Fatal opioid overdoses in healthcare settings in England: a case series analysis

PROTOCOL

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1 Background

Studies in several countries have found raised risk of fatal opioid overdose immediately after release from prison,[1–8] and a protective effect of opioid agonist therapy (such as methadone or buprenorphine) during this period.[7] Studies in Scotland show that the period after hospital discharge is also associated with higher risk.[9,10] The increased risk may relate to reduced tolerance during these periods and interruption of opioid agonist therapy. These studies use cohorts of people who use opioids who are followed after a period in prison or hospital, and report mortality rates stratified by duration after release.

Some evidence also indicates that illicit drug use and fatal overdoses occur in healthcare settings (not only after discharge). In a survey of 1,028 people who inject drugs and had been hospitalised in Vancouver, 44% reported illicit drug use on a hospital ward,[11] and those reporting inadequate pain relief were more likely to report use of illicit drugs.[12] Smaller studies of hospital patients with injecting-related bacterial infections in the US also found that high proportions used illicit drugs while admitted.[13–15] Qualitative research in Canada and the US found that inpatients used drugs to prevent opioid withdrawal and to supplement pain relief medication, while a 'zero-tolerance' approach leads to concealment of drug use, rushing of procedures, and larger doses.[16–18] As such, healthcare settings may be considered a 'risk environment' in terms of illicit drug use.[16]

We are not aware of studies in the UK that examine illicit drug use in healthcare settings. Some acute hospitals in the UK have reported that patients have died following use of illicit drugs on wards (anecdotally), and there are media reports of some such instances.[19–21] In these reports cases are found dead on hospital premises (for example in toilets) and some are found dead shortly after discharge. We do not know the number of times this has occurred, or whether hospital admission is associated with increased risk of fatal overdose.

An initial scoping review of structured data about drug-related deaths held in the National Programme on Substance Abuse Deaths (NPSAD)[22] from 2017 and 2018 found seven cases that

occurred in healthcare settings, some of which occurred while the decedent was living in a mental health hospital.

The risk of fatal overdose in these settings may be modifiable through more timely provision of opioid substitution therapies and/or naloxone, safer injecting spaces (which have been proposed in Canada[23]), or improved protocols for management of people who are dependent on opioids. A study of hospital opioid substitution protocols is currently underway, led by Release and LSHTM, with early findings showing wide variation in protocols.

This study will aim to quantify the risk of fatal overdose associated with inpatient admission to healthcare facilities, to motivate development of interventions such as these.

Specific aims are:

a. To describe fatal overdoses that occur during hospital admission or shortly after hospital discharge

b. To test whether people who use illicit opioids in England are at increased risk of fatal overdose during hospital admission and shortly after discharge from hospital.

2 Method

The study will include two separate analyses: (1) a descriptive case series using data from the National Programme on Substance Abuse and Death (NPSAD); and (2) a self-controlled case series (case-only) analysis of the risk of fatal overdose associated with admission to acute and mental health hospitals, using linked mortality data and Hospital Episode Statistics.

2.1 Descriptive case series using the National Programme on Substance Abuse and Deaths (NPSAD) database

Methods

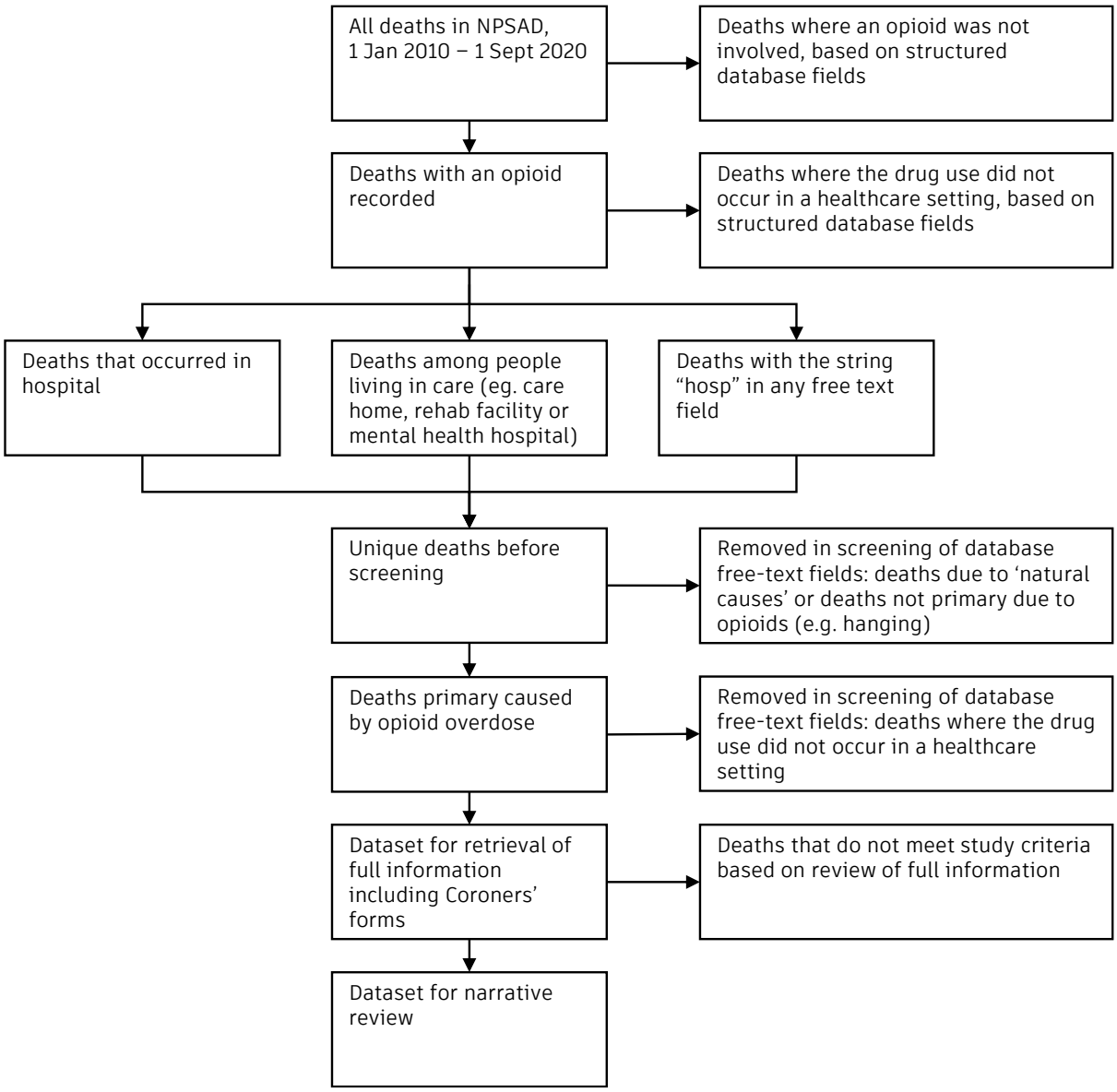
The NPSAD database collates information from Coroners on deaths related to drugs in England, Wales, and Northern Ireland. NPSAD has received information on over 40,000 deaths since 1997. We will search the database for individuals who died between 1 January 2010 and 1 September 2020 due to an opioid overdose during or shortly after an admission to an acute hospital or mental health hospital, and extract information about each case from the Coroner's report. We will not limit to deaths according to intent (accidental, suicide, or unknown).

We will use the following process:

1. Select cases by filtering the database on the following fields:
    a. Drugs, based on toxicology reports: any opioid, including synthetic opioids.
    b. AND 'Place of death' is hospital; OR 'Living' field indicates a healthcare facility, such as a mental health hospital or care home; OR any free text field includes the string 'hosp'.

2. Manually screen the ‘verdict’, ‘detail’ and ‘other information’ fields to identify cases where there is evidence that drug use preceding death occurred during a hospital admission or in the 14 days after discharge. A random 20% of cases will be double-screened by two researchers to check for consistency.
3. Access Coroners’ forms for these cases.
4. Extract the following information:
    a. Age, sex
    b. Location of death
    c. Type of location (e.g. acute / mental health hospital), and whether the death was during or shortly after admission
    d. Any recorded co-morbidities
    e. Drugs that were involved, including the type of opioid, route of administration, and any other drugs, including alcohol and prescription drugs
    f. Whether an intent was recorded (accident, suicide, or unknown)
    g. Short narrative about circumstance of death
5. Conduct narrative analysis to support discussion of the circumstances of deaths.

Figure 1: example flow chart for identifying relevant deaths in NPSAD



Ethics and approvals

The Chair of the King's College London Biomedical & Health Sciences, Dentistry, Medicine and Natural & Mathematical Sciences Research Ethics Subcommittee (BDM RESC) confirmed November 2020 that the NPSAD Programme does not require Research Ethics Committee review as the subjects of the research are deceased. Outputs from this project will be reviewed by the NPSAD team prior to publication or sharing with people outside of the research team to check that data have been reasonably anonymised.

2.2 Self-controlled case series analysis of the risk of fatal overdose associated with admission to acute and mental health hospitals, using linked mortality data and Hospital Episode Statistics

Method

This will be a self-controlled case series where all participants are people who died in England due to use of opioids. The method only includes cases (i.e. people who died), and the analysis focuses on the timing of hospital admissions in relation to the date of death.

The data source will be linked ONS mortality and Hospital Episode Statistics (HES) data in the Public Health England Data Lake.

The approach will be:

1. **Definition of cases (opioid-related deaths)**: Cases will be defined as those with (a) an 'underlying cause of death' of ICD-10 X40-X44, X60-X64, X85, or Y10-Y14 (based on the ONS definition of 'drug-related death'[24]) and an opiate-specific ICD-10 code in any field (T40.0-4 and T40.6), or (b) F11 as the underlying cause of death, whether or not opiate-specific codes are present in other fields. We will include all deaths in England that occurred over the most recent ten years for which data is available, among people aged 18-64.

2. **Processing of linked Hospital Episode Statistics Admitted Patient Care data from episodes into spells or admissions**. Hospital Episode Statistics is arranged such that admissions may be split into more than one record, with each record representing episodes of care led by different doctors. This process will involve merging of contiguous episodes within the same provider, but not across different providers (because a patient may be transferred from one hospital to another when an overdose occurs).

3. **For hospital admissions that end in death, classification of location of overdose into those that happened in the community and those that happened in hospital**. Admissions due to drug overdoses will be identified as (a) those with a code listed in step 1 in the primary position (DIAG_3_01), or (b) admissions for non-drug related causes that may result from overdose (such as cardiac arrest), with another diagnosis code indicating drug use (see figure 3, box). Previous research suggests that hospital coding departments usually use codes T40.1-T40.3 if a patient was admitted due to methadone or heroin overdose.[25] For deaths that occur in hospital where the admission was due to an overdose, the date of overdose will be reclassified to occur on the day of admission and in the location immediately prior to admission (which may be in the community or another hospital). In these cases, the final admission will be excluded from analysis. Figure 2 shows how the exposure status of deaths will be classified.

4. **Description of data, including:**

    a. Characteristics of individuals, including the age at death, sex, decile of Index of Multiple Deprivation, and geographical region. For comparison, ONS data shows that 17,455 opiate-related deaths occurred between 2009 and 2018, and of these

74% were male and the mean age was 42.[26] We also expect deaths to be disproportionately among people living in deprived areas.

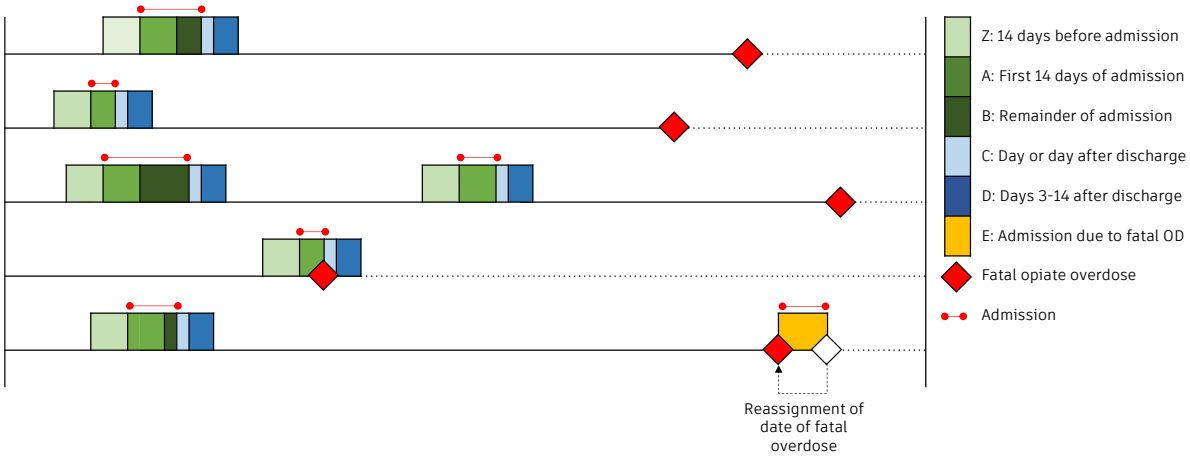
b. Characteristics of deaths, including the ICD-10 codes, intent (suicide or accidental, if ICD-10 information is available), and location of deaths in relation to the risk periods.

c. Characteristics of all admissions in the dataset, including the number of admissions per individual, duration of admissions, diagnostic data in admissions, type of provider (acute vs. psychiatric hospitals).

5. **Self-controlled case series (SCCS)**. A SCCS is a design that only includes individuals who experience an event (in this study people who have died due to an opioid overdose). The analysis is based on the temporal relationship between the event and a transient exposure (in this study hospital admission).[27] Advantages of the method are that (a) it is easier to construct a series of opioid-related deaths than a cohort of people who are at risk of opioid-relate deaths, and (b) it controls unmeasured time-invariant confounders (which in this study may include long-term morbidities that are may be associated with hospitalisation, as well as demographic characteristics such as sex and ethnicity). The study will include the following design features:

   a. Division of the participant time-lines into risk periods: (A) the 14 days after hospital admission (or shorter if the admission is shorter than 14 days); (B) the remainder of admission; (C) the day or day after discharge; (D) days 3-14 after discharge, (Z) the 14 days before admission (see 'limitations' section for an explanation of risk period 4), (E) admissions due to drug overdose that end in death, and (F) other periods (the reference category).

Figure 2: illustrative timeline of risk periods for 5 participants



   b. Arrangement of the data into 'long' form so that each patient has multiple rows, with a new row for each change in exposure period or age group. Age groups will be defined as 18-24, and then 5-year groups up to 60-64.

   c. Three analyses of the data, which address the problem that follow-up ends at the event (death).[28] We will report the results of the three analyses and discuss reasons for differences in the results.

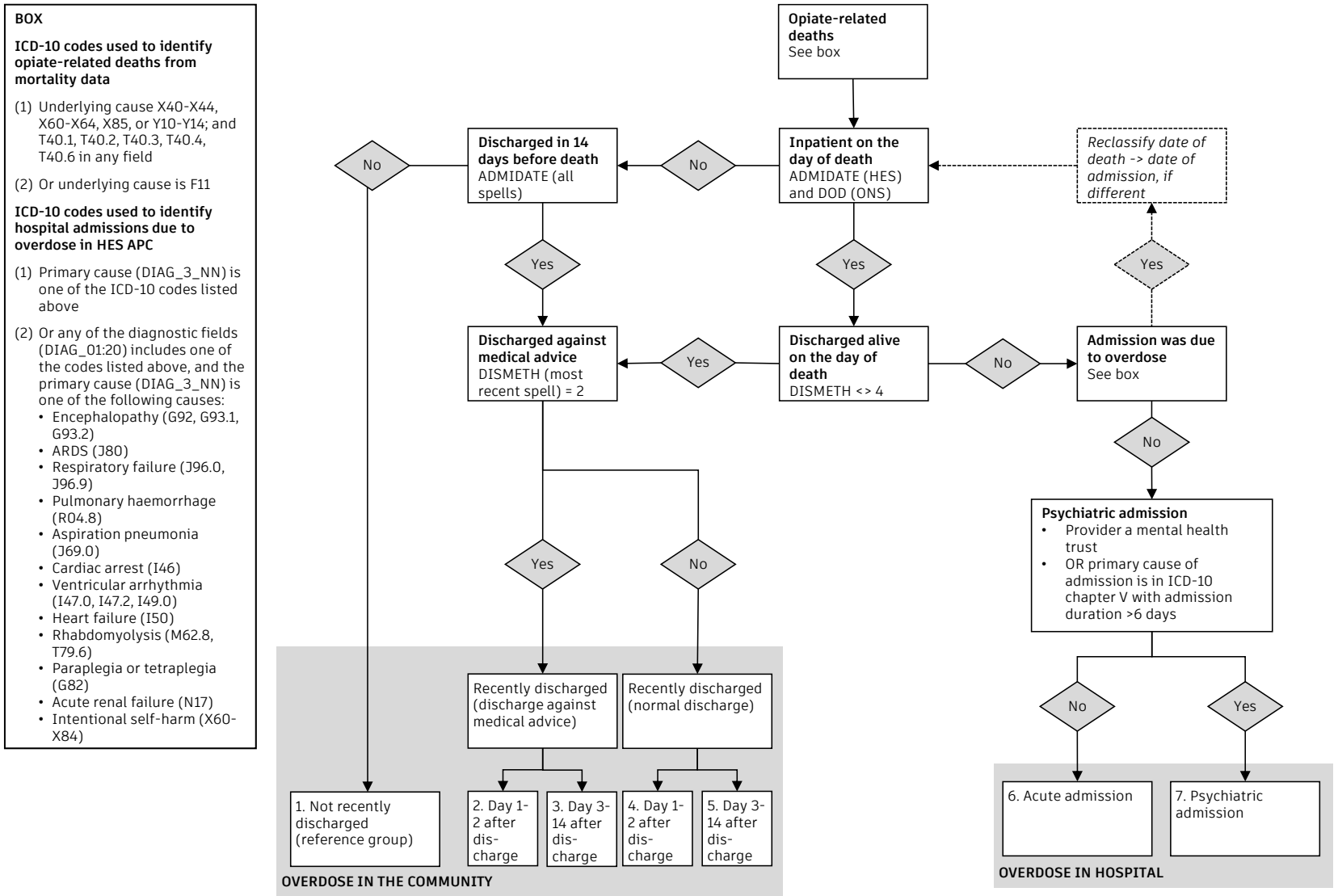
i. Use of the standard SCCS model, with follow-up ending at death. If hospital admission is associated with increased risk of the event, we anticipate that this analysis will produce risk ratios that are biased towards the null (i.e. understated).

ii. Use of the standard SCCS model, with follow-up ending at 31 December 2019 for each participants. Periods after death are included as exposure-free time. If hospital admission is associated with increased risk of the event, we anticipate that this analysis will produce risk ratios that are biased away from the null (i.e. overstated).

iii. Use of the method developed by Farrington et al[29] for SCCS with curtailed event-dependent exposures, which uses a series of analyses in which each exposure is assumed to be the final exposure. This approach is designed to produce unbiased estimates when follow-up ends at the event.

d. We anticipate there may be an interaction between sex and the risk associated with hospital admission, and will stratification the analysis by sex.

Figure 3: Classification of cases by exposure status



Limitations

1. **Missing deaths.** The linked HES-mortality dataset only includes deaths for individuals that "exist in HES" (i.e. have a prior hospital admission or A&E visit). The SCCS method only requires exposed cases so this is not a major problem, but we will attempt to report the number of missing deaths by comparing the data to an unlinked mortality database.

2. **Misclassification of hospital admissions ending in death according to overdose vs. other causes.** This may occur, for example, if diagnoses were changed to incorporate events that occur after admission, including death. For example, if a patient was admitted for treatment of an injecting-related abscess and then used drugs while admitted and died as a result, the diagnostic codes in HES may be adjusted to include the overdose. This may mean we incorrectly classify the patient as being admitted for the overdose, when in fact the admission was due to another cause.

3. **Limitations related to the case definition:**

    a. The ICD-10 codes will capture some deaths related to pain relief rather than non-therapeutic or illicit drug use (e.g. heroin use). In future, it may be possible to improve the specificity of the case definition using linkage to NDTMS.

    b. The ICD-10 code T40.6 ('poisoning due to other and unspecified narcotics') may occasionally relate to non-opioid related deaths.

    c. ICD-10 codes do not allow reliable distinction of different opioids (such as heroin- or methadone-specific deaths), particularly where T40.2 ('other opioids, including codeine and morphine') is used.

    d. Some opioid-related deaths may not have a specific ICD-10 code, and instead have a general code such as T50.9 ('poisoning by other and unspecified drugs'). These deaths will not be captured in the study.

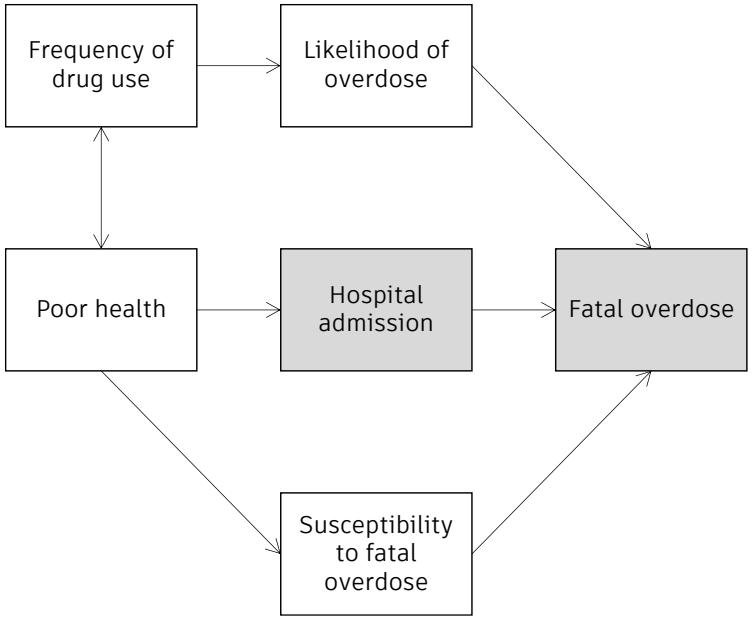
4. **The design estimates relative effects only.** The design is case-only and therefore cannot estimate the rate or risk of fatal overdose in the population.

5. **It may be difficult to evaluate intent.** Although some ICD-10 codes give information about intent (i.e. whether a death was accidental or a suicide), these may not be consistent or reliable. The descriptive analysis will show what proportion of deaths were deemed accidental vs. suicides, but we will not analyse this further.

6. **Some time-varying confounders will not be measurable**. While the SCCS eliminates time-invariant confounders, there may be time-varying confounders that are not measured. In particular, changes in drug use may be associated with both increased risk of hospital admission (for example if an increased frequency of injecting led to increased risk of skin infections), and also increase the risk of fatal overdose. A possible mechanism of time-varying confounding is shown in figure 4. The period before admission (risk period Z) may provide insight into time-varying confounding. For example, if both the pre-admission period and admission have a similar raised risk of

fatal overdose, we could assume that the increased risk associated with admission is related to time-varying confounders such as those in figure 4.

Figure 4: time-varying confounding



Ethics and approvals

The self-controlled case series using linked ONS mortality and Hospital Episode Statistics data has been approved by the PHE Research Ethics and Governance Group (PHE REGG), ref R&D412, on 26 October 2020. The use of PHE 'Data Lake' data for this analysis is approved by the PHE Alcohol, Drugs, Tobacco and Justice Division.

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