 'general physical health'	*Improving access to treatment for non-communicable diseases* Any intervention, including integrated care, linkage, supported referral, care navigation, in-reach, screening, and case finding; and aiming to improve care for diabetes, cardiovascular diseases, respiratory disease, cancer, or liver disease
Context	Routine care provided in the community in any country, with a comparison to the general population	Evaluation of interventions developed in any country

Studies that only reported measures of patient satisfaction or disease prevalence were excluded. There were no exclusions in terms of publication year, language, or country.

7.3.2 Search strategy

I searched MEDLINE via the Ovid interface from inception to 18 September 2019 using search terms in Table 4. I conducted title and abstract screening and accessed potentially relevant full texts. Where full texts met inclusion criteria, I extracted the details of the population, outcomes or interventions, and main findings. I also reviewed references of full-texts.

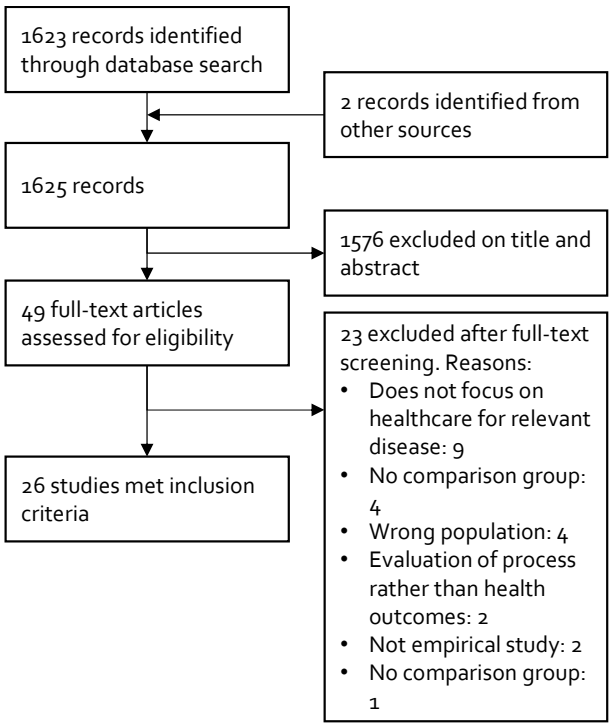
Table 4: Search terms for scoping review

Step	Concept	Terms	Results on 18 September 2019
1	Population: people who use drugs associated with dependence	heroin OR opiate* OR crack OR methamphetamine OR methadone OR pwid OR inject* adj2 drug* OR "substance misuse" OR "substance abuse" OR "substance use" OR "drug dependence" OR "drug use disorder*"	147,308
2	Physical health, specifically cardiovascular disease, cancer, respiratory disease or liver disease	"health status" OR "physical health" OR "medical disorder*" OR "medical status" OR cardiovascular OR cvd OR stroke OR "myocardial infarction" OR "heart failure" OR cardia* OR hypertension OR diabetes OR neoplasm* OR cancer OR respiratory OR copd OR emphysema OR bronchitis OR "lung disease" OR "chronic obstructive pulmonary" OR asthma OR "liver disease" OR fibrosis OR cirrhosis	6,105,695
3	Access or quality of routine care	(quality adj3 health*) OR (quality adj3 medical) OR (outcomes adj3 care) OR (unmet adj3 need*) OR accessibility OR (access adj3 medical) OR (access adj3 health*) OR acceptability	384,167
4	Interventions to improve healthcare	screening OR "case finding" OR linkage OR referral OR "secondary prevention" OR (improv* adj2 access) OR "integrat* care" OR (on-site adj3 care) OR "model* of care" OR "in reach" OR inreach	881,211
5	Final search	1 AND 2 AND (3 OR 4)	1,623

7.4 Results

After deduplication, the search returned 1,623 results. Title and abstract screening identified 49 results for full-text review. 2 studies were identified from references of included studies that did not already appear in the database search. 26 studies met the PCC inclusion criteria. Figure 11 shows a flow-chart of the number of included studies.

Figure 11: Flow-chart of included studies



7.4.1 Question 1: What research has been undertaken into access to routine physical healthcare for people who use drugs?

15 studies evaluated the access to routine physical healthcare for people who use illicit drugs. Only 1 of these studies looked specifically at people who use illicit opioids,[161] with the rest using samples of people with 'substance use disorder', often including a mixture of different drugs and alcohol. 8/15 studies were from the US; 2/15 from Canada; 2/15 from Australia; 1/15 from Finland; 1/15 from Denmark; and 1/15 was a literature review. Studies are listed in Table 5.

The studies used samples with a defined need for healthcare (such as screening in the general population, or diabetes management for people with diabetes), and then compared people who use drugs with the general population in terms of the probability of receiving an defined intervention.

8/15 studies focused on cancer screening, with 6/8 finding lower take-up among people who use drugs. 3/15 studies measured differences in secondary prevention after a cardiovascular event, cathaterisation and revascularisation after myocardial infarction, with all 3 finding lower probability of care for people who use drugs. 2/15 studies looked at diabetes management, of which 1 found

lower probability of treatment for people who use drugs (e.g. patients were less likely to receive retinal examinations) and the other found limited differences. 2 studies looked at mortality after cancer diagnosis, with both finding that participants who use illicit drugs have higher mortality rates after adjustment for disease severity, which may relate to treatment quality.

2/15 studies did not find substantial differences in healthcare access between people who use drugs and the general population.[162,163] Authors of these 2 studies suggested that their findings may relate to additional healthcare provided at the service where people who use drugs were recruited.

Table 5: Studies of healthcare access for common non-communicable diseases among people who use illicit drugs

Study	Title	Country	Population	Outcomes	Findings
Browne 2019[162]	Clinical Care Quality Among Veterans Health Administration Patients With Mental Illness Following Medical Home Implementation	United States	360,495 veterans with "substance use disorder" compared to patients without any mental illness	Cancer screening, immunisations, management of diabetes, hypertension, ischaemic heart disease, heart failure	Minor differences between patients with and without substance use disoder
Spithoff 2019[161]	Quality of primary care among individuals receiving treatment for opioid use disorder	Canada (Ontario)	20,406 patients in opioid agonist therapy and a matched comparison group not receiving opioid agonist therapy	Cancer screening in the whole sample. Among those with diabetes: retinal eye examination, cholesterol test, or blood test	Opioid group had more frequent physician visits, but was less likely to receive cervical, breast or colorectal cancer screening. Among participants with diabetes, opioids associated with lower probability of monitoring
Mander-backa 2018[164]	The effect of history of severe mental illness on mortality in colorectal cancer cases: a register-based cohort study	Finland	909 patients with incident colorectal cancer and comorbid "substance use disorder", compared to 39,326 cases without substance use disorder	Death due to colorectal cancer	The substance use disorder group had 1.22 (95% CI 1.09-1.37) times the mortality rate after adjustment for disease stage at presentation.
Jensen 2016[165]	Psychiatric morbidity and non-participation in breast cancer screening	Denmark (Central Region)	1,427 women with "substance abuse" compared to women with no psychiatric disease	Non-participation in breast cancer screening	The substance abuse group had 1.69 (95% CI 1.59–1.80) times the prevalence of non-participation
Soccio 2015[163]	Pap smear screening, pap smear abnormalities and psychosocial risk factors among women in a residential alcohol and drug rehabilitation facility.	Australia (Sydney)	36 women living in a residential drug and alcohol treatment service, compared to 66 women attending a community screening clinic (general population)	Late cervical screening	Similar proportion with late screening, contrary to hypothesis of higher proportion among women who use drugs

Study	Title	Country	Population	Outcomes	Findings
Chhatre 2014[166]	Substance use disorder and its effects on outcomes in men with advanced-stage prostate cancer.	United States	1,509 men age 66+ diagnosed with advanced prostate cancer and comorbid "substance abuse disorder", compared to 12,768 men without substance abuse disorder	All-cause and cancer-specific mortality	Substance use disorder was associated with hazard ratio of 1.5 (95% CI 1.3-1.7) of all-cause mortality, after adjusting for cancer grade, treatment and co-morbidities
Tilley 2013[167]	Women with substance use under-screened for pap smears.	Australia (Sydney)	76 women living at a residential drug treatment service, compared to 89 women attending a community clinic (general population)	'Underscreening' (last attended more than 4 years ago)	39% of women screened at the drug treatment service were under-screened, compared to 15% from the community sample
Beck 2013[168]	Alcohol and drug use disorders among patients with myocardial infarction: associations with disparities in care and mortality.	Canada (Calgary)	73 patients with "substance use disorder" admitted with acute myocardial infarction, compared to 3,375 patients without substance use disorder	Catheterisation, revascularisation, and in-hospital mortality	After adjustment for clinical characteristics, the substance use disorder group had 2.02 (95% CI 1.10–3.69) times the odds of in-hospital mortality, 0.75 (95% CI 0.55–1.01) times the odds of catheterisation, and 0.85 (95% CI 0.65–1.11) times the odds of revascularisation
Abrams 2012[169]	Cervical cancer screening and acute care visits among Medicaid enrollees with mental and substance use disorders.	United States (Maryland)	6,122 women with "substance use disorder", compared to 85,375 women with no psychiatric diagnosis	Cervical cancer screening	The substance use disorder group had 0.80 (95% CI 0.75-0.85) times the odds of having a cervical cancer screen
Lasser 2011[170]	Is unhealthy substance use associated with failure to receive cancer screening and flu vaccination? A retrospective cross-sectional study.	United States (Boston)	975 patients with "unhealthy substance use", compared to 9020 patients without unhealthy substance use	Flu vaccination, pap smear, mammogram and colorectal cancer screening	Those with unhealthy substance use had 0.81 (95% CI 0.67-0.97) times the odds of flu vaccination, 0.68 (95% CI 0.52-0.89) times the odds of mammogram, and no evidence of differences in pap smear and colorectal cancer screening
Mitchell 2009[159]	Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies.	NA (systematic review)	10 studies	Various	All 10 studies found lower quality healthcare for people with "substance use disorders"
Li 2007[171]	Are patients with coexisting mental disorders more likely to receive CABG surgery from low-quality cardiac surgeons? The experience in New York State.	US (New York State)	560 patients receiving coronary artery bypass graft with comorbid "substance use disorders", compared to 36,628 patients without substance use disorders	Receiving surgery from a 'low quality' or 'high quality' surgeon, based on risk-adjusted mortality quintile	Patients with dual diagnosis of psychiatric and substance use disorders were more likely than patients without mental health diagnoses to be treated by 'low quality' surgeons

Study	Title	Country	Population	Outcomes	Findings
Frayne 2005[172]	Disparities in diabetes care: impact of mental illness.	United States	Patients with diabetes and comborbid "substance use disorders" (number not specified), compared to patients without comorbid substance use disorders	No HbA1c test done; no LDL-C test done; no eye examination done; no monitoring	All outcomes were more likely among patients with substance use disorders (i.e. care quality was worse)
Druss 2002[173]	Quality of preventive medical care for patients with mental disorders.	United States	4536 patients with "substance use disorders" compared to 79,367 patients with no psychiatric disorder	Immunisations and cancer screening	Patient with substance use disorders only had lower likelihood of influenza vaccine (OR 0.77; 0.70-0.85) and prostate cancer screening (OR 0.75; 0.32-0.57 [sic]). Associations with other immunisations and cancer screenings were not significant. Patients with both psychiatric and substance use disorders had lower likelihood of all immunisations and cancer screenings (ORs ranging from 0.52-0.87).
Druss 2000[174]	Mental disorders and use of cardiovascular procedures after myocardial infarction.	United States	1,138 patients with acute mycardial infarction and comorbid "substance use disorders", compared to 108,288 patients without substance use disorder	Catheterisation, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG)	Substance use disorder was associated with 0.78 times the probability of catherterisation after adjusting for clinical characteristics. Among patients undergoing catherisation, substance use disorder was associated with 0.78 times the probability of PTCA and 1.00 times the probability of CABG.

[sic] – error in original
OR = odds ratio

7.4.2 Question 2: What research has been undertaken into interventions that improve physical healthcare for people who use drugs?

11 studies evaluated interventions that aim to improve physical healthcare for people who use drugs. 7/11 used samples of people in opioid agonist therapy, with the rest having general 'substance use disorders'. 6/11 studies were from the United States; 2/11 from the UK; 1/11 from Australia; 1/11 from Switzerland; and 1/11 was a literature review. Studies are listed in Table 6.

7/11 studies evaluated a model of integrated care in which primary care and drug treatment services are co-located. 6/7 of these studies were conducted in the US and 1 was a literature review. The findings of these studies varied. 2 similar studies compared patients in community drug treatment services that have on-site primary care with patients in services without on-site primary care. One found that on-site primary care is associated with substantially lower hospital visits, while the other showed that on-site primary care is not associated with any difference in health outcomes. These results together may suggest that healthcare can be shifted between settings but this does not necessarily improve outcomes for patients. A randomised controlled trial of integrated primary care and community drug treatment found no effect on drug abstinence or total medical costs.

3/11 studies reported the results of spirometry among clients of community drug and alcohol services. It was difficult to classify these studies as prevalence studies (which would not be eligible for this review), or as screening studies (which would be eligible). They show that screening using spirometry is feasible in this setting and I therefore included them.

1/11 study reported results of a general 'health screening tool' and referral process for clients of a community drug and alcohol services, but results were difficult to interpret due to the lack of a comparison group and lack of information on the outcome of referrals.

Table 6: Studies evaluating interventions that aim to improve physical healthcare for people who use illicit drugs

Study	Title	Country	Population	Intervention	Findings
Grischott 2019[47]	Chronic obstructive pulmonary disease (COPD) among opioid-dependent patients in agonist treatment. A diagnostic study	Switzerland (Zurich)	125 opioid agonist patients	Case-finding for COPD using spirometry	30% had COPD; authors recommend diagnostic spirometry in all opioid agonist patients age >40
Burhan 2019[46]	Screening Heroin Smokers Attending Community Drug Services for COPD	UK (Liverpool)	753 people who smoke heroin recruited from a community drug treatment service	Case-finding for COPD using spirometry	35% had COPD; authors recommend screening of people who smoke heroin
Mitchell 2016[175]	Respiratory health screening for opiate misusers in a specialist community clinic: a mixed-methods pilot study, with integrated staff and service user feedback	UK (Sheffield)	34 people who smoke heroin recruited from a community drug treatment service	Case-finding for COPD using spirometry	14% had COPD; qualitative findings show willingness among patients and staff to participate in respiratory screening
Jackson 2016[176]	Towards holistic dual diagnosis care: physical health screening in a Victorian community-based alcohol and drug treatment service.	Australia (Victoria)	40 people who use alcohol and other drugs attending a community drug treatment service	Physical health screening tool and referral to primary care or other relevant service	Participants had high prevalence of chronic health problems. Referrals were made but the outcome of referrals was not known.
Haddad 2015[177]	Buprenorphine maintenance treatment retention improves nationally recommended preventive primary care screenings when integrated into urban federally qualified health centers.	United States (Connect-icut)	266 opioid-dependent patients entering buprenorphine treatment at primary health centres	Integrated care (buprenorphine delivered in primary care settings)	Patients prescribed buprenorphine in primary care often had better participation in screening programmes than patients treated in specialist behavioural health services
Islam 2012[178]	The accessibility, acceptability, health impact and cost implications of primary healthcare outlets that target injecting drug users: a narrative synthesis of literature.	NA (literature review)	35 studies	Primary health centres that specifically serve people who inject drugs	Studies show that these models are more accessible that conventional primary care, due to non-judgemental attitudes and open access appointments

Study	Title	Country	Population	Intervention	Findings
Fareed 2010[179]	On-site Basic Health Screening and Brief Health Counseling of Chronic Medical Conditions for Veterans in Methadone Maintenance Treatment.	United States (Atlanta)	102 people on methadone treatment	Onsite health screening and brief health counselling	May show acceptability of the intervention (through high compliance with appointments), but there is no control group and outcomes are difficult to evaluate
Friedmann 2006[180]	Do mechanisms that link addiction treatment patients to primary care influence subsequent utilisation of emergency and hospital care?	United States	2,113 people entering substance abuse treatment	Onsite primary care in community methadone services and long-term residential programmes	Patients in community methadone services with on-site primary care had lower odds of an A&E visit over 12 months (OR 0.50; 0.31-0.81) and hospitalisation (OR 0.30; 0.15–0.50). Patients in long-term residential programmes with on-site medical care had lower odds of an A&E visit (OR 0.46, 0.25–0.84) and hospitalisation (OR 0.40, 0.21-0.74).
Friedmann 2003[181]	Effect of primary medical care on addiction and medical severity in substance abuse treatment programs.	United States	2,878 patients entering substance abuse treatment	Onsite medical care or off-site medical care	Onsite medical care was associated with greater improvements in drug-related outcomes, but there was no evidence of differences in "medical severity" (a composite score of general health).
Weisner 2001[182]	Integrating primary medical care with addiction treatment: a randomized controlled trial.	United States	592 patients admitted to a drug treatment programme	Integrated medical and addictions care (vs. separate provision)	Integrated care had no effect on drug abstinence or the cost of medical care. The study concludes that integrated care can be cost-effective but this is based on a sub-group analysis of individuals with "substance abuse-related medical conditions".
Selwyn 1993[183]	Utilisation of on-site primary care services by HIV-seropositive and seronegative drug users in a methadone maintenance program.	United States (New York City)	476 people who inject drugs	Integrated primary care and opioid agonist therapy	Results may suggest that integrated care is acceptable due to level of utilisation, but do not evaluate the outcomes of the intervention

7.5 Discussion

Key findings

There are few studies into the access to physical healthcare or interventions that aim to improve physical healthcare for people who use illicit drugs. Previous studies were mostly done in the United States. Existing evidence suggests that illicit drugs is associated with relatively poor access to cancer screening and some studies suggest lower probability of treatment after diagnosis with cardiovascular disease or diabetes. Some studies have evaluated integrated community drug treatment and primary care, with varying results.

7.5.1 Strengths and limitations

The 'scoping review' approach taken in this review allowed inclusion of relevant studies with a wide range of methodologies and populations. The review method was less rigorous than the systematic review presented the previous chapter. This was partly due to limitations in time and resources and partly because the aim was to achieve a reasonable understanding of existing literature rather than do an exhaustive search. In particular, a more robust review would include:

(a) Additional research databases and grey literature. To test whether important studies were excluded from MEDLINE, I ran a similar search on EMBASE and reviewed results that were not included in the original Medline search. I also searched Google Scholar with terms such as "healthcare access heroin". I did not identify additional eligible studies, though this was a post-hoc and brief appraisal.

(b) Engagement with other researchers in this field to identify further possible references.

(c) Double-screening of titles and abstracts and data extraction by multiple researchers, to reduce errors and improve reliability.

(d) A consultation stage in which the gaps and priorities for future research are discussed with people who use drugs and professionals working in relevant health services, as recommended in guidance for scoping reviews.[184]

7.5.2 Interpretation and relevance for policy, practice, and research

The research summarised in this review shows that physical healthcare for people who use illicit drugs has been investigated previously and some interventions have been developed. It is likely that these studies represent a small proportion of actual activity and other service models and interventions have been developed without formal academic evaluation. For example, in my Patient and Public Involvement, participants discussed a 'lung health clinic' for people in community drug and alcohol services at South London and Maudsley NHS Foundation Trust, which does not have associated publications.[185]

The methods used by studies in the first section of this review (looking at the access to physical healthcare) address an issue identified in the systematic review presented in the previous chapter. In

the systematic review, the frequency of healthcare utilisation was difficult to interpret without the context of health needs. The studies of healthcare access in this scoping review recruited patients with a specific health need (such as a diagnosis of diabetes) and assessed whether relevant interventions (such as eye and foot examinations) happened. This approach allows evaluation of healthcare access or quality (rather than simply volume).

Although the results show that physical healthcare for people who use illicit drugs has been investigated previously, there are some major limitations in how this literature can inform physical healthcare for people who use heroin and crack cocaine in England:

(1) Both questions examined in this scoping review revealed small and patchy literatures. Studies of healthcare access focus on cancer screening with few studies focusing on other interventions.

(2) Studies typically used samples of people diagnosed with a 'substance use disorder', which may refer to any drug and in particular means that samples may have large proportions of people in treatment for alcohol dependence.

(3) A large proportion of studies were conducted in the United States, where drug treatment services and general health services are structured differently.

(4) Studies evaluating interventions focused on integrated drug treatment and primary care, with no research into other models, such as in-reach, supported referral, or case management (though some studies of case management for people who use illicit drugs were excluded from the review because they reported process-level outcomes such as engagement with drug treatment services[186] rather than treatment of a non-communicable disease).

Together, these factors mean it is difficult to draw clear conclusions from the existing literature or generalise to people who use heroin and crack cocaine in England.

The lack of evidence and guidance for improving the physical health of people who use drugs has also been observed by an author in Australia,[176] who said that: "the poorer health outcomes experienced by people with mental illness have led to new directions in policy for routine physical health screening of service users. By contrast, little attention has been paid to the physical health needs of consumers of alcohol and other drug services, despite a similar disparity in physical health outcomes compared with the general population," and by an author in the US,[179] who said "although patients with history of heroin dependence and in methadone maintenance treatment are at increased risk for chronic medical conditions like hepatitis C and diabetes, there are minimal federal guidelines for medical care, except than a physical exam upon admission, and basic screening for some infectious diseases e.g. HIV and Hepatitis C for those patients."

As noted by the author mentioned above,[176] there is more research into physical healthcare for people with serious mental illnesses such as schizophrenia and bipolar disorder. There are parallels between this population and people who use heroin and crack cocaine. Both populations have high rates of smoking, harmful drinking, and poor nutrition. Both face stigma in health services. Both have high mortality rates.[187] There is also an overlap between the populations, with one estimate suggesting that 46% of people who use community drug treatment services in the UK have an severe mental health problem.[188]

Since the late 1990s there has been increasing recognition of physical health problems among people with severe mental health problems, with over 100 systematic reviews of the prevalence of physical

comorbidities.[189] A review of healthcare provision for people with severe mental health problems[158] said that "while much attention has been focused on suicide and homicide which are associated with higher rate ratios, the public health burden associated with major chronic diseases is much higher [...] The majority of excess deaths in this population are due to physical illnesses, in particular cardiovascular disease, respiratory illness and cancer." This is a similar situation to people who use illicit drugs, where attention has focused on fatal drug poisonings and infections rather than chronic diseases.

Despite the high health needs among people with severe mental health problems, research has found, for example, inferior care for heart attacks and diabetes.[190] Suggested reasons for poor healthcare include stigma among healthcare professionals, misattribution of somatic symptoms to mental health problems (diagnostic overshadowing), and a lack of understanding of mental health problems.[190] However, unlike for people who use illicit drugs, research and policy have been developed to address this problem. Interventions include offering health checks; specialist health promotion, with a systematic review finding 39 RCTs of physical activity interventions for this population;[191] integration or co-location of mental and physical health services; care managers or advocates; and providing training for physical healthcare staff to help them understand the needs of this population. NHS England has committed to improving take-up of health checks, and local commissioners must now fund "full annual physical health assessment and appropriate follow-up care", plus support for healthier behaviours, for 60% of patients on the GP severe mental health register, with £83m funding from NHSE for this activity per year.[192]

It is not clear why more research and investment has been focused on physical health for people with severe mental health problems than people who use heroin and crack cocaine. 3 possible reasons are (a) more people have severe mental health problems. The Adult Psychiatric Morbidity Survey estimated that 0.7% of the people in England have a psychotic disorder and 2.0% have bipolar disorder;[3] (b) there may be perceptions that people who use illicit drugs will not engage with health services and drug-related problems must be addressed first; (c) the population that uses illicit drugs is ageing and chronic diseases have only become prominent in recent years. The approaches developed for people with severe mental illnesses may provide a starting point when designing interventions for people who use illicit drugs.

7.5.3 Conclusion

In contrast to the extensive research into healthcare for people with severe mental health problems, there is limited research into healthcare for people who use illicit drugs. Existing research suggests that access to physical healthcare is likely to be worse that for the general population, though effective interventions to improve healthcare for this population have not yet been identified.

Linking statement

This chapter has shown there is very little published research into physical healthcare for people who illicit drugs. However, services that support his population may have developed their own interventions without formal evaluation, or have expertise that can inform more effective service models. I therefore led a qualitative study of clinicians who work in community drug treatment services in the UK exploring this issues, which is reported in the next chapter.

8 The role of community drug and alcohol services in physical healthcare for people who use heroin and crack cocaine: a qualitative study of clinical staff

8.1 Summary

Background: There is limited research into interventions that aim to improve physical healthcare for people who use heroin and crack cocaine. Staff at community drug treatment services may have expertise in this area.

Methods: I did a qualitative analysis of semi-structured interviews with 16 clinicians working in community drug and alcohol services in the UK. Interviews were conducted between May 2019 and March 2020. Interviews focused on the physical health needs and healthcare access for clients who use opioids. Topics included participants' role in physical healthcare, barriers and enablers to better healthcare, and 'ideal' models of healthcare for their clients.

Results: Participants discussed 3 main themes. First, clients who use illicit opioids have physical health needs that are often first identified in community drug and alcohol services. Participants attempted to improve access to healthcare by liaising directly with local health services and undertaking other forms of health advocacy, but report limited success. Many referrals ended in non-attendance. Second, most participants felt their role should be supporting access to mainstream health services rather than providing healthcare directly. This was because community drug and alcohol services lack skills and resources to provide equivalent care. However, some felt frustrated at being unable to provide time-sensitive treatments such as antibiotics for a skin or chest infection. In contrast, a minority of participants felt that people who use heroin and crack cocaine would be best served by an integrated 'one-stop-shop' model, but felt this model is currently unlikely to receive funding. Third, participants felt isolated from other health services, in part due to commissioning arrangements in which funding is provided through local government rather than the NHS.

Conclusion: Clinicians participating in this study serve a patient group with unmet physical health needs, but lack the resources to respond effectively to these needs.

This study has been published in the journal BMJ Open.[193]

8.2 Background

Key points

- Community drug and alcohol services serve clients with unmet physical health needs
- There is some evidence that these services have developed models to address this problem
- This study explores how clinical staff working in these services perceive their role in the management of their clients' physical health, focusing on clients who use heroin and crack cocaine

Community drug and alcohol services (CDAS) provide an important point of contact between people who use illicit opioids and other NHS services. In the United Kingdom, CDAS primarily aim to help their clients to stop or reduce their use of alcohol and drugs through psychosocial interventions and pharmacological therapy such as methadone and buprenorphine for opioid dependence. However, some services recognise that their clients have additional health needs that are not met by mainstream services, and offer ancillary services or work in partnership with other local services to design specialist pathways.

For example, CDAS in Liverpool[46] and South London[194] have run pilots of spirometry clinics for clients who use opioids, and referred those with chronic obstructive pulmonary disease to local respiratory services. Blood-borne virus testing is a standard element of induction into opioid agonist therapy,[195] and the NHS England specification for hepatitis C treatment envisages that outpatient care will be delivered in partnership with CDAS.[196] Some nurses who work in CDAS with a primary focus on blood-borne viruses have expanded their remit into areas including wound care, sexual health, and vaccinations.[197]

However, these examples may not capture the diversity of work underway, or the overall position of CDAS in the provision of healthcare for their clients. My Patient and Public Involvement discussions with staff at community drug and alcohol services in London suggested they were aware of their clients' unmet health needs and had tried various strategies to improve the situation, but had not formally evaluated these projects. I therefore did a qualitative study with clinicians working in CDAS to understand their perceptions of physical healthcare for their clients.

I did this study together with Dr. Molly Bradbury, who was studying for an MSc in Population Health at UCL. Dr. Bradbury and I designed the study together. I recruited participants, we both interviewed participants, and we developed a qualitative coding framework together. Dr. Bradbury submitted her own analysis of the interviews for her MSc.

8.3 Methods

We conducted a qualitative study including semi-structured one-to-one interviews with clinicians working in CDAS in the UK, and thematic analysis of transcribed interviews.

8.3.1 Setting and participants

We used purposive sampling, which selects participants who are especially knowledgeable or experienced in the area of interest, based on pre-defined criteria.[198] Inclusion criteria were that participants: (a) were qualified doctors or nurses; (b) work in a 'tier 3' CDAS in the UK; and (c) have at least 3 years of clinical experience. 'Tier 3' services provide outpatient treatment for drug and alcohol dependence, including opioid agonist therapy (methadone or buprenorphine). Potential interviewees were identified through regional policy forums, provider networks, and through snowball sampling (where an interviewee suggests another interviewee). They had the opportunity to ask researchers about the study prior to participation, and provided written consent. We aimed to include participants from a mixture of clinical roles, geographical regions, and provider types (including NHS trusts and independent charities). The recruitment period was May to December 2019 and interviews were conducted between May 2019 and March 2020.

8.3.2 Data collection

Participants were offered face-to-face or telephone interviews according to their preference. We developed a topic guide prior to the first interview, with topics including (a) clients' health and healthcare access; (b) participants' role in terms of physical healthcare; (c) barriers and enablers to better physical healthcare; and (d) 'ideal' models of physical healthcare. Interviews focused on clients who use heroin or crack cocaine. We allowed participants to discuss other topics that they felt were relevant, and updated the topic guide several times during data collection as we identified new themes.

8.3.3 Transcription, data management, and analysis

Interviews were recorded and transcribed verbatim. We used field notes taken immediately after interviews to identify emerging themes. For example, some participants discussed their relationship to other health services and professions, and we therefore asked about the importance of these relationships in subsequent interviews. After interviews were completed, we analysed transcripts using the principles of thematic analysis, following the process described by Braun and Clarke.[199] We read all transcripts several times and then used an 'open coding' process to create 293 codes, using NVivo 12. I coded half the interviews and Dr. Bradbury coded the other half, with 2 interviews double-coded and discussed to check for reliability in the coding approach. We deduplicated codes and grouped them into a framework that identified the most important themes, perceptions that were consistent across participants, and areas where participants had different perceptions.

8.3.4 Ethics and approvals

The project was approved by the UCL Research Ethics Committee on 1 April 2019 (Ref: 13275/002). In addition, the project was approved by the research committees of participants' employers, where required.

8.4 Results

8.4.1 Participants

17 individuals agreed to participate, including 4 consultant psychiatrists, 4 nurses or nurse practitioners, 1 nurse consultant, 5 GPs with a special interest in addiction medicine, 2 psychiatry specialty trainees, and 1 drug worker from a nursing background. 12 interviews were conducted face-to-face and 5 were conducted by phone. 10 participants were in London and the South-East, 2 in South-West England, 1 in North-West England, 1 in Wales and 3 in Scotland. 2 were employed by the same service and some were employed by multiple services, and in total we captured 17 separate CDAS. 13 of these services were run by the NHS, and 4 by charities. 1 participant (a GP with a special interest in addition medicine) was not currently employed by an eligible service and was excluded from analysis, leaving 16 transcripts for analysis. There were no other withdrawals from the study.

We identified 3 overarching themes: (a) physical health needs are often first identified in CDAS, but clinicians report limited success helping their clients access healthcare; (b) clinicians working in CDAS see their role as supporting access to mainstream services; and (c) clinicians working in CDAS feel isolated from other health services, and find it difficult to provide joined-up care.

8.4.2 Theme 1: physical health needs are often first identified in CDAS, but clinicians report limited success helping their clients access healthcare

All participants discussed the health needs of their clients in detail, reporting that their health is typically worse than people of the same age in the general population. In particular, several participants discussed the high prevalence of chronic respiratory problems and the lack of diagnosis and treatment. Participants said that many clients are unlikely to seek help for symptoms of physical health problems; often do not attend healthcare appointments; have difficulty getting diagnoses; and often have poor access to treatment pathways for long term conditions. Some participants also discussed the variation in healthcare access:

> We have got some service users who are very well engaged with primary care and attend regular diabetes reviews or asthma reviews or COPD reviews … Equally we have a larger majority of people whose health is quite poor and they don't engage with those services. [Nurse Consultant]

When asked where their clients seek medical care, participants said that the CDAS (i.e. their own service) and hospital A&E are often the first points of contact. Participants said that clients present to CDAS because they are open-access and non-judgmental. They emphasised the importance of building trust with their clients, and not cancelling appointments or otherwise penalising clients who do not attend. All participants described extensive barriers to healthcare for their clients, particularly relating to stigma, with one participant saying that "GPs just put up barriers because they think the main reason they come is to get hold of drugs" [GP1]. Participants felt their approach contrasted with this:

> We are here, open-door policy, friendly, no barriers. They will come again and again for physical problems. It is then up to us to get them to see the GP or to get them to go to the hospital. [Consultant Psychiatrist 2]

On identifying a physical health problem, participants would recommend that clients visit their GP, or help them make appointments, but reported that clients often did not attend:

> You can signpost people to GPs but they don't then go. Or they actually find it really hard to get appointments. So we tend to do quite a bit of ringing the surgery and booking in appointments. But that doesn't guarantee they'll go. [Drug Worker]

Most participants expressed a duty to act as health advocates for their clients. The most common examples were helping clients book GP and outpatient appointments, reading and responding to letters, and encouraging other health services to see clients at a time when the client is more likely to attend (sometimes immediately). Other examples included peer support, in which emotional and practical support is provided by trained volunteers with personal experience of using heroin or crack cocaine, and when staff at CDAS play a coordinating role in intensive healthcare interventions:

> People end up in a really bad way and everyone is really worried. An example being when they have tuberculosis or they have endocarditis ... All of a sudden specialist services realise the key to this person is the substance misuse service, because that's the place they actually attend. [GP 1]

Some elements of physical healthcare were unanimously considered 'core' to CDAS. All participants described physical health assessments for new clients and at variable intervals, and screening for blood-borne viruses (though the actual tests varied, and not all services tested for hepatitis B and HIV). The physical health assessments were often focused on the safety of opioid agonist therapy:

> It happens around the addiction if you see what I mean. It is all focused on whether they are well enough to have Subutex or methadone ... It's not about wider health issues. I mean you'd probably struggle to get them to do anything about an infected leg ulcer for example ... It's not their area of expertise, it's not an area they are comfortable with. [Nurse Practitioner 2]

8.4.3 Theme 2: clinicians working in community drug and alcohol services see their role as supporting access to mainstream services

All participants agreed that the best care is provided by mainstream GPs and hospitals, and an equivalent service could not be provided by CDAS. Participants saw their main role as supporting access to mainstream services. Participants gave 3 reasons for this. First, medical staff in CDAS are primarily from a psychiatry background:

> I'm a psychiatrist. I'm not a general practitioner. I'm way out of practice for general health, I can't do that. Apart from checking pulse and blood pressure. I'm not able to do much more than that. [Consultant Psychiatrist 4]

The complexity of clients' health needs, particularly related to liver disease, respiratory disease, and chronic infections, meant that specialist skills are often needed, beyond what could be delivered within CDAS:

> As soon as someone's liver starts failing that becomes much more complex. Anyone who is not having treatment for their HIV, the potential illness that they can have are not going to be easy to manage. So it makes sense to make sure they are supported in the specialist services. And that's what the focus is, to get them into the right services. [Nurse Practioner 2]

Second, some participants expressed their clients' right to the same health services as the general population. They said that clients want to be treated like everyone else and should have the opportunity to build relationships with their GP. One participant said provision of integrated care,

with co-located healthcare and drug and alcohol services, would mean "telling that person that you're in addiction services, and you're different" [GP 2]. Some participants felt that engaging with health services is part of 'recovery capital' (which refers to an individual's resources to reduce drug use, and achieve personal goals[200]), and provision of 'one-stop-shop' type healthcare may impede recovery:

> Initially it seemed odd to me that we couldn't do that coincidental stuff. So you turn up for your substance misuse appointment but you've run out of your asthma inhalers. Now a GP, if you turned up with your infected toenail but said can you check my [blood pressure], most GPs would see that as an opportunity ... It was initially quite difficult for me to get my head around that I couldn't do that stuff ... But I think if more of their medical care starts getting delivered from the substance misuse services to some extent we are further isolating them from normal care streams. We're not enabling them to make use of all of the services that are provided for them ... Trying to support the client into accessing regular services is probably more sustainable than simply abandoning ship and delivering everything to them in an institutional way. [GP 1]

Third, participants discussed constrained financial resources and the need to focus on providing treatment for drug dependence. They felt that additional responsibilities would not be safe and would duplicate other services. One participant discussed cuts over recent years and the difficulty of providing more holistic care:

> You have to figure out ways of focusing on the core of your business, and you need to define that, you don't have a lot of time for additional stuff ... Unless there is an injection of cash, which is very very unlikely, we are going to end up neglecting our core business to do something that someone else is supposed to be doing. [Consultant Psychiatrist 3]

Despite their efforts to advocate for their clients, all participants acknowledged that clients have poor access to NHS services. In contrast to the participants who felt that CDAS should focus on supporting better access to mainstream health services, a minority felt that CDAS should provide a 'one-stop-shop' service in which primary care is provided alongside drug treatment. These participants often focused on the needs of clients with the greatest barriers to healthcare, including those experiencing homelessness, those using a lot of illicit drugs, those with serious mental health problems, and those with no recourse to public funds. For example, one participant discussed the benefits of a previous CDAS model that offered GP appointments and wound care:

> We have a lady who is coming here who had a [deep vein thrombosis]. I could see it's flaring up. She came in and there was an ulcer which looked bad. Each time she comes in it was can you please see your GP ... I used to work in a service that had a GP clinic in there. That was really good ... People who had ulcers could have their wound dressed. They come for the drug service but they get everything in there. [Nurse Practitioner 1]

Although the majority of participants felt that integrated models of care are not desirable, most nonetheless described existing models in which some physical healthcare is provided in the CDAS in partnership with other local health services. This usually involved hepatitis C treatment. Some participants described visiting specialists running clinics at CDAS premises, which was described as 'in-reach', while others were commissioned to deliver hepatitis C treatment themselves. Some participants described other hospital outpatient services – including respiratory and gastroenterology services - that reserved clinics for CDAS clients, and CDAS staff booked appointments. These models were felt to improve accessibility, but were often temporary because they relied on specific individuals or short-term project funding.

In terms of medications, most participants were only able to prescribe opioid agonist therapy (i.e. methadone and buprenorphine), and some wanted to prescribe a wider range of medications in an opportunistic manner. Some were able to prescribe specific medications through Patient Group

Directives (template prescriptions used for patients meeting specific criteria), with participants mentioning antibiotics for skin and respiratory infections, tetanus and hepatitis B vaccinations, and long-acting reversible contraception. Perceptions about broader prescribing were mixed. One participant wanted to make simple prescriptions where they were needed, and complained that commissioners dictated the limited prescribing options. Others felt that a more general prescribing function would be undesirable because it would demand more clinical skills, would duplicate primary care, and could change their relationship with clients. They observed the difficulty that GPs sometimes encounter when negotiating prescriptions such as gabapentinoids and benzodiazepines; drugs that are often used alongside heroin and crack cocaine.

8.4.4 Theme 3: clinicians working in community drug and alcohol services feel isolated from other health services, and find it difficult to provide joined-up care

All participants felt their services were poorly funded, and some felt their funding was insufficient to provide good quality core services. Participants related cuts to their funding related to the Health and Social Care Act 2012, which led to CDAS being funded through local authorities rather than the NHS. Participants said that these cuts led to reduced staffing and a more limited scope of services:

> The previous service I used to work in, we had nurses that worked in our needle exchange service. They did full leg ulcer treatment. They did full dressings. And would see any of our clients across the service … I haven't recently in services seen quite so much of that, simply because I think most services around the county are struggling to deliver on what budget you're given. [Nurse Practitioner 4]

Many participants expressed frustration about cuts, describing them as counterproductive because they would lead to greater healthcare use in other parts of the healthcare system. Some participants felt that cuts were related to stigma towards people who use illicit drugs, with a perception that austerity in the UK had been disproportionately applied to CDAS. Participants were pessimistic about the prospects for better funding:

> The less you support people the less you help people in that situation. They become more chaotic and the more chaos means that they access services in a way that's more expensive. It's a bit counterproductive. But yeah. That's a political question. [Nurse Practitioner 2]

As well as reducing funding, participants described short 'commissioning cycles' as a barrier to investment and development of relationships with other health services:

> Why would I embark on a long and painful process of meeting with all kinds of people and writing policies and buying hardware and equipment and getting remote logins if we lose the contract next year and it will all just get scrapped? [GP 1]

Participants discussed feelings of isolation from other health services. Fragmented approaches to commissioning mean that CDAS are not able to provide holistic care for their patients, and can only refer patients to other health services. Referring to commissioning via local authorities, one participant said:

> That happened back in 2012 with the Health and Social Care Act. But it means we are only really allowed to prescribe opioid substitution medications, that's the only thing on our license … There's a lot of 'not out of my budget' approaches. The commissioner has decided that's what we can prescribe so that's it. So sometimes we see people and they need antibiotics, or they need an inhaler refill … And we can just refer them to the GP. And more often than not they don't go. [Psychiatry Specialty Registrar 1]

Most participants felt their communication with other health services was poor, describing difficulty finding out about interactions between clients and other health services. All participants felt that communication with GPs enabled better drug treatment and general physical healthcare, but most felt that this communication was partial and varied by GP surgery. Some participants, particularly those working in services not provided by the NHS, reported that these difficulties were due to incompatible computer systems or a lack of data sharing protocols.

8.5 Discussion

Key findings

Participants in this study reported that clients have extensive unmet physical health needs. They said they are sometimes their clients' only point of contact with health services, but they have limited resources to provide care beyond provision of opioid agonist therapy. Efforts to advocate for clients, such as actively pursuing referrals, have limited success. Most participants did not think that community drug and alcohol services should be responsible for physical healthcare, mostly because they do not have the skills and resources to provide care of an equivalent standard to mainstream health services.

8.5.1 Strengths and limitations

To my knowledge this is the first study of the role of CDAS in the provision of physical healthcare. The sample included participants from different clinical backgrounds and grades, different types of service provider (with a mixture of NHS and charity organisations), and different regions of the UK.

The study has 6 key limitations:

First, despite the variation within the sample, participants may have selected characteristics or perceptions compared to all clinicians working in CDAS. Participants may be particularly engaged with physical health problems, because I recruited through policy forums and networks where the general health of people who use drugs is discussed. Several participants worked in urban areas such as London, Glasgow, and Cardiff, where there are clusters of specialist health services for marginalised populations. Participants working in these areas described the benefits of referring clients to open access health services designed for people experiencing homelessness, for example. For these reasons, participants may represent CDAS that are more likely to offer integrated physical health services, and other CDAS may offer even less. Conversely, one of the peer reviewers for the published version of this study[193] said they are aware of "treatment services across the country that provide a version of the 'one-stop shop' mentioned in the paper (e.g. embedded GPs, integrated clinics)", and our sample may be unusually negative about this approach (peer reviews are publicly available here: https://bmjopen.bmj.com/content/bmjopen/11/7/e046577.reviewer-comments.pdf).

Second, the sample was small with 16 participants. I had planned to include more participants, but had to stop recruitment in March 2020 due to the COVID-19 pandemic. A larger sample may have included more diverse views.

Third, given the sampling method and qualitative methodology, the findings cannot be generalised to other clinicians or services.

Fourth, I only included qualified clinicians. This was because clinicians have an expert understanding of available healthcare interventions and potential healthcare models that might work better. Other important groups include clients of CDAS; people who use heroin and crack cocaine who do not access CDAS; non-clinical staff of CDAS such as key workers; clinical staff working in

other services such as primary care and respiratory and gastroenterology services; and CDAS commissioners in local authorities. All of these groups would add important perspectives to this study but it was not possible to include them all in the time available. Other studies have documented the healthcare experiences of people who use illicit drugs.[12,64,72] These studies emphasise structural barriers to healthcare such as stigma among staff or the need to provide an address.

Fifth, the study used a thematic analysis of semi-structured interviews and other qualitative methods may have yielded different insights into this topic. For example, an 'ethnographic' approach might involve observation of CDAS staff to understand their beliefs and values, while a 'grounded theory' approach might use qualitative data to develop a theory that explains processes such as the stigmatisation of patients who use illicit drugs.[201] Within the 5 types of qualitative enquiry described by Creswell,[201] this study fits best into the category of 'phenomenological research', as it aimed to understand the common meaning of the phenomenon "healthcare access" within a certain group of professionals.

Sixth, the study was conducted by 2 researchers who work in health services. I am a Specialty Registrar in Public Health (non-medical) and Dr. Bradbury is Foundation Year doctor working in an acute hospital that has a lot of patients who use illicit drugs. These experiences may have informed the interviewing style and analysis, and might mean that we had a prior belief in the importance of integrated and specialist models of care. A study led by researchers with different backgrounds or by peer researchers may have produced different results.

8.5.2 Interpretation and relevance for policy, practice, and research

Participants had different perceptions of the appropriate role of CDAS in terms of physical healthcare. Most felt that CDAS are not an appropriate place for physical healthcare to be delivered. Many nonetheless provided some elements of physical healthcare. The most common example was treatment for hepatitis C, with other examples including wound care, contraception, and tetanus vaccinations. Where physical healthcare was integrated into CDAS, it appeared to be focused 'public health problems', meaning health problems that may affect wider communities, such as infectious diseases. It may also reflect the commissioning arrangements of CDAS in England, which are funded via public health teams in local authorities.

Participants had different opinions about the desirability of a 'one-stop-shop' approach to healthcare for people who use illicit opioids. A minority of felt that clients would be best supported by a this approach, and these participants tended to focus on the needs of clients with the greatest barriers to healthcare, such as those experiencing homelessness. All participants felt the 'one-stop-shop' model is unrealistic in the current funding and policy environment in the UK. Such models have been developed in some countries for populations including people who use drugs, people living with HIV, and people experiencing homelessness.[178,202–204] A small number of studies in the US have evaluated integrated community drug dependence and primary care services.[180,182,205] The results suggest that such integrated models could reduce hospital utilisation and use of illicit drugs, but did not find evidence of a change in health outcomes (see Chapter 7 for further discussion of these studies). The effectiveness of these models is likely to be highly dependent on local healthcare systems, funding, and implementation.

Participants recognise the poor management of physical health problems for their clients. This is leading to emergency healthcare use, poor health outcomes, and sometimes worse outcomes of drug treatment because clients "self-medicate" or are too unwell to attend appointments with their key worker. There was strong recognition that current health services are not meeting clients' needs. Despite this, the results suggest a professional view that we should make clients fit into existing systems for treating physical health problems rather than develop new models around these specific needs. This perspective appears to conflict with evidence that accessible services for 'inclusion health' groups (i.e. groups that experience social marginalisation and have high barriers to healthcare, such as people who are homeless, in prison, or dependent on illicit drugs) should be open-access, available at the first-point-of-contact, and staffed by people aware of the traumatic experiences that are common in these populations.[206]

All participants in our study discussed financial cuts to their services. Cuts are difficult to measure but were estimated at 30% across CDAS on average between 2012 and 2015, with further cuts planned.[207] These cuts were highlighted in a recent government-sponsored review,[7] which said that "a prolonged shortage of funding has resulted in a loss of skills, expertise and capacity from this sector," that it is likely "many areas are now offering the bare minimum service with large increases in worker caseloads," and that cuts have resulted "in what are seen as 'nice-to-haves' being cut." These 'nice-to-haves' include interventions related to physical health, such as nurse-led wound clinics. Services that are most accessible to people who use illicit opioids, including CDAS, do not have the funding, skills, or mandate to address holistic health needs. They have been heavily affected by financial cuts in local government. As commissioners are based in local government rather than the NHS, they have limited incentive to develop models that might prevent emergency healthcare use. Potential solutions could include commissioning led jointly by local authorities and the NHS, and models of physical care that are codesigned by clients, drug treatment providers, and primary care.

8.5.3 Conclusion

This study adds to existing evidence that people who use heroin and crack cocaine have unmet health needs. It shows that clinicians working in CDAS recognise this problem and act as health advocates for their clients, but report limited success. Participants had different opinions about the best approach to improving healthcare access, but all agreed that more staff and financial resources are needed.

Linking statement

Clinicians participating in this qualitative research said that health services need to be more accessible for people who use illicit drugs. Designing these improvements will require an understanding of the relative importance of health problems and the quality of care currently experienced by people who use drugs. In the next chapter, I will describe how I used electronic health records to develop cohorts that address these questions.

9 Development and validation of 3 cohorts of people who use heroin and crack cocaine, using electronic health records in England

9.1 Summary

Background: Research into the health of people who use illicit opioids has focused on "drug-related" health outcomes such as overdose and blood-borne viral infections. I used electronic health records to develop and validate 3 cohorts that enable research into more holistic health outcomes in this population.

Methods: The 3 cohorts were derived from the Clinical Practice Research Datalink (CPRD) Aurum, CPRD Gold, and the Clinical Records Interactive Search resource at South London and Maudsley NHS Foundation Trust (SLaM). Individuals who use illicit opioids in CPRD were identified using prescriptions of opioid agonist therapy (methadone or buprenorphine) or clinical observations such as "heroin dependence". Individuals in SLaM were included if they had an episode of community-based treatment for heroin or crack cocaine dependence. Dates of death in all 3 cohorts were available via linkage to the Office for National Statistics mortality database. As a method of external validation, I compared characteristics and mortality rates to other samples of this population. As a method of internal validation of the CPRD cohorts, I identified all CPRD participants who were admitted to hospital and discharged with a diagnosis of 'mental and behavioural disorders due to opioid dependence', and checked how many were included in the cohort.

Results: The CPRD Aurum cohort included 82,241 individuals, CPRD Gold included 24,548, and SLaM included 7,286. The cohorts had characteristics expected of people who use illicit opioids in the UK, including the majority being male (69%, 69% and 74% in CPRD Aurum, CPRD Gold, and SLaM respectively), increasing average age of people joining the cohort over time, high prevalence of current tobacco smoking (79% and 76% in CPRD Aurum and Gold), and mortality rates much higher than the general population. Standardised mortality ratios were 7.7 (95% CI 7.4-8.0), 7.7 (95% CI 7.4-8.0), and 7.4 (95% CI 6.9-8.0) in CPRD Aurum, CPRD Gold, and SLaM respectively; similar to other studies of all-cause mortality in this population. Among all patients discharged from hospital with a diagnosis of opioid dependence, 88% in CPRD Aurum and 89% in CPRD Gold were included in the cohorts, and in most cases opioid use was recorded in primary care data before hospitals. This may suggest good sensitivity in terms of more severe opioid use, thought the cohorts may still exclude people with less severe opioid use.

Conclusion: The 3 cohorts together provide many opportunities to study the health and healthcare use of this population. The validation showed that the cohorts have the expected characteristics, though selection biases may still be important depending on the research question.

A description and validation of the cohorts derived from CPRD data is published in the journal Wellcome Open Research.[208] For the SLaM cohort, I have published an overview of mortality and hospital admissions[39] and a case-study of the incidence and treatment costs of severe bacterial infections,[209] both in the journal Drug and Alcohol Dependence.

9.2 Introduction

Epidemiological studies of people who use illicit drugs can be challenging for 3 reasons.

First, there is the difficulty of creating a sample frame. There are no community registers of people who use illicit drugs (partly because drug use is criminalised in many countries). Some studies recruit participants from the community and then use active follow-up (i.e. they contact participants at regular intervals to collect longitudinal data). For example, the MIX study in Melbourne recruited 688 people who inject drugs through street outreach and snowball sampling, and conducts annual follow-up interviews.[111] Similarly, the VIDUS study in Vancouver recruited 2,700 people who inject drugs through street outreach, and interviews participants twice each year.[210] This 'street outreach' approach can capture people who do not use public services, and interviews can capture bespoke information. However, these methods still have selection biases. For example, MIX initially aimed to recruit people not engaged in opioid agonist therapy (OAT), but found this difficult and therefore allowed participants currently on OAT. Due to resource-intensity the sample sizes are limited. Other studies recruit participants from drug treatment or harm reduction services. This is the most common approach to studying this population, and in a recent systematic review of mortality rates among people who use 'extramedical opioids', 57/99 studies recruited participants from these settings.[211] These studies may exclude people who have less problematic drug use and therefore do not need treatment, as well as people who are more 'chaotic' and do not use services. Other common recruitment settings include prisons and A&E departments, which have other selection biases.

Second, drug use varies over time and is difficult to record accurately. Longitudinal surveys address this by repeatedly asking participants about drug use. Other studies often rely on baseline measurements and ignore changes over time.

Third, there is the difficulty of attrition during follow-up. In the MIX study, 71% of participants attended the 12 month interview, with greater attrition in later years. Studies that use data linkage often rely on single-site or sub-national databases,[51,120,212] which may mean that a large proportion of outcomes are missed given the mobility of this population.

Given these difficulties, it is likely that all studies of this population will suffer from important biases. This chapter shows how I developed 3 new cohorts of people who use illicit drugs in the UK, addressing some of the limitations of existing research. In particular, the cohorts include people who have never been in drug treatment, allow research into a wide range of health outcomes, and use high-quality data linkage with national hospital and mortality databases to minimise loss-to-follow-up. The 3 cohorts are derived from the Clinical Practice Research Datalink (CPRD) Aurum, CPRD Gold, and from the Clinical Records Interactive Search resource at South London and Maudsley NHS Foundation Trust.

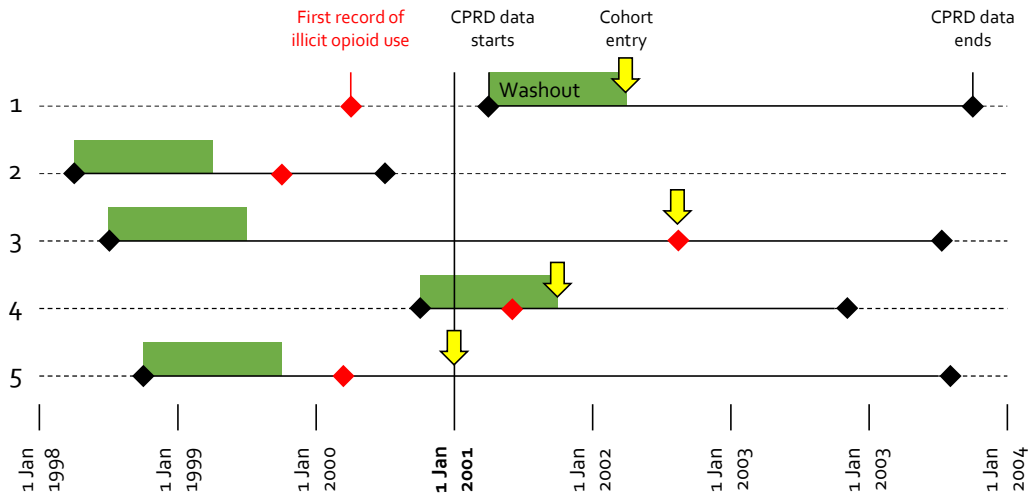
9.3 Methods

9.3.1 Selection of participants: Clinical Practice Research Datalink Aurum and Gold

Data sources. CPRD Aurum and Gold are databases of anonymised electronic health records from primary care, including approximately 13% and 8% of the populations in the UK and England respectively.[213,214] Although the databases include similar clinical information, they differ in terms of data collection software, clinical classification system and geographical coverage. CPRD Gold includes data from GP practices throughout the UK, while CPRD Aurum initially included England only, and more recently practices in Northern Ireland have been added. To maximise comparability I have restricted the cohort to patients registered in England.

Entry and exit dates. I selected patients who were registered at participating GP practices between 1 January 1997 and 31 December 2018 for Gold, and between 1 January 1997 and 31 March 2020 for Aurum. Cohort entry was defined as the latest of (a) 1 January 2001 (because deaths before 1 January 2001 used the ICD-9 classification which makes direct comparisons over time more difficult), (b) 12 months after the first date when good quality data were available for that patient (see description of this 12-month 'washout' period in section 9.3.6), and (c) the date of the first code indicating illicit opioid use. Cohort exit was the earliest of (a) the date when the patient stopped being observed ('last collection date') or participating in CPRD (the patient transferred out of a participating GP practice), (b) death, (c) 30 October 2018, 6 months before the last date when mortality data was available. In addition to these criteria, I excluded patients who were aged under 18 or 65 or older at cohort entry. These individuals are excluded because records of opioid use in children and older people are likely to have a lower predictive value for illicit opioid use, and may instead represent medical opioid use.

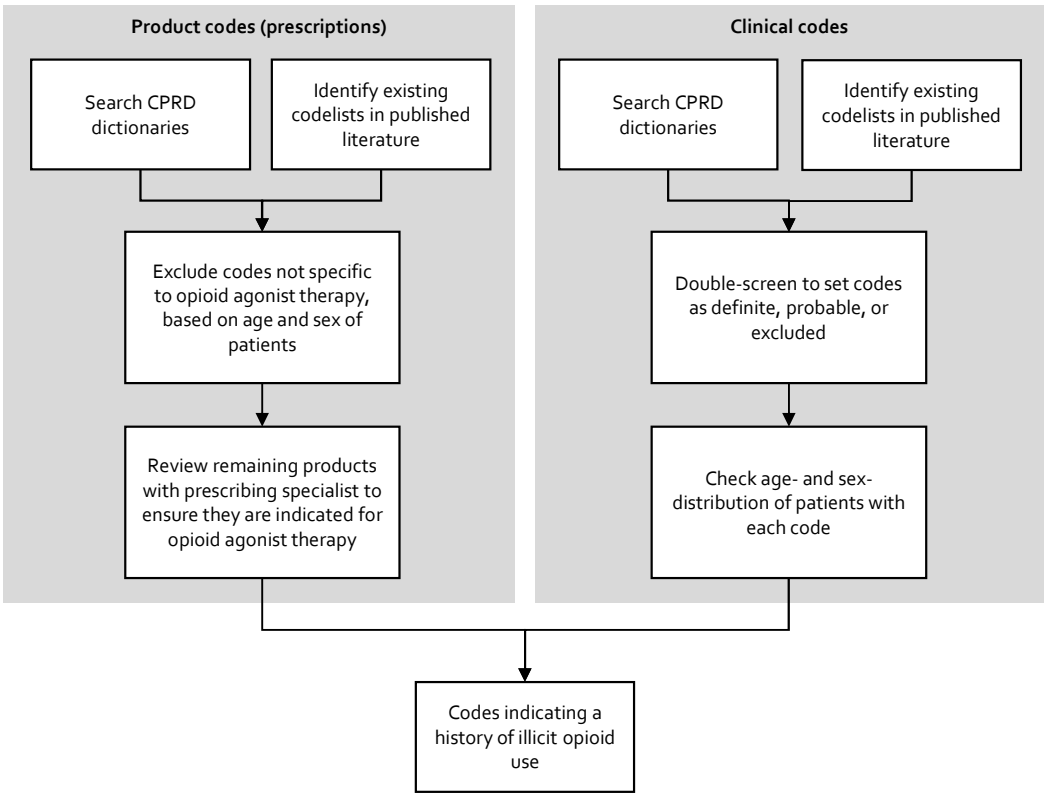
Figure 12: Cohort entry dates for participants in the Clinical Practice Research Datalink (CPRD) with records of illicit opioid use



Participants enter the cohort at the latest of 1 January 2001, 12 months after the earliest date when good quality data is available in CPRD, and the first record of illicit opioid use. In this diagram, participant 2 is excluded because they exit CPRD before 1 January 2001. Participants 1, 4, and 5 are examples of participants with 'prevalent' opioid use (i.e. the first record of illicit opioid use occurs before cohort entry), while participant 3 is an example of a participant with 'incident' opioid use. The majority of participants join on the first record of illicit opioid use, like participant 3.

Selection of patients with a history of illicit opioid use. I focused on patients with a history of opioid use (rather than specifically current use) due to the typically long duration of opioid use[5,6] and the likelihood that patients would not have regularly recorded opioid use. I therefore did not exclude patients with illicit opioid use recorded prior to the cohort entry date, and these patients entered the cohort at the latest of 1 January 2001 and the end of their washout period (Figure 12). CPRD data include 2 main types of codes: product codes and clinical codes. Product codes indicate a prescription made in a primary care setting, whilst clinical codes indicate a diagnosis or other clinical observation (sometimes also a prescription). I selected patients by identifying product codes indicating a prescription of OAT and clinical codes indicating a history of illicit opioid use, such as 'heroin dependence' (see published article for a full list of codes[208]). I prioritised specificity over sensitivity, aiming to use codes that are only applied to the target population. Figure 13 summarises the process for selecting codes.

Figure 13: Selection of codes that indicate a history of illicit opioid use in the Clinical Practice Research Datalink



CPRD – Clinical Practice Research Datalink

Product codes. In the UK, treatment for opioid dependence involves the prescription of methadone or buprenorphine.[215] However, these medications are also licensed for other indications including pain and palliative cough.[216,217] I therefore developed a method to identify medications that are specific to OAT. I searched CPRD dictionaries to identify all methadone and buprenorphine product codes (full search terms are given in the published article[208]). I then followed a 2-step process to identify products that are specific to OAT. First, I described the age- and sex-distribution of patients at the time of the first prescription. Data from specialist drug treatment services shows that the population receiving OAT is three-quarters male and predominantly aged 18–64.[23] In contrast, the population prescribed opioids for pain relief is mainly older and female.[218] I therefore excluded medications where more than half of patients were female, the lower quartile of age was younger than 18 years, or the upper quartile of age was older than 64, as these codes are unlikely to relate specifically to OAT. Second, two prescribing professionals working in a community drug and alcohol service reviewed remaining products to check they are used for OAT.

Clinical codes. CPRD Gold uses Read codes whilst Aurum uses SNOMED codes. I used keywords to search CPRD dictionaries to find Read and SNOMED clinical codes that may indicate illicit opioid use (methadone; buprenorphine; abus*; addict; dependen*; drug user; heroin; inject; misus*; opiate; opioid; overdose). 2 researchers (me and Dr. Prianka Padmanathan, a psychiatry registrar) screened the codes for relevance, with conflicts resolved through discussion. We excluded codes describing prescriptions, tests, or adverse reactions to methadone or buprenorphine where the indication was

unclear. After agreeing a list of codes, we checked the age- and sex-distribution of patients with these codes in the same way as for the product codes.

9.3.2 Selection of participants: Clinical Records Interactive Search at South London and Maudsley NHS Foundation Trust

Data source. The Clinical Records Interactive Search (CRIS) resource at the South London and Maudsley NHS Foundation Trust is a research repository of anonymised data derived from the trust's electronic health record system.[219] The NHS trust is a mental healthcare provider that delivers inpatent and outpatient services, including community drug and alcohol services in some London boroughs. CRIS was established in 2008 and includes structured and free-text records, as well as individual-level linkage to national databases including Hospital Episode Statistics and ONS mortality data.

Entry and exit dates. Cohort entry was defined as the latest of: (a) 1 April 2006, when clinical records at SLaM became fully electronic and data in CRIS is considered reasonably complete; (b) the participant's 18th birthday, (c) the first date of entry into treatment for heroin or crack cocaine dependence. Cohort exit was defined as the earliest of: (a) 2 July 2019; 6 months before the last date when mortality data is available, (b) death.

Selection of patients who use heroin or crack cocaine. Specialist community drug treatment services in England complete a standard form each time a patient starts a treatment episode, and at regular intervals during treatment. This form is called a 'Treatment Outcomes Profile' (TOP) form and includes information about recent drug use, injecting behaviour, criminal activity, and employment and social wellbeing. All information from the TOP form is captured in CRIS. The cohort includes all patients who reported use of "opiate/opioids (illicit)" or "crack".

9.3.3 External validation

I validated the cohorts by comparing them to other samples of people who use illicit opioids. I anticipated the following characteristics:

a) the average age of patients entering the cohort would increase over time, as the cohort of people who use illicit opioids in England is ageing;[24]

b) high prevalence of smoking, with a systematic review finding an average of 84% of people enrolled in addiction services currently smoke;[220] and 70% of patients starting treatment for opioid dependence in England in 2019/20 recorded as current tobacco smokers.[23] For HUPIO, I reported the prevalence of current- and ex-smoking based on existing codelists for smoking histories.[221]

c) disproportionate representation of patients living in more deprived areas, as illicit opioid use and opioid-related deaths are consistently associated with deprivation;[8,9]

d) higher mortality rates than the general population, as studies of mortality in this population consistently show very high mortality rates.[33] I compared the standardised mortality ratios (SMR) for to those reported in existing studies of all-cause mortality among people who use illicit opioids in the UK.

In addition to these characteristics, I reported the proportion of patients with recorded histories of homelessness, prison, and alcohol dependence, based on existing phenotypes[222,223] and searches of clinical codes. I expected these experiences to be common among people with a history of illicit opioid use.[224] However, I did not know how consistently these experiences would be recorded in the datasets, and therefore did not use these variables for validation purposes.

9.3.4 Internal validation of HUPIO (comparison of primary care and hospital data)

HUPIO participants were identified using primary care records that show prescriptions of opioid agonist therapy or clinical observations such as 'heroin dependence'. As well as primary care data, CPRD includes hospital data, and hospital patients may receive diagnoses of opioid dependence either as a primary reason for admission (such as when patients are admitted for detoxification or management of severe opioid withdrawal) or as a secondary observation when patients are admitted for another reason. I decided not to include hospital diagnoses in the cohort definition because these patients are likely to be unusual in terms of health and healthcare use (as some would start follow-up at a hospital admission), but they provide an opportunity to validate the phenotype. I assessed the sensitivity of the HUPIO phenotype by selecting all patients in CPRD with a hospital diagnosis of 'mental and behavioural disorders due to use of opioids' (ICD-10 F11) and reported the proportion included in the HUPIO cohorts. I also reported whether the first primary care record of illicit opioid use was before the first hospital admission where opioid dependence was recorded, in the 30 days after this admission, or later. This was to test whether patients are captured in HUPIO independently of hospital records, or as a result of hospital treatment (e.g. from discharge summaries sent to GPs).

9.3.5 Capturing opioid dependence in hospital data

Previous research has used hospital admissions with a primary diagnosis of bacterial infections and a secondary diagnosis of 'mental and behavioural disorders due to opioids' (ICD-10 F11) to monitor time trends in injecting-related infections.[225,226] I reported the proportion of hospital admissions among HUPIO participants where the diagnosis F11 was recorded, stratified by the primary cause of admission. The primary cause of admission was grouped by ICD-10 chapter, with bacterial infections (defined as cutaneous abscess L02*, cellulitis L03*, and phlebitis or thrombophlebitis I80*, endocarditis I011, I39*, I330, 1400, I410, septicemia A40*, A41*, osteomyelitis or septic arthritis M86*, M00*, M465, or necrotizing fasciitis M762) and drug poisonings (defined as T39-44, X60-64, X85, Y10-14) in separate groups.

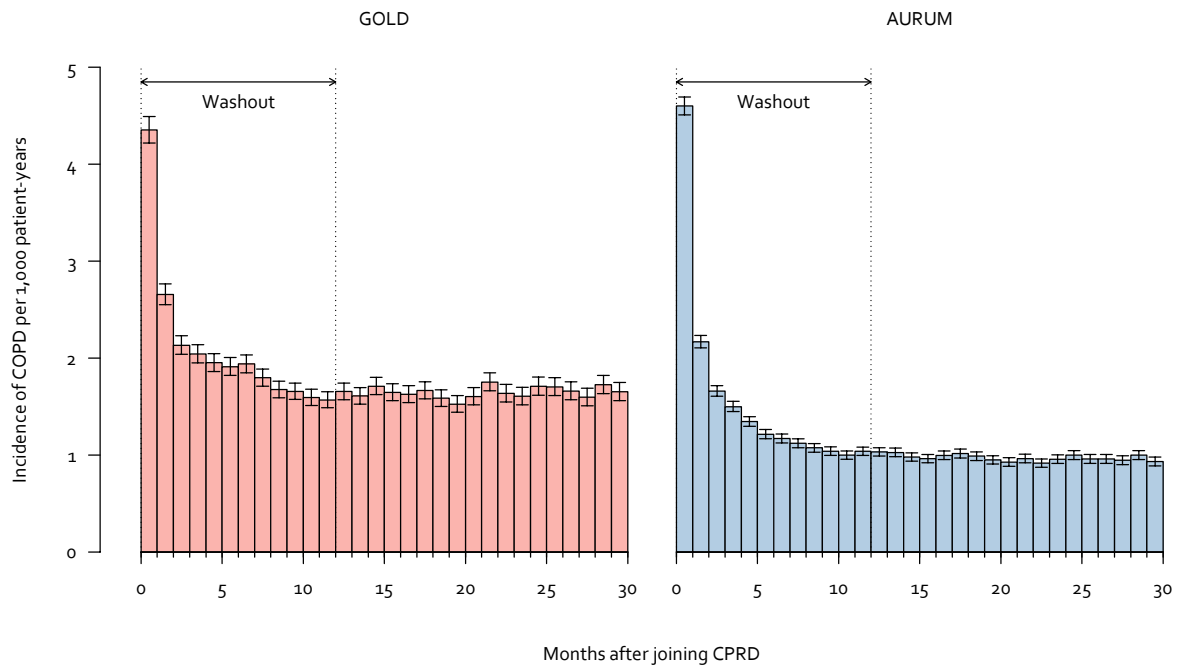
9.3.6 General population comparison groups

Some of the planned analyses of these 2 cohorts require comparison with the general population. Different data is available in each database, which informs the design of comparison groups.

CPRD includes patients registered at GP practices. Those without a history of illicit opioid use provide a comparison group. An important feature of the cohort is that the "exposed" group enters the cohort when their history of illicit opioid use is first observed. This is unlikely to be the date when they first started using opioids (rather it is the date when it was first recorded by their GP), but the date is independent of the date they join CPRD. By contrast, the comparison group does not have an obvious cohort entry date. The date when patients first join CPRD is a problematic cohort entry date

for 2 reasons. First, the date of joining CPRD is likely to be the date when a patient joins a GP practice, and records may be transferred from a previous practice and assigned the date of transfer rather than the date when the event occurred. Second, a patient may join a practice when they are unwell and want to see a GP. Previous research has observed that many diseases have unusually high incidence shortly after joining a research database.[227] Figure 14 shows the incidence of COPD in CPRD Gold and Aurum, stratified by time period after joining the database, using data supplied by CPRD for the generation of the HUPIO cohort. The high incidence of COPD in the months after joining CPRD likely to be an artefact.

Figure 14: 'Lewis' plot of COPD incidence in CPRD Gold and Aurum. Error bars are 95% confidence intervals



COPD – chronic obstructive pulmonary disease
CPRD – Clinical Practice Research Datalink

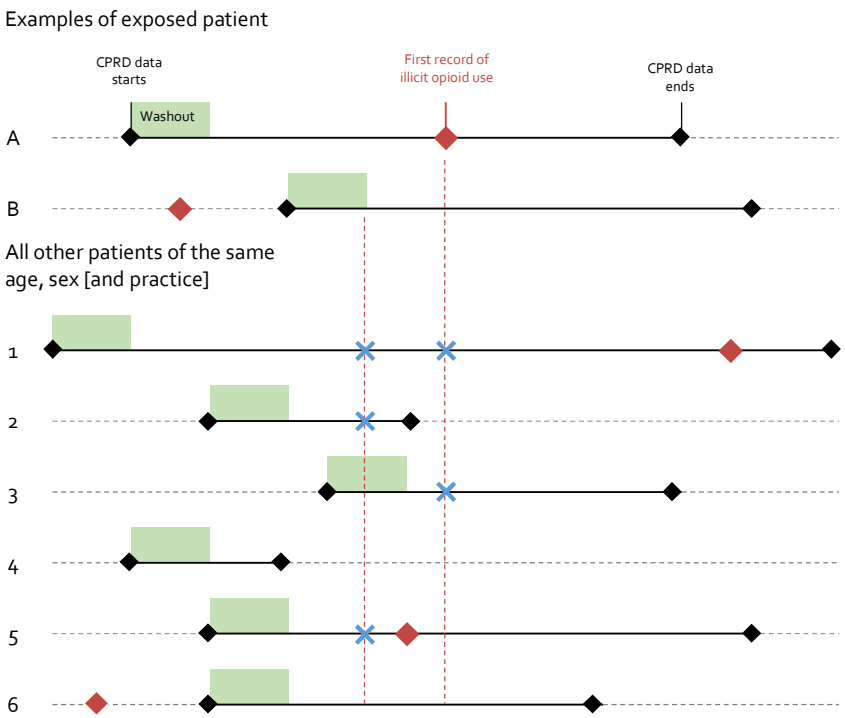
To provide the comparison group with a cohort entry date that is independent of the CPRD start date, each member of the HUPIO cohort was matched with 3 patients without a history of illicit opioid use, and the matched patients were assigned the same cohort entry date. To avoid 'conditioning on the future', the matched patients are sampled from the population that is unexposed at the time of cohort entry (rather than participants who never use opioids), and may later become exposed. Selecting a comparison group from participants who have no records of illicit opioid use at any time could mean that (a) the comparison group is not representative of the whole sample; and (b) the comparison group is biased towards participants with shorter follow-up (since these participants are less likely to opioid use recorded after cohort entry). The issue of 'conditioning on the future' is relatively minor in comparison to the cohort entry date, because the exposure is rare. The design is called 'exposure density sampling'.[228] It is comparable to the more commonly-used 'incidence density sampling' design used in nested case-control studies, but is intended for cohort studies where participants are selected on exposure status rather than caseness. As well as matching on cohort entry date, the comparison group was matched on age (within 3 years), sex, and GP

practice. Although not essential, matching on these additional factors improves the efficiency of the analysis as an unmatched comparison group would be much older, a greater proportion would be female, and less deprived. If matching did not include these factors, adjusted analysis would put a lot of weight on comparators who are young, male, and live in deprived areas. Matching on GP practice also helps to control for differences in clinical practice.

In addition to giving participants matched cohort entry dates, a "washout" period of 12 months was used to avoid the unusual data on joining the database. The washout period means that participants' earliest possible entry date is 12 months after joining CPRD.

Figure 15 provides an illustration of the matching process.

Figure 15: Exposure density sampling to create a comparison group of patients without a history of illicit opioid use. Blue crosses represent potential matches from which the unexposed group is sampled



In this figure, participant A joins the cohort when they first use illicit opioids. Participant B has a record of illicit opioid use prior to joining CPRD. The cohort is designed to capture people with a history of illicit opioid use (rather than new opioid use) and therefore participant B is included. They enter the cohort after the washout period, and are matched with patients of the same age and sex who are unexposed on that day. Participant 1 may be matched to both participants A and B, and may therefore be duplicated in the comparison group. Participant 5 may be matched to participant B because they are unexposed at the time when participant B joins the cohort, but will be censored or change exposure status at their first record of illicit opioid use and therefore is not available to be matched with participant A.

SLaM data include people who have used mental health services. There is therefore no 'general population' group in this dataset. It would be possible to compare people in treatment for heroin and crack cocaine dependence with people who use other mental health services, but this comparison would be difficult to interpret because the comparison group would have specific health needs. Therefore, a matched comparison group similar to the HUPIO comparison group could not be created. Instead, age- and sex-specific rates of hospital admission and death in the general population are used to estimate standardised ratios. This approach is more limited, and modelling

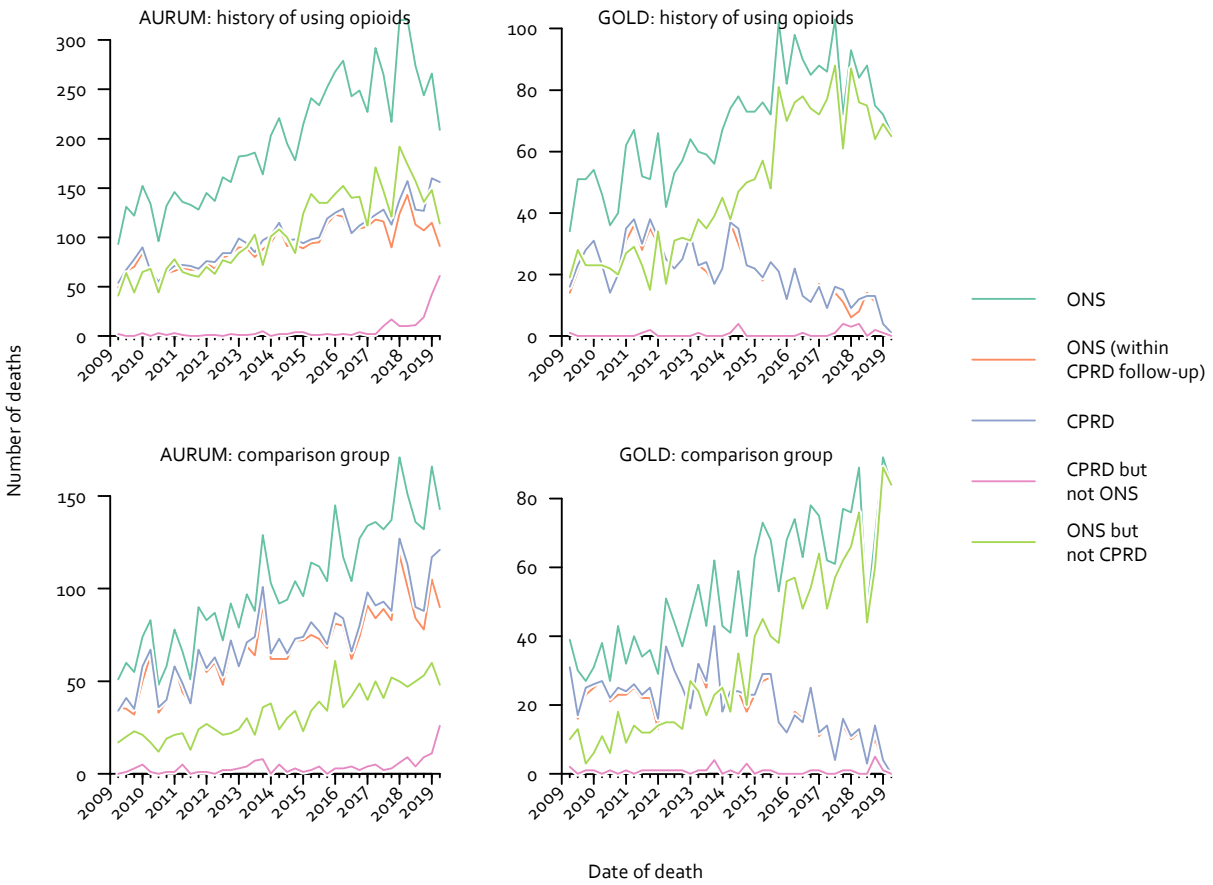
approaches that compare exposed and unexposed groups using individual-level data, such as Cox proportional hazards regression, are not possible. The SLaM database does include hospital admissions and deaths for people living in South London (including those who have not used any mental health services), and these data can be combined with publicly available population estimates to create cause-specific reference rates. To calculate mortality reference rates, I requested mortality data from the Office for National Statistics giving the count of deaths by year of death, underlying cause, sex, and single-year-of-age for people resident in London between 2001 and 2019.[229]

9.3.7 Sources of mortality data

For both CPRD and SLaM datasets, NHS Digital do deterministic linkage to ONS mortality data using NHS number, sex, date of birth, and postcode.[219,230] For CPRD, linked mortality data were available for deaths registered on or before 1 May 2019, and for SLaM data were available for deaths registered on or before 30 December 2019.

CPRD also includes all-cause mortality data recorded in primary care. This data sometimes differs from linked ONS data. In particular, deaths are only recorded in CPRD during follow-up within CPRD (or sometimes shortly after the end of follow-up, making mortality rates difficult to estimate using these data). A large proportion of deaths captured by linked ONS data are not captured in CPRD, as many deaths occur after the end of CPRD follow-up. In addition, a small number of deaths captured in CPRD are not captured in ONS. For example, in our study population, 1,341/10,385 (13%) deaths were recorded in primary care data within CPRD Aurum but were not captured by ONS. Figure 16 shows that these deaths are concentrated in the final months of follow-up. They are likely to represent delays to death registration, for example because a coroner is involved. There are few such deaths in CPRD Gold because there are few participants remaining in the database in recent months. To minimise bias resulting from delays to registration, I censored analyses 6 months before the final linkage date, i.e. 30 October 2018 for CPRD and 2 July 2019 for SLaM.

Figure 16: Number of deaths captured by linked ONS mortality records and in CPRD primary care data by quarter, 2009-2019



9.3.8 Estimation of mortality rates and standardised ratios

In both cohorts, I calculated mortality rates among people who use illicit drugs by (a) calculating the duration of follow-up in the cohort, stratified by sex, single-year-of-age, and calendar year. I accounted for ageing by expanding follow-up for each participant into days, and summarising the number of days by sex, single-year-of-age and calendar year; (b) applying mortality rates in the HUPIO comparison groups (for the HUPIO cohorts) or the general population of London[229] (for SLaM) to these strata to calculate a number of expected deaths; (c) I estimated the standardised mortality ratio by dividing the number of observed deaths by expected deaths. I calculated 95% by assuming a Poisson distribution in the number of observed deaths.

9.3.9 Ethics and approvals

The analysis of CPRD was approved by the MHRA (UK) Independent Scientific Advisory Committee and 19_142R, under Section 251 (NHS Social Care Act 2006). These approvals also apply to the analyses reported in Chapters 10 and Chapter 11. This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare

products Regulatory Agency. Hospital Episode Statistics data is Copyright © 2021, re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

This study was carried out as part of the CALIBER © resource (https://www.ucl.ac.uk/health-informatics/caliber and https://www.caliberresearch.org/). CALIBER, led from the UCL Institute of Health Informatics, is a research resource providing validated electronic health record phenotyping algorithms and tools for national structured data sources.

The SLaM dataset was approved as an anonymised dataset for secondary analyses by the Oxfordshire Research Ethics Committee C (reference number: 08/H0606/71+5). This analysis (and analyses in subsequent sections of this report) was approved by the South London and Maudsley NHS Foundation Trust Biomedical Research Centre CRIS Oversight Committee (reference number: 17–073).

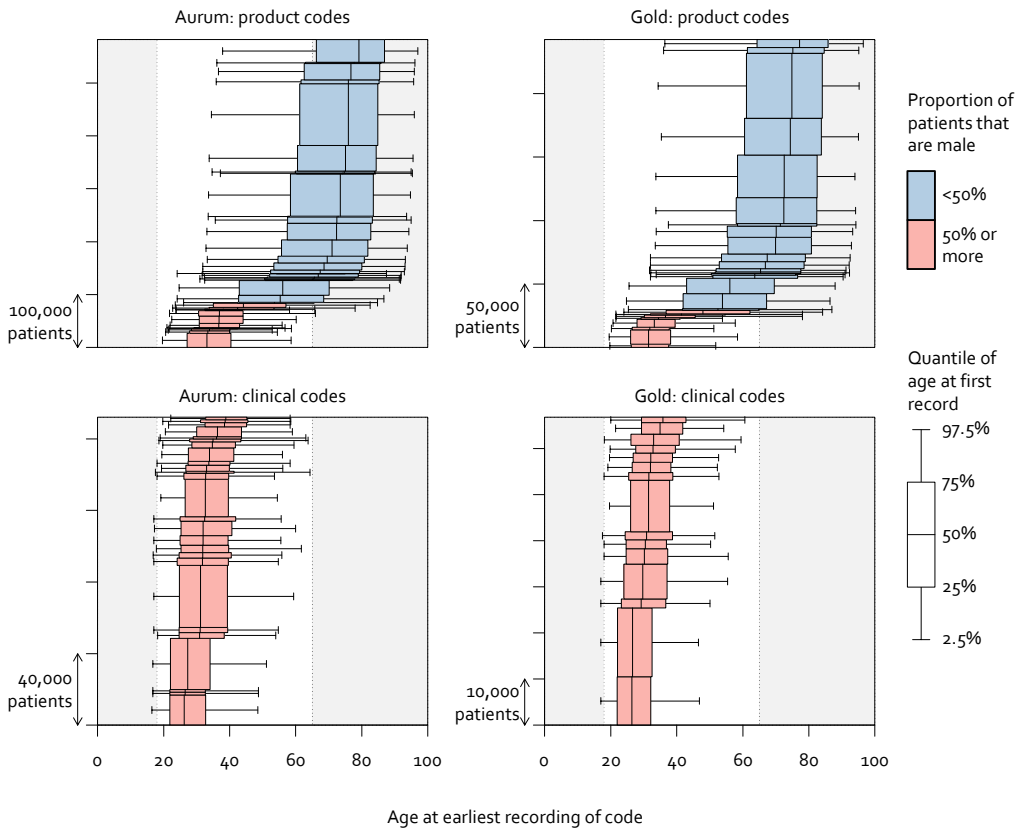
9.4 Results

9.4.1 CPRD codes identifying illicit opioid use

Based on keyword searches for codes relating to prescriptions of methadone and buprenophine, I found 175 codes in CPRD Gold and 136 codes in CPRD Aurum. The age and sex distribution of patients prescribed these medicines fell into 2 distinct groups: those mainly prescribed to younger men, and those mainly prescribed to older women (Figure 17). Codes excluded based on the age and sex distribution were mostly transdermal buprenorphine patches, which are not indicated for OAT. The 2 prescribing professionals confirmed that all remaining codes are used to OAT.

Based on keyword searches of clinical codes, I found 1,098 Read codes (for CPRD Gold) and 1,800 SNOMED codes (for CPRD Aurum). After independently reviewing these codes, we agreed that 71/1,098 Read codes and 154/1,800 SNOMED codes indicated a history of using illicit opioids. A small number of codes were either prescribed to a majority of female patients or had an upper quartile of age older than 64. All of these codes represented dependence on medications prescribed for analgesia (for example 'misuse of Codeine tablets'), which were excluded.

Figure 17: Age and sex distribution of CPRD codes that may indicate a history of illicit opioid use (only codes recorded for more than 1,000 patients are shown)



Each box is a code. Codes where the lower quartile was younger than 18 or the upper quartile was older than 64 were excluded. Colour represents sex distribution. Codes where less than half of patients were male were excludes. The figure shows that product codes (representing prescriptions of methadone or buprenorphine) fell into two groups: those prescribed mostly to younger men (assumed to be OAT) and those mostly prescribed to older women (assumed to for pain relief).

The final codelist is available in the published article[208] and via the CALIBER portal (https://portal.caliberresearch.org/phenotypes/lewer-hupio-mzxe2uzxdzvybsabtjbhrk). I called the cohort of people identified by this cohort 'HUPIO' (healthcare use by people who use illicit opioids). Examples of codes used to identify patients with a history of illicit opioid use are shown in Table 7.

Table 7: Codes that indicate a history of using illicit opioids: top 10 in CPRD Aurum and CPRD Gold

Database	Rank*	Type	SNOMED / Read code	Description	Individuals in cohort
Aurum	1	Medcode	44291000006113	Opioid type drug dependence	33,993
	2	Medcode	346947018	Heroin dependence	28,223
	3	Prodcode	888541000033115	Methadone 1mg/ml oral solution	26,288
	4	Medcode	630131000006118	Drug addictn therap-methadone	20,852
	5	Medcode	388831000006113	[X]Heroin addiction	16,711
	6	Prodcode	2003041000033115	Methadone 1mg/ml oral solution sugar free	13,547
	7	Prodcode	1835341000033111	Buprenorphine 2mg sublingual tablets sugar free	9,659
	8	Medcode	295157010	Opioid drug dependence NOS	7,794
	9	Prodcode	1835441000033117	Buprenorphine 8mg sublingual tablets sugar free	7,771
	10	Medcode	346949015	Methadone dependence	7,425
Gold	1	Medcode	689	Heroin dependence	11,319
	2	Medcode	4564	[X]Heroin addiction	7,715
	3	Prodcode	2952	Methadone 1mg/ml oral solution	6,606
	4	Medcode	6111	Drug addictn therap-methadone	5,952
	5	Medcode	16243	Opioid type drug dependence	5,038
	6	Prodcode	9728	Methadone 1mg/ml oral solution sugar free	3,073
	7	Medcode	10538	[X]Drug addiction - opioids	2,295
	8	Prodcode	10077	Subutex 2mg sublingual tablets (Indivior UK Ltd)	2,164
	9	Prodcode	6210	Subutex 8mg sublingual tablets (Indivior UK Ltd)	1,717
	10	Medcode	16374	Methadone dependence	1,645

* Ordered by the number of CPRD participants with each code.

9.4.2 Characteristics of cohort participants

The CPRD Aurum cohort included 82,241 individuals with a history of using illicit opioids, the CPRD Gold cohort included 24,548, and the SLaM cohort included 7,286. The derivation of the 2 CPRD cohorts is shown in Figure 18. The main reason for excluding individuals with records of illicit opioid use was that linked external data was not available (27,274/117,720, 23.6% of participants in CPRD Aurum; and 22,973/47,874, 48.0% of participants in CPRD Gold). The availability of linked data is primarily determined at practice-level rather than individual-level, and in the majority of practices either 0% or 100% of patients had linked data (Figure 19). Participants excluded on this basis were similar to other participants in terms of age, sex, and date of cohort entry (results not shown).

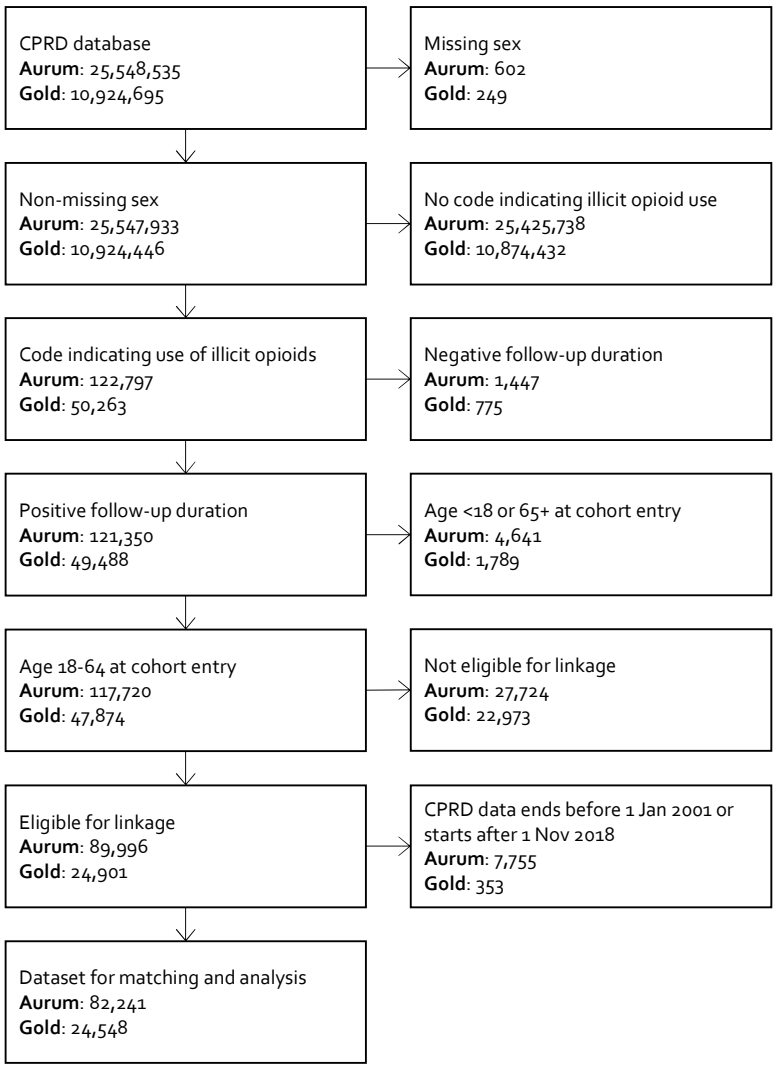
The median ages at cohort entry were 35.3, 34.3, and 37.0 respectively in CPRD Aurum, CPRD Gold and SLaM. When stratified by date, the median age of patients entering the cohorts was similar. The older average ages in Aurum and SLaM is explained by patients entering the cohort at later dates

than in Gold, and the increasing average age of the population. shows the increasing average age of participants.

Approximately 70% of participants in all 3 cohorts were male; similar to 72% of patients in opioid agonist treatment in England in 2018,[23] and 72% of participants in the Unlinked Anonymous Monitoring Survey of People who Inject Drugs.[45] In CPRD Aurum, the only cohort for which deprivation data was available at the time of analysis, there was a clear association between deprivation and a history of opioid use, with over 40% of patients living in the most deprived quintile of neighbourhoods.

In the CPRD cohorts, approximately three-quarters of patients were current smokers (at the most recent record of smoking) and a further 10% were ex-smokers. Table 8 shows characteristics of participants at cohort entry.

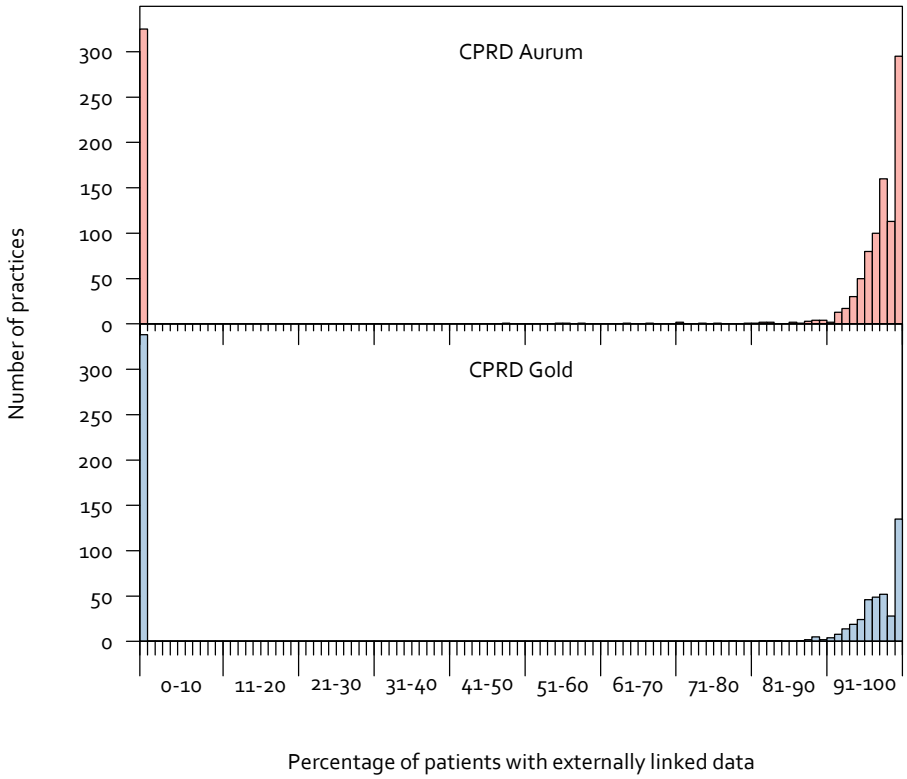
Figure 18: Derivation of eligible cohorts in CPRD Aurum and CPRD Gold



CPRD = Clinical Practice Research Datalink

'Negative follow-up' occurs when the participant exits CPRD before they are eligible to join the cohort. This is most commonly caused by the 12-month washout period.

Figure 19: Proportion of CPRD participants with externally linked data, by GP practice



CPRD = Clinical Practice Research Datalink

Table 8: Characteristics of cohort participants (those with a history of using illicit opioids only; i.e. comparison groups are not shown)

Variable	Level	CPRD Aurum 2001-2018 n (%)	CPRD Gold 2001-2018 n (%)	SLaM 2006-2019 n (%)
Total		82,241 (100.0)	24,548 (100.0)	7,268 (100.0)
Follow-up (years)**	Median [IQR]	8.2 [3.8-13.3]	9.9 [6.1-14.4]	9.3 [5.6-10.8]
Age at cohort entry	18-24	8,782 (10.7)	3,157 (12.9)	600 (8.3)
	25-34	31,347 (38.1)	9,810 (40.0)	2,457 (33.8)
	35-44	26,579 (32.3)	7,462 (30.4)	2,793 (38.4)
	45-54	11,815 (14.4)	3,097 (12.6)	1,195 (16.4)
	55-64	3,718 (4.5)	1,022 (4.2)	223 (3.1)
	Median [IQR]	35.3 [29.2-42.5]	34.3 [28.3-41.5]	37.0 [30.5-43.3]
Sex	Female	25,435 (30.9)	7,563 (30.8)	1,871 (25.7)
	Male	56,806 (69.1)	16,985 (69.2)	5,415 (74.3)
Region	East Midlands	1,426 (1.7)	817 (3.3)	0 (0.0)
	East of England	2,506 (3.0)	2,134 (8.7)	0 (0.0)
	London	12,040 (14.6)	2,654 (10.8)	7,286 (100.0)
	North East	4,717 (5.7)	864 (3.5)	0 (0.0)
	North West	16,897 (20.5)	5,377 (21.9)	0 (0.0)
	South Central	7,315 (8.9)	2,384 (9.7)	0 (0.0)
	South East Coast	3,544 (4.3)	2,124 (8.7)	0 (0.0)
	South West	16,241 (19.7)	3,946 (16.1)	0 (0.0)
	West Midlands	13,709 (16.7)	3,201 (13.0)	0 (0.0)
	Yorkshire & The Humber	3,797 (4.6)	1,047 (4.3)	0 (0.0)
	Missing	49 (0.1)	0 (0.0)	0 (0.0)
Smoking	Current	64,873 (78.9)	18,613 (75.8)	*
	Ex-smoker	5,427 (6.6)	1,616 (6.6)	*
	Missing	6,274 (7.6)	2,725 (11.1)	*
	Never	5,667 (6.9)	1,594 (6.5)	*
Index of Multiple Deprivation	1 (least deprived)	5,690 (6.9)	1,722 (7.0)	*
	2	8,623 (10.5)	2,738 (11.2)	*
	3	12,315 (15.0)	4,024 (16.4)	*
	4	20,280 (24.7)	5,810 (23.7)	*
	5 (most deprived)	35,189 (42.8)	10,207 (41.6)	*
	Missing	144 (0.2)	47 (0.2)	*
Homelessness		4,139 (5.0)	858 (3.5)	2,007 (27.5)
Prison		5,737 (7.0)	1,633 (6.7)	*
Alcohol dependence		15,238 (18.5)	3,560 (14.5)	1,916 (26.3)

SLaM = South London and Maudsley NHS Foundation Trust. IQR = interquartile range. * Data not available. ** Follow-up duration is for linked datasets, i.e. ONS mortality and Hospital Episode Statistics. Follow-up for primary care records is typically shorter.

Figure 20: Age of new entrants by year

CPRD = Clinical Practice Research Datalink

9.4.3 Mortality ratios

The SMRs for CPRD Aurum, CPRD Gold and SLaM were 7.7 (95% CI 7.4-8.0), 7.7 (95% CI 7.4-8.0), and 7.4 (95% CI 6.9-8.0) respectively. More detailed mortality rates and ratios are provided in Chapter 10. These ratios were similar to or higher than SMRs reported in other studies of mortality among people who use illicit opioids in the UK (Table 9).

Table 9: Summary of standardised mortality ratios, compared to other studies of mortality among people who use illicit opioids in the UK

Cohort	Location	Years	Recruitment method	Observed deaths	Expected deaths	SMR (95% CI)
HUPIO (CPRD Gold)	England	2001-2018	Primary care records	9,834	1,280.2	7.7 (7.5-7.8)
HUPIO (CPRD Aurum)	England	2001-2018	Primary care records	3,375	438.4	7.7 (7.4-8.0)
South London & Maudsley	South London	2006-2019	Community treatment for heroin use	732	98.5	7.4 (6.9-8.0)
Pierce 2015[40]	England	2005-2009	Opioid users in contact with drug treatment, prison and probation, and drug testing on arrest	3,974	695	5.7 (5.5-5.9)
Merrall 2012[231]	Scotland	1996-2001	People in contact with drug treatment services (65% using opiates)	777	121.0	6.4 (6.0-6.9)
		2001-2006		1,813	378.2	4.8 (4.6-5.0)

9.4.4 Internal validation of HUPIO: sensitivity of primary care codes

In the entire CPRD Gold and Aurum databases, 89% and 88% of patients who had a diagnosis of 'mental and behavioural disorders due to opioid use' in hospital also had a primary care record showing illicit opioid use (Table 10). For most patients, the first relevant primary care record precedes the first hospital admission where opioid dependence in recorded. Only a small proportion had the first relevant primary record in the 30 days after the first hospital admission (2% in Gold and 3% in Aurum). This suggests that HUPIO has good sensitivity in terms of more severe opioid use, and in most cases GPs capture illicit opioid use independently of information captured by hospitals. However, HUPIO may not capture people with less severe problems.

Table 10: Patients in CPRD with a hospital admission where ICD10 F11 (opioid dependence) was recorded, and the proportion who also appear in the 'HUPIO' primary care cohort

		CPRD Gold	CPRD Aurum
Patients in database with HES linkage		6.2 million	18.8 million
Number admitted with F11 in any diagnostic position after 1 Jan 1998		13,344	46,663
Of which: have a code in primary care data indicating illicit opioid use	Total with relevant code	11,905 (89%)	41,043 (88%)
	Before first admission	9,579 (72%)	31,325 (67%)
	Within 30 days after first admission	299 (2%)	1,256 (3%)
	More than 30 days after first admission	2,027 (15%)	8,462 (18%)

HES = Hospital Episode Statistics

9.4.5 Diagnoses of opioid dependence during hospital admissions among HUPIO participants

Among HUPIO participants (CPRD Aurum and Gold combined) with a history of using illicit opioids, opioid dependence was recorded in 20% of hospital admissions (Table 11). This ranged from 5.0% in admissions due to genitourinary diseases to 52.8% for injecting-related injuries (Table

11). In the comparison group, opioid dependence was recorded in 0.6% of admissions. Future research could use these values to model the number of hospital admissions among people who use illicit opioids nationally. For example, in a recent study I reported time-trends in injecting-related admissions in England using national Hospital Episode Statistics.[225] I counted admissions with a primary diagnosis of a bacterial infection and a secondary diagnosis of opioid dependence. In 2015/16 there were approximately 5,000 such admissions. If we assume that 52.8% of injecting-related infections were captured by this definition, we can estimate there were 5,000/0.528 = 9,469 admissions due to injecting related infections in England in 2015/16.

Table 11: Number of hospital admissions among HUPIO participants by primary cause of admission and proportion with a secondary diagnosis of 'mental and behavioural disorders due to use of opioids' (ICD-10 F11)

Primary diagnosis of admission by ICD-10 chapter	History of using illicit opioids (%)	Comparison group (%)
Total	110,453/551,178 (20.0)	1,349/230,290 (0.6)
Drug poisoning	1,728/11,281 (15.3)	34/3,195 (1.1)
Injecting-related injury	19,296/36,516 (52.8)	219/10,433 (2.1)
I Certain infectious and parasitic diseases	1,673/9,156 (18.3)	19/6,526 (0.3)
II Neoplasms	2,177/21,053 (10.3)	15/68,436 (<0.1)
III Blood and blood-forming organs	1,061/10,563 (10.0)	12/12,172 (0.1)
IV Endocrine; nutritional and metabolic	1,479/7,966 (18.6)	16/11,330 (0.1)
IX Circulatory	4,095/20,346 (20.1)	34/31,362 (0.1)
V Mental and behavioural	6,516/31,061 (21.0)	122/11,061 (1.1)
VI Nervous system	1,411/10,041 (14.1)	29/17,034 (0.2)
VII Eye and adnexa	265/3,618 (7.3)	3/10,970 (<0.1)
X Respiratory system	11,872/39,019 (30.4)	132/23,607 (0.6)
XI Digestive system	10,688/69,031 (15.5)	117/94,868 (0.1)
XII Skin and subcutaneous tissue	2,560/8,200 (31.2)	26/11,771 (0.2)
XIII Musculoskeletal system and connective tissue	4,831/34,928 (13.8)	67/54,205 (0.1)
XIV Genitourinary system	2,547/51,320 (5.0)	30/80,334 (<0.1)
XIX Injury; poisoning and other external causes	18,770/70,655 (26.6)	274/38,060 (0.7)
XV Pregnancy; childbirth and the puerperium	6,302/27,040 (23.3)	27/72,738 (<0.1)
XVIII Symptoms; signs and abnormal findings	11,904/74,836 (15.9)	164/70,027 (0.2)
XXI Factors influencing health status & contact with services	1,278/14,548 (8.8)	9/32,161 (<0.1)

I also found that the proportion of admissions where F11 was recorded was stable over time (Table 12), supporting surveillance studies of time trends in hospitalisation in this population that use secondary diagnoses of F11.

Table 12: Number of hospital admissions among HUPIO participants and proportion with a secondary diagnosis of opioid dependence (ICD-10 F11), by calendar year of admission date

Year	All admissions (%)	Injecting-related infections (%)
2001	1,260/5,277 (23.9)	271/501 (54.1)
2002	1,666/6,960 (23.9)	346/603 (57.4)
2003	2,312/9,675 (23.9)	506/919 (55.1)
2004	2,798/12,133 (23.1)	565/1,018 (55.5)
2005	3,298/15,112 (21.8)	571/1,098 (52.0)
2006	4,148/17,794 (23.3)	741/1,247 (59.4)
2007	4,277/19,645 (21.8)	816/1,460 (55.9)
2008	5,412/23,577 (23.0)	885/1,631 (54.3)
2009	6,027/27,290 (22.1)	780/1,532 (50.9)
2010	7,050/30,850 (22.9)	928/1,603 (57.9)
2011	7,215/34,293 (21.0)	784/1,520 (51.6)
2012	7,472/36,837 (20.3)	935/1,773 (52.7)
2013	7,986/39,565 (20.2)	999/2,024 (49.4)
2014	9,191/44,030 (20.9)	1,345/2,545 (52.8)
2015	10,045/47,847 (21.0)	1,528/2,889 (52.9)
2016	10,584/51,052 (20.7)	1,861/3,489 (53.3)
2017	10,468/53,085 (19.7)	2,094/4,046 (51.8)
2018	11,911/57,994 (20.5)	2,338/4,531 (51.6)
2019	5,393/27,550 (19.6)	1,003/2,087 (48.1)

9.5 Discussion

Key findings

I developed 3 new cohorts of people who use illicit opioids and showed that they have similar characteristics to other samples of this population, with increasing age, approximately three-quarters male, high prevalence of tobacco smoking, and very high all-cause mortality rates. The validation is particularly important for the HUPIO cohort because it uses a new method of identifying people who use illicit opioids.

9.5.1 Strengths and limitations

To my knowledge, HUPIO is the first study to develop a method for identifying people with a history of illicit opioid use within primary care records. Earlier studies have focused specifically on people prescribed opioids,[232,233] general illicit drug use or dependence (i.e. including people who use substances other than opioids),[234,235] and people prescribed OAT.[236,237] The latter is a limited subset of this population, particularly given that OAT in England is not always prescribed by GPs. These studies have included patients prescribed any methadone or buprenorphine product and excluded those with doses suggesting indications other than OAT (such as pain or palliative cough). Yet over 70% of daily doses for these medications are missing from CPRD,[238] and therefore require imputation or exclusion. The method developed in this study avoids the need for imputation by using products that are specific to OAT. In addition, the use of clinical observations such as 'heroin dependence', which account for the majority of participants in HUPIO, mean that people who use illicit opioid but have never been in structured drug treatment are included. This is a rarely-studied population.

The main strength of CPRD in relation to other research datasets for this population is that it offers unique insights into primary healthcare. It can be linked to external datasets to obtain information on care in hospitals, cancer services, and mental health services, as well as causes of mortality.

The cohort of patients at SLaM have all been in community-based treatment for heroin use. People who use such services have been studied many times, including in large linkage-based studies of healthcare use and mortality in the UK.[40,231,239] This resource therefore adds to an existing body of research, rather than adding a new type of resource.

The cohorts have 3 key limitations.

First, data are derived from routine healthcare records and many useful variables are not available. For example, in CPRD there is no systematic recording of the type and frequency of drug use, and the degree of drug dependence. The data on smoking presented in Table 8 suggests that some characteristics of this population are well-captured by GPs, as fewer than 10% had no records and the prevalence of smoking is comparable to that found in other studies. Other characteristics may be less well-captured, for example fewer-than-expected patients had records of homelessness or prison. The SLaM data includes standard regular assessments by support workers (known as "Treatment Outcome Profiles"), and this dataset therefore includes better insight into drug use of participants. However, it does not include data on tobacco smoking.

Second, use of crack cocaine appears poorly captured. The HUPIO cohort was initially conceived as a cohort of people who use heroin or crack cocaine. However, very few codes relating to crack cocaine were identified. This may be because (a) there is no commonly used treatment for crack cocaine dependence (unlike for opioid dependence); (b) crack cocaine may be coded as 'cocaine', and including these codes would greatly reduce the specificity of the codelist due to the high prevalence of powder cocaine use. The final codelist therefore focuses on people who use illicit opioids only. For similar reasons, people accessing drug treatment may be less likely to disclose their use of crack cocaine than heroin, and therefore use of crack cocaine may be under-reported in the SLaM dataset.

Third, depending on the research question, selection biases are likely to be important. To be included in the HUPIO sample, individuals need to be registered with a GP, attend an appointment, and disclose their drug use. At present, we do not know what proportion of this population is registered with a GP. In one study of homeless people who inject drugs in London; a subgroup likely to have relatively high barriers to GP registration, 70% provided GP details,[240] suggesting that a large proportion of this population is registered. However, disclosure of drug use is likely to differ. Groups more likely to disclose drug use may include those prescribed OAT (either in primary care or specialist drug and alcohol services), and those who are more unwell and therefore have more GP appointments. This latter factor may lead to an overestimation in differences in morbidity and mortality when comparing people with a history of illicit opioid use to the general population. Qualitative research has found both practice-level and individual-level barriers to disclosing and recording illicit drug use.[241] In particular, patients and GPs who feel more stigma towards illicit drug use may be less likely to discuss the issue.

The SLaM dataset only includes people who have started a structured treatment programme. People often use heroin for many years before starting treatment. Data from the National Drug Treatment Monitoring System show that among 119,881 people in treatment and "stating a problem with heroin" in 2019/20,[23] the mean reported duration between earliest heroin use and treatment start was 20 years (based on linear interpolation of age categories in the published data). People who use heroin and never seek treatment are also excluded. This may include people with less problematic drug use and therefore lower need for treatment, and also people with more problematic drug use or other life circumstances that make it difficult to engage with services.

9.5.2 Interpretation and relevance for policy, practice, and research

These datasets offer new opportunities to study the health and healthcare of people who use illicit opioids in England. The 3 cohorts offer large samples with long follow-up, allowing studies of rare outcomes. The CPRD and SLaM cohorts have different recruitment methods, and therefore comparisons between results may provide insight into the importance of different types of bias.

9.5.3 Conclusion

The 3 cohorts presented in this chapter together provide many opportunities to study the health and healthcare use of this population. The validation showed that the cohorts have the expected characteristics, though selection biases may still be important depending on the research question.

Linking statement

This chapter has explained the development of 3 cohorts of people who use illicit opioids. The next 2 chapters present epidemiological analyses of these cohorts: first a description of causes of death and how they have changed over time, and second a case study of treatment and outcomes after diagnosis of chronic obstructive pulmonary disease.

10 Causes of death among people who use illicit opioids: analysis of 3 cohorts in England

10.1 Summary

Background: The average age of people who use illicit opioids such as heroin is increasing in many high-income countries. This has been suggested as a reason for the increasing number of opioid-related deaths and changing health needs. This study aims to describe causes of death and changes in mortality by age and time period for people who use illicit opioids in England.

Methods: I studied 3 cohorts: (a) 82,241 individuals in the Clinical Practice Research Datalink (CPRD) Aurum with illicit opioid use recorded between 1 January 2001 and 30 October 2018, with an age/sex/practice-matched comparison group with no records of illicit opioid use; (b) 24,548 individuals in CPRD Gold selected in the same way; (c) 7,286 people entering community-based treatment for heroin dependence at South London and Maudsley NHS Foundation Trust (SLaM) between 1 January 2006 and 2 July 2019. Dates and causes of death were provided by the Office for National Statistics. I described rates of death and calculated cause-specific standardised mortality ratios (SMRs). In the combined CPRD cohort, I used Poisson regression to estimate associations between age, calendar year, and cause-specific death.

Results: Mortality rates and the distribution of causes of death were similar across the 3 cohorts. In CPRD Aurum, 9,834/92,241 participants (10.6%) died over a median of 8.2 years of follow-up, with an SMR of 7.7 (95% CI 7.5-7.8). In CPRD Gold, 3,375/24,548 participants (13.7%) died over a median of 9.9 years of follow-up, with an SMR of 7.7 (95% CI 7.4-8.0). In the SLaM cohort, 732/7,286 participants (10.0%) died over a median of 9.3 years of follow-up, with an SMR of 7.4 (95% CI 6.9-8.0). In each cohort approximately one third of deaths had an underlying cause of drug poisoning, one-tenth were accidents and suicide, half were due to non-communicable diseases, and the rest were infections and other causes. Cause-specific mortality rates were all substantially higher than among people of the same age and sex in the general population, with the highest SMRs for viral hepatitis, chronic obstructive lung disease, and HIV. In the combined CPRD cohort the rate of fatal drug poisoning at age 20 was 271 (95% CI 229-312) per 100,000 person-years, accounting for 60% of deaths, while non-communicable diseases together caused 31 (95% CI 16-45) deaths, accounting for 7% of deaths. The rate of fatal drug poisonings increased steadily with age, reaching 507 (95% CI 452-562) per 100,000 person-years at age 50, accounting for 23% of deaths. Deaths due to non-communicable diseases increased more rapidly to 1,155 (95% CI 880-1431) at age 50, accounting for 52% of deaths. Mirroring national surveillance data, the rate of fatal drug poisonings in the cohort increased by 55% between 2010-12 and 2016-18, and this increase was not sensitive to adjustment for age.

Conclusion: People who use illicit opioids have excess mortality risk across all causes of death. Population ageing does not explain an increasing number of fatal drug poisonings. However, ageing is leading to increasing numbers of premature deaths due to non-communicable diseases.

Results for the CPRD data have been published in the journal The Lancet Public Health.[242]

10.2 Background

Key points

- People who use illicit opioids in England are getting older and some studies show increasing rates of death due to non-communicable diseases
- The number of fatal drug overdoses in England has increased recently and some argue this also relates to ageing in the population

Illicit opioids such as heroin are associated with an extremely high risk of death and international systematic reviews have found mortality rates of 10-15 times the general population.[14,15,33] However, the most common causes of death have changed over time. There were 'epidemics' of heroin use in the UK in the 1980s and 1990s and the population was mostly people in their 20s who had recently started using drugs.[18] In this era, most deaths were due to drug overdoses, infections, and suicides.[243–245] Although the number of new users has tailed-off since the late 1990s, many people who started using opioids in the 1980s and 1990s have continued to use drugs. In 2019, approximately 70% of people accessing treatment in England for 'problematic heroin use' first used heroin before 2000, and the average age of people accessing treatment was 42.[246] As the population has got older, health needs and causes of death have changed. Recent cohort studies continue to show high mortality rates, but many more deaths are now caused by non-communicable diseases.[39,40]

Alongside ageing, another feature of the health of this population is a recent increase in the number of drug-related deaths. The number of heroin or morphine-related deaths in England increased by 57% between 2010 and 2018, from 1,391 to 2,189.[9] Opioid-related deaths are also increasing in Scotland, Australia, and North America.[148,247,248] This is now considered a public health crisis, but the causes of this crisis are likely to differ between countries. For example, in North America, the recent increase is linked to synthetic opioids including fentanyls[148] in the illicit drug market but these drugs are not yet common in the UK. One explanation proposed for the increase in the UK is that the long-term trend of ageing and increasing frailty in this population is leading to greater risk of death after using respiratory depressants such as opioids.[249] However, most surveillance data are from national death records, and it is difficult to determine whether the increasing deaths are due to population ageing, a growing population of people using drugs, or other factors.

Existing cohort studies of people who use illicit opioids show varying associations between age and risk of fatal drug poisoning, with some finding no association[247,250–253] and others finding that risk increases with age.[40,254] Studies consistently find that the risk of death due to non-communicable diseases is more strongly associated with age than the risk of death due to drug poisoning. As a result, non-communicable diseases cause a minority of deaths in younger samples and a majority in older samples.[40,41,250–257] Few studies have attempted to isolate changes in mortality over time from ageing in study cohorts. An exception is a study in Scotland that found age-specific rates of drug-related death increased between 2009 and 2018, concluding that the recent increase in drug-related deaths is not solely due to population ageing.[247]

This chapter uses the cohorts described in Chapter 9 to address the following research questions:

- What is the mortality rate among people who use illicit opioids in England, and how does it compare to people of the same age and sex in the general population?
- What are the most common causes of death among people who use illicit opioids in England, and how do they compare to the general population in both relative and absolute terms?
- How have all-cause and cause-specific mortality rates changed in the past 20 years, and are changes explained by population ageing?

10.3 Methods

This is a cohort study of the rate of all-cause and cause-specific death, comparing people with a history of using illicit opioids to people of the same age and sex in the general population. The methods are repeated in the 3 cohorts described in Chapter 9: CPRD Aurum, CPRD Gold, and South London & Maudsley NHS Foundation Trust (SLaM).

10.3.1 Entry and exit dates for participants with a history of using illicit opioids

Participants in CPRD entered the study at the latest of 1 January 2001, 12 months after entry to CPRD, and the first record of illicit opioid use. I restricted the study to time after 2001 to allow consistent coding of deaths using ICD-10 (deaths before 2001 are coded using ICD-9). I used a 'washout' period of 12 months to avoid the unusual period after joining a database such as CPRD. This period is unusual because it often coincides with registration at a doctor's surgery, and may be associated with poor health, diagnosis, or recording of pre-existing health problems.[227] Participants exited at the earliest of death and 30 October 2018.

Participants in the SlaM dataset entered the study at the latest of 1 April 2006, the participant's 18th birthday, and the first date of entry into treatment for heroin dependence. Participants exited at the earliest of death and 2 July 2019.

10.3.2 Categorisation of mortality data

I classified deaths using the ICD-10 code for the underlying cause of death. I first classified deaths as drug poisonings, using the Office for National Statistics definition,[9] and deaths due to other causes. I classified the remaining deaths in subgroups that were either (a) identified as major causes of premature mortality in England in a previous study,[258] or (b) identified as major causes of death in a previous study of people in treatment for heroin dependent in South London.[39] The groups were: infections (with subgroups HIV and viral hepatitis), cancers (with subgroups digestive, respiratory, lymphoid and hematopoietic, female genital, and breast), disease of the nervous system, circulatory diseases (with subgroups ischaemic heart disease and stroke), respiratory diseases (with subgroups chronic obstructive pulmonary disease and influenza/pneumonia), digestive diseases (with subgroup liver), and external causes (with subgroups accidents and self-harm). ICD-10 codes for these groups are shown in Table 13.

Table 13: ICD-10 codes for causes of death (note that codes for subgroups are also included in chapters)

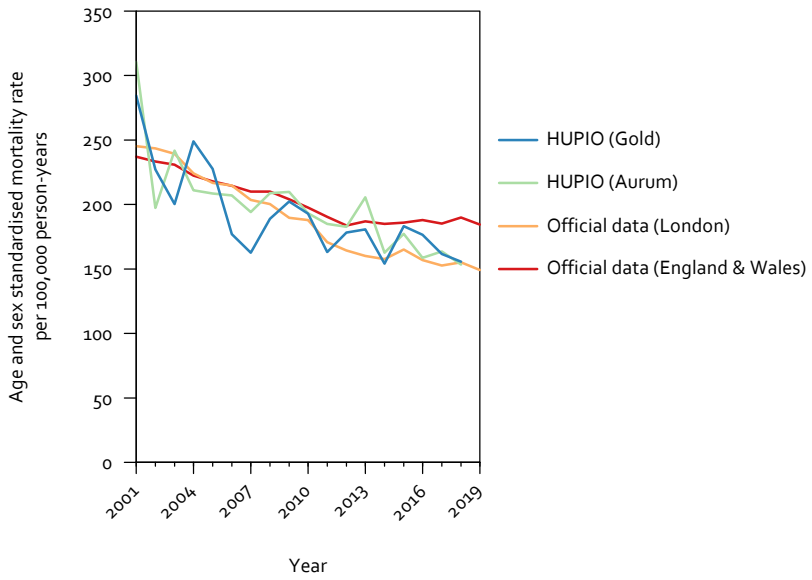
Cause	ICD-10 code of underlying cause of death
Drug-related deaths	F11:16, F18:19, X40:44, X60:64, X85, Y10-14
I: Infections	A00:98, B00:99
HIV	B20:24
Viral hepatitis	B15:19
II: Cancers	C00:97, D00:48
Breast	C50
Digestive	C15:26
Female genital	C51:58
Respiratory	C30:39
Lymphoid & haemopoietic	C81:96
VI: Nervous system	G00:98
IX: Circulatory diseases	I00:99
Ischaemic heart disease	I20:25
Stroke / cerebrovascular disease	I60:69
Other forms of heart disease	I30:52
X: Respiratory diseases	J00:98
COPD	J40:44
Influenza and pneumonia	J09:18
XI: Digestive diseases	K00:92
Liver diseases	K70:76
XX: External (ex. drug-related)	V00:97, W00:98, X00:39, X45:X59, X65:X84, X86-X99, Y00:Y09, Y15:98, U50
Accidents	V00:97, W00:98, X00:39, X45:X59
Suicide	X65:84, Y15-34

COPD = chronic obstructive pulmonary disease

10.3.3 Comparison groups

Comparison groups of people who do not use illicit opioids are described in more detail in Chapter 9. Briefly, CPRD participants are compared to a matched cohort of patients without records of illicit opioid use, using a process called 'exposure density sampling'.[228] This allows for analysis requiring individual-level data. The SLaM dataset does not include people from the general population, and therefore comparisons are made using mortality rates calculated from general population data. This means that analyses rely on standardisation rather than regression-based methods. The mortality rates in the CPRD comparison group are similar to those in the general population (Figure 21).

Figure 21: Age- and sex-standardised mortality rates in comparison (general population) groups



10.3.4 Calculation of mortality rates and ratios

I expanded follow-up for each participant such that a new observation period began with each calendar time period (2001-03, 2004-06, 2007-09, 2010-12, 2013-15, and 2016-18), birthday, and every third anniversary after cohort entry. This method is called 'Lexis expansion'[259] and allows analysis of disease risk on multiple timescales. An example of data expanded in this way and then aggregated across a study population is given in Table 14. This was done by expanding follow-up for each individual into days, determining the age-at-last birthday, calendar year, and duration after cohort entry for each day, then counting the number of days by these categories. My code for doing this procedure is here: https://github.com/danlewer/hupio/blob/main/lexis/lexis_expansion.R.

To calculate cause-specific standardised mortality ratios (SMRs) in the CPRD cohorts, I calculated age, sex, and calendar time period-specific mortality rates in the comparison group, and then applied these rates to the number of person-years in the exposed group. This gave the number of expected deaths. The SMR is the observed divided by the expected deaths. I estimated 95% confidence intervals using a nonparametric bootstrap method[260] in which I resampled participants 1,000 times with replacement, calculated the SMR for each resample, and reported the 0.025 and 0.975 quantiles of the SMR. I used this method because the common approach in which the standard error of the SMR equals the square root of the observed deaths divided by the expected deaths (or equivalent exact Poisson approach) assumes no error in the expected deaths, while the present estimates have less precision, particularly for rare causes of death such as HIV. The bootstrap method accounts for variance in the reference group and gives wider confidence intervals.

For the SLaM dataset, the SMR is calculated using cause-specific mortality rates in the general population of London, based on data provided by ONS specifically for this project.[229] These rates can be assumed to be precise, and therefore I calculated 95% confidence intervals by assuming a Poisson distribution in the count of observed deaths.

Table 14: Example Lexis aggregated data

History of illicit opioids*	Sex	Age group*	Calendar year*	Years after cohort entry*	Person-years	All-cause deaths	COPD deaths	[... Other causes of death]
Yes	Male	30-34	2015	[0-3)	1979	33	0	
Yes	Male	30-34	2015	[3-6)	1824	12	0	
Yes	Male	30-34	2015	[6-9)	1507	11	0	
Yes	Male	30-34	2015	[9-12)	1075	3	1	
Yes	Male	35-39	2015	[0-3)	2502	36	2	
Yes	Male	35-39	2015	[3-6)	2599	37	2	
Yes	Male	35-39	2015	[6-9)	2439	28	1	
Yes	Male	35-39	2015	[9-12)	2122	19	1	
[...]								

* Time-varying within individuals. Follow-up for each individual has been divided into days, with each day assigned to an age group, calendar year, and duration after cohort entry
COPD – Chronic Obstructive Pulmonary Disease

10.3.5 Analysis of change in causes of death over time

For analyses of changes in mortality rates over time, I only used the CPRD datasets. This was because the SLaM dataset did not have sufficient power to analyse changes in rates over time. I also combined the CPRD Aurum and Gold data to simplify the results and to maximise power. For this analysis, I further grouped causes of death to create a mutually exclusive categorisation.

I calculated crude and directly standardised cause-specific mortality rates by time period. Standardisation was based on the average age and sex profile of the whole cohort. Confidence intervals for the standardised rates were estimated using a method based on the gamma distribution[261] and implemented in the R function epitools::ageadjust.direct.

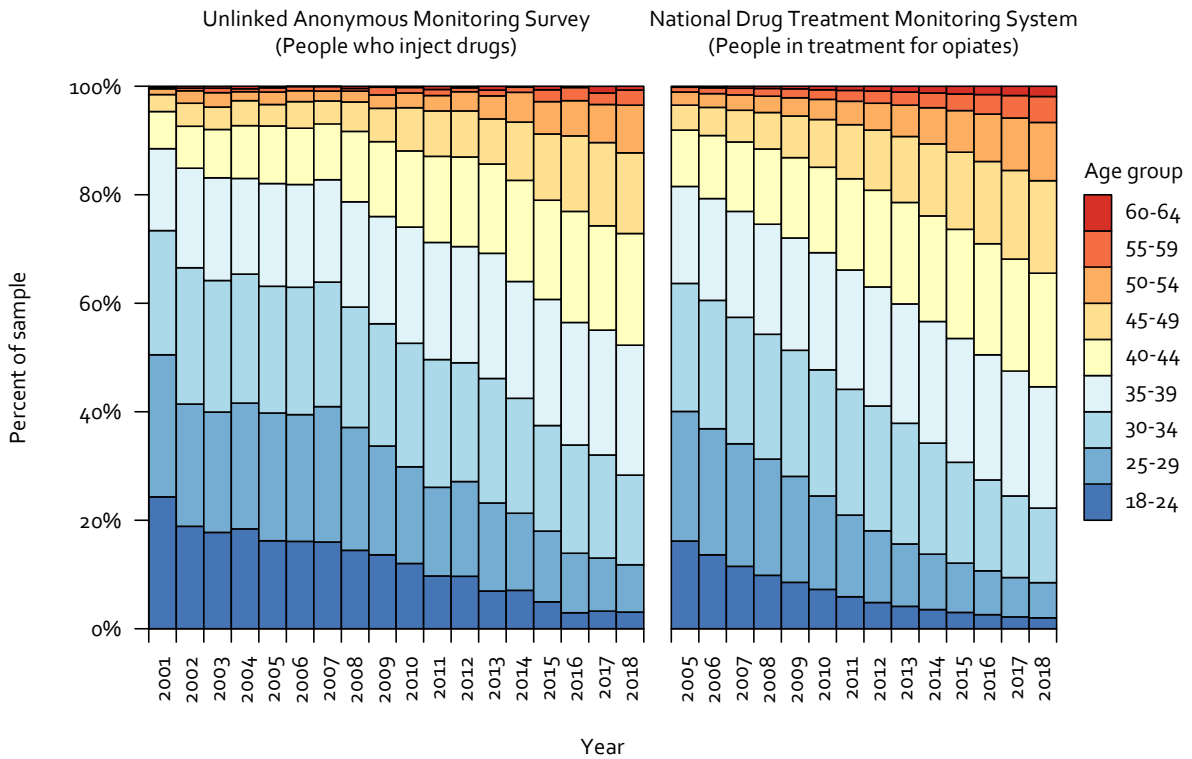
I then estimated the independent association between calendar time period and mortality using a Poisson model for each cause of death. The dependent variable was the count of deaths, and the independent variables were opioid history, age (linear and quadratic terms), sex, an interaction term between opioid history and calendar time, an interaction term between opioid history and time after cohort entry, and an offset for the log person-years. I used the marginal rates from the model to estimate the number of deaths in a cohort of 100,000 individuals with the same characteristics as the entire sample of people who use opioids (in terms of age, sex, and time after cohort entry) for each calendar time period.

10.3.6 Analysis of changes in causes of death by age

I used the same model to estimate the association between age and causes of death. To contextualise this association at a population level, I used the model to predict the number of deaths in an exemplar population taken from the Unlinked Anonymous Monitoring Survey of Infections and Risk among People who Inject Drugs.[11] This population structure is shown in Figure 22, and for context compared to people entering treatment for opiate dependence (showing that the populations have similar age structures after 2005).[246] In this population, the proportion aged under 40 was 89% in 2001 and 52% in 2018. The purpose of this analysis is to estimate the independent effect of

population ageing on population-level cause-specific mortality rates, and therefore test the theory that population ageing is contributing to an increase in fatal drug poisonings.

Figure 22: Age of participants in the Unlinked Anonymous Monitoring Survey of People who Inject Drugs (left panel) and people in treatment for opiate dependence in England (right panel)



10.4 Results

The number of people with a history of using illicit opioids in CPRD Aurum, CPRD Gold, and SlaM was 82,241, 24,548, and 7,286 respectively (Table 15). The 3 cohorts had similar age and sex at cohort entry, with participants in SlaM being slightly older on average and with a slightly larger proportion of men. The average age of people joining the cohorts increased over time and the year-stratified ages were similar (see section 9.4.1).

Table 15: Characteristics of participants in analysis of mortality rates

Cohort	Variable	Participants with a history of using illicit opioids	Comparison group
CPRD Aurum	Number at baseline	82,241	246,723
	Follow-up years (median [IQR])	8.2 [3.8-13.3]	9.1 [4.4-14.1]
	Age at cohort entry (median [IQR])	35.3 [29.2-42.5]	35.4 [29.3-42.6]
	Male (%)	56,806 (69.1)	170,418 (69.1)
CPRD Gold	Number at baseline	24,548	73,644
	Follow-up years (median [IQR])	9.9 [6.1-14.4]	10.7 [6.9-15.1]
	Age at cohort entry (median [IQR])	34.3 [28.3-41.5]	34.4 [28.3-41.6]
	Male (%)	16,985 (69.2)	50,955 (69.2)
South London & Maudsley NHS Foundation Trust	Number at baseline	7,286	*
	Follow-up years (median [IQR])	9.3 [5.6-10.8]	*
	Age at cohort entry (median [IQR])	37.0 [30.5-43.3]	*
	Male (%)	5,415 (74.3)	*

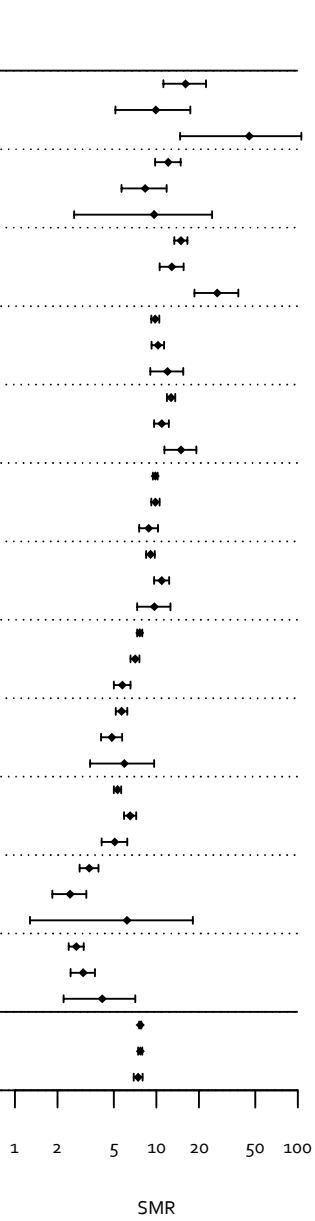
* Comparisons in analysis of the SlaM dataset are based on general population mortality rates rather than an individual-level comparison group. IQR – Interquartile Range

10.4.1 Mortality rates and ratios

Age and sex-stratified crude mortality rates were similar across the 3 cohorts, with greater variation in the SlaM cohort due to small numbers of participants in some strata (Figure 23). Standardised mortality ratios were also similar across the 3 cohorts (Figure 22 and Figure 23). As expected, crude mortality rates increased with age and standardised mortality ratios reduced with age. Female participants had lower crude mortality rates.

Figure 23: Observed and expected deaths stratified by cohort, age, and sex

Age group	Sex	Source	Follow-up (years)	Observed deaths	Deaths per 1000 PYs	Expected deaths	SMR (95% CI)
18-24	Female	Aurum	8,624	35	4.1	2.2	16.1 (11.2-22.3)
		Gold	3,147	12	3.8	1.2	9.9 (5.1-17.3)
		SLaM	593	**	8.4	**	45.3 (14.7-105.7)
	Male	Aurum	12,712	93	7.3	7.7	12.1 (9.8-14.8)
		Gold	4,731	31	6.6	3.7	8.3 (5.7-11.8)
		SLaM	919	**	4.4	**	9.6 (2.6-24.7)
25-34	Female	Aurum	64,830	342	5.3	23.0	14.9 (13.4-16.6)
		Gold	22,817	107	4.7	8.3	12.8 (10.5-15.5)
		SLaM	4,617	33	7.1	1.2	26.9 (18.5-37.8)
	Male	Aurum	127,455	972	7.6	99.1	9.8 (9.2-10.4)
		Gold	46,645	376	8.1	36.7	10.3 (9.2-11.3)
		SLaM	9,482	57	6.0	4.8	12.0 (9.1-15.5)
35-44	Female	Aurum	80,284	839	10.5	66.2	12.7 (11.8-13.6)
		Gold	27,980	280	10.0	25.7	10.9 (9.6-12.2)
		SLaM	6,067	61	10.1	4.1	14.9 (11.4-19.2)
	Male	Aurum	207,215	2,421	11.7	246.8	9.8 (9.4-10.2)
		Gold	71,164	873	12.3	88.7	9.8 (9.2-10.5)
		SLaM	17,327	174	10.0	19.7	8.8 (7.6-10.2)
45-54	Female	Aurum	42,705	770	18.0	84.8	9.1 (8.4-9.7)
		Gold	14,748	264	17.9	24.2	10.9 (9.6-12.3)
		SLaM	3,379	57	16.9	5.9	9.7 (7.3-12.5)
	Male	Aurum	112,679	2,311	20.5	303.4	7.6 (7.3-7.9)
		Gold	36,799	746	20.3	105.6	7.1 (6.6-7.6)
		SLaM	13,297	214	16.1	37.3	5.7 (5.0-6.6)
55-64	Female	Aurum	15,076	457	30.3	80.5	5.7 (5.2-6.2)
		Gold	5,580	136	24.4	28.1	4.8 (4.1-5.7)
		SLaM	680	16	23.5	2.7	5.9 (3.4-9.6)
	Male	Aurum	31,147	1,160	37.2	218.5	5.3 (5.0-5.6)
		Gold	10,273	393	38.3	60.2	6.5 (5.9-7.2)
		SLaM	2,871	95	33.1	18.7	5.1 (4.1-6.2)
65+	Female	Aurum	4,257	169	39.7	50.4	3.4 (2.9-3.9)
		Gold	1,830	54	29.5	22.0	2.5 (1.8-3.2)
		SLaM	53	**	56.1	**	6.2 (1.3-18.1)
	Male	Aurum	5,917	265	44.8	97.6	2.7 (2.4-3.1)
		Gold	2,095	103	49.2	33.9	3.0 (2.5-3.7)
		SLaM	207	**	62.7	**	4.1 (2.2-7.1)
Total	Total	Aurum	712,902	9,834	13.8	1280.2	7.7 (7.5-7.8)
		Gold	247,809	3,375	13.6	438.4	7.7 (7.4-8.0)
		SLaM	59,494	732	12.3	98.5	7.4 (6.9-8.0)



Pys = person-years. SMR = standardised mortality ratio. ** Redacted to prevent disclosure of small counts.

10.4.2 Causes of death

The distribution of causes of death was similar across the 3 cohorts, and cause-specific standardised mortality ratios were also similar. Drug poisoning accounted for 3,232/9,834 deaths (33%) in CPRD Aurum; 1,143/3,375 (34%) in CPRD Gold, and 266/732 (36%) in SlaM. There was strong evidence that the rates of all causes of death were higher among people with a history of using illicit opioids than in the general population (i.e. the cause-specific standardised mortality ratios were greater than 1), except for some rarer causes of death such as diseases of the nervous system, where there was confidence intervals were wide in the SlaM cohort (Figure 23). As expected, the relative risk of drug

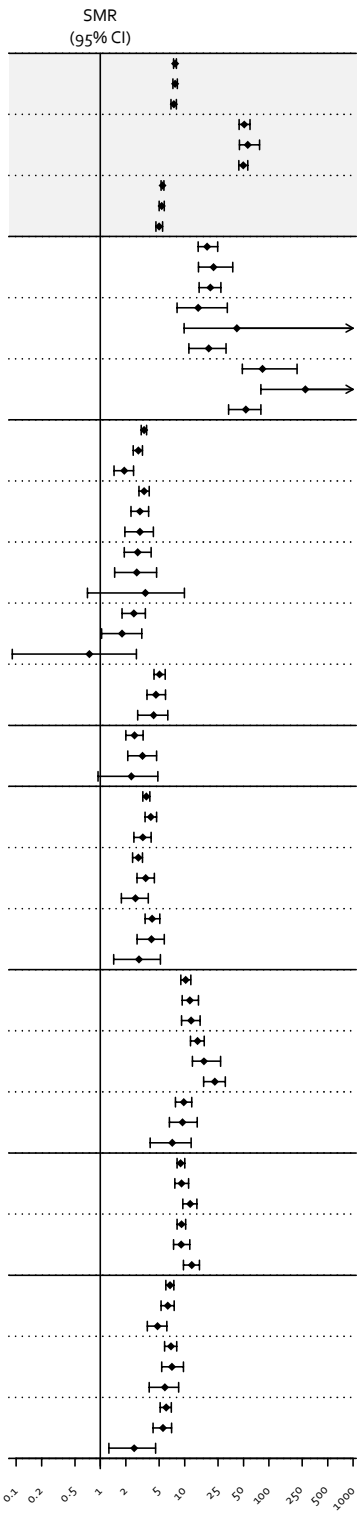
poisoning was very high (pooled SMR = 52) and across the 3 cohorts drug poisoning caused 4,552/12,133 excess deaths (37.5%).

Among other causes of deaths, the highest relative risks were for death due to viral hepatitis (pooled SMR = 97) and HIV (pooled SMR = 17). However, these causes of death are rare in the general population, which may mean that relative risks overstate the importance of these diseases. From an absolute perspective, viral hepatitis caused 322/12,133 excess deaths (2.7%) across the 3 cohorts and HIV caused 77/12,133 (0.6%).

In contrast, some long-term conditions had lower relative risks but caused larger numbers of excess deaths. For example, cardiovascular diseases had a pooled SMR of 3.6, but caused 878/12,133 excess deaths (7.2%).

Figure 24: Observed and expected deaths, stratified by source and cause of death

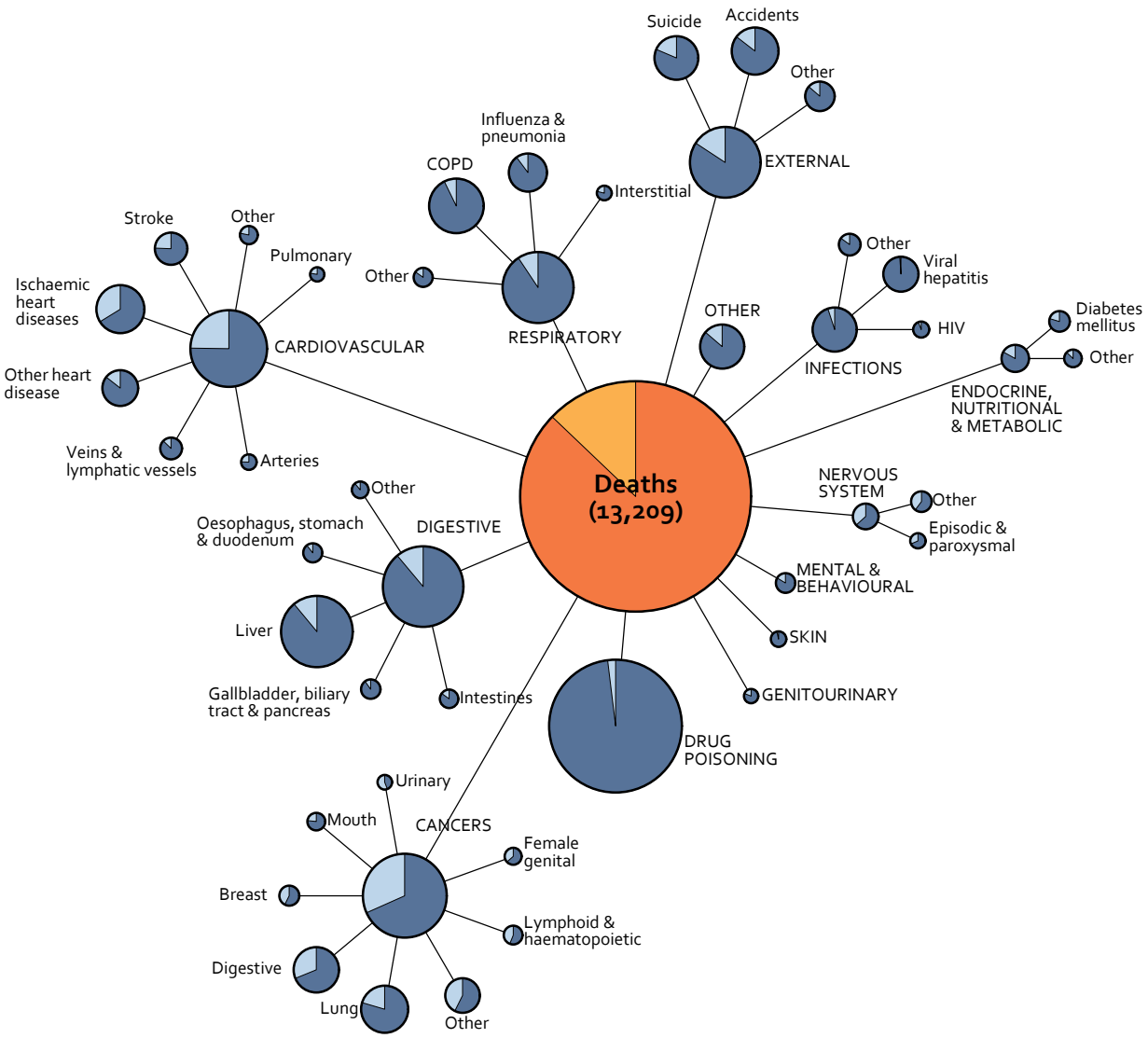
Underlying cause of death	Source	Observed deaths	Percent of deaths	Expected deaths	SMR (95% CI)
All cause	Aurum	9,834	100.0	1272.1	7.7 (7.4-8.0)
	Gold	3,375	100.0	437.0	7.7 (7.2-8.2)
	SLaM	732	100.0	98.5	7.4 (6.9-8.0)
Drug poisoning	Aurum	3,232	32.9	63.5	50.9 (44.4-59.6)
	Gold	1,143	33.9	20.3	56.4 (44.7-77.6)
	SLaM	266	36.3	5.3	49.9 (44.1-56.2)
Not drug poisoning	Aurum	6,602	67.1	1208.6	5.5 (5.2-5.7)
	Gold	2,232	66.1	416.7	5.4 (5.0-5.7)
	SLaM	466	63.7	93.2	5.0 (4.6-5.5)
I: INFECTIONS	Aurum	357	3.6	19.3	18.5 (14.5-24.6)
	Gold	128	3.8	5.8	22.1 (14.6-37.2)
	SLaM	**	**	**	20.3 (14.9-26.9)
HIV	Aurum	52	0.5	3.6	14.5 (8.2-32.1)
	Gold	13	0.4	0.3	41.8 (9.9-Inf)
	SLaM	**	**	**	19.3 (11.3-31.0)
Viral hepatitis	Aurum	222	2.3	2.6	83.9 (48.6-217.2)
	Gold	81	2.4	0.3	271.8 (80.3-Inf)
	SLaM	22	3.0	0.4	53.2 (33.4-80.6)
II: CANCERS	Aurum	1,328	13.5	402.4	3.3 (3.1-3.5)
	Gold	420	12.4	149.4	2.8 (2.5-3.2)
	SLaM	58	7.9	30.3	1.9 (1.5-2.5)
Digestive	Aurum	382	3.9	115.4	3.3 (2.9-3.8)
	Gold	129	3.8	43.7	2.9 (2.3-3.7)
	SLaM	28	3.8	9.5	3.0 (2.0-4.3)
Female genital	Aurum	51	0.5	18.4	2.8 (1.9-4.0)
	Gold	21	0.6	7.8	2.7 (1.5-4.6)
	SLaM	**	**	**	3.4 (0.7-10.0)
Lymph	Aurum	68	0.7	27.3	2.5 (1.8-3.4)
	Gold	20	0.6	11.1	1.8 (1.0-3.1)
	SLaM	**	**	**	0.7 (0.1-2.7)
Respiratory	Aurum	417	4.2	82.6	5.0 (4.3-5.9)
	Gold	131	3.9	28.7	4.6 (3.6-5.9)
	SLaM	25	3.4	5.8	4.3 (2.8-6.3)
VI: NERVOUS	Aurum	115	1.2	45.4	2.5 (2.0-3.2)
	Gold	48	1.4	15.1	3.2 (2.1-4.7)
	SLaM	**	**	**	2.3 (0.9-4.8)
IX: CIRCULATORY	Aurum	844	8.6	240.6	3.5 (3.2-3.9)
	Gold	299	8.9	75.1	4.0 (3.4-4.7)
	SLaM	74	10.1	23.2	3.2 (2.5-4.0)
Ischaemic heart	Aurum	414	4.2	147.2	2.8 (2.4-3.2)
	Gold	158	4.7	45.7	3.5 (2.7-4.4)
	SLaM	31	4.2	11.9	2.6 (1.8-3.7)
Stroke	Aurum	199	2.0	48.4	4.1 (3.4-5.0)
	Gold	61	1.8	15.1	4.0 (2.7-5.7)
	SLaM	11	1.5	3.8	2.9 (1.4-5.1)
X: RESPIRATORY	Aurum	926	9.4	89.5	10.3 (9.1-11.9)
	Gold	321	9.5	27.8	11.5 (9.4-14.6)
	SLaM	64	8.7	5.4	11.9 (9.2-15.2)
COPD	Aurum	507	5.2	35.7	14.2 (11.7-17.2)
	Gold	174	5.2	10.3	16.9 (12.4-26.7)
	SLaM	46	6.3	2.0	22.9 (16.8-30.6)
Flu & pneumonia	Aurum	269	2.7	27.6	9.8 (7.8-12.2)
	Gold	92	2.7	9.7	9.5 (6.6-14.1)
	SLaM	14	1.9	2.0	7.2 (3.9-12.0)
XI: DIGESTIVE	Aurum	1,223	12.4	136.2	9.0 (8.1-10.0)
	Gold	388	11.5	42.3	9.2 (7.6-11.2)
	SLaM	109	14.9	9.4	11.6 (9.5-14.0)
Liver	Aurum	969	9.9	105.8	9.2 (8.1-10.3)
	Gold	303	9.0	33.4	9.1 (7.4-11.5)
	SLaM	84	11.5	6.9	12.2 (9.7-15.1)
XX: EXTERNAL	Aurum	1,008	10.3	150.0	6.7 (6.0-7.4)
	Gold	359	10.6	57.1	6.3 (5.3-7.5)
	SLaM	58	7.9	12.2	4.8 (3.6-6.2)
Accidents	Aurum	403	4.1	58.7	6.9 (5.8-8.0)
	Gold	147	4.4	20.7	7.1 (5.3-9.7)
	SLaM	26	3.6	4.5	5.8 (3.8-8.5)
Suicide	Aurum	476	4.8	79.1	6.0 (5.1-6.9)
	Gold	169	5.0	30.7	5.5 (4.2-7.0)
	SLaM	11	1.5	4.4	2.5 (1.3-4.5)



95% confidence intervals for Aurum and Gold are estimated using a nonparametric bootstrap method. For causes of death that are rare in the general population, the upper confidence limit can be +infinity. This means that the 97.5% quantile of SMR estimates were +infinity, i.e., there were zero deaths in the comparison group in at least 2.5% of resamples. ** Redacted to prevent disclosure of small cell counts.

Figure 25 is a graphical summary of causes of death in the CPRD Aurum and CPRD Gold cohorts combined. In this diagram, the size of the circles is proportional to the total number of deaths for each underlying cause of death, while the darker sections each circle represent the number of excess deaths (calculated using age- and sex-specific mortality rates in the comparison group), such that the light sections represent the expected deaths. The figure shows ICD-10 subgroups with 50 or more deaths in the combined CPRD cohorts.

Figure 25: Expected and excess deaths, by cause, in a cohort of people who use illicit opioids in England, 2001-2018 (combined CPRD Aurum and CPRD Gold cohorts)



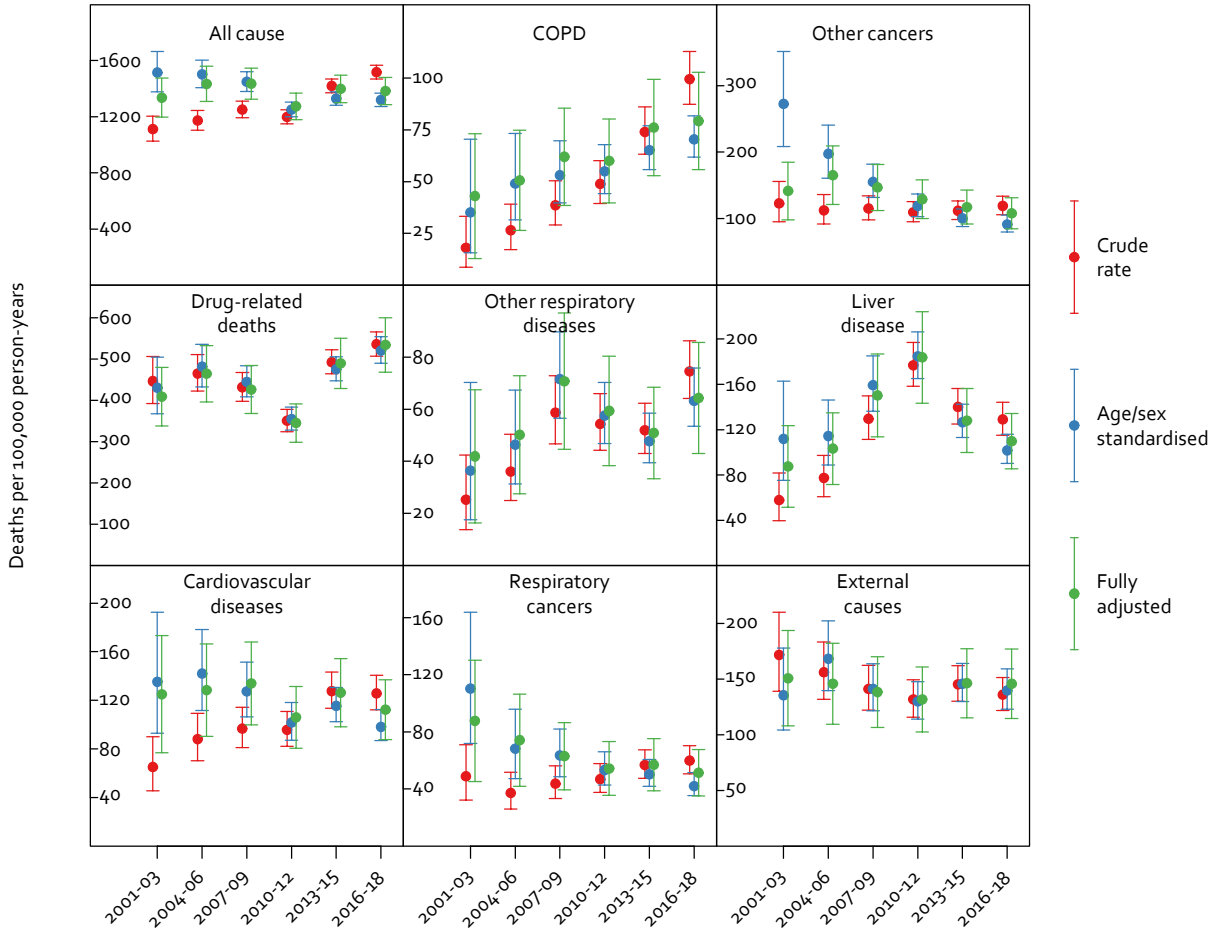
The size of the circles is proportional to the total number of deaths for each cause, while the darker section of the circle represents the number of excess deaths (calculated using age- and sex-specific mortality rates in the comparison group). COPD = chronic obstructive pulmonary disease

10.4.3 Changes in causes of death over time

Comparison between crude and age-adjusted mortality rates showed that ageing in the cohort contributes significantly to changes in crude rates over time. Figure 26 shows cause-specific mortality rates, comparing crude rates, age/sex adjusted rates (using direct standardisation), and age/sex/follow-up adjusted rates (using Poisson regression; subsequently referred to as 'fully adjusted'). The purpose of fully-adjusted rates is to account for differences in the duration of follow-up: in later calendar years, participants have been in the cohort for longer and may therefore be more likely to have stopped using drugs. COPD, ischaemic heart disease, cancers, and liver disease are strongly related to age, and therefore adjustment inflates rates in earlier years and deflates rates in later years (as the cohort is ageing and rates were standardised to the average population structure). Drug-related deaths and deaths due to accidents and suicides are much less age-related, and crude and adjusted estimates are therefore similar. For most causes of death, age/sex-adjusted and fully-adjusted rates are similar, though age/sex-adjusted rates for 'other cancers' are higher in early years. This relates to interactions between age of death and timing of deaths during follow-up, and may also result from chance distributions in the dataset.

The trend in deaths due to drug poisonings mirrors the trend reported in national surveillance data,[9] with an increase from 2010-12 onwards. The rate of deaths due to liver disease increases and then decreases, with a peak in 2010-12. The rate of death due to COPD increases approximately 2-fold, and this increase persists after adjustment for ageing. Time trends in mortality rates due to other diseases (circulatory diseases, other respiratory diseases, respiratory cancers, other cancers, suicides/accidents, and other causes) were either approximately constant or unclear due to wide confidence intervals.

Figure 26: Crude and age-adjusted rates of death by cause and period. Error bars are 95% confidence intervals



COPD = Chronic Obstructive Pulmonary Disease

The Poisson regression model shows that the time after cohort entry is an important determinant of mortality risk among participants with a history of using illicit opioids. In unadjusted analysis, both time after cohort entry and calendar time are associated with increased all-cause mortality rates, both for participants with a history of using illicit opioids and the comparison group. This is expected because age increases over time. After adjusting for age, calendar time is associated with reducing mortality rates in the comparison group (in keeping with reducing mortality rates in the general population), and there is a small increase in mortality rates as follow-up progresses. In contrast, among participants with a history of using illicit opioids there appears to be little association between calendar time and mortality after adjustment for age, while time after cohort entry is associated with reducing mortality. This may relate to reducing drug-related risks over time within individuals (Table 16).

Table 16: Associations between all-cause mortality and age, period (calendar year) and cohort (time since study entry and birth cohort), comparing patients with and without a history of using illicit opioids

Variable	Level	Stratum*	Unadjusted incidence rate ratio (95% CI)	Fully adjusted incidence rate ratio (95% CI)
History of using illicit opioids (ref: no history)			7.216 (6.998-7.442)	8.401 (7.231-9.796)
Age (linear)**			2.567 (2.516-2.619)	2.849 (2.790-2.910)
Age (quadratic)**			0.778 (0.759-0.797)	1.039 (1.015-1.063)
Sex	Male (ref: female)		1.261 (1.221-1.303)	1.304 (1.262-1.347)
Calendar year	2001-03 (ref)	Comparison	1	1
	2004-06		1.096 (0.935-1.289)	0.927 (0.784-1.099)
	2007-09		1.222 (1.055-1.421)	0.892 (0.763-1.046)
	2010-12		1.321 (1.147-1.527)	0.803 (0.689-0.939)
	2013-15		1.523 (1.329-1.755)	0.787 (0.677-0.919)
	2016-18		1.647 (1.439-1.895)	0.711 (0.611-0.831)
	2001-03 (ref)	Opioids	1	1
	2004-06		1.054 (0.956-1.163)	1.069 (0.966-1.184)
	2007-09		1.136 (1.038-1.246)	1.065 (0.969-1.172)
	2010-12		1.090 (0.999-1.192)	0.942 (0.859-1.036)
	2013-15		1.305 (1.199-1.423)	1.033 (0.943-1.133)
	2016-18		1.418 (1.304-1.544)	1.022 (0.933-1.121)
Years after cohort entry	[0-3) (ref)	Comparison	1	1
	[3-6)		1.204 (1.113-1.302)	1.077 (0.992-1.171)
	[6-9)		1.373 (1.267-1.488)	1.093 (1.002-1.192)
	[9-12)		1.704 (1.568-1.851)	1.221 (1.114-1.338)
	[12-15)		1.940 (1.772-2.123)	1.225 (1.106-1.355)
	15+		2.328 (2.095-2.584)	1.322 (1.171-1.490)
	[0-3) (ref)	Opioids	1	1
	[3-6)		0.924 (0.881-0.968)	0.806 (0.768-0.847)
	[6-9)		0.964 (0.916-1.014)	0.741 (0.703-0.781)
	[9-12)		0.992 (0.938-1.049)	0.687 (0.647-0.729)
	[12-15)		1.096 (1.028-1.168)	0.643 (0.599-0.688)
	15+		1.234 (1.140-1.335)	0.620 (0.568-0.676)

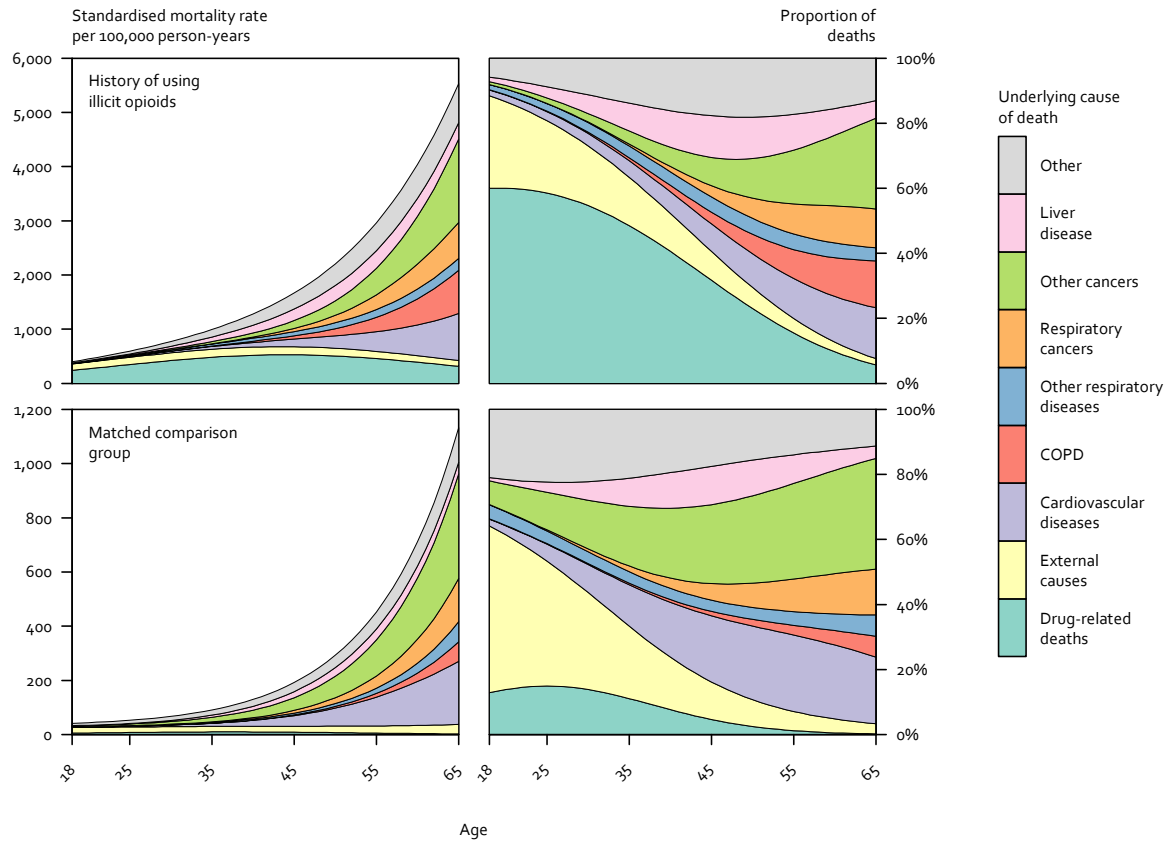
* In unadjusted and age-adjusted results, coefficients are estimated by fitting models on data stratified by exposure. In fully adjusted results, coefficients are estimated from models with interaction terms. ** Age-at-last-birthday is standardised as (age – mean(age)) / sd(age), such that the rate ratio represents an increase of one standard deviation in the variable.

10.4.4 Changes in causes of death by age

Among participants who use illicit opioids, deaths due to drug poisoning, accidents, and suicides were dominant at younger ages but the rate of death due to these causes was not strongly associated with age. The rate of death due to drug poisoning increased slightly to a peak at 44 and then slightly decreased. Deaths due to liver disease peaked at age 58 and then decreased. The rate of death due to circulatory diseases, respiratory diseases, and cancers all increased with age, and therefore the proportion of deaths due to drug poisoning decreased. Among participants who use illicit opioids, at age 20, drug poisonings accounted for 60% of deaths. At age 50, 23% of deaths were drug poisonings

(Figure 27 and Table 17). I found similar trends in the comparison group, but with lower absolute rates and a much smaller proportion of drug-related deaths, especially at older ages.

Figure 27: Standardised cause-specific mortality rates, by age, comparing participants with and without a history of using illicit opioids. Note different y-axes for panels on the left showing standardised rates.



COPD = chronic obstructive pulmonary disease

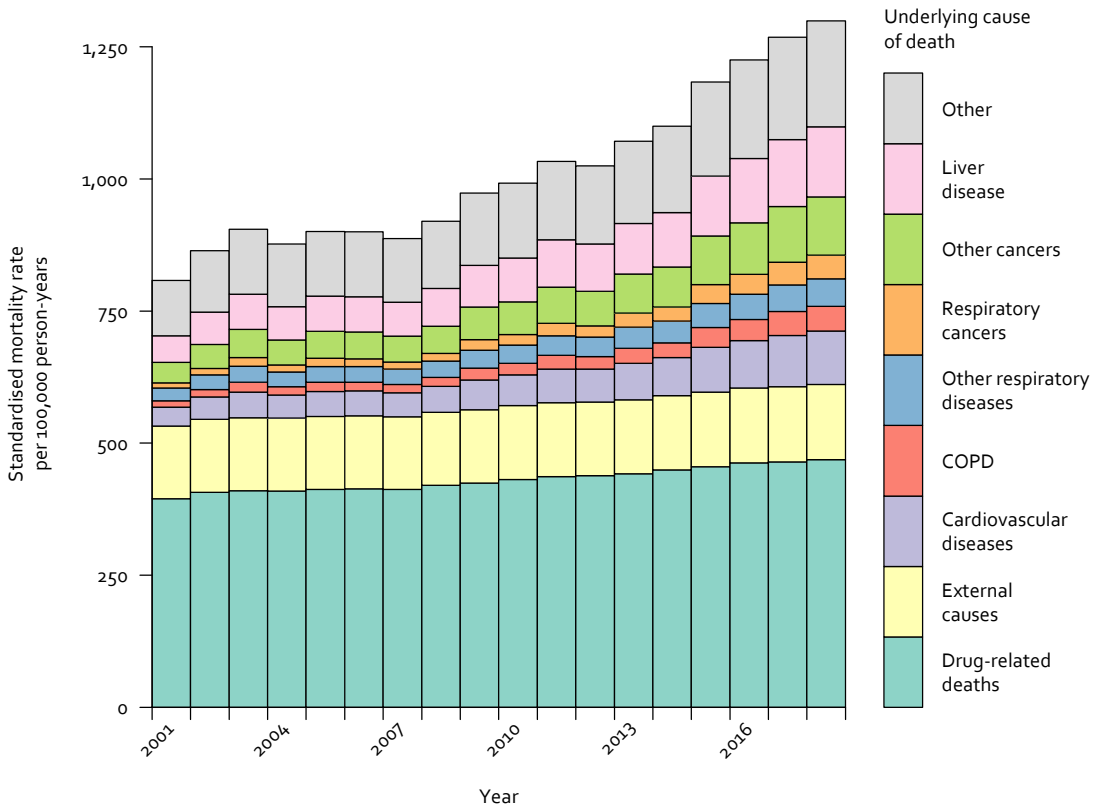
Table 17: Standardised mortality rates for selected ages, participants with a history of using illicit opioids, comparing deaths due to drug poisoning and non-communicable diseases

	Fatal drug poisonings		Non-communicable diseases*	
Age	Deaths per 100,000 person-years (95% CI)	% of deaths	Deaths per 100,000 person-years (95% CI)	% of deaths
20	271 (230-313)	60.0	31 (16-45)	6.8
25	348 (306-390)	58.5	62 (40-84)	10.5
30	422 (377-467)	54.7	121 (88-155)	15.7
35	483 (432-533)	48.5	227 (172-281)	22.8
40	520 (466-575)	40.6	405 (311-499)	31.6
45	529 (473-585)	31.7	696 (533-858)	41.7
50	507 (452-563)	23.0	1,155 (880-1,431)	52.4
55	459 (403-515)	15.5	1,860 (1,408-2,311)	62.7

* Cancers, cardiovascular, respiratory, and liver diseases

I then applied age-specific mortality rates to an exemplar population to show the independent effect of population ageing on patterns of death. Comparing 2010 (when the rate of opiate-related deaths was lowest in the population[262]) to 2018, population ageing was associated with an increase in fatal drug poisonings from 431 deaths (95% CI 374-489) per 100,000 person-years to 469 (409-528); an increase of 8.6%. Over the same period deaths due to cardiovascular, respiratory, liver diseases, and cancers combined increased from 280 deaths (199-360) per 100,000 person-years to 487 (358-616); an increase of 74%. Over the whole period, population ageing was associated with a tripling in the rate of death due to non-communicable diseases (Figure 28).

Figure 28: Age-specific mortality rates applied to an exemplar population of people who use illicit drugs in England (from the Unlinked Anonymous Monitoring Survey of Infections and Risk among People who Inject Drugs)



COPD = chronic obstructive pulmonary disease

10.5 Discussion

Key findings

In this cohort of people who use illicit opioids drawn from primary care data, all causes of death were more common than in the general population. Causes of death traditionally considered 'drug-related,' such as blood-borne viral infections and drug poisoning, had the highest relative risks but non-communicable diseases together caused more excess deaths. The age structure of the population is changing, with the average age increasing faster than the general population. This means that the population's health needs are shifting towards respiratory diseases, cardiovascular diseases, and cancers, but does not explain an increase in the rate of fatal drug poisonings.

10.5.1 Strengths and limitations

Associations between mortality and time/age in our results are consistent with those observed in other data, providing external validity. For example, the trend in deaths due to drug poisonings in our cohort is similar to the trend in population rates calculated from national mortality records (Figure 29). Non-communicable diseases are strongly age-related, with deaths due to liver disease peaking around age 60 and then reducing.

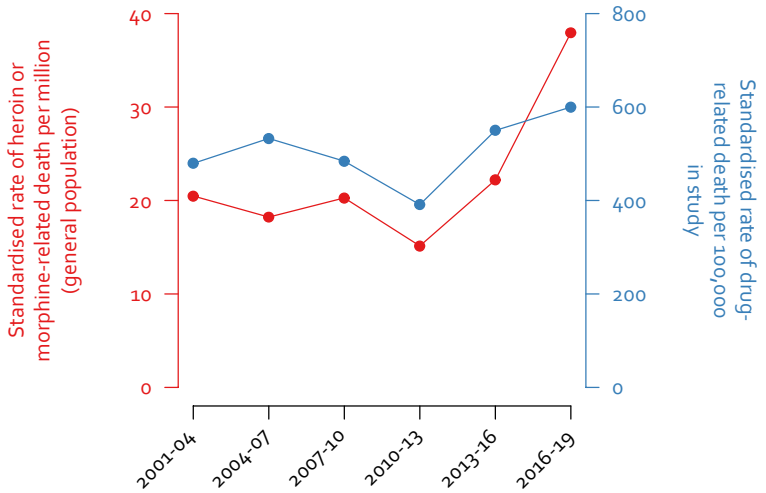
The distribution of causes of death was similar in the 3 cohorts, which provides additional validation of the CPRD cohorts, since the SLaM cohort uses a well-known recruitment method (people in structured treatment for heroin use), while the CPRD methods are more novel.

The study has 6 key limitations.

First, neither dataset included longitudinal data on progression of opioid dependence or cessation of drug use. I mitigated this by accounting for the association between the time after cohort entry and mortality risk. Among people who use illicit opioids but not the general population, I found that time after cohort entry was associated with reducing mortality rates after adjusting for age, possibly relating to cessation of drug use or other factors leading to a more 'stable' lifestyle over time. By including these effects in analysis, I provide more robust evidence that changes over time are not explained or biased by cessation of drug use in the cohort.

Second, there are methodological limitations to analyses of these time-varying factors. In common with many analyses of concurrent age, period, and cohort associations with disease risk, I expanded follow-up into discrete windows and used the independent variance (or overlaps) of these windows to isolate the associations. This method may be sensitive to the time periods selected, and it is difficult to test this in sensitivity analysis.[263] There may also be other important timescales that were not included in this analysis, such as birth cohorts, which may be associated with different types of drug use.

Figure 29: Population rate of opiate-related deaths in England compared to standardised rate of fatal drug poisonings in the HUPIO cohort



The population rate is calculated from mortality data published by ONS[9] and population estimates published by Nomisweb. Rates are directly standardised using the average population aged 15-79 between 2001 and 2019. Rates in the study are standardised using the method described above. Data and code for this chart are available at https://github.com/danlewer/hupio/tree/main/general_pop_rates.

Third, although the large CPRD cohorts allowed analysis of cause-specific mortality rates, there was limited power to estimate changes in cause-specific mortality over time with precision. For example, the results did not show whether cardiovascular mortality rates reduced among participants with a history of using illicit opioids, as they did in the general population.

Fourth, the classification of deaths uses the International Classification of Diseases and given the broad scope of this analysis, it was not possible to validate this classification or explore alternative groupings. It is possible that some deaths are misclassified, for example when someone dies suddenly and alone it can be difficult to determine the cause of death. This may mean that the rate of drug-related deaths in this cohort is either under- or over-estimated. Other causes of death may have a number of different possible classifications. For example, if someone with a chronic hepatitis C infection dies due to liver cirrhosis, the underlying cause of death may be either of those diagnoses.

Fifth, all 3 cohorts have selection biases. In validation,[208] the CPRD sample had similar demographic characteristics and mortality rates to other studies of this population, and 90% of patients in hospital receiving a diagnosis of "opioid dependence" were also captured by primary care records. This suggests that the cohort is a good sample of people with more severe opioid use or dependence. However, it may under-represent people who use opioids for shorter periods, less frequently, or have not sought treatment. These groups may be less likely to disclose illicit drug use to their doctor, and therefore less likely to be included in this study. The SLaM study is limited to people in treatment for heroin use, and therefore excludes people who have never sought treatment. In England, an estimated three-quarters of people who use illicit opiates have had at least one episode of treatment and half are currently engaged with treatment.[264] Those who have never engaged with treatment may include both higher risk patients who are not accessing harm reduction services, and lower risk patients who have lower need for services. Given the high proportion of the population who have

used drug treatment services and the long follow-up, the results for the SLaM cohort are likely to be a reasonable estimate of mortality rates among people who use heroin in London.

Sixth, determinants of mortality among people who use opioids vary between countries. For example, in North America prescription and illicit synthetic opioids have contributed to increasing opioid-related death.[148] In many low- and middle-income countries opioid agonist therapy and other harm reduction measures are less available.[265] Therefore, these results are not intended to be transportable to other countries. The transition in the predominant causes of death from drug poisoning and other 'external' causes to non-communicable diseases has also been observed among people in opioid agonist therapy in Australia, which is also a population with increasing average age.[41,266]

10.5.2 Interpretation and relevance for policy, practice, and research

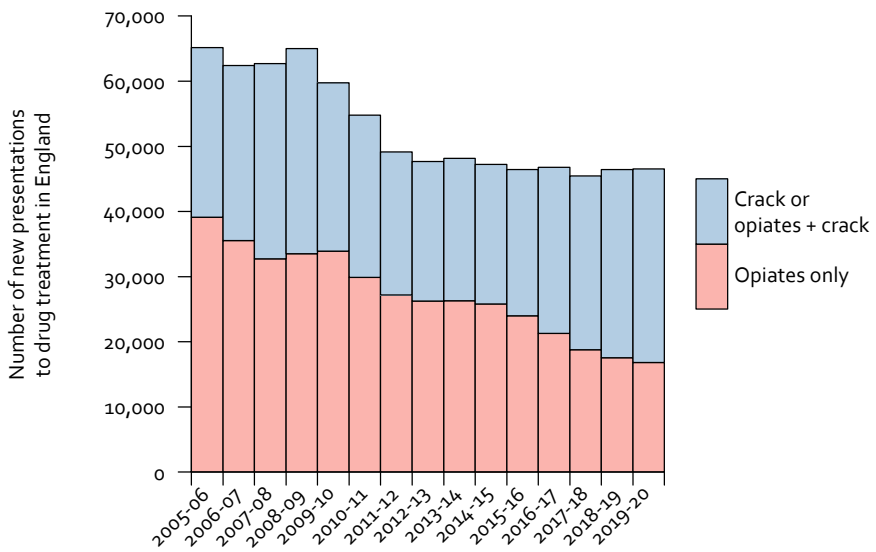
I found higher mortality rates across all causes of death, including many diseases with no obvious causal pathway from opioid use. This reflects a deprived and marginalised population with multiple determinants of poor health throughout life. It emphasises the need for interventions that improve general living conditions such as housing, and basic health improvement such as support for smoking cessation.

Several explanations have been previously proposed for the increasing number of drug-related deaths.[7,24,249] These include an ageing cohort of people who use drugs, increasing availability and purity of heroin, reducing investment in community drug treatment and other services that support this population, and reducing retention in opiate treatment. These results suggest that ageing is not an important driver of the increase in drug-related deaths, and other factors are likely to be more important than demographic factors.

Reductions in deaths due to liver disease may relate to the roll-out of direct acting antiviral treatment for hepatitis C, which historically has been common among people who use illicit opioids due to transmission when sharing injecting equipment.[11] This fits with the timing of the roll-out, which started in 2014. National surveillance data shows that the number of deaths due to hepatitis C related liver disease fell by 25% between 2015 and 2019, while the prevalence of hepatitis C RNA among people who inject drugs is falling.[267]

We found increasing mortality rates due to COPD, which persisted after adjusting for ageing in the study population. Deaths due to respiratory cancers did not increase in parallel and this may suggest it is caused by increases in smoking crack cocaine[268] and other drugs that damage the lungs through particles and thermal injury[35] (i.e. the mechanism does not appear to include carcinogenesis). Data from drug treatment services in England shows that the proportion of people starting treatment for heroin and/or crack cocaine who use crack cocaine increased from 40% in 2005/06 to 64% in 2019/20 (Figure 30).[246] The increase does not appear to relate to changing coding practices, as other respiratory diseases such as pneumonias and asthma that may be substitute diagnoses did not show a corresponding decrease.

Figure 30: New presentations to drug treatment services in England for heroin and/or crack cocaine use, 2005-06 to 2019-20



Source: National Drug Treatment Monitoring System, Public Health England[246]

Non-communicable diseases are likely to get more important in this population as the population continues ageing. Historical research has focused on prevention of overdoses, infections, and crime, and there are effective and cost-effective interventions that target these outcomes.[53,57,58] However, there is little research into interventions that can improve access to care for non-communicable disease in this population despite well-documented barriers.[13,269] There is a need for research into interventions that can improve healthcare access. Community drug treatment services are sometimes the only point of contact between people who use illicit opioids and health services, and cuts have meant that these services now provide a narrow service with little scope for holistic care.[7] These services need resources to care for clients with increasing health and social needs.

10.5.3 Conclusion

People who use illicit opioids in England have much higher mortality rates than the general population, and this excess mortality risk exists across all causes of death. Population ageing explains an increasing number of deaths due to non-communicable diseases but not an increasing number of fatal drug poisonings.

Linking statement

This chapter summarised mortality in 3 cohorts of people who use illicit opioids. It showed that mortality rates are extremely high. COPD is an important and increasing cause of death in this population, and the next chapter focuses on relative rates of COPD diagnosis and death and treatment after patients are diagnosed.

11 Burden and treatment of COPD among people who use illicit opioids: a matched cohort study in England

11.1 Summary

Background: Chronic obstructive pulmonary disease (COPD) is common among people who use illicit opioids. Health outcomes and treatment have not been previously studied.

Methods: I did a cohort study of 106,789 people in the Clinical Practice Research Datalink Aurum (CPRD) and Gold with illicit opioid use recorded between 1 January 2001 and 30 October 2018. I also sampled a 1:3 age/sex-matched comparison group of CPRD participants with no records of using illicit opioids. Diagnoses of COPD were derived from electronic information recorded by GPs, and mortality data was provided by the Office for National Statistics. I used Cox proportional hazards regression to estimate the association between illicit opioid use and (a) incidence of new COPD diagnosis, (b) death due to COPD. Among participants with a new diagnosis of COPD, I estimated the probability of 5 evidence-based treatments: (a) seasonal influenza vaccine, (b) pneumococcal vaccine, (c) pulmonary rehabilitation, (d) bronchodilators and/or corticosteroids, and (e) support with smoking cessation; and 4 adverse events: (a) acute exacerbations of COPD, (b) unplanned hospital admissions, (c) all-cause death, and (d) death with underlying cause of respiratory disease.

Results: After excluding participants with a previous diagnosis of COPD, 4,018/104,365 (3.8%) in the opioid group were diagnosed with COPD over a median 3.2 years of follow-up, compared to 3,331/319,000 (1.0%) over a median 5.5 years in the comparison group. Illicit opioid use was associated with 5.89 (95% CI 5.62-6.18) times the hazard of COPD diagnosis. 746/106,789 (0.7%) participants in the opioid group and 193/320,367 (0.06%) participants in the comparison group died with an underlying cause of COPD, and the hazard ratio was 14.59 (95% CI 12.28-17.33). Among participants diagnosed with COPD, those with comorbid illicit opioid use were more likely to be current smokers, underweight, have worse lung function, and more severe breathlessness. After adjustment for these differences, illicit opioids were associated with increased hazard of all adverse outcomes. For example, adjusted hazard ratios were 1.96 (95% CI 1.82-2.11) for hospitalised exacerbations and 2.18 (95% CI 1.80-2.64) for death due to respiratory disease. The probability of evidence-based treatment was similar for people who use illicit opioids and the comparison group, though few participants in either group received pneumococcal vaccine, smoking cessation support, or pulmonary rehabilitation.

Conclusion: Death due to COPD is 15 times more common among people who use illicit opioid than the general population. This inequality does not appear to be explained by differences in treatment after diagnosis, but later diagnosis may contribute. A strategy to prevent and treat COPD should include better diagnosis in accessible settings and prioritisation of smoking cessation by services that support this population.

11.2 Background

Key points

- COPD is a major cause of illness and death among people who use illicit opioids
- This is probably due to smoking of tobacco and drugs such as heroin and crack cocaine
- People who use heroin and crack cocaine experience barriers to healthcare generally, but treatment for COPD in this population has not been investigated

Chronic obstructive pulmonary disease (COPD) is a diverse respiratory condition characterised by airflow obstruction that is not fully reversible. It causes substantial morbidity and mortality in the general population of most countries,[270] is strongly associated with older age and tobacco smoking,[271] and is especially prevalent among people who use heroin and crack cocaine. Cross-sectional spirometry studies in community drug and alcohol services have found prevalence of COPD, defined as forced exhaled volume in 1 second (FEV1) less than 70% of forced vital capacity, of: 91/184 (49%) among people who smoke heroin in Liverpool,[272] 260/753 (35%) in a larger sample of people who smoke heroin in Liverpool,[46] 36/129 (28%) among patients at opioid agonist treatment clinics in Switzerland,[47] and a pooled value of 18% from an international systematic review of COPD prevalence among people who smoke opiates.[273] These values are particularly high given that participants in these studies are often in their 30's and 40's, and COPD is usually rare in people in this age group.

In Chapter 10 I showed that COPD is the underlying cause in 5%-6% of deaths among people who use illicit opioids in England. The rate of death due to COPD is increasing as the population ages, and I also found evidence that the age-specific COPD mortality risk is increasing, possibly due to increasing use of crack cocaine alongside opiates.

The high burden of COPD in this population is likely due to smoking of tobacco and illicit drugs. Tobacco smoking is extremely common among people who use illicit opioids,[220] and the duration and intensity of smoking may also be longer than for an average smoker. Smoking crack cocaine and heroin can cause additional damage to lungs through direct thermal injury, irritation of the airways by particles, and opiate-stimulated histamine release.[274–276]

I talked to 3 respiratory physicians in preparation for this analysis and each said that people who use heroin and crack cocaine are an important patient group. They felt that standard service models are not accessible for this group and therefore the quality of care is lower. I am not aware of previous research that has investigated COPD treatment in this population. One respiratory physician in South London tried to improve access by working with a local community drug treatment service. She set up a 'lung health clinic' in which clients with symptoms such as breathlessness or cough could be assessed on-site and referred to respiratory services.[185]

Although the need for better prevention and treatment in this population is already clear, there are few evidence-based approaches to improve care. Spirometry studies show that patients are willing to participate and receive a diagnosis, but treatment is mainly in primary care and referrals may not be successful (as participants in the qualitative study in Chapter 8 reported). This study aims to inform more accessible models of care by using primary care data to identify gaps in COPD treatment.

The research questions are:

1) Is illicit opioid use associated with a higher incidence of diagnosed COPD?
2) Is illicit opioid use associated with a higher rate of death due to COPD?
3) What is the likelihood of receiving evidence-based treatment after a new diagnosis of COPD among people with a history of using illicit opioids, and how does this compare to COPD patients without a history of illicit opioid use?
4) What is the likelihood of COPD exacerbations and death after a new diagnosis of COPD among people with a history of using illicit opioids, and how does this compare to COPD patients without a history of illicit opioid use?
5) Are people with a history of using illicit opioids who die due to COPD less likely to receive a diagnosis in primary care prior to death than other people?

I expected to find that illicit opioid use is associated with higher frequency of COPD diagnosis and death, worse access to treatment, and more adverse events after diagnosis.

11.3 Methods

This study included analysis of 2 matched cohorts comparing people with and without a history of using illicit opioids: (a) COPD incidence and mortality among people with no prior COPD diagnosis; (b) treatment and outcomes after among those with a new diagnosis of COPD. The analysis follows a published protocol.[277]

11.3.1 Data source

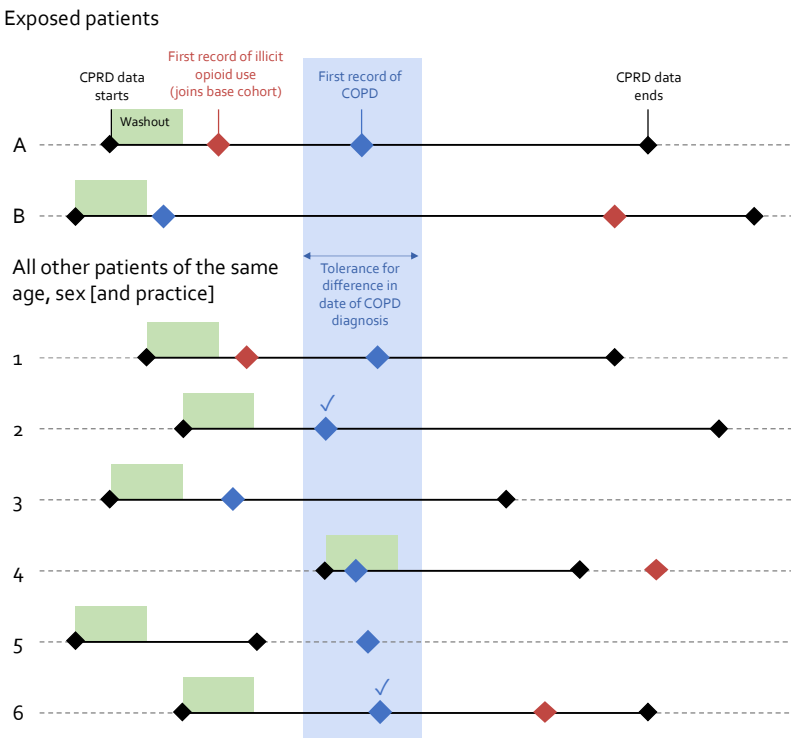
I used data from the Clinical Practice Research Datalink (CPRD) Aurum and Gold.[213,214] These databases contain pseudo-anonymised data from general practices in England covering approximately 13% and 8% of the population respectively. I limited our analysis to individuals eligible for linkage to external databases. After deriving study variables I combined data from the 2 databases.

Participants with a history of using illicit opioids were defined as those aged 18-64 with prescriptions of opioid agonist therapy (methadone or buprenorphine) or clinical observations such as 'heroin dependence'. A full codelist and validation is published and described in Chapter 9, showing that this sample has similar demographic characteristics and all-cause mortality rates as other samples of people who use illicit opioids.[208] The entry date was the latest of 1 January 2001, 12 months after entry to CPRD, or the first record of illicit opioid use. The importance of the 12-month washout period is explained in Chapter 9.

For each participant, I sampled with replacement 3 patients of the same sex and age (+/- 3 years) and from the same practice, with no previous records of illicit opioid use. The matched participants were assigned the same cohort entry date as the corresponding participant with a history of opioid use. This process is called 'exposure density sampling',[228] and is designed to minimise biases related to the definition of cohort entry.

Participants with a history of illicit opioid use and incident COPD were selected for a second stage of analysis. A new comparison group was drawn from the full CPRD database: people with incident COPD but no history of illicit opioids, with matching by age at diagnosis (+/- 3 years), sex, and date of COPD diagnosis (+/- 12 months). This matching process is shown in Figure 15. I planned to additionally match patients by GP practice, but there were insufficient patients with COPD and no history of illicit opioids in some practices.

Figure 31: Exposure density sampling to create a comparison group of people with a COPD diagnosis but no history of illicit opioid use



In this example, patient A has a new diagnosis after cohort entry, while patient B has prevalent COPD at cohort entry and is excluded. Ticks represent potential matches from which the unexposed group for patient A is sampled.

11.3.2 Definition of COPD

New diagnoses of COPD in CPRD Gold were based on a validated list of diagnoses that has an estimated positive predictive value of 87%.[278] There is currently no validated COPD phenotype for SNOMED (the clinical taxonomy used in CPRD Aurum) and I created a new phenotype by searching for terms in the SNOMED data dictionary using the keywords "copd", "chronic obstruct*", "bronchitis", "emphysema", and then screening the results. The list of SNOMED codes is available at: https://github.com/danlewer/hupio/blob/main/codelists/aurum_copd.csv/.

11.3.3 Outcomes for participants with COPD

Based on the NICE guidance NG115 'chronic obstructive pulmonary disease in over 16s: diagnosis and management',[279] I defined 5 treatment outcomes: (a) seasonal influenza vaccination, (b) pneumococcal vaccine, (c) pulmonary rehabilitation, (d) COPD-specific medication, (e) support with smoking cessation. Except for seasonal influenza vaccine, participants were classified as receiving the intervention in the first 12 months after diagnosis or not (i.e. binary outcomes). For seasonal influenza vaccine, I analysed each flu season (1 September – 31 March) after COPD diagnosis separately. Participants diagnosed with COPD during a flu season who received a vaccine prior to diagnosis were considered vaccinated. Lists of prescriptions and clinical codes for each outcome are provided in the pre-published protocol for this study.[277]

Table 18: Outcomes: COPD treatment

Intervention	Prescriptions and clinical events	Ineligible groups
Seasonal influenza vaccine	• Prescription of vaccine • Record of vaccine given in another setting	None
Pneumococcal vaccine	• Prescription of vaccine • Record of vaccine given in another setting	Patients with a pneumococcal vaccine before diagnosis of COPD
Pulmonary rehabilitation	• Pulmonary rehabilitation class • Referral for pulmonary rehabilitation	None
COPD-specific medication	• Inhaled corticosteroids • Oral corticosteroids • Bronchodilators	None
Smoking cessation support	• Referral to a specialist stop smoking team • Prescription of varenicline • Prescription of bupropion • Prescription of nicotine replacement therapy • Delivery of behavioural support to stop smoking	Patients who do not have records of current smoking at the time of COPD diagnosis

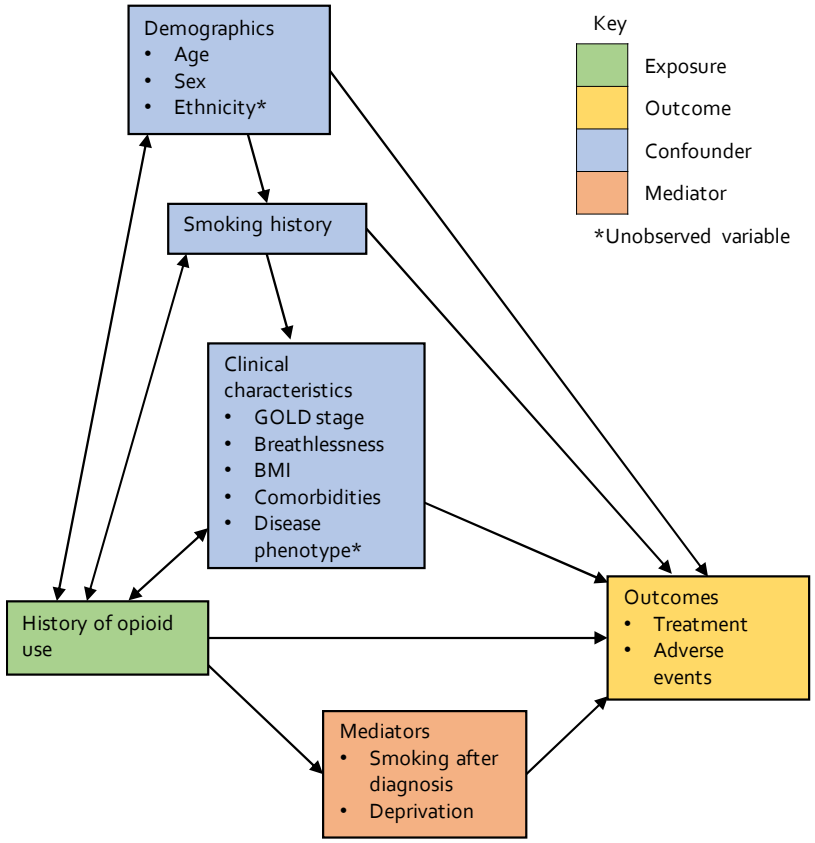
I defined 4 adverse outcomes after diagnosis of COPD: (a) acute exacerbations of COPD, defined as a hospital admission with a primary diagnosis of COPD (ICD-10 J41-J44), or COPD with acute infection or acute exacerbation in any diagnostic position (J44.0 or J44.1); a definition that has been validated;[280]; (b) unplanned hospital admissions with a primary diagnosis of respiratory disease (J00-J99); (c) all-cause death; (d) death with underlying cause of respiratory disease (J00-J99).

11.3.4 Covariates

For analysis of incidence of COPD and death due to COPD, analyses were minimally adjusted (i.e. adjusted for factors in the matching design: age, sex, and calendar year), and then additionally adjusted for smoking status in a mediation analysis.

For analyses of treatment and adverse outcomes after a new diagnosis of COPD, I selected covariates based on an a-priori causal model. The variables interact in the same way for both groups of outcomes (COPD treatment and adverse outcomes). An important feature of this model is that it considers the impact of a history of using illicit opioids (or membership of the population using illicit opioids) on the study outcomes, rather than the direct effects of drug use. An alternative study looking at the direct effects of illicit opioids might consider pathways such as interactions between opioids and COPD medications, or the effect of opioid intoxication on appointment attendance. This study considers the total effect of a history of illicit opioids on COPD incidence and treatment, including factors such as patients' expectations, stigma among staff, and related barriers to healthcare such as imprisonment. An example of a question that this study aims to answer is: "when a GP diagnoses a patient with COPD, does the fact the patient uses heroin affect their probability of getting a pneumococcal vaccine?" The causal model is shown in Figure 32.

Figure 32: Causal model showing how a history of illicit opioid use may affect the probability of treatment and adverse outcomes after a diagnosis of chronic obstructive pulmonary disease



BMI = body mass index. Disease phenotype refers to the type of COPD disease, most commonly defined as chronic bronchitis or emphysema.

Based on this model, I identified confounders as age, sex, ethnicity, smoking history (i.e. smoking before diagnosis), and clinical characteristics of COPD. In the theoretical model, these variables are associated with opioid use and independently cause the outcomes.

- I defined smoking status as current-, ex-, or never-smoker, using the most recent recorded status before cohort entry.
- I measured body mass index using the most recent data available before cohort entry.
- I defined comorbidities as the count of unique ICD-10 chapters 2-14 and 17 (excluding chapters such as 'infections' that may not represent a long-term condition) recorded in hospital data in the 3 years before COPD diagnosis. This approach to measuring comorbidity has been used in other studies.[79] I used hospital data to measure comorbidity because engagement with primary care is likely to differ by history of opioid use, and therefore comorbidity based on primary care data may be biased. I chose the count of ICD-10 chapters over the commonly-used Charlson Index because the Charlson Index excludes many important diseases and is outdated, for example it assumes there is no effective treatment for HIV infection.

- COPD GOLD stage[281] was based on forced exhaled volume in 1 second (FEV1) /predicted FEV1 (i.e. spirometry). Predicted FEV1 was derived from the patient's age, height, sex, and ethnicity[282] (with the algorithm defined here: https://gist.github.com/danlewer/dcc13f0d01d2a0dd4c8266690927b9fa).
- Breathlessness was defined using the MRC dyspnoea scale,[283] where 1 = no breathlessness except with strenuous exercise, 2 = shortness of breath when hurrying on a level, 3 = walks slower than people of the same age or has to stop for breath when walking, 4 = stops for breath after walking about 100 metres, 5 = too breathless to leave the house.

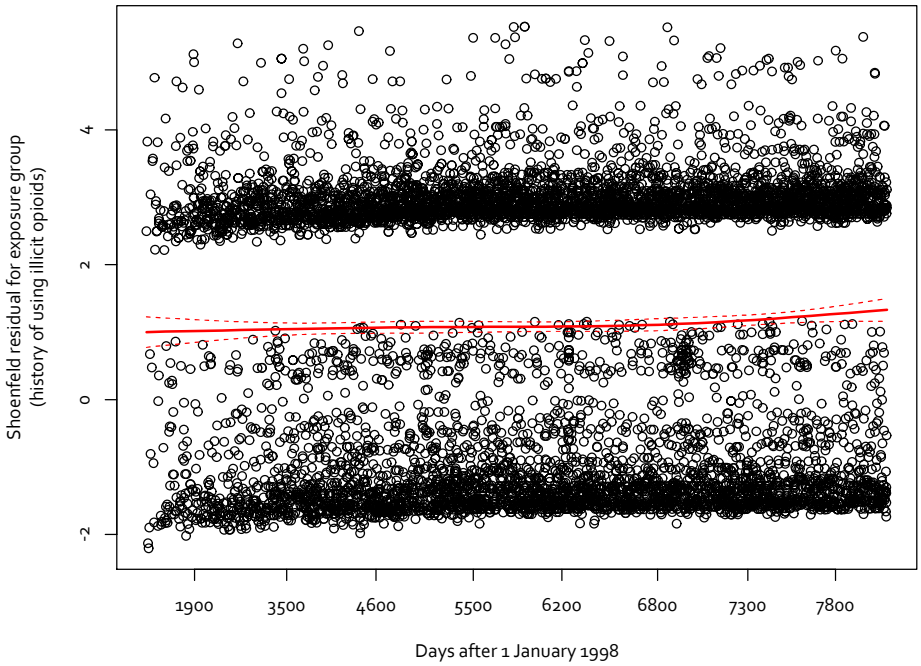
In the model, deprivation is considered a mediating variable. This is because a history of using illicit opioids is likely to affect many socioeconomic circumstances, including the neighbourhood where someone lives and their employment status. Although deprivation is associated with illicit opioid use and may affect COPD-related outcomes, based on this model I decided not to consider it is a confounding variable because this may lead to over-adjustment. I did participants' Index of Multiple Deprivation[284] (a composite measure of neighbourhood characteristics such as crime and employment) for descriptive purposes. Ethnicity and disease phenotype (the subtype of COPD such as chronic bronchitis or emphysema) are potential confounders; however they are not consistently recorded in primary care data.

11.3.5 Analysis

The analysis had 4 stages:

(1) **Frequency of death due to COPD**. I used survival analysis of the time between cohort entry and death with underlying cause of COPD, with censoring at death due to other causes or 30 October 2018. Following the recommended analysis for exposure density sampled data,[228] individuals were deduplicated (as the comparison group is sampled with replacement) and assigned the earliest cohort entry, and data expanded so that history of opioid use and age were time-varying. I used a left-truncated Cox proportional hazards model with times relative to 1 January 2001. The model was first adjusted for age and sex, and then additionally adjusted for smoking as a mediation analysis (i.e., to what extent does recorded smoking status explain inequalities in mortality due to COPD?). Participants were matched on age and sex, and adjustment by age and sex is to account for potential imbalances that arise due to differential follow-up. I assessed the proportional hazards assumption by testing the non-linearity of association between time and Schoenfeld residuals (using the R function survival::cox.zph), then visually assessing linearity using a plot (example in Figure 33 - in this case the assumption of proportional hazards is considered reasonable).

Figure 33: Example plot of Schoenfeld residuals vs. time. The outcome for this plot is death with underlying cause of Chronic Obstructive Pulmonary Disease



(2) **Frequency of new diagnosis of COPD.** I reported the prevalence of COPD at cohort entry and then excluded these participants. I then used the same approach as in step (1) to estimate the association between history of illicit opioid use and incident COPD. Participants were censored at death or exit from CPRD.

(3) **Probability of diagnosis of COPD before death due to COPD.** It is possible that some people never receive a diagnosis before death, and therefore were never treated. I calculated the proportion of people who died due to COPD that received a previous diagnosis of COPD, and the time between diagnosis and death.

(4) **Treatment after new diagnosis of COPD.** Among participants with a new diagnosis of COPD, I used Poisson regression to estimate risk ratios with a binary dependent variable showing whether the participant received each intervention, and independent variables of history of illicit opioid use and an offset for the log follow-up time (usually 365 days, but sometimes less where follow-up ended less than 1 year after diagnosis). For seasonal influenza vaccines, participants are eligible for a vaccine every season and have a new follow-up period starting on 1 September each year. I included each season separately and used a mixed Poisson model with random intercepts for the individual identifier to account for duplicated individuals in this analysis. I used the R function lme4::glmer for the mixed model.[285]

(5) **Adverse outcomes after new diagnosis of COPD.** Among participants with a new diagnosis of COPD, I used the same approach as in step (1) to estimate the association between history of illicit opioid use and each outcome. Participants were censored at 30 October 2018.

11.3.6 Approach to missing data

In preliminary descriptions of the dataset to support the analysis protocol,[277] I identified missing data in smoking status, COPD stage, breathlessness symptoms, and BMI. Analysis of the frequency of death due to COPD and diagnosis of COPD only use smoking status, in a mediation analysis. Analyses of outcomes after diagnosis of COPD use all 4 variables with missing data. I described the distribution of missing data in terms of other key variables, to explore the plausibility of data being 'missing completely at random' (meaning that observed values are representative of a sample with no missing data), or if missingness is associated with other observed variables.[286] I anticipated that data would not be 'missing completely at random'. For example, we might expect that younger participants or those with less severe symptoms would be more likely to have missing smoking status, because they are less likely to visit their GP. Therefore, I used the 'missing at random' assumption, under which missing data can be explained using observed variables, to generate multiple imputed complete datasets. I used the R package 'Amelia'[287] to generate 20 complete datasets for each analysis. Most analyses used Cox proportional hazards regression, and in these imputation models I included the event indicator (1 or 0) and the Nelson-Aalen estimator of the cumulative baseline hazard[288] calculated using the R function mice::nelsonaalen in the imputation formula. I then conducted analysis on each imputed dataset and combined the estimates (e.g. log hazard ratios) and standard errors using Rubin's rule.[289]

In the study protocol[277] I planned to use a 'missing indicator' method in which missing observations are assigned a 'missing' category and included in analysis. The logic was that missingness might be independently associated with outcomes, such that data is 'missing not at random'. For example, engagement with GPs or general health (unobserved variables) might be associated with spirometry being conducted at diagnosis, or smoking status being recorded, and also be associated with outcomes such as influenza immunisation. However, simulation studies have shown that the 'missing indicator' method does not help when data are 'missing not at random', is often biased, and can even cause bias where data are 'missing completely at random'.[290,291] I therefore chose to use multiple imputation for the main analysis, and compare the main results with analyses using a complete case method and the planned missing indicator method.

11.4 Results

11.4.1 Characteristics of participants

The whole cohort included 106,789 participants with a history of using illicit opioids and 320,367 matched participants with no history of using illicit opioids. The median age at study entry was 35.1 and 69.1% were male. Participants with a history of using illicit opioids were more likely to be underweight (5.1% vs. 2.1%), less likely to be overweight or obese (31.1% vs. 43.5%), more likely to be current smokers (78.2% vs. 33.7%), had more comorbidities on average (mean 1.2 vs. 0.4), and were more likely to live in deprived neighborhoods (42.5% vs. 29.1% living in the most deprived quintile by Index of Multiple Deprivation). Table 19 summarises the characteristics of participants used in analysis of incident COPD and COPD-related death.

Table 19: Characteristics of participants for analysis of incident COPD diagnosis and COPD-related deaths

Variable	Level	History of using illicit opioids n (%)	Comparison group n (%)
Total		106,789 (100.0)	320,367 (100.0)
Follow-up (linked data)*	Median [IQR]	8.7 [4.3-13.5]	9.5 [5.0-14.4]
Follow-up (CPRD)*	Median [IQR]	3.2 [1.2-7.3]	5.5 [2.5-10.4]
Age at cohort entry	Median [IQR]	35.1 [29.0-42.3]	35.1 [29.0-42.4]
Sex	Male	73,791 (69.1)	221,373 (69.1)
	Female	32,998 (30.9)	98,994 (30.9)
Body mass index (kg/m2)	Underweight (<18.5)	5,463 (5.1)	6,827 (2.1)
	Healthy [18.5-25)	44,389 (41.6)	105,814 (33.0)
	Overweight [25-30)	20,339 (19.0)	83,682 (26.1)
	Obese [30-40)	11,127 (10.4)	48,735 (15.2)
	Severely obese (40+)	1,779 (1.7)	7,195 (2.2)
	Missing	23,692 (22.2)	68,114 (21.3)
	Median [IQR]	23.7 [21.0-27.5]	25.6 [22.7-29.3]
Smoking at index	Never	7,261 (6.8)	146,342 (45.7)
	Ex	7,043 (6.6)	39,818 (12.4)
	Current	83,486 (78.2)	107,846 (33.7)
	Missing	8,999 (8.4)	26,361 (8.2)
Comorbidities	0	53,626 (50.2)	246,001 (76.8)
	1-2	33,975 (31.8)	61,001 (19.0)
	3-4	12,544 (11.7)	10,448 (3.3)
	5-7	5,506 (5.2)	2,609 (0.8)
	8+	1,138 (1.1)	308 (0.1)
	Median [IQR]	0 [0-2]	0 [0-0]
	Mean [sd]	1.2 [1.8]	0.4 [0.9]
Index of multiple deprivation	1 - Least deprived	7,412 (6.9)	44,051 (13.8)
	2	11,361 (10.6)	52,047 (16.2)
	3	16,339 (15.3)	57,411 (17.9)
	4	26,090 (24.4)	73,151 (22.8)
	5 - Most deprived	45,396 (42.5)	93,268 (29.1)
	Missing	191 (0.2)	439 (0.1)
Prevalent COPD		2,424 (2.3)	1,367 (0.4)
Deaths due to COPD	Number [rate per 100,000 person-years]	746 [78]	193 [6]
Incident COPD	Number [rate per 100,000 person-years]	4,018 [766]	3,311 [151]

* Follow-up for 'linked data' refers to follow-up until the final date when externally linked data (i.e. ONS mortality and Hospital Episode Statistics) is available; while follow-up for 'CPRD' refers to follow-up until the final date when primary care data (used for diagnosis of COPD) is available.

The cohort with a new diagnosis of COPD included 3,903 with a history of using illicit opioids and 19,515 matched participants with no history of using illicit opioids. The median age at diagnosis was 48.8 in the opioid group 49.1 in the comparison group, and 64.2% were male. Participants with a history of using illicit opioids were more likely to be underweight (11.1% vs. 3.8%), less likely to be overweight or obese (43.9% vs. 60.9%), more likely to be current smokers (86.1% vs. 65.6%), had more comorbidities on average (mean 2.4 vs. 1.7), and more severe COPD at diagnosis (median FEV1/predicted 63.0% vs. 70.0%; and 30.7% vs. 16.8% had MRC breathlessness scores of 3-5). Table 20 summarises characteristics of participants with a new diagnosis of COPD.

Table 20: Characteristics of patients with a new diagnosis of COPD

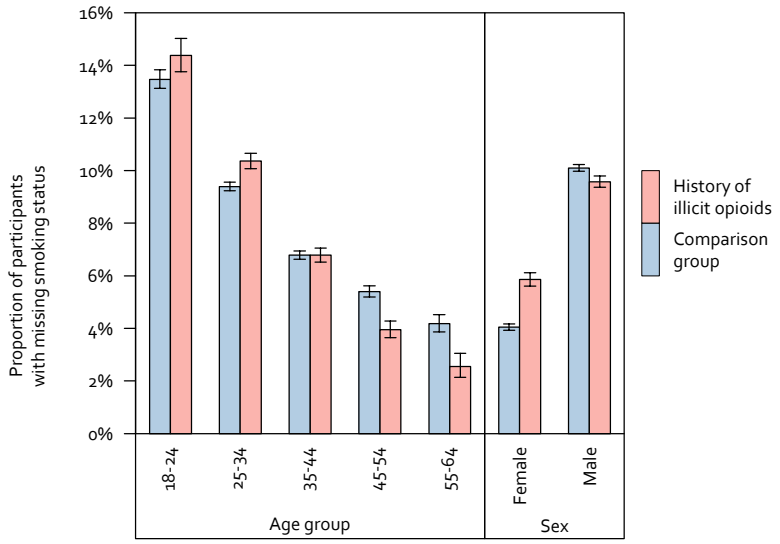
Variable	Level	History of using illicit opioids n (%)	Comparison group n (%)
Total		3,903 (100.0)	19,515 (100.0)
Follow-up (linked data)*	Median [IQR]	3.2 [1.0-6.5]	3.7 [1.2-7.1]
Follow-up (CPRD)*	Median [IQR]	3.0 [1.2-5.7]	3.6 [1.7-6.6]
Age at diagnosis	Median [IQR]	48.8 [43.4-54.4]	49.1 [43.7-54.9]
Sex	Male	2,507 (64.2)	12,535 (64.2)
	Female	1,396 (35.8)	6,980 (35.8)
Body mass index (kg/m2)	Underweight (<18.5)	434 (11.1)	739 (3.8)
	Healthy [18.5-25)	1,623 (41.6)	6,473 (33.2)
	Overweight [25-30)	880 (22.5)	5,874 (30.1)
	Obese [30-40)	689 (17.7)	4,982 (25.5)
	Severely obese (40+)	146 (3.7)	1,025 (5.3)
	Missing	131 (3.4)	422 (2.2)
	Median [IQR]	24.2 [20.5-29.1]	26.8 [23.0-31.3]
Smoking at index	Never	61 (1.6)	2,276 (11.7)
	Ex	433 (11.1)	4,106 (21.0)
	Current	3,359 (86.1)	12,803 (65.6)
	Missing	50 (1.3)	330 (1.7)
Comorbidities	0	1,258 (32.2)	8,522 (43.7)
	1-2	1,019 (26.1)	5,465 (28.0)
	3-4	893 (22.9)	3,371 (17.3)
	5-7	580 (14.9)	1,820 (9.3)
	8+	153 (3.9)	337 (1.7)
	Median [IQR]	2 [0-4]	1 [0-3]
	Mean [sd]	2.4 [2.4]	1.7 [2.1]
COPD Gold spirometry stage: forced exhaled volume in 1 second (FEV1) / predicted (%)	Mild (80%+)	611 (15.7)	4,476 (22.9)
	Moderate (50%-80%]	1,298 (33.3)	7,654 (39.2)
	Severe (30%-50%]	605 (15.5)	1,966 (10.1)
	Very severe (<30%)	191 (4.9)	340 (1.7)
	Missing	1,198 (30.7)	5,079 (26.0)
	Median [IQR]	63.0 [46.0-78.0]	70.0 [57.0-83.0]
MRC dyspnoea scale	Grade 0 (least severe)	331 (8.5)	4,199 (21.5)
	Grade 1	957 (24.5)	5,278 (27.0)
	Grade 2	747 (19.1)	2,384 (12.2)
	Grade 3	377 (9.7)	783 (4.0)
	Grade 4 (most severe)	73 (1.9)	114 (0.6)
	Missing	1,418 (36.3)	6,757 (34.6)
Index of Multiple Deprivation	1 - least deprived	187 (4.8)	2,109 (10.8)
	2	304 (7.8)	2,866 (14.7)
	3	520 (13.3)	3,511 (18.0)
	4	937 (24.0)	4,687 (24.0)
	5 - most deprived	1,952 (50.0)	6,325 (32.4)
	Missing	3 (0.1)	17 (0.1)

* Follow-up for 'linked data' refers to follow-up until the final date when externally linked data (i.e. ONS mortality and Hospital Episode Statistics) is available; while follow-up for 'CPRD' refers to follow-up until the final date when primary care data is available.

11.4.2 Distribution of missing data

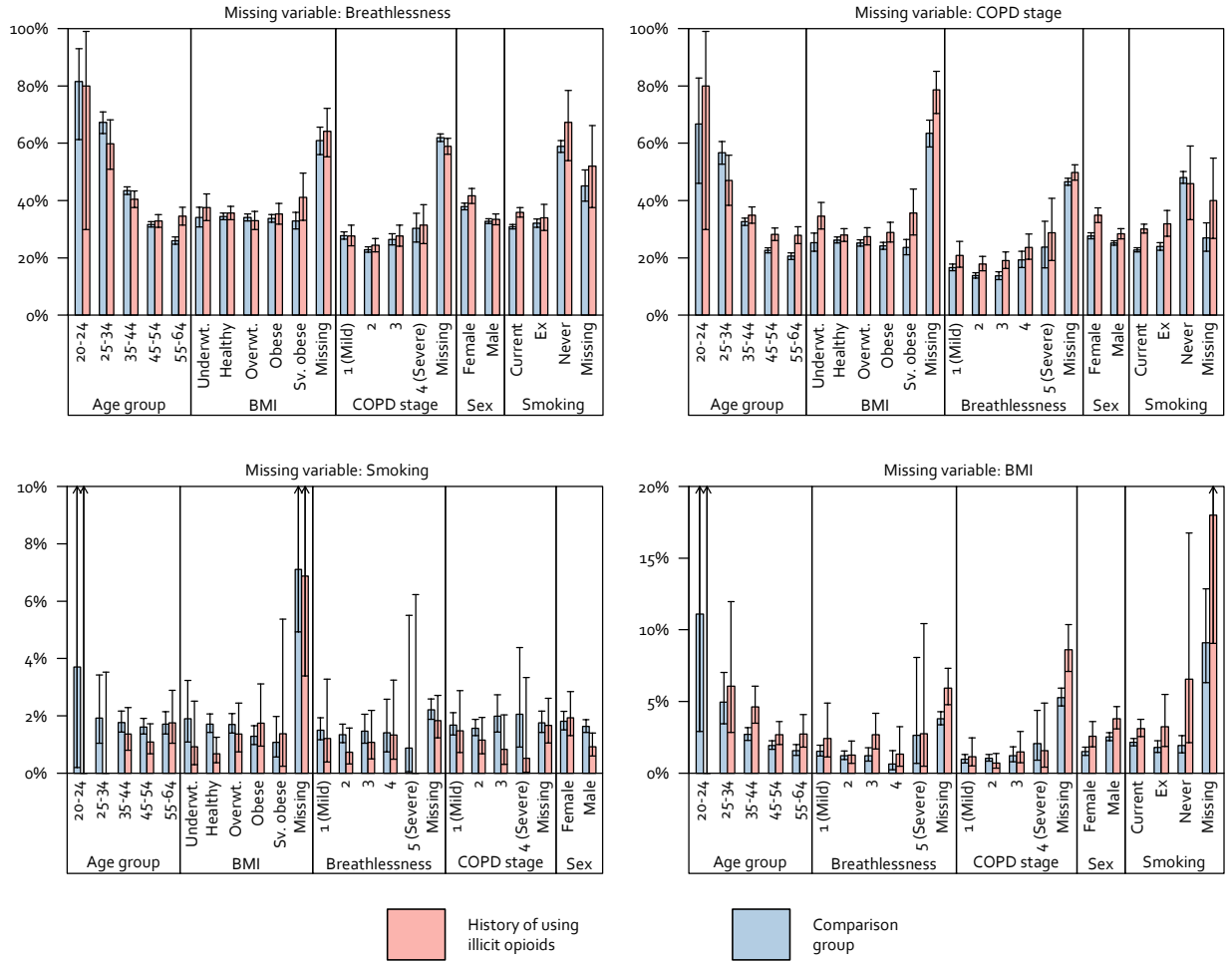
In the whole cohort of 106,789 participants with a history of using illicit opioids and 320,367 matched participants, missing smoking status was more common among younger participants and among men (Figure 34).

Figure 34: Proportion of participants (95% confidence intervals) with no records of smoking status at baseline in the whole cohort, by age, sex, and history of illicit opioid use. Error bars show 95% binomial confidence intervals.



In the cohort of people with a new diagnosis of COPD, data were missing for the MRC breathlessness scale, COPD stage (FEV1/predicted FEV1), smoking status, and BMI. The distribution of this missing data is shown in Figure 35. Missing breathlessness, COPD stage, and BMI were associated with younger age. Missingness in one variable was associated with missingness in other variables. Missing data for breathlessness and COPD stage were associated with never smoking.

Figure 35: Distribution of missing data in the cohort with a new diagnosis of COPD. Error bars show 95% binomial confidence intervals

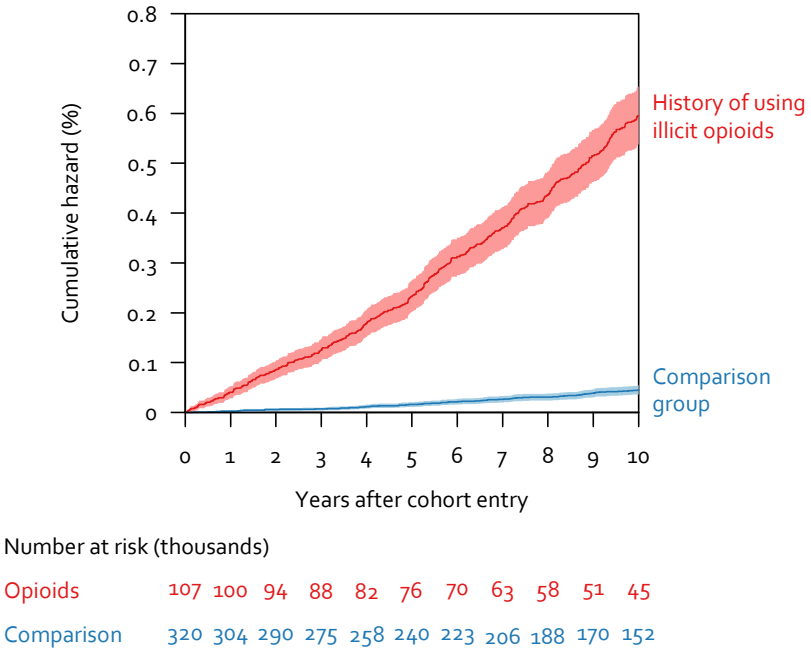


COPD = chronic obstructive pulmonary disease. BMI = body mass index. "Underwt." = underweight; "Overwt." = overweight; "Sv. obese" = severely obese. COPD stage is measured using forced exhaled volume in 1 second (FEV1) as percentage of predicted (see methods). Breathlessness is measured using the MRC breathlessness (dyspnoea) scale (see methods).

11.4.3 Death with an underlying cause of COPD

Among patients with a history of using illicit opioids, 746/106,789 (0.7%) died with an underlying cause of COPD over a median 8.7 years of follow-up. This compared to 193/320,367 (0.06%) over a median 9.5 years of follow-up in the comparison group. Kaplan Meier estimates suggested a cumulative incidence of 0.60% (95% CI 0.54%-0.65%) and 0.04% (95% CI 0.03%-0.05%) after 10 years in the opioid and comparison groups respectively (Figure 36).

Figure 36: Kaplan-Meier estimates of the cumulative hazard of death with an underlying cause of COPD, comparing participants with and without a history of using illicit opioids (shaded area shows 95% confidence interval)



The Cox proportional hazards model showed that participants with a history of illicit opioids had 14.59 (95% CI 12.28-17.33) times the hazard of death with an underlying cause of COPD. After adjustment for smoking status at cohort entry, the hazard ratio was 8.84 (95% CI 7.39-10.56). As expected, smoking and age were strongly associated with death due to COPD (Table 21).

Table 21: Hazard ratio of death with underlying cause of COPD (95% CI)

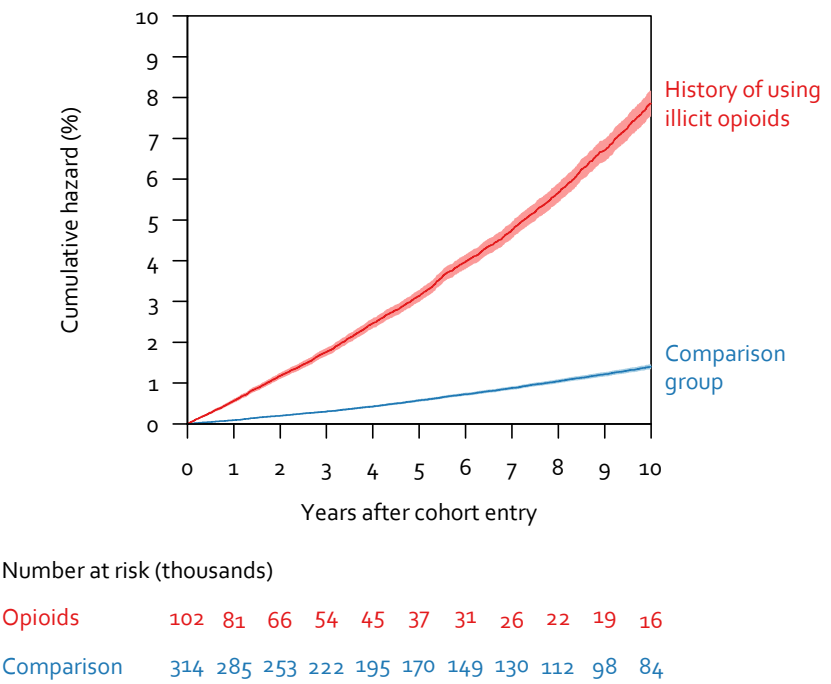
Variable	Level	Adjusted for age and sex only*	Additionally adjusted for smoking status
History of illicit opioids		14.59 (12.28-17.33)	8.81 (7.36-10.54)
Age group	Under 25	4.26 (0.78-23.31)	4.71 (0.86-25.76)
	25-34 (ref)	1	1
	35-44	13.58 (4.98-37.03)	13.75 (5.04-37.51)
	45-54	67.67 (25.16-182.03)	74.02 (27.51-199.14)
	55-64	272.78 (101.60-732.39)	343.89 (128.03-923.68)
	65+	469.37 (173.50-1269.84)	763.62 (281.94-2068.27)
Female sex (ref: male)		1.03 (0.89-1.19)	1.09 (0.94-1.26)
Smoking	Never (ref)	1	1
	Ex	6.59 (4.27-10.18)	4.66 (3.01-7.22)
	Current	20.13 (13.89-29.18)	8.12 (5.55-11.90)

* Hazard ratios for illicit opioid use and smoking status are adjusted for age and sex. Age is adjusted for sex, and sex is adjusted for age. Hazard ratios in the 'additionally adjusted for smoking status' column are adjusted for all other variables.

11.4.4 Incidence of new COPD diagnoses

Among patients with a history of using illicit opioids, 2,424/106,789 (2.3%) had a diagnosis of COPD before joining the cohort, compared to 1,367/320,367 (0.4%) in the comparison group. Among participants with no previous diagnosis of COPD, 4,018 participants with a history of using illicit opioids were diagnosed during a median 3.2 years of follow-up, with a rate of 766 per 100,000 person-years, compared to 3,311 cases in the comparison group over a median of 5.5 years of follow-up, with a rate of 193 per 100,000 person-years. Kaplan Meier estimates suggested a cumulative incidence of 7.53% (95% CI 7.22%-7.83%) and 1.34% (95% CI 1.29%-1.39%) after 10 years in the opioid and comparison groups respectively (Figure 37).

Figure 37: Kaplan-Meier estimates of the cumulative hazard of new COPD diagnosis, comparing participants with and without a history of using illicit opioids (shaded area shows 95% confidence interval)



The Cox proportional hazards model showed that participants with a history of illicit opioids had 5.89 (95% CI 5.62-6.18) time the hazard of a new COPD diagnosis. After adjustment for smoking, the hazard ratio was 3.26 (95% CI 3.11-3.43). As expected, smoking and age were strongly associated with COPD diagnosis (Table 22).

Table 22: Hazard ratio of diagnosis of COPD (95% CI)

Variable	Level	Adjusted for age and sex only	Additionally adjusted for smoking status*
History of illicit opioids		5.89 (5.62-6.18)	3.29 (3.13-3.46)
Age group	Under 25	0.23 (0.10-0.51)	0.24 (0.11-0.54)
	25-34 (ref)	1	1
	35-44	6.10 (5.24-7.10)	6.29 (5.40-7.33)
	45-54	16.37 (14.09-19.02)	18.60 (16.01-21.61)
	55-64	29.92 (25.70-34.85)	39.16 (33.62-45.62)
	65+	30.74 (25.92-36.45)	48.19 (40.61-57.18)
Female sex (ref: male)		1.13 (1.07-1.18)	1.27 (1.21-1.34)
Smoking	Never (ref)	1	1
	Ex	4.02 (3.56-4.55)	3.52 (3.11-3.98)
	Current	13.97 (12.68-15.39)	9.00 (8.14-9.94)

* Hazard ratios for illicit opioid use and smoking status are adjusted for age and sex. Age is adjusted for sex, and sex is adjusted for age. Hazard ratios in the 'additionally adjusted for smoking status' column are adjusted for all other variables.

11.4.5 Comparison of different approaches to missing data

The main analysis uses multiple imputation of missing data, which is explained in section 11.3.6. I repeated the analysis using (a) complete cases only, and (b) the 'missing indicator' method planned in the analysis protocol. The association between illicit opioids and diagnosis of COPD or death due to COPD using each of these methods are shown in Table 23. The 3 different approaches give the same results when adjusting for age and sex only, as data for these variables were complete. The results vary slightly when additionally adjusted for smoking. The covariate coefficients varied more under different methods. For example, using multiple imputation current smokers had 21.13 (95% CI 13.89-29.18) times the hazard of death due to COPD when compared to never smokers; while in the complete case analysis the hazard ratio was 26.09 (95% CI 17.62-38.62). Similarly, analyses of outcomes after a new diagnosis of COPD had very similar primary results under different approaches to missing data, with greater variation in covariate coefficients.

Table 23: Hazard ratios (95% confidence intervals) of death due to COPD or new diagnosis of COPD, comparing participants with a history of illicit opioid use to the comparison group, using different approaches to missing data

Outcome	Adjustment	Multiple imputation	Complete case analysis	Missing indicator method
Death with underlying cause of COPD	Age and sex	14.59 (12.28-17.33)	14.59 (12.28-17.33)	14.59 (12.28-17.33)
	Age, sex, and smoking	8.81 (7.36-10.54)	8.71 (7.23-10.48)	8.84 (7.39-10.56)
New diagnosis of COPD	Age and sex	5.89 (5.62-6.18)	5.89 (5.62-6.18)	5.89 (5.62-6.18)
	Age, sex, and smoking	3.29 (3.13-3.46)	3.23 (3.08-3.40)	3.26 (3.11-3.43)

11.4.6 Relationship between smoking and the raised frequency of COPD among people who use illicit opioids (post-hoc exploratory analysis)

The results in Table 21 and Table 22 suggest that smoking at baseline partially explains (or mediates) the higher frequency of COPD diagnosis and death among people who use illicit opioids. Previous research suggests that approximately 80% of COPD cases in high income countries can be attributed to tobacco smoking, with other cases attributable to air pollution, occupational exposures, diet, and other factors.[270,292]

As a post-hoc exploration of the relationship between tobacco smoking and the raised frequencies of COPD among people who use illicit opioids, I calculated rates of COPD diagnosis and death in 2-by-2 tables comparing smoking status (dichotomised by grouping current and ex-smokers vs. never-smokers, and excluding those with missing data) with opioid exposure (Table 24 and Table 25). I calculated rate ratios within smoking and opioid strata with Wald confidence intervals using the R function epitools::rateratio.

Both analyses showed that smokers have higher rates of COPD than non-smokers, and participants with a history of using illicit opioids have substantially higher rates within smoking strata (Table 24 and Table 25). The higher frequencies among non-smokers who use illicit opioids may be due to differential misclassification, in which some participants recorded as ‘never-smokers’ have smoked in the past and this mistake is more common in the opioid group, or differential unmeasured risks such as air pollution or smoking other substances such as heroin and crack cocaine. Higher frequencies among smokers who use illicit opioids may be due to heavier or longer smoking histories (i.e. more pack-years), differential unmeasured risks, or an interaction between opioid use and tobacco smoking that increases the harm from a given amount of smoking.

Although the rate ratios comparing smokers and non-smokers differ by history of illicit opioid use (Table 24 and Table 25), a model with an interaction between these variables is difficult to specify. A multiplicative model would show an interaction in which opioid use is associated with a lower relative risk of smoking. This is because the frequency of COPD among never-smokers is substantially higher in the opioid group. Conversely, an additive model would show an interaction in which opioid use is associated with greater risk difference. A similar situation has been observed in the interaction between tobacco smoking and socioeconomic status on the risk of lung cancer. The frequency of lung cancer among never-smokers is higher in low socioeconomic groups and therefore the relative risk of smoking appears lower for low socioeconomic groups in some studies, though the absolute risks (i.e. the difference in frequency of lung cancer between smokers and never-smokers) are higher.[293]

Existing knowledge about COPD in high income countries suggests that the large majority of cases are likely due to tobacco smoking. The most obvious explanation for the raised frequency of COPD among people who use illicit opioids is smoking of tobacco and other drugs, though there may be other contributing factors. The contribution of smoking to the inequality in COPD associated with opioid use is difficult to estimate from this study because (a) the measurement of smoking is limited and does not capture duration, intensity, or smoking after study entry, and (b) it is difficult to model the interaction between smoking and opioid use.

Table 24: Rate of death with underlying cause of COPD, comparing smoking and history of using illicit opioids. Cells show numbers of deaths/person-years and rate per 100,000 person-years (95% confidence interval)

	Comparison group	History of using illicit opioids	Rate ratio (95% CI)
Never smokers	12/1,368,596 0.88 (0.45-1.53)	14/59,761 23.43 (12.81-39.31)	26.67 (12.22-59.13)
Current and ex-smokers	148/1,379,112 10.73 (9.07-12.61)	628/784,487 80.05 (73.91-86.57)	7.45 (6.25-8.94)
Rate ratio (95% CI)	12.09 (7.01-23.07)	3.38 (2.07-6.02)	

Table 25: Rate of new COPD diagnosis, comparing smoking and history of using illicit opioids. Cells show numbers of deaths/person-years and rate per 1,000 person-years (95% confidence interval)

	Comparison group	History of using illicit opioids	Rate ratio (95% CI)
Never smokers	538/1,013,774 0.53 (0.49-0.58)	136/40,448 3.36 (2.82-3.98)	3.65 (3.51-3.80)
Current and ex-smokers	4,053/1,018,554 3.98 (3.86-4.10)	6,207/427,492 14.52 (14.16-14.89)	6.34 (5.23-7.63)
Rate ratio (95% CI)	7.50 (6.86-8.21)	4.31 (3.66-5.14)	

11.4.7 Likelihood of diagnosis before death

Patients with a history of using illicit opioids who died due to COPD were less likely to receive a diagnosis before death than other patients (Table 26). Among those who did get a diagnosis, the time between diagnosis and death was shorter for participants with a history of using illicit opioids.

Table 26: COPD-related deaths and the proportion who have a diagnosis of COPD before death

History of using illicit opioids	Number of deaths*	Number with diagnosis of COPD before death	Percent with diagnosis before death	Median years between diagnosis and death (IQR)
Yes	748	484	64.7	3.9 (6.6-9.8)
No	246	177	72.0	4.4 (8.4-12.3)

* Only deaths during CPRD follow-up are included (i.e. the period for which primary care data is available), as COPD diagnosis was derived from primary care data.

11.4.8 Outcomes after diagnosis of COPD

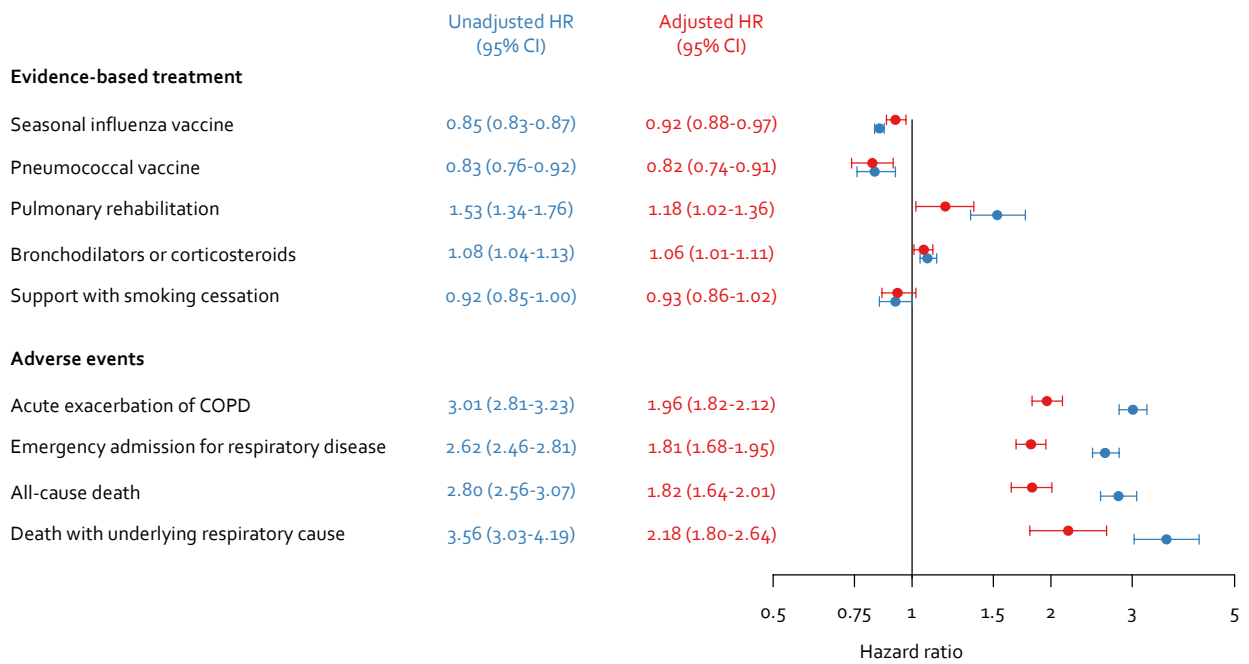
The proportions of participants with COPD who received treatment was similar for those using illicit opioids and in the comparison group (Table 27). The proportion receiving each treatment varied, with the higher proportions for medications (bronchodilators and corticosteroids) and lower for pulmonary rehabilitation, pneumococcal vaccines, and smoking cessation support. Adjusting for smoking status and disease severity using Poisson regression did not substantially change these associations. For some treatments (such as pulmonary rehabilitation) I found a 'significant' association between opioid use and probability of treatment (i.e. the p-value was smaller than 0.05), but the associations were small.

Patients with a history of using illicit opioids before COPD diagnosis had approximately 3 times the risk of each of the adverse outcomes (acute exacerbations and death). In Cox proportional hazards models adjusting for smoking status and disease severity, these associations were partially attenuated and participants with a history of illicit opioids had approximately double the adjusted hazard of each outcome (Figure 38).

Table 27: Patients with a new diagnosis of COPD: number eligible for secondary prevention interventions and proportion receiving each intervention within 12 months of diagnosis

Treatment	Season (years after COPD diagnosis)	History of using illicit opioids	Comparison group
Seasonal influenza vaccine	1	1,798/3,833 (46.9%)	8,258/16,476 (50.1%)
	2	1,629/3,167 (51.4%)	8,056/14,473 (55.7%)
	3	1,302/2,547 (51.1%)	6,812/12,055 (56.5%)
	4	1,039/2,007 (51.8%)	5,792/10,021 (57.8%)
	5+	3,447/6,332 (54.4%)	21,942/35,861 (61.2%)
Pneumococcal vaccine		467/3,203 (14.6%)	2,732/15,700 (17.4%)
Pulmonary rehab		270/3,903 (6.9%)	880/19,515 (4.5%)
Bronchodilators or corticosteroids		3,164/3,318 (81.1%)	14,559/16,590 (74.6%)
Smoking cessation support		672/2,855 (23.5%)	2,815/11,027 (25.5%)

Figure 38: Hazard ratios of evidence-based treatment and adverse events after diagnosis of COPD, comparing participants with a history of illicit opioid use to those without



Unadjusted hazard ratios are adjusted for age and sex only. Adjusted hazard ratios are additionally adjusted for smoking status, COPD GOLD group (FEV1/predicted), MRC dyspnoea/breathlessness scale, and BMI.

11.5 Discussion

Key findings

In this sample of primary care patients in England, illicit opioids were associated with 6 times the rate of new COPD diagnosis and 15 times the risk of death with an underlying cause of COPD. There was evidence that illicit opioids were associated with later diagnosis of COPD, reflected in more severe disease at diagnosis and a shorter duration between diagnosis and death. There was no inequality in treatment after diagnosis, though illicit opioids were associated with substantially higher frequency of acute exacerbation and death, even after adjusting for disease severity at diagnosis.

11.5.1 Strengths and limitations

Other studies have estimated COPD prevalence,[46,47,272] incidence,[294] and mortality[39,40] among people who use illicit opioids. To my knowledge, this is the first study that investigates treatment in this population. It uses 2 well-known measures of disease severity (COPD GOLD stages[281] and the MRC dyspnoea scale[283]), which were well-recorded with approximately two-thirds of participants having each measurement at the time of diagnosis. The study uses 5 treatments recommended in UK guidelines (seasonal influenza vaccine, pneumococcal vaccine, pulmonary rehabilitation, medication, and support with smoking cessation), providing evidence across these interventions that illicit opioids are not associated with healthcare access after diagnosis in this sample. This was contrary to my hypothesis that healthcare access would be poor among people who use illicit opioids.

The study has 8 key limitations.

First, there is selection bias in the study of COPD incidence and mortality, in which the target population is people who use illicit opioids in England. As discussed in Chapter 9, to be included individuals need to be registered with a GP, attend an appointment, and disclose their drug use. Groups more likely to disclose drug use may include those prescribed opioid agonist therapy (either in primary care or specialist drug and alcohol services), and those who are more unwell and therefore have more GP appointments. This latter factor may mean COPD frequency is overstated, i.e. the difference between the general population and all people who use illicit opioids may be smaller than these results suggest.

Second, there is selection bias in the study of treatment and outcomes after diagnosis. This analysis is intended to show what happens after cases are identified in primary care and therefore selection bias is less problematic. However, some diagnosed cases may not be captured by the case definition. For example, data from Wales suggests that around 1 in 3 patients on GP COPD registers do not have recorded spirometry values[295] (consistent with the proportion of missing data in Table 20) and it is possible that some patients also do not have the diagnostic codes used in our case definition. The direction of effect of this type of bias is difficult to predict. The opioid group in this study may be unusually motivated to access care (because disclose of illicit drug use to a GP may be a marker for good engagement with primary care). Therefore, the lack of inequality in treatment after diagnosis may be partly explained by this type of selection bias.

Third, some COPD treatment may be provided in other settings, including specialist respiratory services and 'in-reach' clinics at community drug treatment services (which were described by some participants in the qualitative study in Chapter 8). Differential access to care for COPD outside of primary care could cause bias in either direction.

Fourth, eligibility criteria for some COPD treatments was difficult to determine. Eligibility was easily determined for support with smoking cessation (current smokers), pneumococcal vaccine (participants without a previous vaccine), and seasonal influenza vaccine (everyone). For COPD medications and pulmonary rehabilitation the clinical decision to provide treatment is based on additional patient characteristics and preferences that were not captured in this study – i.e. the definition of eligibility may not match 'clinical reality'. The proportion of patients receiving treatments and the differences between the opioid and comparison group may partly reflect such unmeasured characteristics.

Fifth, there is likely to be residual confounding due to limitations in the measurement of variables. In particular, smoking status was defined as never-, ex-, or current-smoking at cohort entry. Smokers who use illicit opioids are likely to have longer and heavier smoking histories and some smoke other substances such as cannabis, crack cocaine, and heroin. As discussed in section 0, these factors mean it is difficult to estimate the contribution of smoking to opioid-related inequalities in COPD. In addition, smoking after diagnosis may vary between the opioid and comparison group. It is possible that people who use illicit opioids are less likely to quit after a new diagnosis. This could contribute to the substantially higher rates of acute exacerbations and death after diagnosis after adjusting for disease severity and smoking at baseline. Future research could use codes for ex-smoking after diagnosis to compare evidence that patients with COPD have quit smoking. Another limitation relates to the measurement of disease severity. The COPD GOLD stages, MRC breathlessness scale, and body-mass index are associated with survival probability[270,296] and the need for treatment, but they may only partially capture the severity of COPD and their prognostic value may differ between populations.

Sixth, there is likely to be residual confounding due to unmeasured differences between the opioid and comparison group in terms of disease severity at diagnosis. The causal model in Figure 32 includes disease phenotype and ethnicity as potential confounding variables that were not measured. A study of people who smoke heroin showed that emphysema is the dominant COPD phenotype,[276] so it is possible that COPD patients with a history of illicit opioid use are more likely to have emphysema than other COPD patients. Although primary care data includes codes that specify emphysema and chronic bronchitis, the vast majority of participants had generic 'COPD' diagnoses and I was therefore unable to subclassify COPD phenotypes. Ethnicity codes are available in primary care and hospital data,[297,298] but deriving a single ethnicity value for each participant can be complex and biased, and I decided that these issues outweighed the likely weak confounding effect of ethnicity on this study.

Seventh, missing data in covariates may have caused bias. My use of multiple imputation assumes that data is 'missing at random'. Observed data is likely to provide some insight into missing data, however unobserved variables are also likely to be important. For example, participants in the analysis of outcomes after a new diagnosis may be more likely to have missing spirometry values if they have less severe disease, meaning that the probability of an individual having missing data for a particular variable depends on the value of that variable. More fundamentally, participants who are healthier or have lower engagement with their GP may be more likely to have missing data for all variables. In other words, data are unlikely to be entirely 'missing at random' or 'missing not at

random', but a combination. The direction of bias caused by missing data is difficult to estimate. The results under different approaches to dealing with missing data (Table 23) show that (a) the decision on how missing data are analysed does not appear to have an important impact on the primary results in this study; (b) missing data are likely to cause more bias for covariate coefficients than the primary results.

Eighth, this study focuses on healthcare access, which is only one concept of healthcare quality. Many theoretical articles have sought to define healthcare quality. They typically propose a classification of types of healthcare quality. For example, Donabedian differentiated measures of (a) 'structure' – staff, buildings, technologies, and other tangible healthcare assets; (b) 'process' – delivery of healthcare interventions; and (c) 'outcomes' – changes in health.[299] Campbell provided a distinction between (a) 'access', which is similar to Donabedian's 'process' and includes measures of "whether individuals can access health structures and processes of care which they need"; and (b) 'effectiveness', or "the extent to which care delivers its intended outcome".[300] In addition to access and effectiveness, Maxwell discussed relevance to need, equality, social acceptability, and efficiency.[300] In the present study, outcomes such as immunisations, pulmonary rehabilitation, and support for smoking cessation relate to 'process' or 'access'. Donabedian wrote that the study of healthcare process is "justified by the assumption that one is interested not in the power of medical technology to achieve results, but in whether what is now known to be 'good' medical care has been applied."[299] This is why I chose evidence-based interventions that are recommended in national guidance, though the results do not show whether these interventions actually improved patient outcomes. It could be argued that the association between illicit opioid use and adverse outcomes such as acute exacerbations and death (Figure 38), which persisted after adjusting for disease severity at diagnosis, suggests that medical interventions are not effective among people who use illicit opioids. However, the relationship between healthcare and outcomes is complex. Future research might focus on other dimensions of healthcare quality, such as the acceptability of healthcare interventions in this population and whether patients complete recommended treatment.

11.5.2 Interpretation and relevance for policy, practice, and research

This study shows a high burden of COPD among people who use illicit opioids. Death with an underlying cause of COPD is several times more common than among people of the same age and sex in the general population. People who use illicit opioids in England are ageing and the burden of COPD is likely to increase. Given the large inequality and specific health needs in this population, reducing this burden will require a dedicated strategy for primary and secondary prevention of illness and death due to COPD.

I will discuss 4 possible reasons for this inequality and their implications for policy and practice: (a) inequalities in diagnosis; (b) inequality in treatment after diagnosis; (b) interaction with other health conditions; (d) heavier smoking, both before and after diagnosis.

(a) Inequalities in diagnosis. The results suggest substantial undiagnosed COPD. Cross-sectional spirometry studies have found that 30%-40% in studies of people who use illicit opioids have COPD,[46,47] compared to 2.3% in this study with COPD diagnosed in primary care at baseline (Table 19). These values are based on sources with different definitions of COPD meaning they are difficult to compare,[271,301] but the very large difference suggests that many cases are not diagnosed. There may also be substantial undiagnosed COPD in the general population. There are relatively few studies of COPD prevalence among younger adults. An international systematic review estimated a

pooled prevalence of 3.1% in adults aged under 40,[301] compared to 0.4% of participants in the comparison group of this study with COPD diagnosed in primary care at baseline.

There were 2 sources of evidence for inequality in diagnosis. First, where people died and COPD was identified as a contributing cause, those who used illicit opioids were less likely to have received a diagnosis prior to death (Table 26). The low proportion of diagnoses made prior to death (approximately two-thirds diagnosed prior to death) further supports substantial undiagnosed COPD in both the opioid group and the general population. Second, disease severity measured by spirometry and the MRC breathlessness scale was worse on average in the opioid group, which may suggest later diagnosis. Together, this inequality in diagnosis may reflect missed opportunities for treatment.

The inequality in diagnosis may be addressed through spirometry in accessible locations such those providing injecting equipment and opioid agonist therapy; an approach that has been piloted in Sheffield, Liverpool, and London[46,49,185,272] and appears acceptable to patients. However, this is screening and prior to implementation should meet certain criteria,[302] including having a viable treatment pathway and evaluation in an RCT. I cannot identify a potential harm from this type of screening, but screening often has unanticipated harms or poor value for money.

(b) Inequalities in treatment after diagnosis. Contrary to my hypothesis, I did not find evidence of inequality in treatment after diagnosis. This may suggest that people who use opioids have similar care as other patients once diagnosed, or reflect selection bias in which those diagnosed are a 'motivated' subgroup. If other people who use illicit opioids were proactively diagnosed, we may find that the additional cases have lower probability of treatment. The results also show low absolute levels of access for some evidence-based interventions, both in the opioid and comparison group. A small proportion of patients (approximately 1-in-20 in this study) were referred for pulmonary rehabilitation, which has been previously observed.[303,304] Previous research has found that patient-level reasons for non-attendance include transport, lack of perceived benefit, continued smoking after diagnosis, and depression,[305] though the present results suggest that few patients are referred in the first place. Approximately 1-in-7 patients received a pneumococcal vaccine. Many more received the seasonal influenza vaccine (approximately half of participants each season, similar to official data which showing that 45% of people in England aged 16-64 and in a clinical risk group got a vaccine in 2019/20[306]), which may suggest that low access to pneumococcal vaccine is because there is no annual campaign and awareness of eligibility criteria and guidance may be low among GPs. The exception is bronchodilators and inhaled/oral corticosteroids, which were prescribed to approximately 4-in-5 patients in the 12 months after diagnosis. This suggests that participants who use illicit opioids are engaged with primary care there are likely to be opportunity to offer other interventions.

In early planning of this study, I anticipated that the results in Figure 38 would show specific inequalities in healthcare that could be addressed through alternative treatment models such as "in-reach" partnerships between respiratory and community drug treatment services. The results did not suggest inequality in care after diagnosis. Instead, the results show large inequalities in both the frequency and outcomes of COPD that are unlikely to be explained by healthcare access after diagnosis.

(c) Interaction with other health conditions. COPD is associated with greater risk of many health problems after onset, including muscle wasting, cardiovascular diseases, depression, and chronic infections, with plausible mechanisms for COPD causing these problems.[270,307] People who use illicit

opioids have a raised baseline risk of these diseases, which has been observed in many studies[308] and in the baseline prevalence of long-term conditions in this study (Table 19). The worse outcomes after diagnosis for people who use opioids may be explained by comorbidities that are triggered by COPD or interact with COPD to increase the risk of death. This would suggests that people who use illicit opioids are more vulnerable to COPD, and therefore investment in prevention should be prioritised. In theory, we could study some of these mechanisms using the present dataset. For example, we could look at incidence of cardiovascular diseases after diagnosis of COPD and whether it explains differences in mortality. However, these pathways are complex and would require a focused study.

(d) Heavier smoking histories and smoking after diagnosis. Most COPD cases in high-income countries are caused by tobacco smoking.[270,292] While I have not been able to attribute higher frequency of COPD among people who use illicit opioids to a specific risk factor, it is likely related to smoking of tobacco and illicit drugs. Among people without COPD, smoking cessation is associated with lower incidence of COPD,[309] and among people with COPD of any severity it is associated with slower decline in lung function and reduced mortality.[310] The Global Initiative for Chronic Obstructive Lung Disease advises that stopping smoking is the most effective therapeutic approach for preventing or reducing the progression of COPD.[281]

Historically, smoking cessation has been considered difficult or unrealistic among people who use illicit drugs, and there have been few attempts to reduce the high smoking prevalence. In 2019/20, only 2.4% of people starting opioid agonist therapy in England who said they smoke tobacco were provided some kind of smoking cessation intervention.[23] However, some randomised controlled trials of traditional smoking cessation aides (such as nicotine replacement therapy, motivational interviewing, and varenicline/bupropion) among people in treatment for substance use have found sustained reductions in smoking.[311] E-cigarettes might be even more effective, as qualitative data suggests they may be more appealing in this population than traditional therapies.[312] The provision of e-cigarettes is currently being evaluated in a cluster randomised controlled trial in a parallel population of people using homeless day centres[313] and this study may inform approaches to smoking cessation for people who use heroin and crack cocaine. At the very least, people who use illicit opioids who are diagnosed with COPD should be supported to quit smoking.

11.5.3 Conclusion

Death due to COPD is 15 times more common among people who use illicit opioid than the general population. This inequality does not appear to be explained by differences in treatment after diagnosis, but later diagnosis may contribute. A strategy to prevent and treat COPD should include better diagnosis in accessible settings and prioritisation of smoking cessation by services that support this population.

12 Conclusion

This final chapter has 3 sections. I will:

(1) Revisit my research questions and summarise how my work has answered them. I designed a focused study for each research question, but other elements of the thesis contribute to each question, and at some points my plans changed during the research.

(2) Summarise how my research has added to existing knowledge in this field.

(3) Provide recommendations for policy, practice, and future research.

12.1 How does this work address my research questions?

RQ1: How do people who use heroin and crack cocaine use health services?

The systematic review reported in Chapter 6 shows that the frequency of healthcare utilisation in this population is much higher than in the general population, particularly for emergency care such as A&E visits. It also shows that the rate of primary care consultation may be higher than in the general population, even after discounting consultations related to opioid agonist therapy and other "drug-related" issues, contrary to some expectations.

The cohorts developed in Chapter 9 include data on healthcare utilisation. The cohorts derived from the Clinical Practice Research Datalink include primary care data and linkage to hospital episodes, while the cohort from South London and Maudsley NHS Foundation Trust includes linkage to hospital episodes. I had originally planned to describe rates of healthcare utilisation using these data and define "patterns" or "modalities" of healthcare utilisation, such as people who never visit health services, or people who visit A&E often but never see their GP. I thought this would help us understand how this population uses the NHS and therefore plan more accessible services. However, after doing the systematic review I realised that healthcare utilisation is determined by both health needs and healthcare access, and it is difficult to draw conclusions about healthcare access based on based on healthcare utilisation alone. Furthermore, in the cohorts developed in Chapter 9, health needs can only be observed through information recorded in healthcare records. If someone never visits their GP, we would not know if that is because they are healthy or have poor healthcare access.

For these reasons, I decided instead to conduct a more focused study of treatment for people with a new diagnosis chronic obstructive pulmonary disease (COPD), addressing a new research question (RQ4). I followed the approach of studies identified in the scoping review reported in Chapter 7, which looked treatment for cardiovascular disease and diabetes among people who use drugs and alcohol in the US. This approach is narrower but allows clearer conclusions about healthcare access and leads more directly to practical recommendations. I chose chronic obstructive pulmonary disease after observing the high relative and absolute mortality risks, with approximately 5% of all deaths in this population having an underlying cause of COPD and a COPD-specific mortality rate approximately 15 times the general population.

I did summarise hospital admissions in the South London and Maudsley NHS Foundation Trust dataset. This analysis is not included in this thesis but is published in the journal Drug and Alcohol Dependence.[39] The results showed that participants who use heroin were admitted to hospital 3.1 times more often than people of the same age and sex in the general population. Only 14% of admissions were primary "drug-related" (such as overdoses, intoxication, and withdrawal). All causes of hospital admission had raised frequency, with particular high relative rates of admission due to mental health problems, respiratory diseases, skin infections, and head injuries. The exception was admissions due to cancer, which were actually less common than in the general population despite higher cancer-related mortality (as reported in Chapter 10). This may be an avenue for further research.

RQ2: What approaches to improving physical healthcare for people who use heroin and crack cocaine have already been developed?

The scoping review reported in Chapter 7 showed that other researchers have recognised the issue of unmet health needs in this population and some interventions have been evaluated. These include integrated primary care and drug treatment services in the US, spirometry-based screening and referral to respiratory pathways in the UK, and a health screening and referral process in Australia. However, there are few studies and limited evidence of the effectiveness of these interventions.

The qualitative study reported in Chapter 8 found that all participants felt that clients have poor healthcare access and unmet physical health needs. Some had set up projects to address this problem, such as "in-reach" models where specialists (such as respiratory or gastroenterology doctors) run clinics at a drug treatment service, partnerships with hospital outpatient services where a block of appointments is reserved for clients of a drug treatment service, nurse-led wound clinics, and various types of health advocacy. These projects were usually unfunded, led by motivated individuals without long-term support from commissioners, and not evaluated. Therefore they were difficult to sustain and often short-lived, particularly in the context of financial cuts and staffing losses. It is likely that many such projects have been done around the country. The qualitative study also found differing perceptions about models of care that would be more accessible for this population, with many sceptical about a 'one-stop-shop' model, mainly because they felt it would not be properly funded.

RQ3: What are the main causes of death among people who use heroin and crack cocaine and how have they changed over time?

The cohort studies reported in Chapter 10 described causes of death among people who use illicit opioids in England. As discussed in Chapter 9, I was not able to include people who use crack cocaine in the definition of the cohorts derived from the Clinical Practice Research Datalink because crack cocaine appears poorly recorded in primary care records, and not distinguishable from powder cocaine (which is used by different groups). I therefore focused on illicit opioids, and most participants in this study will have a history of using heroin. The results show that one-third of deaths are caused by drug poisoning. Non-communicable diseases in combination cause about half of deaths. Cause-specific mortality rates are all higher in people who use opioids than in the general population, reflecting a deprived and marginalised population with multiple determinants of poor health throughout life. The highest relative risks were for viral hepatitis, chronic obstructive lung disease, and HIV. The study provides evidence that population ageing is contributing to increasing rates of death due to non-communicable diseases (except liver disease, which appears to be reducing in this population, possibly due to successful treatment of chronic hepatitis C infections); but the recent increase in drug-related deaths (reported in national surveillance data[262]) is more likely to be explained by environmental factors such as the availability of harm reduction services and the availability and purity of drugs. This may suggest that the increasing rate of fatal drug poisonings can be reversed, but the importance of non-communicable diseases in this population is likely to continue increasing as the average age increases.

RQ4: Do people who use heroin and crack cocaine experience inequality in treatment for chronic conditions?

The case study in Chapter 11 investigates treatment after a new diagnosis of COPD. It shows that use of illicit opioids (again I was not able to include crack cocaine in the definition of participants) is associated with more severe disease at diagnosis, but similar probability of treatment after diagnosis. This was contrary to my hypothesis that healthcare access would be poor in this population. It is possible that population subgroups with poor healthcare access were not included in this study, i.e. there may be people who use heroin and crack cocaine with COPD who are not known to their GPs and have very poor healthcare access. However, in this sample, the inequalities in COPD incidence and mortality does not appear to be explained by healthcare factors. This does not mean that healthcare quality is good and some of the results suggested poor healthcare. For example, only 65% of people who died with an underlying cause of COPD had any records of COPD in primary care, and only 24% of patients with COPD who smoke were offered support with smoking cessation within 12 months of diagnosis. But these values are not better for patients in the general population, suggesting that illicit opioids are not associated with relatively poor access to GPs (rather access to COPD treatment generally appears low). This study therefore did not identify obvious gaps in COPD treatment for this population or a need for a different model of treatment. The inequality in COPD incidence and mortality shows that smoking cessation should be prioritised in the whole population of people who use heroin and crack cocaine.

12.2 What does this research add to existing knowledge?

Table 28 summarises existing knowledge in each of the 4 topic areas covered by this thesis, and what this work adds.

Table 28: Existing knowledge and what this work adds

Research area	What is already known	What this work adds
Healthcare utilisation by people who use illicit drugs (RQ1)	• People who use illicit drugs have high rates of hospital utilisation • Rates of unplanned or emergency healthcare utilisation are especially high • Use of illicit drugs is associated with barriers to healthcare related to stigma, bureaucracy, and basic priorities that compete with health	• Rates of healthcare utilisation vary widely by setting and population • Contrary to some perceptions, people who use illicit drugs may visit GPs more often than the general population
Healthcare interventions for people who use illicit drugs (RQ2)	• Health interventions have focused on "drug-related" outcomes such as prevention of overdoses and blood-borne virus transmission	• Various models that aim to improve access to physical healthcare have been piloted, but few have been evaluated • Clinicians works in drug treatment services feel they do not have the resources to meet their clients' health needs
Mortality rates among people who use illicit drugs (RQ3)	• Mortality rates among people who use illicit opioids are extremely high – up to 10 times the general population • Studies in the 1980s and 1990s show that most deaths in this population were due to overdoses and infections, while more recent studies show more deaths due to non-communicable diseases • The number of fatal drug poisonings is increasing in England (as well as in other countries)	• All causes of death are more common in people who use illicit opioids than the general population • Ageing in the population means that the rate of death due to cardiovascular disease, respiratory disease, and cancers is increasing • The rate of death due to liver disease may now be decreasing • The recent increase in fatal drug poisonings is unlikely to be explained by population ageing
Treatment for chronic conditions among people who use illicit drugs (RQ4)	• People who use illicit drugs encounter barriers to healthcare and access to treatment for chronic conditions may be poor • People who use drugs and alcohol in the US may have lower rates of cancer screening and lower probability of treatment after diagnosis of cardiovascular diseases and diabetes	• Among people diagnosed with COPD, use of illicit opioids is associated with more severe disease at diagnosis • After a diagnosis of COPD, use of illicit opioids is not associated with lower probability of treatment • After a diagnosis of COPD, use of illicit opioids is associated with worse health outcomes after adjusting for severity at baseline. This may relate to unmeasured clinical factors or exposures after diagnosis such as continued smoking

12.3 Recommendations for policy, practice, and research

People who use heroin and crack cocaine have poor healthcare access and high rates of death due to chronic physical health problems. The population is ageing and these problems are becoming more important. Current clinical guidelines for community drug and alcohol services recognise the increasing health needs in this population, promote joint working with other health services, and specify a range of health assessments and tests with referrals to GPs and hospitals.[195] There appears to be a mismatch between this guidance and the care typically provided, with widespread recognition that health needs are not being met. Staff have differing opinions about specific solutions, but agree that the cause of limited support for physical health is insufficient staff and financial resources. The current model of support for this population is likely to lead to continued poor health outcomes, avoidable deaths, and reliance on emergency healthcare.

There is currently a media and policy focus on 'drug-related deaths'. The number of deaths in England where an opiate is mentioned on the death certificate increased by 54% between 2010 and 2020, from 1,384 to 2,138.[262] The results in Chapter 10 show that there are more excess deaths in this population due to non-communicable diseases, but surveillance of these deaths is difficult because vital statistics do not record that someone who died due to a chronic respiratory disease or a heart attack (for example) used illicit drugs. The recent 'Black Review' of drug markets[7] and treatment[314] highlighted the crisis in drug-related deaths, social problems such as homelessness and crime that are associated with drugs, and that the services providing treatment for people who use heroin and crack cocaine are "not fit for purpose and urgently need repair". It recommended an approximate doubling in funding for treatment services, alongside additional spending on support with employment and housing, and various changes to commissioning and governance of services that support this population. A section on physical healthcare says that "the healthcare system needs to find ways to reach these vulnerable patients to provide screening and treatment. Several models are available for consideration, including specialist clinics within substance misuse services and assertive outreach for repeat attenders at emergency departments."[314]

It is possible that these recommendations will lead to a reversal in the historic disinvestment in this sector, and this is now an opportunity to ensure that services meet the changing needs of this population. Drawing on the findings of this research, my 3 recommendations for policy and practice are:

1. A commitment by the Department for Health and Social Care and NHS England to improve access to physical healthcare for people who use heroin and crack cocaine, parallel to the commitment made to improve healthcare for people with severe mental health problems.
2. More testing and evaluation of accessible models of healthcare for this population, such as on-site primary care at community drug and alcohol services. These pilots should be linked to national funding and guidance processes, so that effective models can be rolled-out. Many local services have set up projects that help people who use heroin and crack cocaine access health services, but they are typically small-scale, unfunded, not evaluated, and reliant on individuals. Consequently they are often short-term and there is a limited evidence base for interventions that could prevent or treat chronic physical diseases in this population (in contrast to the good evidence base for interventions that prevent or treat so-called 'drug-related diseases').

3. **Investment and prioritisation of smoking cessation in services that support people who use heroin and crack cocaine.** To date, there has been little investment in smoking cessation, given the high prevalence of tobacco smoking in this population and the large number of smoking-related deaths. While there may be additional barriers to smoking cessation compared to other groups of smokers, evidence suggests that traditional types of support such as nicotine replacement therapy are effective in this population and e-cigarettes may be more effective.

The research has also led to specific research questions that could be investigated in future research:

1. **Why do people who use heroin and crack cocaine have lower rates of hospital treatment for cancer despite higher cancer-related mortality rates?** This is likely to relate to late diagnoses and poor healthcare access. The CPRD dataset described in Chapter 9, which can be linked to cancer registries, could support a detailed investigation of the types of cancer that are diagnosed late and inform interventions such as targeted screening programmes.
2. **Do people who use heroin and crack cocaine experience inequalities in treatment for chronic health problems?** Chapter 11 addresses this question for chronic obstructive pulmonary disease, and future research could replicate the method for other diseases such as ischaemic heart disease and diabetes.
3. **Among people who use heroin and crack cocaine, how do mortality rates change over a 'drug use career'?** The results in Chapter 10 show that, after adjusting for ageing, mortality rate among participants with a history of using illicit opioids reduced during the study follow-up. This was in contrast to the comparison group, which had stable mortality rates after adjusting for ageing. Analysis of the contributions of different causes of death may provide insight into changing risks over a 'drug use career'. For example, the reducing age-specific mortality risk may be driven by reducing risk of fatal drug poisoning, which could reflect less risky drug use or cessation of drug use.
4. **How do people who use illicit drugs and staff in health services think that physical healthcare could be made more accessible?** Chapter 8 presents a qualitative study addresses this question but only includes staff of community drug and alcohol services.
5. **What are the rates and 'modalities' of healthcare utilisation among people who use heroin and crack cocaine?** The systematic review in chapter 6 shows there is limited research into certain aspects of healthcare utilisation, particularly primary care. In this thesis I decided to focus on treatment access rather than frequency, though the cohorts described in Chapter 9 offer new opportunities to describe how this population uses the NHS.
6. **Among people who inject drugs, are local bacterial infections such as cutaneous abscesses predictive of systemic infections such as endocarditis?** Participants in Chapter 8 described the importance and poor healthcare for bacterial infections. Analysis of the South London and Maudsley cohort described in Chapter 9 has shown the high frequency and treatment cost of these infections.[209] Case reports have suggested that some patients have repeated infections, progressing from localised to more invasive infections. The CPRD dataset could be used to analyse co-occurence of different types of infection, and also the role of GPs in treating these infections.
7. **Can harm reduction and other forms of support be provided more effectively at hospital discharge?** My Patient and Public Involvement groups highlighted the importance of hospital discharge and the problems that people who use heroin and crack cocaine can face at this

time. As a result, I did an analysis of fatal drug poisonings in relation to hospital discharge, and found that approximately 1-in-14 such deaths occur in the 2 weeks after a hospital discharge.[2] This shows the importance of developing and evaluating interventions that improve discharge planning and linkage to community services for this patient group.

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